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UTILIZATION OF DIAGNOSTIC EFFICACY OF A-METHYLACYL COA RACEMASE (AMACR) AND P63 IN DIFFERENTIAL DIAGNOSIS OF PROSTATE CANCER AND BENIGN PROSTATIC HYPERPLASIA

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Abstract

Background: Diagnosis of prostatic tumours, especially the suspicious cases of precancerous lesions are usually subjective, using conventional morphology in Haematoxylin and Eosin stained tissue section. This method is also prone to diagnostic errors or misdiagnosis both in benign and malignant cases. Morphological investigation via light microscopy remains the gold standard for the diagnosis of prostatic carcinoma. Intra-observer variability in diagnosis and difficult cases may benefit from immunohistochemical staining using panel of markers.
Aim: The potentials of p63 and α--methylacyl CoA racemase (AMACR) in differentiating cases of benign prostatic hyperplasia (BPH) from prostate cancer was studied.
Method: Eighty-five previously diagnosed archived prostate tumour tissues comprising of 41 malignant and 44 benign lesions were retrieved for the Histopathology Laboratory of a tertiary healthcare facility. The samples were reviewed and processed for immunostaining (IHC) using p63 and AMACR monoclonal antibodies.
Results: There was 85.9% (73) agreement between morphological diagnosis using conventional Haematoxylin and Eosin technique and IHC, and 14.10% (12) discordance. Of this discordance, 4 (33.30%) were found in cancer of the prostate and 8 (66.70%) were found in benign prostatic

hyperplasia; 37 (90.2%) of previously H&E diagnosed CAP showed strong (3+) immunoreactivity for AMACR while 4(9.8%) were positive for p63. Similarly, previously H&E diagnosed BPH showed 36(81.8%) strong immunoreactivity for p63 and 8(18.2%) for AMACR. Grade V cancers occurred highest with 41% while grade II was the lowest with 5% occurrence. The Gleason's scores ranges for 4+4 to 5+5, while the age of patients ranges from 48 to 86 years with mean age of 68.3 years.

Conclusion: Whereas morphological method remains the gold standard for diagnosis of prostatic lesions, it is not devoid of diagnostic errors. Therefore, p63 and AMACR biomarkers may be of great value in definitive diagnosis and confirming small foci of adenocarcinoma, resolving suspicious lesions and excluding benign mimickers.

Key Words: Prostate, Cancer, Benign, p63, AMACR

Introduction

Prostate cancer is the most frequently diagnosed malignancy in men worldwide after lung cancer, and the 5th leading cause of cancer related deaths in men[1]. Worldwide, the incidence and mortality of prostate cancer increases with increasing age [2]. Black men of African descent have the highest prostate cancer incidence and mortality rates and are more likely to develop disease earlier in life when compared to other racial and ethnic groups[3].

Tissue examination of a prostate needle biopsy or transurethral resection specimen from prostate is mandatory for the diagnosis of prostate cancer and allows patients to receive appropriate therapy. The diagnosis of prostate tumours using conventional Haematoxylin and Eosin staining method may be subjective and prone to misdiagnosis both in benign and malignant cases[4]. Misdiagnosis could be traced to difficult and inaccurate tissue diagnosis due to the increased presence of very small cancer focus leading to either limited amount of suspicious glands and minimal atypism[5], the presence of many benign mimickers of malignancy or as a result of sampling variations[6]. This is more so because a single morphologic feature dose not reliably establish prostatic adenocarcinoma diagnosis. The establishment of a pathologic diagnosis requires the presence of a combination of multiple histologic features of tumor cells which include; pattern of growth, nuclear atypia, absence of basal cells, and the presence of characteristic extracellular material in malignant glands[7]. The consequences associated with incorrect diagnosis, such as unnecessary prostatectomy or radiation associated with adverse complications owing to a false-positive diagnosis or delay of effective treatment owing to a false-negative diagnosis, are undesirable. Although the light microscopic morphological findings remain adjudged as the gold standard for the diagnosis of prostatic carcinoma, intra-observer variability in diagnosis and difficult cases may benefit from immunohistochemical studies[5]. The accuracy of pathologic diagnosis of prostate cancer may be improved by the application of a more objective and reliable tumour-specific markers[6].

PSA is not a cancer-specific marker, as it is present in benign and malignant prostatic epithelial cells[8]. Serum PSA levels frequently are elevated in benign conditions such as benign prostatic hyperplasia (BPH)

and prostatitis[8]. Consequently, patients with an elevated serum PSA level must undergo a biopsy to confirm or exclude the presence of prostate cancer. Other biomarkers, including prostate acid phosphatase (PAP), prostate-specific membrane antigen, prostate inhibin peptide, PCA-1, PR92, prostate-associated glycoprotein complex, PD41, 12-lipoxygenase, p53, p27, hepsin, PIM-1 kinase, and EZH2 are expressed in prostate carcinoma[9]. However, up to now, these markers are not usually used by pathologists to distinguish benign from malignant glands because of lack sensitivity or specificity for prostate carcinoma in formalin-fixed tissue samples[10].

Benign prostate glands contain secretory epithelial cells that express PSA and PAP and basal cells that lie beneath the secretory cells[11]. Basal cells are oriented parallel to the basement membrane and might be inconspicuous in benign glands[12]. Because basal cells are absent in prostate adenocarcinoma, high-molecular-weight cytokeratin (34ßE12) and p63 immunostains specific for basal cells have been used as ancillary tools for the diagnosis of prostate cancer[13]. The identification of the basal cells of prostate glands indicates the presence of benign glands[13]. However, a limitation of using this negative marker for the diagnosis of carcinoma is that basal cells can have a patchy or discontinuous distribution in some benign lesions (adenosis). Consequently, negative staining for basal cells in a few glands suggestive of cancer is not proof of their malignancy[14]. P63 has advantages over 34betaE12, because 34betaE12 is highly susceptible to effect of formalin fixation and IHC procedures such as antigen retrieval pre-treatment, resulting in variable staining arising from loss of staining in the benign glands and can cause misdiagnosis of prostatic adenocarcinoma[15].

P504S was a 382-amino-acid protein, which had been identified as human α-methylacyl coenzyme A racemase (AMACR)[16]. AMACR is an essential enzyme in the beta-oxidation of branched-chain fatty acids. High expression of AMACR protein is found in prostate adenocarcinoma but not in benign prostate tissue by immunohistochemical staining in paraffin-embedded tissue[16]. The expression of AMACR is also detected in prostate premalignant lesions, such as prostate intraepithelial neoplasia (PIN)[16]. The p63 protein, a homologue of the tumor-suppressor p53, is highly expressed in the basal or progenitor layer of many epithelial tissues[17]. P63 is detected in prostate basal cells in normal prostate glands and PIN. However, it is negative in prostate adenocarcinoma[18]. Thus p63 is useful as a differential marker for benign prostate glands and adenocarcinoma (negative marker). The combination of AMACR and p63 may be extremely useful for diagnosing PIN and small focus adenocarcinoma, especially in difficult or suspicious cases for malignancy and cases with limited tissues. This antibody cocktail may eliminate the need for high-molecular-weight cytokeratin (34ßE12).

This study therefore, sought to evaluate the specificity and sensitivity of p63 (negative marker) which is specific for basal cells in benign glands and a more objective and reliable molecular marker for prostate adenocarcinoma such as AMACR (positive marker). The study was also aimed to substantiate the existence of diagnostic inaccuracies or misdiagnosis using only the conventional H&E staining of needle biopsy and transurethral resection of prostate (TURP) samples.

Materials And Methods

Study design

A 5-year retrospective study explored the immunohistochemical evaluation of AMACR and P63 in previously diagnosed

samples of benign and malignant formalin processed, paraffin wax embedded prostate tissue blocks from 2013 to 2018 retrieved from the Histopathology Department of Nnamdi Azikiwe University Teaching Hospital Nnewi was carried out. Also retrieved from the available records were patients' biodata. Ethical approval for the study was obtained from the ethics committee of the hospital before commencement of the study.

Sample collection

Excluding damaged tissue blocks and tissue blocks that were not core needle biopsies, a total of 85 tissue blocks were selected from the hospital archives. All the cases were reviewed during which the tissue blocks were categorized into two, namely 41 malignant and 44 benign cases. The paraffin blocks were trimmed, 3 microns thick sectioned using rotary microtome and three serial sections were mounted on three different slides.

Haematoxylin and Eosin (H&E) Staining[19]

The sections were stained using H&E staining method and photomicrographs of sections taken using Amscope digital camera eyepiece attached to an Olympus optical microscope. Two independent blind reviewers reviewed the slides to confirm morphological diagnosis.

Immunohistochemical (IHC) staining[20]

Tissue sections were subjected to IHC evaluation of AMACR and P63 using anti-AMACR and anti-P63 monoclonal antibodies along with positive and negative controls. Immunoractivity were detected using rabbit horseradish antiperoxidase/diamino benzidene (HRP/DAB) detection IHC kit. Immunoractivity was semi-quantitatively scored[21]. Antibodies and detection kits were products of ABCAM Plc Uk, sourced through Biotec Nigeria.

Data Analysis

Data obtained were analyzed and results presented in tables, pie charts, bar charts and plates.

Results

There was 73(85.9%) agreement between H&E and IHC staining methods and 12(14.10%) discordance (Figure 1). Of this discordance, 4(33.30%) were found amongst cancer of the prostate while 8(66.70%) were found in benign prostatic hyperplasia (Figure 2). Thirty-seven (90.2%) of previously H&E diagnosed CAP showed strong (3+) immunoreactivity for AMACR while 4(9.8%) were strongly positive for p63. Similarly, previously H&E diagnosed BPH showed 36(81.8%) strong immunoreactivity for p63 and 8(18.2%) for AMACR (Table 1). Grade V cancers occurred highest with 41% while grade II was the lowest with 5% occurrence (figure 3). The Gleason's scores ranges for 4+4 to 5+5, while the age of patients ranges from 48 to 86 years with mean age of 68.3 years. The morphology and the ICH expression patterns are shown in plates 1-3.

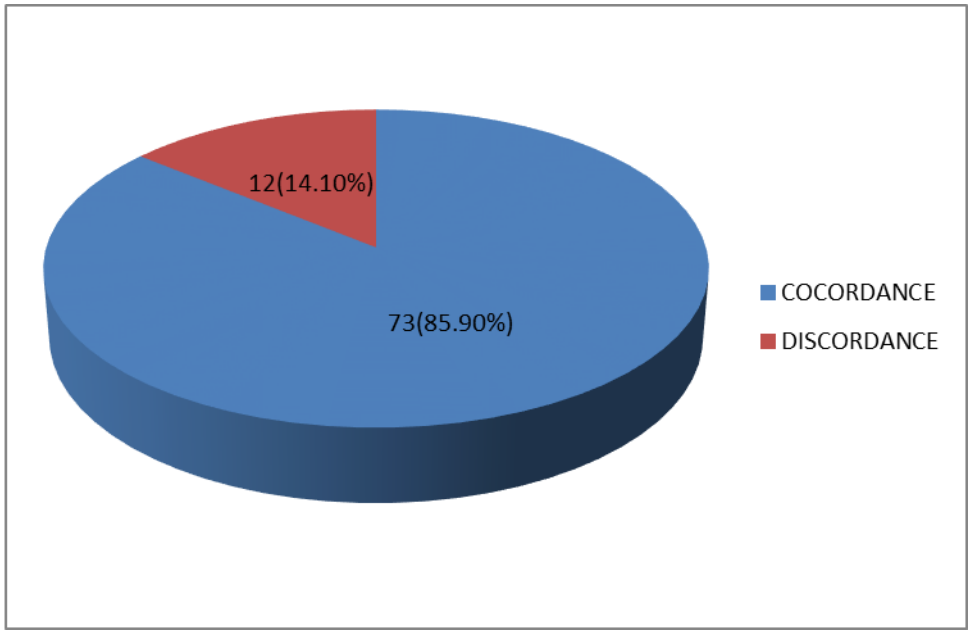


Figure 1: Degree of agreement (concordance) and disagreement (discordance) Between H and E and IHC.

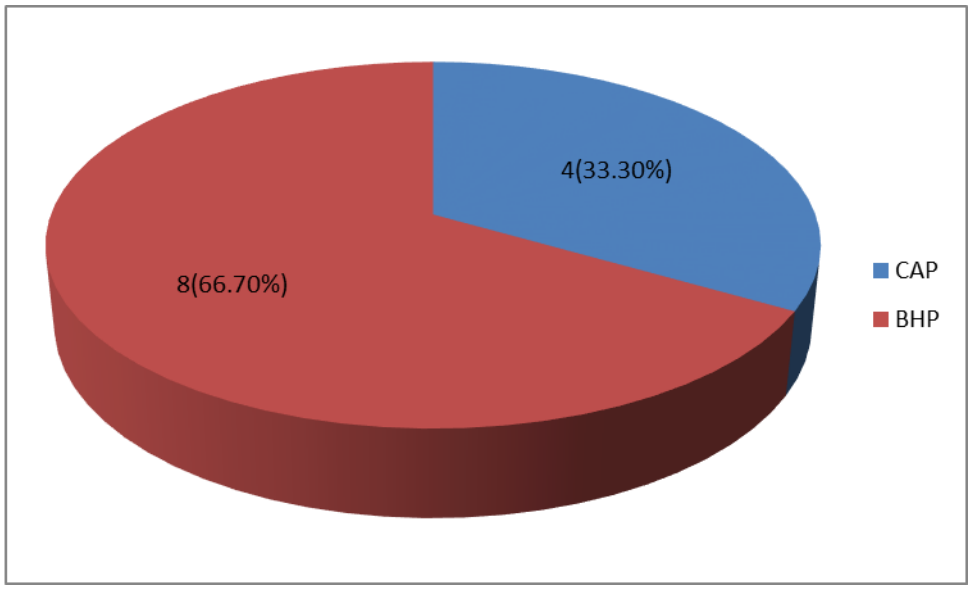


Figure 2: Percentage of discordance between H and E diagnosed CAP and BPH after application of AMACR and P63 markers.

Table 1: Differential Diagnosis of IHC on Benign Prostatic Hyperplasia (BPH) and Cancer of the prostate (CAP) using AMACR and p63

Lesion type/staining techniques	H&E		AMACR		P63	
	Positive n(%)	Negative n(%)	Positive n(%)	Negative n(%)	Positive n(%)	Negative n(%)
BPH	44(100)	0 (0.0)	8(18.2)	36(81.8)	36(81.8)	8(18.2)
CAP	41(100)	0 (0.0)	37(90.2)	4(9.8)	4(9.8)	37(90.2)

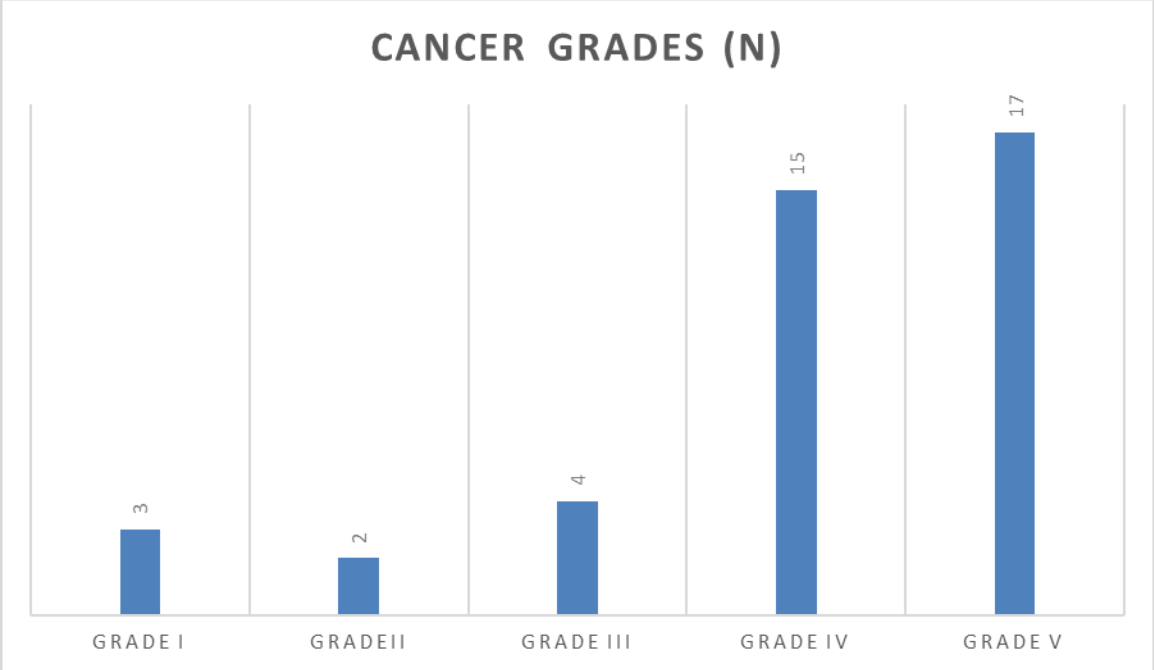
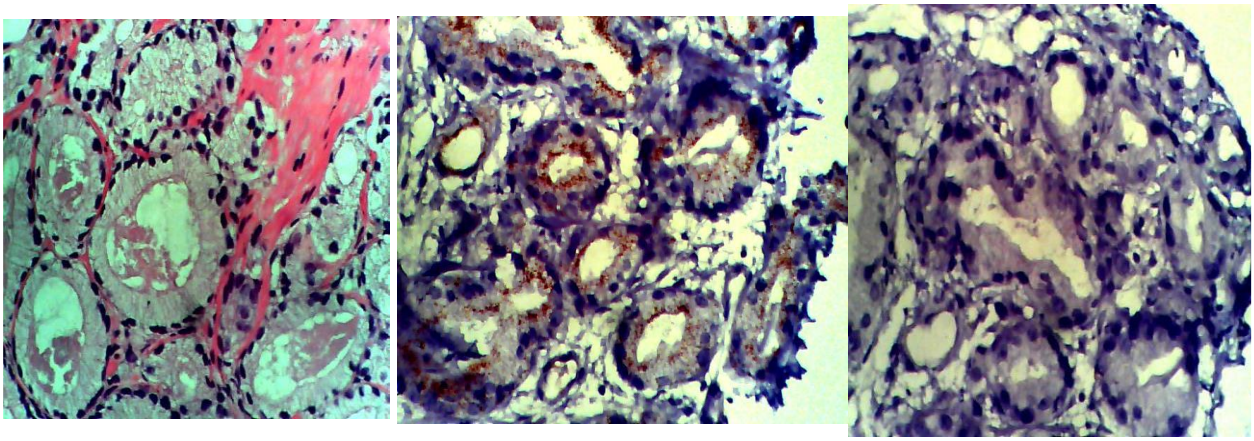
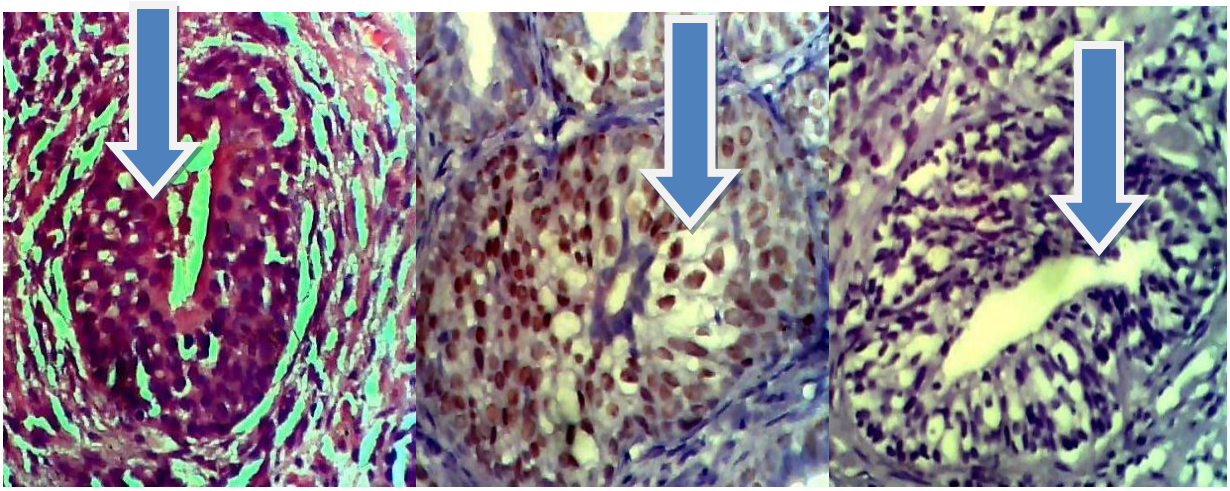


Figure 3: Grades of CAP samples



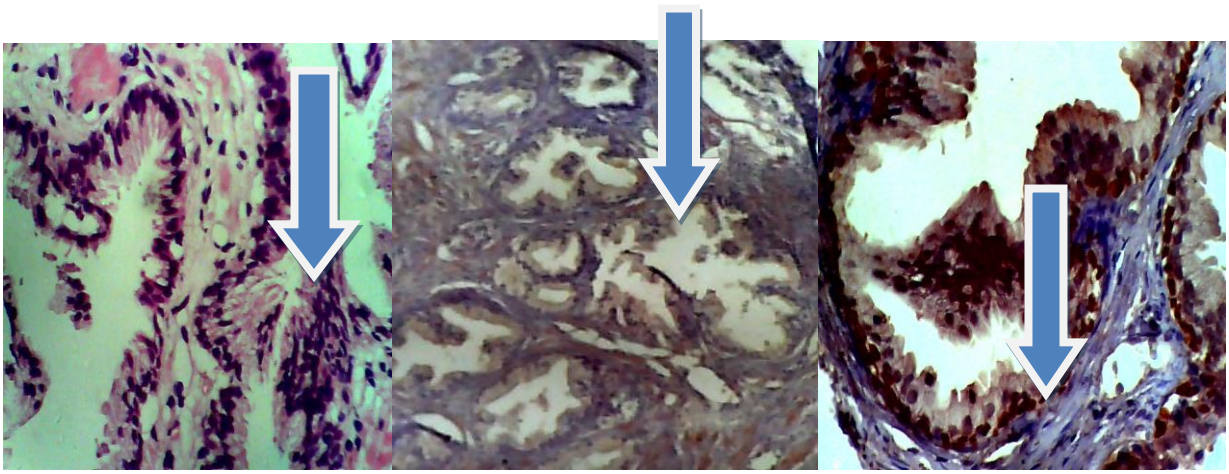
BPH H and E Diagnosis AMACR= POSITIVE P63= NEGATIVE

PLATE I Photomicrograph of a case with a BPH at H and E diagnosis mimicking an Adenosis was finally diagnosed as LOW GRADE ADENOCARCINOMA (Discordance) using AMACR and P63 Immunohistochemistry.x40. There was immunostaining in the luminal cells of the malignant lesions by anti AMACR monoclonal antibodies.No staining by anti p63 monoclonal antibodies .Note AMACR POSITIVE and P63 NEGATIVE.



CAP H and E P63=POSITIVE AMACR= NEGATIVE

PLATE II Photomicrograph of a case with a Cancer of the prostate (intraductal type) at H and E diagnosis was finally diagnosed as BASAL CELL HYPERPLASIA (Discordance) using AMACR and P63 Immunohistochemistry.x40. The basal cell nucei of the benign lesions were immunostained positive by anti-p63 monoclonal antibodies.No immunostaining was seen in the luminal cells of the malignant lesions.Note: AMACR NEGATIVE and P63 POSITIVE.



BPH H and E AMACR =NEGATIVE P63= POSITIVE

PLATE III Photomicrograph showing a case with BPH diagnosis at H and E was also supported (concordance) using AMACR and P63 Immunohistochemistry.x40. The basal cell nucei of the benign lesions were immunostained positive by anti-p63 monoclonal antibodies.No immunostaining was seen in the luminal cells of the malignant lesions by anti AMACR monoclonal antibodies: Note AMACR NEGATIVE and P63 POSITIVE.

Discussion

In agreement with the findings of this study there was an increased significant differential diagnosis in benign prostatic samples and malignant prostatic samples when AMACR and p63 were used as adjunct diagnostic tools, corroborating the report of Rashed *et al*[22] who observed increased statistically significant difference in AMACR index between benign and malignant prostatic lesions. This finding is also in congruence with the finding of Okonkwo *et al*[23] who also carried out the similar study on routinely diagnosed prostatic carcinoma and equivocal diagnoses. The above researchers, though, not undermining the value of morphological diagnosis, revealed a major shortcoming while advocating for inclusion of adjunct IHC markers.

The present study revealed high percentage of diagnosis agreement of 73/85(85.9%) and lower disagreement of 12/85(14.10%) between H&E and IHC methods. This agreed with a previous by Singh *et al*[24] who reported 27/40(67.5%) agreement and 13/40(32.5%) discordance between H&E and IHC. The high level of agreements reported from both studies further proved that H&E method still remains very sensitive diagnostic method. Nonetheless, the record of 12% discordant diagnosis may be an indication of the vulnerability of the method to minimal misdiagnosis, due largely to its subjectivity nature. The higher percentage of discordance in the benign lesions compared to the malignant ones, reported in the current study also corroborates the finding of Singh *et al*[24], who reported 11/13 benign to malignant and 1/13 malignant to benign. One could adduce that the likelihood of having false negative benign results in prostatic diagnosis using only the routine H&E technique is more than false negative malignant results. This portends grave consequences and underscores the importance of using IHC ancillary technique alongside H&E.

The sensitivity and specificity results on diagnostic utility of p63 and α-methyl acyl Co A racemase (AMACR) in resolving suspicious foci in prostatic needle biopsy and transurethral resection of prostate specimens obtained from the current study was generally high and this finding is in agreement with several other studies[25,26,27,28,29]. These authors in separate studies reported high immunoreactivity of AMACR in prostate cancer as compared with benign lesions of prostate.

The current study reported that immonoreactivity of AMACR favours only malignant lesions while only benign lesion showed p63 immunostaining with no case of cross reactivity. This is in congruence with the report of Okonkwo *et al*[23] and Herawi and Epstein[18]. There is abundant literature evidence that luminal cells of high grade prostate cancer do not express p63 but express AMACR whereas basal cells of benign prostatic lesions express p63, they do not express AMACR. This further underscores the value of these panel of tumour markers in definitive diagnosis of prostate lesions. While not jettisoning the efficacy of morphological diagnosis using H&E, including AMACR and p63 in the routine diagnosis regimen may sensitivity of prostatic lesion diagnosis to 100%. This not improves patients' outcome through appropriate management but save time and cost.

The reported patients' mean age of 68.3 years agrees with the generally agreed and reported vulnerable age for prostatic lesions. The pattern grades and the Gleason's scores observed in the current study corroborates the report of earlier studies[23,30].

Conclusion

Morphological diagnosis of prostatic lesions showed high level of sensitive and specific

but with an unacceptable percentage of discordant diagnosis. P63 and AMACR tumour markers showed high percentage of sensitive and specificity for detection of BPH and CAP respectively, when compared to routine H&E method. Therefore, to achieve all times definitive diagnosis of prostate lesions, effective resolution of suspicious cases of prostate cancer and BPH, promote early diagnosis, make uncertain diagnoses less frequent and obviate the need for a number of repeated biopsies, inclusion of p63 and AMACR IHC panel in routine diagnosis may be the answer.

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