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Correlation between tumor-infiltrating lymphocyte density and disease-free survival rate in basal cell carcinoma patients at Dr. Soetomo General Hospital, Surabaya

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Abstract: Basal cell carcinoma has a high risk of recurrence and can be associated with other types of cancer linked to ultraviolet radiation, impacting clinical outcomes, increasing morbidity, and shortening Disease-Free Survival (DFS) rates. Tumor-infiltrating lymphocytes (TILs) are considered predictors of immune response that are useful in suppressing tumor growth by infiltrating tumor cells. TILs were used as a predictive factor in the survival rate of basal cell carcinoma, with the result that high density was a good marker of immune system activation around the tumor and was associated with better prognosis. This study employed a retrospective cohort observational analytic research design to correlate the density of TILs with the DFS rate of basal cell carcinoma patients who had undergone wide excision at Dr. Soetomo General Hospital Surabaya from January 2017 to December 2023, with a total sample of 40 patients. Among the 40 samples, a group with strong TILs density was identified from a total of 14 samples, with 9 samples (22.5%) having DFS ≥ 5 years. In the weak TILs density group, there were 26 samples, with 9 samples (22.5%) having DFS for 1 year, 7 samples (17.5%) having DFS for 2 years, and 8 samples (20%) having DFS for 3 years. The analysis of the correlation between TILs density and DFS found that the stronger the TILs density, the longer the DFS time (p value = 0.002, RR 1.683). There was a significant correlation between TILs density and disease-free survival in patients with basal cell carcinoma who had undergone wide excision and/or radiotherapy.

Keywords: *Basal cell carcinoma, disease-free survival (DFS), tumor-infiltrating lymphocytes (TILs).*

1. Introduction

Basal cell carcinoma is an epithelial malignancy with slow-growing characteristics and rarely metastasizes but it is capable of causing large soft tissue damage [1]. In the United States, the prevalence of basal cell carcinoma reaches 50% of all malignancies. Globally, there were more than one million new cases in 2018 and 6% mortality rate related to basal cell carcinoma [2].

The main management of basal cell carcinoma is currently surgical modalities such as wide excision, electrodesiccation and curettage, and cryotherapy. These surgical methods are used for localized basal cell carcinoma and show a high cure rate within 5 years, generally above 95%. Each has a different postoperative recurrence rate, with wide excision at 10.1%, electrodesiccation and curettage at 7.7%, radiotherapy at 8.7%, and cryotherapy at 7.5% [3].

The high recurrence rate is still a challenge so it is very important to understand the proliferation mechanism of the tumor and its immunogenicity because immunosuppression is a strong risk factor, in addition to exposure to ultraviolet (UV) light [4]. The prognosis of basal cell carcinoma is related to the occurrence of recurrence after initial management. Mortality in cases of basal cell carcinoma is rare

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with an age-based estimate of about 0.12 per 100,000 patients. The risk of mortality is influenced by a decreased immune system, other comorbidities and increasing age [3, 4].

Tumor infiltrating lymphocytes (TILs) are now being considered as a useful predictor of immune response in terms of suppressing tumor growth by infiltrating tumor cells and can be determined by assessing the extent and density of lymphocytes infiltrating tumor cells.[4] In basal cell carcinoma, the role of TILs is still not fully understood. Several studies have been conducted to see if TILs can be used as a predictive factor in the survival rate of basal cell carcinoma patients with the result that higher density is a marker of good immune system activation around the tumor and is associated with better prognosis. In advanced basal cell carcinoma, there was an unsatisfactory response to immunotherapy due to low TILs density [5].

Several other researchers have shown that evaluating the immune density around the tumor is an important factor in the prognosis of basal cell carcinoma because the immune response to tumor properties can affect tumor progression and growth. A high number of TILs indicates a strong antitumor immune response that contributes to better survival. Based on the location of the lesion, the composition and density of TILs are also associated with survival and a lower risk of metastasis, thus affecting the prognosis of patients [2, 6].

2. Method

This study used a retrospective cohort observational analytic research design to correlate Tumor Infiltrating Lymphocyte (TILs) density with disease free survival rate of basal cell carcinoma patients who had undergone wide excision at Dr. Soetomo General Hospital Surabaya from 2017 to 2023. The population of this study were all patients with basal cell carcinoma who received treatment at Dr. Soetomo General Hospital Surabaya in 2017 to 2023. The samples of this study were all patients diagnosed with basal cell carcinoma at Dr. Soetomo General Hospital Surabaya who met the inclusion and exclusion criteria of the study. Inclusion criteria were patients diagnosed with basal cell carcinoma after diagnosis and patients with carcinoma who had undergone extensive excision and/or radiotherapy who experienced recurrence while the exclusion criteria were patients with incomplete medical record data according to the research variables and patients who did not undergo extensive excision. This study used Tumor Infiltrating Lymphocyte (TILs) density variables in stromal tumors taken from postoperative histopathology examinations in basal cell carcinoma patients at Dr. Soetomo General Hospital Surabaya. The obtained data were processed based on the research variables using SPSS 23.0 for windows and presented in the form of tables, diagrams and cross tabulations.

3. Result

Based on Table 1 the study subjects consisted of 19 men (47.5%) and 21 women (52.5%). The age distribution of the research subjects was in the range of the 4th decade to the 6th decade with the highest number in the 6th decade as many as 30 samples (75%), followed by the 5th decade as many as 6 samples (15%), then the 4th decade as many as 4 samples (10%) Table 1. This study also found 13 samples (32.5%) with nodular subtypes, followed by basosquamous subtypes as many as 12 samples (30%), adenoid and infiltrating subtypes each as many as 6 samples (15%) and sclerosing subtypes as many as 3 samples (7.5%). The distribution of the location of basal cell carcinoma in the study subjects with the highest number in the nasal and orbital, each as many as 15 samples (37.5%), followed by the temporal and cheek regions with 4 samples each (10%) and the labial region as many as 2 samples (5%).

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Table 1.
Sample characteristics.

Characteristics	n	Percentage
Gender		
Male	19	47.5
Female	21	52.5
Age		
40-49	4	10.0
50-59	6	15.0
≥ 60	30	75.0
Subtype		
Nodular	13	32.5
Basosquamous	12	30.0
Sclerosing	3	7.5
Adenoid	6	15.0
Infiltrating	6	15.0
Location		
Nasal	15	37.5
Temporal	4	10.0
Cheek	4	10.0
Orbita, Palpebra, Infraorbita	15	37.5
Labialis	2	5.0

Based on Table 2, the most female group was 21 samples (52.5%), with a distribution of disease-free survival rates of 3 years as many as 6 samples (15%), ≥ 5 years as many as 5 samples (12.5%), 1 year as many as 4 samples (10%), while disease free survival rates of 2 years and 4 years were 3 samples each (7.5%).

Based on the results of this study, in the age distribution, it was found that the highest number was the age of the 6th decade (≥ 60 years) as many as 30 samples (70%), with the distribution of the most disease free survival rate of 3 years, namely 8 samples (20%), followed by 2 years and ≥ 5 years each 7 samples (17.5%), 1 year as many as 6 samples (15%), and 4 years as many as 2 samples (5%).

In the distribution of histopathological subtypes, it was found that the most were nodular subtypes as many as 13 samples (32.5%), with a distribution of disease-free survival rates of 3 years and ≥ 5 years each 4 samples (10%), followed by 1 year and 4 years each 2 samples (5%), and 2 years as many as 1 patient (2,5%).

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Table 2.
Correlation between characteristics with disease free survival.

Characteristics	n	*Disease Free Survival*					P *value*
		1 years	2 years	3 years	4 years	≥ 5 years	
Gender							
Male	19	5 (12.5%)	4 (10%)	3 (7.5%)	1 (2.5%)	6 (15%)	0.74
Female	21	4 (10%)	3 (7.5%)	6 (15%)	3 (7.5%)	5 (12.5%)	
Age							
40-49	4	1 (2.5%)	0	0	2 (5%)	1 (2.5%)	0.41
50-59	6	2 (5%)	0	1 (2.5%)	0	4 (10%)	
≥ 60	30	6 (15%)	7 (17.5%)	8 (20%)	2 (5%)	7 (17.5%)	
Subtype							
Nodular	13	2 (5%)	1 (2.5%)	4 (10%)	2 (5%)	4 (10%)	0.85
Basosquamous	12	4 (10%)	3 (7.5%)	3 (7.5%)	1 (2.5%)	1 (2.5%)	
Sclerosing	3	1 (2.5%)	0	0	0	2 (5%)	
Adenoid	6	1 (2.5%)	2 (5%)	0	1 (2.5%)	2 (5%)	
Infiltrating	6	1 (2.5%)	1 (2.5%)	2 (5%)	0	2 (5%)	
Location							
Nasal	15	1 (2.5%)	2 (5%)	6 (15%)	2 (5%)	4 (10%)	0.25
Temporal	4	0	1 (2.5%)	0	1 (2.5%)	2 (5%)	
Cheek	4	3 (7.5%)	0	0	0	1 (2.5%)	
Orbita. Palpebra. Infraorbita	15	5 (12.5%)	4 (10%)	3 (7.5%)	0	3 (7.5%)	
Labialis	2	0	0	0	1 (2.5%)	1 (2.5%)	

In this study, the distribution of locations obtained the most was in the nasal and orbital regions, with a distribution of disease free survival rates for 3 years as many as 6 samples (15%) in the nasal region, and for 1 year as many as 5 samples (12.5%) in the orbital region.
Table 2. Relationship between Subject Characteristics and Disease Free Survival

The relationship between various characteristics of the study subjects and TILs density in Table 2. illustrates that both male and female groups mostly have weak TILs density (13.5% in men and women). In the age distribution, 21 samples (52.5%) had weak TILs density in the ≥ 60 years age group, 4 samples (10%) in the 50-59 years age group, and 1 sample (2.5%) in the 40-49 years age group. In the subtype distribution, it was found that the basosquamous subtype had the most weak TILs density, namely 10 samples (25%), followed by the nodular subtype as many as 8 samples (20%). While in the nodular subtype there were 5 samples (12.5%) that had strong TILs density. In the location distribution, it was found that the orbital region had the highest density of weak TILs, namely 14 samples (35%), followed by the nasal region as many as 8 samples (20%), cheek region as many as 3 samples (7.5%), and temporal region as many as 1 sample (7.5%). While in the nasal region there were 7 samples (17.5%) that had strong TILs density, followed by the temporal region as many as 3 samples (7.5%).

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Table 3.
Correlation between characteristics with TILs density.

Characteristics	n	TILs Density		P *value*
		Strong (≥ 45%) n = 14	Weak (<45%) n = 26	
Gender				
Male	19	6 (15%)	13 (32.5%)	0.68
Female	21	8 (20%)	13 (32.5%)	
Age				
40-49	4	3 (7.5%)	1 (2.5%)	0.19
50-59	6	2 (5 %)	4 (10%)	
≥ 60	30	9 (22.5%)	21 (52.5%)	
Subtype				
Nodular	13	5 (12.5%)	8 (20%)	0.05
Basosquamous	12	2 (5%)	10 (25%)	
Sclerosing	3	2 (5%)	1 (2.5%)	
Adenoid	6	3 (7.5%)	3 (7.5%)	
Infiltrating	6	2 (5%)	4 (10%)	
Location				
Nasal	15	7 (17.5%)	8 (20%)	0.16
Temporal	4	3 (7.5%)	1 (2.5%)	
Cheek (Cheek)	4	1 (2.5%)	3 (7.5%)	
Orbita. Palpebra. Infraorbita	15	1 (2.5%)	14 (35%)	
Labialis	2	2 (5%)	0 (0%)	

Based on Table 3 in the group of research subjects with strong TILs density from a total of 14 samples, 9 samples (22.5%) had Disease Free Survival ≥ 5 years. While in the group with weak TILs density there were 26 samples, 9 samples (22.5%) had Disease Free Survival for 1 year, 7 samples (17.5%) had Disease Free
Survival for 2 years, and 8 samples (20%) had Disease Free Survival for 3 years.

Table 4.
Correlation between TILs density with disease free survival.

TILs density	n	Disease free survival					P value
		1 years	2 years	3 years	4 years	≥ 5 years	
Strong ≥ 42%	14	0	0	1 (2.5%)	4 (10%)	9 (22.5%)	0.002*
Weak < 42%	26	9 (22.5%)	7 (17.5%)	8 (20%)	0	2 (5%)	

The relationship between TILs density and Disease-Free Survival was analyzed using the Chi-Square Test, and it was found that the stronger the TILs density, the longer the Disease- Free Survival time. Conversely, the weaker the TILs density, the shorter the Disease-Free Survival (p value = 0.002, RR 1.683).

Table 5.
TILs density as a predictor factor.

TILs density	n	Disease free survival					*P value*
		1 years	2 years	3 years	4 years	≥ 5 years	
Strong ≥ 42%	14	0	0	1 (2.5%)	4 (10%)	9 (22.5%)	0.002*
Weak < 42%	26	9 (22.5%)	7 (17.5%)	8 (20%)	0	2 (5%)	

4. Discussion

The incidence of skin malignancies worldwide continues to rise, with basal cell carcinoma being the most common case of skin cancer, with a 3% annual increase in cases every decade. Globally, there were

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more than one million new cases in 2018 and 6% deaths related to basal cell carcinoma. This is due to the increasing old age population as the most common age of basal cell carcinoma patients and also UV exposure. Epidemiologic data in Indonesia itself is still very rarely studied. Although basal cell carcinoma tends to grow slowly, there are 1 to 20% of cases that experience recurrence after surgery and are more aggressive, making it more difficult to treat [2].

Data from Dr. Soetomo general hospital shows that recurrence in basal cell carcinoma is 20% over 5 years. Based on several previous studies, there are factors that play a role in recurrence, such as excision margins, tumor subtype, size, depth of tumor invasion and length of exposure to UV light. In addition, some studies have used TILs as a predictor of immune response which is useful in terms of suppressing tumor growth by infiltrating tumor cells and can be determined by assessing the density of stromal lymphocytes infiltrating the tumor cells [4]. In basal cell carcinoma, the role of TILs is still not fully understood. Therefore, in this study, the variable focused on is the stromal density of TILs as a predictor of the length of Disease-Free Survival of basal cell carcinoma patients who experience recurrence. Disease Free Survival is related to the length of time recurrence occurs in patients with basal cell carcinoma.

In this study, it was found that women were the most research subjects with a total of 21 samples (52.5%) compared to men as many as 19 samples (47.5%). These results differ from a study conducted by Demirseren, et al. [7] in 320 patients with basal cell carcinoma reported that men generally have a risk of basal cell carcinoma twice as high as women. However, a study conducted by Dika et al showed that basal cell carcinoma in old age patients was more common in women, while in young patients it was more common in men. This is due to occupational factors, where male patients at a young age are more and longer exposed to sunlight so that it is associated with the appearance of lesions at a young age compared to female patients[7].

In this study, it was found that the 6th decade age group (≥ 60 years) was the largest, namely 30 samples (75%), followed by the 4th decade age group (40-49 years) as many as 6 samples (15%), and the 5th decade age group (50-59 years) as many as 4 samples (10%). This is consistent with the increasing incidence of basal cell carcinoma with age. The study conducted by Demirseren, et al. [7] found that the largest number was the age group 40- 79 years with an average age of 62 years. The incidence of basal cell carcinoma is higher in older age groups, which can be caused by DNA damage due to cumulative exposure to UV rays as well as a decrease in the efficiency of immune surveillance and DNA repair mechanisms with the aging process. The damaging effects of sun exposure begin at an early age and the results can be invisible in 20- 30 years. Cases of basal cell carcinoma are rare in young populations but an increased incidence in children and young adults has been reported [8].

Recurrence rates of basal cell carcinoma were higher in aggressive histopathologic subtypes, head region, positive surgical margins, and male gender. Lower recurrence rates were found in the neck, body and extremity regions. The duration of the lesion since the first clinical evaluation and age had little effect on recurrence [9]. A study mentioned that tumor size (T staging) has a significant effect on prognosis. Recurrence in basal cell carcinoma increases by about 7% for every millimeter of tumor diameter, while other factors include UV-sensitive skin, age >60 years at first diagnosis, histological subtype and immunological status [10].

Based on several previous studies, there are factors that play a role in recurrence, such as excision margins, tumor subtype, size, depth of tumor invasion and duration of exposure to UV light. In this study, histopathological subtype and tumor location were found to be associated with recurrence of basal cell carcinoma, where recurrence will be related to the length and brevity of Disease-Free Survival time in patients with basal cell carcinoma.[8]

In the distribution of histopathological subtypes, it was found that the most was the nodular subtype (32.5%) and the least was the sclerosing subtype (7.5%). In second place is the basosquamous subtype (30%), followed by adenoid and infiltrating subtypes (15%), with a distribution of disease-free survival rates of 3 years and ≥ 5 years for 4 samples each (10%), followed by 1 year and 4 years for 2 samples each (5%), and 2 years for 1 patient (2.5%). This is consistent with the study reported by Abbas,

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et al. [11] where the nodular subtype was the most frequent histopathologic type representing 69.1% of all cases. Although nodular carcinoma develops slowly, advanced tumors can become large and ulcerate which is classically referred to as "rodent ulcer" [4].

Subtypes in basal cell carcinoma are divided into high-risk and low-risk subtype groups. The aggressive-patterned high-risk group (infiltrating, morphoeaform, micronodular, sclerosing subtypes) has perineural invasion, which is usually larger in size, and mostly affects the trunk, extremities and midface. The high-risk subtype group has a poor prognosis associated with the presence of perineural invasion with high recurrence. The low-risk subtypes, such as the nodular and superficial subtypes, do not have perineural invasion, and most lesions appear on the scalp, forehead, cheeks and neck [4].

In this study, the distribution of locations was found to be most prevalent in the nasal and orbital regions (37.5%) and least frequent in the labial region (5%), with a distribution of disease-free survival rates for 3 years as many as 6 samples (15%) in the nasal region, and for 1 year as many as 5 samples (12.5%) in the orbital region. This finding is in accordance with a study conducted by Chow, et al. [12] who reported that the nasal is the most frequent predilection then the next is the cheek. Predilection of basal cell carcinoma is dominant in the body that is often exposed to sunlight, 75-85% of tumors are found in the head and neck [13]. The recurrence rate is higher in tumors with predilection in the orbital, nasal and auricular regions. This can be attributed to the lack of tissue composition, proximity to vital structures, and the cosmetic side that must be considered in the treatment of tumors in these predilections. Recurrence rates may also increase with the size of the tumor itself [9].

In this study, it was found that there was a significant relationship between TILs density and DFS. Patients with strong TILs density (≥ 42%) as much as 22.5% had a longer DFS of ≥ 5 years compared to the group of research subjects with weak TILs density (< 42%) as much as 22.5% also had a shorter DFS of 1 year, followed by 3 years as much as 20% and 2 years as much as 17.5%. Figure 5.1 shows a picture of the sample with strong TILs density (45%) with a DFS rate of 4 years, while Figure 5.2 shows a picture of the sample with weak TILs density (5%) with a DFS rate of 1 year. Analysis using the Chi-Square Test showed that the stronger the TILs density, the longer the DFS time that could be achieved (p-value = 0.002, RR = 1.683). Conversely, in patients with weak TILs density, DFS tended to be shorter.

Disease Free Survival is a determination used in medical research to measure the time from successful treatment of a cancer disease to recurrence or the occurrence of new disease or death from any cause [14]. It provides information on how long a patient remains disease-free after treatment, without experiencing recurrence or the development of new tumors. Recurrence will be related to the length and brevity of Disease Free Survival time in patients with basal cell carcinoma [15]. Research on the relationship of TILs to DFS in basal cell carcinoma has not been conducted. In research on the relationship of TILS to DFS in breast cancer, it was found that higher numbers of TILs were also associated with better disease- free survival, indicating the importance of immunotherapy in breast cancer groups [16]. A study conducted by Alfieri, et al. [17] showed that the median DFS was 633.9 days in 68 patients with basal cell carcinoma. In addition, the study showed that higher numbers of tumor infiltrating lymphocytes (TILs) were associated with better DFS [17].

In basal cell carcinoma, the role of TILs is still not fully understood. Several studies have been conducted to see if TILs can be used as a predictive factor in the survival rate of basal cell carcinoma patients with the result that higher density is a marker of good immune system activation around the tumor and is associated with a better prognosis. In advanced basal cell carcinoma, there was an unsatisfactory response to immunotherapy due to low TILs density [5]. Based on the location of the lesion, the composition and density of TILs are also associated with survival and a lower risk of metastasis, thus affecting the prognosis of patients [4, 6].

This study also observed that robust TILs density plays an important role in better prognosis for patients with basal cell carcinoma, prolonging the disease-free period and improving overall clinical outcomes. These findings emphasize the importance of taking TILs density into account in the management and therapy planning for patients with basal cell carcinoma, as well as the potential use of

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immunotherapy to enhance immune response and prolong DFS. The combination of these various treatment strategies suggests that a comprehensive therapeutic approach can significantly improve the clinical outcomes of patients with basal cell carcinoma.

5. Conclusion

From the results of this study there is a significant relationship between the density of Tumor Infiltrating Lymphocytes (TILs) and the number of Disease-Free Survival (p value = 0.002, RR 1.683) in basal cell carcinoma patients who have undergone extensive excision surgery and / or without radiotherapy according to the stage at Dr. Soetomo general hospital Surabaya.

Transparency:

The authors confirm that the manuscript is an honest, accurate, and transparent account of the study; that no vital features of the study have been omitted; and that any discrepancies from the study as planned have been explained. This study followed all ethical practices during writing.

Conflict of Interest:

The authors declare that there is no conflict of interest in writing this research report.

Author Contribution:

The author is responsible for the preparation and writing of this research report.

Copyright:

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