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Review Article

High-risk cutaneous squamous cell carcinoma (CSCC): Challenges and emerging therapies

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ABSTRACT

Cutaneous squamous cell carcinoma (CSCC) is a common type of skin malignancy that affects people who have been exposed to sunlight for a long time. It has been associated to a high mutational load, making treatment problematic, especially for individuals with high-risk CSCC characteristics. Patients with high-risk CSCC are difficult to define since definitions are still imprecise. Firstly, we review the evidence to see how relevant locoregional involvement is in terms of patient survival and recurrence risk. Second, we go through the difficulties and obstacles that come with sentinel lymph node biopsy (SLNB) and their importance in the management of locally progressed CSCC. Methods and findings from a variety of lymph node investigations are described. There is yet no empirical evidence for the involvement of SLNB in CSCC. Finally, we discussed the most recent developments in the treatment of CSCC. The mainstays of treatment are surgery and radiation. To slow the disease progression, cancer medicines have switched to disrupting particular signaling pathways. Advanced nations have more easily accessible drugs like Cetuximab (epidermal growth factor receptor inhibitor) and Cemiplimab (anti-programme receptor-1 antibodies), which are utilized in advanced CSCC. The response rate varies based on the patient, although there is still a lack of proof. This article discusses the misconception that CSCC is a tumor with a favorable prognosis, as well as the difficulties in treating high-risk CSCC.

1. Introduction

The most prevalent non-melanoma skin cancer is cutaneous squamous cell carcinoma (CSCC), which has a higher death rate.[1] The malignant proliferation of epidermal keratinocytes is a hallmark of CSCC. Persistent exposure to sunlight is an imperative factor related with CSCC.[2] CSCC include an incredible mutational burden, including different signaling pathways; activation of the NF-kB, MAPK, and PI3K/AKT/mTOR pathway which mediates the epidermal growth factor receptor (EGFR) overexpression,[3,4] genetic changes to the suppressors genes such as p53, CDKN2A and NOTCH and oncogenes (RAS).[5] This latter advancement has made a difference to the shape and altered the scene in CSCC (see Fig. 1).

In the United States, an average of 3.5 million patients are detected with NMSC every year, with 75% occurring on exposed areas of the head and neck. The frequency of CSCC varies widely by geographic location, with higher rates at lower latitudes and a lifetime possibility of 9%–14% among men and 4%–9% among women.[6] The challenge is gathering complete epidemiological data as most developing countries especially the Asian region have poor cancer registry documentation. Most of the incidence depicts demographic profiles in developed countries, but data on disease specific death (DSD), disease specific survival (DSS), overall survival (OS) and roles on sentinel lymph node biopsy (SLNB) are still scarce.

1.1. Locally advanced cutaneous squamous cell carcinoma and high-risk features

Larger portion of patients with CSCC have good prognosis and are healed by excision or local radiation therapy, however a small subset of them displays more aggressive behavior, with a tendency of local invasion and metastasis.[7] Sun L, et al, during a 20 year period, looked at a group of patients who had disease recurrence after surgery and postoperative radiotherapy to evaluate survival

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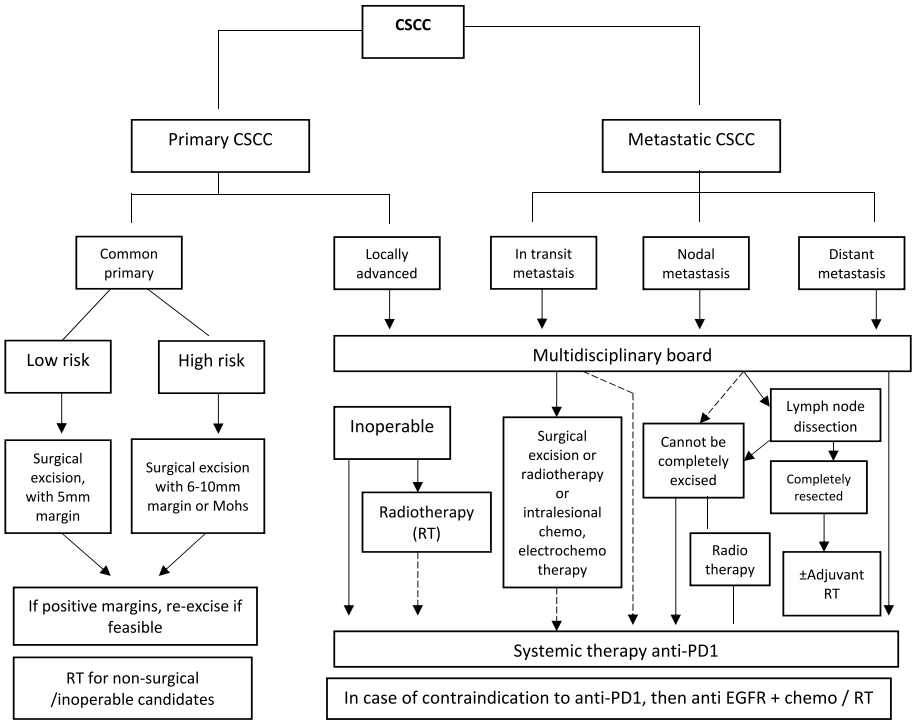

Fig. 1. Main therapeutic indications for CSCC based on European Interdisciplinary meet. Strength of consensus 90% (Stratigos et al, 2020).

rates following recurrence and relationship between immunological state and outcome. In this study, they only included CSCC patients with lesions at the head and neck region, and metastatic CSCC and CSCC in situ were excluded. A total of 72 patients met the inclusion criteria (out of total of 205), with 40 patients (55.6%) being immunocompromised and 32 patients (44.4%) being immunocompetent; median time for disease recurrence postoperative radiotherapy was 10.1 months (immunocompetent) and 9.1 months (immunosuppressed); for both groups, immunosuppressed, n = 31 (77.5%) and immunocompetent, n = 21, locoregional recurrence was the most prevalent first pattern of failure. 27 of the 72 patients had incomplete data on salvage therapy, which the researchers were unable to assess. Nine patients were able to undergo salvage surgery (7 patients had local-only recurrence, 2 nodal-only recurrence) while 36 patients were not considered due to the extent of the disease (n = 21 palliative radiotherapy, n = 4 palliative chemotherapy, n = 2 cetuximab, n = 9 hospice care with no further therapy). The median survival for those amenable to surgery was 26.1 months compared to 4.7 months in those not amenable to surgical survival. When comparing those who had salvage surgery alone with those who had both surgery and radiation, there is no significant difference in median survival. This emphasizes the significance of stepping up treatment early on to avoid recurrence.

In another study in Minnesota, they compared and revealed that the 10 years survival for advanced CSCC with lymph node involvement to be less than 20 percent, and those with distant metastases make up fewer than 10% of the total. Uncontrolled nodal illness, rather than distant metastases, is the leading cause of death in CSCC patients. Local recurrence usually happens within two years of the initial diagnosis. After a surgical resection, those with high-risk traits have a 13 percent-41 percent chance of locoregional recurrence and a 7 percent-16 percent chance of distant metastases. High risk CSCC is defined by aggressive biologic behavior and a greater likelihood of locoregional recurrence and in rare cases distant metastases. Numerous studies have linked high-risk factors to poor outcome, but defining high-risk CSCC remains a challenge with definitions ranging from broad to ambiguous.[8] A meta-analysis by Zeng et al, reviewed 48 studies (with 28,627 patients) showed that common features related to local recurrence include: poorly differentiated tumor, perineural involvement, Breslow >2 mm, diameter of tumor >20 mm, and location of tumor at temple. Risk of metastasis higher: poorly differentiated tumor, with perineural involvement, Breslow >2 mm, Diameter >20 mm, location at ear, lip and temple. Disease specific death (DSD) are seen: poorly differentiated tumor, perineural involvement, Breslow >2 mm.

There are a few classifications used, which slightly defers in the T (tumor) classification for CSCC. According to the American Joint Committee on Cancer's (AJCC) version 8 staging, tumors are classified depending on the tumor size in terms of the clinical diameter and a series of risk factors. T1 and T2 tumors are distinguished by a tumor diameter of more than 2 cm. A tumors diameter > 4 cm, mild bone erosion, and perineural or deep invasion (>6 mm or beyond the subcutaneous fat) are all high risk markers that can lead to T3 upstaging. The Union for International Cancer Control (UICC) is another regularly used classification: tumor diameter <2 cm and >2 cm used to differentiate between T1 and T2, any invasion of deep structures becomes T3 (axial skeleton: T4); and Brigham & Women's Hospital (BWH) classification where number of risk factors present denominates the T classification (as per Table 1.below).[9,10]

1.2. Role of sentinel lymph node biopsy

Microscopic diagnosis of melanoma by sentinel lymph node biopsy (SLNB) and early complete of node dissection improves regional control, reduces the overall number of positive nodes, and increases survival in patients with nodes positive. The effective identification of occult lymph node metastases with SLNB has been

Table 1
Differences in tumor classification based on commonly used classification (Ruiz ES, et al, 2019).

Tumor Staging System	Definition
AJCC	
T1	Tumor ≤2 cm in greatest dimension
T2	Tumor >2 cm but not greater than 4 cm in greatest dimension or with two or more high-risk factors[a]
T3	Tumor >4 cm in greatest diameter or minor bone invasion/perineural invasion or deep invasion
T4a	Tumor with gross cortical bone/marrow invasion
T4b	Tumor with skull bone invasion and/or skull base foramen involvement
UICC	
T1	Tumor ≤2 cm or less in greatest dimension
T2	Tumor >2 cm in greatest dimension
T3	Tumor with invasion of deep structures (eg, muscle, cartilage, bone [excluding axial skeleton], orbit)
T4	Tumor with invasion of axial skeleton or direct perineural invasion of skull base
BWH	
T1	0 high-risk factors[b]
T2a	1 high-risk factor
T2b	2-3 high-risk factors
T3	≥4 high-risk factors or bone invasion

Additional information.
[a] AJCC high-risk factors include thickness greater than 2 mm, Clark level IV, perineural invasion, primary site ear, primary site non-hair bearing lip, or histology with poor differentiation.
[b] Tumor diameter 2 cm, poorly differentiated histology, perineural invasion 0.1 mm, or tumor invasion beyond fat are all high-risk indicators for BWH (excluding bone invasion which automatically upgrades tumors to BWH stage T3).

examined in patients with high-risk localized CSCC tumors, however, the histopathological analysis of SLNB for the management and outcome of patients remain unclear.[11] A retrospective study by Ilmonen S, et al studied whether sentinel lymph node status and early detection of nodal disease impacts survival amongst patient with high-risk CSCC (n = 63). It revealed that though SLNB was feasible but carries little value in that group (SLNB positive in 4 patients (6.3%), SLNB negative with recurrence in 5 patients). The SLNB was done as a single procedure with the excision, patients were given Technetium-99 m-labeled colloidal albumin in 0.2 ml intradermally injected into the main tumor site on both sides, followed by lymphoscintigraphy with static pictures 30 min and 2 h later. Intraoperatively, the surgeon utilized a gamma-detecting probe to harvest all radioactive nodes until no localized residual activity was identified. All tissues were analyzed after the formalin-fixed sentinel node samples were cut at 1–2 mm intervals. Microscopic diagnosis of melanoma by sentinel lymph node biopsy (SLNB) and early complete node dissection improves regional control, reduces unpleasant effects, reduces the overall number of positive nodes, and increases survival in patients with nodes positive. The effective identification of occult lymph node metastases with SLNB has been examined in patients with high-risk localized CSCC tumors.[12]

Aside from that, Ahadiat O, et al compiled a database of all high-risk CSCC patients treated at their facility and looked at the usage of SLNB, among other things. SLNB operations were performed on fewer than 0.1 percent of all patients with high-risk CSCC over the 10-year research period, whereas full lymph node dissections were performed on 14 percent of all patients with high-risk CSCC. 56.7 percent of patients who had full lymph node dissections had microscopic tumor spread to local lymph nodes, whereas 43.3 percent had no metastases. In high-risk CSCC, preventive lymph node dissection was found to be overused, whereas SLNB was shown to be underutilized in this research.[13]

In a validation study by Schmitt et al, 13 case series and 6 case reports (N = 130) were included in the study. Comparing the T staging in AJCC 7th edition, T2 patients had a positive SLNB rate of 11.2% while T4 was 60%. When the same patients were reclassified using the BWH classification, tumors with 2–3 risk traits (T2b) had an SLNB positive rate of 29%, whereas tumors with all four risk factors (T3) had a lymph node metastasis rate of 50%. These findings show that AJCC T2 category may reflect a heterogenous population with a small subgroup that require additional stratification. The 2 cm threshold has been demonstrated to be an independent risk factor for CSCC metastasis in several studies, but none looked to the risk of positive SLNB findings.[14,15] According to Veness et al, 30% of 266 individuals with metastatic illness in their study group had initial lesions bigger than 2 cm, whereas 60% of lesions less than 2 cm had a diameter that measured thicker than 4 mm.[16] In this research, the reported positive rate of SLNB in the setting of high-risk CSCC was 12.3 percent.[17]

The research suggests that the low predictive value of sentinel lymph node status is due: complex anatomy involving bilateral or contralateral drainage in up to 10% patients (requires more technical skills from surgeon), previous tumor surgery and scar formation causes alteration or blocks the natural lymph routes, proximity of primary injection sites interfere when defining true sentinel nodes intraoperatively because of shine through effect. It is premature to rule out the role of SLNB in predicting the outcome of CSCC as most research is mostly based on a single center, included a limited number of patients and was retrospective in nature.[18]

In a systematic review published by Sahovaler et al (includes 20 observational studies and 1 randomized phase III study) they studied risk factors for overall survival (OS), locoregional control (LRC), locoregional recurrence (LRR), and disease specific survival (DSS) for CSCC patients with locoregional lymph node metastasis. The analysis comprised a total of 21 trials (representing 3534 patients). Immunosuppression (hazard ratio [HR] of death, 2.66; 95 percent CI, 2.26–3.13), extracapsular spread (HR, 1.90; 95 percent CI, 1.12–3.23), adjuvant radiotherapy (HR,0.45; 95 percent CI, 0.27–0.78), lymph node ratio (HR, 1.91; 95 percent CI, 1.09–3.35), and advanced age were all significant risk factors associated with OS (HR, 1.03; 95 percent CI, 1.00–1.07). Reduced DSS is also linked to immunosuppression and adjuvant radiotherapy. The review found a significant link between lymph node ratio (LNR) and nodal categorization with specific outcomes, however there was high heterogeneity across the included studies and findings were inconsistent, thus it was not published.[19]

1.3. Current treatment modalities

The European Interdisciplinary Cancer team has rolled out their latest guideline on CSCC based on a consensus meeting in September 2019. Suggestions were based on systematic

examination of the literature, guideline and expert consensus. Surgical excision with postoperative margin evaluation or microscopically controlled surgery (Mohs) are the first-line treatments for primary CSCC. To reduce the risk of local recurrence and metastasis, safety margins containing clinically normal-appearing tissue around the tumor after surgical excision and negative margins as documented in the pathology report are required. There should be no flap replacement until the margin has been cleared definitively. For operable instances, a re-excision should be performed if the margins are affected. For CSCC with cytologically or histologically verified regional nodal involvement, lymph node dissection is advised. For inoperable CSCC or nonsurgical candidates, radiotherapy should be explored as a curative therapeutic option.[20]

Current cancer therapy strategies have pointed to the infiltration of signalling pathways that are important in the disease's process. One of the first systemic medicines to be tried was epidermal growth factor receptor (EGFR) inhibitors. Elevated EGFR expression has been seen in advanced CSCC with a frequency (43 percent-100 percent) that is related to the probability of metastatic disease. Monoclonal antibodies that block the receptor's extracellular domain (example; cetuximab, panitumumab, nimotuzumab, zalutumumab) and small-molecule tyrosine kinase inhibitors (TKIs) that block tyrosine kinase activity and thus inactivate downstream cellular pathways that are two types of EGFR inhibitors (example; gefitinib, erlotinib, afatinib, lapatinib, neratinib, dacomitinib). Cetuximab is a human-mouse chimeric monoclonal antibody that suppresses EGFR by targeting the extracellular region of the protein and disrupting intracellular signalling via the RAS/MAP kinase pathway. It is being studied primarily for advanced CSCC. In Europe, Cetuximab is licensed for advanced or metastatic head and neck CSCC in combination with radiation or platinum-based chemotherapy. Cetuximab is classified as a radiosensitizer since it has a synergistic impact with radiation. Cetuximab alone was compared to Cetuximab coupled with Cisplatin or radiation in a prospective trial of 20 patients with locally advanced CSCC (60–70Gy). Combination therapy had higher response rates versus Cetuximab alone (disease control rate, 92% versus 50%, respectively, and response rates, 53% versus 33%, respectively). In a single study centre by Joseph et al, 8 inoperable CSCC cases were given both Cetuximab and radiotherapy. Cetuximab (first dose): 400mh/m2 7 days before radiation, then weekly dosages of 250mg/m2 for the course of radiotherapy. Six individuals had a full response, one had a partial response, and one experienced illness progression. In the trial, the two-year progression-free survival rate was 83.3 percent. In comparison to traditional chemotherapy, anti-EGFR medicines are often well tolerated. Majority of adverse effects are cutaneous, dose-dependent and affect cosmetically sensitive regions, affecting the patient's quality of life significantly. A papulopustular or acneiform rash, which emerges during the first 1–2 weeks of starting medication, xerosis pruritus and hand or nail toxicity are among them. Cetuximab, in combination with chemotherapy or radiation, can be used as a second-line treatment following Cemiplimab (first line). It might also be used before chemotherapy for older individuals with comorbidities, who may be unable to handle chemotherapy.[21]

Anti-programmed death receptors-1 (PD-1) antibodies are a type of the immune checkpoint inhibitor (immunotherapy) that has been approved for patients with metastatic or locally advanced CSCC who are not candidates for curative surgery or radiation, with Cemiplimab being the first systemic agent for advanced CSCC to be approved by the Food and Drug Administration/European Medicines Agency. In a phase I/II clinical trial reported by Migden et al treated 26 patients with locally advanced CSCC or metastatic CSCC and 59 patients with regionally or distant metastatic CSCC from the phase II part of the study with the PD-1 inhibitor Cemiplimab at a dose of 3 mg/kg every 2 weeks intravenously. Every eight weeks, the patient's responses were evaluated. Patient who had organ transplantation, as well as those suffering from hematologic malignancies or other immunosuppressive diseases, were excluded from the study. The phase I cohort had the best overall response rate of 50%, while phase II cohort had a response rate of 48% (with 7 percent achieving a complete response). Patients with localized or distant metastatic illness had similar response rates. While PD-1 inhibitors have a greater response rate than any other therapy for metastatic CSCC, their usage in patients on immunosuppressive medications or with hematologic malignancies is still limited. Because these drawbacks affect a lesser number of patients, further PD-1 inhibitor studies should be conducted in the future in the aim of making this medicine the gold standard therapy for patients with locally progressed and metastatic CSCC.[22]

Another technique of intervention is electrochemotherapy, which includes injecting a cytotoxic drug (either bleomycin or cisplatin) intravenously, followed by the insertion of a needle electrode into the tumor mass and pulse application. The efficacy varies depending on disease control and local response, which is claimed to be in the 20–70 percent range in most situations. In CSCC, electrochemotherapy can be utilized to slow tumor development while also managing bleeding and other mass-related symptoms. Electrochemotherapy (bleomycin) for skin tumors was evaluated in a European multi-institutional prospective (EURECA) experiment which included 50 CSCC patients of the head and neck who were not appropriate for surgery, chemotherapy, or radiation as determined by a multidisciplinary board. Complete response was achieved in 55 percent of CSCC patients at two months, partial response in 24%, stable illness in 15%, and progression in 4%. Skin ulceration, hyperpigmentation and suppuration were the most common side effects. The efficacy is determined on the tumor's size (smaller tumor better results and the angulation of the needle electrode inserted to the tumor). So far, there have been few investigations on this kind of intervention.[23]

2. Conclusion

Our review's main message is that we should be wary of assuming that CSCC is a tumor with good prognosis merely because it generally has a favorable outcome. In reality, because of its high prevalence, difficult and dispersed cases are likely to repeat frequently. The treatment of metastatic CSCC is still a difficulty. The new generations of pharmaceuticals that target many signaling pathways, particularly immunotherapeutic treatments, offers up new treatment options for CSCC patients, and we may expect these to become more prevalent in the next wave of customized and precision medicine protocols. Patients should be encouraged to participate in clinical trials so that new medications might be discovered and adopted in the future.

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