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Guidelines

European interdisciplinary guideline on invasive squamous cell carcinoma of the skin: Part 2. Treatment

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Abstract In order to update recommendations on treatment, supportive care, education and follow-up of patients with invasive cutaneous squamous cell carcinoma (cSCC), a multidisciplinary panel of experts from the European Dermatology Forum, the European Association of Dermato-Oncology and the European Organization of Research and Treatment of Cancer was formed. Recommendations were based on evidence-based literature review, guidelines and expert consensus. Treatment recommendations are presented for common primary cSCC (low risk, high risk), locally advanced cSCC, regional metastatic cSCC (operable or inoperable) and distant metastatic cSCC. For common primary cSCC (the most frequent cSCC type), first-line treatment is surgical excision with postoperative margin assessment or microscopically controlled sugery. Safety margins containing clinical normal-appearing tissue around the tumour during surgical excision and negative margins as reported in the pathology report are necessary to minimise the risk of local recurrence and metastasis. In case of positive margins, a re-excision shall be done, for operable cases. Lymph node dissection is recommended for cSCC with cytologically or histologically confirmed regional nodal involvement. Radiotherapy should be considered as curative treatment for inoperable cSCC, or for non-surgical candidates. Anti-PD-1 antibodies are the first-line systemic treatment for patients with metastatic or locally advanced cSCC who are not candidates for curative surgery or radiation, with cemiplimab being the first approved systemic agent for advanced cSCC by the Food and Drug Administration/European Medicines Agency. Second-line systemic treatments for advanced cSCC include epidermal growth factor receptor inhibitors (cetuximab) combined with chemotherapy or radiation therapy. Multidisciplinary board decisions are mandatory for all patients with advanced disease who require more than surgery. Patients should be engaged with informed decisions on management and be provided with best supportive care to optimise symptom management and improve quality of life. Frequency of follow-up visits and investigations for subsequent new cSCC depend on underlying risk characteristics.

1. Information about the guideline

The European Interdisciplinary Guidelines on invasive squamous cell carcinoma of the skin were written as a uniform text and then published in 2 separate but integral parts: Part 1 on definitions, epidemiology, etiopathogenesis, diagnosis, risk classification, staging and prevention and Part 2 on treatments, supportive care, patient education and follow-up. Information about the Guidelines is detailed in Stratigos *et al.* Part 1, including the information about societies in charge, financing of the guidelines, scope, target population, objectives and formulation of sections, audience and period of validity, and methodology.

Recommendations were based on the level of best quality available evidence and good clinical practice

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(GCP). Expert consensus was provided wherever adequate evidence is not available (detailed in Stratigos.Part 1 ____). The levels of evidence were graded according to the Oxford classification [1]. The grades of recommendation were classified as follows:

A: Strong recommendation. Syntax: 'shall'.
B: Recommendation. Syntax: 'should'.
C: Weak recommendation. Syntax: 'may/can'.
X: Should not be recommended.
0: Recommendation pending. Currently not available or sufficient evidence to make a recommendation in favour or against.

1.1. Consensus building process

The meeting was held in Athens, Greece, on 6th and 7th September 2019. A structured consensus process was used to discuss and agree upon, with final outcomes: (1) the approval of the text and (2) a consensus rate of agreement of at least 80%, for recommendations provided in structured boxes and the Fig. 1. Voting of the recommendations included the selection of 'Agree', 'Disagree' or 'Abstential' vote, and the possibility of providing comments in case of disagree/abstential. Consensus voting on recommendations and finalisation of the draft was conducted among co-authors through emailing between 20th September 2019 and 30th October 2019.

After the consensus voting, there were two recommendations that had a lower than 80% consensus rate: the recommendation for 'Safety margins for surgical excision' and the Fig. 1. Also, it was decided to add a recommendation box for adjuvant RT. Comments were received from co-authors, the recommendations were revised and a second round of voting was conducted for these three recommendations.

1.2. Disclaimer

Medicine is subject to a continuous development process. This entails that all statements, especially with regard to diagnostic and therapeutic procedures, can only reflect current scientific knowledge at the time of printing of these guidelines. Utmost care was applied with respect to stated therapeutic recommendations and the selection as well as dosage of drugs. Nevertheless, users are prompted to use package inserts and expert information by the manufacturers as backup and, in case of doubt, consult a specialist. Pursuant to public interest, questionable discrepancies shall be communicated to the Guideline Program in Oncology (GPO) editors. The user himself/herself remains responsible for all diagnostic and therapeutic applications, medications and doses. Registered trademarks (protected product names) are not specified in these guidelines. From the absence of respective indications, it may thus not be inferred that product names are unprotected.

2. General considerations for the treatment of cSCC

Clearance of the tumour is the main goal of surgery which is the primary treatment of cSCC. Additionally, preservation of function and cosmesis are relevant objectives of treatment. Most cSCC are successfully treated with surgical excision alone with a good prognosis and cure rates greater than 90% [2].

Radiotherapy (RT) may be considered as a primary treatment in patients who are not candidates for surgery (e.g. locally advanced disease, comorbidities or declined surgery) or in cases when curative surgery is not possible or could be disfiguring.

Adjuvant therapy is defined as additional treatment, either systemic or radiation therapy, given after complete resection at the primary surgical treatment, with the aim to reduce the risk of recurrence.

Systemic treatment options with a curative intent for advanced cSCC include immunotherapy, epidermal growth factor receptor (EGFR) inhibitors, chemotherapy and electrochemotherapy. The programmed death receptor-1 (PD-1) blocking antibody, cemiplimab, was approved by the Food and Drug Administration (FDA) in 2018, and by the European Medicines Agency (EMA) in 2019, for patients with metastatic cSCC (mcSCC) or locally advanced cSCC (lacSCC) who are not candidates for curative surgery or curative radiation, and represents the only approved systemic therapy for cSCC. Platinum-based chemotherapy was used as the standard of care in the past. EGFR inhibitors have been reported for advanced cSCC and most studies concern cetuximab, with considerable heterogeneity and small numbers of included patients. Cetuximab may be combined with RT or chemotherapy [3].

A multidisciplinary approach is mandatory for all patients with advanced disease. Participation of patients in clinical trials should be encouraged, taking into consideration the limitations of current regimens due to risk of associated toxicity, and the older age and comorbidities often encountered in patients with advanced cSCC. A retrospective study from the German Dermatologic Cooperative Oncology Group, based on 190 patients with advanced cSCC, reported that 59% of lacSCC patients did not receive any therapy after diagnosis and that only 32 patients (29 mcSCC, 3 lacSCC)

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received systemic anti-tumour therapies, under the need for access to more effective systemic treatments for patients with advanced cSCC [4].

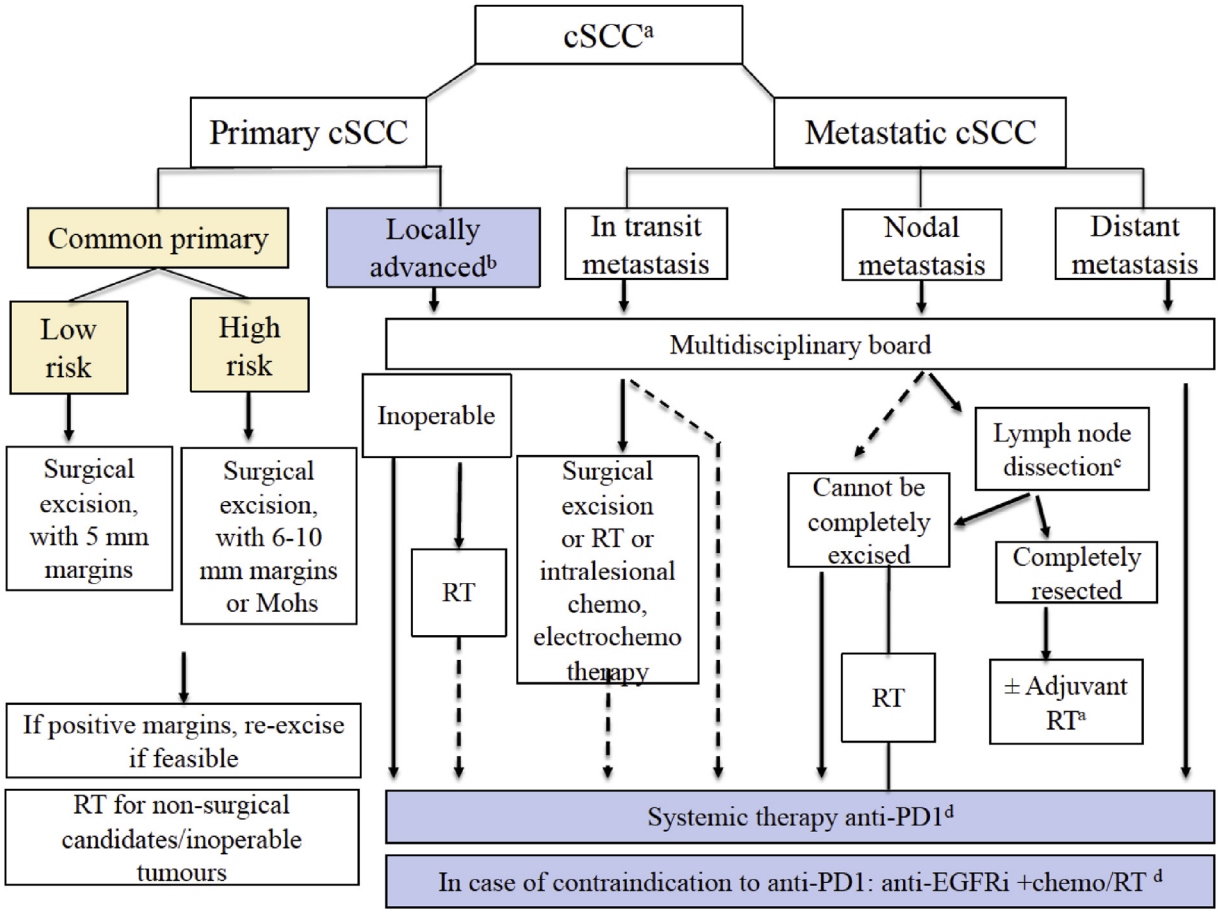
The same principles of management as for common primary cSCC do also apply for recurrent cSCC.

3. Surgery for common primary cSCC

Surgical excision is considered the first-line treatment of primary cSCC, regardless of the age-group and anatomic location. Surgery provides a high rate of clinical and microscopic complete resection (R0 surgery).

Two different surgical procedures may be offered in patients with primary cSCC: conventional surgery with safety margins and micrographically controlled surgery (MCS). MCS provides the highest rate of R0 resection, above 90%, and lower recurrence rates (0%–4%) compared to conventional surgery (3.1%–8.0%) [5–11]. The following procedures of MCS have been described: Mohs micrographic surgery (MMS) based on intraoperative frozen sections and procedures based on paraffin-embedded section analysis ("slow" Mohs, 3D histology, complete peripheral and deep margin assessment). These time-consuming procedures are usually reserved for patients with high-risk tumours, in whom MCS provides the best guarantee for complete tumour resection and with optimal anatomic and functional preservation. The possibility of false-negative margins after frozen section analysis of cSCC should be taken into consideration, and further confirmation of paraffin-embedded sections is recommended [12,13].

Frequently, a reconstructive procedure (i.e. flap or graft closure) is necessary to repair the surgical defect resulting from tumour resection, but reconstruction should never be done before histological confirmation of clear margins. The surgical management of tumours requiring extensive excisions should be performed by surgeons (dermatosurgeons, plastic surgeons or head and neck surgeons) with appropriate expertise in reconstructive procedures.



Fi.1. Main therapeutic indications for cSCC. Strength of consensus: 90%. [a]For detailed indications and recommendations of treatment, refer to relevant section text in the Guidelines. [b]Locally advanced by definition not amenable to curative surgery or curative RT. [c]Lymph node dissection as indicated. [d]All systemic treatments are off-label, except for anti-PD-1 agent cemiplimab that is approved by FDA/EMA for patients with locally advanced or metastatic cSCC who are not candidates for curative surgery or curative radiation. cSCC, cutaneous squamous cell carcinoma; RT, radiotherapy; EGFRi, epidermal growth factor receptor inhibitors; FDA, Food and Drug administration; EMA, European Medicines Agency.

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3.1. Standard excision with postoperative margin assessment

Surgical excision including appropriate safety margins of clinically normal skin with postoperative margin assessment is the standard treatment of invasive cSCC [11]. Safety margins containing clinical normal-appearing tissue around the tumour during surgical excision [14] and negative margins as reported by the pathology report are necessary to minimise the risk of local recurrence and metastasis [9,15,16].

Conventional excision with a clinically tumour-free margin should be followed by postoperative pathologic assessment of resection margins. This can be performed both by intra-paraffin-embedded cross sections for most cases and by operative frozen section evaluation in other high-risk tumours for definitive evaluation. Despite the fact that intraoperative frozen section evaluation of the whole specimen has been reported as an accurate procedure, with a short duration and low complication rate for the complete removal of facial cSCC [17], false-negative frozen section margin analysis should be taken into account [18], requiring further confirmation with paraffin-embedded sections.

Safety excision margins should be adapted to the risk of subclinical extensions and recurrence [19], as defined by high-risk factors including clinical (tumour diameter $>$ 2 cm, high-risk sites), histological (thickness $>$ 6 mm or invasion beyond subcutaneous fat, perineural invasion [PNI], poor differentiated, desmoplasia) and patient-related criteria (immunosuppression) (EADO list of high-risk criteria, Stratigos *et al.* Part 1). In clinically well-defined low-risk cSCCs with a diameter of less than 2 cm, a margin of 4 mm has achieved cure rates of 95%–97% in prospective studies [14,20]. Nevertheless, tumour diameter is only an approximate reflection of the actual degree of tumour aggressiveness and additional histological features may increase the risk of margin involvement, even in smaller tumours [21]. Therefore, guidelines consistently propose margins between 4 mm and 6 mm for tumours lacking high-risk features [16,22–25]. The European consensus group suggests a 5-mm margin for low-risk lesions (Fig. 1).

For high-risk cSCC, however, although wider safety margins are recommended (compared to those for low-risk cSCC), there is currently no unified defined recommendation on appropriate safety margins. The American Academy of Dermatology (AAD) and National Comprehensive Cancer Network guidelines recommend wider margins for high-risk cSCC, without further specifying, primarily due to the wide variability of characteristics that may define a high-risk cSCC and underlying tumour or patient-specific factor [26,27]. Additional guideline recommendations vary between 6 and 13 mm or favour micrographically controlled excisions as first-line treatment instead [22,24,25,28–30]. For cSCCs $>$ 2 cm in maximum clinical diameter and/or other high-risk factors (EADO list of high-risk factors, Stratigos *et al.* Part 1), an excision margin of at least 5 mm is required [14]. The European consensus group suggests 6–10 mm safety margins for cSCC with high-risk factors. As the independent prognostic effect of high-risk factors has not been consistently reported, a specific recommendation on the clinical safety margins cannot be given, but should fall within the 6–10 mm range and be based on individual risk assessment and tumour- and patient-related characteristics.

In patients with skin areas covered by a cluster of multiple invasive cSCCs (e.g. on the dorsal hands or scalp), *en bloc* excision of the involved field with subsequent skin grafting can be offered as an effective treatment.

The depth of excision should include the subcutaneous tissue (together with the underlying galea-aponeurosis in scalp locations) while sparing the perichondrium or periosteum, provided these structures are not affected by the tumour [23].

In case of positive margins, a re-excision shall be done, for operable cases. Wider excision should be considered when margins appear more limited than the recommended safety margins, as described in the pathology report, after considering the tissue shrinkage during the process (Fig. 1).

3.2. Micrographically controlled surgery

MCS is the collective term used for a surgical technique of removing skin cancer, processing skin tissue in horizontal sections and examining them under a microscope. This procedure is repeated until all borders are tumour free. Two techniques are being used in Europe: MMS and 3D histology [12], the first one making use of frozen sections whereas the second one uses paraffin sections with diverse modifications of sectioning the tissue specimen [13]. MMS is more time-consuming and labour-intensive than conventional excision and therefore more expensive. There is no randomised trial that compares MMS or other 3D techniques with conventional surgical excision for cSCC [11]. However, in prospective and retrospective studies, the value of MMS has been shown, especially for head and neck tumours [5–8,11]. More recently, two retrospective studies supported the value of MMS in prevention of local recurrence. In one study, including 647 high-risk cSCC, there were 19 local recurrences (2.9%), 31 nodal metastases (4.8%), 7 distant metastases (1.1%), and 7 disease-specific deaths (1.1%) [9]. Two factors, poor differentiation and invasion beyond the subcutaneous fat, were positively associated with local recurrence, nodal metastasis, and disease-specific death. The other retrospective study including 579 patients with 672 cSCCs of the head and neck (380 treated with MMS and 292 with

SE) concluded that MMS might be superior to standard excision for cSCCs of the head and neck because of a lower recurrence rate after adjustment for tumour size and deep tumour invasion (3% versus 8%) [10].

An advantage of MMS is that the tumour can be removed on the same day and a reconstruction can be performed shortly after. In conclusion, MMS and 3D histology are effective treatments for high-risk cSCC. As MMS and 3D histology are tissue conservative methods, they may be of particular value for cSCC in the head and neck area.

4. Surgery for regional nodal disease

The evidence about the management of regional nodal disease in patients with cSCC is limited and largely based on studies performed in head and neck mucosal SCC [31]. It is likely that patients with nodal metastases from cSCC should be managed surgically similarly to patients with other skin cancers (melanoma or Merkel cell carcinoma). For all tumours not amenable to surgery (due to patient-related factors or when the intention of a R0-resectability cannot be achieved), non-operative therapies should be considered by a multidisciplinary tumour board decision.

Therapeutic regional lymph node dissection for lymph nodes clinically detected or following imaging is the preferred surgical treatment [16,26,29,32–40]. A radical lymph node dissection of the affected areas should be performed. The extent of surgical resection is determined by the interdisciplinary tumour board. The 3 levels of axillary lymph nodes should be removed in cases of axillary nodal disease. In the groin, the procedure should include the superficial and deep inguinal lymph nodes. If the nodal disease occurs on the neck, the 5 levels of nodes should be included in the dissection. Neck dissection in addition to superficial parotidectomy should be performed if the parotid gland is affected, because a lower disease-specific survival was observed with radiation therapy alone [41]. It is unclear whether a more selective procedure will affect the disease-free survival and the overall survival.

Elective (prophylactic) lymph node dissection is not recommended in the management of lymph node–-negative cSCC patients, due to the low rate of nodal metastases, associated morbidity from the dissection and limited evidence in patients with mucosal head and neck SCC, a type of cancer with a significantly higher rate of nodal involvement [42,43]. A meta-analysis (17 studies) in patients with mcSCC to the parotid with no clinically evident cervical disease reported that the overall prevalence of occult disease was 22.5%. The authors suggested that elective neck dissection is recommended in patients with mcSCC to the parotid due to the prevalence of occult cervical disease. The extent of dissection is determined by the surgeon in collaboration with the interdisciplinary tumour board [44].

Recommendation 1.

Surgical treatment of primary cSCC	Evidence-based recommendation
Grade of recommendation: A	As standard therapy, an excision with histological control shall be performed. The aim of cSCC surgery shall be a complete excision (R0) with histological confirmation of peripheral and deep excision margins. Large tumours or tumours on high-risk sites can undergo a punch or incisional biopsy for histological confirmation and planning of a subsequent complete excision. In case of positive margins, a re-excision shall be done, for operable cases
Level of evidence: 2	Guideline adaptation [16] Systematic review [15] Retrospective study [9] Strength of consensus: 100%

Recommendation 2.

Surgery and safety margins	Evidence-based recommendation
Grade of recommendation: B	Low-risk cSCC should be excised with a clinical safety margin of 5 mm cSCC with high-risk factors* should be excised with a clinical safety margin of 6–10 mm or by MMS/MCS
Level of evidence: 2-3	Guideline adaptation [22–25,29] Strength of consensus: 85%

*As the independent prognostic effect of high-risk factors has not been consistently reported, a specific recommendation on the clinical safety margins cannot be given, but should fall within the 6- to 10 -mm range and be based on individual risk assessment and a constellation of tumour- and patient-related characteristics.

Recommendation 3.

GCP	As long as an R0 resection is not histologically confirmed, wound closure with local tissue movements (flaps) should be avoided Strength of consensus: 90%

Recommendation 4.

Therapeutic lymph node dissection	Evidence-based recommendation
Grade of recommendation: B	A regional therapeutic lymph node dissection should be performed in clinically or radiologically detected lymph node metastasis that is confirmed with cytology or biopsy. The extent of surgical resection is determined by the surgeon in collaboration with the interdisciplinary tumour board.
Level of evidence: 3	Review [32,33] Prospective study [34] Retrospective study [35–40] Guidelines [16,26,29] Strength of consensus: 95%

Recommendation 5.

Elective lymph node dissection for cSCC	Evidence-based recommendation
Grade of recommendation: X	Elective lymph node dissection should not be performed for cSCC.
Level of evidence: 4	Evidence for elective lymph node dissection for N0 cSCC is lacking [32]. Strength of consensus: 100%

Recommendation 6.

Elective neck lymph node dissection for mcSCC to the parotid	Evidence-based recommendation
Grade of recommendation: C	Elective neck dissection may be discussed and offered for mcSCC of the parotid
Level of evidence: 3	Meta-analysis [44] Strength of consensus: 95%

5. Treatment alternatives to surgery for selected cases with common primary cSCC

5.1. Curettage and electrodessication

There are no prospective studies comparing curettage and electrodessication (C&E) with other treatments. A systemic review and pooled analysis of observational studies reported low recurrence rates for small cSCC (<2 cm) [11]. Expert consensus in the AAD guidelines state that C&E may be considered for small, low-risk primary cSCC (based on National Comprehensive Cancer Network risk stratification) [16,26]. Curettage and cautery (2 cycles) in experienced hands can be performed in small, low-risk tumours and in selected cases (patients with multiple cSCCs) but surgery is always to be preferred to this blind method. Lesions on terminal hair-bearing skin (scalp, pubic, axillary regions and the beard area in men) should be excluded from treatment with C&E [16,26].

5.2. Other destructive treatments: Cryosurgery, lasers, PDT

Surgery should be discussed and considered with preference to other destructive options, because recurrences may lead to surgery in even poorer conditions. There is inadequate evidence regarding efficacy of PDT for invasive cSCC and it cannot be recommended [45]. A systematic review and pooled analysis of observational studies reported low recurrence rates after cryotherapy but most cSCC included were small and low risk, and the quality of evidence was low [11]. The AAD guidelines state that cryosurgery may be considered for low-risk cSCC when more effective therapies are contraindicated or impractical, which is rather uncommon [26]. Nevertheless, in selected cases of low-risk cSCC in patients with extensive field cancerisation, cryotherapy can be offered [46,47].

5.3. Intralesional cytostatic drugs

In keratoacanthomas, when the clinical features are typical, intralesional injection of cytostatic drugs (methotrexate, 5-fluorouracil or bleomycin, or interferon) may be considered to reduce scarring in a self-healing lesion. However, an advantageous benefit-risk ratio has not been demonstrated, particularly when compared with surgery [48–50]. If complete regression is not achieved, the lesion should be surgically removed for covering the risk that this supposed keratoacanthoma could in fact be a more aggressive SCC.

6. Radiotherapy

6.1. Primary definitive RT

Definitive primary RT represents a good alternative and curative treatment strategy to surgery for small cSCCs. RT may be considered as a primary treatment in patients who are not candidates for surgery (e.g. lacSCC, presence of comorbidities or decline of surgery) or in cases when curative surgery is not possible or could be disfiguring or burdened by poor functional outcome,

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Recommendation 7.

Destructive modalities	Consensus-based recommendation
GCP	Destructive modalities such as C&E, cryotherapy, PDT and lasers should not be performed in the treatment of primary invasive cSCC. Exceptions can be considered in small-sized and/or multiple cSCCs in low-risk areas where surgery is not possible or has unacceptable consequences Strength of consensus: 95%

especially cSCCs located on the face (i.e. eyelid, nose and lip) or large lesions on the ear, forehead or scalp.

Prospective randomised trials comparing the effectiveness of primary RT in local tumour control and patient survival compared to other local therapy modalities are not available. A meta-analysis (2013) of 14 observational studies of RT for 1018 primary cSCCs reported a pooled average local recurrence rate of 6.4% [11].

Modern RT represents a versatile treatment modality and depending on tumour and/or patient factors, it can be delivered as an external beam technique or via the direct application of brachytherapy. External beam RT may involve electron beams or photons, with either superficial energy RT in the range of 50−500 kV or deeply penetrating megavoltage in the range of 4−18 MV (photons or electrons). Treatment can be delivered to a small superficial area (e.g. nasal ala) or a large complex volume (e.g. whole scalp or skull base).

Total prescribed dose and fractionation should reflect the differences in radiobiological effectiveness between different radiation modalities. Recommended are doses of 45−50 Gy in fractions of 2.5−3 Gy for tumours of <2 cm and doses of 60−66 Gy in fractions of 2 Gy or 50−60 Gy in fractions of 2.5 Gy for tumours of >2 cm.

RT is an overall safe procedure, although it can be associated with complications such as an acute, often erosive, radiation-induced dermatitis and chronic onset of depigmentation and telangiectasia. The latter will become more visible over the years so RT should not be recommended for younger patients. Higher doses per fraction lead to higher rates of late toxicity [51]. Therefore, accelerated fractionation schedules should be reserved for elderly, frail patients, or when cosmetic outcome is of less importance.

Prescribed dose must encompass all visible tumour plus an appropriate variable margin (clinical target volume), sparing as much as possible of the surrounding healthy structures [52,53]. Irrespective of treatment intent (definitive, adjuvant and palliative), dosimetric and technical considerations should be surveyed by a certified radiation oncologist.

RT may be combined with systemic therapies including chemotherapy (chemoradiation) or cetuximab in more advanced cases.

6.2. Postoperative adjuvant RT

Definitive postoperative RT should be considered after surgical excision for cSCC with positive margins and re-excision not possible [16,25,29,56].

Adjuvant RT is offered as part of clinical practice in many medical centres for patients with high-risk cSCC, particularly for tumours with microscopic or clinical PNI. Current practice is influenced by the standard use of adjuvant RT for mucosal SCC of the head and neck. However, there is a lack of significant evidence, including randomised controlled trial data, showing a clear benefit of adjuvant RT in this setting [15,16,54,56−61]. An important limitation of existing studies of the use of adjuvant RT for primary common cSCC is the fact they do not specify the results of histological margin assessment or include patients treated with RT for cSCC with positive margins and those with negative margins. A retrospective analysis by Harris *et al.* in 349 patients indicated that patients with cSCC on the head and neck region with regional metastases or PNI had improved disease-free survival and overall survival (OS) after adjuvant RT [56]. The systematic review of Jambusaria-Pahlajani *et al.* (2009) reported no difference in outcomes for cSCC with microscopic PNI between those treated with surgery alone versus surgery plus adjuvant RT. It was suggested that the degree of PNI may be a factor affecting outcomes. Also, the importance of clear surgical margins was underlined, as unreported or positive margins may confound outcomes [15].

For patients with cSCC in the head and neck region with regional metastases, a recent meta-analysis performed by Sahovaler *et al.* (20 observational studies and 1 randomised phase III study [62]) confirmed the

Recommendation 8.

Definitive primary RT	Evidence-based recommendation
Grade of recommendation: B	Primary RT should be considered as an alternative to surgery for inoperable or difficult-to-operate tumours or in the absence of consent to surgical excision
Level of evidence: 3	Systematic review/meta-analysis, high risk of bias [11] Retrospective studies in small numbers and heterogeneous group of patients [54,55] Strength of consensus: 100%

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improved disease-specific survival (DSS) and OS of adjuvant RT. In this meta-analysis, PNI was not associated with poorer OS, while extracapsular extension was [63].

The risk of bias is significant in these articles, being based mostly on a retrospective design, also patients with worse prognosis and comorbidities may not have received adjuvant RT [63], and the possibility that patients who received adjuvant RT may not have had clear surgical margins and may have had other poor prognostic factors [15]. The great variation in results, however, suggests that a subset of patients may derive benefit from adjuvant RT. However, it remains difficult to select this subgroup of patients.

7. Adjuvant systemic therapy

There are no solid data to support the use of adjuvant systemic treatment in localised cSCC after RO resection [62,65–69]. There was no improvement in time to recurrence or time to second primary tumours with adjuvant 13-cis-retinoic acid plus interferon alpha [67]. Adjuvant chemotherapy (oral capecitabine and other systemic cytotoxic drugs) or targeted therapies (EGFR inhibitors) should not be recommended, because robust evidence about efficacy based on survival data is lacking [68]. A retrospective study in patients with resected high-risk cSCC investigated RT combined with cetuximab (n = 29) or RT alone (n = 39). There were better progression-free survival rates for the combination therapy than with RT alone (2 years: 72% versus 53%, 5 years: 66% versus 29%, respectively) [69]. Currently, there is no robust evidence to support the use of adjuvant systemic treatment for cSCC, but clinical trials on the PD-1 antibodies cemiplimab and pembrolizumab are currently being conducted.

Recommendation 9.

Adjuvant RT	Evidence-based recommendation
Grade of recommendation: B	Adjuvant RT should be considered in cSCC of the head and neck with regional nodal metastases and extracapsular extension Postoperative RT should be considered after surgical excision for cSCC with positive margins and for which re-excision is not possible
Level of evidence: 3	Meta-analysis (20 observational studies and 1 randomised phase III study) [63] Randomised phase III study [62] Retrospective studies [31,56,64] Strength of consensus: 85%

8. Neoadjuvant therapy

Neoadjuvant therapy aims to reduce the size of a tumour before surgery, so that there is a smaller surgical defect and easier reconstruction. There is a limited number of small studies on neoadjuvant EGFR inhibitor therapy [70–73]. A recommendation cannot be given on the use of neoadjuvant therapy due to lack of adequate evidence. Publication of results for neoadjuvant cemiplimab are awaited.

9. Treatment for in-transit metastases

Satellite or in-transit metastases should be removed surgically if the number, size and location allow complete removal of the metastatic sites. According to a case series, adjuvant radiation therapy can be helpful in such cases [74]. For multiple unresectable metastases on the limbs, amputation used to be a common option; however, currently it is no longer performed as it has no proven impact on the prognosis and several local and systemic alternatives are available to prevent mutilation [74]. Local options include RT, intralesional chemotherapy (5-fluorouracil, bleomycin or methotrexate), intralesional recombinant interferon alpha, electrochemotherapy or isolated limb perfusion [74–77]. Systemic options include oral retinoids, chemotherapy (platin-based regimens), EGFR inhibitors and anti-PD-1 immunotherapy [74,75]. The only systemic drug approved in this setting is the anti-PD-1 agent cemiplimab [78]. Reduction or withdrawal of immunosuppressive drugs should be considered in iatrogenically immunosuppressed patients [74].

10. Systemic treatments for advanced cSCC

10.1. Immunotherapy: immune checkpoint inhibitors

Until recently, no systemic therapy was formally approved for the treatment of mcSCC. Similar to other ultraviolet radiation–driven skin cancers, cSCC is among the cancers with the highest rate of somatic mutations [79] and mutated proteins can serve as neoantigens that can be recognised by the immune system [80]. Increased PD-1 and PD-ligand 1 (PD-L1) expression with immunohistochemistry has been reported in cSCC compared to normal skin, but with no correlation to clinical response [81]. Also, immune inhibitory molecules have been shown in the cSCC microenvironment [82,83].

In a phase I/II clinical trial recently reported by Migden *et al.* [78], 26 patients from a phase I extension cohort with lacSCC or mcSCC and 59 patients with regionally or distant mcSCC from the phase II part of the study were treated with the PD-1 inhibiting antibody, cemiplimab, at a dose of 3 mg/kg every 2 weeks

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intravenously. Patients were assessed for response every 8 weeks. Patients who had undergone organ transplantation and patients with hematologic malignancies or any immunosuppressive conditions were excluded. The best overall response rate was 50% in the phase I and 48% in the phase II cohort (with 7% achieving a complete response). Response rates were similar between patients with regional or distant metastatic disease. At a median follow-up of 11.1 months in the phase I cohort and 7.9 months in the phase II cohort, median disease-free survival and overall survival were not reached at the time of data cut-off (Table 1).

The treatment was generally well tolerated with only 7% of patients stopping therapy due to adverse events. The most commonly reported adverse events were diarrhoea (27%), fatigue (24%), nausea (17%), constipation (15%), and rash (15%). Forty-two percent of patients had an adverse event reported as being grade 3 or higher as defined by the Common Terminology Criteria for Adverse Events, version 4.03 which included diarrhoea, fatigue, constipation, anaemia and pneumonitis. In 3 of 11 patients in the phase II cohort who died during the study, death was associated with a non-treatment emergent adverse event [78].

Based on this study, cemiplimab was approved in September 2018 by the FDA and in July 2019 a conditional approval was granted by EMA, for patients with mcSCC or lacSCC who are not candidates for curative surgery or curative radiation. The approved dose is 350 mg cemiplimab, every 3 weeks, administered as an intravenous infusion over 30 min [84] (Fig. 1). A similar study with pembrolizumab has been recently reported and publication of results is awaited.

While PD-1 inhibitors show a significantly higher response rate than any other treatment for mcSCC, there is currently limited use in patients on immunosuppressive medication (organ transplant recipients [OTRs], autoimmune disease) and no comprehensive information in patients with underlying hematologic malignancies such as chronic lymphocytic leukaemia [85]. Because these limitations are present only in a smaller number of patients [4], PD-1 inhibitors will be the future gold standard therapy for the large majority of patients with lacSCC or mcSCC. In renal OTRs, when the prognosis is poor and no other modalities are possible, PD-1 inhibition can be considered and has been used in melanoma. A systematic review of immunotherapies (nivolumab, pembrolizumab and ipilimumab) for 57 solid OTRs with metastatic cancers reported that 37% of patients experienced organ rejection and 14% died as a result of graft rejection. There were no data for cemiplimab [86].

10.2. EGFR inhibitors

Elevated EGFR expression has been demonstrated in advanced cSCC with a frequency (43%–100%) proportional to the metastatic risk [87]. Genetic activation of EGFR by mutation was reported in a small subset of cSCC (2.5%) [88]. Available targeted EGFR inhibitors include antibody-based inhibitors of the extracellular domain of EGFR (cetuximab, panitumumab) and small-molecule tyrosine kinase inhibitors including erlotinib, gefitinib and lapatinib.

Cetuximab is a human-mouse chimeric monoclonal antibody that inhibits EGFR by targeting the extracellular domain of the EGFR and by blocking the intracellular signalling via the RAS/MAP kinase pathway.

Recommendation 10.

Immunotherapy for lacSCC or mcSCC	Evidence-based recommendation
Grade of recommendation: A	Patients with mcSCC or lacSCC who are not candidates for curative surgery or curative radiation should receive first-line treatment with a PD-1 antibody*.
Level of evidence: 2	Phase 1 and 2 study of cemiplimab [78]. Phase 1 and 2 of pembrolizumab [87,88]. Strength of consensus: 100%

*Cemiplimab is currently the only approved medication in Europe, while pembrolizumab is investigated in clinical studies.

Table 1
Response outcomes of prospective studies of systemic therapies for treatment in curative intent for advanced cSCC published from 2000 till 31st May 2019: anti-PD-1 agent cemiplimab.

Reference	Trial design	Patients (N)	cSCC type	Treatment schema	Response	Survival
Migden *et al.* (2018)	Phase 1, open-label, multicentre	26	10 Locally advanced 8 Regional metastasis 8 Distant metastasis	Cemiplimab	Best ORR 50% 13 PR	Not reported
	Phase 2, non-randomised, global, pivotal study	59	14 Regional metastasis 45 Distant metastasis		Best ORR 48% 4 CR 24 PR	1-y OS: not reached (estimated 81%) 1-y PFS: not reached (estimated 53%)

cSCC, cutaneous squamous cell carcinoma; CR, complete response; PR, partial response, SD, stable disease; PD, progressive disease; DCR, disease control rate (CR + PR + SD); ORR, overall response rate (CR + PR); y, year; PFS, progression-free survival; OS, overall survival.

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Cetuximab is the EGFR inhibitor mainly investigated for advanced cSCC, while panitumumab has been assessed in a small number of patients [89,90]. There is very limited evidence for erlotinib, gefitinib and lapatinib [91,92].

10.2.1. Cetuximab combined with chemotherapy or RT

Cetuximab is EMA approved for advanced or metastatic head and neck SCC combined with RT and with platinum-based chemotherapy, respectively. Cetuximab has been used off-label, either alone [93−96] or combined with RT or cisplatin, for advanced cSCC in a small number of patients [3,97−101].

Cetuximab is considered a radiosensitiser as it has a synergistic effect in combination with RT [65,102]. A prospective study of 20 patients with lacSCC compared cetuximab alone versus cetuximab combined with cisplatin or RT (60−70 Gy). Combination therapy had higher response rates versus cetuximab alone (disease control rate, 92% versus 50%, respectively, and response rates, 53% versus 33%, respectively). However, there was short duration of response (OS, 11.1 months; progression-free survival, 5.7 months) [103]. Another prospective trial of cetuximab combined with curative RT in 8 patients (median age of 81 years and adequate performance status) with inoperable cSCC reported good tolerance and durable disease control [3] (Table 2).

Anti-EGFR inhibitors are generally well tolerated compared to standard chemotherapy. Most adverse events are cutaneous, are dose dependent and affect aesthetically sensitive areas with a great impact on patient's quality of life. They include a papulopustular/acneiform rash which usually appears within the first 1−2 weeks of initiating treatment, xerosis, pruritus and hand/nail toxicity [93].

Cetuximab may be used as second-line treatment after cemiplimab (first-line), combined with chemotherapy or RT. It may also be considered before

Table 2
Response outcomes and dosing regimens of prospective studies of systemic therapies for treatment in curative intent for advanced cSCC published from 2000 till 31st May 2019: EGFR inhibitors and chemotherapy.

Reference	Trial design	Patients (N)	cSCC type	Treatment regimens	Response	Survival
Anti-EGFR antibodies						
Maubec *et al.* (2011)	Phase II open-label, uncontrolled, multicentre trial	36	33 Unresectable 3 Metastatic	Cetuximab Initial dose of 400 mg/m^2 followed by weekly doses of 250 mg/m^2 for at least 6 w	ORR: 28% DCR: 69% 2 CR 8 PR	Mean OS: 8.1 m Median PFS: 4.1 m
Preneau *et al.* (2014)	Open label, single-centre, non-randomised	20	Locally advanced	6 Cetuximab Initial dose of 400 mg/m^2 followed by weekly doses of 250 mg/m^2 9 Cetuximab as above + carboplatin 300 mg/m^2 monthly 5 Cetuximab + RT Cetuximab as above, RT: 60−70 grey	ORR: C: 33% C−C: 37.5% C-RT: 80% DCR: C: 50% C−C: 87.5% C-RT: 100%	OS: 11.1 m C: 2.5 C−C: 5.6 C-RT: 3 PFS: 5.7 m C: 1.3 C−C: 2.8 C-RT: 1.6
Joseph *et al.* (2018)	Single-centre	8	Inoperable	Cetuximab + RT Cetuximab at initial dose of 400 mg/m^2 7 d before RT, followed by weekly doses of 250 mg/m^2 for the duration of RT	6 CR 1 PR 1 PD	2-y PFS: 83.3% 2-y SSS: 87.5%
Foote *et al.* (2014)	Phase II, uncontrolled, single-centre trial	16	14 Locally advanced 2 Metastatic	Panitumumab 6 mg/kg every 2 weeks for maximum of 9 cycles	ORR: 31%	Median OS: 11 m Median PFS: 8 m
EGFR tyrosine kinase inhibitors						
William *et al.* (2017)	Phase II, uncontrolled	40/37 E valuable	27 Locoregionally recurrent 4 Locally advanced 9 Metastatic	Gefitinib 250 mg/d orally	ORR 16% ORR in mcSCC: 0 DCR 51%	Median OS: 12.9 m Median PFS: 3.8 m
Gold *et al.* (2018)	Phase II, uncontrolled, single-centre trial	29	Locoregionally recurrent or metastatic cSCC	Erlotinib 150 mg/d orally (dose reduction management specified in the study)	ORR 10% DCR 72% 3 PR, 18 SD, 8 PD	Median OR: 13 m Median PFS: 4.7 m

cSCC, cutaneous squamous cell carcinoma; mcSCC, metastatic cSCC; C, cetuximab monotherapy, C−C, cetuximab combined with carboplatin; C−RT, cetuximab combined with radiotherapy; CR, complete response; PR, partial response; SD, stable disease; PD, progressive disease; DCR, disease control rate (CR + PR + SD); ORR, overall response rate (CR + PR); d, day; m, months; w, weeks, y, year; PFS, progression-free survival; OS, overall survival; SSS, SCC-specific survival.

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chemotherapy for elderly patients with comorbidities, who may not tolerate chemotherapy (Fig. 1).

Currently, there are no systemic chemotherapies approved for advanced cSCC patients. The chemotherapeutic agents that have been used for advanced cSCC either as monotherapy or polychemotherapy include platinum agents (i.e. cisplatin or carboplatin), 5-fluorouracil, bleomycin, methotrexate, adriamycin, taxanes, capecitabine, doxorubicin, gemcitabine and ifosfamide. Data about such treatments are weak and inconsistent and are limited by the small number of treated patients, heterogeneity of treatment regimens and different outcome assessments [104–109]. Platinum-based therapy has been used as one of the standard chemotherapeutic options in the management of advanced cSCC [93,110]. A recent systematic review of mcSCC reported only 60 cases of mcSCC treated with cisplatin monotherapy published from 1989 to 2014, underlying the paucity of data [93]. Complete response was described in 22% and partial response in 23%, resulting in an overall response of 45%. The median disease-free survival for patients who attained a complete response was 14.6 (range, 3–112) months [93].

Polychemotherapies seem more effective than monochemotherapy but result in more side effects and poor tolerance. In general, responses are mostly short-lived and are followed by rapid recurrence and do not lead to a curative effect.

10.3. Electrochemotherapy

Electrochemotherapy for cSCC consists of intravenous injection of a cytotoxic agent (usually bleomycin or cisplatin) followed by insertion of needle electrode in the tumour mass and pulse application [111]. Efficacy of electrochemotherapy in terms of disease control and local response has been reported in a range of 20%–70% of cases [112–115]. Electrochemotherapy can also be used in cSCC to reduce tumour progression with the benefit of controlling bleeding and mass-related symptoms. A European multi-institutional prospective (EURECA) trial studied electrochemotherapy (bleomycin) for skin tumours, including 50 cSCC of the head and neck not suitable for surgery or chemotherapy/RT, as decided by multidisciplinary board. At 2-months follow-up, complete response was achieved in 55% of cSCC, partial response in 24%, stable disease in 15%, and progression in 4%. Main adverse events included skin ulceration, hyperpigmentation, and suppuration [116].

Recommendation 11.

EGFR inhibitors	Evidence-based recommendation
Grade of recommendation: C	Cetuximab may be used for patients with lacSCC and mcSCC, who have failed to respond or are intolerant to immunotherapy. Cetuximab combined with chemotherapy or RT is favoured over cetuximab monotherapy.
Level of evidence: 3	Small number of patients in prospective studies [96,103]. A small number of patients with mcSCC treated [93,97,98,103,109]. Only two prospective non-randomised study in small number of patients [3,103]. Small number of patients from retrospective studies [98,99]. Strength of consensus: 80%

Recommendation 12.

Chemotherapy for lacSCC or mcSCC	Evidence-based recommendation
Grade of recommendation: C	Chemotherapy can be used when patients fail to respond or are intolerant to anti-PD-1 immunotherapy. Platinum-based agents can be preferred. Chemotherapy may be more effective when used in combination with EGFR inhibitors or radiation therapy.
Level of evidence: 3-4	Systematic review of 60 cases of mcSCC treated with cisplatin [93]. Strength of consensus: 90%

11. Clinical trials

Patient participation in clinical trials is encouraged. Pembrolizumab is being evaluated in clinical trials for lacSCC or mcSCC, either alone (NCT02964559, NCT03284424) or in combination with abexinostat, a broad-spectrum phenyl hydroxamic acid inhibitor of histone deacetylase (NCT03590054), or cetuximab (NCT03082534), or Oncolytic MG1 Expressing MAGE-A3 (MG1-MAGEA3) with Adenovirus Vaccine Expressing MAGE-A3 (NCT03773744). Also, cemiplimab is being evaluated for recurrent stage II-IV head and neck cSCC (NCT03565783), or as intralesional therapy for recurrent cSCC (NCT03889912) [117]. A phase II study testing a fixed-dose regimen and alternative dosing intervals of cemiplimab is ongoing (NCT02760498).

There are ongoing clinical trials on the efficacy of anti-PD-1 agents in the adjuvant setting for high-risk or lacSCC, for cemiplimab (NCT03969004) [118] and for pembrolizumab (NCT03057613, NCT03833167) [117].

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Furthermore, a neoadjuvant systemic treatment with cemiplimab is tested in early clinical trials in cSCC and head/neck cancers (NCT03916627). A small-sized phase-1 trial on intralesionally applied cemiplimab for a pre-operative use in cSCC patients is also actively recruiting (NCT03889912).

12. Best supportive care

When no further curative therapy is possible, palliative therapy (surgery, RT, electrochemotherapy) aims to control tumour extension and relieve symptoms [111,116]. RT is particularly helpful as a palliative treatment, in order to relieve pain, to stop haemorrhage and to limit tumour extension to adjacent critical areas such as the orbits or oral cavity [119]. In these cases, a combined treatment of RT with chemotherapy or with cetuximab or other EGFR inhibitors may be used. A number of different combination schemes are reported in the literature [104]. These treatments are anecdotal with no sufficient evidence to recommend them.

To improve overall quality of life in the palliative setting, consideration should be given to nutritional, psychological, social and existential needs. Furthermore, psychosocial support is crucial. Advance care planning, conversations about wishes, needs and values of individual patients should be started. Consider consultation with a palliative care specialist/team [120].

Supportive care of patients with a skin tumour includes prevention of infection with daily irrigation of the tumour with lukewarm tap water or with a solution containing sodium chloride solution of 0.9% or povidone iodine in a 2% or 10% solution [121]. For fetor, dressings containing silver sulphadiazine or metronidazole cream/lotion and oral metronidazole may be considered [121,122]. Applying zinc oxide paste or silicone gel on the surrounding skin can prevent maceration due to tumour exudate. Application of calcium alginate dressings, dressings with xylometazoline or adrenaline (1:1000) or silver nitrate can temporarily stop bleeding [122]. Pain may affect quality of life significantly and should be addressed appropriately [123]. The World Health Organization ladder of pain is a helpful tool for adequate pain management [124]. The first step is treatment with paracetamol or non-steroidal anti-inflammatory drugs and when insufficient, opioids may be added. In case of local pain, a nerve block might diminish pain. In smaller wounds, application of morphine gel can be considered [125,126].

13. Follow-up

Patients with cSCC should be closely followed up for the early detection of recurrences and for the development of new keratinocyte cancer and melanoma. The relative risk for development of melanoma after diagnosis of a keratinocyte cancer was reported to be 1.99 for men and 2.58 for women based on 2 large cohort studies [128]. In a cohort of 1426 cSCC patients in the United States, 5- and 10-year risks of further cSCC were estimated to be 42.1% and 69.1%, respectively [129], and the standardised incidence ratio was estimated to be 15.0 (14.0–16.0) in a systematic review [130]. The risk is significantly higher for immunosuppressed individuals in whom cSCC is frequently multiple [131,132].

Patients with a history of cSCC should be followed closely, particularly during the first few years after diagnosis. There is no standardised follow-up schedule for patients with cSCC. Follow-up examination is largely based on risk ascertainment of the primary cSCCs, local recurrence or metastatic spread.

Recommendations on follow-up scheme are presented in Table 3. Follow-up in all patients should include regular physical examination, including inspection of the entire skin and inspection and palpation of the excision site, the in-transit route and the regional lymph nodes. Histopathologically diagnosed low-risk cSCC in elderly patients on sun-exposed sites may not need long-term follow-up and if follow-up is deemed necessary, the frequency and the length of follow-up need to be established after careful assessment of the risk factors.

Patients with high-risk cSCC (as defined in EADO guidelines [Stratigos Part 1]) should be followed up every 3–6 months for the first 2 years, and every 6–12 months for years 3–5, and annually thereafter. A lymph node ultrasound should be performed every 3–6 months in the first 2 years depending on risk stratification and

Recommendation 13.

Best supportive care	Evidence-based recommendation
Grade of recommendation: B	• Before the introduction of anti-PD-1, all therapies in advanced cSCC were considered to be palliative. • To improve overall quality of life in the palliative setting, one should be aware of nutritional, psychological, social and existential needs • Supportive care of patients with a skin tumour includes the reduction in symptoms, the prevention/treatment of an infection, the control of haemorrhage and adequate pain management
Level of evidence: 2	Systematic review and meta-analysis [127] Strength of consensus: 95%

Table 3
Consensus-based recommendations for follow-up time schedule for patients with cSCC proposed by EDF-EADO-EORTC.

cSCC risk factors	Clinical examination	Imaging examination for non-palpable regional lymph nodes	Main underlying risk
Low-risk primary	Every 6–12 m for 5 y	Not recommended	Low risk of recurrence or new skin cancers
High-risk[a] primary	Every 3–6 m for 2 y Every 6–12 m: 3 y to 5 y Annually thereafter	Lymph node US every 3–6 m for 2 y (depending on risk assessment and previous findings)	Risk of local recurrence or new skin cancers Risk of regional metastases
LacSCC or mcSCC	Every 3 m for 5 y Every 6–12 m thereafter	Lymph node US every 3–6 m for 5 y and then every 6–12 m Imaging (CT, MRI, or PET–CT) every 3–6 m for 3 y and then based on individual symptoms and stage	High risk of regional and distant metastases
Immunosuppression[b]	Every 3–6 m lifelong + according to the characteristics of individual primary tumours	According to the characteristics of individual primary tumours	Mainly very high risk of new skin cancers and recurrence

cSCC, cutaneous squamous cell carcinoma; mcSCC, metastatic cSCC; lacSCC, locally advanced cSCC; y, years; m, months; US, ultrasound; EDF, European Dermatology Forum; EADO, European Association of Dermato-Oncology; EORTC, European Organization of Research and Treatment of Cancer; CT, computed tomography; MRI, magnetic resonance imaging; PET, positron emission tomography.

[a] High-risk cSCC patient as defined by EADO guidelines. As the independent prognostic effect of high-risk factors has not been consistently studied, an individual risk assessment is advised to guide follow-up decisions.

[b] Organ transplant recipients; chronic lymphocytic leukemia or with xeroderma pigmentosum.

previous findings [5]. As the independent prognostic effect of high-risk factors has not been consistently reported, follow-up should be based on individual risk assessment and tumour- and patient-related characteristics, with special consideration to those with more than one risk factor.

In patients with lacSCC or mcSCC and after surgery of loco-regional metastases, clinical examination should be performed every 3 months in the first 5 years and then every 6–12 months. An ultrasound examination of the draining lymph node region is advised every 3–6 months for 5 years and then every 6–12 months. Imaging (computed tomography/magnetic resonance imaging/positron emission tomography–computed tomography) should be performed every 3–6 months in the first 3 years and then based on the assessment of individual symptoms.

For patients at high risk of other primaries (immunosuppression, haematological comorbidities, genetic predisposition, prior multiple cSCC), a close clinical follow-up schedule, every 3–6 months lifelong, should be applied, depending on the total number of tumours and the frequency of development of new tumours.

14. Patient education

When diagnosing common primary cSCC, the clinician will need to give information about the type of cSCC diagnosed and the risk of relapse or metastasis. Patients should be reminded that most cSCCs are well-differentiated tumours which have a low risk of recurrence and/or metastasis. Patients may need support from clinical nurse specialists in case of disfiguring surgery or the delivery of bad news and need to be offered access to support services when deemed necessary. Self-examination should be discussed for the diagnosis of new primary and detection of lymph nodes in the draining basins.

Patients with SCCs should also be informed of different treatment modalities and these need to be discussed when appropriate with the patient before treatment. The potential consequences of foregoing treatment should also be explained. Patient should be

Recommendation 14.

Follow-up	Consensus-based recommendation
GCP	• cSCC patients shall be followed up for recurrences and development of new non-melanoma skin cancer and melanoma. • Follow-up in all patients shall include regular clinical examination, including inspection of the entire skin and inspection and palpation of the excision site, the in-transit route and the regional lymph nodes. • Frequency of follow-up visits and imaging depend on underlying risk characteristics for cSCC: low-risk or high-risk common primary, advanced or regional disease, immunosuppression setting (detailed in Table 3). Strength of consensus: 95%

made aware that RT is not a good treatment modality in young age-groups as RT scars usually worsen over time and there is a risk of secondary malignancies.

A crucial point to remind first-line physicians and patients with is that age is certainly not a good argument to reduce or skip surgical treatment of SCC, under the argument that he/she is too old for a complete surgery. Knowing that the tumour kinetics is usually faster than the natural general degradation even in very old people, the usual consequence is a bigger lesion that has to be treated anyway a few months later, because of its impact on comfort and social life. A simple cSCC in a very old patient becomes a disaster to manage in an older patient.

An information leaflet should be provided giving facts about SCCs and these tumours are the second most common skin cancer after basal cell carcinomas. Risk factors should be explained such as chronic sun exposure, genetic and host factors such as fair skin, immunosuppression, or the presence of syndromes with increased susceptibility to skin cancers such as xeroderma pigmentosum and albinism. In patients with cSCCs and family history of uterus and/or bowel cancer, clinicians should discuss genetic counselling and testing for DNA mismatch repair genes. If the gene mutation is confirmed, the patient will be offered colon and uterus cancer screening and it is important that these patients are managed by cancer geneticists and other specialists.

Patients may have different types of follow-up schedules depending on age, location of tumour, histological subtype, and other host factors such as immunosuppression. The risk of recurrence should be discussed taking account of the tumour characteristics and other risk factors. Patients should be advised how to perform self-examination. For immunosuppressed patients, it is recommended that patients are followed up for life, ideally in dedicated clinics with experience in the management of these complex patients.

A qualitative study looked at the needs and preferences of patients with cSCC regarding treatment and follow-up care: patients mentioned that clear information on self-inspection would reduce the need for follow-up visits and that they wished information preferably on paper. Patients preferred periodic follow-up visits with a possibility to come in-between visits in case of suspicious new lesions and believed it was too hard to self-detect cancer or make self-skin examination of the whole body [133].

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Conflict of interest statement

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