



# Evidence-Based Consensus Recommendations for the Evolving Treatment of Patients with High-Risk and Advanced Cutaneous Squamous Cell Carcinoma

Guilherme Rabinowits<sup>1</sup>, Michael R. Migden<sup>2,3</sup>, Todd E. Schlesinger<sup>4</sup>, Robert L. Ferris<sup>5,6,7,8</sup>, Morganna Freeman<sup>9</sup>, Valerie Guild<sup>10</sup>, Shlomo Koyfman<sup>11</sup>, Anna C. Pavlick<sup>12</sup>, Neil Swanson<sup>13</sup>, Gregory T. Wolf<sup>14</sup> and Scott M. Dinehart<sup>15</sup>

Cutaneous squamous cell carcinoma is the second most common skin cancer in the United States. Currently, there is no standardized management approach for patients with cutaneous squamous cell carcinoma who develop metastatic or locally advanced disease and are not candidates for curative surgery or curative radiation. To address this issue, the Expert Cutaneous Squamous Cell Carcinoma Leadership program convened an expert steering committee to develop evidence-based consensus recommendations on the basis of a large, structured literature review. Consensus was achieved through modified Delphi methodology. The steering committee included five dermatologists, three medical oncologists, two head and neck surgeons, one radiation oncologist, and a patient advocacy group representative. The steering committee aligned on the following clinical topics: diagnosis and identification of patients considered not candidates for surgery; staging systems and risk stratification in cutaneous squamous cell carcinoma; the role of radiation therapy, surgery, and systemic therapy in the management of advanced disease, with a focus on immunotherapy; referral patterns; survivorship care; and inclusion of the patient's perspective. Consensus was achieved on 34 recommendations addressing 12 key clinical questions. The Expert Cutaneous Squamous Cell Carcinoma Leadership steering committee's evidence-based consensus recommendations may provide healthcare professionals with practically oriented guidance to help optimize outcomes for patients with advanced cutaneous squamous cell carcinoma.

*JID Innovations* (2021);1:100045 doi:10.1016/j.xjidi.2021.100045

<sup>1</sup>Division of Hematology Oncology, Miami Cancer Institute/Baptist Health South Florida, Miami, Florida, USA; <sup>2</sup>Department of Dermatology, The University of Texas MD Anderson Cancer Center, Houston, Texas, USA; <sup>3</sup>Department of Head and Neck Surgery, The University of Texas MD Anderson Cancer Center, Houston, Texas, USA; <sup>4</sup>Dermatology & Laser Center of Charleston, Summerville, South Carolina, USA; <sup>5</sup>Department of Otolaryngology, University of Pittsburgh, Pittsburgh, Pennsylvania, USA; <sup>6</sup>Department of Immunology, University of Pittsburgh, Pittsburgh, Pennsylvania, USA; <sup>7</sup>Department of Radiation Oncology, University of Pittsburgh, Pittsburgh, Pennsylvania, USA; <sup>8</sup>UPMC Hillman Cancer Center, University of Pittsburgh, Pittsburgh, Pennsylvania, USA; <sup>9</sup>City of Hope Comprehensive Cancer Center, Duarte, California, USA; <sup>10</sup>AIM at Melanoma Foundation, Plano, Texas, USA; <sup>11</sup>Department of Radiation Oncology, Cleveland Clinic, Cleveland, Ohio, USA; <sup>12</sup>Sandra and Edward Meyer Cancer Center, Weill Cornell Medicine, New York City, New York, USA; <sup>13</sup>Oregon Health & Science University, Portland, Oregon, USA; <sup>14</sup>Department of Otolaryngology-Head and Neck Surgery, Michigan Medicine, University of Michigan, Ann Arbor, Michigan, USA; and <sup>15</sup>Arkansas Dermatology & Skin Cancer Center, Little Rock, Arkansas, USA

Correspondence: Guilherme Rabinowits, Division of Hematology Oncology, Miami Cancer Institute, 8900 North Kendall Drive, Miami, Florida 33176, USA. E-mail: [GuilhermeR@baptisthealth.net](mailto:GuilhermeR@baptisthealth.net)

Abbreviations: cSCC, cutaneous squamous cell carcinoma; EXCeL, Expert Cutaneous Squamous Cell Carcinoma Leadership

Received 7 December 2020; revised 3 June 2021; accepted 7 June 2021; accepted manuscript published online XXX; corrected proof published online XXX

Cite this article as: *JID Innovations* 2021;1:100045

## INTRODUCTION

Cutaneous squamous cell carcinoma (cSCC) is the second most common skin cancer (NCCN, 2019; Work Group et al., 2018), with an estimated annual incidence of ~700,000 in the United States requiring ~1 million medical procedures (on the basis of the Medicare database only) and resulting in over 8,000 deaths per year. The incidence is increasing, with reports estimating that new cases of cSCC have increased by up to 263% over the past 30 years and are likely to increase further with a growing elderly population (Karia et al., 2013; Que et al., 2018a).

In addition, there is an increased focus on skin cancer screening, which may lead to higher rates of detection (Karia et al., 2013). Owing to increased sun exposure, the incidence of cSCC is also greater in the southern regions of the United States, where the number of annual deaths is estimated to be similar to that of melanoma and other common cancer types (Karia et al., 2013). Reported incidence rates range from 60 per 100,000 person-years in Canada to 290 per 100,000 person-years in Arizona (Green and Olsen, 2017).

Most patients with cSCC have localized, low-risk (for recurrence or metastasis) disease that can be treated with complete surgical resection (Mohs micrographic surgery or wide excision) with 5-year disease-free rates of  $\geq 90\%$  (NCCN, 2019). However, the risk of nodal metastasis in cSCC

ranges from 4% to 6% (Brantsch et al., 2008; Czarniecki et al., 1994; Fox et al., 2019; Joseph et al., 1992; Schmults et al., 2013; Work Group et al., 2018), and a small percentage of patients with cSCC develop metastatic or locally advanced disease (collectively referred to as advanced disease in the remaining part of this paper) and are not good candidates for potentially curative surgery (Migden et al., 2018). In these patients, radiation therapy, chemotherapy, and targeted therapies have been used to manage the disease (NCCN, 2019; Work Group et al., 2018). However, there is a lack of robust clinical data supporting these treatment options, and there is no standardized management approach (NCCN, 2019; Work Group et al., 2018).

Although the overall mortality rate of patients with cSCC is approximately 1–3%, the total number of deaths from cSCC has been estimated to be similar to that from melanoma (Brantsch et al., 2008; Eigentler et al., 2017; Hillen et al., 2018; Karia et al., 2013; Schmults et al., 2013). Patients with advanced cSCC have a very poor prognosis, with high recurrence rates (nearly 50% with large-caliber perineural invasion), metastasis rates (32.8% with poorly differentiated tumors), and mortality rates (a 5-year and 10-year survival rates of ~60% and <20%, respectively, in patients with regional lymph node involvement and 10-year survival rate <10% in those with distant metastases) even with the addition of adjuvant radiation therapy or chemotherapy (Alam and Ratner, 2001; Clayman et al., 2005; Green and Olsen, 2017; Hillen et al., 2018; Mendez and Thornton, 2018; Que et al., 2018a; Rowe et al., 1992). In addition, patients often have a poor QOL from disfiguring and functionally impairing surgeries and from the psychosocial impact of the disease (Arunachalam et al., 2011; Berens et al., 2017).

The aim of the Expert Cutaneous Squamous Cell Carcinoma Leadership (EXCeL) program was to address key clinical questions in the treatment of advanced cSCC by (i) helping to identify the characteristics of patients with advanced cSCC who are not candidates for surgery; (ii) providing a framework for current treatment options and the role of a multidisciplinary team in managing advanced disease; and (iii) developing evidence-based consensus recommendations with respect to cSCC tumor staging, work up, treatment, and surveillance. In this study, we report the evidence-based consensus recommendations of the EXCeL multidisciplinary steering committee, synthesized through a validated approach that includes a comprehensive literature review and a modified Delphi process.

## RESULTS

To address the clinical questions identified by the steering committee, a literature search was performed, and a total of 5,471 publications (Tables 1–14) went through an initial abstract screening. The steering committee developed and voted on 36 recommendations relating to the 12 key clinical questions. The recommendations, together with their consensus percentages and levels of evidence, are presented in Tables 15–20, and the evidence supporting them is briefly summarized in the following section. A consensus was reached on 34 of 36 recommendations, with nine achieving 100% consensus. Consensus could not be reached on two

statements owing to the lack of available data to support or refute them.

### Diagnosis and identification of patients considered not candidates for surgery

The steering committee defined locally advanced cSCC as a local tumor where surgery or radiation is unlikely to obtain clearance of the tumor or where the patient is not a candidate for surgery or radiation owing to an inability to safely reconstruct the wound or owing to high morbidity unacceptable to the patient (based on a multidisciplinary discussion as well as discussion with the patient) (Table 16). This definition was selected because it corresponds to experience in daily clinical practice and because similar criteria have been used in previous clinical studies of nonmelanoma skin cancer (Hillen et al., 2018; Migden et al., 2018; Reigneau et al., 2015; Sekulic et al., 2012).

Cutaneous in-transit and regional lymph node metastases are the most common metastatic presentation in cSCC, followed by distant metastases (Work Group et al., 2018). On the basis of expert opinion, in-transit metastases have a different prognosis from distant metastases, and therefore, the steering committee recommends that in-transit metastases should be classified as locally advanced cSCC. Metastatic cSCC should be defined as any disease that has spread to a distant organ, to a lymph node, or to subcutaneous tissues beyond the draining lymphatics of the primary tumor location (Table 16). No evidence-based publications give a specific definition of resectability in cSCC.

For cSCCs with high-risk features (such as invasion of subcutaneous tissue or histologic grade  $\geq 2$ , which may increase the risk of developing recurrent or metastatic disease) or cSCC in high-risk locations (scalp, ears, eyelids, nose, lips), current guidelines recommend that lesions with a diameter <1 cm, of 1–1.9 cm, and  $\geq 2$  cm would require excisions with at least 4 mm, 6 mm, and 9 mm clinical margins, respectively (NCCN, 2019). The steering committee recommends that a patient's appropriateness for surgery should be assessed on a case-by-case basis by a surgeon with experience in treating patients with advanced cSCC. Inappropriate patients include those with a low probability of cure with surgery (with or without additional radiation therapy) as well as patients with comorbid medical conditions that may pose a higher risk of complications from surgery or anesthesia. In complex cases, a second opinion may be warranted. Evidence indicates that all cases of advanced cSCC (locally advanced and metastatic) require, when possible, the involvement of a multidisciplinary team consisting of at least dermatologists, radiation oncologists, medical oncologists, and surgeons from one or more of the following specialties: head and neck surgeons, Mohs surgeons, and surgical oncologists (Baum et al., 2018; DI Stefani et al., 2017). The steering committee also recommends involving patients in multidisciplinary team discussions and incorporating their preferences into the decision-making process (Table 16).

### Staging systems and risk stratification in cSCC

Two validated staging systems for cSCC are available (Amin et al., 2017; Jambusaria-Pahlajani et al., 2013; Karia et al., 2014; Roscher et al., 2018). Most physicians tend to use either the American Joint Committee on Cancer or the

**Table 1. Question 1 Search Term String Results**

**1. What Indicates a Diagnosis of LA cSCC over Metastatic cSCC?**

| No | Searches   | Objective   | Results   |
|----|--|---|-----------|
| 1  | (Skin[tw] OR cutaneous[tw] OR skin neoplasms[MeSH]) AND (carcinoma, squamous cell [MeSH] OR squamous cell carcinoma <sup>1</sup> [tw] OR SCC[tw]) OR cSCC[tw] OR squamous cell skin cancer <sup>1</sup> [tw]   | Permutations of cSCC  | 23,561    |
| 2  | Diagnosis[MeSH] OR diagnosis[tw] OR diagnose <sup>1</sup> [tw] OR diagnostic[tw] OR work up[tw]  | Permutations of diagnosis   | 9,606,646 |
| 3  | Neoplasm metastasis[MeSH] OR neoplasm recurrence, local [MeSH] OR recurrence[tw] OR recurrent[tw] OR advanced[tw] OR metastatic[tw] OR metastasize[tw] OR metastatise[tw] OR metastasized[tw] OR metastasised[tw] OR metastases[tw] OR contiguous[tw] OR (stage [III OR IV OR IIIa OR IIIb]) | Permutations of advanced disease  | 1,326,104 |
| 4  | 1 AND 2 AND 3  |   | 3,536     |
| 5  | 1 AND 2 AND 3; limited to past 10 y; limited to English  |   | 1,534     |
| 6  | (Skin[tw] OR cutaneous[tw] OR skin neoplasms[MeSH]) AND (carcinoma, squamous cell/diagnosis[MeSH] OR squamous cell carcinoma <sup>1</sup> [ti] OR SCC[ti] OR cSCC[ti] OR (squamous cell[ti] AND skin cancer[ti]))  | Increase specificity by including SCC in title or with MeSH subheading of diagnosis | 7,559     |
| 7  | 2 AND 3 AND 6; limited to past 10 y; limited to English  |   | 770       |

Abbreviations: cSCC, cutaneous squamous cell carcinoma; LA, locally advanced; MeSH, Medical Subject Headings; No, number; SCC, squamous cell carcinoma; tw, text word.

For congress searches in 2017–2018, no relevant publications were identified. Please note that the question in the table has been reviewed, supplemented, and refined by the steering committee for the voting process; the final list of clinical questions is presented in Table 15.

<sup>1</sup>Metastatic or LA cSCC.

Brigham and Women’s Hospital staging system (Jambusaria-Pahlajani et al., 2013; Karia et al., 2014). Unlike American Joint Committee on Cancer staging, the Brigham and Women’s Hospital staging does not address nodal, metastatic, and advanced stage groups (Karia et al., 2014; Work Group et al., 2018). However, Brigham and Women’s Hospital staging focuses on the presence of more than one high-risk factor and may avoid inappropriate upstaging of low-risk disease (Karia et al., 2014). The steering committee recommends combining aspects of both staging systems to help identify patients with advanced cSCC who are at risk of recurrence, metastasis, and/or death (Table 17). Although current tumor staging systems do not define the criteria for

locally advanced cSCC, they do use features commonly seen in those tumors. The steering committee recommends that current tumor staging should not have a prominent role in making systemic treatment decisions in advanced cSCC.

No formal guidelines for synoptic pathology reporting to assist in tumor staging and clinical decision making are available, although some recommendations are included in the current clinical guidelines (NCCN, 2019; Work Group et al., 2018). The steering committee recommends that several key pathology requirements on the basis of histologic risk factors for recurrence and/or metastatic cSCC be included (Table 17). These evidence-based risk factors include tumor diameter ( $\geq 2$  cm) (Haisma et al., 2016;

**Table 2. Question 2 Search Term String Results**

**2. How Would You Determine Noncandidacy for Surgery for Patients with Advanced<sup>1</sup> Disease?**

| No | Searches  | Objective                          | Results   |
|----|---|------------------------------------|-----------|
| 1  | (Skin[tw] OR cutaneous[tw] OR skin neoplasms[MeSH]) AND (carcinoma, squamous cell[MeSH] OR squamous cell carcinoma <sup>1</sup> [tw] OR SCC[tw]) OR cSCC[tw] OR squamous cell skin cancer <sup>1</sup> [tw]   | Permutations of cSCC               | 23,561    |
| 2  | (Candidate <sup>1</sup> [tw] OR candidacy[tw] OR eligible[tw] OR eligibility[tw] OR indication <sup>1</sup> [tw] OR indicated[tw] OR contra-indicat <sup>1</sup> [tw] OR contraindicat <sup>1</sup> [tw] OR fatigue[tw]) AND (surgical[tw] OR surgery[tw] OR resect[tw] OR resection[tw] OR resected[tw] OR excision[tw] OR excise <sup>1</sup> [tw] OR unresectable[tw]) | Permutations of surgical candidacy | 244,113   |
| 3  | Neoplasm metastasis[MeSH] OR neoplasm recurrence, local[MeSH] OR recurrence[tw] OR recurrent[tw] OR advanced[tw] OR metastatic[tw] OR metastasize[tw] OR metastatise[tw] OR metastasized[tw] OR metastasised[tw] OR metastases[tw] OR contiguous[tw] OR (stage [III OR IV OR IIIa OR IIIb])   | Permutations of advanced disease   | 1,326,104 |
| 4  | 1 AND 2 AND 3   |                                    | 277       |
| 5  | 1 AND 2; limited to past 10 y; limited to English language  |                                    | 109       |

Abbreviations: cSCC, cutaneous squamous cell carcinoma; MeSH, Medical Subject Headings; No, number; tw, text word.

For congress searches in 2017–2018, no relevant publications were identified. Please note that the question in the table has been reviewed, supplemented, and refined by the steering committee for the voting process; the final list of clinical questions is presented in Table 15.

<sup>1</sup>Metastatic or locally advanced cSCC.

**Table 3. Question 3 Search Term String Results**

**3. How Should Different Staging Systems Be Used in Practice for the Management of Advanced cSCC?**

| No | Searches  | Objective                                | Results   |
|----|---|--|-----------|
| 1  | (Skin[tw] OR cutaneous[tw] OR skin neoplasms[MeSH]) AND (carcinoma, squamous cell[MeSH] OR squamous cell carcinoma <sup>1</sup> [tw] OR SCC[tw]) OR cSCC [tw] OR squamous cell skin cancer <sup>1</sup> [tw]  | Permutations of cSCC                     | 23,561    |
| 2  | (Neoplasm staging[MeSH] OR staging[tw] OR stage[tw] OR staged[tw] OR classify [tw] OR classification[tw] OR classified[tw] OR diagnosis[tw] OR diagnose <sup>1</sup> [tw] OR diagnostic[tw] OR work up[tw])   | Permutations of staging                  | 5,803,431 |
| 3  | Neoplasm metastasis[MeSH] OR neoplasm recurrence, local[MeSH] OR recurrence[tw] OR recurrent[tw] OR advanced[tw] OR metastatic[tw] OR metastasize[tw] OR metastatise[tw] OR metastasized[tw] OR metastasised[tw] OR metastases[tw] OR contiguous[tw] OR (stage [III OR IV OR IIIa OR IIIb]) | Permutations of advanced disease         | 1,326,104 |
| 4  | Guideline[publication type] OR ‘practice guidelines as topic’[MeSH] OR guideline <sup>1</sup> [tw] OR ‘clinical decision-making’[MeSH] OR treatment decision[tw] OR practice[tw] OR ‘disease management’[MeSH] OR real world[tw] OR ‘evidence-based practice’[MeSH]                         | Permutations of use in clinical practice | 1,262,607 |
| 5  | 1 AND 2 AND 3 AND 4   |  | 143       |
| 6  | 1 AND 2 AND 3 AND; limited to past 10 y; limited to English   |  | 89        |

Abbreviations: ACMS, American College of Mohs Surgery; cSCC, cutaneous squamous cell carcinoma; MeSH, Medical Subject Headings; No, number; tw, text word.

For congress searches in 2017–2018, one abstract was identified in ACMS 2017. Please note that the question in the table has been reviewed, supplemented, and refined by the steering committee for the voting process; the final list of clinical questions is presented in Table 15.

<sup>1</sup>Metastatic or locally advanced cSCC.

NCCN, 2019; Thompson et al., 2016), thickness (Breslow)/ level of tissue invasion (Eigentler et al., 2017; NCCN, 2019; Thompson et al., 2016; Work Group et al., 2018), and differentiation (Haisma et al., 2016; NCCN, 2019; Thompson et al., 2016; Work Group et al., 2018) as well as the presence of desmoplasia (Eigentler et al., 2017; NCCN, 2019); perineural invasion (NCCN, 2019; Thompson et al., 2016; Work Group et al., 2018); lymphovascular invasion (Gore et al., 2016; NCCN, 2019; Work Group et al., 2018); the invasion of fascia, muscle, or bone (Work Group et al., 2018); and the extent of lymphocyte infiltration (Kyrgidis et al., 2010), which is often difficult to measure and quantify reliably. The significant prognostic impact of the extent of lymphocyte infiltration in patients with cSCC will need further research.

The steering committee recommends obtaining adequate, high-quality biopsy tissue and/or excisional specimens (which may include Mohs excision frozen tissue histologically interpreted by the Mohs surgeons) to accurately assess these histological parameters.

In addition, any physician evaluating cSCC specimens should be encouraged to document the results in a synoptic pathology report, when adequate tissue has been submitted.

Sentinel lymph node biopsies as a prognostic factor have been investigated in several studies, although data are only currently available from small studies, and the prognostic value of this technique has not yet been established (NCCN, 2019; Stratigos et al., 2015; Work Group et al., 2018).

Additional patient characteristics that confer an increased risk of poor outcomes in cSCC include immunosuppression

**Table 4. Question 4 Search Term String Results**

**4. What Is the Role of Synoptic Pathology Reports in the Diagnosis of cSCC?**

| No | Searches  | Objective   | Results   |
|----|---|---|-----------|
| 1  | (Skin[tw] OR cutaneous[tw] OR skin neoplasms[MeSH]) AND (carcinoma, squamous cell[MeSH] OR squamous cell carcinoma <sup>1</sup> [tw] OR SCC[tw]) OR cSCC[tw] OR squamous cell skin cancer <sup>1</sup> [tw] | Permutations of cSCC  | 23,561    |
| 2  | Diagnosis[MeSH] OR diagnosis[tw] OR diagnose <sup>1</sup> [tw] OR diagnostic[tw] OR work up[tw]   | Permutations of diagnosis   | 9,606,646 |
| 3  | Synoptic  | Synoptic in all fields  | 1,296     |
| 4  | 1 AND 2 AND 3   |   | 0         |
| 5  | (Pathology[MeSH] OR pathology[tw] OR pathologic[tw] OR pathological[tw]) AND (report[tw] OR reports[tw] OR reporting[tw])   | Increase sensitivity by using the term pathology reports rather than synoptic | 768,964   |
| 6  | 1 AND 2 AND 5   |   | 2,662     |
| 7  | 1 AND 2 AND 5; limited to past 10 y; limited to English   |   | 1,097     |

Abbreviations: cSCC, cutaneous squamous cell carcinoma; MeSH, Medical Subject Headings; No, number; tw, text word.

For congress searches in 2017–2018, no relevant publications were identified. Please note that the question in the table has been reviewed, supplemented, and refined by the steering committee for the voting process; the final list of clinical questions is presented in Table 15.

<sup>1</sup>Metastatic or locally advanced cSCC.

**Table 5. Question 5 Search Term String Results**

**5. What Patient/Tumor Characteristics Suggest Increased Risk for Recurrence or Metastatic Disease?**

| No | Searches  | Objective                        | Results   |
|----|---|----------------------------------|-----------|
| 1  | (Skin[tw] OR cutaneous[tw] OR skin neoplasms[MeSH]) AND (carcinoma, squamous cell[MeSH] OR squamous cell carcinoma <sup>1</sup> [tw] OR SCC[tw]) OR cSCC[tw] OR squamous cell skin cancer <sup>1</sup> [tw]   | Permutations of cSCC             | 23,561    |
| 2  | Neoplasm metastasis[MeSH] OR neoplasm recurrence, local[MeSH] OR recurrence[tw] OR recurrent[tw] OR advanced[tw] OR metastatic[tw] OR metastasize[tw] OR metastatise[tw] OR metastasized[tw] OR metastasised[tw] OR metastases[tw] OR contiguous[tw] OR (stage [III OR IV OR IIIa OR IIIb]) | Permutations of advanced disease | 1,326,104 |
| 3  | Risk factors[MeSH] OR risk assessment[MeSH] OR risk factor[tiab] OR characteristic[tiab] OR protective[tw] OR protect[tw] OR predict <sup>1</sup> [tw] OR prognostic[tw]  | Permutations of risk factor      | 3,046,737 |
| 4  | 1 AND 2 AND 3   |                                  | 1,028     |
| 5  | 1 AND 2 AND 3; limited to past 10 y; limited to English   |                                  | 575       |

Abbreviations: ACMS, American College of Mohs Surgery; AHNS, American Head and Neck Society; ASCO, American Society of Clinical Oncology; ASTRO, American Society for Radiation Oncology; cSCC, cutaneous squamous cell carcinoma; MeSH, Medical Subject Headings; No, number; tw, text word.

For congress searches in 2017–2018, one abstract was identified in ACMS 2017, two in ACMS 2018, two in AHNS 2017, two in AHNS 2018, one in ASCO 2018, one in ASTRO 2017, and three in ASTRO 2018. Please note that the question in the table has been reviewed, supplemented, and refined by the steering committee for the voting process; the final list of clinical questions is presented in Table 15.

<sup>1</sup>Metastatic or locally advanced cSCC.

(e.g., solid organ transplant recipients or patients with chronic lymphocytic leukemia or HIV), tumor location (temple, ear, vermilion lip, periorbital, anogenital), concomitant conditions (albinism, xeroderma pigmentosum, recessive dystrophic epidermolysis bullosa), and the involvement of a high proportion of evaluated lymph nodes and/or extracapsular extent of tumor in lymph nodes (Chalya et al., 2012; Hirshoren et al., 2017; Tseros et al., 2016).

Several tumor-specific characteristics (including genetic, protein, and cellular infiltrate markers) may be associated with an increased risk of recurrence or metastasis in cSCC.

These include high antigen Ki-67 levels (Cañueto et al., 2018, 2017a), PD-L1 expression (García-Díez et al., 2018; Garcia-Pedrero et al., 2017; Roper et al., 2017), podoplanin expression (Cañueto et al., 2017b; Hesse et al., 2016; Kreppel et al., 2013), and loss of E-cadherin and protein-coding gene *IPP5PA* function (Hesse et al., 2016; Sekulic et al., 2010). However, without further validation and consensus on the levels of these biomarkers that would confer increased risk, the steering committee recommends that these and other molecular tests under investigation should not be adopted as risk assessment or staging tests at this time.

**Table 6. Question 6 Search Term String Results**

**6. What Tests Can Be Performed to Identify Patient/Tumor Characteristics Suggestive of Increased Risk for Recurrence and/or Metastatic Disease?**

| No | Searches   | Objective                        | Results   |
|----|--|----------------------------------|-----------|
| 1  | (Skin[tw] OR cutaneous[tw] OR skin neoplasms[MeSH]) AND (carcinoma, squamous cell[MeSH] OR squamous cell carcinoma <sup>1</sup> [tw] OR SCC[tw]) OR cSCC[tw] OR squamous cell skin cancer <sup>1</sup> [tw]  | Permutations of cSCC             | 23,561    |
| 2  | Neoplasm metastasis[MeSH] OR neoplasm recurrence, local[MeSH] OR recurrence[tw] OR recurrent[tw] OR advanced[tw] OR metastatic[tw] OR metastasize[tw] OR metastatise[tw] OR metastasized[tw] OR metastasised[tw] OR metastases[tw] OR contiguous[tw] OR (stage [III OR IV OR IIIa OR IIIb])            | Permutations of advanced disease | 1,326,104 |
| 3  | Risk factors[MeSH] OR risk assessment[MeSH] OR risk factor[tiab] OR characteristic[tiab] OR protective[tw] OR protect[tw] OR predict <sup>1</sup> [tw] OR prognostic[tw]   | Permutations of risk factor      | 3,046,737 |
| 4  | Test[tw] OR tests[tw] OR assess[tw] OR assessment <sup>1</sup> [tw] OR evaluat <sup>1</sup> [tw] OR examination <sup>1</sup> [tw] OR exam[tw] OR exams[tw] OR work up[tw] OR biomarkers[MeSH] OR biomarker <sup>1</sup> [tw] OR marker <sup>1</sup> [tw] OR gene expression [tw] OR gene signature[tw] | Permutations of tests            | 8,373,416 |
| 5  | 1 AND 2 AND 3 AND 4  |                                  | 587       |
| 6  | 1 AND 2 AND 3 AND 4; limited to past 10 y; limited to English  |                                  | 363       |

Abbreviations: cSCC, cutaneous squamous cell carcinoma; MeSH, Medical Subject Headings; No, number; tw, text word.

For congress searches in 2017–2018, two abstract was identified in ACMS 2018. Please note that the question in the table has been reviewed, supplemented, and refined by the steering committee for the voting process; the final list of clinical questions is presented in Table 15.

<sup>1</sup>Metastatic or locally advanced cSCC.

**Table 7. Question 7 Search Term String Results**

**7. When Should Radiation Therapy Be Considered for Locally Advanced Disease?**

| No | Searches  | Objective                        | Results |
|----|---|----------------------------------|---------|
| 1  | (Skin[tw] OR cutaneous[tw] OR skin neoplasms[MeSH]) AND (carcinoma, squamous cell[MeSH] OR squamous cell carcinoma <sup>1</sup> [tw] OR SCC[tw]) OR cSCC[tw] OR squamous cell skin cancer <sup>1</sup> [tw] | Permutations of cSCC             | 23,561  |
| 2  | Locally advanced[tw] OR locoregional[tw] OR loco-regional[tw] OR regionally advanced[tw] OR locally advanced[tw] OR regionally advanced[tw] OR (stage [III OR IIIa OR IIIb])                                | Permutations of locally advanced | 41,066  |
| 3  | Radiation[MeSH] OR chemoradiation[MeSH] OR carcinoma, squamous cell/ radiotherapy[MeSH] OR radiotherapy[tw] OR radiation[tw] OR chemoradiotherapy[tw] OR chemoradiation[tw] OR brachytherapy[tw]            | Permutations of radiation        | 950,173 |
| 4  | 1 AND 2 AND 3   |                                  | 400     |
| 5  | 1 AND 2 AND 3; limited to past 10 y; limited to English   |                                  | 197     |

Abbreviations: ASCO, American Society of Clinical Oncology; ASTRO, American Society for Radiation Oncology; cSCC, cutaneous squamous cell carcinoma; EADO, European Association of Dermato Oncology; MeSH, Medical Subject Headings; No, number; tw, text word.

For congress searches in 2017–2018, one abstract was identified in ASCO 2017, three in ASTRO 2018, two in EADO 2017, and two in EADO 2018. Please note that the question in the table has been reviewed, supplemented, and refined by the steering committee for the voting process; the final list of clinical questions is presented in [Table 15](#).

<sup>1</sup>Metastatic or locally advanced cSCC.

**The role of radiation therapy in the management of advanced cSCC**

The current evidence-based guidelines propose primary radiation therapy in patients with cSCC for whom surgery is not an option (NCCN, 2019; Work Group et al., 2018). Adjuvant radiation therapy (after surgery) is also proposed as a potential option for cSCC tumors with uncertain surgical margins or extensive perineural or large nerve involvement or in patients at high risk for regional or distant metastasis or in those with large or multiple lesions. In addition, adjuvant radiation therapy has been associated with longer recurrence-free and disease-free survival in primary tumors with invasion of three or more nerves in a single study (Sapir

et al., 2016). On the basis of expert opinion, the initial recommendation within statement 1 in question 7 ([Table 18](#)) indicated that adjuvant radiation was associated with a lower risk of local recurrence in primary tumors with large-caliber (>0.1 mm) nerve invasion. This statement reached 75% of agreement. A case-controlled study published after the recommendations were finalized has shown no improvement in outcomes with adjuvant radiation for patients with large-caliber (≥0.1 mm) nerve invasion or with other risk factors (Ruiz et al., 2020, 2019). Therefore, these data resulted in the revised statement 1 in question 7 that reached 91% of consensus. Because recent high-grade evidence regarding the role of radiation is lacking

**Table 8. Question 8 Search Term String Results**

**8. What Factors Should Be Considered before Performing Surgery or Further Surgery?**

| No | Searches  | Objective   | Results   |
|----|---|---|-----------|
| 1  | (Skin[tw] OR cutaneous[tw] OR skin neoplasms[MeSH]) AND (carcinoma, squamous cell[MeSH] OR squamous cell carcinoma <sup>1</sup> [tw] OR SCC[tw]) OR cSCC[tw] OR squamous cell skin cancer <sup>1</sup> [tw]   | Permutations of cSCC  | 23,561    |
| 2  | Surgical[tw] OR surgery[tw] OR electrosurgery[tw] OR cryosurgery[tw] OR resect[tw] OR resection[tw] OR resected[tw] OR excision[tw] OR excise <sup>1</sup> [tw] OR unresectable[tw] OR Mohs[tw] OR Mohs surgery[MeSH] OR surgical procedures, operative[MeSH]                               | Permutations of surgery   | 4,216,406 |
| 3  | Neoplasm metastasis[MeSH] OR neoplasm recurrence, local[MeSH] OR recurrence[tw] OR recurrent[tw] OR advanced[tw] OR metastatic[tw] OR metastasize[tw] OR metastatise[tw] OR metastasized[tw] OR metastasised[tw] OR metastases[tw] OR contiguous[tw] OR (stage [III OR IV OR IIIa OR IIIb]) | Permutations of advanced disease  | 1,326,104 |
| 4  | 1 AND 2 AND 3   |   | 1,266     |
| 5  | 1 AND 2 AND 3; limited to past 10 y   |   | 1,313     |
| 6  | (Skin[tw] OR cutaneous[tw] OR skin neoplasms[MeSH]) AND (carcinoma, squamous cell/diagnosis[MeSH] OR squamous cell carcinoma <sup>1</sup> [ti]) OR SCC[ti] OR cSCC[ti] OR (squamous cell[ti] AND skin cancer[ti])   | Increase specificity by including SCC in title or with MeSH subheading of diagnosis | 7,559     |
| 7  | 2 AND 3 AND 6; limited to past 10 y; limited to English   |   | 605       |

Abbreviations: ASTRO, American Society for Radiation Oncology; cSCC, cutaneous squamous cell carcinoma; MeSH, Medical Subject Headings; No, number; SCC, squamous cell carcinoma; tw, text word.

For congress searches in 2017–2018, one abstract was identified in ASTRO 2018. Please note that the question in the table has been reviewed, supplemented, and refined by the steering committee for the voting process; the final list of clinical questions is presented in [Table 15](#).

<sup>1</sup>Metastatic or locally advanced cSCC.

**Table 9. Question 9 Search Term String Results**

**9. How Should Response/Failure of Radiation Therapy or Surgery Be Assessed?**

| No | Searches   | Objective                             | Results   |
|----|--|---------------------------------------|-----------|
| 1  | (Skin[tw] OR cutaneous[tw] OR skin neoplasms[MeSH]) AND (carcinoma, squamous cell[MeSH] OR squamous cell carcinoma <sup>1</sup> [tw] OR SCC[tw]) OR cSCC[tw] OR squamous cell skin cancer <sup>1</sup> [tw]  | Permutations of cSCC                  | 23,561    |
| 2  | (Surgical[tw] OR surgery[tw] OR electrosurgery[tw] OR cryosurgery[tw] OR resect[tw] OR resection[tw] OR resected[tw] OR excision[tw] OR excise <sup>1</sup> [tw] OR unresectable[tw] OR Mohs[tw] OR Mohs surgery[MeSH] OR surgical procedures, operative[MeSH] OR (radiation[MeSH] OR chemoradiation [MeSH] OR carcinoma, squamous cell/radiotherapy[MeSH] OR radiotherapy [tw] OR radiation[tw] OR chemoradiotherapy[tw] OR chemoradiation[tw] OR brachytherapy[tw])) | Permutations of surgery and radiology | 4,949,076 |
| 3  | Treatment outcome[MeSH] OR response[tw] OR respond[tw] OR responses [tw] OR failure[tw] OR failed[tw]  | Permutations of response/failure      | 4,343,270 |
| 4  | Neoplasm metastasis[MeSH] OR neoplasm recurrence, local[MeSH] OR recurrence[tw] OR recurrent[tw] OR advanced[tw] OR metastatic[tw] OR metastasize[tw] OR metastatise[tw] OR metastasized[tw] OR metastasised[tw] OR metastases[tw] OR contiguous[tw] OR (stage [III OR IV OR IIIa OR IIIb])  | Permutations of advanced disease      | 1,326,104 |
| 5  | 1 AND 2 AND 3 AND 4  |                                       | 1,103     |
| 6  | 1 AND 2 AND 3; limited to past 10 y  |                                       | 505       |

Abbreviations: cSCC, cutaneous squamous cell carcinoma; MeSH, Medical Subject Headings; No, number; tw, text word.

For congress searches in 2017–2018, no relevant publications were identified. Please note that the question in the table has been reviewed, supplemented, and refined by the steering committee for the voting process; the final list of clinical questions is presented in Table 15.

<sup>1</sup>Metastatic or locally advanced cSCC.

(predominantly retrospective analyses) (Coombs et al., 2018; Dean et al., 2011; Harris et al., 2019; NCCN, 2019; Raza et al., 2015; Ross et al., 2009; Strassen et al., 2017; Teli et al., 2009; Work Group et al., 2018), the involvement of a multidisciplinary team and discussions involving the patients are recommended when considering radiation therapy. Recommendations from the steering committee for the use of radiation therapy in advanced cSCC are summarized in Table 18.

**The role of systemic therapy in the management of advanced disease, with a focus on immunotherapy**

Currently, there is no standard of care for neoadjuvant or adjuvant systemic therapy in patients with high-risk cSCC. Primary evidence relating to systemic therapies (excluding immunotherapy) is mostly limited to small studies (Bertino et al., 2016; Campana et al., 2016; Cavalieri et al., 2018; Di Monta et al., 2017; Espeli et al., 2016; Gold et al., 2018; Goyal et al., 2017; Jenni et al., 2016; Lu and Lien, 2018;

**Table 10. Question 10 Search Term String Results**

**10. When Should Systemic Therapy Be Considered?**

| No | Searches   | Objective                        | Results   |
|----|--|----------------------------------|-----------|
| 1  | (Skin[tw] OR cutaneous[tw] OR skin neoplasms[MeSH]) AND (carcinoma, squamous cell[MeSH] OR squamous cell carcinoma <sup>1</sup> [tw] OR SCC[tw]) OR cSCC [tw] OR squamous cell skin cancer <sup>1</sup> [tw]   | Permutations of cSCC             | 23,561    |
| 2  | Antineoplastic agents[MajR] OR 'drug therapy, combination'[MeSH] OR electrochemotherapy[MeSH] OR photochemotherapy[MeSH] OR chemoradiotherapy[tw] OR chemoradiation[tw] OR 'epidermal growth factor receptor'[tw] OR EGFR[tw] OR systemic[tw] OR targeted[tw] OR immunotherapy [MeSH] OR immunotherapy[tw] OR 'immune therapy'[tw] OR checkpoint[tw] OR immunologic[tw] OR PD-1[tw] OR PD-L1[tw] OR 'programmed death'[tw] | Permutations of systemic therapy | 1,782,746 |
| 3  | Neoplasm metastasis[MeSH] OR neoplasm recurrence, local[MeSH] OR recurrence [tw] OR recurrent[tw] OR advanced[tw] OR metastatic[tw] OR metastasize[tw] OR metastatise[tw] OR metastasized[tw] OR metastasised[tw] OR metastases[tw] OR contiguous[tw] OR (stage [III OR IV OR IIIa OR IIIb])   | Permutations of advanced disease | 1,326,104 |
| 4  | 1 AND 2 AND 3  |                                  | 1,212     |
| 5  | 1 AND 2 AND 3; limited to past 10 y; limited to English  |                                  | 692       |

Abbreviations: AHNS, American Head and Neck Society; ASCO, American Society of Clinical Oncology; cSCC, cutaneous squamous cell carcinoma; EADO, European Association of Dermato Oncology; ESMO, European Society for Medical Oncology; MeSH, Medical Subject Headings; No, number; SITC, Society for Immunotherapy of Cancer; tw, text word.

For congress searches in 2017–2018, one abstract was identified from AHNS 2017, three from ASCO 2017, four from ASCO 2018, one from EADO 2017, four from EADO 2018, two from ESMO 2018, one from Las Vegas Dermatology Seminar, and one from SITC 2017. Please note that the question in the table has been reviewed, supplemented, and refined by the steering committee for the voting process; the final list of clinical questions is presented in Table 15.

<sup>1</sup>Metastatic or locally advanced cSCC.

**Table 11. Question 11 Search Term String Results**

**11. When Should Immunotherapy Be Considered?**

| No | Searches  | Objective                        | Results   |
|----|---|----------------------------------|-----------|
| 1  | (Skin[tw] OR cutaneous[tw] OR skin neoplasms[MeSH]) AND (carcinoma, squamous cell [MeSH] OR squamous cell carcinoma <sup>1</sup> [tw] OR SCC[tw]) OR cSCC[tw] OR squamous cell skin cancer <sup>1</sup> [tw]  | Permutations of cSCC             | 23,561    |
| 2  | Immunotherapy[MeSH] OR immunotherapy[tw] OR ‘immune therapy’[tw] OR checkpoint [tw] OR immunologic[tw] OR PD-1[tw] OR PD-L1[tw] OR ‘programmed death’[tw]   | Permutations of immunotherapy    | 510,506   |
| 3  | Neoplasm metastasis[MeSH] OR neoplasm recurrence, local[MeSH] OR recurrence[tw] OR recurrent[tw] OR advanced[tw] OR metastatic[tw] OR metastasize[tw] OR metastatise[tw] OR metastasized[tw] OR metastasised[tw] OR metastases[tw] OR contiguous[tw] OR (stage [III OR IV OR IIIa OR IIIb]) | Permutations of advanced disease | 1,326,104 |
| 4  | 1 AND 2 AND 3   |                                  | 225       |
| 5  | 1 AND 2 AND 3; limited to past 10 y; limited to English   |                                  | 102       |

Abbreviations: ASCO, American Society of Clinical Oncology; cSCC, cutaneous squamous cell carcinoma; EADO, European Association of Dermato Oncology; ESMO, European Society for Medical Oncology; MeSH, Medical Subject Headings; No, number; SITC, Society for Immunotherapy of Cancer; tw, text word.

For congress searches in 2017–2018, two abstracts were identified from ASCO 2017, four from ASCO 2018, four from EADO 2018, one from ESMO 2018, one from Las Vegas Dermatology Seminar, and one from SITC 2017. Please note that the question in the table has been reviewed, supplemented, and refined by the steering committee for the voting process; the final list of clinical questions is presented in Table 15.

<sup>1</sup>Metastatic or locally advanced cSCC.

Mevio et al., 2012; Nottage et al., 2017; Tanvetyanon et al., 2015; Trodello et al., 2017; William et al., 2017), with only one Oxford level of evidence 2 study investigating radiation therapy plus chemotherapy after resection in patients with high-risk cSCC (Porceddu et al., 2018). Preliminary evidence indicates that electrochemotherapy and radiation therapy (with or without platinum-based chemotherapy) in patients where surgery is not an option as well as targeted single therapies (cetuximab, erlotinib, gefitinib, dacomitinib, and lapatinib) show activity in patients with advanced cSCC. Further trials are needed to determine clear roles for these therapies in any treatment algorithm.

Immunotherapies for the treatment of advanced cSCC have been investigated in clinical trials (Amoils et al., 2019; Borradori et al., 2016; García-Díez et al., 2018; Grob et al.,

2020; Kudchadkar et al., 2018; Migden et al., 2018; Younes et al., 2019). The PD-1 inhibitors cemiplimab (Migden et al., 2018; Regeneron Pharmaceuticals, 2018) and pembrolizumab (Grob et al., 2020; Merck & Co., 2020) are the two Food and Drug Administration–approved immunotherapies for use in patients with advanced cSCC who are not candidates for surgery or radiation therapy.

Evaluation of immunotherapy in immunosuppressed patients with cSCC (e.g., with concomitant HIV or chronic lymphocytic leukemia) is limited to case studies and one recent phase I/IIa study, but it indicates no unexpected safety issues (Borradori et al., 2016; Younes et al., 2019). Studies suggest that testing for the PD-L1 expression does not help to formulate treatment or predict prognosis in patients with advanced cSCC (Amoils et al., 2019; García-Díez et al.,

**Table 12. Question 12 Search Term String Results**

**12. How Should Response to/Failure of Immunotherapy Be Assessed?**

| No | Searches  | Objective                        | Results   |
|----|---|----------------------------------|-----------|
| 1  | (Skin[tw] OR cutaneous[tw] OR skin neoplasms[MeSH]) AND (carcinoma, squamous cell [MeSH] OR squamous cell carcinoma <sup>1</sup> [tw] OR SCC[tw]) OR cSCC[tw] OR squamous cell skin cancer <sup>1</sup> [tw]  | Permutations of cSCC             | 23,561    |
| 2  | Immunotherapy[MeSH] OR immunotherapy[tw] OR ‘immune therapy’[tw] OR checkpoint [tw] OR immunologic[tw] OR PD-1[tw] OR PD-L1[tw] OR ‘programmed death’[tw]   | Permutations of immunotherapy    | 510,506   |
| 3  | Neoplasm metastasis[MeSH] OR neoplasm recurrence, local[MeSH] OR recurrence[tw] OR recurrent[tw] OR advanced[tw] OR metastatic[tw] OR metastasize[tw] OR metastatise[tw] OR metastasized[tw] OR metastasised[tw] OR metastases[tw] OR contiguous[tw] OR (stage [III OR IV OR IIIa OR IIIb]) | Permutations of advanced disease | 1,326,104 |
| 4  | Treatment outcome[MeSH] OR response[tw] OR respond[tw] OR responses[tw] OR failure [tw] OR failed[tw]   | Permutations of response/failure | 4,343,270 |
| 4  | 1 AND 2 AND 3 AND 4   |                                  | 94        |
| 5  | 1 AND 2 AND 3 AND 4; limited to past 10 y; limited to English   |                                  | 48        |

Abbreviations: ASCO, American Society of Clinical Oncology; cSCC, cutaneous squamous cell carcinoma; EADO, European Association of Dermato Oncology; MeSH, Medical Subject Headings; No, number; tw, text word.

From congress searches in 2017–2018, one abstract was identified from ASCO 2018 and two from EADO 2018. Please note that the question in the table has been reviewed, supplemented, and refined by the steering committee for the voting process; the final list of clinical questions is presented in Table 15.

<sup>1</sup>Metastatic or locally advanced cSCC.



**Table 13. Question 13 Search Term String Results****13. When Should Immunotherapy Be Combined with Surgery/Radiation/Other Systemic Therapies?**

| No | Searches  | Objective   | Results   |
|----|---|---|-----------|
| 1  | (Skin[tw] OR cutaneous[tw] OR skin neoplasms[MeSH]) AND (carcinoma, squamous cell [MeSH] OR squamous cell carcinoma <sup>1</sup> [tw] OR SCC[tw]) OR cSCC[tw] OR squamous cell skin cancer <sup>1</sup> [tw]  | Permutations of cSCC  | 23,561    |
| 2  | Immunotherapy[MeSH] OR immunotherapy[tw] OR 'immune therapy'[tw] OR checkpoint [tw] OR immunologic[tw] OR PD-1[tw] OR PD-L1[tw] OR 'programmed death'[tw]   | Permutations of immunotherapy                               | 510,506   |
| 3  | (Antineoplastic agents[MajR] OR 'drug therapy, combination'[MeSH] OR electrochemotherapy[MeSH] OR photochemotherapy[MeSH] OR 'epidermal growth factor receptor'[tw] OR EGFR[tw] OR systemic[tw] OR targeted[tw]) OR (surgical[tw] OR surgery [tw] OR electrosurgery[tw] OR cryosurgery[tw] OR resect[tw] OR resection[tw] OR resected [tw] OR excision[tw] OR excise <sup>1</sup> [tw] OR unresectable[tw] OR Mohs[tw] OR Mohs surgery [MeSH] OR surgical procedures, operative[MeSH]) OR (radiation[MeSH] OR chemoradiation[MeSH] OR carcinoma, squamous cell/radiotherapy[MeSH] OR radiotherapy[tw] OR radiation[tw] OR chemoradiotherapy[tw] OR chemoradiation[tw] OR brachytherapy[tw]) | Permutations of surgery or radiotherapy or systemic therapy | 5,985,311 |
| 4  | Neoplasm metastasis[MeSH] OR neoplasm recurrence, local[MeSH] OR recurrence[tw] OR recurrent[tw] OR advanced[tw] OR metastatic[tw] OR metastasize[tw] OR metastatise[tw] OR metastasized[tw] OR metastasised[tw] OR metastases[tw] OR contiguous[tw] OR (stage [III OR IV OR IIIa OR IIIb])   | Permutations of advanced disease                            | 1,326,104 |
| 4  | 1 AND 2 AND 3 AND 4   |   | 150       |
| 5  | 1 AND 2 AND 3 AND 4; limited to past 10 y; limited to English   |   | 74        |

Abbreviations: cSCC, cutaneous squamous cell carcinoma; MeSH, Medical Subject Headings; No, number; tw, text word.

From congress searches in 2017–2018, no relevant publications were identified. Please note that the question in the table has been reviewed, supplemented, and refined by the steering committee for the voting process; the final list of clinical questions is presented in Table 15.

<sup>1</sup>Metastatic or locally advanced cSCC.

2018). There is insufficient evidence to provide recommendations on (i) the use of immunotherapy in combination with surgery, radiation therapy, or other systemic therapies and (ii) the appropriate duration of immunotherapy. Further studies are therefore needed.

Throughout the literature, treatment failure is often defined as local, regional, or distant recurrence with varying definitions, although local recurrence is often defined as disease present in the field of previous treatment (for radiation therapy and surgery) (Manyam et al., 2015; Porceddu et al., 2018; Schmults et al., 2013; Varra et al., 2018; Xu et al., 2018). In the single phase I study evaluating immunotherapy in cSCC, patients were monitored using both clinical evaluation and whole-body imaging (computed

tomography, magnetic resonance imaging, or positron emission tomography–computed tomography scan at 8-week intervals), and complete response was confirmed using biopsies of the target lesions (Migden et al., 2018). For head and neck cSCC, regular follow-up (including physical examination and radiographic imaging at the physician's discretion) is required because most patients develop recurrence or metastases within 2 years (Kropp et al., 2013; Lin et al., 2012; Lu and Lien, 2018; O'Bryan et al., 2013; Que et al., 2018b; Roozeboom et al., 2013; Schmidt et al., 2015; Schmults et al., 2013; Silberstein et al., 2015; Xu et al., 2018). Although there is no established protocol for follow-up in cSCC, various studies report evaluating patients every 3 months for the first 2 years

**Table 14. Question 14 Search Term String Results****14. When Would a Multidisciplinary Team Consultation Be Most Useful to Obtain a Consensus on Patient Care?**

| No | Searches   | Objective                              | Results |
|----|--|--|---------|
| 1  | (Skin [tw] OR cutaneous[tw] OR skin neoplasms[MeSH]) AND (carcinoma, squamous cell [MeSH] OR squamous cell carcinoma <sup>1</sup> [tw] OR SCC[tw]) OR cSCC[tw] OR squamous cell skin cancer <sup>1</sup> [tw]  | Permutations of cSCC                   | 23,561  |
| 2  | Patient care team[MeSH] OR disease management[MeSH] OR interdisciplinary communication[MeSH] OR multidisciplinary[tw] OR multidisciplinary[tw] OR interdisciplinary[tw] OR inter-disciplinary[tw] OR multidisciplinary team[tw] OR multidisciplinary team[tw] OR referral[tw] OR referral and consultation[MeSH] OR shared decision-making[tw] | Permutations of multidisciplinary team | 225,598 |
| 3  | 1 AND 2  |  | 404     |
| 4  | 1 AND 2; limited to past 10 y; limited to English  |  | 245     |

Abbreviations: cSCC, cutaneous squamous cell carcinoma; MeSH, Medical Subject Headings; No, number; tw, text word.

From congress searches in 2017–2018, no relevant publications were identified. Please note that the question in the table has been reviewed, supplemented, and refined by the steering committee for the voting process; the final list of clinical questions is presented in Table 15.

<sup>1</sup>Metastatic or locally advanced cSCC.

**Table 15. The Final List of Key Areas of Focus and Clinical Questions Identified by the EXCeL Multidisciplinary Steering Committee**

**Areas of Focus and Clinical Questions**

|  |   |
|--|---|
| Focus 1: Diagnosis and identification of patients considered not candidates for surgery                    |   |
| 1  | What indicates a diagnosis of locally advanced cSCC over metastatic cSCC?   |
| 2  | How would you determine ‘non-candidacy for surgery’ for patients with advanced disease? <sup>1</sup>  |
| Focus 2: Staging systems and risk stratification in cSCC   |   |
| 3  | How should different staging systems be used in practice for the management of advanced cSCC?   |
| 4  | How should synoptic pathology reporting be used in the diagnosis of cSCC?   |
| 5  | What patient/tumor characteristics suggest increased risk for recurrence or metastatic disease?   |
| 6  | What supplemental tests can be performed to identify tumor characteristics suggestive of increased risk for recurrence and/or metastatic disease? |
| Focus 3: The role of radiation therapy in the management of advanced cSCC                                  |   |
| 7  | What is the role of curative radiation therapy in advanced cSCC?  |
| Focus 4: The role of systemic therapy in the management of advanced disease, with a focus on immunotherapy |   |
| 8  | What systemic therapies are utilized at various stages of treatment in patients with advanced cSCC?   |
| 9  | How should response to/failure of treatments be assessed?   |
| 10   | When should immunotherapy be combined with surgery/radiation/other systemic therapies?  |
| Focus 5: Referral patterns, survivorship care, and inclusion of the patient’s perspective                  |   |
| 11   | When would a multidisciplinary team consultation be most useful to obtain a consensus opinion on patient care?                                    |
| 12   | What are the follow-up survivorship recommendations for patients with advanced cSCC?  |

Abbreviations: cSCC, cutaneous squamous cell carcinoma; EXCeL, Expert Cutaneous Squamous Cell Carcinoma Leadership.  
<sup>1</sup>Metastatic or locally advanced cSCC.

(Gauden et al., 2013; Porceddu et al., 2018; Schmidt et al., 2015).

Full consensus recommendations from the steering committee on the role of systemic therapies in advanced cSCC are summarized in Table 19. Overall, on the basis of current clinical evidence and further to recent clinical guidelines (Grob et al., 2020; Migden et al., 2018; NCCN,

2019; Stratigos et al., 2015; Work Group et al., 2018), the steering committee recommends that immunotherapy be considered first line for patients with advanced cSCC, with chemotherapy or targeted therapy to be considered in patients who are not candidates for immunotherapy (such as patients with lung, heart, and liver transplant), who have progressed on immunotherapy, or who have unresolved or

**Table 16. Evidence-Based Consensus Recommendations: Diagnosis and Identification of Patients Ineligible for Surgery**

| Key Question/Recommendation  | Consensus, % <sup>1</sup> |
|--|---------------------------|
| <b>Focus 1: Diagnosis and identification of patients considered not candidates for surgery</b>   |                           |
| 1. What indicates a diagnosis of locally advanced cSCC over metastatic cSCC?   |                           |
| 1. Locally advanced cSCC is a local tumor where surgery or radiation is unlikely to obtain clearance of the tumor or where the patient is not a candidate for surgery or radiation owing to an inability to safely reconstruct the wound or owing to high morbidity unacceptable to the patient. (Strength of recommendation: 3; Oxford level of evidence: 3)  | 82                        |
| 2. Metastatic cSCC can be defined as a disease that has spread from the original site to a distant organ or in subcutaneous tissues beyond the draining lymph nodes of the primary cSCC location. (Strength of recommendation: 2; Oxford level of evidence: 2)<br>Note: In-transit metastasis (biopsy-proven cSCC in dermal and subcutaneous tissue in the area between the primary cSCC and its draining lymph nodes) is classified as a locally advanced disease. (Expert opinion)   | 87.5                      |
| 2. How would you determine ‘non-candidacy for surgery’ for patients with advanced disease? <sup>2</sup>  |                           |
| 1. Appropriateness for surgery can be best assessed by a surgeon, including but not limited to Mohs surgeons, head and neck surgeons, and oncologic surgeons with experience in treating patients with advanced cSCC. A multidisciplinary discussion of therapeutic options with oncologists, radiation oncologists, and patients’ primary physicians can be helpful in weighing the risks and benefits of various treatment approaches, also considering patient comorbidities. For complex cases, second opinions are encouraged. (Expert opinion) | 89                        |
| 2. The appropriateness of resection should be discussed with the patient. This discussion should include the likelihood of tumor clearance with surgery and any significant risk of morbidity to determine whether the morbidity is acceptable to the patient. (Expert opinion)  | 89                        |

Abbreviation: cSCC, cutaneous squamous cell carcinoma.

<sup>1</sup>Defined as the percentage of respondents rating the recommendations 7–9 on a 9-point scale.

<sup>2</sup>Metastatic or locally advanced cSCC.

**Table 17. Evidence-Based Consensus Recommendations: Tumor Staging and Risk Stratification**

| <b>Focus 2: Staging systems and risk stratification in cSCC</b>   | <b>Consensus,<br/>%<sup>1</sup></b> |
|---|-------------------------------------|
| 3. How should different staging systems be used in practice for the management of advanced cSCC?  |                                     |
| 1. Staging systems help to identify patients with advanced cSCC who are at risk of local recurrence, metastasis, and/or death. They may be useful to compare outcomes in some but not all clinical trials. (Expert opinion)   | 78                                  |
| 2. The panel recommends using the AJCC and BWH systems as follows (Strength of recommendation: B; Oxford level of evidence: 2):<br>The BWH T staging system may be used to estimate the risk of recurrence and metastasis and identify patients who may benefit from radiologic nodal staging or increased surveillance for recurrence<br>AJCC8 N2 identifies patients at increased risk of regional treatment failure after surgery with or without radiation. These patients may benefit from consideration of systemic therapy if such failure occurs or if the nodal disease is inoperable<br>Metastases to distant organs identify patients in need of systemic therapy  | 78                                  |
| 3. On the basis of the current evidence, tumor staging does not have a prominent role in determining the appropriateness for systemic therapy, including immunotherapy in patients with advanced cSCC. However, nodal and metastasis staging systems do play a role. (Expert opinion)   | 78                                  |
| 4. Current tumor staging systems do not define the criteria for locally advanced tumors, but they utilize tumor features that are commonly seen in locally advanced tumors. (Expert opinion)  | 78                                  |
| 4. How should synoptic pathology reporting be used in the diagnosis of cSCC?  |                                     |
| 1. Synoptic pathology reports specifying the presence or absence of specific histologic features should be used to assist clinical tumor staging and guide further decisions about additional therapy beyond surgery in patients with advanced cSCC. (Expert opinion)   | 89                                  |
| 2. A synoptic pathology report for cSCC should include the following minimum key requirements:<br>Clinical preoperative tumor diameter (provided to the pathologist by the surgeon)<br>Millimeter thickness or tissue level of invasion: (i) Millimeter depth measured from the granular layer of the adjacent normal epidermis to the base of tumor (Breslow thickness) and (ii) tissue level depth of tumor invasion (e.g., dermis, fat, fascia)<br>Tumor differentiation (well, moderate, poor, undifferentiated)<br>Desmoplasia<br>Perineural invasion specifying (i) nerve caliber $\geq 0.1$ mm or (ii) invasion of a nerve lying deep to the dermis<br>Extent of lymphocyte infiltration (immunoscore)<br>Lymphovascular invasion<br>Specify whether the tumor may represent a metastasis (Expert opinion) | 89                                  |
| 3. To accurately stage cSCC using the criteria listed previously regarding synoptic pathology reporting, a quality tissue biopsy and/or excisional specimen (which may include Mohs excision frozen tissue histologically interpreted by the Mohs surgeon) should be evaluated for histologic risk factors. When possible, biopsy specimens should include the tumor base. (Expert opinion)   | 100                                 |
| 4. Non-Mohs excision specimens should be evaluated histologically for the risk factors listed in recommendation 2 regarding synoptic pathology reporting. For Mohs excisions, information from tumor debulking specimens (before the first Mohs layer) may be combined with findings on Mohs layers for optimal synoptic reporting and tumor staging. (Expert opinion)  | 100                                 |
| 5. What patient/tumor characteristics suggest increased risk for recurrence or metastatic disease?  |                                     |
| 1. Tumor diameter $\geq 2$ cm, presence of desmoplasia, tumor thickness (millimeter depth measured from the granular layer of the adjacent normal epidermis to the base of tumor [Breslow thickness]), tissue level of invasion, the caliber of perineural invasion, bone erosion, and poor differentiation are independent risk factors for local recurrence, metastasis, and/or death from the disease in patients with cSCC. (Strength of recommendation: B; Oxford level of evidence: 2a)   | 89                                  |
| 2. Certain tumor locations and characteristics confer risk for poor disease outcomes in patients with cSCC, which include the temple, ear, vermillion lip (lipstick area), periorbital, anogenital, or immunosuppression. (Strength of recommendation: B; Oxford level of evidence: 2a–2b)  | 78                                  |
| 3. Immunosuppression and certain conditions such as albinism, xeroderma pigmentosum, and recessive dystrophic epidermolysis bullosa are associated with higher risks of local recurrence, metastasis, and/or tumor-specific survival in patients with cSCC. (Strength of recommendation: B; Oxford level of evidence: 1b–2b)<br>Immunosuppressed patients include but are not limited to (i) patients with CLL, (ii) patients with drug-induced immunosuppression or HIV, (iii) patients with a solid-organ transplant, and (iv) patients with chronic graft versus host disease (Expert opinion)   | 89                                  |

(continued)

Table 17. Continued

| Focus 2: Staging systems and risk stratification in cSCC   | Consensus, % <sup>1</sup> |
|--|---------------------------|
| 4. Sentinel lymph node biopsy may detect occult metastasis in patients with high-risk cSCC; however, its ability to impact therapeutic outcomes is not yet established. (Strength of recommendation: B; Oxford level of evidence: 2a–3a)   | 87.5                      |
| 5. A high proportion of involved lymph nodes is associated with worse survival in patients with advanced cSCC. (Strength of recommendation: B; Oxford level of evidence: 2b)<br>When available, the following parameters should be considered as adjuncts to clinical nodal staging and prognosis: (i) number and level of lymph nodes, (ii) size of tumor foci within nodes, (iii) extranodal involvement, and (iv) laterality.<br>(Expert opinion)   | 87.5                      |
| 6. What supplemental tests can be performed to identify tumor characteristics suggestive of increased risk for recurrence and/or metastatic disease?   |                           |
| 1. Currently, testing of cSCCs for genetic alterations, protein expression, or specific cellular infiltrate is largely experimental with respect to predicting poor outcomes. Markers such as high Ki-67, PD-L1, and podoplanin expression and loss of E-cadherin and INPP5A have been associated with poor outcomes. However, additional validation and consensus on the level of relevant expression are needed before adopting these as clinical tests. (Strength of recommendation: C; Oxford level of evidence: 2b–4) | 75                        |
| 2. Molecular tests are currently being investigated and should not be used to make treatment decisions. Future development of molecular staging tests may provide better risk stratification. However, until more conclusive evidence is available, molecular tests should not be used to guide treatment or referral decisions. (Expert opinion)  | 100                       |

Abbreviations: AJCC, American Joint Committee on Cancer; BWH, Brigham and Women's Hospital; CLL, chronic lymphocytic leukemia; cSCC, cutaneous squamous cell carcinoma.

<sup>1</sup>Defined as the percentage of respondents rating the recommendations 7–9 on a 9-point scale.

clinically significant immunotherapy-related adverse events.

#### Referral patterns, survivorship care, and inclusion of the patient's perspective

The exact role of a multidisciplinary team for the management of cSCC has not yet been elucidated. All cases of metastatic disease should involve a multidisciplinary team in addition to palliative care specialists (Fu et al., 2016; Mittal and Colegio, 2017). The steering committee added that a multidisciplinary team consultation may be useful at any time a patient needs more than a single specialist to be involved in their care and for any patient with locally advanced disease or who could be treated with more than one therapy option (surgery, radiation therapy, surgery in combination with radiation therapy, etc.).

The current guidelines for follow-up/survivorship care in advanced cSCC recommend in-office screening at least once a year or more often, adjusting the frequency on the basis of individual patient risk (Work Group et al., 2018). Clinical assessment of lymph node basins is also recommended for high-risk cSCC owing to an increased risk of other non-melanoma or melanoma skin cancers. Guidelines also recommend that patients are counseled about the risk of new skin cancers and are advised on the benefits of regular self-screening, including all skin surfaces and lymph nodes, as well as on the need for sun protection and avoidance. Prophylactic oral retinoid therapy is recommended in select patients at high risk of multiple squamous cell carcinomas, including solid organ transplant recipients. However, the side effects of oral retinoids may be significant, and the therapeutic effects are limited to the duration of treatment. Despite the greater tolerability, there is limited evidence to make recommendations on prophylaxis with nicotinamide,

$\alpha$ -difluoromethylornithine, and celecoxib (Baum et al., 2018; Chen et al., 2015; Gilmore, 2018).

Recommendations from the steering committee for the role of a multidisciplinary team, the members of a multidisciplinary team, and patient follow-up/survivorship care are summarized in Table 20.

#### Recommendations not achieving steering committee consensus

There was a lack of consensus on only two of the recommendations, both related to the role of curative radiation therapy in advanced cSCC, highlighting specific areas where further research is needed (Table 18).

#### DISCUSSION

cSCC is the second most common skin cancer, with advanced cSCC representing an under-recognized health issue with no standardized management approach. The EXCeL program convened an expert steering committee to develop evidence-based recommendations relating to the management of advanced cSCC, which may help clinical decision making and optimize patient outcomes. By identifying gaps in the evidence base, these outputs may also help to guide further clinical research into optimizing management approaches in advanced cSCC.

The steering committee reached 100% consensus on nine consensus recommendations that broadly fell into four categories: (i) disease staging—the importance of specimen quality and synoptic reporting in evaluating disease staging and the need for further evidence to support molecular staging tests (before their use in clinical decision making); (ii) immunotherapy—the need for further studies of immunotherapies in the neoadjuvant and adjuvant setting and the enrollment of patients to support these studies; (iii) the assessment of treatment response/failure; and (iv) the

**Table 18. Evidence-Based Consensus Recommendations: The Role of Radiation Therapy in Advanced cSCC**

| Focus 3: The Role of Radiation Therapy in the Management of Advanced cSCC   | Consensus,<br>% <sup>1</sup> |
|---|------------------------------|
| <b>7. What is the role of curative radiation therapy in advanced cSCC?</b>  |                              |
| 1. Radiation therapy for advanced cSCC may be considered in the following settings: <ul style="list-style-type: none"> <li>a. Adjuvant radiation therapy may be considered in patients with uncertain surgical margins (e.g., multifocal or large-caliber nerve invasion or lymphovascular invasion) or with a recurrent tumor.</li> <li>b. Definitive radiation therapy versus systemic therapy may be considered when gross disease is present and is not amenable to surgical resection. However, the efficacy of radiation has not been investigated in grossly unresectable cSCC. Imaging is strongly suggested when clinical evaluation for assessment of response is insufficient after definitive radiation therapy. Imaging modalities may include CT, PET, PET–CT, MRI, and ultrasound and should be selected on the basis of clinical information and available evidence</li> <li>c. Adjuvant radiation may be considered for local control of microscopic residual disease that cannot be surgically resected</li> </ul> Note: Given the approval of cemiplimab, the curative confidence and morbidity of definitive, single modality radiation therapy should be considered, discussed with the patient, and weighed against those of systemic options such as immunotherapy. (Expert opinion) | 91                           |
| 2. Patients with cSCC arising within a burn scar/chronic inflammation should consider adjuvant radiation therapy in addition to surgical excision. (Strength of recommendation: C; Oxford level of evidence: 2b)  | 50                           |
| 3. Patients with recurrent, locally aggressive cSCC may be considered for adjuvant radiation therapy in addition to surgical excision for their recurrent disease when surgery is possible. (Strength of recommendation: B; Oxford level of evidence: 2b)<br>Note: Efficacy of adjuvant radiation therapy in improving outcomes in recurrent cSCC has not been investigated.  | 62.5                         |
| Abbreviations: cSCC, cutaneous squamous cell carcinoma; CT, computed tomography; MRI, magnetic resonance imaging; PET, positron emission tomography.  |                              |
| <sup>1</sup> Defined as the percentage of respondents rating the recommendations 7–9 on a 9-point scale.  |                              |

multidisciplinary team—its members and its role in helping patients and physicians know the available treatment options and in weighing the risks and benefits and its involvement in assessing treatment response and/or failure.

On the basis of the available clinical evidence, the steering committee recommends that immunotherapy now be considered the first-line systemic therapy.

In September 2018, cemiplimab, a human mAb that blocks PD-1 binding to PD-L1, was approved by the United States Food and Drug Administration for the treatment of advanced cSCC in patients who are not candidates for curative surgery or curative radiation therapy (Migden et al., 2018; Regeneron Pharmaceuticals, 2018).

The efficacy of cemiplimab in patients with advanced cSCC was evaluated in two open-label multicenter, non-randomized, multicohort studies (Regeneron Pharmaceuticals, 2018). Treatment with cemiplimab led to a response rate of 46.7% in patients with metastatic cSCC and 48.5% in patients with locally advanced cSCC. Complete responses were observed in 5.3% of patients with metastatic disease, and partial responses were reported in 41.3% and 48.5% of patients with metastatic and locally advanced diseases, respectively.

Results from updated analyses showed that treatment with cemiplimab conferred durable clinical benefits to patients with advanced cSCC (Rischin et al., 2020). Response rates of 50.8% and 42.9% were reported in patients with metastatic cSCC and receiving 3 mg/kg cemiplimab once every 2 weeks or 350 mg once every 3 weeks, respectively. Patients with locally advanced cSCC and receiving 3 mg/kg cemiplimab once every 2 weeks experienced a response rate of 44.9%.

The median duration of response and the median overall survival have not been reached.

In June 2020, another anti-PD-1 antibody, pembrolizumab, was approved in the United States for the treatment of patients with recurrent or metastatic cSCC that is not curable by surgery or radiation (Grob et al., 2020; Merck & Co., 2020). Recent results for pembrolizumab showed an objective response rate of 34.3% (95% confidence interval = 25–44) with a median follow-up time of 11.4 months in patients having recurrent or metastatic cSCC, the majority with previous exposure to systemic therapy (86.7%) or radiation (74.3%). The median progression-free survival was 6.9 months. The median overall survival and the median duration of response were not reached.

As such, the steering committee defined locally advanced cSCC as a local tumor where surgery or radiation is unlikely to obtain clearance of the tumor or where the patient is not a candidate for surgery or radiation owing to an inability to safely reconstruct the wound or owing to high morbidity unacceptable to the patient (Table 16) to avoid a narrow definition that might exclude patients otherwise eligible for immunotherapy (Migden et al., 2018). The assessment of appropriate immunotherapy treatment sequencing duration is also recommended.

On the basis of expert opinion, the steering committee recommends that in-transit metastases should be classified as locally advanced cSCC (Table 16). In support of this recommendation, recent findings from multivariate analyses of patients with high-risk cSCC showed that patients with in-transit metastases had a high rate of disease progression similar to that of patients with other locally advanced cSCC

**Table 19. Evidence-Based Consensus Recommendations: The Role of Systemic Therapy (Immunotherapy Focused) in Advanced cSCC**

| <b>Focus 4: The Role of Systemic Therapy in the Management of Advanced Disease, with a Focus on Immunotherapy</b>  | <b>Consensus, %<sup>1</sup></b> |
|--|---------------------------------|
| 8. What systemic therapies are utilized at various stages of treatment in patients with advanced cSCC?   |                                 |
| Immunotherapy <sup>2</sup>   | 87.5                            |
| 1. Cemiplimab is the only FDA-approved therapy for use in patients with locally advanced or metastatic cSCC who are not candidates for surgery or radiation. The approval was based on phase I/II data. Cemiplimab should be used as first-line therapy in patients requiring systemic treatment. (Expert opinion)   |                                 |
| 2. Appropriate use of cemiplimab in immunosuppressed patients has not been established because they have been excluded from trials published thus far. However, cemiplimab treatment is not necessarily precluded in these patients. Treatment decisions should weigh the risk of death and disability from the tumor versus the risk of immunotherapy, which can provoke exacerbations of autoimmune conditions (e.g., lupus, colitis) and organ rejection in organ transplant recipients, which can lead to rapid death in patients with lung, heart, and liver transplant. Although cemiplimab was not studied in patients with CLL and other hematologic malignancies/dyscrasias, it is likely to have a similar safety profile in these patients to that in those studied. (Expert opinion)   | 87.5                            |
| 3. On the basis of the current evidence, the degree of PD-L1 expression is not associated with the degree of response in patients with advanced cSCC. Therefore, PD-L1 should not be used as a decision-making tool for administering cemiplimab in these patients. Notably, subset analyses in other disease states have shown a correlation between PD-L1 expression and clinical benefit. (Expert opinion)  | 87.5                            |
| 4. In the neoadjuvant and adjuvant settings, treatment of cSCC with immunotherapy is under investigation through clinical trials. Enrollment of eligible patients in these trials is strongly encouraged. (Expert opinion)   | 100                             |
| Chemotherapy or targeted therapies   | 87.5                            |
| 1. Chemotherapy or targeted therapy can be considered in patients who are not candidates for immunotherapy, who have progressed on immunotherapy, or who cannot tolerate immunotherapy-related adverse events. However, response rates are low and generally of short duration. The adverse event profile may be more serious, depending on the choice of therapy. (Expert opinion)  |                                 |
| 2. Currently, there is no standard of care for neoadjuvant or adjuvant systemic therapy in advanced cSCC. In patients with locally advanced and metastatic cSCC, immunotherapy should be considered first line (with the caveats earlier mentioned), followed by targeted therapy and/or chemotherapy. (Expert opinion)  | 75                              |
| 3. Because no adjuvant, neoadjuvant, or second-line options are approved, sequencing of systemic therapy is not established for advanced cSCC. Development of and enrollment in clinical trials is strongly encouraged. (Expert opinion)   | 87.5                            |
| 9. How should response to/failure of treatments be assessed?   |                                 |
| 1. For patients who are disease free, follow-up with the treating physician who administered/performed the most recent treatment or with another designated team member should occur regularly during the first 2 y after treatment. Where possible, multidisciplinary follow-up should be employed. For patients with high-risk disease <sup>3</sup> treated with surgery alone or in combination with radiation, follow-up every 3–6 months is advised depending on disease extent and severity. For patients who required systemic therapy, follow-up every 3–4 months is recommended. Monitoring for possible late adverse events of therapy should be undertaken. Optimal radiologic surveillance is undefined but may be considered every 4–6 months for the first 2 y for survivors of high-risk cSCC <sup>3</sup> . (Expert opinion) | 100                             |
| 2. The best way to monitor response to immunotherapy is with both clinical assessment and serial imaging (every 12 weeks): (i) clinical assessment and lesion measurement (photography and physical examination), (ii) visceral/nodal/deep local disease (radiographic imaging), and (iii) pathology (option if adequate samples can be obtained that will determine treatment endpoints and therefore impact management; e.g., complete response, disease progression). (Expert opinion)  | 100                             |
| 3. The treating physician should be aware of the rare potential for pseudoprogression and expected toxicities that may occur in patients with advanced cSCC receiving immunotherapy. Clinical judgment and discussion around the continuation of treatment should occur with physicians with expertise in immunotherapy and cSCC and, when possible, within a multidisciplinary team. (Expert opinion)   | 100                             |

(continued)

Table 19. Continued

| <b>Focus 4: The Role of Systemic Therapy in the Management of Advanced Disease, with a Focus on Immunotherapy</b>  | <b>Consensus,<br/>%<sup>1</sup></b> |
|--|-------------------------------------|
| 10. When should immunotherapy be combined with surgery/radiation/other systemic therapies?   |                                     |
| 1. Future studies may elucidate the role of immunotherapy in combination with surgery, radiation, or other systemic therapies in neoadjuvant or adjuvant settings in patients with advanced cSCC. (Expert opinion) | 89                                  |
| Abbreviations: CLL, chronic lymphocytic leukemia; cSCC, cutaneous squamous cell carcinoma; FDA, Food and Drug Administration.  |                                     |
| <sup>1</sup> Defined as the percentage of respondents rating the recommendations 7–9 on a 9-point scale.   |                                     |
| <sup>2</sup> The statements in this section were determined before the approval of pembrolizumab.  |                                     |
| <sup>3</sup> Locally advanced or metastatic cSCC.  |                                     |

but not as high as that of patients with metastatic disease (Smile et al., 2021).

Another key aspect of the steering committee recommendations was the importance of multidisciplinary team involvement throughout the treatment process, which is also reflected in the recently updated clinical guidelines. The multidisciplinary team should include at least a medical oncologist, dermatologist, a surgeon (Mohs surgeon, head and neck or oncologic surgeon), and radiation oncologist and should be conducted for any patient with locally advanced disease or who could be receiving more than one treatment option. The recommendations of the multidisciplinary team should be discussed between the treating physician and the patient, particularly around incorporating patient preferences into the decision-making process. At a minimum, the steering committee recommended multidisciplinary team involvement in the following situations: during initial treatment decisions

after diagnosis of locally advanced cSCC (particularly about appropriateness for surgery [specialized surgeons], radiation therapy [radiation oncologists], locoregional/distant metastatic disease and immunosuppressed patients [medical oncologists], and more complex cases); in discussions about continuation of treatment in terms of toxicities (for chemotherapy, radiation therapy, and immunotherapy); and in the assessment of treatment response and/or failure (every 3–6 months during the first 2 years after the active treatment period, depending on the extent and severity of the disease).

Several areas where there is still a lack of consensus in cSCC and where further research is needed included those relating to the role of curative immunotherapy in the neoadjuvant and adjuvant setting and in combination with radiation therapy; the role of radiation therapy in the curative-intent setting for patients who are not surgical candidates; and the role of the standard of care combination therapies,

Table 20. Evidence-Based Consensus Recommendations: cSCC Referral Patterns and Patient Perspective

| <b>Focus 5: Referral Patterns, Survivorship Care, and Inclusion of the Patient's Perspective</b>   | <b>Consensus,<br/>%<sup>1</sup></b> |
|--|-------------------------------------|
| 11. When would a multidisciplinary team consultation be most useful to obtain a consensus opinion on patient care?   |                                     |
| 1. The goal of the multidisciplinary team is to help patients and treating clinicians know their options and weigh risks and benefits for all treatment modalities: surgery, radiation therapy, and systemic treatment. (Expert opinion)<br>Note: A multidisciplinary team consultation is most useful any time a patient may require more than a single specialist to be involved in their care.  | 100                                 |
| 2. Patients with locally advanced or metastatic cSCC may benefit from a multidisciplinary team discussion, including experts in cSCC from the areas of surgery, medicine, and radiation. Such experts include (but are not limited to) medical oncologists, dermatologists/dermato-oncologists, surgical oncologists (including head and neck and Mohs surgeons), and radiation oncologists. (Expert opinion)  | 100                                 |
| 12. What are the follow-up survivorship recommendations for patients with advanced cSCC?   |                                     |
| 1. Recommendations on follow-up/survivorship care include the following:<br>New primaries: in-office screening for new primary skin cancers should be performed at least once per year, adjusting the frequency on the basis of individual patient risk. Patients with a previous SCC are also at increased risk of developing cutaneous melanoma and basal cell carcinoma, and patients with multiple previous SCCs are at a higher risk of developing metastasis.<br>Concurrent patient self-surveillance: patients should be educated about the importance of sun protection and regular self-examination of the skin.<br>Transplant patients: patient education regarding sun avoidance and self-examination should begin shortly after transplantation.<br>Use of oral retinoids (acitretin, isotretinoin) is effective in reducing new cSCC tumor formation in patients with extensive actinic damage who have a history of multiple cSCCs. (Expert opinion) | 78                                  |

Abbreviations: cSCC, cutaneous squamous cell carcinoma; SCC, squamous cell carcinoma.

<sup>1</sup>Defined as the percentage of respondents rating the recommendations 7–9 on a 9-point scale.

**Table 21. Members of the EXCeL Steering Committee**

| Name                           | Institution   |
|--------------------------------|---|
| Scott M. Dinehart (Cochair)    | Arkansas Skin Cancer Center, Little Rock, Arkansas                                      |
| Guilherme Rabinowits (Cochair) | Miami Cancer Institute, Miami, Florida  |
| Robert L. Ferris               | University of Pittsburgh Medical Center Hillman Cancer Center, Pittsburgh, Pennsylvania |
| Morganna Freeman               | City of Hope Comprehensive Cancer Center, Duarte, California                            |
| Valerie Guild <sup>1</sup>     | AIM at Melanoma Foundation, Plano, Texas  |
| Shlomo Koyfman                 | Cleveland Clinic, Cleveland, Ohio   |
| Michael R. Migden              | MD Anderson Cancer Center, Houston, Texas   |
| Anna C. Pavlick                | Weill Cornell Medicine, Meyer Cancer Center, New York City, New York                    |
| Todd E. Schlessinger           | Dermatology & Laser Center of Charleston, Charleston, South Carolina                    |
| Chrysalynne D. Schmults        | Brigham and Women’s Hospital, Harvard Medical School, Boston, Massachusetts             |
| Neil Swanson                   | Oregon Health & Science University, Portland, Oregon                                    |
| Gregory T. Wolf                | Michigan Medicine, University of Michigan, Ann Arbor, Michigan                          |

Abbreviation: EXCeL, Expert Cutaneous Squamous Cell Carcinoma Leadership.  
<sup>1</sup>Valerie Guild is deceased (May 21, 2020).

treatment sequencing, and the validation of biomarker and molecular tests to aid tumor staging and prognosis. Data are needed to better define the optimal treatment for patients who are not candidates for immunotherapy, who have progressed on immunotherapy, or who cannot tolerate immunotherapy-related adverse events. Currently, several trials are ongoing to help elucidate the role of these treatment modalities for patients with advanced cSCC.

Overall, there is a paucity of clinical research evidence supporting the use of nonsurgical therapeutic options for the management of advanced cSCC. As a result, there is currently no standardized management approach. The EXCeL program’s expert-agreed, evidence-based recommendations may help to address this by providing healthcare professionals with practically oriented recommendations to help optimize outcomes for patients with advanced cSCC.

**MATERIALS AND METHODS**

**EXCeL steering committee**

In October 2018, the EXCeL multidisciplinary steering committee of experts was convened, which included five dermatologists (including four Mohs surgeons), three medical oncologists, two head and neck surgeons, one radiation oncologist, and a patient advocacy

group representative (Table 21). The aim of the steering committee was to develop evidence-based consensus recommendations for the diagnosis and management of cSCC using a modified Delphi methodology (Figure 1) (Jones and Hunter, 1995). The steering committee identified five key areas of focus, including diagnosis, staging systems and risk stratification, different treatment modalities in advanced cSCC, referral patterns, and patient perspective (Table 15).

**Key clinical questions**

The steering committee identified 14 key clinical questions for each area of focus to be answered in order to develop consensus recommendations. These questions were then ranked and refined by the steering committee to a final list of 12 overarching questions (Table 15).

**Literature search**

Bibliographic fellows were nominated by the steering committee from among research fellows and residents (Table 22) to perform a comprehensive and structured literature review. Searches were performed between December 2018 and February 2019 and focused on evidence published in peer-reviewed publications from the past 10 years and/or presented at major international dermatology and

**Figure 1. Illustrative representation of the modified Delphi process used to reach consensus.**





**Table 22. Bibliographic Fellows Selected by the EXCeL Steering Committee**

| Name              | Title   | Institution  |
|-------------------|---|--|
| Saqib Ahmed       | Fellow, Micrographic Surgery and Dermatologic Oncology                        | MD Anderson Cancer Center, Houston, Texas, United States                         |
| Kristin Bibee     | Clinical Instructor, Dermatology  | University of Pittsburgh School of Medicine, Pittsburgh, Pennsylvania            |
| Jessie Hou        | Fellow, Mohs Surgery and Procedural Dermatology                               | University of California, Irvine, California, United States                      |
| Richard Lin       | Dermatology Resident  | NYU Langone Health, New York City, New York, United States                       |
| Jessica Moskovitz | Fellow, Head and Neck Surgical Oncology                                       | University of Pittsburgh Medical Center, Pittsburgh, Pennsylvania, United States |
| Patrick Mulvaney  | Resident, Harvard Combined Dermatology  | Massachusetts General Hospital, Boston, Massachusetts, United States             |
| Tejas Patel       | Attending Dermatologist   | Bridgeview Dermatology, Brooklyn, New York, United States                        |
| Erik Petersen     | Fellow, Micrographic Surgery and Dermatologic Oncology                        | MD Anderson Cancer Center, Houston, Texas, United States                         |
| SyriL Keena Que   | Director and Assistant Professor, Dermatologic Surgery and Cutaneous Oncology | Indiana University School of Medicine, Carmel, Indiana, United States            |
| Gaurav Singh      | Resident, Dermatology   | NYU Langone Health, New York City, New York, United States                       |

Abbreviation. EXCeL, Expert Cutaneous Squamous Cell Carcinoma Leadership.

oncology congresses in the past 2–3 years. These included the annual meetings of the American Society of Clinical Oncology, the European Academy of Dermatology and Venereology, the American Academy of Dermatology, and the Society for Investigative Dermatology.

The bibliographic fellows identified search terms and constructed search strings relating to each individual question, which were then tested and refined (Tables 1–14). Search strings were defined on the basis of the PICO (patient problem, intervention, comparison, and outcome) method (Richardson et al., 1995). Electronic searches were performed using PubMed and Google Scholar, and any duplicate records were removed. Publications were then screened for eligibility by the bibliographic fellows using a two-step process. In the first step, information from the titles and abstracts of the publications was screened to identify articles of relevance (to the clinical question being investigated) using predefined inclusion and exclusion criteria. All randomized controlled trials, prospective and retrospective studies, case series with multiple patients, peer-reviewed articles, and major international conference abstracts were included. Some preclinical studies were included if deemed to be of high enough relevance. Conversely, single-case studies, narrative reviews, editorials, and false-positive articles (those identified by the searches but of limited relevance on closer inspection) were excluded. In the second step, full-text copies of all relevant publications identified during the first step were obtained and reviewed against the same inclusion and exclusion criteria.

Key data extracted from selected publications included study characteristics (design, patient population, study period, patient characteristics [age, sex], follow-up), intervention (type, dose, timeframe, administration), comparators, outcomes, limitations, conclusions, and/or recommendations.

PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) (Moher et al., 2009) data extraction and reporting guidelines were observed, and Oxford Centre for Evidence-Based Medicine criteria were used to assess the quality of evidence level for each paper (OCEBM, 2011).

### Development of evidence-based recommendations and voting process

A report summarizing the collected evidence for each of the 14 key clinical questions was prepared, including evidence ratings where appropriate and draft evidence-based recommendations. The report,

key clinical questions, and draft recommendations were then reviewed, supplemented, and refined by the steering committee for the voting process (including a live steering committee meeting in February 2019), leaving 12 final key questions and 36 consensus statements (Table 15–20).

During each round of voting, steering committee members anonymously assigned each recommendation an agreement score between 1 (strong disagreement) and 9 (strong agreement). These scores were then collated into two ranges: 1–3 and 7–9. Consensus was achieved if  $\geq 75\%$  of participants scored the recommendation within the 7–9 range and if  $\leq 25\%$  scored it within the 1–3 range. If consensus was not achieved, the recommendation was revised to address any comments/issues, and another round of voting was conducted. If consensus was not achieved after three rounds of voting, a lack of consensus was recorded.

In April 2019, the steering committee convened and discussed, further refined, and finalized the consensus recommendations during three online voting sessions. An additional online vote was performed in February 2020 to revise question 7, statement 1. The purpose of this vote was to ensure the accuracy of the statement. The patient advocate participated in the discussion leading to final recommendations before voting.

### Data availability statement

No datasets were generated or analyzed during this study.

### ORCIDs

Guilherme Rabinowits: <http://orcid.org/0000-0001-5783-491X>  
 Michael R. Migden: <http://orcid.org/0000-0003-3293-1208>  
 Todd E. Schlessinger: <http://orcid.org/0000-0002-1128-9626>  
 Robert L. Ferris: <http://orcid.org/0000-0001-6605-2071>  
 Morganna Freeman: <http://orcid.org/0000-0003-0314-7270>  
 Shlomo Koefman: <http://orcid.org/0000-0002-2275-5346>  
 Anna C. Pavlick: <http://orcid.org/0000-0001-7088-0742>  
 Neil Swanson: <http://orcid.org/0000-0003-2837-754X>  
 Gregory T. Wolf: <http://orcid.org/0000-0002-3219-9515>  
 Scott M. Dinehart: <http://orcid.org/0000-0002-6147-9604>

### AUTHOR CONTRIBUTIONS

Conceptualization: GR, MRM, TES, RLF, MF, VG, SK, ACP, NS, GTW, SMD; Funding Acquisition: GR, MRM, TES, RLF, MF, VG, SK, ACP, NS, GTW, SMD; Investigation: GR, MRM, TES, RLF, MF, VG, SK, ACP, NS, GTW, SMD; Methodology: GR, MRM, TES, RLF, MF, VG, SK, ACP, NS, GTW, SMD; Supervision: GR, MRM, TES, RLF, MF, VG, SK, ACP, NS, GTW, SMD; Validation: GR, MRM, TES, RLF, MF, VG, SK, ACP, NS, GTW, SMD; Visualization: GR, MRM, TES, RLF, MF, VG, SK, ACP, NS, GTW, SMD; Writing - Original Draft Preparation: GR, MRM, TES, RLF, MF, VG, SK, ACP, NS, GTW, SMD; Writing - Review and Editing: GR, MRM, TES, RLF, MF, VG, SK, ACP, NS, GTW, SMD

**ACKNOWLEDGMENTS**

Funding for the Expert Cutaneous Squamous Cell Carcinoma Leadership program was provided by the Sanofi Genzyme and Regeneron Alliance. The Expert Cutaneous Squamous Cell Carcinoma Leadership steering committee (composed of all listed authors) is solely responsible for all aspects of developing the consensus statements. Editorial and organizational supports were provided by Lighthouse (a Lucid Group Company) and paid by the Sanofi Genzyme and Regeneron Alliance. The authors maintained complete control over the direction and content of the manuscript. No payments were made to the authors for the writing of this manuscript, and the authors approved the final content of the manuscript. The authors would like to recognize the valuable participation of Chrysalyn D. Schmults in the consensus program because she was part of the consensus panel and critically revised the paper providing substantial contributions. Finally, the authors would like to recognize the contributions of VG, who passed away (21 May 2020), to both this manuscript and her important work on behalf of patients with skin cancers.

**DISCLAIMER**

Sanofi Genzyme and Regeneron Alliance had no input into the consensus statements or manuscript content. The funding source had no role in drafting or voting on the statements.

**CONFLICT OF INTEREST**

GR reports consulting and advisory relationships with Castle Biosciences, EMD Serono, Merck, Pfizer, Regeneron Pharmaceuticals, and Sanofi Genzyme. In addition, he holds Regeneron Pharmaceuticals and Syros Pharmaceuticals shares. MRM reports honoraria from Eli Lilly, Novartis, Regeneron Pharmaceuticals, and Sun Pharma and research funding from Genentech and Sanofi Genzyme. TES reports research funding from AbbVie, Aclaris Therapeutics, Arcutis Premier Research, Arcutis Biotherapeutics, Akros Pharma, Allergan, AOBiome Therapeutics, Biofrontera, Boehringer Ingelheim, Bristol-Myers Squibb, Cara Therapeutics, Castle BioScience, Celgene, Centocor Ortho Biotech, ChemoCentryx, Coherus Biosciences, Corrona, Dermavant, Dermira, DT Pharmacy & DT Collagen (Melasma), Eli Lilly, Galderma (Nestle), Genentech, Janssen Pharmaceuticals, Kinex, Kiniksa, Leo, Merz, Novartis, Pfizer, Regeneron Pharmaceuticals, Sanofi, Sisaf, Tetra Derm Group, LLC (Wound Healing), Trevi; honoraria and consulting relationships from/with AbbVie, Aclaris Therapeutics, Allergan, Almirall LLC, Bristol-Myers Squibb, Eli Lilly & Co., EPI Health, Galderma, Merz Pharma, Novartis, Ortho Dermatologics, Pharmatecture, Prolacta Bioscience, Regeneron Pharmaceuticals, Sun Pharma, and UCB Pharma; advisory relationships with Allergan, Almirall, LLC, Bioderma Laboratories, Biofrontera, Greenway Therapeutics, Remedy, and Suneva Medical; and speaker bureau with Aclaris Therapeutics, Almirall, LLC, Dermira, EPI Health, Regeneron Pharmaceuticals, Sanofi Genzyme, Sun Pharma, and Suneva Medical. RLF reports honoraria from Aduro Biotech, Nanobiotix, Torque Therapeutics, EMD Serono, GlaxoSmithKline, Iovance Biotherapeutics, MacroGenics, Numab Therapeutics AG, Oncorus, Ono Pharmaceutical Co, Pfizer, PPD, and Regeneron Pharmaceuticals; honoraria and research funding from AstraZeneca/MedImmune, Bristol-Myers Squibb, and Merck; honoraria, research funding, and stock from Novasentia; research funding from Tesaro; and consultancy with Sanofi and Zymeworks. MF reports scientific advisory boards and consulting relationships with Bristol-Myers Squibb and Novartis and consulting relationship and research funding with/through Merck and Regeneron Pharmaceuticals. SK reports research funding from Bristol-Myers Squibb and Merck and consultancy for Regeneron. ACP reports advisory boards and consulting relationships and research funding with/through Bristol-Myers Squibb, Merck, Regeneron Pharmaceuticals, and Sanofi Genzyme. NS reports consulting relationship with Genentech, Regeneron Pharmaceuticals, and Sanofi Genzyme. GTW reports honoraria from Merck and Regeneron Pharmaceuticals and research funding from Brooklyn Immunotherapeutics. SMD reports advisory boards and consulting relationships with Regeneron Pharmaceuticals and Sanofi Genzyme, consulting relationship with Genentech, advisory boards with Verrica Pharmaceuticals, and Speaker and Consultant with Castle Biosciences. The remaining authors state no conflict of interest.

**REFERENCES**

Alam M, Ratner D. Cutaneous squamous-cell carcinoma. *N Engl J Med* 2001;344:975–83.

Amin MB, Greene FL, Edge SB, Compton CC, Gershenwald JE, Brookland RK, et al. The eighth edition AJCC cancer staging manual: continuing to build a

bridge from a population-based to a more "personalized" approach to cancer staging. *CA Cancer J Clin* 2017;67:93–9.

- Amoils M, Kim J, Lee C, Sunwoo JB, Colevas AD, Aasi SZ, et al. PD-L1 expression and tumor-infiltrating lymphocytes in high-risk and metastatic cutaneous squamous cell carcinoma. *Otolaryngol Head Neck Surg* 2019;160:93–9.
- Arunachalam D, Thirumorthy A, Devi S, Thennarasu. Quality of life in cancer patients with disfigurement due to cancer and its treatments. *Indian J Palliat Care* 2011;17:184–90.
- Baum CL, Wright AC, Martinez JC, Arpey CJ, Brewer JD, Roenigk RK, et al. A new evidence-based risk stratification system for cutaneous squamous cell carcinoma into low, intermediate, and high risk groups with implications for management [published correction appears in *J Am Acad Dermatol* 2018;79:1173.e1]. *J Am Acad Dermatol* 2018;78:141–7.
- Berens AM, Akkina SR, Patel SA. Complications in facial Mohs defect reconstruction. *Curr Opin Otolaryngol Head Neck Surg* 2017;25:258–64.
- Bertino G, Sersa G, De Terlizzi F, Occhini A, Plaschke CC, Groselj A, et al. European Research on Electrochemotherapy in Head and Neck Cancer (EURECA) project: results of the treatment of skin cancer. *Eur J Cancer* 2016;63:41–52.
- Borradori L, Sutton B, Shayesteh P, Daniels GA. Rescue therapy with anti-programmed cell death protein 1 inhibitors of advanced cutaneous squamous cell carcinoma and basosquamous carcinoma: preliminary experience in five cases. *Br J Dermatol* 2016;175:1382–6.
- Brantsch KD, Meisner C, Schönfisch B, Trilling B, Wehner-Caroli J, Röcken M, et al. Analysis of risk factors determining prognosis of cutaneous squamous-cell carcinoma: a prospective study. *Lancet Oncol* 2008;9:713–20.
- Campana LG, Testori A, Curatolo P, Quaglino P, Mocellin S, Framarini M, et al. Treatment efficacy with electrochemotherapy: a multi-institutional prospective observational study on 376 patients with superficial tumors. *Eur J Surg Oncol* 2016;42:1914–23.
- Cañueto J, Cardeñoso E, García JL, Santos-Briz Á, Castellanos-Martín A, Fernández-López E, et al. Epidermal growth factor receptor expression is associated with poor outcome in cutaneous squamous cell carcinoma. *Br J Dermatol* 2017a;176:1279–87.
- Cañueto J, Cardeñoso-Álvarez E, Cosano-Quero A, Santos-Briz Á, Fernández-López E, Pérez-Losada J, et al. The expression of podoplanin is associated with poor outcome in cutaneous squamous cell carcinoma. *J Cutan Pathol* 2017b;44:144–51.
- Cañueto J, Martín-Vallejo J, Cardeñoso-Álvarez E, Fernández-López E, Pérez-Losada J, Román-Curto C. Rapid growth rate is associated with poor prognosis in cutaneous squamous cell carcinoma. *Clin Exp Dermatol* 2018;43:876–82.
- Cavaliere S, Perrone F, Miceli R, Ascierio PA, Locati LD, Bergamini C, et al. Efficacy and safety of single-agent pan-human epidermal growth factor receptor (HER) inhibitor dacomitinib in locally advanced unresectable or metastatic skin squamous cell cancer. *Eur J Cancer* 2018;97:7–15.
- Chalya PL, Mabula JB, Rambau P, McHembe MD, Kahima KJ, Chandika AB, et al. Marjolin's ulcers at a university teaching hospital in Northwestern Tanzania: a retrospective review of 56 cases. *World J Surg Oncol* 2012;10:38.
- Chen AC, Martin AJ, Choy B, Fernández-Peñas P, Dalziel RA, McKenzie CA, et al. A phase 3 randomized trial of nicotinamide for skin-cancer chemoprevention. *N Engl J Med* 2015;373:1618–26.
- Clayman GL, Lee JJ, Holsinger FC, Zhou X, Duvic M, El-Naggar AK, et al. Mortality risk from squamous cell skin cancer. *J Clin Oncol* 2005;23:759–65.
- Coombs AC, Butler A, Allison R. Metastatic cutaneous squamous cell carcinoma of the parotid gland: prognostic factors. *J Laryngol Otol* 2018;132:264–9.
- Czarnecki D, Staples M, Mar A, Giles G, Meehan C. Metastases from squamous cell carcinoma of the skin in southern Australia. *Dermatology* 1994;189:52–4.
- Dean NR, Sweeney L, Magnuson JS, Carroll WR, Robinson D, Desmond RA, et al. Outcomes of recurrent head and neck cutaneous squamous cell carcinoma. *J Skin Cancer* 2011;2011:972497.
- Di Monta G, Caracò C, Simeone E, Grimaldi AM, Marone U, Di Marzo M, et al. Electrochemotherapy efficacy evaluation for treatment of locally

- advanced stage III cutaneous squamous cell carcinoma: a 22-cases retrospective analysis. *J Transl Med* 2017;15:82.
- DI Stefani A, Del Regno L, Piccerillo A, Peris K. Practical indications for the management of non-melanoma skin cancer patients. *G Ital Dermatol Venereol* 2017;152:286–94.
- Eigentler TK, Leiter U, Häfner HM, Garbe C, Röcken M, Breuninger H. Survival of patients with cutaneous squamous cell carcinoma: results of a prospective cohort study. *J Invest Dermatol* 2017;137:2309–15.
- Espeli V, Ruegg E, Hottinger AF, Modarressi A, Dietrich PY. Weekly multi-agent chemotherapy (CMF-b) for advanced non-melanoma skin cancer. *Anticancer Res* 2016;36:2359–64.
- Fox M, Brown M, Golda N, Goldberg D, Miller C, Pugliano-Mauro M, et al. Nodal staging of high-risk cutaneous squamous cell carcinoma. *J Am Acad Dermatol* 2019;81:548–57.
- Fu T, Aasi SZ, Hollmig ST. Management of high-risk squamous cell carcinoma of the skin. *Curr Treat Options Oncol* 2016;17:34.
- García-Díez I, Hernández-Ruiz E, Andrades E, Gimeno J, Ferrándiz-Pulido C, Yébenes M, et al. PD-L1 expression is increased in metastasizing squamous cell carcinomas and their metastases [published correction appears in *Am J Dermatopathol* 2019;41:537]. *Am J Dermatopathol* 2018;40:647–54.
- García-Pedrero JM, Martínez-Cambolor P, Díaz-Coto S, Munguía-Calzada P, Vallina-Alvarez A, Vazquez-Lopez F, et al. Tumor programmed cell death ligand 1 expression correlates with nodal metastasis in patients with cutaneous squamous cell carcinoma of the head and neck. *J Am Acad Dermatol* 2017;77:527–33.
- Gauden R, Pracy M, Avery AM, Hodgetts I, Gauden S. HDR brachytherapy for superficial non-melanoma skin cancers. *J Med Imaging Radiat Oncol* 2013;57:212–7.
- Gilmore SJ. Nicotinamide and skin cancer chemoprevention: the jury is still out. *Australas J Dermatol* 2018;59:6–9.
- Gold KA, Kies MS, William WN Jr, Johnson FM, Lee JJ, Glisson BS. Erlotinib in the treatment of recurrent or metastatic cutaneous squamous cell carcinoma: a single-arm phase 2 clinical trial. *Cancer* 2018;124:2169–73.
- Gore SM, Shaw D, Martin RC, Kelder W, Roth K, Uren R, et al. Prospective study of sentinel node biopsy for high-risk cutaneous squamous cell carcinoma of the head and neck. *Head Neck* 2016;38(Suppl. 1):E884–9.
- Goyal U, Prabhakar NK, Davuluri R, Morrison CM, Yi SK. Role of concurrent systemic therapy with adjuvant radiation therapy for locally advanced cutaneous head and neck squamous cell carcinoma. *Cureus* 2017;9:e1784.
- Green AC, Olsen CM. Cutaneous squamous cell carcinoma: an epidemiological review. *Br J Dermatol* 2017;177:373–81.
- Grob JJ, Gonzalez R, Basset-Seguín N, Vornicova O, Schachter J, Joshi A, et al. Pembrolizumab monotherapy for recurrent or metastatic cutaneous squamous cell carcinoma: a single-arm Phase II trial (KEYNOTE-629). *J Clin Oncol* 2020;38:2916–25.
- Haisma MS, Plaat BEC, Bijl HP, Roodenburg JLN, Diercks GFH, Romeijn TR, et al. Multivariate analysis of potential risk factors for lymph node metastasis in patients with cutaneous squamous cell carcinoma of the head and neck. *J Am Acad Dermatol* 2016;75:722–30.
- Harris BN, Pipkorn P, Nguyen KNB, Jackson RS, Rao S, Moore MG, et al. Association of adjuvant radiation therapy with survival in patients with advanced cutaneous squamous cell carcinoma of the head and neck [published correction appears in *JAMA Otolaryngol Head Neck Surg* 2019;145:196]. *JAMA Otolaryngol Head Neck Surg* 2019;145:153–8.
- Hesse K, Satzger I, Schacht V, Köther B, Hillen U, Klode J, et al. Characterisation of prognosis and invasion of cutaneous squamous cell carcinoma by podoplanin and E-cadherin expression. *Dermatology* 2016;232:558–65.
- Hillen U, Leiter U, Haase S, Kaufmann R, Becker J, Gutzmer R, et al. Advanced cutaneous squamous cell carcinoma: a retrospective analysis of patient profiles and treatment patterns—results of a non-interventional study of the DeCOG. *Eur J Cancer* 2018;96:34–43.
- Hirshoren N, Danne J, Dixon BJ, Magarey M, Kleid S, Webb A, et al. Prognostic markers in metastatic cutaneous squamous cell carcinoma of the head and neck. *Head Neck* 2017;39:772–8.
- Jambusaria-Pahlajani A, Kanetsky PA, Karia PS, Hwang WT, Gelfand JM, Whalen FM, et al. Evaluation of AJCC tumor staging for cutaneous squamous cell carcinoma and a proposed alternative tumor staging system. *JAMA Dermatol* 2013;149:402–10.
- Jenni D, Karpova MB, Mühleisen B, Mangana J, Dreier J, Hafner J, et al. A prospective clinical trial to assess lapatinib effects on cutaneous squamous cell carcinoma and actinic keratosis. *ESMO Open* 2016;1:e000003.
- Jones J, Hunter D. Consensus methods for medical and health services research. *BMJ* 1995;311:376–80.
- Joseph MG, Zulueta WP, Kennedy PJ. Squamous cell carcinoma of the skin of the trunk and limbs: the incidence of metastases and their outcome. *Aust N Z J Surg* 1992;62:697–701.
- Karia PS, Han J, Schmults CD. Cutaneous squamous cell carcinoma: estimated incidence of disease, nodal metastasis, and deaths from disease in the United States, 2012. *J Am Acad Dermatol* 2013;68:957–66.
- Karia PS, Jambusaria-Pahlajani A, Harrington DP, Murphy GF, Qureshi AA, Schmults CD. Evaluation of American Joint Committee on Cancer, International Union Against Cancer, and Brigham and Women's Hospital tumor staging for cutaneous squamous cell carcinoma. *J Clin Oncol* 2014;32:327–34.
- Kreppel M, Krakowezki A, Kreppel B, Drebbler U, Wedemeyer I, Mauch C, et al. Podoplanin expression in cutaneous head and neck squamous cell carcinoma—prognostic value and clinicopathologic implications. *J Surg Oncol* 2013;107:376–83.
- Kropp L, Balamucki CJ, Morris CG, Kirwan J, Cognetta AB, Stoer CB, et al. Mohs resection and postoperative radiotherapy for head and neck cancers with incidental perineural invasion. *Am J Otolaryngol* 2013;34:373–7.
- Kudchadkar RR, Yushak ML, Lawson DH, Delman KA, Lowe MC, Goings M, et al. Phase II trial of pembrolizumab (MK-3475) in metastatic cutaneous squamous cell carcinoma (cSCC). *J Clin Oncol* 2018;36:9543.
- Kyrgidis A, Tzellos TG, Kechagias N, Patrikidou A, Xirou P, Kitikidou K, et al. Cutaneous squamous cell carcinoma (SCC) of the head and neck: risk factors of overall and recurrence-free survival. *Eur J Cancer* 2010;46:1563–72.
- Lin C, Tripcony L, Keller J, Poulsen M, Martin J, Jackson J, et al. Perineural infiltration of cutaneous squamous cell carcinoma and basal cell carcinoma without clinical features. *Int J Radiat Oncol Biol Phys* 2012;82:334–40.
- Lu SM, Lien WW. Concurrent radiotherapy with cetuximab or platinum-based chemotherapy for locally advanced cutaneous squamous cell carcinoma of the head and neck. *Am J Clin Oncol* 2018;41:95–9.
- Manyam BV, Gastman B, Zhang AY, Reddy CA, Burkey BB, Scharpf J, et al. Inferior outcomes in immunosuppressed patients with high-risk cutaneous squamous cell carcinoma of the head and neck treated with surgery and radiation therapy. *J Am Acad Dermatol* 2015;73:221–7.
- Mendez BM, Thornton JF. Current basal and squamous cell skin cancer management. *Plast Reconstr Surg* 2018;142:373e–87e.
- Merck & Co. KEYTRUDA® (pembrolizumab) [Package Insert]. Whitehouse Station NJ: Merck & Co; 2020.
- Mevio N, Bertino G, Occhini A, Scelsi D, Tagliabue M, Mura F, et al. Electrochemotherapy for the treatment of recurrent head and neck cancers: preliminary results. *Tumori* 2012;98:308–13.
- Migden MR, Rischin D, Schmults CD, Guminski A, Hauschild A, Lewis KD, et al. PD-1 blockade with cemiplimab in advanced cutaneous squamous-cell carcinoma. *N Engl J Med* 2018;379:341–51.
- Mittal A, Colegio OR. Skin cancers in organ transplant recipients. *Am J Transplant* 2017;17:2509–30.
- Moher D, Liberati A, Tetzlaff J, Altman DG, PRISMA Group. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *PLoS Med* 2009;6:e1000097.
- NCCN. National Comprehensive Cancer Network clinical practice guidelines in oncology: squamous cell skin cancer. Version 2.2020. 2019 (accessed November, 2019), [https://www.nccn.org/professionals/physician\\_gls/default.aspx](https://www.nccn.org/professionals/physician_gls/default.aspx).
- Nottage MK, Lin C, Hughes BG, Kenny L, Smith DD, Houston K, et al. Prospective study of definitive chemoradiation in locally or regionally advanced squamous cell carcinoma of the skin. *Head Neck* 2017;39:679–83.
- O'Bryan K, Sherman W, Niedt GW, Taback B, Manolidis S, Wang A, et al. An evolving paradigm for the workup and management of high-risk cutaneous squamous cell carcinoma. *J Am Acad Dermatol* 2013;69:595–602. e1.

- OCEBM. Levels of Evidence Working Group. The Oxford 2011 levels of evidence. Oxford Centre for Evidence-Based Medicine. 2011 (accessed XXX), <http://www.cebm.net/index.aspx?o=5653>.
- Porceddu SV, Bressel M, Poulsen MG, Stoneley A, Veness MJ, Kenny LM, et al. Postoperative concurrent chemoradiotherapy versus postoperative radiotherapy in high-risk cutaneous squamous cell carcinoma of the head and neck: the randomized phase III TROG 05.01 trial. *J Clin Oncol* 2018;36:1275–83.
- Que SKT, Zwald FO, Schmults CD. Cutaneous squamous cell carcinoma: incidence, risk factors, diagnosis, and staging. *J Am Acad Dermatol* 2018a;78:237–47.
- Que SKT, Zwald FO, Schmults CD. Cutaneous squamous cell carcinoma: management of advanced and high-stage tumors. *J Am Acad Dermatol* 2018b;78:249–61.
- Raza SM, Ramakrishna R, Weber RS, Kupferman ME, Gidley PW, Hanna EY, et al. Nonmelanoma cutaneous cancers involving the skull base: outcomes of aggressive multimodal management. *J Neurosurg* 2015;123:781–8.
- Regeneron Pharmaceuticals. LIBTAYO® (cemiplimab-rwlc) [Package Insert] Tarrytown, NY: Regeneron Pharmaceuticals; 2018.
- Reigneau M, Robert C, Routier E, Mamelle G, Moya-Plana A, Tomasic G, et al. Efficacy of neoadjuvant cetuximab alone or with platinum salt for the treatment of unresectable advanced nonmetastatic cutaneous squamous cell carcinomas. *Br J Dermatol* 2015;173:527–34.
- Richardson WS, Wilson MC, Nishikawa J, Hayward RS. The well-built clinical question: a key to evidence-based decisions. *ACP J Club* 1995;123:A12–3.
- Rischin D, Khushalani NI, Schmults CD, Guminski AD, Chang AL, Lewis KD, et al. Phase II study of cemiplimab in patients (pts) with advanced cutaneous squamous cell carcinoma (cSCC): longer follow-up. *J Clin Oncol* 2020;38:10018.
- Roozeboom MH, Lohman BG, Westers-Attema A, Nelemans PJ, Botterweck AA, van Marion AM, et al. Clinical and histological prognostic factors for local recurrence and metastasis of cutaneous squamous cell carcinoma: analysis of a defined population. *Acta Derm Venereol* 2013;93:417–21.
- Roper E, Lum T, Palme CE, Ashford B, Ch'ng S, Ranson M, et al. PD-L1 expression predicts longer disease free survival in high risk head and neck cutaneous squamous cell carcinoma. *Pathology* 2017;49:499–505.
- Roscher I, Falk RS, Vos L, Clausen OPF, Helsing P, Gjersvik P, et al. Validating 4 staging systems for cutaneous squamous cell carcinoma using population-based data: a nested case-control study. *JAMA Dermatol* 2018;154:428–34.
- Ross AS, Whalen FM, Elenitsas R, Xu X, Troxel AB, Schmults CD. Diameter of involved nerves predicts outcomes in cutaneous squamous cell carcinoma with perineural invasion: an investigator-blinded retrospective cohort study. *Dermatol Surg* 2009;35:1859–66.
- Rowe DE, Carroll RJ, Day CL Jr. Prognostic factors for local recurrence, metastasis, and survival rates in squamous cell carcinoma of the skin, ear, and lip. Implications for treatment modality selection. *J Am Acad Dermatol* 1992;26:976–90.
- Ruiz ES, Koyfman SA, Kass J, Schmults CD. Surgery and salvage limited-field irradiation for control of cutaneous squamous cell carcinoma with microscopic residual disease. *JAMA Dermatol* 2019;155:1193–5.
- Ruiz ES, Koyfman SA, Que SKT, Kass J, Schmults CD. Evaluation of the utility of localized adjuvant radiation for node-negative primary cutaneous squamous cell carcinoma with clear histologic margins. *J Am Acad Dermatol* 2020;82:420–9.
- Sapir E, Tolpadi A, McHugh J, Samuels SE, Elalfy E, Spector M, et al. Skin cancer of the head and neck with gross or microscopic perineural involvement: patterns of failure. *Radiother Oncol* 2016;120:81–6.
- Schmidt C, Martin JM, Khoo E, Plank A, Grigg R. Outcomes of nodal metastatic cutaneous squamous cell carcinoma of the head and neck treated in a regional center. *Head Neck* 2015;37:1808–15.
- Schmults CD, Karia PS, Carter JB, Han J, Qureshi AA. Factors predictive of recurrence and death from cutaneous squamous cell carcinoma: a 10-year, single-institution cohort study. *JAMA Dermatol* 2013;149:541–7.
- Sekulic A, Kim SY, Hostetter G, Savage S, Einspahr JG, Prasad A, et al. Loss of inositol polyphosphate 5-phosphatase is an early event in development of cutaneous squamous cell carcinoma. *Cancer Prev Res (Phila)* 2010;3:1277–83.
- Sekulic A, Migden MR, Oro AE, Dirix L, Lewis KD, Hainsworth JD, et al. Efficacy and safety of vismodegib in advanced basal-cell carcinoma. *N Engl J Med* 2012;366:2171–9.
- Silberstein E, Sofrin E, Bogdanov-Berezovsky A, Nash M, Segal N. Lymph node metastasis in cutaneous head and neck squamous cell carcinoma. *Dermatol Surg* 2015;41:1126–9.
- Smile TD, Xiong DX, Varra V, Winter IW, Beal BT, Gastman BR, et al. Disease progression in cutaneous squamous cell carcinoma patients with satellitosis and in-transit metastasis. *Anticancer Res* 2021;41:289–95.
- Strassen U, Hofauer B, Jacobi C, Knopf A. Management of locoregional recurrence in cutaneous squamous cell carcinoma of the head and neck. *Eur Arch Otorhinolaryngol* 2017;274:501–6.
- Stratigos A, Garbe C, Lebbe C, Malvehy J, del Marmol V, Pehamberger H, et al. Diagnosis and treatment of invasive squamous cell carcinoma of the skin: European consensus-based interdisciplinary guideline. *Eur J Cancer* 2015;51:1989–2007.
- Tanvetyanon T, Padhya T, McCaffrey J, Kish JA, Deconti RC, Trotti A, et al. Postoperative concurrent chemotherapy and radiotherapy for high-risk cutaneous squamous cell carcinoma of the head and neck. *Head Neck* 2015;37:840–5.
- Teli MA, Khan NA, Darzi MA, Gupta M, Tufail A. Recurrence pattern in squamous cell carcinoma of skin of lower extremities and abdominal wall (Kangri cancer) in Kashmir valley of Indian subcontinent: impact of various treatment modalities. *Indian J Dermatol* 2009;54:342–6.
- Thompson AK, Kelley BF, Prokop LJ, Murad MH, Baum CL. Risk factors for cutaneous squamous cell carcinoma recurrence, metastasis, and disease-specific death: a systematic review and meta-analysis. *JAMA Dermatol* 2016;152:419–28.
- Trodello C, Pepper JP, Wong M, Wysong A. Cisplatin and cetuximab treatment for metastatic cutaneous squamous cell carcinoma: a systematic review. *Dermatol Surg* 2017;43:40–9.
- Tseros EA, Gebski V, Morgan GJ, Veness MJ. Prognostic significance of lymph node ratio in metastatic cutaneous squamous cell carcinoma of the head and neck. *Ann Surg Oncol* 2016;23:1693–8.
- Varra V, Woody NM, Reddy C, Joshi NP, Geiger J, Adelstein DJ, et al. Sub-optimal outcomes in cutaneous squamous cell cancer of the head and neck with nodal metastases. *Anticancer Res* 2018;38:5825–30.
- William WN Jr, Feng L, Ferrarotto R, Ginsberg L, Kies M, Lippman S, et al. Gefitinib for patients with incurable cutaneous squamous cell carcinoma: a single-arm phase II clinical trial. *J Am Acad Dermatol* 2017;77:1110–3.e2.
- Work Group, Invited Reviewers, Kim JYS, Kozlow JH, Mittal B, Moyer J, et al. Guidelines of care for the management of cutaneous squamous cell carcinoma. *J Am Acad Dermatol* 2018;78:560–78.
- Xu MJ, Lazar AA, Garsa AA, Arron ST, Ryan WR, El-Sayed IH, et al. Major prognostic factors for recurrence and survival independent of the American Joint Committee on Cancer eighth edition staging system in patients with cutaneous squamous cell carcinoma treated with multimodality therapy. *Head Neck* 2018;40:1406–14.
- Younes A, Brody J, Carpio C, Lopez-Guillermo A, Ben-Yehuda D, Ferhanoglu B, et al. Safety and activity of ibrutinib in combination with nivolumab in patients with relapsed non-Hodgkin lymphoma or chronic lymphocytic leukaemia: a phase 1/2a study. *Lancet Haematol* 2019;6:e67–78.



This work is licensed under a Creative Commons Attribution-NonCommercial-NoDerivatives 4.0 International License. To view a copy of this license, visit <http://creativecommons.org/licenses/by-nc-nd/4.0/>