ORIGINAL ARTICLE

Is extended biopsy protocol justified in all patients with suspected prostate cancer?

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Abstract

Objective: To determine the significance of an extended 10-core transrectal biopsy protocol in different categories of patients with suspected prostate cancer using digital guidance.

Materials and Methods: We studied 125 men who were being evaluated for prostate cancer. They all had an extended 10-core digitally guided transrectal prostatic biopsy done for either an elevated serum prostate-specific antigen (PSA) or an abnormal digital rectal examination finding or both. Sextant biopsy samples were collected first, followed by additional four lateral biopsies in all patients. Both groups of specimens were analyzed separately. The cancer detection rates of both sextant and extended 10-core biopsy protocols at different PSA levels and digital rectal examination (DRE) findings were determined and compared. The level of significance of difference in cancer detection was determined using Pearson's Chi square test with level of significance set at <0.05.

Results: The overall cancer detection by the extended technique was 61 (48.8%) cases while the sextant protocol detected cancer in 52 cases. The 10-core extended protocol yielded an increase in cancer detection rate of 14.8% but the improvement in detection rate was only statistically significant in the sub-set of patients with PSA between 4.1 and 10 ng/mL, with or without abnormality on DRE, with an overall increase detection rate of 33%.(*P*=0.04)

Conclusion: Our study has shown that a 10-core prostate biopsy protocol significantly improves cancer detection in patients with suspected early cancer. It should therefore be the optimum biopsy protocol for patients with gray-zone PSA value, with or without abnormal DRE.

Key words: Biopsy, detection rate, digital rectal examination, extended, prostate cancer, prostate-specific antigen, sextant

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Introduction

Carcinoma of the prostate is the second leading cause of death due to neoplastic diseases and accounts for approximately 10% of all malignant neoplasms in men worldwide.[1] This disease is an age-related pathology and as such destined to be increasingly relevant in an aging general population.[2] The preemptive measures and strategies being developed are aimed at diagnosing tumors at an earlier stage with the aim of improving survival. The major tools for early diagnosis include the prostate-specific antigen (PSA) level, digital rectal examination (DRE), and imaging studies.[3]

With the emphasis on early detection of prostate cancer, the importance of prostate biopsy methods have been recognized. A sextant (six-core) biopsy is generally regarded as adequate to make the diagnosis as demonstrated by Hodge *et al.*,[4] and it is still being practiced by most urologists. However, some researchers have demonstrated an increase in cancer detection if an extended biopsy protocol, which incorporates biopsy of the peripheral zone into the traditional para-sagittal sextant biopsies, is employed (ranging from eight to 26 cores).[5-8] Systematic biopsy of the peripheral zone (PZ), which can be obtained by laterally directing the biopsy needle in the prostate, has been found to increase the

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detection rate of prostate cancer significantly.[9] However, no study on the usefulness of extended biopsy protocol has been done in our environment or sub-region to the best of our knowledge. There is, therefore, a need to evaluate the biopsy protocols with different number of cores, with the aim of determining the optimal biopsy protocol for patients at risk of prostate cancer in our environment. The main aim of this study was to determine the significance of extended 10-core biopsy protocol on cancer detection in different categories of patients being evaluated for prostate cancer.

Materials and Methods

This study was carried out prospectively amongst 125 men who were being investigated for cancer of the prostate between January and December 2010. Informed consent from the patients and approval from the ethical committee of Lagos University Teaching Hospital were obtained. They all had a DRE, PSA measurement, and prostate scan followed by prostate biopsy. Indications for prostate biopsy included presence of one or combination of elevated PSA and abnormal DRE, irrespective of findings on trans-abdominal ultrasound of the prostate. All patients had an extended transrectal digitally guided prostate biopsy using a size 16 spring-loaded semi-automated Tru-Cut biopsy after rectal lubrication with 2% xylocaine hydrochloride jelly. All patients also had intravenous Pentazocin 30 mg, Diazepam 5 mg, and Ciprofloxacin 200 mg stat before the procedure. "Sextant biopsies" were obtained from the apex, middle, and base of each lateral lobe para-sagittally. Additional four core biopsies, two cores from each lateral lobe, were obtained in all patients to make extended 10-core biopsies from the far lateral portion of the prostate by directing the needle laterally under digital guidance. These additional four cores were put together in a separate bottle and labeled as the "Lateral biopsies". Samples were analyzed separately by the same pathologist to avoid inter-observer error. The results of biopsy histopathology were documented as malignant, benign, or prostatic intra-epithelial neoplasia (PIN). The overall histopathology from combination of the two biopsy protocols' specimens termed "Extended biopsies" was reported as well as the results of Sextant biopsies separately.

A structured pro forma was used to obtain relevant patients' information including the demographic data, examination findings, results of PSA, indication(s) for biopsy, and histopathology results. The data obtained from all patients on the pro forma were analyzed with Statistical Package for the Social Science (SPSS), version 16. The results were displayed in tables and charts. Cancer detection rates of sextant and extended biopsy protocols were determined and compared at different PSA ranges and different DRE findings. Level of significance of difference in cancer detection was determined using Pearson's Chi square test with level of significance set at <0.05.

Results

A total of 125 patients were enrolled for the study. Ages of patients ranged from 47 to 95 years with a mean age of 67.2 ± 10.5 years. Ninety-three (74.4%) were men above 60 years of age. Men in their seventh decade of life accounted for 41.6% of the entire study population. [Table 1]

The PSA range was 0.6 to 149 with a mean of 23.4 ± 18.46 ng/mL. Majority of study population, consisting of 78 patients (62.4%), had elevated serum PSA of above 10.0 ng/mL. Thirty-six (28.8%) had borderline (gray zone) PSA of 4.1–10.0 ng/mL while 11 (8.8%) had a normal PSA level of less than 4 ng/mL. [Table 2]

Indications for prostate biopsy were elevated PSA alone in 41 (32.8%) patients, abnormal DRE alone in 12 (9%), and combination of elevated PSA and abnormal DRE finding(s) in 72 (57.6%). A total of 84 (67.2%) patients had palpable abnormalities in the prostate while a total of 113 (90.4%) had elevated PSA.

Sixty-one (48.8%) of the 125 patients had malignant histology, 60 (48%) were benign, while 4 (3.2%) had PIN. All malignant biopsies were adenocarcinomas.

Amongst the 61 patients diagnosed to have cancer by the extended (combination) technique, only 52 of them were detected by the sextant technique of biopsy with an improvement of cancer detection in nine patients, amounting to an increase of 14.8%. This was found to be statistically significant with a *P*-value of 0.046. [Figure 1]

Table 1: Ages of patients

Age range	Frequency (N)	Percent (%)
41–50	6	4.8
51–60	26	20.8
61–70	52	41.6
71–80	30	24.0
81–90	8	6.4
91–100	3	2.4
Total	125	100

Table 2: Distribution of ranges of PSA

Ranges of PSA (ng/mL)	Frequency (N)	Percent (%)
0–4.0	11	8.8
4.1–10.0	36	28.8
10.1–20.0	26	20.8
20.1–30.0	15	12.0
30.1–40.0	10	8.0
40.1–50.0	8	6.4
>50.0	19	15.2
Total	125	100

Cancer detection rates of sextant and extended biopsy protocols were determined at different levels of PSA. There was statistically significant increase in detection rate of 33% by the extended protocol at PSA range of 4.1–10 ng/mL with *P*-value of 0.04. Detection was improved in PSA range of 10.1–20.0 ng/mL by 20% but was not significant (0.067). There was no significant difference in detection rate at all levels of PSA above 10 ng/mL. ($P>0.05$) [Figure 2]

Amongst the 45 patients with normal DRE, sextant protocol detected cancers in 12 (26.7%) patients while 16 (35.6%) were detected by the extended protocol with an improvement in detection rate of 25%. This is statistically significant with *P*-value of 0.047. Cancer detection rates amongst individuals with abnormal DRE were 40 (50%) and 45 (56.3%) by sextant and extended protocols, respectively, with an improvement of 11.1%. This is not statistically significant. ($P=0.186$.)

Cancer detection by sextant and extended protocols in relation to the DRE findings amongst patients with gray-zone PSA showed detection rates of 12.5% (2/16) and 25% (4/16), respectively, with an improvement of 50% in patients with normal DRE findings. Detection rates were 30% (6/20) and 40% (8/40), respectively, with an increase of 25% in those with abnormal DRE findings. Both were statistically significant with *P*-values of 0.037 and 0.049, respectively.

The range of Gleason score was 3–10 with a mean of 6.3 amongst the 61 patients diagnosed to have cancer. In 38 patients, the scores and the grades were exactly the same for cancers detected by both sextant and extended biopsies. The Gleason grades were different but with same score in 5 cases. Both grades and score differed in 6 cases with an average increase in the Gleason score of 0.8. Nine (14.8%) cases were detected by extended biopsies only. The average Gleason score for these additional cases was 6.4 with no significant difference with others. Four (66.7%) of these six cases were in the gray zone with an average score of 6.37. There was no significant difference in the scores of additional cases detected by the extended biopsies in patients with PSA between 4 and 10 ng/mL and other PSA ranges as well.

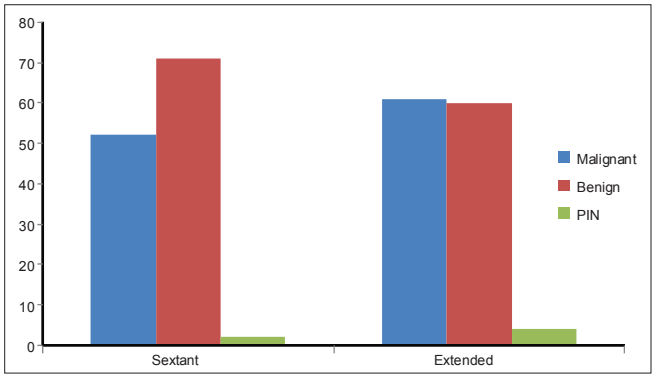

Figure 1: Comparison of overall detection by biopsy protocols

Discussion

Prostate cancer is a global disease and its detection has greatly been facilitated by the discovery of PSA measurements.[10] The optimal biopsy protocol for patients has been a matter of debate with emphasis on biopsy protocol that maximizes cancer detection with minimal discomfort and an acceptable complication rate.

In this study, men above 60 years of age constituted about three-quarters of the study population, signifying that prostatic diseases are common among the elderly.[1,2] The mean age of 67.2 years in this study agrees with findings of other researchers in the literature.[11-13]

Elevated total PSA level was the commonest indication for biopsy. Forty-one (33%) patients had elevated PSA only while 72 (58%) had elevated PSA in addition to abnormal DRE findings. Prior to the PSA era, nearly 70% of men diagnosed with prostate cancer already had extra-prostatic or metastatic disease, as an abnormality in the prostate had to be palpably evident before a biopsy was performed.[14] With the advent of PSA evaluation, majority of patients are diagnosed at an early stage, including asymptomatic patients who had biopsy after PSA screening in the advanced countries. This is, however, not entirely true in sub-Saharan Africa where the benefit of PSA as a screening tool has not been fully used. This is reflected in this study as majority, 84 (67.2%) patients, had palpable abnormalities in the prostate at presentation while only 41 (32.8%) had biopsy on account of PSA alone. However, this is in contrast to a study carried out by Awojobi *et al*.[15] in Ibadan more than two decades ago where abnormal DRE was the sole indication for biopsy in more than 65% of patients. This implies that development of PSA measurement has significantly changed the way men with suspected prostate cancer are evaluated in our environment and has also enabled diagnosis of prostate cancer in men with early-stage disease without clinical evidence of malignancy.

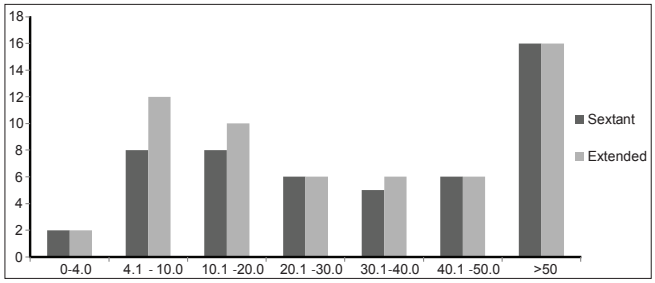

Figure 2: Comparison of cancer detection by techniques at different PSA ranges

The overall cancer detection rate was 48.8% in this study. This is higher than the findings in most other studies where detection rates vary from 18.6 to 42.6%. This may not be unconnected with late presentation in our environment.[12,16] This fact is supported by the fact that 78 (62.4%) patients in this study had PSA of > 10ng/mL.

Among the 61 patients that were positive for malignancy by extended biopsy protocol, sextant protocol detected cancers in 52 patients. Considering cancer detection rate of both biopsy protocols at different PSA levels, we observed that there was a statistically significant improvement in detection rate by the extended over the sextant protocol in patients with PSA range of 4.1–10 ng/mL. In this subset, the sextant technique detected eight (8) cancers only while the extended technique detected a total number of twelve (12) cases. This is a 33.3% increase in prostate cancer detection rate by the addition of the four lateral biopsies in this category of patients and was found to be statistically significant ($P=0.04$). This may be due to small size and volume of the disease in early stages as opposed to large size and volume in advanced malignancies, which can be readily detected by sextant or targeted biopsies. In addition, the peripheral zone, which is usually left unsampled in sextant para-sagittal biopsies, is believed to be the site of origin for most early cancers before extension to other aspects of the prostate.[17,18] However, for PSA ranges above 10 ng/mL, cancer detection rates were not affected significantly by increased number of cores. Though detection was improved by extended protocol in patients with PSA between 10.1 and 20.0 ng/mL, the improvement was found to be statistically insignificant. ($P=0.067$) Based on the mean PSA value of 23.4 ng/mL in this study, it could be assumed that most of the patients were likely to have advanced disease with greater tumor size/volume. This is probably responsible for the similar detection rates by sextant and extended biopsy protocols in all categories of patients with elevated PSA level more than 10.0 ng/mL. Djavan *et al.*[19] in their study also documented that sextant biopsy is sub-optimal in patients with gray-zone PSA between 4 and 10ng/mL and suggested extended biopsy protocol for these patients. This finding also suggests that sextant protocol would still be appropriate in advanced cases.

It is a well-known fact that the ability of serum PSA to distinguish between benign and malignant conditions is particularly poor in the intermediate range of 4.1 and 10 ng/mL.[10] Thus, additional PSA parameters like PSA velocity, PSA density, and PSA adjusted for transitional zone have been suggested to improve the sensitivity and specificity of PSA. This study has demonstrated that performing an extended prostate biopsy is another important way of improving cancer detection in these patients.[8]

There was significant improvement in the diagnostic yield of 25% by the extended 10-core biopsy technique over the conventional sextant technique with a *P*-value of 0.048 in men with normal DRE findings, irrespective of their PSA values. This was not so in patients with clinically palpable abnormalities where detection was increased by 11.1%. This may be due to the fact that clinical evidence of malignancy on DRE often connotes advancement with possible increased tumor volume in contrast to early cancers without palpable abnormality because of small tumor size. This shows that DRE finding is another important factor in determining the best biopsy technique for patients. An extended 10-core technique is, therefore, highly recommended in patients who have normal DRE, irrespective of their serum PSA level.

In this study, there was a significant total improvement of 33% in diagnostic yield in patients with gray-zone PSA, with or without abnormality on DRE. However, the improvement is much higher in patients with both gray-zone PSA and a normal DRE, with an increase in cancer detection of 50% as opposed to 25% increase in those with gray-zone PSA and palpable abnormality. Therefore, one can safely conclude that a PSA of 4.1–10.0 ng/mL in the presence of a normal DRE is a very strong indication for an extended 10-core prostatic needle biopsy.

The range of Gleason score was 3–10 with a mean of 6.3. This implies that most of the patients had moderate grade histology. Though there were few disparities in the Gleason scores and grades, cancers detected by both sextant and extended protocols were similar in patients in all PSA ranges. Cancers detected by extended protocol only also have similar characteristics in patients with PSA between 4 and 10 ng/mL and in other PSA ranges. However, the significance of this cannot be stated with certainty and further studies with higher number of study populations will be required. Also, the result of this study does not establish any direct relationship between PSA levels and Gleason scores.

Conclusion

With an overall improvement in detection rate of 33% in patients with gray-zone PSA irrespective of the DRE findings and a 50% improvement in patients with gray-zone PSA and normal DRE findings, this suggests that an extended 10-core biopsy technique should be the appropriate or optimal biopsy protocol in patients with gray-zone PSA. This biopsy technique is much more important in patients with a gray-zone PSA and normal DRE findings. The use of the traditional sextant protocol in patients with high PSA and abnormal DRE findings is still recommended.

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