

## **VEGF-B EXPRESSION AS A PREDICTIVE BIOMARKER FOR NEOADJUVANT CHEMOTHERAPY RESPONSE IN LOCALLY ADVANCED STAGE BREAST CANCER**

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### **ABSTRACT**

**Background:** Breast cancer is one of the most common malignancies in women. In Indonesia, most cases are diagnosed at an advanced stage, which makes therapy success more challenging. Neoadjuvant chemotherapy is a commonly used initial approach to shrink tumor size before surgical intervention. However, not all patients show a good response to this therapy. One important mechanism in cancer progression is angiogenesis, which is regulated by growth factors such as VEGF-B. VEGF-B plays a role in blood vessel formation and is associated with more aggressive tumor characteristics. Therefore, VEGF-B expression has the potential to be used as a predictive biomarker for chemotherapy response. **Methods:** This study used a prospective cross-sectional design involving 30 patients with locally advanced breast cancer at RSUP Dr. Hasan Sadikin, Bandung. All patients received three cycles of neoadjuvant chemotherapy with the CAF regimen (cyclophosphamide, doxorubicin, and 5-fluorouracil), followed by modified radical mastectomy. VEGF-B expression was assessed through immunohistochemical examination of biopsy samples. Chemotherapy response was evaluated based on clinical changes in tumor size and classified as complete response, partial response, or no response. Data analysis was performed using Spearman's test, chi-square, and multivariate logistic regression. **Results:** The average age of the patients was 47.9 years. Two patients (5%) showed a complete response, 20 patients (50%) had a partial response, and 18 patients (45%) did not respond. Most patients had high tumor grade (52.5%). Moderate VEGF-B expression was found in 60% of patients, and strong expression in 40%. There was a significant relationship between age ( $p = 0.023$ ), tumor grade ( $p = 0.027$ ), and VEGF-B immunoexpression ( $p = 0.026$ ) with chemotherapy response. Logistic regression analysis showed that VEGF-B expression (OR = 0.16; 95% CI: 0.03–0.82) and age (OR = 3.33; 95% CI: 1.30–8.60) were significant predictors of therapy success. **Conclusion:** High VEGF-B expression is associated with a decreased response to neoadjuvant chemotherapy. In addition, younger age also showed a tendency toward a lower response. VEGF-B may be considered a potential predictive biomarker in the early evaluation of locally advanced breast cancer patients to improve therapy personalization and treatment effectiveness.

**Keywords:** Angiogenesis, biomarker, immunohistochemistry, breast cancer, VEGF-B

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**INTRODUCTION**

Breast cancer is one of the main malignancies in women, with high morbidity and mortality rates, especially in developing countries. In Indonesia, most breast cancer cases are diagnosed at advanced stages, unlike in developed countries where most cases are found at early stages. Previous research shows that approximately 23% of patients are found at stage IIIA and 40% at stage IIIB<sup>1</sup>. At RSUP Dr. Hasan Sadikin Bandung, the increase in the frequency of advanced breast cancer was reported from 12.5% in 1989–1991 to 17.4% in 1992, making it the second leading cause of cancer death after cervical cancer. At RSUP Dr. Hasan Sadikin Bandung, the increase in the frequency of advanced breast cancer was reported from 12.5% in 1989–1991 to 17.4% in 1992, making it the second leading cause of cancer death after cervical cancer (Lukitto, P., 1995) (Heriyanto, L. & Suardi, D.R., 1995).

Advanced local stage breast carcinoma is defined as a tumor larger than 5 cm with involvement of the skin, chest wall, or metastasis to regional lymph nodes such as the axilla, supraclavicular, or internal mammary (stage T3/T4 and/or N2). Locally advanced breast carcinoma is defined as a tumor larger than 5 cm with involvement of the skin, chest wall, or metastasis to regional lymph nodes such as the axilla, supraclavicular, or internal mammary nodes (stage T3/T4 and/or N2) (Harris, R.J. et al., 1999).

The current standard therapy involves neoadjuvant chemotherapy to shrink the tumor, followed by surgical intervention and adjuvant chemotherapy. Although this strategy is effective for some patients, not all show a good clinical response to neoadjuvant chemotherapy. Context: Although this strategy is effective for some patients, not all show a good clinical response to neoadjuvant chemotherapy. The evaluation of the chemotherapy response is generally classified into complete response, partial response, no response, and disease progression (Wood, W.C., et al 2005).

Evaluation of chemotherapy response is generally classified into complete response, partial response, no response, and disease progression. One of the factors that plays a role in determining the response is the histopathological grade of the tumor. Higher grades are reported to more often respond to chemotherapy, although they do not fully predict the success of the therapy (Wood, W.C., et al 2005). This raises the question: are there other biological factors that can be used as more accurate predictors of chemotherapy response. This raises the question: are there other biological factors that can be used as more accurate predictors of chemotherapy response.

Angiogenesis, the formation of new blood vessels by tumors, plays a crucial role in cancer growth and metastasis. Angiogenesis, which is the formation of new blood vessels by tumors, plays a crucial role in the growth and metastasis of cancer (Miller, D.K & Dull, C, 2004). One of the main mediators of this process is Vascular Endothelial Growth Factor

(VEGF), particularly the VEGF-B isoform, which is known to be involved in vasculogenesis and angiogenesis. Previous studies have shown that increased expression of VEGF is associated with tumor aggressiveness and poor prognosis (Fidler, I.J et al., 2005)

A deeper understanding of the role of VEGF-B as a predictive biomarker has the potential to make significant contributions to the personalization of breast cancer therapy, as well as improving clinical outcomes through early prediction of chemotherapy effectiveness. Further understanding of the role of VEGF-B as a predictive biomarker has the potential to make significant contributions to the personalization of breast cancer therapy, as well as improving clinical outcomes through early prediction of chemotherapy effectiveness. The aim of this study is to evaluate the expression of VEGF-B through immunohistochemistry as a predictive factor for the response to neoadjuvant chemotherapy in patients with locally advanced breast cancer. It is hoped that the results of this study can contribute to the selection of more personalized and effective therapies in the future.

## **METHODS**

### **Research Design**

This study is a prospective observational study with a cross-sectional approach, conducted on patients with locally advanced breast cancer at the Oncology Surgery Division of RSUP Dr. Hasan Sadikin Bandung, during the period from March 1, 2006, to March 1, 2007.

### **Population and Sample**

The population in this study consists of patients with locally advanced breast cancer who sought treatment and underwent incisional biopsy, followed by neoadjuvant chemotherapy, and then modified radical mastectomy (MRM) at the Oncology Surgery/Head and Neck Division of FK UNPAD/RS Dr. Hasan Sadikin Bandung, between March 1, 2006, and March 1, 2007. The study sample included patients with histopathological diagnosis of invasive ductal carcinoma obtained through incisional biopsy, who had undergone neoadjuvant chemotherapy with the CAF regimen (cyclophosphamide 600 mg/m<sup>2</sup>, doxorubicin/adriamycin 60 mg/m<sup>2</sup>, and 5-fluorouracil 600 mg/m<sup>2</sup>), followed by MRM surgery at the Oncology Surgery-Head and Neck Division-PERJAN RS Dr. Hasan Sadikin Bandung, and met the inclusion and exclusion criteria, with a total of 30 cases. Includes patients with locally advanced breast cancer who have not received any previous therapy, have a histopathological diagnosis of invasive ductal carcinoma, underwent three cycles of neoadjuvant CAF chemotherapy, and have available medical records and paraffin blocks. Includes patients with other histopathological types, those who did not complete the full CAF chemotherapy regimen, or those with incomplete data.

### **Procedure**

The diagnosis of breast cancer began with a physical examination, two-dimensional measurements, and evaluation of the axillary lymph nodes, followed by an incisional biopsy of the tumor. Imaging studies, including chest X-ray, abdominal ultrasound, and bone scan, were then performed to determine the disease stage. Tumor tissue obtained from the biopsy was examined using routine pathology (hematoxylin-eosin staining) to identify the tumor type and grade by Toi et al. Subsequently, immunohistochemical analysis was conducted to

evaluate VEGF-B expression at the Department of Anatomic Pathology, Faculty of Medicine, Universitas Padjadjaran/Dr. Hasan Sadikin Hospital, Bandung. This involved sectioning the paraffin-embedded specimens and performing immunohistochemical staining using the monoclonal antibody NCL-VEGF.

The immunohistochemical procedure included deparaffinization, graded rehydration, blocking, application of primary and secondary antibodies, and use of an enzyme substrate to produce contrasting staining. VEGF staining results were assessed using a light microscope at 100x magnification, based on staining intensity and distribution criteria, which were scored from negative to strong. Based on the immunoexpression scores, VEGF expression was categorized from negative to strong. In addition, tolerance to neoadjuvant chemotherapy with the CAF regimen was evaluated. Chemotherapy was administered in three cycles, with three-week intervals between cycles. The response to chemotherapy was assessed by WHO standart and patients showing complete or partial response proceeded to surgery. Those who did not respond or were deemed inoperable continued treatment with an alternative chemotherapy regimen.

### Data Analysis

The collected data were analyzed using SPSS version 23. The chi-square test was employed to assess associations between categorical variables, such as tumor grade, VEGF-B expression levels, and age groups, in relation to chemotherapy response. Additionally, multivariate logistic regression analysis was conducted to identify independent predictors of neoadjuvant chemotherapy outcomes. A p-value of less than 0.05 was considered statistically significant for all analyses.

## RESULTS AND DISCUSSION

### Characteristics of the Research Subjects

Between March 1, 2006, and February 28, 2007, a total of 40 patients diagnosed with locally advanced breast cancer met the inclusion criteria. The patients' ages ranged from 34 to 68 years, with a mean age of 47.9 years. The majority (90%) were under 60 years of age, distributed as follows: 11 patients (27.5%) were aged 30–39 years, 9 patients (22.5%) were aged 40–49 years, 15 patients (37.5%) were aged 50–59 years, and only 5 patients (12.5%) were older than 60.

Regarding treatment response, 2 patients (5%) achieved a complete response, 20 patients (50%) had a partial response, and 18 patients (45%) showed no response to neoadjuvant chemotherapy. When reclassified into two categories, 22 patients (55%) were responders (complete or partial response), while 18 patients (45%) were non-responders. Histopathological evaluation showed that high-grade tumors were predominant. Grade III tumors were present in 21 patients (52.5%), grade II in 14 patients (35%), and grade I in 5 patients (12.5%). This finding suggests that poorly differentiated tumors were more common among the studied cohort.

Immunohistochemical analysis of VEGF-B expression revealed that all tumors exhibited moderate to strong staining. Specifically, 24 patients (60%) demonstrated moderate expression (+2), and 16 patients (40%) showed strong expression (+3). No cases with negative or weak expression were identified, indicating a generally elevated VEGF-B expression profile across the study population.

These results suggest that younger age, high tumor grade, and elevated VEGF-B expression were frequently observed among patients with locally advanced breast cancer undergoing neoadjuvant chemotherapy. Further statistical analysis was performed to assess the associations between these variables and treatment response.

Table 1. Respondent Characteristics Table

Characteristics	Percentage (%)
<b>Age</b>	
30-39	11(27,5%)
40-49	9 (22,5%)
50-59	15 (37,5%)
60<	5 (12,5%)
<b>Region</b>	
Left	22 (55%)
Right	18 (45%)
<b>Chemotherapy response</b>	
Complete Response	2 (5%)
Partial Response	20 (50%)
No response	18 (45%)
<b>Gradasi</b>	
Gradasi I	5 (12,5%)
Gradasi II	14 (35%)
Gradasi III	21 (52,5%)
<b>Imunoekspresi VEGF</b>	
Positif 3	16 (40%)
Positif 2	24 (60%)
Positif 1	—
Negative	—

Table 2. Results of VEGF immunoexpression examination based on immunohistochemical staining in patients with locally advanced ductal breast carcinoma

Imunoekspresi VEGF	Sum	%
0	0	0
+1	0	0
+2	24	60%
+3	16	40%

### The relationship between tumor grade and VEGF immunoexpression in patients with locally advanced breast carcinoma

The association between tumor grade and VEGF-B immunoexpression in patients with locally advanced breast cancer is summarized in Table 3. Grade III tumors were the most common (52.5%), followed by grade II (37.5%) and grade I (10%). In grade III, 66.7% of tumors exhibited moderate VEGF-B expression (+2), while 33.3% showed strong expression (+3). Similarly, grade II tumors presented moderate and strong VEGF-B

expression in 64.3% and 35.7% of cases, respectively. Interestingly, in grade I tumors, a reverse trend was observed, with 80% showing strong expression and only 20% showing moderate expression.

No negative or weak (+1) VEGF-B expression was observed in any grade category, indicating a generally elevated expression of VEGF-B in all tumor grades. Despite these distribution patterns, statistical analysis using the chi-square test revealed no significant correlation between tumor grade and VEGF-B expression levels ( $p = 0.147$ ). This suggests that while VEGF-B expression is consistently high across different histological grades, it may not be directly influenced by the differentiation status of the tumor. These findings are in accordance with Foekens' study, which also reported a lack of significant association between VEGF expression and tumor grade, indicating that VEGF-B may act as an independent biological factor in tumor angiogenesis and chemoresistance rather than merely reflecting histological aggressiveness.

Table 3. The relationship between tumor grade and VEGF immunoexpression in patients with locally advanced breast carcinoma

Gradasi	Imunoekspresi VEGF			
	Negatif	+1/Weak	+2/Moderate	+3 /Strong
I	0	0	1(20%)	4(80%)
II	0	0	9(64,3%)	5(35,7%)
III	0	0	14(66,7%)	7(33,3%)

Explanation  $X^2 = 3.829$ ;  $p = 0.147$

Table 4. The relationship between hormonal status and chemotherapy response in patients with locally advanced breast carcinoma

	Response to neoadjuvant chemotherapy			Sum	p
	No response	Partial response	Complete Response		
Pre menopause	12	11	0	23	0,161
Post menopause	6	9	2	17	
Sum	18	20	2	40	

An analysis of the association between hormonal status and response to neoadjuvant chemotherapy revealed no statistically significant relationship ( $p = 0.161$ ). Among premenopausal patients, 12 (30%) did not respond to treatment, 11 (27.5%) achieved a partial response, and none showed a complete response. In contrast, among postmenopausal patients, 6 (15%) were non-responders, 9 (22.5%) had a partial response, and 2 (5%) achieved a complete response.

Although postmenopausal patients appeared to have slightly better overall outcomes, including all complete responses observed in the study, the difference was not statistically significant. These findings suggest that hormonal status alone may not be a reliable predictor of neoadjuvant chemotherapy response in patients with locally advanced breast cancer.

**The relationship between age, grade, and VEGF immunoexpression with the response to neoadjuvant chemotherapy in locally advanced breast carcinoma**

The association between age groups and response to neoadjuvant chemotherapy in patients with locally advanced breast cancer is presented in Table 5. Overall, 2 patients (5%) achieved a complete response, 20 patients (50%) had a partial response, and 18 patients (45%) did not respond. When stratified by age, none of the patients under 40 years old achieved a complete response, while 3 (7.5%) had a partial response and 8 (20%) did not respond. In the 40–50 years group, 5 patients (12.5%) had a partial response and 4 (10%) were non-responders, with no complete responses. Notably, all complete responses (n = 2; 5%) occurred in the group over 50 years, which also included 12 partial responders (30%) and 6 non-responders (15%).

Statistical analysis demonstrated a significant association between age group and chemotherapy response (p = 0.023), suggesting that older patients had a better likelihood of responding to neoadjuvant treatment. This may reflect differences in tumor biology or hormone sensitivity across age groups.

In contrast, the relationship between hormonal status and chemotherapy response did not reach statistical significance (p = 0.161), as previously noted.

Regarding histological grade, the majority of responders were observed in grade III tumors, with 15 out of 21 patients (71.5%) responding. Grade II accounted for 4 responders (28.6%) out of 14 patients, while grade I showed 3 responders (60%) among 5 patients. Although response rates appeared to vary across grades, the statistical significance of this relationship is not explicitly reported in the table referenced.

Analysis of the association between VEGF-B immunoexpression and chemotherapy response also revealed meaningful findings (Table 5). No patients exhibited negative (0) or weak (+1) VEGF-B expression. Among those with moderate VEGF-B expression (+2), 8 patients (20%) did not respond, 14 (35%) had a partial response, and 2 (5%) achieved a complete response. In the strong expression group (+3), 10 patients (25%) were non-responders and 7 (15%) were partial responders; no complete responses were recorded in this category.

A statistically significant association was identified between VEGF-B expression level and chemotherapy response (p=0.026), suggesting that higher VEGF-B expression may correlate with reduced treatment efficacy. These results align with findings by Foekens, supporting VEGF-B's potential role in chemoresistance through its involvement in tumor angiogenesis.

Table 5. The relationship between age, grade, and VEGF immunoexpression with the response to neoadjuvant chemotherapy in locally advanced breast carcinoma

variable	Clinical response to neoadjuvant chemotherapy			Analysis	
	No response	Partial response	Complete response		
Age	< 40 years	8	3	0	rs = 0,359 p= 0,023
	40-49	4	5	0	
	>50	6	12	2	
gradasi	I	2	3	0	rs= 0,308

<b>Imunoekspresi VEGF</b>	II	10	4	0	p= 0,027
	III	6	13	2	
	0/negatif	0	0	0	rs= 0,309 p= 0,026
	+1/weak	0	0	0	
	+2/moderate	8	14	2	
	+3/strong	10	6	0	

Explanation rs = Spearman rank correlation coefficient.

### Analysis Results

Univariate analysis revealed several noteworthy associations. A significant relationship was observed between patient age group and clinical response to neoadjuvant chemotherapy ( $p = 0.026$ ), indicating that age may influence treatment outcomes. Tumor grade was also significantly associated with chemotherapy response ( $p = 0.043$ ), suggesting that more poorly differentiated tumors might respond differently to treatment. Additionally, VEGF-B immunoexpression showed a borderline significant association with chemotherapy response ( $p = 0.069$ ), implying a potential trend that warrants further investigation. These findings are summarized in Table 6.

Table 6. Univariate analysis of the relationship between age, grade, and VEGF immunoexpression with neoadjuvant chemotherapy response in patients with locally advanced breast carcinoma.

		<b>Clinical response neoadjuvant chemotherapy</b>		<b>Analysis</b>
		<b>No response</b>	<b>response</b>	
<b>Age in Years</b>	< 40	8	3	$X^2 = 4,976$ $p = 0,026$
	40-49	4	5	
	> 50	6	14	
<b>Grade</b>	I	2	3	$X^2 = 6,291$ $p = 0,043$
	II	10	4	
	III	6	15	
<b>Imunoekspresi VEGF</b>	0/ negatif	0	0	$X^2 = 3,30$ $p = 0,069$
	+1/ Weak	0	0	
	+2/ Moderate	6	16	
	+3/ Strong	10	6	

Since the variables age group, tumor grade, and VEGF-B immunoexpression all had  $p$ -values  $< 0.25$  in the univariate analysis, they were subsequently included in a multivariate logistic regression model to identify independent predictors of clinical response to neoadjuvant chemotherapy. The result of this multivariate analysis are presented in Table 7.

From the analysis, the odds ratio (OR) for the age group was 3.33, indicating that older patients were more likely to respond to chemotherapy compared to younger patients. VEGF-B immunoexpression demonstrated an OR of 0.16, suggesting that higher VEGF-B expression levels were associated with a significantly lower likelihood of a favorable chemotherapy response. In contrast, tumor grade did not emerge as a significant predictor in the model, as indicated by a  $p$ -value of 0.640.

*VEGF-B expression as a predictive biomarker for neoadjuvant chemotherapy response in locally advanced stage breast cancer (Lopo Triyanto)*



These findings highlight the independent predictive value of age and VEGF-B expression on chemotherapy response, while suggesting that tumor grade, despite its clinical relevance, may not serve as an independent predictor when adjusted for other factors.

Table 7. Results of multivariate analysis of the relationship between age, grade, and VEGF immunoexpression with the response to neoadjuvant chemotherapy in patients with locally advanced breast carcinoma based on multiple logistic regression

Variable	Coefficient $\beta$	SE ( $\beta$ )	P value	OR(95%/CI)
Age (Years)	1,202	0,484	0,013	3,33(1,30-8,60)
Imunoekspresi VEGF	-1,817	0,828	0,028	0,16(0,03-0,82)

Constant = 1.947

Explanation = Accuracy = 67.5%

SE = Standard Error

For the gradient variable,  $p = 0.640$  was obtained.

The study by Foekens et al. (2001) focuses on advanced-stage breast cancer, where VEGF-B may play a more significant role in the development of resistance to systemic therapy due to its involvement in more active angiogenesis at the later stages of the disease. In advanced stages, tumors are typically more aggressive and can develop mechanisms to evade the effects of therapy, making factors like VEGF-B more relevant (Foekens, A.J et al., 2001).

In contrast, the study by Linderholm (1998) focuses on patients with node-negative breast cancer, meaning patients who do not show lymph node involvement. Patients with node-negative breast cancer generally have a better prognosis and less aggressive tumors compared to those with advanced-stage breast cancer or lymph node involvement. Therefore, VEGF-B may not play the same role in therapy resistance in patients with more localized cancer (Linderholm, B et al., 1998).

VEGF-B is a growth factor that plays a key role in angiogenesis, the process by which new blood vessels are formed. In the context of cancer, angiogenesis supports tumor growth by enhancing the supply of oxygen and nutrients. In advanced-stage breast cancer, the blood vessels formed during angiogenesis often exhibit structural abnormalities or "defects," which can impede the delivery of chemotherapy or other therapeutic agents, thereby contributing to therapy resistance. This defective vasculature results in poor distribution of drugs throughout the tumor, limiting the effectiveness of therapies (Wood, W.C., et al 2005).

In contrast, in node-negative patients, where tumors are generally smaller and have a lower likelihood of metastasis, the role of angiogenesis may be less pronounced. This could explain why VEGF-B appears to have a lesser impact on therapy resistance in this subgroup. The absence of extensive tumor vascularization in early-stage cancers might reduce the importance of angiogenesis-related factors such as VEGF-B in determining therapeutic outcomes (Linderholm, B et al., 1998).

Additionally, genetic variability among individuals can influence both the expression of VEGF-B and the response to therapy. Variations in the VEGF-B gene or other genes related to angiogenesis may alter how tumors interact with therapies, further complicating the relationship between VEGF-B and therapy resistance. These genetic differences could

help explain why the role of VEGF-B in therapy resistance is not consistent across all patients (Harris, R.J. et al., 1999).

Furthermore, the tumor microenvironment in advanced breast cancer is far more complex than in early-stage disease. The interactions between tumor cells, immune cells, and the extracellular matrix can significantly impact the efficacy of therapies. VEGF-B may contribute to this complexity by facilitating the development of mechanisms that help tumors resist treatment, such as promoting anti-apoptotic pathways or altering metabolic processes (Harris, R.J. et al., 1999).

However, this study has several limitations. For instance, the relatively small sample size and the lack of consideration of other molecular factors, such as HER2 and estrogen/progesterone receptors (ER/PR), which are also critical determinants of chemotherapy response, limit the generalizability of the findings. Therefore, future research involving larger cohorts and a more comprehensive analysis of molecular markers is essential to validate these conclusions.

Given the disparities in results between the two studies, further investigation is necessary to elucidate the role of VEGF-B within a broader clinical context. Large-scale cohort studies and additional exploration of the interactions between VEGF-B and other angiogenesis-related factors will be crucial in understanding its role in therapy resistance. Future research could also focus on integrating VEGF-B with other biomarker panels to construct more robust predictive models for neoadjuvant chemotherapy response.

## CONCLUSION

VEGF-B expression has been shown to be a significant predictive factor for neoadjuvant chemotherapy response in patients with locally advanced breast cancer. High VEGF-B expression is associated with reduced therapeutic response. While age and tumor grade demonstrated some correlation with treatment outcomes, only VEGF-B remained statistically significant in multivariate analysis. These findings support the role of VEGF-B as a potential predictive biomarker to guide more personalized treatment strategies. Further studies with larger sample sizes and broader biomolecular approaches are warranted for validation.

## REFERENCE

- Adams, J. et al., 2000. Vascular endothelial growth factor (VEGF) in breast cancer: comparison of plasma, serum, and tissue VEGF and microvessel density and effects of tamoxifen. *Cancer Research*, 60, pp.2898–2905.
- Beretta, G., 1991. *Cancer Treatment Medical Guide*. 10th ed. Trivulzio-PAT Institute, Milan, Italy.
- Ramli, M., 2000. Kanker payudara, deteksi dini dan penatalaksanaan masa kini. *Muktamar V/PIT XII*, Peraboi.
- Cotran, R.S., Kumar, V. and Robbins, S.L., 1994. *Pathologic Basis of Disease*. 5th ed. Philadelphia: WB Saunders, p.275.
- Conn, G. et al., 1990. Amino acid and cDNA sequences of a vascular endothelial cell mitogen that is homologous to platelet-derived growth factor. *Proceedings of the National Academy of Sciences*, 87(7), pp.2628–2632.
- Dvorak, H.F. et al., 1995. Vascular permeability factor/vascular endothelial growth factor, microvascular hyperpermeability, and angiogenesis. *American Journal of Pathology*, 146, pp.1029–1039.

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- Enholm, B., 2004. Vascular Endothelial Growth Factors B and C: Gene Regulation and Gene Transfer in Vivo. Academic Dissertation, University of Helsinki, Finland.
- Eppemberger, U. et al., 1998. Markers of tumor angiogenesis and proteolysis independently define high- and low-risk subsets of node-negative breast cancer patients. *Journal of Clinical Oncology*, 16, pp.3129–3136.
- Folkman, J., 1995. Tumor angiogenesis. In: Mendelsohn, J., Howley, P.M., Israel, M. and Liotta, L.A., eds. *The Molecular Basis of Cancer*. Philadelphia: WB Saunders Co, pp.206–223.
- Ellis, L., Randinsky, R. and Fidler, I., 2001. Recent advances in the biology of cancer invasion and metastasis. In: Bland, K., Daly, J. and Karakousis, C., eds. *Surgical Oncology*. New York: McGraw-Hill, pp.101–117.
- Fidler, I.J., Langlay, P.P., Kerbel, R.S. and Ellis, M.L., 2005. Angiogenesis. In: DeVita, V.T., Hellman, S. and Rosenberg, S.A., eds. *Cancer: Principles and Practice of Oncology*. 7th ed. Vol 2. Philadelphia: Lippincott, pp.129–138.
- Foekens, A.J. et al., 2001. High tumor level of vascular endothelial growth factor predicts poor response to systemic therapy in advanced breast cancer. *Cancer Research*, 61, pp.5407–5414.
- Gasparini, G., 2000. Prognostic value of vascular endothelial growth factor in breast cancer. *The Oncologist*, 5, pp.37–44.
- Gasparini, G. et al., 1997. Prognostic significance of vascular endothelial growth factor protein in node-negative breast carcinoma. *Journal of the National Cancer Institute*, 89, pp.139–147.
- Heriyanto, L. and Suardi, D.R., 1995. Frekuensi karsinoma payudara di RSHS Bandung 1993–1994. Unpublished. Pertemuan Ilmiah Tahunan IKABI, Bali.
- Harris, R.J. et al., 1999. *Diseases of the Breast*. 2nd ed. Lippincott Williams and Wilkins.
- Heer, K. et al., 2001. Serum vascular endothelial growth factor in breast cancer. *Clinical Cancer Research*, 17, pp.3491–3494.
- Issakh, B., Achmad, D. and Lukitto, P., 2002. Hubungan antara derajat histopatologi dengan respons radioterapi pada karsinoma lanjut lokal di RSUP Dr. Hasan Sadikin Bandung. *Jurnal Ilmu Bedah Indonesia*, 30(2).
- Kostopoulos, I., 2006. Evaluation of the prognostic value of ER-2 and VEGF in breast cancer patients participating in a randomized study with dose-dense sequential adjuvant chemotherapy. SpringerLink.
- Kresno, S.B., 2002. Angiogenesis dan metastasis dalam onkologi. Bagian Patologi Klinik FKUI, Jakarta.
- Kumamoto, K., Ohki, K. and Ooya, K., 2002. Association between vascular endothelial growth factor (VEGF) expression and tumor angiogenesis in ameloblastomas. *Journal of Oral Pathology & Medicine*, 31, pp.28–34.
- Kaban, K. et al., 2002. Angiogenesis as a target for cancer therapy. *Hematology/Oncology Clinics of North America*, 16, pp.125–171.
- Lukitto, P., 1995. Pola Penyakit Kanker di RSHS Bandung tahun 1972–1974. Kumpulan Naskah Ilmiah Kongres IKABI ke V, Jakarta.
- Lee, S.J. et al., 2002. Expression of vascular endothelial growth factor in invasive ductal carcinoma of the breast and the relation to angiogenesis and p53 and HER-2/neu

- protein expression. *Applied Immunohistochemistry & Molecular Morphology*, 10(4), pp.289–295.
- Linderholm, B. et al., 1998. Vascular endothelial growth factor is of high prognostic value in node-negative breast carcinoma. *Journal of Clinical Oncology*, 16, pp.3121–3128.
- Miller, D.K. and Dull, C., 2004. Breast cancer: the role of angiogenesis and antiangiogenic therapy. *Hematology/Oncology Clinics of North America*, 18, pp.1071–1086.
- Neufel, G. et al., 1999. Vascular endothelial growth factor (VEGF) and its receptors. *FASEB Journal*, 13, pp.9–22.
- Rosen, L.S., [n.d.]. Clinical experience with angiogenesis signaling inhibitors: focus on vascular endothelial growth factor (VEGF) blockers.
- Rosen, L.S., [n.d.]. Clinical Experience with Angiogenesis Signaling Inhibitors: Focus on Vascular Endothelial Growth Factor (VEGF) Blockers.
- Schneider, P.B. and Miller, D.K., 2005. Angiogenesis of Breast Cancer. *Journal of Clinical Oncology*, 23, pp.1782–1790.
- Salven, P. et al., 1998. Vascular endothelial growth factors VEGF-B and VEGF-C are expressed in human tumors. *American Journal of Pathology*, 153(1), pp.9–22.
- Sudarsa, W., Manuaba, W. and Sampaipayung, D., 2002. Respons locally advanced breast cancer (LABC) terhadap pemberian kemoterapi neoadjuvan. *Jurnal Ilmu Bedah Indonesia*, 30(2).
- Sastroasmoro, S. and Ismael, S., eds., [n.d.]. *Dasar-dasar metodologi penelitian klinis*. 2nd ed. Jakarta: Sagung Seto.
- Toi, M. et al., 1996. Quantitative analysis of vascular endothelial growth factor in primary breast cancer. *Cancer*, 77(6), pp.1101–1106.
- Veikkola, T., Karkainen, M., Claesson-Welsh, L. and Alitalo, K., 2000. Regulation of angiogenesis via vascular endothelial growth factor receptor. *Cancer Research*, 60, pp.203–212.
- Wood, W.C., Muss, H.B., Solin, L.J. and Olopade, O.I., 2005. Malignant Tumors of the Breast. In: DeVita, V.T., Hellman, S. and Rosenberg, S.A., eds. *Cancer: Principles and Practice of Oncology*. 7th ed. Vol 2. Philadelphia: Lippincott, pp.1145–1177.
- Weidner, N. et al., 1992. Tumor angiogenesis: a new significant and independent prognostic indicator in early-stage breast carcinoma. *Journal of the National Cancer Institute*, 84, pp.1875–1887.