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Dennis William Pratama
*Training Program in Surgery, Department of Surgery, Faculty of Medicine, Universitas Indonesia, dr. Cipto Mangunkusumo General Hospital Jakarta*, dennismd06@gmail.com

Ahmad Kurnia
*Division of Oncology Surgery, Department of Surgery, Faculty of Medicine, Universitas Indonesia, dr. Cipto Mangunkusumo General Hospital Jakarta*

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# Wide Excision of Non–Melanoma Skin Cancer at dr. Cipto Mangunkusumo General Hospital, 2012–2015: Recurrence and Prognostic Factors

Dennis W. Pratama, [1] Ahmad Kurnia.[2]

1. Training Program in Surgery, 2. Division of Oncology Surgery, Department of Surgery, Faculty of Medicine, Universitas Indonesia, dr. Cipto Mangunkusumo General Hospital Jakarta.

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## Abstract

**Introduction.** Skin cancer is one of many kinds of cancer which incidence increases globally. Basal cell carcinoma (BSC) and squamous cell carcinoma (SCC) are the most common prevalence of non–melanoma skin cancer, and also are the most common cancer among skin cancer. The main therapy for such skin cancer is wide excision within its safety margin added by adjuvant therapy. Despite adequate therapy, people with skin cancer still have a risk of recurrence. This study assesses the prognostic factors of recurrence among people with non–melanoma skin cancer who underwent wide excision surgery.
**Method**. This study was a retrospective cohort with survival analysis. The patient's data who underwent wide excision surgery were from Perhimpunan Ahli Bedah Onkologi Indonesia (PERABOI) registry and medical record from Oncology Surgery Division in RSCM from January 2012–December 2015. Data selection was done based on inclusion and exclusion criteria.
**Results**. There were 187 patients with non–melanoma skin cancer who underwent wide excision surgery; the recurrence was detected on 15% of the case. Most of the patients were ≥45 years old with the most common histopathological feature of the skin cancer was basal cell carcinoma. We did a survival analysis with Cox regression and the result was previous history of skin cancer (RR 6.903; 95% CI 2.925–16.292), perineural invasion (HR 3.818; 95% CI 1.561–9.340), location of the lesion (HR 0.071; 95% CI 0.022–0.228), and size of the tumor (HR 1.842; 95% CI 1.244–2.729) was the factors that increased recurrence.
**Conclusion**. History of previous skin cancer, perineural invasion, location of the lesion, and size of the tumor were the prognostic factors for recurrence among patients with non–melanoma skin cancer who underwent wide excision surgery.

**Keywords**: *non–melanoma skin cancer, basal cell carcinoma, recurrence, squamous cell carcinoma, wide excision surgery*

## Introduction

Basal cell carcinoma (BSC) and squamous cell carcinoma (SCC) are the most common non–melanoma skin cancer group, as well as the most common malignant tumor found[1,2] contributed less than 0.1% mortality of cancer.[3,4,5] Aside from death, cancer–related diseases led the patient suffered; pain and discomfort arising from cancer, the side effects of treatment. In addition, the high burden of costs is the things contribute to this suffering.

Wide excision with a safety margin in accordance with histopathology type completed by the adjuvant therapy is the treatment for skin cancer. However, the risk of recurrence that may found let the suffering increased. A cohort study of Margaret et al (2011) in the United States reporting the recurrence rate of 4.0%.[6] Study of Khan et al (2014) showed that age, tumor size, immune conditions, and modality of therapy were the affecting factors for the recurrence. Study of the National Comprehensive Cancer Network reporting tumor location and size, tumor boundary, previous cancer history, patient immunological status, perineural involvement, and tumor histopathology subtype were the predictors of recurrence.[6,9]

Investigations on the affecting factors of the recurrence have been widely reported. In contrast, the recurrence rates and affecting factors in Indonesia have not been reported. Thus, the recurrence of non–melanoma skin cancer following wide excision was the aim of the study

## Method

A retrospective cohort study with survival cox analysis proceeded to find out the association of age, tumor size, previous cancer history, perineural invasion, histopathology of skin cancer, and predilection to the recurrence in patients underwent wide excision in Division of Oncology Surgery in CMGH during the period of 2012 to 2015. Data collected from Perhimpunan Ahli Bedah Onkologi Indonesia (PERABOI) registry and medical record from Oncology Surgery Division at CMGH were subjected to statistical analysis. Chi-square was used to determine the correlation of risk factors with the recurrence, Fischer test was the alternative if the analysis were not qualified for the Chi-square test. The relative risk (RR) describes the correlation of each variable to the recurrence.

**Results**

In the observation period (2012–2015) there were 381 cases of skin cancer recorded. Out of 213 non–melanoma, a total of 187 subjects with complete data enrolled in the study. Mostly (87.2%), the age of the subject of ≥45 years and 7% with a history of cancer in the family.

Table 1. Distribution of demographic characteristics of skin cancer in the period of January 2012 – December 2015 (n = 187)

| Variable | Total (%) |
|---|---|
| Age | |
| – <45 years | 24 (12.8) |
| – ≥ 45 years | 163 (87.2) |
| Occupation | |
| – Indoor | 114 (61.0) |
| – Outdoor | 73 (39.0) |
| Family history of cancer | |
| – Yes | 13 (7.0) |
| – No | 174 (93.0) |

Table 2. Distribution of clinical characteristics of skin cancer in the period of January 2012 – December 2015

| Variable | Total (%) |
|---|---|
| Age | |
| – <45 years | 24 (12.8) |
| – ≥45 years | 163 (87.2) |
| Previous cancer | |
| – Yes | 21 (11.2) |
| – No | 166 (88.8) |
| Histopathology of skin cancer | |
| – BSC | 98 (52.4) |
| – SCC | 89 (47.6) |
| Cancer–related neurological symptoms | |
| – Present | 73 (39) |
| – Absent | 114 (61) |
| Predilection | |
| – Face | 134 (71.7) |
| – Trunk and upper extremities | 14 (7.5) |
| – Lower extremities | 39 (20.9) |
| Tumor size | |
| – <2 cm | 33 (17.6) |
| – >2≤ 5 cm | 85 (45.5) |
| – >5 cm | 69 (36.9) |

Subjects with BSC were found predominant (52.4%) with the predilection in the face; of which is the predisposing area of high–risk skin cancer. Among the recorded risk factors to the recurrence in this non–melanoma underwent wide excision surgery, there was only the variable of age showing nonrelated to recurrence (p = 0.258; RR 0.569; 95% CI 0.206–1.570) (table 3). Based on the results using Cox regression analysis, the variables showing a significant relationship with the recurrence was: the history of previous cancer, cancer–related neurological symptoms, tumor size, and predilection. Previous history of cancer with HR 6.903, 95% CI 2.925–16.292), tumor size of ≥5 cm with HR 1.842, 95% CI 1.244–2.729), and cancer–related neurological symptoms with HR 3.818; 95% CI 1.561 –9.340) were the prognostic factors for the recurrence. The likelihood of such subjects to have recurrence is 95%. The cancerous lesions in the low–risk areas were found as a protective factor of recurrence (HR 0.071, 95% CI 0.022–0.228).

Table 3. Relationship of clinical characteristics of skin cancer patients with recurrence at RSCM during period January 2012 – December 2015

| Variable | Recurrence | | RR (95% CI) | P |
|---|---|---|---|---|
| | Yes | No | | |
| Age | | | | |
| – <45 years | 6 | 18 | 0.569 | 0.258* |
| – ≥45 years | 26 | 137 | (0.206–1.570) | |
| History of previous cancer | | | | 0.001* |
| – Yes | 10 | 11 | 5.950 | |
| – No | 22 | 144 | (2.263–15.646) | |
| Histopathology | | | | |
| – SCC | | | | |
| – BSC | 23 | 66 | 2.956 | 0.003** |
| | 9 | 89 | (1.255–6.965) | |
| Cancer–related neurological symptoms | | | | |
| – Present | 21 | 52 | 3.731 | 0.001** |
| – Absent | 11 | 103 | (1.696–8.433) | |
| Predilection | | | | |
| – *High risk* | 28 | 107 | 3.086 | 0.034** |
| – *Low risk* | 4 | 48 | (1.01–8.646) | |
| Tumor size | | | | |
| – ≤5 cm | 14 | 104 | 2.622 | 0.013*** |
| – >5 cm | 18 | 51 | (1.208–5.689) | |

Table 4. Multivariate logistic regression analysis

| Variable | Coefficient | p value | OR(95%CI) |
|---|---|---|---|
| Previous cancer history | 2.631 | 0.000 | 13.885 (4,.008–48.107) |
| Cancer–related neurological symptoms | 2.003 | 0.000 | 7.414 (2.705–20.321) |
| Tumor size | 1.276 | 0.010 | 3.583 (1.364–9.408) |
| Predilection | 3.196 | 0.000 | 4.440 (5.279–113.151) |
| Constanta | –6.152 | 0.000 | |

**Discussion**

A better understanding of the recurrence risk factors let a more holistic, comprehensive management and follow-up may be provided. Out of 187 non-melanoma skin cancer enrolled in the study, the recurrence was found in a total of 32 subjects. On the analysis, age was not significantly associated with the recurrence (p = 0.258) and found in contrast to study by Khan et al (2014) reporting a median age of 78 years as the risk factors for post-radiotherapy recurrence of non-melanoma cancer.[9] Studies of Lin et al (2012) showed that age had no effect on the recurrence of BSC and SCC in the age group >70 years compared with age ≤70 years (p = 0.09; RR 1.76; 95% CI 0.92-3.37).[21] Out of 187 subjects of non–melanoma enrolled in this study, the age at most for skin cancer was over 45 (86.6%) like study of Ocanha (2009) on BSC showing the highest prevalence of skin cancer in the female group (54.7%) with the average age of 65 years at the initial diagnosis constituted.[17] Study of Szewczyk (2014) also on BSC showed males were predominated (63%) with age ranged of 32–96 years (median age 73 years).[18]

Study of Wiser (2016) reporting the highest prevalence of SCC on the face and neck in the group of men with a mean age of 75 years. The study showed that gender was significantly associated with the occurrence of SCC in the face and neck (p <0.001).[19] Chren (2011) study on 495 non-melanoma showed the highest number of male subjects (97%) with an average age at the time of diagnosis was 71 years.[6] The pathophysiology explains the relationship between gender and the occurrence of non-melanoma skin cancers remains unclear but may be influenced by the habits and occupation. Males tend to have jobs with high sun exposure let the risk of developing non-melanoma skin cancer increased.[19, 24]

Out of the non-melanoma skin cancer subjects in the study, a total of 61% were the indoor workers and did not fit to the previous study reporting that the outdoor workers were at greater risk of developing skin cancer. Other study reports a specific association of BSC to intermittent sun exposure and excessive sunlight exposure during childhood and SCC to chronic and continuous sunlight exposure.[20] In this study, most subjects were BSC and indoor workers, Indonesian specific skin color may have an impact different from those reported. A further investigation may be required to have the best explanation for the difference.

Most subjects (93%) in this study have no family cancer history. The history of cancer in the family is a risk factor in relation to mutant genes that were inherited in nature. With sufficient exposure to sunlight, particularly continuous exposure to UVA and UVB rays may lead to precancerous lesions as these lights leading to the mutations of p53 (tumor suppressor gene).[12,15]

BSC was found predominated (52.4%) in this study as those reported (accounting 75% of all non-melanoma skin cancers).[20] The histopathology type showed the association with the recurrence. Bivariate analysis showed that SCC was 2.96 times greater risk for the recurrence rather than BSC (p = 0.003; RR 2.956; 95% CI 1.255-6.965). Another important finding in the study was the predilection. In this study, 71.7% were located in the face, in accordance with reports showing the face as a high-risk area for the predilection of skin cancer.[15] Our bivariate analysis showing this cancer located in the face has 3 times greater for recurrence than those located in low-risk areas (p = 0.034; RR 3.086; 95% CI 1.01-8.646). This is consistent with the previous study by Bogelund (2007) showing that tumor sites are associated with recurrence rates. BSC in the head region showed at a greater risk for recurrence (OR 2.8; 95% CI 1.5-5.3).[22] A systematic review (Lansbury, 2013) showed that SCC located at the ear is at greater risk for recurrence than other areas (14.1%, 95% CI 10, 2-18,5).[23] The head referred to a high-risk area; as it exposed to anything more than other parts.

The size of the tumor in this study is divided into 3 categories, with the most category is the tumor on the skin sized 2 - ≤5 cm that is as much as 45.5%. In the process of data analysis, we merged the categories because the results of the analysis did not meet the requirements of the chi-square test for a 3x2 table so that obtained a new category that sized ≤5 cm and> 5cm. From the results of the analysis, there was a significant correlation between tumor size and recurrence in non-melanoma skin cancer patients (p = 0.013; RR 2.622; 95% CI 1.208-5.689). This is in accordance with a research by Khan et al (2014) for non-melanoma skin cancer patients undergoing radiotherapy. The study showed that the larger the size of the tumor, the greater the risk of recurrence (P = 0.0004, RR 2.578, 95% CI 1.529-4.348).[9] Whatever modalities are used in the treatment of non-melanoma skin cancer, the larger the size of the tumor, the risk of recurrence will be even greater. The larger the size of the tumor will make it more difficult for the surgical process because the tumor invades to the important structures so that the risk of recurrence will increase if the margin of the incision of the tumor is not a clear margin.

Neurological involvement of skin cancers occurs due to the perineural infiltration process (the tumor spreads to the perineurium of the nerve). The incidence of perineural invasion in BSC patients ranging from 0.18% to 10%, whereas in SCC the incidence is 2.5% to 14 %.[21] Symptoms of perineural invasion include pain, dysesthesia or hypoesthesia. In this study, it was found that cancer-related neurologic symptoms were among the risk factors for recurrence (P = 0.001; RR 3.731; 95% CI 1.696-8.433) .[21]

Study of Lin et al (2012) showed that the degree of tumor invasion of the perineurium nerve associated with tumor recurrence within 5 years, local invasion of perineurium nerve has better outcomes than the widespread invasion (p = 0.02; RR 2.18; 95% CI 1.11-4.31).[21] Perineural invasion of skin cancers is associated with increased recurrence possibilities due to skipping lesions in the region along the nerve so that despite the excision is resulting in a clear margin, the risk of recurrence remains high. The factors associated with perineural involvement include male gender, tumor size greater than 2 cm, location on the face, and previous history of cancer lesions.[25]

In this study, we carried out survival analysis with Cox regression to determine the factors that can be predictors of recurrence in non-melanoma skin cancer patients who have undergone wide excision. The results shown that previous cancer history was the largest predictor of recurrence in patients (HR 6.903; 95% CI 2.925-16.292). It is also known that cancer lesions in low-risk areas are a protective factor of recurrence (HR 0.071, 95% CI 0.022-0.228). This is related to the low intensity of sunlight exposure in low-risk areas of the skin.

The history of previous skin cancer, cancer-related neurological symptoms, tumor size, and location of cancer have a strong relationship with recurrence in post wide excision non-melanoma skin cancer patients; the location of primary cancer contributes the most to the recurrence. Cancers located in high-risk areas are three times greater for recurrence (p = 0.034, 95% CI 1.01-8.646). This is due to the extremely high intensity of sun exposure in high-risk areas. The second largest risk factor was previous cancer history. The non-melanoma skin cancer patients who had previous other cancers and then performed wide excision then 6.9 times greater risk for recurrence compared with patients with de novo cancer (p = 0.000; 95% CI 2.925-16.292). Those with a history of previous other cancers already have a mutant gene in the body let the risk of recurrence increased. Those with perineural invasion will have a 3.8 times greater risk of recurrence (p = 0.003, 95% CI 1.561-9.340) and those with tumor size> 5cm will be 1.84 times greater risk of recurrence (p = 0.002; 95% CI 1.244-2.729). Cumulative risk if the subject has all the four risk factors for recurrence is 95%.

## Conclusion

In the period of January 2012 to December 2015 in CMGH, there were 213 cases of non-melanoma skin cancer, 15% of whom had recurrences. Factors that affect the recurrence of non-melanoma skin cancer after wide excision include previous cancer history, perineural invasion, cancer location, and cancer size. The cumulative risk of recurrence for non-melanoma skin cancer patients after wide excision located in high-risk areas, having previous cancer history, perineural invasion, and tumor size >5 cm is 95%.

## Disclosure

Author disclose there was no conflict of interest.

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