



Original article

ACTA FAC. MED. NAISS. 2004; 21 (4): 195-200

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MARGIN SIZE IN BASOCELLULAR SKIN CARCINOMA RESECTION: IMPACT ON RELAPSE

SUMMARY

Seventy six patients were analysed in the paper after surgical treatment of basocellular facial skin carcinoma, tumor clinical characteristics, their incidence related to sex, age and site. Patients with relapse were specially monitored. Histopathologic smears with marginal remnants of tumor cells were analysed. Relapses occurred equally in patients in whom radical treatment was achieved and in those in whom radical treatment was not achieved, meaning that relapse of basocellular carcinoma does not depend on the degree of intended radical treatment but also on other factors.

Key words: basocellular carcinoma, facial skin, relapse

INTRODUCTION

Basocellular carcinomas (BCC) are common pathologic entities affecting facial skin and engaging a large number of physicians of different specialties in everyday practice. They represent a significant problem in modern medical science, both regarding theoretic elucidations of the process as a biologic phenomenon and regarding practical, clinical aspects.

Markedly increased incidence of facial BCC induced increased interest in the BCC study. According to the International Union Against Cancer, there are 70–80 new cases of skin cancer per 100.000 individuals. It is considered that the number is much higher since a significant number of cases is not reported and registered.

Skin BCC originates from epidermal basal cells and there are several different variants with possible confluence among them. It is situated only in the skin. There are several histopathologic and clinical forms of BCC. Clinically, these classifications do not bear much importance and these tumors are divided into infiltrant and limited/circumscribed types.

Several authors described BCC metastases. Up to the present, around 200 cases of metastasizing were reported. Metastases were described in the subcutaneous tissue, bones, lungs, liver, lymph nodes of the neck (1–3).

Traditional diagnostic methods do not provide enough information on tumor features. Radiography visualizes only the bone structures and computerized tomography is not appropriate from both ethical and economic reasons for this kind of diagnosis. Based on sonography, BCC characteristics cannot be clearly visualized.

Surgical excision is the mainstay of BCC therapy. Induced defects are closed either with direct suture or flaps and grafts, depending on the wound size. Reconstructions are sometimes very complicated – when a BCC invades bone structures it is very destructive. Today, it is believed that Mohs' surgical technique is the most successful in BCC management, then surgical and radiotherapy. However, this technique is very complex, requires specially trained personnel and it is not suitable for routine practice.

The basic problem remains unresolved though, since Fleming (4) states that he has found BCC relapse in cases with tumor presence in the margins of histopathologic smear in 39% cases after 5 years and in 33% if the tumor was observed in the deep margin.

Further study of tumor characteristics as well as its treatment remains a challenge for the future.

Aim of the study was to establish clinical BCC forms, incidence in the groups investigated related to sex, age and site, and to establish whether the margin size (distance from the incision to clinically evident tumor) influences BCC relapse.

MATERIAL AND METHODS

In the period 1990–2000, 216 patients with skin BCC were surgically treated at the Department of Maxillofacial surgery, Dentistry clinic and Health Care Centre in Pirot.

A detailed analysis of the clinical data on the disease course was performed and all patients were divided into two large groups.

1. Group without relapse (n=190)
2. Group with relapse (n=26)

Further, biopsies of 76 BCC patients were analysed. The samples were fixated in 10% formaldehyde or 70% during at least 24 h, processed in the apparatus for automatic tissue processing, and embedded in paraffin and microtomed up to the 4 µm thickness.

Out of the total number, we analysed 76 patients in which 76 operations were done. Eleven interventions were performed in general endotracheal anesthesia, and 65 in local anesthesia (2% cystocain with adrenaline). Sliding flap was the reconstruction method in 33 cases, rotational in 16, transpositional in 10, insular in 3, McGregor's in 2, Mustard's in 2, bilobar in 1, rhomboidal in 2 and frontal on arteria supratrochlearis in 3 cases.

Most of the patients were operated in 1990 and 1991; afterwards, only those with relapse were selected and monitored. Relapsed cases were considered those with the exact date of surgery, exact site and histopathologic results (from medical history). At the marked site, an incision from earlier surgery could be observed, and merked relapse site is in continuity with earlier incision. The criteria for forming the group without relapse were that the excision is primary (with the intent of completeness) and that there was no previous therapy. Excisions were made in order to be complete, with all free margins ie. without any macroscopic element of residual tumor at any border.

RESULTS

In the period observed, 346 patients were treated with facial skin BCC, out of which 24 relapses (6.93%).

Detailed data analysis enabled us to select the group of 76 patients (40 men; 36 women). Sexual BCC distribution is presented in table 1.

Table 1. Sexual BCC distribution

Sex	BCC without relapse	BCC with relapse	Total
Male	32	8	40
Female	20	16	36
Total	52	24	76

Obtained frequency differences were not statistically significant ($\chi^2=27$; $df=p>0.05$).

Age range for males was 54–91 years, and in women 41–96 years. Average age was the same in men and women, but with relapses in younger age groups in both sexes. Sexual and age BCC distribution is presented in table 2.

Table 2. BCC distribution by sex and average age

Sex	Average age		Total
	BCC without relapse	BCC with relapse	
Male	74.90	67.00	70.95
Female	76.57	63.81	70.19
Total	75.53	64.87	70.20

As for clinical forms (table 3), nodular form is most common (in 37 cases and more common in men). It is clinically manifest as a nodulus. Its surface is rough, with frequent hyperkeratosis on the surface. Ulcerous form is the second most common (more common in women). It is clinically manifest as an ulceration, with variable size and irregular shape, rough bottom, raised edges, involving whole skin-depth. Other clinical forms are rare.

Obtained frequency differences are not statistically significant ($\chi^2=1,1$; $df=1$; $p=0.294$; $p>0.05$).

Nodular form is more frequent in men in the group without BCC relapse, while in those with relapsed BCC it is more common in women (table 4). Ulcerous form is also more frequent in men in the group without relapse and in women in the relapse group. Pigmentous and superficial forms of BCC are very rare, and ulcerous terebrans form is also rare, though very destructive locally.

Table 3. Distribution of all BCCs according to their clinical appearance.

Clinical form	All BCCs		Total
	Male	Female	
Ulcerous	17	19	36
Nodular	22	15	37
Ulcerous terebrans	1	0	1
Pigmentous	0	0	0
Superficial		2	2
Total by sex	40	36	76

Table 4. BCC distribution with and without relapse according to the clinical form

Clinical form	BCC without relapse		BCC with relapse		Total
	Male	Female	Male	Female	
Ulcerous	10	7	7	12	36
Nodular	21	11	1	4	37
Ulcerous terebrans	1	0	0	0	1
Pigmentous	0	0	0	0	
Superficial	0	2	0	0	2
Total by sex	32	20	8	16	76
Total all BCCs	52		24		76

The differences obtained are not statistically significant ($\chi^2=0.22$; $df=1$; $p=0.64$; $p>0.05$).

Table 5 presents the BCC distribution by its site. They are more frequent on the nose, then in the zygomatic region and nasolabial sulcus.

Revision of histopathologic findings helped us to investigate the presence of cancer plaques in the incision edges and the results are presented in table 6.

The differences in incidence of cancer plaques in the incision edges we obtained were not statistically significant ($\chi^2=1.91$ $df=1$ $p>0.25$.)

DISCUSSION

Women are more frequently affected with BCC (60.91%:39.09%) but in the age group up to 60

years this proportion is reversed (20.89:25.58), though this sex difference was not statistically significant. In rural areas, women are also more commonly affected (64.17%:62.79%), while in urban surroundings the proportion is reversed (5).

Table 5. BCC distribution by its site

BCC site	Relapsed BCC	BCC without relapse	Total
Nose	5	15	20
Nasolabial sulcus	4	5	9
Zygomatic region	3	5	8
Temporal region	4	2	6
Mental region	1	4	5
Lower eyelid	1	4	5
Forehead	3	1	4
Upper eyelid	0	2	2
Lower lip	1	1	2
Retroauricular region	0	3	3
Medijalni canthus	0	2	3
Upper lip	1	2	3
Neck	0	2	2
Preauricular region	0	2	2
Cheek	0	1	1
Auricula	0	1	1
Total	24	52	76

Table 6. Distribution of all BCCs with or without relapse by the incision edge status

BCC	Positive edges	Negative edges	Total
BCC without relapse	33	19	52
BCC with relapse	12	12	24

Most authors agree that BCCs and malignant melanomas are more frequent in women, while planocellular carcinoma is more common in men (6,7).

The difference in BCC distribution by the factor of age was not statistically significant. This fact compels us to think that in younger age groups, in addition to UV radiation, some other yet undefined factors play a significant role in BCC etiopathogenesis (5).

Possible factors important for BCC may be the disturbances of genetic structures. Four kinds of genes are disturbed in tumors:

1. Oncogenes, enhancing tumor growth.
2. Antioncogenes, impeding malignant tumor development, are recessively inherited. MST1 (multiple tumor suppressor) gene, significant in breast cancer, is situated on 9p21 chromosome and it codes for the inhibitor (p16) of cyclin-dependent kinase 4, which regulates cell cycle.
3. Genes which impede metastasizing
4. Genes regulating apoptosis, genetically programmed cell death

Human PTC gene is a tumor suppressor and development regulator. Some BCC patients have embryonal mutations in PTC gene and they are at increased risk of anomalies such as spina bifida and craniofacial deformities, skin BCC and brain tumors. PTC mutations are frequent in BCCs which mainly have both PTC copies inactivated(8).

The existence of cancer genes indicates that the biologic type of BCC does not depend only on the surgical intervention but on the malignant potential present also in apparently normal epidermal cells.

The second generally accepted fact is that BCC most commonly affects the skin of head and neck(9). Facial middle third is the most common site. In the Timok region, head and neck cutaneous BCC are found in 88.4% cases. It is most common on the nose, lower eyelid etc. Facial areas most exposed to UV radiation are most frequently affected. Female part of the population is affected 1.34 times more(10). During the 14 years' investigation at the Howard University, there were 58 skin malignancies in black population – only 1.5% of all tumors. BCCs were found in 7 patients or 12%, out of which 6 cases on the scalp (85.7%). In China, in those with tumorous facial skin changes, 20% of the patients had tumors below the line connecting the tragus and lip corner, while 44.4% had planocellular cancer above this line (11).

In the material studied, BCCs were most common on the nose – 20, and then on the nasolabial sulcus – 9, zygomatic region – 8. They were least frequent on the auricula and cheek – 1 case each.

BCCs were situated on the face in 94.53% of the cases. Out of that on the nose in 40%, then in the zygomatic region – 36.36%, frontal region – 10%. Facial BCCs were similarly common in females, while in men BCCs is most frequent in the zygomatic region, then nose and temporal region (5).

Regardless of the differences in BCC incidence in various regions, there was no correlation between the anatomical site of the primary tumor and its relapse (12).

As for the clinical picture, authors usually describe 5 BCC forms. Such a classification does not

have much relevance for clinical practice; they are usually divided into infiltrant and circumscribed/limited types. Ulcus rodens is clinically hardly distinguished from ulcus terebrans, except for their clinical course after longer monitoring (which is therapeutically suboptimal). Clinically, pigmentous and superficial BCCs are also hardly distinguishable. At clinical presentation, two forms are usually clearly recognizable – ulcerous and nodular – most common in the investigated material. There were 37 nodular cases (27 men; 15 women) and 36 with ulcerous form (17 men; 19 women) (table 3). For both forms BCC is more frequent in men in those without relapse, while in those with relapse it is more common in women (table 4).

Relapses after complete excision are relatively common – 0.5% to 48%, depending on the therapy (3).

The problem of relapses after surgical excision is partly alleviated through the Mohs technique of intraoperative microscopic examination of the specimen and evaluation of the completeness of surgery. Mohs' technique requires much material and organisational resources. The technique has its indications and relative contraindications (13).

In the studied material, relapses occurred in individuals averagely aged 64.87 years (67.00 for men; 63.81 for women), while for BCC without relapse average age was 75.53 years (74.90 for men; 76.57 for women).

According to some authors, skin BCC more frequently relapses in men (30 men vs 20 women, out of 50 in total).

In the studied material relapses were more common in women (16) than in men (8) out of total 24 patients. The difference is not statistically significant, since this is probably a small patient series.

Various factors influence relapses, but it is believed that BCCs which relapse are more aggressive from the start and that their behaviour can be foreseen based on the histomorphological character (14).

There is an interesting observation that relapses were not found in operated tumors sized <2 cm in diameter (15). Relapses are most commonly situated on the dorsal aspect of the nose, medial canthus and nasolabial groove (15). Nasal relapses were most common in the studied group (5 patients), nasolabial sulcus (4 patients), temporal region (4), zygomatic region (3), forehead (3).

In BCCs with tumor presence on the edges of the histopathologic specimen relapses occur in 39% of the cases after 5 years' period.

Surgical treatment is a predominant modality. Surgical excision should be defined by a precise, clear diagnosis of the lesion and marginal status. Postoperative defect can be reconstructed primarily, delayed primarily or secondarily. Excision has clear

advantages in BCC treatment because of the histologic control of tumor nature and resection borders, rapid wound healing and good cosmetic results (16). It can be used for all BCC types and all tumor sites. With this method a part of healthy tissue is sacrificed and it is less appropriate for multiple lesions. Reconstruction of some structures is also necessary in order to obtain good functional and cosmetic result. A disadvantage of surgical excision is only in the poorer histologic control of treatment completeness compared to Mohs technique (17,18).

There are no clear and definite opinions on the margin size. For smaller tumors 3-5 mm will do fine, while for larger tumors the margin is also wider. For relapses, the suggested margin width is 1.5–3 cm (18–22).

Epstein suggested the margin of 2 mm as appropriate for tumors smaller than 1 cm, nodular and well delineated. Such a margin is not appropriate for larger lesions, aggressive and poorly circumscribed tumors, the evolution of which is characterized with so called subclinical spread.

Other authors think that tumors smaller than 2 cm and well delineated require margin of 4 mm. For tumors larger than 2 cm with subclinical spread margins cannot be precisely defined (22,23).

Based on these as well as other reports, margins of 2-4 mm may be recommended for nodular, well delineated tumors sized up to 2 cm. For those larger than 2 cm, excision with margin of 1 cm or more is usually suggested. Also, for these tumors (>2 cm, with aggressive course, relapsing), Mohs' technique offers best chances for cure and maximally preserves healthy tissue.

Reconstructive interventions, especially if complex, should be undertaken only if the excision margins are clearly defined, ie. if the excision was done all the way into the healthy tissue.

In the studied material, revision of histopathologic smears was performed; cancer plaques was found in the excision edges, meaning that surgical treatment was not radical enough in the first act. In BCCs without relapse positive margins were found in 33 out of 52 cases, and in recidivant BCCs 12 out of 24 were positive. However, frequency differences obtained were not significant (Table 6), suggesting that BCC relapse does not depend on the radicality of first act surgery.

A typical BCC who will eventually relapse is situated on the sun-exposed skin in males aged 60 years; it does not have ulcerated surface, its thickness is up to 3 mm with Clark's IV invasion degree, infiltrant with microscopic type growth, without cysts, poorly formed peripheral palisades, with cellular pleomorphism, small groups of cells, angular shape and infiltrant invasion borders. In the studied material, BCCs more frequently metastasize in women, averagely aged 70.19 years, and are commonly ulcerous clinically.

CONCLUSION

Based on the results obtained, the following facts can be emphasized: most common clinical BCC forms are nodular and ulcerous; there is not any statistically significant correlation between these forms and tumor relapse, nor any sex-related differences between relapsing BCCs and those which did not relapse. In spite of adequate surgery, histologic analysis demonstrated the presence of cancer plaques in the resection edges in 59.21% cases of removed BCCs. However, these cancer plaques did not significantly influence BCC relapses, meaning that margin size in tumor resection does not have any decisive role regarding relapse.

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UTICAJ VELIČINE MARGINE KOD RESEKCIJE BAZOCELULARNIH KARCINOMA KOŽE NA NJIHOVO RECIDIVIRANJE

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SAŽETAK

U radu se analizira 76 pacijenata nakon hirurškog tretmana bazocelularnog karcinoma kože lica, kliničke karakteristike tumora, njihova incidenca po faktorima pola, starosti i lokalizacije. Pacijenti sa relapsom posebno su nadzirani. Analizirani su histopatološki preparati sa ostacima tumorskih ćelija na marginama. Do relapsa je podjednako dolazilo kod pacijenata kod kojih je radikalnost tretmana bila postignuta i onih kod kojih to nije, što znači da relaps bazocelularnog karcinoma ne zavisi od stepena planiranog radikalnog tretmana, već i od drugih faktora.

Ključne reči: bazocelularni karcinom, koža lica, relaps