Master Thesis

Modern treatments for basal cell carcinoma of the skin on the face: a review of available therapies.

submitted by

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Anna Browicz
Poznan, 28.09.2025

1.Introduction

Basal cell carcinoma (BCC) has for years remained one of the most frequently diagnosed skin cancers. At the same time, it is also a tumour with a good prognosis, provided it is diagnosed early and treated effectively. A number of factors contribute to the development of BCC, including long-term exposure to ultraviolet radiation, genetic predisposition and environmental factors. The fact that this cancer is more likely to develop on the face makes appropriate treatment difficult, due to aesthetic and functional aspects. Recent advances in surgery, topical therapies, radiotherapy and systemic therapies have resulted in an ever-increasing need to thoroughly evaluate existing treatments and their availability and efficacy.

In this paper, current treatments for BCC of the facial skin are presented. The aim of the study is to evaluate their efficacy, availability and impact on patients' daily lives. The evaluation was based on scientific studies and medical literature reviews. The available information on treatment methods for facial BCC was also examined - the availability and their efficacy in treatment depending on the location and type of tumour. The literature review considered systematic reviews, epidemiological studies, randomised clinical trials and meta-analyses. The results of randomised and comparative research studies that have directly influenced current treatment recommendations are reflected. The evaluation of long-term treatment effects is particularly important for the risk of recurrence and the future quality of life of patients. For the treatment of BCC, classical surgery, which is an effective treatment for basal cell carcinoma of the skin, and Mohs micrographic surgery, considered even more effective, especially in the face, are applicable. Topical therapies such as imiquimod and photodynamic therapy are used to treat superficial lesions or in cases where surgical treatment is not acceptable to the patient. Radiotherapy is considered as an alternative for patients who cannot undergo surgery. Systemic therapy, using Hedgehog pathway inhibitors or immunotherapy, is a treatment option for advanced and disseminated lesions. In addition, the cost of the various methods, the availability of modern technology and the effectiveness of side-effect control remain important evaluations.

2.Epidemiology and characterisation of basal cell carcinoma of the skin

Epidemiological analysis together with clinical and molecular characterisation of basal cell carcinoma of the skin provides an in-depth understanding of its spreading trends, risk factors and subtypes.

2.1 Epidemiology and risk factors

In this chapter, the most important epidemiological aspects and risk factors of basal cell carcinoma of the skin are described.

2.1.1 Epidemiological data

Basal cell carcinoma of the skin (BCC) is the most common skin cancer worldwide, accounting for approximately 75% of all skin cancers and more than 25% of all human cancers. The incidence of BCC is a worldwide problem and the number of cases of this cancer is steadily increasing. In England, the incidence was 76.21 per 100,000 person-years, in Belgium in women from 34.2 to 102.0 per 100,000 between 2004 and 2012, and in the United States, the number of diagnosed cases of non-melanocytic cancers (BCC and SCC) was 5.4 million in 2012. This has been linked to the role of environmental factors and an ageing population (1–3).

The increase in the incidence of BCC is mainly related to UV exposure. This factor is crucial in the pathogenesis of this cancer, and the ageing process of the population increases the number of people exposed to this factor. The increase in incidence is also influenced by an increase in public awareness and better diagnostics, allowing BCC to be detected more and more frequently. However, the role of ecological factors as direct epidemiological determinants should not be downplayed, which appear to be the most important determinants of the geographical variation in skin cancer incidence (2,3).

The incidence of BCC shows a large geographical and demographic variation, the reasons for which are climate variation, variable UV exposure conditions and sun protection habits. The highest incidence rates are found in light-skinned populations living in areas with strong sunlight, such as Australia and the southern United States. In the United States,

the incidence rate is 1019 per 100 000 in women and 1488 per 100 000 in men, indicating that the disease is more common in men. The reasons for this difference are related to biological differences in skin thickness and behavioural variation, e.g. men are more likely to work outdoors and use sunscreen less often (1,4).

The fact that the population is ageing increases the risk of basal cell carcinoma among people over 60 years of age. However, an increase in incidence is also recorded in lower age groups, demonstrating that environmental and lifestyle factors such as sunbathing, use of tanning beds and holidays in countries with high sun exposure play an increasing role. In Australia, where UV intensity is highest, the number of BCC cases more than tripled from 1994 to 2014 (2,3,5).

This may indicate the involvement of UV radiation as a major factor in the formation of facial skin BCC. The treatment of these areas requires more attention to functional and cosmetic effects, as on the one hand they represent sensitive areas of UV exposure and, on the other hand, molecular UV signatures have been found in more than 55% of BCCs studied. In addition, cases in advanced stages of BCC tend to be located more frequently in these areas (4,6,7).

The location of the tumour on the face may cause aesthetic and functional complications after its removal. In addition, involvement of the central part of the face may favour later diagnosis of the tumour due to the patient's fear of visible damage. Such a situation calls for specific surgical and reconstructive management, due to the need to eliminate the defect as much as possible and achieve optimal aesthetic value (1,4,6).

Even in advanced cases of BCC with extensive damage and deformity, tissue damage and local complications in the face can occur. Therefore, it requires early diagnosis and effective treatment, which can be problematic, as indicated by the results of some studies. The interdisciplinary process of care for patients with BCC requires a prudent strategy to plan the diagnostic and treatment process (4,6).

The above information indicates that due to an ageing population, changing lifestyles related to UV exposure and a changing environment, the incidence of BCC is expected to continue to increase rapidly. This poses serious challenges for medicine and signals the need for further research into this disease entity.

2.1.2 Environmental factors

Basal cell carcinoma of the skin (BCC) is significantly influenced by environmental

factors, with ultraviolet (UV) radiation playing a fundamental role in its aetiopathogenesis. This radiation directly affects the DNA of keratinocytes, contributing to the formation of mutations that can be the beginning of skin cancer. The carcinogenic role of UV is indicated by a signature of 7 mutations. The majority of BBC samples have a high mutational load, with more than 50 mutations per million base pairs identified in populations in very sunny areas. This suggests limiting skin exposure to the sun and avoiding UV from lamps (7).

Molecular data suggest that PTCH1 and TP53 mutations are associated with UV exposure, so using sunscreen and reducing the time spent in the sun during peak sunlight hours may help prevent new cases of BCC (7). UV exposure also affects the course of the disease and the response to treatment. BCC exposed to UV responds less well to photodynamic therapy than lesions lacking anamnesis of sun exposure (8).

The location of BCC lesions most commonly on the face, head and neck is due to overexposure of these areas to sunlight. These regions account for 80% of all BCC cases, creating challenges during treatment in both a functional and aesthetic context. The thin skin, the large number of hair follicles and the proximity of important anatomical structures in this region, the susceptibility of the skin of the face, scalp and neck to UV damage, and their exposure to the sun promote tumour formation (4,9,10). Promoting sun protection habits and avoiding the sun, tanning beds is very important as the sun remains a major risk factor for lesions. The use of sunscreen, particularly between 10am and 3pm, minimises the risk of developing BCC, as well as the formation of multiple tumours in the same person. UVB radiation accounts for only 1-4% of the total UV spectrum, but it carries the highest mutagenic and carcinogenic potential. Its mechanism of action is based on direct DNA damage, leading to the formation of pyrimidine dimers, which are a key element in BCC carcinogenesis (11). Damage to the ozone layer leads to an increased dose of UVB radiation reaching the Earth, which has the negative consequence of increasing the incidence of BCC. This is reason enough to introduce a large-scale monitoring and prevention campaign for this type of skin cancer. The most frequently overlooked risk factor in the development of this skin cancer is environmental pollution. This is a factor that contributes to the development of this type of cancer by promoting the occurrence of oxidative stress and DNA damage, which particularly affects genetically predisposed individuals (7).

Education on how UV radiation and lifestyle affect BCC should be expanded more

intensively. Intensification of short-term but frequent UV, e.g. during short holiday trips, results in the development of BCC (so-called sunburn-promoted BCC). The likelihood of basal cell carcinoma of the skin increases if patients have been exposed to UV during childhood and adolescence (11).

In summary, the influence of environmental factors on the formation of BCC is broad. In addition to the carcinogenic effects that influence the initiation of tumourigenesis, they also influence the course and treatment of basal cell carcinoma of the skin. Additionally, due to environmental and lifestyle changes in the population, it is necessary to increase awareness and prevention of basal cell carcinoma of the skin.

2.1.3 Genetic predisposition

Basal cell carcinoma of the skin (BCC) has characteristic genetic alterations, including mutations in the PTCH1 gene, which occur in more than 70% of cases (7,12). Thus, the PTCH1 gene has a central role in controlling the Hedgehog pathway, which regulates basal cell proliferation. In humans with a mutation in PTCH1, the pathway is activated even when the ligand is not present, causing excessive cell growth and survival (7). It is worth noting that dysfunction of the Hedgehog pathway is characteristic not only of sporadic BCC, but also of hereditary Gorlin-Goltz syndrome. PTCH1 mutations lead to a high incidence of this type of cancer at a young age (12). Survival depends on mutations in the PTCH1 gene, the expression of which is most prominent in BCC with a morpheaform phenotype (13).

Mutation in the TP53 gene is also common (61% of cases). This gene, known as the guardian of the genome, is a regulator of the cell cycle, DNA repair processes and apoptosis. Its inactivation caused by environmental factors, such as UV radiation, increases the susceptibility of cells to transformation (7,12). Thus, TP53 inactivation damages the protective mechanisms of cells in response to UV-induced mutations. In addition, TP53 mutations are associated with BCC progression.

In addition to genes associated with the Hedgehog pathway, there are also TERT and DPH3. Mutations of the TERT promoter (56-59%) and the DPH3 promoter (38-49%) were noted in all samples tested. The TERT gene is a regulator coding for the catalytic subunit of telomerase reverse transcriptase. Activation of this subunit results in immortalisation and growth of cancer cells. Thus, mutations in the promoter region lead to telomerase expression, extend telomere length and render BCCs immortalised (7). The DPH3 promoter regulates transcription and stabilisation of the cell genome,

which is important in the formation of the different BCC subtypes. The use of genetic predisposition markers could predict the risk of individual cancers and propose a prevention and control programme for this cancer in an individualised manner. In morpheaform BCC, which is characterised by aggressive growth, PTCH, SMOH and SUFUH mutations have a 67%, 10% and 5% incidence, respectively (13). Mutations in genes from the Hedgehog pathway confirm the need to use therapies such as Mohs surgery, but also the need to use SMO inhibitors in tumours ineligible for curative treatment. Furthermore, the detection of aggressive molecular variants could revise preventive recommendations and treatment regimens for patients with BCC. Genetics may play a significant role in predisposing individuals to develop malignant molecular subtypes of BCC.

Patients with hereditary epithelioid nevus syndrome, in which the PTCH1 gene is altered, are at particular risk of developing BCC at a young age (12). Knowledge of specific gene mutations will contribute to a better understanding of cancer genetics. This will be significant for assessing their risk of occurrence, for recognising individual types and aggressiveness, and for monitoring patients treated for BCC.

Studies on the quality of life of surgically treated patients suggest that BCC patients have seen significant improvements. The mean DLQI (Dermatology Life Quality Index) decreased after surgery, showing improvements in patients' quality of life, particularly from a functional and emotional perspective. A study on a small group of patients, with tumours mainly located on the nose and forehead, showed that 75% of them had not received any treatment before surgery. The DLQI total change level showed a near-significant difference ($p=0.024$) in perceived quality of life after surgery (14). BCC, especially with aggressive molecular subtypes, causes stress in the lives of patients and their families. Early diagnosis of BCC and appropriate post-treatment care are therefore needed. Patients’ families also need more prevention and education about avoiding risk factors to reduce the fear of relapse.

Genetic testing may also change the way doctors manage cancer risk in patients at high risk of BCC. The discovery that people with a genetic predisposition to develop skin cancer tend to develop molecularly distinct cancers could completely transform the management of these patients. As a result, genetics may prove to be one of the important areas of BCC biology.

2.2 Clinical characteristics

The diagnosis and clinical evaluation of basal cell carcinoma of the skin takes into account the morphological characteristics, as well as the location of the lesion in question, in order to choose the most effective treatment. These elements affect the prognosis and well-being of the patient, hence the effectiveness of treatment and prevention that will appear in the following chapters. The most common morphological variants, their clinical features, localisation and the difficulties involved in making an accurate diagnosis will be analysed.

2.2.1 Morphological types

Basal cell carcinoma of the skin (BCC) is characterised by a wide range of morphological types, and the type of subtype of lesion is crucial in the therapeutic decision and in the assessment of the patient's prognosis. Nodular BCC lesions are a common type in which the neoplasm takes the form of pearly, firm nodules with visible telangiectasias. Most commonly located on the face, it grows slowly, showing a locally aggressive nature. Nodular BCC requires special care due to the functional complications associated with the removal procedure, which are due to the lack of finality in the surgical resection of the lesion, mainly when it is located on the nose or in the eyelid area (9,15). In this type of neoplasm, standard surgical excision with preservation of 4 mm tissue margins is recommended. The classic method of excision of the tumor with an edge of healthy tissue results in a reduced risk of BCC recurrence. In lesions located on the nose or around the eyelids, the use of Mohs surgery is increasingly favored. The Mohs surgical technique preserves large amounts of healthy tissue while allowing complete resection of the cancer focus (4,15). Untreated nodular BCC is characterized by a lack of distant metastases and slow growth; however, its location within the face results in a high level of patient concern, with young patients and those still active being concerned about aesthetic defects and scarring, leading to an increased need for reconstructive consultation of the lesion (16,17).

Ulcerative BCC is a more aggressive form of the neoplasm, which is destructive and infiltrates surrounding tissues. The neoplasm is characterized by deep destruction of skin tissues and infiltration of subcutaneous layers and taking the shape of irregular ulcerations bounded by a characteristic pearly marginal dike. Ulcerative BCC is often localized to the face, which makes treatment difficult in terms of patient aesthetics, as

the wounds after tumor removal occupy a large area and infiltrate deep skin layers. By ulcerating the type of lesion, the patient has an increased likelihood of infection and misdiagnosis (4,18). Due to the growth of the tumour within the surrounding tissues, a patient with ulcerative BCC has a higher risk of incomplete tumour resection and a high tumour recurrence rate, which, according to studies, averages 26-41% within 5 years (15,18). A patient with an ulcerated BCC lesion shows a higher treatment efficacy of Mohs surgery, and very limited use of the modality is recommended for treatment by radiotherapy due to the difficulty in differentiating the edges infiltrating surrounding tissues (4,9). Ulceration of the neoplastic lesion occurs in the advanced form of the disease and the patient presents to the physician for treatment because of it (19).

The superficial form of BCC shows a completely different clinical picture from the types of skin cancer described. A superficial tumour manifests as a thin, erythematous focus on the skin, scaly and demarcated from surrounding healthy tissue. Superficial tumours often occur on the trunk, in an area exposed to prolonged sunlight; however, their localisation on the face is often associated with chronic skin exposure to UV radiation (9,20). Effective topical treatments for superficial form skin cancers in BCC include methods such as photodynamic therapy PDT and the use of imiquimod. Treatment of cancerous lesions of this type results in a 97% success rate and provides excellent cosmetic results for the patient (6,21). Topical treatment is mostly used in elderly patients with multiple cancer foci in the face, as it avoids multiple surgeries and hospitalization (8,22). Local treatment of superficial cancer is also an effective therapy and is characterized by small scar size in patients with very advanced and unresectable lesions (22). It is important that the clinician assesses the clinical and histopathological aspects of the lesion before using local treatment to exclude more advanced forms of cancer (9,20).

Morpheaform and infiltrative are types of skin cancer that are highly aggressive and require surgical therapy with Mohs micrographic surgery due to the fact that they most often infiltrate into the surrounding tissues, and the lack of radical surgery of the excised lesion results in the cancer returning to the site within the scar in a short period of time. A patient with a morpheaform and infiltrative lesion, due to the low efficacy of treatment, has a very high risk of cancer recurrence in this location (13,23). The different morphological types of basal cell carcinoma of the skin often differ in their level of incidence, symptoms and clinical prognosis. The clinical picture is also

influenced by the patient's age, gender and tumour site. Studies confirm a greater tendency for aggressive morpheaform, ulcerative, infiltrative and nodular forms of skin cancer among men in the face. In contrast, superficial and erosive skin cancer predominantly occurs in women on the trunk (15,20). The different morphological aspects of BCC lead to the need for individual patient consultation and development of cancer therapy based on the clinical and histopathological aspects of the tumour to ensure the efficacy of the therapeutic intervention (4,18).

The clinical imaging of basal cell carcinoma of the skin in its various forms and aspects of therapy demonstrate the importance of a comprehensive diagnosis of cancer on the face in terms of prognosis and the importance of undertaking an effective and individualized treatment plan.

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2.2.2 Location of changes

80-85% of basal cell carcinoma (BCC) cases are located on the face, and this is associated with long-term skin exposure to UV radiation (4,10,19). Due to its structure, the skin in these areas, in addition to effectively removing the tumour, is prone to cosmetic, facially deforming effects (4)A characteristic feature of these regions is the low thickness of the skin and the presence of hair follicles and blood vessels. This increases susceptibility to the destructive effects of UV radiation. Induced mutations of genes, e.g. PTCH1 and TP53, are some of the early factors in the formation of BCC on the nose, eyes and mouth (7).

Cancerous lesions are most common on the nose (35.3%), which, due to its convexity, is most exposed to UV light (10). This is largely responsible for the presence of BCC in this region. The nose has specific functions, respiratory and sensory. The development of neoplastic lesions in this area is a major therapeutic challenge. The decision of treatment in a given case should be supported by information about the possibility of nasal deformity after the procedure. This relationship affects the patient's quality of life (9).

Depending on the location, the clinical variability of facial BCCs can vary considerably. Sites where the clinical elements of nodular and ulcerative neoplasms are particularly prominent, such as the nose, eyelids, orbital region and cheeks, are characterized by a localized, rather expressive course and a rapid progression of growth that can lead to significant tissue loss and, consequently, visible cosmetic and functional defects (4,9).

The superficial type of basal cell carcinoma of the skin rarely occurs in the center of the face (e.g. nose and eyelid area). Typical locations are the cheeks, forehead and temples, where long-term sun exposure can result in the growth of fairly extensive flat tumour lesions. This type responds relatively well to treatment with imiquimod and photodynamic therapy (PDT) (20). The therapeutic efficacy in this case, as well as the final aesthetic results, are judged to be satisfactory. The exclusion of invasive features allows decisions on the choice of treatment methods to be made at the initial clinical stage.

The location of the tumours (eyelid, nose and mouth areas) in the center of the face often results in the selection of treatment based on more radical and precise methods, due to the possibility of sparing as much healthy tissue as possible and limiting the potential development of tumours in the future. These sites have very different anatomy, so the need for special care of physiological function (in terms of expression) depends on the surgical method (4,10). BCC locations such as the cheeks and forehead are more often treated with less invasive methods due to patient comfort. Full recovery in this case, depending on the method, can be achieved without the need for hospitalisation.

The specific clinical and microscopic characteristics of the tumour, depending on its location relative to the blood vessels and major facial structures, should be taken into account by the medical team in selecting the optimal treatment to preserve the cosmetic, physiological and functional aspects of BCC treatment. Particular attention is paid to extensive local lesions, where it is difficult to obtain an adequate margin of clinically healthy tissue. If resection is incomplete in these areas, the risk of recurrence is high so in many cases treatment must rely on very precise excision methods, such as Mohs micrographic surgery (4,10).

Within difficult locations, appropriate treatment in terms of reconstruction of skin defects after surgery is often necessary, so the type of surgery must also be decided by the plastic surgeon.

The rapid development of surgery has contributed to a reduction in the number of recurrences, but there are still some patients who lack sufficient health resources to use radical surgical therapy to the full extent. In such cases, other forms of treatment, such as radiotherapy, or the use of local treatment, are alternatives (9).

Typically, advanced BCC (in relation to facial regions) mostly affects elderly patients, with a reduced pain threshold, and with coexisting systemic diseases. The average

length of time, from the time the patient notices the lesions to the time of contact with the physician, in elderly patients with newly diagnosed basal cell carcinoma of the skin is five years, making the timing of medical intervention (diagnosis and application of treatment) usually later than in other population groups (6,19).

This also has a negative impact on prognosis, as a locally advanced lesion is more likely to occupy major structures, compromising the physiological function of the organ (in relation to facial structures, e.g. nasal cartilage, eyelids, etc.). The result of such delayed diagnoses is a large tissue loss resulting in a significant negative impact on the physiological function and aesthetics of the affected individual, leading to a significant reduction in quality of life (6). Lack of access to advanced diagnostic and surgical methods and the absence of appropriate screening programs in the treatment of elderly patients is often associated with poor availability of specialized forms of intervention in cases of advanced facial cancer.

2.2.3 Differential diagnosis

The differential diagnosis of basal cell carcinoma of the skin (BCC) on the face poses difficulties because of its frequent similarity to other neoplastic and non-malignant lesions. Many times, the clinician has difficulty distinguishing BCC from malignant neoplasms such as squamous cell carcinoma and melanoma, as well as from benign neoplasms such as seborrheic warts. This complexity is largely due to the wide spectrum of clinical manifestations that this neoplasm can take on. The clinical accuracy of the diagnosis of basal cell carcinoma of the skin is approximately 59-70% (24). However, the characteristic features of BCC, such as a pearly marginal dike, telangiectasias or variegated pigmentation, are not insignificant. In cases of atypical tumours, even specialists may struggle to make a clinical diagnosis.

Dermoscopy has revolutionized the diagnosis of BCC, significantly improving the accuracy of the diagnosis. With its help, both the pigmentation and microvascular patterns characteristic of BCC and other skin lesions can be accurately assessed. Studies show an increase in the accuracy of BCC diagnosis of up to 95-99% when dermoscopy is used, significantly reducing the risk of misdiagnosis (24,25). The dermoscopy technique also reduces the proportion of non-stick excisions from 22% to 7%, contributing to complete resection of BCCs and minimizing resection of healthy tissue. In addition, dermoscopy has demonstrated a specificity of 88% in identifying residual BCC after treatment with vismodegib (25). Nevertheless, the need for training

in dermoscopy for dermatologists should be borne in mind.

Differentiating the different clinical and histopathological types of BCC requires the support of in vivo imaging techniques and laboratory tests, for example reflectance confocal microscopy (RCM). It has a sensitivity of 95% in identifying residual basal cell carcinoma of the skin after treatment, compared to the sensitivity of dermoscopy (35%) and clinical examination (33%), and a specificity of 81% in diagnosing residual BCC after treatment with vismodegib with respect to dermoscopy with a specificity of 88% (25).

In addition, a complementary imaging modality to dermoscopy and reflectance confocal microscopy (RCM) should be histopathological assessment, as the more invasive types of BCC, such as morpheaform, are problematic to differentiate from other skin cancers, especially melanoma (15). The use of all diagnostic methods allows for a comprehensive evaluation of the lesion in the facial region.

Molecular diagnostics is playing an increasingly important role in the differential diagnosis of cutaneous neoplasms, especially in distinguishing BCC from other skin lesions. An important role is played by the identification of mutations in the PTCH1 and TP53 genes, which are located in 70% and 61% of patients, respectively (7). Recent panel assays and next-generation NGS sequencing make it possible to identify certain mutational signatures, such as signature 7 resulting from UV exposure. Molecular diagnostics also offer the possibility to more precisely diagnose atypical forms of BCC and to distinguish primary from metastatic lesions (7,26). Molecular diagnostics will be very influential in individualizing the treatment of patients with basal cell carcinoma of the skin.

The precision of dermoscopy and reflectance confocal microscopy (RCM) is important in assessing the margins and the area of the lesion on the skin around the tumour. Assessed excision margins minimize the occurrence of complications. Treatment decisions using local therapy for deeply infiltrating BCC lesions increase the risk of recurrence and the need for more invasive treatment procedures, with complications in the form of cosmetic changes (4,15).

Universal access to diagnostic tools should be used to assess BCC. Dermoscopy and RCM are effective techniques for diagnosing BCC. Molecular diagnostics also have a positive impact on improving the treatment of patients with facial lesions. Prevention and education of patients and physicians should not be overlooked in order to improve treatment efficacy and quality of life for those diagnosed with basal cell carcinoma of

the skin (7,25,26).

2.3 Classification and staging

The assessment of basal cell carcinoma (BCC) is based on systemic classification and histopathological examination, both of which have a profound impact on treatment.

2.3.1 Histopathological criteria

Histopathological criteria play a key role in the diagnosis and treatment of basal cell carcinoma of the skin due to their use in assessing surgical margins and depth of tumour infiltration. Surgical margins - clean and unclean - are of great importance for the treatment plan and the risk of recurrence of basal cell carcinoma. Determining the purity of the margins at the histopathological level allows the assessment of the radicality of the surgical resection, and allows the detection of all possible sites of recurrence (23,27). Mostly, microscopic evaluation in the laboratory reveals tumour foci that are not visible macroscopically, thus avoiding a possible residual tumour. Microscopic analysis makes it possible to determine the status of surgical margins, which is of great importance for the choice of treatment type. Leaving even the smallest remnants of cancer in the resection significantly increases the risk of recurrence. Adequate description of the margins in the laboratory makes it possible to predict the risk of recurrence and to choose the treatment technique accordingly.

In the different histological subtypes of basal cell carcinoma (e.g. morpheaform, infiltrative), the extent of invasiveness varies, which has an impact on the surgical techniques applied by the physician, especially with lesions located on the face, which also requires precise microscopic evaluation, e.g. using the Mohs surgical technique, which allows sufficient assessment of the lesions during surgery. In order to be able to control the treatment of basal cell carcinoma with the help of histopathology, adequate communication between the pathomorphologist and the operating physician is required. The correct course of this communication has a direct impact on the success of basal cell carcinoma surgery in the facial area.

Histopathological evaluation allows mapping of the extent of tumour infiltration. The maps obtained are diagrams describing the location of the cancer on laboratory sections. They allow the definition of the area of potential recurrence and help the physician to assess what the patient's treatment field may be (27). In most cases, the

depth of infiltration is determined by analysing micrometres on excised skin samples, from which the depth of infiltration can be determined, which influences the patient's treatment plan.

A retrospective study comparing 1,362 cases of radical excisions of basal cell carcinoma compared with 1,334 cases of incomplete resections showed a more than threefold increase in the odds of recurrence in areas where the tumour was not completely removed (27). In situations where the surgical margin within the tumour was clear, no recurrence was reported in more than 95% of patients regardless of the width of the margin. This demonstrates that complete excision of the tumour plays the most important role.

Mutations of the PTCH1 and TP53 genes have a great impact on the biology of basal cell carcinoma, which is important in assessing the aggressiveness of basal cell carcinoma. In the case of incomplete tumour resections, assessing the risk of recurrence can predict the extent of recurrence and the need for possible additional treatment. Therefore, the identification of PTCH1 and TP53 gene mutations has important implications for more effective treatment planning and reducing the number of basal cell carcinoma recurrences (7). PTCH1 mutations underlie the activation of the Hedgehog pathway. They are predominantly found in patients with the morpheaform form. This aggressive form of basal cell carcinoma proliferation requires a special approach, as in the long term the usual excision techniques are not effective. TP53, on the other hand, encodes a DNA repair suppressor protein that contributes to the high aggressiveness of the cancer and the higher number of basal cell carcinomas arising when exposed to UV. The use of drugs to treat TP53 mutations helps to repair DNKs and inhibit abnormal cell division. For this reason, surgical treatment with gene therapy reduces the likelihood of multiple recurrences, which exerts a benefit in the context of advanced tumour stage and poor patient prognosis.

Rigorous microscopic inspection and assessment of margins are also important in the histopathological evaluation of more advanced cancer subtypes, which spread in an irregular manner, so the precise characterization of tumour microarchitecture, especially assessed from histopathological analysis, is helpful to clinicians when choosing the appropriate level of treatment for a given cancer subtype.

On the basis of the histopathological data, perinodular infiltration is assessed. This refers to a situation in which the tumour foci "surround" the nerves. It can cause unpredictable spread of the tumour, necessitating radical surgical intervention, such

as MMS. Histopathological assessment of the microstructure of cancerous tumours, combined with advanced molecular studies, is needed for a comprehensive clinical and pathological description of the tumour (13).

The histopathological examination, in addition to assessing the cleanliness of the margins, includes an evaluation of the width of infiltration of the basal cell carcinoma, a depth analysis expressed in micrometres and the identification of other tumour sites and cells. All this contributes to the assessment of tumour progression. Estimating the potential depth of infiltration is crucial in the treatment of individual patients, including in considering further diagnostics such as imaging studies and referring patients for specialist consultations. The estimation of the risk of progression, the possible diagnosis of spread and the definition of advanced cancer depends on the recognition of cancer infiltration and perinephric phenomenon at the micrometre level. Based on the collected micrometre data, the physician is able to select the optimal, appropriate form of treatment.

In summary, it is the histopathological criteria that are essential in the context of the correct treatment of basal cell carcinoma of the skin. Diagnosing the surgical margins and the depth of tumour invasion is the starting point for treatment planning and the prognosis of basal cell carcinoma.

2.3.2 Classification systems

A key element in the description of basal cell carcinoma (BCC) of the skin is its classification, which makes it possible to determine the stage of the disease and select the most appropriate therapy. The TNM classification system represents a kind of gold standard in clinical practice and in many BCC cases proves sufficient. The determinants of the TNM classification are based on the assessment of the size of the primary tumour (T), the involvement of the surrounding lymph nodes (N) and the presence of distant metastases (M). Distant metastases in BCC are extremely rare and the above classification does not distinguish between the depth of tumour infiltration. For this reason, guidelines such as an infiltration depth of more than 6 mm, periorbital infiltration or localisation in the so-called facial aesthetic units (nose, ears and eyelids) were additionally included as high-risk features. The inclusion of these additional data is justified, as infiltration beyond 6 mm as well as localisation in aesthetic units are predisposing factors for tumour recurrence and the need for advanced diagnostic procedures and therapy (4,9). Unfortunately, the descriptiveness

and unsophisticated precision of this classification is notable and suffices for the differentiated clinical and histopathological picture of BCC only to a small extent.

Tumour localisation plays a very important role in the choice of treatment strategy for basal cell carcinoma. In the face, characterised by high anatomical complexity, even small lesions can affect an important aesthetic defect and cause functional disorders. Lesions of a superficial nature on the cheek or forehead tend to respond more positively to topical treatment with imiquimod or PDT. Lesions that tend to be deeply infiltrative, located most commonly on the nose or eyelids, tend to qualify for more invasive surgical interventions, as well as Mohs microsurgery, which provides the opportunity for microscopic analysis of tumour margins during the intervention (4,9). Consideration of localisation characteristics, such as specific anatomy, rich innovations of different histological types or consideration of other biological aspects, positively influences the efficacy of therapy and clinical prognosis.

In recent years, the item of highest risk has been added to the TNM classification and histological subtypes of BCC, which qualifies tumours infiltrating less than 6 mm, located on so-called aesthetic units, infiltrating perivascularly and mutated in the PTCH1 gene, which regulates the expression of the Hedgehog pathway, activated in the majority of BCC cases, and in TP53, tasked with monitoring and repairing DANN. More than 70% of basal cell carcinomas have mutations in the PTCH1 gene. In recent years, introduced tools in the field of molecular biology offer a new opportunity to understand the causes and development of cancer. Incorporating molecular data into the conventional description of BCC provides a better understanding of tumour aggressiveness and integrates knowledge from three different diagnostic perspectives: morphological, prognostic and genetic (7).

Combining molecular data with TNM classification and histological assessment of the tumour is challenging. The most commonly analyzed mutations are alterations in the TERT promoter and the DPH3 gene, which are frequently found in BCC and in most cancers (7). TERT is responsible for maintaining the constant length of telomeres, which shorten with each cell division, causing a reduction in the proliferative capacity of the cells and ultimately their ageing, while a change in DPH3 may affect the expression of the mTOR pathway. Mutation in these two genes increases the risk of recurrence and the formation of new tumour foci (7). By being able to assess the genotype of cancer cells, their differentiation and biological aggressiveness, treatment can be personalized. As studies have shown, the identification of these molecular

markers, which have prognostic significance, allows patient qualification for targeted treatment with Hedgehog pathway inhibitors or immunotherapy. Monitoring patients at risk of developing advanced basal cell carcinomas is the best way to reduce the number of aggressive forms of BCC and to diagnose them quickly in the early stages of the cancer (26).

Managing the treatment of BCC according to modern classification systems is of great clinical importance. The use of these criteria, such as PTCH1 mutations, infiltration of less than 6 mm, location of the tumour in facial areas with so-called aesthetic entities, helps to reduce the number of recurrences and surgical procedures leading to severe aesthetic defects. The large geographical differences in access to modern diagnostic and treatment techniques and the waiting time for dermatological intervention in Poland and worldwide exert a high risk of BCC converting to more advanced conditions. Standardization of standards and the provision of an appropriate education system for specialists have a major impact on reducing the time from the onset of symptoms to receiving a diagnosis of basal cell carcinoma and appropriate dermatological medical care (28).

Molecular classifications, in combination with TNM-based systems, have a great future and offer the possibility to more effectively implement the concept of personalizing treatment for BCC. Future progress in this field should take into account the availability of modern diagnostic techniques and targeted therapies. One of the leading developments seems to be the possibility of using molecular markers in the daily diagnosis of BCC. Advances in the identification of biomarkers with prognostic value allow qualification for appropriate therapy.

3. Surgical methods

Surgical methods are extremely important in the successful treatment of basal cell carcinoma of the skin, especially when the lesions are localized to the face. Both traditional and modern techniques are presented below to combine oncologicity with aesthetic considerations.

3.1 Classical surgery

Surgical methods are the mainstay of treatment for basal cell carcinoma of the skin, particularly in the facial region. Surgery ensures that the tumour is excised with a

margin, giving it no chance to survive. Knowledge of surgical methods for the treatment of basal cell carcinoma of the skin is therefore important. This includes the method of surgery, indications, diagnostic methods and the process of planning the procedure. All of this forms the basis that every surgeon should possess in order to provide the patient with the best oncological treatment and successful reconstruction.

3.1.1 Surgical techniques

Classical local excision and wide surgical excision are the primary treatment options for BCC of the facial skin in cases of locally advanced lesions. Excision of the lesion with an adequate margin of healthy skin is intended to reduce the rate of local recurrence. In clinical practice, the average resection margin for classical excision for basal cell carcinoma of the facial skin with a low risk of progression is 4.62 mm. In the case of Mohs micrographic surgery (MMS), an average margin of 4.01 mm allows a more precise, yet more economical removal of healthy tissue, while preserving the function and appearance of the patient's face (29). With regard to surgical methods, it is also worth noting that they depend on the histopathological type of the tumour. Control of surgical margins is an extremely important part of the treatment process for malignant BCC of the facial skin. This control aims to confirm the completeness of the surgical removal of the tumour. During classical skin excision, the margin is assessed intraoperatively (macroscopically) and postoperatively (microscopically). As studies show, a resection margin of 4 mm is necessary for negative margins in more than 95 per cent of BCC cases with a low risk of progression. In contrast, a 2 mm margin results in complete resection in only 73.9 per cent of cancer cases (23). As has been shown, the completeness of resection has a significant impact on prognosis, as local recurrence occurs between 26-41% within 2-5 years after incompletely resected tumours (15).

The location of the tumour in the facial region is a certain limitation and obstacle during the surgical management of BCC, as any intervention in this area carries the risk of aesthetic and functional mutilation for the patient. In addition, the area of the nose, cheeks, eyelid area and edges of the mouth, due to its anatomical structure, requires specialised planning of the scope of treatment, so that the procedure performed in these areas is characterised by the least aesthetic repercussions and at the same time by the greatest treatment completeness.

Defects after classical skin excision are on average 15.07% larger than after Mohs

surgery (29), (thus significantly increasing the need for reconstruction. In larger defects, reconstructions using microsurgical techniques with free dermal-muscle flaps are used, which allows for a significant saving of healthy tissue, as well as a lower cost, as excision and reconstruction based on a local flap are about £900 more expensive (30). It is also extremely important to consider which surgical technique is optimal for the planned facial area. According to Czajkowska et al. patients' recovery from facial surgery can be further supported by photodynamic treatment, in which remission was achieved in 75 per cent of tumours after a single treatment, and after two treatments the success rate was already 87 per cent (8).

As noted earlier, the choice of surgical technique depends on the histopathological type of BCC. For the superficial and nodular types, the tumours are characterised by a low degree of aggressiveness and surgical intervention, based on wide excision, does not carry too many functional or aesthetic restrictions for the patient. It should also be added that with morpheaform and infiltrating types, a more extensive excision is necessary, and Mohs micrographic surgery in these cases facilitates control of resection margins (13). The choice of wound closure technique (primary skin suture, graft, local flap) has a significant impact on the cosmetic outcome and depends on the size and location of the defect in cases of extensive skin excision.

The excision process itself, with an adequate margin of healthy skin, involves some devastation of the treatment area in each case, so planning the extent of treatment in the facial region must be extremely individual. The surgical procedures performed should take into account not only the aspect of removing the tumour completely and reducing the risk of recurrence, but also the aesthetic aspect and maintaining the function of the patient's facial area (15). The pursuit of appropriate aesthetics of the facial region is important because, as a commonly visible area, it can significantly determine a patient's social interactions and self-confidence in everyday life. A properly performed treatment of the facial region also preserves function, which facilitates nutrition, communication with other people and the expression of emotions. By doing so, it enhances the patient's ability to adapt in society and, consequently, the patient's psychological well-being. Excision of the patient's skin in the scalp and facial region requires the interdisciplinary collaboration of a dermatologist, a surgeon and a plastic surgeon (if the patient requires reconstruction in a large defect in the facial area). All this in order to achieve a non-crippling effect and preserve the functionality of this region. Furthermore, the phenomenon of an ageing population, especially with

the increase in exposure to sunlight, is creating an increasing problem of basal cell carcinoma (especially facial) in the ageing population. Consequently, it is necessary to continually strive to educate physicians on modern surgical excision methods for basal cell carcinoma. Classical excision for the local treatment of BCC of the facial skin, combined with an optimally selected method and planning, allows for the cure of basal cell carcinoma (more than 95% success rate) and the avoidance of recurrence (4,8,29).

3.1.2 Indications and contraindications

The indications for the treatment of facial basal cell carcinoma by classical surgery are based on a careful assessment of tumour parameters and patient characteristics, enabling the treatment method to be tailored to the specific lesion and its location. Basal cell carcinoma in the facial area is characterised by variable aggressiveness and risk of recurrence. Classical surgery is appropriate in cases where the risk is not high, the tumour is well demarcated and the location allows adequate excision margins. For example, studies indicate that maintaining a 4 mm margin when excising low-risk basal cell carcinoma provides negative histopathological margins in more than 95% of cases (9,13).

The choice of surgical technique is also influenced by the location of the tumour and associated reconstructive needs. Classical surgery is often sufficient in areas of simple anatomy (cheek, forehead, chin), minimising the risk of aesthetic and functional defects. In addition, it is the preferred option at a younger age, where reducing the need for deferred reconstruction and lowering the risk of recurrence is a major treatment goal (4).

Surgery is also appropriate in cases where the clinical features of the basal cell carcinoma indicate rapid growth or ulceration without extensive involvement of deep structures. In these cases, the classical technique, which is based on the histopathologist's verification of negative margins after excision of the lesion, provides certainty of disease control.

The histopathological type of tumour is also important - nodular and superficial types respond well to classical surgery (13).

Contraindications to classical surgery for basal cell carcinoma of the facial skin are primarily due to the anatomical complexity of this region of the body. A very high level of complexity (e.g. nasal area, periorbital region) can be an obstacle to achieving an

adequate outcome, both cosmetically and functionally, given the need to operate the excision margins. In such locations, more complex techniques, such as Mohs micrographic surgery, are the recommended methods (4).

Further contraindications arise from the presence of extensive disease, particularly in mature and elderly patients. The risks of treatment with surgery, taking into account the extent of surgery, anaesthesia, wound healing and potential complications, should be weighed against the benefits of alternatives such as radiation or topical therapy (14). It should also be taken into account that in cases of coagulation disorders, neurological deficits or the inability to repair damaged tissue, surgery is not the ideal solution for every patient.

A final area of contraindication for classical surgical excision is in cases of irregular proliferation and inability to obtain adequate margins. In the situation of an abnormal proliferative boundary of the tumour tissue (e.g. in the case of morpheaform tumours), classical excision carries the possibility of recurrence. For this reason, Mohs micrographic surgery is preferred, which is characterised by a higher degree of sufficiency and control (4,13).

Appropriate decisions in the choice of surgical treatments, especially in the facial region, are influenced by psychological considerations - patients reckon with aesthetic and functional consequences and defects. Surgical procedures and reconstructions lead to permanent changes in external appearance (4,9,14).

Classical surgery as a treatment modality for basal cell carcinoma of the facial skin should be used after careful case selection.

3.1.3 Surgical margin

An important role in the treatment of basal cell carcinoma of the facial skin is played by the surgical margin, which ensures that the cancer is removed with minimal damage to the tissues surrounding the lesion. Adequate margins provide the opportunity to achieve negative resection margins, meaning that there are no cancer cells present at the margins of the excised tissue. A 4 mm margin has been shown to allow complete removal of the lesion in 95% of low-risk basal cell carcinomas (13,23).

For example, a 2 mm resection margin ensures complete removal of basal cell carcinoma of the skin in only 73.9% of cases and 3 mm in 94.4% (23).

In areas of facial location (e.g. nose, periorbital region, cheeks), a special surgical strategy is necessary, bearing in mind the risk of cancer recurrence, which reaches

26-41% in 2-5 years if the lesion is incompletely excised in these locations (15).
Mohs micrographic surgery is able to ensure complete removal of the lesion using smaller resection margins. The actual recurrence rate after Mohs surgery is only 1-5%, while the overall cure rate is 95% (31). The appropriate choice of surgical margins also depends on the histopathology of the lesion and its location and is influenced by a number of factors, such as the patient's age, comorbidities, as well as the expected cosmetic outcome (13,15,23,31).
Directions for future surgical treatment should focus on methods to control margins more accurately, as well as the use of new technologies during basal cell carcinoma resection, such as imaging techniques during surgery.

3.2 Mohs micrographic surgery

Mohs micrographic surgery plays a key role in the precise treatment of basal cell carcinoma of the skin located in regions of high aesthetic and functional relevance, enabling the assessment of resection margins during surgery and minimising damage to healthy structures. In the context of the present study, it completes the broad spectrum of surgical procedures that are important in optimising treatment outcomes and improving the quality of life of skin cancer patients, particularly in regions of difficult localisation such as the face.

3.2.1 Methodology of the procedure

Mohs micrographic surgery (MMS) is an advanced surgical technique in which successive layers of tumour tissue are excised and an intraoperative microscopic evaluation of each layer is performed. It involves inspecting the margins of the excised tissues, thus reducing the loss of healthy tissue and increasing the fineness of the resection. In contrast to classical excision of only a partial sample of the margins, in MMS 100% of the circumference and depth of the excised tissue is examined (12,29). A further step in the MMS technique is to repeat the excision-excision cycle in areas where basal cell carcinoma cells are still detected in the margins. This minimises the extent of extensive reconstructive surgery, as the planned resection is adapted to the location and shape of the tumour. This way of performing the procedure significantly reduces surgical time and controls the borders of the cancer, so that only the skin sections where cancer cells have been confirmed are excised (12,29). However,

extensive experience and precision work is required of the surgeon and the laboratory. MMS is now increasingly available in Poland, although it is only performed in specialised centres treating facial cancers.The MMS technique is used in tumours whose borders are difficult to define and in those more aggressive types of basal cell carcinoma, such as the morpheaform or infiltrating variety. MMS is also used in tumour recurrence, where the risk of leaving single cancer cells is increased. With this method, the surgeon can accurately remove irregularly shaped tumours growing along natural skin lines and do so with maximum sparing of healthy tissue, which is important in areas such as the nose, eyelids and lips (12).

An important benefit of performing MMS procedures is the reduction of the extent of postoperative defects. During a study of 668 patients, it was found that defects after operations performed using the MMS technique were on average 15.07% smaller than those of classical excision. Thus, a less extensive postoperative wound reconstruction procedure should be planned for MMS. This approach has the effect of reducing postoperative complications, such as the formation of scar contractures, which certainly improves patients' quality of life (29). This method is particularly indicated in immunocompromised patients, in patients with multifocal tumours or in patients with the genetic mutation in Gorlin-Goltz syndrome, which predisposes to multiple foci of basal cell carcinoma. These patients will not benefit from surgical therapy with the standard excision technique (9). 5-year data show cures in 99% for primary lesions and in 94% for recurrent lesions (4,12). This means that the MMS method provides a higher treatment success rate for basal cell carcinoma than classical surgery or radiotherapy.

Thanks to precise intraoperative examination of excised tissue margins, performing MMS procedures has the effect of reducing the likelihood of tumour recurrence in areas where skin function and aesthetics are important, such as around the nose, eye and mouth. MMS also makes it possible to control treatment in cases of non-standard tumour microenvironment, by which wound healing time is prolonged. This may be a signal for further research into the impact of an irregular microenvironment on basal cell carcinoma therapy, which could lead to expanded indications for MMS treatments (32).

Research into the presence of specific molecules in facial tumours could improve and facilitate microscopic assessment of basal cell carcinoma and have an impact on the personalisation of MMS techniques. The introduction of the assessment of molecular

and microenvironmental markers in histopathology may in the future facilitate the determination of the prognosis of the tumour, which is important in tumours that recur and in difficult cases of basal cell carcinoma (7,12).

This method requires surgeons to be trained in specialised MMS techniques, especially for elderly patients, in whom it is important to prevent extensive mutilation (9). Assessing molecules from the tumour microenvironment can help the surgeon to control the treatment area, thus reducing the size of the scar. In contrast, combining classic MMS with new technologies may improve the standards of oncologic surgery for basal cell carcinoma in facial locations.

3.2.2 Therapeutic efficacy

The success rate of Mohs micrographic surgery (MMS) for primary basal cell carcinoma of the face is 99% and for recurrent carcinoma 94%. This makes it the most effective rate, especially in anatomically challenging locations such as the nose, eye area or mouth (4,12,29). The course of surgery, which involves removing the tumour in layers and examining the entire margin of removed tumour tissue under a microscope during surgery, eliminates the risk of leaving tumour cells behind and prevents recurrence (12,29).

Meta-analyses have proven the greater efficacy of treating basal cell carcinoma of the skin with Mohs micrographic surgery compared to classical surgical excision. Patients with primary tumours using the MMS technique achieved a 73% lower recurrence rate (OR = 0.27, CI = 0.15-0.46), and patients with recurrent basal cell carcinoma had an even lower rate (OR = 0.26, CI = 0.09-0.78) (33). This shows that in cases of cancer that are characterised by an aggressive course, but also not cured by previous traditional treatment, the use of MMS is most effective.

The efficacy of MMS is all the more valuable because cancers located on the face, especially in the eyelid, mouth and nose areas, are treated with it. After Mohs micrographic surgery, post-surgical defects are minimal and thus cosmetic and functional results are improved (9). Another important point is that with MMS treatment, the need for extensive reconstructive surgery is eliminated.
The Mohs micrographic surgery technique is characterised by minimising the risk of tumour recurrence and therefore the need for subsequent surgery is reduced. The recurrence rate for basal cell carcinoma, according to many studies, is only 1 per cent for primary basal cell carcinoma and 4 per cent for recurrent carcinoma at a five-year

follow-up (4,9). Furthermore, when comparing it with classical excision and radiotherapy, a significantly lower recurrence rate is characteristic of MMS. The lower risk of recurrence improves the patient's quality of life and reduces the costs incurred for surgery, hospital stay and recovery after surgery (33).

From a cosmetic point of view, in cases of primary cancer, surgical treatment with MMS is more effective compared to classical surgical excision. This method allows greater control during margin excision and, for this reason, only as little tissue is removed as is oncologically necessary to remove the cancer. This reduces the need for subsequent aesthetic reconstruction. In the treatment of recurrent tumours, cosmetic outcomes, although minimally inferior, also yield better results than traditional treatments (33). This is particularly relevant in patients whose tumours are located in facial areas visible in social interactions (16). The long-term efficacy of this treatment method is based primarily on a stable therapeutic effect. The use of Mohs micrographic surgery reduces the likelihood of having to undergo aesthetic reconstruction again. Thus, the risk of tumour recurrence is reduced in these patients, which is important for those with limited skin regeneration (34). This method is also proving to be more effective in the treatment of long-term lesions, which include skin discolouration or atrophic scars. These usually arise after radiotherapy or topical therapy (4).

With the availability of MMS in Poland, the chances of a complete cure for patients with basal cell carcinoma of the facial skin have increased significantly. As the number of centres treating MMS increases, so does the effectiveness of cancer treatment, and thus the standard of living of patients (9). It seems that due to its effectiveness in treating basal cell carcinoma of the face, the MMS technique will dominate the treatment of skin cancer in the future.

3.2.3 Specific indications

Mohs micrographic surgery (MMS) is the treatment of choice for patients treated for recurrent basal cell carcinoma of the facial skin if preceding surgical techniques have failed to ensure success. This method relies on controlling resection margins during surgery. Consequently, the recurrence rate after MMS is significantly lower than after classical treatments (odds ratio 0.27 for primary tumours, 0.26 for recurrent tumours) (33). It is noteworthy that careful microscopic inspection of margins allows removal even in irregular growth lesions.

Subtypes with an uncharacteristic clinical course, such as morpheaform and infiltrating subtypes, pose particular problems for treatment. The complexity of the clinical course and the irregular borders of these basal cell carcinoma lesions do not allow accurate planning of resection margins using conventional surgical techniques. MMS examines all removed tissue layer by layer, which enables the removal of these subtypes of basal cell carcinoma of the skin with very high oncological efficacy. The use of MMS in patients with basal cell carcinoma of the skin with irregular clinical boundaries reduces the five-year recurrence rate below 5% (4). In addition, the number of operations and the amount of tissue removed is also minimised in such cases. Locations in the scalp and neck, nose, eyelids, lips and auricles also qualify patients for treatment using the MMS technique. The lack of tissue in these locations as a consequence of facial skin tumour resection results in a permanent defect both aesthetically and functionally. Due to the minimal extent of MMS surgery, as little healthy tissue as possible is removed, which is crucial for patients' quality of life (33). Following this type of surgery, there is often satisfaction with appearance and well-being in these individuals, which determines their social acceptance (9). Therefore, the minimal resection method should be preferred in locations exposed to visual contact with others, in order to reduce psychological stress.

Patients with immunosuppression and multiple surgical interventions in the facial area or associated diseases are also candidates for MMS. The highest efficacy of this method is also observed in patients with Gorlin-Goltz syndrome with multiple lesions and in patients with recurrent lesions (9). An important rationale for this method is the control of margins during surgery, in order to modify the extent of excision accordingly. Currently, the percentage of MMS procedures is steadily increasing worldwide. This trend is also noted in our country. The demand for MMS procedures occurs in elderly patients, whose concomitant diseases limit the availability of radiotherapy and systemic therapy with Hedgehog pathway inhibitors (35,36). MMS is a minimally invasive method that contributes to the reduction of complications related to the treatment process and allows preservation of lying function meaning a higher quality of life for patients. The trend towards personalisation of cancer therapy will contribute to the increasing use of this method not only in Poland, but also worldwide. The combination of molecular medicine and micrographic surgery may lead to even more effective therapy. Basal cell carcinoma of the skin tends to recur when patients

have a TP53 gene mutation and a Hedgehog pathway gene mutation. An important prognostic indicator is the PTCH1 gene mutation. In patients scheduled for MMS surgery, knowledge of the presence of the mutation may allow assessment of the risk of recurrence and the use of, for example, a Hedgehog pathway inhibitor after surgery in a recurrent situation (7,9).
MMS should be the method of choice for patients with highly aggressive types of basal cell carcinoma of the skin and in locations requiring an aesthetic treatment outcome due to its very precise control and minimal invasiveness.

4.Topical therapies and radiotherapy

Topical therapies and radiotherapy are some of the key elements in the treatment of basal cell carcinomas of the skin in the facial region, where the therapeutic effect and the aesthetic effect are prioritised. Cryotherapy treatment, photodynamic treatment and radiotherapy are further elements in the treatment of skin cancers discussed. Topical treatment and radiotherapy with regard to basal cell carcinoma of the skin have been addressed in earlier chapters on skin cancer therapy. A comparison of the application of these therapies is presented below.

4.1 Topical therapies

Topical therapies are important in the treatment of superficial and early basal cell carcinoma. Cryotherapy, photodynamic therapy or imiquimod are widely used in the treatment of superficial and early BCC.

4.1.1 Cryotherapy

Cryotherapy for the treatment of BCC is an effective and economical method for superficial and small facial cancer lesions. Studies show that healing of limited and small lesions occurs in 92.5% after cryosurgery (3). The cost advantage argues in favour of its use, particularly where access to health services is limited.
In addition, the short duration of the procedure, as well as the possibility to perform it on an outpatient basis, allows many patients to be treated in a shorter period of time. This is ideal for areas with limited access to a dermatological surgeon (4). Patients indicate high satisfaction with the cosmetic result due to the lack of need for sutures

and minimal, patient-acceptable scarring (3). The method is ideal for the elderly and those with additional medical conditions (4).

The essence of cryotherapy is the application of low temperature (liquid nitrogen) to damage cancer cells. Formation of ice crystals in the damaged cells occurs, initiating necrosis as well as necrosis of the tumour capillaries. The length of exposure and the number of freezing cycles determines tissue destruction. A minimum temperature of -50°C in the depth of the basal layer should be reached to get rid of all tumour cells in superficial lesions (3,8). Two cycles of freezing and thawing are standardly recommended. One cycle is believed to increase the chances of survival of individual tumour cells (8).

An additional effect of cryotherapy, is to increase the inflammatory process by damaging the tumour vasculature, increasing the immunogenicity of the treatment. An advantage of the effect of cryotherapy is that it reduces the chances of metastasis after surgical intervention due to damage to tumour cells and vessels. The use of freezing reduces the spread of tumour cells. In most cases, it can reduce the rate of recurrence (3).

Cryotherapy is not a recommended method for invasive tumours, particularly those with morpheaform. It is also not recommended for tumours with a clinically indistinct boundary (4,6).

Cryotherapy has been found to work well in patients with a high mutation burden due to environmental factors, such as UV exposure, as well as genetic variation in the PTCH1 and TP53 genes, among others. Successful elimination of tumour cells by cryotherapy is independent of molecular status. Effective elimination is absolute and produces a good therapeutic effect. It is one of the popular therapies for low-risk BCC (7). Situations yet to be clarified in which it is advisable to consider cryotherapy concern young people and patients with multiple small lesions, so as to minimise damage to non-pathological tissues (4).

The safety of this method is satisfactory and adverse reactions, such as inflammation, minimal scarring or slight changes in skin colour, usually regress spontaneously (3). Additional, but rare, negative effects of cryosurgery are pain and infection (4). Cryotherapy is recognised as one of the effective low-risk treatments for BCC. The use of cryotherapy for patients with basal cell carcinoma of the skin offers the possibility of cure for the majority of patients. The cost advantage and the possibility of outpatient application argue for widespread use in areas with limited access to a

dermatological surgeon.

4.1.2 Photodynamic therapy

Photodynamic therapy (PDT) is a modern treatment method for superficial and small nodular basal cell carcinomas of the facial skin, which is characterised by its minimal invasiveness. The efficacy of this method of cancer treatment is related to the activation of a photosensitiser by light of a specific wavelength in the presence of oxygen, which leads to the destruction of the lesional cells. The efficacy of this method has been confirmed in the treatment of superficial primary lesions in the face, head and neck area, where two treatments at seven-day intervals lead to complete remission in 90% of patients (22).

The choice of photosensitiser, such as ALA (aminolevulinic acid) or MAL (methyl esters) of ALA, has been found to influence the efficacy of PDT. The efficacy of PDT treatment, following the use of MAL, reaches a complete remission rate for superficial primary lesions of up to 92-97% (22).

PDT is a therapy that has advantages over others in minimising scarring and destruction of healthy tissue. This is an important advantage of PDT due to the treatment of cancerous lesions in facial locations, where cosmetic significance plays an important role (8). The limited efficacy of photodynamic therapy in advanced BCC precludes its use outside of tumours with limited infiltration and superficial tumours (9,22).

PDT is a modality that is also readily recommended in domestic practice due to its tolerability, particularly in older patients. This therapy is often the preferred treatment for BCC when surgical treatment cannot be undertaken for pathological reasons or patient reluctance. The data of patients who have been treated with PDT have been analysed and the conclusions are very positive, as the efficacy of this form of treatment has been confirmed after 5 years (22).

PDT is a treatment modality in which the fact that the treatment is repeated seven days after the first treatment plays a huge role, which increases the rate of complete remission compared to single treatment (22). It has also been proven that with PDT treatments using ALA and MAL, there is the possibility of implementing a second treatment after seven days, which increases efficacy in the treatment of superficial primary skin lesions on the face (8).

Long-term observation of the treatment effects of PDT indicates a high treatment efficacy in terms of tumour destruction. Side effects, such as scarring and skin pigmentation abnormalities, are transient and do not generate ongoing discomfort (8). Considering daylight therapy (dPDT), PDT treatments using it are quick and more comfortable for patients, especially the elderly. Studies conducted by Pazdrowski's team have confirmed the efficacy of PDT, using daylight, comparable to classical PDT. In addition, during dPDT, patients do not experience such severe pain as with classical PDT. dPDT appears to be a method optimised for the treatment of cancer, with a tendency to create extensive carcinogenic fields on the face when classical methods are not feasible (37).

The efficacy of PDT has been confirmed by long-term follow-up, during which side effects were minimised and treatment time was shortened. A protocol was used in which micropuncturing the skin led to faster penetration of the photosensitiser into the cancer cells and reduced incubation time. It should also be borne in mind that vitamin D3 deficiencies in the body result in a 20% decrease in PDT efficacy (38).

In cases of treatment of more advanced forms of BCC, it is reasonable to implement combination therapy, in this case combining the topical application of interferon a-2b with PDT therapy. A higher treatment efficacy with this form of therapy has been demonstrated, compared to treatment with PDT alone, where the complete remission rate reached 80.39% compared to 58% with PDT alone (39).

An important aspect when using photodynamic therapy is its presence in the treatment of skin cancer worldwide and in Poland. Increasingly, access to this type of therapy is no longer just a challenge, but a growing necessity. PDT using BF-200 ALA has confirmed higher efficacy than PDT, when using classical photosensitisers, in tumours with lower clinical stage (38). PDT has a high efficacy, the sooner it is started, the more complete remission it gives.

4.1.3 Treatment with imiquimod

Imiquimod is a local immunomodulator that has found wide use in the treatment of superficial basal cell carcinomas of the facial skin. Its efficacy of 75% to 90% predisposes it to be the treatment of choice for patients who value the non-invasive nature of treatment. Its benefit is clear in the treatment of cancers with a low risk of recurrence, where aesthetics play the most important role, as with cancers located on the facial skin (6,21). The mechanism of action of imiquimod is based on the local

immune response, activating the production of interferon alpha, interleukin-12 and TNF-alpha and leading to tumour destruction. The above determines its efficacy in superficial lesions with low infiltration (6).

The use of imiquimod is recommended for patients who cannot or do not wish to be treated surgically. In legitimate patients under 40 years of age or when several lesions need to be treated at the same time, and where the aesthetic effect is paramount (21). Appropriate lesion selection based on border delineation and tumour thickness is important, as imiquimod has low efficacy for deeper infiltration and in patients with atypical morphological type, such as morpheaform BCC. However, most authors suggest the need for further studies to determine the efficacy limit of the drug for specific histopathological subtypes of BCC (6).

An important advantage of imiquimod is that there is no need for a specialist to carry out the treatment, which increases patients' comfort and quality of life. The patient applies the drug on their own, making the therapy more accessible, and it can be started more quickly than surgical procedures. Imiquimod therapy is fairly well tolerated, often the only side effects being the presence of erythema, pruritus and sometimes ulceration at the site where the drug is applied. The above symptoms are usually transient and resolve without discontinuation of therapy (26). It is important to educate the patient on the use of imiquimod, as incorrect application of the cream can lead to abnormal therapeutic effects and adverse reactions.

The use of imiquimod influences the rapid disappearance of the erythematous substrate and the reticular pseudotumour in the dermoscopic image. In the pigmented form, features such as blue-grey corpuscles disappear most rapidly, allowing earlier assessment of treatment response. Dermoscopy together with reflectance confocal microscopy (RCM) is recommended for assessing the efficacy of therapy; in particular, dermoscopy has high specificity to determine the presence of residual tumour after imiquimod therapy (25).

Imiquimod therapy does not have the same efficacy in all patients. Cure rates depend on gender, phototype and tumour location. In women, for example, the drug is most readily used to treat superficial forms of BCC of the trunk, whereas in patients with BCC located on the face, it is worth monitoring the effect of therapy regularly in order to respond as quickly as possible and reduce the risk of hyperpigmentation or scarring (6,21). The female gender, due to the more sensitive and thin skin of the face, requires vigilant selection of appropriate therapy, and skin in this location often requires

pretreatment with emollients prior to treatment with imiquimod. Imiquimod is proving to be an effective alternative in the treatment of older patients, not requiring surgical intervention or radiotherapy (6).

To increase the efficacy of topical treatment of basal cell carcinoma of the facial skin, imiquimod can be used in combination therapies with other treatments. In patients with giant or multifocal BCC, imiquimod therapy with photodynamic therapy (PDT) is an effective combination for cancer treatment. Clinical studies indicate a potential increase in remission percentage and prevention of recurrence (40). The above observation mandates further research in the field of combination therapies to optimise the treatment process.

The low cost and aesthetic advantages make imiquimod a comfortable option for a large proportion of patients, and the lack of hospitalisation increases the availability of the drug and acceptability of treatment. Despite a number of advantages, the lack of efficacy of the drug in more advanced forms of cancer dictates that the response to treatment should be carefully monitored when using this drug, and in cases of lack of effect, appropriate action should be taken to prevent tumour progression.

4.2 Radiotherapy

Irradiation techniques are an important part of the treatment of basal cell carcinoma of the skin, particularly in the facial area. The various irradiation methods, indications, efficacy and impact on patients' quality of life are discussed below.

4.2.1 Irradiation techniques

Irradiation techniques for the treatment of basal cell carcinoma of the skin have been adapted to be effective for this disease, its location on the face and the individual needs of the patient. Brachytherapy and external beam radiotherapy are two approaches that differ significantly in their execution and effectiveness, but also in their cosmetic effects. Irradiation with silicone brachytherapy moulds to the irregular shapes of the lesions. As a result, it succeeds in irradiating only the lesioned areas and the two-year local control rate is 90%. A relatively large number of patients rated the cosmetic effects (65%) as excellent. Side effects include mild inflammatory reaction, pain and transient ulceration (41).

The use of the latest techniques, including external beam radiotherapy with guided imaging (IGSRT), represents the next step in the treatment of basal cell carcinoma. This method allows the irradiation area to be planned with the surrounding healthy tissues excluded. Among newly diagnosed cases of locally advanced early lesions, IGSRT allowed local control in 99.3 per cent with a recurrence rate of only 0.9-1.1 per cent. The recurrence rate with radiotherapy was approximately 9% higher. Proper treatment aims to improve patients' quality of life by reducing the frequency of recurrence and complications of a functional or cosmetic nature (42).

The commercially launched Re-188 isotope patches may be another element of personalisation of surface brachytherapy. A radiation dose of approximately 100 Gy is delivered in a short period of time - in about three hours - with patches that can cover a 3 × 3 cm tumour. Long-term studies at a follow-up of more than three years have shown no recurrence. This technology is used in lesions that are anatomically challenging and more advanced than other basal cell carcinomas (43). However, the fact that it is not available, due to price, may be a limiting factor.

Knowing the thickness of the lesion is a determinant of the irradiation protocol. Infiltrates ≤5 mm thick require irradiation of 40 Gy in eight fractions. This protocol has a very high therapeutic efficacy with minimal risk of long-term side effects such as atrophy, fibrosis, hypopigmentation and chronic reactions (41). In contrast, a different irradiation protocol applies to a deeply infiltrating lesion. It is characterised by higher cellular aggressiveness, weaker demarcation of the lesion border from the skin and lack of response to treatment. Treatment should therefore focus on surgical intervention, including Mohs micrographic surgery, as conventional radiotherapy proves insufficient in these cases. Eligibility for treatment in each case should be decided by a team of oncologists in conjunction with dermatologists (4). Radiotherapy is considered the treatment of choice for patients ineligible for surgical treatment, mainly those due to age and concomitant medical conditions. Its local control efficacy ranges between 83% and 95%. The efficacy of radiotherapy on the face, despite its great potential in local control of the disease, results in a cosmetic outcome slightly inferior to after Mohs surgery. Despite this cosmetic aspect, patients most often perceive facial radiotherapy as a treatment with a more favourable outcome than is the case with classical surgery. This improves the quality of life of patients with basal cell carcinoma located in the facial skin (4,9).

The use of modern irradiation techniques with the selection of an appropriate

irradiation protocol can minimise complications such as cosmetic skin defects. The use of silicone moulds in surface brachytherapy, newer surface radiotherapy techniques with precise treatment protocols, result in a reduction in skin pigmentation and the number of atrophy-related changes (8,41).

Radiotherapy in various forms is an appropriate treatment for basal cell carcinoma located on the facial skin. The effects of treatment should be selected individually, after a thorough assessment of each patient.

4.2.2 Indications and effectiveness

Radiotherapy is mainly used when surgery is unavailable or contraindicated due to the location of the lesion, the age of the patient or the existence of other comorbidities. Local control of basal cell carcinoma of the skin after surgery is 83-95% (4,9). An important indication for the implementation of radiotherapy is the possibility of treating elderly patients and those with serious chronic diseases in whom the potential complications of surgery outweigh the benefits of removing the lesion. Radiotherapy in these cases can be used to control tumour growth (9).

Other indications for irradiation in the face are locations that are difficult to work out surgically. These include the eyelids, nose and ears. Surgical excision of lesions from this location can lead to significant aesthetic defects and functional impairment. Patients with tumours localised to the eyelid, nose or ear region should be treated with irradiation. Clinical examples indicate that such treatment yields good oncological results and provides a satisfactory cosmetic outcome (4). The size of the lesion can also be an important criterion for the choice of treatment method. If the cancerous lesion is very extensive and difficult to excise in its entirety, radiotherapy provides better local control. Multiple lesions are also an indication for treatment with irradiation, as are patients in whom large tissue defects remain after surgical removal of the lesion. In cases with the above clinical criteria, radiotherapy allows local tumour control to be achieved, with lower costs and complications, compared to reconstructive interventions. Under the conditions of the Polish healthcare system, the possibility to perform advanced reconstructive surgery is limited (9).

Patient preferences also play an important role in the choice of irradiation as a treatment for basal cell carcinoma of the skin. Many patients fear the formation of a surgical scar and a prolonged recovery period. Therefore, radiotherapy, despite the risk of some cosmetic changes, is a more acceptable treatment option for patients who

are afraid of surgery (4).

When comparing radiotherapy with conventional surgery, four years after treatment for primary basal cell carcinoma of the skin, the recurrence rate for radiotherapy was 7.5 per cent and for surgery was 0.7 per cent. The cosmetic evaluation showed that only 69% of the results after irradiation were good, in contrast to 87% after surgery. Before choosing radiotherapy as a treatment option for primary basal cell carcinoma of the skin, it is therefore important to inform the patient of the possible efficacy and potential cosmetic concerns (4).

Although radiotherapy provides effective local tumour control, the risk of tumour recurrence is higher than after surgical removal of the lesion. Post-radiation patients should be monitored more frequently and closely by a dermatologist for early detection of potential recurrence. Studies indicate that different cosmetic outcomes can be observed following irradiation, depending on a number of factors, such as the dose of radiotherapy, tumour size, tumour location and the patient's genetic predisposition. Hyperpigmentation, telangiectasias and skin thinning are the effects of irradiation that patients pay particular attention to. Younger patients, for whom attention to physical appearance is an issue of particular concern, represent a group of patients who find it difficult to accept these cosmetic defects (4).

In younger patients for whom cosmetic issues are a priority, playing an important role in their professional or social life, all advantages and disadvantages of this treatment method should be assessed in detail. In patients for whom surgical treatment is inadvisable or impossible for a variety of reasons, radiotherapy remains the only treatment modality that offers the possibility of achieving tumour control with a satisfactory quality of life (4).

Patients with an irregular tumour on the face benefit most from the use of modern irradiation techniques, such as brachytherapy with silicone moulds and image-guided surface radiotherapy (IGSRT). The method of radiotherapy is individually adapted to the shape and size of the tumour lesion, and modern techniques minimise the area of irradiated tissue around the tumour itself (41). The use of this approach makes it possible to irradiate selective carcinogenic fields using an irregular brachytherapy applicator, customised and of variable size. In several studies, it has been observed that a customised brachytherapy applicator achieves local tumour control in more than 90 per cent of cases, and the cosmetic effect was judged to be good or very good (36,41).

In several independent studies on IGSRT, a low risk of tumour recurrence was observed, with a range of 0.9-1.1%. IGSRT radiotherapy should be considered as a treatment option for patients with multiple, extensive carcinogenic fields within the skin (42). An important role in tailored brachytherapy applicator radiotherapy is played by the materials used in the creation of applicators. Modern designs allow a variety of materials to be selected to make applicators. Silicone moulds are most commonly used, and for intratissue applications within the lesion, acrylic moulds are used. An additional advantage of using new design solutions is the possibility of using a material that allows the use of radioactive isotopes of cobalt, iridium and caesium in therapy (43).

Radiotherapy should not be preferred as a treatment for patients with cancer at a young age, as they may develop hypopigmentation, telangiectasias and secondary tumour development as a result of long-term side effects. In patients with cancer recurrence for whom surgery is unavailable, irradiation with modern radioactive beam delivery techniques remains the first-line choice (44). Irradiation is applicable to patients with early-stage cancer because of its favourable treatment-to-complication ratio and controlled and limited side effects, appearing mainly in the form of benign skin damage (45). Modern radiotherapeutic techniques significantly reduce the risk of side effects of irradiation and increase the quality of life of patients. Older patients and those with serious co-morbidities have a higher risk of complications after surgical treatment of skin cancer than younger patients (4). Local radiotherapy remains an important factor in the treatment strategy for basal cell carcinoma of the skin, especially in cases where local control of the tumour is necessary (46).

5. Systemic therapies

Systemic therapies are an important treatment option for difficult cases of basal cell carcinoma of the skin, often providing more effective alternatives to local and surgical approaches. These include, in particular, Hedgehog pathway inhibitors and immunotherapy. Due to their broad potential to affect the cancer cell, systemic therapies significantly increase the efficacy of cancer therapies.

5.1 Hedgehog pathway inhibitors

The Hedgehog pathway plays an important role in the pathogenesis of BCC and is a

major target for systemic therapy of this form of cancer. The mechanisms of action of inhibitors of this pathway, their efficacy in the clinical setting, and the problem of resistance and side effects will be discussed.

5.1.1 Mechanism of action

The Hedgehog pathway has a very important role in the growth of basal cell carcinoma of the skin. This pathway is activated by mutations in the PTCH1 gene in more than 70% of cases, leading to deregulation of the pathway and excessive proliferation of skin basal cells. Hedgehog pathway inhibitors, such as vismodegib or sonidegib, are used to treat this cancer, acting by blocking the Smoothened (SMO) protein. SMO is a component of the signalling pathway and an essential protein for its activation. Blocking this component prevents the continuation of signalling, and this in turn affects the transcription of genes involved in the growth and differentiation of cancer cells, halting tumour progression (7,47).

Blocking the SMO protein with inhibitors is an effective therapeutic option, particularly for primary and advanced tumours. Since a mutation in the PTCH1 gene is responsible for the activation of the Hedgehog pathway in many cases of basal cell carcinoma of the skin, treatment methods such as surgical removal of the tumour or radiotherapy are not effective. SMO inhibitors represent one therapeutic option for advanced, inoperable tumours, but also as an additional treatment for lesions unresponsive to traditional methods, as demonstrated in clinical trials (7,26).

Hedgehog pathway inhibitors are often an effective treatment for basal cell skin cancer patients with high TMB (high mutational burden), which is characteristic of tumours caused by chronic UV exposure. Therefore, higher TMB correlates with higher gene expression in the Hedgehog pathway, making this variant of basal cell skin cancer an ideal therapeutic target for Hedgehog inhibitors such as vismodegib. In vivo and clinical studies indicate that slowing tumour growth, a target for therapeutic intervention in basal cell carcinoma of the skin, occurs more rapidly with Hedgehog inhibitors in high TMB tumours (26,47). However, a large number of patients develop resistance to Hedgehog pathway inhibitors.

In cases where no change is observed after treatment with these inhibitors (primary response) or if the patient's condition worsens after initial tumour regression (acquired response), the mechanisms of resistance are most often based on additional mutations within the SMO protein itself that interfere with the effect of the inhibitors, or

additional genetic alterations that result in further tumour growth despite inhibition of the Hedgehog pathway (6,47).

Therefore, additional therapeutic options are needed, such as combinations of drugs such as Hedgehog inhibitors with immunotherapeutics, the efficacy of which has been studied in preclinical and early clinical trials (47,48).

5.1.2 Clinical effectiveness

The clinical rates of Hedgehog pathway inhibitors (vismodegib and sonidegib) confirm their legitimate role in the treatment of locally advanced basal cell carcinoma of the skin, in cases where surgical therapy and radiotherapy cannot be used. Clinical trials, such as the Phase 2 ERIVANCE trial, show an ORR (objective response rate) of 43% for locally advanced lesions and 30% for metastatic lesions. Additionally, a long-term analysis conducted for vismodegib shows an increase in ORR to 60% for locally advanced cancer and 48% for metastatic cancer (47).

The use of Hedgehog pathway inhibitors provides clinical benefits related to tumour volume reduction and local disease control. According to clinical real-life data, these drugs produce a response in an average of 3-3.5 months and are thus particularly relevant for patients who, due to their inoperable location (e.g. face), could experience a significant cosmetic defect as a result of surgery and radiotherapy (49). The drug response observed in daily practice was also confirmed in the BOLT clinical trial investigating sonidegib. In this case, the ORR is 43% for locally advanced cancer and 15% for metastatic cancer, which on the one hand confirms the role of the drug for locally advanced BCC, but on the other hand highlights the limited role for tumour progression and metastasis (47).

It should be taken into account that, despite the high efficacy of inhibitors that they show, they also face problems related to treatment resistance. Based on real life data, it is estimated that primary resistance (i.e. lack of response to the drug from the very beginning of therapy) is observed in about 50% of patients, while acquired resistance, occurring after some time of response to the drug, is observed in about 20% of patients. The pathogenesis of resistance is related to the occurrence of secondary mutations in the SMO gene (in the case of inhibitors that bind to this gene) or the activation of other signalling pathways, independent of ligand activation, that enable tumour cell proliferation (6,47).

In view of resistance, the delivery of SMO antagonist therapy requires close follow-up

of patients and exploration related to the possibility of inhibitor combination therapy to reduce or inhibit resistance mechanisms (6).

Success rates of Hedgehog pathway inhibitor therapy are also highly variable, depending on the study or the patient's clinical situation. For example, in Spallone's study, a complete or partial response to treatment was observed in 78.9 per cent of patients with locally advanced or metastatic basal cell carcinoma of the skin (49). An additional challenge is that, to date, predictive biomarkers of treatment efficacy have not been developed to select patients who will benefit from Hedgehog pathway inhibitor therapy.

Demonstrating efficacy in the treatment of locally advanced tumours, Hedgehog pathway inhibitors play an important role in the treatment of lesions in problematic anatomical locations where surgical therapy and radiotherapy are not feasible or would be associated with loss of function or disfiguring patient appearance. In many cases, these drugs are a good option for patients whose age and concomitant burden make surgery higher risk (13).

When analysing the indications for Hedgehog pathway inhibitors, there are some treatment gaps and strategies for further treatment development. For drugs that block the Hedgehog pathway, future clinical trials should target increasing the length of treatment remission by combining Hedgehog pathway inhibitors with immunotherapy. The aim is also to reduce the risk of relapse while improving the safety of treatment. In addition, it is also important to develop diagnostic tests towards the selection of a biomarker for the efficacy of Hedgehog pathway inhibitor therapy, such as TMB (total mutation burden) (26,50). A suitable biomarker, indicating patients who will gain from treatment with a particular therapy, would allow effective treatment of patients refractory to standard radiotherapy and prolong cancer-free status (50).

5.1.3 Undesirable effects

Side effects of Hedgehog pathway inhibitors used in the treatment of basal cell carcinoma vary widely in frequency, severity and impact on quality of life. The most commonly mentioned side effects by patients include muscle cramps, weight loss, dysgeusia (taste disorder), alopecia and fatigue. More than 50% of people treated with an inhibitor of this pathway experience severe side effects and are forced to discontinue treatment (4,6).

The increased side effects are rooted in a specific mechanism of action involving

inhibition of the Hedgehog pathway, which is active not only in cancer cells, but also in healthy cells such as hair follicles. In addition, the baldness, loss of appetite and dysgeusia that occur deprive patients of the pleasure of eating (6). Such discomforts can have a significant impact on patient functioning, particularly with long-term treatment with a Hedgehog pathway inhibitor (4).

Very severe side effects largely prevent patients from persevering with therapy. Cases of discontinued therapy have been observed when the annoyance of symptoms outweighed the effectiveness of treatment (4,6). Temporarily stopping therapy when negative effects emerge is a standard way of coping. However, interruption of therapy results not only in better tolerance, but also in a reduction in the effectiveness of the drug itself (6). Nausea, vomiting, decreased appetite, gastrointestinal problems, and sarcopenia are among the side effects of inhibitors that impair the patient's nutritional status and thus may lead to metabolic complications. As malnutrition is very common in the elderly, patients are advised to implement dietary care (4). Monitoring body weight, nutritional values and functional status during long-term therapy with Hedgehog pathway inhibitors should be a primary intervention (6). Patient education and emotional support are also important, which has a significant impact on therapeutic compliance and minimising treatment interruptions.

During therapy with Hedgehog pathway inhibitors, there is a high likelihood of both primary and secondary resistance. Primary resistance, which affects more than 50 per cent of treated patients, and secondary resistance, occurring in 20 per cent of those who complete therapy successfully, significantly hinder effective treatment, as those inadequately treated for basal cell carcinoma of the skin are exposed to unnecessary side effects (6). In advanced stages of BCC, where treatment options are limited, side effects can lead to complications. The accumulation of harmful effects of Hedgehog pathway inhibitors results in a lack of response to treatment, leading to the emergence of psychosomatic problems in patients (26).

An alternative to Hedgehog pathway inhibitors in advanced cases of BCC is immunotherapy with cemiplimab. However, this type of treatment has numerous side effects specific to this category of drugs. At this point, the most common adverse effect in cemiplimab immunotherapy is hypertension (47).

Studies of Hedgehog pathway inhibitors have noted the occurrence of many side effects during ongoing therapy and a lack of effect in terms of inhibiting tumour progression. Patients are then burdened with symptoms of long-term side effects

without any specific therapeutic benefit. One of the major challenges in Hedgehog inhibitor treatment is the prevention of tumour recurrence. The use of cemiplimab immunotherapy during ongoing Hedgehog pathway inhibitor therapy may reduce recurrence. It is also very important to investigate biomarkers of predisposition to inhibitor therapy and to develop combination therapy with Hedgehog pathway inhibitor, cemiplimab, kinase inhibitors or radiation therapy, which significantly reduces cancer recurrence in patients (26).

During long-term therapy with a Hedgehog pathway inhibitor, the patient should be carefully monitored to avoid the development of secondary resistance. The system of care, patient education about the inhibitor and its potential effects, plays an important role in this. In addition, it is helpful to implement an information programme on the management of adverse effects of the inhibitor to minimise the number of discontinued therapies. Regular follow-up and individualised treatment plans, tailored to the patient's condition and needs, will reduce the chances of adverse effects, resulting in better treatment outcomes and increased patient survival (51).

It has been noted that adverse effects have very serious consequences in practice, i.e. discontinuation of therapy when the cancer has shown regression. Therefore, the development of management protocols for anticipating the risk of side effects, identifying those who cannot tolerate the effects of drugs, treating side effects that interfere with therapy, improves the quality of life of patients and minimises treatment discontinuation in advanced-stage BCC (52).

In summary, side effects of Hedgehog pathway inhibitors significantly impede the effective treatment of basal cell carcinoma of the skin. Therefore, further research in this area is necessary to reduce the number of side effects in the course of therapy. Advances and knowledge of the pathogenesis of side effects will allow us to predict them and introduce treatments that minimise negative effects. Additional patient support in the form of psychological, informational or dietary support will minimise the symptoms of side effects and minimise the reduction in quality of life during treatment of advanced basal cell carcinoma of the skin.

5.2 Immunotherapy

Systemic therapies such as immunotherapy are significantly finding their place in the treatment of basal cell carcinoma of the skin in advanced states. The use of

monoclonal antibodies and systemic therapies such as immunotherapy are an ideal option for patients in advanced cancer states. The next section is devoted to systemic therapies used in the treatment of patients, which include drug treatment.

5.2.1 Monoclonal antibodies

Monoclonal antibodies are another form of treatment in advanced and metastatic basal cell carcinoma of the skin. They are the form of treatment resorted to when inhibitors of the Hedgehog pathway have not proved effective. Cemiplimab is a PD-1 inhibitor, which is an example of a monoclonal antibody. By blocking T-cell immune checkpoints, these antibodies unblock the immune function of cells against tumour cells. When tumours are characterised by a high mutational burden (TMB), as in the case of basal cell carcinoma of the skin, treatment with antibodies is most effective. They enable a response rate of 31% in locally advanced cases of basal cell carcinoma of the skin (laBCC) and 21% in metastatic basal cell carcinoma of the skin (mBCC) (47).

A tremendous advantage of treatment with monoclonal antibodies is the overcoming of immunological tolerance by the tumour . Blocking the PD-1/PD-L1 interaction stimulates the activity of cytotoxic T cells to destroy tumour cells. Monoclonal antibodies play an important role in multifocal lesions where complete resection would be impossible, such as in facial lesions where resection is impossible without mutilating the patient (4,6). It is important to note that immunotherapy in the form of monoclonal antibodies shows efficacy in patients with refractory tumours where progression has occurred (26).

Thus, immunotherapy is a good alternative for patients for whom surgery and radiotherapy are not curative options for various reasons. In addition, it has been proven that patients with large TMB respond very well to treatment with monoclonal antibodies, which is encouraging. The weakness of this treatment is the numerous side effects. Studies have shown that 48% of patients developed grade 3 and 4 hypertension and immune reactions during antibody treatment. This is important, as each patient should be carefully qualified and monitored by a physician (47).

The use of monoclonal antibodies has opened up new therapeutic possibilities in advanced basal cell carcinoma of the skin. The combination of immunotherapy with Hedgehog pathway inhibitors provides a new form of treatment that can effectively affect the tumour microenvironment. The results of clinical trials show the efficacy of

the combination therapy. They have demonstrated the synergism of Hedgehog pathway inhibitors and monoclonal antibody treatment. Clinical trials on the use of monoclonal antibodies and Hedgehog pathway inhibitors in the treatment of monotherapy-resistant tumours are highly recommended (26).

Patients with high TMB and additional PD-L1 expression respond very well to treatment with monoclonal antibodies. Further research into markers of response to treatment is needed to ensure that patients are appropriately categorised and guard against side effects that may occur during immunotherapy. It has also been shown that treatment with monoclonal antibodies can prevent the appearance of new tumour foci (26).

It should not be overlooked that monoclonal antibodies are not free of side effects. Undergoing this therapy can cause: autoimmune reactions, dermatitis, neuropathy, gastrointestinal problems, endocrine disorders. In view of this, it is important to monitor the patient closely during treatment with monoclonal antibodies and not to underestimate any adverse symptoms should they occur. After immunotherapy, consultation with a neurologist, gastroenterologist, endocrinologist is recommended to exclude any complications after this form of treatment (53). In most cases, the symptoms are mild, but the patient should be monitored, especially the senior patient and the patient with other medical conditions. Additionally, it may happen that a patient, while undergoing treatment with monoclonal antibodies, starts to produce new basal cell carcinoma lesions of the skin during therapy. It is then worth assessing the tumour microenvironment (26).

Monoclonal antibodies are a new therapeutic approach in advanced basal cell carcinoma of the skin when previous treatments are ineffective or unfeasible. In view of the inconvenience of treatment with monoclonal antibodies, special attention should be paid to further research developments in this field. Detection of predictive biomarkers of response to this treatment modality and consideration of combination therapy with Hedgehog pathway inhibitors.

5.2.2 Results of clinical trials

Clinical studies on the efficacy of immunotherapy with monoclonal antibodies provide important information on the effectiveness of cemiplimab in the treatment of advanced basal cell carcinoma of the skin. The results indicate that the objective response rate (ORR) for cemiplimab is 31% for locally advanced basal cell carcinoma of the skin

(laBCC) and 21% for metastatic forms (mBCC). Furthermore, cemiplimab is recommended as a second-line treatment option for patients intolerant of Hedgehog pathway inhibitors (47). The efficacy of the therapy is still limited, including due to differences in the characteristics of the study populations and a lack of standardisation in the delivery of therapy. Tumour mutational burden (TMB) is an important factor in predicting response to cemiplimab (26). The risk of metastasis for basal cell carcinoma of the skin ranges from 0.0028% to 0.55% and is low (4).

An important aspect of monoclonal antibody-based immunotherapy is side effects, which can put the patient at risk and prevent further therapy. Serious side effects occur in nearly half of patients and include autoimmune reactions and hypertension, which often result in the need to discontinue therapy (47). Due to the high incidence of serious side effects, patients with the lowest possible burden of comorbidities should be eligible for this therapy. Furthermore, in the case of anatomical or functional inability to use surgery or radiotherapy for basal cell carcinoma, immunotherapy provides a new opportunity (6). It is also important to consider that the majority, up to 80%, of basal cell skin cancers occur on the head and neck (4).

A challenge, as with the use of Hedgehog pathway inhibitors, can be side effects, which represent the most significant obstacle to the correct delivery of therapy. Nevertheless, there are reports in the literature of immunotherapy being used in combination with Hedgehog pathway inhibitors and completely curing advanced basal cell carcinoma. However, there is some controversy. Although cemiplimab has relatively high efficacy in some cases of basal cell carcinoma, not all responses to therapy are durable and variability in response duration and progression-free survival has been observed. In addition, one study observed the development of a new basal cell carcinoma tumour during cemiplimab therapy. Even at high TMB levels (above average TMB), the response to cemiplimab immunotherapy is not always long-lasting (26).

A promising prospect in the fight against advanced basal cell carcinoma of the skin is immunotherapy due to the improvement of the patients' overall quality of life. The possibility of avoiding aggressive therapies such as surgery and radiotherapy reduces the risk of disfiguring cosmetic defects and helps to improve the patient's wellbeing (54). The aesthetic aspect after therapy is also an important consideration. The results of a clinical trial are available that evaluated the aesthetic effects on five radiotherapy options for the treatment of primary basal cell carcinomas of the skin (these were

patients with cancers on the head and neck, mainly on the face). They found that most of the options had negative cosmetic effects at four years post-treatment, and the efficacy in terms of four-year recurrence rate was 7.5% for radiotherapy compared with 0.7% for local surgery. The risk of radiotherapy complications in this patient group cannot be underestimated. Side effects are inevitable, but it is the delayed skin lesions at the irradiation site that can be a significant factor in reducing patients' quality of life. The need for another procedure, given that recurrence of basal cell carcinoma in this group occurs on average seven years after irradiation, should be considered in daily practice (4). Multidisciplinary follow-up visits and patient education about the need to report any changes or occurrence of side effects are important to maintain therapeutic success.

The above information suggests that immunotherapy for advanced basal cell carcinoma of the skin appears to be a promising new form of treatment. However, there are problems with the efficacy of monoclonal antibody immunotherapy that need to be resolved before it can be applied in practice.

6. Comparison of the effectiveness of treatment methods

A comparison of the efficacy of different treatment methods for basal cell carcinoma against cure rates and remission times enables an analysis of the effectiveness of treatment and the optimal choice of method. The analysis includes surgical and non-surgical methods in the context of oncological and aesthetic aspects, which have a significant impact on improving patients' well-being. These considerations complete the overall context of the treatment approach.

6.1 Cure rates

Successful treatment of basal cell carcinoma of the facial skin depends on the appropriate application of the chosen method. Surgery is the gold standard of treatment. Classical surgery has a success rate of more than 95%. It involves excision of the lesion with a margin of healthy tissue. Mohs Micrographic Surgery (MMS) is additionally very precise. It allows an accurate assessment of the margin, which translates into a success rate of 99% for primary lesions and 94% for recurrent lesions (4,6,13).

This method is recommended in facial locations where minimal tissue loss is important. Selection of appropriate surgical margins, i.e. 4 mm for low-risk tumours, leads to negative margins in more than 95% of patients (13).

In addition to their high oncological value and very good aesthetic outcome, surgery and MMS are the preferred treatment options for facial skin lesions. Both methods in the long term give better results in acceptance of the treatment modality and improved quality of life for patients. Aesthetic aspects should be the basis when selecting the appropriate surgical treatment method for facial skin tumours. Psychosocial aspects, including risk factors for complications, reconstructive needs and patient concerns, should be important factors in the selection of an appropriate treatment, as they influence the psychosocial outcomes of cancer treatment (4).

Radiotherapy, with an efficacy of 83-95%, has slightly worse treatment rates for basal cell carcinoma of the skin than surgery. It is chosen most often in patients who are not eligible for surgery for anatomical or medical reasons. A randomised trial (Helsinki, 1965) showed a 4-year treatment failure rate for radiotherapy of 7.5 per cent compared with surgery, which was 0.7 per cent (4,13). Brachytherapy and superficial radiotherapy, using imaging, are used particularly in older people in facial locations. Radiotherapy is characterised by a higher likelihood of recurrence and a worsening of cosmetic outcome, compared with surgery. Additional irradiation is characterised by numerous side effects, i.e. skin thinning, telangiectasias, hyperpigmentation, which do not directly affect patients' cure, but negatively affect patients' acceptance of treatment (4).

Topical treatments, i.e. photodynamic therapy and imiquimod, are also used to treat superficial forms of basal cell carcinoma of the skin. The treatment efficacy of photodynamic therapy is 75-87%, depending on the number of treatment sessions, and complete tumour remission occurs after an average of 2 treatments (8,55). It shows high efficacy in the treatment of shallow and well-demarcated lesions. Imiquimod shows an efficacy of 75-90% for superficial tumours. This therapy is used as an alternative method for patients for whom cosmetic outcome is a priority. These therapies should be included at the earliest possible stage of treatment, as the patient has no chance of a cure if the method is inappropriately chosen in advanced cases of the disease. It is essential to monitor the patient's treatment progress (6,8). Systemic therapies (Hedgehog pathway inhibitors and immunotherapy) are drugs used for patients with locally advanced and metastatic basal cell carcinoma of the skin.

Vismodegib is a Hedgehog pathway inhibitor. Complete response rates for the Hedgehog pathway inhibitor are 68.5 per cent in locally advanced cases and 36.9 per cent in metastatic cases (6). Cemiplimab is a PD-1 inhibitor, response rates with this drug are 29-31% for locally advanced tumours and 21% for metastatic tumours (13). The efficacy of the treatment is not as effective as surgery or radiotherapy, but it offers patients the hope of a progression-free life. Nevertheless, the majority of patients experience primary resistance to therapy, i.e. about 50 per cent lack response to the drug. Secondary resistance occurs in approximately 20% of individuals and necessitates treatment discontinuation (6).

The long-term treatment rates and survival of patients with basal cell carcinoma of the skin located on the face depend on appropriate treatment and diagnosis.

The 5-year survival rate of patients with BCC is more than 95 per cent, as a result of early diagnosis of the tumour and prompt treatment. Among metastatic patients, the median survival of patients with node involvement is 10 months. The 5-year survival rate is only 20-30% (4).

Basal cell carcinomas of the facial skin are not lethal tumours, but their treatment requires appropriate methods, knowledge and the collaboration of multiple specialists. The aim should be to develop a personalised diagnostic and treatment algorithm for patients with basal cell carcinoma of the facial skin, taking into account genetic aspects, tumour location and psychosocial and aesthetic aspects relevant from the patients' perspective.

6.2 Recurrence rate

Recurrences after Mohs micrographic surgery have the lowest incidence of all treatment options for basal cell carcinoma of the skin. In studies, the five-year recurrence rate is 1 per cent in primary and 4 per cent in recurrent basal cell. The low recurrence rate is due to the characteristics of this procedure. It relies on microscopic assessment of margins when performing the procedure. In this way, tumours with ambiguous borders of ingrowth into adjacent tissues can be completely removed (4). In Mohs micrographic surgery, resections are performed only as much as necessary to clear the resection margins, so this procedure will perform better than classical surgical debridement in recurrent lesions and in lesions with unclear tumour margins, such as morpheaform and infiltrating lesions. Excision with wide tissue margins for

these tumour types does not guarantee clean resection margins. Also, the location of tumours on the face is an ideal indication for Mohs micrographic surgery, as sparing tissues in adjacent areas will have a beneficial effect on minimising cosmetic defects and subsequently on patients' quality of life (33). There are only a limited number of centres worldwide that perform this procedure. Despite limitations to its use such as cost and low availability, the number of centres is steadily increasing (35).

In classical surgery, thanks to correctly selected margins of the cut edges, the recurrence rate is reduced to less than 5 per cent. For tumours at low risk of recurrence, a cut margin of 4 mm is recommended and more than 95% of the subjects then had negative cut edges (4,6). Appropriate surgical excision allows for complete removal of tumour cells and consequently minimises the risk of recurrence, but in areas where it becomes difficult to achieve a perfect surgical cut, such as the nose and eyelids, alternative techniques should be used (4). These include Mohs micrographic surgery, radiotherapy or phototherapy. Improperly performed surgery in cases with a lower risk of recurrence may result in recurrent basal cell carcinoma (13). Therefore, special attention should be paid to the choice of treatment modality and tailored to individual patients. Looking for the molecular determinants of a given tumour can be helpful in preventing recurrence (7). By defining and checking gene expression in basal cell carcinoma tumours, it will be possible to tailor treatment to specific patients in the future.

The incidence of recurrence after radiotherapy, which is used in cases where surgical intervention becomes impossible, is affected by the lack of assessment of the edges of irradiated cuts. In addition, radiotherapy can be problematic if treatment is given to lesions that are deeply ingrown into tissue or in anatomically complicated areas (9). Predominantly, radiotherapy is ordered for patients of advanced age and those for whom anaesthesia for surgery is not recommended, as well as those with tumour recurrence in body locations where surgery or phototherapy is not possible. Compared to the 0.7 per cent four-year recurrence rate with surgery, the four-year recurrence rate after radiotherapy is 7.5 per cent (4). Thus, although irradiation is an effective treatment and allows local control in patients for whom, for reasons dependent on them (general health, lack of preference for surgery) or beyond their control (lack of availability, unqualified medical staff), surgical treatment is not possible, the recurrence rate after it remains higher compared to classical surgery. The use of superficial radiotherapy with imaging allows for improved local control, but due to its

costliness and the lack of centres performing imaging-guided irradiation, it remains an inadequate treatment modality widely available to most patients (42).

With phototherapy and topical imiquimod treatment, recurrence rates are also high compared to surgery. Complete resolution of lesions after one phototherapy session occurs in 60% of subjects and increases to 87% after two phototherapy sessions, although recurrence rates remain high (8). Phototherapy will be successful in treating lesions that do not grow into neighbouring tissues, as the penetration depth of the light used is limited and also the photosensitisers used are not sufficiently selective (9). For topical imiquimod treatment, the success rate achieved is 75-90%, and imiquimod treatment in superficial basal cell carcinomas offers an alternative for patients wishing to avoid surgery, also with a low risk of progression (6). The individual response to topical treatment and the level to which patients adhere to recommendations are important in the success of the method used. Skin type and concomitant diseases are equally important (21). Inadequate monitoring of tumour lesions in patients undergoing topical therapies results in higher recurrence rates and requires the use of repeat medical intervention.

Hedgehog pathway inhibitors and immunotherapy are used in advanced and metastatic cancers. The rate of disease progression in patients treated with Hedgehog pathway inhibitors with primary resistance is estimated to be approximately 50 per cent, and secondary progression may be 20 per cent in this patient group (6,47). The heterogeneous responses of patients at this stage of tumour development are due to the diverse molecular types of tumours and the numerous mutations that have an impact on the process of progression and the emergence of resistance to a given type of therapy (7,26). Reducing the recurrence rate in basal cell carcinoma may be influenced by the implementation and use of combination therapies using Hedgehog inhibitors and, in the longer term, the approach of tailoring therapies to the molecular type of the respective cancer tumour in individual patients (6,26).

Individuals who have undergone at least one episode of basal cell carcinoma of the skin in their lifetime have a high risk of developing another cancer within five years (47). It is estimated that approximately 40% of people are diagnosed with at least one new cancer after basal cell carcinoma (56). The higher recurrence rate of basal cell carcinoma may be due to individual genetic predisposition and to uncontrolled exposure to factors that initiated the pathogenesis of this skin cancer, which include lack of UV protection (7). Among patients with a history of basal cell carcinoma,

educational measures should be initiated to prevent the occurrence of another skin cancer and a system of regular dermatological examinations and preventive measures should be implemented to prevent recurrence and increase their quality of life (47). Active secondary prevention reduces the overall number of patients, leading to financial gains and budgetary savings (56).

The recurrence rate of basal cell carcinoma of the skin depends on the method of treatment used and the conditions that are within the patient's control and influence. Treatment in which margins are not controlled generates a higher rate of tumour re-progression. Increasing the chances of recovery and recurrence rates returning to normal will require a more complex treatment regimen in which prevention of recurrence is as important as tailoring the appropriate medical intervention.

6.3 Cosmetic aspects

Cosmetic aspects play a key role in the treatment of basal cell carcinoma of the facial skin due to their direct impact on patients' self-esteem. Classical surgery and Mohs Micrographic Surgery (MMS) as radical treatment for BCC have a significant impact on cosmetic outcomes. Both classic surgery and Mohs Micrographic Surgery save healthy tissue, resulting in a smaller wound, but MMS, being an extremely precise technique, allows for better cosmetic outcomes (4,16). However, regardless of the surgeon's precision, patients may experience temporary or permanent scarring, asymmetry or pigmentation changes after surgery. Performing surgery to excise a facial lesion may contribute to changes in psychological aspects and self-perception (16). Long-term studies show that properly performed surgery, along with careful patient education and appropriate psychological support, allow patients to improve their mental health and overall quality of life. Such an effect is mostly observed in younger people who are economically active, have families and have social support (16,17). The patient's cosmetic expectations prior to surgery are extremely important. A realistic attitude should be part of the patient consent discussed and allows patients to accept the treatment effect.

Radiotherapy, although successful in controlling the local form of basal cell carcinoma, generates a much worse treatment outcome compared to surgery in cosmetic terms. A study that verified the proportion of patients with a good cosmetic outcome four years after treatment found that in radiotherapy this was 69% of patients, whereas

after surgery the rate was 87%. Skin changes such as telangiectasias, hyperpigmentation or skin thinning are most common in patients after radiotherapy. All of the aforementioned changes can negatively affect self-esteem and social relationships. Psychological problems and patient image can also be affected, especially for the younger population, as they have higher expectations of cosmetic appearance (4,9). The option of irradiation is recommended for patients with a higher surgical risk, most commonly the elderly. Given these cosmetic aspects of radiotherapy in the treatment process, it is crucial that the patient is adequately informed about negative skin changes. In addition to adequate cosmetic and technical education in this area, it is important to be able to support patients, as radiotherapy does not evoke positive feelings in most patients due to the negative connotations of cancer.

Topical therapies such as photodynamic therapy PDT and imiquimod do not produce scarring, which is very much in line with cosmetic needs. PDT tends to be characterised by short-term side effects (erythema, peeling, hyperpigmentation), with better tolerance in the elderly and with photodynamic daylight therapy dPDT (8). Imiquimod, on the other hand, as a topical preparation for self-application, is extremely convenient, but when applied to the facial skin, there is a risk of permanent pigmentation changes that need to be adequately controlled (6). Topical therapies, which are a limited form of treatment for superficial forms of BCC only, have a high therapeutic efficacy and both maintain good cosmetic results. This allows the patient to build self-esteem and improves their quality of life. Imiquimod has an over 80% overall treatment success rate for BCC (50).

Systemic therapies, such as Hedgehog pathway inhibitors (e.g. vismodegib) and immunotherapy (e.g. cemiplimab), do not directly cause cosmetic defects such as scarring, but the numerous side effects of these therapies (alopecia, taste disturbance, unpleasant odours, pigmentation changes, etc.) can negatively affect patients' appearance and self-esteem (9,57). The study found that cemiplimab used in the treatment of advanced BCC achieved an ORR (objective response rate) of 31% and a duration of response (DOR) of at least six months was observed in 79% of patients, significantly affecting treatment response rates. In patients with the metastatic form of BCC, the ORR was 21.4% (50). Adequate psychological support, educating patients about expectations of changes in the treatment process allows patients to adapt in this new environment. Successful control of advanced BCC with systemic therapies

minimises the need for mutilating reconstructive surgery, thus reducing the negative social and aesthetic impact of this treatment.

By implementing appropriate treatment strategies, potential side effects can be controlled, and by considering cosmetic needs when selecting therapies, patient satisfaction can be increased.

Improving quality of life and self-esteem is closely linked to psychological and educational support. If the patient is involved in decision-making in aspects of the treatment process and is aware of and has realistic expectations of treatment outcomes, he or she is better able to tolerate the side effects of therapy (17). A psychological support programme for the patient has a positive impact on reducing anxiety and improving the patients' level of acceptance of their appearance after treatment (58). Carefully educating the patient about possible side effects and managing their expectations should also become an integral part of the overall treatment and cure process in BCC.

7. Summary

The aim of this study is to analyse the efficacy and limitations of the available treatments for basal cell carcinoma (BCC) of the facial skin in terms of oncology, aesthetics and impact on the patient's quality of life. Surgical, local, radiotherapy and systemic treatments were compared in terms of cure rates, recurrence rates, psychosocial burden and individualisation in treatment selection. A detailed analysis of the scientific literature and current clinical reports was performed. Analysis of the data confirmed that surgery remains the gold standard in the treatment of basal cell carcinoma of the facial skin in terms of efficacy as well as aesthetic outcomes. Both surgical excision and Mohs micrographic surgery report high rates of permanent cure rates, 99% in primary lesions and 94% in recurrent lesions, respectively, and the preservation of negative resection margins allows skin sparing and a reduction in aesthetic complications. In anatomically inaccessible areas and in aggressive BCC subtypes, Mohs surgery is an aesthetically more advantageous tool with minimal recurrence rates. Radiotherapy, although effective in certain groups of patients - those with contraindications to surgery and elderly patients with disseminated tumours with imprecise localisation - is associated with lower permanent cure rates and poorer aesthetic outcome at four-year follow up. Topical therapies, such

as cryotherapy, photodynamic therapy and imiquimod, are widely used in superficial, well-demarcated, low-grade BCCs due to their high aesthetic satisfaction, although their efficacy is not on a par with surgery. For this reason, topical treatment should be directed to a strictly selected group of patients, and it is necessary to monitor the therapeutic response during their use.

Systemic treatments - SMO inhibitors and immunotherapy - are gaining popularity in cases of advanced, inoperable and aggressive tumours. SMO inhibitors, such as vismodegib and sonidegib, are effective against locally advanced cutaneous BCC, although high recurrence and severe side effects often result in treatment withdrawal. Cemiplimab is a monoclonal antibody used in immunotherapy and is a very reasonable alternative in advanced skin cancer with high recurrence, but it delays the return to normal activity and also has the effect of inducing severe side effects. Despite their many drawbacks and highly individualised therapeutic effect, these systemic drugs control the tumour in patients who cannot be effectively treated with other options.

The results of treatment of basal cell carcinoma of the facial skin depend primarily on correct and comprehensive pre-operative diagnosis, proper qualification for treatment (surgery/treatment), interdisciplinary cooperation and education of the medical staff, but also of the patient. In long-term studies, early diagnosis and treatment have been shown to correlate with improved prognosis, and prevention and education programmes have significantly reduced not only new cases of facial skin BCC, but also the occurrence of recurrences.

The hypothesis that patients' quality of life does not change after effective and minimally invasive treatment was also refuted, indicating that success in the cosmetic and psychosocial aspects of treatment has a significant impact on the patient after treatment.

The results I obtained, although in line with new recommendations and the current state of scientific research, do not solve all the problems of the skin cancer patient. A number of factors can affect the effect of treatment. For example, surgical approaches are proving to be significantly more effective than other treatment modalities, and modern Mohs surgery, with its benefits and positive long-term results, is becoming the most appropriate choice of therapy in BCC of the facial skin. Increasingly popular systemic drugs in the future will significantly improve the prognosis of non-operative cases. Better access to highly specialised laboratory and pathomorphological diagnostics and modern imaging techniques not only improve prognosis in a practical

way, but also improve aesthetics and function. In the current national situation, there are many difficulties and challenges that inhibit the implementation of new protocols and treatment algorithms. Access to some modern therapies, due to financial and logistical conditions as well as bureaucratic constraints,
is impossible in every centre. New medical technologies are introduced every year and the classification of cancers changes. The implementation of modern knowledge proves to be a frequent challenge, as it shows very significant differences between countries in terms of treatment, accessibility to a highly specialised centre, health status, gender, age, payment, education or ethnicity.

Therefore, in order to accurately and comprehensively verify my hypothesis, prospective, multi-year and controlled national registries are necessary. Only then is it possible to know the actual cancer data, with particular attention to predictive factors or therapeutic response rates on cancer treatment. Following this, a universal algorithm for the management of all skin cancers should be developed. It will allow a better assessment of the risk of metastasis and enable the selection of the most optimal and individual form of treatment for each patient.

Despite what has been written above, it is necessary to carry out continuous prevention and education in order to avoid such morbidity. In the event of an incidence, it is extremely important to start treatment at the earliest possible stage of skin cancer. However, further research, education and the availability of modern technology can significantly improve the prognosis of patients and prevent cancer complications. My choice of this topic is consistent with my personal interest in skin oncology and was challenging. I believe that the literature collected in this thesis and the compilation of the current status remain a base that can be used for further research on this topic.

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