

An evaluation of neglected tumors: Giant basal cell carcinomas

 Ozgur Agdogan¹,  Alper Ural²

¹Istanbul Reyap Hospital, Clinic of Plastic Surgery, Istanbul, Turkey

²Department of Plastic Reconstructive and Aesthetic Surgery, Faculty of Medicine, Kahramanmaraş Sutcu Imam University, Kahramanmaraş, Turkey

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Abstract

Aim: Giant basal cell carcinomas (GBCCs) which constitute approximately 1% of basal cell carcinoma are aggressive tumors characterized by deep tissue invasion, high risk of metastasis, and poor prognosis. We aimed to analyze demographics, treatment, and outcome of patients with GBCCs in this study.

Material and Methods: Between 2017 and 2020, nine patients applied to Department of Plastic and Reconstructive Surgery and underwent surgical treatment for GBCC were included in the study. Age, sex, localization, tumor size, treatment and comorbid diseases of the patients were reviewed retrospectively.

Results: Six patients were male and three patients were female. The mean age was 68.6 ±3.8 years, ranging from 62 to 78 years. The tumors were located on cheek (n=4), frontotemporal region (n=2), cheek nose lower eyelid junction (n=1), scalp (n=1) and dorsum of the hand (n=1). The largest of the lesions was 8x10 cm and the smallest was 4x6 cm. The defect sizes following tumor removal ranged from 24 to 80cm² with an average of 43,6 cm². Nodular GBCC was the most common histological subtype (n=6), followed by superficial (n=2) and morpheaform (n=1). Two patients were skin grafted after excision of GBCC whereas cheek rotation flaps (n=2), cervicofacial flaps (n=3) and pedicled forehead flaps (n=2) were utilized for reconstruction.

Conclusion: Since health insurance covers oncologic surgery and there is an extreme ease to reach a health professional in our country, the most common reason to still encounter GBCC seems like negligence. GBCCs are rare, but they need proper interventions when detected. Aggressive surgery should not be avoided for better outcomes.

Keywords: Basal cell cancer; malignant neoplasms neglected diseases; reconstructive surgery

INTRODUCTION

Non-melanocytic skin carcinomas account for one-third of cancers diagnosed annually, and over 75% of non-melanotic skin cancers are basal cell carcinomas (BCC) (1, 2). BCC have slow growth pattern and non-aggressive behavior; however, histological subtypes such as morpheaform, micronodular and infiltrative are more aggressive. BCC, which has a lifetime risk of developing over 30%, arises from pluripotent cells of the epidermis and grows at a rate of 1.0 mm in diameter per year (2,3,4). GBCCs, defined as BCCs that are 5 cm or greater in diameter, are characterized by rapid growth pattern, deep tissue invasion, increased metastasis risk and poor prognosis (5). GBCCs, which constitute approximately 0.4-1 % of basal cell carcinomas, is more common in men over sixty years of age (3,6). While BCC frequently occupies the head and neck region, GBCCs are reported to be found more often in areas usually covered by clothes

since elderly patients are prone to receive treatment for the disease if socially disturbing but delay it unless the tumor bleeds or becomes malodorous (1,7). Even it may take GBCC ten years or more to evolve from BCC, the fact that mean survival is only 8 to 10 months once metastasized, necessitates early diagnosis and treatment of GBCC (6,8).

The American Joint Committee on Cancer (AJCC) describes GBCC as a BCC larger than 5 cm in diameter and super giant basal cell carcinoma if it has a diameter larger than 20 cm, nevertheless some authors define GBCC as BCCs larger than 10 cm in diameters (9,10,11). The TNM system classifies them all as T3 tumors (5). The most important feature to determine the degree of tumoral invasion is the size, however the depth of invasion is not considered an absolute determinant of prognosis (4,5). The metastasis rate increases proportionally with tumor size; therefore, GBCCs (1.9%) have a higher rate of metastasis compared to BCCs (5).

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Corresponding Author: Alper Ural, Department of Plastic Reconstructive and Aesthetic Surgery, Faculty of Medicine, Kahramanmaraş Sutcu Imam University, Kahramanmaraş, Turkey, E-mail: alper_ural@yahoo.com

The two main reasons of late presentation for seeking treatment are negligence and psychophysical impairments (5). The presence of miasis in some giant skin tumors can be also considered as an evidence of neglect (9, 12). Low socioeconomic status, inadequate self care, low educational status and poor hygienic conditions can be frequently encountered in patients presenting with giant skin tumors (3,6,7). The treatment modalities for GBCC are surgery, topical immunotherapy, cryotherapy and radiotherapy (RT), however the most common treatment method is surgery (7). Surgical treatment of GBCC can also be challenging since surgical resection of GBCC with proper margins often results in large and complex soft tissue defects and necessitate individualized reconstructive options including skin grafts, local flaps, perforator flaps, regional flaps and free flaps (1,3,6,7,11). To the best of our knowledge, studies' concerning GBCC is scarce in our country. Therefore, in this study, we aimed to analyze the demographics, treatment and outcomes of patients with GBCCs in our population.

MATERIALS AND METHODS

Between 2017 and 2020, nine patients applied to Department of Plastic and Reconstructive Surgery underwent surgical treatment for GBCC were included in the study. Patients whose histopathological reports were incompatible with basal cell carcinoma and those did not receive surgical treatment for GBCC were excluded. Informed consent was obtained from each patient. Age, sex, localization, tumor size, treatment, anamnestic characteristics and comorbid diseases of the patients were analyzed retrospectively. The mean age and mean flap area size was calculated. The longest follow-up was

two years whereas the shortest follow up period was six months.

RESULTS

The mean age was 68.6 ± 3.8 years, ranging from 62 to 78 years. Six patients were male and three patients were female. The most common anatomical site was the cheek. The tumors were located on cheek (n=4), frontotemporal region (n=2) cheek nose lower eyelid junction (n=1), scalp (n=1) and dorsum of the hand (n=1). The main complaints of the patients were decreased quality of life, discomfort, itching, bleeding and malodor. The largest of the lesions was 8x10 cm and the smallest was 4x6 cm in size following tumor removal, defect sizes ranged from 24 to 80cm² with an average of 43,6 cm². Nodular GBCC was the most common histological subtype (n=6), followed by superficial (n=2) and morpheaform (n=1) types. Two patients were residents in rural areas and seven were in urban. Two patients were skin grafted after excision of GBCC whereas cheek rotation flaps (n=2), cervicofacial flaps (n=3) and pedicled forehead flaps (n=2) were utilized for reconstruction of the defects in seven patients following GBCC removal. Recovery of eight patients were uneventful, however local wound infection seen in one of the patients who has diabetes mellitus. We managed it using topical ointments, antibiotics and daily dressings. Postoperative radiation therapy was not given to any of our patients. All of the patients included in the study were referred to medical oncology department. Patients were evaluated in terms of age, gender, location of the lesion, main complaint, diameter of the lesion, residence, and comorbid diseases. The details are shown in Table 1.

Table 1. Patients were evaluated in terms of age, gender, localization of the tumor, main complaint, diameter of the lesion, residence and comorbid diseases

Case	Age	Gender	Localization	Complaint	Tumor size(cm)	Residence	Comorbid disease
1	65	M	Frontotemporal	Decreased life Quality	8x10	Urban	-
2	78	M	Hand	Impaired cosmesis	6x6	Urban	Gastric cancer
3	78	F	Nose, Eyelid, Cheek	Itching	5x8	Urban	Hypertension
4	64	M	Scalp	Malodor	4x6	Urban	-
5	71	F	Cheek	Bleeding	5x7	Urban	Alzheimer
6	67	M	Cheek	Bleeding	5x8	Urban	Anemia
7	62	F	Cheek	Impaired cosmesis	8x10	Urban	-
8	71	M	Cheek	Malodor	4x7	Rural	DM
9	62	M	Frontotemporal region	Decreased life quality	5x6	Rural	-

Case 1

A 65-year-old male patient admitted as a result of non healing wound on the left forehead and cheek since 20 years. Detailed story revealed it has enlarged recently and bleeds sometimes. The major cause of presentation was the blood stains on his pillow and shirt formed by tumor bleeding. Our patient was a farmer and lived in urban. His examination revealed an irregular bordered, fistulated and bleeding ulcer about 8x10 cm in size on left frontotemporal area involving the lateral eyebrow. Any palpable lymph node was not found. An incisional biopsy was performed for suspected malignancy and diagnostic

purposes. Histopathologic evaluation confirmed the diagnosis of basal cell carcinoma. Head and neck imaging was also carried out by computed tomography (CT) due to giant basal cell carcinoma. Tumor was excised with 1 cm intact margins. The defect was reconstructed with a split thickness skin graft. Six months after the first operation, a crusty lesion appeared on the left eyebrow. Excisional biopsy was performed considering a possible relapse, however no sign of malignancy was determined as a result of histopathologic evaluation. The stab wound due to biopsy was left to secondary healing and the patient was followed up with 3 month regular intervals (Figure 1).

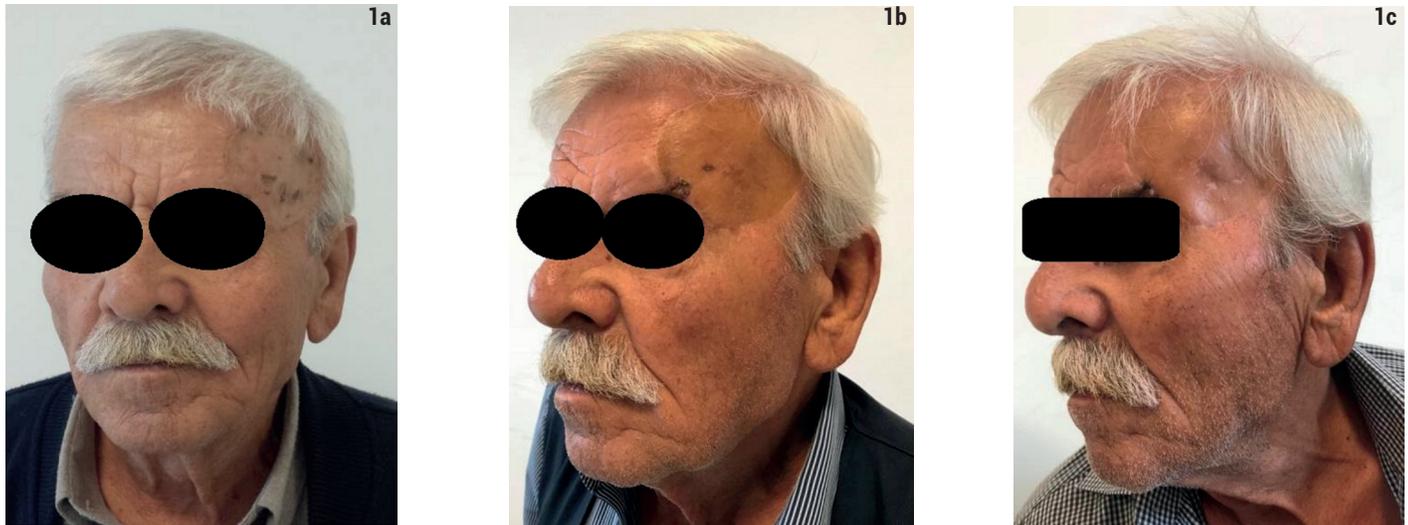


Figure 1. Postoperative 2 month (a), 6 month (b) and 18 month(c) follow up view

Case 3

A 78-year-old female patient was brought by her relatives because of the bleeding of the tumour involving the left side of the nose, left eyelid, and left cheek, which has existed for about 10-15 years. Her main complaint was itching. She was taken care by her sons due to insufficiency of self care. In her examination, a 5x8 cm sized irregularly bordered chronic wound was observed on the left side of the nose involving left medial canthus,

and cheek. There were no palpable lymph nodes. An incisional biopsy was performed from 2 different points for suspected malignancy and diagnostic purposes. Histopathologic evaluation confirmed the diagnosis of BCC. The patient was using medicine for hypertension. GBCC was excised with a 1 cm intact margin and the resultant defect was reconstructed using forehead flap under general anesthesia (Figure 2). She had an uneventful recovery and showed no signs of relapse during follow ups.



Figure 2 a. Giant basal cell carcinoma of the cheek involving nose and eyelid b. The defect after GBCC removal c: Reconstruction via supratrochlear pedicled forehead flap is seen on immediate postoperative photo d. Two months postoperative view

Case 7

A 62-year-old woman applied because of non healing wound on the left cheek about 15 years. Her basic complaint was impaired cosmesis. She was surprisingly also a healthcare worker. An 8x10 cm diametered hyperpigmented, fistulated, cicatricial and irregularly bordered chronic wound was found on the left cheek. There were no palpable lymph nodes. Incisional biopsy was performed for diagnosis and

histopathologic evaluation confirmed the diagnosis of basal cell carcinoma. Head and neck imaging was also carried out by computed tomography (CT) due to giant basal cell carcinoma. Neither deep tissue invasion nor cervical lymph node involvement was determined by CT evaluation. GBCC was excised with a 1 cm intact margin and the resultant defect was reconstructed with a cervicofacial fasciocutaneous flap (Figure 3). She had an uneventful recovery and showed no signs of relapse during follow ups.



Figure 3 a: A 62 year-old woman with GBCC on lateral cheek extending to temporal region b: Aggressive excision of tumor c: Flap design d: Two months postoperative view e: Flap shows good texture and color match on postoperative sixth month

DISCUSSION

Basal cell carcinoma is the most common skin cancer of caucasian population however, GBCCs are not frequently seen since most patients receive treatment before the tumors reach large sizes (6). Nonetheless, late presenting patients with GBCC can still be encountered. Environmental factors, such as exposure to sunlight, radiation, trauma, smoking and exposure to chemicals like arsenic and coal-tar are important risk factors associated with basal cell carcinoma (2). The causes of GBCC development are not exactly clear but rural area residency, alcohol consumption, occupation, psychophysical disorders, low socioeconomic and educational status, poor social or family support have been reported to give rise to GBCC (3). Morpheiform and infiltrating histopathologic subtypes have a higher risk of evolution to GBCC and perivascular or perineural invasion can increase the spread (3).

Negligence of some patients probably relies on GBCC symptoms are mild unless tumor begins to impair quality of life. An untreated GBCC can often result in anemia and hypoproteinemia by bleeding as well as serious infection and even sepsis. GBCCs, especially located on midface and scalp can be more aggressive due to its proximity to cartilage and bone since they have tendency to ulcerate and bleed in this particular areas (5). In our series, male sex predominancy was obvious similar to previous studies (6,7). In addition, mean age of our patients is calculated as $68,6 \pm 3.8$ in this study. Our findings are therefore consistent with the reported mean age of 67.7 years in the literature (3). According to the literature, back

and face are the most common sites of GBCCs, although we observed a higher incidence for the facial area. Eight GBCC was located on head whereas one of our patient had GBCC on dorsal of his hand.

The main complaints of our patients were; decreased quality of life, discomfort, itching, bleeding, discharge and malodor. Two of the patients complained about the decreased quality of life while again two of them complained about their worsened appearance began to cause social discomfort. Therefore, 'impaired aesthetic appearance' is notable complaint for some patients to should be taken into account. However, applying to hospital and seeking for medical care just because of cosmetic aspect of such a devastating disease is nothing but ignorance. Despite six of our patients lived in urban they also delayed seeking treatment until the symptoms of GBCC have been inevitable. As it is extremely easy to reach family physicians or even county hospitals and health insurance covers all types of oncologic surgeries in our country, the reason why the patients have let their tumors grow to such large dimensions seems explainable only by ignorance as abovementioned. The only exception was one of our patient having Alzheimer disease brought by her son. Surgical treatment is the gold standard treatment and excision with 1 cm intact surrounding margins is recommended for GBCC (5,13). It is crucial to remove GBCC completely when detected since GBCC can metastasize to lymph nodes, bone and has a mean survival of approximately 8-10 months once lung metastasis exists (5,13).

No relationship was found between the risk of metastasis and the histopathological subtype (5,14). In a study investigating 50 GBCC patients, 72% of cases were reported as an aggressive histopathological pattern, 26% as a nodular variant and 2% as a superficial pattern (5,15). However, in another meta-analysis, 53% of GBCCs were nodular, followed by 20% with infiltrative pattern and 9% of morphea form (3,5,6). GBCCs larger than 5 cm in diameter have an incidence of 25% increased metastasis risk whereas GBCCs larger than 10 cm in diameter are associated with approximately 50% increased metastasis and risk of death (11, 16). The tumor dimensions were 5-10 cm sized in our series and no recurrence, invasion and/or metastasis findings were observed during follow-ups. During follow ups, only one of our patients developed a lesion on his eyebrow area in the 6th month after the initial operation. However, histopathological evaluation showed no evidence of malignancy. The most common metastasis sites for GBCC are the lymph nodes, lung, bone, skin and liver. Tumors larger than 3 cm in diameter; located on the midface, nose, or ears; aggressive histological subtypes including metatypical, morpheic and infiltrating subtypes are described as high risky (17). In addition, deep extension; perineural invasion; long-existing neglected tumors, Mohs surgery and recurrence of tumor after prior treatment have been associated with high risk(18).

Treatment modalities for GBCC consist of neoadjuvant therapy, cryotherapy, radiotherapy, topical and systemic chemotherapy, topical immunotherapy and surgery (7). Sanmartín et al. recommended oral acitretin and topical imiquimod usage together as a neoadjuvant therapy in order to reduce the tumor volume preoperatively since they work synergistically (19). Due to the high recurrence rate, no electrocauterization or CO₂ laser is recommended as therapeutic options (3,5). Cryosurgery may be feasible option only for superficial and small sized tumors (5,15). Radiotherapy should be considered as a palliative treatment, whereas chemotherapy is an alternative choice for metastatic or inoperable tumors (5). GDC-0449, an antineoplastic agent that inhibits the hedgehog signaling pathway, use in advanced GBCC and vismodegib, which acts in the same pathway, use has been reported in elderly and inoperable patients (11,20,21).

Although surgical excision is the principle treatment modality for BCC, patient preference and some other factors can lead to the choice of RT as the primary treatment modality. In a recent 5-year retrospective study, local control, cure and complete response rates of BCCs treated with RT were reported to be 93-96% whereas the recurrence rates were between 4-16% (22, 23). In a randomized trial which RT was compared to surgery, it was reported that RT treatment resulted with higher recurrence rates compared to surgery (7.5% vs. 0.7%), causing worse cosmetic results and more postoperative complications including even skin necrosis (24). RT is more efficient in primary cases, nodular histological subtypes and small sized tumors (22,23).

RT is a convenient adjuvant treatment option for palliation and local control in high-risk BCCs. Although RT is generally feasible for patients over 60 years of age with comorbid disease due to concerns about long-term sequelae, it should be borne in mind that RT is contraindicated in genetic conditions prone to skin diseases such as basal cell nevus syndrome, xeroderma pigmentosum and connective tissue diseases such as lupus and scleroderma (25). The postoperative RT has been widely accepted in reducing the rate of recurrence in high-risk patients. In certain patients, local control with postoperative RT can be achieved by 100% and adjuvant RT will be appropriate even if tissue margins are positive following a BCC removal (26). Therefore, the role of RT is of a great importance in primary BCC treatment and recurrent BCCs in terms of reducing the risk of relapse after excision.

The gold standard treatment for giant basal cell carcinomas is surgery, however the best results can only be achieved by working simultaneously with an oncologist. One more issue that should also be emphasized is that most of the patients in this study delayed seeking medical care or surgery not because of poverty or distance to health centers. Since health insurance covers oncologic surgery and there is an extreme ease to reach a health professional in our country, the most common reason to still encounter GBCC seems like negligence.

CONCLUSION

GBCCs are rare, but they necessitate proper interventions like wide resection and reconstruction operations as soon as patients are detected since this malignancy has a higher metastasis risk and poor prognosis. Therefore, one must conclude that 'less is more' is not relevant for GBCCs and aggressive surgery should not be avoided for better outcomes and survival rates.

Patient informed consent : Informed Consent forms are obtained for each patient

Conflict of interest: The authors declare that they have no competing interest.

Financial Disclosure: There are no financial supports.

Ethical approval: Since our study's design was a retrospective case series, ethics committee approval was not required.

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