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Diagnostic role of HMWCK in differentiation of Prostatic malignancy from its benign lesions

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Abstract

Background: Globally, prostate cancer ranks second in terms of frequency of diagnosis and is the sixth most common cause of cancer-related mortality in men. Markers such as HMWCK help to differentiate the malignant prostate cancer form the benign lesions. Hence, present study aimed to evaluate the diagnostic role of HMWCK in the differentiation of prostatic malignancy from its benign mimickers. **Material and Method**: This cross-sectional study was conducted among 40 cases for period of 2years from Nov 2016 to May 2018 at department of Pathology, Bangalore Medical College, Bengaluru. It included the include 40 prostate biopsies/transurethral resection of prostate (TURP) specimens/prostatectomies received from the Department of Urology, Bangalore Medical College. The staining for light microscopy done with routine H&E to arrive at diagnosis. The HMWCK cellular localisation, as basal cells of prostatic glands, urothelium, positive control is of prostate cancer. All the patient's data were analysed using SPSS 21.0 operating on windows 10 and data are represented using tables, figures and histopathological diagrams. **Result**: A total of 40 prostate samples included in present study. Twenty-four (60%) were TURP and sixteen (40%) were core biopsy specimens. The cases were distributed in the age group of 40–95 years. The majority of cases were in the age group of 70-80yrs. Immunohistochemistry was done using HMWCK markers in the cases of BPH, Prostatic intraepithelial neoplasia, and carcinoma. The HMWCK showed a significant sensitivity, specificity, NPV and PPV to diagnose the malignant tumor from pre-malignant and benign lesions of prostate. **Conclusion**: HMWCK is a reliable marker with consistently positive in normal benign prostate gland or epithelial cells. Hence it is recommended for use of the IHC marker to support the diagnosis of prostate carcinoma.

Keywords: Carcinoma, HMWCK, Prostate, Markers, Immunostain, Benign

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Introduction

Globally, prostate cancer ranks second in terms of frequency of diagnosis and is the sixth most common cause of cancer-related mortality in men. Since 2008, it has been responsible for 14% (903,500) of newly diagnosed cases and 6% (258,400) of male cancer fatalities.[1,2] Prostate tissue examination is required for the diagnosis of prostate cancer. However, if the cancer focus is very small (<1 mm), tissue diagnosis may be challenging and inaccurate because a pathologic diagnosis requires the presence of multiple tumour cell histological

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features, such as growth pattern, nuclear atypia, absence of basal cells, and the presence of distinctive extracellular material in malignant glands.[3]

There are multiple mimickers of benign lesion of prostate such as adenosis, atrophy and partial atrophy. High molecular weight cytokeratin (HMWCK) is a marker to detect the presence of malignancy. In such cases, the over diagnosis may cause unnecessary treatment of men without the prostate cancer, which may lead to incontinence or impotency.[4] The immunostains specific to the basal cells of prostate have been used in diagnosis of postate cancer. If there is presence of basal cells of prostate glands, indicate the presence of benign glands.[5] A positive immunohistochemical marker which is specific to the cancer of prostate along with negative basal cell marker are of great value to increase the level of confidence required to establish a definitive diagnosis of malignancy with the use of HMWCK. Present study aimed to evaluate the diagnostic role of HMWCK in the differentiation of prostatic malignancy from its benign mimickers

Material and Method

This cross-sectional study was conducted among 40 cases for period of 2years from Nov 2016 to May 2018 at department of Pathology, Bangalore Medical College, Bengaluru. It included the include 40 prostate biopsies/transurethral resection of prostate (TURP) specimens/prostatectomies received from the Department of Urology, Bangalore Medical College.

Procedure: All the specimens obtained were fixed in buffered neutral formalin for a period of 12-24 hrs and then the entire specimen was submitted for processing. For grossing, The weight of the specimen was noted and the findings were recorded as per the format. The entire bits were submitted for processing. Which included the steps as dehydration, clearing by chloroform, paraffin impregnation, embedded in paraffin wax, sections were cut by microtome setting of 4 microns, sections were floated in 60degree temperature, mounted on slide and for immunohistochemical analysis sections were mounted on poly-L-Lysine coated slides. The staining for light microscopy done with routine H&E to arrive at diagnosis. The HMWCK cellular localisation, as basal cells of prostatic glands, urothelium, positive control is of prostate cancer.

Statistical analysis: all the data were analysed using SPSS 21.0 operating on windows 10. The results on continuous measurements are presented on Mean ± SD (Min-Max) and results on categorical measurements are presented in Number (%). Significance is assessed at 5 % level of significance.

Result

A total of 40 prostate samples included in present study. Twenty-four (60%) were TURP and sixteen (40%) were core biopsy specimens. The cases were distributed in the age group of 40–95 years. The majority of cases were in the age group of 70-80yrs. Out of forty cases, thirteen were BPH, three were atypical small acinar proliferation, two were atypical adenomatous hyperplasia, nine were high grade intraepithelial neoplasia, thirteen were prostatic adenocarcinoma. Immunohistochemistry was done using HMWCK markers in the cases of BPH, Prostatic intraepithelial neoplasia, and carcinoma.

Table 1: Showing demographic details and histopathology report of all patients

		Frequency	Percent
Age	<40yr	01	2.5
	51-60yr	06	15.0
	61-70yr	11	27.5
	71-80yr	17	42.5
	81-90yr	04	10.0

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	>90yr	01	2.5
Type	Core biopsy	16	40
	TURP	24	60
HPR	Atypical adenomatous hyperplasia	02	5
	Atypical small acinar proliferation	03	7.5
	Benign prostatic hyperplasia	13	32.5
	High grade prostatic intraepithelial neoplasia	09	22.5
	Prostatic adenocarcinoma	13	32.5
HPR	Benign	13	32.5
	Malignant	13	32.5
	Premalignant	14	35

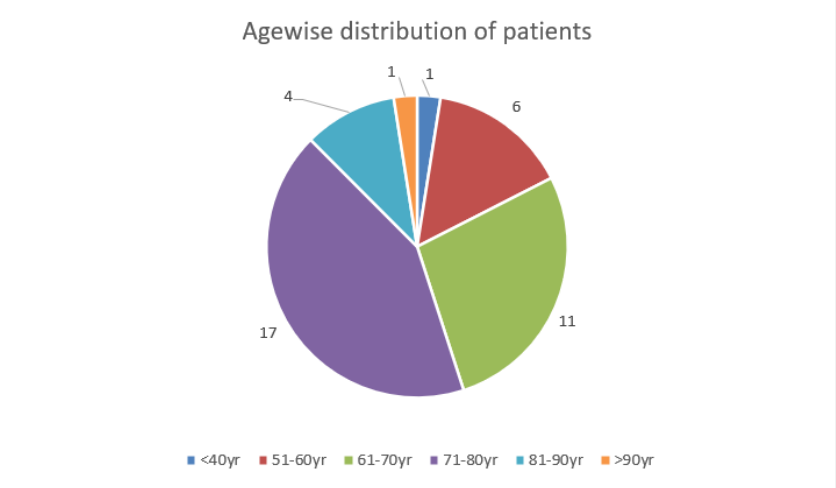

Figure 1: Agewise distribution of patients included in present study

Table 2: IHC staining pattern of HMWCK in correlation with histopathology report

	Total			
	Continuous positivity	**Negative**	**Patchy positivity**	**Total**
Benign	13	0	0	13
	100%	0.0%	0.0%	100.0%
Premalignant	1	2	11	14
	7.1%	14.4%	78.5%	100.0%
Malignant	0	13	0	13
	0%	100%	0%	100.0%
Total	14	15	11	40
	35%	37.5%	27.5%	100.0%

Table 3: Distribution of study subjects according to Age Specific PSA levels and HMWCK among Histopathology classification

HPR				**Age specific PSA**		**Total**
				Normal	**Abnormal**	
Benign	HMWCK	Continuous positivity		10	3	13
				76.9%	23.07%	100.0%
	Total			10	3	13
				76.9%	23.07%	100.0%

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Malignant	HMWCK	Continuous positivity		0	0	0
				0.0%	0.0%	0.0%
		Negative		0	13	13
				0%	100%	100.0%
		patchy positivity		0	0	0
				0.0%	0.0%	0.0%
	Total			0	13	13
				0%	100	100.0%
Premalignant	HMWCK	Negative		0	1	1
				0.0%	100.0%	100.0%
		Continuous positivity		0	1	1
				0.0%	100.0%	100.0%
		patchy positivity		4	8	12
				33.3%	66.7%	100.0%
	Total			4	10	14
				28.5%	71.4%	100.0%

Table 4: Diagnostic accuracy of AMACR to differentiate malignant lesions of prostate

		HPR	
		Malignant	**Pre-malignant**
HMWCK	Positive	13	12
	Negative	0	13
		Percent	**95% CI**
Diagnostic characteristics of HMWCK	Sensitivity	100%	(77.19 – 100)
	Specificity	92.86%	(68.53 – 98.73)
	Positive predictive value	92.86%	(68.53 – 98.73)
	Negative predictive value	100%	(34.24 – 100)
	Diagnostic accuracy	96.3%	(81.72 – 99.34)
		HPR	
		Malignant	**Benign**
HMWCK	Positive	0	13
	Negative	13	0
		Percent	**95% CI**
Diagnostic characteristics of HMWCK	Sensitivity	100%	(77.19 – 100)
	Specificity	100%	(77.19 – 100)
	Positive predictive value	100%	(77.19 – 100)
	Negative predictive value	100%	(77.19 – 100)
	Diagnostic accuracy	100%	(77.19 – 100)

The HMWCK showed a significant sensitivity, specificity, NPV and PPV to diagnose the malignant tumor from pre-malignant and benign lesions of prostate.

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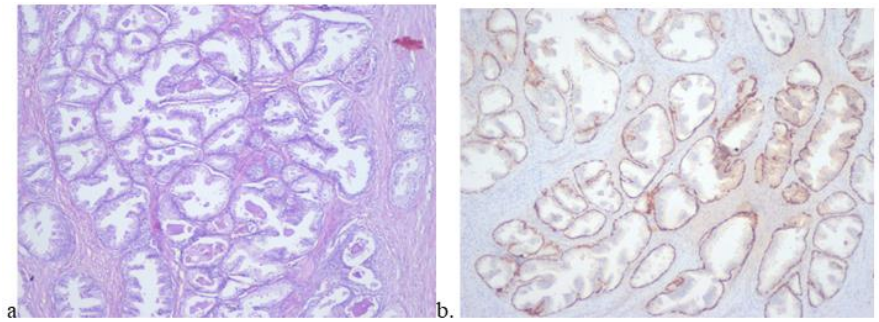

Figure 2: a. Photomicrograph of histology of BPH; b. HMWCK showing basal cell positivity in BPH

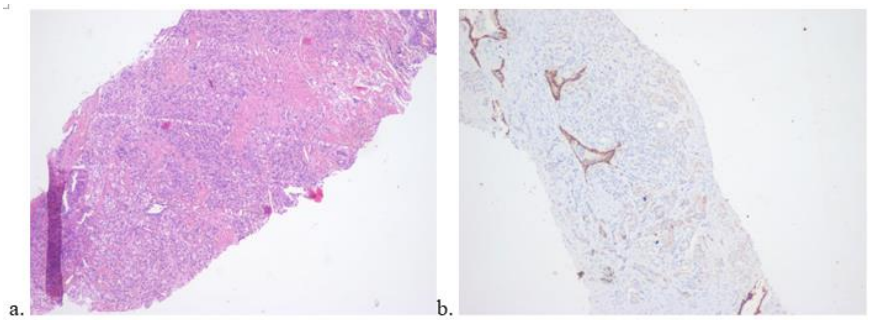

Figure 3: a. Photomicrograph of histology of adenocarcinoma of prostrate; b. HMWCK negative staining in prostatic adenocarcinoma

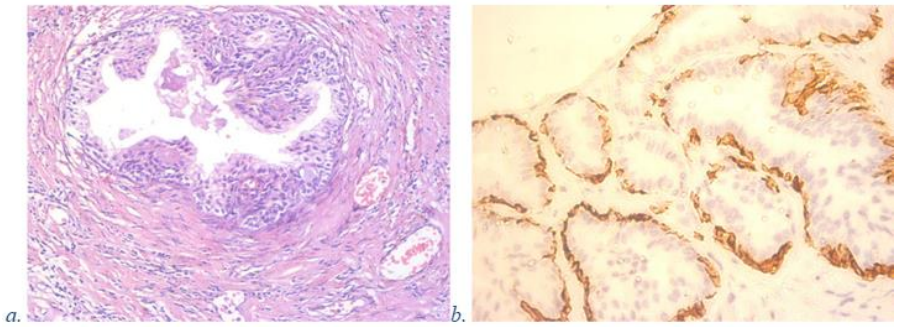

Figure 1: a. Photomicrograph of histology of HGPIN; b. HMWCK showing patchy positivity or discontinuous staining of basal cells of HGPIN

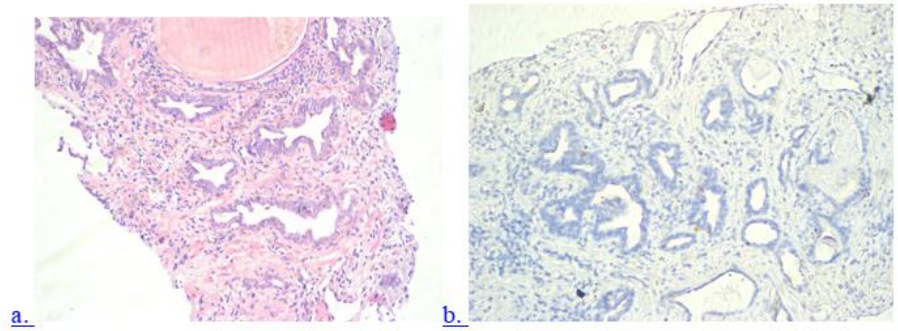

Figure 2: a. Photomicrograph of histology of ASAP; b. HMWCK showing negative staining in ASAP

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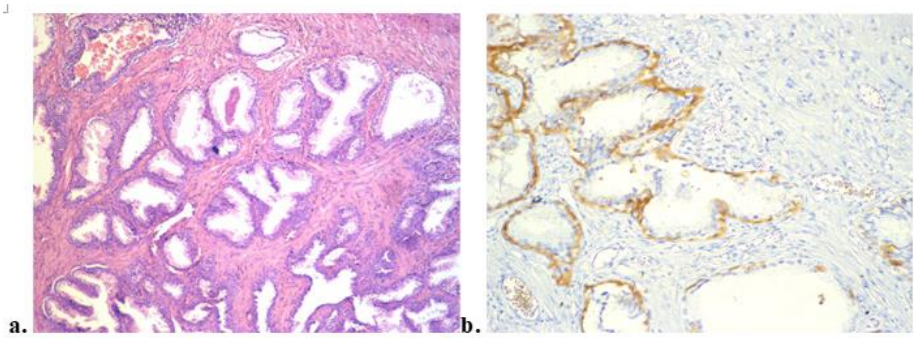

Figure 6: a. Photomicrograph of histology of FAAH; b. HMWCK showing discontinuous staining of basal cells in FAAH

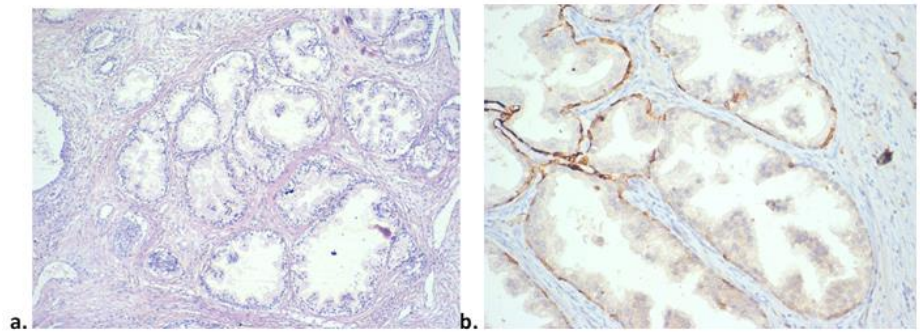

Figure 7: a. Photomicrograph of histology of AAH; b. HMWCK showing discontinuous basal cell staining in AAH

Discussion

Prostate needle biopsies have increased significantly since the introduction of prostate-specific antigen screening, as has the incidence of challenging biopsies including tiny foci of adenocarcinoma and atypical glands suggestive but not definitive of cancer. Rather of relying solely on a single diagnostic characteristic, prostate cancer is diagnosed using classic histological criteria, such as architecture, nuclear features, and auxiliary features (if needed).[6] Prostate cancer can be mistaken for basal cell hyperplasia, particularly in needle biopsies. A nodular growth of homogeneous spherical glands connected to a cellular stroma is typically the defining feature. Morphologically, there are still tiny lumina that are bordered by many layers of black basal cells with sparse cytoplasm and round or oval spindled hyperchromatic nuclei. These lumina are lined by secretary cells with transparent cytoplasm.[7]

Approximately 40-50% of patients with limited cancer had moderately advanced or advanced carcinoma on final radical Prostatectomy.[8] Therefore, under diagnosis of a small focus of prostatic adenocarcinoma might delay early treatment and cause severe adverse consequences for patients. Benign glands contain basal cells, which are absent in cancerous glands and hence the use of basal cell markers (HMWCK 34βE12,) to label the basal cells when faced with an ambiguous lesion.

HMWCK positivity in BPH is correlated with Deepika Jain et al,[9] Uma S et al,[8] Kumarseran K et al.[8] Present study all the 13 cases of BPH, showed continuous positivity for HMWCK. In pre-malignant cases, present study documented a percentage positivity of 85.6%, which was similar to study by Uma S et al.[8]

Present study correlated with the study done by Kiril Trpkov et al,[10] Jain D et al[9] and Uma SR et al.,[8] with percentage negativity of 100% for malignant cases. In concordance, HMWCK were negative in prostate cancer cell and positive in normal prostate gland and epithelium. There is a strong correlation with negative in cancer cell and positive in benign cell of prostate.[11]

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Conclusion

The study concluded that the HMWCK is a reliable marker with consistently positive in normal benign prostate gland or epithelial cells. Hence it is recommended for use of the IHC marker to support the diagnosis of prostate carcinoma especially in the cases with smaller biopsy where the diagnostic dilemma are present due to presence of both the malignant cell and benign cell in routine examination of biopsy under microscope.

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Conflict of interest: Nil

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