Overview of guideline recommendations for the management of high-risk and advanced cutaneous squamous cell carcinoma

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Abstract Cutaneous squamous cell carcinoma (cSCC) is the second most common form of skin cancer. National and international associations have issued evidence- and consensus-based guidelines to offer clinicians a framework to optimally manage patients with invasive cSCC. Current updated guidelines regarding the recommendations on the management of patients with high-risk and advanced cSCC include EDF/EADO (European) Guidelines 2020, US National Comprehensive Cancer Network guidelines 2021, American Academy of Dermatology guidelines 2018, British Association of Dermatology guidelines 2020 and German guidelines 2020. This review presents the guideline recommendations on the definition of high-risk and advanced cSCC, surgical treatment and safety margins, definitive and adjuvant radiotherapy and systemic treatments. The recommendations across guidelines may converge, diverge or in some cases not be able to provide a recommendation, highlighting open questions to be answered by future studies.

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features present, as proposed by the Brigham and Women’s Hospital (BWH) T classification system. In the BWH system, the combination of two or more high-risk factors (among clinical diameter $\geq 2$ cm, PNI of $\geq 0.1$ mm calibre, poor differentiation, and invasion beyond subcutaneous tissue) significantly increases the risk of negative outcomes and defines a high-stage cSCC (T2b, T3). Bone invasion upstages the tumour to T3.5,14

The therapeutic recommendations for high-risk cSCC by the European guidelines are summarized in Fig. 1.

**Surgical treatment for high-risk cSCC**

In all guidelines, surgical excision is considered the first-line treatment for resectable primary cSCC and aims at clinical and microscopic complete resection (R0 surgery) with clear (negative) histological margins.

Standard surgical excision with histological confirmation of peripheral and deep margins is the first-line treatment option for resectable primary cSCC. The European guidelines recommend standard excision and postoperative margin assessment or Mohs’ micrographic surgery (MMS) for high-risk cSCC.9 The NCCN guidelines recommend standard excision and postoperative margin assessment for high-risk cSCC, or MMS or resection with complete circumferential peripheral and deep margin assessment (CCPMDMA), preferred for very high-risk cSCC.10 In the AAD guidelines, MMS is recommended for high-risk csCC, and standard excision may be considered for select high-risk cSCCs.

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**Figure 1** Main therapeutic indications for high-risk and advanced cutaneous squamous cell carcinoma (cSCC). (Reused from Stratigos et al.,9 with permission). In addition, it is noted that since the publication of this figure, anti-PD-1 agent pembrolizumab has been approved by US FDA for patients with recurrent or metastatic cSCC that is not curable by surgery or radiation. EGFRi, EGFR inhibitors; La, locally advanced; RT, radiotherapy. aFor detailed indications and recommendations of treatment, refer to relevant section text in the European Guidelines. bLocally advanced by definition not amenable to curative surgery or curative RT. cLymph node dissection as indicated. dAll 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.
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sentinel lymph node biopsy

European guidelines do not recommend SLNB for cSCC outside of the setting of clinical trials. NCCN guidelines recommend to discuss and consider SLNB in very high-risk cSCCs that are recurrent or have multiple risk factors and have normal examination of the draining nodal basin. The AAD and German guidelines do not issue any recommendation as the value of SLNB for cSCC is unknown, and the BAD guidelines recommend to consider SLNB for specific, high-risk, primary cSCC in the context of a clinical trial/SSMDT.11-13

primary definitive radiotherapy for high-risk cSCC

Definitive primary radiotherapy (RT) represents an alternative to surgery and effective curative treatment for small cSCCs. RT may be considered as a primary treatment in patients who are not candidates for surgery (e.g., locally advanced cSCC, presence of comorbidities or decline of surgery) or in cases where curative surgery is not possible or could be disfiguring or burdened by the poor functional outcome, especially cSCCs located on the face (i.e., eyelid, nose and lip) or large lesions on the ear, forehead or scalp. RT is often reserved for patients older than 60 years of age because of concerns about long-term sequelae if used in younger patients. It is proposed to inform patients <60 years of age, especially organ transplant recipients, of the very low risk of radiation-induced, in-field malignancy in the future.12

Adjuvant treatment for high-risk cSCC

High-risk cSCC is by definition node-negative. Adjuvant (postoperative) RT at the primary tumour site is RT following resection of all macroscopic tumour with or without microscopic residual disease, and it is the only adjuvant therapy recommended for selected cases of high-risk cSCC in some guidelines. The rational for its use is the possibility to reduce the risk of local recurrence.

The European guidelines recommend postoperative RT after the surgical excision for cSCC with positive margins and in cases where re-excision is not possible. The NCCN guidelines recommend multidisciplinary consultation and consider adjuvant RT for local, high-risk cSCC with negative margins, if extensive perineural, larger, or named nerve involvement, or if other high-risk features exist. It is noted, however, that ‘the outcome benefit of adjuvant RT following resection of any cSCC with negative surgical margins is uncertain’.10

In BAD guidelines, it is recommended to offer adjuvant RT to people with incompletely excised cSCC, where further surgery is not possible and in those at high risk for local recurrence (PNI, i.e. multifocal, named nerve and/or diameter of nerve >0.1 mm, below the dermis, and immunosuppression or recurrent disease). Adjuvant RT may be recommended for completely excised T3 tumours, with multiple high-risk factors including >6 mm thickness and invasion beyond subcutaneous fat. It is recommended to not offer postoperative RT for patients with completely excised T1 or T2 cSCC and with microscopic, dermal only, nerve diameter <0.1 mm PNI.12

In the German guidelines, postoperative RD should be performed for R1 or R2 resection (if re-excision not feasible) and in the presence of the following risk factors: surgical margins <2mm and re-excision not feasible, extensive PNI.13

Guidelines on the management of advanced cSCC

A definition for locally advanced cSCC is given in the European guidelines; advanced cSCC is classified as locally advanced (lacSCC) and metastatic (mcSCC) including locoregional metastatic (in-transit and regional nodal metastasis) or distant metastatic cSCC, respectively. LacSCC is defined as non-metastatic cSCC, not amenable to either surgery or radiotherapy with reasonable hope for cure, because of multiple recurrences, large extension, bone erosion or invasion, or deep infiltration beyond subcutaneous tissue into muscle or along nerves, or else tumours in which curative resection would result in unacceptable complications, morbidity or deformity. For staging and management of advanced cSCC, consultation in a multidisciplinary tumour board is necessary.

Surgical treatment for advanced cSCC

Regional therapeutic lymphadenectomy in patients with regional operable lymph node metastasis is associated with improved locoregional disease control.
The BAD and AAD guidelines recommend to offer therapeutic regional lymphadenectomy for cSCC with regional lymph node metastases that are resectable.\(^{11,12}\) The European, German and NCCN guidelines recommend therapeutic regional lymphadenectomy for cSCC with clinically or radiologically detected regional nodal metastasis.\(^{9,10,13}\) Also, the German guidelines state that there are currently insufficient data regarding the value of regional lymphadenectomy following positive SLNB.\(^{13}\) In addition, RT with or without concurrent systemic therapy may be indicated after regional lymph node dissection and are discussed below.

### Primary definitive radiotherapy for advanced cSCC

In the European and German guidelines, RT should be performed in patients with inoperable disease.\(^{9,13}\) In the NCCN guidelines, for patients with cSCC and inoperable nodal disease, multidisciplinary consultation should discuss RT with or without systemic therapy.\(^{16}\) In the AAD guidelines, it is recommended to consider combination chemoradiation for inoperable disease with regional nodal metastasis.\(^{11}\) The BAD guidelines recommend to consider regional lymphadenectomy or regional lymph node basin irradiation in selected people with cSCC for disease control even in the presence of distant metastases, especially in those undergoing multi-modality treatment.\(^{12}\)

### Systemic treatments for advanced cSCC

Systemic treatment options with a curative intent for advanced cSCC include immune checkpoint inhibitors, epidermal growth factor receptor (EGFR) inhibitors and chemotherapy/electrochemotherapy. A multidisciplinary decision approach is mandatory for all patients with advanced disease.\(^9\)

The only approved systemic treatments for advanced cSCC are anti-programmed death receptor-1 (PD-1) agents, cemiplimab and pembrolizumab. Cemiplimab was approved by the US FDA in 2018 and by the European Medicines Agency (EMA) in Europe in 2019, for patients with metastatic cSCC or locally advanced cSCC who are not candidates for curative surgery or curative radiation. The approved regimen is a fixed dose of 350 mg every 3 weeks by IV infusion.\(^{15}\) Efficacy has been shown in clinical trials reporting objective response of 50% for a cohort of patients with lacSCC or mcSCC in the phase 1 study and of 47% for mcSCC in the primary analysis of the pivotal phase 2 study (median follow-up: 11 months).\(^{16}\) Rischin et al. reported long-term outcomes of the pivotal study in 59 patients with mcSCC, with objective response rate of 49.2% at a median follow-up pf 16.5 months. Importantly, the median duration of response was not reached, underscoring a sustained efficacy. A duration of response at 12 months was sustained by 88.9% of responders.\(^{15}\) Immune-related adverse events (including maculopapular rash, hypothyroidism, diarrhoea and pneumonitis) occurred in around 60% and of grade 3 or higher in 13%.\(^{15}\) Mignon et al.\(^{17}\) reported similar objective response rates of 44% for the group of patients with lacSCC in the pivotal trial. Pembrolizumab was approved by the FDA in 2020, for patients with recurrent or metastatic cSCC that is not curable by surgery or radiation. The approved regimen is a fixed dose of 200 mg every 3 weeks by IV infusion. In the pivotal phase 2 clinical trial in 105 patients with recurrent or metastatic cSCC, there was an objective response rate of 34.3%, while the median duration of response was not reached (median follow-up: 9.5 months).\(^{18}\) Another phase 2 study evaluated pembrolizumab as first-line, systemic therapy for patients with unresectable cSCC and reported a higher objective response rate of 41% (median follow-up: 22.4 months).\(^{19}\) Among contraindications, solid organ transplant recipients and patients with significant autoimmune disease or haematological malignancy were excluded from the clinical trials with anti-PD-1 agents for cSCC.

Platinum-based chemotherapy was used for advanced cSCC 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 chemotherapy or radiotherapy.\(^{9,20}\)

The guideline recommendations for systemic treatment for advanced cSCC are presented in Table 1. The European guidelines recommend first-line systemic treatment with a PD-1 antibody for patients with mcSCC or lacSCC, who are not candidates for curative surgery or curative RT (with a strong recommendation). 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 EGFRi or RT.\(^9\) The NCCN guidelines give various recommendations for systemic therapy according to the extent of disease and whether systemic therapy will be used alone or with RT. Recommended systemic therapy options for use with RT, include (i) preferred regimens: cisplatin or clinical trial, (ii) other recommended regimens: none and (iii) useful in certain circumstances: EGFR inhibitors (e.g. cetuximab), or cisplatin + 5-FU, or carboplatin. Recommended options for systemic therapy alone include (i) preferred regimens: cemiplimab, pembrolizumab or clinical trial, (ii) other recommended regimens: carboplatin + paclitaxel and (iii) useful in certain circumstances: cetuximab, or capcitabine, or cisplatin, or cisplatin + 5-FU, or carboplatin.\(^10\) The BAD guidelines recommend to consider immune checkpoint inhibitor treatment in patients with lacSCC where curative surgery or RT is not reasonable, or those with mcSCC, except OTRs or those who have significant autoimmune conditions (with a weak recommendation).\(^{12}\) Chemotherapy and EGFRi are second-line treatments in the European and BAD guidelines, to consider in patients with mcSCC with contraindications to immune checkpoint inhibitors.\(^9,12\) The German guidelines do not recommend...
| Surgery | European 2020⁸,⁹ | US NCCN 2021¹⁰ | US AAD 2018¹¹ | UK BAD 2020¹² | German 2020¹³ |
|---------|------------------|-----------------|---------------|--------------|-------------|
| Surgical regional lymphadenectomy for cSCC with clinically or radiologically detected regional nodal metastasis (GOR: B) | Therapeutic regional lymphadenectomy for cSCC with regional nodal metastasis (GOR: 2A) | Therapeutic regional lymphadenectomy for cSCC with regional nodal metastasis (GOR: B) | Therapeutic regional lymphadenectomy for cSCC with regional nodal metastasis (GOR: strong) | Therapeutic regional lymphadenectomy should be performed in clinically manifest LN metastasis (GOR: B) |
| Primary RT | RT should be performed in patients with inoperable disease (GOR: B) | Inoperable regional nodal metastasis should be treated with RT after multidisciplinary board (and consider concurrent systemic therapy after MDT) (GOR: 2A) | Consider combination chemoradiation for inoperable disease with regional lymph node metastasis (GOR: B) | Consider regional lymphadenectomy or regional lymph node basin irradiation in selected people with cSCC for disease control even in the presence of distant metastases, especially in those undergoing multi-modality treatment (GOR: GPP) | RT should be performed in patients with inoperable disease (GOR: B) |
| Systemic treatments | First-line treatment with a PD-1 antibody for patients with mcSCC or lacSCC who are not candidates for curative surgery or curative RT (GOR: A) (cemiplimab currently the only approved medication in Europe and USA, pembrolizumab approved in USA) | For lacSCC in non-surgical candidates, to consider for use in combination with RT, after MDT, preferred regimens: cisplatin or clinical trial (GOR: 2A) | Consider ICI in people with lacSCC where curative surgery or RT is not reasonable, or those with mcSCC, except OTR or those who have significant autoimmune conditions (GOR: Weak) | Systemic treatment should be reviewed in patients with recurrent local or locoregional disease if no surgical or RT options are available (GOR: expert consensus) |
| 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 (GOR: C) | For lacSCC in which curative surgery and curative RT are not feasible, recommend MDT to consider systemic alone, preferred regimens: cemiplimab, pembrolizumab, or clinical trial (GOR: 2A) | EGFR inhibitors and cisplatin, as a single agent or in combination therapy may be considered for metastatic disease (GOR: B) | Consider chemotherapy or EGFR inhibitors in people with mcSCC with contraindications to ICI (GOR: Weak) | No controlled or randomized studies on the benefit of systemic treatment for mcSCC. If used, systemic treatment should preferably be administered in the context of clinical trials (GOR: expert consensus) |
| 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 EGFRi or RT (GOR: C) | For new inoperable regional nodal metastasis, to consider concurrent systemic therapy with RT, after MDT. Options: cisplatin, clinical trial. Useful in certain cases: EGFRi, cisplatin + 5-FU, carboplatin (GOR: 2A) | | | |

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a specific systemic treatment for advanced cSCC. It is stated that systemic treatment should be reviewed in patients with recurrent local or locoregional disease if no surgical or RT options are available. Also, according to expert consensus, there are no controlled or randomized studies on the benefit of systemic treatment for metastatic cSCC, and if used, systemic treatment should preferably be administered in the context of clinical trials, while the decision to administer systemic treatment and its choice should be made by an interdisciplinary tumour board.13

**Adjuvant treatment for advanced cSCC**

The only adjuvant treatment recommended for advanced cSCC is postoperative RT after a therapeutic lymphadenectomy for cSCC with clinically apparent (via palpation or imaging) regional lymph node metastasis, depending on the number and size of nodal metastasis and the presence of extracapsular extension (ECE; Table 2).

In the European guidelines, adjuvant systemic therapy is not recommended for fully resected regional disease, except in the context of clinical trials.9 In the NCCN guidelines, adjuvant systemic therapy is not recommended for most cases of fully resected regional disease, unless within a clinical trial. RT may be considered with or without systemic therapy for completely resected ECE or similar high-risk regional disease.10

**Conclusions**

There are various common recommendations across guidelines. Surgery with a curative intent is recommended as the treatment of choice for resectable high-risk or advanced (regional nodal metastatic) cSCC aiming to the complete removal of the tumour with uninvolved (negative) pathological margins. In case of involved (positive) histological margins, a re-excision is recommended if feasible in all guidelines. Definitive RT should be considered for non-surgical candidates. The only adjuvant treatment recommended for advanced cSCC is postoperative RT after a therapeutic lymphadenectomy for cSCC with clinically apparent (via palpation or imaging) regional lymph node metastasis. For immunosuppressed patients, it is recommended to consider modification or reduction in immunosuppression as appropriate. A multidisciplinary tumour board discussion is mandatory for all patients with advanced cSCC. The European guidelines recommend first-line systemic treatment with a PD-1 antibody for patients with mcSCC or IaSCC, who are not candidates for curative surgery or curative RT (in the absence of contraindications). Cemiplimab is the PD-1 antibody currently licensed in Europe for this indication. Also, the participation of patients in clinical trials should be encouraged.

The guidelines screen and grade a huge and quickly accumulating amount of evidence in order to provide physicians with evidence- and expert consensus-based guidance in clinical decisions. The recommendations across guidelines may converge,
Table 2  Guidelines on adjuvant treatment for advanced cSCC

| European 2020 | US NCCN 2021 | US AAD 2018 | UK BAD 2020 | German 2020 |
|---------------|--------------|-------------|-------------|-------------|
| **Adjuvant RT** | Adjuvant RT should be considered in cSCC of the head and neck with regional nodal metastases and ECE (GOR: B) | For cSCC of trunk and extremities, following therapeutic regional lymphadenectomy: adjuvant RT may be considered especially if multiple involved nodes or ECE (GOR: 2A) | Surgical resection, with or without adjuvant RT (GOR: B) and possible systemic therapy recommended for regional lymph node metastasis (GOR: B) | Offer adjuvant RT following therapeutic regional lymphadenectomy for cSCC with high-risk pathology (e.g. two or more nodes, large nodes and ECE, UICC8 ≥ pN1) (GOR: Strong) | Postoperative RT should be performed in: R1 or R2 resection (if re-excision not feasible) extensive lymph node involvement (>1 affected LN, LN metastasis >3 cm, capsular penetration) intraparotid LN involvement (GOR: B) |
| **Adjuvant systemic therapy** | Adjuvant systemic therapy is not recommended for fully resected regional disease. Ongoing clinical trials | | Adjuvant systemic therapy is not recommended for most cases of fully resected regional disease, unless within a clinical trial (GOR: 2A) | | There is currently insufficient data regarding the value of regional lymphadenectomy following positive SLNB |

cSCC, cutaneous squamous cell carcinoma; RT, radiotherapy.
diverge or in some cases fail to provide any solid recommendation, underscoring current gaps in scientific knowledge.

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