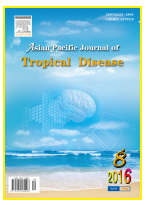
HOSTED BY
ELSEVIER

Contents lists available at ScienceDirect

Asian Pacific Journal of Tropical Disease

journal homepage: www.elsevier.com/locate/apjtd



Original article doi: 10.1016/S2222-1808(16)61103-9

Mid-face location of primary basal cell carcinoma related to cancer aggressivity

Prasetyadi Mawardi[1,2*], Handono Kalim[3,4], Kusworini Handono Kalim[4,5], Loeki Enggar Fitri[4,6], Karyono Mintaroem[4,7], Ambar Mudigdo[2,8], Oyong[2,8], Brian Wasita[2,8]

[1]*Dermatovenereology Department, Medical Faculty, Sebelas Maret University, Surakarta, Central Java, Indonesia*

[2]*Dermatovenereology Department, Moewardi Public Hospital, Surakarta, Central Java, Indonesia*

[3]*Internal Medicine Department, Faculty of Medicine, University of Brawijaya, Malang, East Java, Indonesia*

[4]*Saiful Anwar Public Hospital, Malang, East Java, Indonesia*

[5]*Clinical Pathology Department, Faculty of Medicine, University of Brawijaya, Malang, East Java, Indonesia*

[6]*Parasitology Department, Faculty of Medicine, University of Brawijaya, Malang, East Java, Indonesia*

[7]*Pathology Department, Faculty of Medicine, University of Brawijaya, Malang, East Java, Indonesia.*

[8]*Pathology Department, Medical Faculty, Sebelas Maret University , Surakarta, Central Java, Indonesia*

ARTICLE INFO

Article history:
Received 7 Jun 2016
Received in revised form 22 Jun, 2nd revised form 27 Jun 2016
Accepted 10 Jul 2016
Available online 15 Jul 2016

Keywords:
BCC
Mid-face
Aggressive
Ultraviolet B

ABSTRACT

Objective: To study the aggressiveness of basal cell carcinoma (BCC) on the mid-face location.
Methods: A total of 30 patients were diagnosed using specimen biopsy with hematoxylin-eosin stain at Moewardi Public Hospital in Surakarta, Central Java, Indonesia. The age, gender distribution, site of the lesion, as well as clinic-pathological appearance were analyzed.
Results: There were 30 patients consisting of 46.7% males and 53.3% females with ages ranging from 33 to 91 years old and with the most common occupation, such as farmers (53.6%) and housewives (26.7%). Morpheaform subtypes BCC were more frequent than other types. Based on the predilection, most of the BCC were found to be in the mid-face (76.7%) and using determined criteria of histopathological examination, the aggressive appearance was 77% and non-aggressive BCC was 23%. The BCC on the mid-face location was more aggressive than the other sites ($P < 0.05$).
Conclusions: BCC is the most common skin tumor in humans with rare metastases, which might cause significant damage due to its local recurrences and aggressiveness. BCC on the mid-face is significantly more aggressive than that on the other predilection sites.

1. Introduction

Basal cell carcinoma (BCC) is the most common skin tumor in humans[1]. BCC is locally aggressive which may invade the skin and adjacent structure including the muscles and bones and it has the low metastatic potential[2]. The highest incidence of BCC is in Australia with the ratios of 1 041 in 100 000 male population, and 745 in 100 000 female population. The incidence of skin cancer has markedly increased over the past decade. At this time, There are 2 up to 3 million of BBC that are non melanoma skin cancer[3]. In Indonesia, BCC is in the 3rd rank after breast cancer and cervix cancer[4]. In Moewardi Public Hospital, it is the most frequent of the skin cancers[5].

Ultraviolet B (UV-B, 290–320 nm wavelength) irradiation is a major etiologic and risk environmental factor in the pathogenesis of melanoma and non-melanoma skin cancer, including BCC[6]. Photocarcinogenesis follows a multistage model of cancer development in which UV-induced DNA damage leads to mutations resulting in activation of oncogenes

*Corresponding author: Prasetyadi Mawardi, Dermatovenereology Department, Medical Faculty, Sebelas Maret University, Surakarta, Central Java, Indonesia.
Tel: + 628164250638
E-mail: prasetyadimawardi@gmail.com

The study protocol was performed according to the Helsinki declaration and approved by Medical Faculty, Sebelas Maret University, Surakarta, Central Java, Indonesia. The ethical clearance number: 934/XII/HREC/2015.

The journal implements double-blind peer review practiced by specially invited international editorial board members.

or silencing of tumor suppressor genes[7]. UV-B proton induces DNA damage, particularly on neighboring pyrimidine bases thymine and/or cytosine. It stimulates several pro-inflammatory cytokines production, such as tumor necrosis factor-α, interleukin-1 and interleukin-6 in the skin and they are considered to be closely related to the progression of UV-induced carcinogenesis. Macrophage migration inhibitory factor is originally identified as a lymphokine that concentrates macrophages at inflammatory loci. Macrophage migration inhibitory factor inhibits p53-dependent apoptotic processes after UV-B exposure[8]. Lesions occur mainly on the sun-exposed skin,in about 80% of patients. They appear in the heads and in half of the patients and affect the skins of cheeks and the noses[9].

The BCC classification is complex and lacks uniformity of terminology and clear definitions. There is considerable variability in the morphology of BCC and as a consequence, a number of histopathological subtype has been defined[10-11]. Clinical manifestation is various lesion with a pearl transparent rim, destructive ulcerative lesion called ulcus rodents, pale foci with various degrees of induration, erythematous foci with obvious telangiectasia or cystic nodules. The most common BCC was nodular, followed by superficial and sclerosing or morpheic form[10-11].

In this study, BCC was classified as aggressive and non-aggressive. BCC generally has a clinical course characterized by slow growth, minimal soft tissue invasion and a high cure rate. However, BCC behaves aggressively with deep invasion, recurrence and potential regional and distant metastasis. Several factors include tumor size, duration and histology and perineural spread have been postulated as markers of the aggressive BCC phenotype[12]. Although the mortality rate is low, BCC may grow aggressively through creating extensive tissue destruction. Its frequency of metastasis is less than 0.1%[13]. Though BBC is eminently curable when the diagnosis is made promptly and the lesion is treated in the early phase, it constitutes an enormous financial burden on the health care system[5].

This study mainly focused on the tumor aggressiveness and its correlation to its predilection. By determining the localization of tumor aggressiveness we can prevent and evaluate the risk of recurrence after BCC treatment.

2. Materials and methods

A total of 30 BCC patients were diagnosed using specimen biopsy with hematoxylin-eosin. All patients were treated at the Moewardi Public Hospital in Surakarta, Central Java, Indonesia. The histologic pattern of BCC was divided into several major types: superficial, nodular, morpheic, pigmented, basosquamous and mixed. BCC on the face was divided by three sections: upper-face, mid-face and lower-face. The upper-face area included anterior hairline until glabella. The mid-face area included glabella going down to sub-nasal and the lower-face area included sub-nasal to mentalis[13]. Aggressive BCC based on histologic examination showed damaged basal membrane from nested tumors in palisading form or noncircular nested tumor with a smaller degree of peripheral palisade or loss palisading, spiky and jagged, or atypical basaloid tumor cells. While, the characteristic of non aggressive BCC are circular nested tumor with greater degree peripheral palisading or undamaged basal membrane of nested tumor[14,15]. The results of the study were statistically analyzed with the Kruskal-Wallis test ($P < 0.05$).

3. Results

In this study, we found BBC predominantly in females than males (54.3% and 46.7%, respectively). The age range of the patients was 33–91 years old with the most common occupation of farmers (53.3%) and housewives (26.7%). According to the duration of the illness, most patients had symptoms more than 3 years and affected people over 50 years old (Table 1).

Table 1
The characteristics of patients. *n* (%).

Variable	Patients
Gender	
Male	14 (46.7)
Female	16 (53.3)
Age (years)	
30–39	1 (3.3)
40–49	2 (6.7)
50–59	12 (40.0)
60 years old or more	15 (50.0)
Occupation	
Farmer	16 (53.3)
Civil servant	2 (6.7)
Entrepreneur	3 (10.0)
Housewife	8 (26.7)
Others	1 (3.3)
Duration of disease (years)	
1–3	3 (10.0)
3–5	15 (50.0)
> 5	12 (40.0)

Based on histopathology analysis, we found morpheaform subtype BCC (40%) was more dominant than other subtypes, which was followed by basosquamous, nodular, qigmented, mixed and superficial subtype BCC with percentages of 24%, 16%, 8%, 8% and 4%, respectively.

Based on the predilection, the most common BCC was in the mid-face. There were 28 patients who had BCC in their mid-face, and 23 patients were categorized as aggressive BCC and 5 patients had not aggressive BCC. In addition, the predilection of

BCC in the upper-face and lower-face was found in one patient only and there was no aggressive BCC (Figure 1).

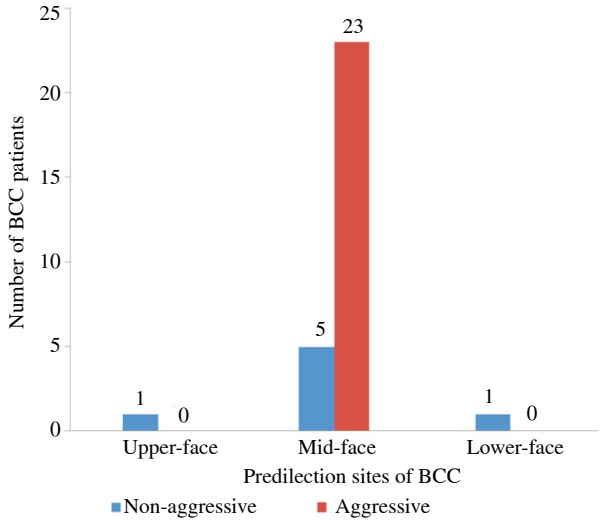


Figure 1. Numbers of BCC patients based on predilection.

The aggressiveness of BCC was found in 77% patients and non-aggressiveness was found in 23% patients. Aggressive BCC based on histologic examination showed damaged basal membrane from nested tumors in palisading form or noncircular nested tumor with a smaller degree of peripheral palisade or loss palisading, spiky and jagged.

4. Discussion

BCC is the most common skin cancer with increasing prevalence, especially in lighter skinned individuals. The incidence of BCC is estimated to be 80% of all skin cancers[15].

Several studies have shown that BCC is often found in men than women[15]. This may reflect a higher rate of sun exposures of males because of the employment pattern[16,17]. However, in this study, it is more common in women (53.3%) than men (46.7%). This is in accordance with a study done by Nisa *et al.*[5], where BCC is more often found in women than men. Historically, men were affected twice as often as women, although these differences are becoming less significant with a change in lifestyle, so the incidence in women is increasing due to a changing fashion in clothing and time spent outdoor for a recreational pattern or occupation reason[18].

Based on the occupation, most of the patients are farmers, which is considered as an occupation with high UV light exposure. Many studies have shown the close correlation between UV exposure and BCC incidence. The concept that UV exposure was the main etiological agent in the pathogenesis of non-melanoma skin cancer has been proposed since the early 20th century[15]. UV radiation is one of the most significant factors demonstrated by the global highest incidence around equator area, whilst Finland has the lowest incidence of all European countries[19]. UV radiation harms the DNA and its repair system as well as changes the immune system as a result of progressive genetic change and neoplasm formation. UV-B radiation absorbed by DNA is the main endogenous chromophore[15]. There are also increasing evidence that UV radiation affects extra nuclear molecular targets located in the cytoplasm and the cell membrane, including cell surface receptors, kinases, phosphatases and transcription factors. UV-B also alters the antigen-presenting function of Langerhans cells that leads to immunosuppression[15]. UV-B induced DNA damage and caused mutation in TP-53 tumor suppressor gene which resides on band 17p13.1 have found in some cases of BCC[18].

By age group, this study showed that patients over 50 years old were the most common affetced group. The rate of BCC has increased in the older age groups. The peak incidence is between 60 and 80 years old. More than 80% of patients are over 50 years old. Although recently it has been observed that the incidence in the population under 40 years old has increased as well. The suppressed immunity, as well as reduced DNA repairmen and regeneration properties occurring in the elderly also contribute to the raise of BCC incidence[20].

Of all 30 patients, BCC sites were on their faces with most of them in the mid-face. The most typical site of BCC is uncovered skin which is directly exposed to the sun. Thus, BCC is often observed in head and neck areas. BCC growth is characteristically slow, evolving for months to years in general, and tends to have the most aggressively behaving cell[17].

According to the histopathological findings, morpheaform, basosquamous, infiltrative and nodular subtypes were common in this study[21]. They found sclerosing or morpheic form was the rarest[22]. In addition, the morpheaform subtype mostly occurred on the head[23]. The mixed subtype in this study was lower as compared to other studies about 11%–40%[24]. Morphoeic or sclerosing BCC is an aggressive variant of BCC and resembles foci of systemic sclerosis. It is most frequently located on the face and has a form of a yellow-white lesion which is not subject to disintegration with ill-defined borders. In its central part, sclerosis, scarring and telangiectasia are usually present. It may grow fast and reach several centimeters within a few months or remain unchanged for many years[20]. Significant links were found between non-circular nests, smaller degrees of peripheral palisading and tumor aggressiveness. Mackiewicz-Wysocka *et al.*[14] and Patel *et al.*[15] also found that fibrous stroma was benign and that hyalinization was present in the stroma of more aggressive tumors.

Most authors used two basic criterias to classify histological types, growth pattern and histological differentiation[10].

Classification based on the histological growth pattern is useful during creation of the concepts of low-risk and high-risk types of BCC[25]. Great probabilities of subclinical spread, aggressive local behavior of the tumor with a more frequent occurrence of local recurrences due to incomplete excision are characteristics of high-risk types[24,25]. The morpheiform, basosquamous, infiltrative and mixed tumor subtypes are more aggressive than other subtypes.

In this study, we found the incidence of aggressive BCC was statistically higher than non-aggressive BCC with the predilection on the mid-face ($P < 0.05$).

BCC is the most common skin tumor in humans. Although BCC metastasizes rarely, it can lead to significant damage due to its local and aggressiveness recurrences. Morpheaform subtype is mostly found than the other subtypes. BCC on the mid-face is significantly more aggressive than BCC on the other predilection.

Conflict of interest statement

We declare that we have no conflict of interest.

References

[1] Nitzki F, Zibat A, König S, Wijgerde M, Rosenberger A, Brembeck FH, et al. Tumor stroma-derived Wnt5a induces differentiation of basal cell carcinoma of the Ptch-mutant mice via CaMKII. *Cancer Res* 2010; **70**: 2739-48.

[2] Baheti AD, Tirumani SH, Giardino A, Rosenthal MH, Tirumani H, Krajewski K, et al. Basic cell carcinoma: a comprehensive review for the radiologist. *AJR Am J Roentgenol* 2015; **204**: W132-40.

[3] Mateoiu CC. Contributions to the study of basic cell carcinoma. Histological and immunohistochemical study [dissertation]. Craiova: University of Medical and Pharmacy; 2011, p. 3-5.

[4] Kanoko. Basal Cell Carcinoma. 4th Annual Scientific Meeting of Indonesian Society of Dermatovenereology Perdoski. Semarang; 2002.

[5] Nisa M, Mawardi P, Darmawan N. Basal cell carcinoma in Dr. Moewardi Hospital. 12th Annual Scientific Meeting of Indonesian Society of Dermatovenereology Perdoski. Surakarta; 2012.

[6] Pittayapruek P, Meephansan J, Prapapan O, Komine M, Ohtsuki M. Role of matrix metalloproteinases in photoaging and photocarcinogenesis. *Int J Mol Sci* 2016; doi: 10.3390/ijms17060868.

[7] Seebode C, Lehmann J, Emmert S. Photocarcinogenesis and skin cancer prevention strategies. *Anticancer Res* 2016; **36**(3): 1371-8.

[8] Shimizu T. The role of macrophage migration inhibitory factor (MIF) in ultraviolet radiation-induced carcinogenesis. *Cancers (Basel)* 2010; **2**: 1555-64.

[9] Dourmishev LA, Rusinova D, Botev I. Clinical variants, stages, and management of basal cell carcinoma. *Indian Dermatol Online J* 2013; **4**(1): 12-7.

[10] Patterson JW. *Weedon's Skin Pathology*, 4th ed. London: Churchill Livingstone-Elsevier; 2015, p. 806-7.

[11] Vantuchová Y, Čuřík R. Histological types of basal cell carcinoma. *Scr Med (Bron)* 2006; **79**(5-6): 261-70.

[12] Deshmukh P, Sharma YK, Dogra BB, Chaudhari ND. Superficial large basal cell carcinoma over face, reconstructed by v-y plasty. *J Cutan Aesthet Surg* 2014; **7**(1): 65-6.

[13] Abbas OL, Borman H. Basal cell carcinoma: a single-center experience. *ISRN Dermatol* 2012; **2012**: 246542.

[14] Mackiewicz-Wysocka M, Bowszyc-Dmochowska M, Strzelecka-Węklar D, Dańczak-Pazdrowska A, Adamski Z. Basal cell carcinoma - diagnosis. *Contemp Oncol (Pozn)* 2013; **17**(4): 337-42.

[15] Patel P, Adsay V, Andea A. Basal cell carcinoma with progression to metastatic neuroendocrine carcinoma. *Rare Tumors* 2010; **2**(1): e8.

[16] Jarell AD, Mully TW. Basal cell carcinoma on the ear is more likely to be of an aggressive phenotype in both men and women. *J Am Acad Dermatol* 2012; **66**(5): 780-4.

[17] Nakayama M, Tabuchi K, Nakamura Y, Hara A. Basal cell carcinoma of the head and neck. *J Skin Cancer* 2011; **2011**: 496910.

[18] Bader RS. Basal cell carcinoma. [Online] Available from: http://emedicine.medscape.com/article/276624-overview [Accessed on September 15th, 2015]

[19] Samarasinghe V, Madan V, Lear JT. Focus on basal cell carcinoma. *J Skin Cancer* 2011; **2011**: 328615.

[20] Dębski T, Lembas L Jethon J. Basal Cell Carcinoma. In: Agullo FJ, editor. *Current concepts in plastic surgery*. Croatia: InTech; 2012, p. 13-48.

[21] Yalcin O, Sezer E, Kabukcuoglu F, Kilik AI, Sari AG, Cerman AA, et al. Presence of ulceration, but not high risk zone location, correlates with unfavorable histopathological subtype in facial basal cell carcinoma. *Int J Clin Exp Pathol* 2015; **8**(11): 15448-53.

[22] Kirzhner M, Jakobiec FA, Borodic G. Desmoplastic trichoepithelioma: report of a unique periocular case. *Ophthal Plast Reconstr Surg* 2012; **28**(5): e121-3.

[23] Nalin AS, Mary GJ, Sreedhar S, Raj PR, George GB. Pigmented basal cell carcinoma: a case report. *IJSS Case Rep Rev* 2015; **2**(5):4-6.

[24] Kim HS, Park JM, Mun JH, Song M, Ko HC, Kim BS, et al. Usefulness of dermatoscopy for the preoperative assessment of the histopahologic aggressiveness of basal cell carcinoma. *Ann Dermatol* 2015; **27**(6): 682-7.

[25] Trakatelli M, Morton C, Nagore E, Ulrich C, Del Marmol V, Peris K, et al. Update of the European guideline for basal cell carcinoma management. *Eur J Dermatol* 2014; **24**(3): 312-29.