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REVIEW

Guidelines for the diagnosis and treatment of basal cell carcinoma: a GRADE approach for evidence evaluation and recommendations by the Italian Association of Medical Oncology

P. Queirolo[1], M. Cinquini[2], G. Argenziano[3], F. Bassetto[4], P. Bossi[5], A. Boutros[6], C. Clemente[7], V. de Giorgi[8,9], M. Del Vecchio[10], R. Patuzzo[11], K. Peris[12,13], P. Quaglino[14], A. Reali[15], I. Zalaudek[16] & F. Spagnolo[17,18]*

[1]Division of Melanoma, Sarcomas and Rare Tumors, European Institute of Oncology, Milan; [2]Istituto di Ricerche Farmacologiche Mario Negri IRCCS, Milan; [3]Dermatology Unit, Department of Mental and Physical Health and Preventive Medicine, University of Campania Luigi Vanvitelli, Naples; [4]Clinic of Plastic Surgery, Department of Neuroscience, Padua University Hospital, Padua; [5]Medical Oncology, Department of Medical and Surgical Specialties, Radiological Sciences and Public Health University of Brescia, ASST-Spedali Civili, Brescia; [6]Department of Internal Medicine and Medical Specialties, School of Medicine, University of Genoa, Genoa; [7]UO SMEL-2, Surgical Pathology, Department of Pathology and Laboratory Medicine, IRCCS-Policlinico San Donato, Milan; [8]Dermatology Unit, Azienda USL Toscana Centro, Florence; [9]Section of Dermatology, Department of Health Sciences, University of Florence, Florence; [10]Department of Medical Oncology, Fondazione IRCCS Istituto Nazionale dei Tumori, Milan; [11]Fondazione IRCCS Istituto Nazionale Dei Tumori, Melanoma and Sarcoma Unit, Milan; [12]Dermatology, Department of Translational Medicine and Surgery, Università Cattolica del Sacro Cuore, Rome; [13]Dermatology, Department of Medical and Surgical Sciences, Fondazione Policlinico Universitario A. Gemelli IRCCS, Rome; [14]Department of Medical Sciences, Clinic of Dermatology, University of Turin, Turin; [15]Radiation Oncology Department, Michele e Pietro Ferrero Hospital, Verduno; [16]Dermatology Clinic, Maggiore Hospital, University of Trieste, Trieste; [17]Oncologia Medica 2, IRCCS Ospedale Policlinico San Martino, Genoa; [18]Department of Integrated Surgical and Diagnostic Sciences (DISC), University of Genoa, Genoa, Italy

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Basal cell carcinoma (BCC) is the most common form of cancer, with a high impact on the public health burden and social costs. Despite the overall prognosis for patients with BCC being excellent, if lesions are allowed to progress, or in a small subset of cases harboring an intrinsically aggressive biological behavior, it can result in local spread and significant morbidity, and conventional treatments (surgery and radiotherapy) may be challenging. When a BCC is not amenable to either surgery or radiotherapy with a reasonable curative intent, or when metastatic spread occurs, systemic treatments with Hedgehog inhibitors are available. These guidelines were developed, applying the GRADE approach, on behalf of the Italian Association of Medical Oncologists (AIOM) to assist clinicians in treating patients with BCC. They contain recommendations with regard to the diagnosis, treatment and follow-up, from primitive tumors to those locally advanced or metastatic, addressing the aspects of BCC management considered as priorities by a panel of experts selected by AIOM and other national scientific societies. The use of these guidelines in everyday clinical practice should improve patient care.

Key words: basal cell carcinoma, skin cancer, keratinocyte carcinoma, GRADE, guidelines

INTRODUCTION

Keratinocyte carcinomas, characterized by the malignant proliferation of epidermal keratinocytes, are the most common form of cancer.[1] As in the USA and most European countries, data on the incidence of keratinocyte carcinomas from a unified national registry are not available in Italy. High incidence of keratinocyte carcinomas, heterogeneity of treatments and low mortality are a challenge in obtaining accurate incidence data and consistent registration in cancer registries. Important consequences are that the public health burden and social costs associated with keratinocyte carcinomas are probably underestimated. In the AIRTUM 2019 report, 64 000 new cases of basal cell carcinomas (BCCs) and 19 000 new cases of cutaneous squamous cell carcinoma (CSCC) were estimated for year 2018.[2] In a recent paper from the United States Global Burden of Disease, the incidence and prevalence per 100 000 persons for BCC were 525 and 51.2, respectively, whilst disability adjusted life years (DALY) and mortality rates were 0.2 and zero, respectively.[3]

Overall, the prognosis for patients with BCC is excellent; however, if BCC is allowed to progress, or in a small subset of cases harboring an intrinsically aggressive biological behavior, it can result in local spread and significant morbidity, and treatment with surgery and radiotherapy may be challenging. When a BCC is not amenable to either surgery or radiotherapy with a reasonable curative intent

*Correspondence to: Prof. Francesco Spagnolo, Oncologia Medica 2, IRCCS Ospedale Policlinico San Martino, Largo R. Benzi 10, 16132, Genova, Italy. Tel: +390105558901

E-mail: francesco.spagnolo85@gmail.com (F. Spagnolo).

[i.e. locally advanced BCC (laBCC)], systemic treatments with Hedgehog inhibitors are available. BCC may also spread to distant sites, although metastatic BCC (mBCC) with histologically confirmed metastases is extremely rare, with an estimated incidence of 0.0028%-0.55%.[4-6]

These guidelines were developed, applying the GRADE approach,[7] on behalf of the Italian Association of Medical Oncologists (AIOM) to assist clinicians in treating patients with BCC. They contain recommendations with regard to the diagnosis, treatment and follow-up, from primitive tumors to those locally advanced or metastatic, addressing the aspects of BCC management considered as priorities by a panel of experts selected by AIOM and other national scientific societies. The use of these guidelines in everyday clinical practice should improve patient care.

METHODS

The panel of AIOM guidelines on BCC

The AIOM guidelines on basal cell carcinoma are updated every year by a panel composed of academics and clinicians with expertise in medical oncology, surgery, dermatology, radiotherapy and pathology, and clinical research methodology. The draft of the updated guidelines is then sent to external reviewers before the final publication on the AIOM website (www.aiom.it). The external reviewers are nominated by AIOM and other relevant scientific societies (Italian Melanoma Intergroup; Italian Society Of Medical, Surgical And Aesthetic Dermatology and of Sexually Transmitted Diseases; Italian Association of Radiotherapy and Clinical Oncology; Italian Society of Pathology; Italian Society of Oncologic Surgery; Italian Society of Medical and Interventional Radiology).

Development of clinical question

The clinical question was developed according to the P.I.C.O. acronym requiring the definition of: population (P), intervention (I), comparison (C) and outcomes (O).

Panel members decided to address the following clinical questions:

- Question 1: Should sunscreen creams with solar protection factor $\geq$30 be recommended in subjects who are exposed to solar ultraviolet radiation (UVR) to reduce the incidence of BCC?
- Question 2: Should dermoscopy be recommended in subjects with suspicious skin lesions compared with visual inspection only for the detection of BCC?
- Question 3: Should reflectance confocal microscopy be recommended in subjects with suspicious skin lesions compared with dermoscopy only for the detection of BCC?
- Question 4: Should a surgical excision with $\geq$3 mm clinical margins be recommended in subjects with operable BCC compared with surgical excision with $<$3 mm clinical margins?
- Question 5: Should Mohs surgery be recommended in subjects with recurrent or high-risk BCC compared with standard surgical excision?
- Question 6: Should electrochemotherapy be recommended in subjects with BCC and relative contraindications to conventional treatments (surgery and radiotherapy) compared with standard surgical excision or radiotherapy?
- Question 7: Should standard surgical excision be recommended in subjects with non-recurrent, operable BCC compared with imiquimod?
- Question 8: Should standard surgical excision be recommended in subjects with non-recurrent, operable BCC compared with topical 5-fluorouracil?
- Question 9: Should standard surgical excision be recommended in subjects with non-recurrent, operable BCC compared with photodynamic therapy?
- Question 10: Should standard surgical excision be recommended in subjects with non-recurrent, operable BCC compared with cryotherapy?
- Question 11: Should standard surgical excision be recommended in subjects with non-recurrent, operable BCC compared with laser treatments?
- Question 12: Should standard surgical excision be recommended in subjects with non-recurrent, operable BCC compared with cauterization?
- Question 13: Should standard surgical excision be recommended in subjects with non-recurrent, operable BCC compared with radiotherapy?
- Question 14: Should radiotherapy be recommended after surgical excision of BCC with positive margins compared with re-excision?
- Question 15: Should baseline radiological tumor assessment be recommended in subjects with laBCC and mBCC?
- Question 16: Should radiological tumor assessment be recommended in the follow-up of subjects with laBCC and mBCC?
- Question 17: Should treatment with Hedgehog pathway inhibitors be recommended in subjects with laBCC and mBCC compared with follow-up/best supportive care?

Panel members decided to define, as the population of interest, the Italian population at high risk of developing BCC, or who have received a diagnosis of BCC.

Identification of outcomes

Panel members identified, through a prioritization process, the outcomes of benefit and harm, judging them as 'critical' or 'important' for the decision-making.

Search strategy and selection of evidence

For each question, a systematic literature search was carried out searching PubMed, Embase and Cochrane Library without language or date restriction up to December 2019. The full search strategy is available as Supplementary material, available at https://doi.org/10.1016/j.esmoop.2023.102037. Main articles were cross-referenced to check that all the relevant literature was fully identified. The PRISMA flow-chart for each question is reported as

Supplementary material, available at https://doi.org/10.1016/j.esmoop.2023.102037.

To answer the proposed questions, systematic reviews or randomized controlled trials were searched. If not found, non-randomized studies were retrieved. Narrative reviews, and case reports, were excluded.

Quality of evidence evaluation

According to the GRADE approach, an evaluation of the certainty of evidence for each selected outcome was carried out. The GRADE evaluation encompasses five main domains: study limitations, imprecision, indirectness, inconsistency and publication bias. Based on the study design, the certainty level starts at a prespecified level (high certainty for randomized controlled trials). The detection of limitations in one or more of the five domains can lead to downgrading the certainty of evidence. The final judgment can be one of the following: high, moderate, low and very low. A summary of the certainty of evidence and a quantitative synthesis of the effects for each outcome are reported in a dedicated evidence profile table.

Evidence to decision framework

The evidence to decision (EtD) framework provides a transparent and structured approach to support the decision-making process.[8] It allows summarizing the evidence in relation to the priority of the problem, the substantiality of the desirable and undesirable effects, balance of the effects, certainty of evidence, patients values and preference, use of resources, equity, acceptability and feasibility.

Benefit/harm balance and clinical recommendation

At this point of the decision-making process, the panel voted one of the following options for the balance between benefits and harms of the intervention and the comparison: favorable, uncertain/favorable, uncertain/unfavorable and unfavorable. The panel also voted on the strength of the recommendation according to the following options: strong in favor, conditional in favor, conditional against, strong against the intervention.

The AGREE reporting checklist was followed to guide the reporting of the present recommendation.[9]

GRADE QUESTIONS

Primary prevention

The main risk factor associated with the development of BCC is exposure to UVR. The incidence of BCC is higher in subjects with fair skin, and with history of chronic solar UVR exposure. Numerous epidemiological studies highlighted that the incidence of BCC is lower in subjects with dark skin and in those who are less exposed to solar UVR. In an Australian study, the analysis of the incidence of keratinocyte carcinomas in Australia showed that the rate of solar UVR-induced keratinocyte carcinomas was essentially 100%, and that a fraction of these tumors could be prevented with regular sunscreen use.[10] As some outside workers (e.g. farmers, road workers, lifeguards, …) are chronically exposed to solar UVR due to occupational reasons, BCC may be considered as an occupational disease in this subset of workers.[11] In a recent review and meta-analysis, including one prospective cohort study and 18 case-control studies, 95% of studies reported higher risks among outdoor workers.[12]

The association between nodular BCC and chronic UVR exposure is supported by the prevalent localization on the head and neck region, and the increased incidence with ageing. Superficial BCC is instead more associated with intermittent sun exposure and predominant location on the trunk. In addition to chronic exposure, epidemiological data show that solar UVR exposure at a young age is an important predictive factor for the subsequent development of BCCs.[13] Frequent use of indoor tanning is also a relevant risk factor, and the most important one in young subjects.[14,15] In addition to UVR, a subset of BCCs may be associated with other risk factors such as immunosuppression, ionizing radiation and arsenic exposure.

The prevalent role of UVR in the risk of development of BCC highlights the importance of primary prevention measures. Strategies of primary prevention should rely on both proper photo-protection and sun exposure, and should include different scopes such as increased awareness, avoiding excessive sun exposure and/or protection through clothing, and the correct use of sunscreen creams. Numerous case-control studies tried to analyze the impact of sunscreen creams on the development of skin cancer, but the results are discordant. In a review by Burnett and Wang,[16] the analysis of literature data highlighted that use of sunscreen creams may reduce the incidence of CSCC, without compromising the blood levels of vitamin D. The regular and proper use of sunscreen creams also reduced the incidence of actinic keratoses, which are well known markers of damage from chronic UVR exposure.[17] In the study conducted by Olsen et al.,[10] the fraction of skin cancers that could be prevented by regular use of sunscreen was estimated, and it was as high as 14% for melanoma and 9.3% for CSCC, but no estimates were provided for BCC.

Eleven randomized studies investigating the effects of behavioral counseling to prevent skin cancer were included in a meta-analysis conducted by Lin et al.,[18] showing how counseling could reduce solar and artificial UVR exposure, and increase the use of sunscreen creams. In the same analysis, 35 observational studies focusing on the association of solar UVR exposition and skin cancer were identified, but only in one study did the regular use of sunscreen creams show reduction in the incidence of CSCC, with no significant difference for BCC.

Question 1. Should sunscreen creams with solar protection factor $\geq$30 be recommended in subjects who are exposed to solar UVR to reduce the incidence of BCC?

Recommendation. In subjects who are exposed to solar UVR, sunscreen creams with solar protection factor $\geq$30 may be considered as a first option measure to reduce the incidence of BCC.

Strength of recommendation. Conditional in favor.

Overall quality of evidence. Moderate.

Motivation/comments on the benefit/risk balance. In the Cochrane systematic review by Sánchez et al.,[19] only one randomized study assessing the role of photo-protection for the prevention of keratinocyte carcinomas was identified. In this randomized trial (named the Nambour trial from the Australian region where it was conducted), 1621 participants were randomized to four groups:

- daily applications of sunscreen creams with solar protection factor ≥15 plus beta-carotene supplementation
- daily applications of sunscreen creams with solar protection factor ≥15 plus beta-carotene supplementation placebo
- beta-carotene supplementation only
- beta-carotene supplementation placebo only

The following outcomes were defined by the panel of experts as essential for the assessment of risks and benefits balance: incidence of BCC; incidence of solar or actinic keratosis (as a marker of actinic damage).

The results of the study did not demonstrate any difference in the incidence nor in the number of BCCs between the four groups (total diagnosed BCCs: 1621; risk ratio 1.03, 95% confidence interval [CI] 0.74-1.43).

Despite the randomized trial not demonstrating any significant effects of the intervention for the prevention of BCC, the panel voted for a favorable damage/benefit ratio, supporting their use to prevent BCC in subjects who are exposed to solar UVR (see Notes to recommendation 1). The panel did not identify any probable uncertainty or variability on how the population may evaluate the analyzed outcomes. See Supplementary material (Question 1), available at https://doi.org/10.1016/j.esmoop.2023.102037, for evidence to decision results, quality of evidence and implications for future results.

Notes to recommendation 1. Due to the challenges related to the evaluation of the efficacy of sunscreen creams for the prevention of BCC in randomized trials, other types of studies were taken into consideration to answer the question. Current literature data demonstrate an association between use of sunscreen creams and reduction of CSCC and actinic keratosis incidence, but results on the prevention of BCC are discordant.[10,16,17] The primary endpoint of the Nambour trial was incidence of keratinocyte carcinomas after a follow-up of 4.5 years,[19,20] which was probably too short to detect any impact of sunscreen creams on the incidence of BCC. In an analysis with longer follow-up, in fact, a trend towards an increased time between the diagnosis of the first BCC and the subsequent has emerged in the group using sunscreen creams.[21]

In addition to clinical data, preclinical evidence demonstrates with a high level of certainty that solar UVR exposition is the main risk factor for the development of BCC and CSCC. The exposition modality most frequently associated with keratinocyte carcinomas is chronic, cumulative exposition, and may be associated with some outside occupations or may be recreational. The fact that BCC develops earlier in life compared with CSCC, and that it often arises in the trunk in addition to the chronically exposed anatomical areas, suggests that BCC requires an inferior cumulative dosage of UVR than that necessary to induce a CSCC.

Secondary prevention

BCC most commonly arises on chronically sun-exposed anatomical sites (such as head and neck, dorsum of the hands, forearms), but may also arise on the trunk and other less sun-exposed anatomical regions. BCC may have heterogeneous clinical presentations depending on location, skin type, ulceration and presence of pigmentation.

Differential diagnosis between BCC and other skin lesions is not always easy. Both neoplastic (such as melanoma, B-cell cutaneous lymphoma, CSCC, actinic keratosis, Bowen's disease, keratoacanthoma and adnexal tumors), and non-neoplastic skin lesions (such as seborrheic keratosis, hemangioma, dermal nevus, dermatofibroma, telangiectatic granuloma, fibrous papule, sebaceous hyperplasia, molluscum contagiosum, psoriasis, eczema) must be included in the differential diagnosis of BCC.

Dermoscopy may be used to increase the diagnostic sensibility of skin lesions. In cases of BCC diagnosis, it may help in the differentiation of BCC from melanoma, invasive and *in situ* CSCC, and benign tumors.[22,23] Dermoscopic criteria for BCC are the absence of brown reticular lines (pigment network), branching and linear vessels (arborising and superficial telangiectasias), multiple erosions, ulceration, bluish-gray clods of variable size (ovoid nests and globules and focused dots), radial lines connected to a common base (leaf-like areas), radial lines converging to a central dot or clod (spoke-wheel areas) and clods within a clod (concentric structure).[24]

Question 2. Should dermoscopy be recommended in subjects with suspicious skin lesions compared with visual inspection only for the detection of BCC?

Recommendation. In subjects with suspicious skin lesions, the use of dermoscopy should be recommended as the first option compared with visual inspection only for the detection of BCC.

Strength of recommendation. Strong in favor.

Overall quality of evidence. High.

Motivation/comments on the benefit/risk balance. In the multicenter, two-arm, randomized study conducted by Argenziano et al.[25] and published in 2006, the diagnostic accuracy for skin tumors of dermoscopy *versus* visual inspection only was assessed in a cohort of general practitioners undergoing a 1-day dermoscopy training based on a specific three-point checklist. This study has been conducted in one center in Italy and one in Spain. General practitioners who underwent dermoscopy training were

randomized into two groups: in the control group, the doctors had only the possibility to conduct a visual inspection of their patients, whereas doctors in the experimental group could make use of dermoscopy in addition to visual inspection. The study consisted of four steps: in step 1 (1-day training courses), 88 general practitioners were trained in two 2-h sessions on the clinical and dermoscopic diagnosis, respectively, of keratinocyte carcinomas; in step 2 (general practitioners randomization and patients screening), doctors were randomized to either the control or experimental group; in step 3, (expert evaluation), all patients were evaluated by two blinded dermatologists; in step 4 (surgical excision and histologic exam), all lesions considered as malignant by the general practitioners were surgically removed and subjected to histologic analysis. Among 2522 patients, a statistically significant difference was observed in terms of diagnostic sensitivity (79.2% versus 54.1%) and negative predictive value in favor of dermoscopy compared with visual inspection only. Specificity and positive predictive value were not different (71.8% versus 71.3%). The histologic exam of the excised lesions revealed that in the control group, 23 lesions were not properly diagnosed at visual inspection versus only 6 lesions for the dermoscopy group.

The panel did not identify any probable uncertainty or variability on how the population may evaluate the analyzed outcomes. The balance between outcomes of benefit and outcomes of damage favors the use of dermoscopy in addition to visual inspection compared with visual inspection only. Dermoscopy is easy to implement in centers where it is not commonly used, without a relevant impact on costs or logistic challenges. See Supplementary material (Question 2), available at https://doi.org/10.1016/j.esmoop.2023.102037, for table of evidence, quality of evidence and implications for future results.

Question 3. Should reflectance confocal microscopy be recommended in subjects with suspicious skin lesions compared with dermoscopy only for the detection of BCC?

Recommendation. In subjects with suspicious skin lesions, the use of reflectance confocal microscopy for the detection of BCC may be considered as the first option compared with dermoscopy only.

Strength of recommendation. Conditional in favor.

Overall quality of evidence. Moderate.

Motivation/comments on the benefit/risk balance. The studies by Alarcon et al.[26] and Pellacani et al.,[27] both published in 2014, showed that the use of reflectance confocal microscopy may reduce the number needed to treat (NNT), measured as the rate of equivocal lesions which are excised for each melanoma. Specifically, Alarcon et al.[26] observed a reduction of non-necessary surgical procedures following reflectance confocal microscopy with an NNT reduction from 3.73 with dermoscopy only to 2.87 with dermoscopy followed by reflectance confocal microscopy. Similarly, Pellacani et al.[27] reported a reduction of NNT from 14.6 to 6.8 without and with reflectance confocal microscopy, respectively. Among the 836 lesions included in both studies, however, only 31 (3.7%) were BCCs, limiting the assessment of reflectance confocal microscopy for the diagnostic accuracy of BCC specifically.

In the multicenter study by Nelson et al.,[28] published in 2016, 87 patients with 100 BCCs were assessed. Patients who had a suspected BCC by visual inspection and dermoscopy were included in the study; all lesions were analyzed with dermoscopy and reflectance confocal microscopy evaluation. All collected images were evaluated by eight experts. An improvement of the diagnostic sensitivity was shown with reflectance confocal microscopy compared with dermoscopy only (76.5% versus 67.6%, respectively); the positive predictive value was 98.6% for reflectance confocal microscopy and 97.0% for dermoscopy. The difference, however, was not statistically significant. The main limitations of this study are the retrospective design and the assessment based on images of lesions already suspected for being BCCs.

In the study conducted by Witkowski et al.[29] and published in 2016,the diagnostic accuracy of dermoscopy versus reflectance confocal microscopy was assessed for pink BCC. Two hundred and sixty consecutively registered pink BCCs (with $<$10% pigmentation), clinically equivocal, were analyzed for a period of 2 years. Dermoscopic and reflectance confocal microscopy images of each lesion were assessed by two blinded experts who should define the diagnosis and clinical management. The sensitivity and specificity of dermoscopic diagnosis were 85.1% and 92.4%, respectively, for a positive predictive value of 89.8%. The sensitivity and specificity of reflectance confocal microscopy were 85.1% and 93.8%, respectively, for a positive predictive value of 91.5%. Combined dermoscopy plus reflectance confocal microscopy positive predictive value was 94.6%.

The panel did not identify any probable uncertainty or variability on how the population may evaluate the analyzed outcomes. The balance between outcomes of benefit and outcomes of damage favors the use of reflectance confocal microscopy compared with only dermoscopy. However, reflectance confocal microscopy is not widely accessible across Italy. See Supplementary material (Question 3), available at https://doi.org/10.1016/j.esmoop.2023.102037, for table of evidence, quality of evidence and implications for future results.

Treatment of primary BCC

Treatment of primary BCC mostly relies on surgical excision with histologic examination.[30] The excisional biopsy is preferably carried out with a 3-4 mm margin of healthy surrounding tissue and extended to the subcutaneous tissue; in cases of very large lesions or anatomic regions at high reconstructive complexity (such as face, hands), incisional or punch biopsies are frequently used to confirm the diagnosis of BCC with a histologic exam before radical excision.[30]

Surgical treatment of primary BCC achieves optimal results in terms of rate of cure and rate of relapse.[30] In selected cases, however, other treatment modalities may be used based on patient preferences and clinical conditions (which can be a contraindication to surgery) and/or on tumor characteristics, such as anatomical location, dimension, number of lesions. The most commonly used non-surgical treatments for primary BCC include curettage and electrodessication, cryotherapy, CO_2 laser ablation, intralesional or topical agents, photodynamic therapy. Punch or incisional biopsies allow the histologic examination of the lesion before treatment to avoid using these non-surgical therapies improperly.

A recent Cochrane meta-analysis confirmed that overall non-surgical treatments are less effective than surgery in low-risk BCC, however recurrence rates are acceptable and cosmetic outcomes are probably superior. Even if the grade of evidence is low to moderate, imiquimod shows the best evidence to support its activity.[31]

Curettage and electrodessication, despite the simple and fast application, do not allow for a proper histologic evaluation of the lesion, and no strong literature data support the therapeutic success of this approach in terms of rate of relapse.[32] In particular, the main limitations of curettage and electrodessication are: scalp lesions, due to the possible hair follicles involvement; lesions involving the hypodermis; high-risk BCC.[32]

Cryotherapy uses the cytotoxicity of liquid nitrogen to freeze and destroy cutaneous lesions, whereas CO_2 laser ablation destroys tumor cells through a rapid intracellular temperature increase. Both techniques achieved similar results in terms of rate of relapse and aesthetic results, and have the same limitations as curettage and electrodessication.[33] In a three-arm study, 240 patients with BCC were randomized to receive either surgery or cryotherapy or pulse CO_2 laser ablation. Cryotherapy and pulse CO_2 laser ablation achieved similar results in terms of 3-month complete remissions and aesthetic outcomes, but were both inferior compared with surgery.[33]

The most commonly used topical treatments include 5-fluorouracil cream, imiquimod and photodynamic therapy[34]:

- Topical 5-fluorouracil is most frequently used as a 5% cream for the treatment of low-risk superficial BCC only, as it has shown low cure rates for nodular or high-risk BCC. Despite patients having to avoid solar UVR exposition during treatment (3-4 weeks), the main advantage of this treatment modality is the good aesthetic results;[34]
- Imiquimod is commonly used as a 5% formulation cream for the treatment of superficial and small nodular BCC in low-risk anatomical areas, where a relapse would not be associated with a relevant local morbidity, in patients with contraindication to surgical excision or with low life expectancy. This treatment modality may be associated with erythema and with some very rare systemic adverse events such as fatigue, exfoliative dermatitis and flu-like symptoms. Imiquimod is generally applied once daily, five to seven times a week for 6 weeks;[35]
- Photodynamic therapy is based on the application of a photosensitizer to the tumor lesion followed by illumination of the lesion with visible light, resulting in subsequent selective tumor cell death. The therapeutic protocol usually consists of two sessions 1 week apart, which may be repeated in cases of incomplete clinical response. Superficial lesions are the most responsive to this treatment modality, which usually results in excellent or good aesthetic results.[36]

The effectiveness of photodynamic therapy compared with imiquimod or fluorouracil in patients with histologically confirmed superficial BCC was assessed in a single-blind, non-inferiority, randomized multicenter trial. Patients were randomly assigned to receive treatment with methyl aminolevulinate photodynamic therapy (two sessions with an interval of 1 week), imiquimod cream (once daily, five times a week for 6 weeks), or fluorouracil cream (twice daily for 4 weeks). A total of 601 patients were randomized to receive photodynamic therapy, imiquimod, or fluorouracil. At 12 months after treatment, 52 of 196 patients treated with photodynamic therapy, 31 of 189 treated with imiquimod, and 39 of 198 treated with fluorouracil had tumor residue or recurrence. The proportion of tumor-free patients at both 3- and 12-month follow-up was 72.8%, 83.4% and 80.1%, respectively. In summary, topical fluorouracil was non-inferior and imiquimod was superior to photodynamic therapy.[34] This finding was confirmed at a 3-year follow-up analysis.[37]

In selected cases of BCC at high risk of relapse, and/or arising in anatomical areas requiring a minimally invasive approach, non-conventional surgical treatments such as Mohs micrographic surgery and complete circumferential peripheral and deep margin assessment (CCPDMA) are available in specialized centers.[38-40] In terms of cure and relapse rates, Mohs micrographic surgery achieves better results than CCPDMA.[38-40] In a prospective, multicenter case series which included all patients in Australia treated with Mohs micrographic surgery for BCC, who were monitored by the Skin and Cancer Foundation between 1993 and 2002, cure rates at 5 years were 98%-99% for primary BCCs and 95% for recurrent lesions.[41]

Electrochemotherapy (ECT) is a local treatment modality for cutaneous and subcutaneous tumors, where electric pulses are used to cause increased permeability of cell membranes in the tumor mass, enabling dramatically enhanced effectiveness of bleomycin and other hydrophilic chemotherapy drugs.[42,43] In a European prospective study including patients with skin tumors arising in the head and neck area, ECT was used for the treatment of 105 patients with recurrent or locally advanced tumors. Response rate was higher for BCC (97%) compared with other tumor types (74%).[42] In a retrospective, single-center analysis, 84 patients with BCC not amenable to conventional treatments received ECT, with a complete response rate of 50%.[43] In a recent report from the INSPECT group on $>$2000 tumor lesions, the response rate in 282 cases of BCC was 96%, with 85% complete response rate.[44] In a randomized non-

inferiority study comparing ECT with the gold standard surgery, the two treatments showed statistical equivalence in terms of recurrence (one in the surgery group and five in the ECT group at 5-year follow-up).[44]

Question 4. Should a surgical excision with ≥3 mm clinical margins be recommended in subjects with operable BCC compared with surgical excision with <3 mm clinical margins?

Recommendation. In subjects with operable BCC, a surgical excision with ≥3 mm clinical margins should be considered as the first option compared with surgical excision with <3 mm clinical margins.

Strength of recommendation. Strong in favor.

Overall quality of evidence. Moderate.

Motivation/comments on the benefit/risk balance. In the meta-analysis published in 2010 by Gulleth et al.,[45] 37 studies assessing the surgical margins of BCC were included, for a total of 16 066 treatment-naive lesions in 10 261 patients. The diameters of BCC included in the meta-analysis were 11.7 mm ± 5.9 mm (from 3 to 30 mm) and the excisional margins were on average 3.9 ± 1.4 mm (from 1 to 10 mm). We focused on the comparison between a ≥3 mm clear margin or a narrower margin, and to respond to this question we defined recurrence rate and functional-aesthetic results as essential outcomes, and quality of the scars, pathological accuracy, pathological scarring and wound breakdown as important outcomes. Gulleth's meta-analysis showed a relative risk of 1.60 on comparison between 3 mm excisional biopsy with 4 mm excisional biopsy in BCC, namely 15 more recurrences every 1000 excisions (95% CI 1-37 more recurrences). The relative risk was 2.40 when 2 mm was compared with 4 mm, namely 55 more recurrences every 1000 excisions (95% CI 27-97 more recurrences). No data were available regarding the outcomes of damage such as scarring and cosmetic results.

The panel did not identify any probable uncertainty or variability on how the population may evaluate the analyzed outcomes. The balance between outcomes of benefit and outcomes of damage favors the surgical excision of operable BCCs with ≥3 mm clinical margins compared with <3 mm clinical margins. The intervention is equally accessible over all the country. See Supplementary material (Question 4), available at https://doi.org/10.1016/j.esmoop.2023.102037, for evidence to decision results, quality of evidence and implications for future results.

Question 5. Should Mohs surgery be recommended in subjects with recurrent or high-risk BCC compared with standard surgical excision?

Recommendation. In subjects with recurrent or high-risk BCC, Mohs surgery may be considered as the first option compared with standard surgical excision.

Strength of recommendation. Conditional in favor.

Overall quality of evidence. Very low.

Motivation/comments on the benefit/risk balance. One randomized trial comparing Mohs with standard surgery was identified.[46-48] The results of the study were reported for the first time in 2004 by Smeets et al.,[48] then by Mosterd et al.[47] in 2008 with longer follow-up and, finally, by van Loo et al.[46] in 2014 with a 10-year follow-up time. The study analyzed the outcomes of 408 primary BCCs (204 treated with conventional surgery and 204 with Mohs micrographic surgery; among these, 68 patients with 78 primary BCCs were not randomized) and 204 recurrent BCCs (102 treated with conventional surgery and 102 with Mohs micrographic surgery; among these, 42 patients with 42 primary BCCs were not randomized). Patients included in this study had at least one treatment-naive ≥1 cm BCC located in the H area (i.e. periorbital, eyelids, periauricular, temple, ears, central face, lips, and nose), or a BCC with a high-risk histotype (morpheaform, micronodular, trabecular, infiltrative or basosquamous); in the recurrent BCC group, patients with at least one recurrent BCC of the face were included, both if it was a first or second recurrence.[47] As for primary tumors, 5-year follow-up was completed by 251 patients (129 BCCs treated with Mohs micrographic surgery and 141 with conventional surgery), whereas in the recurrent BCC group, 137 patients (75 BCCs treated with MMS and 59 with conventional surgery) completed 5-year follow-up.[47] In the report published in 2014 by van Loo et al.,[46] 10-year follow-up data were available for only 140 lesions (accounting for 35.3% of all primary tumors) in 129 patients.

The panel identified relapse rate and rate of complete excisions confirmed at pathologic examination as essential outcomes of benefit, and number of re-interventions as an important outcome of benefit. The essential outcome of damage was duration of surgical procedures, whereas aesthetic and functional results were defined as important outcomes of damage.

In the analysis reported by van Loo et al.,[46] after a mean follow-up of 10 years, a relative risk (RR) = 0.27 (95% CI 0.08-0.94) in favor of Mohs compared with conventional surgery was observed, namely eight fewer relapses every 100 procedures (95% CI 10-1 fewer relapses). As for rate of complete excisions confirmed at pathologic examination, the analysis reported by Smeets et al.[48] showed that RR = 1.12 was achieved with Mohs surgery (95% CI 0.95-1.32), equivalent to eight more complete excisions with Mohs compared with conventional surgery (95% CI from 3 fewer to 22 more complete excisions). The surgical complications were reported in the analysis published by Mosterd et al.[47] in 2008 with a mean follow-up of 5 years. The RR was 0.43 (95% CI 0.20-0.94), namely 11 fewer surgical complications with Mohs surgery every 100 procedures (95% CI 15-1 fewer procedures). The number of re-interventions and duration of procedures were not evaluated in any analysis.

Considering the lower risk of surgical complications with Mohs surgery, and the better results in terms of outcomes of benefits, the balance between risks and benefits favors Mohs compared with conventional surgery. The panel did not identify any probable uncertainty or variability on how the population may evaluate the analyzed outcomes. Mohs surgery must be carried out by a highly specialized and trained multidisciplinary team, however, and it is not easily implementable in many centers across the country. Thus, the recommendation in favor of Mohs surgery may cause inequity and low accessibility to such treatment. See Supplementary material (Question 5), available at https://doi.org/10.1016/j.esmoop.2023.102037, for evidence to decision results, quality of evidence and implications for future results.

Question 6. Should ECT be recommended in subjects with BCC and relative contraindications to conventional treatments (surgery and radiotherapy) compared with standard surgical excision or radiotherapy?

Recommendation. In subjects with BCC and relative contraindications to conventional treatments (surgery and radiotherapy), ECT should not be considered as the first option compared with standard surgical excision or radiotherapy.

Strength of recommendation. Conditional against.

Overall quality of evidence. Very low.

Motivation/comments on the benefit/risk balance. The outcomes of benefit defined as essential by the panel were rate of relapse, rate of complete responses, overall survival, relapse-free survival and overall subjective satisfaction. Scarring, pain, rate of infection, rate of any-grade adverse events, rate of grade 3-5 adverse events and duration of adverse events were considered as essential outcomes of damage.

Only one randomized study, published by Clover et al.[44] in 2020, addressed this question. One hundred patients with primary BCCs were randomized to either ECT (52 patients) or surgery (48 patients). Some 45 and 42 patients, respectively, received the allocated treatment. Patients were followed up to 6 months for complete response evaluation, and up to 5 year for the duration of response. Less complete responses were achieved with ECT compared with surgery (RR: 0.93, 95% CI 0.82-1.06), and a higher relapse rate (14% versus 3%, for an RR: 4.86; 95% CI 0.60-39.63). The risk of superficial ulceration, surgical infections and post-operative pain were higher for ECT compared with surgical excision. No results in terms of overall survival, relapse-free survival and overall subjective satisfaction were reported. In addition to that, due to the small sample size and the low number of events, results were not statistically significant. Nevertheless, the panel judged the damage/risk balance as probably in favor of the control treatment (i.e. conventional surgery).

The panel did not identify any probable uncertainty or variability on how the population may evaluate the analyzed outcomes. The intervention should be easy to implement in centers in which it is not available yet without great costs, and should be acceptable by all stakeholders;[49] however, to date, such a treatment modality is not equally distributed across Italy. See Supplementary material (Question 6), available at https://doi.org/10.1016/j.esmoop.2023.102037, for evidence to decision results, quality of evidence and implications for future results.

Considerations on subgroups of patients. ECT may be considered as an option compared with conventional surgery and radiotherapy in selected cases of BCC, especially those located around the eye and on the nose,[50] and when multiple lesions must be treated.

Question 7. Should standard surgical excision be recommended in subjects with non-recurrent, operable BCC compared with imiquimod?

Recommendation. In subjects with non-recurrent, operable BCC, surgical excision should be recommended as the first option compared with imiquimod.

Strength of recommendation. Conditional in favor.

Overall quality of evidence. Very low.

Motivation/comments on the benefit/risk balance. The SINS (Surgery versus Imiquimod for Nodular and Superficial basal cell carcinomas) study was a non-inferiority, randomized trial with parallel groups the results of which were reported across three publications. In the first report, published in 2010 by Ozolins et al.[51] the study design and methods were described; the second publication (Bath-Hextall et al.,[52] 2014) reported the results with a 3-year follow-up; finally, in the third paper (Williams et al.,[53] 2017), the results with a 5-year follow-up were reported.

A total of 501 patients were enrolled in the study, and 401 were included in the 3-year modified 'intention-to-treat-group'. Patients were included if they had at least one superficial or nodular BCC (morpheaform histotype was excluded), <2 cm wide, which had not received a previous treatment and was not arising in a high-risk anatomical area (nose, ear, eye, eye lids, temple). Patients were randomized to receive either topical imiquimod 5% cream or surgery. Imiquimod was applied for 6 weeks in cases of superficial BCC and 12 weeks for nodular BCC. Surgical excision was carried out with a 4 mm clinical margin.

The outcomes of benefit defined as essential by the panel were response rate, relapse rate, time to recurrence and aesthetic results; acute and chronic sequelae and overall toxicities were considered as essential outcomes of damage.

At a minimum follow-up of 5 years, response rate was 98% in patients receiving surgery and 83% in those treated with imiquimod (RR: 1.18, equal to 15 more responses every 100 patients, 95% CI 9-22 more responses). As for relapse rate, an RR of 0.21 (95% CI 0.05-0.94) in favor of surgery (4 fewer relapses every 100 patients, 95% CI 0-5 fewer relapses). Non-optimal cosmetic results were

observed in 16.4% of patients in the surgery group compared with 34.7% for imiquimod (RR: 0.47; 95% CI 0.31-0.70), acute sequelae such as discomfort in, respectively, 7% and 9.6% (RR: 0.72; 95% CI 0.39-1.33) and bleeding in 3.5% and 8.4% (RR: 0.41; 95% CI 0.19-0.92). On the contrary, pain located at the lesion site was more frequent in patients treated with surgery than those receiving imiquimod (7.4% versus 4.8%; RR: 1.54; 95% CI 0.75-3.15), as well as swelling (8.3% versus 4%; RR: 2.07; 95% CI 0.98-4.35).

Overall, the balance between risks and benefits was in favor of surgery. The panel did not identify any probable uncertainty or variability on how the population may evaluate the analyzed outcomes. The intervention is easily accessible across the country and should be acceptable by all stakeholders. See Supplementary material (Question 7), available at https://doi.org/10.1016/j.esmoop.2023.102037, for evidence to decision results, quality of evidence, and implications for future results.

Considerations on subgroups of patients. The results of the SINS study showed the superiority of surgery compared with imiquimod, but highlighted that imiquimod may also obtain long-term responses in a high rate of patients. For this reason, imiquimod could be considered as an option in selected patients with low-risk, superficial BCC when multiples lesions must be treated, and/or in presence of comorbidities increasing the complexity and risks of surgical intervention.

Question 8. Should standard surgical excision be recommended in subjects with non-recurrent, operable BCC compared with topical 5-fluorouracil?

Recommendation. In subjects with non-recurrent, operable BCC, surgical excision should be recommended as the first option compared with topical 5-fluorouracil.

Strength of recommendation. Conditional in favor.

Overall quality of evidence. Expert opinion.

Motivation/comments on the benefit/risk balance. No studies comparing surgery with topical 5-fluorouracil were identified through our systematic literature search. In the absence of data documenting the activity of topical 5-fluorouracil for the treatment of BCC, such a treatment modality is not recommended in subjects with non-recurrent, operable BCC. See Supplementary material (Question 8), available at https://doi.org/10.1016/j.esmoop.2023.102037, for quality of evidence and implications for future results.

Question 9. Should standard surgical excision be recommended in subjects with non-recurrent, operable BCC compared with photodynamic therapy?

Recommendation. In subjects with non-recurrent, operable BCC, surgical excision should be recommended as the first option compared with photodynamic therapy.

Strength of recommendation. Strong in favor.

Overall quality of evidence. Low.

Motivation/comments on the benefit/risk balance. To respond to this question, the panel identified through a systematic literature search two meta-analyses published by Wang et al.[54] in 2015 including a total of 1583 patients and by Zou et al.[55] in 2016 including 596 patients. The different population size reflected the different inclusion criteria of the two meta-analyses. Wang's meta-analysis included randomized trials assessing photodynamic therapy compared with other treatment modalities (mostly surgery, but also other therapies such as imiquimod);[54] Zou's analysis included only randomized trials comparing photodynamic therapy with surgery in patients with histologically confirmed nodular BCC.[55]

The outcomes of benefit defined as essential by the panel were response rate, relapse rate, time to recurrence, aesthetic results; acute and chronic sequelae, and overall toxicities were considered as essential outcomes of damage.

In the analysis reported by Wang et al.,[54] photodynamic therapy was associated with a lower rate of complete responses compared with surgery (RR: 0.93; 95% CI 0.89-0.98), with a higher 1-year relapse rate (RR: 12.42; 95% CI 2.34-66.02) and 5-year relapse rate (RR: 6.79; 95% CI 2.43-18.96).

The meta-analysis reported by Zou et al.[55] focused on the efficacy of photodynamic therapy versus surgery in patients with nodular BCC. Five randomized trials were included in this analysis for a total of 596 patients with histologically confirmed nodular BCC. The results did not demonstrate a significant difference between the two treatments, but photodynamic therapy showed an increased cumulative risk of relapse. As for the overall rate of relapse, both meta-analyses reported results favoring surgery, with an RR: 0.16 (95% CI 0.06-0.45) in Wang's report,[54] and an RR: 0.12 (95% CI 0.04-0.33) in Zou's analysis.[55]

Overall, the balance between risks and benefits was in favor of surgery. The panel did not identify any probable uncertainty or variability on how the population may evaluate the analyzed outcomes. The intervention is easily accessible across the country, and should be acceptable by all stakeholders. See Supplementary material (Question 9), available at https://doi.org/10.1016/j.esmoop.2023.102037, for evidence to decision results, quality of evidence and implications for future results.

Considerations on subgroups of patients. In Wang's report, the subgroup analysis showed that surgery benefit was not confirmed considering nodular BCC only (RR: 0.93; 95% CI 0.85-1.01); in addition to that, no significant differences were found when only BCCs arising in the face were analyzed (RR: 0.99; 95% CI 0.89-1.10). Finally, the clinical activity of photodynamic therapy strictly depended on the type of photosensitizing agent.[54] In the comparisons

between photodynamic therapy and imiquimod, the efficacy of these two treatments was similar. The results of the meta-analyses showed the superiority of surgery compared with photodynamic therapy, but highlighted that photodynamic therapy may also obtain long-term responses in a subgroup of patients. For this reason, photodynamic therapy could be considered as an option in selected patients with low-risk BCC, especially when multiples lesions of the face must be treated, and/or in presence of comorbidities increasing the complexity and risks of surgical intervention.

Question 10. Should standard surgical excision be recommended in subjects with non-recurrent, operable BCC compared with cryotherapy?

Recommendation. In subjects with non-recurrent, operable BCC, surgical excision should be recommended as the first option compared with cryotherapy.

Strength of recommendation. Strong in favor.

Overall quality of evidence. Low.

Motivation/comments on the benefit/risk balance. Only one randomized study answering this question was found through our systematic literature search. In this study, published by Thissen et al.[56] in 2000, 96 patients were enrolled if they had a <2 cm wide superficial or nodular BCC, located in the head and neck area. Patients were randomized to receive either conventional surgical excision or cryotherapy.

The outcomes of benefit defined as essential by the panel were response rate, relapse rate, time to recurrence and aesthetic results; acute and chronic sequelae, and overall toxicities were considered as essential outcomes of damage.

No outcomes of damage as defined by the panel were reported in the paper. The authors reported aesthetic results and 1-year relapse rate.

One-year relapse rate was in favor of surgery, with three patients relapsing in the cryotherapy group versus no patients among those undergoing surgical excision (RR: 0.170; 95% CI 0.009-3.230, $\leq$5 relapses every 100 treated patients; 95% CI from 6 fewer relapses to 14 more). All patients receiving surgery had histologic examination, whereas this information was lacking in those who received cryotherapy.

Overall, the balance between risks and benefits was in favor of surgery. The panel did not identify any probable uncertainty or variability on how the population may evaluate the analyzed outcomes. The intervention is easily accessible across the country, and should be acceptable by all stakeholders. See Supplementary material (Question 10), available at https://doi.org/10.1016/j.esmoop.2023.102037, for evidence to decision results, quality of evidence and implications for future results.

Question 11. Should standard surgical excision be recommended in subjects with non-recurrent, operable BCC compared with laser treatments?

Recommendation. In subjects with non-recurrent, operable BCC, surgical excision should be recommended as the first option compared with laser treatments.

Strength of recommendation. Conditional in favor.

Overall quality of evidence. Expert opinion.

Motivation/comments on the benefit/risk balance. No studies comparing surgery with laser treatments were identified through our systematic literature search. In the absence of data documenting the activity of laser treatments for BCC, such a treatment modality is not recommended in subjects with non-recurrent, operable BCC. See Supplementary material (Question 11), available at https://doi.org/10.1016/j.esmoop.2023.102037, for quality of evidence and implications for future results.

Question 12. Should standard surgical excision be recommended in subjects with non-recurrent, operable BCC compared with cauterization?

Recommendation. In subjects with non-recurrent, operable BCC, surgical excision should be recommended as the first option compared with cauterization.

Strength of recommendation. Conditional in favor.

Overall quality of evidence. Expert opinion.

Motivation/comments on the benefit/risk balance. No studies comparing surgery with cauterization were identified through our systematic literature search. In the absence of data documenting the activity of cauterization for the treatment of BCC, such a treatment modality is not recommended in subjects with non-recurrent, operable BCC. See Supplementary material (Question 12), available at https://doi.org/10.1016/j.esmoop.2023.102037, for quality of evidence and implications for future results.

The role of radiotherapy

Exclusive radiotherapy is commonly used for the treatment of inoperable BCC; in cases of lesions developing in anatomical locations where surgery could cause unacceptable aesthetic results or negatively impact on patients' quality of life;[57] in cases of frail patients with limited life expectancy, or patients with multiple comorbidities which limit the range of treatment modalities.[58,59] Radiotherapy is generally contraindicated in patients with genodermatosis such as xeroderma pigmentosum, and some soft tissues diseases such as scleroderma and lupus.[60] Three large retrospective studies assessed the efficacy of exclusive radiotherapy as first-line treatment of BCC arising in the head and neck area. Overall, 3609 patients received radiotherapy within these studies. Regardless of the radiotherapy technique and fractionation schedules, the cure rates at 5 years were 96%,[61] 95.8%[62] and 94.8%.[63]

Adjuvant radiotherapy after surgical excision of primary BCC is not commonly used due to the very low overall risk

of relapse. The role of adjuvant radiotherapy has been investigated, however, in cases of BCC with large subcutaneous extension, bone involvement, postsurgical residues after multiple treatments, lymph node involvement and perineural invasion.[64]

BCCs may be irradiated through different modalities, using low-energy photons, 4-12 MeV electrons, interstitial brachytherapy[65,66] or high conformation techniques (three-dimensional conformal radiotherapy [3D-CRT] or intensity-modulated radiotherapy [IMRT]). The energy to be used is defined based on the thickness of the lesion assessed through ultrasound or CT scan, while volume may be evaluated clinically and should include a 1 cm margin for <2 cm wide BCCs, and a 1.5 cm margin for wider lesions.[59] Margins are tailored when BCCs arise in specific anatomical regions such as nasolabial folds and preauricular area. Numerous fractionation schedules are described in literature, with hypofractionated schedules with 35 Gy in 5-7 fractions three times a week[62] or 25-30 Gy in 5-6 weekly fractions,[58,59] moderate hypofractionation with 45 Gy in 9 fractions along 3 weeks[63] or conventional fractionation.[67]

Question 13. Should standard surgical excision be recommended in subjects with non-recurrent, operable BCC compared with radiotherapy?

Recommendation. In subjects with non-recurrent, operable BCC, surgical excision should be recommended as the first option compared with radiotherapy.

Strength of recommendation. Strong in favor.

Overall quality of evidence. Moderate.

Motivation/comments on the benefit/risk balance. One randomized study comparing surgery and radiotherapy for the treatment of primary BCC was identified through our systematic literature search.[68] In this one study, published by Avril et al.[68] in 1997, 347 patients with BCCs arising in the face and <4 cm wide were randomized to either surgery (174 patients) or radiotherapy (173 patients). After a mean follow-up of 41 months, the relapse rate was 0.7% (95% CI 0.1% to 3.9%) with surgery and 7.5% (95% CI 4.2% to 13.1%) with radiotherapy. The hazard ratio was 0.18 (95% CI 0.06-0.56) and the RR 0.12 (95% CI 0.02-0.98). In the group of patients treated with radiotherapy, 55% received brachytherapy, 33% contact therapy and 12% a conventional technique. Good cosmetic results were achieved in 87% of patients in the surgery group versus 69% with radiotherapy. Surgical complications such as scar retraction were more frequent in the first year after treatment, and their frequency tended to be progressively lower afterwards. Telangiectasias and dyschromias were the most frequently reported complications in the radiotherapy group; their frequency was stable on follow-up.[68]

The study demonstrated a significant advantage of surgical excision over radiotherapy in terms of local disease control for <4 cm wide BCCs arising in the head and neck area. It must be noted, however, that some of the radiotherapy treatment modalities used in the study are currently overcome. The panel did not identify any probable uncertainty or variability on how the population may evaluate the analyzed outcomes. The intervention is equally accessible across the country. See Supplementary material (Question 13), available at https://doi.org/10.1016/j.esmoop.2023.102037, for evidence to decision results, quality of evidence and implications for future results.

Question 14. Should radiotherapy be recommended after surgical excision of BCC with positive margins compared with re-excision?

Recommendation. After surgical excision of BCC with positive margins, radiotherapy should not be recommended as the first option compared with re-excision.

Strength of recommendation. Conditional against.

Overall quality of evidence. Very low.

Motivation/comments on the benefit/risk balance. The assessments were based on the following outcomes of benefit and damage: rate of relapse, relapse-free survival, quality of life, rate of acute and chronic sequelae. Due to the paucity of literature, two case series were analyzed to answer this this question.

In the series published in 2004 by Wilson et al.,[69] all consecutive patients with BCC treated between 1990 and 1999 at the Unit of Oral and Maxillofacial Surgery of St. Richard's and Worthing & Southlands Hospital and a minimum follow-up of 1 year were included in the analysis. Among these patients, 235 BCCs were incompletely excised. The authors compared the outcomes of radiotherapy, surgery or observation only for these lesions: 84 BCCs were treated with radiotherapy, 11 were re-excised, and 140 were followed up based on age, comorbidities, patients' preference, entity of margins involvement, anatomical area, histological subtype and surgeon's preference. In both patients treated with surgery or radiotherapy, no relapses were observed, whereas among 140 BCCs in the observation only group, 29 relapsed after 5-76 months (mean 25 months).[69]

In the study published in 1991 by Liu et al.,[70] the outcomes of radiotherapy and observation only were compared in patients with incompletely excised BCCs treated between 1970 and 1985 at Princess Margaret Hospital in Toronto. Patients with evidence of macroscopic relapse were excluded from the analysis, as well as patients with no follow-up. Overall, 187 patients were included in the study: among these patients, 119 with incompletely excised BCC were treated with radiotherapy, 1 with surgery and 67 were followed up without any further treatment. At 10 years, 9.2% of patients receiving treatment had a relapse, compared with 59.7% in the observation group (RR: 0.15; 95% CI 0.08-0.28), equal to 51 fewer relapses every 100 incomplete excisions (95% CI from 55 to 43 fewer relapses).[70]

The panel did not identify any probable uncertainty or variability on how the population may evaluate the

analyzed outcomes. The intervention is equally available across the country, and should be acceptable by all stakeholders. See Supplementary material (Question 14), available at https://doi.org/10.1016/j.esmoop.2023.102037, for evidence to decision results, quality of evidence and implications for future results.

Management of locally advanced and mBCC

The choice of a medical approach mainly relies on a shared definition of laBCC. Essentially, the definition of laBCC overlaps with the field of application of systemic treatments. As a matter of fact, this term was not used before the introduction of effective targeted treatments for BCC. Locally advanced BCC includes a heterogeneous range of lesions not amenable for treatment with surgery and radiotherapy with curative intents. Thus, the definition of laBCC may include a range of subjectivities and interpretations deriving from the experience, oncologic competence and personal approach of the specialists treating such disease.[71] This assessment is often based on the discussion within a multidisciplinary group, including surgeons (dermatologist, plastic surgeon, head and neck surgeon, …), radiotherapist and medical oncologist.

Surgery may be contraindicated based on several factors:

- low chances of achieving a curative resection due to the extension and/or anatomical location of the tumor. The rate of BCCs >5 cm wide are rare,[72] and are usually associated with psychiatric disorders, immunosuppression or negligence
- complexity in terms of reconstructive phase. Despite being in a very limited proportion of cases, thanks to the advances of plastic and reconstructive surgery, the clinical conditions of patients and/or the local extension and type of tissue invasion of the tumor may be contraindications to the reconstructive phase
- substantial deformity or morbidity caused by surgery. In cases of tumors arising in some anatomical areas, such as eye, ear, nose and extremities, the radical surgical excision may be contraindicated due to anticipated unacceptable cosmetic and functional results
- recurrent tumors after two or more surgical resections, where another surgical procedure may be associated with a high risk of relapse
- any clinical condition or comorbidities which may be contraindications to surgical options

Radiotherapy may also be contraindicated when it was already used in the same anatomical area, when the extension of the area to be treated is too wide and in presence of clinical contraindications such as risk of developing second tumors, DNA repair pathogenic conditions, genodermatosis.

Systemic treatments are indicated in cases of laBCC and mBCC. Before the introduction of targeted therapies, chemotherapy was the only treatment available in this setting.[73,74] Numerous drugs and combination regimens have been used, despite their outcomes being published only in case reports and small case series, with no proper investigations in prospective clinical trials. Cisplatin was the most commonly used chemotherapy; combination regimens included etoposide, 5-fluorouracil, bleomycin, cyclophosphamide and Adriamycin.[75] A response rate as high as 75% was reported in literature for both locally advanced and metastatic cases; however, important limitations are the high risk of selection bias and small sizes of the case series. Systemic retinoids have also been used for the treatment of multiple BCCs[76]: in a study including 12 patients with Gorlin syndrome, isotretinoin p.o. was administrated with a response rate of 16%; however, treatment was not well tolerated, with 41% of patients interrupting treatment due to drug toxicity. As for epidermal growth factor receptor (EGFR) inhibitors, only very limited data are available from case reports, insufficient to state any indications for the use of this class of drugs for advanced BCC.[77] Finally, treatments targeting the Hedgehog pathway achieved encouraging results in phase I trials and received the approval by the regulatory agencies for the treatment of advanced BCC.[78-81] Specifically, vismodegib received approval from the Food and Drug Administration, European Medicines Agency (EMA) and Agenzia Italiana del Farmaco (AIFA) for the treatment of both laBCC and mBCC, after achieving a response rate of 67% and 38%, respectively, with a median time to best response of only 2.6-2.8 months. Most adverse events were low grade (grade 1-2 according to the Common Terminology Criteria for Adverse Events grading system). The adverse events most frequently reported were muscle cramps, alopecia, dysgeusia, loss of weight, fatigue, loss of appetite, diarrhea and nausea. Time to occurrence of adverse events was about to 2 months for the majority of adverse events, and longer for alopecia and gastrointestinal disorders (∼4 months), and loss of weight (∼6 months). However, despite adverse events being mostly low grade, the long duration of toxicity is a challenge for an optimal compliance to treatment, and a relevant proportion of patients interrupted therapy due to adverse events in clinical trials. Mean duration of treatment with vismodegib was 13 months.[82]

More recently, sonidegib, another inhibitor of the Hedgehog pathway, was approved by the regulatory agencies for the treatment of laBCC.[83-85] The BOLT study enrolled 230 patients, 79 and 151 in the 200 mg and 800 mg groups, respectively. The overall response rates by central review were 56% for laBCC and 8% for mBCC in the 200 mg group and 46% for laBCC and 17% for mBCC in the 800 mg group. The 200 mg dosage is the currently approved one. The pattern of toxicities was similar to that observed with vismodegib, and no new safety concerns emerged at the 42 month analysis.[85]

The clinical differences between vismodegib and sonidegib in patients with laBCC are unclear, as no head-to-head randomized trials were conducted. Moreover, there were important differences in the designs of their pivotal studies, BOLT for sonidegib and ERIVANCE for vismodegib, most importantly related to the assessment of response. In the ERIVANCE study, the conventional Response Evaluation

Criteria in Solid Tumors (RECIST) was used, and in the BOLT trial, the more stringent modified RECIST was used to assess responses. In a recent consensus paper, clinical experts in the management of laBCC concluded that both vismodegib and sonidegib were associated with similar clinical activity and patterns of toxicities, despite their pharmacokinetic profiles showing important differences, such as volume of distribution and half-life. Further studies are needed to understand how these differences may impact clinical practice.[86]

Treatment breaks are commonly used to reduce the severity and duration of Hedgehog pathway inhibitor-related adverse events. No specific recommendations on the optimal application of treatment breaks exist, however, and it mostly relies on the experience of clinicians. According to AIFA, treatment breaks for a maximum of 4 and 3 consecutive weeks for vismodegib and sonidegib, respectively, are allowed for the management of treatment-related toxicities. Studies investigating the effects of longer treatment breaks have been conducted, but to date such schedules are not approved.[87]

Itraconazole, an antifungal drug, also inhibits the Hedgehog signaling pathway. In a study assessing the effect of itraconazole on the Hedgehog pathway and on tumor size in human BCC tumors, a total of 29 patients were enrolled, 19 of whom were treated with itraconazole. Four partial responses and four stable disease were achieved, showing that itraconazole has anti-BCC activity in humans. To date, however, itraconazole is not approved for the treatment of advanced BCC due to the very limited data about its activity and safety.[88]

Question 15. Should baseline radiological tumor assessment be recommended in subjects with laBCC and mBCC?

Recommendation. In subjects with laBCC and mBCC, baseline radiological tumor assessment may be recommended as the first option compared with no baseline radiological tumor assessment.

Strength of recommendation. Conditional in favor.

Overall quality of evidence. Expert opinion.

Motivation/comments on the benefit/risk balance. No studies comparing baseline radiological tumor assessment with no assessment in subjects with laBCC and mBCC were identified through our systematic literature search. The lack of evidence was expected due to the recent introduction of the definition for laBCC and the extreme rarity of mBCC. Since patients with laBCC often harbor tumors with deep tissue involvement, the panel determined that whether a baseline radiological assessment is necessary in patients with advanced BCC was a question worth addressing. In addition to that, since the identification of a locally advanced and/or metastatic disease may precede the administration of a systemic treatment, the detection of an additional neoplastic disease at baseline radiological assessment may help for the evaluation of risks and benefits in a population characterized by an old mean age. A baseline assessment is also necessary to properly evaluate the response to systemic treatments in cases of laBCC with deep tissue involvement and mBCC. Based on these considerations, and despite the lack of evidence in literature, the panel believes that the balance of risks and benefits of a baseline radiological tumor assessment in patients with laBCC and mBCC is favorable. The panel did not identify any probable uncertainty or variability on how the population may evaluate the analyzed outcomes. The intervention is equally available across the country, and should be acceptable by all stakeholders. See Supplementary material (Question 15), available at https://doi.org/10.1016/j.esmoop.2023.102037, for quality of evidence and implications for future results.

Question 16. Should radiological tumor assessment be recommended in the follow-up of subjects with laBCC and mBCC?

Recommendation. In the follow-up of subjects with laBCC and mBCC, radiological tumor assessment may be recommended as the first option compared with no radiological tumor assessment.

Strength of recommendation. Conditional in favor.

Overall quality of evidence. Expert opinion.

Motivation/comments on the benefit/risk balance. No studies comparing radiological tumor assessment in the follow-up of subjects with laBCC and mBCC with no radiological assessment were identified through our systematic literature search. Since laBCC and mBCC are often the results of previous treatment failures, however, and for laBCCs, their involvement of deep tissue is often clinically meaningful, the panel, despite the lack of evidence in literature, believes that the balance of risks and benefits of a radiological tumor assessment in the follow-up of patients with laBCC and mBCC is favorable, and that the type and frequency of assessments should be at clinicians' judgment. The panel did not identify any probable uncertainty or variability on how the population may evaluate the analyzed outcomes. The intervention is equally available across the country, and should be acceptable by all stakeholders. See Supplementary material (Question 16), available at https://doi.org/10.1016/j.esmoop.2023.102037, for quality of evidence and implications for future results.

Question 17. Should treatment with Hedgehog pathway inhibitors be recommended in subjects with laBCC and mBCC compared with follow-up/best supportive care?

Recommendation. In subjects with laBCC and mBCC, treatment with Hedgehog pathway inhibitors should be recommended as the first option compared with follow-up/best supportive care.

Of note, both vismodegib and sonidegib received the approval by the regulatory agencies for the treatment of laBCC, whereas only vismodegib received the indication for mBCC.

Starting from April 2021, updates were made to the AIFA register of sonidegib to allow the switch to the molecule in patients pretreated with Hedgehog pathway inhibitors should the prescriber deem it necessary to adopt the schedule every other day for a better management of the adverse reactions.

Strength of recommendation. Strong in favor (the panel decided to adopt a strong recommendation in favor of treatment with Hedgehog pathway inhibitors despite a very low quality of evidence for the following reasons: the absence of a therapeutic standard for locally advanced BCC and mBCC has made it impossible to conduct randomized clinical trials; in daily clinical practice, to date there is no therapeutic alternative to the use of Hedgehog pathway inhibitors for the treatment of locally advanced BCC and mBCC).

Overall quality of evidence. Very low.

Motivation/comments on the benefit/risk balance. The outcomes of benefit defined as essential to answer this question were disease control rate, response rate, duration of response and progression-free survival. The rate of any-grade and grade 3-5 adverse events, and their duration, were considered as essential outcomes of damage, in addition to specific adverse events such as loss of weight and muscle spasms.

Three non-randomized trials were identified through our systematic literature search.[83,84,89] Due to the lack of a control arm, it was not possible to estimate the relative and absolute effects of treatment with regard to the predefined outcomes. Considering the high response and disease control rate, and an impact of toxicities judged as moderate, however, the panel voted for a balance between risks and benefits favoring the systemic treatment with Hedgehog inhibitors compared with follow-up/best supportive care.

The panel did not identify any probable uncertainty or variability on how the population may evaluate the analyzed outcomes. The intervention is equally available across the country, and should be acceptable by all stakeholders. See Supplementary material (Question 17), available at https://doi.org/10.1016/j.esmoop.2023.102037, for evidence to decision results, quality of evidence and implications for future results.

Final considerations

On 20 May 2021, the EMA's Committee for Medicinal Products for Human Use (CHMP) adopted a positive opinion recommending a change to the terms of the marketing authorization for cemiplimab. The CHMP adopted new indications as follows: cemiplimab as monotherapy is indicated for the treatment of adult patients with locally advanced BCC or mBCC who have progressed or are intolerant to a Hedgehog pathway inhibitor. The positive opinion on the new indication was based on data from a multicenter phase II study, in which 84 patients were enrolled and treated with cemiplimab between November 2017 and January 2019. The primary endpoint was objective response. At a median follow-up of 15 months, an objective response by independent central review was observed in 26 (31%; 95% CI 21 to 42%) of 84 patients. The median time to response was 4.3 months (interquartile range: 4.3-7.2 months), with an 80% disease control rate (95% CI 70% to 88%) and a durable disease control rate of 60%. The median progression-free survival was 19 months (95% CI 9 months-not evaluable). The safety profile was consistent with the known adverse events associated with anti-programmed cell death protein 1 (PD-1) agents, even considering the advanced age of the included patients (median age: 70 years). The observed immune-related toxicities were manageable, with a total of nine (11%) serious immune-related adverse events, particularly colitis and adrenal insufficiency.[90] The positive opinion by the EMA CHMP was followed by the approval by the European Commission in June 2021.

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