Correlation of Doppler Indices of Prostatic Lesions with Prostate Specific Antigen in Abakaliki, Nigeria

C.N. Ikeh[1], M.O. Orji[1], E. Uchendu[1], C.M. Asaleye[2], C.U. Ibewuike[1], O.S. Oboke[1], C.A. Odoemene[3].

[1]Department of Radiology, Alex Ekwueme Federal University Teaching Hospital Abakaliki, Nigeria.

[2]Department of Radiology, Obafemi Awolowo University Teaching Hospitals Complex, Ile-Ife, Nigeria.

[3]Department of Surgery, Alex Ekwueme Federal University Teaching Hospital Abakaliki, Nigeria.

ABSTRACT

BACKGROUND: Prostatic lesions are common health challenges worldwide with prostate cancer rated as second commonest malignancy in male. Prostate Specific Antigen (PSA) is a sensitive but nonspecific marker for prostatic lesions. Transrectal ultrasonography with Doppler interrogation is an affordable imaging technique that has shown remarkable improvement in differentiating benign from malignant prostatic lesions with the potential of improving its sensitivity and specificity in future.

AIMS AND OBJECTIVES: The aim of this study was to evaluate the relationship between Doppler indices and PSA in patients with prostatic lesions in Abakaliki.

MATERIALS AND METHODS: This was a cross sectional study that lasted for 8months in which 74 men aged 45 to 89years who had suspected prostatic lesions on digital rectal examination (DRE) with or without raised PSA were evaluated using transrectal Doppler ultrasonography. A Medison Accuvix A30 ultrasound machine was used for the evaluation and all the participants subsequently had biopsy with available results.

All data were analyzed using Statistical Package for Social Sciences (SPSS) version 20. Tables, charts and scatter diagrams were used to present results. Means of continuous variables were compared using t-test. Test of relationships were done using Pearson's correlation analysis and $p \leq 0.05$ was considered statistically significant. Linear regression was used to explain the relationship between dependent and independent variables.

RESULTS: Histopathology results showed that 49patients had benign prostatic hyperplasia while 25patients had adenocarcinoma of the prostate. The mean end diastolic velocity (EDV) was significantly greater in malignant prostatic lesions when compared with benign lesions (4.52±3.00cm/s versus 3.06±2.24cm/s, p=0.021). The mean pulsatility index (PI) was significantly lower in malignant lesions as compared with benign lesions (1.73±0.75 versus 2.25±0.98, p=0.023). The mean [peak systolic velocity (PSV) and

resistivity index (RI)] showed no significant difference in malignant lesions when compared to benign lesions (PSV, 19.54±7.75cm/s versus 17.00±8.51cm/s, p=0.215; RI, 0.77±0.12 versus 0.82±0.11, p=0.067). There was significant positive correlation between PSA and EDV in benign lesions (r=0.309, p=0.031) but not in malignant lesions (r=0.134, p=0.525). Other Doppler indices (PSV, RI and PI) were not significantly correlated with PSA in both benign (r=0.222, -0.193, -0.197; p=0.125, 0.183, 0.175 respectively) and malignant (r=-0.085, -0.240, -0.080; p=0.686, 0.247, 0.704 respectively) prostatic lesions.

CONCLUSION: End diastolic velocity (EDV) and PI may assist in differentiation of benign from malignant prostatic lesions. End diastolic velocity correlated positively with PSA only in benign lesions and therefore may be used to monitor patients with benign prostatic lesions.

KEY WORDS: Doppler ultrasound, Prostate, Prostate specific antigen, transrectal ultrasound.

INTRODUCTION

Prostatic lesions occur often in males especially with advancement in age above 50 years.[1]These lesions range from the benign ones like prostatitis and benign prostatic hyperplasia (BPH) to malignant ones like cancer of the prostate. Prostatic cancer is ranked as the second most common malignant tumour and the sixth most common cause of cancer-related deaths in men globally.[1]

Prostate Specific Antigen (PSA) is an organ specific marker that is usually elevated in prostatic lesions.[2] Because the serum level of PSA is raised in both benign and malignant diseases of the prostate, it is therefore nonspecific but it is the most commonly used tumour marker for screening prostate cancer and any value greater than 4ng/ml is suspicious of prostatic lesion.[3] The serum concentration of PSA of cancerous tissue appears to be thirty-fold larger than the normal prostatic epithelium and ten-fold that of BPH.[3] Prostate specific antigen (PSA) alone has a cancer detecting rate of 4.6%, positive predictive value of 32% and low specificity for prostate cancer.[3]

Transrectal ultrasound (TRUS) is a relatively affordable, widely used and well tolerated tool for imaging the prostate. TRUS has been regarded as an extension of the urologist's finger for early detection of prostate cancer.[4] Ultrasound has been applied in structural analysis such as prostate volume measurement, study of echotexture, tissue elasticity illustration, to deliver treatments such as brachytherapy and to monitor cryotherapy treatment for prostate cancer.[4] Like many other malignant tumours, prostate cancer displays increased angiogenesis, giving rise to increased micro vessel density with an increased tortuosity of the tumour blood vessels.[5] These vascular changes have made detection of prostatic tumours with color or power Doppler examination possible. Any focal asymmetry in blood flow within the peripheral zone of the prostate raises a high index of suspicion for a focal lesion.[5] Introduction of colour and power Doppler ultrasound has improved the specificity of ultrasound- guided prostate biopsy.[5]

Kwon et al[6] in 2016 demonstrated an increase in resistivity index (RI) in patients with BPH although the actual reason for this increase has not been established, but may be due to increase in intraprostatic pressure caused by prostatic hypertrophy because the growing hypertrophic prostate pushes the capsule outward. This finding agrees with Kojima et al[7] who found that there was a significant increase of the RI in 40 cases of BPH (0.72 ± 0.05) compared to 37 cases with a normal prostate volume (0.64 ± 0.04), (P < 0.0001). Frauscher et al[8] showed a similar result that the RI was significantly elevated in BPH patients in comparison to the normal group. Osama et al[9] observed that there was a relative difference in the RI of prostatic vasculature in different prostatic pathologies. The mean RI value of 0.579 (range, 0.45 - 0.80) for cancer cases was slightly lower than the mean values for cases with atypia, inflammation, and benign disease, which were 0.601 (range, 0.49 - 0.86), 0.621 (range, 0.54 - 0.77) and 0.616 (range, 0.40 - 1.00), respectively. In Taiwan, a significant difference was noted between the Doppler indices (PSV, EDV, RI) of benign and malignant prostatic lesions measured at the neurovascular bundle vessel (NVB). [10]

Studies had shown that there is a slight correlation between Doppler indices and PSA. Yuh et al[10] observed that for patients with PSA <10 ng/ml, the EDV value of left NVB vessels was significantly higher at the malignant sides than those at the benign ones (6.8 ± 5.4 cm/s *vs* 4.2 ± 3.0 cm/s, *p*=0.013). The RI value of left NVB vessels was significantly lower at the malignant sides than those at the benign ones (0.69 ± 0.11 *vs* 0.80 ± 0.12, *p*=0.0006). But among patients with PSA between 10 and 20 ng/ml, the malignant halves exhibited significantly higher EDV values and lower RI values of bilateral NVB vessels as compared with the benign halves (all *p*-values<0.05). The PSV values at the left NVB site were significantly higher in the malignant prostate halves than those in benign prostate ones (25.0 ± 11.1 mL/second *vs* 20.0 ± 9.1 mL/second, *p*=0.046). Among patients with PSA more than 20 ng/mL, the EDV values at the right NVB site were significantly higher in the malignant prostate halves than those in benign prostate ones (7.3 ± 5.5 mL/second *vs* 4.1 ± 2.4 mL/second, *p*=0.017). The RI values at the right NVB site were significantly lower in the malignant prostate halves than those in benign prostate ones (0.71 ± 0.12 *vs* 0.79 ± 0.12, *p*=0.012).

This study aimed at using Doppler ultrasound to differentiate benign from malignant prostatic lesions and evaluate the relationship between Doppler indices and PSA which might improve the selection of patients for prostate biopsy procedures in future.

The Gray-scale B-mode was used to visualize the morphology of the prostate while the Doppler provided the information about vascularity of the tissues. The routine application and reporting of Doppler parameters may assist in improving the specificity of prostatic lesions and contribute to monitoring of these lesions.

METHODOLOGY

STUDY   DESIGN

This was a cross–sectional study to ascertain the difference in Doppler indices of benign and malignant lesions of the prostate and correlate these indices with serum PSA level in patients with suspected prostatic lesions who presented in departments of: surgery, general outpatient and Radiology of Alex Ekwueme Federal University Teaching Hospital Abakaliki, Nigeria.

STUDY AREA

Alex Ekwueme Federal University Teaching Hospital Abakaliki is a tertiary institution that serves the major towns in Ebonyi State including Abakaliki, Afikpo and the surrounding rural areas. The hospital has 604 beds. The general outpatient department serves a very large number of patients coming from these areas. Ebonyi state has a population of about 2.39million and men account for about 1.16million.[11] On the average, about 3 new patients with prostatic lesions were seen in the Urology clinic of FETHA every week.

STUDY POPULATION

The subjects for this study included men who presented in departments of: surgery, general outpatient and Radiology of FETHA with lower urinary tract symptoms (LUTS) secondary to suspected prostatic disease with abnormal digital rectal examination findings or raised PSA. All patients referred for prostate scan with abnormal prostate findings on DRE were scanned and their reports given back to them to see their doctors but those that were eventually recruited for the study were those who gave their consent and were within the age range of 45 to 89years.

STUDY DURATION

This study lasted for a period of 8months from January 2018 to August 2018.

INCLUSION   CRITERIA

1. Men who presented with abnormal prostate findings on DRE.

2. Men with raised serum PSA level > 4.0ng/ml.

3. Patients with prostate biopsy result.

EXCLUSION CRITERIA

1. Men who did not give consent.

2. Men with anal stenosis or fissure and those who were not co-operative.

3. Patients with no suspected prostatic lesions.

4. Patients who refused to do prostate biopsy.

5. Patient on 5-α-reductase inhibitor therapy.

6. Patient on urinary catheter.

EQUIPMENT

Prostate scan was carried out with transrectal probe (5 - 9 MHz) of Accuvix A30 (MEDISON LV Korea 2013).

TECHNIQUE

All transrectal ultrasonography in this study were done only by a Consultant Radiologist to eliminate inter observer variability. The Radiologist was blinded of the patient's biopsy report prior to the scan to avoid bias. Doppler values were obtained at the right and left capsular arteries twice within 15minutes by the same investigator and the average was used for comparison to increase reliability of the data.

Positioning: After explaining the procedure and consent obtained, the patient was positioned in a left lateral decubitus position with the knees flexed. The privacy of the patient was maintained throughout the procedure.

Probe preparation and insertion: Digital rectal examination (DRE) was done prior to the insertion of the probe to exclude contraindication to the procedure like anal stenosis and fissure. The probe was covered with double condom sheaths for protection and contact jelly poured into the sheath to reduce air interface and establish good contact with the probe for transmission of sound waves. The sheathed probe after K-Y jelly application was inserted into the anus and angled posteriorly following the curve of the rectum.

Scanning: The prostate was scanned both in transverse and longitudinal planes to assess the morphology. The transverse scan was done starting from above the bladder base at the level of seminal vesicles to the level of the apex of the prostate while the longitudinal scan was done from right to left lateral aspect of the gland. Prior to transrectal scan, each patient was asked to void and made attempt to completely empty his bladder.

DOPPLER IMAGING: Doppler window was applied on B-Mode image and was adjusted to cover the entire periphery and most of the central area of the gland in order to assess the symmetry and flow throughout the prostate. Using a broad-bandwidth 5–9MHz dedicated endorectal probe**,** Doppler spectral waveform of the capsular artery at neurovascular bundle (NVB) was measured bilaterally at fixed angle of 56° and sample volume (gate) of 2mm. The pulse repetition frequency was set to 800 Hz, with a wall filter of 50 Hz. The capsular arteries at the neurovascular bundle sites were examined at the point just before they enter the prostate rather than the intraprostatic branches penetrating into the gland. Once the pulsatile waveforms of a given Doppler spectrum become stable for the consecutive five repeats, the peak-systolic velocity (PSV), end-diastolic velocity (EDV), resistive index (RI) and pulsitility index (PI) of each site was measured and recorded in the study sheet. During the entire ultrasonographic scan, care was taken to avoid excess probe pressure on the rectal wall to prevent compression of the neurovascular bundles and to minimize discomfort to the patient. The gray-scale and Doppler images of the prostate are shown in Figures 1-3.
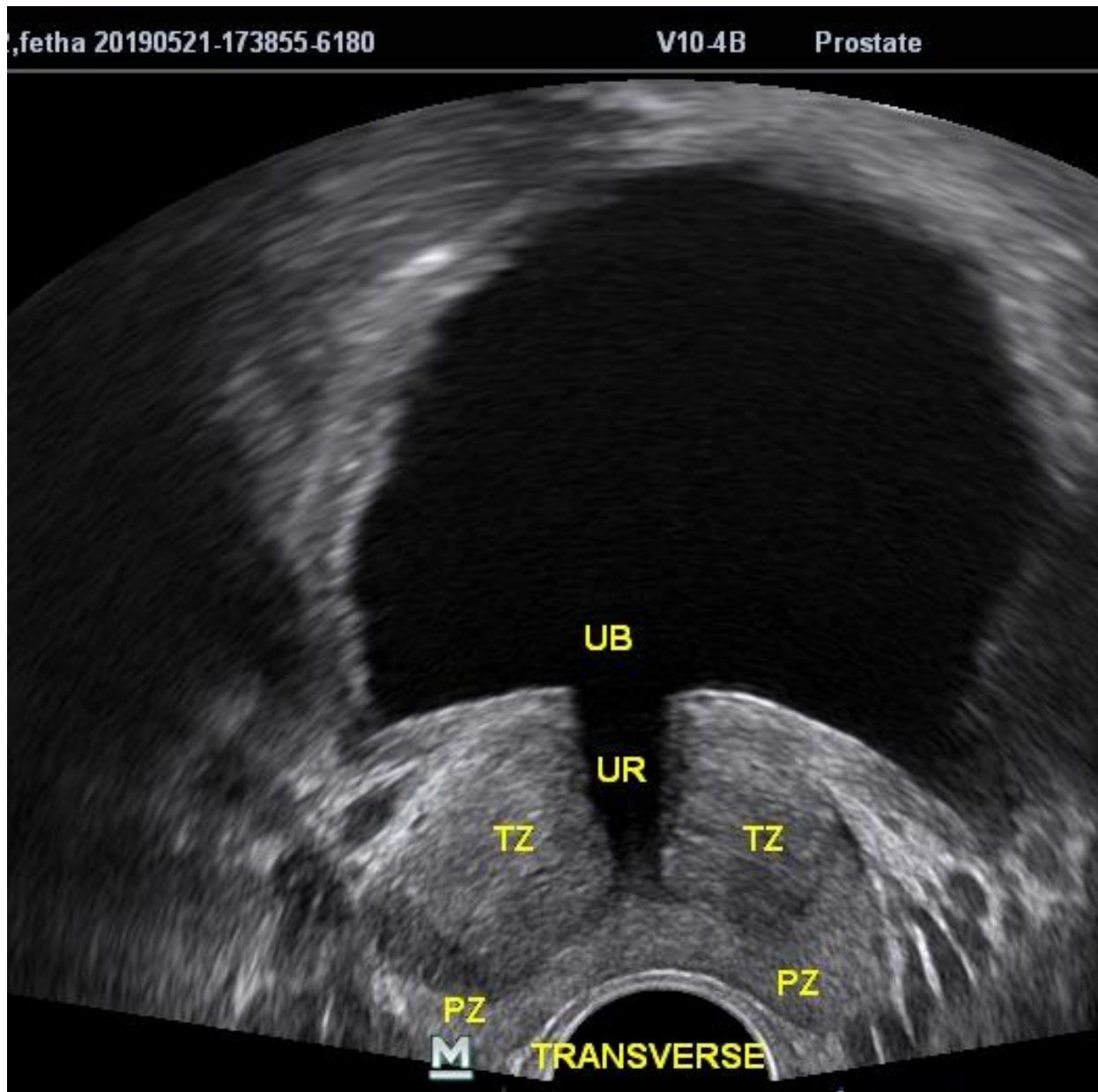
Figure 1: Axial B- Mode Ultrasound of the prostate showing prostatic zones.

PZ   =   Peripheral Zone.

TZ   =   Transitional Zone.

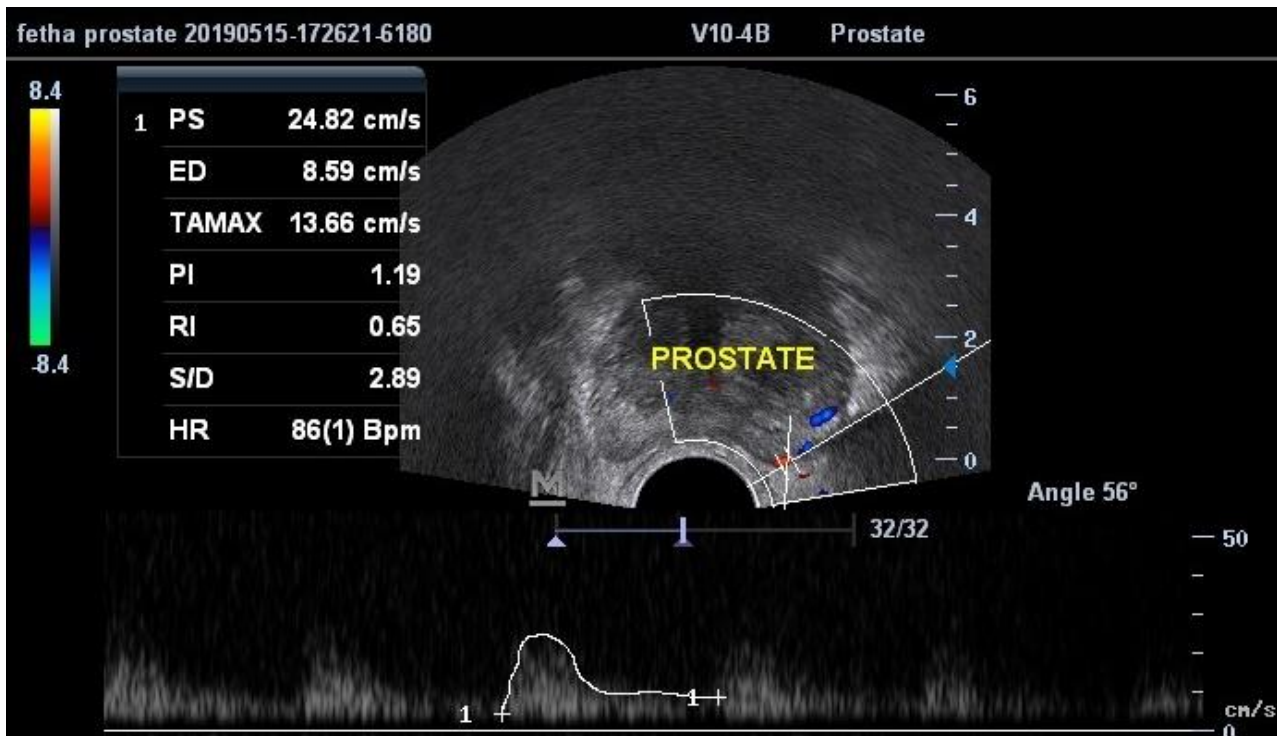UR =   Urethra

UB =   Urinary Bladder

Figure 2: Doppler scan of the prostate (Transverse View) showing the Doppler waveform of   the capsular artery.
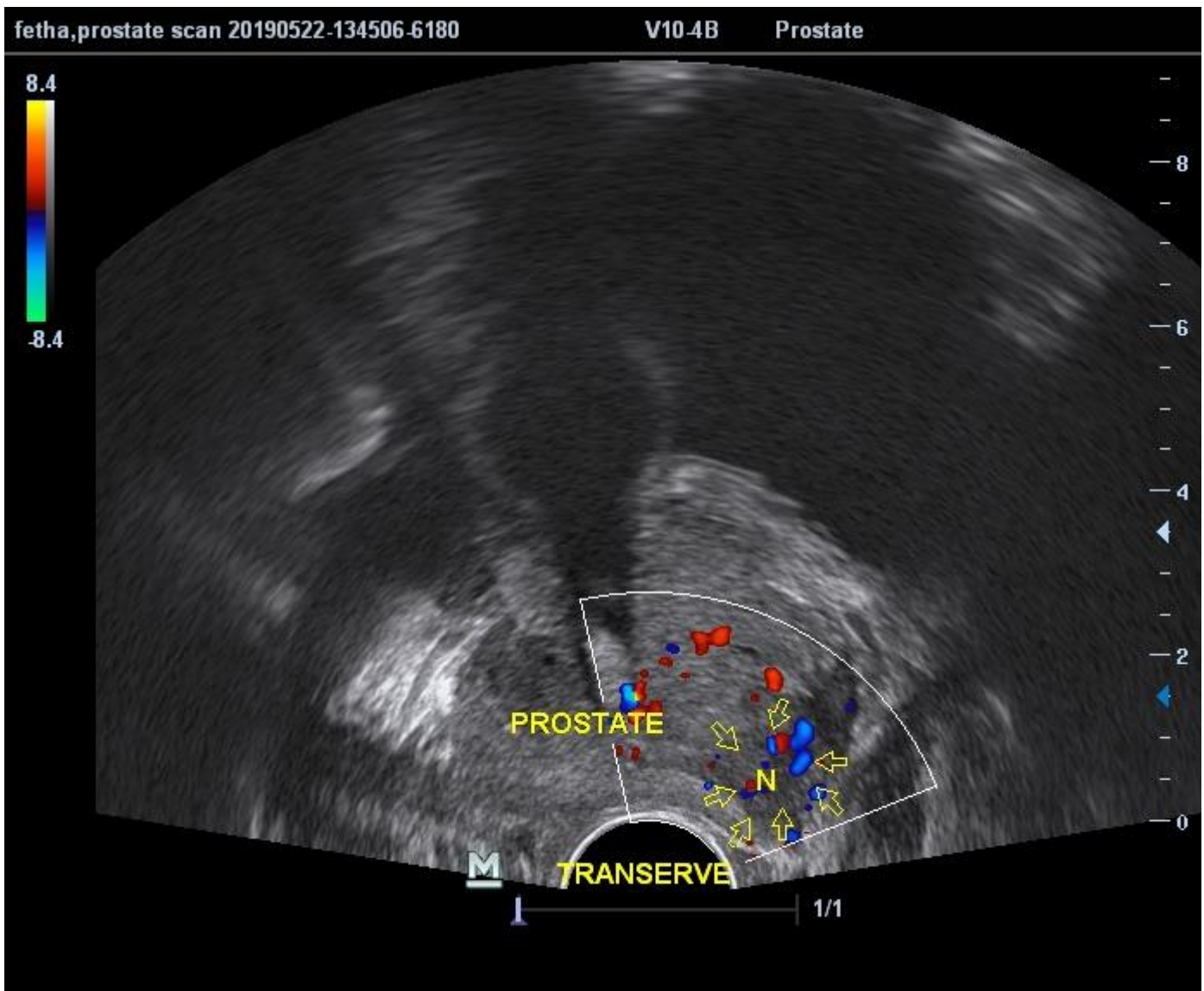
Figure 3: Colour Doppler scan of the prostate (Transverse View) showing a hypoechoic nodule with increased vascularity at the left peripheral zone.

ETHICAL CONSIDERATIONS

Approval for this research was obtained from the Health Research and Ethics Committee of Alex Ekwueme Federal University Teaching Hospital Abakaliki. Informed consent was also obtained from each patient after the study objectives, procedure and full implications of the procedure were made known to them. Participation was voluntary and information obtained during the study was used only for research purposes.

PSA ASSAY

Blood samples of participants were collected in the hospital laboratory by the Lab. scientist and PSA assay was done using an ELISA kit (TECO).

PROSTATE BIOPSY

Transrectal digitally directed 12-core prostate biopsies were taken by Urologist in the theatre for each participant. Samples obtained were sent to the Pathologist for histology reports. The result of the biopsy was later collected and recorded in the data sheet.

DATA   ANALYSIS

The data were analyzed using Statistical Package for Social Sciences (SPSS) for windows version 20 package. Tables and charts were used to present the results. Statistical tests were considered significant at p-value less or equal to 0.05.

Descriptive statistics which include: frequency, percentage, mean and standard deviation were used to summarize the data. Student t-test and Chi-squared test were used to compare continuous and categorical variables. Pearson's correlation analysis was used to test for relationship between variables.

RESULTS

Seventy-four (74) adult male patients between the ages of 45 – 89years who had prostatic lesions were studied. The modal age group

for prostatic lesion was 61– 75years which accounted for 45(60.8%) of the studied population while the least number 14 (18.9%) of

the participants were in the age group of 76-89years. The age distribution of the participants is shown in table 1.

Table 1: The demographic variables of the study population

Demographic	Frequency	Percentage (%)	Cumulative percentage (%)
Age Group			
45 – 60years	15	20.3	20.3
61 – 75years	45	60.8	81.1
76 – 89years	14	18.9	100.0

Out of 74 patients recruited for the study, 49(66.2%) patients had benign lesions while 25(33.8%) patients had malignant lesions as shown in table 2 below. The mean age for benign lesions was 67.2± 8.0 years while that for malignant lesions was 69.9±9.2 years but there was no statistical significant difference (p=0.651). The modal age group was 61-75years for both benign and malignant lesions.

The details of the age distribution is illustrated in table 3.

Table 2: The biopsy results of the participants

Prostatic lesions	Frequency	Percentage (%)	Cumulative percentage (%)
Benign prostatic hyperplasia (BPH)	49	66.2	66.2
Prostatitis	0	0	66.2
Adenocarcinoma	25	33.8	100.0
Metastasis	0	0	100.0

Table 3: Age distribution of participants with benign and malignant lesions

Age Group	Benign (n=49)	Malignant (n=25)	Total (n=74)	χ^2	df	P-value
45 – 60years	11(22.4%)	4 (16.0%)	15(20.3%)	0.859	2	0.651
61 – 75years	30(61.2%)	15(60.0%)	45(60.8%)			
76 – 89years	8(16.3%)	6 (24.0%)	14(18.9%)			
Mean($\pm$SD)years	67.2($\pm$8.0)	69.9($\pm$9.2)	68.1($\pm$8.5)			

The mean ($\pm$SD) PSA for benign lesions was 17.90$\pm$32.00ng/ml while that of malignant lesions was 84.90$\pm$135.80ng/ml which was significant (p=0.002). The mean PSA was 67.00ng/ml higher in malignant than benign lesions. The detail of the PSA is shown in table 4 below.

Table 4: Measurement of PSA in benign and malignant lesions

Measurements	Benign (n=49)		Malignant (n=25)		Mean Diff	t-test	Df	P-value
	Range	Mean ±SD	Range	Mean ±SD				
PSA (ng/ml)	0.20-134.00	17.90±32.00	0.50-613.40	84.90±135.80	67.00	3.300	72	0.002

There was no significant difference between the mean PSV of benign and malignant lesions (17.00±8.51cm/s versus 19.54±7.75cm/s; p=0.215) as illustrated in table 5.

There was significant difference between the mean EDV of benign and malignant lesions (3.06±2.24cm/s versus 4.52±3.00cm/s, p=0.021). The mean EDV was 1.46cm/s higher in malignant lesions than benign lesions. This is also illustrated in figure 4.

Although the mean RI of benign lesions (0.82±0.11) appeared higher than that of malignant lesions (0.77±0.12), there was no significant difference (p=0.067).

There was significant difference between the mean PI of benign and malignant lesions (2.25±0.98 verses1.73±0.75; p=0.023). The mean PI of benign lesion was 0.52 higher than that of malignant lesion. This was also illustrated in Figure 4.

Table 5: Doppler indices of capsular artery in benign and malignant prostatic lesions

Measurements	Benign (n=49)		Malignant (n=25)		Mean Diff	t-test	Df	P-value
	Range	Mean±SD	Range	Mean±SD				
PSV(cm/s)	7.60-52.05	17.00±8.51	8.54-32.67	19.54±7.75	2.54	1.251	72	0.215
EDV (cm/s)	0.00-9.61	3.06±2.24	1.17-16.29	4.52±3.00	1.46	2.358	72	0.021
RI	0.60-1.00	0.82±0.11	0.42-0.96	0.77±0.12	0.05	1.862	72	0.067
PI	0.42-4.68	2.25±0.98	0.53-3.21	1.73±0.75	0.52	2.323	72	0.023
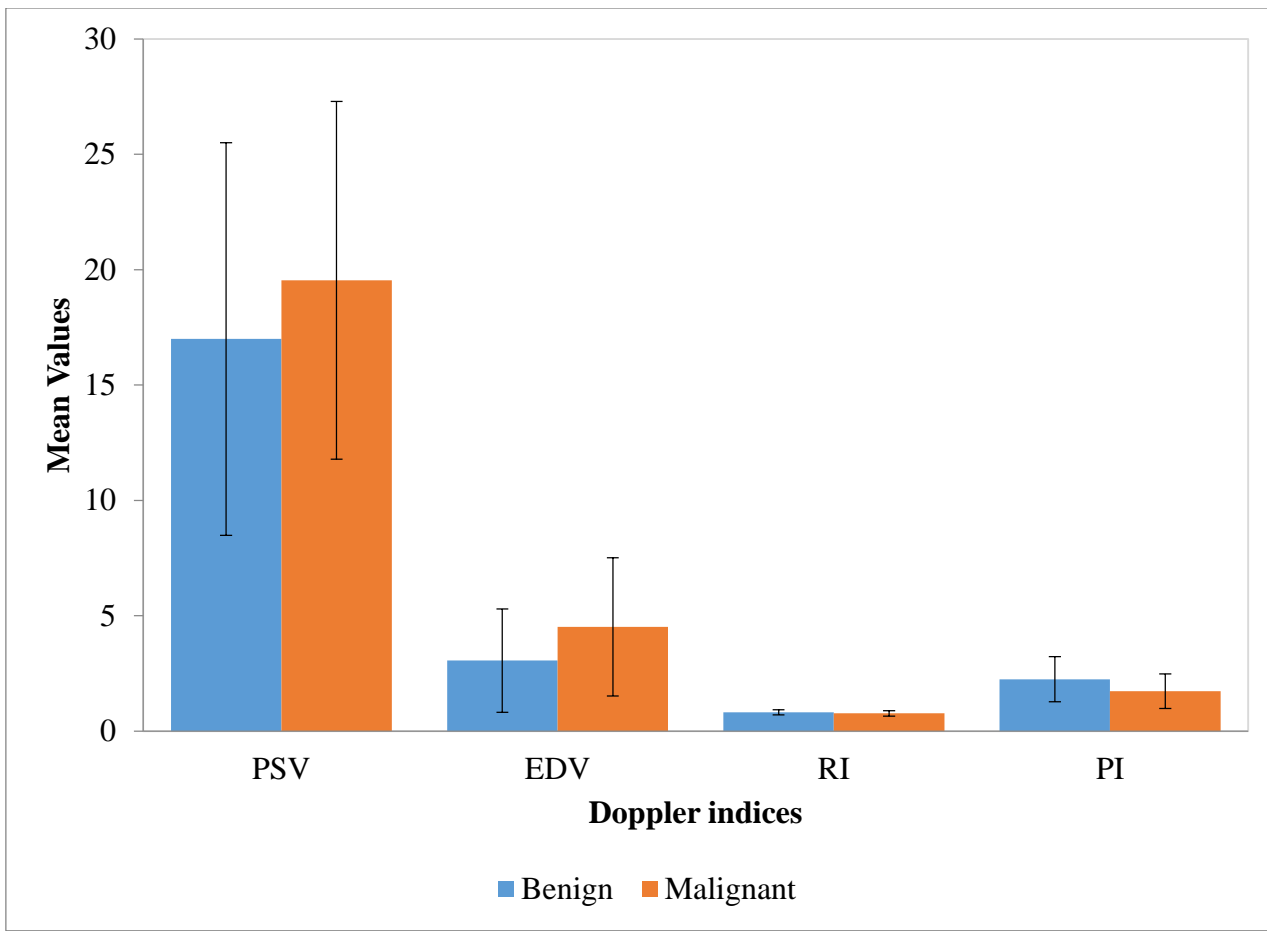
Error bars : ± 1 SD

Figure 4: A bar chart showing the mean (SD) PSV, EDV, RI, PI in benign and malignant prostatic lesions.

There was no significant correlation between PSA and PSV in both benign and malignant lesions (r=0.222, -0.085; p=0.125, 0.686 respectively) as shown in table 6.

There was significant positive correlation between PSA and EDV in benign lesions (r=0.309, p=0.031) but no significant correlation in malignant lesions (r=0.134, p=0.525). This implied that in benign lesions, increase in PSA resulted to increase in EDV as illustrated in table 6.

There was no significant correlation between PSA and RI in both benign and malignant lesions (r=-0.193, -0.240; p=0.183, 0.247 respectively).

There was no significant correlation between PSA and PI in both benign and malignant lesions

(r= -0.197, -0.080; p=0.175, 0.704 respectively).

Table 6: The correlation between PSA and Doppler indices (PSV, EDV, RI and PI) in benign and malignant lesions

Biopsy result			PSV	EDV	RI	PI
Benign	PSA value (ng/ml)	Pearson Correlation	0.222	0.309	-0.193	-0.197
		P-value	0.125	0.031	0.183	0.175
		N	49	49	49	49
Malignant	PSA value (ng/ml)	Pearson Correlation	-0.085	0.134	-0.240	-0.080
		P-value	0.686	0.525	0.247	0.704
		N	25	25	25	25

There was a direct relationship between PSA and EDV (r = 0.309). As EDV increased, PSA also increased.

Majority of the EDV values clustered below 4.00cm/s while the PSA values clustered below 25ng/ml as was shown in Figure 5.
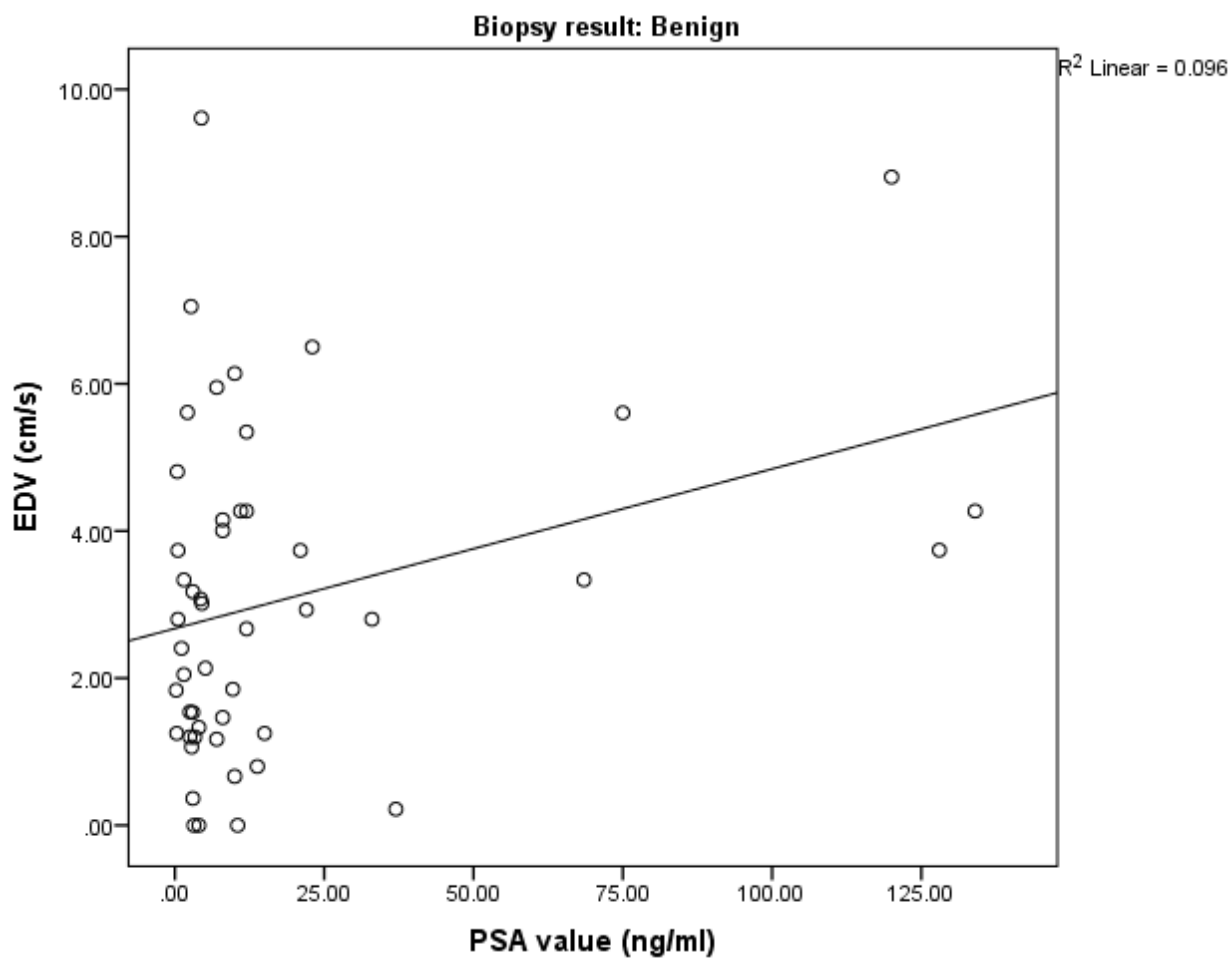

Figure 5: A scatter plot with trend line of relationship between PSA and EDV in benign lesions.

DISCUSSION

A total number of 74 adult men within the age range of 45 to 89years with the mean (±SD) age of 68.1(±8.5) years who had prostate lesions were recruited in this study. The modal age group was 61-75years which accounted for 60.8% of the studied population. This was similar to Anunobi et al[12] in 2011 that quoted a mean age of 67years with peak incidence age group of 60-69years for prostatic lesions. Other studies done in Nigeria and Pakistan showed similar modal age group with none contradicting this present study.[13,14] These similarities could suggest that prostatic lesions might be part of aging processes.

Benign prostatic hyperplasia (BPH) accounted for 49(66.2%) while cancer of the prostate (CaP) accounted for 25(33.8%) of the studied population which agreed with the common knowledge that BPH is the commonest prostatic lesion in adult males. Another study done in Nigeria by Nwafor et al[13] noted that BPH accounted for 62.8% and was distantly followed by CaP that accounted for 29.3% of histology results which was similar to findings in this study. However, Aslams et al[14] in Pakistan noted a much higher proportion for BPH 42(87.5%) as against CaP 6(12.5%). This variation might be due to difference in geographical location.

There was significant statistical difference in the mean PSA of patients with benign (17.90±32.00ng/ml) and malignant (84.90±135.80ng/ml) prostatic lesions with p-value=0.002. Although the PSA values in these two conditions were elevated compared to the normal value of ≤4.0ng/ml, it was markedly higher in malignant lesions.[15] The study done by Stamey et al[3] noted a similar exceedingly higher PSA value in CaP than in BPH. Another study done in Enugu, Nigeria by Udeh et al[16] noted a statistical significant difference in PSA value between BPH and CaP in favour of CaP which also agreed with the findings of this index study. The difference in PSA level between these two prostatic lesions was attributed to distortion of the basement membrane of prostatic epithelium by prostate cancer resulting in higher production of PSA.[16] Though Ekeke et al[17] observed that most patient with PSA >10ng/ml had advanced prostate cancer, this might not be generally true since BPH could also give such high PSA values.

Significant differences were noted in the mean EDV and PI of benign and malignant lesions with p=0.021 and p= 0.023 respectively. The PSV and RI showed no significant statistical difference in benign and malignant lesions. Two different studies done in India and Korea by Jyotsna et al[18] and Cho et al[19] respectively noted a similar finding that the mean RI was not significantly different in benign and malignant prostatic lesions. In New York, Rifkin et al[20] also noted a similar finding. A study done in Taiwan by Yuh et al[10] noted a significant difference between the Doppler indices (PSV, EDV, RI) of benign and malignant prostatic lesions measured at the neurovascular bundle vessels (NVB). Their EDV finding which was significantly higher in malignant lesions agreed with the present study while PSV and RI did not agree. This partial agreement might be due to larger sample size used in their study when compared to present study (292patients verses 74patients). Osama et al[9] in Egypt also observed a relative difference in the RI of prostatic vasculature in different prostate pathologies. They noted that the mean RI value for cancer cases was slightly lower than the mean RI for benign cases. A similar observation was made by Kwon et al[6] in 2016 in South Korea that there was an increase in resistivity index

(RI) in patients with BPH. Although the actual reason for this increased RI in BPH patients had not been established, it might be due to increase in intraprostatic pressure caused by the growing hypertrophied gland that pushed the capsule outwards thereby compressing the neurovascular structures.[7] Onwuchekwa et al[21] did a study in Nigeria and found that CaP cases showed a localized increased flow with low resistivity index compared to BPH cases. The increased flow with low RI seen in CaP might possibly be due to neovascularity associated with malignant changes which was also seen in cancer of other organs like kidney and liver.[22,23]

There was a significant positive correlation between EDV and PSA in benign lesions only (r=0.309, p= 0.031). Other Doppler indices (PSV, RI and PI) were not significantly correlated with PSA in both benign and malignant lesions. At the moment, there is no available local or international literature on the relationship between Doppler indices and PSA to compare these findings. However, this result might be due to the fact that blood samples for PSA were not collected same day the Doppler scans were done. Some patients did their PSA months after their Doppler scan were done and vice versa due to financial constraints.

CONCLUSION

End diastolic velocity (EDV) and PI may assist in differentiation of benign from malignant prostatic lesions. In benign

lesions, EDV correlated with PSA and therefore can used to monitor patients with BPH.

Competing interest

There is no conflict of interest.

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Authors

Chiedozie N. Ikeh, Department of Radiology, Alex Ekwueme Federal University Teaching Hospital Abakaliki, Nigeria, Email: edozienkem@gmail.com

Michael O. Orji, Department of Radiology, Alex Ekwueme Federal University Teaching Hospital Abakaliki, Nigeria, Email: drorji2003@yahoo.com

Emmanuel Uchendu, Department of Radiology, Alex Ekwueme Federal University Teaching Hospital Abakaliki, Nigeria, Email: emmauchendu@yahoo.com

Christiana M. Asaleye, Department of Radiology, Obafemi Awolowo University Teaching Hospitals Complex, Ile-Ife, Nigeria, Email : casaleye@yahoo.com

 Callistus U. Ibewuike, Department of Radiology, Alex Ekwueme Federal University Teaching Hospital Abakaliki, Nigeria, Email: etoovic2002@yahoo.com

Ozoemena S. Oboke, Department of Radiology, Alex Ekwueme Federal University Teaching Hospital Abakaliki, Nigeria, Email: obokeozoemema@yahoo.com

Charles A. Odoemene, Department of Surgery, Alex Ekwueme Federal University Teaching Hospital Abakaliki, Nigeria, Email: odoemenec@yahoo.com

Correspondence Author
Dr. Ikeh Chiedozie Nkemakonam, Department of Radiology, Alex Ekwueme Federal University Teaching Hospital Abakaliki, Nigeria, Email: edozienkem@gmail.com