Int J Clin Exp Pathol 2015;8(11):15448-15453
www.ijcep.com /ISSN:1936-2625/IJCEP0016294

Original Article

Presence of ulceration, but not high risk zone location, correlates with unfavorable histopathological subtype in facial basal cell carcinoma

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Received September 16, 2015; Accepted October 24, 2015; Epub November 1, 2015; Published November 15, 2015

Abstract: Background: Basal cell carcinoma (BCC) has been stratified into low- and high-risk according to their propensity for local recurrence. Risk factors for recurrence include histologic subtype, anatomic location (i.e. H-zone of the face), horizontal diameter, and patient health status. Objective: To assess if favorable (superficial, nodular, adenoid and trabecular) and unfavorable (infiltrative, morpheaform, micronodular, metatypical, basosquamous) histopathological subtypes of BCC do correlate with anatomic location on the face (facial high risk versus non-high risk zones). Methods: Histopathological specimens of all facial BCCs, which were histopathologically diagnosed in the Pathology Department of Şişli Etfal Training Hospital, between the years 2008 and 2014 were retrospectively studied. Histopathological aggressive and non-aggressive subtypes as well as the presence of ulceration were correlated with facial high-risk (i.e. H-zone) and low risk anatomical locations. Results: Of 184 BCC of unfavorable subtypes, 101 cases were identified in facial high-risk anatomical region (H-zone) compared to 83 cases at non H-zone (P = 0.553). On the other hand the ulceration rate was significantly higher for unfavorable histological subtypes than in the favorable histopathological subtype group (P = 0.042). Regarding anatomic site, ulceration frequency was not significantly different for the H-versus non-high risk zones (P = 0.335). Conclusions: A correlation of unfavorable histopathological subtype of BCC and high-risk anatomical location (i.e. H-zone) was not observed in our study. Our results however confirmed a significantly higher rate of ulceration in the subgroup of aggressive histopathological BCC forms. Thus, factors other than histopathological subtype (such as narrow excision margin related to difficult surgical technique in H-zone, microcirculation, vasculature and host inflammatory response) may be responsible for the high recurrence rate in facial H-zone-located BCCs.

Keywords: Ulcer, facial BCC

Introduction

Basal cell carcinoma (BCC) is the most common malignancy worldwide among Caucasians and its incidence and prevalence is increasing. Recent studies suggest that BCC is not a single disease entity. It has been hypothesized that BCC occurring at certain body sites or that BCC of a particular histopathological subtype may be associated with certain clinical behaviour and may even have a different aetiology [1-3].

Specific locations on the face (i.e. nasolabial fold, nasal, orbital and auricular areas) have been described as high-risk zone or H-zone for BCC as they are associated with a higher risk of tumour recurrence compared with the non H-zone. While some histopathological subtypes of BCC such as superficial, nodular, adenoid and trabecular are considered favorable or less aggressive, certain forms such as infiltrative, morpheaform, micronodular, metatypical and basosquamous are regarded as aggressive or less favorable in terms of tumor recurrence. To our knowledge, little is known regarding the link between the histopathological subtypes of BCC and facial risk zones locations. In this study, we investigated the correlation of aggressive and favorable BCC histopathological subtypes to tumor location in facial H-zone and non H-zones.

Table 1. Patient demographics in 408 facial BCC

	N	Average age, year	Facial H-zone	Facial non-H zone
Men	234	70.01 ± 11.79	124	110
Women	174	71.99 ± 12.51	98	76
Total	408	70.85 ± 12.13	222	186

Table 2. Correlation of histopathological subtypes (HS) and ulceration with facial anatomical zones

	High-risk HS	Low-risk HS	Ulcerated	Non-ulcerated
H-zone	101	116	85	132
Non H-zone	83	98	66	125

HS: Histopathological subtype.

Table 3. Various histopathological subtypes of BCC, identified in biopsy specimens

Subtype	N
Nodular	288
Infiltrative	113
Adenoid	37
Pigmented	36
Micronodular	22
Superficial	19
Metatypical	17
Morpheaform	14
Clear cell	11
Keratotic	8
Trabecular	5
Keloidal	5
Basosquamous	5
Pleomorphic	1

Material and methods

Histopathological specimens of all BCCs diagnosed in the Pathology Department of Şişli Etfal Training Hospital, between the years 2008 and 2014 were retrospectively studied. The exclusion criteria included extrafacial location and unspecified localization within facial anatomical zones. While nasolabial fold, nasal, orbital and auricular areas are defined as high-risk (H-zone) anatomical region, other areas were recorded as non H-zone. Patient data including gender and age at diagnosis were recorded as well.

Histopathological specimens were reviewed to ascertain subtypes of BCC and presence of ulceration. While infiltrative, morpheaform, micronodular, metatypical, and basosquamous subtypes have been classified as unfavorable (high risk) histopathological group, other subtypes such as nodular, superficial, adenoid and, trabecular forms were regarded as favorable (low risk) group. Since BCCs with mixed histology should be treated according to their most aggressive histopathological subtype, we evaluated the mixed histology including any high-risk pattern into the high-risk histopathological subtype [4].

Data from microscopical analysis were expressed as mean ± standard error. The logistic regression and kira test was used to determine the statistical significance between high-risk histopathological subtypes and anatomic location and ulceration. The statistical analysis was performed by using SPSS statistical software. *P* values of less than 0.05 were considered statistically significant.

Results

A total of 408 specimens obtained in 346 patients met the inclusion criteria for this study. Patient's demographic data are shown in **Table 1**. The median age at time of diagnosis was 70.85 ± 12.13, 70.01 ± 11.79 years for men (n = 234) and 71.99 ± 12.51 years for women (n = 174). The number of specimens restricted to facial high risk location (H-zone) was 124 for men (53%) and 98 for women (56%).

While a total of 101 aggressive BCC subtype were identified in facial high-risk anatomical region (H-zone), 83 cases of the unfavorable histopathological subtypes were located within the non H-zone. The correlation of aggressive histopathological subtype with facial H-zone did not reach statistical significance (P = 0.553). On the other hand the ulceration rate was higher in the high-risk histopathological subtype than that of low-risk histopathological subtype (P = 0.042) (**Table 2**). Likewise, presence of ulceration did showed no correlation with facial zone locations (observed in 85 specimens from H-zone compared with 66 specimen in non H-zone; P = 0.335). Correlation of histopathological subtype and gender was also statistically not significant (P = 0.368).

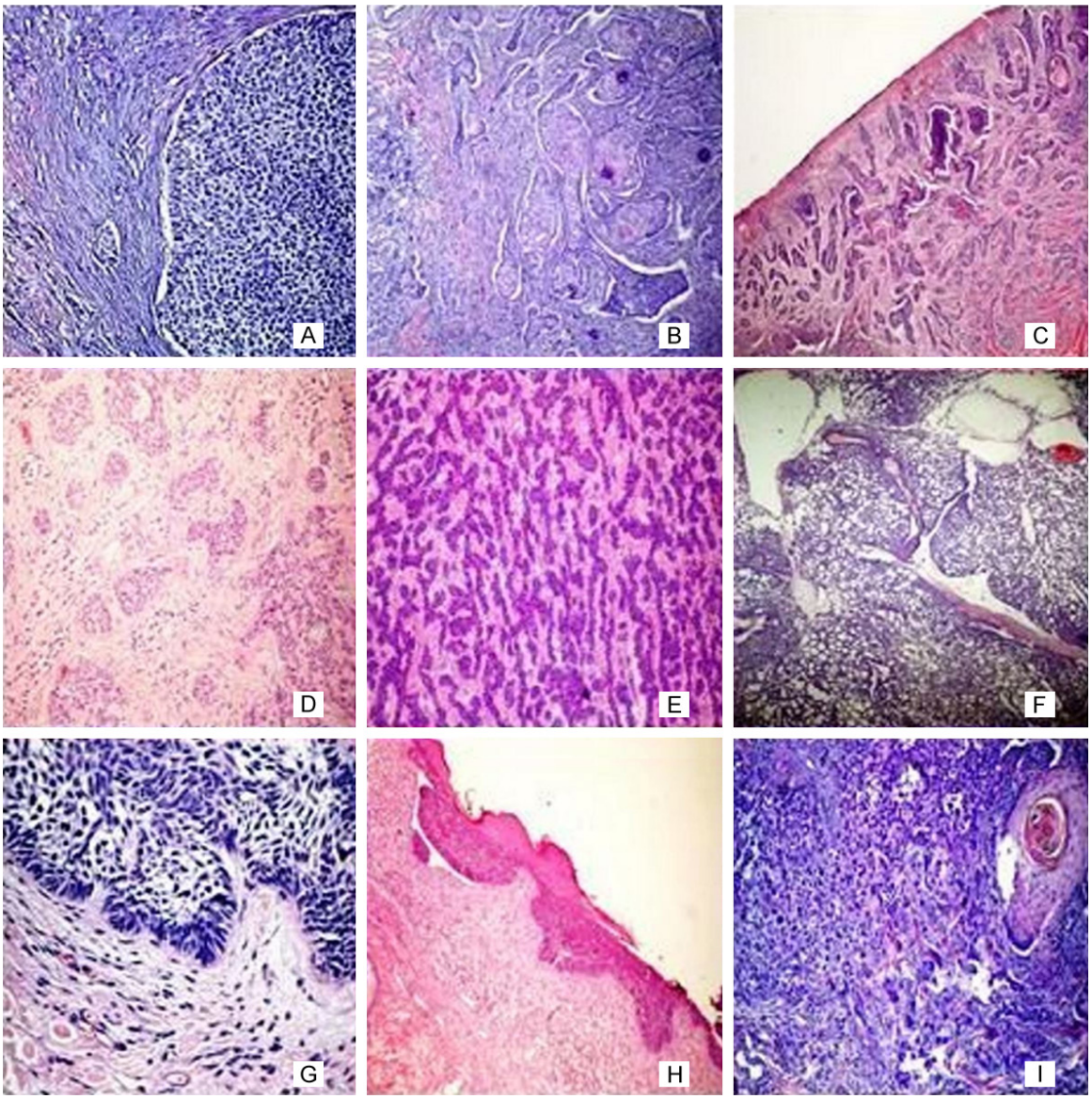

Figure 1. Various histopathological subtypes were identified such as (A) Nodular; (B) Infiltrative; (C) Morpheaform; (D) Micronodular; (E) Trabecular; (F) Adenoid; (G) Clear Cell; (H) Superficial; (I) Pleomorphic Bccs.

Detailed histopathological examination for identifying histopathological subtypes revealed various forms as nodular BCC being the most common subtype (**Table 3**; **Figure 1**). We observed BCC with mixed histology in 205 out of 408 specimens (50.25%) with the combination of nodular and infiltrative BCC as the most common associated subtypes.

Discussion

BCC is the most common cancer in Caucasians, occurring in one of every five to six individuals in a lifetime, and the incidence is still rising every year. BCC affects mainly fair-skinned adults over 40 years old. The median age at time of diagnosis was 70.01 ± 11.79 years formen and 71.99 ± 12.51 years forwomen in our study. Exposure to ultraviolet light, especially of the type B spectrum (UV-B), is the major environmental factor in the pathogenesis of BCC because it induces mutation of tumour suppressor genes [5].

The head and neck region appears to be the most common anatomical site for BCC. In a review of 239 BCC patients, in 179 (74.9%) patients the tumour was located in the head

and neck, followed by the trunk (10.55), upper (9.6%) and lower (4.2%) limbs [5]. The same study revealed that the nasal region was the most affected location on the face, which is also consistent with our study. BCCs have been stratified as low-risk or high-risk according to their propensity for local recurrence. Risk factors that predict local tumor recurrence include histologic subtype, anatomic location (i.e. H-zone of the face), horizontal diameter, and patient health status [6]. In a study investigating the difference in anatomic location and histopathological subtypes of BCC in adults younger than 60 or ≥90, subtype was independently associated with anatomical site (i.e. superficial BCC more common on truncal location) but not with age or sex [7]. However, correlation of histopathological subtypes with facial high-risk zones, as in our study has not been described in this previous study. In the study by Dixon et al., age, distance to resection margins, contour of invading edge, shape of cell groups, growth pattern, degree of peripheral palisading, and nuclear pleomorphism correlated with tumour recurrence, whereas depth of invasion, degree of inflammation, actinic change, tumour necrosis, nuclear hyperchromasia, mitosis, amount of melanin, amount of amyloid, and size of cell groups did not [8].

Welsch et al. highlighted the correlation of various histopathological subtypes with the depth of invasion in 100 BCC biopsy specimens and found that micronodular tumours had the greatest mean depth, followed by infiltrative, nodular, and superficial subtypes. In another study correlating the depth of tumour invasion with histopathological subtypes of BCC, the Clark level was comparable between micronodular and infiltrative BCC, while nodular BCC showed a more superficial level compared with both groups [9].

It was a surprising finding that we did not observe correlation between tumor location within the high risk anatomical zones (i.e. H-zone) with high risk (adverse) histopathological subtypes, as would be expected. To our knowledge, there have been no previous studies addressing this aspect in BCC. However, ulceration rate was statistically significant in the high-risk histopathological subtype, compared to the low risk group, but correlation of ulceration with anatomical high-risk zone (i.e. H-zone) was not detected. We hypothesize that other factors other than the histopathological subtype (such as microcirculation, vasculature and host inflammatory response) might be responsible for the high recurrence rate in facial H-zone BCC. In a recent article highlighting the host inflammatory response in various histopathological subtypes of BCC, the mean inflammatory infiltrate was found to be significantly lower for high-risk subtype of BCC, but the overall frequency of dense infiltrates and/or absence of infiltrates were not statistically different [10]. However, consistent differences between low- and high-risk BCC subtypes for molecular biomarkers of tumor progression have not been demonstrated such as gains in *TP53* mutations and expression, loss of E-cadherin expression, loss of bcl-2 expression, or nuclear location of α-catenin expression. Instead of distinct molecular aberrations driving BCC progression, development of a permissive tissue environment and/or escape from immune surveillance may play more significant roles in the transformation of indolent to aggressive BCC phenotypes [10].

Jarell et al. investigated the subtype of BCCs in 471 lesions located on the ear and revealed that the majority of auricular BCCs are of a more aggressive phenotype (i.e. morpheaform, micronodular, infiltrative, morpheaform, basosquamous and metatypical) [1]. In our current study, we did not find any such correlation between the aggressive BCC subtypes with facial H-zone region.

Another study investigating the prognosis of 216 BCC lesions on the face, local recurrences were identified predominantly within the first year after ablative surgery [11]. Relative to the small number of sclerodermiform BCC (i.e. 10% of the patients) this subtype was the most frequent tumour that developed local recurrences. A study highlighting the recurrence rates in 720 BCC lesions terated with Mohs' micrographic surgery, prognostic factors for recurrence were found to be the aggressive histopathological subtype, recurrent BCC and more than four Mohs' stages [12]. The treatment approach of BCC may also differ based on location and histopathological subtype. Whereas according to the Dutch guidelines, low risk superficial and nodular BCCs on the trunk <10 mm should be excised with a margin of 3 mm,

high risk BCCs located at the H-zone, infiltrative or micronodular subtypes, recurrences or BCCs >10 mm should be excised with a margin of 5 mm [13].

BCC with mixed histology is a variant which demonstrates two or more pathologic patterns of BCC within the same tumor, such as superficial BCC in the papillary dermis and infiltrative BCC in the deeper reticular dermis. The incidence of BCC with mixed histology varied between 11% and 41% in various studies. In a recent research, this morphology was detected most commonly in the nose, followed by the ear, cheek, and the scalp [14]. We observed BCC with mixed histology in 205 out of 408 specimens with the combination of nodular and infiltrative BCC as the most common associated subtypes. In a study regarding the characteristics of mixed type BCC compared with other subtypes in 825 patients, anatomic distribution of mixed type was most common on the facial region and the most frequent combined subtypes were nodular-infiltrative, followed by nodular-micronodular and nodular-adenoid forms [15]. An interesting feature was the mean diameter of the mixed type, which was larger than that of the non-mixed type.

Pigmented BCC is contains melanin pigment due to melanocytic colonization of the tumour. A recent study investigating the subtypes of pigmented BCCs, nodular/nodulocystic forms constituted the most common subtypes with a percentage of 79.1%, followed by micronodular (16.7%) and adenoid subtypes (4.2%) [16]. Our study revealed melanin pigmentation in 36 out of 408 BCC lesions, with a decreasing order in nodular, adenoid, infiltratve, keratotic, metatypical, basosquamous and superficial subtypes.

In summary, this study did not show any correlation between aggressive histopathological subtypes of BCC and location within high-risk anatomical facial zones (i.e. H-zone). The ulceration rate was significantly associated with aggressive histopathological subtypes. Other factors (other than H-zone location, e.g. narrow excision margin related to difficult surgical technique in H-zone, microcirculation, vasculature and host inflammatory response) are likely responsible for the high recurrence rate observed in facial H-zone located BCCs.

Disclosure of conflict of interest

None.

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