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Measurement of Microvessel Density Using CD105 (Endoglin) as a Marker in Prostatic Adenocarcinoma

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Abstract

Introduction Angiogenesis has been proposed as a promising prognostic marker in a variety of tumours. Microvessel density (MVD) measurement is the most reliable method for the semiquantitative evaluation of angiogenesis. Endoglin (CD105) is a recognised marker of proliferating endothelium and is expressed in intra-tumoral as well as peri-tumoral vessels. It is upregulated in various cancers including prostate cancer, therefore, it is an upcoming prime marker for prognosis, tumour imaging and antiangiogenesis therapy.

Aim The study was done to evaluate microvessel density (MVD) by using CD105 (endoglin) as an IHC marker in prostatic adenocarcinoma and to find its relationship with Gleason score and grade groups.

Materials and methods This was an observational cross-sectional study under which a total of 31 histopathologically diagnosed cases of prostatic adenocarcinoma on TURP chips were included and were graded according to Gleason score and grades. IHC using endoglin (CD105) was done to detect the highest-density areas of stained vessels (hot spots). The highest value obtained in three hot spot fields was reported as microvessel density (MVD) and its relationship with Gleason score and grade groups was analysed.

Results Most common age group was 71-80 years (48.39% cases). Maximum cases (45.16%) had a Gleason score of 9. The maximum mean MVD CD105 score was found in the Gleason grade group 5 (45.32%) while the minimum was in grade group 1 (24%). Comparison of mean MVD CD105 scores in different Gleason grade groups revealed a significant association of MVD CD105 with Gleason grade groups.

Conclusion Endoglin measures microvessel density and its expression correlated with Gleason score and grade group. Hence it can be used as a potential prognostic marker in adenocarcinoma prostate.

Key words prostatic adenocarcinoma, angiogenesis, CD105, Gleason grade, microvessel density

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Introduction

Carcinoma of the prostate is one of the most common malignancies amongst men worldwide and is responsible for 10% of cancer deaths [1]. Globally prostate cancer is the second most frequent malignancy (after lung cancer) while in India it is the sixth most common cancer with an age-adjusted incidence rate of 10.2/100,000 and age-adjusted mortality rate of 4.2/100,000 population [2-4]. Many genetic and molecular alterations have been observed in prostatic carcinoma including angiogenesis which is important for tumour growth, progression and metastasis [5]. Parameters like the clinical stage, serum level of prostate-specific antigen (PSA) and histological differentiation, reported as the Gleason score help in stratifying patients for further likelihood of progression and type of therapy required. However, in patients with an intermediate Gleason score (GS 6 and GS 7), accurate prediction of outcome is often difficult. Therefore, there is a need for biomarkers which can predict the clinical behaviour and course of prostatic carcinoma [6]. Angiogenesis has been proposed as a promising prognostic marker in a variety of tumours. The counting of microvessel density (MVD) is one of the most representative methods to quantify angiogenesis in human cancer tissues histologically by observing the IHC expression of various endothelial markers like CD34, CD31, and CD105 (endoglin). Endoglin is a transmembrane glycoprotein which is upregulated in several cancers including prostatic cancer. It is highly expressed in activated vascular endothelial cells but weakly or not at all expressed in normal quiescent vessels. Endoglin is a marker of proliferating endothelium which is expressed in intratumoral and peritumoral vessels. Because of these features, it is upcoming as a prime marker for prognosis, tumour imaging and antiangiogenesis therapy [7]. Presently there are only limited studies on the clinical significance and pathological roles of MVD measured by CD105-positive vessels in prostate cancer tissues. Most of them have identified CD 105 as a significant and independent predictor of progression and marker of recurrence in prostate cancer patients as well as in various other malignancies including breast, rectal and hepatocellular carcinomas [8-13]. This study was conducted to measure and evaluate microvessel density using CD105 (endoglin) as a marker for angiogenesis in prostatic adenocarcinoma and to determine its relationship with Gleason score and grade groups. The current emphasizes the angiogenic role of endoglin (CD105) in adenocarcinoma prostate signifying its role as a prognostic marker.

Materials and methods

This study was an observational prospective study conducted in the Department of Pathology over nineteen months after getting approval from the institutional ethical committee. A total of thirty-one cases of transurethral resection of the prostate (TURP) chips were included. All inadequate biopsies and cases with marked inflammation obscuring the epithelium were excluded. Needle core biopsies were also excluded due to limited tissue. There were no prostatectomy cases received during the study period. The tissue received in histopathology in neutral buffered was grossed as per the standard protocol of the histopathology section. The tissues were processed in an automated tissue processor. These were paraffin-embedded, sectioned and stained with Hematoxylin -Eosin stained sections followed by light microscopic examination. The adenocarcinoma cases were graded and categorized using Gleason's scoring system [14-15]. One section each from a representative block was subjected to IHC marker endoglin (CD105). Representative sections of 2-3 microns were cut and taken on poly-1-lysine-coated slides. Brown-stained positive endothelial cell or endothelial cell cluster with or without lumen was considered as a single, countable microvessel. Slides were examined at low power magnification to find high-density areas of stained vessels (hot spots). The number of microvessels was then counted in high power in three such hot spots. The highest value obtained amongst the three fields was reported as microvessel density (MVD). All data were statistically analysed using SPSS 22.0 software. The difference between the two groups was determined using a t-test and the level of significance was at $p<0.005$.

Observations and results

The study included 31 cases of adenocarcinoma prostate. Maximum subjects were in the age group of 71-80 years (48.39%) followed by the age group of 61-70 years (29.03%). The least cases were in the age group 51-60 years (3.23%). The age range of subjects was from 52 to 93 years and the mean age was 74.58±7.82 years.

Gleasons scoring

Maximum cases had a Gleason score of 9 (14/31; 45.16%) followed by a Gleason score of 7 amongst which 3+4=7 (5/31; 16.1%) were more common than 4+3=7 (2/31; 6.5%). Four cases showed the highest Gleason score of 10 (4/31; 12.90%). Maximum cases (18/31; 58.0%) were in grade group 5 with Gleason scores of 9 & 10 followed by an equal number of cases (5/31; 16.1%) in grade groups 2 and 4 (**Table 1**, **Figure 1, 2**).

Mean microvascular density (MVD) CD105

The Mean MVD CD105 score was 39.03 with minimum and maximum of 16 and 90 respectively.

Correlation of mean MVD CD105 and gleason grades

Mean MVD CD105 scores in Gleason grades 1, 2, 3, 4 and 5 were 24.00, 29.60, 25.50, 27.50 and 45.32 respectively. Maximum MVD CD105 score was found in Gleason grade group 5 while minimum in grade group 1 (**Figure 3, 4**). When mean MVD CD105 score was compared according to Gleason grade group, the statistical association of MVD CD105 with the Gleason grade group was significant (p value <0.05) (**Figure 5**).

Correlation of mean MVD CD105 with perineural invasion (PNI) and lymphovascular invasion(LVI)

Perineural invasion was present in fourteen cases (45.2%) while it was absent in seventeen cases 54.8%. The majority had no evidence of lymphovascular invasion (80.6%), only six cases showed lymphovascular invasion. However, when the mean MVD CD105 score was compared according to the presence and absence of LVI and PNI, the difference was statistically insignificant (p-value - 0.53, 0.34) (**Figure 6**).

Discussion

Prostate cancer has shown an increase in age adjusted incidence worldwide with nearly seventy-five per cent occurring at the age of 65 years and above [16]. In the present study, the maximum number of subjects were from the age group of 71-80 years (48.39%) followed by the age group 61-70 years (29.03%), Similar results were reported by Wikstroma et al., where the mean age was 72 years (range 53-90 years) however a lesser mean age (59.2±6.3 years) were reported by El-Gohary et al [17, 18]. The higher mean age observed may be due to delays in check up and lack of awareness. In the present study, the most common Gleason

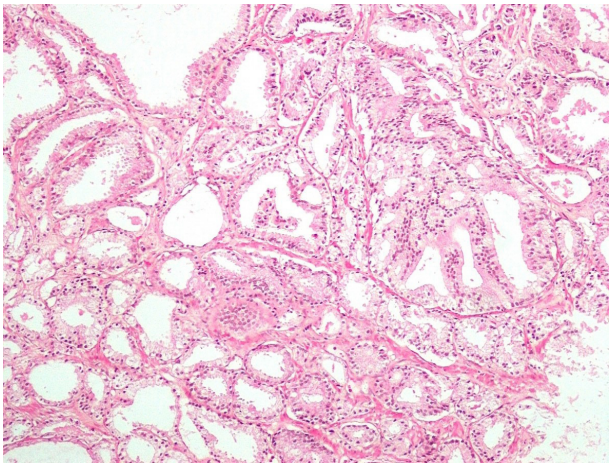

Figure 1. Prostatic adenocarcinoma grade group 2; Gleason score 3+4=7 (100X; H&E).

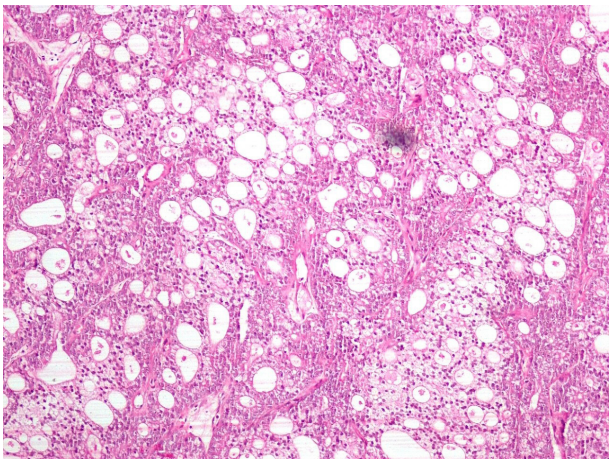

Figure 2. Glands in a diffuse pattern along with cribriform glands grade group 5; Gleason score 5+4=9 prostatic adenocarcinoma (100X; H&E).

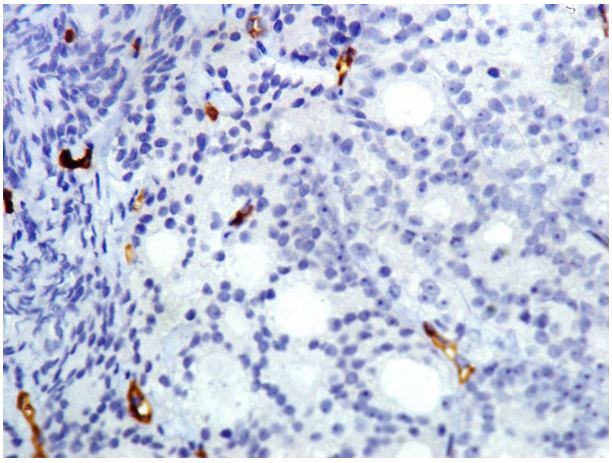

Figure 3. CD105 focus on hot spot areas around the cribriform pattern (100X; IHC).

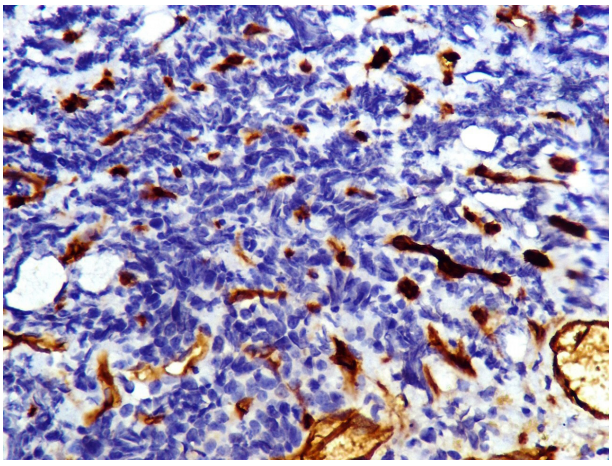

Figure 4. CD105 stained microvessels in hot spot areas in prostatic adenocarcinoma (400X; IHC).

grade group was 5 (18/31; 58.0%) followed by an equal number of cases (5/31; 16.13%) in grade groups 2 and 4. The results were comparable with the study by Wikstroma et al., where the maximum cases had Gleason grade 5 [17]. Vidal et al., in their study, showed an equal proportion of cases in grade group 1 (27/46) and grade group 4 and 5 (27/46) [19]. Whereas El-Gohary et al, Jain et al & Rathod et al reported Gleason scores 6 &7 to be more common pattern [18, 20, 21]. Although limited data is

Table 1. Distribution of cases according to Gleason's score and grade group.

Gleason grade group	Gleason's score	No. of study subjects	Percentage%
1	≤6	1	3.2
2	3+4=7	5	16.13
3	4+3=7	2	6.5
4	8	5	16.13
5	9	14	45.16
	10	4	12.90
Total	-	31	100

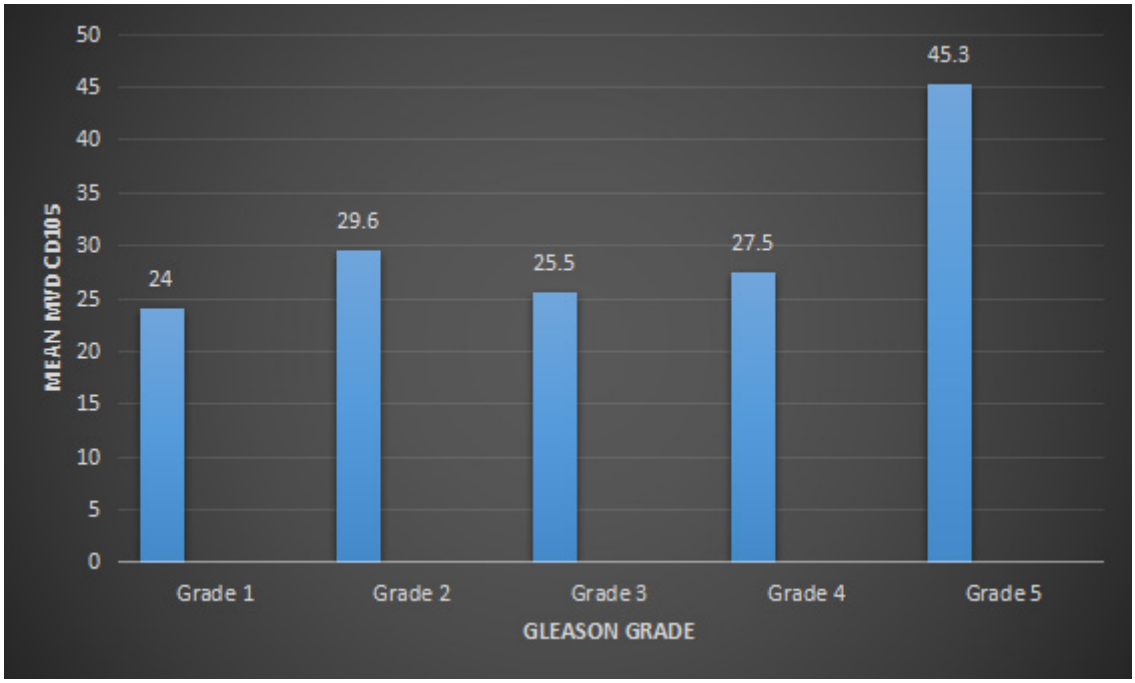

Figure 5. Correlation of cases according to Gleason Grade group and MVD by CD105.

available regarding the change in grade over time, a few studies suggest group grade increases with time [17-21]. Endoglin (CD105) stains small immature vessels formed during tumorogenesis, therefore, can be used for measuring microvessel density (MVD) and as a marker for prostate cancer [7, 13]. In this study, the mean MVD CD105 scores among the study subjects were 39.03±15.45 with minimum and maximum of 16 and 90 respectively. It was found that the mean MVD CD105 score increases with an increase in Gleason grade i.e. maximum MVD CD105 score was found in Gleason grade 5 while minimum in grade 1 except in

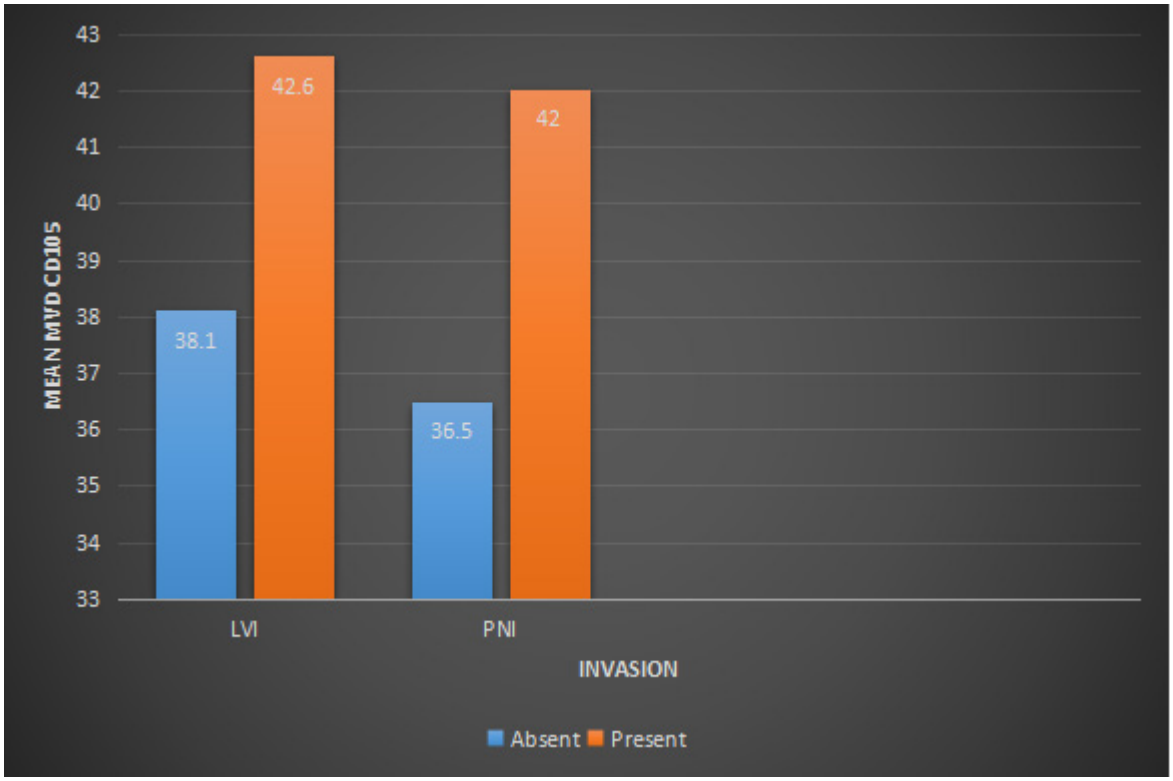

Figure 6. Correlation of cases according to LVI and PNI status and MVD by CD105.

grade 2 where mean MVD CD105 score was found to be more compared to grade 3. Higher gleason grade is associated with a higher endovascular proliferation and CD105 is a proliferation and hypoxia-induced protein expressed in endothelial cells of new blood vessels of tumour cells, thus showing an increased expression with increased Gleason Grade [18, 19]. The difference between groups 2 and 3 might be due to difference in subject distribution among various grade groups. There were only 2 cases in grade group 3 with MVD score of 25 and 26. In grade group 2, there were 5 cases with MVD scores of 22, 22, 24, 35 and 45. When mean MVD CD105 scores in different Gleason grades were compared, the difference was significant (p-value <0.05). The results were in congruence with the studies by Upadhyaya et al, Weidner et al, Miyata et al and El-Gohary et al [18, 22, 23]. In the present study, less number of cases showed LVI (19.4%) while PNI were present in approximately half of the cases which was comparable to the study by Patil et al [24]. Mean MVD CD105 was also slightly higher in subjects with the presence of LVI in comparison to those with the absence of LVI which is analogous to the study by El-Gohary et al and Mean MVD CD105 was slightly higher in subjects with the presence of PNI in comparison to the absence of PNI were in congruence with a study by Egemen Akıncıoğlu et al. However no statistically significant correlation was found between mean MVD and LVI or PNI [18, 25].

Conclusion

Prostatic adenocarcinoma is one of the most common malignancies in the elderly male. Tumour growth and progression depend upon neoangiogenesis. Endoglin (CD105) stains well the microvessels within and around the tumour. Hence, it can be used as a marker to measure MVD. The present study showed a significant association of MVD with Gleason score and grades indicating its potential use as a prognostic marker in prostatic adenocarcinoma. It might be a valuable predictive parameter in patients with a higher risk of developing metastatic disease. However, more studies including long-term term follow up of patients along with the inclusion of classical prognostic markers are necessary to validate above observations and establish the role of CD105 as a potential biomarker.

Acknowledgements

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Ethical policy

All procedures performed in this study were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. Informed consent was obtained from all individual participants included in the study. Approval from institutional ethical committee was taken.

Availability of data and materials

All data generated or analysed during this study are included in this publication.

Author contributions

SHA, MK: Conception; GS, SHA, MK: Performance of work; SHA, SEA, SK, SAA: Interpretation of data; SHA, GS, MK: Writing the article.

Competing interests

We have no disclosures that are related to the current study.

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