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Determination of the Frequency of Scalp Basal Cell Carcinoma Subtypes Based on Histopathology and Other Related Variables and its Comparison between Patients with and without Chronic Radio-Dermatitis

Farideh Jowkar[*], MD, Fateme Sari Aslani[**], MD, Leila Samipour[***], MD, Fateme Mohebpour[****], MD, Maryam Hadibarhaghtalab[****♦], MD, Negin Fazelzadeh Haghighi[****], MD, Kaveh Taghipour[****], MD

[*]*Department of Dermatology, Molecular Dermatology Research Center, Shiraz University of Medical Sciences, Shiraz, Iran*

[**]*Department of Pathology, Shiraz University of Medical Science, Shiraz, Iran*

[***]*Student Research Committee, Shiraz University of Medical Sciences, Shiraz, Iran*

[***]*Molecular Dermatology Research Center, Shiraz University of Medical Sciences, Shiraz, Iran*

♦Corresponding Author
Maryam Hadibarhaghtalab, MD
1st Floor, Faghihi Hospital, Department of Dermatology,
Molecular Dermatology Research Center,
Shiraz University of Medical Sciences, Shiraz, Iran
Email: Maryam_hadibarhaghtalab@yahoo.com

Abstract

Background: Basal cell carcinoma (BCC) is the most prevalent type of skin cancer in Iran. The determination of subtype of BCC plays an essential role in the diagnosis, recurrence rate, and outcome of patients. The present study was conducted to investigate the relationship between histopathologic subtypes and demographic data, history of radiation exposure, and past medical history in the Iranian population.

Method: This retrospective cross-sectional study evaluated the patients with BCC referred to Faghihi hospital Shiraz Iran from 2012 to 2017. We examined all the patients with definite histologically diagnosed scalp BCC. The prevalence of different subtypes and its association with other variables were compared between the patients with and without chronic radio-dermatitis. A *P*-value of less than 0.05 was considered to be significant.

Results: A total number of 161 patients with a cumulative of 439 BCC lesions participated in the study. The mean age of the patients was 64.2 (± 12.38) years old. Among the patients, 113 (70.2%) were men and 48 (29.8%) were women. The total prevalence of macro-nodular, micro-nodular, and mixed aggressive was 70.2%, 49.1%, and 41.6%, respectively. Multivariate logistic regression analysis showed that excessive sun exposure increased the chance of developing micronodular and mixed aggressive lesions by 3.21 (P=0.006) and 4.88 (P<0.001) times, respectively.

Conclusion: BCC was more aggressive in chronic radio-dermatitis patients than that in non-radio-dermatitis patients. Moreover, it was significantly different regarding age, gender, appearance, and job distribution compared to non-radio-dermatitis patients. Thus, we could suggest that BCC in chronic radio-dermatitis should be regarded as a high-risk disease unless proven otherwise.

Keywords: Carcinoma, Basal cell, Radiation injuries, Dermatitis, Radiodermatitis

Introduction

Basal cell carcinoma (BCC) is the most common skin cancer in the Iranian population.[1-3] The incidence of non-melanoma skin cancer in Iran is estimated to be 10-15 cases per 100,000. BCC accounts for 75% of all skin cancers.[4] Skin cancer incidence has been steadily increasing by 7.22% per year in Iran.[5] Bcc is usually slow-growing and rarely metastatic. Despite its low mortality rate, local tissue destruction could lead to disfigurement and in turn, a significant emotional burden to patients and enormous costs for healthcare systems.[6]

Chronic radio-dermatitis is the skin and soft tissues' delayed inflammatory response to radiation exposure. In addition to concurring environmental and genetic risk factors, chronic Ultraviolet (U.V.) exposure is known to be the most common risk factor for the development of BCC.[7, 8] The diminishing U.V. exposure is one of the best targets for primary prevention. However, the relationship between the pattern of exposure and histology is ambiguous.[9] BCC arising due to radiation is at a higher risk of recurrence or metastasis and more challenging to treat.[10]

Despite common molecular pathways, histopathologic, and gross morphologic, heterogeneity of BCCs are striking features.[11] The histological subtype of BCC affects diagnosis, recurrence rate, choosing the best treatment strategy, and outcome of the patients. The clinical and histopathological characteristics of BCC have been relatively well studied in other populations, yet not in Iran.

This study aimed to determine the prevalence of different histopathologic subtypes and its relationship with demographic data, history of radiation exposure, past medical history of tinea capitis, and malignancies other than BCC.

Method

This retrospective cross-sectional study was conducted in Faghihi hospital, a referral hospital for dermatological oncology affiliated to Shiraz University of Medical Sciences, south of Iran, from March 2012 to February 2017. We examined all the patients who had a histologically proven scalp BCC. In this work, BCC was diagnosed according to the standard criteria mentioned in previous studies.

Patients and tumor characteristics were collected from patients' medical records and pathology reports via a data-gathering form. The patients' data included demographic data, gender, age at the time of diagnosis, and therapy. Tumor characteristics were histologic subtypes, including nodular, micro-nodular, superficial, infiltrating, fibro-epithelial, keratotic, basosquamous, pigmented, infundibulocystic, adenoid, cystic, sclerosing, metatypical, and mixed. These subtypes were defined according to Weedon 2002 categorization.[12]

A telephone survey was conducted to assess any history of radiation exposure, the existence of hair at the site of lesion, occupational and recreational sun exposure, previous history of alopecia at a young age (specific history of tinea capitis X-ray epilation treatment), chemotherapy, radiotherapy, and any other malignancies.

The pathology slides sent from other centers for confirmation were excluded. Moreover, the subjects with diseases susceptible to skin cancer, such as xeroderma pigmentosum and basal cell nevus syndrome, those unavailable for the interview or with incomplete charts, those without a clear history of radiation exposure, and the patients who refused to take part in the study were excluded.

The research protocol and questionnaire used in this study were reviewed and approved by the Ethics Committee of the Shiraz University of Medical Sciences (No. 14731). The study was conducted according

to the principles of the declaration of Helsinki. Informed consent was taken orally to use the data in research purposes anonymously.

The patients were divided into two groups based on their history of chronic radiation exposure. The prevalence of different subtypes and other variables were compared between these two groups. Descriptive statistics for categorical and continuous variables were reported as frequency (percent) and mean (S.D.), respectively. To determine the significance of the association of clinical presentation, demographic and histologic subtypes, independent T-test, logistic regression, multivariate regression, chi-square, or Fisher exact test were used as appropriate. SPSS software version 23.0 (IBM SPSS Inc., Chicago, IL, USA) was utilized for all the statistical analyses. A *P*-value of less than 0.05 was considered to be statistically significant.

Result

A total of 410 patients with histologically confirmed BCCs were diagnosed and only 161 cases were eligible for the study. Out of these 161 patients, 439 BCC lesions were confirmed. Among the patients, 113 (70.2%) were men and 48 (29.8%) were women. The mean age was 64.2 (± 12.38) years old (66.3 ± 11.69 years old for men and 59.4±12.76 years old for women). Men's age was significantly higher than that of women (*P*=0.001). 5% of the patients were younger than 40 years old and 95% older than the age of 40.

Concerning gender, infiltrative lesions were more common in male (*P*= 0.013 O.R= 4.48).

Among various subtypes, macronodular lesions with 70.2 % occurrence were the most prevalent. Afterwards, mixed aggressive (49.1%) and micronodular (41.6%) followed, respectively (Table 1).

Among these 161 patients, 74 were diagnosed with chronic radio-dermatitis (three undergoing radiotherapy, 68 tinea capitis patients were exposed to radiation, and 69 with a history of radiation exposure in childhood).

In multivariate regression, micronodular (*P* < 0.001, odds ratio (OR) = 9.5) and mixed aggressive (*P* < 0.001, OR = 9.7) lesions were significantly more prevalent among chronic radio-dermatitis patients. On the other hand mixed non-aggressive (*P* = 0.023, OR = 2.8) lesions were more prevalent in non-radio-dermatitis patients. Due to the small number of infundibulocystic, basosquamous, sclerotic, morphoeic, and keratotic lesions, there were no statistical tests feasible, which were excluded from the analysis. Moreover, there were not any statistically significant differences among the demographical items, such as age, number of bcc lesions in radiodematitis group versus non radio dermatitis (*P*>0.005) (Table 2).

Excessive sun exposure increased chances of developing micro nodular and mixed aggressive lesions lesion by 3.2 (*P*=0.006) and 4.9 (*P*<0.001) times, respectively. Mixed non-aggressive lesions were higher in the patients with low sun exposure (*P*=0.035) (Table 3).

In those with past medical history of tinea capitis, macro nodular (*P*-value= 0.031, OR= 2.2), micro nodular (*P*<0.001, OR= 3.5), and mixed (*P*<0.001, OR= 3.4) lesions were considerably more common.

Working outdoors, unlike working indoors, increased micro nodular (*P*=0.008, OR=2.6) and mixed non-aggressive (*P*<0.001, OR= 4.1) lesions. Those who worked indoors however developed further mixed non-aggressive lesions (*P*=0.006, OR= 1.3).

History of other malignancies were associated with less micro nodular (*P*=0.025, OR= 10.6) and more infiltrative

(*P*=0.017, OR= 4.0) and basosquamous (*P*=0.011, OR= 24.3) subtypes (Table 4).
Past medical history of childhood radiation was found to be linked with further macro-nodular (*P*=0.024, OR= 2.3), micro nodular (*P*<0.001, OR= 3.7), and mixed aggressive (*P*<0.001, OR= 3.6) lesions.

Discussion

The current research is the first investigation in Iran to report subtypes specific incidence rate of BCC and their relationship with other related variables in patients with and without a history of chronic radio-dermatitis.
In our study, the male to female ratio was 2.35. Concerning sex, infiltrative lesions were higher in males. In most studies, men are the predominant population.[5, 13, 14] In a study conducted in Jordan, scalp BCC affected males more than females.[15] This similar finding may be on account of our similar population in the Middle East.
Previous studies have shown that 95% of patients with BCC are between 40 and 79 years of age. BCC is quite rare under the age of 40 and is somewhat sporadic in adolescents.[16-18] This is established in our study, with only a few patients below the age of 25 and more than 95% of patients aged above 40 years old.[19]
Macro-nodular, mixed-aggressive, and micro-nodular were the most common lesions, respectively. According to Arits et al., the most common subtype is nodular; meanwhile, superficial and infiltrative lesions are less frequent.[20, 21] This finding could be due to the difference in our study population.
Excessive sun exposure increased the chances of developing micronodular and mixed aggressive lesions. Mixed non-aggressive lesions were higher in the patients with low sun exposure. Razi et al. showed that excessive sun exposure increases the incidence of skin cancer by 4.8 times.[5] UVB radiation harms DNA and its repair system and alters the immune system bringing about progressive genetic changes and the development of a neoplasm. UV-induced mutations in the TP53 tumor-suppressor gene have been reported in about half of BCC patients. The mutations that initiate the Hedgehog intercellular signaling pathway genes, including PTCH, Sonic hedgehog, and Smoothened, play a significant role in cutaneous neoplasm. Furthermore, Boaventura P et al. indicated that D310 D-Loop mutation rate in BCC could be associated with a higher irradiation dose, suggesting the role of radiation in the frequency of this mutation.[22]
Working outdoors, unlike working indoors, increased micronodular and mixed aggressive lesions. Those who work indoors, however, developed further mixed non-aggressive lesions. A meta-analysis in 2011 implied that BCC in UV-exposed workers increases by 40%.[23] Pelucchi et al. reported that occupational U.V. exposure is correlated with more nodular subtype with an O.R of 1.53.[24] This could be due to the fact that outdoor workers usually have more U.V. exposure (both occupational and leisure) and less sunscreen use and health knowledge. This leads to higher sun exposure, more photodamage, and an amplified possibility of developing skin cancers.
Past medical history of childhood radiation, mostly as a treatment for tinea capitis, is linked with more macro-nodular, micronodular, and mixed aggressive lesions. Pelucchi et al. found that a personal history of radiotherapy multiplies the chance of nodular and superficial subtypes 2.57 and 2.2 times, respectively.[24]
Micro nodular and mixed aggressive lesions were significantly higher among chronic radio-dermatitis patients. On the other hand, mixed non-aggressive lesions were more prevalent in non-radio-dermatitis patients. A study conducted in 2008 showed the most

prevalent subtypes among radiation-induced BCC to be macronodular, pigmented, and micronodular, respectively.[25] Oshinsky et al. in 2011 showed that nodular, superficial, infiltrative, and basosquamous lesion is the most prevalent.[23] In a study on radiation-induced BCC in 2018, the most prevalent pathologies were nodular, superficial, micronodular, and mixed.[26]

We acknowledge several limitations of our study, including its retrospective nature and the inability to assess the association between the outcomes and patients' skin types and phenotypes. Another limitation of this study was that U.V. exposure was not measured quantitatively, but only subjectively and qualitatively.

Future longitudinal multicenter prospective studies of BCC patients, including skin types and phenotypes and quantitatively measured U.V. exposure, can provide unbiased estimates of prevalence and identify patients at risk for more aggressive subtypes of BCC.

Conclusion

Chronic radio-dermatitis could lead to more aggressive subtypes of BCC. These subtypes can vary widely based on age, gender, appearance, and job distribution. Thus, in the setting of chronic radio-dermatitis, any BCC should be considered as high-risk unless proven otherwise. Practically, these outcomes imply that ultraviolet radiation exposure should be downgraded. Avoidance of midday sun exposure, protective outfits, and sunscreens could be suggested.

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Conflicts of Interest

None declared.

References

1. Amoori N, Mirzaei M, Cheraghi M. Incidence of cancers in Kuzestan province of iran: trend from 2004 to 2008. *Asian Pac J Cancer Prev.* 2014;15(19):8345-9. doi: 10.7314/apjcp.2014.15.19.8345.
2. Vakili M, Pirdehghan A, Adimi M, Sadeghian M, Akhondi M. Epidemiology and trend of cancer in Yazd, a central province of Iran, 2005-2009. JRHS. 2014;14(3):210-3.
3. Keyghobadi N, Rafiemanesh H, Mohammadian-Hafshejani A, Enayatrad M, Salehiniya H. Epidemiology and trend of cancers in the province of Kerman: southeast of Iran. Asian Pac J Cancer Prev. 2015;16(4):1409-13. doi: 10.7314/APJCP.2015.16.4.1409
4. Zargari O. Radiation-induced basal cell carcinoma. Dermatol Pract Concept. 2015;5(2):109-12. doi: 10.5826/dpc.0502a22.
5. Razi S, Enayatrad M, Mohammadian-Hafshejani A, Salehiniya H, Fathali-Loy-Dizaji M, Soltani S. The epidemiology of skin cancer and its trend in Iran. IJPM. 2015;6:64. doi: 10.4103/2008-7802.161074.
6. Lomas A, Leonardi-Bee J, Bath-Hextall F. A systematic review of worldwide incidence of nonmelanoma skin cancer. Br J Dermatol. 2012;166(5):1069-80. doi: 10.1111/j.1365-2133.2012.10830.x.
7. Feller L, Khammissa R, Kramer B, Altini M, Lemmer J. Basal cell carcinoma, squamous cell carcinoma and melanoma of the head and face. Head Face Med. 2016;12(1):11. doi: 10.1186/s13005-016-0106-0.
8. Kim Y, He YY. Ultraviolet radiation-induced non-melanoma skin cancer: Regulation of DNA damage repair and inflammation. Genes Dis. 2014;1(2):188-98. doi: 10.1016/j.gendis.2014.08.005.
9. Epstein EH. Basal cell carcinomas: attack of the hedgehog. Nat. Rev. Cancer. 2008;8(10):743. doi: 10.1038/nrc2503.
10. Hassanpour SE, Kalantar-Hormozi A, Motamed S, Moosavizadeh SM, Shahverdiani R. Basal cell carcinoma of scalp in patients with history of childhood therapeutic radiation: a retrospective study and comparison to nonirradiated patients. Ann. Plast. Surg.. 2006;57(5):509-12. doi: 10.1097/01.sap.0000229002.09605.5d.

11. Raasch B, Buettner P, Garbe C. Basal cell carcinoma: histological classification and body-site distribution. Br. J. Dermatol. 2006;155(2):401-7. doi: 10.1111/j.1365-2133.2006.07234.x.
12. Weedon D. Tumors of the epidermis. Skin pathology. 2002:753-802.
13. Razi S, Rafiemanesh H, Ghoncheh M, Khani Y, Salehiniya H. Changing trends of types of skin cancer in Iran. Asian Pac J Cancer Prev. 2015;16(12):4955-8. DOI: 10.7314/APJCP.2015.16.12.4955.
14. Boaventura P, Oliveira R, Pereira D, Soares P, Teixeira-Gomes J. Head and neck basal cell carcinoma prevalence in individuals submitted to childhood X-ray epilation for tinea capitis treatment. Eur J Dermatol. 2012;22(2):225-30. doi:10.1684/ejd.2012.1670.
15. Al-Qarqaz F, Marji M, Bodoor K, Almomani R, Al Gargaz W, Alshiyab D, et al. Clinical and Demographic Features of Basal Cell Carcinoma in North Jordan. J. skin cancer. 2018;2018:5. doi: 10.1155/2018/2624054.
16. Lesiak A, Slowik-Rylska M, Rogowski-Tylman M, Sysa-Jedrzejowska A, Norval M, Narbutt J. Risk factors in Central Poland for the development of superficial and nodular basal cell carcinomas. Arch Med Sci.. 2010;6(2):270-5. doi: 10.5114/aoms.2010.13907.
17. Deja M, Teresiak E, Buczynska-Górna M, Karas A, Jenerowicz D. Analysis of the appearance of different histological types of basal cell carcinoma, localization of the lesions, the age and sex of patients. Postepy Dermatol Alergol. 2004;21(5):231.
18. Gursan N. Bazal hucreli karsinomlarin klinik ve histopatolojik degerlendirilmesi. Turk J Dermatopathol. 2000;9:23-8.
19. 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. Postepy Dermatol Alergol. 2018;35(1):47-52. doi: 10.5114/ada.2018.73164.
20. Arits A, Schlangen M, Nelemans P, Kelleners-Smeets N. Trends in the incidence of basal cell carcinoma by histopathological subtype. J. Eur. Acad. Dermatol. Venereol.. 2011;25(5):565-9. doi:10.1111/j.1468-3083.2010.03839.x.
21. Scrivener Y, Grosshans E, Cribier B. Variations of basal cell carcinomas according to gender, age, location and histopathological subtype. Br. J. Dermatol. 2002;147(1):41-7. doi: 10.1046/j.1365-2133.2002.04804.x.
22. Boaventura P, Pereira D, Mendes A, Batista R, da Silva AF, Guimarães I, et al. Mitochondrial D310 D-Loop instability and histological subtypes in radiation-induced cutaneous basal cell carcinomas. J. Dermatol. Sci. 2014;73(1):31-9. doi: 10.1016/j.jdermsci.2013.09.002.
23. Bauer A, Diepgen T, Schmitt J. Is occupational solar ultraviolet irradiation a relevant risk factor for basal cell carcinoma? A systematic review and meta-analysis of the epidemiological literature. Br. J. Dermato. 2011;165(3):612-25. doi: 10.1111/j.1365-2133.2011.10425.x
24. Pelucchi C, Di Landro A, Naldi L, La Vecchia C. Risk factors for histological types and anatomic sites of cutaneous basal-cell carcinoma: an italian case–control study. JID. 2007;127(4):935-44. doi: 10.1038/sj.jid.5700598.
25. Meibodi NT, Maleki M, Javidi Z, Nahidi Y. Clinicopathological evaluation of radiation induced basal cell carcinoma. Indian J Dermatol.. 2008;53(3):137. doi: 10.4103/0019-5154.43222.
26. Oshinsky S, Baum S, Huszar M, Debby A, Barzilai A. Basal cell carcinoma induced by therapeutic radiation for tinea capitis-clinicopathological study. Histopathology. 2018;73(1):59-67. doi: 10.1111/his.13497.

Table 1. Frequency of each subtype

Subtype	Macro nodular	Mixed-aggressive	Micro nodular	pigmented	Adenoid	Mixed-nonaggressive	Infiltrative	Superficial	other
Frequency	113 70.2%	79 49.1%	67 41.6%	45 28%	40 24.8%	31 19.1%	29 18%	24 14.9%	11 6.8%

Table 2. Comparison of the frequency of histopathologic subtypes of basal cell carcinoma of the scalp in patients with and without chronic radiodermatitis

Subtypes	Non-Chronic Radiodermatitis (n =87, 209 lesions)	Chronic Radiodermatitis (n=74, 230 lesions)	*P*-value[1]
macro-nodular	54 (62.1%)	59 (79.7%)	0.1
micro-nodular	26 (29.9%)	41 (55.4%)	<.001
superficial	13 (14.9%)	11 (14.9%)	0.41
adenoid	20 (23.0%)	20 (27.0%)	0.27
infiltrative	13 (14.9%)	16 (21.6%)	0.55
infundibulocystic	1 (1.1%)	1 (1.4%)	-
basosquamous	3 (3.4%)	0	-
Keratotic	3 (3.4%)	2 (2.7%)	-
mixed aggressive	32 (36.8%)	47 (63.5%)	<.001
mixed non-aggressive	21 (24.1%)	10 (13.5%)	0.023
pigmented	22 (25.3%)	23 (31.1%)	0.99
Metatypical	1 (1.1%)	0	-
[1] Pearson's Chi-square test			

Table 3. Comparison of variables related to scalp basal cell carcinoma in each histopathologic subtype

		Macro-nodular	*P*-value[1]	Micro-nodular	*P*-value	Superficial	*P*-value	Adenoid	*P*-value
gender	male	81(71.7%)	0.25	47 (70.1%)	0.99	14 (58.3%)	0.17	28(70%)	0.98
	female	32(28.3%)		20 (29.9%)		10 (41.7%)		12(30%)	
sun exposure	low	27 (23.9%)	0.74	9 (13.4%)	<0.01	5 (20.8%)	0.49	10 (25%)	0.71
	medium	3(2.7%)		2 (3%)		0		2(5%)	
	high	83(23.5%)		56 (83.6%)		19 (79.2%)		28(70%)	
baldness	no	61 (54%)	0.64	31 (46.3%)	0.16	9 (37.5%)	0.1	24(60%)	0.29
	yes	52 (46%)		36 (53.7%)		15 (62.5%)		16(40%)	
job	inside	37(32.7%)	0.18	16 (23.9%)	< 0.01	7 (29.2%)	0.45	18(45%)	0.17
	outside	76(67.3%)		51 (76.1%)		17 (70.8%)		22(55%)	
	Age [3]	-	0.193[2]	-	0.346	-	0.467	-	0.264

Pearson's Chi-square test
Wilcoxon rank-sum test (U statistic - *P*-value)
mean ± SD

Table 4. Comparison of scalp basal cell carcinoma-associated variables in each histopathologic subtype

		Infiltrative	*P*-value[1]	Mixed aggressive	*P*-value	Mixed non-aggressive	*P*-value	Pigmented	*P*-value
gender	male	26(89.7%)	0.01	60 (75.9%)	0.12	18 (58.1%)	0.10	28(62.2%)	**0.17**
	female	3(10.3%)		19 (24.1%)		13 (41.9%)		17(37.8%)	
sun exposure	low	5 (17.2%)	0.58	9 (11.4%)	< .001	12 (38.7%)	0.05	9 (20%)	**0.60**
	medium	1(3.4%)		2 (2.5%)		2 (6.5%)		1(2.2%)	
	high	23(79.3%)		68 (86.1%)		17 (54.8%)		35 (77.8%)	
baldness	no	9 (31%)	0.01	34 (43%)	.001	23 (74.2%)	0.01	26 (57.8%)	**0.43**
	yes	20 (69%)		45 (57%)		8 (25.8%)		19 (42.2%)	
job	inside	7(24.1%)	0.14	16 (20.3%)	0.01	18 (58.1%)	< .001	15 (33.3%)	**0.66**
	outside	22(75.9 %)		63 (79.7%)		13 (41.9%)		30 (66.7%)	
	Age [3]	-	0.606 [2]	-	0.394	-	0.784	-	**0.139**

[1]Pearson's Chi-square test
[2]Wilcoxon rank-sum test (U statistic - *P*-value)
[3]mean ± S.D.