Cutaneous Squamous Cell Carcinoma

Abigail Waldman, MD, MHS*, Chrysalyne Schmults, MD, MSCE

KEYWORDS

• Cutaneous squamous cell carcinoma • Treatment • Diagnosis • Skin cancer

KEY POINTS

- Cutaneous squamous cell carcinoma (cSCC) is a common skin cancer that presents as a scaly, red, or bleeding lesion on sun-exposed areas.
- UV exposure, fair skin, and immunosuppression increase incidence of cSCC.
- Recurrence and metastasis are associated with tumor diameter greater than 2 cm, depth greater than 2 mm or beyond subcutaneous fat, extensive or large-caliber perineural involvement, and poor differentiation on histopathology.
- AJCC 8 is used for TNM staging for cSCC of the head and neck. BWH offers an alternative T staging system.
- Management is primarily surgical with rare indications for adjuvant chemoradiation based on risk factors.

INCIDENCE AND EPIDEMIOLOGY

Cutaneous squamous cell carcinoma (cSCC) is the second most common nonmelanoma skin cancer. It accounts for 20% of skin cancer and results in 1 million cases in the United States each year resulting in up to 9000 estimated deaths.[1–4]

Depending on the latitude, the incidence of cSCC ranges from 5 to 499 per 100,000 patients.[5–8] The lifetime risk of developing SCC is 14–20% in a non-hispanic white population in the United States.[9,10] This number continues to increase annually with an estimated 50% to 200% increase in incidence in the last three decades and will likely continue to increase because of the aging population.[11]

CLINICAL PRESENTATION

cSCC presents as a red scaly plaque, typically in sun-exposed areas. Lesions are typically solitary (**Fig. 1**A); however, they rarely can present as multiple "in transit" metastases (**Fig. 1**B).

Disclosure Statement: No disclosures.
Department of Dermatology, Brigham and Women's Hospital, 1153 Centre Street, Suite 4J, Boston, MA 02130, USA
* Corresponding author.
E-mail address: awaldman10@bwh.harvard.edu

Hematol Oncol Clin N Am 33 (2019) 1–12
https://doi.org/10.1016/j.hoc.2018.08.001
hemonc.theclinics.com

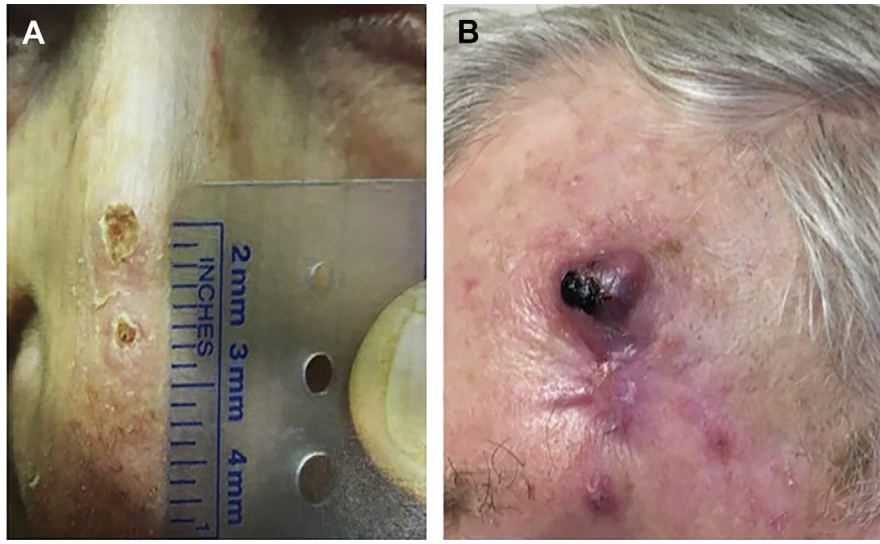

Fig. 1. Clinical presentation of SCC. (*A*) Primary locally invasive cSCC. (*B*) Multiple nodules representing in transit metastases.

WORK-UP

Diagnosis is made by a skin biopsy deep enough to allow the pathologist to comment on depth of invasion, perineural or lymphovascular invasion, differentiation, and connection to the overlying epidermis.[12] Local lymph nodes and parotid when appropriate should be evaluated by clinical examination and should be sampled if clinically involved.[13] The value of sentinel lymph node biopsy in cSCC without clinically apparent lymph nodes is currently unknown.[14–17] The patient should also be assessed for nerve involvement signified by neurologic pain or palsy. Generally, imaging is not required unless the clinical picture is suggestive of involvement of large-caliber nerves, muscle or bone, lymph node involvement, or when high-risk features are present.[12,13] When indicated, compute tomography with contrast is useful for evaluation of lymph node, soft tissue, or bone involvement. MRI is preferred to evaluate perineural invasion or orbital and intracranial extension.[18]

HISTOPATHOLOGY

On histopathology, cSCC differentiation may vary from well to poorly differentiated. Well-differentiated tumors exhibit interconnecting follicular infundibular type squamous epithelium. Mitosis may be rare or absent. Poor differentiation indicates that it is difficult to determine a keratinocyte lineage (**Fig. 2**).[19,20]

Low- or Moderate-Risk Histologic Variants

- Keratoacanthomas: a well-differentiated squamous proliferation with a crateriform appearance
- Verrucous carcinomas: well-differentiated SCC with prominent hyperkeratosis and “club-like tongues” of intradermal growth
- Clear cell: greater than 25% squamoid epithelial cells with cytoplasmic vacuolation (PAS+[periodic acid-schiff])

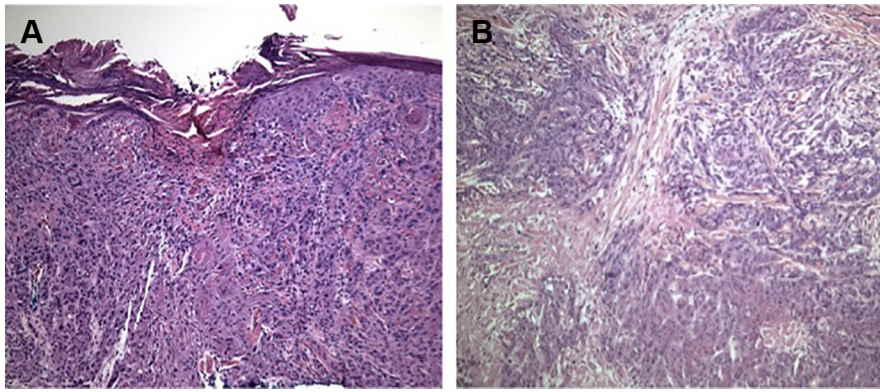

Fig. 2. Histopathology of cSCC. (*A*) (hematoxylin-eosin, original magnification ×4). (*B*) (hematoxylin-eosin, original magnification ×10).

Higher Risk Histologic Variants

- Acantholytic SCC: well-differentiated SCC with acantholysis
- Spindle cell SCC is a poorly differentiated variant with closely packed fascicles of pleomorphic spindle cells with high mitotic activity
- Adenosquamous carcinoma: mixed squamous and glandular differentiation originating from epidermis with interconnecting nests of anaplastic squamoid cells and desmoplastic stroma with 5% to 80% glandular differentiation (highlighted with CEA and CK7 immunostaining)

Uncommon Variants

- SCC with sarcomatoid differentiation
- Lymphoepithelioma-like carcinoma
- Pseudovascular SCC
- SCC with osteoclast-like giant cells

Immunohistochemistry is not typically needed except in the cases of poorly differentiated SCC or uncommon variants. Cutaneous SCC stains positive with p63, p40, MUC1 (epithelial membrane antigen), CK5/6, MNF116, and high-molecular weight 34 E12. BerEp4 should be negative in SCC.[20]

RISK FACTORS

The most significant risk factors resulting in cSCC include UV exposure, older age, fair skin (Fitzpatrick skin types I-III), and immunosuppression. UV (primarily UV-B) from the sun or tanning beds induces skin cancer by causing DNA damage.[21–25] The incidence of SCC doubles with each 8° to 10° in latitude.[26,27] Skin types that burn after UV exposure (related to Fitzpatrick skin type) are predisposed to developing cSCC.[28]

Other Risk Factors

cSCC is more common in men than women (3:1 ratio). The incidence increases with age, with an average age of onset in the mid-60s.[29] Immunosuppression can play a major role in cSCC, with solid transplant recipients suffering 65 to 250 times the risk of cSCC compared with the general population.[30–33] The rate of cSCC formation is related to the number of immunosuppressive agents, the type of immunosuppressant agent, and the amount of sun exposure or skin cancers before transplant.[32] Patients

with chronic lymphocytic leukemia have an 8- to 10-fold increased risk for developing cSCC.[34,35] Patients exposed to vismodegib have eight times the risk of cSCC compared with control patients.[36]

Rare Risk Factors

Oncogenic human papillomavirus types 16 and 18 are associated with periungual and anogenital cSCC.[37] Environmental exposures associated with cSCC include arsenic, polycyclic aromatic hydrocarbons (tar, pitch, and soot), nitrosamines, and alkylating agents. Any exposure to ionizing radiation is associated with more aggressive cSCC, with high rates of recurrence and a 10% to 30% rate of metastasis.[38,39] The presence of rare familial syndromes (including xeroderma pigmentosum, albinism, epidermolysis bullosa, epidermolysis verruciformis, Ferguson Smith epithelioma, Rothmund-Thomson syndrome, Bloom syndrome) can predispose an individual to multiple cSCCs at a young age.[40]

GENETICS

cSCC carries more mutations than other common malignancies, with more than four times the mutation rates in melanoma.[41] Tumor protein 53 (*TP53*),[42] cyclin-dependent kinase inhibitor 2A mutations (*CDKN2A*), *Ras* mutations, and mutations of Notch homolog 1 are involved in cSCC carcinogenesis.[41,43] Genetic mutations found to be differentially expressed in cSCC include CXCL8 (IL8), MMP1, HIF1A, ITGA6, and ITGA2.[20,44]

MORTALITY

Although most cSCC are treated locally with no sequelae, a small subset result in tumor-specific mortality. In the United States, the annual disease-specific mortality is estimated to be 1.5% to 2% with up to 4% mortality rates reported in other countries; 5604 to 12,572 people with cSCC developed nodal metastases with an estimated 9000 deaths.[2,45] Factors associated with local recurrence and metastases are listed in **Table 1**.

Diameter

A tumor diameter greater than 2.0 cm doubles the risk of cSCC recurrence and triples the rate of metastasis compared with lesions less than 2 cm in diameter. Tumor

Table 1
cSCC tumor characteristics that increase the risk of recurrence and/or metastasis

Risk Factors	Recurrence	Metastasis
Diameter >2 cm	2 times	3 times
Depth >2 mm or beyond subcutaneous fat	10 times	11 times
Perineural involvement (>0.1 mm caliber nerve)	23 times	12 times
Poor differentiation	3 times	2 times
Recurrent	2–3 times	Up to 23 times for certain sites (ear/lip)
Site	2 times (ear)	3 times (ear), 5 times (vermillion/mucosal lip)
Arising in scar	not available	12 times
Immunosuppression	6 times	2 times

diameter greater than 2 cm is the risk factor most highly associated with disease-specific death and a 19-fold higher risk of death from cSCC compared with tumors less than 2 cm.[46]

Depth

Depth of disease is highly associated with recurrence and metastasis, with tumors of Breslow thickness greater than 2 mm having a 10-fold higher risk of local recurrence and tumors extending beyond subcutaneous fat having a local recurrence rate of 28% and an 11-fold higher risk of metastasis compared with more superficial tumors.[4,46,47]

Perineural Involvement

The overall incidence of perineural involvement in cSCC is 2% to 14%.[48,49] Perineural invasion of large-caliber nerves (involved nerves measuring $\geq$0.1 mm) is associated with increased nodal metastases and disease-specific mortality.[49,50] Tumors with large-caliber perineural invasion have local recurrence and metastatic risks of 47% and 35%, respectively, after wide local excision.[48,51]

Differentiation

The presence of poor differentiation indicates a poorer prognosis, with local recurrence risk more than triple when compared with well differentiation (7% vs 2%) and a metastatic risk approximately double (7% vs 3%) that of well-differentiated cSCCs.[4]

Previously Treated/Recurrent Cutaneous Squamous Cell Carcinoma

Once a cSCC has recurred, it has a much worse prognosis, with risk of spread to regional lymph nodes and distant metastases cited as 45% for ear cSCC and 32% for lip SCC.[51] Recurrent cSCCs are two to three times as likely to recur again after excisional surgery and Mohs micrographic surgery when compared with primary tumors.[52]

Site

cSCC of the ear has been reported to have a local recurrence risk of 5% after Mohs micrographic surgery, 19% after non-Mohs modalities, and a metastatic risk of 9% after greater than 5 years of follow-up. SCC of the lip has a reported metastatic risk of 14% after greater than 5 years of follow-up.[51,53]

Cutaneous Squamous Cell Carcinoma Arising in Scar

cSCCs arising from a leg ulcer, burn scar, radiation dermatitis, and other chronic wounds have a reported metastatic risk of 26%.[51]

Immunosuppression

cSCCs in immunosuppressed patients may display more rapid growth; recur locally in 13% of patients; and have a 5% to 8% risk of metastasis, usually in the second year after excision.[54–56] Prognosis is usually worse for older patients with tumors located on head and neck skin, when multiple tumors are present, and when there is a history of high exposure to the sun.[57–61]

STAGING

American Joint Committee on Cancer-8

In October 2016, the American Joint Committee on Cancer (AJCC) introduced the eighth edition of its cancer staging systems.[62] The AJCC-8 staging system classifies cSCC of the head and neck by local tumor burden (T), nodal status (N), and metastatic disease (M).[61,63] Stage T1 are tumors less than 2 cm. T2 are tumors 2–3.9 cm. T3

tumors are ≥4 cm or with minor bone erosion or large caliber perineural invasion or deep invasion >6 mm. T4a tumors invade to cortical bone or marrow and T4b invade the skull base or skull base foramen.

Brigham and Women's Hospital Tumor Classification System

The Brigham and Women's Hospital staging system, proposed in 2013, offers an alternative tumor (T) classification system but does not include N or M staging criteria.[64] High-risk features in this T classification system include tumor diameter greater than or equal to 2 cm, tumor invasion beyond the subcutaneous fat, perineural invasion of nerves greater than or equal to 0.1 mm in caliber, and poor differentiation. T stage is assigned as follows: T1, no high-risk features; T2a, one high-risk feature; T2b, two to three high-risk features; and T3, all four high-risk features or bone invasion.[62]

TREATMENT

cSCC is stratified into low risk or high risk. Guidelines are available to help guide treatment including those by the National Comprehensive Cancer Network (NCCN)[13] and the American Academy of Dermatology (AAD) guidelines (**Table 2**).[12]

There are two main types of margin analysis commonly used for surgically excised cSCC: sectional assessment used in standard excision, and complete circumferential peripheral and deep margin assessment (CCPDMA). Sectional assessment describes traditional "bread loaf" assessment and allows for visual assessment of approximately 1% of the marginal surface of a specimen, whereas CCPDMA involves *en face* sectioning that allows for histologic examination of nearly 100% of the marginal surface. The two main methods of CCPDMA used in keratinocyte carcinomas are Mohs micrographic surgery and the Tubingen method.

According to AAD and NCCN guidelines, for local low-risk SCC, first-line treatments include standard excision with 4- to 6-mm clinical margins and postoperative margin assessment.[12,13] For standard excision, recurrence rates are 8.10% for primary low-risk SCC.[51] If margins are positive, additional re-excision or Mohs surgery is considered depending on the location[13] For small tumors not in hair-bearing areas, curettage and electrodessication may be indicated.[12,65,66] Unlike in situ disease, no data support the use of cryotherapy, topical creams, or photodynamic therapy for the primary treatment of dermally invasive SCC.[12]

For high-risk cSCC, the AAD and NCCN guidelines recommend Mohs micrographic surgery, which boasts a 3% recurrence rate for primary cSCC and significantly improved outcomes for high-risk SCCs compared with standard assessment (see **Table 2**).[12,13,51]

Table 2
Mohs micrographic surgery versus standard "bread loaf" pathology assessment recurrence rates

	Mohs, %	Standard Excision, %
Primary cSCC	3.10	8.10
Recurrent SCC	10	23
Perineural involvement	0	47
SCC >2 cm	25.20	41.70
Poorly differentiated	32.60	53.60

Data from 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(6):976–90.

NCCN guidelines state that other measures of CCPDMA, such as the Tubingen method, can be used. When CCPDMA is not available, wide local excision with delayed closure is acceptable. Radiation should only be used as primary treatment in those patients who are not surgical candidates.[13] Radiation may be used as adjuvant therapy in some cases where extensive perineural invasion or large-caliber nerve invasion is present. Multidisciplinary approach is taken when positive margins are noted after Mohs micrographic surgery.[12,13]

Management for local regional or distant metastatic cSCC requires multidisciplinary involvement. NCCN recommends excision ± lymphadenectomy or parotidectomy when lymph nodes are involved.[13,67] Adjuvant chemoradiation may be considered pending margin evaluation or if extracapsular extension of lymph nodes is noted.[13,17,68,69] The AAD offers specific recommendations of epidermal growth factor receptor inhibitors or cisplatin when systemic therapy is needed; however, therapy is constantly evolving. The NCCN recommends consideration of clinical trials and anti-PD1 immunotherapy (eg. pembrolizumab, cemiplimab) is under active investigation.[12,70–74] For inoperable disease, chemoradiation plus palliative care is recommended. However, a recent study showed no benefit for chemoradiation with carboplatin based chemotherapy over radiation alone.[11,69]

PREVENTION

Photoprotective measures including sunscreen application have been shown to decrease SCC by 40%.[75,76] Other measures of prevention include those aimed at managing field cancerization (large defects of DNA damaged skin): 5-fluorouracil, imiquimod, topical retinoids, diclofenac sodium, ingenol mebutate, chemotherapy wraps, photodynamic therapy, nicotinamide and acitretin or capecitabine for very high-risk, immunosuppressed patients.[12]

MONITORING

A patient with at least one cSCC is at risk for additional cSCC and other for skin cancers, including basal cell carcinoma and melanoma.[77,78] The 5-year probability of another non-melanoma skin cancer (NMSC) after diagnosis of a first is 40.7%, the 10 year is 59.6%, and after more than one cSCC it is 82% and 91.2%.[79] After a diagnosis of local SCC, the NCCN guidelines suggest follow-up and screening every 3 to 12 months for 2 years after initial diagnosis and then every 2 years. For regional disease, suggested follow-up is every 1 to 3 months for 1 year, every 2 to 4 months for second year, every 4 to 6 months for the third year, and then every 6 to 12 months for life.[13,80] Concurrent patient and family member self-surveillance for cSCC and other skin cancers may be of additional utility in detecting new primary tumors.[81]

REFERENCES

1. Rogers HW, Weinstock MA, Feldman SR, et al. Incidence estimate of nonmelanoma skin cancer (keratinocyte carcinomas) in the U.S. population, 2012. JAMA Dermatol 2015;151(10):1081–6.
2. Karia P. 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.
3. Schmults C. Factors predictive of recurrence and death from cutaneous squamous cell carcinoma. A 10-year, single-institution cohort study. JAMA Dermatol 2013;149:541–7.

4. Brantsch K. Analysis of risk factors determining prognosis of cutaneous squamous cell carcinoma: a prospective study. Lancet Oncol 2008;9:713–20.
5. Brewster DH, Bhatti LA, Inglis JH, et al. Recent trends in incidence of nonmelanoma skin cancers in the east of Scotland, 1992-2003. Br J Dermatol 2007; 156(6):1295–300.
6. Andersson EM, Paoli J, Wastensson G. Incidence of cutaneous squamous cell carcinoma in coastal and inland areas of Western Sweden. Cancer Epidemiol 2011;35(6):e69–74.
7. Staples MP, Elwood M, Burton RC, et al. Non-melanoma skin cancer in Australia: the 2002 national survey and trends since 1985. Med J Aust 2006;184(1):6–10.
8. Nguyen KD, Han J, Li T, et al. Invasive cutaneous squamous cell carcinoma incidence in US health care workers. Arch Dermatol Res 2014;306(6):555–60.
9. Miller DL, Weinstock MA. Nonmelanoma skin cancer in the united states: incidence. J Am Acad Dermatol 1994;30(5 Pt 1):774–8.
10. Stern RS. Prevalence of a history of skin cancer in 2007: results of an incidence-based model. Arch Dermatol 2010;146(3):279–82.
11. Muzic JG, Schmitt AR, Wright AC, et al. Incidence and trends of basal cell carcinoma and cutaneous squamous cell carcinoma: a population-based study in Olmsted County, Minnesota, 2000 to 2010. Mayo Clin Proc 2017;92(6):890–8.
12. Work Group, Invited Reviewers, Kim JYS, Kozlow JH, Mittal B, et al. Guidelines of care for the management of cutaneous squamous cell carcinoma. J Am Acad Dermatol 2018;78(3):560–78.
13. NCCN guidelines in oncology: squamous cell skin cancer. 2018. Available at: https://www.nccn.org/professionals/physician_gls/pdf/squamous.pdf. Accessed July 4, 2018.
14. Allen JE, Stolle LB. Utility of sentinel node biopsy in patients with high-risk cutaneous squamous cell carcinoma. Eur J Surg Oncol 2015;41(2):197–200.
15. Durham AB, Lowe L, Malloy KM, et al. Sentinel lymph node biopsy for cutaneous squamous cell carcinoma on the head and neck. JAMA Otolaryngol Head Neck Surg 2016;142(12):1171–6.
16. Ahadiat O, Higgins S, Sutton A, et al. SLNB in cutaneous SCC: a review of the current state of literature and the direction for the future. J Surg Oncol 2017; 116(3):344–50.
17. Navarrete-Dechent C, Veness MJ, Droppelmann N, et al. High-risk cutaneous squamous cell carcinoma and the emerging role of sentinel lymph node biopsy: a literature review. J Am Acad Dermatol 2015;73(1):127–37.
18. MacFarlane D, Shah K, Wysong A, et al. The role of imaging in the management of patients with nonmelanoma skin cancer: diagnostic modalities and applications. J Am Acad Dermatol 2017;76(4):579–88.
19. Paolino G, Donati M, Didona D, et al. Histology of non-melanoma skin cancers: an update. Biomedicines 2017;5(4) [pii:E71].
20. Murphy G, Beer T, Cerio R, et al. Keratinocytic/epidermal tumors. In: Elder D, Massi D, Scolyer R, et al. World Health Organization classification of Tumours, Fourth Edition. Volume 11. Geneva (Switzerland): WHO Press, World Health Organization. 31–43.
21. Barnard IRM, Tierney P, Campbell CL, et al. Quantifying direct DNA damage in the basal layer of skin exposed to UV radiation from sunbeds. Photochem Photobiol 2018. https://doi.org/10.1111/php.12935.
22. Ikehata H, Mori T, Douki T, et al. Quantitative analysis of UV photolesions suggests that cyclobutane pyrimidine dimers produced in mouse skin by UVB are more mutagenic than those produced by UVC. Photochem Photobiol Sci 2018; 17(4):404–13.

23. Schmitt J, Seidler A, Diepgen TL, et al. Occupational ultraviolet light exposure increases the risk for the development of cutaneous squamous cell carcinoma: a systematic review and meta-analysis. Br J Dermatol 2011;164(2):291–307.
24. Schmitt J, Haufe E, Trautmann F, et al. Is ultraviolet exposure acquired at work the most important risk factor for cutaneous squamous cell carcinoma? Results of the population-based case-control study FB-181. Br J Dermatol 2018;178(2):462–72.
25. Diepgen TL, Fartasch M, Drexler H, et al. Occupational skin cancer induced by ultraviolet radiation and its prevention. Br J Dermatol 2012;167(Suppl 2):76–84.
26. Scotto J, Cotton G, Urbach F, et al. Biologically effective ultraviolet radiation: surface measurements in the United States, 1974 to 1985. Science 1988;239(4841 Pt 1):762–4.
27. Scotto J, Kopf AW, Urbach F. Non-melanoma skin cancer among caucasians in four areas of the United States. Cancer 1974;34(4):1333–8.
28. English DR, Armstrong BK, Kricker A, et al. Case-control study of sun exposure and squamous cell carcinoma of the skin. Int J Cancer 1998;77(3):347–53.
29. Xiang F, Lucas R, Hales S, et al. Incidence of nonmelanoma skin cancer in relation to ambient UV radiation in white populations, 1978-2012: empirical relationships. JAMA Dermatol 2014;150(10):1063–71.
30. Krynitz B, Edgren G, Lindelof B, et al. Risk of skin cancer and other malignancies in kidney, liver, heart and lung transplant recipients 1970 to 2008: a Swedish population-based study. Int J Cancer 2013;132(6):1429–38.
31. Sinnya S, Zwald FO, Colegio OR. Skin cancer in the crosshairs: highlights from the biennial scientific retreat of international transplant skin cancer collaborative and skin care in organ transplant recipients Europe. Transplant Direct 2015;1(7):e26.
32. Zwald FO, Brown M. Skin cancer in solid organ transplant recipients: advances in therapy and management: part II. management of skin cancer in solid organ transplant recipients. J Am Acad Dermatol 2011;65(2):263–79 [quiz: 280].
33. Omland SH, Gniadecki R, Haedersdal M, et al. Skin cancer risk in hematopoietic stem-cell transplant recipients compared with background population and renal transplant recipients: a population-based cohort study. JAMA Dermatol 2016; 152(2):177–83.
34. Velez NF, Karia PS, Vartanov AR, et al. Association of advanced leukemic stage and skin cancer tumor stage with poor skin cancer outcomes in patients with chronic lymphocytic leukemia. JAMA Dermatol 2014;150(3):280–7.
35. Mehrany K, Weenig RH, Lee KK, et al. Increased metastasis and mortality from cutaneous squamous cell carcinoma in patients with chronic lymphocytic leukemia. J Am Acad Dermatol 2005;53(6):1067–71.
36. Mohan SV, Chang J, Li S, et al. Increased risk of cutaneous squamous cell carcinoma after vismodegib therapy for basal cell carcinoma. JAMA Dermatol 2016;152(5):527–32.
37. Faust H, Andersson K, Luostarinen T, et al. Cutaneous human papillomaviruses and squamous cell carcinoma of the skin: nested case-control study. Cancer Epidemiol Biomarkers Prev 2016;25(4):721–4.
38. Torchia D, Massi D, Caproni M, et al. Multiple cutaneous precanceroses and carcinomas from combined iatrogenic/professional exposure to arsenic. Int J Dermatol 2008;47(6):592–3.
39. Balmain A, Yuspa SH. Milestones in skin carcinogenesis: the biology of multistage carcinogenesis. J Invest Dermatol 2014;134(e1):E2–7.
40. Jaju PD, Ransohoff KJ, Tang JY, et al. Familial skin cancer syndromes: increased risk of nonmelanotic skin cancers and extracutaneous tumors. J Am Acad Dermatol 2016;74(3):437–51 [quiz: 452–4].

41. Pickering CR, Zhou JH, Lee JJ, et al. Mutational landscape of aggressive cutaneous squamous cell carcinoma. Clin Cancer Res 2014;20(24):6582–92.
42. Wikonkal NM, Brash DE. Ultraviolet radiation induced signature mutations in photocarcinogenesis. J Investig Dermatol Symp Proc 1999;4(1):6–10.
43. South AP, Purdie KJ, Watt SA, et al. NOTCH1 mutations occur early during cutaneous squamous cell carcinogenesis. J Invest Dermatol 2014;134(10):2630–8.
44. Egashira S, Jinnin M, Ajino M, et al. Chronic sun exposure-related fusion oncogenes EGFR-PPARGC1A in cutaneous squamous cell carcinoma. Sci Rep 2017;7(1):12654.
45. Fears TR, Scotto J. Changes in skin cancer morbidity between 1971-72 and 1977-78. J Natl Cancer Inst 1982;69(2):365–70.
46. Thompson AK, Kelley BF, Prokop LJ, et al. Risk factors for cutaneous squamous cell carcinoma recurrence, metastasis, and disease-specific death: a systematic review and meta-analysis. JAMA Dermatol 2016;152(4):419–28.
47. Karia PS, Jambusaria-Pahlajani A, Harrington DP, et al. 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(4):327–34.
48. Goepfert H, Dichtel WJ, Medina JE, et al. Perineural invasion in squamous cell skin carcinoma of the head and neck. Am J Surg 1984;148(4):542–7.
49. Carter JB, Johnson MM, Chua TL, et al. Outcomes of primary cutaneous squamous cell carcinoma with perineural invasion: an 11-year cohort study. JAMA Dermatol 2013;149(1):35–41.
50. Ross AS, Whalen FM, Elenitsas R, et al. Diameter of involved nerves predicts outcomes in cutaneous squamous cell carcinoma with perineural invasion: an investigator-blinded retrospective cohort study. Dermatol Surg 2009;35(12):1859–66.
51. 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(6):976–90.
52. Harris BN, Bayoumi A, Rao S, et al. Factors associated with recurrence and regional adenopathy for head and neck cutaneous squamous cell carcinoma. Otolaryngol Head Neck Surg 2017;156(5):863–9.
53. Wang DM, Kraft S, Rohani P, et al. Association of Nodal Metastasis and Mortality With Vermilion vs Cutaneous Lip Location in Cutaneous Squamous Cell Carcinoma of the Lip. JAMA Dermatol 2018;154(6):701–7.
54. Winkelhorst JT, Brokelman WJ, Tiggeler RG, et al. Incidence and clinical course of de-novo malignancies in renal allograft recipients. Eur J Surg Oncol 2001;27(4):409–13.
55. Cheng JY, Li FY, Ko CJ, et al. Cutaneous squamous cell carcinomas in solid organ transplant recipients compared with immunocompetent patients. JAMA Dermatol 2018;154(1):60–6.
56. Wheless L, Jacks S, Mooneyham Potter KA, et al. Skin cancer in organ transplant recipients: more than the immune system. J Am Acad Dermatol 2014;71(2):359–65.
57. Kanitakis J, Karayannopoulou G, Roux A, et al. Histopathologic features predictive of aggressiveness of post-transplant cutaneous squamous-cell carcinomas. Anticancer Res 2015;35(4):2305–8.

58. Garrett GL, Lowenstein SE, Singer JP, et al. Trends of skin cancer mortality after transplantation in the United States: 1987 to 2013. J Am Acad Dermatol 2016; 75(1):106–12.
59. Lam JKS, Sundaresan P, Gebski V, et al. Immunocompromised patients with metastatic cutaneous nodal squamous cell carcinoma of the head and neck: poor outcome unrelated to the index lesion. Head Neck 2018;40(5):985–92.
60. Rizvi SMH, Aagnes B, Holdaas H, et al. Long-term change in the risk of skin cancer after organ transplantation: a population-based nationwide cohort study. JAMA Dermatol 2017;153(12):1270–7.
61. Que SKT, Zwald FO, Schmults CD. Cutaneous squamous cell carcinoma: incidence, risk factors, diagnosis, and staging. J Am Acad Dermatol 2018;78(2): 237–47.
62. Amin M, Edge S, editors. AJCC cancer staging manual. 8th edition. New York: Springer; 2017.
63. Xu MJ, Lazar AA, Garsa AA, 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(7):1406–14.
64. Jambusaria-Pahlajani A, Kanetsky PA, Karia PS, et al. Evaluation of AJCC tumor staging for cutaneous squamous cell carcinoma and a proposed alternative tumor staging system. JAMA Dermatol 2013;149(4):402–10.
65. Lansbury L, Bath-Hextall F, Perkins W, et al. Interventions for non-metastatic squamous cell carcinoma of the skin: systematic review and pooled analysis of observational studies. BMJ 2013;347:f6153.
66. Lansbury L, Leonardi-Bee J, Perkins W, et al. Interventions for non-metastatic squamous cell carcinoma of the skin. Cochrane Database Syst Rev 2010;(4):CD007869.
67. Hirshoren N, Ruskin O, McDowell LJ, et al. Management of parotid metastatic cutaneous squamous cell carcinoma: regional recurrence rates and survival. Otolaryngol Head Neck Surg 2018;159(2):293–9.
68. Navarrete-Dechent C, Veness MJ, Droppelmann N, et al. Cutaneous squamous cell carcinoma and the emerging role of sentinel lymph node biopsy. G Ital Dermatol Venereol 2018;153(3):403–18.
69. Porceddu SV, Bressel M, Poulsen MG, 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(13):1275–83.
70. Migden MR, Rischin D, Schmults CD, et al. PD-1 blockade with cemiplimab in advanced cutaneous squamous-cell carcinoma. N Engl J Med 2018;379(4): 341–51.
71. Gold KA, Kies MS, William WN Jr, et al. Erlotinib in the treatment of recurrent or metastatic cutaneous squamous cell carcinoma: a single-arm phase 2 clinical trial. Cancer 2018;124(10):2169–73.
72. Potenza C, Bernardini N, Balduzzi V, et al. A review of the literature of surgical and nonsurgical treatments of invasive squamous cells carcinoma. Biomed Res Int 2018;2018:9489163.
73. Yanagi T, Kitamura S, Hata H. Novel therapeutic targets in cutaneous squamous cell carcinoma. Front Oncol 2018;8:79.
74. Que SKT, Zwald FO, Schmults CD. Cutaneous squamous cell carcinoma: management of advanced and high-stage tumors. J Am Acad Dermatol 2018; 78(2):249–61.

75. van der Pols JC, Williams GM, Pandeya N, et al. Prolonged prevention of squamous cell carcinoma of the skin by regular sunscreen use. Cancer Epidemiol Biomarkers Prev 2006;15(12):2546–8.
76. Olsen CM, Wilson LF, Green AC, et al. Cancers in Australia attributable to exposure to solar ultraviolet radiation and prevented by regular sunscreen use. Aust N Z J Public Health 2015;39(5):471–6.
77. Wheless L, Black J, Alberg AJ. Nonmelanoma skin cancer and the risk of second primary cancers: a systematic review. Cancer Epidemiol Biomarkers Prev 2010; 19(7):1686–95.
78. Song F, Qureshi AA, Giovannucci EL, et al. Risk of a second primary cancer after non-melanoma skin cancer in white men and women: a prospective cohort study. PLoS Med 2013;10(4):e1001433.
79. Wehner MR, Cidre Serrano W, Nosrati A, et al. All-cause mortality in patients with basal and squamous cell carcinoma: a systematic review and meta-analysis. J Am Acad Dermatol 2018;78(4):663–72.e3.
80. Johnson MM, Leachman SA, Aspinwall LG, et al. Skin cancer screening: recommendations for data-driven screening guidelines and a review of the US Preventive Services Task Force controversy. Melanoma Manag 2017;4(1):13–37.
81. Robinson JK, Friedewald J, Gordon EJ. Perceptions of risk of developing skin cancer for diverse audiences: enhancing relevance of sun protection to reduce the risk. J Cancer Educ 2016;31(1):153–7.