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Basal cell carcinoma of the nasal pyramid excision margins: a retrospective study

IVAN VATAMANESKU[1)], SORIN VIOREL PARASCA[2)], OTILIA MARIA PARASCA[3)], FLORIN ALEXANDRU VAIDA[4)], MIHAELA-CEZARINA MEHEDINŢI[5)], FLORIN GROSU[6)], MARIUS EUGEN CIUREA[7)]

[1)]*PhD Student, Doctoral School, University of Medicine and Pharmacy of Craiova, Romania*

[2)]*Department of Plastic Surgery, "Carol Davila" University of Medicine and Pharmacy, Bucharest, Romania; Department of Plastic Surgery, Clinical Emergency Hospital for Plastic Surgery and Burns, Bucharest, Romania*

[3)]*Student, "Carol Davila" University of Medicine and Pharmacy, Bucharest, Romania*

[4)]*Division of Biostatistics and Bioinformatics, Department of Family Medicine and Public Health, School of Medicine, University of California, San Diego, USA*

[5)]*Department of Histology and Cell Biology, Faculty of Medicine, "Lower Danube" University of Galaţi, Romania*

[6)]*Department of Histology, "Victor Papilian" Faculty of Medicine, "Lucian Blaga" University of Sibiu, Romania*

[7)]*Department of Plastic Surgery, University of Medicine and Pharmacy of Craiova, Romania*

Abstract

Basal cell carcinoma (BCC) is the most frequent skin cancer and its location in the nasal pyramid poses treatment problems. The main issue is how large the resection margins should be. The article presents a retrospective study on patients with BCCs of the nose. Thirty-seven patients were included and the correlations between incomplete resections and tumor dimensions, resection margins or histological sub-type were investigated. Of the 37 patients, only five had tumor-positive excision margins, but no correlation with the above-mentioned factors could be found. An overall tendency to over-resection was detected, contrary to the tendency depicted in the literature, but the incomplete resection rate (13.5%) is comparable with other reports. Further studies are needed, on a larger population in order to generate guidelines to better medical practice on this matter.

Keywords: basal cell carcinoma, nasal pyramid, surgical margins.

Introduction

Basal cell carcinoma (BCC) is the most common malignant tumor and its localization in the face poses the greatest challenge to treating physicians [1, 2]. Complete surgical excision is the treatment of choice for most BCCs providing definitive cure [1]. The nasal pyramid is one of the locations considered to be of high risk by the *National Comprehensive Cancer Network* (NCCN) from the United States of America (USA) due to its high rate of recurrence, esthetical considerations and difficulty of reconstruction after excision (many resulting defects need three-dimensional reconstruction) [3, 4]. Medical authorities in USA indicate Mohs' surgery as the golden standard for treating BCCs of the nose [3, 5]. Unfortunately, this type of surgical excision is unavailable on a large scale in many European countries, including Romania, due to its high costs and necessity of highly trained personnel [6]. Therefore, medical professionals have to choose certain resection margins that will assure a complete excision of the tumor without producing huge esthetical harm to this sensitive area. Which are the best resection margins is still a matter of debate among dermatologists and plastic surgeons, with many studies conducted to solve this problem [6, 7]. As long as such studies are missing from the Romanian literature, the authors have decided to provide a retrospective study on BCCs of the nose resection margins from a local Plastic Surgery Department in the present article.

Patients, Materials and Methods

A retrospective study on BCCs of the nose resection margins was conducted in the No. 2 Department of Plastic Surgery, Clinical Emergency Hospital for Plastic Surgery and Burns, Bucharest, Romania.

A formal approval for the study was obtained from the Ethics Committee of the Institution.

Sources for data gathering and definition of the study group

There were reviewed the medical charts and pathology reports of the patients admitted between January 1st and December 25th, 2017, with skin tumors of the nasal pyramid. Of the 47 patients who were treated in this period, we removed three patients for lacking pathology reports, and other six patients with other types of tumors (two squamous cell carcinomas, one melanocytic nevus, two seborrheic keratosis and one granulomatous chronic dermatitis). In one female patient, the pathologist due to mechanical artifacts could not assess the margins, and the patient was excluded from the study. The final study group consisted of 37 patients, 15 males and 22 females, with mean age of 71 years.

Data gathering

For each patient in the group, the following data were collected: tumor dimensions (in mm), resection margins (in mm), histological type of the tumor, and whether the

resection margin was tumor-free. A follow-up of at least 11 months of the patients with positive margins was conducted in order to detect recurrences of the tumor. Tumor dimensions were grouped in four classes: less than 6 mm, 7–10 mm, 11–20 mm, and over 20 mm. Resection margins were grouped as: 3 mm margin, 4 mm margin, 5 mm margin, and over 5 mm margin. The dimensions were collected from the medical charts and not from the pathology reports, because shrinkage of the specimen distorts the measurements in a random fashion (it depends on gender, skin texture, age, a.s.o.). The histological types were grouped according to *NCCN* into: low-risk (nodular, superficial) and high-risk (infiltrating, micronodular, metatypical, and with perineural infiltration). None of the patients had pre-operatory pathological exams, so the amount of resection was based only on tumor dimensions.

Data analysis

The following possible associations were investigated: (*1*) the relationship between tumor dimensions and size of resection margins; (*2*) the relationship between tumor size and complete or incomplete resection (the authors decided to take into account only lateral positive margins and not the deep positive margins, therefore two patients with deep positive margins but with tumor-free lateral margins were counted as negative lateral margins); (*3*) the relation between tumor resection margins and complete or incomplete excision; (*4*) the relation between histological type (low-risk or high-risk) and tumor-free resection margins.

Statistical analysis

All the relations were analyzed by a biostatistician using Fisher's exact test and were further tested using Goodman–Kruskal test for detecting monotonous trends. In order to assess the overall incomplete resection proportion with a 95% confidence interval (CI), the binomial law for proportions' distribution was applied.

Histopathological analysis

For the histopathological (HP), positive and differential diagnosis, the resection material from each patient was fixed in 10% buffered formalin solution, and sent to the Laboratory of Pathology. The biological material was embedded in paraffin, microtome sectioned at 4 μm thick, and stained with Hematoxylin–Eosin (HE) and trichrome green light, following the Goldner–Szekely (GS) technique.

Immunohistochemical analysis

For evaluation of particular characteristics of the tumors, we also performed an immunohistochemistry, using antibodies: anti-pan-cytokeratin (CK) AE1/AE3 (monoclonal mouse anti-human CK, clones AE1/AE3, 1:100, Dako), anti-Ki67 (monoclonal mouse anti-human Ki67, clone MIB-1, 1:50, Dako), anti-epithelial membrane antigen (EMA) (monoclonal mouse anti-human, clone E29, 1:50, Dako), anti-p53 (monoclonal mouse anti-human p53 protein, clone DO-7, 1:100, Dako), anti-cluster of differentiation (CD) 3 (monoclonal mouse anti-human CD3, clone F7.2.38, 1:25, Dako), anti-CD20 (monoclonal mouse anti-human CD20cy, clone L26, 1:50, Dako).

Results

In our group of 37 patients with BCCs of the nose (15 males, 22 females), five patients had incomplete lateral resection (positive lateral resection margins) (two males and three females), meaning 13.5% (with a 95% CI 4.5–28.8%). The macroscopic aspects of tumors ranged from nodular, superficial, to deep, necrotic and ulcerated (Figures 1 and 2).

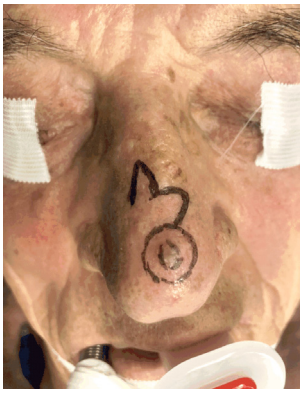

Figure 1 – ***Nodular, slightly prominent tumor on the nose, 3 mm resection margin.***

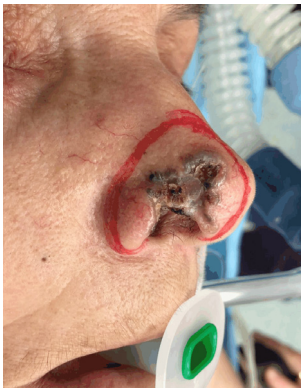

Figure 2 – ***Ulcerative, necrosed, infiltrative tumor, with heterogeneous margins, located under the right nasal wing, 5 mm resection margin.***

Table 1 summarizes the excision margins in each tumor dimensions group. It can be observed that most tumors (14, representing 37.84%) had 7–10 mm dimensions. Also, "neglected tumors", those with dimensions larger than 20 mm, were seven, representing 18.92%. No statistically significant difference was detected between the groups (p=0.13, Fisher's exact test and p=0.66, Goodman–Kruskal test). That means that tumor dimensions are not the primary criterion for choosing excision margins.

Table 1 – ***Resection margins' dimensions in each tumor dimension group***

Tumor dimensions / resection margins	3 mm	4 mm	5 mm	Over 5 mm
Under 6 mm	1	0	8	0
7–10 mm	1	3	10	0
11–20 mm	1	3	3	0
Over 20 mm	1	1	3	2

Table 2 describes the proportion of incomplete resections in each tumor dimension group. No statistically significant difference could be detected (p=0.85, Fisher's exact test). Most incomplete resections were found in tumors with a diameter of 7–10 mm. Here, there were three incomplete resections from the 14 surgeries, representing 21.4%.

Table 2 – ***Proportions of incomplete lateral resection related to tumor dimensions***

Tumor dimensions	Incomplete resection cases / total cases (percentage)	*p*-value
Under 6 mm	1/9 (11.1%)	0.85
7–10 mm	3/14 (21.4%)	
11–20 mm	1/7 (14.3%)	
Over 20 mm	0/7 (0%)	

Table 3 shows the proportion of incomplete resections in relation to the size of resection margins. In our study, most incomplete resections were performed at 5 mm resection margins. Once again, no significant difference was found (p=0.83, Fisher's exact test and p=0.47, Goodman–Kruskal test).

Table 3 – ***Proportions of incomplete lateral excision related to resection margins' dimensions***

Resection margins	Incomplete resection cases / total cases (percentage)	*p*-value
3 mm	1/4 (25%)	0.83
4 mm	1/7 (14.3%)	
5 mm	3/24 (12.5%)	
Over 5 mm	0/2 (0%)	

Table 4 depicts the frequency of different sizes of the resection margins dimensions for histological high-risk and low-risk, with no statistically significant difference between the groups (p=0.29, Fisher's exact test and p=0.52, Goodman–Kruskal test). This fact was expected taking into account that the surgeons did not have any pre-operatory data regarding the histological risk.

Table 4 – ***Resection margins' dimensions for each group of histological risk***

Histological risk	3 mm margins	4 mm margins	5 mm margins	Over 5 mm margins	*p*-value
High	1/15	5/15	8/15	1/15	0.29
Low	3/22	2/22	16/22	1/22	

We found two out of 15 cases of incomplete resections in the high histological risk group and three out of 22 cases of incomplete resections in the low risk group, with no statistically significant difference between groups (p=1, Fisher's exact test).

One patient with incomplete resection had a recurrence in the interval of follow-up and it was resected again with tumor-free margins.

The microscopic examination of the surgical resection pieces highlighted the presence of various forms of BCCs; most of them were included in the nodular form (Figure 3), but there were also identified superficial BCCs (Figure 4), adenoid ones (Figure 5), adenoid-cystic ones (Figure 6) and even metatypical carcinomas.

As it may be observed from our images, the BCCs were formed of basaloid cells that are similar to the basal non-differentiated cells of the epidermis, arranged in palisades, separated by a basal membrane from the surrounding stroma. The tumoral cells presented a reduced basophil cytoplasm and rich in chromatin nuclei. The examination with high power objectives showed that most of the tumoral cells presented typical mitoses. Also, the usual microscopic examination did not highlight the presence of desmosomes, a characteristic aspect for BCCs.

Some large-sized nodular tumors presented central necrosis (Figure 7), while the ulcerative tumors presented peripheral necrosis made of cell and tissue residues, infiltrated with leukocytes of the granulocyte, macrophage and lymphocyte type (Figure 8).

The tumoral stroma presented an inflammatory infiltrate with a heterogeneous arrangement, more or less intense, mainly formed of lymphocytes, plasma cells and macrophages. In the ulcerative tumors, the inflammatory infiltrate contained large quantities of neutrophil granulocytes and macrophages and a reduced number of lymphocytes and plasma cells (Figures 9 and 10).

Immunohistochemical (IHC) examinations highlighted an intense reaction of the tumoral cells to pan-CK AE1/AE3, both for the nodular and adenoid forms of the BCCs (Figures 11 and 12). In comparison, Ki67 tumoral proliferation factor presented a low index, about 3–5%, both in nodular and in adenoid forms (Figures 13 and 14).

p53 protein had an extremely variable IHC expression, from negative to intensely positive, regardless of the HP form of BCCs (Figures 15 and 16). In about 50% of the BCC cases studied, its expression was positive.

EMA had, most of the time, a low or negative IHC expression in all forms of BCCs (Figures 17 and 18).

Of the two types of cells studied, present in the stromal inflammatory infiltrate, the most numerous were the T-lymphocytes (Figures 19 and 20).

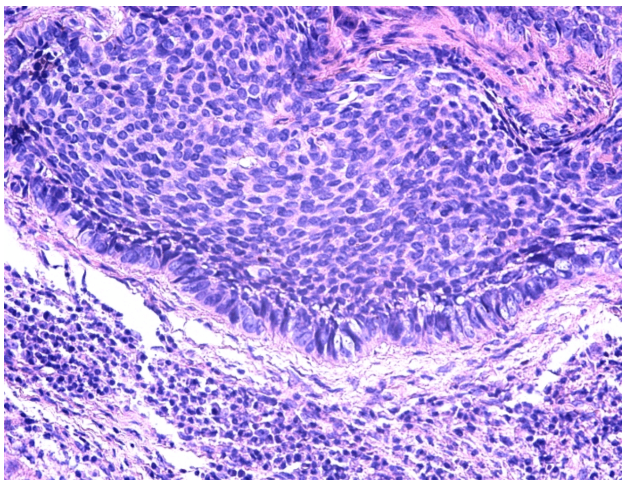

Figure 3 – ***Nodular basal cell carcinoma. HE staining, ×200.***

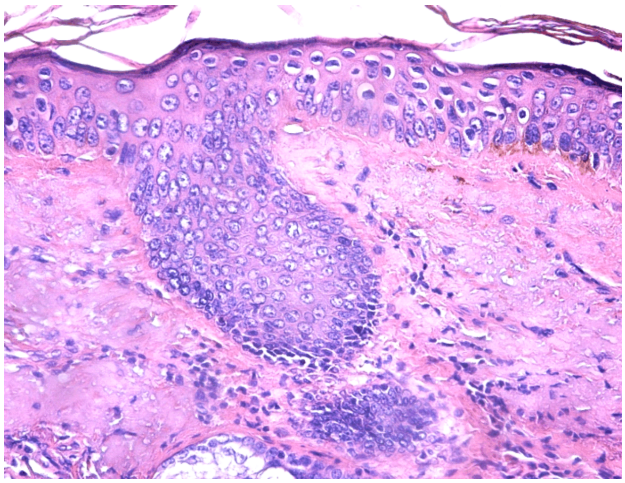

Figure 4 – ***Superficial basal cell carcinoma. HE staining, ×200.***

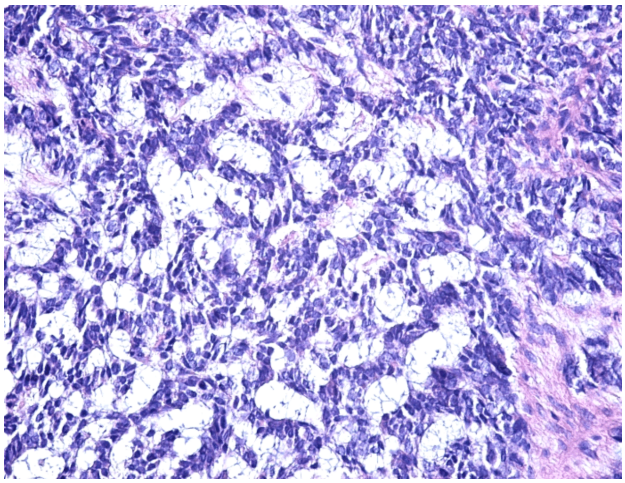

Figure 5 – ***Adenoid basal cell carcinoma. HE staining, ×200. HE: Hematoxylin–Eosin.***

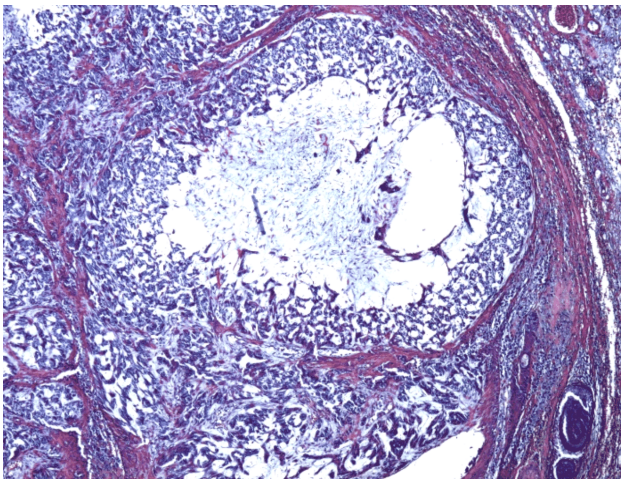

Figure 6 – ***Basal cell carcinoma, the adenoid-cystic form. GS trichrome staining, ×40. GS: Goldner–Szekely.***

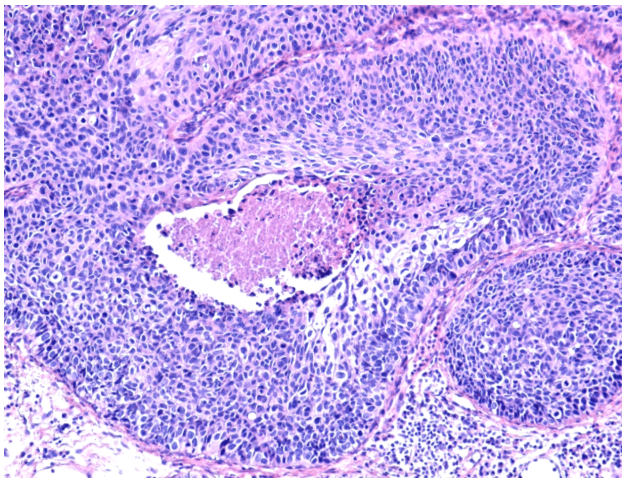

Figure 7 – ***Basal cell carcinoma, the nodular form, with central necrosis. HE staining, ×100.***

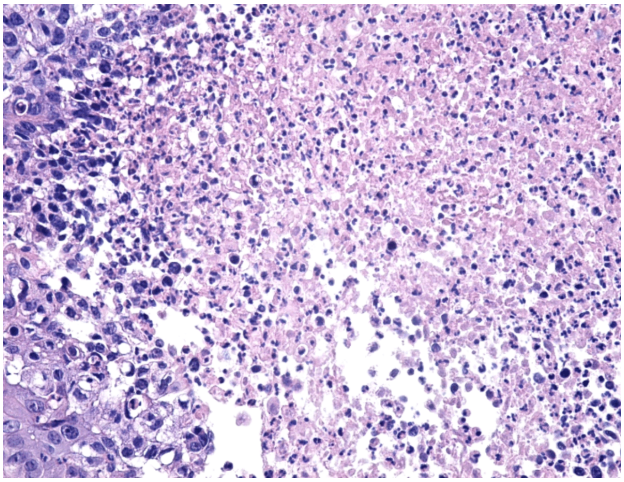

Figure 8 – ***Peripheral area of a nodular, ulcerative basal cell carcinoma, where there is highlighted the presence of a necrosis area infiltrated with granulocyte leukocytes and macrophages. HE staining, ×200.***

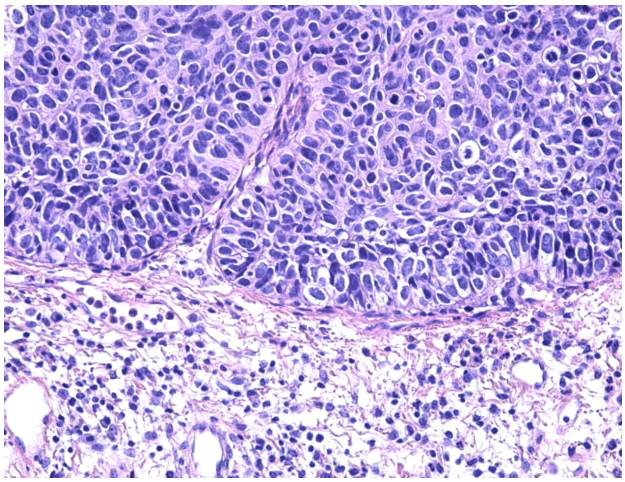

Figure 9 – ***Tumoral stroma with a moderate inflammatory infiltrate. HE staining, ×200.***

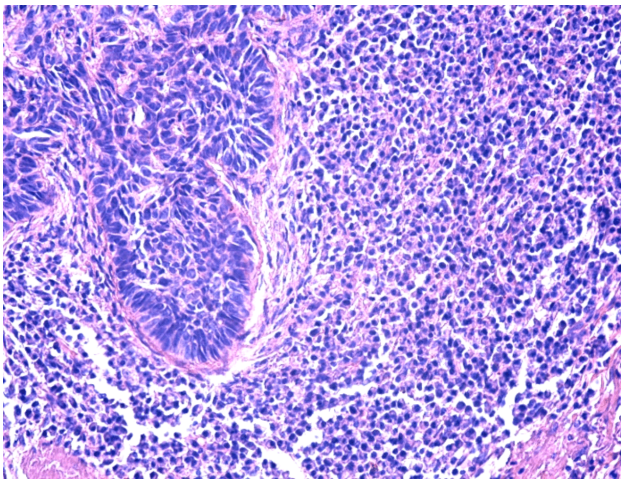

Figure 10 – ***Tumoral stroma with an abundant inflammatory infiltrate mainly formed of lymphocytes. HE staining, ×200.***

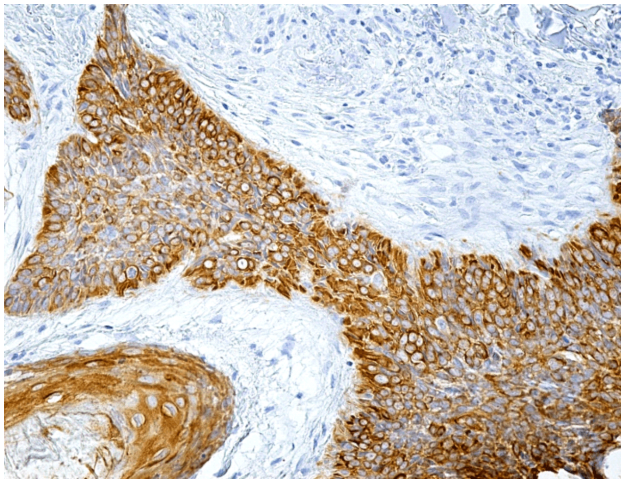

Figure 11 – *Nodular basal cell carcinoma with an intense reaction of the tumoral cell to anti-pan-CK AE1/AE3 antibody. Immunomarking with anti-pan-CK AE1/AE3 antibody, ×200. CK: Cytokeratin.*

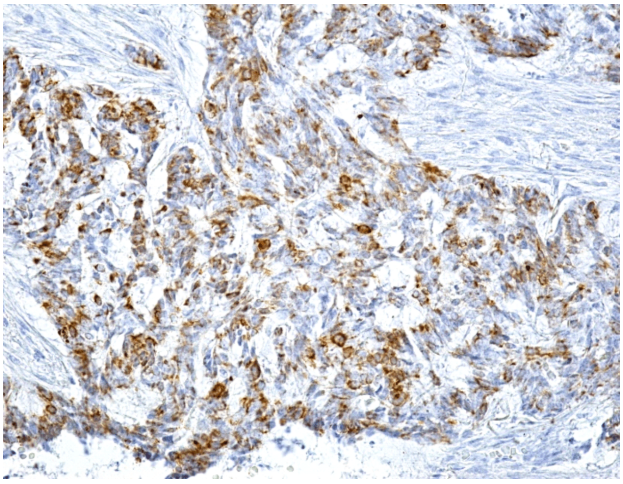

Figure 12 – *Adenoid basal cell carcinoma, with a moderate reaction to pan-CK AE1/AE3. Immunomarking with anti-pan-CK AE1/AE3 antibody, ×200. CK: Cytokeratin.*

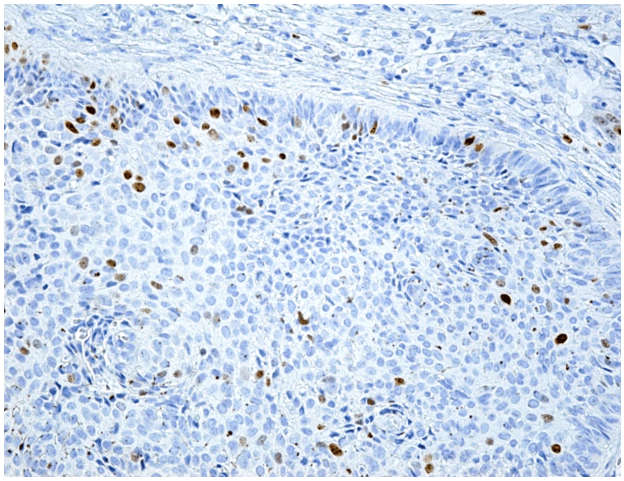

Figure 13 – *Basal cell carcinoma, with a low number of cells in mitosis, marked by anti-Ki67 antibody. Immunomarking with anti-Ki67 antibody, ×200.*

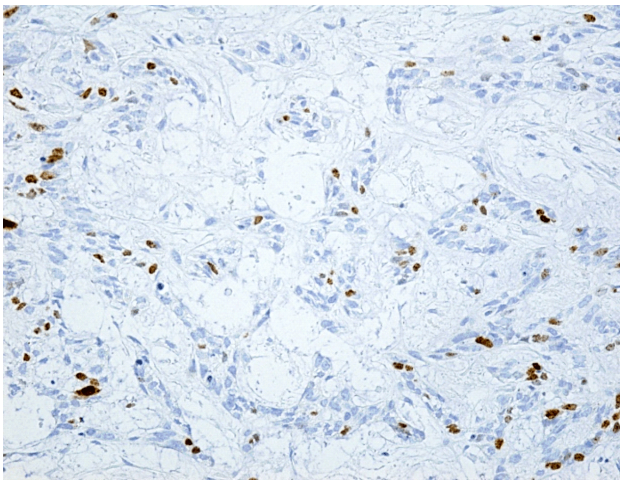

Figure 14 – *Adenoid basal cell carcinoma, with a low cellular Ki67 proliferation index. Immunomarking with anti-Ki67 antibody, ×200.*

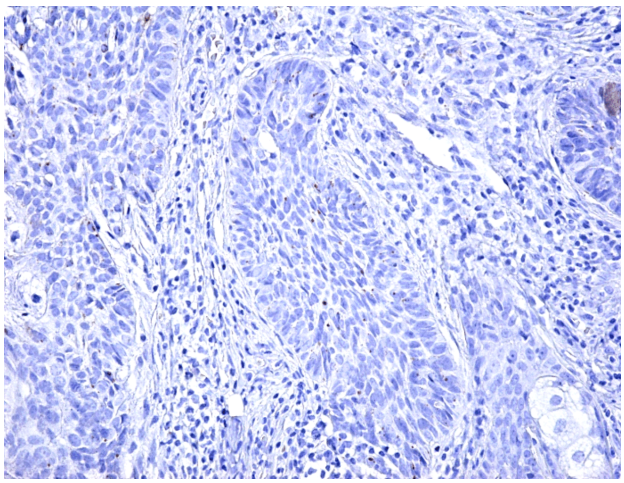

Figure 15 – *Nodular basal cell carcinoma, with a negative reaction to p53. Immunomarking with anti-p53 antibody, ×200.*

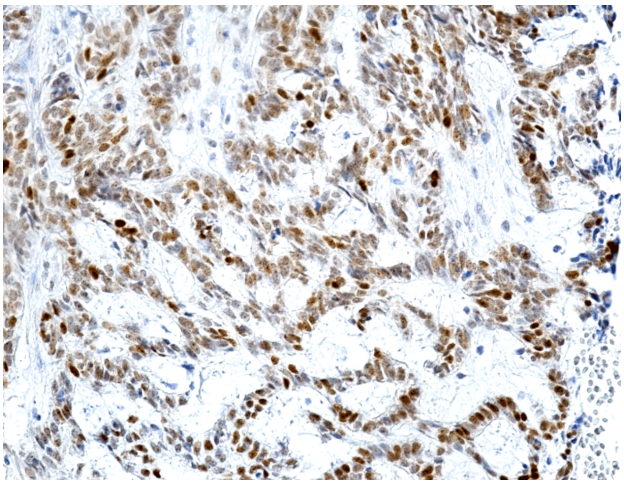

Figure 16 – *Adenoid basal cell carcinoma, with an intense reaction to p53. Immunomarking with anti-p53 antibody, ×200.*

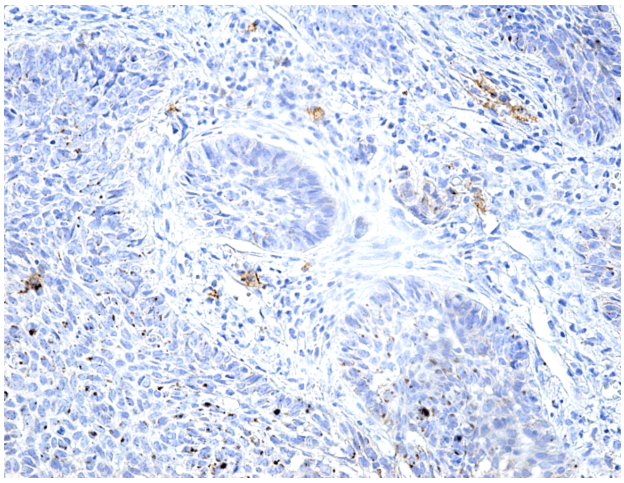

Figure 17 – ***Basal cell carcinoma with an absent immunohistochemical expression of EMA. Immunomarking with anti-EMA antibody, ×200. EMA: Epithelial membrane antigen.***

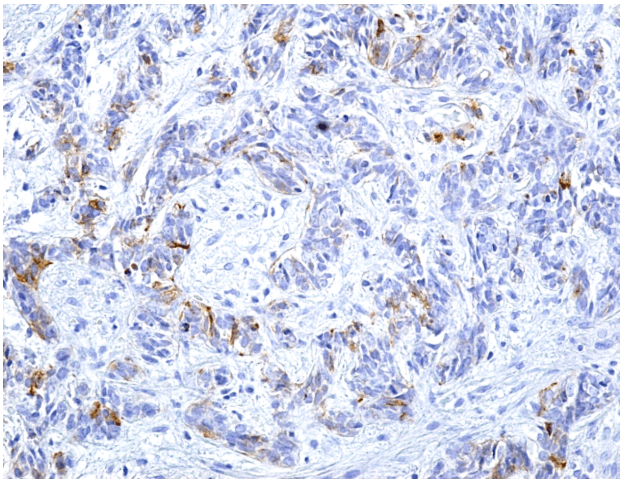

Figure 18 – ***Adenoid basal cell carcinoma with a moderate reaction to EMA. Immunomarking with anti-EMA antibody, ×200.***

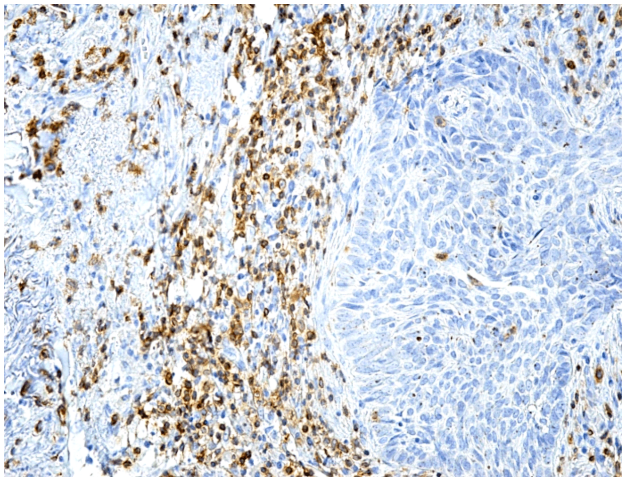

Figure 19 – ***Inflammatory infiltrate in the tumoral stroma rich in T-lymphocytes. Immunomarking with anti-CD3 antibody, ×200. CD34: Cluster of differentiation 34.***

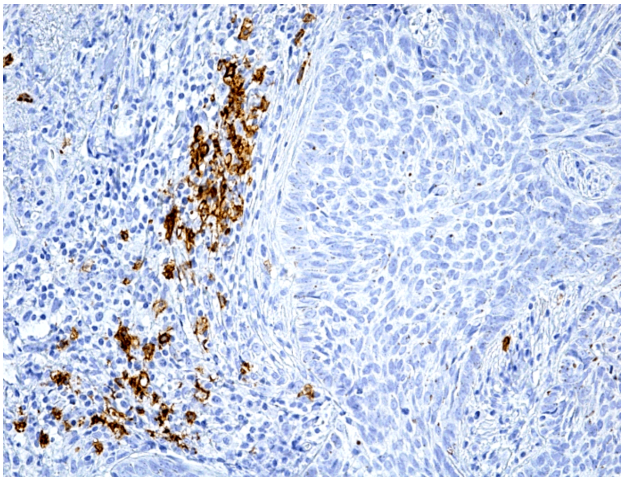

Figure 20 – ***Nodular basal cell carcinoma with a moderate number of B-lymphocytes in the inflammatory infiltrate of the tumoral stroma. Immunomarking with anti-CD20 antibody, ×200. CD20: Cluster of differentiation 20.***

Discussions

BCC is a challenging health problem, being the most common human malignant tumor [1, 2]. Worldwide, its incidence reached about 2.7 million cases and it is ever growing [8–10]. All the studies show that this form of cancer represents about two-thirds of all the skin cancers in Caucasian people [11–13]. The onset and progression of BCC is mainly connected to the exposure of skin to solar ultraviolet (UV) radiations. Therefore, these tumors occur on the head and neck skin, mainly on the nose and face, mainly in adult men working outdoors, aged over 50 years old [14, 15]. The studies in the last decades showed that the BCC incidence has increased by 10% per year and it is diagnosed more and more often in people aged less than 40 years old) [16, 17]. The high incidence of BCC in people aged less than 50 years old may be due to a prolonged exposure to sunlight, either at work or during recreational activities, due to the reduction of the ozone layer, to artificial UV exposure in beauty saloons, due to a change in the dressing code, to a low immunity in some individuals, and others [18, 19].

Face is considered a location that raises important treatment problems, with nasal pyramid seen as a high-risk area [1–4]. At this level, complete excision of the tumor stays in balance with the reconstructive challenges and the esthetic outcome. Mohs' microsurgery is the best solution to this problem, but it is, unfortunately, unavailable in Romania's public health system, while even in well-developed Western European countries it is not largely available [20]. Current practice is excision with certain safety margins followed by pathological validation of the excision. Pathology is the referee between wide excision and tissue preservation, although questions are raised regarding its absolute value. Thus, classical bread loafing technique in preparing the specimen was found to diagnose positive margins in facial BCC in

only 44% of cases compared to "en face" slicing [21, 22]. Pathology was found to have only 76% negative predictive value in BCC with negative margins [22]. Despite current incertitude, pathology remains the golden standard.

When excising a BCC, one has to answer two fundamental questions: (*1*) where are the macroscopic margins of the tumor? and (*2*) how large the safety margins should be? The tumor margins are perceived differently among specialties according to a recent study stating that dermatologists have the best rate of tumor-free margins followed by plastic surgeons and general practitioners in Netherlands [23]. Moreover, several reports suggest that enhanced direct examination using loupes [23], dermoscopy [7, 24], or "wet blotting technique" (wetting the tumor and surrounding skin with water before examination) [22] leads to better identification of tumor borders and allow for lesser safety margins. In our Department, the surgeons do not use any of these techniques leading to larger excision margins compared with recent literature reports (5 mm and above margins comprise for 70.2% of total cases in our series).

There is a tendency for reducing excision margins in BCC of the face in the latest reports: 3 mm for BCCs of the nose [5], 2 mm margins for tumors less than 1 cm [7]. As stated above, this tendency was not seen in our group, surgeons aiming for safety, possessing a large armamentarium of methods to close the defect. The statistical analysis of our series showed that there was no statistical difference between groups with 3 mm, 4 mm, or 5 mm margins in terms of incomplete excision, which means that we could reduce the margins in smaller tumors (less than 20 mm) with good tumor clearance. Lack of correlation between histological subtype and incomplete resections makes the necessity of preoperative biopsies somehow dubitable and was reported by a French study too [5]. It is probably explained by the fact that nose is a high-risk location by itself and histological risk has less importance here [25]. One interesting finding was that the excision margins were not dictated by the tumor dimensions, which probably lead to the tendency to over-resection depicted in our study. The authors believe that some guidelines should be followed regarding this matter. Overall positive margin frequency in our group was 13.5% (95% CI 4.5–28.8%), which is well between the limits reported by similar studies conducted in this region of the face [26–28]. We found one recurrence with a follow-up of at least 11 months, which is similar with other reports [29], but we feel that the follow-up period was to short and maybe some patients with recurrence did not return to our Department.

We consider that HP and IHC examinations are essential both for establishing the positive and differential diagnosis with other benign or malignant skin lesions, and for evaluating the margins of surgical resection of the tumor and establishing the prognosis [30, 31]. It is known that BCC very rarely causes metastases, but it can infiltrate and destroy local or neighboring tissues with the tumor, or even relapse in the case of incomplete surgical excisions [32–34].

The present study has some limitations linked mainly to the number of patients and the subjectivity of the collected data, so the conclusions lack power. Nevertheless, further studies could be performed having this article as a starting point. Guidelines are needed in our country on this matter and they should be based on evidence.

Conclusions

BCCs of the nasal pyramid are a challenge and in our study, there was a tendency for over-resection, but incomplete resections could not be linked to tumor dimensions, subtype, or selected margins.

Conflict of interests

None of the authors has any conflict of interests to disclose.

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Corresponding authors

Sorin Viorel Parasca, Lecturer, MD, PhD, Department of Plastic Surgery, "Carol Davila" University of Medicine and Pharmacy, 37 Dionisie Lupu Street, Sector 2, 020021 Bucharest, Romania; Phone +40723–513 914, e-mail: sorinparasca@yahoo.com

Mihaela-Cezarina Mehedinţi, Professor, MD, PhD, Department of Histology and Cell Biology, Faculty of Medicine, "Lower Danube" University of Galaţi, 35 Alexandru Ioan Cuza Street, 800010 Galaţi, Romania; Phone +40724–851 671, e-mail: mihaela_hincu10@yahoo.com

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