Clinical and Pathological Features of the Giant, Invasive Basal Cell Carcinoma of the Scalp

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Background: The giant, invasive basal cell carcinoma of the scalp is a rare clinical form of this tumor that appears on the skin, but may spread to some of the following structures: soft tissues of the scalp, bones, meninges, and the brain. In literature, so far, it is known as the GBCC. It is caused by aggressive BCC subtypes.

Methods: We will present here a research of clinical and pathological features of 47 pathological specimens in 31 patients where the following features were examined: the dimension of the tumor, the dimension of the tissue segment, tumor area, segmentation area, resection margin width, microscopic resection margin status, tumor invasion level, and the outcome.

Results and Conclusions: We have concluded that microscopic resection margin dimensions from 1 to 10 mm are safe and that relapse occurrences in giant, invasive BCCs of the scalp depend on microscopic resection margin dimensions, resection margin status, tumor invasion levels, risky occupation, and risky behavior of the patient.

Key Words: Giant; invasive basal cell carcinoma; scalp; relapse; resection margins

Abbreviations: AJCC, American Joint Committee of Cancer; NMSC, Non-melanoma skin cancer; MIN, Microscopic dimensions of resection margins; INH KCS, Institute for neurosurgery of the Clinical Center of Serbia; KOPRH KCS, Clinic for Burns, Plastic and Reconstructive Surgery of the Clinical Center of Serbia; GBCC, Giant basal cell carcinoma; BCC, Basal cell carcinoma; BSC, Carcinoma basosquamosum; BCCs, Superficial form of BCC; BCNS, Basal cell nevus syndrome; 5-FU, 5-Fluorouracil (Efudix); EHO, Echosonography; NMR, Nuclear magnetic resonance imaging; CT, computed tomography

Basal cell carcinoma (BCC) is the most frequent malignant skin tumor.[1 4] It is characterized by high incidence and low mortality rate (<0.1%),[2] with rare occurrence of metastasis (<0.1%).[5,6] Exposure to ultraviolet radiation is a main predisposing factor for BCC development. Individual characteristics associated with the increased risk are light skin, slow tanning on the sun, and blond or red hair. Nevertheless, in 20% of patients BSS occurs on the skin areas that are not sun exposed.[3]

BCC arises from immature, pluripotent cells lodged in the basal layer of epidermis and follicular epithelium, sebaceous glands, and other adnexa of skin. It is characterized by a local infiltrative and sometimes destructive growth.[7]

There are 3 recognizable growth forms: nodular, superficial, and morpheaform.[2] These histological types may have clinical manifestations in more than 10 clinical forms.[7] For surgeons, the most important classification is the classification to aggressive and non-aggressive. The first group includes infiltrative, morpheaform, micronodular, basal, and squamous as well as mixed forms of infiltrative/morpheaform and nodular-infiltrative,[2,8 10] and the non-aggressive group includes pigmented and nodular subtype and superficial only conditionally.[2,11,12] There is evidence that the superficial subtype carries a high relapse risk after routine excision, curettage, or topical treatment due to the multicentric expansion.[2]

The most common areas where BCC occurs are on the head and neck 70% 98.4%,[13 17] then arms and back, frequently sun-exposed sites. BCC occurs on the scalp, 21% 29%[13 17] mostly in temporal and retroauricular areas.[18]

The giant, invasive basal cell carcinoma of the scalp is a rare clinical form of this tumor. Apart from the skin, it spreads to one of the following structures: scalp soft tissue, bones, meninges, and the brain. In literature, so far, it is known as GBCC. It is caused by aggressive BCC subtypes with possible metastasis. It is the exception to the rule. Surgery is the only treatment and that means major mutilating surgeries and reconstruction surgeries.

Since 1973 till today, there are 74 reported cases of patients with BCC that grow into the scalp and skull; this type is known as giant (if the tumor is more than 5 cm), invasive, aggressive (considering the way it spreads), or ulcus terebrans (characterized by ulceration)[15,19 26] (Fig. 1). How can these tumors be classified? The size is more than F1
2 cm, apart from the skin, and they spread to the soft tissue of the scalp, sometimes the bones, and sometimes the brain. There is no precise classification and treatment protocol.

The American Joint Committee of Cancer has developed a classification system for SCC and other skin cancers (cutaneous squamous cell carcinoma and other cutaneous carcinomas).

There are separate staging systems in the seventh edition of the American Joint Committee on Cancer's (AJCC) *AJCC Cancer Staging Manual* for carcinomas of the eyelid versus other skin surfaces (Table 1). T1 AQ2

Publications on the giant, aggressive BCC of the scalp show histological BCC subtypes,[2,8 12] types of reconstructive surgery,[15,24,27 30] and tendency to metastasis.[31] Even after detailed research, we have not found publications that elaborate respective tumor margins.

PATIENTS AND METHODS

Between 1998 and 2007, we processed 111 pathological specimens from 42 operated patients with giant, invasive BCC of the scalp. We have performed the statistical analysis in 31 patients and we have processed 47 tumors (pathohistologic process according to specific criteria using parameters from Table 2). The first group included T2
patients with relapse, from number 1 to 24 (had generally 3 operations under general anesthesia before undergoing a surgery in our institution), and other patients with primary tumors, from number 26 to 38 (column 1, Table 2). We have studied and measured the following features: tumor dimensions, dimension of the segment of tissue, tumor area, segmentation area [according to the formula tumor

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size = log 10 (D1 × D2)],[32] width of resection margins in patients with and without relapse, microscopic status of resection margins (if the tumor spread to margins or not), as well as BCC subtypes, tumor invasion level, risk factors, and treatment results.

We have processed the obtained results using statistical methods for data analysis: the Student *t* test, the equality of variance test, the Mann-Whitney *U* test, and the Pearson product-moment correlation coefficient. The clinical and epidemiological features were studied and will be elaborated in another research project.

RESULTS AND DISCUSSION

From 1998 till 2006, there were 1980 reported cases of BCC of the scalp (29.1%) and 6804 (70.9%) reported BCC cases in other locations that had undergone surgery and histopathological examination. Since 1980, 684 (34.5%) reported cases of BCC of the scalp were from the group of invasive subtypes; the other 1296 (65.5%) cases were noninvasive subtypes (superficial, nodular, pigmented, etc). Out of 684 cases of BCC of the scalp, 42 patients had 53 tumors, pT4 stage, in total 7.7%.

In terms of sampling, there were significantly more patients of older age, average age 63 years,[33,34] significantly more male patients, 66.7% in comparison to 33.3%,[3,35] and all were Caucasian.[1,33,36,37] The majority of patients had relapse, and were exposed to risk factors (many years of sun exposure, farmers) and/or risky behaviors (alcoholism and/or laceration several years prior to the tumor). This data concur with results of previous research.[2,3,33,38]

When it comes to subtypes, all histological subtypes were aggressive in the group with and without relapse. The infiltrative subtype occurred with significant probability in 66%, nodular-infiltrative in 23%, and 11% other.

Several researches, conducted on patients with large or giant BCCs, confirm that these tumors cause aggressive forms of BCC. The most common of the scalp (but also in other locations) is also an infiltrative subtype 35%, morpheaform 10.9%, micronodular 4.4%, and basal and squamous 2.7%.[2,11,12] The aggressive growth model has more than 86% of tumors with mixed histology,[8] and from all recurrent BCC, 65% belong to the aggressive type.[2]

TABLE 1. Primary Tumor (T) for Non-Eyelid Carcinoma[a,b]

TX	Primary tumor cannot be assessed
T0	No evidence of primary tumor
Tis	Carcinoma in situ
T1	Tumor ≤2 cm in greatest dimension with <2 high-risk features[c]
T2	Tumor >2 cm in greatest dimension or Tumor any size with ≥2 high-risk features[c]
T3	Tumor with invasion of maxilla, mandible, orbit, or temporal bone
T4	Tumor with invasion of skeleton (axial or appendicular) or perineural invasion of skull base

[a]Reprinted with permission from AJCC: Cutaneous squamous cell carcinoma and other cutaneous carcinomas. In: Edge SB, Byrd DR, Compton CC, et al., eds.: *AJCC Cancer Staging Manual*. 7th ed. New York, NY: Springer, 2010, pp 301–314.
[b]Excludes cutaneous squamous cell carcinoma of the eyelid.
[c]High-risk features for the primary tumor (T) staging.

When we are speaking about treatment outcome, relapse occurred in 64.5% of patients in comparison to 35.5% with no relapse. Patients with relapse were monitored from 5 to 72 months (average of 38.7 months) and patients with no relapse were monitored from 12 to 84 months (average 44.6 months). For patients with Exitus letalis (4 patients with relapse and 1 patient without relapse), the survival rate was on average 7.4 months. No metastases were found in deceased patients.

There are no data in literature that examine the positive and negative outcomes in giant, aggressive BCCs apart from data on the survival of patients with BCC metastasis. Review papers, published by authors from England, included 205 patients with BCC metastasis; patients live, on average, another 8 months after the first signs of metastasis have been noticed.[31]

Histopathological Features of Giant, Invasive BCC of the Scalp and Relapse

Tumor dimensions were taken into consideration. The large diameter of tumors in the group with relapse was on average 34.2 mm; in the group without relapse, it was on average 57.9 mm. We have compared the value of the large diameter of tumor and proven that the size is not statistically significant. We had a similar result after examination of small-diameter tumors. The small diameter of tumors in the group without relapse was on average 38.3 mm; in the group with relapse, it was on average 23.4 mm.

The segmentation and tumor area were further analyzed. By applying the correlation analysis techniques, it has been confirmed that there is a linear connection between the growth of the segmentation area and the tumor area because the result was a high Pearson correlation ratio of 0.936.

In patients with and without relapse, the segmentation area is significantly larger than in cases without relapse; the relapse is less likely to occur if the removed tumor-affected tissue is large (Chart 1). F2

And finally, according to the hypothesis, the resection margin dimensions (minimal distance between the sample edge and the tumor—MIN) serve as criteria to determine whether the tumor has been completely removed or not. In the group with relapse (MIN) it has a maximum of 10 mm, on average 2.4 mm; in the group without relapse, it has a maximum of 8 mm, on average 3.5 mm (Chart 2). F3

The reason for these findings may lie in the fact that the identification and visualization of the resection line is far more difficult

Fig 1 4/C

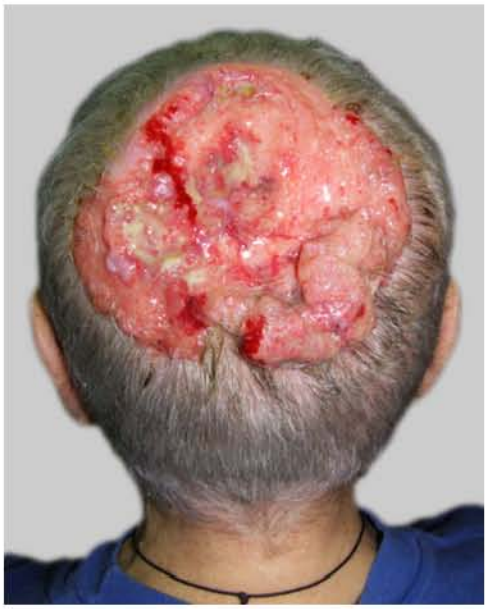

FIGURE 1. An example of the giant, invasive relapse of BCC of the scalp.

TABLE 2. Clinical and Pathological Features of BCC, pT4 Stage

Case	Br. Tu.	DI >	DI <	PI	DT >	DT <	PT	MIN, mm	Subtype	Invasion	Margins	Outcome
1	1	24	13	244.92	10	8	62.8	2	nod.-infilt.	fascia	+	rec
1	2	23	14	252.77	15	10	117.1	1	nod.-infilt.	galea	+	rec
1	3	14	7	76.93	10	5	39.25	1	infiltrative	galea	+	rec
1	4	18	10	141.3	11	7	60.4	1	infiltrative	galea	+	rec
1	5	22	14	241.78	14	9	98.9	1	nod.-infilt.	galea	+	rec
1	6	54	43	1822.77	40	7	219	4	infiltrative	fascia	close	rec
1	7	35	34	934.15	13	9	91.8	7	infiltrative	fascia	close	rec
1	8	15	9	105.97	5	3	11.7	1	infiltrative	fascia	+	rec
1	9	20	13	204.1	8	5	31.4	1	infiltrative	fascia	+	rec
3	10	118	67	6206.21	85	60	4003.5	4	infiltrative	muscle	+	rec
3	11	60	36	1695.6	50	30	1177.5	1	infiltrative	fascia	+	rec
4	12	42	36	1186.9	40	34	1067.6	1	nod.-infilt.	galea	+	rec
4	13	23	14	252.7	15	10	117.7	1	nod.-infilt.	galea	+	rec
4	14	65	30	1530.7	50	27	1059.7	1	morfea	fascia	No tu	rec
AQ3 4	15	67	38	1998.6	50	30	1177.5	1	morfea	fascia	Close	rec
4	16	58	34	1548	48	30	1130.4	1	morfea	fascia	Close	rec
5	17	70	70	3846.5	40	20	628	1	infiltrative	cartilage	+	exitus l.
6	18	50	40	1570	35	25	686.8	1	infiltrative	cartilage	+	rec
7	19	62	48	2336.1	30	20	471	1	metatip.	muscle	+	rec
8	20	43	30	1012.6	16	15	188.4	4	infiltrative	muscle	+	rec
8	21	47	20	737.9	20	15	235.5	1	infiltrative	muscle	close	rec
9	22	33	24	621.7	25	15	294.3	2	metatip.	muscle	+	rec
9	23	40	25	785	25	18	353.25	4	metatip.	muscle	+	rec
10	24	50	40	1570	38	25	745.7	4	infiltrative	muscle	+	rec
11	25	150	120	14.130	120	100	9420	2	infiltrative	muscle	+	rec
12	26	40	40	1256	25	8	157	1	infiltrative	muscle	+	exitus l.
14	27	70	45	2472.7	62	36	1752	5	infiltrative	galea	+	rec
14	28	12	7	65.9	12	7	65.9	1	infiltrative	brain	+	exitus l.
15	29	24	17	320.2	16	10	125.6	1	nod.-infilt.	fascia	+	rec
16	30	98	80	6154.4	87	67	5829	4	nod.-infilt.	muscle	close	rec
17	31	40	30	942	35	30	942	3	nod.-infilt.	muscle	+	rec
18	32	67	50	2629.7	40	40	1256	1	infiltrative	galea	+	rec
20	33	90	40	2826	27	15	317.9	1	infiltrative	muscle	+	rec
21	34	46	40	1444.4	20	20	314	10	infiltrative	muscle	+	rec
23	35	40	15	471	4	4	12.56	6	nod.-mikr.	muscle	+	rec
24	36	107	90	7559.5	90	70	4945.5	6	infiltrative	muscle	+	exitus l.
26	37	150	85	10,008.8	140	80	8792	2	infiltrative	muscle	+	primary t.
27	38	45	38	1342.3	40	34	1067.6	1	nod.-infilt.	galea	+	exitus l.
28	39	50	42	1648.5	40	30	942	1	infiltrative	muscle	+	primary t.
29	40	110	100	8635	80	50	3140	1	infiltrative	bone	no tu	primary t.
30	41	95	70	5220.2	90	70	4945.5	1	nod.-infilt.	periost	close	primary t.
31	42	75	30	1766.2	50	20	785	4	metatip.	muscle	close	primary t.
33	43	70	57	3132.5	52	30	1224.6	8	infiltrative	fascia	close	primary t.
34	44	110	35	3022.2	18	10	141.3	6	infiltrative	muscle	+	primary t.
35	45	42	26	857.2	25	18	353.2	4	infiltrative	muscle	close	primary t.
37	46	30	30	706.5	12	9	84.7	5	infiltrative	muscle	close	primary t.
38	47	105	95	7830.3	90	70	4945.5	5	infiltrative	muscle	+	primary t.

DI > indicates large diameter of the tissue segment; DI <, small diameter of the tissue segment; PI, segmentation area; DT >, large diameter of the tissue segment; DT<, small diameter of the tissue segment; PT, segmentation area; no tu, no tumor; close, at 0.5 mm from the resection edge; +, positive, affected by tumor (depth, width, and both); MIN, minimal distance of the tumor from the resection edge; rel, relapse; primary t., primary tumor; exitus l., exitus letalis.

and less precise when planned in relapse cases because of the scar from the previous surgery, in comparison to the scission planning in case of primary tumor.

According to the prospective study including 757 BCCs, diameter up to 2 cm in 600 patients, it has been confirmed that the incidence of incomplete excision depends upon the performance of the surgeon, the minimum excision margin, and the BCC subtype. This research has shown that incomplete excision occurred in 27 tumor cases (4%) with macroscopic dimensions from 1 to 5 mm. This research did not include groups with relapse.[39]

There is no available research on macroscopic dimensions of resection margins in giant BCC, especially those of the scalp.

In the group with relapse, there is significantly greater probability of margin status marked with number 3.

In the group with relapse, it is certain that these patients will relapse (that means third surgery in general anesthesia and further

disease progression). In the group without relapse, the group of primary tumors, 45.4% of patients are likely to relapse because the margins are positive; the remaining 54.6% of patients have a tumor at a distance of less than 0.5 mm from the nearest resection line. These patients did not relapse during the average monitoring period of 44.6 months, which means that even the free margin of 0.5 mm results in less frequent relapse. These patients have tumors that have spread to the muscle or galea. If these patients were diagnosed with a bone tumor or tumor in the endocranial content, the margin of 0.5 mm would probably not have been enough for the patient not to relapse. This can be elaborated during future research of resection margins of bones.

A total of 2.8% of patients had relapse tumors (1 pathological specimen), and 9.2% (1 pathological specimen) of patients with primary tumors will probably not relapse because the resection edges had no tumor. In case of perineural spread of tumor, there will be no relapse. The subtype in these 2 pathological specimens is infiltrative (bone) and morpheaform (fascia). All relapsed patients underwent a second surgery, and in 80.5% it will not be the last due to the tumor at margins of excision. For patients with no relapse, it was the first surgery.

In patients without relapse (with primary tumor), if in 45.4% there are positive margins, it means that it is just a matter of time when they will relapse.

There is an increased risk of relapse in patients with tumors that are located at a distance less than 0.5 mm from the resection line.

MIN (minimum distance of the tumor from the resection line) is 1 8 mm, with an average of 3.6 mm in 45.4% of primary tumors (5 pathological specimens) and 1 10 mm in 16.7% of relapsed patients (6 pathological specimens); the tumor is located at a distance of less than 0.5 mm. These findings indicate that the tumor (histological margin) is located between 1 mm and 10 mm from the macroscopically visible (surgical) tumor margin.

There is no available research in the literature related to surgical and histological margins in giant BCC.

CONCLUSIONS

The research imperative was to draw conclusions on the length of the resection line in millimeters (histological margin) so that the tumor can be radically removed without the risk of relapse. There is no doubt that it has to be between 1 and 10 mm in comparison to the surgical or microscopic tumor margin.

We have concluded that the relapse does not depend upon the dimensions of a tumor or BCC subtype. In fact, relapse in giant, invasive BCC of the scalp depends upon macroscopic dimensions of resection margins, resection margin status (with or without tumor), tumor invasion level, risky occupation, and risky behavior of the patient (chronic alcohol intoxication and injuries of the scalp).

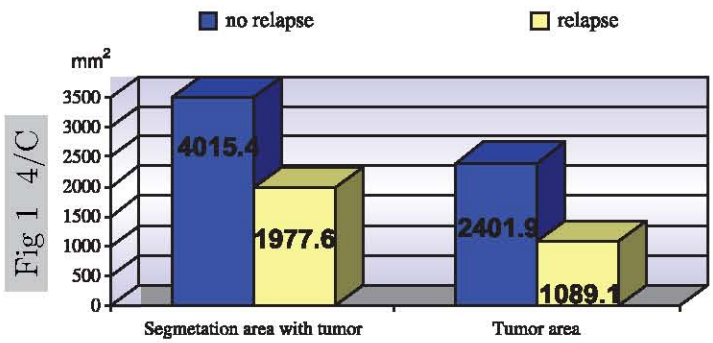

Fig 1 4/C

CHART 1. The segmentation area and the tumor area in the group with and without relapse.

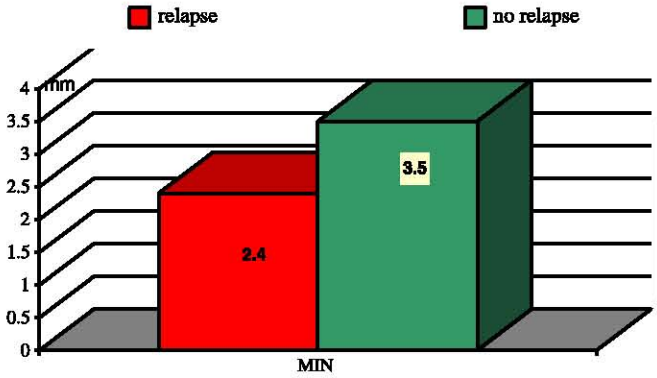

Fig 2 4/C

CHART 2. Average macroscopic resection margin dimensions (mm).

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