Detection of Prostate Cancer: Comparison of cancer detection rates of Sextant and Extended Ten-core Biopsy Protocols.

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Summary

Aims and Objectives: To compare the cancer detection rates of sextant and ten-core biopsy protocol amongst patients being evaluated for prostate cancer.

Patients and methods: This is a prospective study involving 125 men with suspicion of prostate cancer. They all had an extended 10-core transrectal digitally-guided prostatic biopsy using Tru-Cut needle. Indications for biopsy were presence of one or more of the following: elevated Prostate Specific Antigen (PSA), abnormal Digital Rectal Examination (DRE) findings and abnormal prostate scan. Sextant biopsies were collected first, followed by four lateral biopsies in all patients. Both groups of specimen were kept and analyz\sed separately by the same pathologist. The cancer detection rates of sextant and extended (combination of sextant and lateral) 10-core biopsy protocols were determined and compared. Pearson's Chi square and McNemar tests at two degrees of freedom with level of significance set at 0.05 (P <0.005) were used to determine the statistical significance.

Results: The overall cancer detection rate of 10-core prostate biopsy was 48.8%. Of all positive biopsies, the sextant biopsy protocol detected 52 cancers (85.2%) while the lateral biopsy protocol detected 58 cases (95.1%). Three (3) cancers were detected by the sextant protocol only while the lateral protocol detected nine (9) cancers where sextant technique was negative for malignancy. Ten-core extended protocol showed a statistically significant increase of 14.8% over the traditional sextant. (P=0.046). The overall complication rate of ten-core biopsy was 26.4% and the procedure was well tolerated in most patients.

Conclusion: We conclude that a ten-core prostate biopsy protocol significantly improves cancer detection and should be considered as the optimum biopsy protocol.

Keywords: sextant, extended, biopsy, PSA, DRE, prostate cancer, detection rate

Carcinoma of the prostate (CaP) is a common malignant disease in men over sixty years of age[1, 2]. It is a significant health care burden due to its high incidence, mortality and the cost associated with its detection and treatment[3]. Various epidemiological data have supported the high incidence and mortality of this malignancy amongst the blacks [4, 5].

Currently, histo-pathological examination of a needle core-biopsy of prostatic tissue is the "gold standard" modality by which a suspected diagnosis of prostate carcinoma is confirmed. Transrectal ultrasound (TRUS) guided needle biopsy is the procedure of choice for obtaining high-quality tissue cores for histo-pathological analysis [6]. However, in developing countries such as ours where transrectal ultrasound probe is not readily available thus digitally-guided prostate biopsy has been the usual procedure over the years[7]. The main indications for prostate biopsy are elevated prostate-specific antigen (PSA), abnormal digital rectal examination(DRE) findings and abnormal findings on

imaging studies [6].

Prostate biopsy techniques have evolved considerably. The initial targeted or lesion directed biopsies gave way to systematic para-sagittal sextant (6 – core) biopsy when Hodge et al[8] in 1989 demonstrated its superiority over lesion-directed biopsies. This is still being practised by most urologists worldwide. Recently, many researchers have shown an improvement in the cancer detection rate if an extended biopsy protocol is employed [9-12]. These extended biopsy protocols range from eight to twenty-six cores.

Clinically, the sampling error of the sextant biopsy template has been evident by the 20% to 30% cancer detection rate in men undergoing a repeat transrectal ultrasound guided biopsy[10, 13]. This has led investigators to question the sampling adequacy of the standard sextant prostate biopsy template and to propose alternate "extended pattern" biopsy schemes to improve prostate cancer detection. The alternate prostate biopsy templates aim to improve sampling of the prostate by either increasing the number of core biopsies taken and/or by directing the biopsies more laterally to better sample the anterior horn (the far lateral regions of the peripheral zone). Most of the studies on different prostatic biopsy protocols were done under transrectal ultrasound guidance [9-11]. Therefore, this study aims at determining the significance of increasing number of cores on cancer detection using digitally-guided technique. It compares the cancer detection rates of sextant and extended ten-core prostate biopsy techniques.

Patients and methods

This prospective study was carried out amongst 125 men who were being investigated for cancer of the prostate at the Lagos University Teaching Hospital, Idi-araba, Lagos. Ethical committee approval was obtained as well as informed consent from all the patients. 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, abnormal digital rectal examination findings and abnormal imaging on trans-abdominal scan of the prostate. We discontinued non-steroidal anti-inflammatory drugs (NSAIDs) for ten (10) days before the biopsy in those on such medications. Before the procedure, all patients had intravenous Pentazocin 30mg for analgesia, Diazepam 5mg as sedative and Ciprofloxacin 200mg stat as antibiotic prophylaxis. Biopsy was then performed in left lateral position using a size 16 spring-loaded semi-automated Tru-Cut biopsy needle about ten minutes after rectal lubrication with about 10 ml of 2% xylocaine hydrochloride jelly. The left index finger was introduced into the rectum with the spring-loaded biopsy needle to guide the positioning of the Tru-Cut needle on the prostate. 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 ten-core biopsies from the far lateral portion of the prostate. The initial six cores of tissue from the six zones were put together in one specimen bottle containing formalin and labeled as the 'Sextant biopsies'(Protocol A) while the additional four cores were put together in a separate bottle and labeled as the 'Lateral biopsies' (Protocol B). The tissue samples in the two bottles were sent for histopathology and were analysed separately by the same pathologist to avoid inter-observer errors. The results of biopsy histopathology were reported as malignant, benign (benign prostatic hyperplasia and prostatitis) and prostatic intra-epithelial neoplasia (PIN). The overall histopathology from combination of the two biopsy protocols' specimens termed 'Extended biopsies' (Protocol C) was documented as well as the results of sextant and lateral biopsies. The histological type and Gleason grade/score of biopsies that were found to be malignant were also reported.

Relevant information was obtained using a structured pro forma including the demographic data, mode of presentation, examination findings and indication(s) for biopsy. Urine cultures were done before and after the procedure in all the patients and the results were documented. Complications and tolerability of the procedure, results of histopathology from sextant and extended biopsies were recorded separately including histological type, Gleason's grades and score. Patients were followed-up at the out-patient clinic six days after the procedure where history was taken and examination done to document complications.

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 as well as complication rates. Pearson's chi-square and McNemar tests at 2 degrees of freedom with level of significance (P) set at 0.05 ($P < 0.05$) were used to determine the statistical significance.

Results

One hundred and twenty-five (125) patients were recruited for the study. Ages of patients ranged from 47-95 years with a mean age of 67.2 ± 10.5 years. Ninety two (73.6%) were above 60 years of age. The peak age range was 61 – 70 years and accounted for 52 patients (41.6%) of the entire study population. (Figure 1)

Three (2.4%) patients were asymptomatic while 122 (97.6%) presented with various symptoms. Lower urinary tract symptoms (LUTS) alone were the presentation in majority of patients, 69(55.2%). Other presentations include features of local spread such as haematuria and haematospermia and distant metastasis including weight loss, limb weakness, bone pain, limb swelling and chronic cough as depicted below. (Table i)

The PSA range was 0.6 to 149 with a mean of 23.4 ± 18.46 ng/ml. The indications for prostate biopsy are shown

in figure 2. No patient had a biopsy for abnormal imaging alone. (Figure 2)

Histopathology in sixty one (48.8%) of the 125 patients was reported as malignant, 60(48%) were benign, while 4 (3.2%) had prostatic intra-epithelial neoplasia (PIN). All malignant biopsies were adenocarcinomas. Of these sixty-one patients with prostate cancer, sextant technique (Protocol A) detected 52(85%) and lateral biopsy technique (Protocol B) detected 58 (95%). Both sextant and lateral protocols yielded the same result. Three (2.4%) cancer cases were detected by sextant only but not by lateral biopsies while 9/61(14.8%) were detected by the lateral biopsy protocol only and not by the sextant protocol. (Figure 3)

The overall cancer detection rate by 10-core extended technique (protocol C) (sextant plus lateral) was 61 (48.8%). There was statistically significant increase in detection of 14.8% by 10-core extended over the sextant technique (P=0.046). There were however, no statistically significant differences in detection rate between sextant and lateral protocols (P =0.067) as well as between lateral and extended protocols (P=0.114). (Figure 4)

All the 61 malignant biopsies were assigned Gleason grade and score. The range of score was 3-10 with a mean score of 6.37 with a standard deviation (SD) of 1.53. Of 49(100%) patients detected by both sextant and lateral protocols, 38(77.6%) had the same Gleason grades and score while there was disparity in the Gleason grades but same score in 5(10.2 %). Gleason grades and score were both different in 6(12.2%) patients with a mean increase of 0.8 in score from the lateral biopsies. Pain level and tolerability of the procedure assessed by pain visual analogue scale showed that 20(16%) patients did not experience pain at all while 105(84%) patients had varying degrees of pain. Mild, moderate and severe pain were experienced in 66(52.8%), 26(20.8%) and 13(10.4%) patients respectively.

There were a total of fifty-eight (58) complications occurring in thirty-three (33) patients with an overall complication rate of 26.4%. Haematuria was the commonest complication occurring in 19(15.2%) patients while the least was haematospermia in 1(0.8%). Six (4.8%) patients had urinary tract infection with Escherichia coli being responsible for 4(66.7%) while Klebsiella spp. and Proteus spp. were responsible for 1 (16.7%) each. The frequency of each complication is shown in table ii below.

Table i: **Distribution of modes of presentation**

Symptoms	Frequency (n)	Per cent (%)
Asymptomatic	3	2.4
Lower Urinary Tract Symptoms Only	69	55.2
Local Invasion Only	2	1.6
Distant Metastasis Only	4	3.2
LUTS plus Local Invasion	7	5.6
LUTS plus Distant Metastasis	24	19.2
LUTS plus Local Invasion plus Distant Metastasis	16	12.8
Total	**125**	**100.0**

Table ii: **Complications of 10 core extended prostate biopsy**

Complications	Frequency (n)	Per cent (%)
Haematuria	19	15.2
Rectal bleeding	10	8.0
Deep perineal pain	9	7.2
Fever	8	6.4
Urinary tract infection	6	4.8
Epididymo-orchitis	2	1.6
Haematospermia	1	0.8

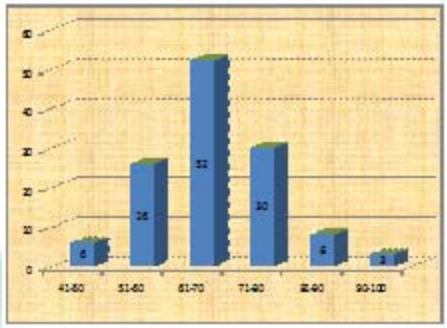

Figure 1: Age range distribution of patients

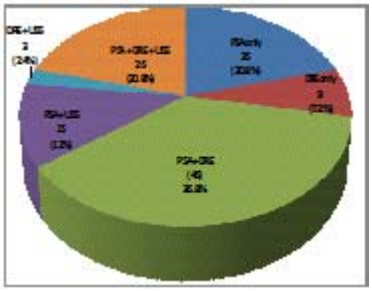

Figure 2: Indications for prostate biopsy

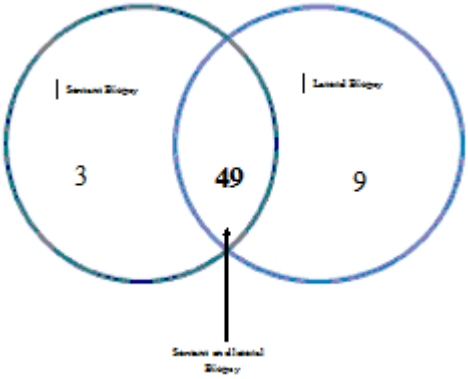

Figure 3: Pattern of cancer detection by different biopsy protocols

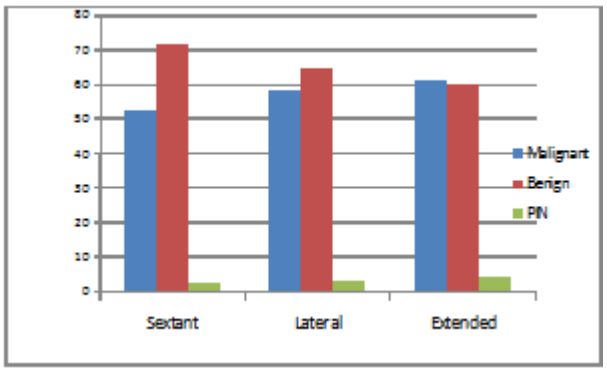

Figure 4: Comparison of cancer detection by biopsy protocols

Discussion

Great advances in the diagnosis of prostate cancer have evolved through the past century, most notably, prostate specific antigen (PSA) measurement[3, 14]. This has led to a dramatic increase in number of biopsies performed and diagnosis of prostate cancer at early stages. Nevertheless, considerable controversy still exists regarding the number, site and the best biopsy protocol for prostate biopsy. In this study, the peak age range of the patients was the seventh decade (61 – 70 years) of life with a mean age of 67.2 years. This is similar to the mean age of 68years reported by Osegbe[15] in Lagos over a decade ago and 66.3years in the study by Dawam et al[16] amongst Nigerians with CaP in Zaria. The disease is that of the ageing male, it is therefore not surprising that elderly men above 60 years of age made up the greater percentage (74.4%) of the study population. Some other studies have also reported similar distribution[17, 18].

Elevated PSA was the commonest indication for prostate biopsy. Twenty-six (20.8%) patients had elevated PSA only while 88(70.4%) had elevated PSA in addition to other indications. 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.[19] With the advent of PSA evaluation, 75% of men have non-palpable cancer while fewer than 3% of men have metastases at the time of diagnosis in the western countries[19, 20]. Unfortunately, this has not been the case in sub-Saharan Africa where the benefit of PSA as a screening tool has not been fully utilised[7, 18]. This was also reflected in this study as only 3(2.6%) patients were asymptomatic and 26(20.8%) patients were biopsied on account of PSA alone while 80 (64%) had palpable abnormalities in the prostate at presentation. A widespread public health education and screening is recommended to enhance early presentation and improve cancer detection at early stages in Nigerians.

Combination of elevated PSA and abnormal DRE was the commonest combination of indication for the biopsies. This agrees with the findings of most workers that the above two tools are the commonly employed tools for screening for prostate cancer and for recommending a prostate biopsy [8, 9, 12]. 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 18.6-42.6% [9-11, 13]. The typical late presentation in our environment may be responsible for this. This is demonstrated in this study where 78(62.4%) patients had PSA of e"10ng/ml which is far greater than the proportion documented in those studies where patients with PSA d" 10ng/ml predominate [9, 12, 13].

Of all the 61 patients that were positive for malignancy, sextant protocol detected 52 (85.2%) and lateral biopsy protocol detected 58 (95.1%).This showed an improvement of 6(10.3%) of the lateral over the sextant protocol. This was however not statistically significant. (P >0.067) The surprisingly high detection rate from the lateral biopsies, even though less number of cores were taken when compared with the standard sextant biopsies (four against six) emphasises the importance of sampling cores from these regions. This is in keeping with the finding of Philips et al[21]. Extended biopsy protocol (combination of the two techniques) showed an overall improvement of 9 (14.8%) over the sextant protocol which was statistically significant. (P <0.046). This suggests that lateral biopsy protocol on its own is not significantly better than sextant protocol but has an additive value on the sextant biopsies to produce a significant improvement in the rate of cancer detection.

The increase in detection rate of 14.8% in this study is very similar to the findings of Matsubara et al[12] where the improvement in detection of extended protocol over the sextant was reported to be 14.6%. Most other studies have however reported values ranging from 16 to 35% [9, 13, 22]. This may be due to the higher sensitivity of TRUS-guided biopsy technique utilised in those studies over digitally guided biopsy used in this study. However, not all studies have demonstrated the superiority of extended biopsy protocol as Naughton et al [23] found no significant improvement in cancer detection when a 12-core extended biopsy protocol incorporating the lateral peripheral zone (PZ) was prospectively compared with routine sextant biopsies alone.

Three (4.9%) cancer cases were detected by the sextant biopsies only but not by the lateral biopsies while 9(14.8%) cancers were detected by the lateral biopsy protocol only. These twelve cancer cases which accounted for 19.7% of all cancer cases could have been missed if either protocol were used alone without the other. This may be due to the fact that lateral biopsy protocol mainly targets the PZ which is not taken into consideration in the sextant protocol. Since the majority of prostate cancers (70%) originate from the PZ which is not always included in the sextant protocol which takes para-sagittal biopsies, sextant biopsies may therefore be inadequate [24, 25]. In contrast to the findings of other studies,[9, 11, 21] improvement in detection by lateral biopsy over the sextant protocol

was not statistically significant in this study. The disparity may be due to the procedure being digitally-guided with inability to locate targeted aspect of the prostate accurately. Combining the two as extended protocol however, showed a significant improvement in detection rate over the traditional sextant technique. Thus, both sextant and lateral biopsies should be complementary even in digitally-guided biopsy procedure.

The range of Gleason score was 3 – 10 with a mean of 6.34. This implies that most of the patients had at least moderate grade histology. The Gleason scores and grades were not exactly the same in the 49 patients whose cancers were detected by both sextant and lateral biopsy protocols. In 38 (77.6%) patients, the scores and the grades were the same. The Gleason grades were different but with same score in 5(10.2%) cases. Both grades and score differed in 6(12.2%) cases with an average increase in the Gleason Score of 0.8 from the lateral biopsies. This suggests that the higher the number of tissue cores available the greater the ability to determine the accurate Gleason score of the tumour. This implies that the extended protocol makes available more significant foci of tumours for analysis which are often missed in the sextant protocol only. This is important because it has been shown that the degree of differentiation of the cancer is related to its aggressiveness and rapidity of progression [26, 27]. It is therefore necessary to use the biopsy protocol that will give the closest result to the true Gleason score. However, the significance of this disparity cannot be stated with certainty and further studies with higher number of study population will be required.

All patients diagnosed to have CaP in this study had adenocarcinoma as the histological type. This is very similar to findings of other researchers which stated that adenocarcinoma constitutes more than 95% of all cases of prostate cancer [28, 29]. The incidence of PIN in this study was 3.2% which falls within the range of 1.5-16.5% reported by Renshaw et al [28].

There is theoretical concern of increase in complication rate of prostate biopsy if extended protocols with more number of biopsies are employed. The overall complication rate of 26.4% is within the range documented in literature [30, 31]. Generally, the increase in biopsy cores did not result in increased post-biopsy morbidity as the complication rates in this study were comparable to reported rates in the sextant protocol [8, 30, 31]. In the present series, there was no relationship between biopsy outcome (benign or malignant) and the incidence of complications. Haematuria was found to be the commonest complication which occurred in 19(15.2%) patients followed by rectal bleeding in 10 (8%). Other studies reported similar findings [31, 32]. These complications were mostly self-limiting. However, one patient had profuse rectal bleeding necessitating transfusion with two pints of blood. There were no major infective complications like septicaemia as reported in some series [33, 34]. Antibiotic prophylaxis employed in this study might be responsible for this finding. There were six cases of culture confirmed urinary tract infection following the procedure. Gram negative organisms were responsible for all the urinary tract infection associated with biopsy. This agrees with findings of other studies [33, 34]. Thus, a 10-core prostate biopsy can safely be performed without necessarily increasing the complication rate.

Ten-core extended prostate biopsy was well tolerated in most patients. About 16% of patients did not experience pain at all during the procedure while majority, 72.8% of patients had mild/moderate pain. Severe pain was experienced in 11.2% who described the procedure as severely painful. Ten-core extended prostate biopsy can therefore be described as a tolerable and safe procedure.

Conclusion

The improvement in detection rate of 14.8% obtained in this study suggests that a ten-core prostate biopsy protocol significantly improves cancer detection in patients with suspected cancer of the prostate without an associated significant increase in complication rate. Therefore, it should be the optimum biopsy protocol rather than sextant para-sagittal biopsies. A widespread public health education and screening is also recommended to enhance early presentation and improve cancer detection at early stages in Nigerians.

References

1. Greenlee R. T., Murray T., Bolden S. Cancer statistics. *CA Cancer J Clin* 2000; **50:** 7-10.
2. Yeboah E. D. The prostate gland. In: Badoe EA, Archampong EQ, da Rocha-Afodu JT, editors. Principles and practice of surgery including pathology in the tropics. 3rd ed. Accra: Assemblies of God Literature Centre; 2000. p. 850-83.
3. Brawer M. K., Chetner M. P., Beatie J., Buchner D. M., Vessella RL *et al*. Screening for prostatic carcinoma with prostate specific antigen. *J Urol* 1992; **147(3):** 841-5.
4. Jackson M. A., Ahluwalia B. S., Ghestimat M. Y. Characterization of prostate carcinoma amongst blacks:A continuation report. *Cancer* 1977; **61(1):** 167-70.
5. Wynder E. L., Mabuchi K., Whitmore W. F., Jr. Epidemiology of cancer of the prostate. *Cancer* 1971; **28(2):** 344-60.
6. Ramey J. R., Halpern E. J., Gomella L. G. Ultrasonography and Biopsy of the Prostate. In: Wein AJ, editor. Campbell-Walsh Urology. 9th ed. Philadelphia: Saunders Elsevier; 2007. p. 2883-95.
7. Onuora V., Adekanye A., Obarisiagbon E., Oguike T., Akumabor P. Digitally guided transrectal biopsy of the prostate. *Nig J Surg Sc* 2004; **14(1)**: 35-9.
8. Hodge K. K., McNeal J. E., Terris M. K., Stamey T. A. Random systematic versus directed ultrasound guided transrectal core biopsies of the prostate. *J Urol* 1989; **142(1):** 71-4.
9. Durkan G. C., Sheikh N., Johnson P., Hildreth A. J., Greene D. R. Improving prostate cancer detection with an extended-core transrectal ultrasonography-guided prostate biopsy protocol. *BJU Int* 2002; **89(1):** 33-9.

10. Levine M. A., Ittmann M., Melamed J., Lepor H. Two consecutive set of transrectal ultrasound guided sextant biopsies of the prostate for detection of prostate cancer. *J Urol* 1998; **159:** 471-5.
11. Damiano R., Autorino R., Perdona S., De Sio M., Oliva A. *et al*. Are extended biopsies really necessary to improve prostate cancer detection? *Prostate cancer and prostatic diseases* 2003; **6(3):** 250-5.
12. Matsubara A., Mutaguchi K., Yasumoto H., Takeshima Y., Teishima J. *et al*. Transrectal ultrasound-guided 10-core biopsy of the prostate for Japanese patients. *Hiroshima J Med Sci* 2006; **55(2):** 65-70.
13. Fink K. G., Hutarew G., Pytel A., Esterbauer B., Jungwirth A. *et al*. One 10-core prostate biopsy is superior to two sets of sextant prostate biopsies. *BJU Int* 2003; **92(4):** 385-8.
14. Brawer MK. Prostate specific antigen: current status. *CA Cancer J Clin* 1999; **49(5):** 264-81.
15. Osegbe D. N. Prostate cancer in Nigerians: Facts and non-facts. J *Urol* 1997; **157(4):** 1340 - 43.
16. Dawam D., Rafindadi A. H., Kalayi G. D. Benign prostatic hyperplasia and prostate carcinoma in native Africans. *BJU Int* 2000; **85(9):** 1074-7.
17. Ogunbiyi J. O., Shittu O. B. Increased incidence of prostate cancer in Nigerians. *J Natl Med Assoc* 1999; **91(3):** 159-64.
18. Nwofor A. M. E., Oranusi C. K. Cancer of the prostate: experience at Nnewi, Southeast, Nigeria. *Niger J Clin Pract* 2004; **7:** 65-8.
19. Higashihara E., Nutahara K., Kojima M. Significance of serum free prostate specific antigen in the screening of prostate cancer.*J Urol.*1996; **156(6):** 1964-8.
20. Stamey T. A., Yang N., Hay A. R. Prostate-specific antigen as a serum marker for adenocarcinoma of the prostate. *N Engl J Med.* 1987; **317(15):** 909-16.
21. Philips J., Ragavan N., Desousa J., Foster C. S., Javle P. Effect of peripheral biopsies in maximizing early prostate cancer detection in 8-,10- or 12-core biobsy regimens. *BJU Int* 2004; **93:** 1218-20.
22. Ravery V., Goldblatt L., Royer B., Blanc E., Toublanc M., *et al*. Extensive biopsy protocol improves the detection rate of prostate cancer. *J Urol* 2000; **164(2):** 393-6.
23. Naughton C. K., Miller D. C., Mager D. E., Ornstein D. K., Catalona W. J. A prospective randomized trial comparing 6 versus 12 cores: Impact on cancer detection. *J Urol* 2000; **164(2):** 388-92.
24. Presti J. C., Jr., Kane C. J., Shinohara K., Carrol P. R. Neoplasms of the Prostate Gland. In: Tenagho E. A., McAninch J. W., editors. Smith's General Urology. 17th ed. New York: McGraw-Hill Companies,Inc.; 2008. p. 348-76.
25. McNeal J. E., Redwine E. A., Freiha F., Stamey T. A. Zonal distribution of prostatic adenocarcinoma. Correlation with histologic pattern and direction of spread. *Am J Surg Pathol* 1988; **12(12):** 897-906.
26. Gleason D. F., Mellinger G. T. Veterans Administration Cooperative Urological Research Group: Prediction of prognosis for prostatic adenocarcinoma by combined histologic grading and clinical staging. *J Urol.* 1974; **111**: 58-64.
27. Pan C. C., Potter S. R., Partin A. W., Epstein JI. The prognostic significance of tertiary Gleason patterns of higher grade in radical prostatectomy specimens: a proposal to modify the Gleason grading system. *Am J Surg Pathol* 2000; **24(4):** 563-9.
28. Renshaw A. A., Schultz D., Cote K., Loffredo M., Ziemba D. E. *et al*. Accurate Gleason grading of prostatic adenocarcinoma in prostate needle biopsies by general pathologists. *Arch Pathol Lab Med* 2003; **127(8):** 1007-8.
29. Epstein J. I. Pathology. In: Kantoff P, Carroll PR, D'Amico AV, editors. Prostate Cancer: Principles and Practice. 1st ed. Philadelphia: Lippincott Williams and Wilkins; 2002. p. 464-81.
30. Berger A. P., Gozzi C., Steiner H., Frauscher F., Varkarakis J, *et al*. Complication rate of transrectal ultrasound guided prostate biopsy: a comparison among 3 protocols with 6, 10 and 15 cores. *J Urol* 2005; **173(2):** 663-4.
31. Vallencien G., Prapotnich D., Veillon B. Systematic prostatic biopsies in 100 men with no suspicion of cancer on digital rectal examination. *J Urol* 1991; **146:** 1308-12
32. Herget E. J., Saliken J. C., Donnelly B. J. Transrectal ultrasound-guided biopsy of the prostate: Relation between ASA use and bleeding complications. *Can Assoc Radiol J* 1999; **50:** 173-76.
33. Rodriguez L. V., Terris M. K. Risks and complications of transrectal ultrasound guided prostate needle biopsy: A prospective study and review of the literature. *J Urol* 1998; **160(2):** 2115-20.
34. Lindert K. A., Kabalin J. N., Terris M. K. Bacteremia and bacteriuria after transrectal ultrasound guided prostate biopsy. *J Urol* 2000; **164(1):** 76-80.