Cutaneous squamous cell carcinoma

Incidence, risk factors, diagnosis, and staging

Syril Keena T. Que, MD,[a] Fiona O. Zwald, MD,[b] and Chrysalyne D. Schmults, MD, MSCE[a]
Boston, Massachusetts, and Washington, District of Columbia

Learning objectives
After completing this learning activity, participants should be able to describe the incidence of cSCC and define factors that are independently associated with poor outcomes on multivariate analysis of cSCC; outline the various staging systems for cSCC, the features that upstage a cSCC, and the rate of local recurrence, metastatic disease, and disease specific death at each stage; and identify aggressive cSCC that require further work-up and treatment.

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Cutaneous squamous cell carcinoma (cSCC), a malignant proliferation of cutaneous epithelium, represents 20% to 50% of skin cancers. Although the majority of cSCCs are successfully eradicated by surgical excision, a subset of cSCC possesses features associated with a higher likelihood of recurrence, metastasis, and death. The proper identification of these aggressive cSCCs can guide additional work-up and management. In the first article in this continuing medical education series, we discuss the incidence, recurrence rates, mortality rates, and risk factors associated with cSCC and review the staging systems used to stratify patients into high- and low-risk groups. The second article in this series reviews the treatment options for cSCC, with focused attention on the management of high-stage tumors. (J Am Acad Dermatol 2018;78:237-47.)

Key words: 5-fluorouracil, imiquimod, ingenol mebutate; acitretin; American Joint Commission on Cancer; Brigham and Women's Hospital staging system; capecitabine; *CDKN2A*; cetuximab; chemotherapy; classification; cSCC; CT; cutaneous squamous cell carcinoma; familial cancer syndromes; high-risk; management; MRI; N1S3 staging; nicotinamide; nivolumab; *NOTCH1*; p53; PD-1; pembrolizumab; photodynamic therapy; radiation therapy; Ras; retinoids; risk factors; sentinel lymph node biopsy; sirolimus; staging.

EPIDEMIOLOGY AND ESTIMATES OF INCIDENCE

Key points

- **Cutaneous squamous cell carcinoma is the second most common nonmelanoma skin cancer after basal cell carcinoma, and in some studies approaches the incidence of basal cell carcinoma**
- **The incidence of cutaneous squamous cell carcinoma is increasing yearly in the United States**

From the Department of Dermatology,[a] Brigham and Women's Hospital, Harvard Medical School, Boston, and the Medstar Georgetown Melanoma and Skin Cancer Center,[b] Georgetown University, Washington, DC.

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Correspondence to: Syril Keena T. Que, MD, Department of Dermatology, Brigham and Women's Hospital, 1153 Centre St, Boston, MA 02130. E-mail: keenaq@gmail.com.

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Abbreviations used:

AJCC-8:	American Joint Committee on Cancer, 8th edition
BCC:	basal cell carcinoma
BWH:	Brigham and Women's Hospital
CDKN2A:	cyclin-dependent kinase inhibitor 2A
cSCC:	cutaneous squamous cell carcinoma
EGFR:	epidermal growth receptor factor
HPV:	human papillomavirus
MAPK:	mitogen-activated protein kinase
N1S3:	revised nodal staging system for head and neck cSCC
PD1:	programmed cell death protein 1
SOTR:	solid organ transplant recipient
TP53:	tumor protein p53

- **Estimates of mortality rates of cutaneous squamous cell carcinoma approximate that of renal and oropharyngeal carcinomas and melanoma in the southern and central United States**

Cutaneous squamous cell carcinoma (cSCC) is the second most common nonmelanoma skin cancer/keratinocyte carcinoma. While cSCC traditionally accounted for 20% of skin cancers, a recent study cited a 1:1 ratio between basal cell carcinoma (BCC) and SCC in the Medicare fee-for-service population.[1] Data from the Rochester Epidemiology Project, conducted by the Mayo Clinic, showed an overall 263% increase in the incidence of cSCC between the 1976 to 1984 and 2000 to 2010 periods.[2] Rates are likely increasing with the growing elderly population[3] and the increased focus on skin cancer screening.

Unfortunately, cSCC is not included in the US national tumor registries, making it difficult to know the exact incidence and mortality rates in our country. European data show that the age-standardized incidence of cSCC ranges from 9 to 96 per 100,000 male inhabitants and 5 to 68 per 100,000 female inhabitants (2002-2007 estimates).[4-6] In Australia, the incidence of cSCC was as high as 499 per 100,000 for men and 291 per 100,000 in women (2002 estimates).[7] In 2011, the cSCC mortality incidence in Australia was 2 per 100,000 individuals.[8] A study in Denmark estimated that 3% to 4% of cSCCs diagnosed in 1984 were associated with cSCC-specific mortality.[9]

In the United States, a 2012 estimate by Karia et al[10] suggested that 5604 to 12,572 people with cSCC developed nodal metastases and 3932 to 8791 people died from cSCC in the United States in that year. The incidence of cSCC was higher in the southern and central United States, where the estimated mortality rate approximates that of renal and oropharyngeal carcinomas and melanoma.

Given its increasing incidence and potential for poor outcomes, cSCC is emerging as a public health problem. Understanding the features of cSCC associated with poor prognosis can help dictate an appropriate work-up and management strategy.

PATHOGENESIS AND ETIOLOGIC RISK FACTORS

Key points

- **Genes commonly mutated in patients with cutaneous squamous cell carcinoma include *TP53*, *CDKN2A*, *Ras*, and *NOTCH1***
- **Risk factors that predispose to the development of cutaneous squamous cell carcinoma include light skin (Fitzpatrick skin types I-III), age, male sex, exposure to sunlight or other ultraviolet radiation, immunosuppression, human papillomavirus, chronic scarring conditions, familial cancer syndromes, and environmental exposures, such as arsenic**

Molecular basis

cSCC carries more mutations than other common malignancies—5 times the mutation rates in lung cancer[11] and >4 times the mutation rates in melanoma.[12] Through the accumulation of these mutations and other cellular changes, an area of skin (usually in response to ultraviolet light damage) can progress through increasing levels of dysplasia and transform into a cSCC.

Tumor protein 53 (*TP53*) is the most commonly mutated tumor suppressor gene in patients with cSCC. Most of the *TP53* mutations in cSCC are C→T single-base transition mutations at dipyrimidine sites.[13] *TP53* mutations enable tumor cells to resist apoptosis and expand clonally at the expense of neighboring normal keratinocytes. Other mutations commonly involved are cyclin-dependent kinase inhibitor 2A mutations (*CDKN2A*), involved in cell cycle control proteins[14]; *Ras* mutations, involved in cellular signal transduction; and mutations of Notch homolog 1, a tumor suppressor gene that acts as a gatekeeper event in cSCC carcinogenesis.[15] Most cSCCs have a multitude of other mutations in addition to these 4. Also, mutations in *TP53* and *Ras* have been found in sun-damaged skin (actinic keratosis).[16-19] This suggests that mutations in *TP53*, *CDKN2A*, and *Ras* may be early events from ultraviolet light damage that set the stage for cSCC development, but other additional mutations are likely required for tumor formation and growth.

Understanding this molecular basis can help pave the way for targeted therapy in the future, although the sheer number of mutations in cSCC may make single-agent targeted therapy infeasible. At the

moment, there is no therapy designed specifically for cSCC. Therapies under investigation for the treatment of cSCC include epidermal growth receptor factor (EGFR) inhibitors, which impact the Ras–Raf–mitogen-activated protein kinase (MAPK) pathway, and programmed cell death protein 1 (PD1) inhibitors, which stimulate T cells to attack tumors.

Medications that target other skin cancers, such as melanoma and BCC, can paradoxically lead to the development of cSCCs. For example, patients exposed to vismodegib, a smoothened inhibitor used for advanced basal cell carcinoma, have 8 times the risk of cSCC compared to control patients.[20] The hypothesis is that targeted inhibition of smoothened by vismodegib selects for tumor cells that proliferate through the Ras–MAPK pathway. The use of a BRAF inhibitor for metastatic melanoma is associated with the eruption of squamoproliferative lesions, including keratoacanthomas, and is hypothesized to also activate the MAPK pathway.[21,22] More research is needed to understand how these therapies work and why cSCC develops.

Risk factors

The most significant risk factors resulting in cSCC include sun exposure, age, fair skin, and immunosuppression. cSCC is most common in white individuals and 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.[23] Though less common in Hispanic, black, and Asian patients, cSCC is the most common skin cancer in these populations.[24] In black patients, cSCC results in a high mortality rate (18%) because of delayed diagnosis and the occurrence of cSCCs on sites of previous trauma or scarring, which carries a worse prognosis.[25]

Immunosuppression can play a major role in cSCC, with solid organ transplant recipients (SOTRs) bearing 65 to 250 times the risk of cSCC compared with the general population.[26-28] The rate of cSCC formation is proportional to the number of immunosuppressive agents a SOTR is taking at any given time.[26] Heart and lung transplant recipients tend to have a higher risk of cSCC than renal transplant recipients because of the more intensive immunosuppression regimens and the older age of these patients.[29] The risk of cSCC development is greater for SOTRs in general than it is for hematopoietic stem cell transplant recipients.[30] Patients with chronic lymphocytic leukemia, who lack a competent cell-mediated and humoral immunity, also have an 8- to 10-fold increased risk for developing cSCC.[31-33] cSCC seems to be highly immunologically mediated, and therefore boosting T cell–mediated antitumor responses may be particularly helpful in controlling advanced cSCC. A PD1 inhibitor is currently under investigation in a phase 2 trial dedicated to cSCC,[34] and this will be discussed further in the second article in this continuing medical education series.

Oncogenic human papillomavirus (HPV) can be associated with cSCC, particularly periungal and anogenital cSCC. HPV types 16 and 18 possess E6 and E7 proteins that prevent apoptosis and allow for continuous replication of viral DNA by regulating p53 and retinoblastoma, respectively.[35] cSCCs of SOTRs also commonly express HPV types 8, 9, and 15, suggesting a potential role for HPV in the development of cSCC among SOTRs.[36] However, HPV is not transcriptionally active in cSCC; if HPV is involved in pathogenesis, it is likely involved during the induction, not the maintenance, of cSCC.[37]

Environmental exposures associated with cSCC include arsenic[38] (sometimes present in well water and previously used in pesticides containing lead arsenate), polycyclic aromatic hydrocarbons (tar, pitch, and soot), nitrosamines, and alkylating agents.[39] In addition, any exposure to ionizing radiation is associated with more aggressive cSCC, with high rates of recurrence and a 10% to 30% rate of metastasis.[40]

The presence of rare familial syndromes associated with photosensitivity or defective DNA repair can predispose an individual to multiple cSCCs at a young age. For a more detailed discussion of these syndromes, we refer the reader to Jaju et al.[41]

CLINICAL AND HISTOPATHOLOGIC DIAGNOSIS

Key points

- **Histopathologic subtypes of cutaneous squamous cell carcinoma that are well-differentiated with low metastatic potential include keratoacanthoma and verrucous carcinoma**
- **This includes Buschke–Lowenstein tumors found in the genitalia and groin and epithelioma cuniculatum, which is found on the plantar surface of the foot**
- **Histopathologic subtypes of cutaneous squamous cell carcinoma with poor prognosis include desmoplastic cutaneous squamous cell carcinoma, adenosquamous cutaneous squamous cell carcinoma, and cutaneous squamous cell carcinoma associated with scarring processes**

Dermoscopic clues

Dermoscopy can help to establish the diagnosis of cSCC. cSCC is characterized under dermoscopy by 2

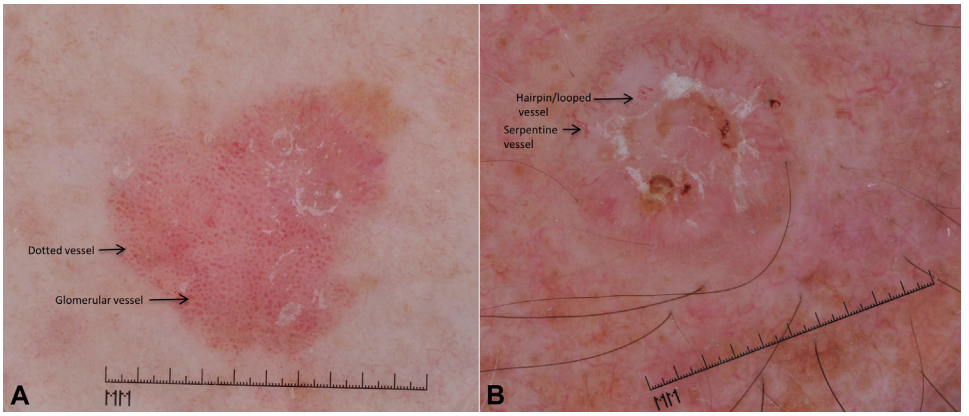

Fig 1. A, Cutaneous squamous cell carcinoma with dotted and glomerular vessels. **B**, Cutaneous squamous cell carcinoma with hairpin and serpentine vessels. Photographs courtesy of Ashfaq A. Marghoob, MD.

vascular patterns: small dotted vessels and glomerular vessels. Pigmented cSCC in situ can also have small brown globules and a gray-brown homogenous pigmentation on dermoscopic examination.[42] Invasive cSCC tends to have looped/hairpin and serpentine vessels[43] (Figs 1 and 2).

Histopathologic subtypes

Well-differentiated histologic subtypes with low metastatic potential include keratoacanthoma and verrucous carcinoma. Histologically, keratoacanthomas typically have a crateriform appearance and a large central keratin plug with a pronounced, well-differentiated squamous proliferation. The verrucous carcinoma subtype includes the Buschke–Lowenstein tumor found in the genitalia and groin and epithelioma cuniculatum found on the plantar surface of the foot. Histologically, verrucous carcinomas have an endophytic component with well-differentiated squamous epithelium and pushing borders.[44]

Some histologic subtypes of cSCC bear a poor prognosis. Desmoplastic cSCC is highly infiltrative, recurs 10 times more frequently, and metastasizes 6 times more frequently than other cSCC variants.[45] A prospective cohort study by Brantsch et al[46] found desmoplasia to be a prognostic factor for local recurrence in cSCC (hazard ratio 16.11 [95% confidence interval 6.57-39.49]). The adenosquamous variant, characterized by secretory tubular structures, is another subtype reported to have a high risk of local recurrence, metastasis, and death.[47]

FACTORS ASSOCIATED WITH LOCAL RECURRENCE AND METASTASES

Key points

- **Tumor diameter >2.0 cm is the risk factor most highly associated with disease-specific death**
- **Perineural involvement of nerves >0.1 mm in caliber is associated with increased nodal metastases and increased mortality risk**

Lymph node metastases from head and neck cSCC have a high cure rate when identified and treated early.[48,49] Risk factors that predispose an individual to a higher rate of local recurrence and metastasis are discussed below.

Diameter. A tumor diameter >2.0 cm doubles the risk of cSCC recurrence and triples the rate of metastasis compared to lesions <2 cm in diameter.[24] Based on a systematic review by Thompson et al,[50] tumor diameter >2 cm is the risk factor most highly associated with disease-specific death and a 19-fold higher risk of death from cSCC compared to tumors <2 cm.

Depth. The risk factor most highly associated with recurrence and metastasis is tumor depth, with tumors of Breslow thickness >2 mm having a 10-fold higher risk of local recurrence and tumors extending beyond subcutaneous fat (into deeper layers, such as the fascia, muscle, perichondrium, and periosteum) having an 11-fold higher risk of metastasis compared with more superficial tumors.[50] One study involving 653 patients over a median follow-up of 43 months[46] showed that tumors ≤2 mm did not metastasize; cSCCs between 2.1 and 6.0 mm metastasized 4% of the time; and cSCCs ≥6.0 mm metastasized 16% of the time. The depth of cSCC is sometimes described by tissue plane, rather than millimeters, on pathology reports. In anatomic terms, extension beyond subcutaneous fat is associated with high rates of local recurrence (28%) and nodal metastasis (27%).[51]

Perineural involvement. The overall incidence of perineural involvement in cSCC is 2% to 14%.[52-55] Perineural invasion of large-caliber nerves (involved nerves measuring ≥0.1 mm) is associated with increased nodal metastases and disease-specific

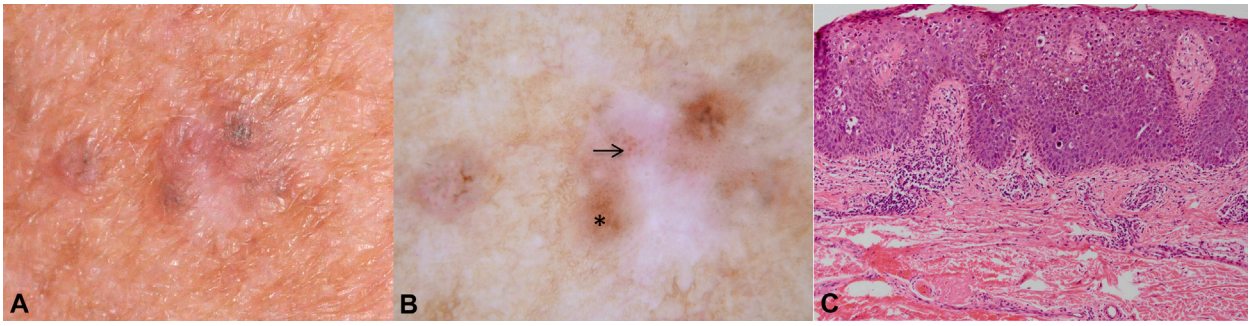

Fig 2. A, Pigmented cutaneous squamous cell carcinoma, clinical image. **B**, Pigmented cutaneous squamous cell carcinoma, dermoscopic image showing focal areas of gray-brown homogenous pigmentation (*) and dotted vessels (black arrow). **C**, Histopathologic results showing pigmented squamous cell carcinoma in situ with increased melanin deposition throughout the epidermis and melanophages. Photographs courtesy of Harold S. Rabinovitz, MD.

mortality.[54,56,57] Tumors with significant perineural invasion have local recurrence and metastatic risks as high as 47% and 35%, respectively, after wide local excision.[53] Mohs micrographic surgery, which is often combined with radiation therapy, brings the recurrence risk close to 0 and the risk of metastasis to 6%.[54]

Histologic differentiation. In 1921, Broders[58] devised a histologic grading system for cSCC from grades 1 through 4 based on the ratio of histologically differentiated versus undifferentiated cells. Grade 1 represents a lesion where 75% of cells are well-differentiated, grade 2 has 50% of cells well-differentiated, grade 3 has 25% to 50% of cells well-differentiated, and grade 4 has <25% well-differentiated cells.[59] In practice, many pathologists use the phrase well-differentiated to mean that nearly all the cells are well-differentiated, moderate differentiation to indicate there are areas without clear keratinization, horn pearls, and other classic features of cSCC, and poor differentiation to indicate that it is difficult to determine a keratinocyte lineage.

The presence of poor differentiation indicates a poorer prognosis, with 1 study indicating a local recurrence risk more than triple (7% vs. 2%) and a metastatic risk approximately double (7% vs. 3%) that of well-differentiated cSCCs.[46]

Previously treated/recurrent cSCC. 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.[24] Recurrent cSCCs are twice as likely to recur again after excisional surgery when compared with primary tumors.[60] After treatment with Mohs micrographic surgery, recurrent cSCCs can still recur ≤10% of the time.[61]

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 >5 years of follow-up. SCC of the lip has a reported recurrence risk of 2% after Mohs micrographic surgery, 11% after non-Mohs modalities, and a metastatic risk of 14% after >5 years of follow-up.[24]

cSCC arising in scar. cSCCs arising from a leg ulcer, burn scar, radiation dermatitis, discoid lupus, and other chronic wounds have a reported metastatic risk of 26%.[24]

Immunosuppression. cSCCs in immunosuppressed patients may display more rapid growth, recur locally in 13% of patients,[62] and have a 5% to 8% risk of metastasis, usually in the second year after excision.[63] 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. However, metastases can occur even in patients who undergo transplantation in childhood.[64]

Fig 3, adapted from Thompson et al,[50] summarizes the effect of each high-risk feature on clinical outcome.

VARIOUS CLASSIFICATION SCHEMES AND CLINICAL APPLICATION

Key points

- **The American Joint Committee on Cancer's (AJCC) most recent staging system, AJCC-8, published in October 2016, uses tumor diameter ≥2 cm as the distinguishing factor between T1 and T2 tumors**
- **High-risk features in AJCC-8 staging, which result in upstaging to T3, include tumor diameter ≥4 cm, minor bone erosion, invasion of nerves 0.1 mm in caliber or in subcutis, or deep invasion (≥6 mm or beyond the subcutaneous fat)**

Outcome	Risk Factor	No. of Studies	Risk Ratio	(95% CI)	*P* Value	I^2 Statistic, %
Recurrence	Breslow thickness >2 mm	1	9.64	1.30-71.52	.03	NA
	Invasion beyond subcutaneous fat	3	7.61	4.17-13.88	<.01	0
	Breslow thickness >6 mm	1	7.13	3.04-16.72	<.01	NA
	PNI	6	4.30	2.80-6.60	<.01	15
	Diameter >20 mm	5	3.22	1.91-5.45	<.01	58
	Temple	1	3.20	1.12-9.15	.03	NA
	Poor differentiation	11	2.66	1.72-4.14	<.01	42
	Immunosuppression	6	1.51	0.81-2.81	.20	39
	Lip	4	1.28	0.41-3.97	.67	52
	Ear	6	1.28	0.56-2.90	.56	59
Metastasis	Invasion beyond subcutaneous fat	5	11.21	3.59-34.97	<.01	74
	Breslow thickness >2 mm	3	10.76	2.55-45.31	<.01	23
	Breslow thickness >6 mm	2	6.93	4.02-11.94	<.01	NA
	Diameter >20 mm	8	6.15	3.56-10.65	<.01	57
	Poor differentiation	18	4.98	3.30-7.49	<.01	76
	PNI	12	2.95	2.31-3.75	<.01	55
	Temple	7	2.82	1.72-4.63	<.01	0
	Ear	13	2.33	1.67-3.23	<.01	6
	Lip	13	2.28	1.54-3.37	<.01	27
	Immunosuppression	6	1.59	1.07-2.37	.02	0
	Cheek	5	1.30	0.61-2.77	.49	47
Disease-specific death	Diameter >20 mm	1	19.10	5.80-62.95	<.01	NA
	Poor differentiation	4	5.65	1.76-18.20	<.01	86
	Ear	2	4.67	1.28-17.12	.02	NA
	Lip	2	4.55	1.41-14.69	.01	NA
	Invasion beyond subcutaneous fat	4	4.49	2.05-9.82	<.01	76
	PNI	3	4.06	3.10-5.32	<.01	0
	Temple	1	1.80	0.22-14.79	.58	NA
	Immunosuppression	1	0.35	0.05-2.58	.30	NA

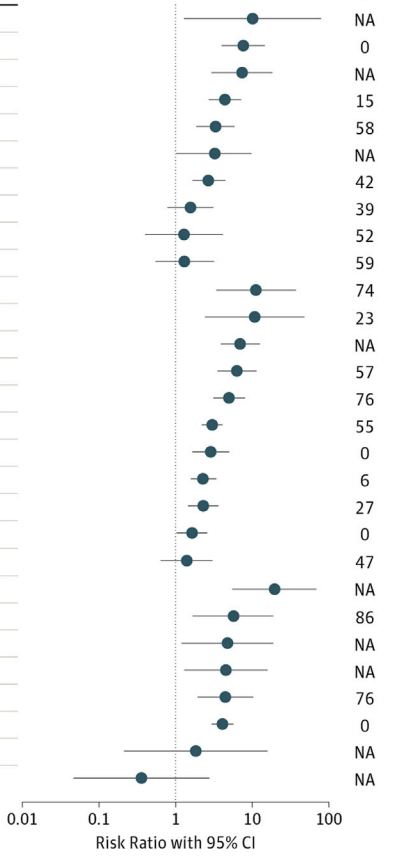

Fig 3. Effect of each cutaneous squamous cell carcinoma high-risk feature on recurrence, metastasis, and disease-specific death. Obtained with permission from Thompson et al.[50]

- **T4 is reserved for major bone involvement or skull base invasion**
- **An alternative staging system, the Brigham and Women's Hospital (BWH) staging system, contains a high-risk T2b category, which requires the presence of ≥2 risk factors and includes only about 5% of cSCCs but accounts for 72% of nodal metastases and 83% of deaths from cSCC**
- **The N1S3 nodal staging system, introduced in 2010, specifies that the diameter of metastatic foci in lymph nodes and number of involved nodes play an important role in clinical outcome**

How is cSCC tumor staging relevant to my everyday clinical practice?

The goal of cancer staging is to risk stratify patients into groups where patients have similar clinical outcomes within a given group and progressively worse outcomes as the stage increases. Staging can help identify patients that require further work-up, adjuvant radiation, and chemotherapy. In addition, staging criteria can help select high-risk cSCC patients for inclusion in clinical trials.

What are the current staging systems for cSCC?

AJCC-8

In October 2016, the AJCC introduced the 8th edition of its cancer staging systems. AJCC-8 includes a revision of the cSCC staging system, which was developed within the head and neck committee and therefore only applies to cSCCs located on head and neck skin and vermillion lip. It is not specified how cSCCs located elsewhere on the body are to be staged. The AJCC-8 staging system classifies cases by local tumor burden (T), nodal status (N), and metastatic disease (M). The T category is based on tumor risk factors that have been shown in multivariate analysis to be independent risk factors for local recurrence, metastasis, or disease-specific death.

Key features of tumor staging. Tumor diameter is the key distinguishing feature between T1 and T2 tumors, with tumors 2 to 3.9 cm in clinical

Table I. American Joint Committee on Cancer (AJCC) cutaneous SCC staging system for tumors of the head and neck skin 8th edition

T category	T criteria	N category	N criteria for pathologic N	M category	M criteria
TX	Primary tumor cannot be identified	NX	Regional lymph nodes cannot be assessed	M0	No distant metastasis
Tis	Carcinoma in situ	N0	No regional lymph node metastasis	M1	Distant metastasis
T1	Tumor <2 cm in greatest dimension	N1	Metastasis in a single ipsilateral lymph node, ≤3 cm in greatest dimension and ENE^{-}*		
T2	Tumor ≥2 cm but <4 cm in greatest dimension	N2	Metastasis in a single ipsilateral lymph node ≤3 cm in greatest dimension and ENE^{+}; or >3 cm but not >6 cm in greatest dimension and ENE^{-}; or metastases in multiple ipsilateral lymph nodes, none >6 cm in greatest dimension and ENE^{-}; or in bilateral or contralateral lymph nodes, none >6 cm in greatest dimension and ENE^{-}		
T3	Tumor ≥4 cm in clinical diameter OR minor bone erosion OR perineural invasion OR deep invasion†	N2a	Metastasis in single ipsilateral or contralateral node ≤3 cm in greatest dimension and ENE^{+}; or in a single ipsilateral node >3 cm but not >6 cm in greatest dimension and ENE^{-}		
T4	Tumor with gross cortical bone/marrow, skull base invasion, and/or skull base foramen invasion	N2b	Metastasis in multiple ipsilateral nodes, none >6 cm in greatest dimension and ENE^{-}		
T4a	Tumor with gross cortical bone/marrow invasion	N2c	Metastasis in bilateral or contralateral lymph nodes, none >6 cm in greatest dimension and ENE^{-}		
T4b	Tumor with skull base invasion and/or skull base foramen involvement	N3	Metastasis in a lymph node >6 cm in greatest dimension and ENE^{-}; or in a single ipsilateral node >3 cm in greatest dimension and ENE^{+}; or multiple ipsilateral, contralateral, or bilateral nodes, any with ENE^{+}		
		N3a	Metastasis in a lymph node >6 cm in greatest dimension and ENE^{-}		
		N3b	Metastasis in a single ipsilateral node >3 cm in greatest dimension and ENE^{+}; or multiple ipsilateral, contralateral, or bilateral nodes, any with ENE^{+}		

Obtained with permission from *AJCC Cancer Staging Manual,* 8th edition, Springer International Publishing, New York, New York, © 2017.
ENE, Extranodal extension.
*Extension through the lymph node capsule into surrounding connective tissue, with or without stromal reaction.
†Deep invasion is defined as invasion beyond subcutaneous fat or >6 mm (as measured from granular layer of adjacent normal epidermis to the base of the tumor). Perineural invasion is defined as tumor cells within the nerve sheath of a nerve deeper than the dermis or measuring ≥0.1 mm, or presenting with clinical or radiographic involvement of named nerves without skull base invasion.

diameter being T2 and tumors ≥4 cm in diameter being classified as T3 tumors.

Nodal metastases are described by the N category. A solitary parotid or regional lymph node metastasis measuring ≤3 cm is categorized as N1. Nodes are further classified as N2a to N2c and N3a to N3b on the basis of size, the number of lymph nodes, and the presence of extranodal extension. Metastases in

Table II. Brigham and Women's Hospital tumor staging system

Stage	No. of high-risk factors*
T1	0
T2a	1
T2b	2-3
T3	≥4

*Brigham and Women's Hospital high-risk factors include tumor diameter ≥2 cm, poorly differentiated histology, perineural invasion ≥0.1 mm, or tumor invasion beyond the subcutaneous fat (excluding bone invasion which automatically upgrades tumor to Brigham and Women's Hospital stage T3).

distant organs or sites outside the regional lymph nodes are staged as present (M1) or absent (M0).

Table I provides greater detail on the AJCC-8 staging system.

Strengths. The new AJCC-8 staging system (2016) is based on multiple studies published since AJCC-7 (2010), which show the most relevant prognostic risk factors for cSCC. The low number of cases meeting T3 and T4 criteria had been a criticism of AJCC-7. The expansion of the T3 category in AJCC-8 will likely lead to more cases and more poor outcomes occurring in this category. The N category currently reflects the evidence-based data showing decreased survival with increasing node size, increased number of nodes, and extracapsular extension.

Weaknesses. Given that this staging system has recently been introduced, its prognostic accuracy has yet to be validated. Validation of the full tumor-node-metastasis system will require large population-based cohort studies because of the rarity of cSCC nodal and distant metastases.

Clinical applications. cSCCs that are AJCC-8 stage T2 or higher likely have an elevated risk of poor clinical outcomes and may warrant more advanced work-up and management. Staging the nodal basin (via ultrasound, computed tomography scan, or sentinel lymph node biopsy) may be considered for AJCC T2 to T4 cSCCs if a risk of nodal metastasis is considered to be present. We refer the reader to the second article in this continuing medical education series for a more thorough discussion of these options. Clear surgical margins should be obtained whenever feasible. Close clinical follow-up for recurrence should be considered.

Brigham and Women's Hospital Tumor classification system

The Brigham and Women's Hospital (BWH) staging system, proposed in 2013, offers an alternative tumor (T) classification system (Table II) but does not include N or M staging criteria.

Table III. Other staging systems for lymph nodes*

Parotid/neck (O'Brien et al,[67] 2002)	N1S3 (Forest et al,[68] 2010)
Parotid gland	
P1: Node ≤3 cm	I: Single nodal metastasis ≤3 cm
P2: Node >3 cm but ≤6 cm or multiple nodes	II: Multiple nodes with ≥1 node(s) ≤3 cm or single nodes >3 cm
P3: Node >6 cm or facial nerve involvement, skull base invasion	III: Multiple nodes with ≥1 node >3 cm
Neck	
N0: Clinically negative neck	
N1: Single node ≤3 cm (ipsilateral)	
N2: Single node >3 cm, multiple or contralateral nodes	

*Adapted with permission from O'Brien et al[67] and Forest et al.[68]

Key features of the BWH T classification. High-risk features in this T classification system include tumor diameter ≥2 cm, tumor invasion beyond the subcutaneous fat, perineural invasion of nerves ≥0.1 mm in caliber, and poor differentiation. T stage is assigned as follows: T1, 0 high-risk features; T2a, 1 high-risk feature; T2b, 2 to 3 high-risk features; and T3, all 4 high-risk features or bone invasion.

Clinical applications. Two studies consisting of a total of 2074 cSCCs showed the BWH T classification to have improved prognostic discrimination over AJCC-7 with BWH T2b cSCCs carrying an elevated risk of nodal metastases (24% and 37%) and disease-specific death (16% and 20%) because of cSCC.[51] Published cases of BWH T2b cSCCs have a sentinel lymph node positivity risk ranging from 29% to 37%.[65,66]

Strengths. The BWH T classification takes into account that tumors <2 cm can also metastasize and includes other factors independently associated with poor prognoses on multivariate analysis, weighting these factors as equal to tumor diameter. This appears to result in better prognostication than the AJCC-7 T classification. The majority of poor clinical outcomes occur in BWH stage T2b cSCCs.

Weaknesses. The BWH T classification is based on 2 single-institution cohorts. It should ideally be compared against the new AJCC-8 T classification in a larger population-based cohort.

Are there alternative systems for staging lymph node metastases?

An alternative nodal (N) classification system, developed by O'Brien et al[67] for cSCC, separated parotid and neck disease (Table III). This group showed that patients with cervical nodes ≥3 cm in diameter or with multiple positive neck nodes had a significantly worse prognosis than those with a single positive node. However, this staging system is complex, and it is unclear whether there is any benefit in separating parotid and neck nodal involvement.

An improved and simplified N classification system, the N1S3 system, was developed by Forest et al[68] in 2010 using a cohort of 215 patients with head and neck cSCC and validated using a different group of 215 patients. This system considers nodes from the parotid and neck together and is simpler than the AJCC-8 nodal staging criteria.

N1S3 N classification is as follows: I, single nodal metastasis ≤3 cm; II, multiple nodes ≤3 cm or a single node >3 cm; and III, multiple nodes with ≥1 node >3 cm.

Patients with stage I were reported to have 90% disease-specific survival at 5 years. This percentage decreased to 75% disease-specific survival for stage II disease and 42% survival for stage III disease.

In conclusion, the first article in this series serves as an introduction to the risk factors, histologic features, and staging criteria used to classify cSCC. While there is currently no standard definition of high-risk cSCC, certain patient and tumor characteristics are more likely to lead to poor clinical outcomes. These characteristics are captured in the cSCC staging systems, specifically the AJCC-8 and the BWH T classification systems.

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Answers to CME examination

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