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Metastatic Squamous Cell Carcinoma: Epidemiology and Available Systemic Therapies

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Abstract Metastatic cutaneous squamous cell carcinoma rarely since surgery cures the majority of primary tumors. Metastatic cutaneous squamous cell carcinoma causes significant morbidity and mortality. Identifying characteristics of patients and the primary tumor may help to predict risk for metastasis and aid in the prevention, detection, or treatment of metastatic squamous cell cancer. Due to the rarity of metastatic cutaneous SCC, there are few prospective trials examining tumor characteristics associated with metastasis. Furthermore, the rarity and morbidity of metastatic squamous cell carcinoma make randomized controlled therapeutic trials difficult. We examine the risk factors and systemic treatments for metastatic cutaneous squamous cell carcinoma.

Keywords Squamous cell carcinoma · Metastatic skin cancer · Mohs micrographic surgery · EGFR inhibitors

Introduction

Squamous cell carcinoma (SCC) is the second most common cutaneous malignancy worldwide. Conventional surgical therapies cure 95 % of cutaneous SCC. Four percent of cutaneous SCC tumors metastasize, leading to significant patient morbidity and mortality [1]. Identifying high-risk tumors and designing treatments is challenging due to the lack of data to guide care. This article examines the epidemiology and systemic therapies for metastatic cutaneous SCC.

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Epidemiology of Metastatic Squamous Cell Carcinoma

Squamous cell carcinoma (SCC) most commonly presents in sun damaged skin of the head and neck in fair skinned, older patients. Squamous cell carcinoma is the second most common cutaneous malignancy behind basal cell carcinoma. Between 186,157 and 419,843 new cases of squamous cell carcinoma are estimated in 2012 [2]. The incidence of squamous cell carcinoma is estimated, as the data is not captured by tumor registries. Most SCC tumors are small, localized skin cancers that are cured with surgical excision or Mohs micrographic surgery. A small percentage of SCC is recalcitrant to surgical therapies may display aggressive biology with local recurrences and/or lymphatic spread. An estimated 5604 to 12,572 patients developed nodal metastasis, and 3932 to 8791 will die from SCC in the United States in 2012 [2]. Identifying patients at risk for metastatic SCC is a diagnostic challenge for physicians. Small retrospective trials have identified tumor characteristics associated with high-risk tumors, but no large trials have supported the observations. Tumor size, anatomical location, depth, perineural invasion, and intravascular invasion have all been associated with metastatic SCC. The rarity and mortality of cutaneous metastatic SCC make long term prospective trials difficult.

For the past 20 years, the American Joint Committee on Cancer (AJCC) staging system grouped all non-melanoma skin cancers (NMSC) together, including SCC. NMSC staging focused on lesion size without incorporating tumor features. In June 2011, the seventh edition of the AJCC staging criteria established a separate staging system for cutaneous SCC. The newest edition is more congruent with the mucosal SCC staging system and is based on "data-derived, evidence based medicine" [3••]. The new staging

criteria incorporates features associated with high risk tumors such as histological subtype, depth of tumor invasion, perineural and intravascular invasion, tumor recurrence, anatomical site and patient immune status. The updated staging system designates a high risk lesion as greater than 2 cm in diameter or having two or more high-risk features. The tumor characteristics incorporated in the AJCC staging system are "believed to be associated with high-risk SCC", but convincing data supporting these characteristics as prognosticators for metastasis is lacking [3••].

Tumor Size

Squamous cell carcinomas that are larger in size are more likely to recur and metastasize. In tumors greater than 2 cm in diameter, the local recurrence rate doubled and metastasis rate tripled. SCC on the trunk and extremities measuring greater than 2 cm has an eight-fold risk of recurrence and metastasis. In a prospective study of 266 cutaneous SCC patients with lymph node metastasis, tumor size was not relevant with the majority of tumors less than 2 cm. Examination of a Danish tumor registry containing 915 cutaneous SCC showed the risk of metastasis significantly increased in tumors greater than 1.5 cm. Further studies examining tumor size are needed to determine the importance of tumor size in metastasis.

Perineural and Intravascular Invasion

Perineural invasion is associated with a poor prognosis including increased risk of local recurrence, distant metastasis and disease-specific death [4]. Debate exists regarding the importance of the size of the nerve involved. Perineural invasion of named nerves is accepted as significant disease with poor prognosis. The significance of small caliber nerve invasion is controversial. In a retrospective cohort of 48 patients with perineural invasion, involvement of nerves >0.1 mm had higher rates of local recurrence, nodal metastases, distant metastases and disease-specific death [5]. A retrospective cohort study examining 114 cases of perineurally invasive SCC showed that tumors with large nerve (>0.1 mm in caliber) invasion were significantly more likely to have other risk factors leading to recurrence and metastasis [6••]. Sixty-eight tumors had perineural invasion of small nerves (<0.1 mm). One tumor with perineural invasion of small caliber nerves had a single local recurrence. On univariate analysis, large nerve invasion was associated with increased risk of nodal metastasis (HR, 5.6{95 % CI 1.1-27.9}) and death from disease (HR 4.5 {95 % CI, 1.2-17.0}). When perineural invasion was combined with other risk factors such as lymphovascular invasion, invasion beyond subcutaneous fat, and tumor diameter greater than 2 cm, overall prognosis was poor. Tumors with multiple high-risk features are more likely to have a poor prognosis.

Tissue processing during Mohs micrographic surgery allows for 100 % of histological margin examination. The central portion of the tumor is not examined unless the tumor is debulked and processed serially such as in a "bread loafing" technique. While histological margin examination in Mohs micrographic surgery is standardized, the processing of the central tumor varies by surgeon. Examination of the central tumor is especially valuable in cases where tumor extirpation is achieved in the first stage of Mohs micrographic surgery. In suspected high-risk tumors, submitting Mohs tissue blocks for paraffin sectioning allows for further tumor characterization and staging [7•].

Histologic Characteristics and Anatomical Location

Depth of tumor invasion and histologic degree of differentiation are associated with cutaneous SCC recurrence and metastasis. SCC with greater than 2 mm thickness is associated with an increased risk of metastasis. A retrospective study of 615 SCC tumors treated with Mohs micrographic surgery showed 4 % of patients developed metastasis and 3 % of patients had a local recurrence [8]. Tumors 2 mm or less did not metastasize. Metastasis occurred in 4 % of tumors between 2.1 mm and 6.0 mm thickness and in 16 % of tumors with a thickness greater than 6 mm [8].

Well differentiated tumors have the highest cure rate, while poorly differentiated tumors have a 37 % cure rate and an increased risk of metastasis [4, 9]. Poorly differentiated SCC is more likely to metastasize to regional lymph nodes and 10 times more likely to recur than well differentiated SCC.

Anatomical location of the primary squamous cell carcinoma can be associated with subsequent metastasis with the lip and ear as high-risk sites [1]. Head and neck tumors are more likely to metastasize as compared to trunk and extremity squamous cell carcinomas. Large, ulcerated, neglected tumors of the trunk and extremities are associated with metastasis [10•].

Immunocompromised Patient

Solid organ transplant recipients (SOTR) have a 65-fold increased incidence of SCC as compared to the general population [11]. The degree and duration of immunosuppression are important factors in the development of SCC. Patients on three immunosuppressive medications are more likely to develop SCC as compared to patients on two drug regimens. Seven percent of SOTR develop SCC one year following transplant. The incidence of SCC in the SOTR climbs to forty percent at 11 years post-transplant [12]. SOTR have a 66 % risk of developing a second skin cancer within five years from their first SCC tumor [12]. SOTR have aggressive tumors with poorly differentiated histology,

deep invasion and increased risk of metastasis [13]. Distant and in-transit metastases are more common in transplant patients [14]. Once metastasis has occurred, the prognosis for SOTR is poor with 30 % disease associated mortality. Reducing immunosuppression is an important part of metastatic SCC treatment in the solid organ transplant recipient.

Impaired immune function as in lymphocytic diseases such as chronic lymphocytic leukemia (CLL) and small-cell lymphocytic lymphoma (SLL) is associated with metastatic SCC. Only 5 % of CLL and SLL patients will develop SCC, but the tumors they develop are high- risk, aggressive SCC [15]. A quarter of SCC in SLL and CLL patients will recur or metastasize. Forty percent of CLL/SLL patients with metastatic SCC will die from skin cancer.

A multidisciplinary approach is needed for immunocompromised patients with catastrophic and metastatic squamous cell carcinoma. The immune mechanisms underlying the increased risk of aggressive SCC in the immunosuppressed have not been established.

Treatment of High Risk SCC

The treatment of high-risk SCC is difficult as there are no evidence based guidelines to direct care. The expert consensus published by the National Comprehensive Cancer Network (NCCN) recommends tumors with one risk factor have treatment with wide local excision with 1-cm margins or with Mohs micrographic surgery [16]. The NCCN consensus cites the following risk factors for high-risk SCC: large tumor diameter, depth beyond papillary dermis, ill-defined margins, recurrence, immunosuppression, history of radiation at the site, rapid growth, neurological symptoms, perineural or vascular invasion, moderately or poorly differentiated histology, infiltrative or acantholytic pattern, or mucin production [17]. The updated American Joint Committee on Cancer (AJCC) designates a high risk lesion as greater than 2 cm in diameter or having two or more high-risk features [3••].

Achieving tumor-free margins during the initial surgery is vital for decreasing the risk of subsequent metastasis and recurrence in high-risk SCC lesions. Adjuvant radiation for high-risk SCC following surgical treatment remains controversial. There have been no rigorous prospective trials examining adjuvant radiation therapy for high-risk SCC surgically treated. A small retrospective study of cutaneous SCC patients with incidental perineural involvement benefited from elective nodal irradiation with a five year regional neck control rate of 100 % as compared to 82 % (p=0.0652) in the nonirradiated cohort [18]. In tumors with additional high-risk features in addition to perineural involvement, adjuvant radiation therapy was not beneficial [19]. Well designed, randomly controlled, prospective clinical trials are necessary to examine adjuvant radiation therapy in high risk SCC.

The use of sentinel lymph node (SLN) in staging of high risk cutaneous SCC remains unproven. SLN biopsy is an investigational staging tool in clinically node-negative high-risk cutaneous SCC patients [20•]. Well-designed prospective studies with long term follow up are needed to discern the role of SLN in clinically negative node patients with high risk SCC.

Metastatic Squamous Cell Carcinoma

Lymph node metastasis from cutaneous SCC can present within the first two years from treatment of the primary tumor. The distribution of nodal metastases is approximately divided equally between the parotid alone, the parotid and neck, and the neck alone [21]. The location of the primary SCC determines the site of nodal metastases with facial lesions spreading to level I and II cervical nodes and the anterior scalp, ear, and forehead/temple lesions tending to spread to the parotid and level II nodes[22]. The prognosis for patients with nodal metastasis depends on the number of involved nodes and extracapsular extension. Disease specific survival (DSS) and overall survival (OS) are worse for patients with distant disease compared to those with different stages of regional disease. After 5 years, only 25 % of patients with metastasis to two lymph nodes and 35 % of patients with three lymph node disease die from their cancer compared with 89 % of patients with distant metastases [23]. Patients with lymph node metastasis greater than 3 cm in size have a worse prognosis [24]. Metastasis to one lymph node, less than 3 cm with no extracapsular nodal spread, has a good prognosis with the 5-year regional control rate of 92 % and DSS of 100 %. The DSS decreased to 93 % when extracapsular nodal spread was present [25••].

The treatment of metastatic squamous cell carcinoma is challenging due to tumor biology and the lack of standardized treatment algorithms. Surgical resection of the metastasis and draining lymph nodes is the first step in treatment. Dissection of the superficial parotid with sparing of the facial nerve is recommended as the parotid contains multiple lymph nodes. The use of adjuvant radiation following surgery has been recommended in the NCCN guidelines [17]. Small retrospective studies have supported combined surgery and adjuvant radiation for metastatic disease treatment. A retrospective review of metastatic cutaneous SCC patients treated with surgery vs. radiation and surgery showed that after surgery alone 11 patients (55 %) developed a recurrence compared with 23 patients (23 %) after surgery and radiation [26•]. Tumor recurrence despite combined surgical and radiation therapy has a poor prognosis [19]. In contrast, patients with head and neck lymph node metastasis involving one node with no extracapsular extension did not benefit from radiation following lymph node dissection [25••]. Prospective, randomized controlled trials are needed to

determine the benefit of radiation therapy following surgical resection of metastatic SCC.

Systemic Therapies

Systemic treatments have been described for aggressive squamous cell carcinoma not conducive to conventional therapies. There are no rigorous, well controlled clinical trials examining the efficacy of systemic therapies in cutaneous metastatic SCC. Importantly, systemic treatments are used in aggressive tumors recalcitrant to surgical and radiation therapies. An intrinsic biological difference is present in these refractory tumors making interpretation of the scarce data even more difficult.

Chemotherapy for Cutaneous Squamous Cell Carcinoma

Chemotherapeutic agents have been described as treatments for aggressive, metastatic squamous cell carcinoma. Data supporting the use of systemic chemotherapy in the treatment of metastatic cutaneous SCC is lacking. The rarity of metastatic cutaneous SCC make large randomized controlled trials difficult. Treatment recommendations are based on case series and reports, an adjuvant phase III trial and four single arm phase II trials. Cytotoxic chemotherapies (bleomycin, doxorubicin, 5-fluorouracil, and cisplatin) has been described. An underpowered, randomized trial comparing bleomycin with other cytotoxic agents (cyclophosphamide, vincristine, methotrexate, and procarbazine) as treatment for 70 patients with SCC, six with cutaneous SCC, showed no statistically significant difference between the two treatment groups [27]. A prospective observational study of fourteen patients with advanced cutaneous SCC treated with cisplatin, 5-FU, and bleomycin showed four patients had a complete response (CR) and seven had a partial response [28]. Cisplatin and 5-FU without bleomycin decreased locoregional progression of SCC in seven patients with inoperable primary tumors [29]. Capecitabine, an orally bioavailable fluoropyrimidine chemotherapy agent converted to 5-fluorouracil, combined with subcutaneous interferon α in four patients with advanced cutaneous SCC resulted in two patients with CR and two with PR. Capecitabine has been described as a single agent in solid organ transplant patients to reduce the incidence of new primary squamous cell carcinomas [30••]. Metastatic SCC patients treated with capecitabine after failing cisplatin based therapies had a median overall survival of seven months [31••]. Further studies are needed to optimize treatment regimens and to determine efficacy.

Interferon α and Retinoic Acid

Interferon (IFN) is a proinflammatory cytokine with antitumor and viral downstream effects. Retinoids alter keratinocyte differentiation and proliferation. When combined, IFN and retinoids have been beneficial in the treatment of unresectable SCC [32]. In a prospective, phase II clinical trial combining cisplatin with IFN and 13 cis retinoic acid, six of 35 patients had a CR and six had a PR. Patients with metastatic disease did not see the benefit of those with advanced locoregional tumors. Interferon and retinoic acid was combined as an adjuvant treatment for patients with high-risk SCC treated with surgical excision. Sixty-six patients with tumors having one or more high-risk features were treated with surgery followed by a combination of 13 cis retinoic acid and interferon for 6 months or no adjuvant therapy [33]. Adjuvant radiation therapy was used in patients with perineural invasion, two positive lymph nodes, positive margins, or extracapsular nodal disease. At a median follow up of 21.5 months, adjuvant therapy with 13 cis retinoic acid and interferon did not improve time to recurrence.

Epidermal Growth Factor Receptor (EGFR) Inhibitors

Cutaneous squamous cell carcinomas express epidermal growth factor receptors, a member of the ErbB family of tyrosine kinase receptors [34]. EGFR Downstream signaling events includes cellular proliferation and angiogenesis. EGFR inhibitors have been efficacious in the treatment of advanced head and neck squamous cell carcinomas. Two pathways of EGFR activation are therapeutic targets–the receptor extracellular domain and the signaling pathway.

EGFR Monoclonal Antibodies

Cetuximab (Erbitux, C225) is a chimeric anti-epidermal growth factor receptor monoclonal antibody that binds the EGFR extracellular domain inhibiting receptor ligand binding and activation. Trials in patients with metastatic and recurrent head and neck SCC show cetuximab in combination with platinum and 5-fluoruracil had an increase in mean overall survival as compared to patients treated with chemotherapy alone (10.1 vs. 7.4 months, respectively, $p=0.04$) [35]. In a study of 424 patients with stage III or IV advanced head and neck cancer randomized to high-dose radiotherapy plus weekly cetuximab or high-dose radiotherapy alone, the median duration of locoregional control was 24.4 months versus 14.9 months (p: 0.005), respectively [36]. Mean duration of overall survival was 49 months for the combination therapy, versus 29.3 months for radiotherapy alone (p=0.03) [36].

Due to its therapeutic benefit in head and neck SCC, cetuximab has been used to treat advanced cutaneous squamous cell carcinomas [37]. There are no randomized, controlled clinical trials examining the efficacy of cetuximab in cutaneous SCC. The largest cetuximab study included 36 patients with advanced or metastatic cutaneous SCC [38]. Patients were treated with cetuximab 400 mg/m2 initial dose followed by 250 mg/m2 weekly. MRI or CT scans were performed every six weeks to assess therapy response. The endpoints were disease control rate (DCR) at 6 weeks and best objective response rate (ORR) using the RECIST criteria [39]. Statistical analyses were carried out both in the intent to treat (ITT) and per protocol (PP) populations [38]. DCR at 6 wks was 69 % in the ITT population and 81 % in the PP population (21 SD, 3 PR and 1 CR). Fourteen patients died: 6 due to disease progression; 4 were considered as NOS, and 3 sudden deaths were of unknown causes.

A retrospective review of eight cases of advanced or unresectable cutaneous SCC treated with cetuximab or cetuximab with radiation showed the efficacy of combined therapies. Four of the eight patients had metastatic disease. Of the patients treated with radiation and chemotherapy, three of the four patients had a complete response and one had a partial response [40•].

Cetuximab's primary side effect is a pruritic papulopustular acneiform rash that resolves following treatment [41]. Rash severity is a possible predictor of tumor responsiveness as head and neck SCC patients who developed the acneiform rash had better clinical outcomes. Rare case reports describe interstitial lung disease in 1 % of patients treated with gefitinib and erlotinib. Two lung transplant recipients with metastatic cutaneous SCC treated with cetuximab died from diffuse alveolar damage [42]. Safety and efficacy of EGFR inhibitors in transplant recipients have not been established.

Well-designed prospective, randomized controlled trials are needed to determine the efficacy, dosing and combined therapies for cutaneous SCC .

EGFR Tyrosine Kinase Inhibitors

Geftinib (Iressa, ZD1839) and erlotinib (Tarceva, OSI-774) are tyrosine kinase inhibitors that block EGFR receptor binding to early signaling molecules. There are no randomized controlled trials examining the EGFR tyrosine kinase inhibitors efficacy in cutaneous SCC treatment. Two patients with unresectable cSCC treated with erlotinib responded to therapy with a complete and partial response [43]. Gefitinib treatment of produced a 15 % partial response rate and 45 % stable disease rate in a prospective trial of patients with recurrent or metastatic cSCC [44]. A phase II trial of gefitinib in 15 patients with advanced SCC failed to achieve an objective response [45]. Combining gefitinib with the mTor inhibitor sirolimus was beneficial in shrinking an advanced extremity SCC in a patient declining amputation [46].

Conclusion

Metastatic squamous cell carcinoma is a deadly tumor claiming an estimated 2500 lives per year in the United States. The rarity of metastatic SCC makes identification of risk factors and therapeutic algorithms difficult. Tumor characteristics associated with metastasis have been described, but the data has not been validated in large, prospective trials. The new seventh-edition AJCC staging system creates the necessary framework for tumor data collection. Understanding metastatic squamous cell tumor biology and characteristics may lead to new therapeutic targets. Present systemic therapies for metastatic squamous cell carcinoma are few. Chemotherapies and EGFR inhibitors are used with varying success. The rarity of metastatic disease prohibits large, randomized controlled clinical trials. As the incidence of squamous cell carcinoma increases, so will the number of metastatic tumors. Multicenter collaboration is needed to determine the efficacy of systemic treatments for this aggressive tumor.

Conflict of Interest A Hanlon declares no conflicts of interest relevant to this article.

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