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Basal cell carcinoma – principles of treatment

Базоцелуларни карцином – принципи лечења

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Базоцелуларни карцином – принципи лечења

SUMMARY

Basal cell carcinoma (BCC) is one of the most common malignant tumors in human medicine and the most common skin malignancy, with the largest number of lesions found on exposed parts of the skin, on the face, head, and neck. The average age of the patients is 60 years, with an increasing incidence in younger ages and an increased incidence in males.

The incidence of BCC is increasing and doubles every 25 years. Annually, there are approximately 1,000,000 newly diagnosed cases worldwide. The frequency of malignant skin tumors depends on the influence of external factors such as UV radiation and other biological properties of the skin with a higher incidence in fair-skinned people (Fitzpatrick type I and type II skin types).

BCC is a slow growing malignant tumor that arises from the basal layer of the epidermis, the outer layer of hair follicles, or the sebaceous glands. BCC can be locally invasive and, if neglected, can infiltrate surrounding structures (muscles and cartilage) and vital structures, which can ultimately lead to death.

The clinical presentation is very diverse and dependent on the histological subtype. Prevention is the most important and effective approach towards reducing the burden of BCC. The best treatment for BCC is surgical excision with confirmation and verification of surgical margins. The therapeutic goal is oncologic radical resection of the tumor, followed by reconstruction of the affected area for structure and optimal aesthetic result.

Keywords: carcinoma; basal cell; therapeutics; prognostic factors

САЖЕТАК

Базоцелуларни карцином (*BCC*) је један од најчешћи малигни тумор у хуманој медицини и најчешћи малигном коже, највећи број лезија се налази на експонираним деловима коже, на лицу, поглавини и врату. Просечна старост пацијената је 60 година с тенденцијом појаве у све млађој животној доби и чешће код мушкараца.

Инциденца је у порасту и удвостручује се на 25 година. Број новооткривених случајева на годишњем нивоу у свету је приближно 1.000.000. Учесталост малигних тумора коже је зависна од утицаја спољних фактора, на првом месту УВ зрачења, а потом и биолошких својстава коже (особе светле пути, тип I и II по Фицпатрику).

BCC је спорорастући малигни тумор који настаје из базалног слоја епидермиса, спољног слоја фоликула длаке или себацеалних жлезда. *BCC* може бити локално инвазиван и уколико се занемари може инфилтрисати околне структуре (мишиће, хрскавицу- кост) и виталне структуре и може довести до смрти.

Клиничка слика је веома разнолика и зависи од хистолошког подтипа. Превенција представља најважнији и најефикаснији начин лечења. Хируршко лечење ексцизијом с хистолошком потврдом и провером хируршких маргина је стандардна терапија *BCC*. Циљ лечења је онколошки радикално уклањање тумора, реконструкција функције захваћене регије – структуре и оптималан естетски резултат.

Кључне речи: базоцелуларни карцином; лечење; прогностички параметри

INTRODUCTION

Malignant epithelial skin tumors, also known as non-melanocytic skin cancer (NMSC) are one of the most common malignant neoplasms in human medicine. NMSCs comprise 95% of all skin cancers and are considered to have the most favorable prognosis with a high 5-year survival rate [1, 2]. It is predicted that more than 50% of people over the age of 50 will be diagnosed with some type of skin tumor [3]. Biological behavior varies where most often they will have a relatively benign course, while others progress to extreme morbidity, mutilation, metastasis, and even death [2 ,4, 5].

In 2020, there were 1,198,073 new cases of NMSCs recorded worldwide. Of that number, 80% or approximately 1,000,000 cases were classified as basal cell carcinomas (BCC) [1, 2]. In 2018, the number of newly discovered NMSCs within the territory of the Republic of Serbia for males and females were 1830 and 1715, respectively [3].

EPIDEMIOLOGY

It has been widely accepted that 80% of NMSCs are BCC, and up to 20% are classified as squamous cell carcinoma (SCC) [1, 4, 5].

The greatest number of BCC lesions are located on areas of exposed skin (i.e. face (particularly on the upper two-thirds), head and neck (90% of neoplasms)) [4, 5, 6]. The average age of patients is 60 years, with an increasing incidence in younger ages, and a higher incidence in males [7–11].

NMSCs are predominantly found in the Caucasian population (> 99%) among a fair-skinned population (Fitzpatrick type I and II skin types, which are more prone to solar burns), in geographic regions with a high level of insolation (incidence is directly proportional to the degree of exposure to UV radiation) [6].

Over the past thirty years, the incidence of NMSC has increased by 20–80%, and continues to increase at a rate that doubles every 25 years [1, 6, 8]. The number of newly diagnosed cases annually in Europe ranges from 40 to 80 per 10,000 inhabitants in Scandinavian countries and Mediterranean counties, respectively [8]. In Australia, skin neoplasms account for 50% of all tumors in the white population with an incidence of 1600 per 10,000 people [8].

ETIOLOGY

The most important etiological factors are the biological properties of the skin (i.e. skin type) and the influence of external factors, primarily exposure to ultraviolet radiation, natural and artificial (i.e. sunbeds). Among other external factors that play a role in cutaneous carcinogenesis are: X-ray radiation, alpha and beta radiation, chemical agents (tar, resins, soot, arsenic, aniline, asbestos), atmospheric pollutants, psoralen and nitrogen mustard, and immunosuppressive therapy [1, 9]. Neoplasms can appear in areas of chronic skin diseases such as: actinic keratosis, degenerative skin atrophy, and scars, most often after burns. Neoplasms

can also occur as part of the syndrome: Xeroderma pigmentosum, nevoid basal cell carcinoma syndrome also known as Gorlin-Goltz syndrome, and albinism [1, 12]. Furthermore, the dose of UVB exposure during childhood and adolescence is directly proportional to the risk of developing BCC [1, 12, 13].

In regard to the pathogenesis of NMSCs, only the wavelengths in the UV spectrum (100 to 400nm) are of clinical significance. The sun is a natural source of UV radiation; however, the long-term effects of exposure to sunlamps and sunbeds cannot be ignored, which may also explain the increasing incidence of NMSC in younger women, with the highest relative increase in women aged 40–49 (246%) and 30–39 (191%) [14, 15]. The amount of radiation produced by fluorescent lamps and other "cold" UV light sources is not clinically significant [16].

Solar radiation that penetrates to the Earth's surface generally does not contain UVC radiation. More than 95% of solar UV radiation is within the ultraviolet-visible (UVA) wavelength range, while the small remaining amount of UVB is responsible for acute sunburn, as well as most chronic sun damage and malignant degeneration of human skin. A condition known as *erythema ab igne*, caused by chronic exposure to radiant heat, strongly simulates chronic UV injury [4, 5, 17].

Actinic damage, direct and local or indirect and systemic, is the only universally recognized risk factor for the development of all types of NMSCs [7, 8]. The distribution of NMSCs and individual susceptibility to UV-induced tumors is inversely proportional to the melanocyte content of the skin (highest density of melanocytes are on chronically photo-exposed parts (i.e. face), smallest density of melanocytes are typically on unexposed skin regions (i.e. soles and stomach) and the constitutive higher production of melanin pigment that is transported to keratinocytes to provide protection from UV radiation [6, 16]. UVB rays are most carcinogenic and have the greatest immunological impact, but UVA rays are known to significantly accentuate the acute damage caused by UVB rays and enhance their carcinogenic effect [17, 18, 19].

The process of UV radiation-induced skin damage starts at birth, accumulates over time, and can eventually lead to the emergence of BCC [19, 20, 21]. Given the role that sun and wind exposure play in the carcinogenesis of BCC, there is an increased risk of BCC in certain occupations associated with extended outdoor exposure (i.e. farmers, sailors) [22, 23].

PATHOGENESIS

BCC was first described by Jacob in 1827 using the term "rodent ulcer" [20]. In 1903, Krompecher later described the histological characteristics of what was initially considered a true epithelial carcinoma [21, 24, 25].

BCC is a slow-growing malignant tumor that arises from the basal layer of the epidermis, the outer layer of the hair follicle, or the sebaceous glands. It grows locally, infiltratively, and destructively, affecting the adjacent skin and subcutaneous tissue, which can lead to significant functional and cosmetic defects. Locally, BCC can be very invasive. If neglected, it can infiltrate the surrounding structures (muscles, cartilage, bone), develop a superimposed infection, and even lead to death [1]. Furthermore, BCC metastasizes extremely rarely (0.0028–0.55%) [26, 27].

BCC, when experimentally transplanted without dermal tissue, does not survive [28]. A possible explanation is that the altered stroma of scar tissue helps pluripotent cells transform into malignant cells, which would further explain the appearance of tumors in areas of trauma, ulceration, and burns [29, 30].

Experimentally, BCC has previously been induced in rats through the use of chemical carcinogens; however, no tumor occurrences were ever observed when there was only exposure to UV light. One-third of all BCCs occur in areas of the body with little to no exposure to the sun [30, 31].

CLINICAL PRESENTATION

BCC has a very diverse clinical presentation manifesting macroscopically as macular, papular, nodular, and in the form of a solid plaque, sometimes accompanied by ulceration (skin-color or transparent), lightly erythematous, with raised edges where telangiectasias can be observed (Figure 1) [1].

Aggressive BCCs are characterized by a combination of potential clinical manifestations such as subclinical growth, aggressive local spread, incomplete excision, and recurrence [1, 19, 20].

In 1996, Weber defined the "H" zone of the face, the at-risk region where BCCs are found most frequently (Figure 1). BCC can be divided into two categories: low and high risk of recurrence after therapy. The key clinical features used to make this distinction are location,

size, margins, immune status of the patient, and histopathological parameters (subtype, depth of invasion, perineural, and perivascular invasion) (Figure 2) [21, 22].

Tumor staging is determined using TNM staging classifications. In Europe, staging is used for all skin regions according to Union for the International Cancer Control (UICC) 2017, while in the US the American Joint Committee on Cancer (AJCC) 2017 system uses the classification only for tumors of the head and neck region. (Table 1)

BCCs in certain anatomical locations, such as the periperiorbital, perinasal, and periauricular regions, often recur (20–25%) [1, 17, 32]. This may be due to: embryonic fusion planes, the tendency for the tumor to spread peripherally below the superficial layers of the skin (i.e. subclinical extension), and the difficulty in accurately assessing the extent of tumor extension during surgical excision (i.e. the lack of adequate margins) [33, 34].

Recurrent BCC becomes more aggressive as the number of treatments increases, as evidenced by a change in tumor histology from nodular to infiltrative with each new treatment attempt [34]. Tumor size greater than 5 cm is associated with a 25% increased risk for metastasis, and tumors that are greater than 2 cm in size are associated with a poorer prognosis [35, 36].

HISTOPATHOLOGICAL CHARACTERISTICS

BCC is characterized by cells with a scant cytoplasm, smaller hyperchromatic (darkly stained) nucleus without a prominent nucleolus. The peripheral layer of the tumor typically forms a palisade arrangement with a cleft that forms the adjacent stroma. BCC can be divided into low and high risk types based on certain histopathological characteristics that have prognostic significance (Table 2), primarily in relation to local recurrence, given that metastasis is extremely rare. Superficial BCC, despite always being classified as low risk, tends to recur due its multifocal growth pattern (Figure 3a), with some peripheral nests. Due to their small dimensions they can often be clinically undetected and found beyond the tumor's margins typically manifesting in the form of erythematous macules.

Variants of nodular BCC (i.e. cystic, adenoid) can sometimes cause dilemmas in differential diagnosis due to the similarities with certain adnexal tumors. According to the World Health Organization (WHO) classification of low-risk tumors, pigmented BCC is also noted, which is essentially not a separate histopathological subtype, but rather a clinical presentation of different (usually superficial and nodular) types of BCC that exhibit brown

pigmentation and can simulate melanocytic lesions, including melanoma. The pigment is most often found in melanophages, less often in BCC cells or in multiple dendritic melanocytes in BCC nests (Figure 3b). Sometimes, clinically visible pigmentation represents the accumulation of hemosiderin.

Infiltrative BCC is characterized by irregular nests (Figure 3c), while morpheaform BCC grows in the form of narrow bands spanning the width of several rows of cells, in a dense collagenous stroma, making it difficult to clinically distinguish the border in relation to scar tissue in recurrences. Micronodular BCC features small nests of basaloid cells (up to 0.15 mm in diameter) that often extend in depth and width beyond clinically detectable margins (Figure 3d) [27, 37]. Basosquamous (metatypical) BCC shows fields of atypical squamous cells with the appearance of SCC which has a higher recurrence rate and metastatic capacity.

BCC often exhibits different types of structural features within the same tumor, from the same risk category (eg. superficial peripherally and nodular centrally; infiltrative and morpheaform, or in combination with micronodular or basosquamous), or from different categories (usually superficial nodular and deeper in tissue infiltrative or micronodular). There are no clear indicators for the tendency of recurrence in BCC exhibiting a combination of types from different risk groups; however, it is best to determine the risk according to the most aggressive component [37]. More aggressive variants are usually found deeper in the tissue, making it difficult to perform adequate dermatoscopy [38].

Deep invasion (i.e. beyond the subcutaneous fatty tissue or >6mm from the granular layer of the surrounding skin) is a factor that transforms T1 or T2 tumors into T3. However, thickness as a risk for local recurrence and metastasis was determined by study performed on SCC [39].

Unlike perineural, vascular invasion is not always mentioned as a factor influencing the staging of skin tumors, primarily for the basosquamous type, although in practice it can also be observed in other variants of BCC [37].

The status of resection margins can be defined as tumor presence at the resection line, close to the resection line (<1 mm), and tumor-free (>1 mm) [37].

DIAGNOSIS

Clinical presentation and a thorough patient history of exposure to risk factors and duration of lesion presence are often sufficient for the diagnosis of BCC. Examination to evaluate the location and size of the lesion is necessary, and dermoscopy can also be used to

accurately assess skin lesions. Definitive diagnosis is established via biopsy and pathohistological verification. Smaller lesions are removed entirely with surrounding parts of the healthy skin and subcutaneous tissue, which is commonly the case and a definitive treatment. For larger lesions, a punch biopsy is performed [1, 4, 5].

CT and MRI are only used in more advanced tumors. Timely detection and therapy is associated with an excellent prognosis (high cure percentage and low recurrence rate) [1, 5].

TREATMENT

Prevention is the most important and effective therapeutic approach. It consists of: education, the use of protective creams, and maximum reduction of sun exposure, particularly during hours with a high UV index [33, 34]. Premalignant lesions should be treated before the full clinical form of the tumor develops. An initially suspected BCC lesion should be biopsied for histological confirmation [1].

The goal of treatment is radical resection of the tumor, reconstruction of the function of the affected region for structure and optimal aesthetic result [1, 17].

Therapeutic modalities can be classified into two categories: surgical methods and non-surgical methods [1, 4, 5, 9]. Surgical treatment is the modality of choice since it has significant advantages, mainly in regard to histological control and the lowest frequency of recurrence (Table 3). Surgical techniques include: classic surgical excision with postoperative determination of surgical margins, Mohs micrographic surgery, and destructive surgical techniques [1, 19, 20].

Factors that affect treatment decision are heavily dependent on the tumor's size, location, histological type, invasion to surrounding structures, in depth spread, patient age, number of tumors, clarity of edges, whether it is a primary tumor or recurrence, and any previous therapy. Surgical treatment of facial skin cancer after tumor excision also includes reconstruction of the defect (Figure 4) [1, 19]. When the surgical excision is incomplete, a reexcision must be performed taking into account the patient's general health status, tumor type, and location [1, 17, 19].

Surgical techniques

Surgical treatment via excision with histological confirmation or Mohs surgery with confirmed surgical margins is considered the standard therapy for BCC [4, 5, 40]. Surgical excision enables histological confirmation of tumor removal and leads to good results in both low-risk and high-risk tumors. For BCC, the primary plan is surgical excision to reduce the risk of recurrence. The recommended surgical margins for well defined, low-risk tumors (<2cm in size) are 4–5 mm and 6–10 mm for high-risk tumor types as well as larger lesions and recurrences [1, 19, 20].

Mohs surgery is a surgical technique that, with the help of three-dimensional microscopic control, complete excision of the cancerous lesion with the entire subclinical extension of the tumor can be achieved allowing for histological control of margins while achieving maximum therapeutic effect and tissue preservation [40]. Depending on the tumor's size, histological type and recurrence, Mohs surgery is recommended for high-risk tumors in regions of the face. A disadvantage is that it is time-consuming, requires special training and significant financial resources [19, 20].

Destructive techniques

Other surgical therapies include more destructive techniques such as: electrodesiccation and curettage (ED&C), cryosurgery, "shave excision," and laser therapy [28, 30]. These techniques are typically used in elderly patients with multiple lesions located primarily on the body and extremities, but rarely on the face. A major drawback to these techniques is that they do not provide complete histological confirmation and have low therapeutic effect [21, 22, 23, 41].

Non-surgical therapeutic modalities include: photodynamic therapy (PDT), radiotherapy, local therapy: intralesional application of interferon, and pharmacologic therapy (imiquimod, retinoids, 5-fluouracil). For more advanced cases, hedgehog signaling pathway inhibitor drugs such as Vismodegib and Sonidegib are used [42]. The disadvantage of destructive and non-surgical modalities is the loss of histological control and a higher percentage of recurrence compared to surgical treatment modalities [1, 25, 26].

All patients with a history of BCC require lifelong follow ups, regardless of treatment modality (Figure 5). The risk of developing another BCC lesion is highest in the first three years after initial treatment. Patients with low-risk tumors and histologically negative margins

can be followed up annually while patients with high-risk tumors without histological confirmation of negative margins, or those that have been treated with non-surgical methods, with recurrent tumors, positive surgical margins or have an increased risk of developing BCC should be followed up more frequently. All patients with BCC must be educated about sun protection, trained in self-examination, and be advised to have annual exams performed by their dermatologist [1, 43].

PROGNOSIS

BCC has an excellent prognosis, with a high cure rate and low recurrence rate, with timely detection and therapy. Worldwide mortality attributed to BCC is estimated to be 10,000 people annually. Well planned treatment is over 95% effective. In 50% of patients, there is a possibility of developing a second BCC within 5 years. Recurrences occur in 5% of patients, most often within 4 to 12 months after initial treatment. The likelihood of recurrence is dependent on the histological subtype and therapy (i.e., positive surgical margins) [1]. Similar to other chronic conditions, for successful treatment outcome affirmation of prevention (education and UV protection), early diagnosis, and planned therapy-surgical treatment and regular follow ups are pivotal [41, 44].

CONCLUSION

NMSCs are one of the most common malignant neoplasms in the human population, of which BCC makes up 80% of skin tumors.

The most important etiological factors are: genetic predisposition, exposure to: UV radiation, radiotherapy, and chemical agents. BCC can also occur in scarred areas, on sebaceous nevi, after long-term immunosuppression, and as part of syndromes and genetic anomalies (i.e. Xeroderma pigmentosum, Gorlin-Goltz syndrome, and albinism).

Diagnosis of BCC is highly reliant on the clinical presentation and definitive diagnosis is established by pathohistological verification.

The goal of the treatment is radical resection of the tumor, reconstruction of the function of the affected region for structure and optimal aesthetic result. Surgery is the treatment of choice, offering significant advantages over other treatment modalities, due to histological control, lowest recurrence rate, and cure rate of up to 95%.

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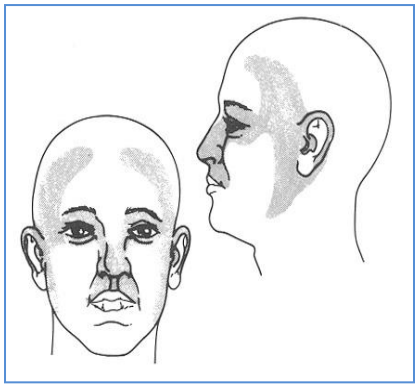

Figure 1. Weber "H" zone;

used with permission from: Dimitrijević MV. Epitelni maligni tumori kože. In: Dimitrijevic MV, et al. Maksilofacijalna hirurgija. Medicinski Fakultet, Beograd; 2020. p.165–70

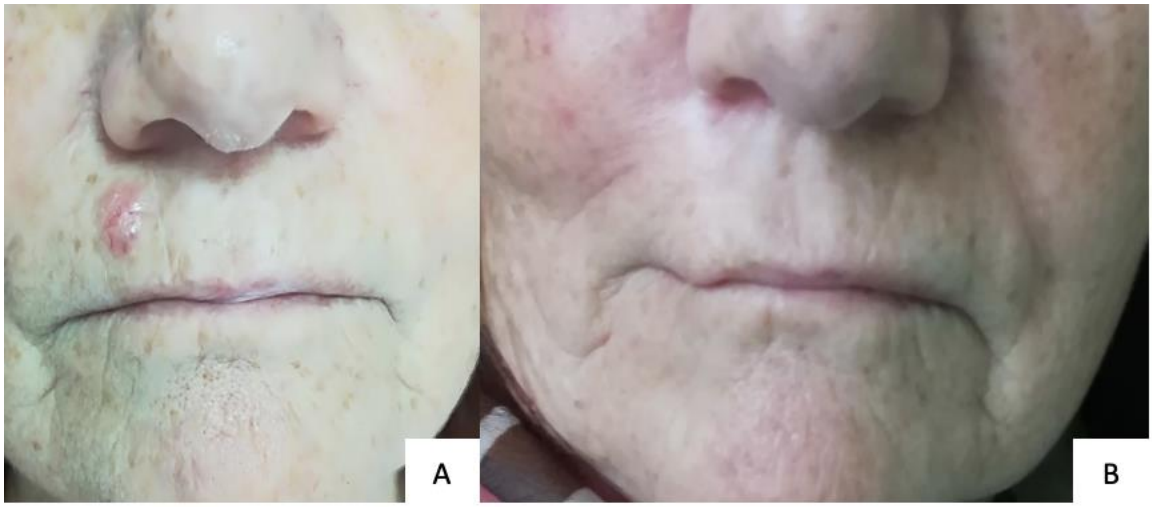

Figure 2. Basal cell carcinoma pre-operative (A) versus post-operative (B);

from the private collection of Dimitrijević MV

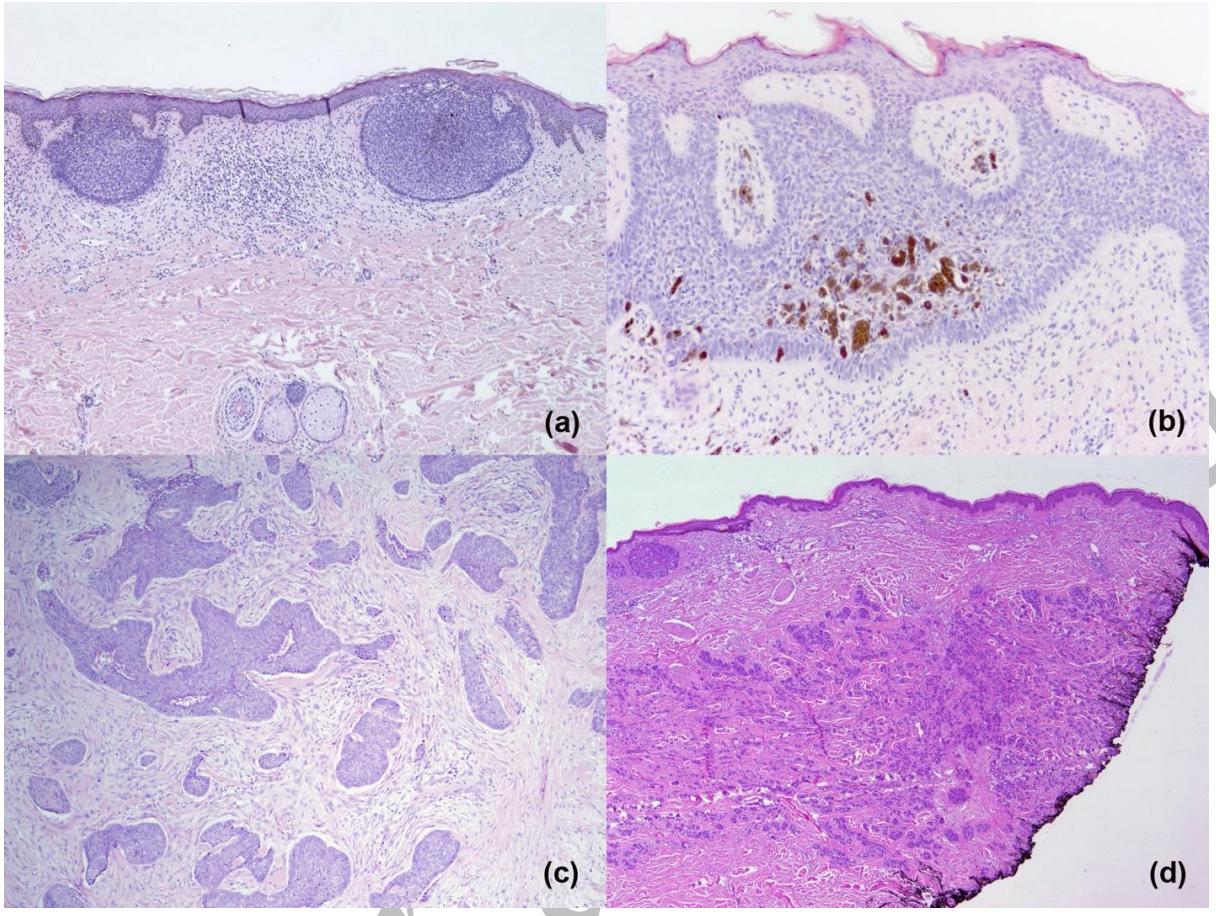

Figure 3. Histopathological types of basal cell carcinoma; superficial (a) with multifocal, small, superficial nests; pigmented (b) with melanin pigmentation in the stromal melanophages and tumor cells; infiltrative (c), and micronodular (d) which is found on the peripheral lines of the resection marked by the black edges (hematoxylin and eosin staining, magnification 40× (a, d), 100× (b, c);

from the private collection of Brašanac DČ

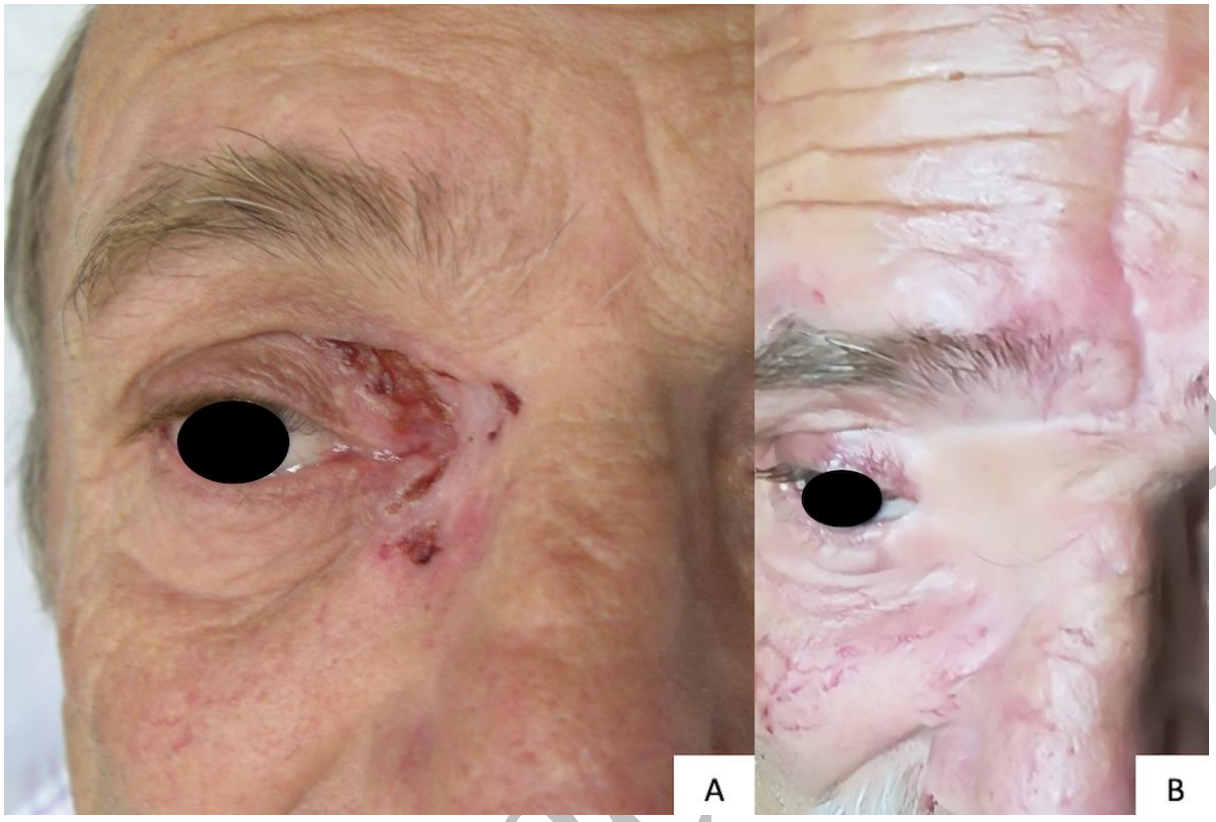

Figure 4. Basal cell carcinoma pre-op (A) versus post-op (B);

from the private collection of Dimitrijević MV

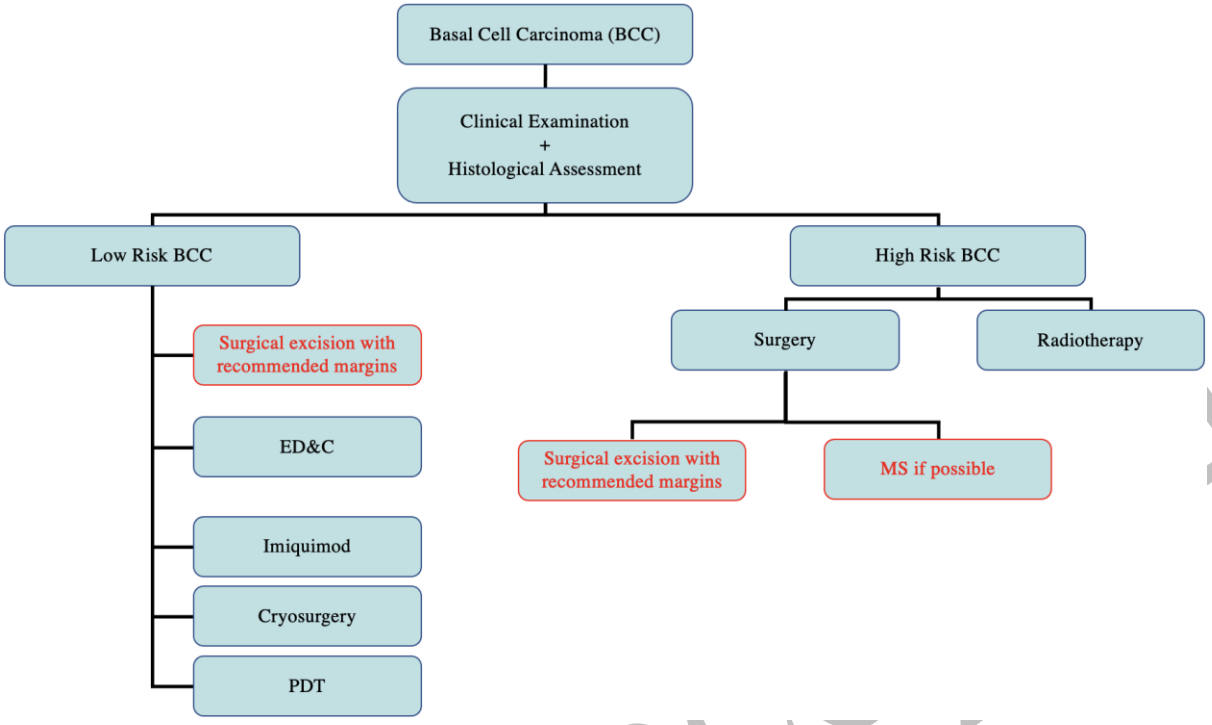

Figure 5. Basal cell carcinoma treatment modalities;

ED&C – electrodesiccation and curettage; MS – Mohs micrographic surgery; PDT – photodynamic therapy; red text – standard therapy; black text – other therapeutic modalities; modified from reference 23

Table 1. TNM classification of malignant skin tumors (UICC, 2017)

TX	Tumor cannot be assessed
T0	No evidence of primary tumor
TIS	Carcinoma *in situ*
T1	Tumor is up to 2 cm in the greatest diameter
T2	Tumor is > 2 cm but < 4 cm in the greatest diameter
T3	Tumor is > 4 cm in the greatest diameter, or with minimal bone erosion, or with one or more high risk parameters (i.e. invasion into the deeper superficial layers of the skin, perineural invasion)
T4A	Tumor with significant invasion to the bone: core and/or marrow
T4B	Tumor with skull base or axial skeleton invasion including foraminal involvement and/or vertebral foramen involvement to the epidural space

T – primary tumor site;

N and M categorization corresponds to the same categories of other localized malignant tumors of the head and neck [Brierley JD, Gospodarowicz MK, Wittekind CH (eds). TNM Classification of Malignant Tumours (8th edition). Oxford, UK: Wiley-Blackwell, 2017]

Table 2. Histopathological prognostic parameters of basal cell carcinoma

1. Histopathological subtype
1.1 Low risk
1.1.1. Superficial
1.1.2. Nodular and variants
1.1.3. Rarer types (infundibulocystic/harmartomatous, fibroepithelioma of Pinkus)
1.2 High risk
1.2.1. Infiltrative
1.2.2. Morpheaform (morphologic, sclerotic)
1.2.3. Micronodular
1.2.4. Basosquamous (metatypical)
2. Depth (level) of invasion
3. Perineural invasion
4. Vascular invasion
5. Status of resection margins

Modified from references 27 and 37

Table 3. Advantages of surgical treatment

1. Histological verification and confirmation that the tumor is excised completely to “healthy” level
2. Tumor can be removed regardless of location and size
3. Aesthetic results are superior and is a significant factor in the regions of the head and neck
4. Shorter duration of therapy
5. Treatment expenses
6. The induction of new tumors is avoided unlike in radiotherapy

Table 4. Criteria for successful treatment of basal cell carcinoma

1. Prevention (patient education, UV protection)
2. Early diagnosis
3. Planned therapy – surgical intervention
4. Regular follow-ups

