Prostate Cancer

Extended 12-Core Prostate Biopsy Increases Both the Detection of Prostate Cancer and the Accuracy of Gleason Score

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Abstract

Objective: To evaluate the effect of extended 12-core prostate biopsy in improving the detection rate of prostate cancer and increasing the accuracy of Gleason score.

Methods: This study included 113 patients who underwent TRUS-guided lateral sextant biopsy (group I) and 176 patients who underwent extended 12-core biopsy (group II). Inclusion criteria for prostate biopsy were elevated serum PSA levels (> 3.0 ng/ml) and/or suspicious digital rectal examination (DRE).

Results: Clinical characteristics were similar in both groups. Cancer was detected in 28 (24.8%) and 64 (36.4%) patients in group I and II respectively, $\chi^2 = 4.26, p = 0.039$. Among patients with cancer in group I, 14 were treated by radical prostatectomy (RP). The median Gleason sum was 6 (range 3–8) and 7 (range 5–9) for needle and prostatectomy specimens respectively. There was an agreement between the biopsy and prostatectomy Gleason sum in 7 (50%) patients while the biopsy Gleason sum was lower in 7 (50%) cases. Among patients with cancer in group II, 27 were treated by RP. The median and the range of Gleason sum was the same for needle and prostatectomy specimen (median 6, range 4–9). There was an agreement between the biopsy and prostatectomy specimen in 23 (85.2%) patients while the biopsy sum was lower than prostatectomy in 4 (14.8%) patients. The agreement between the biopsy and prostatectomy specimen was significantly higher in group II (82.5%) than group I (50%), Fisher’s Exact Test, $p = 0.026$.

Conclusion: Extended 12-core prostate biopsy significantly increases both the detection rate of prostate cancer and the accuracy of biopsy Gleason score.

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1. Introduction

The wide spread use of prostate specific antigen (PSA) and transrectal ultrasound (TRUS)-guided needle biopsy dramatically improved the detection rate of early prostate cancer [1,2]. The TRUS-guided sextant biopsy technique introduced by Hodge et al. [1] has become the gold standard method for the diagnosis of prostate cancers. Recently, many reports have shown that sextant biopsies do not detect all significant cancers [3–5] and more cores should be taken to have better cancer detection rate. Gleason sum is an important predictor factor of outcome of prostate cancer treatment [6] and therefore, correct grading helps in decision making for appropriate treatment. However, the accuracy of Gleason sum obtained from prostate biopsies poorly correlate with Gleason sum of RP [7]. Recently, it was reported that extended needle biopsy can improve the concordance with the final Gleason sum obtained from the RP. [8,9]. In this study, we evaluate the possible effect of extended 12-core prostate biopsy in improving detection rate of prostate cancer and increasing the accuracy of Gleason score.

2. Materials and methods

This study was conducted on two groups of patients suspected of having prostate cancer who underwent TRUS-guided biopsy. The first group included 113 patients who underwent laterally directed sextant biopsy in the period of February 2000 to June 2002. The second group included 176 patients who underwent extended 12-core biopsy in the period of July 2002 to December 2004. Inclusion criteria for biopsy were elevated serum PSA (above 3.0 ng/ml) and/or suspicious DRE. None of our patients was exposed to TRUS-biopsy before included in the study. PSA was measured by Chemiluminescence Technique (DPC, NJ, USA) using Immulite Autoanalyser. All the specimens were processed within 3 hours of collection and assayed within 12 hours.

TRUS was performed with the patient in the left decubitus position, using a Cheetah 2003 scanner with a 7–10 MHz biplaner attached probe, type 8551 (B&K Medical AS, Glostrup, Denmark). All the DRE and TRUS-biopsy were performed by the same urologist (A.E.). Twenty ml of Lidocaine gel was introduced intra-rectally 15 minutes before the procedure. Prostate volume was routinely measured during TRUS using ellipsoid volume calculation (height × width × length × π/6) (0.52). Biopsies were taken during longitudinal scanning, using 18-G tru-cut biopsy needles loaded on a biopsy gun. The sextant biopsies were taken laterally in the prostate from the base, midlobe and apex. In extended 12-core biopsy scheme, beside the lateral sextant cores, 3 cores were taken from each side from the far lateral areas of the prostate at the base, midlobe and near the apex. In either schemes, patients who had hypo-echoic areas or palpable lesions not visible on ultrasound were subjected to additional directed 2 biopsies.

All the needle and prostatectomy specimens were examined by the same reference Uro-pathologist (M.K.) who was blinded to the cases. Chi-Square test ($\chi^2$-test) was used for comparison between qualitative variables. Fisher’s Exact Test was used for comparing two qualitative variables whenever Chi-Square test was not appropriate (if the expected value of 25% of the cells was less than 5). $p < 0.05$ was considered statistically significant.

3. Results

Median patient age was 64 (range 49–79) and 63 years (range 48–81) for group I and II respectively. Median pre-biopsy PSA was 7.9 (range 2.4–13.3) and 7.4 ng/ml (range 2.2–12.4) and median prostate volume was 39 (range 23–65) and 43 cc (range 20–71) for group I and II respectively. Table 1. The indication of biopsy was due to abnormal DRE in 36 (31.9%) and 50 (28.4%) patients, high PSA in 61 (54%) and 98 (55.7%) patients and high PSA with abnormal DRE in 16 (14.1%) and 28 (15.9%) patients of group I and group II respectively. Out of the first group, 28 (24.8%) patients had prostate cancer, 14 of them were treated by RP whereas 64 (36.4%) patients of group II had cancers, 27 of them were treated by RP.

The overall cancer detection rate by was significantly higher in group II (36.4%) than in group I (24.8%), $\chi^2 = 4.26, p = 0.039$, Table 2. Only in 2 patients of group I and in 1 patient of group II, the cancer was detected only in the directed biopsies. Excluding these patients did not change the findings ($\chi^2 = 5.01, p = 0.025$), so, they were not excluded from the statistical analysis. Within group I, patients with prostates ≥50 cc constitute 31.9% (36/113) whereas patients with prostates <50 cc constitute 68.1% (77/113) with cancer detection rate of 19.5% (7/36) and 27.2% (21/77) respectively ($\chi^2 = 0.81, p = 0.36$). Within group II, patients with prostates ≥50 cc constitute 35.8% (63/176) whereas patients with prostates <50 cc constitute 64.2% (113/176) with cancer detection rate of 38% (24/63) and 35.4% (40/113) respectively ($\chi^2 = 1.39, p = 0.23$). Cancer detection rate in

| Table 1 – Clinical data of patients undergoing 6 and 12-core biopsy |
|---------------------|---------------------|---------------------|
|                      | Group I Median (range) | Group II Median (range) | $p$ value |
| Age (years)         | 64 (49–79)            | 63 (48–81)            | 0.41     |
| PSA (ng/ml)         | 7.9 (3–13.1)          | 7.4 (3–12.1)          | 0.39     |
| Prostate volume (cc)| 39 (23–65)            | 43 (20–71)            | 0.42     |
prostates \( \geq 50 \text{ cc} \) was significantly higher in group II (38\%) than group I (19.5\%), \( \chi^2 = 3.71, p = 0.049 \), Table 2. In group II, cancer was detected at the sextant biopsy in 47 (26.7\%) patients, at the extra 6-core in 12 (6.8\%) patients and at both of them in 5 (2.9\%) patients.

Median age for patients with histologically proven prostate cancer was 62 (range 51–74) and 60 years (range 49–73) for group I and II respectively. Median pre-biopsy PSA was 8.2 (range 2.7–13.2) and 7.5 ng/ml (range 2.4–12.4) whereas the median prostate volume was 40 (range 24–63) and 45 cc (range 21–71) for both groups respectively.

In group I, the median Gleason sum for needle biopsy was 6 (range 3–8) while in prostatectomy specimen was 7 (range 5–9). There was an agreement between the Gleason sum detected in biopsy and that detected in prostatectomy specimen in 7 (50\%) patients while in the other 7 (50\%) patients the biopsy Gleason sum was lower than prostatectomy specimen. The difference between the two Gleason sum was 1 in 5 (35.7\%) patients and 2 in 2 (14.3\%) patients, Table 3.

In group II, the median and range of Gleason sum was the same for biopsy and prostatectomy (median 6, range 4–9). There was an agreement between the biopsy and prostatectomy specimen in 23 (85.2\%) patients. Gleason sum detected in biopsy was lower than that of prostatectomy in 4 (14.8\%) cases. The difference between the two Gleason sum was 1 in 3 (11.1\%) patients and 2 in 1 (3.7\%) patient, Table 3.

Comparing both groups, the agreement between the biopsy and prostatectomy specimen was significantly higher in group II (85.2\%) than in group I (50\%), Fisher’s Exact Test, \( p = 0.026 \). Similarly, regarding primary Gleason pattern, biopsy and prostatectomy agreement was 25 of 27 (92.6\%) and 9 of 14 (64.3\%) for 12-core and sextant biopsy respectively, Fisher’s Exact Test, \( p = 0.031 \).

### 4. Discussion

TRUS-guided systematic prostate biopsy remains the standard test for diagnosing early prostate cancer. The parasagittal sextant biopsy technique introduced by Hodge et al. [1] has become standard and been shown to outperform directed biopsies. However, several studies have shown that parasagittal biopsies provides insufficient material to adequately detect all significant cancers [3–5,10]. These results were reproduced by Epstein et al. who found no cancer in 31\% of repeated random sextant biopsies that were performed on a set of 193 radical prostatectomies [11]. In 1995, Stamey suggested shifting the sextant biopsies more laterally in order to sample better the peripheral zone where most of the cancers is located [12]. However, even with this modification, recent reports have shown that a single set of lateral sextant biopsies may miss clinically detectable prostate cancer in up to 34\% of men. [5,13] and that a larger numbers of cores should be taken to have better cancer detection rate.

Various studies consistently demonstrated that, in cases with a small focus of cancer in a sextant biopsy set, less than 10\% of patients have a small cancer in the prostate and consequently more than 90\% have a cancer of a size that generally has to be considered significant [14–16]. A small focus of cancer on biopsy therefore cannot be used as a basis for less aggressive treatment. The reason for the limited predictive value of a small focus of cancer on

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N.B. Higher Gleason sum at radical prostatectomy are highlighted and underlined.
biopsy is probably the same for the fact that some prostate cancers are not detected at all, namely sampling error. It has subsequently been reported that, the 10 and the 12-core biopsy significantly increased cancer detection rate without significant morbidity and without increasing the number of insignificant cancer [10,17–19]. Invariably, increasing the number of biopsies has seemed the best and most logical way to decrease sampling error and therefore increase the capacity of biopsy sets to predict cancer. In our study, the extended 12-core biopsy significantly increased cancer detection rate compared to the sextant biopsy. This series shows the clear advantage of 12-core biopsy over sextant biopsy.

The influence of prostate volume on the positive yield of the systematic biopsy is logical and has been proved in more than one study. Brawer recently concluded that positive yield of the systematic biopsy decreases significantly when gland volume is >55.6 c.c. [20]. In another study, there was a significant decreased yield of sextant biopsy with increasing gland volume [21]. The highest positive biopsy rate (39.6%) was among prostates ≤20 c.c. and the lowest positive biopsy rate (10.1%) was obtained in glands between 80–90 c.c. [21]. In both studies, the range of prostate volumes was very wide (4.5–311.5 cc in Brawer series) and the significant difference in cancer detection was found between extremes of volumes.

In our study, the range and median of prostate volumes in both groups were comparable. Cancer detection rate in prostates ≥50 cc was significantly higher in group II than in group I which is expected due to better sampling. Within each group, there was no significant difference in cancer detection rate between prostates ≥50 cc and <50 cc. This may be due to narrow range of prostate volumes and less number of patients compared to the other series. The increased yield with in group II is a function of more extended sampling and can not be attributed to differences in prostate volumes. No prospective study using the prostate volume as a determinant of the number of cores obtained was performed. This would provide the answer to the question whether the increased yield with more cores is a function of better sampling but this seems obvious.

The grade of prostate cancer is the strongest predictor of its clinical course. It is often underestimated on needle biopsy and an important reason for this undergrading lies in sampling error. Prostate cancer is often heterogeneous, consisting mostly of generally well differentiated tumors that contain foci of high grade cancer. These foci of high grade cancer are easily missed by biopsies [14,16]. Consequently, in cases where prostate cancer is found on biopsies, undergrading will occur more frequently than overgrading. Also, prostate cancer is a multifocal disease with multiple tumor foci could be detected in more than half of the RP specimens [22,23]. The needle biopsy may not contain a cancer focus of the biologically most relevant tumor. Furthermore, grading error on needle biopsy could arise from inter-observer variability and subjectivity in the interpretation of tumor pattern with subsequent failure to appreciate foci of high grade cancer.

Probable because of the fact that multiple factors influence grading error in needle biopsy, reported frequencies of cases in which prostate cancer grade is underestimated on prostate biopsy show a wide variation and range from 23% to 50% [7,9,24]. In this study, there was 50% undergrading of Gleason sum on needle biopsy in patients of group I compared to 14.8% in patients of group II. Since all the needle biopsies and the prostate specimens were examined by the same pathologist, observer variability has no role in these undergrading results. The significantly less undergrading in group II could only be attributed to better sampling reducing the sampling error which is obviously more frequent with sextant biopsy. There was no overgrading in this series, may be due to the small number of patients as undergrading occurs more frequently than overgrading.

There is a trend to treat tumors that are thought to be small and well differentiated less aggressively. This trend may be dangerous, because tumors that are thought to be small and well differentiated on biopsy, could turn out to be large and poorly differentiated because of sampling error. Our data demonstrates that, increasing the number of biopsies leads to an increase in the cancer detection rate and enhancement in the prediction of tumor grade in the RP specimen.

In conclusion, extended 12-core prostate biopsy significantly increases both the detection rate of prostate cancer and increases the accuracy of biopsy Gleason score.

References


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The likelihood to detect prostate cancer depends on three factors: the location of biopsies, the number of biopsies taken and the volume of the prostate. A good biopsy protocol should consider all of these.

The optimal biopsy pattern is still not found and there are many controversies i.e: should we perform random biopsies or lesion-directed? How many cores should we take for optimal diagnosis? Which prostate areas should be biopsied to give the best results? How can we avoid to find clinically insignificant tumors. How many lateral biopsies should be performed?

Many authors like Bauer et al., Presti et al., Gore et al., Ravery et al., Wendi et al. showed the superiority of an extended biopsy protocol in respect to the traditional sextant biopsy regarding the overall cancer detection rate and the agreement between Gleason score of biopsies and final pathological specimen. More sceptic authors advocate that with extended protocols more clinically insignificant tumors are detected and the chance of being diagnosed with prostate cancer is 6 times higher than its likelihood of dying of it.

On the other side Eskew et al. could not find any association between an extended biopsy technique and the detection of smaller or clinically insignificant tumors but Babaian et al. did so.

However there is a lack of evidence what, how and when we should do. Every centre is actually performing its own protocol, modifying it lateron, obtaining improved results. But generally there is a lack of standardization and the different series are difficult to compare. Therefore the field of speculation is wide.

This paper is emphasizing the superiority of an extended protocol but implicates all limitations mentioned before.