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The relationship between histopathological subtypes and recurrence in basal cell carcinoma patients: A case-control study

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Abstract: Basal cell carcinoma is an epithelial malignancy characterized by indolent growth and a rare tendency to metastasize, but it can cause significant soft tissue damage. Worldwide, basal cell carcinoma is the most commonly diagnosed type of skin cancer, accounting for approximately 25% of all skin cancers due to the aging population and increased exposure to sunlight. Recurrence of basal cell carcinoma after complete surgical excision is rarely reported, and risk factors are not well studied. Histopathological subtype is an important factor in determining excision margins and further management, as it provides predictive information regarding tumor behavior and the risk of recurrence. This study aims to determine the relationship between histopathological subtypes and the incidence of recurrence in basal cell carcinoma patients at Dr. Soetomo General Hospital Surabaya for the period from January 2017 to December 2023. All patients between January 2017 and December 2023 whose primary BCCs were excised with free surgical margins according to histopathology reports were included, and a case-control study was conducted using medical files to record patients' age, sex, tumor site, size, histopathology variant, and recurrence. Based on the chi-square odds ratio calculation, the high-risk subtype increased the chance of recurrence by 13 times (OR 3.9-42.9) compared to the low-risk subtype. There was no significant relationship between recurrence and the patient's sex, age, or tumor site. There is a relationship between histopathological subtypes and recurrence in basal cell carcinoma at Dr. Soetomo General Hospital Surabaya for the period from January 2017 to December 2023.

Keywords: *Basal Cell Carcinoma, Histopathological Subtypes, Recurrence Rate.*

1. Introduction

Basal cell carcinoma is an epithelial malignancy characterized by its indolent growth and rarely metastasized but capable of causing major soft tissue damage. In 70% of cases, the predilection for this type of cancer occurs often in the head and neck area, especially the nose, cheeks, and nasolabial folds. This is because this area is often exposed to sunlight, which is a major risk factor for basal cell carcinoma [1].

Worldwide, basal cell carcinoma is the most commonly diagnosed type of skin cancer, accounting for around 25% of all skin cancers due to the aging population and increasing exposure to sunlight. Patients diagnosed with basal cell carcinoma for the first time have a high risk of recurrence and may develop other types of cancer associated with ultraviolet radiation, thereby impacting clinical outcomes, increasing morbidity and requiring repeated therapeutic interventions which increase the burden of health care costs [2].

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Even though the fatality rate is low, the incidence of basal cell carcinoma is also increasing by 10% per year, reaching 3-4 million cases. Basal cell carcinoma has a slow growth rate so that patient follow-up to assess disease free survival for five years after surgery should easily be detected. The recurrence rate after surgery is 3% at 2.5 years and 12% at 10 years and it was found that 56% of recurrence cases occurred more than five years after therapy [3].

Based on data from Dr. Soetomo Surabaya, there were 208 cases of basal cell carcinoma that underwent wide excision and 20% of them experienced recurrence during 2015-2023, however the etiology of this incident is unclear since it is not well-studied, possibly because some sufferers underestimate the impact of this cancer and inadequate recording because of its high frequency and low death rate. Therapy for basal cell carcinoma aims to eradicate the tumor and restore function and cosmetic aspects as best as possible, therefore it is important to know the histopathological subtype because it can influence the choice of therapy and prognosis. The therapeutic approach with wide excision is the main curative therapy in basal cell carcinoma, it is important to achieve adequate surgical margins, which is limits that depend on the size of the lesion, anatomical location, clinical picture, ulceration and depth of penetration, but radiotherapy is an inseparable modality in definitive and adjuvant therapy [4, 5].

Safety margin of 4 mm – 5 mm is recommended for low risk histopathological subtype lesions or high risk lesions with a predilection other than the face, and a minimum of 6 mm for low risk type recurrent lesions, and ≥1 cm for high risk subtype lesions considering tumor extension and characteristics of the patients [6, 7].

To address the clinical aspects in prognosis of patients wih basal cell carcinoma, histopathological subtype holds the pivotal role in 5-year survival. Mosterd et al published a study in 2009 that nodular and superficial subtypes are clinically and histopathologically well defined and can be treated satisfactorily with recent modalities, and they are referred to as low risk subtypes. Meanwhile, the high risk subtypes including sclerosing, micronodular and infiltrative are more difficult to assess on a macro and micro basis and are associated with low tumor clearance. These three subtypes also have higher recurrence rates. Tumors that are histologically intermediate between basal cell carcinoma and squamous cell carcinoma are called basosquamous or metatypical basal cell carcinoma and also have a tendency to recur and unfavorable outcome [8-12].

Although basal cell carcinoma can be eradicated well at an early stage, good clinical outcomes and high recurrence rates are still a challenge so it is very crucial to understand the mechanism of tumor proliferation and appropriate therapeutic management (3). Histopathology will provide an overview of the excised margins, the histology of the tumor, and the depth of tumor invasion hence it is not only can establish accurate diagnosis of basal cell carcinoma, but also provides predictive information regarding tumor behavior and the risk of recurrence (9, 10). Emphasizing the histopathology subtypes as a significant risk factor associated in recurrence for it will be able to provide clinicians with an overview of the management of basal cell carcinoma, so as to increase awareness in post-operative follow up.

2. Materials and Methods

A retrospective observational study that examines the relationship between exposure and its consequences in order to obtain an explanation of disease risk factors in Dr. Soetomo General Hospital Surabaya, Indonesia. It was designed as a case control study. Characteristic of the samples including demography, histopathological subtype variants, and recurrence. Recurrence in BCC may presents with local erythema, induration or ulceration at the previous site of the primary tumor, meanwhile metastasis in regional lymph nodes is not considered as a recurrence. Patients whose met the criteria of recurrence prior surgical wide excision referred as the case group, whereas the remaining did not have any characteristic as recurrence referred to as control group.

The study included patients whose initial BCCs were excised with free histological margins and post operative follow up conducted from medical record from January 2017 to December 2023. The

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exclusion criteria were incomplete medical records and the patients died due to other than BCC. A total of 64 patients met the inclusion criteria and both groups were analyzed.

For the selected criteria, the following characteristics were recorded: gender, age, subtype variants, localization, and dimension (cm). taking into considerations their location, tumors were divided into three risk localization categories: i) high risk area including mask area (central face, eyelids, eyebrows, periorbital area, nose, lips, chin, mandible, temples, preauricular and postauricular area, ear), genitalia, hands, feet; ii) middle risk including cheeks, forehead, scalp, neck; iii) low risk including trunk and extremities.

The data analysis and interpretation were performed using the SPSS version 26. Quantitative variables were tested for normality or distribution using Kolmogorov-Smirnov test and were expressed as median. Qualitative variables were characterized by number and percentage. Comparisons between groups were carried out using the Mann-Whitney test, T-test, and Chi-square test, whenever suitable. Univariate analysis utilizing odds ratio (OR) was used to identify the ability of a variable to predict the risk of recurrence with $p<0,05$ was considered to indicate statistical significance.

3. Results

This study has 64 subjects that is divided into recurrent group (group A) and non-recurrent group (group B). The data was then analyzed based on sociodemographic data and research variables. A total 64 subjects of whom 29 were men and 35 were women. The overall mean age was 66,7 ± 12,44 years, with the youngest and oldest patients aged 32 and 94 years. The gender and age distributions are presented in Table 1.

Table 1.
The gender and age distributions.

	Frequency (N=64)	**Percentage (%)**
Gender		
Men	29	45,31%
Women	35	54,69%
Age		
Decade 2 (21-30 years)	0	0,00%
Decade 3 (31-40 years)	1	1,56%
Decade 4 (41-50 years)	5	7,81%
Decade 5 (51-60 years)	11	17,19%
Decade 5 (61-70 years)	21	32,81%
Geriatrics (>70 years)	26	40,63%
	Mean (SD)	Median (Min-Max)
Age (Years)	66,7 (□12,44)	65 (32-94)

The study revealed that there were 16 men and 16 women in group A and 13 men and 19 women in group B, while according to this data there was no significant relationship BCC recurrence and gender ($p = 0,45$) with an odds ration 1,4 ($\alpha = 95\%$). Patients who experienced recurrence had the same gender proportion, namely 16 subjects. The most common age diagnosed with BCC was geriatrics with mean age experienced recurrence was 65.2 ± 12.2 years and non-recurrence was 68.5 ± 12.6 years. However there was no significant relationship between recurrence and age ($p = 0,93$) (Table 3).

The most common location of the BCC was the nose (24, 37.5%), followed by periorbital area (15, 23.4%), cheeks (7, 10.9%), and temples (6, 9.3%). According to the localization, high risk area in group A was found more (28, 87.5%) rather than in group B (26, 81.3%) and middle risk area in group A was less (4, 12.5%) rather than in group B (6, 18.8%). There was no low risk area in this study. Details was shown in Table 2. Statistically, no significant relationship between the location of the primary tumor and recurrence of BCC ($p = 0.49$; OR = 0.61) (Table 3).

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The mean dimension of the primary tumor in this study was 2,85 ± 2,59 cm. In group A the mean tumor size was 3.44 ± 2.56 cm and in group B was 2.32 ± 2.53 cm, the average tumor size of patients who experienced recurrence was larger compared to those who did not. Correlation analysis was carried out between BCC recurrence and tumor size, as expected tumor size was strongly correlated with recurrence rate (p = 0,04) (Table 3).

Table 2 indicates that the most common subtype was the low risk type (34, 53.1%) included nodular (23, 35.9%), superficial (9, 14.06%), achantothic (1, 1.5%) and adenoid (1, 1.5%). Meanwhile, the high risk subtype was found (30, 46.8%), with the details being basosquamous (18, 28.1%), infiltrative (7, 10.9%), and sclerosing (5, 7.8%). Of all the cases of BCC in this study, in group A there were high risk subtype (24, 75%) and low risk subtype (8, 18.8%) meanwhile in group B the high risk subtype was found (6, 15%) and low risk (26, 81.3%). The analysis showed the significant relationship between histopathological subtype and recurrence (p = <0.001), it was found that the high risk subtype increase the chance of recurrence (OR = 13) (Table 3).

Table 2.
Characteristics of basal cell carcinoma.

	Frequency (N=64)	**Percentage (%)**
Location		
Auricular	4	6.25%
Cheeks	7	10.94%
Forehead	3	4.69%
Frontotemporal	1	1.56%
Lips	2	3.13%
Nose	24	37.50%
Nasolabial	2	3.13%
Temple	6	9.38%
Periorbita	15	23.44%
Subtype		
High risk	30	46.88%
Sclerosing	5	7.81%
Infiltrative	7	10.94%
Basosquamous	18	28.13%
Low Risk	34	53.13%
Superficial	9	14.06%
Nodular	23	35.94%
Achanthotic	1	1.56%
Adenoid	1	1.56%
Recurrence		
Recurrence	32	50.0%
Non-recurrence	32	50.0%
	Mean (SD)	Median (Min.-Max.)
Largest dimension (cm)	2.85 (±2.59)	3 (0.05-8)

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Table 3.
Risk factors of recurrence in basal cell carcinoma.

Patient variables		Recurrence		Total	p-value	OR
		Yes	No			
Gender	Men	16	13	29	0.45	1.4 (0.5 – 3.9)
		55.2%	44.8%	45.3%		
	Women	16	19	35		
		45.7%	54.3%	54.6%		
Age		65.2±12.2	68.5±12.6	64	0.93	
				100%		
Location	High risk area	28	26	54	0.49	0.6 (0.1-2.2)
		87.5%	81.3%	84.3%		
	Middle risk area	4	6	10		
		12.5%	18.8%	15.6%		
Tumor size		3.44±2.56	2.32±2.53	64	0.04	
				100.0%		
Histopathological Subtype	High risk	24	6	30	<0.001	13 (3.9-42.9)
		75%	15%	46.8%		
	Low risk	8	26	34		
		18.8%	81.3	53.1%		

4. Discussions

In this study, we found that the majority of gender was women (35, 54.69%) compared to men (29, 45.31%). with the geriatric group >70 years as the largest percentage, (26, 40.63%) with an average age of 66.7 ± 12.44 years. The incidence of BCC increases with age. At old age, BCC is found more often in women, while at young age it is found more often in men. This may be explained by occupational factors and men's habits of being more exposed to sunlight so that lesions appear decades earlier than in women [3, 10, 11, 13, 14].

There was no statistically significant relationship between gender and the incidence of recurrence (p = 0.45; OR 1.4). In general, the incidence of BCC is higher in men than in women, possibly due to high exposure due to work or living habits. However, this difference becomes less significant with changes in lifestyle, such as tanning or smoking habits. In several studies, it was found that the incidence of BCC was greater in young women (<40 years) and older men (>60 years) because women paid more attention to the condition of their skin [10, 13-15].

In group A, the mean age was 65.2±12.2, while in group B the mean age was 68.5±12.6 (p=0.93). The age of patients who experienced recurrence was younger than those who did not experience recurrence, but this was not statistically significant as a risk factor for recurrence. Older age affects the decline in biological functions resulting in reduced ability of DNA to repair itself, genomic instability, decreased immune system function, chronic inflammation. This is what underlies the discovery of accumulation of damaged DNA and chronic inflammation in aging skin due to changes in the integrity of the skin matrix. In this study, no statistically significant relationship was found because the distribution of the research sample was more in the geriatric category with the total sample average being >65 years old and there were multifactorial factors in the incidence of recurrence such as tumor size, tumor location and choice of therapy for BCC [10, 11, 16].

BCC has a predilection for exposed area of the body. The most frequent location of the BCC in our study was the nose (24, 37.5%) and orbita (15, 23.4%) namely the high risk area, which is a high risk location for recurrence because of the anatomical location which is relatively difficult to carry out wide excision and reconstruction which requires a multidisciplinary team. The next most frequent location was cheeks (7, 10.9%) which were included in medium risk area. The mean largest tumor size in this study was 2.85 ± 2.59 cm with tumor-free excision margins obtained histopathologically through frozen section examination. This study did not report primary or recurrent lesions outside the head and neck

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region. Statistically, there was no significant relationship between tumor location and recurrence of BCCs (p = 0.491; OR 0.16). This is contrary to previous study which stated that tumor locations in the perinasal and periorbital areas have a worse prognosis with a greater frequency of recurrence due to the higher risk of incomplete excision (13, 14, 20). In this study, we obtained a wide distribution of tumor location, this could occur because of the predilections for tumors in the head and neck area overlap so that the nomenclature of lesion diagnosis becomes subjective. A clinician and a pathologist may provide different localization of tumor site.

The mean tumor size in the case group was 3.44 ± 2.56 cm which was larger than that in the control group 2.32 ± 2.53 cm. This is statistically significant with the incidence of recurrence (p = 0.04). This result was similar to other studies showing that lesions larger than 2 cm have a greater risk of recurrence, larger tumors often have perineural invasion, deeper Clarks levels and aggressive tumor features. Large tumors tend to have deep invasion that affects the surrounding soft tissue structures including nerve fibers [16-19].

There is a statistically significant relationship between histopathological subtype and recurrence (p<0.001; OR 13) whereas the high risk histopathological subtype has a 13 times greater risk of recurrence compared to the low risk histopathological subtype. The low risk subtype does not have perineural invasion, while the high risk subtype is generally larger, mostly affecting the trunk, extremities and midface. Histologically, high risk BCC is poorly defined with perineural invasion and a high tendency for recurrence. (10). Perineural invasion reflects tumor extension and direct growth along the nerve sheath and fibers while nerve fibers are not directly affected by tumor growth due to the elasticity of the perineural and endoneural spaces, this explains why tumors that invade the perineural have minimal symptoms until they reach the final stage. BCC is considered a neurotrophic cancer so that on histopathological examination characteristics of perineural invasion can be found [15, 17].

BCC is not an aggressive tumor with a life-threatening potential, it is important to be treated appropriately. Histopathological examination is not only a definitive diagnosis of a BCC lesion but also provides information on factors predicting the nature of the tumor and the risk of recurrence, so the clinicians could provide an attentive follow-up after the surgery [6, 18, 20].

The study's limitation include the low number of case analyzed because most patients did not present for follow up and lack of data regarding characteristics of the tumor. For these reasons, follow-up visits are crucial both for the clinicians and patients, also close examination for tumor extension and routine examination for histopathological subtype is mandatory.

5. Conclusion

Histopathological subtype plays an important role in the therapeutic management of BCC. It may provide guidelines to determine the excision margin as recommended in low risk subtype ≥4-10 mm and in high risk subtype ≥10mm, also adduction to adjuvant radiotherapy. The results of this study also show that there is significant relationship between histopathologial subtype of BCC with its recurrence since it provides tumor behavioural. Age and location of the tumor do not appear as considerable risk factors but the size of the primary tumor does. Follow up after operation is mandatory to maintain regular examinations.

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.

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