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Relationship Between Vascular Endothelial Growth Factor Expression and Gleason Score in Prostate Carcinoma

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ABSTRACT

Prostate cancer is the most common cancer in men worldwide and ranks second in the Laboratory of Anatomical Pathology, Dr. Mohammad Hoesin with the highest incidence, especially at the age of more than 60 years. Factors that play a role as a prognostic factor and therapy in prostate carcinoma, including VEGF. The role of VEGF expression in prostate carcinoma as a prognostic and histopathological factor which is an important predictor for the progression of prostate carcinoma. This study aims to determine the relationship between VEGF expression and Gleason score in prostate carcinoma. This study was a cross-sectional observational study. Thirty samples diagnosed with prostate adenocarcinoma were derived from the results of the tranurethral resection of the prostate (TRUP) and prostatectomy. Samples were taken from the archives in the Anatomic Pathology section of Dr. Mohammad Hoesin Palembang (period January 1, 2011 to December 31, 2013. Then the sample was stained with VEGF antibody, identified and analyzed the VEGF relationship with the Gleason.z score. The positivity of VEGF expression in prostate adenocarcinoma tended to be more prevalent in the Gleason score group ≥ 7 (43.3%) than in the Gleason score group <(10%). There was no significant relationship between VEGF expression and high Gleason score (p> 0.05). There was no significant relationship between VEGF expression and Gleason score in prostate adenocarcinoma

1. Introduction

Prostate carcinoma is the most common carcinoma in men worldwide. In America, it is the second leading cause of death in men over the age of 40. The publication of data from the *American Cancer Society* in 2012 stated that there were 241.720 (28.5%) new cases of prostate carcinoma and 28.170 (9.3%) of which caused death.[1]

The Cancer Registration Agency of the Indonesian Anatomical Pathology Doctors Association reported prostate carcinoma ranked first in 2009 as much as 15% of all anatomical pathology centers in Indonesia, and ranked second in the Anatomical Pathology laboratory of Dr. Mohammad Hoesin as many as 44 cases (13.8%) with the highest incidence, especially those aged over 60 years. In 2010 the data from Dr. Mohammad Hoesin, prostate carcinoma ranks first as much as 21.75% of all primary carcinomas in men.[2]

Factors that act as prognostic and therapeutic factors in prostate carcinoma, including VEGF. VEGF is a proangiogenic factor that has a role as a mitogen in endothelial cells and induces proliferation and increases vascular permeability. In addition, VEGF affects the angiogenesis process required for growth and metastasis of a cancer.[3,4]

Based on the research of Ferrer *et al*[5], it was found that VEGF overexpression in prostate carcinoma in 80% of cases. The role of VEGF expression in prostate carcinoma as a prognostic factor was also stated by Strohmeyer *et al.*[6] stated that there was a relationship between VEGF expression and histopathological *grading* which is an important predictor factor for the progression of

prostate carcinoma. In addition, Melanie et al[7] research stated that there was a relationship between high VEGF expression and Gleason score (p = 0.02) and survival (p = 0.035).

There is still controversy between VEGF expression and Gleason degree in prostate carcinoma as stated by Luczynska *et al*[8] study which stated that there was no significant correlation between both VEGF expression and the degree of gleason and *staging* / *TNM* in prostate carcinoma.

So far there is evidence of resistance to conventional therapies including anti-androgen therapy chemotherapy and radiotherapy. The use of antiangiogenesis therapy as an adjuvant therapy combined with conventional therapy can increase oxygenation in a hypoxic state and the effectiveness of radiation therapy and the effectiveness of chemotherapy.[9,10]

This study is based on many previous studies on VEGF gene expression in prostate carcinoma. So far there has been no research on the description of VEGF expression, especially in prostate carcinoma at dr. Mohammad Hoesin / Faculty of Medicine, Sriwijaya University, Palembang. This study tries to present new data and information and to strengthen the results of research that has been done previously by other researchers.

2. Methods

This study is an observational analytic study with a *cross sectional* approach, to determine the relationship between *VEGF* expression and the histopathological characteristics of prostate carcinoma. The research sample is a specimen that has been diagnosed as prostate adenocarcinoma from the results of TURP and prostatectomy stored in the Pathologic Anatomy Diagnostic Center, Faculty of Medicine, Sriwijaya University / RSUP Dr. Mohammad Hoesin Palembang from October 1, 2013 to March 31, 2014. Through the calculation of the sample size N = ((Zα) pq/d_2, with a value of n = 30. The research sample was taken by systematic random sampling. The study sample was reviewed by 2 pathologists. Assessment of the histopathological degree of prostate carcinoma is based on five architectural patterns according to `` The 2005 International Society of Urological Pathology Modified Gleason System ". moderate differentiation if the total gleason score is 5-6 and poor differentiation if the total gleason score is 710.[11]

Paraffin blocks of research samples were re-cut for streaking immunohistochemically with VEGF primary antibody. Paraffin blocks were cut to a thickness of 4μ, deparaffinized and rehydrated. The preparations were immersed in a 0.5% H_2O_2 solution in methanol for 30 minutes, heated in a microwave using anti-VEGF antibodies and incubated for 1 hour in a *humidify chmaber* at room temperature. The results of the immunohistochemical streaks were examined by two pathologists

Semquantitative assessment of the VEGF immunoreactive score by summing the results of the assessment of the staining intensity (I) and expansion (P) of the tumor VEGF, cells stained in ≥ 500 cells in 5-10 large fields of view (400x magnification), with a cut-off point value > 25%. The value is negative if the sum of the immunoreactivity scores is ≤ 2, and positive if the immunoreactivity score is between 3-7.[12]

The data obtained were analyzed using multivariate methods, namely all the variables studied would be grouped in the form of a frequency distribution table and to determine the differences in the distribution of categories, analysis was carried out using *chi-square* (2x3). All data analysis used the SPSS version 16.0.

3. Results and Discussion

The highest frequency of prostate carcinoma was in the age group 71-80 years as many as 14 cases (46.67%), followed by the age group 61-70 years with 8 cases (26.67%). Based on table 1, the highest frequency of prostate carcinoma was in the 71-80 years age group as many as 14 cases (46.67%), followed by the 61-70 years age group as many as 8 cases (26.67%). Based on Table 2, it can be seen that prostate carcinoma with poor differentiation was found in 27 cases (90%), followed by moderate-differentiated prostate carcinoma in 3 cases (10%). In this case, no well-differentiated prostate carcinoma was found.

Table 3 shows the frequency distribution of 30 samples of prostate carcinoma cases according to VEGF expression, the distribution of VEGF expression with the highest positivity was 16 cases (53.33%), followed by lower positivity in 13 cases (43.33%), and the lowest with a score. VEGF 5 in 1 case of prostate carcinoma (3.33%). Based on table 4 above, in poorly differentiated prostate carcinoma (gleason score ≥7), the VEGF immunoreactivity score was approximately the same (VEGF score 6 and 7) in 43.33% of cases. Whereas prostate carcinoma with a Gleason score <7 (moderate differentiation) showed the highest VEGF immunoreactivity score of 7 in 10% of cases, this confirmed that there was no difference between VEGF expression in both moderate and poorly differentiated carcinomas.

Table 1. Distribution of prostate carcinoma by age group (n = 30)

Age group	Frequency	Percentage (%)
40 – 50 years	1	3.33 %
51 – 60 years	6	20 %
61 – 70 years	8	26.67 %
71 – 80 years	14	46.67 %
81 – 90 years	1	3.33 %
Total	30	100 %

Table 2. Distribution of prostate carcinoma based on the degree of histopathological differentiation.

Degree of histopathological differentiation	Frequency	Percentage (%)
Good differentiation (Gleason score 2-4)	-	-
Moderate differentiation (Gleason score 5-6)	3	10 %
Poor differentiation (Gleason score 7-10)	27	90 %
Total	30	100 %

Table 3. Frequency distribution of the sum of VEGF immunoreactivity scores in prostate carcinoma.

VEGF immunoreactivity score (p) + (i)	Frequency	Percentage
Negative	-	-
3	-	-
4	-	-
5	1	3.33 %
6	13	43.33 %
7	16	53.33 %
Total	30	100%

Table 4. Distribution of VEGF immunoreactivity scores based on Gleason score

Gleason score	VEGF immunoreactivity score (summation of intensity and expansion)					
	Negative	3	4	5	6	7
< 7				-	-	3 (10%)
≥ 7		-		1 (3.33 %)	13 (43.33 %)	13 (43.33 %)

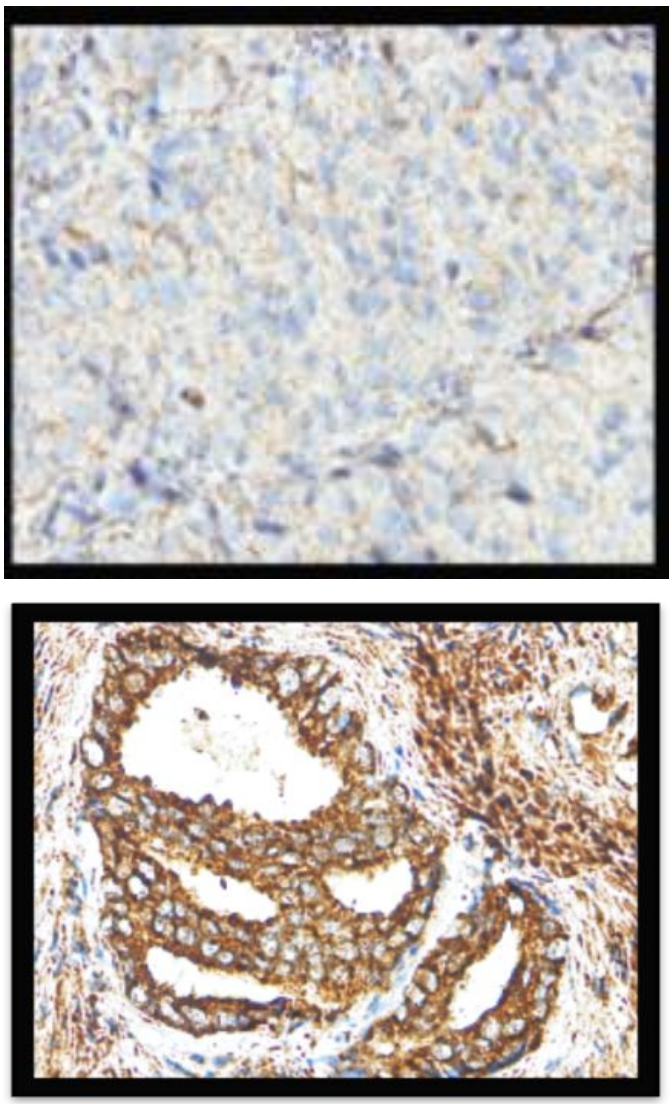

Figure 1 VEGF expression, (a) negative and (b) positive VEGF immunoreactivity, 400x magnification

The role of *VEGF* as a prognostic value has been comprehensively investigated by the study of Wang et al and Zhan et al by means of meta-analysis, it was found that overexpression of *VEGF* was associated with *overall survival.*[13,14] Although heterogeneity and publication bias were found in the analysis, they did not significantly influence it. One of the growth factors that play an important role in metastatic conditions, especially *VEGF,* with the finding that a high level of *VEGF* expression in serum is associated with a worse prognosis and ability to metastasize in bone. The binding between *VEGF* via the *VEGFR2* receptor stimulates the migration of tumor cells, by activating adhesion molecules such as fibronectins

and sialoproteins in the extracellular matrix, as well as regulating integrin activity.[15,16]

The highest frequency of prostate carcinoma was in the age group 71-80 years as many as 14 cases (46.67%), followed by the age group 61-70 years with 8 cases (26.67%). This is not much different from the research of Wang *et al*,[13] Soulitzis *et al*,[17] Ohlmann *et al*,[18] and Green *et al*. The highest frequency of prostate carcinoma was found in the age category > 65 as many as 89 cases (60%).[7]

Prostate carcinoma with poor differentiation was found mostly in 27 cases (90%), followed by moderate-differentiated prostate carcinoma in 3 cases (10%). In this case, no well-differentiated prostate carcinoma was found. The results of this study are consistent with Kwak *et al,* where there is a distribution of poorly differentiated prostate carcinoma (Gleason score ≥ 7) as many as 30 cases (85%), compared to those with good differentiation (Gleason score ≤ 6) as many as 5 cases (15%).[19]

The frequency distribution of 30 samples of prostate carcinoma cases according to *VEGF* expression, obtained the distribution of *VEGF* expression with the highest positivity of 16 cases (53.33%), followed by lower positivity in 13 cases (43.33%), and the lowest with a VEGF score of 5 at 1 cases of prostate carcinoma (3.33%). The assessment of the sum of the immunoreactivity scores in this study has a similarity with Green et al's research based on the sum of the percentage expansion and intensity and the low VEGF expression category, which is a score <5 and high VEGF expression, which is a score of 5-8.[7]

In poorly differentiated prostate carcinoma (gleason score ≥ 7), VEGF immunoreactivity scores were approximately the same (VEGF scores 6 and 7) in 43.33% of cases. Whereas prostate carcinoma with a Gleason score < 7 (moderate differentiation) showed the highest VEGF immunoreactivity score of 7 in 10% of cases, this confirmed that there was no difference between VEGF expression in both moderate and poorly differentiated carcinomas.

This contradicts the study of West *et al*.[3] there is a heterogeneous difference in the intensity of *VEGF*, where good and moderate carcinomas have lower *VEGF* expression, compared to poorly differentiated prostate carcinomas, with the same *cut-off point* value of 25%. The study of Gyftopaulus et al, [49] found weak and moderate *VEGF* expression, especially in poorly differentiated prostate carcinoma. This difference is due not only to differences in the study sample but also to the assessment of the *VEGF* immunoreactivity score.

From the results of data analysis, it was found that there was no significant relationship between VEGF expression and Gleason score in prostate carcinoma (p = 0.23). The high score for VEGF immunoreactivity was not associated with the high Gleason score in prostate carcinoma. In poorly differentiated prostate carcinoma with serial number 10, with a gleason score of 7, a lower positive VEGF expression was obtained, namely yellow intensity with 76-100% expansion of the stained tumor mass (sum of immunoreactivity score = 5), the exact mechanism of the cause has not can be ascertained, the possibility of genetic factors such as variations in genetic polymorphisms play an important role. In another case of poorly differentiated prostate carcinoma, a gleason score of 8, negative results on VEGF immunohistochemical streaks, reconstitution of these cases was performed and a positive result was obtained (VEGF score 7).

This study is in line with several opinions such as Luczynska et al, who stated that there was no significant relationship between VEGF expression and Gleason score (p = 0.697), and grading (p = 0.233) where *pTNM 1* was higher than *pTNM3* and *pTNM4*.[8]

There is a discrepancy between this study and the number of literates, such as the study of Lekas et al which stated that there was a significant relationship between the high expression of VEGF in prostate carcinoma with bad differentiation degrees compared to the degree of good and moderate differentiation (p <0.001), with a cut-off point of 25% .[20] Aslan *et al*[42] compared the VEGF expression with the gleason score obtained a significant relationship (p = 0.007), in poorly differentiated prostate carcinoma, the Gleason score 8-10 obtained a higher level of VEGF expression compared to the Gleason score which was well and moderately differentiated[12].

4. Conclusion

There is no significant relationship between VEGF expression and Gleason score so that VEGF cannot be used as a prognostic factor Conflict of interest

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