We are IntechOpen, the world's leading publisher of Open Access books Built by scientists, for scientists

6,900
Open access books available

185,000
International authors and editors

200M
Downloads

Our authors are among the

154
Countries delivered to

TOP 1%
most cited scientists

12.2%
Contributors from top 500 universities



WEB OF SCIENCE™

Selection of our books indexed in the Book Citation Index in Web of Science™ Core Collection (BKCI)

Interested in publishing with us?
Contact book.department@intechopen.com

Numbers displayed above are based on latest data collected.
For more information visit www.intechopen.com



2

Basal Cell Carcinoma

Tomasz Dębski, Lubomir Lembas and Józef Jethon
Department of Plastic Surgery,
The Medical Centre of Postgraduate Education in Warsaw
Poland

1. Introduction

Neoplastic lesions of the skin are among the most common human malignancies. They originate from different skin tissues and structures such as:

- epidermis
- skin appendages (hair follicles, sebaceous glands, eccrine sweat glands, apocrine sweat glands)
- pigment cells (melanocytes)
- mesenchymal structures (fibrous tissue, fatty tissue, blood and lymphatic vessels, muscles)
- nerves and APUD cells of the neuroendocrine system
- lymphatic system cells.

The vast majority of neoplasms originating from the above skin structures are benign neoplasms. They are characterised by slow local growth and lack of intensive tissue damage.

The remaining part of neoplastic lesions consists of skin malignancies including carcinomas (originating from the epidermis and skin appendages), melanomas (originating from pigment cells), lymphomas (originating from the lymphatic system cells) and sarcomas (originating from other skin cells) Other classification of malignancies is as follows:

Non-Melanoma Skin Cancer (NMSC) and Melanoma Malignum (MM.) NMSC include skin cancers (96% of skin malignancies), lymphomas and sarcomas (1% of skin malignancies.) The remaining 3% is MM which is characterised by high malignancy and accounts for 75% of all deaths due to skin neoplasms (Kordek et al., 2004 ; The Burden of Skin Cancer, 2008).

Despite the fact that there are different classifications available in literature, one thing that does not change is that cancer is the most common histopathological form of malignancies. Almost all skin cancers originate in the epidermis. Cancers arising in the skin appendages constitute a very low per cent. From a histological point of view the epidermis is stratified epithelium with several layers of cells. Depending on an epidermal layer (the basal cell or squamous cell layer) skin cancers are divided into:

- Basal Cell Carcinoma (BCC) originating from the basal cell layer of the epidermis and sheaths of hair follicles. It constitutes 80% of all skin cancers.

- Squamous Cell Carcinoma (SCC) originating from cells in the Malpighi layer and it accounts for 20% of skin cancers (Kordek et al.,. 2004).

Although both BCC and SCC originate from the epidermis, their biology is completely different and therefore they cannot be discussed together. For that reason the authors of this review have decided to present problems associated only with one of them, namely BCC.

BCC is of the most common human malignancies, and its incidence has been rising within the last decade (Preston & Stern, 1992). Although it is not life-threatening, its local malignant features, especially in the area of the face may cause significant functional and aesthetic disturbances what has a profound effect on the quality of life of patients. If BCC is left untreated, it can infiltrate not only adjacent tissues but also bones and even deeper structures like brain (Franchimont, 1982). Moreover, extremely rare distant metastases of this neoplasm have been described (Lo et al., 1991).

BCC diagnostics and treatment is managed by physicians of different specialities (dermatologists, plastic surgeons, general surgeons, oncologists, ophthalmologists, ENT specialists, and even general medicine specialists) who promote therapeutic options which are closely related to their specialities and are often controversial. Available literature reports different therapeutic methods including non-invasive techniques such as local application of Imiquimod-containing ointments (Mark et al., 2001), photodynamic therapy (Clark et al., 2003), radiation therapy (Kwan et al., 2004), CO_2 laser ablation (Nouri et al., 2002), cryosurgery (Giuffrida et al., 2003), cautery (Spiller WF & Spiller RF, 1984) and curettage (Reyman, 1985) or surgical excision of a lesion with a margin of clinically normal surrounding tissues (Walker & Hill, 2006).

Functional and aesthetic results, treatment efficacy, side effects and effects on the quality of life are different and depend on the method that has been used.

Method selection depends on lesion morphological features and patient's condition and preferences. The majority of methods to treat BCC described so far may be used only in some, highly selected cases. The only universal method that can be used to treat all cases of BCC is surgical excision with a margin of clinically normal surrounding tissues.

Due to high efficacy of this method, its versatility, good functional and aesthetic results, low risk of complications, availability, low costs, and what is the most important, the ability of postoperative histological assessment of excision completeness, surgical treatment is currently the most common method to treat BCC.

2. Epidemiology

Among all human malignancies skin cancer occurs the most frequently and it accounts for almost 1/3 of all detectable neoplasms (Kordek et al., 2004). Despite the fact that since the early 1990s the global incidence of neoplasms has been decreasing the rate of incidence of skin cancer has been rising and it is estimated to be 10-15% annually, what is almost ten times higher than the population growth rate (Cole & Rodu, 1996; Kordek et al., 2004; Parkin et al., 1999). It has to be emphasised that there are no precise records especially with regard to BCC and therefore epidemiological data are often understated and not included in global lists of incidence rates of neoplasms (Kordek et al., 2004).

Only in the USA, more than one million cases of skin cancers are detected every year (American Cancer Society, 2008). It is the number almost equal to the number of all other cancers detected annually in this country (American Cancer Society, 2006). It is estimated that one out of five Americans will develop skin cancer (American Cancer Society, 2008), and in almost half of 65-year-olds this cancer will occur at least once in their lives (Robinson, 2005).

Although the data presented above regard all cases of skin cancers it can be assumed that they reflect BCC epidemiology to a large extent, as BCC accounts for almost 80% of all cases of skin cancers (Kordek et al., 2004).

Global statistics unanimously indicate that BCC is one of the most common neoplasms in Europe, Australia and the USA (Miller & Weinstock, 1994), and the number of new cases is increasing every year (Table 1.)

Country	Non-melanoma skin cancers (w/m)	Lung cancer (w/m)	Colon cancer (w/m)	Breast cancer (w)
Finland	399 / 416	20 / 55	43 / 41	137
Switzerland	433 / 560	26 / 78	54 / 75	137
Netherlands	402 / 470	29 / 92	57 / 62	130
United Kingdom	458 / 471	51 / 83	55 / 66	135
USA	459 / 534	59 / 84	55 / 60	144
Australia	403 / 483	27 / 57	58 / 67	114
Poland	320 / 382	23 / 104	40 / 41	73

Table 1. Incidence rate for selected neoplasms based on Globocan 2002 (number of detected cases/year/100 000 citizens) (Global Cancer Statistics Globocan, 2002).

Epidemiology of skin cancer unanimously indicates that it is a significant global problem. However, this problem is not noticed and is underestimated especially because of the fact that mortality related with these neoplasms is low (in the USA 1000-2000 patients/year) (Jemal et al., 2003) and that this neoplasm is not listed in incidence records (data are not complete.) The importance of this problem is mainly affected by the number and dynamics of new cases, a high recurrence rate (even 18%) (Silverman et al., 1991) and generally high costs of treatment (in the USA the costs of treating skin cancers were more than one billion dollars in 2004) (Bickers et al., 2006).

3. Etiopathogenesis

Although currently several factors are suspected to be responsible for BCC the most important roles in cancerogenesis are played by UV radiation and advanced age of patients. They account for more than 90% of neoplastic lesions (Taylor, 1990).

3.1 Aetiological factors

Solar radiation (UV) can be divided into three parts depending on the wavelength: UVA (wavelength of 320-400 nm), UVB (wavelength of 280-320 nm) and UVC (wavelength of 200-280 nm) (Kordek et al., 2004).

The majority of radiation emitted by the Sun is absorbed by the ozone layer of the atmosphere, and consequently, only a low amount reaches the Earth. As due to atmosphere pollution the thickness of the ozone layer is gradually reduced, more and more UV radiation reaches the Earth, therefore the incidence of BCCs can increase (Goldsmith, 1996). This phenomenon may also explain the fact that this neoplasm occurs in younger and younger patients as they earlier achieve a cancerogenesis threshold of Average Accumulated Exposure (The Skin Cancer Foundation, 2008).

Exposure to UVB radiation contributes to the BCC development the most (Boukamp, 2005).

Contrary to common opinions short-term but intensive and long-term but less-intensive exposure are equal (Marks et al., 1990). The dose of UV absorbed in the childhood does not contribute significantly to neoplasm pathogenesis according to the latest reports (Godar et al., 2003).

Long-term UVB actions lead to the formation of mutagenic photoproducts that damage DNA chains in skin cells. DNA damaged in this way is repaired within 24 hours as a result of the effective repair system called NER (nucleotide excision repair system) (Szepietowski et al., 1996). Impairment of this system present in patients with xeroderma pigmentosum inevitably leads to multifocal skin cancer and death at a young age.

Apart from damage to DNA of skin cells UV radiation also causes mutations in a suppressor gene of the p-53 protein. The protein coded by this gene has anti-oncogenic properties as it induces apoptosis in the cells with damaged DNA. As a result of a mutation in this gene the anti-oncogenic properties of the p-53 protein are turned off, therefore the cells with damaged DNA proliferate without control. The presence of a mutation in the p-53 gene is found in 60-100% of cases of skin cancer (Marks, 1995).

The skin inflammatory response induced during the exposure to UV also participates in the process of damaging DNA (Maeda & Akaike, 1998) inducing disturbances of division and mutations in newly produced cells (Hendrix et al., 1996).

The sources of UV radiation include not only solar radiation but also PUVA lamps used to treat psoriasis and albinism as well as tanning lamps.

Due to the fact that tanning lamps are widely accessible and due to fashion trends they have become especially important in BCC etiopathogenesis in the last years. Some of these modern tanning lamps may emit radiation doses which are even 12 times higher than the ones emitted by the Sun (11th ROC: Ultraviolet Radiation Related Exposures, 2008). The risk of BCC in subjects using tanning lamps regularly is twice the risk observed in the general population (Karagas et al., 2002).

The significance of solar radiation in BCC pathogenesis is emphasised by the fact that this neoplasm is found on the skin areas with the most exposure to sunlight, such as the head and neck (85% of all lesions, including 30% within the nose (DeVita et al., 2001; McCormack et al., 1997).

It is claimed that such substances as arsenic, wood tar, gas pitch, synthetic antimalarial agents or psoralens participate in BCC cancerogenesis (Kordek et al., 2004).

3.2 Risk groups

Age. A peak in the incidence is between 60 and 80 years of age. More than 95% of patients are patients above 65 years old (Kordek et al., 2004) although recently it has been observed that the incidence in the population below 40 years old is growing (The Skin Cancer Foundation, 2008). With age the total period of UV radiation exposure (Average Accumulated Exposure) increases, therefore when a given threshold is exceeded cancerogenesis processes are initiated. Moreover, the reduced immunity and reduced DNA repair and regeneration properties occurring in the elderly also contribute to the increasing incidence of BCC in this age group (Pietrzykowska-Chorążak, 1978).

Sex. Men slightly more frequently suffer from BCC (M/F ratio 1.2) (Brodowski & Lewandowski, 2004). It is probably associated with higher exposure to UV radiation what is a result of different working conditions (usually outdoors) and rarer use of sun screens in the case of men (McCarthy et al., 1999). It should be noted that during the last 30 years the rate of women below 40 years of age suffering from BCC has tripled (The Burden of Skin Cancer, 2008).

Race. People with fair skin type, light blue and grey eyes and with light red and fair hair suffer from BCC more frequently than people with dark skin (Gloster & Neal, 2006; Jabłońska & Chorzelski, 2002; McCarthy et al., 1999).

Fair hair, frequent sunburn and freckles in the childhood are features which are especially associated with BCC development (Bouwes et al., 1996).

Previous BCC treatment. After the first case of BCC in one's life the probability of the second one increases ten times (Marcil & Stern, 2000). In 50% of patients with previously diagnosed BCC other foci will form within 5 years since the first manifestation (Brodowski & Lewandowski, 2004). It is estimated that the likelihood of BCC in such patients is almost 140 times higher that the one in the general population (Aston et al., 1997)

Post-organ transplant patients. In post-organ transplant patients BCC is the most frequent neoplasm and accounts for 35% of all neoplasms occurring in this group of patients. It is estimated that post-organ transplant patients suffer from BCC 65-250 times more frequently than the general population. BCC most frequently occurs in patients after heart and renal transplantation (Jensen et al., 1999).

Higher incidence of BCC in this group is associated with long-term immunosuppressive therapy that reduces the number of CD4+ cells (Viac et al., 1992).

The pharmacological immunosuppression combined with UVB radiation that additionally reduces the number of Langerhans cells (immune properties) leads to increased immunosuppression in the skin and increases the risk of neoplasm (Parrish, 1983).

Leukaemic patients due to immune system dysfunctions are the next group at a risk. BCC most frequently occurs in patients with chronic lymphocytic leukaemia (8-13 times more frequently than in the general population) (Manusow & Weinerman, 1975).

Other risk groups. According to recent opinions risk factors that have not been so widely studied include genetic predisposition (Gailani et al., 1996; Gilbody et al., 1994; Schreiber et al., 1990), freckles (Gilbody et al., 1994) and rich-fat diet (Zak-Prelich et al., 2004) which is low in antioxidants and vitamins (Jeacock, 1998).

3.3 Precancerous lesions

Precancerous lesions are morphologically changed tissues (a pathological process) on the basis of which neoplasm develops more frequently than in other unchanged tissues (Kordek et al., 2004).

BCC most frequently develops in the skin without previous lesions. It can significantly more rarely (contrary to SCC) develop on the basis of precancerous lesions. Precancerous lesions leading to BCC development include:

- post-radiation dermatitis is most frequently induced by X-ray radiation and is characterised by irregular skin thickening accompanied by discolouration, hyperpigmentation, teleangiectasia and scared atrophy (Jabłońska & Chorzelski, 2002).
- It is estimated that in 60% of cases it transforms into BCC (Aston et al., 1997).
- nevus sebaceous of Jadassohn is a superficial, protruding, yellow-pink, irregular nonhairbearing lesion on the head or neck. Its diameter rarely exceeds 3 cm. It is very frequently present since birth or early childhood and the likelihood of its transformation into BCC is 15% (Aston et al., 1997) .
- actinic keratosis is characterised by multifocal, dry, yellow-brown, slightly protruding keratic build-up, sometimes brown spots are present, they are often numerous on the forehead and temples (Jabłońska & Chorzelski, 2002). The risk of neoplastic transformation into BCC is 10% (1/1000/year) (Chicheł & Skowronek, 2005).
- chemical keratosis is a result of exposure to arsenic or wood tar.
- xeroderma pigmentosum is present in patients with a defective system of DNA repair (NER) what leads to the development of multifocal skin cancer and death at a young age (Marks, 1995). Lesions resemble intensified freckles and the skin shows atrophy, discolouration and teleangiectasia (Jabłońska & Chorzelski, 2002).
- other rarer precancerous lesions include inflammatory changes with scars and hypertrophied scars after burn injuries (Jabłońska & Chorzelski, 2002).

Although in the majority of patients with BCC it is possible to find at least one of the above factors it has to be remembered that the risk of BCC development increases in proportion to the number of existing risk factors.

For example, in Australia the incidence of this neoplasm is the highest. The reason for that is the fact that this continent is located close to the equator (much sunlight and UV radiation), its population has fair skin type (emigrants from England and Scotland) and the ozone layer above Australia is gradually decreasing (Marks et al., 1993).

4. Clinical picture

Diagnosis of BCC basing on the clinical picture is associated with many problems. Diagnosis precision among experienced dermatologists ranges from 50% to 70% (Kricker et al., 1990; Presser & Taylor, 1987). The sensitivity of a clinical test is estimated to be 56-90%, and its specificity 75-90% depending on physician's experience (Mogenses & Jemec, 2007). Diagnostic accuracy is enhanced by good lightning, magnification and dermatoscope (Costantino et al., 2006).

Based on the data presented above it can be concluded that BCC diagnosis basing only on a clinical picture is difficult and depends on physician's experience to a large extent. It is often

the case that a lesion previously diagnosed as a benign lesion turns out to be BCC following a biopsy and the reversed situation is also common. BCC diagnosis basing on the clinical picture is not of significance in the diagnostic process. A histopathological examination is the only test that can verify and complete the BCC diagnosis.

Several clinical forms of BCC are traditionally distinguished due to various clinical pictures and biological features.

It has to be emphasised that the awareness of their existence may only help distinguish oncologically suspicious lesions, and not diagnose them.

4.1 Clinical forms of BCC (pict. 1)

Nodular BCC (BCC nodosum) (pict. 1a)- This is the most common form of BCC. Its dimensions may range from several millimetres to 1 cm. It is mainly present in the elderly and develops for years. It has a form of a non-inflammatory, glistening nodule or papule with pearly appearance. The bigger it is, the more pearly it becomes and present capillaries are more and more visible, their layout is radial and they form telangiectasias. The skin covering a nodule is very often so thin that even the smallest trauma causes bleeding and ulceration. Repetitive ulceration leads to the formation of a basin in the middle (BCC partim exulcerans) surrounded by an edge consisting of transparent nodules similar to pearls.[44] In its central part clusters with discolouration suggesting melanoma may be visible. In rare cases tenderness occurs. Small nodules that are difficult to distinguish from seborrhoeic warts, moles or psoriasis are a diagnostic problem. Differential diagnosis has to take SCC into account; however, it is darker and lacks a pearly edge, horizontally branching telangiectasias and clusters with discolouration. Lupus tuberculosis is different from nodular BCC in that it has lupus nodules in a scar and lacks a pearly edge; whereas chronic lupus erythematosus can be distinguished by the presence of more advanced inflammation, perifollicular hyperkeratosis and lacks disintegration (Bers & Berkow, 2001; Jabłońska & Chorzelski, 2002).

Pigmented BCC (BCC pigmentosum) - it is an intensely pigmented variant of a nodular form. Differential diagnosis should consider pigmented naevus which is different in that its dimensions do not grow and it lacks a characteristic edge. On the other hand, melanoma grows faster and more frequently occurs in young patients, with dark hair and dark eyes. (Jabłońska & Chorzelski, 2002; The Skin Cancer Foundation)

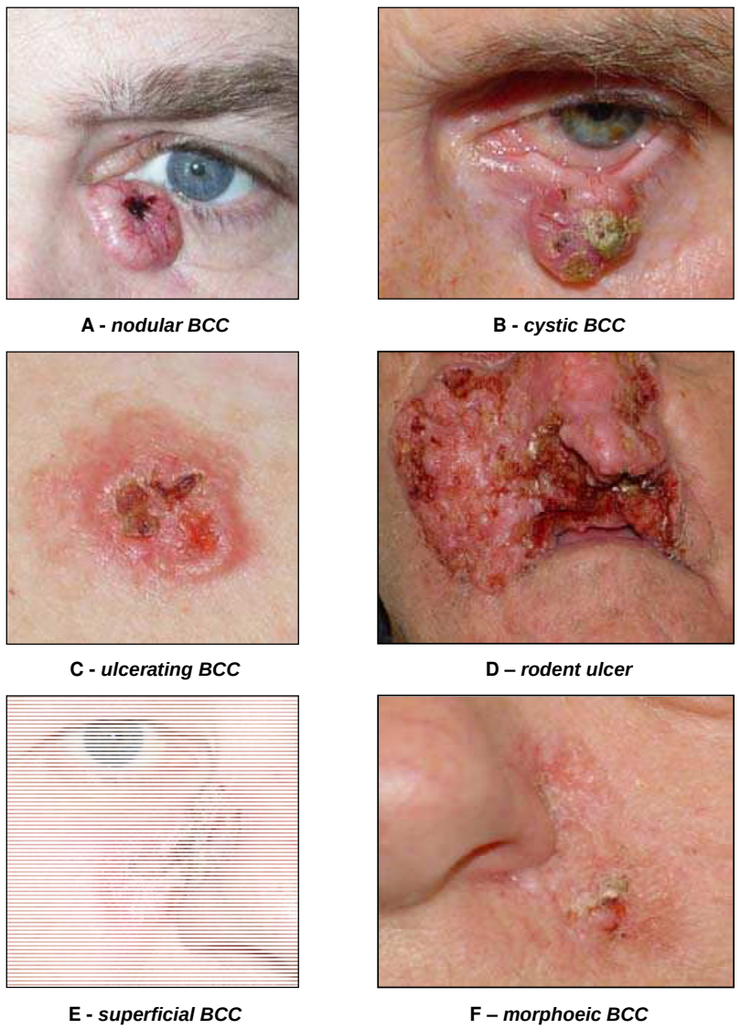
Ulcerating BCC (BCC exulcerans, ulcus rodens) (pict 1c, 1d) is an ulcer with prominent, heaped-up edges, that tends to bleed and infiltrate stroma. It may penetrate deeply and cause damage to the muscles, cartilage, bones or even eye protective apparatus (rodent ulcer.) It is distinguished from SCC by the presence of a pearly fold and slower course (Jabłońska & Chorzelski, 2002; Raasch & Buettner, 2002).

Morphoeic or sclerosing BCC (BCC morpheiforme) (pict. 1f) is an aggressive variant of BCC and resembles foci of systemic sclerosis. It is most frequently located on the face and has a form of a yellow-white lesion not subject to disintegration, with ill-defined borders. In its central part sclerosis, scarring and telangiectasias are often present. It may grow fast and reach several centimetres within a few months or remain unchanged for many years. Due to ill-defined borders and infiltrations reaching even 7 mm outside a macroscopic border this

type of BCC is often resected incompletely and is associated with a high risk of recurrence (Jabłońska & Chorzelski, 2002, Wagner & Casciato, 2000).

Cystic BCC (BCC cysticum) (pict. 1 b) has a form of small, transparent nodules located on the eyelids (Jabłońska & Chorzelski, 2002)

Superficial BCC (BCC superficiale) (pict. 1 e)is a type of BCC that grows especially slowly (months and years, often regression.) It occurs more often in young patients and its form includes numerous, flat, glistening, light pink lesions with well-defined borders, surrounded by a slightly prominent edge. Recent studies regarding a microscopic 3D analysis indicated that different lesions are connected what proves their origin from one focus (Wade & Ackerman, 1978).



A - *nodular BCC* **B - *cystic BCC***

C - *ulcerating BCC* **D – *rodent ulcer***

E - *superficial BCC* **F – *morphoeic BCC***

Photo 1. Clinical forms of BCC

Photo 1. Clinical forms of BCC

Contrary to other variants this type of BCC is not located on the face, but mainly on the trunk and limbs, what suggests that its cancerogenesis threshold due to UV radiation is lower (McCormack et al., 1997). Its characteristic feature is the fact that the intensity of reddening increases when a lesion is stretched and rubbed. When a lesion is stretched, its glistening surface is visible, and it may show a peripheral, pearly ring or pearly islets inside a lesion. Such lesions are rarely itchy, they rarely bleed or form ulcers. They may be formed after arsenic intoxication and coexist with other types of BCCs. Frequently they are mistaken for Bowen's disease and they can be distinguished from it by the presence of glistening surface, lack of hyperkeratosis and a lighter shade. Some lesions may be similar to psoriasis, pigmented lichen planus, eczema, fungal infections, solar keratosis or even amelanotic melanoma (Australian Cancer Network Management of Non-Melanoma Skin Cancer Working Party, 2002; Jabłońska & Chorzelski, 2002; The Skin Cancer Foundation)

Fibroepithelial BCC (fibroepithelioma) is single or multiple reddish nodules, often pedunculated, located mainly on the back. They resemble fibroma from a clinical point of view (Aston et al., 1997; The Skin Cancer Foundation).

Basal cell nevus syndrome (Gorlin syndrome) is an autosomal dominant hereditary disorder the mutation of which is located in the chromosome 9. Its characteristic features include multiple BCCs coexisting with such abnormalities as palmoplantar pits, skin cysts in the mandible, bifid ribs, calcification of the dura, mental impairment (Aston et al., 1997).

Linear basal cell nevus occurs in the form of several streaks consisting of brownish nodules. Contrary to Gorlin syndrome which is clinically similar this disorder is not hereditary and not associated with abnormalities. It is the rarest variant of BCC (Aston et al., 1997).

In conclusion, the diagnosis of BCC based on the clinical picture is not an easy task, therefore each skin lesion exhibiting some dynamic features, namely growing when compared to adjacent structures, with inflammatory changes, bleeding or crusted should be treated as potentially neoplastic and requires further diagnostics.

4.2 Clinical course

The clinical course of BCC is not characteristic and cannot be predicted: a lesion may not change for years, it may grow slowly or extremely fast, infiltration area may enlarge or recede, it may also ulcerate or tend to heal (Franchimont, 1982). The tendency to heal may lead to decreased vigilance of a physician and their patients, what can be the reason why patients with advanced neoplasia (Table 2.) often report at clinics.

BCC is a locally malignant neoplasm and infiltrates tissues in a three-dimensional fashion, forming fingerlike outgrowths not visible to a naked eye originating from the central part of a tumour (Braun et al., 2005). Their course and range are unpredictable, therefore it is extremely difficult to excise a lesion completely (Raasch & Beuttner, 2002). In the most dangerous cases the infiltrate may spread to the dura, bones, nerves and vessels (Franchimont, 1982).

BCC metastasises really rarely as a result of developed extracellular matrix and preserved epithelial basement membrane (Jabłońska & Chorzelski, 2002). In 1894-2004 only 268 such cases were described, what is less than 0.1% (Ionesco et al., 2006; Weedon & Wall, 1975). Metastases were mainly in patients with a long medical history and after radiation therapy

(Domarus & Stevens, 1984), with histopathologically aggressive BCC located in the central face or near the ear (Randle, 1996) and lesions were larger than 2 cm (>3 cm -2% risk of metastases, >5 cm - 25 %, >10 cm-50%) (Snow et al., 1994) BCCs the most frequently spread along lymphatic vessels and its metastases were mainly observed in the lymph nodes, lungs, bones, pleura, spleen and brain (Safai & Good, 1977).

Mortality due to BCC is low and mainly regards people older than 85 years and patients who did not consent to surgical treatment (Weinstock et al., 1991).

TNM Staging System for Non-melanoma Skin Cancer			
T0	No evidence of primary tumour	**Nx**	Regional lymph nodes cannot be assessed
Tis	Carcinoma in situ	**N0**	No regional lymph node metastasis
T1	Tumour 2.0 cm or less in greatest dimension	**N1**	Regional lymph node metastasis
T2	Tumour more than 2.0 cm but not more than 5.0 cm in greatest dimension	**Mx**	Presence of distant metastasis cannot be assessed
T3	Tumour more than 5.0 cm in greatest dimension	**M0**	No distant metastasis
T4	Tumour infiltrating anatomical structures located under the skin such as bones, cartilage, skeletal muscles etc.	**M1**	Distant metastasis present (includes distant lymph nodes)

Staging			
	T	**N**	**M**
0	Tis	N0	M0
I	T1	N0	M0
II	T2 or T3	N0	M0
III	T4 Each T	N0 N1	M0 M0
IV	Each T	Each N	M1

Table 2. Classification TNM and stages of skin cancers based on AJCC 2002 (AJCC, 2002)

5. BCC diagnostics

5.1 Invasive diagnostics (biopsy)

Despite the fact that clinical features are well described and relatively specific, it should be emphasised that only a result of a histopathological examination can confirm the diagnosis and a biopsy is the gold standard in BCC diagnostics. Some specialists recommend to perform a biopsy in all cases when BCC is suspected. Others recommend it only in diagnostically doubtful cases or when a histological type can affect the choice of a

therapeutic method and prognosis (Costantino et al., 2006). There are following types of a biopsy:

Curettage – involves removing neoplastic tissue using a special spoon. Due to the fact that the internal structure of curetted tissues is lost this method is not reliable and currently not recommended (Australian Cancer Network Management of Non-Melanoma Skin Cancer Working Party, 2002).

Shave biopsy – involves cutting the half-thickness skin at a tangent to the skin. It is recommended for superficial BCC, especially if a tumour is multifocal, is present in regression areas and in the case of recurrent disease. A shave biopsy allows for collecting material from a large area. The wound heals fast and leaves no secondary deformations, therefore it can be difficult to locate when a patient returns to continue treatment (a biopsy site should be marked and photographed.) (Australian Cancer Network Management of Non-Melanoma Skin Cancer Working Party, 2002).

Punch biopsy (trepanobiopsy) – a full-thickness skin fragment with the diameter of 4-5 mm is removed with a punch consisting of a metal tube with a sharp edge and a handle.

It is recommended in diagnostics of lesions located in aesthetically and functionally important skin regions (e.g. face.) The repetitive 2-mm punch biopsy may be used to determine poorly demarcated neoplasms (Australian Cancer Network Management of Non-Melanoma Skin Cancer Working Party, 2002).

Incisional biopsy – involves removing a lesion fragment with a healthy skin fragment of usually about 3-4 mm. It is recommended in highly advanced cases and in recurrent disease. It allows for the estimation of infiltration depth, which is of special importance before radiation therapy (Australian Cancer Network Management of Non-Melanoma Skin Cancer Working Party, 2002).

Excisional biopsy – is a diagnostic and therapeutic method. It is recommended in all cases where a defect formed after lesion excision can be sutured without leaving deformities (trunk, limbs.) Not only does it provide information regarding final diagnosis but also informs about the treatment efficacy (completeness). It involves primary excision of a lesion with a margin of clinically normal surrounding tissues. The recommended margin ranges from 2 to 8 mm. Unfortunately, it occurs quite often that clinically normal surrounding tissues are saved to too large an extent and excision is not complete, and as a result neoplastic recurrence is observed (Australian Cancer Network Management of Non-Melanoma Skin Cancer Working Party, 2002).

5.2 Imaging diagnostics

Dermatoscopy includes observing the skin with a dermatoscope consisting of a microscope with 10-100x magnification. In addition, a dermatoscope is equipped with an internal light source that illuminates the skin at an angle of 20°, therefore the picture is enlarged and its resolution is higher. This method is of the greatest importance in the diagnostics of pigmented lesions and melanoma. It makes it possible to distinguish melanoma from pigmented BCC. According to the Monzi criteria pigmented BCC has the following features: lack of pigment network and the presence of one of the following features: maple leaflike areas, spoke wheel areas, large gray-blue ovoid nests, large gray-blue globules,

telangiectasias with arborisation and ulceration (Menzies et al., 2000). In the case of nodular BCC in 82% it is possible to observe branching vessels, and the superficial form has delicate and short telangiectasias (Argenziano et al., 2004).

Imaging tests such as computed tomography or magnetic resonance imaging are used to determine the extent of neoplastic infiltration when cartilage, bone, large nerve (Williams et al., 2001), eyeball (Leibovitch et al., 2005, Meads & Greenway, 2006) or parotid gland (Farley et al., 2006) involvement is suspected.

Other modern methods are only of academic interest and do not play important roles in clinical diagnostics. They include:

High resolution ultrasound examination (20-100 Hz) allowing for imaging the skin up to the depth of even 1.1 mm which may be helpful during evaluation of the depth of lesion infiltration (Vogt & Ermert, 2007).

Optical coherence tomography (OCT) (Olmedo et al., 2006) – the mechanism of action is similar to the ultrasound examination; however, infrared light is used instead of ultrasounds – it is possible to visualise skin layers, appendages and vessels (Welzel et al., 1997) ; nevertheless, it is not possible to see the basement membrane or to evaluate the depth of infiltration (Welzel et al., 2003).

Confocal microscopy (RCM, reflectance confocal microscopy and FLSM, fluorescence confocal laser scanning microscopy) (Ulrich et al., 2008)- involving the detection of endogenous (RCM) or exogenous (FLSM) dye with special light, what makes it possible to visualise cells and cell structures with the precision nearly as good as the one of a histopathological examination (Swindle et al., 2003a; Swindle et al., 2003b).

Photodynamic diagnostics (PDD) involves the detection of light (using electromagnetic waves) emitted from tissues after fluorescence excitation (Morawiec et al., 2004).

Spectrometric diagnostics involves differentiation and evaluation of the excitation spectrum of healthy tissue and tissues with dysplastic or neoplastic lesions (Sieroń et al., 2007).

Fluorescence lifetime imaging methods (FLIM) - this time is different for healthy tissues and neoplastic tissues (Galletly et al., 2008).

6. BCC: Therapeutic options

BCC treatment is managed by physicians of many specialities. Dermatologists often use cryotherapy and remove small lesions located on the face and trunk, small eyelid neoplasms belong to ophthalmologists, lesions on the nose and ear are resected by ENT specialists, whereas dental surgeons remove lesions located in the area of the mouth cavity. Lesions the size of which makes it possible to direct closure are also excised by general surgeons and even by general practitioners in some countries (Australian Cancer Network Management of Non-Melanoma Skin Cancer Working Party, 2002). In the treatment of more extensive and advanced BCC cases in order to cover a defect after neoplasm excision it is necessary to use different reconstruction methods, what is possible only in specialist centres of plastic, maxillary or oncological surgery.

As there are many specialists managing BCC treatment, there are also numerous and different therapeutic options. They can be divided into destructive methods where

neoplastic tissue is destroyed and it is not possible to evaluate a histopathological type or procedure completeness, and surgical methods involving the excision of neoplastic tissue with a margin of clinically normal surrounding tissues.

Destructive methods include:

- local immunotherapy using imiquimod-containing ointment that stimulates and intensifies a local anti-inflammatory reaction what leads to BCC regression (Marks et al., 2001).
- photodynamic therapy, which uses the fact that some photosensitive substances, namely substances absorbing light of specific wavelength accumulate in neoplastic tissues. When they are selectively accumulated in the neoplastic tissue the lesion is exposed to laser light at the wavelength absorbed by a given photosensitive substance. Consequently, the high levels of radiation energy are accumulated in the neoplastic tissue and it becomes destroyed (Morawiec et al., 2004).
- radiation therapy, combining many methods starting from superficial radiation (up to 170 kV) in the case of lesions with the depth up to 6 mm, to electron beam radiation and brachytherapy (Telfer et al., 2008).
- curettage, which is often combined with other methods such as: coagulation (Reymann, 1985), imiquimod (Wu et al., 2006), photodynamic therapy (Soler et al., 2001), cryosurgery (Nordin & Stenquist, 2002) or surgery (Chiller et al., 2000; Johnson et al., 1991).
- cryosurgery, which involves the destruction of neoplastic tissue during one or several cycles of freezing using liquid nitrogen (Graham, 1983).
- CO_2 laser is a new therapeutic option still studied in clinical trials (Telfer et al., 2008).
- local application of fluorouracil (5-FU)-containing ointment, which is a classic cytostatic. Further studies are necessary to evaluate its long-term efficacy (Telfer et al., 2008).

The destructive methods presented above may be used only in some highly selected cases. Appropriate patient qualification combined with experience of a specialist using a given therapeutic method may provide good therapeutic effects.

As BCC, contrary to other malignant neoplasms, is rarely responsible for patient's death, 5-year survival as an outcome measure is not justified. For that reason, in order to assess the efficacy of BCC treatment the recurrence rate during a 5-year follow-up period is used. Moreover, it is necessary to take cosmetic and functional results and treatment comfort into account.

Currently it is difficult to evaluate unanimously which destructive method is the best. It is a result of the fact that current literature lacks in prospective trials comparing different methods and that the criteria of patients' qualification are extremely narrow and suitable only for individual methods, therefore it is not possible to compare them objectively. It is commonly thought that each method is good if it is applied in an appropriate case by an experienced specialist.

Surgical methods include classic excision of a lesion with a margin of clinically normal surrounding tissues and Mohs micrographic surgery that involves staged resection of a lesion with intraoperational histopathological evaluation of its edges.

6.1 Selecting a therapeutic method

In order to determine the indications for different methods, prognostic factors predicting BCC with a high-risk of recurrence have been identified.

6.2 Prognostic factors

Tumour site - a significantly higher risk of recurrence compared to the trunk and neck (recurrence in 0.5%) was observed for BCC located on the face (lateral canthal region – 43% of recurrence, upper lid and eyebrow 33%, nose 19%), ear (24%) and scalp. Some specialists think that it is associated with a specifical anatomical structure of the subcutaneous tissue of these areas, which creates a risk of deeper invasion (Monney & Parry, 2007).

Other specialists make attempts to explain a higher risk of recurrence in the central face (17.5% of recurrence vs 8.6% for other parts of the face) by the fact that a neoplasm changes its way of spreading from horizontal to vertical, what is reflected by the fact that infiltration spreads along embryonic connections between facial buds (Włodarkiewicz & Muraszko-Kuźma, 1998; Wronkowski et al., 1978).

Based on the risk of recurrence, the following areas can be distinguished: high risk of recurrence (H), middle risk of recurrence (M) and low risk (L) (Figure 1.).

However, it has to be emphasised that the above division into risk areas is based on a series of retrospective studies that analysed recurrence sites following surgical treatment. The margin of a clinically normal surrounding tissues resected with a lesion was not taken into account.

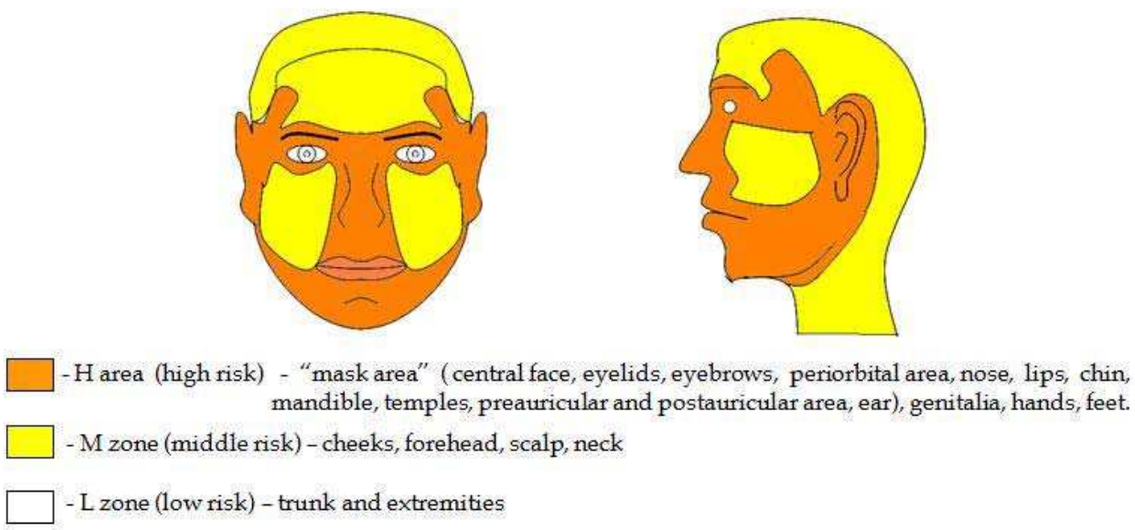


Fig. 1. Recurrence risk areas (Swanson, 1983)

According to the authors more frequent recurrences in the H zone may be associated with the fact that a smaller margin of clinically normal surrounding tissues is applied in these face areas. It is a result of the fact that operators are afraid of poor aesthetical and functional effects. For example, applying a larger margin in the medial canthal region could deform and disturb the functions of the eye protective apparatus. In other risk areas (M or L area)

e.g. on the neck or the trunk it is possible to resect lesions with larger margins of clinically normal surrounding tissues, what has no significant effects on aesthetical and functional results; however, it will significantly increase completeness of excision.

Tumour size and depth of invasion – the recurrence rate increases with the increasing size of a tumour. Depending on a diameter the recurrence rate in a 5-year follow-up period is as follows for the following tumour sizes: <1.5cm-12%, >3cm-23.1% (Dubin & Kopf, 1983). In other studies: <1cm-3.2%, 1-2cm–8%, >2cm recurrence in almost 1/3 of cases (Włodarkiewicz & Muraszko-Kuźma, 1998; Wronkowski et al., 1978).

Moreover, invasion of structures lying under the skin such as cartilages and bones is associated with a higher risk of recurrence.

The guidelines of National Comprehensive Cancer Network (NCCN), an American organisation studying therapeutic algorithms for treatment of neoplasms, combine tumour site and size in order to assess the recurrence risk (Diagram 2.)

Definition of clinical margins – the recurrence risk for lesions with ill-defined clinical tumor borders is higher than for lesions with well-defined borders (Rowe et al., 1989).

Histological subtype of BCC – for some morphological subtypes, e.g. morpheaform, infiltrating, micronodular or mixed types, the recurrence risk is higher (Table 3.) (Costantino et al., 2006 ; Włodarkiewicz & Muraszko-Kuźma, 1998).

Lesion excision with a classic margin is incomplete in 6.4% for a nodular lesion, for a superficial lesion – 3.6%, for a micronodular lesion – 18.6%, for an infiltrating lesion - 26%, for a morpheaform lesion – 33.3% (Mooney & Parry, 2007). Moreover, histological features of infiltration, especially perineural and perivascular involvement, are significant risk factors of recurrence (Costantino et al., 2006).

Non-aggressive growth pattern (well circumscribed, low recurrence rate)	**Aggressive growth pattern (poor circumscribed, high recurrence rate)**
Nodular subtypes (approx. 50%): - nodular-solid (nodularis-solidum) - nodular-adenoid (nodularis adenoides, nodularis cribriforme) - nodular-cystic (nodularis – cysticum)	Infiltrating (5-20%) (infiltrativum, infiltrative non-sclerosing, styloides) Morpheaform (approx.5%) (sclerodermiforme, morpheiforme, morphea-like, sclerosans, sclerotic, cicatrisans, infiltrative sclerosing)
Keratotic (keratoticum)	Micronodular (micronodulare)
Pigmented (pigmentosum)	Metatypic (matatypicum, baso-spinocellulare)
Fibroepithelial (fibroepithelioma, Pinkus tumour)	Superficial multifocal (15%) (superficiale multicentricum, Arning)

Table 3. Clinical-pathological classification of BCC (WHO 2006) and classification based on the recurrence risk (Bieniek et al., 2008; Kossard et al., 2006).

Recurrent BCC – treatment of recurrent BCC is associated with a significantly higher recurrence rate than treatment of primary lesions (Australian Cancer Network Management of Non-Melanoma Skin Cancer Working Party, 2002).

Immunosuppression – is associated not only with a higher risk of BCC in general, but also with a higher recurrence rate.[39]

BCC in patients after organ transplantation and leukaemic patients constitute a special problem.

Other prognostic factors, which are mentioned more rarely: age <35 years (Boeta-Angeles & Bennet, 1998), a reconstruction method after surgical excision (recurrent disease within the first year when full-thickness skin is grafted, after two years when split-thickness skin is grafted and within 4 years after local tissue transfers) (Koplin & Zarem, 1980; Richmond & Davie, 1987). Prognosis for Gorlin syndrome treatment is also poor (Gorlin, 1995).

The presence or lack of such features makes it possible to divide all types of BCC into high or low-risk lesions, therefore it is possible to select an appropriate therapeutic method. The latest guidelines for BCC treatment suggested by the British and American Scientific Societies are outlined (Diagram 1 and 2).

As it can be concluded from the guidelines, all high- and low-risk BCC as well as recurrent BCC may be surgically treated.

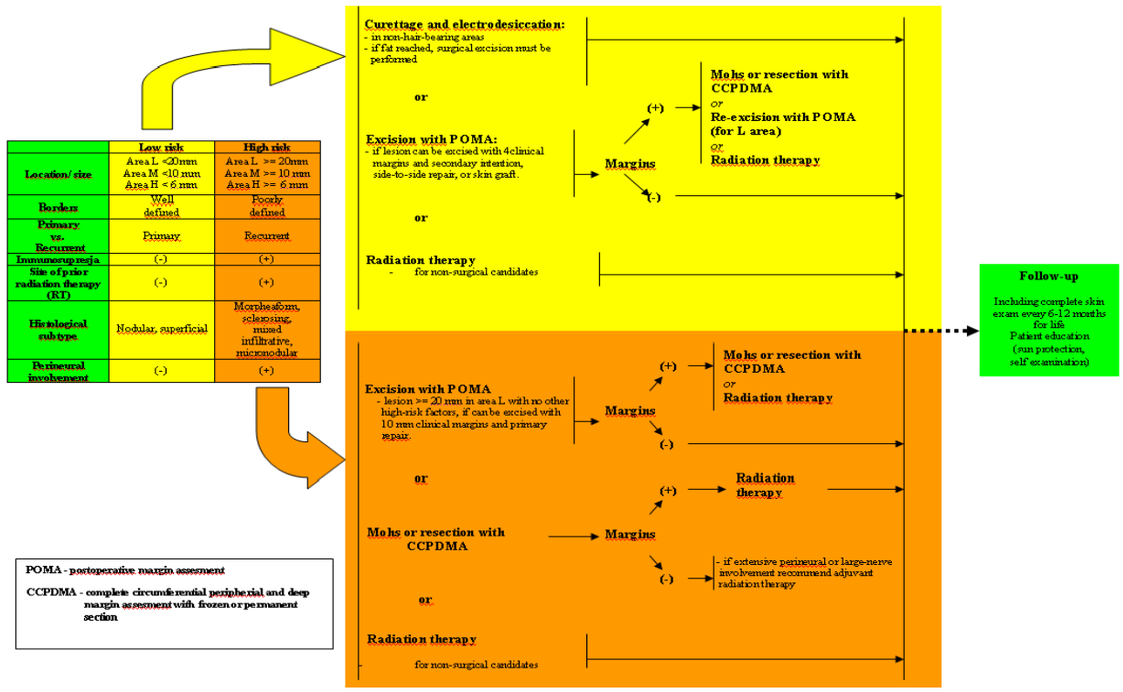


Diagram 1. Guidelines for BCC treatment based on *NCNN Clinical Practice Guidelines in Oncology: Basal Cell and Squamous Cell Skin Cancers* (USA, 01.2009)

Surgery is currently the gold standard for BCC treatment because of high efficacy, its versatility, fast results, good aesthetical and functional outcome, low risk of complication,

availability (the majority of mentioned destructive methods can only be applied in highly specialized clinics), low costs of treatment and what is even more important, the possibility to evaluate procedure completeness (Bath-Hextall et al., 2007).

PRIMARY BCC

BCC type: histology, size*, site**	PDT	Imiquimod	Curettage and cautery	Radiation therapy	Cryosurgery	Excision	Mohs surgery
Superficial, small and low-risk site	++	++	++	?	++	?	X
Nodular, small and low-risk site	+	-	++	?	++	+++	X
Infiltrative, small and low-risk site	X	X	+	+	+	+++	?
Superficial, large and low-risk site	+++	++	++	+	++	+	?
Nodular, large and low-risk site	-	-	++	++	++	+++	?
Infiltrative, large and low-risk site	X	X	-	+	+	+++	++
Superficial, small and high-risk site	+	+	+	++	+	++	+
Nodular, small and high-risk site	-	-	+	++	++	+++	++
Infiltrative, small and high-risk site	X	X	-	+	+	++	+++
Superficial, large and high-risk site	+	+	-	+	+	++	++
Nodular, large and high-risk site	-	X	X	-	+	++	++
Infiltrative, large and high-risk site	X	X	X	X	X	+	+++

RECURRENT BCC

BCC type: histology, size*, site**	PDT	Imiquimod	Curettage and cautery	Radiation therapy	Cryosurgery	Excision	Mohs surgery
Superficial, small and low-risk site	++	+	+	+	++	++	-
Nodular, small and low-risk site	-	X	++	++	++	+++	-
Infiltrative, small and low-risk site	X	X	-	++	++	+++	+
Superficial, large and low-risk site	++	+	+	++	++	+	+
Nodular, large and low-risk site	X	X	-	+	+	+++	+
Infiltrative, large and low-risk site	X	X	-	+	+	++	++
Superficial, small and high-risk site	?	X	+	+	+	++	++
Nodular, small and high-risk site	X	X	+	+	+	+++	++
Infiltrative, small and high-risk site	X	X	X	+	+	++	+++
Superficial, large and high-risk site	?	X	X	+	-	++	++
Nodular, large and high-risk site	X	X	X	-	-	++	+++
Infiltrative, large and high-risk site	X	X	X	-	-	+	+++

+++ probable treatment of choice, ++ generally good choice, + generally fair choice, ? reasonable, but not often needed, - generally poor choice, X probably should not be used

* size: small <2cm, large >2cm
** high-risk site *(central face, especially around the eses, nose, lips and ears), low-risk site (other sites)*
PDT – *photodynamic therapy*

Diagram 2. Treatment of BCC based on *Guidelines for the Management of Basal Cell Carcinoma* (UK, 07.2008 r.)

7. Surgical treatment

7.1 Surgical excision with a margin of clinically normal surrounding tissues

Surgical treatment is the simplest, the most effective and nowadays the most popular method of treatment. Its efficacy evaluated as the recurrence rate in a 5-year follow-up is 2-10% (Cullen et al., 1993; Goldberg et al., 1989; Griffiths et al., 2005; Silverman et al., 1992; Walker et al., 2006). So far only few prospective studies comparing surgical excision with other methods have been published in the literature.

Thissen compared cryosurgery (spray technique and double cycle of freezing) with surgical treatment of nodular and superficial BCC of the head and neck with the diameter of <2cm and observed better therapeutic outcomes in surgically treated patients; however, the differences were not statistically significant (Thissen et al., 2000).

On the other hand, Rhodes compared surgical treatment of nodular BCC located on the face with photodynamic therapy (PDT.) He did not observe significant differences in recurrence rates during the first 3 months; however, in 12- and 24-month follow-up he observed a statistically significant increase in the recurrence rate and worse cosmetic results in the case of PDT (Rhodes et al., 2004). Taking into account long-term results (after 60 months),

recurrence occurred in 14% after PDT and only in 4% after surgical treatment (Rhodes et al., 2007).

Moreover, another study where surgical excision of primary BCCs with the diameter below 4 cm was compared with radiation therapy indicated that during a 4-year follow-up a lower recurrence rate was associated with surgical excision (0.7% vs 7.5%.) Moreover, cosmetic results after surgical excision were more acceptable than the ones after radiation therapy (79% vs 40%), which were associated with discolouration and telangiectasia in more than 65% and radiodystrophy in 41% of cases (Avril et al., 1997; Petit et al., 2000).

An important stage in surgical excision of a lesion is the determination of a macroscopic (clinical) lesion border. It can be done using magnification (3x at least), Wood's lamp or dermatoscope (Costantino et al., 2006). Applying curettage before excision may increase the completeness of a procedure because it may be possible to determine real borders of a tumour more precisely (neoplastic tissues are more curettable) (Chiller et al., 2000; Johnson et al., 1991). When lesion borders have been precisely determined a margin (range) of clinically normal tissue is planned, and they are removed together with a lesion en-block. The specimen resected in this way is subject to histopathological evaluation during which a histopathological subtype of BCC is confirmed as well as procedure completeness. The tissue defect formed after lesion excision is closed according to the reconstructive ladder.

7.2 Margin of clinically normal surrounding tissue

It is obvious that the extent of neoplastic infiltration affects the range of a peripheral and deep margin. On the other hand, the infiltration extent correlates with prognostic factors (Telfer et al., 2008) e.g. for primary morpheaform BCC resected with a 3-mm margin only 66% of radical excisions observed, with a 5-mm margin – 82% and with a 13-15-mm more than 95%. For that reason, the presence of prognostic factors should determine the extent of a margin. Nonetheless, a precise therapeutic algorithm has so far not been established (Telfer et al., 2008). The extent of suggested margins ranges from 2 to 15 mm (Table 4), is established empirically and what is the most important, it does not take prognostic factors into account.

As reports published so far are in the majority retrospective reviews of therapeutic outcomes for different margins, their conclusions should be treated more like advices rather than methodologically proven guidelines.

Although American recommendations of NCCN (National Comprehensive Cancer Network) recommend to remove low-risk BCCs with a 4-mm margin it has to be noted that, what is emphasised by the authors of these recommendations, this guideline was based on lower-level evidence (Clinical Practice Guidelines in Oncology, 2009). It is based on the prospective report by Wolf from 1987 (Table 4) where 117 primary lesions were resected with a 2-mm margin with subsequent histopathological evaluation according to Mohs. If excision was incomplete, the margin of resected tissues was expanded by 1 mm until the procedure was complete. When lesions were excised with 2-mm margins, completeness of 70% was achieved, with 3-mm margins excisions were complete in 85% of cases and when margins were 4 mm completeness was as high as 95%. Although these results are statistically significant, they are poorly reliable because the study did not take into account prognostic factors that have been identified until now. The study lacks in information regarding the site of a tumour, its histopathological subtype and regards only

Author	Suggested margin	Primary /recurrent	Site (%)	Size (mm)	Histological subtype (%)	Incomplete excision(%)	Recurrence (%)
Conway[49]	3-4 mm – intraperative frozen section control	114.0	medial/lateral canthus – 48,2 / 17,5 upper/lower lid – 33,4 / 0,9	mean 13,3 (2-32)	infiltrative – 21 others – 79	no data	0%
	4- 8 mm – conventional histopathological techniques	31.0	medial/lateral canthus – 35,5 / 22,6 upper/lower lid – 41,9 / 0	mean 12,9 (5-18)	infiltrative – 22,6 others – 77,4	no data	9,7
Beirne[50]	5-10 mm	169.0	no data	no data	no data	0 (10 mm margin)	no data
Barf[51]	3-5 mm	468/27	cheek – 18,1 lips – 1,1 forehead – 14,5 nose – 20,9 ear – 1,9 neck – 6,4 extremities- 7,5 trunk – 14,1 orbital region - 4,9 scalp – 4,1	0-5 – 22% 6-10 – 40,3% 11-15 – 20,7% 16-20 – 7,2% ≥20 – 9,8%	no data	6,8	no data
Emmett[52]	3 - 8 mm - nodular 3-10 mm - infiltrative, multifocal, poor-circumscribed >10mm - recurrence	1411/258	head and neck – 75,5% trunk – 8,4% extremities - 16 %	no data	no data	12,7 (primary BCC) 0,7 (recurrent BCC)	no data
Epstein[53]	2mm - size < 10mm	131	b.d.	mean 8 (3-20)	nodular - 73 infiltrative – 6 superficial – 21	6 (1 mm margin) 2 (2 mm margin)	no data
Bisson[54]	3 mm	100	cheek – 19 nose – 25 forehead – 11 ear – 4 temple – 18 neck – 1 extremities – 10 trunk – 5 orbital region – 12 scalp – 2	mean 8,9 (1-30)	nodular – 68 micronodular- 6 superficial – 12 morpheaform -3 infiltrative - 4 others - 7	4	no data
Thomas[54]	4 mm – poor-circumscribed; 3mm -well-circumsriced	91	head and neck – 51	mean 12,1 (53% > 10 mm)	nodular -63 infiltrative – 10 superficial – 16 morpheaform – 2	4	no data
Hsuan[57]	2 mm	55	upper/lower lid – 56 / 11 medial/lateral canthus – 23,6 / 3,6 forehead – 0,5% cheek – 0,5 %	no data	no data	18	no data
Griffith[58]	3mm - well-circumscribed 10mm - poor-circumscribed and >10mm	634/49	cheek – 14,2 ear – 3,2 nose – 21,1 chin – 2,2 forehead - 21,0 neck – 4,9 extremities – 2,9 trunk – 5,5 orbital region – 9 scalp – 6,8	<5 – 38% 6-10 – 38,2% 11-20 – 17,5% 21-30 – 4,5% >30 – 1,8%	no data	no data	0,9
Breuninger[55]	7 mm	1757/259	forehead - 9,6 temple – 9,7 cheek – 10,2 neck – 2,6 nose – 17,1 scalp – 2,6 lower lid – 3,3 ear – 5,4 med./lateral canthus - 5,1 lips – 4,6	<10 – 48% 10-20 – 30% >20 – 9%	solidum -52 morpheaform -13 superficial – 14 mixed – 20	46,7 (2 mm margin) 20,7 (4 mm margin) 14,7 (6-8 mm margin)	no data
Wolf[47]	4 mm - < 2 cm, well-circumscribed , non-aggressive growth pattern	177.0	no data	< 10 - 62% 10-20 – 29% >20 - 9%	no data	5 (4 mm margin) 15 (3 mm margin) 30 (2mm margin)	no data
Griffiths[56]	2-3 mm – well-circumscribed 5 mm - poor-circumscribed	1539	forehead - 10 temple – 14 cheek – 9 ear – 8 nose – 22 lips – 3 orbital region – 9 scalp – 5 neck – 5 trunk – 5 extremities– 10	no data	no data	8,4	
Collin[59]	3-5 mm	226/10	Lower/upper lid – 37,6 / 6,7 medial/ lateral canthus – 38,4 / 7,9	<5 – 25,2% 5-10 – 33,6% 10-20 -37,6% >25 – 3,6%	solidum - >50%	no data	2,3%

Table 4. Range of excision margin – analysis of selected studies.

well-demarcated lesions, and in 91% of cases the tumour diameter was below 2 cm, and the mean was 9 mm. Due to low reliability of studies published so far the need to perform prospective studies according to evidence based medicine (EBM) arises as it is necessary to determine unanimously the range of margins depending on prognostic factors. It is of special importance when BCCs are located in functionally and aesthetically important face areas such as nose (ala nasi, columella, naso-facial sulcus), eyelids, medial and lateral canthus, ear with preauricular and postauricular region, lips philtrum (Chicheł & Skowronek, 2005; Mohs & Parry, 2007). All anatomical regions mentioned above are associated with a high risk of recurrence (H -area– Figure 1), and the differences in suggested margin are extremely important although they are as small as several millimetres. The excision of a lesion with a larger margin may for example result in the removal of lacrimal ducts or cause ectropion. For that reason, during margin selection a surgeon resecting a lesion in these areas (a suggested margin for the face is from 2 to 10 mm) has to take into account such aspects as post-surgical function preservation, possibility of defect closure or, last but not least, achieving acceptable cosmetic results.

As it can be seen, due to varied and often not very reliable recommendations, the decision to choose an oncologically radical margin is extremely difficult and in most cases made based on operator's experience (his knowledge and skills.)

Prospective trials taking into account all factors affecting the range of a margin (including prognostic factors) would systematise the current state of knowledge and contribute to establishing consensus regarding the excision margins, what is indispensable in order to prepare a consistent algorithm for BCC treatment.

The deep margin range is less controversial. The majority of authors recommend to resect BCCs at the depth reaching the fat tissue (Telfer et al., 2008). In BCCs where the skin is directly above deep tissues (cartilages, bones) it is obligatory to perform imaging tests and if necessary, increase the depth of a margin (Australian Cancer Network Management of Non-Melanoma Skin Cancer Working Party, 2002).

7.3 Histopathological evaluation

In order to determine the location of a resected tumour with relation to the adjacent tissues, each specimen indicated for a histopathological examination should be equipped with a surgical marker (suture, cut, dye mark) and a precise diagram presenting its location with relation to the adjacent tissues. As a result, it will be possible to identify sites where excision was incomplete. Moreover, information regarding previous treatment and results of a biopsy are also necessary (Australian Cancer Network Management of Non-Melanoma Skin Cancer Working Party, 2002).

The aim of a histopathological examination is to determine a histological subtype of BCC and excision completeness.

From a histopathological point of view BCC is similar to the basement membrane cells but differs in that the nucleus/cytoplasm ratio is higher.

Moreover, BCC cells do not have intercellular bridges and mitotic figures (Bader, 2008).

According to the latest WHO classification there are several clinical-pathological types of BCC. It includes criteria of a clinical and histopathological picture of different subtypes of BCC (Kossard et al., 2006).

From a clinical point of view it is important to distinguish histopathological subtypes with a aggressive growth pattern, what is of importance when a surgical procedure is planned (Table 3.) In addition, infiltration along vessels and nerves is dangerous, and associated with a high risk of recurrence (Costantiono, 2006).

The literature also describes undifferentiated and differentiated BCC. Little or no differentiation is reffered to as a solid BCC and includes pigmented, superficial, morpheaform and infiltrative subtypes. Differentiated BCC is mainly nodular BCC which often differentiates into cutaneous appendages, including hair, sebaceous or tubular glands (Bader, 2008). For statistical purposes the classification including three types is often used: nodular (solid), fibrosing (desmoplastic) and metatypic (baso-spinocellular) (Bieniek et al., 2008). Based on precise histopathological evaluation it was determined that neoplastic infiltration is irregular and unpredictable; however, it is usually present to a limited extent (Burg et al. 1975).

The margin of clinically normal surrounding tissues viewed under a microscope is on average smaller by 24% from a macroscopic in vivo margin as a result of shrinking and fixing (Thomas et al., 2003).

Hendrix et al. proved that infiltration in the case of infiltrating BCC is on average 7.2 mm, whereas for nodular BCC it is 4.7 mm (primary /recurrent 5.6/10.4 vs 4.3/5.7 respectively) (Hendrix & Parlette, 1996). On the other hand, according to Salasche primary morpheaform BCC can infiltrate tissues even up to the width of 7 mm beyond macroscopic borders of a

lesion (Salasche et al., 1981). Based on Burg's studies microscopic borders of primary BCC infiltration are estimated to be 3-6 mm, and 5-9 mm in the case of recurrent disease (Burg et al., 1975).

The most important factor determining the recurrence is to determine the extent of neoplastic infiltration and its relation to the edge of resection (Australian Cancer Network Management of Non-Melanoma Skin Cancer Working Party, 2002). It regards cases where tumor was identified at peripheral edge of resection and deep edge of resection what is associated with a more than a double risk of recurrence (17% peripheral vs 35% deep surgical edge in a 5-year follow-up period) (Liu et al., 1991).

In order to evaluate the risk of recurrence Pascal (Pascal et al., 1986) made the following classification:

- incomplete excision – a tumor is identified at a surgical edge. It is associated with a 33% risk of recurrence within 5 years follow-up.
- suboptimal excision - tumor is visible at the distance smaller than 0.5 mm from a surgical edge, what microscopically corresponds to one high-power field (400x.) In such cases there is a 12% risk of recurrence within 5 years follow-up.
- complete excision – tumor is visible at the distance larger than 0.5 mm, namely it is not present in one high-power field (400x) involving a surgical edge.

Although resecting a tumor in these cases is described as complete excision it is associated with a 1.2% risk of recurrence within 5 years follow-up.

It is mainly associated with the fact that histopathological techniques are not perfect. Conventional microscoping processing involves vertical sectioning at every 2-4 μm, perpendicular to the tumor surface (breadloaf sectioning -recommended for lesions <16 mm) (Rapini, 1990), when specimens from all four lesion quadrants are resected (cross sectioning – recommended >16 mm) (Rapini, 1990) or from its peripheral parts (peripheral sectioning) (Mohs & Parry, 2007) (Fig. 2: A, B, C.). Consequently, only representative vertical sections are evaluated and it is not possible to evaluate the whole tumor margin. It is claimed that using conventional methods it is possible to evaluate only from 0.01% to 44% of tumor margins (Kimyai-Asadi et al., 2005; Mohs & Parry, 2007).

The basic drawback of this method is an assumption that when a tissue margin in representative sections is considered as tumor-free, the whole lesion is considered to be excised completely. The method suggested by Mohs is significantly more precise than conventional techniques as it allows for collecting sections which are horizontal to the tumor surface, namely it is possible to evaluate the whole margin (Fig. 2:D.)

7.4 Incomplete excision

Incomplete excision of BCC is a situation when a tumor is identified at surgical edge or is at the distance of <0.5 mm from it (one high-power field at 400x magnification.) On average 4.7% - 7% (Griffiths, 1999; Kumar et al., 2000) of cases in the UK and 6.3% in Australia (Dieu & Macleod, 2002; Sussman & Liggins, 1996) are excised incompletely. These numbers prove that a problem is huge and although factors responsible for an increased risk of incomplete excision have already been identified until now it has not been possible to create a consistent algorithm of BCC management. The necessity to improve procedure completeness is

undeniable; however, management following incomplete excision (follow-up, reexcision, radiation therapy) raises many controversies.

Followers of follow-up base their opinions on numerous studies proving that recurrent disease will occur only in 30-41% of cases (De Silva & Dellon, 1985; Park et al., 1994; Sussman & Liggins, 1996) out of all incompletely excised lesions, so as many as 2/3 of tumor tissue left in the skin will not recur.

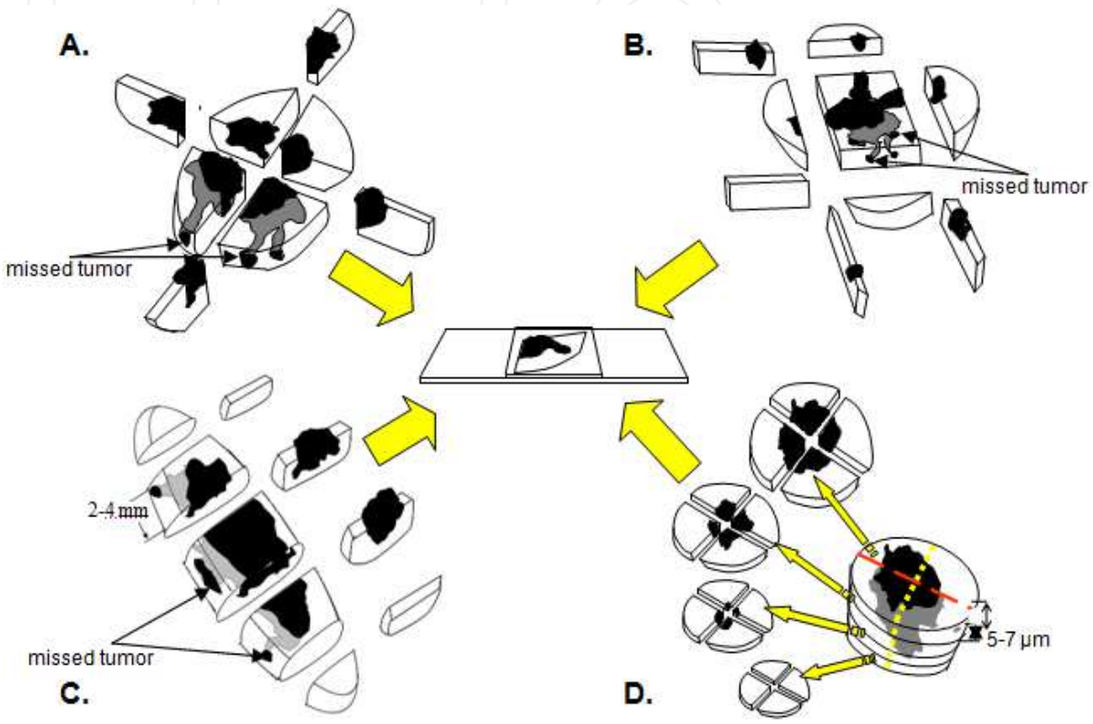


Fig. 2. Methods of microscopic processing: cross sectioning (A), peripheral sectioning (B), breadloaf sectioning (C), Mohs method (D).

In addition, prospective studies where incompletely excised BCCs were reexcised showed the presence of tumor tissue only in 45% (Wilson et al., 2004) and 54% (Griffiths, 1999) using conventional histopathological evaluation and 55% using the Mohs method (Bieley et al., 1992). It means that in almost half of cases the tumor tissue which was left regresses, possibly with the help of the immune system (Bieley et al., 1992).

Is a reexcision of an incompletely excised tumor justified?

Richmond et al. included in their study 92% patients who underwent reexcision of an incompletely excised tumors and 90% patients who were only observed (until recurrence occur, then it was excised immediately.) After a 10-year follow-up period recurrence occurred only in 9% of patients in the first group and in as many as 60% of patients in the other (Richmond & Davie, 1987).

Koplin recommends reexcision only in two cases: when a tumor is identified at surgical edge and when a tumor was excised suboptimally; however, only when expected life-time is long (Koplin & Zarem, 1980).

On the other hand, Robinson recommends only follow-up in the case of incomplete excision of an aggressive histopathological subtypes of BCC located on the nose, cheeks, around the lips, in men >65 years and in the case when a flap or split-thickness skin graft was used to cover a defect. His stand is based on the observation that in cases mentioned above significantly longer time is required for recurrence development (>5 years) than in other cases of BCC excised incompletely (Robinson & Fischer, 1996).

Similar controversies are associated with the use of radiation therapy following incomplete BCC excision. In a 10-year follow-up Liu compared the number of recurrence in the group of patients after immediate post-operative radiation therapy with the group of observed patients. Although in the group of patients subject to post-operative radiation therapy the recurrence rate was significantly lower the evaluation of all treatment aspects (costs analysis, complications) indicated that it is only recommended in cases after recurrence and when deep and lateral margins are involved. In the remaining cases the authors recommend careful observation stating a high presence of patients on follow-up examinations and significantly lower treatment costs as arguments for it (Liu et al., 1991).

On the other hand Wilson et al. recommend radiation therapy or reexcision of a tumor following its incomplete excision when a local flap or full-thickness skin graft was applied and when a deep margin in the H zone was involved. In all such cases recurrence would be difficult to detect and treat. In addition, Wilson does not recommend radiation therapy in young patients, especially in the forehead and scalp due to the risk of neoplastic transformation in scarred lesions in a long-term follow-up. In such cases, as well as in the cases of histologically aggressive BCC reexcision is recommended (Wilson et al., 2004).

Some authors have even more restrictive views on radiation therapy and they recommend it only in small lesions in patients who do not agree surgical treatment or in whom it is not possible to perform a surgery due to their physical condition (Australian Cancer Network Management of Non-Melanoma Skin Cancer Working Party, 2002).

7.5 Recurrence

Recurrence is defined as a new focus of tumor in a scar or in its vicinity formed after excision of a primary tumor occurring within 5 years since the excision and with the same histological type as the primary tumor. The incidence rate after surgical treatment of BCC in a 5-year follow-up is estimated to be 5% for primary and about 13% for recurrence BCC (Hauben et al., 1982). The factors increasing the risk of recurrence have been discussed in the Part II. Recurrence is the most frequent, namely as many as 82% of cases occur in the first five years, and about 30% of cases are present in the first year of observation, 50% in the second and 66% in the third year. The remaining 18% of cases occur in the period from 5 to 10 years since tumor excision (Marcil & Stern, 2000). The recommended follow-up for one patient in order to observe recurrence is 5 years (every 3 months during the first year, then every 6 months) (Liu et al., 1991) although the latest guidelines of the American NCCN recommend follow-up every 6-12 months for the whole lifetime (Clinical Practice Guidelines in Oncology, 2009). During follow-up control it is necessary to educate a patient with the possibilities of active prophylaxis against BCC, especially regarding sun protection. Moreover, it is also necessary to inform a patient about the need of skin self-examination. It is of special importance not only because of recurrence monitoring but also due to the risk of

development of another BCC which is ten times higher in patients with a previous BCC than in the general population (Marcil & Stern, 2000). This risk is also significantly higher in elderly patients, in patients with multiple BCCs and with the lesion diameter > 1cm (Van Iersen, 2005).

In some countries general practitioners manage follow-up control after BCC excision (Park et al., 1994).

Clinical symptoms that should raise suspicion of recurrence:

- scarring with non-healing or recurrent ulceration,
- a scar that is becoming red, desquamating and looks like ichtyosis,
- an expanding scar with telangiectasia inside the scar
- a nodule appearing within a scar
- tissue destruction

Recurrence following non-surgical treatment (radiation therapy, cryotherapy, curettage) is associated with a higher risk of another recurrence or even with the possibility of metastases (Smith & Grande, 1991). Skin lesions due to such treatment (atrophy, hypopigmentation, scarring) make it difficult to assess the extent of recurrence precisely. In addition, recurrence following treating BCC with cryotherapy may be difficult to evaluate due to scarring associated with treatment and the fact that infiltration spreads deeply beneath normally looking skin (Australian Cancer Network Management of Non-Melanoma Skin Cancer Working Party, 2002). Moreover, recurrence diagnostics in skin creases such as the nasolabial sulcus may also be a huge problem. Due to diagnostic difficulties in all cases when recurrence is suspected it is necessary to perform a biopsy to confirm diagnosis.

Recurrence treatment is significantly more difficult than treatment of a primary lesion, and the success rate is considerably lower (Rowe et al., 1989a). The risk of another recurrence is by 50% higher that in the case of a primary lesion (Silverman et al., 1992). Furthermore, it is thought that some incompletely excised lesions recur in a more aggressive growth pattern (a more aggressive histological subtype), especially in the central face (Boulinguez et al., 2004).

Surgical methods are recommended to treat recurrence. Wide BCC excision with a scar and a margin ranging from 5 to 10 mm or Mohs micrographic surgery which is significantly more successful are performed.

7.6 Mohs micrographic surgery (excision controlled histopathologically)

The history how this method came into existence and evolved is tightly associated with its creator. In 1930s Frederic E. Mohs, who was a medicine student at those times, studied the effects of different substances on cancer cells in rats. When he injected 20% zinc chloride solution inside a tumour he accidentally observed tissue necrosis and at the same time in situ tissue fixation. As a result of in vivo tissue fixation with zinc chloride he was able to cut specimens horizontally (parallel to the skin.) As a result he was able not only to assess a tumor histopathologically, but also to assess its whole margin, what formed the base to excision of tumors under microscopic control. After a short period of laboratory tests Mohs replaced 20% zinc chloride solution with the zinc paste applied 24h before tumor excision and started clinical trials on the use of his method in the treatment of skin tumors. As early as in 1941 Mohs presented his first clinical trials in "Archives of surgery" and named his

method chemosurgery (Mohs, 1941) (chemo – as tissue fixation is a result of a chemical reaction between tissues and zinc chloride) (Diagram 3).

It involves curettage of a tumour then applying a thick layer of the zinc paste under occlusive dressing which increases paste penetration and protects the surrounding skin. In the case of tumors with large hyperkeratosis before applying the zinc paste dichloroacetic acid with the keratolytic effects can be used and as a result, after the keratotic layer has been exfoliated, penetration of the zinc paste is greater. Tissues prepared in this way become necrotic after 6-24 hours what creates appropriate conditions for a surgical procedure (no pain, small bleeding at the operation site.) During the first stage a surgeon uses methylene blue, sutures or incisions to mark landmarks that will allow further identification of tumor areas that have been excised incompletely. Then the whole tumor with a 3-mm margin of clinically normal surrounding tissues is excised at the angle of 45^{o}, what makes it possible to "tease up" a epidermal edge and facilitates histopathological evaluation, especially of superficial skin layers. The incision is continued at the angle of 45^{o} around the tumor, and the deep surgical edge is parallel to the skin. After haemostasis a diagram presenting a defect formed after tumor excision and its relation to previously marked landmarks is prepared.

In the next stage, a histopathologist divides a lesion according to landmarks marked by an operator (usually into 4 quadrants), turns it deep surface up and marks edges of all quadrants formed after the division with two different dyes. Consequently, further identification of specimen areas excised incompletely is made easier. After marking quadrant edges the specimen is sectioned parallel to the skin and as a result 5-7 μm sections are obtained, therefore it is possible to assess the whole lesion margin. When a tumor fragment is found in the close vicinity of a surgical edge (suboptimal excision) or when a tumor is identified at surgical edge (incomplete excision) a histopathologist marks an area of incomplete excision in the diagram. Based on this diagram a surgeon locates the area with tumor cells that has been left, and then the whole process of fixation, excision and histopathological evaluation is repeated until complete excision is obtained.

In some cases when lesions were excised incompletely the whole process was repeated several times, what due to long time of tissue fixation with the zinc paste (6-24h) took even several days (high costs of treatment and hospitalisation.) Moreover, application of the zinc paste was painful for patients and induced tissue necrosis and ulceration in the lesion vicinity.

Therefore after tumor excision it was necessary to wait until necrosis areas became defined, and only then it was possible to close formed defect. All these features resulted in the fact that despite high efficacy this method did not gain much popularity. However, Mohs, who believed in the success of his method, focused more on its promotion than improvement. And in 1953 when he was doing a film demonstrating his technique an accident decided about a breakthrough discovery for yet another time. Mohs during resecting BCC of the lower eyelid omitted the stage of tissue fixation with the zinc paste in order to accelerate the whole process for the purposes of the film. Instead he excised BCC under local anaesthesia, then froze it and using cryotome obtained horizontal specimens of 5-7 μm. After their standard staining with haematoxylin-eosin he stated than the quality of specimens obtained in this way is the same when compared to the original method, and the duration of the procedure, costs and lack of ulceration and pain are significantly lower. Moreover, primary

defect closure was possible what decided about the success of this method to a large extent. With time the fresh-tissue technique replaced the fixed-tissue technique that was originally developed by Mohs. The original name of the whole procedure (chemosurgery) was replaced by Mohs Micrographic Surgery (MMS) due to unfavourable associations and in order to confer its meaning, namely mapping out of the specific location of tumor extension by the use of microscopic evaluation.

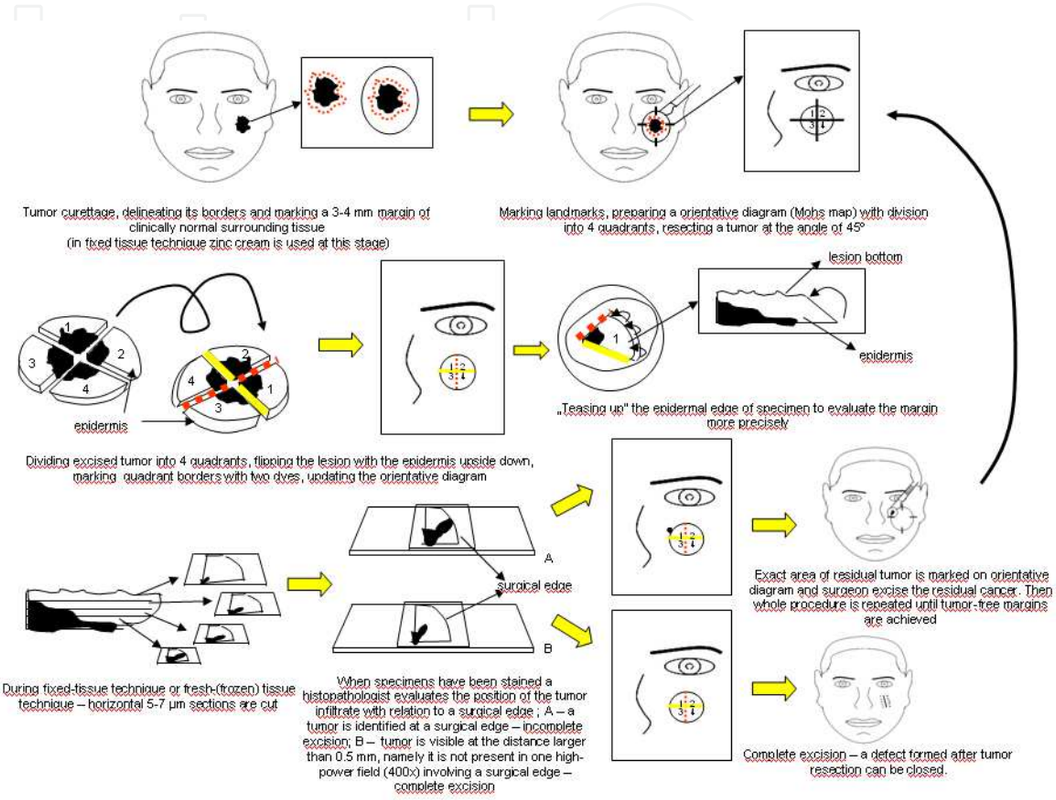


Diagram 3. Mohs micrographic surgery

Currently the fixed-tissue technique is used only in selected cases, mainly in order to eliminate excessive bleeding during lesion excision in areas which are well supplied with blood (e.g. penis.) The fresh-tissue technique has considerably more indications in BCC treatment (Table 5.)

A review of studies published since the mid-1940s confirms the high efficacy of this method reaching even 99% in a 5-year follow-up for primary (Rowe et al., 1989b) and 94.4 % for recurrent BCC (Rowe et al., 1989a). In prospective trials conducted in Australia in 819 patients with periocular BCC no recurrence were observed in 100% patients with primary and in 92.2% with recurrent BCC (Malhotra et al., 2004) in a 5-year follow-up, and in another study with 3370 patients with BCC on the head and neck no recurrence were observed in 98.8% patients with primary BCC and in 96% with recurrent BCC in a 5-year follow-up (Leibovitch et al., 2005).

Apart from its high efficacy other advantages of this method include the minimum amount of excised tissues and the possibility of primary defect closure knowing that a lesion was

excised completely. Despite many advantages Mohs Micrographic Surgery has been fully approved only in the USA, where it is used in about 30% of cases (Gaston et al., 1999).

Indications for Mohs Micrographic Surgery:
• location: H area (Part II), especially in the areas where it is necessary to excise a lesion in a saving manner (tip and ala of the nose, lips, eyelids, ear, hands, feet, genitalia)
• size: lesion with the diameter > 2 cm
• histopathological subtype: BCC with an aggressive growth pattern (tab.4), perineural, perivascular or deep tissues involvement
• recurrent BCC
• BCC in patients with immunosuppression
• BCC in patients with a history of previous radiation therapy
• long-lasting BCC (neglected)
• Gorlin syndrome

Table 5. Indications for Mohs Micrographic Surgery (at least one of the mentioned above) (Mohs & Parry, 2007).

Also in the USA was formed the American College of Mohs Micrographic Surgery and Cutaneus Oncology that currently has more than 800 physicians of different specialities who are qualified to use this method when they have completed a 1-2 year training course. In other countries Mohs micrographic surgery is used more rarely, mainly due to high costs (equipment, service, qualified staff) (Cook & Zitelli, 1998) and more work contribution (Hsuan et al., 2004) (time of one procedure is 3h on average) compared to traditional surgical lesion excision. Moreover, contrary to a classic surgical procedure this method is laborious, time-consuming and exhausting for a patient.

Some researchers defend high costs of treatment using this method by the fact that it is possible to obtain better results, consequently, it is more effective in terms of treatment costs than classic surgery (Hsuan et al., 2004). However, Smeets in a prospective trial comparing this method with surgical excision of a lesion with a 3-mm margin of clinically normal surrounding tissue following 30 months of follow-up did not find statistically significant differences in the treatment efficacy between these two method (Smeets et al., 2004).

8. Conclusion

BCC is one of the most common human malignancies. Epidemiology and the increasing rate of incidence prove that BCC is and will be in the future a significant clinical problem. Studies published recently complete our knowledge on its pathogenesis and present new diagnostic and therapeutic methods. The majority of new therapeutic methods may be used only in highly selected cases.

The only universal method that can be used to treat all cases of BCC is surgical excision with a margin of clinically normal surrounding tissues. However, despite numerous advantages of this method and its versatility it has been impossible to determine until now what margin of clinically normal surrounding tissue should be applied when BCC is excised. It is of special importance when lesions in functionally and aesthetically important face areas are excised. In such cases margin differences as low as 1 mm may affect completeness of excision, its functional results, the method of reconstruction and its aesthetic results as well.

For that reason, the authors think that prospective studies in accordance with EBM are necessary in order to determine unanimously the range of margins depending on the prognostic factors mentioned above.

The results of such studies could allow for the unanimous determination of the excision margins and preparing a consistent and common algorithm of BCC treatment.

9. References

"11th ROC: Ultraviolet Radiation Related Exposures." 27 January 2005. U.S. Department of Health & Human Services. 15 April 2008.

American Cancer Society. Cancer Facts & Figures 2008. Atlanta: *American Cancer Society*; 2008.

American Cancer Society: http:www.cancer.org (2006).

American Joint Committee on Cancer, *AJCC Cancer Staging Manual*, 6th ed. New York: Springer-Verlag 2002.

Argenziano G, Zalaudek I, Corona R et al. Vascular structures in skin tumors: a dermoscopy study. *Arch. Dermatol*. 2004; 140(12): 1485-1489

Aston S.J., Beasley R.W., Thorne C.H. Grabb *and Smith's Plastic Surgery*, 5th Edition, Philadelphia, Lippincott-Raven; 1997

Australian Cancer Network Management of Non-Melanoma Skin Cancer Working Party. Non-melanoma skin cancer: *Guidelines for treatment and management in Australia*; 24 October 2002

Avril MF, Auperin A, Margulis A et al. Basal cell carcinoma of the face: surgery or radiotherapy? Results of a randomized study. *Br J Cancer* 1997; 76:100–6.

Bader RS, Basal Cell Carcinoma: Differential Diagnoses & Workup (2008): http://emedicine.medscape.com/article/276624-diagnosis

Bart RS, Schrager D, Kopf AW, Bromberg J, Dubin N. Scalpel excision of basal cell carcinomas. *Arch Dermatol* 1978(114),V,739-742

Bath-Hextall F, Perkins W, Bong J, Williams H. Interventions for basal cell carcinoma of the skin. *Cochrane Database Syst Rev* 2007; 1:CD003412.

Beirne GA, Beirne CG. Observations on the critical margin for the complete excision of carcinoma of the skin. *Arch Dermatol* 1959;80:344-5

Bers MH, Berkow R, *The Merck Manual of Diagnosis and Therapy*. 2001;Section 10,Chapter 126:1004-1010.

Bickers DR, Lim HW, Margolis D et al. The burden of skin diseases: 2004. *J Am Acad Dermatol* 2006; 55: 490-500.

Bieley HC, Kirsner RS, Reyes BA, Garland LD. The use of Mohs micrographic surgery for determination of residual tumor in incompletely excised basal cell carcinoma. *J Am Acad Dermatol* 1992; 26:754–6.

Bieniek A, Cisło M, Jankowska-Konsur A. Nowotwory skóry. Klinika, patologia, leczenie, *Galaktyka* 2008

Bisson MA, Dunkin CSJ, Suvarna SK, Griffiths RW. Do plastic surgeons resect basal cell carcinomas too widely? A prospective study comparing surgical and histological margins. *Br J Plast Surg* 2002;55:293-7

Boeta-Angeles L, Bennet RG: Features associated with recurrence. Cutaneus Oncology. Malden: *Blackwell Science*; 1998. p. 998

Boukamp P. Non-melanoma skin cancer: what drives tumor development and progression? *Carcinogenesis* 2005; 26: 1657-1667.

Boulinguez S, Grison-Tabone C, Lamant L et al. Histological evolution of recurrent basal cell carcinoma and therapeutic implications for incompletely excised lesions. *Br J Dermatol* 2004; 151:623–6.

Bouwes Bavinck JN, Hardie DR, Green A, Cutmore S, MacNaught A, O'Sullivan B, et al. The risk of skin cancer in renal transplant recipients in Queensland, Australia. A follow-up study. *Transplantation* 1996; 61:715–721.

Braun RP, Klumb F, Girard C et al. Three-dimensional reconstruction of basal cell carcinomas. *Dermatol Surg* 2005; 31:562–6.

Breuninger H, Schippert W, Black B, Rassner G. The margin of safety and depth of excision in surgical treatment of a basalioma. Use of 3-dimensional histologic study of 2016 tumors. *Hautarzt* 1989;40:693-700

Brodowski R, Lewandowski B. Rak skóry twarzy. Przegląd piśmiennictwa. *Przegląd Medyczny Uniwersytetu Rzeszowskiego* 2004;2-3:224-230.

Burg G, Hirsch RD, Konz B, Braun-Falco O. Histographic surgery: accuracy of visual assessment of the margins of basal-cell epithelioma. *J Dermatol Surg* 1975; 1:21–24.

Chicheł A, Skowronek J. Współczesne leczenie raka skóry – dermatologia, chirurgia czy radioterapia? *Współczesna Onkologia*; 2005;9;10; 429-435.

Chiller K, Passaro D, McCalmont T, Vin-Christian K. Efficacy of curettage before excision in clearing surgical margins of nonmelanoma skin cancer. *Arch Dermatol* 2000; 136:1327–32.

Clark C, Bryden A, Dawe R et al. Topical 5-aminolaevulinic acid photodynamic therapy for cutaneous lesions: outcome and comparison of light sources. *Photodermatol Photoimmunol Photomed* 2003; 19:134–41.

Clinical Practice Guidelines in Oncology: Basal Cell and Squamous Cell Skin Cancers V.I.2009: www.nccn.org

Cole P, Rodu B: Declining cancer mortality in the United States. *Cancer* 1996;78:2045

Collin JRO. Basal cell carcinoma in the eyelid region. *Br J Ophtalmol* 1976; 60:806-809

Conway RM, Themel S, Holbach LM. Surgery for primary basal cell carcinoma including the eyelid margins with intraoperative frozen section control: comperative interventional study with a minimum clinical follow up of 5 years. *Br J Ophtalmol* 2004;88:236-8

Cook J, Zitelli JA. Mohs micrographic surgery: a cost analysis. *J Am Acad Dermatol* 1998; 39:698–703.

Costantino D, Lowe L, Brown DL. Basosquamous carcinoma – an under-recognized, high-risk cutaneous neoplasm: case study and review of the literature. *J Plast Reconstr Aesthet Surg* 2006; 59:424–8

Cullen FJ, Kennedy DA, Hoehn JE. Management of basal cell carcinoma: current concepts. *Adv Plast Surg* 1993; 10:187

De Silva SP, Dellon AL. Recurrence rate of positive margin basal cell carcinoma: results of a five-year prospective study. *J Surg Oncol* 1985; 28:72–4.

DeVita VT Jr, Hellman S, Rosenberg SA. Cancer*: Principles and Practice of Oncology*. 6th Edition, Lippincot 2001: Chapter 41.

Dieu T, Macleod AM. Incomplete excision of basal cell carcinomas: a retrospective audit. *Aust NZ J Surg* 2002; 72:219–21.

Domarus H, Stevens P. J. Metastatic basal cell carcinoma. Report of five cases and review of 170 cases in the literature. *J.Am.Acad.Dermatol*. 1984;10:1043-60.

Dubin N, Kopf AW: Multivariate risk score for recurrence of cutaneous basal cell carcinomas. *Arch Dermatol* 1983;119 (5): 373-7.

Emmett AJJ, Broadbent GG. Basal cell carcinoma in Queensland. *Aust NZ J Surg* 1981;51:576-90

Epstein E. How accurate is the visual assessment of basal carcinoma margins? *Br J Dermatol* 1973;89:37-43

Farley RL, Manolidis S, Ratner D. Aggressive basal cell carcinoma with invasion of the parotid gland, facial nerve, and temporal bone. *Dermatol Surg* 2006; 32:307–15.

Franchimont C. Episodic progression and regression of basal cell carcinomas. *Br J Dermatol* 1982;106:305–10.

Gailani MR, Leffell DJ, Ziegler A et al. Relationship between sunlight exposure and a key genetic alteration in basal cell carcinoma. *J Natl Cancer Inst* 1996; 88:349–54.

Galletly NP, McGinty J, Dunsby C, Teixeira F, Requejo-Isidro J. Munro I, Elson DS., Neil MAA, Chu AC. French PMW, Stamp GW. Fluorescence Lifetime Imaging Distinguishes Basal Cell Carcinoma From Surrounding Uninvolved Skin; *Br J Dermatol*. 2008;159(1):152-161.

Gaston DA, Naugle C, Clark DP. Mohs micrographic surgery referral patterns: the University of Missouri experience. *Dermatol Surg* 1999;25:862-6

Gilbody JS, Aitken J, Green A. What causes basal cell carcinoma to be the commonest cancer? *Aust J Public Health* 1994; 18:218–21.

Giuffrida TJ, Jimenez G, Nouri K. Histologic cure of basal cell carcinoma treated with cryosurgery. *J Am Acad Dermatol* 2003; 49:483–6.

Global Cancer Statistics Globocan 2002: http://www-dep.iarc.fr/

Gloster Jr HM, Neal K, Skin cancer in skin of color, *J. Am. Acad. Dermatol.* 2006; 55: 741–760.

Godar DE, Urbach F, Gasparro FP, van der Leun JC. UV Doses of Young Adults. *Photochemistry and Photobiology* 2003; 77(4): 453-457.

Goldberg LH, Hsu SH, Alcalay J. Effectiveness of isotretinoin in preventing the appearance of basal cell carcinomas in basal cell nevus syndrome. *J Am Acad Dermatol* 1989; 21:144–145.

Goldsmith LA. Skin effects of fair pollution. *Otolaryn. Head and Neck Surg* 1996; 114:217.

Gorlin RJ. Nevoid basal cell carcinoma syndrome. *Dermatol Clin* 1995; 13:113–125

Graham G. Statistical data on malignant tumors in cryosurgery: 1982. *J Dermatol Surg Oncol* 1983; 9:238–9.

Griffith BH, McKinney P. An appraisal of the treatment of basal cell carcinoma of the skin. *Plast Rec Surg* 1973;51:563-571

Griffiths RW, Suvarna SK, Stone J. Basal cell carcinoma histological clearance margins: an analysis of 1539 conventionally excised tumours. Wider still and deeper? *J of Plast Rec and Aest Surgery* 2007,60:41-47

Griffiths RW, Suvarna SK, Stone J. Do basal cell carcinomas recur after complete conventional surgical excision? *Br J Plast Surg* 2005; 58:795–805.

Griffiths RW. Audit of histologically incompletely excised basal cell carcinomas: recommendations for management by re-excision. *Br J Plast Surg* 1999; 52:24–8.

Gupta AK, Cardella CJ, Haberman HF, Cutaneus malignant neoplasms In patients with renal transplants. *Arch Dermat*. 1986;122;1288-1293

Hauben DJ, Zirkin H, Mahler D, Sacks M: The biologic behaviour of basal cell carcinoma: analysis of recurrence in excised basal cell carcinoma. Part II. *Plast Reconstr Surg* 1982;69:110-116

Hendrix JD, Harry L, Parlette HL. Micronodular basal cell carcinoma. A deceptive histologic subtype with frequent clinically undetected tumor extension. *Arch. Dermatol*.1996;132:295.

Hendrix JD, Parlette HL, Duplicitous growth of infiltrative basal cell carcinoma. Analysis of clinically undetected tumor extent in a paired case-control study. *Dermatol Surg* 1996;22:535-539

Hsuan JD, Harrad RA, Potts MJ, Collins C. Small margin excision of periocular basal cell carcinoma: 5 year results. Br *J Ophthalmol* 2004; 88:358–60.

Ionesco DN, Arida M, Jukic DM. Metastatic Basal Cell Carcinoma. Four Case Reports, Review of Literature, and Immunohistochemucal Evaluation. *Arch Pathol Lab Med* 2006;130(1): 45-51.

Jabłońska S, Chorzelski T. *Choroby skóry. Dla studentów medycyny i lekarzy*. Wyd. V PZWL; 2002. p. 387-394.

Jeacock DA. *Dietary fats and antioxidants and BCC incidence*. 1998; Uni Qld. MSc.

Jemal A, Murray T, Samuels A, et al.: Cancer statistics, 2003, *CA Cancer J Clin* 2003; 53:5.

Jensen P, Hansen S, Moller B, Leivestad T, Pfeffer P, Geiran O, Fauchald P, Simonsen S, Skin cancer in kidney and heart transplant recipients and different long-term immunosuppressive therapy regimens, J. *Am. Acad. Dermatol*. 1999;40: 177–186.

Johnson TM, Tromovitch TA, Swanson NA. Combined curettage and excision: a treatment method for primary basal cell carcinoma. *J Am Acad Dermatol* 1991; 24:613–17.

Karagas MR, Stannard VA, Mott LA, Slattery MJ, Spencer SK, and Weinstock MA. Use of Tanning Devices and Risk of Basal Cell and Squamous Cell Skin Cancers. *J. Natl. Cancer Inst*. 2002; 94: 224.

Kimyai-Asadi A, Goldberg LH, Jih MH. Accuracy of serial transverse cross-sections in detecting residual basal cell carcinoma at the surgical margins of an elliptical excision specimen. *J Am Acad Dermatol 2005*; 53:469–74.

Koplin L, Zarem HA. Recurrent basal cell carcinoma: a review concerning the incidence, behavior, and management of recurrent basal cell carcinoma, with emphasis on the incompletely excised lesion. *Plast Reconstr Surg* 1980; 65:656–64.

Kordek R, Jassem J, Krzakowski M, Jeziorski A, *Onkologia. Podręcznik dla studentów i lekarzy*. Wyd. II: Via Medica; 2004. p. 191-196

Kossard S, Epstein EH Jr, Cerio R, Yu LL, Weedon D. Basal cell carcinoma. In: LeBoit P, Burg G, Weedon D, Sarasin A. The WHO classification of tumours. Pathology and genetics of skin tumours. *IARC Press*, Lyon 2006:13-19

Kossard S, Epstein EH Jr, Cerio R, Yu LL, Weedon D. Basal cell carcinoma. In: LeBoit P, Burg G, Weedon D, Sarasin A. The WHO classification of tumours. Pathology and genetics of skin tumours. *IARC Press*, Lyon 2006:13-19

Krajowy Rejestr Onkologiczny: http://epid.coi.waw.pl/krn/

Kricker A, English DR, Randell PL, Heenan PJ, Clay CD, Delaney TA, et al. Skin cancer in Geraldton, Western Australia: a survey of incidence and prevalence. *Med J Aust* 1990; 152:399–407.

Kumar P, Orton CI, McWilliam LJ, Watson S. Incidence of incomplete excision in surgically treated basal cell carcinoma: a retrospective clinical audit. *Br J Plast Surg* 2000; 35:563–6.

Kwan W, Wilson D, Moravan V. Radiotherapy for locally advanced basal cell and squamous cell carcinomas of the skin. *Int J Radiat Oncol Biol Phys* 2004; 60:406–11.

Leibovitch I, Huilgol SC, Selva D et al. Basal cell carcinoma treated with Mohs surgery in Australia II. Outcome at 5-year follow-up. *J Am Acad Dermatol* 2005;53:452-7

Leibovitch I, McNab A, Sullivan T et al. Orbital invasion by periocular basal cell carcinoma. *Ophthalmology* 2005; 112:717–23.

Liu FF, Maki E, Warde P, Payne D, Fitzpatrick P. A management approach to incompletely excised basal cell carcinomas of skin. *Int J Radiat Oncol Biol Phys* 1991; 20:423–428.

Lo JS, Snow SN, Reizner GT et al. Metastatic basal cell carcinoma: report of twelve cases with a review of the literature. *J Am Acad Dermatol* 1991; 24:715–19.

Maeda H, Akaike T. Nitric oxide and oxygen radicals in infection, inflammation, and cancer, *Biochemistry* (Mosc) 1998; 63:854-865.

Malhotra R, Huilgol SC, Huynh NT, Selva D. The Australian Mohs database, part II: periocular basal cell carcinoma outcome at 5-year follow-up. *Ophthalmology* 2004;111:631-6

Manusow D., Weinerman B.H., Subsequent neoplasia in chronic lymphocytic leukemia. *JAMA* 1975; 232: 267–269.

Marcil I, Stern RS. Risk of developing a subsequent nonmelanoma skin cancer in patients with a history of nonmelanoma skin cancer: a critical review of the literature and meta-analysis. *Arch Dermatol* 2000; 136:1524–30.

Marks R, Gebauer K, Shumack S et al. Imiquimod 5% cream in the treatment of superficial basal cell carcinoma: results of a multicenter 6-week dose–response trial. *J Am Acad Dermatol* 2001; 44:807–13.

Marks R, Jolley D, Lectsas S, Foley P. The role of childhood exposure to sunlight in the development of solar keratoses and non-melanocytic skin cancer. *Med. J. Aust.* 152 (1990):62-66.

Marks R, Staples M, Giles GG, Trends in non-melanocytic skin cancer treated in Australia: the second national sutvey. *Int J Cancer.* 1993;53:585-590.

Marks R. The epidemiology of non-melanoma skin cancer: who, why and what can we do about it. *J. Dermatol*.1995;22:853.

McCarthy EM, Ethridge KP, Wagner RF, Beach holiday sunburn: the sunscreen paradox and gender differences, *Cutis* 1999; 64:37–42.

McCormack CJ, Kelly JW, Dorevitch AP. Differences in age and body site distribution of the histological subtypes of basal cell carcinoma. A possible indicator of differing causes. *Arch Dermatol* 1997; 133:593–596.

Meads SB, Greenway HT. Basal cell carcinoma associated with orbital invasion: clinical features and treatment options. *Dermatol Surg* 2006; 32:442–6.

Menzies SW, Westerhoff K, Rabinovitz H, Kopf AW, McCarthy WH, Katz B. Surface microscopy of pigmented basal cell carcinoma. *Arch. Dermatol*. 2000; 136(8): 1012-1016

Miller DL, Weinstock MA. Nonmelanoma skin cancer in the United States: incidence. *J Am Acad Dermatol* 1994; 30:774–8.

Mogensen M, Jemec GB. Diagnosis of nonmelanoma skin cancer/keratinocyte carcinoma: a review of diagnostic accuracy of nonmelanoma skin cancer diagnostic tests and technologies. *Dermatol. Surg.* 2007;33(10): 1158-1174.

Mohs FE: Chemosurgery: A microscopically controlled method of cancer excision. *Arch Surg* 1941;42:279-295

Mohs Mooney M, Parry E. Mohs Micrographic Surgery(2007): www.emedicine.com/derm/topic542.htm

Morawiec Z., Rykała J., Kołacińska A., Antoszewski B., Kruk-Jeromin J., Czy metoda fotodynamiczna będzie diagnostyką przyszłości? *Acta Clinica et Morphologica* 2004; 7(1):10-14

NCNN Clinical Practice Guidelines in Oncology: Basal Cell and Squamous Cell Skin Cancers V.I.2009: www.nccn.org

Nelson BR, Railan D, Cohen Scott Moh's micrographic surgery for nonmelanoma skin cancers. *Clin in Plast Surg* 1997;24(4): 705-718

Nordin P, Stenquist B. Five-year results of curettage-cryosurgery for 100 consecutive auricular non-melanoma skin cancers. *J Laryngol Otol* 2002; 116:893–8.

Nouri K, Chang A, Trent JT, Jimenez GP. Ultrapulse CO_2 used for the successful treatment of basal cell carcinomas found in patients with basal cell nevus syndrome. *Dermatol Surg* 2002; 28:287–90.

Olmedo JM, Warschaw KE, Schmitt JM, Swanson DL. Optical coherence tomography for the characterization of basal cell carcinoma in vivo: a pilot study. *J. Am. Acad. Dermatol*. 2006; 3: 408-412

Park AJ, Strick M, Watson JD. Basal cell carcinomas: do they need to be followed up? *J R Coll Surg Edinb* 1994; 39:109–11.

Parkin DM, Pisani P, Ferley J: Global cancer statistics. *CA Cancer J Clin* 1999; 49:33.

Parrish JA. Ultraviolet radiation affects the immune system, *Pediatrics* 1983;71: 129–133.

Pascal RR, Hobby LW, Lattes R, Crikelair GF, Prognosis of "incompletely" versus "completely excised" basal cell carcinoma. *Plast Rec Surg* 1968;41;328-332

Petit JY, Avril MF, Margulis A et al. Evaluation of cosmetic results of a randomized trial comparing surgery and radiotherapy in the treatment of basal cell carcinoma of the face. *Plast Reconstr Surg* 2000; 105:2544–51.

Pietrzykowska-Chorążak A.: Odczyny skórne na promieniowanie UV w zależności od wieku. *Przegl. Dermatolog*. 1978;61:3.

Presser SE, Taylor JR. Clinical diagnostic accuracy of basal cell carcinoma. *J Am Acad Dermatol* 1987; 16:988–990.

Preston DS, Stern RS. Nonmelanoma cancers of the skin. *N Engl J Med* 1992;327:1649–62.

Raasch BA, Buettner PG. Multiple nonmelanoma skin cancer in an exposed Australian population. *International journal of Dermatology* 2002;41(10):652–8.

Randle HW. Basal cell carcinoma: identification and treatment of the highrisk patient. *Dermatol Surg*. 1996;22:255–261.

Rapini RP, Comparison of methods for checking surgical margins. *J Am Acad Dermatol* 1990;23:288-94

Reymann F. 15 years' experience with treatment of basal cell carcinomas of the skin with curettage. *Acta Derm Venereol* (Stockh) 1985; 120 (Suppl.):56–9.

Rhodes LE, de Rie M, Enstrom Y, Groves R, Morken T, Goulden V, et al.Photodynamic therapy using topical methyl aminolevulinate vs surgery for nodular basal cell carcinoma. *Arch Dermatol* 2004;140:17–13.

Rhodes LE, de Rie MA, Leifsdottir R et al. Five year follow-up of a randomized, prospective trial of methyl aminolevulinate photodynamic therapy vs surgery for nodular basal cell carcinoma. *Arch Dermatol* 2007; 143:1131–6.

Richmond JD, Davie RM. The significance of incomplete excision in patients with basal cell carcinoma. *Br J Plast Surg* 1987; 40:63–67.

Robinson JK, Fisher SG: Recurrent basal cell carcinoma: A management dilemma? *Aust NZ J Surg* 1996, 66;276-278

Robinson JK. Sun Exposure, Sun Protection, and Vitamin D. *JAMA* 2005; 294: 1541-43.

Rowe DE, Carroll RJ, Day CL Jr et al. Long-term recurrence rates in previously untreated (primary) basal cell carcinoma: implications for patient follow-up. *J Dermatol Surg Oncol* 1989; 15:315–28.

Rowe DE, Carroll RJ, Day CL. Mohs surgery is the treatment of choice for recurrent (previously treated) basal cell carcinoma. *J Dermatol Surg Oncol* 1989; 15:424–31.

Safai B, Good RA. Basal cell carcinoma with metastasis: review of literature. *Arch Pathol Lab Med*. 1977;101:327–331.

Salasche SJ, Amonette RA. Morpheaform basal-cell epitheliomas. A study of subclinical extensions in a series of 51 cases. *J Dermatol Surg Oncol* 1981; 7:387–394.

Schreiber MM. Moon TE, Fox SH, Davidson J. The risk of developing subsequent nonmelanoma skin cancers. *J Am Acad Dermatol* 1990;23:1114–18.

Sieroń A, Gibiński P, Woźnica T. Spektrometryczny system wczesnego wykrywania i diagnostyki nowotworów. *Acta Bio-Optica et Informatica Medica* 2007; 13(4):

Silverman MK, Kopf AW, Bart RS, Grin CM, Levenstein MS. Recurrence rates of treated basal cell carcinomas. Part 3: Surgical excision. *J Dermatol Surg Oncol* 1992; 18:471–476.

Silverman MK, Kopf AW, Grin CM et al. Recurrence rates of treated basal cell carcinomas. Part 2: curettage-electrodesiccation. *J Dermatol Surg Oncol* 1991; 17:720–6.

Smeets NWJ, Krekels GAM, Ostertag JU, Essers BAB, Dirksen CD, Nieman FHM, et al.Surgical excision vsMohs' micrographic surgery for basal-cell carcinoma of the face: randomised controlled trial. *Lancet* 2004;364:1766–72.

Smith SP, Grande DJ. Basal cell carcinoma recurring after radiotherapy: A unique difficult treatment subclass of recurrent basal cell carcinoma. *J Dermatol Surg Oncol* 1991; 17:26

Snow SN, Sahl, W, Lo, J S, Mohs FE, Warner T, Dekkinga ,JA. et al. Metastatic basal cell carcinoma. Report of five cases. *Cancer*. 1994;73:328-35.

Soler AM, Warloe T, Berner A, Giercksky KE. A follow-up study of recurrence and cosmesis in completely responding superficial and nodular basal cell carcinomas treated

with methyl 5-aminolaevulinate-based photodynamic therapy alone and with prior curettage. *Br J Dermatol* 2001; 145:467–71.

Spiller WF, Spiller RF. Treatment of basal cell epithelioma by curettage and electrodesiccation. *J Am Acad Dermatol* 1984; 11:808–14.

Sussman LA, Liggins DF. Incompletely excised basal cell carcinoma: a management dilemma? *Aust NZ J Surg* 1996; 66:276–8.

Swanson N.A., Mohs surgery: Technique, indications, applications, and the future. *Arch. Dermatol* 1983;119:761-773.

Swindle L, Freeman M, Jones B, Thomas S. Fluorescence confocal microscopy of normal human skin and skin lesions in vivo. *Skin Res Technol* 2003b; 9:167.

Swindle LD, Thomas SG, Freeman M, Delaney PM. View of normal human skin in vivo as observed using fluorescent fiber-optic confocal microscopic imaging. *J Invest Dermatol* 2003a; 121:706–12.

Szepietowski J, Sworszt-Pączek W, Wąsik F, Cisło M, Bliżanowska A. Mnogie raki kolczystokomórkowe u chorego z łuszczycą. *Przegl. Dermatol* 1996;83:127.

Taylor CR et al. "Photoaging/Photodamage and Photoprotection" *J. Am Acad Dermatol* 1990: 22.

Telfer NR; Colver GB; Morton CA; Guidelines for the Management of Basal Cell Carcinoma. *Br J Dermatol*. 2008;158(7): 35-48

The Burden of Skin Cancer. National Center for Chronic Disease Prevention and Health Promotion. 13 May 2008.

The skin Cancer Foundation: Skin Cancer Facts 2008: www.skincancer.org

Thissen MRTM, Nieman FHM, Ideler AHLB. Cosmetic results of cryosurgery versus surgical excision for primary uncomplicated basal cell carcinomas of the head and neck. *Dermatological Surgery* 2000; 26:759–64.

Thomas DJ, King AR, Peat BG. Excision margins for nonmelanotic skin cancer. *Plast Reconstr Surg* 2003;112:57-63

Ulrich M., Astner S., Stockfleth E., Röwert-Huber J. Noninvasive Diagnosis of Non-melanoma Skin Cancer: Focus on Reflectance Confocal Microscopy, *Expert Rev Dermatol*. 2008;3(5):557-567.

Van Iersel CA, van de Velden HV, Kusters CD et al. Prognostic factors for a subsequent basal cell carcinoma: implications for follow up. *Br J Dermatol* 2005; 153:1078–80.

Viac J, Chardonnet Y., Euvrard S, Chignol MC, Thivolet J. Langerhans cells, inflammation markers and human papillomavirus infections in benign and malignant epithelial tumors from transplant recipients, *J. Dermatol.* 1992; 19: 67–77.

Vogt M, Ermert H. High Resolution Ultrasound In: Bioengineering of the Skin. Skin, Skin imaging and Analysis; second edition, KP Wilhelm, P Elsner, E Berardesca, H Maibach (eds.). *Informa Healthcare USA Inc*, NY, USA, 2007; 17–29.

Wade T., Ackerman A.B.: The many faces of basal-cell carcinoma. *J. Dermatol. Surg. Oncol.* 1978;4:23.

Wagner RF, Casciato DA: Skin cancers. In: Casciato DA, Lowitz BB, eds.: *Manual of Clinical Oncology*. 4th ed. Philadelphia: Lippincott; 2000. p. 336-373.

Walker P, Hill D. Surgical treatment of basal cell carcinomas using standard postoperative histological assessment. *Australas J Dermatol* 2006; 47:1–12.

Weedon D, Wall D. Metastatic basal cell carcinoma. *Med J Aust*. 1975;2: 177–179.

Wei Q, Matanoski GM, Farmer ER, Strickland P, Grossman L. Vitamin supplementation and reduced risk of basal cell carcinoma. *J Clin Epidemiol* 1994; 47:829–836.

Weinstock MA, Bogaars HA, Ashley M, Litle V, Bilodeau E, Kimmel S. Nonmelanoma skin cancer mortality: a population-based study. *Arch Dermatol*. 1991; 127:1194–1197.

Welzel J, Bruhns m, Wolff H. Optical coherence tomography in contact dermatitis and psoriasis. *Arch Dermatol Res* 2003; 295:50–5.

Welzel J, Lankenau E, Birngruber R et al. Optical coherence tomography of the human skin. *J Am Acad Dermatol* 1997; 37: 958–63.

Williams LS, Mancuso AA, Mendenhall WM. Perineural spread of cutaneous squamous and basal cell carcinoma: CT and MR detection and its impact on patient management and prognosis. *Int J Radiat Oncol Biol Phys* 2001; 49:1061–9.

Wilson AW, Howsam G, Santhanam V et al. Surgical management of incompletely excised basal cell carcinomas of the head and neck. *Br J Oral Maxillofac Surg* 2004; 42:311–14.

Włodarkiwicz A, Muraszko-Kuźma M. Czynniki zwiększonego ryzyka wznowy w raku podstawnokomórkowym skóry. *Przegl. Dermatol.* 1998,85,405.

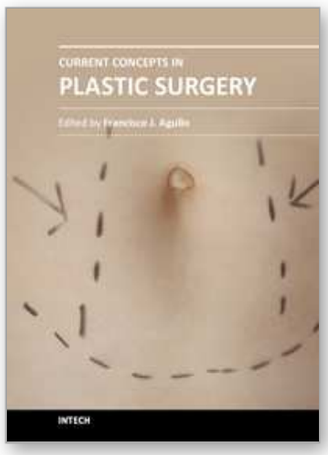
Wolf DJ, Zitelli JA, Surgical margins for basal cell carcinoma. *Arch Dermatol* 1987;123:340-4

Wronkowski Z, Dąbska M, Kułakowski A. *Rak skóry*. PZWL, Warszawa 1978.

Wu JK, Oh C, Strutton G, Siller G. An open-label, pilot study examining the efficacy of curettage followed by imiquimod 5% cream for the treatment of primary nodular basal cell carcinoma. *Australas J Dermatol* 2006; 47:46–8.

Zak-Prelich M, Narbutt J, Sysa-Jedrzejowska A. Environmental risk factors predisposing to the development of basal cell carcinoma. *Dermatol Surg* 2004; 30:248–52.

IntechOpen



Current Concepts in Plastic Surgery

Edited by Dr. Frank Agullo

ISBN 978-953-51-0398-1
Hard cover, 264 pages
Publisher InTech
Published online 23, March, 2012
Published in print edition March, 2012

Plastic surgery continues to be a rapidly growing field in medicine. There have been multiple recent advancements in the field. Specifically, there has been a continuously growing interest in fat grafting, body contouring, minimally invasive surgery, and plastic surgery education. At the same time, there have been continued advances and modifications in surgical techniques, which translate into better and improved results for our patients while increasing safety and efficacy. The title of the book is Current Concepts in Plastic Surgery and, as such, it highlights some of the "hot topics" in recent years. We have invited renowned specialists from around the world to share their valued expertise and experience. Most of the chapters will expose the reader to multiple techniques for achieving desired results, with emphasis on the author's preferred methodology.

How to reference
In order to correctly reference this scholarly work, feel free to copy and paste the following:

Tomasz Dębski, Lubomir Lembas and Józef Jethon (2012). Basal Cell Carcinoma, Current Concepts in Plastic Surgery, Dr. Frank Agullo (Ed.), ISBN: 978-953-51-0398-1, InTech, Available from: http://www.intechopen.com/books/current-concepts-in-plastic-surgery/basal-cell-carcinoma1

INTECH
open science | open minds

InTech Europe
University Campus STeP Ri
Slavka Krautzeka 83/A
51000 Rijeka, Croatia
Phone: +385 (51) 770 447
Fax: +385 (51) 686 166
www.intechopen.com

InTech China
Unit 405, Office Block, Hotel Equatorial Shanghai
No.65, Yan An Road (West), Shanghai, 200040, China
中国上海市延安西路65号上海国际贵都大饭店办公楼405单元
Phone: +86-21-62489820
Fax: +86-21-62489821

© 2012 The Author(s). Licensee IntechOpen. This is an open access article distributed under the terms of the Creative Commons Attribution 3.0 License, which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited.

IntechOpen

IntechOpen