Abstract
Basal cell carcinoma (BCC) is the most common type of skin cancer, thus numerous therapeutic approaches have been developed. Optimal treatment outcome should comprise complete removal of the tumor to the margin of normal tissue with the best possible aesthetic result. Surgical treatment remains the “gold standard” in therapy of BCC, showing excellent cure rates when used within the guidelines. However, it is not always possible to perform surgical excision, since it can be contraindicated in patients with certain comorbidities or in case of extensive size and/or difficult location of the tumor. Therefore, a variety of treatment modalities have been developed including cryotherapy, radiation therapy, photodynamic therapy, topical therapies, laser therapy and recently established systemic therapy. Radiation therapy is commonly performed in patients who are not good candidates for surgery and in cases when extensive or complex surgical procedure is required, often resulting in poor cosmetic outcome. Other treatment options including topical therapies, photodynamic therapy (PDT), cryotherapy, electrodesiccation and curettage are suitable for superficial and/or multiple lesions. Laser treatment, although potentially promising, is still not a widely used treatment modality for BCC, usually used only for small BCCs in low-risk anatomical areas. Finally, systemic therapy, vismodegib, is an orally administered Hedgehog pathway inhibitor, recently approved for treatment of metastatic and curettage are suitable for superficial and/or multiple lesions. Laser treatment, although potentially promising, is still not a widely used treatment modality for BCC, usually used only for small BCCs in low-risk anatomical areas. Finally, systemic therapy, vismodegib, is an orally administered Hedgehog pathway inhibitor, recently approved for treatment of metastatic and locally advanced BCC. The advantages, disadvantages and limitations, as well as cosmetic outcomes of each of these treatment modalities are widely discussed and reviewed in this article. Special emphasis is given to the importance of individual patient approach, taking into consideration all of the possible risks and benefits and patient quality-of-life issues when choosing a treatment modality. Conclusively, this paper aims to present a comprehensive review of current treatment modalities of BCC.

ABBREVIATIONS

INTRODUCTION
Basal cell carcinoma (BCC) is the most common cancer in humans. Taking into account the increasing incidence rate of this locally invasive malignant epidermal skin tumor by 3-10% per year, it is becoming a growing public health problem [1]. Although it can occur at any age, the incidence of BCC increases markedly after the age of 40 [2]. Basal cell carcinomas (BCCs) develop slowly and metastasize extremely rarely, with an incidence ranging from 0.0028% to 0.55% [3]. Nevertheless, early diagnosis is important due to the fact that 74% of all BCCs occur on the head and neck, and their nature to locally invade can lead to significant cosmetic disfigurement and even destruction of vital structures [4]. The most significant etiological factors are fair skin type and exposure to ultraviolet radiation. Other risk factors include immune suppression, increasing age, male gender, exposure to arsenic, prior treatment with ionizing radiation, scars and certain hereditary disorders [5]. In a patient presenting with multiple early onset lesions, possible connection to specific syndromes (Xeroderma Pigmentosum, Gorlin-Gotz, Bazex-Dupré-Christol or Rombo) should be investigated [6]. In contrast to the usual predilection sites on chronically sun-exposed skin for the general population, in immune suppressed patients, BCCs appear on the UV non-exposed skin of the body and upper limbs [7]. The distinction between several clinical and histological subtypes of basal cell carcinoma is important for the prognosis and treatment considering different patterns of behavior. Nodular BCC accounts for 60-80% and is most commonly found on the head [7]. Other less frequent types of BCC are superficial BCC, sclerodermiform (morphoform or morphoeic), cystic,
infiltrated, micro nodular, pigmented and fibro epithelioma of Pinkus [7]. Considering the high prevalence rate of BCC and its aggressive growth pattern, timely treatment is essential in order to minimize complications and provide complete removal of the tumor with the best cosmetic result. Optimal treatment option is generally chosen based upon several factors, primarily including the size and location of the tumor, as well as the patient’s age, comorbidities and histological tumor type. In the following sections, each of the current treatment approaches, as well as new promising therapies for BCC will be thoroughly discussed. The aim of this review is to present optimal treatment modalities which should be chosen based on tumor characteristics, such as size, localization and histological subtype, and patient related factors such as age and comorbidities that all have a significant impact in making a decision about treatment.

SURGICAL EXCISION

Standard surgical excision remains a “gold standard” for primary BCC, providing complete removal of the tumor, as well as the pathohistological analysis in order to make sure that the tumor is fully excised. Although the possibility of histological examination of tumor margins to establish clearance is an advantage of surgical treatment, complete margin control is not possible. Standard vertical section processing of excision specimens enables examining only the peripheral and deep surgical margins, representing at best only 44% of the entire margin, which could partly explain the reason for recurrence of tumors reported as “fully excised” [8]. Disadvantages of this method include scars, possibility of pigmented changes, infection or poor wound healing, more commonly seen in elderly and immune compromised patients. The decision regarding the size of a adequate surgical margin can be difficult, especially when the procedure is performed on the face or in case of an extensive lesion. Some authors have indicated that excision of small (less than 10 mm) lesions with a 2 mm peripheral surgical margin cleared 70%, margins of 3 mm cleared 84%, and margins of 5 mm cleared 95% of all tumors [9]. They have also emphasized the need for wider surgical margins in morphoeic and large BCCs, as results of their study have indicated that the rate of complete excision for primary morphoeic BCC was 66% for a 3 mm margin, and 82% for 5 mm, and >95% for 13–15mm [4]. Furthermore, recurrent BCC tends to be more difficult to treat than a primary lesion. A study analyzing histological sections of recurrent BCCs has reported that 24% became histologically more aggressive, 20% originally nonaggressive BCCs became aggressive during recurrence and 31% originally aggressive BCCs showed a more aggressive component during recurrence [9]. Surgical excision should therefore always be performed with a sufficient safety margin in order to enable complete excision and minimize recurrence rate.

MOHS MICROGRAPHIC SURGERY

Mohs surgery is most frequently used for extensive and destructive lesions located on the face and recurrent BCC. High cure rates (5-year cure rate for primary BCC 99% and 94.4% for recurrent BCC), together with maximal preservation of normal tissue is the reason why this procedure is the treatment of choice for high risk BCCs located on the face [10,11]. The principle is microscopic control at the time of removal of the tumor. The undersurface of each layer of the excised tissue is examined by frozen section until the margins are free of the tumor. The disadvantages of this method are that it requires special laboratory facilities and trained personnel, and also the duration of procedure [12]. It is therefore performed only in specialized centers and should be considered in cases of recurrences after radiotherapy or surgery, high risk anatomical sites, large tumors and whenever there is a need for maximal tissue preservation.

CURETTAGE AND CAUTERY

Electro desiccation and curettage is a method commonly used to treat primary nodular and superficial BCC of less than 1.0 cm in diameter [13]. After the tumor is scraped off with a curette, the area is treated with electrocautery in order to eradicate residual tumor and control bleeding. Usually, two to three treatments are recommended in order to remove the tumor completely. [14,15]. Since this technique does not provide a sample for histological diagnosis, it is advised to make preoperative biopsy to confirm the diagnosis and determine the histological subtype [4]. In a study comparing the efficacy of curettage plus cryosurgery and surgical excision in nonaggressive BCC of the head and neck, recurrences occurred in 17.6% after curettage, and in 8.2% after surgical excision [16]. These results indicate that surgical excision should be preferred to curettage in treatment of primary, nonaggressive BCC of the head and neck due to lower recurrence rates, better cosmetic results and reduced wound healing time [16]. Curettage and cautery is contraindicated in lesions larger than 1 cm in diameter, localized around the eyes, nostrils and ears, as well as for ulcerated lesions and morphoeform BCC [12]. Curettage has also been combined with imiquimod, photodynamic therapy (PDT) and cryosurgery in attempt to increase treatment efficacy [11].

CRYOTHERAPY

The principle of cryotherapy is the induction of cell necrosis by exposing the tissue to low temperatures using liquid nitrogen. This procedure does not provide a histological specimen, so it is advisable to make a biopsy prior to the procedure. Cryotherapy is the most useful in treatment of low risk BCCs with well-defined borders. Nevertheless, good results are obtained even following the treatment of high risk lesions either as a monotherapy or in combination with curettage [4]. Cryotherapy results in peripheral erythema, pain, edema, bulla formation and exudation, usually healing with a fine atrophic scar. Most common long-term side effects are pigmented changes [17]. Cryotherapy should be avoided in areas of hair growth (scalp and beard area) and in patients with conditions sensitive to low temperature (Raynaud’s syndrome, cold panniculitis, cryoglobulinemia) [13]. Although there are variations regarding the technique and the number of cycles performed, the general recommendation is two freeze-thaw cycles [15]. Mallon and Dawber compared cure rates after one and two freeze-thaw cycle schedules, showing a cure rate of 79.4% when facial lesions were treated with a single freeze-thaw cycle, while for double freeze-thaw cycle the cure rate was 95.3% [18]. Treatment of superficial truncal BCCs with a single freeze-thaw cycle achieved a cure rate of 95.5% [18]. The results have suggested that facial BCCs require a double freeze-thaw cycle with liquid nitrogen, while truncal lesions may require only one treatment cycle [18]. For treatment of primary BCC, there
is a cumulative 5-year recurrence rate of 4-17% depending on different studies [19]. A particular problem regarding recurrence after using this treatment modality is the development of fibrous scar overlaying the recurrent tumor, which may become extensive before the diagnosis is made [15]. A comparison of cryosurgery with PDT showed histopathologically comparable recurrence rates - 15% for cryosurgery and 25% for ALA-PDT (aminolevulinic acid -mediated photodynamic therapy), but clinical recurrence rates 13% for cryosurgery and only 5% for PDT [20]. Although pain and discomfort were equivalent with the two treatment modalities, healing time was considerably shorter and cosmetic outcome significantly better with PDT [20]. Nevertheless, PDT requires expensive equipment and experience in use, while cryotherapy requires minimal costs and is easier to administer. Surgical excision is still the preferred modality over cryosurgery when lesions are located on the face, as cryotherapy results in less acceptable cosmetic outcome and higher recurrence [19].

LASER TREATMENT

Although lasers have been used in dermatology for nearly 50 years, they are still an uncommon treatment modality for BCC. In a study on patients with Gorlin-Gotz syndrome, ultra pulse CO2 laser was found to be effective in treatment of small BCCs in low-risk areas leaving minimal post-treatment scarring [21]. The evaluation of treatment and cosmetic outcome of super pulsed CO2 laser after curettage for BCC showed 93.7% cure rate after one session, with excellent cosmetic outcomes in 85.8% cases [22]. It was shown that this method is an appropriate alternative treatment for BCC lesions smaller than 2 cm, superficial, pigmented and nodular clinical subtype without an aggressive pathologic pattern [22]. A recent study which evaluated the 595-nm pulsed dye laser (PDL) efficacy and safety in treating superficial BCCs at low-risk anatomical sites, showed complete remission in 78.6% of treated patients, with development of crusts and changes in pigmentation as main adverse events [23]. In another study published this year, the effect of repeated treatment with a combined 585 nm pulsed dye laser (PDL) and 1,064 nm Neodymium Yttrium Aluminum Garnet (Nd:YAG) laser on superficial and nodular subtypes of varying diameters was evaluated, where 58% of all tumors and 75% of tumors of less than 1 cm in diameter, showed complete response [24]. It is important to note that all subjects with incompletely responding BCCs were on various forms of anticoagulation therapy during the treatment, which might have inhibited laser-mediated thrombosis necessary for the clinical effect [24].

RADIOTHERAPY

Radiotherapy (RT) is an effective treatment for primary BCCs, recurrent BCCs after surgery when re-excision is not possible, as adjuvant therapy, in elderly patients and when surgery is contraindicated due to patients comorbidities, difficult location or large size of the tumor. Head and neck area generally tolerate RT well, while patients with tumors located in lower risk areas, such as the trunk and extremities are usually not treated by this modality. RT includes superficial RT (generated at up to 170 kV) which is suitable for lesions of up to 6 mm in depth, electron beam therapy (generated at higher energies) which penetrates deeper tissues and brachytherapy which is useful for lesions arising on curved surfaces [11]. In the past, irradiation was given in a single dose, which resulted in scarring and radio necrosis. Modern techniques of fractioning the dose have greatly improved cosmetic results. Still, radiotherapy should be avoided in certain sites (ear, lower leg, back of hand - possible radio necrosis), in morphoeic BCC (radio resistant) and superficial BCC (poor cosmetic result) [12]. The dose and treatment regimen depend on the size, location, type and depth of the tumor. Primary BCCs irradiated by a “standardized” x-ray therapy schedule have a 5-year recurrence of 7.4%-9.5% [25]. The comparison of radiotherapy to other treatment modalities has shown significant advantage of radiotherapy over cryotherapy (2-year recurrence rate of 4% of tumors treated with radiotherapy and 39% of those treated with cryotherapy), but also the superiority of surgery (recurrence of 7.5% after radiotherapy and 0.7% after surgery with significantly better cosmetic result after surgery) [26,27]. Radiation therapy is contraindicated in genetic disorders which predispose patients to skin cancers, patients with connective tissue diseases (Gorlin’s syndrome, xeroderma pigmentosum, lupus and scleroderma), as well as in patients who have recurrent BCC after previous RT [11,13]. It is also not advisable in younger patients because of theoretical possibility of inducing secondary malignancies and poor cosmetic results.

IMIQUIMOD

Imiquimod is an immune-response modifier acting through the activation of macrophages and other cells by binding to cell surface receptors, inducing secretion of pro-inflammatory cytokines and generation of cytotoxic effects through Th1 cell-mediated immune response [28]. 5% imiquimod cream during 6 weeks was evaluated according to superficial BCC histologic clearance, with results of 100% in twice daily, 87.9% in once daily, 73.3% in twice daily 3 times per week and 69.7% in once daily 3 times per week regimen [29]. It was found that inflammatory skin reactions at the site of application were common and dose related [29]. In addition to superficial BCC (87%), imiquimod 5% cream has also shown response rates nodular BCC (65%) [30]. Better results on superficial BCCs may be explained due to their minimal depth of invasion and the fact that effectiveness of this treatment depends on tissue penetration [4]. Imiquimod can also be used as adjunctive therapy to surgery, prior to excision, providing significant reduction in the size of the tumor, consequently resulting in better postoperative cosmetic result [13]. Imiquimod is not recommended for recurrent disease, but it can be an alternative to surgery in patients with primary superficial BCCs, although long-term clearance is not as good as in other treatment modalities [4].

PHOTODYNAMIC THERAPY

Photodynamic therapy (PDT) is a treatment modality that includes photochemical reactions that occur due to the photosensitizing agent, visible light and oxygen interaction. After a photosensitizer, 5-aminolaevulinic acid (ALA) or methyl aminolevulinic (MAL) is applied to the skin, it is converted to protoporphyrin IX by the tumor cells. In the presence of intense red or blue light, a cytotoxic reaction occurs with reactive oxygen in the cell-membranes of tumor cells and the tumor is destroyed with sparing of uninvolved skin [4]. The advantage of topical PDT over other treatment options is its noninvasiveness, excellent cosmetic results and good tolerability. It is a good alternative
for patients with bleeding tendency and with superficial and multiple tumors [31]. In addition, it can be applied repeatedly without cumulative toxicity [32]. However, a study investigating immediate and long-term effects of ALA-PDT on superficial BCC revealed poor long-term cure rates [31]. Although primary response rate was 86%, after a median follow-up of 19 months recurrence rate was 44%, and 36 months after the therapy, the disease-free rate was only 50% [33]. More encouraging results with a complete response rate of 100% one month after treatment, and relapse rate of 4% after 27 months were seen in a study when two cycles of PDT were applied [34]. When compared to cryotherapy, histological recurrence is 25% for ALA-PDT and 15% for cryotherapy, but clinical recurrence is only 5% for PDT and 13% for cryotherapy [20]. Additionally, PDT shows shorter healing time, better cosmetic outcome and equivalent pain and discomfort [20]. MAL is more lipophilic methyl ester of ALA which shows increased response in nodular lesions. MAL-PDT is a good option for BCCs that are difficult to treat and due to excellent cosmetic results, this treatment is particularly well suited for lesions that would otherwise require extensive surgical procedures [31,35].

5 - FLOROURACIL

Fluorouracil is an antimetabolite that blocks the incorporation of thymidine into DNA and thereby inhibits DNA synthesis, prevents cell proliferation and causes tumor necrosis. It is approved as 5% solution and cream twice daily for at least 6 weeks for the treatment of superficial BCC, usually in low risk sites, when conventional methods are impractical [13]. A systematic review found that fluorouracil produced clearance rates of 90% for superficial BCC, but 97% of patients experienced adverse effects such as erythema, pruritus and pain [36]. In a trial that compared the effectiveness of topical PDT with imiquimod or fluorouracil in patients with superficial BCC, the cure rate for MAL-PDT was 72.8%, for imiquimod 83.4% and for fluorouracil 80.1% [37].

VISMODEGIB

Vismodegib is the first Hedgehog pathway inhibitor approved for treatment of adults with metastatic BCC or locally advanced BCC that has recurred following surgery or patients that are not candidates for radiation [38]. It is a molecule that inhibits signal transduction in the hedgehog signaling pathway, an important regulator in embryogenesis, which is normally inactive in adults. However, certain mutations can cause constitutive signaling, leading to proliferation of basal skin cells and causing carcinoma [39]. After a successful phase I trial in a phase II trial on the efficacy and safety of vismodegib in advanced BCC, a response to a dose of 150 mg was evaluated [40]. In patients with metastatic BCC, the response rate was 30%, in patients with locally advanced BCC 43%, and complete response was seen in 21% [40]. Adverse events in more than 30% of patients included muscle spasms, alopecia, taste disturbance, weight loss and fatigue [40]. Serious adverse events were reported in 25% of patients and seven deaths due to adverse events were noted [41]. An additional Phase II trial evaluated patients with Gorlin-Gotz syndrome with the result of significantly decreased number of new BCCs, as well as decrease in the size of pre-existing ones [42]. Since there may be hundreds to thousands of BCCs in a single patient with Gorlin-Gotz syndrome, which are commonly managed by surgery, vismodegib promises significant life quality improvement in this subset of patients [43]. Vismodegib has a nonlinear pharmacokinetic profile with regard to dose and time, which means that plasma concentration, does not rise with increasing dose levels [39]. That is the result of low solubility of a drug at physiological pH and increase in unbound fraction due

<table>
<thead>
<tr>
<th>Treatment modality</th>
<th>Advantages</th>
<th>Disadvantages and possible risks</th>
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<tbody>
<tr>
<td>Surgical excision</td>
<td>pathohistological analysis optimal cosmetic result in most cases</td>
<td>local anesthesia difficult to perform in the case of extensive lesion or certain localisations (i.e., ear, eyelid)</td>
</tr>
<tr>
<td>Mohs micrographic surgery</td>
<td>pathohistological analysis microscopic margin control maximal preservation of normal tissue optimal for high risk anatomical sites</td>
<td>possible to perform only in specialized centers expensive procedure time consuming local anesthesia</td>
</tr>
<tr>
<td>Curettage and cautery</td>
<td>minimally invasive procedure easy to use minimal costs</td>
<td>lack of histological specimen - need for preoperative biopsy less favorable cosmetic result suitable for nodular and superficial BCC of less than 1.0 cm in diameter</td>
</tr>
<tr>
<td>Cryotherapy</td>
<td>minimally invasive procedure easy to administer minimal pain and discomfort minimal costs</td>
<td>lack of histological specimen - need for preoperative biopsy multiple cycles (2-3 treatments) recommended</td>
</tr>
<tr>
<td>Laser treatment</td>
<td>noninvasive procedure good cosmetic result</td>
<td>lack of histological specimen - need for preoperative biopsy requires expensive equipment</td>
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<tr>
<td>Radiotherapy</td>
<td>suitable for patients where surgery is contraindicated (comorbidities, age, difficult location or large size of the tumor)</td>
<td>possible to perform only in specialized centers multiple cycles recommended not advisable in younger patients requires expensive equipment</td>
</tr>
<tr>
<td>Imiquimod</td>
<td>topical treatment easy to use</td>
<td>suitable only for superficial BCCs higher recurrence rates</td>
</tr>
<tr>
<td>Topical 5-Fluorouracil</td>
<td>topical treatment easy to use suitable for patients where surgery is contraindicated</td>
<td>pain, burning, pruritus, inflammation, swelling, hyperpigmentation, scarring</td>
</tr>
<tr>
<td>Photodynamic therapy</td>
<td>noninvasiveness good tolerability suitable for superficial and multiple tumors good cosmetic result</td>
<td>suitable only for superficial BCCs multiple cycles recommended time consuming requires expensive equipment</td>
</tr>
<tr>
<td>Vismodegib</td>
<td>approved for metastatic BCC and locally advanced BCC</td>
<td>many side effects expensive treatment</td>
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Table 1: Advantages and disadvantages of basal cell carcinoma treatment modalities.
to AAG (alpha-1 acid glycoprotein) saturation [44]. Therefore, concurrent administration of agents that increase gastrointestinal pH (antacids, histamine H2-receptor antagonists, proton-pump inhibitors) should be avoided. Vismodegib is available as 150 mg capsule taken orally once daily. The drug has shown to cause toxicity in animal embryos, so its use is strictly forbidden in pregnancy [39]. Moreover, following discontinuation of the treatment, contraception is mandatory for women at least for seven months after taking the last dose of medication [39].

CONCLUSION

Although various treatment modalities are available, surgery is the “gold standard” for the treatment of vast majority of BCC, providing specimen for histological analysis, low recurrence rate and satisfactory cosmetic result. Mohs surgery is the treatment of choice for extensive, recurrent and high risk lesions, while curettage and cautery are effective in treatment of smaller lesions. When used within guidelines, surgical modalities have cure rates greater than 90%. Radiotherapy is a good alternative to surgery for the elderly, especially for lesions located on the head. Cryotherapy is a localized therapy with minimal invasion and cost, but may have a poor cosmetic result. Laser seems to be a promising alternative therapy, but further studies in this field are needed. Superficial treatment modalities suitable in patients with low-risk BCCs include topical imiquimod, 5-fluorouracil and photodynamic therapy (PDT). Although therapy with PDT is followed by excellent cosmetic results, it acts mostly on superficial lesions, the regimens are not standardized and it is not as effective and shows higher recurrence rate than surgery. Vismodegib is a newly licensed therapeutic option for management of advanced BCC, but more studies are needed regarding cure rates, management of the side effects, possible treatment of microscopic disease, risk of recurrence and long term effects. Taking into account that BCCs mostly occur on the head and face, cosmetic outcome is not an insignificant factor when choosing a treatment modality, especially considering that the disease increasingly affects people of a younger age. There is still a need of controlled clinical studies of different treatment modalities, and careful patient selection is required in order to achieve the goal of complete tumor clearance.

REFERENCES


