

A COMPARATIVE STUDY BETWEEN TRANS-RECTAL ULTRASOUND GUIDED 6-CORE AND 12- CORE PROSTATE BIOPSY FOR DETECTION OF PROSTATE CANCER

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Abstract:

Purpose- This study was performed to assess the comparative accuracy of trans-rectal ultrasound guided 6-core versus 12-core prostate biopsy for detection of prostate cancer.

Materials and Methods: A prospective comparative study between 6 cores and 12 cores prostate biopsy was done by a prospective comparative study from July 2007 to June 2008 in urology outpatient department, Bangabandhu Sheikh Mujib Medical University, Dhaka Medical College Hospital, Popular diagnostic Centre, Dhaka and Comfort Nursing Home, Dhaka. Study population included the patients having raised serum PSA or abnormal DRE attending in the above centres. They were divided into two groups. Group A was scheduled for 6 cores biopsy and Group B for 12 cores biopsy. A total 60 patients of PSA >4ng/ml or abnormal DRE or both were selected for prostate biopsy.

Results: In this study prostate cancer detection rate in 6 core prostate biopsy (Group-A) was 20% and in 12 core prostate biopsy (Group-B) was 46.67%. This study showed significant difference between the two procedures in respect of cancer detection. The 12 cores TRUS-guided prostate biopsy improved the detection rate of prostate cancer by 26.67% when compared with the traditional 6 cores biopsy technique without increasing in the morbidity.

Conclusions: The results of this study shown that the cancer detection rate is higher in transrectal ultrasound guided 12 cores prostate biopsy than transrectal ultrasound guided 6 cores prostate biopsy without increasing the morbidity.

Key words: Trans-rectal ultrasound, core prostate biopsy

Introduction:

Prostate cancer is the most common cancer and the second most common cause of cancer-related death in men in the United States. The probability of developing

prostate cancer in men under the age of 40 years is 1 in 10,000 and for men of 60-79 years it is 1 in 8 cases¹. Diagnosis of prostate cancer requires obtaining cancerous tissue from the prostate gland during biopsy. The standard of reference for diagnosis of cancer of the prostate is by transrectal sonographically guided needle biopsy².

Digital rectal examination (DRE) of the prostate has long been the sole method of physically examining the prostate. Nodularity, hardness, or irregularity on DRE has led to the clinician to perform biopsy of the prostate to determine the presence or absence of carcinoma. Before the era of 6 core biopsy, the diagnosis of prostate cancer relied on three methods: DRE, needle biopsy, and open perineal biopsy. The need for a tissue diagnosis led to the first documented needle biopsy technique of the prostate was transperineal needle aspiration. The major advancement in prostate needle biopsy was the use of transrectal ultra-sonography (TRUS). Digitally guided biopsy missed more than 50% of adenocarcinomas compared with TRUS guided biopsy³.

The modern era of prostate biopsy began with the use of TRUS guided biopsy in a directed versus a random systematic manner. The technique was to direct the biopsy needle to a total of 6 anatomic sites bilaterally—the apex, middle, and base of each side of prostate parasagittally—in addition to any hypoechoic regions noted on TRUS guided. This technique has become the reference of standard and this technique is called the systematic 6 core (sextant) prostate biopsy technique. Noting that a significant volume of prostate was not sampled using the 6 core technique; several studies were designed to investigate the role of more than 6 biopsy core. Believing that 6-biopsy core is inadequate for sufficient sampling of the prostate, Levine et al (1998) sampled the prostates of 137 men with abnormal DRE findings or an elevated PSA level with

two independent consecutive sets of 6 core biopsy. Their protocol noted a 30% increased cancer detection rate after two consecutive sets compared with a single set of 6 core biopsy in the same patients⁴.

With the understanding that 6 core biopsy technique does not sample the lateral peripheral zone tissue, Presti et al (2004) enrolled 483 patients with either abnormal DRE findings or a PSA level of 4.0 ng/mL or greater for peripheral zone tissue in their samples, they added four additional biopsy locations to the standard 6 core technique, two biopsy sites at the lateral position bilaterally¹. Analysis of the cancer detection rate from each site noted that 6 core biopsy techniques missed 20% of cancers³.

In clinical stage T2 carcinomas and in 85% of non-palpable tumors diagnosed on needle biopsy (stage T1c), the major tumor mass is peripheral in location. In the remaining cases, tumors are predominantly located in the transition zone (i.e., periurethrally or anteriorly). Tumors that appear to be unilateral on rectal examination are bilateral in approximately 70% of cases when examined pathologically. Adenocarcinoma of the prostate is multi-focal in more than 85% of cases⁵. The optimal number of biopsy core needed to detect prostate cancer remains controversial. Many investigators have insisted that large number of biopsy core should be obtained. In another study reported cancer detection rate of 26% and 27% in 6 cores and 12 cores prostate biopsy respectively. Some recent studies have suggested that the standard 6 core biopsy (B_x6C) lacks sensitivity. Besides prospective studies have demonstrated that the addition of lateral cores to the (B_x6C) significantly increases detection rate of prostate cancer^{6, 7}.

Higher tumor volume is located in the peripheral zone more lateral to the Bx6C plane. Based on this, Eskew et al (1996) were the first to perform biopsies with more lateral core⁸. Extended multisite directed biopsy (extended biopsy) scheme increases early cancer detection compared with 6 core prostate biopsy⁹.

Prostate cancer is not uncommon in Bangladesh. Exact prevalence of prostate cancer is not known in our country. The present study is designed to compare the effectively of 6 cores and 12 core prostate biopsy for detection of prostate cancer in Bangladeshi men.

Materials and Methods:

This is a hospital based prospective comparative study conducted between July'2007 to June'2008 in the

Urology department, Bangabandhu Sheikh Mujib Medical University, Dhaka Medical College Hospital, Popular diagnostic Centre and Comfort Nursing Home. Study population included by random sampling. Patients were included according to selection and exclusion criteria with a target to recruit finally not less than 30 cases in each group. Group A was scheduled for 6 cores biopsy and Group B was scheduled for 12 cores prostate biopsy.

Patients with hard consistency or nodularity of prostate in DRE and raised serum PSA > 4 ng/ml were included and patient with bleeding disorder, patient with anorectal pathology, presence of active UTI or prostatitis were excluded from the study.

All male patients aged over 50 years having lower urinary tract symptoms (LUTS) attending to Urology OPD were evaluated and potential participants were counseled for prostate biopsy. Informed consent was taken. Before taking biopsy patients were again judged by selection and exclusion criteria.

Patients were prepared by bowel cleansing, prophylactic antibiotics and withdrawing anticoagulant if any. Patients were grouped into A and B. Group A patients were submitted for TRUS guided 6 cores prostate biopsy and Group B patients were submitted for TRUS guided 12 cores prostate biopsy. Then biopsy was taken as per following procedure.

Biopsy Procedure:

Oral fluoroquinolone (Ciprofloxacin) and metronidazole were given at least 2 hours before the procedure and continued for at least 5 days after prostate biopsy. The buttock was flush at the margin of the table to allow easy manipulation of the probe and biopsy gun without obstruction. Enrolled, consented, and prepared patient was positioned in left lateral decubitus on sonography bed and hip flexed at 90° degree. Painting and rectal swabbing was done by using povidone iodine. First DRE was done with well lubricated gloved finger. Then TRUS is done by endorectal ultrasound probe covered by condom. Lubrication was liberal. Compatible needle guide and additional condom were applied to cover TRUS probe and needle guide. Biopsy cores were taken by Monopty gun. TRUS image was superimposed with a trajectory corresponding to the anticipated needle path. The Monopty gun advanced the needle 0.5 cm and sampled the subsequent 2.2 cm of tissue with the tip extending 0.5 cm beyond the area was sampled. Therefore, when sampling the PZ, the needle tip was

placed 0.5 cm posterior to the prostate capsule before firing. Similarly when sampling anteriorly, the needle tip was placed not less than 2.5 cm from the anterior venous plexus before firing to avoid hematoma formation. For Group A patient biopsies were obtained from 6 anatomic sites—the apex, middle, and base of each lobe, parasagittally bilaterally. For Group B patient biopsies were obtained from 12 anatomic sites; 6 sites of 6-core biopsy and 6 additional lateral biopsies in same level. Tissue was preserved in 10% formalin and was sent for histopathology. Routine tissue processing and staining was done. Patients were observed for 2 hours and discharged with cell/phone number so that they could contact for any problems. Patients were advised to come for a follow up with histopathology report and an interview with leading questions on morbidity was taken. Patients were asked to take prescribed antibiotics for 5 days.

Data were collected from history, findings of clinical examination, results of investigations before prostate biopsy, during observations, and at the time of follow up with histopathology report leading questions were asked about morbidity. Data collection sheet containing the selected points were filled up. After meticulous checking and rechecking data compilation and statistical analysis (Chi square test, Student's unpaired 't' test) were done using computer, based on statistical software (SPSS-12) and necessary help was taken from the resource personnel in the field of statistics. A 'p' value < 0.05 was considered as significant.

Observations and Results:

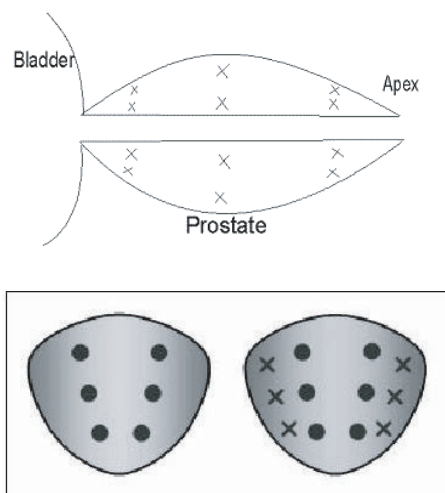


Fig.-1: Sites of taking biopsy from prostate (Biopsy sites of 6 & 12 core)¹⁰

The age distribution of Group-A was 52 to 78 years and Group-B was from 51 to 82 years. The mean age of group-A and Group-B were 65.33 and 67.77 years respectively and SD of age of group-A and Group-B were 15.98 and 24.31 respectively. There was no significant age difference between two groups (Fig.-2).

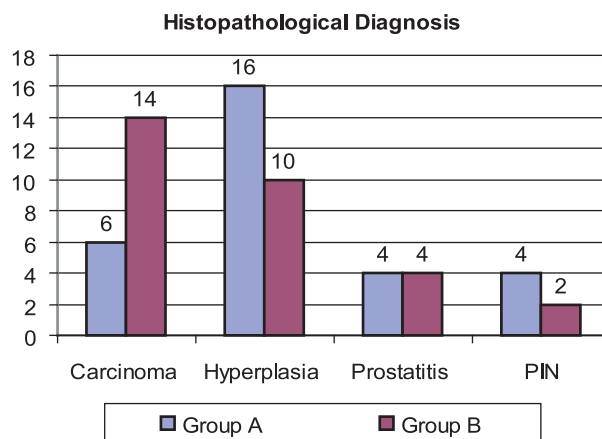


Fig.-2: Proportional Bar diagram of Age Distribution of Patients:

Volume range was 33-64.5 gram for Group A and 32-63 gram for Group B. For Group A mean volume was 47.78 gram and for Group B it was 47.07 gram SD was 8.91 for Group A and 8.95 for Group B. There is no significant difference of volume of prostate between the two groups. (At df = 58 't' value was 0.31, p > 0.05).

Serum PSA level was measured in all patients. PSA level was 3.5-21.5 ng/ml for Group A and 3.8- 19.5 ng/ml for Group B. For Group A mean PSA level was 8.7 ng/ml and for Group B it was 9.28 ng/ml and SD was 3.73 for Group A and 4.55 for Group B. There is no significant difference of PSA level between the two groups (at df = 58't' value was 0.54, p > 0.05).

Per-rectal digital examination was done in all patients. In Group A 24 (80%) patients were found normal DRE finding other than enlarged prostate and 6 (20%) patients were seen abnormal DRE finding, e.g. hard consistency or nodule in prostate. Similarly in Group B 23 (76.67%) patients were found normal DRE finding other than enlarged prostate and 7 (23.33%) patients were seen abnormal DRE finding, e.g. hard consistency or nodule in prostate. With +2 test at df 1 and in 5% significant level +2 value from table is 3.84 which is greater than calculated value (0.98). So DRE finding is not significant in between two groups (p > 0.05).

Table-I
Post procedural fever, dysuria, sepsis, hematuria and per rectal bleeding

Group	Fever	Dysuria	Sepsis	Hematuria	Per rectal Bleeding
A (n=30)	2 (6.67%)	6(20%)	0(0%)	18 (60%)	4 (13.33%)
B (n=30)	3 (10%)	14 (46.47 %)	0(0%)	21 (70%)	6 (20%)

Table-II
Comparison of efficacy of two procedures:

Group	Carcinoma	Non-malignancy	df	χ^2	p value	Inference
A (n=30)	6	24	1	4.563	<0.05	S
B (n=30)	14	16				

χ^2 test = Chi square test

df = degree of freedom

S = significant

In Group A 2 (6.67%) patients developed fever (temperature > 100 °F) and in group B 3 (10%) developed fever up to the follow up period of 72 hours. In Group A 6 (20%) patients developed dysuria and in Group B 14 (46.47%) complained of dysuria after 72 hours follow up. In Group A 18 (60%) patients complained of macroscopic hematuria and in Group B 21 (70%) complained of macroscopic hematuria after 2 hours of prostate biopsy. In Group A, 4 (13.33%) patients continued per rectal bleeding and in Group B, 6 (20%) complained per rectal bleeding after 2 hours of prostate biopsy (Table-I).

All histopathology reports were collected. For Group A carcinoma prostate was diagnosed in 6 (20%) patients and for Group B it was diagnosed in 14 (46.67%) patients. Benign prostatic hyperplasia was diagnosed

in 16 (53.33%) patients in Group A and 10 (33.33%) patients in Group B. Prostatitis were diagnosed in 4 (13.33%) patients in each Group. Prostatic intraepithelial neoplasia (PIN) was diagnosed in 4 (13.33%) patients in Group A and 2 (6.67%) patients in Group B (Figure-3).

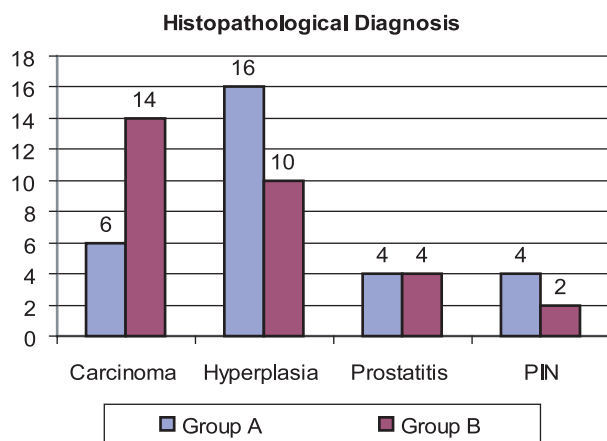


Fig 2: Proportional Bar diagram of Age Distribution of Patients:

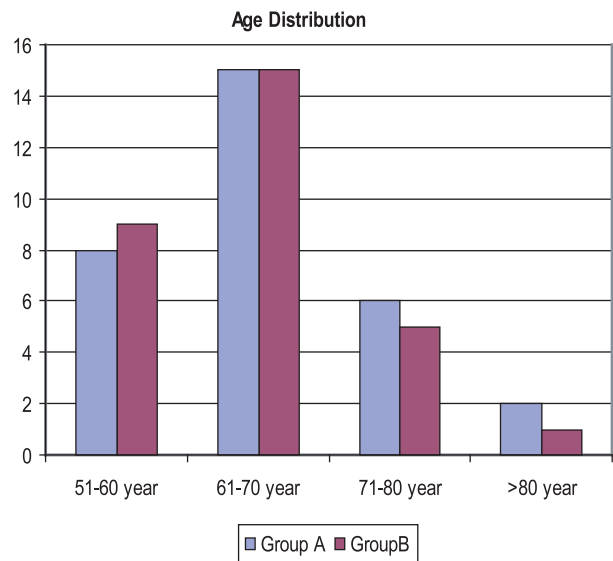


Fig.-3: Histopathological diagnosis

In Group A 6 cases were diagnosed as carcinoma prostate and 24 cases were diagnosed as other diseases. In Group B 14 cases were diagnosed as carcinoma prostate and 16 cases were diagnosed as other diseases (Table-II). With χ^2 test at df 1 and in 5% significant level χ^2 value from table is 3.84 which is smaller than calculated value (4.563). So the result is statistically significant ($p < 0.05$).

Discussion:

Prostate biopsy has become a common office procedure for urologists for a number of years. However, this procedure has changed significantly in recent years due to advances in equipment and continuous efforts to improve the sensitivity of the procedure. Transrectal ultrasound (TRUS)-guided systematic needle biopsy is the most reliable method at present of sampling prostatic tissue. Prostate biopsy is considered in men at high risk for harboring prostate cancer based on DRE and PSA findings. The major role of TRUS is to ensure accurate wide-area sampling of prostatic tissue^{11, 12}. The optimal biopsy technique in terms of the number of biopsies and the needle placement for tissue procurement that minimizes the chance of missing a relevant cancer is controversial.

The sextant technique is inaccurate mainly because it under-samples the peripheral zone of the prostate. In modified sextant biopsy from peripheral zone appears to improve the cancer detection rate. Extended biopsy techniques that utilize additional cores directed to the peripheral zone also have improved prostate cancer detection rather than 6 cores. Taking 10 to 12 tissue cores has become the standard of biopsy².

This study compared the detection rate of prostate cancer and post procedural morbidity between 6 core prostate biopsy and 12 cores prostate biopsy. Present study was conducted in similar background of age, prostate volume, DRE findings and PSA value. Group A patients underwent TRUS guided 6 core prostate biopsy and Group B patients underwent TRUS guided for 12 core prostate biopsy. In this study age limit of patients was 52-78 years for Group A and 51-82 years for Group B. Mean age was 65.33 years for Group A and 65.77 years for Group B. Similar study was conducted by different investigators. Age limit was similar as prostate cancer is more prevalent after 60 years of age; e.g. study of Kim et al (2004) mean age was 63.83 years for 6 core and 62 years for 12 core group respectively¹⁰.

Serum PSA was measured for all patients before prostate biopsy. In this study PSA range was 3.5 -21.5 ng/ml for Group A and 3.8-19.5 ng/ml for Group B with mean PSA was 8.7 ng/ml for Group A and 9.28 ng/ml for Group B. In Group A, 3 patients had PSA level < 4 ng/ml and in Group B, 2 patients had PSA level < 4 ng/ml. They were included in this study due to suspicious DRE finding (e.g. hard prostate or nodule in prostate). During first evaluation volume of prostate was measured by USG. In this study volume range of prostate was 33-64.5 gram

for Group A and 32-63 gram for Group B. Mean volume was 47.78 gram for Group A and 47.07 gram for Group B patients. Per-rectal digital examination was done in all patients. In Group A, 24 (80%) patients were found normal DRE finding other than enlarged prostate and 6 (20%) patients were seen abnormal DRE finding, e.g. hard consistency or nodule in prostate. Similarly in Group B, 23 (76.67%) patients were found normal DRE finding other than enlarged prostate and 7 (23.33%) patients were seen abnormal DRE finding, e.g. hard consistency or nodule in prostate. Most of the patients in this study underwent prostate biopsy is due to raised PSA level.

In current study carcinoma prostate was diagnosed in 6 (20%) patients in Group A and 14 (46.67%) patients in Group B. Benign prostatic hyperplasia was diagnosed in 16(53.33%) patients in Group A and 10 (33.33%) patients in group B. Prostatitis was diagnosed in 4 (13.33%) patients in both group. Prostatic intraepithelial neoplasia (PIN) was diagnosed in 4 (13.33%) patients in group A and 2 (6.67%) patients in group B. In this study cancer detection was 20% for 6 core prostate biopsy (Group A). Result is similar to the study of Mariappon et al, (2004), (i.e. 17%)¹³. In this study cancer detection was 46.67% for 12 core prostate biopsy (Group B). Cancer detection rate was significantly higher in Group B than Group A. Result was similar to the other studies of multiple core prostate biopsies, more than 10 cores (Mariappon et al, 2004). Result was different from the study of Kim et al (2004). Study of Kim et al was conducted in Korea which was a geographical area of low incidence of prostate cancer. Other reasons might be they took sextant biopsy from more peripheral zone and had larger sample size. That study showed cancer detection was 27% for 6 core prostate biopsy and cancer detection was 26% for 12 cores prostate biopsy¹⁰.

In 2004 Naya with co-investigators performed an extended biopsy of prostate and found increased cancer detection rate⁹. In a study conducted by Mariappon et al (2004) showed that increasing core increase cancer detection rate over 6 core biopsy. Presti et al (2000) reported a significant increase of prostate cancer detection rate with increasing biopsy core¹⁴. In 2003 Matalga, Eskew and McCullough showed in a review article that increasing biopsy core increases cancer detection rate, especially when biopsy was taken from more peripheral zone. Levine et al compared 6 and 12 core prostate biopsy by a consecutive 6 and 12 cores

prostate biopsy. Their result showed a 28% increase in cancer detection rate over standard sextant biopsy. This result was statistically significant and similar to present study (26.67%)⁴. The study of Presti et al (2000) detected 42% had prostate cancer. Present study showed a 33.33% patient had prostate cancer¹⁴.

Presti et al (2000) revealed that traditional sextant biopsy missed 20% of prostate cancer⁴. Present study showed that 6 core prostate biopsy missed 26.67% of prostate cancer. Similar findings were found in another review article by Silletti et al (2007). They reported a 30% improvement in prostate cancer detection rate when 10 core or more biopsy were taken and extra biopsy cores were taken from peripheral zone³. Findings were similar to present study. In order to improve the sensitivity of the biopsy, Stamey et al (1999) suggested that the sextant biopsy should be performed slightly more laterally based on cancer mapping of radical prostatectomy specimens (75% of prostate cancer originates from the peripheral zone)^{14, 15}. Chang et al added 4 lateral regions in addition to the sextant biopsy. This revealed that lateral region biopsies found an additional 14% of positive cancer biopsies not diagnosed with regular sextant biopsy¹².

The ability of the standard 6- core biopsy to provide optimal sampling was questioned by recent studies. Uzzo et al (1999) reported on cancer detection rates and their variation with prostate size using a systematic sextant core biopsy regimen. Using a sextant regimen, the cancer detection in glands > 50 g was 23% vs. the cancer detection is 38% in glands < 50 g. Their data suggest that significant sampling error may occur in men with large glands, and more biopsies may be needed under these circumstances. Karakiewicz et al (1999) also evaluated the positive rate of sextant biopsy according to gland size. The positive biopsy rate for glands less than 20 cc was 40% vs. 10% for glands 80-90 cc. Levine et al (2001) also contributed to the evidence of increased sampling error in larger glands¹¹.

They also concluded that biopsy sensitivity did not surpass the sextant biopsy when the regions of the biopsy were not different¹⁶. The addition of lateral cores added tumors to the sextant biopsy in up to 35% of the cases³. In a review study by Matlaga et al (2003) reported the cancer detection rates were 27.6 % (42/152) and 19.7 % (30/152) for the 10-core and 6 core biopsy protocols respectively⁴. Adding the lateral peripheral zone (PZ) to the 6 core biopsy showed a 28.6 % (12/42) increase in the cancer detection rate in patients with positive prostate cancer without increase in the morbidity³. Yamamoto et al Presti et al, 2000 performed biopsy the prostate of 237 patients in the sextant group;

prostate cancer was detected in 47 patients (19.8%)¹⁷. The cancer detection rate, morbidity and complications were similar to present study.

Post procedural morbidity was evaluated and compared in between two groups. In Group A, 2 (6.67%) patients developed fever (temperature > 100° F) and in Group B, 3 (10%) developed fever up to the follow up period of 72 hours. This difference was not significant in between two groups. In Group A, 6 (20%) patients complained dysuria and in Group B, 14 (46.47%) complained dysuria and voiding difficulty after 72 hours follow up. This difference was significant in between two groups but comments can not be drawn with this small study. In Group A, 18 (60%) patients complained naked eye hematuria and in Group B, 21 (70 %) complained naked eye hematuria after 2 hours of prostate biopsy. Similarly 4 (12.33%) patients in Group A complained per rectal bleeding and in Group B, 6 (70 %) patients complained per rectal bleeding after 2 hours of prostate biopsy. These differences were not significant in between two groups.

By reviewing data of previous studies in Japan the Japanese Urological Association showed the rate of rectal bleeding was 5.9%, which was only encountered after transrectal biopsy. Fever (38°C) and sepsis were observed in 1.1% and 0.07%, respectively. Voiding difficulty and urinary retention occurred in 1.9% and 1.2% of cases, respectively. Type and rate of complications were similar to present study and were negligible¹⁸.

In another comparative study between 6 core and 12 core prostate biopsy Djavan et al (2001) showed rectal bleeding (2.1% versus 2.4%), mild hematuria (62% versus 57%), severe hematuria (0.7% versus 0.5%) and vasovagal episodes (2.8% versus 1.4%, respectively). Major complications were rare and included urosepsis (0.1% versus 0%) and rectal bleeding that required intervention (0% versus 0.1%, respectively)¹⁹. This result is similar to present study. In another study Ghani, Dundas, Patel (2004) showed the prevalence of bleeding complications (6, 8- and 12-core, respectively) was: hematuria 44%, 41% and 39%; haemospermia 13%, 16% and 12%; and rectal bleeding 17%, 26% and 27%. Naughton et al, (2000) showed there was no difference of post-biopsy pain between the 6 and 12-core groups. In the 12-core group there was an increase in hemochezia and hemo spermia (24% versus 10% and 89% versus 71% respectively) but no significant difference between groups reporting morbidity as a major problem. These results of morbidity were negligible and comparable to the results of current study²⁰.

There were some limitations in this study as- sample size was small ; consideration of subdivision of prostate volume were not taken like < 40g, 40-60g, >60g ;

consideration of subdivision of PSA value were not taken like < 4ng/ml, 4-10ng/ml, >10ng/ml ; prostate biopsy was performed by different urologists ; histopathology was done by different pathologists. With al, these limitations it was concluded that 12 core prostate biopsy is preferable to 6 core prostate biopsy in diagnosis of prostate cancer.

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