European Review for Medical and Pharmacological Sciences 2021; 25: 4283-4288

Implication of wide surgical excision in minimizing positive margins and consequential secondary excision – a retrospective comparative study involving 106 basal cell carcinoma cases

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Abstract. – OBJECTIVE: The use of current surgical techniques in the management of skin cancers that are not amenable to other treatment options has become the cornerstone of dermatological surgical intervention. Among the many benign lesions and malignant lesions, such as squamous cell carcinomas, melanomas, and Merkel cell carcinomas, the tumors that are commonly excised surgically are the basal cell carcinomas (BCC). Although the majority of BCC lesions spread locally and are rarely metastatic, these lesions may recur, especially, if the excised tissue consists of positive surgical margins. As BCC lesions are more common on the head, face, and neck regions, inadvertent positive margin excisions to help avoid major disfigurement of the regions may contribute to their recurrence. Trichoepithelioma (TE) is a benign tumor that bears a close resemblance to BCC, and therefore, clinicians encounter difficulty in differentiating between TE and BCC lesions. Clinicians have to rely on histopathology and immune-histochemical markers to rule out TE. This differentiation is crucial to make a definitive diagnosis of BCC and subsequently, employ a more aggressive surgical excision approach to treat this invasive tumor as compared with TE. Our focus in this article is to highlight only the surgical excision management of local and or locally invasive BCCs and report the success rate of our hospital's Dermato-venereology clinic (DVC) in Timisoara, Romania. This article highlights the role of an appropriate wide local lesion excision (5 mm) with

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negative surgical margins in the prevention of further surgical interventions, be it for corrective or esthetic reasons.

PATIENTS AND METHODS: This is a retrospective study that summarizes the evaluation of 120 lesions from 106 patients who were treated for BCCs at DVC (University Hospital), using a wide surgical excision method. Following the Romanian Society of Dermatologists guidelines, local non-aggressive BCC lesions were excised with margins of 5 mm and up to 1 cm for the aggressive sclerosing subtype.

RESULTS: The results of the audit of a sample of 120 lesions from 106 patients demonstrated that none of the surgically treated patients had recurrences and only 23 (19.16%) had positive surgical margin lesions. Out of these, 17 (73.91%) lesions underwent second surgical excision, while only three (13.04%) showed the presence of a residual tumor. The evaluation results may encourage dermatologists worldwide to make appropriately sized excision, especially in regions other than the head and neck, to avoid positive surgical margins and eliminate the need for consequent surgery.

CONCLUSIONS: For a better post-surgical prognosis of BCC, the authors recommend the practice of a wide margin excision (5 mm) during the primary surgery to avoid secondary surgery, especially if the tissue in the region is not sparse and chances of causing major disfigurement are minimal. As our findings suggest, only a few cases have the presence of residual tumor in the second surgery, hence authors also advocate the necessity to inform the patients about the merits of a second surgery, clearly mentioning the possibility of the absence of tumor even in the presence of positive margin.

Key Words:
Basal cell carcinoma, Residual tumor, Positive margins, Wide excision, Secondary excision.

Introduction

Squamous cell carcinomas (SCCs) and basal cell carcinomas (BCCs) are considered to be the most common among the non-melanoma skin cancers (NMSCs)[1]. BCCs account for an estimated three - fourths of those, making BCCs the most common human cancer overall[1]. It is mostly localized, slow growing, and rarely metastatic, however, some of the histologic subtypes are locally aggressive[2]. Though BCCs rarely prove to be fatal[3], their delayed diagnosis and/or improper treatment can damage the nearby anatomical structures and make the treatment challenging[4]. Based on the histopathological features, BCCs can be classified as either aggressive-growth or indolent-growth subtypes[5]. The indolent growth subtypes constitute nodular and superficial subtypes whereas aggressive growth subtypes, which have higher recurrence rates and a tendency to cause extensive local spread, constitute morpheaform, infiltrative, micronodular, and basosquamous subtypes[5]. BCCs have a propensity for sun-exposed areas of the body with the head and neck being the most common site and the forehead, cheek, and nose being the most common subsites[6]. Predisposing factors like immunosuppression as seen in human immunodeficiency virus (HIV) sero-positivity and organ transplant recipients, the fair skin tone of type 1 and 2 skin phototype when exposed to natural or artificial ultraviolet (UV) radiations, and genetic disorders such as Gorlin Goltz syndrome, albinism, and Xeroderma pigmentosum have been widely reported as the associated risk factors[7]. However, repeated long-term sun exposure in young adults is considered to be the main risk factor[6]. Repeated exposures of longer durations or having exposures since early years of life, in the long run causes BCCs more commonly, as compared to the overall cumulative exposure over the same period of time[8,9]. The mutation of p53 has been documented in 30-50% of BCCs cases, and therefore, p53 is believed to be involved in the pathogenesis of this disease[8,10-12]. Moreover, exposure to UVB radiations, in particular, tends to induce mutations in p53 tumor suppressor genes.

Although there is uncertainty in terms of the exact etiology of BCCs, its association with the pilosebaceous unit has been well-established[13]. Currently it is believed to originate from the pluripotent cells present in the basal layer of the epidermis or the follicle[13]. The Sonic Hedgehog (SHH) intracellular signaling pathway is believed to be implicated in the pathogenesis of BCCs[14]. This pathway plays a vital role in the regulation of cellular growth and differentiation during embryonic development[14]. However, the loss of the SHH pathway inhibition is linked with the development of BCCs[14]. The SHH ligand and the transmembrane protein known as PTCH1 are considered to be the main components of the SHH pathway. PTCH1 acts as a receptor for the SHH ligand and further binds to a second transmembrane protein called Smoothened (SMO)[14]. Under normal conditions, PTCH1 binds to SMO and inhibits its signal transduction ability, thus blocking downstream events that cause transcription of the

target genes[14]. But when the binding of the SHH ligand to PTCH1 transmembrane receptor protein relieves the PTCH1 mediated SMO inhibition, Hedgehog Pathway activates and causes abnormal cell growth and differentiation[14]. Additionally, the gain of function mutation of SMO and/or mutations causing inactivation of PTCH1 are other factors that contribute to unrestricted SMO signal transduction implicated in the pathogenesis of neoplasms such as the BCCs[14,15].

Diagnosing BCC becomes even more challenging due to its resemblance to a rarely occurring tumor called trichoepithelioma (TE). TE is a rare benign cutaneous tumor that is also derived from hair follicleS[16]. Though TE and BCC are two different clinical entities, evidence points to common pathogenesis[16]. Several studies analyze a common origin of both TE and BCC, and since they share many clinical and histopathologic features, differentiating between them becomes difficult. Studies have indicated the deletions at 9q22.3, which is the location of the PTCH gene of the basal cell nevus syndrome (Gorlin syndrome), as the potential factor in the pathogenesis of sporadic TE as well[16]. Due to many similarities between the two entities, especially between the solitary TE subtype and BCC, and the difficulty encountered in the diagnosis, the clinicians at our hospital thoroughly examined the specimens for differentiating histopathological and immune-histochemical markers to rule out a more invasive BCC tumor. The definitive diagnosis of BCC necessitates a more aggressive surgical excision approach by our team to treat BCC as compared with TE.

The incidence of BCCs is on the rise in regions with a predominantly white population, such as Europe, North America, and Australia[6]. The incidence of BCCs in Europe is 150/100000, which is less than the United States of America and Australia, where incidence is 300/100000 and 1600/100000, respectively[17]. Despite increased incidence, epidemiology data is limited in Romania due to improper record keeping, and therefore, 30-40% of all BCCs cases are not reported. Dermatologists and/or surgeons have the option of managing the localized BCCs by utilizing local therapies such as intra-lesional injections, photodynamic therapy, electrodessication and curettage (EDC), topical therapies including 5-fluorouracil and Imiquimod, Mohs micrographic surgery (MMS), and surgical excision[1]. However, the management of BCC is mostly surgical in the form of MMS, EDC, and surgical excision, reserving topical therapies only for low-risk BCCs.

The main focus of the article was to highlight success rates in treating BCCs lesions, using the wide surgical excision to minimize positive margin tissue. Also, the study reported the epidemiologic and histologic data of BCCs lesions diagnosed in Municipal Emergency University Hospital, Timisoara, Romania.

Patients and Methods

Organization of the Study

In the period included in the study, 120 lesions from 106 patients were treated with wide excision and histopathologically diagnosed as BCCs lesions. Based on the Fitzpatrick skin phototype classification, all the included BCCs patients were of European descent and skin phototype 2. These patients were treated at Municipal Emergency University Hospital, Timisoara, Romania. The patients included in the study had to fulfill two main criteria:

– the treatment applied had to be surgical excisions with wide margins;
– the pathological diagnosis had to be BCCs.

In the first step of the study, following the recommendations of the Dermatological Society of Romania, the cases of BCCs that underwent primary surgical excision of the lesions with wide margins were identified.

To fulfill the objective of our study, we reviewed the medical files of all the patients with clinical suspicion of BCC lesions. We reviewed the files of 2004 patients who were admitted between 1st January 2016 and 31st December 2018 to the Dermatology department, Municipal Emergency University Hospital, Timisoara, Romania. From these, only 106 patients with BCCs lesions underwent surgical excision with wide margins, and 120 lesions' biopsies were sent for pathological lab evaluation. The specimens were fixed in buffered formalin, embedded in paraffin, and prepared with the routine histopathological technique. From the paraffin blocks, 4-micrometer sections were cut and stained with hematoxylin and eosin.

The Ethics approval was obtained, and all the patients included in the study signed the informed consent. The data were collected per the hospital guidelines. The histological subtypes of BCCs were noted from the histological reports filed by the hospital's Pathology unit. For this study, multiple lesions within a single patient were consid-

ered separate BCCs lesions. To avoid duplication, pre-excised biopsied lesions were regarded as one same lesion. The collected relevant patients' data were then reviewed retrospectively.

Results

The analyses of the compiled data showed that BCC patients' gender distribution comprised 50 males and 56 females. We found various histopathological subtypes of BCC among the specimens that were included in the study. The 120 specimens from 106 patients comprised of 65 (54.16%) nodular, 28 (23.33%) superficial, and 9 (7.5%) infiltrating, and the remaining 18 (15%) were of mixed histologic BCCs subtypes. Among these 120 lesions, 80 (66.66%) of lesions were from the head and neck region, followed by 28 (23.33%) from the trunk, and the remaining 12 (10%) were from the limbs. Positive margins were seen in 23 (19.16%) of lesions and the most common site being head and neck regions, accounting for 60.86% (14 lesions). The sub-sites of cheek and forehead accounted for only a few specimens with positive margins, the majority were from the high-risk region sub-sites. The histologic subtype of BCC that accounted for the majority of positive margin specimens was found to be superficial, followed by nodular. The lesions that were found to have positive margins also had lateral margin involvement in 66.66% of specimens while the remaining had deep margin involvement. Out of 23 (19.16%) positive margin excisions, 17 (73.91%) underwent second surgical excision, and only three (13.04%) lesions were found to be positive for the residual tumor. The remaining 13.04% of lesions from three different patients did not undergo second surgical excision and failed to follow up, and hence post-primary surgical recurrence or presence of residual tumor in them could not be reported.

Discussion

The most preferred type of skin biopsy performed at our hospital is mostly excisional; other forms of biopsies such as incisional, punch, and or shave are not considered as effective as the excisional and have poor rates of diagnosis and recurrence.

The results of this study indicated that the percentage of positive margin excisions using the 5 mm margin rule was within the expected low range as reported in the data. It can be assumed that patients who underwent surgical excision of BCCs with 5 mm margins have a minimal or no recurrence rate. However, it is not always possible to make such an excision, especially in areas with sparse tissue such as the peri-orbital area and peri-oral area. In addition, in many instances, the preferences of the patients for esthetic reasons limit the excision size. The findings of the present study of a higher positive margin rate that was significantly associated with the region of head and neck were comparable to other studies on this subject[2,17-19].

The assumptions behind the higher positive margin rates are: 1) the difficulty encountered while removing localized and or locally invasive tumor to avoid damaging the important anatomical structures in the proximity, and 2) the reluctance of the family physicians to make a wide margin excision to avoid disfigurement of the region. In Romania, the family physicians do not perform such procedures and hence all such cases are referred to dermatologists. The available literature also suggests that the problems faced in the complete removal of certain BCCs subtypes, such as infiltrative, morpheaform, and multifocal is due to the difficulty in identifying the margins and diffuse spreading nature of these subtypes[17].

Making excision with 5 mm margins, especially for high-risk BCC (>2 cm), to ensure complete tumor removal minimizes the presence of positive margins and the need for secondary surgery. Following the Romanian Society of Dermatologists recommendation of 5 mm excision margins, our hospital achieves a 95.54 % "clear" margin rates as compared with the British Association of Dermatologist recommendation of 3 mm-4mm excision margins with an 85% "clear" margin rate[2] and of the European dermatological forum (EDF) recommendation of 4 mm excision margins with a 95% clear margin rate[20].

Conclusions

For a better post-surgical prognosis of BCC, the authors advocate the practice of a wide margin excision (5 mm) during the primary surgery to avoid secondary surgery, especially if the site and density of tissue allow such an excision. As our study indicates only few cases with the presence of residual tumor in the second surgery,

it is crucial for the dermatologist to determine thoroughly whether there is a presence of positive margin or not, as well as to communicate effectively the merits of a second surgery to the patients, clearly mentioning the possibility of absence of tumor even in the presence of positive margin.

The use of new emerging molecular therapy for treating locally advanced multifocal or metastatic BCC and topical therapies to treat superficial disease is proving to be effective, however, further studies are required to gauge the long-term effectiveness of all these alternative modalities in decreasing overall BCC related morbidity. In the meanwhile, as MMS and surgical excision remain the standard of care for treating BCCs at most places, wide surgical excisions practiced in our hospital continue to yield higher success rates in the BCC treatment, and is, therefore, worth recommending.

Conflict of Interest

The Authors declare that they have no conflict of interests.

Acknowledgements

These authors contributed equally as Co-first authors: Nilima Rajpal Kundnani, Razvan Vlad Tirziu, and Claudia Borza.

Funding

This research received no grant from any funding agency in the public, commercial or not-for-profit sectors.

Ethics Approval and Informed Consent Statement

Before the beginning of the study, Ethics Approval and informed written consent was obtained from all the relevant persons or authorities. The study was approved by the '*Comisia de Etica a Cercetarii Stiintifice*' (Ethics Committee for Scientific Research) of the University of Medicine and Pharmacy "Victor Babes", Timisoara, in accordance with the Helsinki Declaration – Recommendations Guiding Medical Doctor in Biomedical Research Involving Human Subjects. All the steps of the study were conducted in accordance with the above guidelines, conforming to the standard operational procedures for clinical studies approved for Sp Municipal, (Municipal Emergency University Hospital, Romania). This retrospective study was conducted in our university hospital, and as a part of routine procedure informed written consent forms stating that the data can be used for future medical research purpose, were signed by each patient at the time of admission in the hospital.s.

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