Research Article

Clinicopathologic and Histomorphological Aspect of Basal Cell Carcinoma in Dr. Cipto Mangunkusumo Hospital: A Retrospective Analysis of Twenty Years Experience

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Abstract

Basal cell carcinoma (BCC) is the most common skin malignancy, and the incidence increases over time. However, epidemiological data and analysis of the histopathological characteristic of BCC in Asia and Indonesia are limited. This study evaluates the clinicopathological and histomorphological features of BCC cases at Dr. Cipto Mangunkusumo Hospital (CMH) for the last 20 years (2000-2019). This is a cross-sectional retrospective study, using medical records and slides data screened based on inclusion and exclusion criteria. The re-diagnostic assessment was performed independently by two investigators. Data were analyzed statistically by the chi-square test, Kruskal Wallis, and Mann Whitney tests. There were 896 cases of total 20 years, with an increase of 51.4% between the first and second decades, female: male ratio was 1.34: 1, the median age was 63 y.o (0-99), and 54% patient was 60-79 y.o. The majority of cases are located on the head, face, and neck (95.8%), nodular as the most common histological subtypes (49.2%), with adenoid as the highest number of variants (63.1%). Single vs mixed subtype BCC (58.4% vs 41.6%), low-risk vs high-risk BCC (53.9% vs 46.1%). There were different levels of risk and a number of subtypes based on anatomical location. The differences were also found in the number of subtypes, the aggressiveness of subtypes, and risk levels based on gender and histological subtypes based on anatomical location. Residual tumours were present in 2.8% of cases. Thus the cases of BCC in CMH have increased in the last 20 years, and differences are observed in anatomical distribution, gender, age, risk, number of subtypes, histological subtypes, and aggressiveness.

Keywords: *basal cell carcinoma, retrospective, epidemiology, histomorphological characteristics.*

Aspek Klinikopatologis dan Histomorfologikal Karsinoma Sel Basal di Rumah Sakit Dr. Cipto Mangunkusumo: Analisis Retrospektif 20 Tahun

Abstrak

Karsinoma sel basal (KSB) merupakan keganasan kulit yang paling sering. Namun data epidemiologi dan telaah karakteristik histopatologi KSB di Asia dan Indonesia sangat terbatas. Penelitian ini bertujuan mengevaluasi kasus KSB di Rumah Sakit Dr. Cipto Mangunkusumo (RSCM) dan meninjau gambaran klinikopatologis serta histomorfologinya selama 20 tahun terakhir (2000-2019). Penelitian ini menggunakan desain potong lintang retrospektif dengan mengambil data dari rekam medis dan slide tersimpan. Skrining formulir permintaan patologi berdasarkan kriteria inklusi dan eksklusi. Penilaian diagnosis ulang dilakukan secara independen oleh dua peneliti. Data dianalisis dengan uji chi square, Kruskal Wallis, dan Mann Whitney. Terdapat 896 kasus KSB dalam waktu 20 thn dengan peningkatan 51,4% KSB antara dekade ke-1 dan ke-2, rasio perempuan: laki-laki adalah 1,34:1, median usia 63 tahun (0-99) dan 54% berusia 60-79 tahun. Lokasi anatomis terbanyak di kepala, wajah, dan leher (95,8%), subtipe nodular (49,2%) dengan varian adenoid tertinggi (63,1%). KSB subtipe tunggal vs. campuran (58,4% vs. 41,6%), KSB risiko rendah vs. tinggi (53,9% vs. 46,1%), terdapat beda tingkat risiko dan jumlah subtipe berdasarkan lokasi anatomis, jumlah subtipe, sifat agresivitas subtipe, dan tingkat risiko berdasarkan jenis kelamin, serta beda jenis subtipe dengan lokasi anatomis. Tumor residif terdapat pada 2,8% kasus. Kasus KSB di RSCM meningkat dalam 20 tahun terakhir dan perbedaan diamati pada distribusi anatomi, jenis kelamin, usia, risiko histopatologik, jumlah subtipe, berbagai subtipe histopatologi, dan agresivitasnya.

Kata kunci: *karsinoma sel basal, retropsektif, epidemiologi, karakter histomorfologi.*

Introduction

Basal cell carcinoma (BCC) is the most common skin malignancy, and the incidence increases over time. This malignancy has low mortality but can cause significant morbidity due to local damage. Official statistics in the United States estimate 4.3 million BCC cases annually.[1] Although BCC is common among Caucasians in Europe, the incidence trend increases in several regions, including Asia and South America.[1] A BCC study in an Asian population showed that Asian people tend to develop BCC at a later age with less incidence during their lifetime than Caucasians despite the similar length of daily exposure to sunlight. However, doctors should be aware that BCC potential occurs in Asians and should still promote early screening and detection by introducing knowledge of the risk factors of BCC.[2]

Risk factors for BCC are mainly Fitzpatrick's skin types I and II associated with light eye color, freckles, blonde or red hair, exposure to ultraviolet (UV) radiation, childhood sunburn, family history of skin cancer, use of tanning bed, chronic immunosuppressive conditions, photosensitizing drugs, ionizing radiation, and exposure to carcinogenic chemicals especially arsenic.[1] The pathogenetic process of BCC includes constitutive activation of the intracellular patched/hedgehog signaling pathway that is responsible for regulating cell growth. Various mutations such as inactivation of the *Patched 1* gene (*PTCH1*), activation of the *SMOm* gene, loss of function of the *Suppressor of Fused Homolog* (*SUFU*) gene, or specific damage to the *p53* tumour suppressor gene due to UV can cause hedgehog pathway deviations and eventually form tumours.[3] Currently, knowledge regarding the recurrence rate of the histomorphological characteristics of the tumour is influential in determining the choice of therapeutic modality for BCC.

Epidemiological research related to BCC in Asia and Indonesia is still limited, especially one that covers a long periode of time and large number of cases. Insight into histomorphological data of BCC also need to be known to form a basis of better understanding of this disease. Thus, this study aims to evaluate the case of BCC at Dr. Cipto Mangunkusumo national referral hospital and to review its clinical and histomorphological features over the past 20 years.

Methods

Study Design

This research is a cross-sectional retrospective study conducted at the Department of Anatomical Pathology, Faculty of Medicine Universitas Indonesia (FMUI)/Dr. Cipto Mangunkusumo Hospital (CMH). The study was conducted on a group of patients with a confirmed BCC diagnosis over 20 years (January 2000 to December 2019). Cases form 2020 are purposedly not included to avoid bias due to decrease cases number in hospital in coronavirus disease 2019 (COVID-19) pandemic time.

Sample Characterization and Data Collection

Data were obtained from archives of Department of Anatomical Pathology, FMUI/CMH in the form of pathology examination request forms and histopathology slides with hematoxyllin-eosin (HE) staining. Ethical clearance has been obtained from the Health Research Ethics Committee FMUI/CMH, protocol number KET-183/UN2.F1/ETIK/PPM.00.02/2021.

The samples were taken by consecutive sampling with inclusion criteria patients confirmed with BCC as final diagnosis between January 2000 and December 2019. The exclusion criteria included patients with incomplete slides and patients with a change in diagnosis after re-assessment by pathologist.

The data were collected using the International Classification of Diseases for Oncology (ICD-O) system with the BCC morphological code (M8090/3) and topographic codes for all areas of the skin such as (1) head, face and neck; (2) trunk; (3) upper limbs; and (4) lower limbs. The cases were independently reassessed by dermato-pathologist (RA and MAPH) then a final diagnosis was confirmed. The classification of subtypes is based on the 2018 World Health Organization (WHO) guidelines for skin tumours.[4]

The variables assessed were patient characteristics (gender, age, anatomical site, year of registration, and clinical diagnosis of recurrence tumours), then all cases divided per decade. The histomorphological characteristics of BCC included histological subtype and variant, number of subtypes, recurrence risk and tumour aggressiveness.

Several subtypes of BCC are prognostically relevant, including low-risk or non-aggressive subtype of BCC (nodular, superficial, pigmented, fibroepithelial, infundibulocystic/with adnexal differentiated) and

high-risk BCC (micronodular, infiltrative, sclerosing/ morpheaform, basosquamous, sarcomatoid) with additional high-risk criteria when mixed BCC has a component of the aggressive subtype.[1,5] Each subtype can display further histological variants (keratotic, nodulocystic, and adenoid).[1,4] For cases diagnosed in the period before the use of WHO in 2018, the diagnosis was generally categorized as solid and cystic, so that the diagnosis of solid BCC was transformed into undifferentiated BCC and cystic BCC to nodular BCC.[1,6,7]

Data Analysis

All variables were analyzed with descriptive analysis by comparing the absolute frequency and the percentage statistically. The proportions of two or more categoric variables are compared with the chi-square test with the alternative non-parametric test of the Kruskal-Wallis test and posthoc Mann-Whitney test. The results are statistically significant if the p-value was <0.05 with a 95% confidence interval. The data were statistically processed using SPSS 24.0.

Results

This study describes a 20 years retrospective review of BCC at CMH, Indonesia. Initially, 1,204 cases of BCC were collected, however 308 cases excluded due to various reasons like incorrect coding (55), double specimen from one patient (biopsy and surgery 105), incomplete slides (108), and change of diagnosis (45); thus, 896 cases were analyzed.

Based on Figure 1, it can be seen that the trend of BCC cases has increased in the last two decades. There has been an increase in the proportion of cases both analyzed by age range and gender. The proportion of BCC cases always increases in each age range, with a tendency to be more in the older age group (60–79 years). Female patients are always dominant in number in all decade. The multivariate analysis on the types of histological subtypes of the tumour showed significant differences (p<0.05) with the most locations in the head, face, and neck areas for single or mixed types.

Figure 1. The incidence of BCC cases in CMH from 2000 to 2019 (a) Trend of increasing cases of BCC per year. There was a varied and cumulative increase from decade 1 to decade 2 by 51.4%. (b) The proportion of BCC based on each year's age range and it is higher each year in the old age group (c) The proportion of BCC by gender (d) The number of BCC based on the age groups.

Table 1 shows that overall, BCC with a low-risk level and single subtype are dominant based on histomorphological features. Most subtypes were nodular for the single low-risk type and micronodular and basosquamous for high-risk types. The most common mixed types were BCC with two components of the histological subtype. Our study shows that the combination of nodular and infiltrative subtypes is the most prevalent in mixed BCC (Table 2). On further histomorphological evaluation, the adenoid variant is dominant and only a minority of cases show vascular and perineural invasion. In this study, 2.4% of cases were recurrent BCC based on clinical diagnosis (Figure 2).

Table 1. Clinicopathological Profile of BCC Patients

Clinicopathological Profile	Overall BCC		Recurrent BCC	
	n	%	n	%
Registration year (n = 896)				
Decade 1 (2000-2009)	218	24.3	4	16.0
Decade 2 (2010-2019)	678	75.7	21	84.0
Gender				
Male	383	42.7	14	56.0
Female	513	57.3	11	44.0
Ratio of male: female	1:1.34		1.27:1	
Age groups (years old, n=896)				
Median	63.00 (0–99)		66 (43–80)	
0–19	10	1.1	0	0
20–39	49	5.5	0	0
40–59	285	31.8	11	44.0
60–79	484	54.0	12	48.0
≥80	68	7.6	2	8
Location of the tumour (n=896)				
Head, face, and neck	858	95.8	25	100.0
Trunk	20	2.2	0	0
Upper limbs	11	1.2	0	0
Lower limbs	7	0.8	0	0

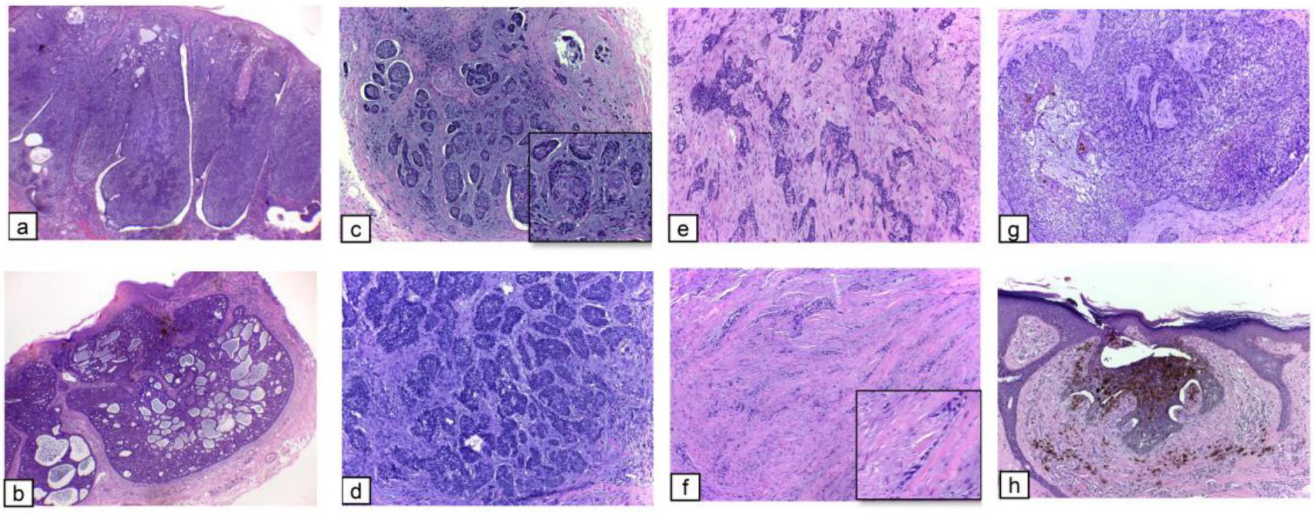

Figure 2. Histomorphological Characteristics of Subtypes and Variants of BCC. (a) Nodular subtype (H&E, 40X).(b) Nodular adenoid variant (H&E, 40x) (c) Nodular keratotic variant (H&E, 100x).(d) Micronodular subtype (H&E, 100x); (e) Infiltrative subtype (H&E, 100x); (f) Sclerosing/morpheaform subtype (H&E, 100x). (g) Sarcomatoid subtype (H&E, 40x); (h) Marked pigmentation with a dark brown melanin (H&E, 40x).

Table 2. Histomorphological Characteristics of BCC Patients

Histomorphological Characteristics	Overall BCC		Recurrent BCC	
	n	%	n	%
BCC subtype group based on risk level (n=896)				
Low-risk subtype	483	53.9	7	28
Nodular	441	49.2	7	28
Superficial	21	2.4	0	0
Infundibulocystic/with adnexal differentiation	1	0.1	0	0
Mixed with non-aggressive histological subtype components	20	2.2	0	0
High-risk subtype	413	46.1	18	72
Micronodular	19	2.1	1	4
Infiltrative	17	1.9	2	8
Sclerosing/morpheaform	4	0.5	0	0
Basosquamous/meta-atypical	19	2.1	2	8
Sarcomatoid/metaplastic	1	0.1	0	0
Mixed with aggressive histological subtype components	353	39.4	13	52
Number of BCC histological subtypes (n=896)				
Single subtype	523	58.4	12	48
Mixed or multiple type with:	373	41.6	13	52
Two component histological subtypes	310	34.6	11	44
Three component histological subtypes	60	6.7	2	8
Four component histological subtypes	3	0.3	0	0
Different subtypes in mixed type BCC (n= 373)				
Mixed type with two histological subtypes	310	83.1	11	84.6
Infiltrative, sclerosing/morpheaform	15	4.0	1	7.7
Micronodular, infiltrative	8	2.1	1	7.7
Micronodular, sclerosing/morpheaform	2	0.5	0	0
Nodular, basosquamous/meta-atypical	4	1.1	1	7.7
Nodular, pigmented	5	1.3	0	0
Nodular, infiltrative	219	58.7	8	61.5
Nodular, infundibulocystic/adnexal differentiation	2	0.5	0	0
Nodular, micronodular	35	9.4	0	0
Nodular, sclerosing/morpheaform	6	1.6	0	0
Nodular, superficial	13	3.5	0	0
Superficial, infiltrative	1	0.3	0	0
Mixed type with three histological subtypes	60	16.1	2	15.4
Micronodular, infiltrative, sclerosing/morpheaform	2	0.5	2	15.4
Nodular, infiltrative, basosquamous/meta-atypical	7	1.9	0	0
Nodular, infiltrative, sclerosing/morpheaform	45	12.1	0	0
Nodular, micronodular, basosquamous/meta-atypical	1	0.3	0	0
Nodular, micronodular, infiltrative	3	0.8	0	0
Nodular, micronodular, sclerosing/morpheaform	2	0.5	0	0
Mixed type with four histological subtypes	3	0.8	0	0
Nodular, micronodular, infiltrative, sclerosing/morpheaform	2	0.5	0	0
Nodular, superficial, infiltrative, sclerosing/ morpheaform	1	0.3	0	0
Histological variants in nodular subtypes, single & mixed (n=786)				
Yes	84	10.7	0	0
Adenoid	53	6.7	0	0
Keratotic	29	3.7	0	0
Cystic	2	0.3	0	0
No	702	89.3	0	0
Lymphovascular and perineural invasion (n = 896)				
Yes	4	0.4	0	0
No	892	99.6	0	0

Table 3 shows that age does not associated histological recurrence risk level and the number of subtypes. (with Multivariate analysis with Kruskal-Wallis test following by bivariate analysis with post-hoc Mann-Whitney test: comparison of head, face, and neck vs trunks (p=0.016)) The head, face, and neck location is the largest and most significant location for the trunk for analysis of the level of risk and the number of subtypes. The proportions of the trunk and upper limbs were also statistically significant for the number of subtype analysis.

Table 3. The Histopathological Subtypes of BCC Based on The Histopathological Recurrence Risk and The Number of Subtypes Towards Age Groups and Location of The Tumour

Age and Tumour Location	Histological Subtypes							
	Histological Reccurence Risk				Number of Subtype			
	High	Low	Total	p-value	Single	Mixed	Total	p-value
Age groups (years old)								
0–19	7 (1.7%)	3 (0.6%)	10 (1.1%)	0.287	3 (0.6%)	7 (1.9%)	10 (1.1%)	0.391
20–39	21 (5.1%)	28 (5.8%)	49 (5.5%)		26 (5.0%)	23 (6.2%)	49 (5.5%)	
40–59	125 (30.3%)	160 (33.1%)	285 (31.8%)		169 (32.3%)	116 (31.1%)	285 (31.8%)	
60–79	233 (56.4%)	251 (52.0%)	484 (54.0%)		286 (54.7%)	198 (53.1%)	484 (54.0%)	
≥80	27 (6.5%)	41 (8.5%)	68 (7.6%)		39 (7.5%)	29 (7.8%)	68 (7.6%)	
Location of the tumour								
Head, face, and neck	405 (98.1%)	453 (93.8%)	858 (95.8%)	0.016*	494 (94.5%)	364 (97.6%)	858 (95.8%)	0.006*
Trunk	4 (1.0%)	16 (3.3%)	20 (2.2%)		19 (3.6%)	1 (0.3%)	20 (2.2%)	
Upper limbs	3 (0.7%)	8 (1.7%)	11 (1.2%)		5 (1.0%)	6 (1.6%)	11 (1.2%)	
Lower limbs	1 (0.2%)	6 (1.2%)	7 (0.8%)		5 (1.0%)	2 (0.5%)	7 (0.8%)	

* Multivariate analysis with Kruskal-Wallis test following by bivariate analysis with post-hoc Mann-Whitney test

Table 4 shows a significant difference (Mann-Whitney test; p=0.005) between histological reccurence risk level and gender, indicating that female is more at risk for BCC.

Table 4. Distribution Histomorphological Characteristics Based on Gender

Histomorphological Characteristics	Male	Female	p-value
Histological reccurence risk of all BCC (n = 896)			
Low	207 (42.9%)	276 (57.1%)	0.005*
High	176 (42.6%)	237 (57.4%)	
Number of subtypes of all BCC (n = 896)			
Single	222 (42.4%)	301 (57.6%)	0.046*
Mixed (Multiple)	161 (43.2%)	212 (56.8%)	
Aggressiveness of mixed type BCC (n = 373)			
Not aggressive	9 (45.0%)	11 (55.0%)	0.029*
Aggressive	152 (43.1%)	201 (56.9%)	

*Mann-Whitney test.

Discussion

Surveying the Increment of BCC cases Case Analysis Based on the Case Registration Decade

In this study, the number of cases per year showed a 51.4% increase between two decades. The highest number of cases was in 2017, reached 96 cases (10.7%), and the lowest was in 2004, 4 cases (0.4%). Previous publications from CMH, Indonesia, stated that between 2014–2017 BCC incidents were 66.9 % of 263 skin malignancies.[8]

The number of cases per year showed a 51.4% increment between two decades. The highest number of cases was in 2017, reached 96 cases (10.7%), and the lowest was in 2004, 4 cases (0.4%). Previous publications from CMH, Indonesia, stated that between 2014–2017 BCC incidents were 66.9 % of 263 skin malignancies.[8]

One of the factors contributed for this gain is possibly due to more accessible access to healthcare in the second decade, related to the expansion of the national health insurance program (Jaminan Kesehatan Nasional; JKN) since 2014.[10] Currently, JKN has covered 83–85% of the Indonesia population.[9] The benefits of JKN are presented in outpatient and inpatient services. The outpatient services access was progressed from 38% to 54% in the period 2003–2015. Meanwhile, inpatients services improvement started from 4.1% to 7.1% in the period between 2007 and 2015.[10]

Case Analysis Based on Gender

In this study, the proportion of patients suffering from BCC was higher in females (57.3%) with a ratio of 1.34:1. This result is in line with research in Poland and India which states that women are more exposed to BCC with a ratio of 1.3:1[11] and 2.3:1[12], respectively.

This retrospective study shows a lower male to female ratio than other studies in the western literature. The incidence of BCC is more common in men than women in the worldwide study, possibly because of greater occupational exposure to UV radiation. However, the number of females suffering from BCC is increasing, such as in India, which has similar regional characteristics to Indonesia according to WHO region grouping.[12] Indonesia's demographic characteristics are similar to India's, where females experience significant cumulative high-intensity UV exposure related to outdoor work, such as cooking in an open kitchen, farming, and trading in traditional markets. Another factor is that male and female skin differ substantially in their structure and biology. Female's skin is structurally thinner, with a lower collagen density in the dermis when compared to men's.[13] This causes differences in the skin's response to environmental stress, including UV exposure.[14]

The number of female patients who are more registered in health facilities is also influenced by the character of women who pay more attention to their skin's health and immediately seek medical help if there are skin lesions or any abnormalities on the face.[15] Females pay special attention to facial skin and extremities'health so that it is easier to detect anomalies by themselves.[16] Females more often visit beauty salons, where the service contributes to finding skin anomalies.[17]

Case Analysis Based on Age

The median age of the patients was 63 (0–99) y.o. The overall mean of patients was 61.54 ± 14.17 y.o.; in men was 61.34 ± 13.76 y.o.; and in women was 61.70 ± 14.48 y.o. This finding with various previous studies with a mean age of 65.6 y.o.[18] The youngest age group in this study was 0-19 years old. The incidence of BCC in children under 15 years of age is infrequent, according to literature.[19] BCC was commonly associated with genetic defects and inherited syndromes in pediatric patients, including basal cell nevus syndrome, Bazex syndrome, albinism, xeroderma pigmentosum, vitiligo, and sebaceous nevus.[19] We only evaluated ten pediatric cases (1.1%) for BCC in our study for the last twenty years.

Understanding age has important implications for the prognosis of life expectancy. Epidemiology occurs in older patients due to two possibilities; first, BCC occurs in old age; or secondly, it arises from poor early detection. Old age is also associated with skin malignancy as the culmination of the accumulation of hereditary genetic disorders or acquired mutations. The type and number of mutations accumulated determine the malignancy potential of a skin lesion.[20] The UV light's ability to cause point mutations, deletions, and micronuclei, have been observed in irradiated skin cells.[1,20] The epidermis bears the brunt of adverse environmental effects on the body, and several mutations occur in each proliferation process. Most of them are quick to repair and do not cause vicious transformations. When the accumulation of genetic disorders can no longer be repaired, the genes that control the cell cycle and DNA repair are disrupted. An imbalance of proliferation and apoptosis regulations occurs so that cells will transform into tumours. This process requires a long process over a long period.[1,20]

The predominance of the elderly in having BCC also has implications for the choice of treatment.[21] Therapy in the geriatric age group is not as simple as in healthy young adults due to their body cells' ability to proliferate in wound healing.[21] People over 65 years of age tend to have their epithelial process inhibited after surgical procedures. This delay can be attributed to decreased proliferation and migration of keratinocytes, fibroblasts, endothelial cells, reduced collagen turnover, and increased fibroblast ageing.[22] This delay in wound healing can lead to an increased risk of infection. Also, epithelialization in geriatrics can be complicated because of common comorbidities, such as diabetes mellitus and vascular disease.[23]

Distribution of BCC According to Anatomical Location

According to our result, the head, face, and neck regions become the most prevalent of BCC, following by trunk, upper limbs, and lower limbs. Similar to our study, Subramaniam et al. also proved that the head, face, and neck region are known to be the centres of BCC tumours, with a relative density of tumours for this region of 4.47 (CI 95%: 4.3–4.64) followed by trunk 1.6 (95% CI: 1.01–1.11), upper limbs 0.72 (95% CI: 0.67–0.78), and lower limbs 0.3 (CI 95%: 0.28–0.33).[24]

Referring to the theory that BCC is strongly associated with UV exposure, this result is relevant because the head, face, and neck areas are most frequently exposed to sunlight.[25] The theory that other BCC precursors originate from hair follicles supports the finding because head, face, and neck region contain more hair follicles than any other region of the body.[26,27] However, a discrepancy in the pattern of UV exposure occurred in this study. The proportion of BCC in the trunk as the body's area is typically covered and becomes less exposed has relatively higher tumour density than in the upper and lower extremities. This result is similar to that from a study conducted in Australia,[24] which posits that BCC incidence in areas that are not exposed to sunlight is potentially related to other mechanisms in BCC development, including genetic syndromes or toxic additives. The predisposition factor of BCC cases in the trunk appears to be specifically associated with gene variation for the enzyme glutathione S-transferase (three forms) and cytochrome P450.[28] Immunosuppression may play an essential role in the development of BCC, as we know that patients in old age has entered a period of immunosenescence and causes immune suppression.

Another point that explains the phenomenon of BCC more in covered areas is based on the new thinking that the incidence of BCC may not be directly proportional to sun exposure where such as the trunk. The first hypothesis, insufficient exposure to sunlight in this closed body part, results in lower melanin production. The risk of sunburn is higher due to inadequate protection from melanin. The second hypothesis, BCC in these areas can occur due to intermittent exposure to high doses of UV rays without being continuously exposed. Another suggestion is that the cells originating from BCC in the trunk and buttocks require a lower total dose of sunlight to become neoplastic. The hypothesis of intermittent high doses of UV is also supported by the frequent occurrence of BCC in the facial periorbita area, even though the area is protected from the forehead compared to other facial subsites.[24]

Analysis of Histological Subtypes and Variants

According to the WHO classification of skin tumours, BCC is divided into two categories based on its reccurence risk (low risk and high risk). A mixed type of BCC can consist entirely of low-risk subtypes (low aggressiveness), all high-risk subtypes (high aggressiveness), as well as a mix of low-risk and high-risk, which will eventually be classified as high risk (high aggressiveness).

Analysis of Single Subtype BCC

Low-risk subtypes of basal cell carcinoma with non-aggressive tissue features include nodular, superficial, infundibulocystic, and pigmented types. In contrast, high-risk subtypes include micronodular, infiltrative, sclerosing/morpheaform, basosquamous, and more aggressive sarcomatoid. Descriptive analysis of low-risk single subtype BCC showed that nodular subtypes were the most prevalent (49.2%). These results are consistent with various previous studies (43–55%[12,29]). The superficial subtypes in this study were 2.3% (previous study 5–8.12%[12,30]) and infundibulocystic 0.1% (previous study 5%[12]). In the high-risk group with aggressive histomorphological features, micronodular and basosquamous subtypes were the most prevalent (2.1%). Previous studies showed a proportion of micronodular (2.4–6.59%[30,31]) and basosquamous/ meta-atypical subtypes (4.76–5%[12,18]). The infiltrative subtype was 1.9%, which was higher in the previous study at 4.76%.[18] The proportion of sclerosing/morpheaform subtypes observed was 0.4%, consistent with previous studies of 0.5%.[30]

The predominance of nodular BCC is likely due to advancing age, with the hypothesis that this subtype is more associated with chronic cumulative sun exposure.[30] The different distribution patterns of most types of BCC occur in the superficial subtypes. This subtype has a predilection site on the trunk with a more protected character from UV rays.[32]

Analysis of Mixed-type BCC

Mixed histological subtypes of BCC in one lesion showed evolution and phenotypic transformation of BCC.[33] The proportion of mixed BCC in this study was 41.6%, higher than in previous studies 17.8–38.5%.[33] Combination of nodular-superficial, nodular-pigmented, and nodular-infundibulocystic were the non-aggressive mixed subtypes in this study. Our study perceived 19 mixed-type combinations, with the four most common combinations being nodular-infiltrative, nodular-micronodular, infiltrative-sclerosing, and nodular-superficial. These results are consistent with studies that found 31 different combinations, with the most combination subtypes being nodular-infiltrative, superficial-nodular, and nodular-micronodular. The mixed-type in our study was observed mainly in the head, neck, and face are similar to the previous study.[29] Overall, mixed BCC was more common in females than males, 56.8% vs 43.2% (p=0.046).

Mixed BCC has been associated with the histological aggressiveness of tumours. A study show mixed-type BCC can have a component of the aggressive histological subtype, including micronodular, infiltrative, sclerosing/ morpheaform, basosquamous/ meta-atypical, or sarcomatoid/ metaplastic. The proportions of aggressive mixed-type in the previous study ranging from 59.1 to 70%.[33] Our results show that mixed BCC, which has an aggressive histological subtype component was 56.9% vs 43.1%, occurring more in the female than the male population, respectively (p=0.029).

According to the literature, most of the mixed-type BCC components had a nodular subtype.[29] This is comparable to our study (Table 1), resulting in 373 cases of mixed-type BCC, with the nodular component dominating 92.5% of the total mixed-type BCC (345/373 cases). The nodular components are spreading in the mixed-type with two histological subtypes (284/310 cases), mixed-type with three histological subtypes (58/60 cases), and a mixed-type with four histological subtypes (3/3 cases). Infiltrative subtypes were also found to be huge and considered as an aggressive form of tumour.[4,29] The combination pattern between nodular and infiltrative was higher (73.46%) in our study compared to previous studies (31.08%).[29]

Analysis of Histological Variants of BCC

Based on the 2018 WHO classification of skin tumours, nodular subtypes have variants of keratotic, cystic, and adenoid,[4,34] as depicted in Figure 2. We found the results that the most significant variants are adenoid (63.1%), keratotic (34.5%), and cystic (2.4%). These results are similar to previous studies where adenoids and keratotic had a proportion of 66.7% and 33.3%, respectively.[29]

Analysis of Single Subtype versus Mixed Subtype

This study found that the proportion of BCC with a single histological subtype (58.4%) was more than the mixed type (41.6%). Previous studies reported different results in which more mixed-subtype BCC was noticed (54%), while in other countries, the proportion varied between 11–39%.[29] The most common mixed lesion was a mixture of two histological subtypes (34.6%). In the analysis based on the location of tumours, there were significant differences between head, face, and neck regions versus the trunk (p=0.001) and between trunk versus upper limbs (p=0.002). It seems that the distribution of the mixed subtypes is more in areas exposed to UV light. These results are consistent with previous research, which found frequent mixed-types in the facial area.[29]

Study Limitations

Our study was a retrospective cross-sectional study reporting the clinicopathological and histomorphological characteristics of the BCC, which lack of data was inevitable and not bias-free. Limitations also arise because pathological reporting in the first decade was not as comprehensive as the second decade of registry year related to different guidelines used for different periods. This issue has been anticipated by conversing data using the latest WHO guidelines. However, for the first time, we have identified the increasing trend of BCC with many patients and extended periods. Our findings reinforce the urgent need to start taking health policy to reduce BCC incidence by raising awareness of skin cancer among young people.

Conclusion

BCC cases in CMH are increasing every year in the last 20 years. There were differences in the distribution of BCC based on gender, age groups, anatomic location, and histological subtypes.

References

1. Dika E, Scarfì F, Ferracin M, Broseghini E, Marcelli E, Bortolani B, et al. Basal cell carcinoma: A comprehensive review. Int J Mol Sci. 2020;21(15):1–11.
2. Moore MG, Bennett RG. Basal Cell Carcinoma in Asians: A Retrospective Analysis of Ten Patients. J Skin Cancer. 2012;2012:1–5.
3. Bonilla X, Parmentier L, King B, Bezrukov F, Kaya G, Zoete V, et al. Genomic analysis identifies new drivers and progression pathways in skin basal cell carcinoma. Nat Genet. 2016;48(4):398–406.
4. Messina J, Epstein EJ, Kossard S, McKenzie C, Patel R, Patterson J, et al. WHO Classification of Skin Tumors. In: Elder DE, Massi D, Scolyer RA, Willemze R, editors. WHO Classification of Skin Tumors [Internet]. Lyon: International Agency for Research on Cancer (IARC); 2018. p. 26–34.
5. Santos AB de O, Andrade NMM de, Brandão LG, Cernea CR. Which features of advanced head and neck basal cell carcinoma are associated with perineural invasion?. Braz J Otorhinolaryngol. 2017;83(1):94–7.
6. Mackiewicz-Wysocka M, Bowszyc-Dmochowska M, Strzelecka-Weklar D, Dańczak-Pazdrowska A, Adamski Z. Basal cell carcinoma - Diagnosis. Wspolczesna Onkol. 2013;17(4):337–42.
7. McDaniel B, Badri T, Steele RB. Basal Cell Carcinoma. In: StatPearls [Internet]. Treasure Island (FL): StatPearls; 2020. Available from: https://www.ncbi.nlm.nih.gov/books/NBK482439/
8. Wibawa LP, Andardewi MF, Ade Krisanti I, Arisanty R. The epidemiology of skin cancer at Dr. Cipto Mangunkusumo National Central General Hospital from 2014 to 2017. J Gen Dermatology Venereol Indones. 2019;4(1):11–6.
9. Agustina R, Dartanto T, Sitompul R, Susiloretni KA, Suparmi, Achadi EL, et al. Universal health coverage in Indonesia: concept, progress, and challenges. Lancet. 2019;393(10166):75–102.
10. Kharisma DD. Indonesian Health System Performance Assessment: The Association between Health Insurance Expansion with Health Status and Health Care Access. J Perenc Pembang: Indones J Dev Plan. 2020;4(3):312–26.
11. Ciążyńska M, Narbutt J, Woźniacka A, Lesiak A. Trends in basal cell carcinoma incidence rates: a 16-year retrospective study of a population in central Poland. Postep dermatologii i Alergol. 2018;35(1):47–52.
12. Ammasaigoundan V, Shariff VNSA, Ramesh A. Basal cell carcinoma- a prospective clinico epidemiological and pathological study. Int J Res Med Sci. 2017;5(6):2712.
13. Oninla OA, Oninla SO, Ajani AA, Report C. Gender Dermatoses: The Role of Sex Hormones in Skin Diseases. 2017;2(2):1–4.
14. Oblong JE. Comparison of the impact of environmental stress on male and female skin. Br J Dermatol. 2012;166 Suppl:41–4.
15. Stephens PM, Martin B, Ghafari G, Luong J, Nahar VK, Pham L, et al. Skin Cancer Knowledge, Attitudes, and Practices among Chinese Population: A Narrative Review. Dermatol Res Pract. 2018;2018:1-9.
16. Chevalier V, Barbe C, Le Clainche A, Arnoult G, Bernard P, Hibon E, et al. Comparison of anatomical locations of cutaneous melanoma in men and women: a population-based study in France. Br J Dermatol. 2014;171(3):595–601.
17. Glithro S, Newell D, Burrows L, Hunnisett A, Cunliffe C. Public health engagement: detection of suspicious skin lesions, screening and referral behaviour of UK based chiropractors. Chiropr Man Therap. 2015;23:5.
18. Gundalli S, Kolekar R, Kolekar A, Nandurkar V, Pai K, Nandurkar S. Study of basal cel carcinoma and its histopathological variants. Our Dermatology Online. 2015;6:399–403.
19. Kuvat SV, Gücin Z, Keklik B, Özyalvaçlı G, Başaran K. Basal Cell Carcinoma in a Child. J Skin Cancer. 2011;2011:1–3.
20. Pellegrini C, Maturo MG, Di Nardo L, Ciciarelli V, Gutiérrez García-Rodrigo C, Fargnoli MC. Understanding the molecular genetics of basal cell carcinoma. Int J Mol Sci. 2017;18:1-16
21. Sreekantaswamy S, Endo J, Chen A, Butler D, Morrison L, Linos E. Aging and the treatment of basal cell carcinoma. Clin Dermatol. 2019;37:373–8.
22. Sgonc R, Gruber J. Age-related aspects of cutaneous wound healing: a mini-review. Gerontology. 2013;59:159–64.
23. Gould L, Abadir P, Brem H, Carter M, Conner-Kerr T, Davidson J, et al. Chronic wound repair and healing in older adults: current status and future research. Vol. 63, Journal of the American Geriatrics Society. 2015. p. 427–38.
24. Subramaniam P, Olsen CM, Thompson BS, Whiteman DC, Neale RE. Anatomical distributions of basal cell carcinoma and squamous cell carcinoma in a population-based study in Queensland, Australia. JAMA Dermatology. 2017;153:175–82.
25. Bauer A, Haufe E, Heinrich L, Seidler A, Schulze HJ, Elsner P, et al. Basal cell carcinoma risk and solar UV exposure in occupationally relevant anatomic sites: Do histological subtype, tumor localization and Fitzpatrick phototype play a role? A population-based case-control study. J Occup Med Toxicol. 2020;15:1–13.
26. Tan ST, Ghaznawie M, Heenan PJ, Dosan R. Basal cell carcinoma arises from interfollicular layer of epidermis. J Oncol. 2018;2018:1-5

27. Grachtchouk M, Pero J, Yang SH, Ermilov AN, Michael LE, Wang A, et al. Basal cell carcinomas in mice arise from hair follicle stem cells and multiple epithelial progenitor populations. J Clin Invest. 2011;121:1768–81.
28. Farage MA, Miller KW, Berardesca E, Maibach HI, Neuhaus IM. Neoplastic Skin Lesions in the Elderly Patient. In: Farage MA, Miller KW, Maibach HI, editors. Textbook of Aging Skin. Berlin, Heidelberg: Springer-Verlag; 2017. p. 803–54.
29. Ghanadan A, Abbasi A, Rabet M, Abdollahi P, Abbasi MA. Characteristics of mixed type basal cell carcinoma in comparison to other BCC subtypes. Indian J Dermatol. 2014;59:56–9.
30. Hakverdi S, Balci DD, Dogramaci CA, Toprak S, Yaldiz M. Retrospective analysis of basal cell carcinoma. Indian J Dermatol Venereol Leprol. 2011;77:261–6.
31. Li CL, Chen YC, Yang KC, Chen LW. Different histopathologic profiles and outcomes between sun-exposed BCC and non-sun-exposed BCC. Sci Rep. 2020;10:1–8.
32. Verkouteren JAC, Smedinga H, Steyerberg EW, Hofman A, Nijsten T. Predicting the Risk of a Second Basal Cell Carcinoma. J Invest Dermatol. 2015;135:2649–56.
33. Bartoš V, Kullová M. Basal cell carcinoma of the skin with mixed histomorphology: acomparative study. Cesk Patol. 2016;52:222–6.
34. Saldanha P, Shanthala PR, Upadhaya K. Cutaneous basal cell carcinoma: A morphological spectrum. Arch Med Heal Sci. 2015;3:24–8.