Cutaneous squamous cell carcinoma

Clinical overview
Cutaneous squamous cell carcinoma (cSCC) is the second most common skin malignancy after basal cell carcinoma (BCC). The ratio of BCC to cSCC in Brisbane is 6:1, but this ratio becomes 2:1 in Northern Queensland with the higher incidence of squamous cell carcinomas. The prognosis is generally favourable. Recurrence and metastasis can occur, with SCC responsible for 20% of all skin-cancer-related deaths.1 Exposure to ultraviolet light is the main cause, although SCC can also arise in the setting of scarred or chronically inflamed skin (such as burns or ulcers). Fair-skinned patients are at higher risk. Other risk factors include male gender, older age and immunosuppression. Sun-exposed sites, such as head, neck and limbs, are most frequently involved.2

The staging of cSCC has undergone significant change in the most recent American Joint Committee on Cancer (AJCC) classification. These changes are the main focus of this bulletin.

Staging of cSCC (7th edition AJCC)
The two most important changes in the staging of cSCC, as outlined in the 7th edition AJCC1, relate to tumour size and the inclusion of ‘high-risk’ factors.

Tumour size
Tumour size is defined as the maximum clinical diameter. In the previous staging system, the important cut-offs were 2 cm and 5 cm. The 5 cm cut-off has been abandoned, due to insufficient data to support this measurement as a significant prognostic factor. In contrast, there is evidence to indicate an increased risk of recurrence and metastasis for tumours >2 cm. SCC >2 cm is staged as T2.

High-risk factors
Although tumour size is important, recurrence and metastasis can still occur in cSCC <2 cm. This has led to the inclusion of ‘high-risk’ factors in the staging system. cSCC with two or more of the following high-risk factors is staged as T2, regardless of tumour size:

- depth of invasion
  - Breslow thickness > 2 mm
  - Clark level ≥ 4
- perineural invasion
- primary site – ear or hair-bearing lip
- differentiation – poorly differentiated or undifferentiated

Immunosuppression
Immunosuppression is not included as a ‘high-risk’ feature in staging as it is a clinical risk factor. Nevertheless, immunosuppressed patients have a significantly increased risk of cSCC. This includes solid organ transplant recipients and patients with lymphoma/leukaemia. In the AJCC 7th edition, the following points are noted regarding cSCC in immunosuppressed patients:

- increased rate of recurrence and metastasis
- more likely to arise at a younger age
- more numerous lesions
- microscopically more likely to demonstrate acantholysis, early invasion, Bowen's disease, infiltrative growth and deep extension
- aggressive behaviour can be observed, even in small tumours.
Perineural invasion
The rate of perineural invasion (PNI) in SCC is reported as 2-14%. The presence of PNI in cSCC is a risk factor for recurrence and metastasis. The following points should be noted:

- Most cases of PNI are clinically asymptomatic. Symptoms can include formation, pain, sensory impairment or loss of nerve function.
- There is no standardised definition of what constitutes PNI microscopically. Most authors require the presence of cytologically malignant cells between the nerve and perineurium (i.e. in the perineural space). In equivocal cases, the presence of tumour completely surrounding a nerve (or surrounding most of the nerve) is supportive.
- Size of the involved nerve is prognostically important. Involvement of small-calibre nerves (diameter < 0.1 mm) is associated with a significantly lower rate of adverse outcomes. PNI involving nerves > 0.1 mm diameter has a higher rate of recurrence and metastasis.
- Involvement of a ‘named’ nerve (such as the cranial nerve) imparts a poorer prognosis. It can be difficult, however, to define where a ‘named’ nerve ends and the ‘un-named’ portion begins. Furthermore, some of the ‘named’ nerves are quite small; for example, the temporal nerve has a diameter of 0.08 mm.
- Management options include surgery and radiotherapy. There is a need for controlled studies to assess the benefit of radiotherapy.

Recently described variants of SCC are follicular and infundibulocystic. These are both derived from the infundibulum (upper part) of the hair follicle and are closely related.

- Follicular SCC comprises strands and nests of tumour cells radiating from a central dilated infundibular structure.
- The crateriform type can resemble keratoacanthoma. Features that favour SCC are radiating tumour cords from the base of the crater, or long and irregularly shaped infundibular canals.
- Infundibulocystic SCC usually presents as a keratotic plaque on the lip. Microscopically, this tumour consists of numerous small or dilated infundibular cysts, sometimes with minimal cytologic atypia. The lesion lacks a central crater and usually shows deep infiltration.

Sub-types of cSCC
Sub-types of cSCC that are associated with more aggressive behaviour include:

- acantholytic SCC (also referred to as adenoid or pseudo-glandular), which is characterised by tumour nests with central discohesion, resembling gland formation
- pseudovascular SCC, which can be mistaken microscopically for angiosarcoma.
- spindle cell SCC.

Summary
Cutaneous SCC is a common tumour. Although most of these lesions do not show aggressive behaviour, recurrence and metastases do occur. The most recent staging system has identified important high-risk prognostic factors relating to tumour size, depth of invasion, anatomic site, differentiation and perineural invasion. In cases with PNI, the size of the involved nerve appears to be important in clinical outcome, with more aggressive behaviour if the involved nerve has a diameter of > 0.1 mm.

References

Blake O’Brien FRCPA
Dr Blake O’Brien completed his medical training at The University of Queensland in 2005, graduating with the University Medal. He commenced as a consultant pathologist at Sullivan Nicolaides Pathology in 2012. His special area of interest is dermatopathology. He has a keen interest in teaching.