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Alpha-Methylacyl-Coa Racemase (Amacr) Expression In Prostatic Lesions – A Tertiary Care Centre Study In North Kerala

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Abstract :
Background*: Prostate cancer is the fourth most common cancer and eighth leading cause of cancer-related death worldwide . Even though the diagnosis of prostatic adenocarcinoma can be made based on morphologic features, it is sometimes difficult to diagnose when the foci of cancer is small. Moreover various benign conditions like adenosis, partial atrophy etc can mimic prostate cancer. AMACR (alpha-methylacyl-CoA racemase) has been described in literature as a potential marker of prostatic adenocarcinoma but is not 100% sensitive. This study is an attempt to evaluate the immunohistochemical expression of AMACR in prostatic lesions in a tertiary care centre of North Kerala and to evaluate the pattern of AMACR expression in varying histological grades of prostatic adenocarcinoma.*
Materials and Methods: *This was a descriptive study and included a total 41 cases of prostatic lesions which included transurethral resection specimens and prostate core biopsies received in the department of Pathology ,Government Medical College , Kannur from July 2021 to July 2022.The clinical data and histopathological slides were reviewed and the lesions were categorized. The representative blocks of biopsies were subjected to immununohistochemical study with AMACR. The results were subsequently analyzed.*
Results*: Of the 41 cases, 21 were prostatic adenocarcinomas and 20 were benign prostatic hyperplasia . Majority of cases belonged to 61-70 years of age group in both benign and malignant cases. The mean age of the study population of prostatic adenocarcinoma was 70 years and 65 years in benign prostatic hyperplasia. Among prostatic adenocarcinomas majority of cases belonged to grade group 5 (7/21 cases) and grade group 1 had the minimum (2/21 cases). AMACR expression was found to be positive in 90.47% cases. Strong (3+) AMACR staining was obtained in 61.9% of prostatic adenocarcinoma cases, moderate (2+) in 23.8% and weak (1+) in 4.8% cases .The 2 cases of AMACR negative prostatic adenocarcinoma belonged to grade group 5. No significant association was obtained between AMACR positivity and prostatic adenocarcinoma grade groups using Chi-square test (p =0.420). 85% of benign prostatic hyperplasia cases showed AMACR negativity and 3 cases showed weak staining. None of the benign prostatic hyperplasia cases showed strong staining.*
Conclusion: *AMACR helps in confirming the diagnosis of prostatic adenocarcinomas but is not always reliable. It can be negative in a small percentage of carcinomas. There is no significant association between AMACR expression and prostatic adenocarcinoma grade groups. Weak positivity can be observed in benign prostatic glands too.*
***Key word* :** *AMACR; prostatic adenocarcinoma ; grade groups .*

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I.Introduction

Prostate cancer is the fourth most common cancer and eighth leading cause of cancer-related death worldwide.[1] Histopathological examination is always necessary to diagnose prostatic adenocarcinoma. It is always challenging to accurately diagnose small foci of prostate cancer and to distinguish cancer from its benign mimickers. It would be better if diagnosis can be supported with more accuracy by a positive diagnostic marker. AMACR stands for alpha-methylacyl-CoA racemase. AMACR is a well-characterized enzyme that plays a key role in peroxisomal beta oxidation of dietary branched-chain fatty acids and bile acid intermediates.[2] Studies have shown that AMACR is overexpressed in majoriy of prostatic adenocarcinomas when compared to benign lesions. However, AMACR is not 100% sensitive, and its expression is not limited to prostatic adenocarcinoma but may also be seen in several of its histologic mimics, resulting in many potential caveats in its use.[3] This study is an attempt to evaluate the immunohistochemical expression of AMACR in prostatic lesions in a tertiary

care centre of North Kerala and also to test the pattern of AMACR expression in varying histological grades of prostatic adenocarcinoma.

II. Materials And Methods

This is a 1 year descriptive study (from July 2021 to July 2022) done in the department of Pathology ,Government Medical Collage Kannur following approval from the institutional ethical committee. 41 cases of prostatic lesions were included in the study .The specimens included –TURP (transurethral resection of prostate) and prostate core needle biopsies.

Study Design: Descriptive study

Study Setting: Government Medical College, Kannur

Study Duration: July 2021-July 2022

Study Population: Cases of prostatic lesions received in the Department of Pathology, GMC Kannur .

Inclusion Criteria:

- All prostatic specimens- needle biopsies, TURP- transurethral resection of prostate specimens

Exclusion Criteria:

- Inadequqte sample (Core biopsies without glandular tissue.)

Sample Size:

Sample size is calculated based on the formulae given below.

$\frac{z2pq}{d^2(PREVELENCE)}$,

z=1.96

d=5% relative precision,

p=86.7%[14]

q=100-p=13.3%,

d=4.3

Based on the above formula, the sample size obtained was 20. Using the convenient sampling method, 41 consecutive samples were included in this study.

The relevant clinical data and details of laboratory investigations were obtained from the request form for histopathological examination. Biopsy specimens were received in 10% neutral buffered formalin. Representative sections were taken, labeled and processed routinely for Hematoxylin and Eosin staining. The slides were examined under the microscope. Prostatic adenocarcinomas were graded according to the 2019 ISUP/WHO Gleason grading of Prostatic carcinoma. IHC was done using AMACR (P504S) Rabbit Monoclonal Antibody. AMACR staining pattern and intensity were noted and evaluated.

Interpretation of Immunohistochemistry:

Positive staining refers to circumferential, granular, luminal/apical to diffuse cytoplasmic staining.

Negative staining refers to absent staining and focal, partial or non-circumferential staining.

The intensity is graded between 0 and 3+ as given below:-

0 - No staining, focal / non circumferential staining

1+ - weak, circumferential, granular, luminal/apical to diffuse cytoplasmic staining

2+ - moderate, circumferential, granular, luminal/apical to diffuse cytoplasmic staining

3+ - strong, circumferential, granular, luminal/apical to diffuse cytoplasmic staining

Statistical analysis

Data was entered into Microsoft excel and analysed using Statistical Package for Social Science software. Qualitative variables were expressed as frequencies and percentage. Chisquare test and Fisher's exact test were used to examine the relationship between categorical variables.

III. Results

Majority of specimens received were TURP specimens accounting for 24 cases, along with 17 cases of prostate core biopsies. Of the total 41 cases 21 were prostatic adenocarcinomas and 20 were cases of benign prostatic hyperplasia .

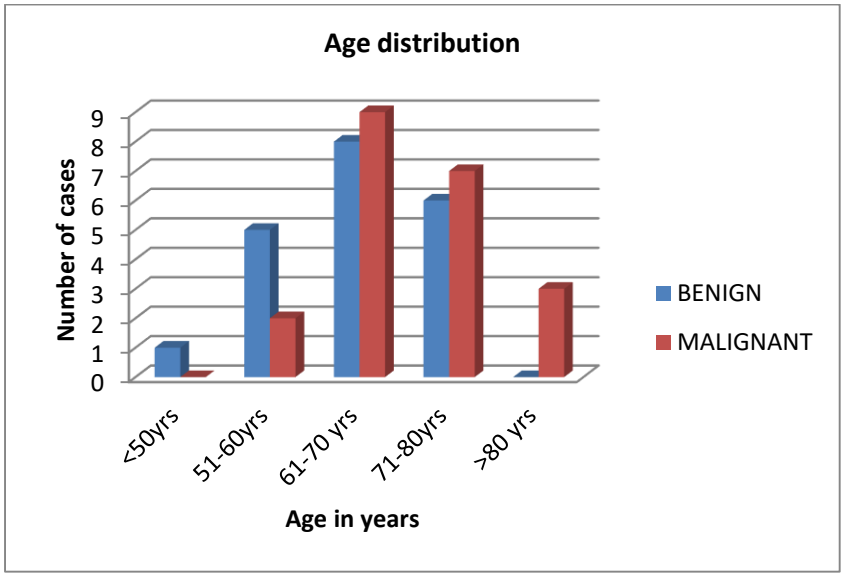

Figure 1: Bar diagram depicting age distribution of the study population .

In this study majority of cases belonged to the age group of 61- 70 years (figure 1). The mean age of study population of prostatic adenocarcinoma was 70 years with minimum age of 61 years and maximum of 85 years. Among benign lesions the mean age was 65 years with an age range of 46 to 76 years.

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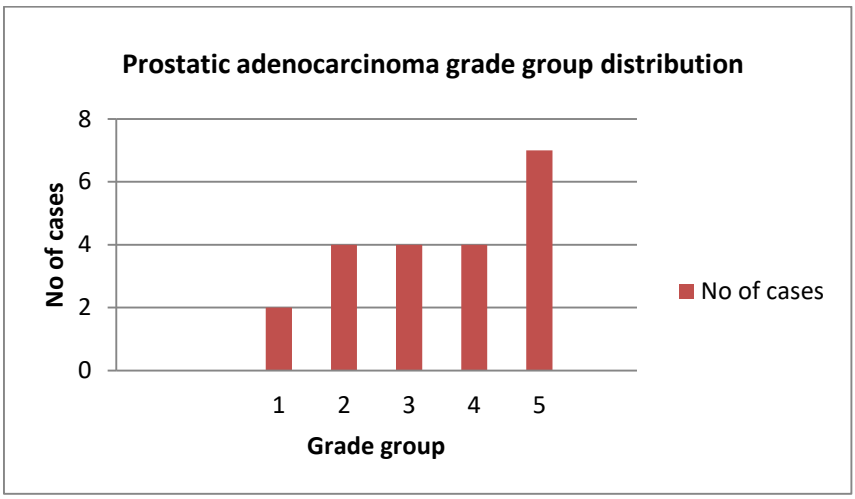

Figure 2: Bar diagram depicting the frequency of prostatic adenocarcinoma grade groups.

Among prostatic adenocarcinomas, the maximum number of cases (7/21 cases) belonged to grade group 5 and the minimum was in grade group 1 (2/21 cases) .(figure 2).

Table 1: AMACR expression in prostatic lesions

AMACR	POSITIVE	NEGATIVE
Prostatic adenocarcinoma	19	2
BPH	3	17

AMACR positivity was observed in 19/21 (90.47%) prostatic adenocarcinomas. It was negative in 17/20 (85%) cases of BPH .

Table 2: AMACR staining intensity in prostatic lesions

		AMACR staining intensity				
Group		0	1+	2+	3+	Total
Prostatic adenocarcinoma	Frequency	2	1	5	13	21

	%	9.5%	4.8%	23.8%	61.9%	
BPH	Frequency	17	3	0	0	20
	%	85.0%	15.0%	0.0%	0.0%	
Total		19	4	5	13	41

Majority of prostatic adenocarcinomas, (61.90% cases) showed 3+ AMACR staining intensity. 2+ and 1+ staining intensity were seen in 23.1%% and 4.8% of cases respectively. 9.5% of cases showed no staining.

None of the benign prostatic lesions showed strong or moderate staining. Weak staining was obtained in 15% of cases.

Using Fisher's exact test ($p<0.001$) significant association was obtained between AMACR positivity in benign & malignant groups. The proportion of malignant group who had 3+ staining was significantly higher than proportion of benign group who had 3+ staining. The proportion of benign group who had no staining was also significantly higher than the proportion of no staining in malignant group.

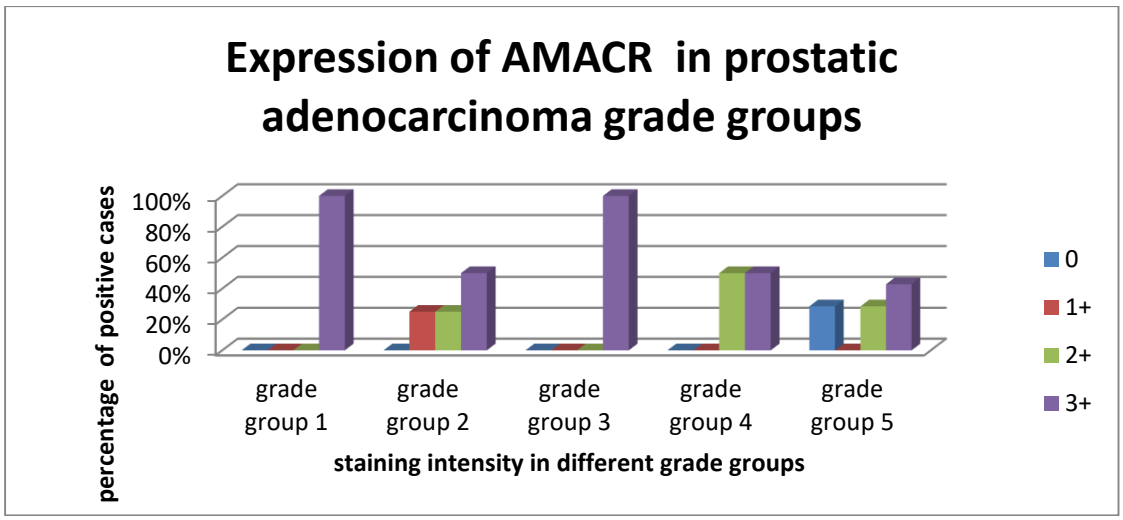

Figure 3: Bar diagram depicting AMACR staining in prostatic adenocarcinoma grade groups.

Grade group 1 and grade group 3 showed 100% 3+ staining.
In grade group 2, 50% of cases showed 3+ and rest of cases showed 1+ and 2+ staining intensity.
In grade group 4, 50% of cases showed 3+ and rest showed 2+ staining .
In grade group 5, 42.8% of cases showed 3+ staining and 28.5% of cases showed 2+ and negative staining intensity respectively.

Table 3: AMACR staining intensity in grade groups

AMACR STAINING INTENSITY	GRADE GROUP				
	1	2	3	4	5
0	0	0	0	0	2
1+	0	1	0	0	0
2+	0	1	0	2	2
3+	2	2	4	2	3
TOTAL	2	4	4	4	7

Using Chi-square test, the p value was found to be 0.420 and hence there is no significant association between AMACR positivity and prostatic adenocarcinoma grade groups.

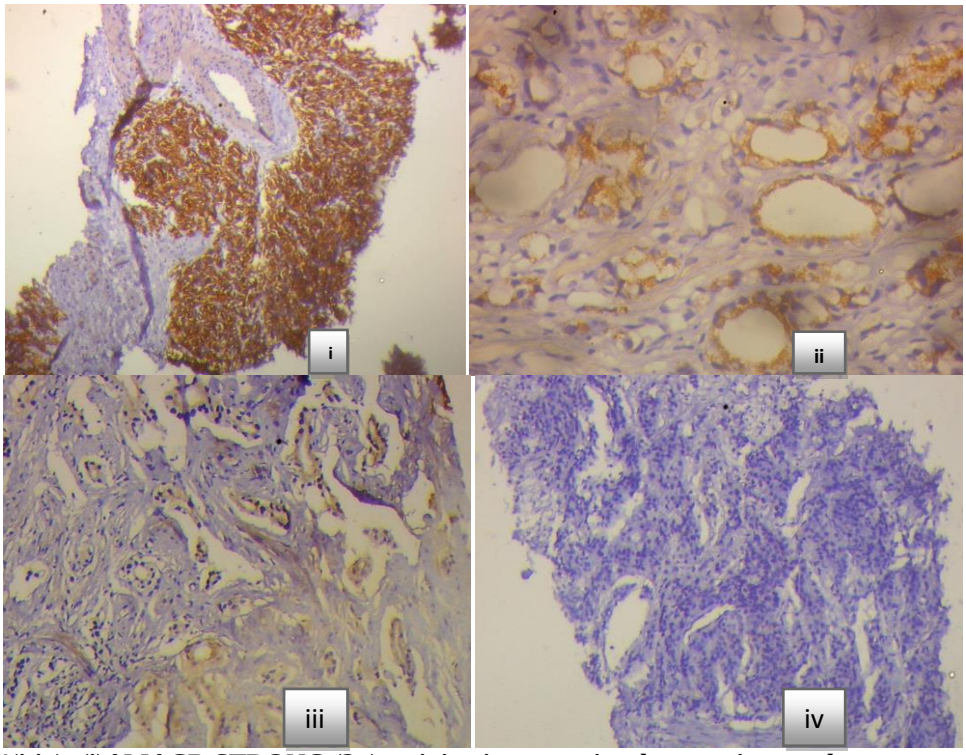

Figure 4(i-iv): (i)AMACR STRONG (3+) staining in prostatic adenocarcinoma gleason pattern 5.(ii) moderate staining in gleason pattern 3.(iii)weak staining in gleason pattern 3. (iv)negative staining in gleason pattern 5

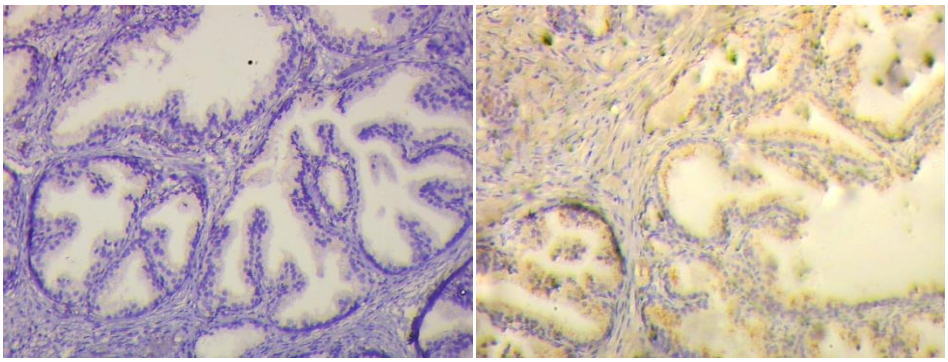

Figure 5 :Benign prostatic hyperplasia showing negative and weak AMACR positivity

IV.Discussion

Alpha-methylacyl-CoA racemase (AMACR) gene product is an enzyme involved in β-oxidation of branched-chain fatty acids. It has been identified as a novel tumor marker for several human cancers including prostate cancer. In this study AMACR expression was analysed in 41 cases of prostatic lesions of which 21 cases were prostatic adenocarcinomas and 20 cases were benign (BPH). The pattern and intensity of AMACR expression was evaluated in all.

Majority of cases were specimens of transurethral resection of prostate (24/41cases). Prostatic adenocarcinomas were detected in 4 cases of TURP specimens. Both benign and malignant lesions were more commonly seen in the age group 61- 70 years which was similar to the study of Koshy et al.[4] The mean age of presentation of prostatic adenocarcinomas and BPH cases in our study was 70 and 65 years respectively. This was similar to the study of Kumar S et al[5] where the mean age of prostatic adenocarcinoma was 68 years.

Majority of prostatic adenocarcinomas belonged to grade group 5 and constituted 7/21 cases. The least number of cases were observed in grade group 1(2/21 cases). This was discordant with the studies conducted by Koshi et al,[4] Puttaswamy K et al & Kumar M[5] et al where grade group 1 had the majority of cases .

AMACR immunoreactivity was detected in 90.47% cases of prostatic adenocarcinoma in the present study which was similar to the studies of Ozgur et al[6] (90.6%), and Rashed H E et al[7] (90%). In most of the previous studies immunoreactivity of AMACR ranged from 82- 100%.

Table 4: Previous studies of AMACR expression in prostatic adenocarcinoma in comparison with the current study.

Study	Year	No: of prostatic adenocarcinoma cases	AMACR positive cases
Vahini et al[8]	2021	26	26 (100%)
Koshy et al[4]	2021	28	27 (96%)
Shrivasthava et al[3]	2019	30	30 (100%)
Kandaswami et al [9]	2017	93	85 (91%)
Goswami et al [10]	2019	50	48 (95%)
Ozgur et al[6]	2013	64	58 (91%)
Rashed et al[7]	2012	30	27 (90%)
Zhong et al [11]	2005	82	78 (95%)
Vincent et al [12]	2004	260	252 (97%)
R Beach et al[13]	2002	186	153 (82%)
Current study		21	19 (90%)

In the current study 3 + AMACR staining intensity was detected in 61.9% cases of prostatic adenocarcinoma .23.8% of cases showed 2+ and 23.8% showed 1 + intensity. This finding was almost similar to the findings of Vahini et al[8] where they found 58% cases with strong (3+) intensity and 4%with weak(1+) intensity .Whereas in the study conducted by Vincent et al [12] 36% of cases showed 3+ intensity & 31% and 30 % of cases showed 2+ and 1+ staining intensity respectively.

No significant association between AMACR staining and prostatic adenocarcinoma Grade groups were detected in the current study. Z Jiang et al[2] ,Vincent et al[12],R Beach et al[13] ,Ozgur et al[6] ,and Rashed et al[7] were also of the same opinion whereas Kumar S et al[5] had obtained a significant association between AMACR overexpression and increasing Gleason scores.

AMACR expression was found to be negative in 2/7 cases of grade group 5 prostatic adenocarcinomas. A similar observation was noted by Kandaswami et al[9] who also stated that AMACR negativity can be present in high grade carcinomas.

In the current study most cases (85%) of benign prostatic hyperplasia showed negative AMACR staining(17/20 cases). 15%(3/20) cases showed 1+ staining . None of the cases expressed 3+ and 2+ AMACR staining which was similar to the previous studies .

Tabe 5: Previous studies of AMACR expression in prostatic benign glands in comparison with the current study

study	year	No of cases	Weak AMACR expression
Kandaswami et al[9]	2019	19	0
Goswami et al[10]	2019	50	2
Zhong jang[11]	2005	56	0
Vincent et al[12]	2004	260	4
Current study		20	3

V.Conclusion

AMACR helps in confirming the diagnosis of prostatic adenocarcinomas but is not always reliable. It can be negative in high grade carcinomas. There is no significant association between AMACR expression and prostatic adenocarcinoma grade groups. Weak positivity can be observed in benign prostatic glands too.

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