Review Article

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Guidelines for Management of Cutaneous Squamous Cell Carcinoma

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Abstract

Cutaneous squamous cell carcinoma (cSCC) is the second most common skin cancer. This review article gives an overview of cSSC in terms of etiology, pathophysiology, epidemiology, prognosis, clinical presentation, work up, treatment and highlights various guidelines like American College of Radiology, Scottish Intercollegiate Guidelines Network's, Dermatological Cooperative Oncology Group of the German Cancer Society, British Association of Dermatologists Guidelines for the management of cSSC.

Kewords: Cutaneous; Squamous cell; Carcinoma.

INTRODUCTION

Background

Cutaneous squamous cell carcinoma (cSCC) is the second most common skin cancer and one of the most common cancers overall in the United States.[1]

Pathophysiology

Malignant transformation of normal epidermal keratinocytes is the hallmark of cSCC. One critical pathogenic event is the development of apoptotic resistance through functional loss of TP53, a well-studied tumor suppressor gene. TP53 mutations are seen in over 90% of skin cancers diagnosed in the United States, as well as in most precursor skin lesions, suggesting that loss of TP53 is an early event in the development of cSCC (Fig. 1).

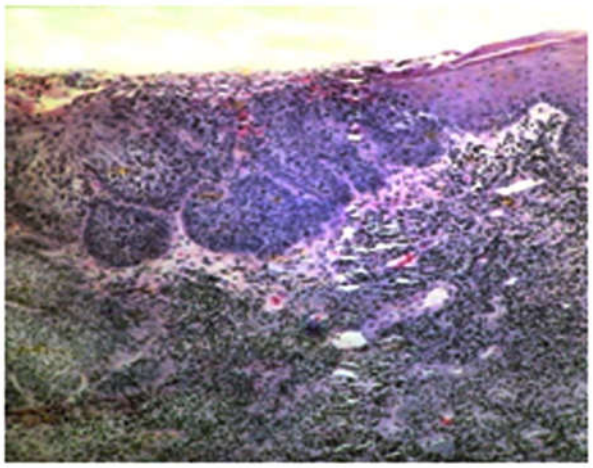

Fig. 1: Squamous cell carcinoma.

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Etiology

Exposure to cancer-promoting stressors and the response of the body to those exposures (host response) promote the development of cSCC. Well-known risk factors include the following:

- UVR exposure
- Immunosuppression
- Exposure to ionizing radiation or chemical carcinogens
- Human papillomavirus (HPV) infection

EPIDEMIOLOGY

Skin cancers are the most frequently diagnosed cancers in the United States. Determining the number of cSCCs is difficult, however, because reporting of these cases to cancer registries is not required. One report estimated that in 2012, there were over 5.4 million non melanoma skin cancers in the United States, with more than 3.3 million people treated.[3]

Geography-related demographics

The highest incidence of cSCC occurs in Australia, where non melanoma skin cancer incidences as high as 1.17 per 100, a rate 5 times greater than all other cancers combined, have been reported.[4]

Race-related demographics

SCC is the second leading cause of skin cancer in white individuals.[5]

Sex and age related demographics

SCC occurs in men 2-3 times more frequently than it does in women, most likely as a result of higher cumulative lifetime UV exposure in men.

PROGNOSIS

Although primary cSCC is not often fatal, it can cause significant morbidity if left untreated.[6]

Like many cancers, cSCC is staged clinically by tumor and node size and metastasis, ie, the TNM staging system, as devised by the American Joint Committee on Cancer (AJCC).[7]

Diameter and thickness

Lesions of invasive SCC measuring smaller than 2 cm in diameter have been associated with a 9.1% rate of metastasis, whereas those larger than 2 cm in diameter have a metastatic rate of up to 30.3%. A prospective study reported a 3 years, disease-specific survival rate of 67% for lesions larger than 4 cm, compared with 93% for tumors smaller than 4 cm.[8]

A study by Eigentler et al indicated that in cases of cSCC, factors contributing to a high risk for tumor-specific death, if a cut-off for tumor thickness of 6 mm or greater is used, include desmoplastic growth and immunosuppression.[9]

Depth

With increasing depth of invasion of the primary SCC tumor, the risk of local recurrence and nodal metastasis increases and the rate of survival decreases.

Cellular differentiation

More poorly differentiated tumors have a worse prognosis in SCC, with reported recurrence rates of 33-54%.[10]

Tumor recurrence

Recurrence risk is increased with high-risk tumors; lesions larger than 2 cm recur at a rate of 15.7% after excision.

Perineural invasion

Perineural invasion has been estimated to occur in up to 7% of persons with cutaneous SCC. The prognosis in such cases is worse, with historical rates of metastasis reported to be as high as 47%. Much lower rates of metastasis (8%) have been reported using Mohs micrographic surgery.[11]

Lymph node ratio

A study by Vasan et al indicated that in patients with metastatic head and neck cSCC, a ratio of positive lymph nodes to resected lymph nodes of over 6% is a risk factor for shorter disease free and overall survival.[12]

CLINICAL PRESENTATION

History

The initial presentation of cutaneous squamous cell

carcinoma (cSCC) typically includes a history of a nonhealing ulcer or abnormal growth in a sun-exposed area.

PHYSICAL EXAMINATION

The following features of the lesion should be noted.

- Location (eg, eyelid SCC is more common on the lower eyelid)
- Size
- Character (eg, smooth/nodular, vascularity, color): SCC may appear as plaques or nodules with variable degrees of scale, crust, or ulceration
- Presence of ulceration

Frequently, the presentation of cSCC is preceded by the presence of actinic keratoses.[13]

TUMOR SIZE AND LOCATION

In addition to general appearance, the size and location of the lesion should be recorded, as both have prognostic and therapeutic importance. For instance, lesions larger than 2 cm and those located on the external ear or lip have been shown to have a higher rate of metastatic spread.

Tumor characteristics

Surface changes on a typical SCC may include scaling, ulceration, crusting, or the presence of a cutaneous horn. Less commonly, the lesion may manifest as a pink cutaneous nodule without overlying surface changes.

Perineural invasion

Up to 14% of cSCCs exhibit perineural invasion. Evidence of cranial nerve dysfunction on examination should raise concern of significant perineural invasion. The most frequently involved cranial nerves are the facial and trigeminal nerves.[14]

Tumor metastasis

Investigate regional spread of head and neck cSCC by palpating for enlarged preauricular, submandibular, and cervical lymph nodes. Regional metastasis occurs in 2-6% of cases of cSCC. In head and neck cSCC, soft tissue metastasis, defined as metastatic spread to non-lymphatic soft tissue, suggests a poorer prognosis than extranodal extension.[15]

INVESTIGATIONS

A biopsy should be performed for any lesion suspected of being a cutaneous neoplasm.

In advanced stage cSCC, CT scanning or MRI can be helpful in defining the extent of disease. CT scanning is useful for determining the presence of bone or soft tissue invasion and for evaluating cervical lymph nodes at risk for metastasis. For evaluation of perineural invasion and orbital or intracranial extension, MRI is the preferred imaging modality.

Biopsy

Small skin lesions in noncritical areas may be amenable to excisional biopsy, in which the entire area of concern is removed. This method has the benefit of being diagnostic as well as potentially therapeutic, without the need for a second procedure.

STAGING

TNM staging system

The TNM staging system for nonmelanoma skin cancers, including cSCC.[7]

TREATMENT AND MANAGEMENT

Low-risk cutaneous squamous cell carcinoma (cSCC) on the trunk and extremities can be treated with electrodessication and curettage (ED & C). For invasive cSCC, surgical excision and Mohs micrographic surgery are the primary treatment options; with appropriate patient selection, these techniques have comparable cure rates. Radiation therapy is typically used as an adjuvant to surgery, to provide improved locoregional control, but it may be used as primary therapy in patients who are unable to undergo surgical excision.

Chemotherapy may be considered as adjuvant therapy in select highest risk cases of cSCC. In particular, emerging evidence suggests that epidermal growth factor receptor (EGFR) inhibitors may be useful adjuncts to surgical treatment. Systemic chemotherapy may be considered for metastatic cSCC.

Electro dessication and Curettage

ED & C is a simple technique that can be used to treat localized, superficial cSCC.

Surgical Excision and Reconstruction

Standard excision with conventional permanent (ie, paraffin embedded) tissue sections is a highly effective and well tolerated therapy for primary cSCCs that lack high risk features and are located in areas where tissue sparing is not critical. Surgical excision offers the advantages of histologic verification of tumor margins, rapid healing, and improved cosmesis.

Simple excision is most valuable in the treatment of small primary SCCs on the trunk, extremities, or neck, where tissue sparing is less essential.[16] Recurrence rates after the excision of low risk lesions range from 5-8%. A 6-mm margin of healthy tissue is recommended for lesions that are larger than 2 cm, invasive to fat, or in high risk locations (ie, central face, ears, scalp, genitalia, hands, feet).

After surgical excision, if the defect is small then primary closure can be done. If defect is large enough to involve subcutaneous layer and fascia then skin grafting can be done. If the defect is very large then local, regional, distant or micro vascular flap should be considered.

Sentinel lymph node biopsy

While positron emission tomography (PET)/CT imaging and ultrasonography can be useful tools in identifying metastatic disease, approximately 7% of patients with no findings on PET/CT scans have been found to have micrometastases when sentinel lymph node biopsy (SLNB) is performed.[17,18]

A systematic review by Ahmed et al showed that among SLNB patients with T2 or greater cSCC of the head and neck area, 13.7% were found to have a positive sentinel lymph node.[19]

Bander et al found that positivity rates for SLNB in high risk cSCC ranged between 11.3% and 24%. [20,21]

Mohs micrographic surgery

Mohs micrographic surgery is a specialized technique for removing many forms of skin cancer, including cSCC. Because of its numerous advantages, Mohs micrographic surgery is the procedure of choice in the following situations:

- SCC in which tissue preservation is needed
- Ill-defined SCC
- Recurrent tumors
- High-risk SCC

Mohs surgery, which was developed by Frederic E. Mohs in the 1930s, is a method of tumor excision in which the surgeon first excises the visible tumor with a small margin of normal tissue.[22]

Radiation Therapy

Radiation therapy as primary treatment for cSCC is typically reserved for patients who are unable to undergo surgical excision. More frequently, radiation therapy is used as an adjuvant to surgery for improved locoregional control. Postoperative radiotherapy is considered for tumors that exhibit perineural invasion or other high risk features and for those that involve regional metastasis.[23]

No comparative studies of surgery versus surgery plus adjuvant radiotherapy for high risk SCC have been performed. With no clear evidence of benefit and the potential of significant morbidity, clinical judgment is required in deciding which patients should receive adjuvant radiation. One systematic review suggests that adjuvant radiation be considered in patients with uncertain or positive surgical margins or advanced nerve involvement.

Systemic Treatment

Chemotherapy

Adjuvant chemotherapy

Adjuvant medication may be considered in select highest-risk cases of cSCC. Options include oral 5-fluorouracil (5-FU) and epidermal growth factor receptor (EGFR) inhibitors.[24]

Chemotherapy

Among the most common non targeted agents used in cSCC are cisplatin and carboplatin, 5-FU, and taxanes. Cetuximab, a chimeric immunoglobulin G1 monoclonal antibody that inhibits EGFR, has been reported as successful in multiple case reports[25,26,27]

Immunotherapy

Approved by the US Food and Drug Administration (FDA) in October 2018, the PD-L1 inhibitor cemiplimab (Libtayo) became the first treatment specifically approved for patients with metastatic or locally advanced cSCC who are not candidates

for curative surgery or curative radiation.[28] The investigators found an objective response rate of 47% among patients with metastatic disease, and 49% in those with locally advanced cSCC.[29]

Approval was based on efficacy data from the multicenter, nonrandomized, open-label KEYNOTE-629 clinical trial. Patients (n=105) received pembrolizumab 200 mg IV every 3 weeks until the disease progressed, toxicity became unacceptable, or a maximum of 24 months had passed, with the cohort demonstrating an objective response rate of 34%.[30]

GUIDELINES SUMMARY

Guidelines of American College of Radiology

Appropriateness Criteria® for the treatment of aggressive nonmelanomatous skin cancer of the head and neck, issued by the American College of Radiology (ACR) in 2014, include the following recommendations[31]

- Cutaneous squamous cell cancer (cSCC) that is resected with negative margins and does not display high risk features can be safely observed postoperatively
- Consider adjuvant radiotherapy for resected SCC that demonstrates perineural invasion, especially multifocal; in cases of extensive perineural invasion or invasion of named nerves, the nerve should be targeted with radiotherapy back to the skull base
- Patients with periparotid nodal disease should be managed by surgical resection with neck dissection, followed by adjuvant radiotherapy
- Concurrent cisplatin-based chemotherapy can be considered in patients with high risk pathologic features (eg, margin positivity or extracapsular extension) or in patients with unresectable, locally advanced disease
- Intensified adjuvant therapies, such as radiotherapy for intermediate risk patients and incorporating systemic therapies concurrently with radiotherapy, may benefit certain classes of patients

SCOTTISH INTERCOLLEGIATE GUIDELINES NETWORK

Recommendations from the Scottish Intercollegiate Guidelines Network's (SIGN's) updated guidelines for the management of primary cutaneous squamous cell carcinoma (cSCC), published in 2014, are summarized below.[32]

The following are considered high risk clinical features:

- Immunosuppression
- Ear as the tumor site
- Horizontal tumor diameter of >20 mm
- Tumor depth >4 mm; >6 mm indicates a very high risk tumor
- Tumor extension beyond the dermis into or through subcutaneous fat
- Perineural invasion
- Desmoplastic subtype
- Poorly differentiated tumor status

The presence of any of the above high-risk features in a patient with primary SCC warrants discussion of the patient in a multidisciplinary team (MDT) meeting.

SCC Treatment Options Include the following:

- ***Surgical excision for high-risk tumors*** - A clinical peripheral margin of 6 mm or greater is indicated when surgically achievable and clinically appropriate.
- ***Surgical excision for low-risk tumors*** - A clinical peripheral margin of 4 mm or greater is indicated when surgically achievable and clinically appropriate.
- ***Mohs micrographic surgery should be considered for selected patients with high-*** risk tumors when tissue preservation or margin control is challenging, as well as for patients with any tumor at a critical anatomic site.
- ***Consider curettage and cautery for patients with low*** risk tumors if healthcare professionals have had appropriate training with a blunt curette.
- Photodynamic therapy should not be used for treatment of primary SSC.
- Consider primary radiotherapy for patients if surgical excision would be extremely challenging or difficult to perform or would be likely to result in an unacceptable functional or aesthetic outcome.
- Consider adjuvant radiotherapy for patients with a high risk of local recurrence or with close or involved margins when further surgery carries an increased risk of complications, including functional or aesthetic morbidity.

For patients with SCC with any high-risk features, posttreatment follow-up appointments every 3-6 months for 24 months should be offered. Depending on the clinical risk, it may be appropriate to also schedule one 3-year follow-up appointment.

GUIDELINES OF DERMATOLOGICAL COOPERATIVE ONCOLOGY GROUP

Guidelines on cutaneous squamous cell carcinoma (cSCC) from the Dermatological Cooperative Oncology Group of the German Cancer Society and the German Society of Dermatology were published in April 2020. They include the following.[33]

Because data are insufficient regarding the value of regional lymphadenectomy following positive sentinel lymph node biopsy (SLNB), do not perform prophylactic lymphadenectomy.

When lymph node metastasis is clinically manifested, the patient should undergo regional (therapeutic) lymphadenectomy.

When local disease is inoperable or not completely resectable, radiation therapy should be performed.

The following cases should prompt use of postoperative radiation therapy:

- R1 or R2 resection (if reexcision is not feasible)
- Extensive lymph node involvement (>1 affected lymph node, lymph node metastasis >3 cm, capsular penetration)
- Intraparotid lymph node involvement
- Existence of the following risk factors should prompt treatment with adjuvant radiation therapy:
- Surgical margins < 2 mm and reexcision is not feasible
- Extensive perineural infiltration

Employ micrographically controlled surgery (MCS) for the treatment of local or locoregional recurrence.

If, over the course of the resection, residual, unresectable tumor tissue (R1 or R2 resection) is in evidence, the affected area should undergo radiation therapy.

If an interdisciplinary tumor board determines inoperability, radiation therapy should be performed.

Guidelines of British Association of Dermatologists

Guidelines on the management of cutaneous squamous cell carcinoma (cSCC) were published in March 2021 by the British Association of Dermatologists.[34]

Pretreatment for cSCC

If there is any diagnostic uncertainty, histologic confirmation of cSCC lesions should be obtained before planning definitive treatment.

Before performing any diagnostic or treatment procedure, the following should be recorded:

- Maximum clinical cSCC lesion dimension (typically diameter, in mm)
- The plane of the deep excision margin
- Whether the tumor is recurrent or whether it is in a field of previous radiotherapy
- The immunocompetency of the patient

Treatment options for primary cSCC

The first-line treatment that should be offered to people with resectable primary cSCC is surgical excision.

Determine peripheral tumor margins under bright lighting with magnification or with dermoscopy.

The following should be offered to patients with cSCC who have one or more involved margins or margins less than 1 mm, in whom patient or tumor factors suggest higher risk:

- Wide local excision (delayed reconstruction likely)
- Mohs micrographic surgery
- Adjuvant radiotherapy

Active treatment can be offered to immunosuppressed cSCC patients who have one or more clear but close (< 1 mm) or involved margins, followed by structured follow up and surveillance.

If patients have symptomatic perineural invasion or radiologic evidence of perineural invasion, their case should be discussed by a specialist skin cancer multidisciplinary team.

Mohs micrographic surgery can also be considered in selected patients with cSCC after discussion by a specialist skin cancer multidisciplinary team; this particularly applies to cases in which tumor margins are difficult to delineate or in locations where tissue conservation is important for function.

Before considering radiotherapy in patients with histologically proven cSCC, discuss the case with a multidisciplinary team—either a local skin cancer multidisciplinary team or a specialist skin cancer multidisciplinary team—with a clinical oncologist present.

Curettage and cautery with curative intent can be considered in immunocompetent patients with low risk, small (< 1 cm), well defined, nonrecurrent cSCC.

Locally advanced, recurrent, and metastatic cSCC

In patients with the following variables, an individualized specialist skin cancer multidisciplinary team should be involved to include multimodality and imaging treatment plans:

- Regional lymph node metastasis
- Immunocompromise with locally advanced and/or metastatic cSCC
- In-transit metastases from cSCC
- Metastatic cSCC, with the patient having experienced further locoregional relapse following lymphadenectomy

Therapeutic regional lymphadenectomy should be offered to patients with head and neck cSCC with regional lymph node metastasis. It should also be offered to patients with non–head and neck cSCC who have regional lymph node metastases in axillary, inguinofemoral, or other peripheral draining nodes.

Adjuvant radiotherapy should be offered after therapeutic regional lymphadenectomy to patients with cSCC who have high risk pathology.

Insufficient evidence to support any recommendation for cSCC

The evidence is insufficient to support any recommendations for the following therapies in the treatment of cSCC:

- Cryotherapy
- Carbon dioxide laser therapy
- Topical therapies

CONCLUSION

Various guidelines like American College of Radiology, Scottish Intercollegiate Guidelines Network's, Dermatological Cooperative Oncology Group of the German Cancer Society, British Association of Dermatologists Guidelines provides evidence based recommendations for the management of cSSC.

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