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# Rates and Determinants of Complications Following Trans-Rectal Prostate Biopsy in Enugu, Nigeria

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***Authors' contributions***

*This work was carried out in collaboration between all authors. Authors FOU and IIN designed the study, performed the statistical analysis, wrote the protocol and the first draft of the manuscript. Authors KNE and ADO reviewed the analysis and contributed to subsequent drafts. Author EIU managed the literature searches, reviewed analysis and contributed to drafts. All authors read and approved the final manuscript.*

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## ABSTRACT

**Aims:** Analysis of the complications of trans rectal prostate biopsy to establish their rates and determinants.
**Study Design:** Retrospective study.
**Place and Duration of Study:** Departments of Urology University of Nigeria Teaching Hospital, Saint Mary's Hospital, Mother of Christ Specialist Hospital, Royal Hospital, and East Side Hospital Enugu between January 2009 and December 2015.
**Methodology:** One hundred and twenty four patients who had transrectal prostate biopsy were assessed. Complications were graded according to the Clavien-Dindo classification. Grade 1 was regarded as minor and grade 2 classified as major.
**Statistical analysis used**: simple means and percentages. Categorical variables were analyzed with the Chi square test. P-value was < 0.05.

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**Results:** Age range was 44 to 90 years, mean (66.6±9.96). Mean PSA value was 13.1ng/ml.
Mean prostate volume was 88.7ml (46 – 210). Minor complications were mostly hemorrhagic, with primary macroscopic hematuria occurring in 43/124 patients (34.6%) and acute urinary retention in 8/124 patients (6.45%).
Major complications seen include urosepsis in 5/124 patients (4.03%) and severe haematuria in 2/124 patients (1.61%).The occurrence of major complications were analyzed by Chi square test against potential determinants; age group, prostate specific antigen (PSA) level and prostate volume (PV).
For age and AUR, there is a significant difference in occurrence of AUR (p=0.01).
For age and urosepsis, the result is significant at (p=0.01). For PSA and AUR, the result is significant at (p=.00). For PSA and urosepsis, the result is significant at (p=.00). For prostate volume and AUR, the result is significant at (p=.00). For PV and urosepsis the result is significant at (p=.03). There was no mortality.
**Conclusion:** Transrectal Prostate biopsy has a low incidence of major complications.
The occurrence of AUR and urosepsis showed significant associations with age, PSA, and prostate volume.

*Keywords: Transrectal; prostate biopsy; complications; determinants; Nigeria.*

## 1. INTRODUCTION

Transrectal ultrasound (TRUS) guided prostate needle biopsy has become the mainstay for tissue diagnosis of prostate adenocarcinoma, [1,2] with more than 500,000 prostate biopsies being performed yearly in the United Sates [1].

The widespread acceptance of this technique followed the demonstration that systematic biopsy significantly increases the diagnostic sensitivity of detection of prostate cancer [2,3]. In some under-resourced settings, digitally directed transrectal prostate biopsy (TRPB) remains a common method of obtaining histopathology specimens especially in patients with abnormal digital rectal examination findings [4,5]. Irrespective of the method of needle guidance, trans-rectal access and the invasive nature of the procedure remain common to both methods. These procedures are generally well tolerated but are associated with some risk of minor and major complications. [3,6-9] As awareness of prostate cancer increases and prostate specific antigen (PSA) testing becomes more available, the number of biopsies performed is likely to increase.

This study aims to assess the complications associated with transrectal prostate biopsy and determine risk factors for their occurrence

## 2. MATERIALS AND METHODS

For the period between January 2009 and December 2015, records of patients who had TRPB at University of Nigeria Teaching Hospital, Saint Mary's Hospital, Mother of Christ Specialist Hospital, Royal Hospital and East Side Hospital, Enugu were identified. Indications for prostate biopsy in this cohort of patients were PSA elevation above 4ng/ml, abnormal digital rectal examination (DRE) findings suggestive of prostate cancer, (hardness, fixity of mucosa, sulci obliteration etc.), abnormal ultrasound findings in the prostate (hypoechoic lesions suggestive of cancer) and clinical evidence of locally advanced/metastatic prostate cancer. The DRE's were performed by senior residents and or consultants to ensure correctness of the clinical impression.

Information extracted were demographics, PSA value, prostate volume (PV), comorbidity and complications if any. Complications observed were graded according to the Clavien-Dindo classification system for postoperative complications [10,11]. Subsequently, grade 1 was regarded as minor and grade 2 and above regarded as major [12].

Ethical principles as stated in the Declaration of Helsinki were complied with.

Biopsy Protocol; Culture proven urinary tract infections were treated and aspirin/antiplatelet agents were stopped two weeks before the TRPB was performed. Parenteral prophylactic antibiotics used were, combinations of ceftriaxone 1gm gentamicin 80mg, and metronidazole 500 mg or ciprofloxacin 200mg and metronidazole 500 mg. These were based on managing unit protocols.

Oral ciprofloxacin was continued for 3 days after biopsy with oral analgesics.

Anaesthesia used was either periprostatic lidocaine injection or caudal block.

18G semi-automatic core biopsy needles were used, with post observation including voiding trial before discharge.

Standard 12 core biopsies were taken. There were no repeat biopsies. Patients were reviewed at one, 2 and 4 weeks after the procedure according to the local unit protocol.

### 2.1 Statistical Analysis

Data were analyzed using SPSS 20 (IBM SPSS Statistics for Windows, Version 20.0.Armonk, NY, USA). The emphasis was on determinations of the effect of age, PSA level, and prostate volume on the occurrence of the 3 complications; acute urinary retention, severe haematuria and urosepsis.

For the purposes of analysis, cut points were set for the 3 parameters to create 4 equal subgroups each, i.e. age (40-49,50-59,60-69,70-79); PSA level (4.9-9.9,10-19.9,20-29.9,>30) and prostate volume (40-79,80-119,120-159,>160). Categorical variables were analyzed with the Chi-square test with significance level set at $p < 0.05$.

## 3. RESULTS AND DISCUSSION

### 3.1 Results

One hundred and seventy one patients were identified, of which forty six (46) were excluded due to incomplete records. One hundred and twenty four (124) patients were analyzed. Patient's age range was 44 to 90 years; mean 66.6 ± 9.96. Mean PSA value was 13.1ng/ml. Mean prostate volume was 88.7ml (46 - 210). Comorbidity seen was controlled hypertension in 58/124 patients (46.8%).

Indications for prostate biopsy were PSA elevation only (above 4ng/ml), in 27/124 patients (21.7%) and abnormal digital rectal examination findings, in 46/124 patients (37.1%).

Abnormal ultrasound findings were present in 21/124 patients (16.9%). Features of locally advanced/metastatic prostate cancer were seen in 11/124 patients (8.87%). In the 46/124 patients with abnormal digital rectal examination findings, the least PSA value was 11.1ng/ml (11.1-34.4). (Table 1).

Grade 1 Clavien - Dindo (minor) complications seen were mostly haemorrhagic, with primary macroscopic haematuria occurring in 43/124 patients (34.6%) and acute urinary retention in 8/124 patients (6.45%). (Table 2). Grade 2 Clavien – Dindo (major) complications were urosepsis in 5/124 patients (4.03%), 2/124 of whom received ceftriaxone, gentamicin and metronidazole combination and 3/124 of whom received ciprofloxacin and metronidazole combination. Severe haematuria in 2/124 patients (1.61%). (Table 2). There was no mortality.

**Table 1. PSA levels in those with abnormal DRE findings**

| S/no | PSA (ng/ml) | S/no | PSA (ng/ml) |
|---|---|---|---|
| 1. | 25.1 | 24. | 34.4 |
| 2. | 21.7 | 25. | 23.3 |
| 3. | 27.1 | 26. | 31 |
| 4. | 17 | 27. | 11.1 |
| 5. | 34 | 28. | 21.6 |
| 6. | 14 | 29. | 12.3 |
| 7. | 18.9 | 30. | 26.5 |
| 8. | 31 | 31. | 13 |
| 9. | 36.1 | 32. | 12 |
| 10. | 12 | 33. | 33 |
| 11. | 11.4 | 34. | 19.4 |
| 12. | 18.7 | 35. | 33.2 |
| 13. | 26.6 | 36. | 22.3 |
| 14. | 20 | 37. | 22 |
| 15. | 14 | 38. | 14 |
| 16. | 20.4 | 39. | 17.8 |
| 17. | 18.1 | 40. | 20.4 |
| 18. | 24.8 | 41. | 13.7 |
| 19. | 14.5 | 42. | 26.3 |
| 20. | 20.2 | 43. | 17 |
| 21. | 14.2 | 44. | 13.2 |
| 22. | 28 | 45. | 13 |
| 23. | 27 | 46. | 19.5 |

Parenteral prophylactic antibiotics given were, ceftriaxone, gentamicin and metronidazole combination in 68/124 (54.8%), while ciprofloxacin and metronidazole combination was given in 56/124 (45.2%). All patients were discharged home on oral ciprofloxacin for 3 days.

**Table 2. Clavien-Dindo classification of post biopsy complications (Major and Minor)**

| Clavien- Dindo Grade 1 (minor) Complication | Number | % | Clavien-Dindo Grade 2 (major) Complication | Number | % |
|---|---|---|---|---|---|
| Acute urinary retention | 8/124 | 6.45% | Haematuria, requiring blood transfusion | 2/124 | 1.61% |
| Primary macroscopic haematuria | 43/124 | 34.6% | Urosepsis | 5/124 | 4.03% |
| Intermittent macroscopic haematuria (post discharge) | 21/124 | 16.9% | | | |
| Mild Bleeding per rectum | 39/124 | 31.4% | | | |
| Bleeding per rectum requiring rectal gauze packing | 11/124 | 8.8% | | | |
| Febrile episode | 11/124 | 8.87% | | | |
| New onset dysuria | 17/124 | 13.7% | | | |
| Urinary tract infection | 19/124 | 15.3% | | | |
| Acute epididymorchitis | 9/124 | 7.25% | | | |
| Anal pain | 16/124 | 12.9% | | | |
| Haemospermia | 17/124 | 13.71% | | | |

The occurrence of urosepsis, acute urinary retention (AUR) and severe haematuria were analyzed by Chi square test against age group, PSA level and prostate volume (PV). For age and AUR, there was significant difference in occurrence of AUR [*P*< .05 (.007)]. For age and urosepsis the result is significant at [*P*< .05 (006)]. For PSA and AUR, the result is significant at [*P*< .05 (003)]. For PSA and urosepsis, the *P* value is .003 and is significant at *P*<.05. For PV and AUR, the result is significant at [*P*< .05(.00002)]. For PV and urosepsis the result is significant at [*P*< 0.05 (.026)]. For age and haematuria 2/2 (100%) of the patients who suffered severe haematuria were > 60 years old and this was not statistically significant ($\chi 2=1.94$, p= .74).

## 3.2 Discussion

Transrectal prostate biopsy is relatively safe, with the probability of severe complications low, but the incidence of infectious complications has recently been rising, along with the potential for more severe complications such as sepsis [13-15].

With increasing awareness of prostate cancer and availability of PSA testing, the number of prostate biopsies performed is likely to increase. Previous work has shown a slight but not statistically significant increase in minor complications as the number of cores taken increase [16,17].

The transrectal approach is widely practiced and it is important to assess its complications and possible determinants in order to enhance patient safety. Other potential benefits include potential reduction in complications, which lead to higher costs. [18] Earlier workers have demonstrated that surgical care costs significantly increase in patients first seen in the emergency department, [19] which is the usual admission route for those patients who present acutely.

Majority of complications seen were grade 1 Clavien – Dindo, (minor). Hemorrhagic complications predominated, consisting of primary macroscopic hematuria, intermittent hematuria post discharge, bleeding per rectum and hemospermia. Previous work had similarly reported hemorrhagic complications as the commonest [7,20].

Rates of hematuria ranging from as high as 62% to 14.4% have been reported [7,21]. In our series, primary macroscopic hematuria occurred in 34.6% and was self-limiting, usually resolving in 5-7 days. These findings are lower than those of Deliveliotis and Naughton, [22,23] but similar to those of Van den Heuvel and Raaijmakers, [20,24] with the common trend being that it is the most common minor complication seen. The varying rates in other series may be due to different number of cores taken, prostate size and possible residual effect of antiplatelet drugs.

Mild rectal bleeding has been reported as high as 98%, [9] with severe bleeding occurring between 2.1% to 8.2%. [7,9] Self-limiting rectal bleeding was observed in our series in 31.4%, with 8.8% (classified as moderate), of patients requiring rectal gauze tamponade as the only intervention. Other workers have reported the use endoscopic sclerotherapy in severe cases where digital and instrument pressure techniques have failed. Hemospermia rates ranging from 9.1% through 38.8% to 53.8% have been reported in other studies, [9,20] we noted a hemospermia rate of 13.7% which is similar to the findings of earlier studies.

Infective complications could occur as a result of manipulation or translocation of faecal flora into the prostate, urine and blood by the biopsy needle [6]. We observed post procedure fever in (n=17, 8.8%), prior publications had noted fever ranging from 1.7% to 6.3% [6,9,20,25] and is thought to be due to bacteraemia and or pyrogens.

New onset dysuria and UTI were noted in (n=17/124; 13.7%) and (n=19/124; 15.3%) respectively, which were higher than the rates noted in previous series [9,25]. We also noted acute epididymoorchitis in (n=9/124; 7.25%).

The role of antibiotic prophylaxis in the prevention of infective complications after transrectal prostate biopsy is well established [26-30]. Two regimens of either ceftriaxone, gentamicin and metronidazole or ciprofloxacin and metronidazole were given according to managing surgeon's preference. This approach has been observed in other climes and speaks to the need to adopt a standardized antibiotic regimen based on local sensitivity studies [12]. The patients who were culture positive pre operatively or had an indwelling catheter, they were placed on the appropriate antibiotic and proceeded to biopsy after the urine became culture negative. The quest to reduce infection rates has led to much work on augmented antibiotic prophylaxis and targeted antibiotic prophylaxis, [31] although these have the potential to lead to the emergence of antibiotic resistant strains [26].

Urosepsis occurred in (n=5/124; 2.4%) and required admission and treatment with parenteral antibiotics. Regarding these infective complications, the most commonly cultured organisms in urine in our series were *E.coli* and *Klebsiella* and this is consistent with earlier findings [32,33]. Given that anaerobes are normal commensals of large bowel and that fatal anaerobic sepsis has been reported after TRPB, [34] it may be useful to include metronidazole in these regimens [9].

Anaesthesia for prostate biopsy has evolved from no anaesthesia to various methods including periprostatic lidocaine injection, intrarectal lidocaine gel, caudal block, epidurals etc [35,36]. Earlier series have suggested that discomfort after this procedure is affected by certain factors including younger age and anxiety [37,38]. Voiding difficulty and acute urinary retention after prostate biopsy are potential sequelae of prostate biopsy [8,38].

Attempts have been made to mitigate this with alpha blocker therapy with some benefit [39,40]. We noted an acute urinary retention rate of (6.45% n=8/124) this is similar to the findings of Deliveliotis et al. [22] but higher than those of Lee et al [1]. These patients were managed with urethral catheterization and commencement of alpha blockers with voiding trial later.

The occurrence of urosepsis, acute urinary retention (AUR) and severe haematuria were analyzed by Chi square test for potential associations with age group, PSA level and prostate volume.

For Age and AUR, there was significant difference in occurrence of AUR, 7 of the 8 patients (87.5%) with AUR in our series were < 60 years old and this was statistically significant ($\chi^2$ =14.0, $p<0.05$). Previous randomized control (RCT) studies have shown that pain scores were lower in younger men <65 years. [37] This "age anaesthetic effect" may play a contributory role in increasing the rates of AUR in younger men < 60 years in our series, due to pain is a risk factor for AUR as has been observed following painful perineal procedures [41,42].

For age and urosepsis, 5/5 (100%) of the patients who suffered urosepsis were >70 years old and this was statistically significant ($\chi^2$ =14.3, $p<0.05$). Urosepsis is one of the less frequent complications of prostate biopsy [6,7] and while no clear associations with age have been shown, we note that in our series, all patients with this complication were > 70 years old. Possibilities may be unidentified comorbidity or other unknown factors. We believe this is a worthy subject to test in future prospective studies with larger cohort of patients.

For PSA and AUR, 7 of the 8 patients (87.5%) with AUR in our series had PSA values >10ng/ml

and this was statistically significant ($\chi^2$ =14.3, p<0.002). The finding of significant association between PSA and AUR is an interesting one. An earlier study in which the mean PSA of subjects was 113.2 ng/ml. showed a high AUR rate of 1.4%, [1] though ours was higher at 6.45%. We note that this will require further evaluation in a prospective series.

For PSA and urosepsis, 5/5 (100%) of the patients who suffered urosepsis had PSA values >20ng/ml and this was statistically significant ($\chi^2$ =17.7, p<0.0005). This association of PSA and urosepsis is intriguing as systematic review of complications of prostate biopsy have not shown elevated PSA as a risk factor [31]. This raises the possibility that other factors may be involved and strengthens the case for a prospective study to address the issue.

For prostate volume (PV) and AUR, 7 of the 8 patients (75%) with AUR in our series had PV >160mls and this was statistically significant ($\chi^2$ =24.3, p<0.00002). This finding is in agreement with that of earlier workers who noted that PV is associated with risk of urinary retention after biopsy [24,43]. This finding may be of value in deciding when prescribe alpha blockers like tamsulosin after transrectal prostate biopsy.

For PV and urosepsis 4 of the 5 patients (80%) with AUR in our series had prostate volumes >120mls and this was statistically significant ($\chi^2$ =9.3, p<0.025). Loeb et al [44] have shown that increased PV is a risk factor for fever and infectious complications. Our findings are in agreement with this and may help identify patients at risk.

For PV and haematuria the result was not significant at p =0.22. 2/2 (100%) of the patients with haematuria requiring blood transfusion had prostate volumes >120ml but this did not reach statistical significance. Interestingly, earlier workers have shown that prostate volume is significantly associated with haematuria [20]. While this did not reach statistical significance, it is probably useful to consider it as risk factor for hematuria, although other factors such as undeclared NSAID or antiplatelet use need consideration.

## 4. LIMITATIONS

Our study limitations include the retrospective nature of the work and relatively small number of subjects. Despite this we believe our findings offer an audit of practice, and can provide the basis and stimulus for a larger prospective study.

## 5. CONCLUSION

Transrectal prostate biopsy has a low incidence of major complications. Minor complications are frequent with haemorrhagic and infective types predominating. The occurrence of AUR and urosepsis showed significant associations with age, PSA, and prostate volume.

## CONSENT

All authors declare that consent for this study was granted by the institutional research ethics committee and was performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki.

## ETHICAL APPROVAL

This study was approved by the University of Nigeria Hospital Research Ethics Committee; approval number NHREC/05/01/2008B/UNTH/CSA.329/Vol.6.

All authors hereby declare that all experiments have been examined and approved by the appropriate ethics committee and have therefore been performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki.

## COMPETING INTERESTS

Authors have declared that no competing interests exist.

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