# The need for a better prognostic staging system in patients with metastatic cutaneous squamous cell carcinoma of the head and neck

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**Purpose of review**

A validated and universal staging system for metastatic cutaneous head and neck squamous cell carcinoma that accurately describes its clinical behaviour is vital for prognostication and management. The current clinical staging system is not specific for the head and neck and makes no allowances for disease extent. The lack of an improved staging system prevents any meaningful research into improved treatment strategies in patients with head and neck cutaneous squamous cell carcinoma.

**Recent findings**

Contemporary evidence supports surgery and adjuvant radiotherapy as current best practice for patients with operable metastatic head and neck cutaneous squamous cell carcinoma. Despite this, patients with poor-prognosis disease are still at risk of locoregional relapse and may benefit from collaborative research. The modified staging system proposed by O'Brien is an important aspect of any further research and is discussed in this article.

**Summary**

The present clinical staging for head and neck cutaneous squamous cell carcinoma is inadequate and the evidence to date supports a recommendation for changing the current system to reflect the heterogeneity and complexity of this disease.

**Keywords**

metastatic cutaneous squamous cell carcinoma, parotid gland, regional lymph nodes, staging system

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**Abbreviations**

**cSCC** cutaneous squamous cell carcinoma
**NMSC** nonmelanoma skin cancer


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## Introduction

The primary treatment of metastatic cutaneous squamous cell carcinoma (cSCC) of the head and neck is surgery (in operable disease) followed by adjuvant radiotherapy. Single modality treatment (surgery or radiotherapy) is less likely to be curative [1]. The choice of treatment can vary, however, and depends on a number of factors including institutional experience, clinician philosophy, and patient factors. The relative rarity of this disease within certain parts of the world has delayed the development of evidence-based management guidelines. Recent evidence from Australian researchers, however, supports best practice as combined treatment in the majority of patients [1,2]. One obstacle to a better understanding of the management of patients with metastatic head and neck cSCC is the absence of an accurate and predictive staging system that reflects the heterogeneity and complexity of this disease. A validated system for staging head and neck cSCC, which accurately reflects its clinical behaviour, is vital for prognostication, treatment and research.

## Background and epidemiology

Nonmelanoma skin cancer (NMSC) is the most common malignancy worldwide. Most NMSCs are basal cell carcinomas (75–80%), followed by squamous cell carcinomas (20–25%) [3]. Accepted patient risk factors for developing cutaneous squamous cell carcinoma include Caucasian background, male gender, age (> 65 years old), outdoor occupation, and immunodeficiency (solid organ transplant recipient, etc.) [4]. The pathogenesis of cSCC relates to chronic ultraviolet damage of the epithelium, with transition from solar keratosis to invasive cancer, and the potential for both local invasion and regional and/or distant spread. The sun-exposed regions of the head and neck (i.e. cheek, scalp, ear, nose, lower lip, etc.) are the most common sites (80–90%) for the development of cSCC [5•]. The incidence of this disease varies across the world but directly relates to the proximity to the equator [6]. Northern European countries have a low annual incidence of approximately 10/100 000, while Australia leads the world with an annual incidence of approximately 300/100 000 [7]. Townsville, a city in northern Queensland, has the highest annual incidence of cSCC in men of approximately 1300/100 000 [3]. The incidence of NMSC is on the rise with a doubling of the rate within Australia within recent years [7]. Environmental factors,

such as the ozone depletion, an ageing world population, and the increasing number of solid organ transplant recipients, have been postulated to be the cause for this dramatic rise [6].

Overall, approximately 2–3% of cSCCs spread to regional lymph nodes of the head and neck, especially parotid lymph nodes [5•]. There are, however, patient, tumour and treatment factors that may predict patients at higher risk (>10–15%) of developing regional spread [8••]. These include size of the primary (>2 cm), thickness (>4–5 mm), perineural invasion, an immunosuppressed state, and recurrence [1,5•,8••]. Knowing the location of an index lesion may allow a clinician to predict the pattern of spread to regional lymph nodes [9]. This evidence comes from both the NMSC and melanoma literature and suggests cutaneous lesions of the head and neck can be separated into two groups, according to a line dividing the tragus [10•]. The majority of cSCCs are located anterior to this line, and include the cheek, ear, nose, periorbital region, lips, temple, anterior scalp and forehead. The most important lymph-node group involved is that located within the parotid gland. Anatomical studies have demonstrated approximately 30 lymph nodes within the parotid gland, the majority of which are superficial to the posterior facial vein and bear an intimate relationship with the facial nerve [11]. Other lymph-node groups involved in this process are those located at neck levels I–IV, with levels I and II being the most commonly affected by metastatic disease [1]. Level V nodes are rarely involved in isolation and are only at risk with cSCCs involving the pinna and posterior scalp [1]. One important group of nodes with a significant risk of harbouring disease that are not included in the classic neck levels are those found along the external jugular vein. Any neck dissection and/or course of radiotherapy should include this group of nodes.

## Why change the staging system?

The current TNM staging system for cSCC ascribes N0 to all patients that have no clinical evidence of regional metastatic disease, and N1 for patients with regional metastatic disease. It is not specific to the head and neck region and does not account for the extent of metastatic disease. It should be noted that the current staging system does not differentiate between a patient presenting with a single small parotid node (good prognosis), a patient presenting with malignant facial nerve palsy, and a patient with metastatic disease involving both the parotid gland and the neck lymph nodes (poor prognosis).

Patients presenting with metastatic cSCC are usually older, with a median age of 65–70 years, and may have associated significant medical co-morbidities [12]. Prognostication is always important when considering complex and prolonged treatments that are often associated with major morbidity and potential mortality. A more predictive staging system, reflecting the heterogeneous nature of this disease, would allow better assessment of the risk–benefit ratio and therefore provide more accurate information to the patient and their family regarding local control of disease and potential for long-term cure.

The incidence of metastatic head and neck cSCC has increased over recent decades, with an increasing number of patients presenting to tertiary head and neck cancer services requiring complex and multidisciplinary treatment. Most patients undergo major ablative surgery (parotidectomy and neck dissection), appropriate reconstruction (if required), and adjuvant radiotherapy to consolidate locoregional control (close margins, extranodal spread, perineural invasion). Despite this, 20–25% will experience relapse, usually locoregional. Most patients will die following relapse. The existence of a more predictive staging system may allow better decision-making by clinicians based on an improved understanding of the disease and the outcome of relevant treatment. Identifying poor-risk patients at higher risk of relapse may allow a more intensive treatment approach, for example, adding chemotherapy to adjuvant radiotherapy, although further research is needed to prove this.

A number of different treatment approaches exist in the management of patients with metastatic cutaneous head and neck SCC. This not only includes variations in the extent of surgery (total compared with superficial parotidectomy, and comprehensive compared with selective neck dissection) but also in different approaches to radiotherapy. This is reflected by the fact that the current literature on the treatment of metastatic cSCC of the head and neck relies on relatively small case series reporting a variety of surgical and nonsurgical approaches. Despite this, the evidence strongly supports complete surgical resection and adjuvant radiotherapy as current best practice in this group of patients. Given the lack of a validated staging system, however, there is significant selection bias based on a variety of disease, patient and institutional factors. It is important to develop and adopt a more prognostic and practical staging system for head and neck cSCC in order to objectively compare and contrast different therapeutic approaches. This is vital, not only for current treatments available but also for research into new and novel strategies that are based on a better understanding of tumour biology. A randomized trial is currently underway in Australia and New Zealand testing the efficacy of platinum-based concomitant adjuvant chemotherapy/radiotherapy in high-risk patients. Participation in multi-institutional and international trials is vital in order to find new and improved treatment strategies. In addition, this would allow the accrual of large numbers of patients for a meaningful and accurate analysis into treatment outcomes, and this will only be

made possible with an improved and uniform staging system allowing standardized and effective communication between clinicians.

## Evidence to support change to the staging system

Professor Chris O'Brien proposed a new staging system for metastatic cSCC in order to address the inadequacy of the current system [12]. He recommended separating parotid gland involvement from those with cervical node metastases. This resulted in the proposed parotid (P) and neck (N) staging system (Table 1). O'Brien *et al.* hypothesized that prognosis varied with the extent of disease. This system was initially tested on 87 previously untreated patients with parotid and cervical cSCC metastases. Most patients had either P1 or P2 disease. Neck disease was present in 21 patients and was staged as either N1 in 11 or N2 in 10 patients. The results from this study concluded that increasing P stage, positive margins, and failure to give adjuvant external beam radiotherapy correlated with a decrease in local control. The presence of advanced neck disease (N2) had an independent negative impact on survival on multivariate analysis. Although local control varied with P stage, it did not correlate with survival in this series. In patients with metastatic cSCC to both the parotid gland and cervical nodes, survival was significantly decreased compared with those patients with parotid disease only (75% compared with 64%, $P = 0.04$) [12].

The Head and Neck Cancer Service at Westmead Hospital independently tested this proposed staging system on 126 patients with metastatic cSCC involving the parotid and/or neck lymph nodes [13]. All patients were treated with surgery (parotidectomy and/or neck dissection) and adjuvant radiotherapy, with a minimum of 2 years follow-up. The results showed that survival varied significantly with advancing P stage. Patients with P3 disease had a worse outcome on multivariate analysis when compared with those with either P1 or P2 disease. Interestingly, the addition of neck disease did not have a negative impact on outcome as described by O'Brien's group. Importantly, this study confirmed the significant benefit of adjuvant radiotherapy. The presence of immunosuppression had a negative impact on survival, with no transplant patient with metastatic cSCC surviving beyond 3 years.

**Table 1 Proposed clinical staging system for metastatic cutaneous squamous cell carcinoma of the parotid and/or neck**

| Proposed clinical staging system |
|---|
| Parotid |
| P0: No clinical disease in the parotid |
| P1: Metastatic node up to 3 cm in diameter |
| P2: Metastatic node >3 cm and up to 6 cm in diameter or multiple nodes |
| P3: Metastatic node >6 cm or disease involving the facial nerve or skull base |
| Neck |
| N0: No clinical disease |
| N1: Single ipsilateral neck node up to 3 cm in diameter |
| N2: Single node >3 cm in diameter or multiple nodes or contralateral nodes |

Reproduced from [12].

Audet *et al.* [14] investigated the usefulness and validity of this staging system in a group of 56 patients at a major Canadian Head and Neck Cancer Centre. The results were in concordance with the series by Palme *et al.* [13], with P stage having a statistically significant impact on disease-specific survival. In patients with parotid disease alone, independent poor prognostic factors on multivariate analysis included tumour size larger than 6 cm and facial-nerve involvement. In patients with one or both of these factors, disease-specific survival was 47% at 5 years. The authors confirmed the importance of disease extent and the benefit of adjuvant radiotherapy.

The results of these three studies prompted a multi-institutional international trial (three Australian and three North American institutions) to test O'Brien's staging system on a larger cohort of patients [15••]. In all, 322 patients were included in this review. All patients had previously untreated metastatic head and neck cSCC with a minimum of 2 years follow-up. Parotid disease was present in 260 (P1, 149; P2, 78; P3, 33) patients, with 43 having concomitant neck disease (N1, 22; N2, 21). Neck disease alone was present in 62 patients (N1, 26; N2, 36). Overall, disease-specific survival was 74% at 5 years. Advanced P stage predicted for a worse outcome when compared with early disease (69% compared with 82%). Concomitant neck disease also had a statistically significant negative impact on survival when compared with patients who only had disease within the parotid gland (61% compared with 79%, $P = 0.027$). Based on results of this study, the authors recommended that the current TNM staging system be modified to separate parotid and cervical metastases. Even with improvements in the staging of these patients, there are other important patient and tumour factors that are not addressed in the proposed new staging system. These include the presence of immunosuppression, particularly seen in patients after solid organ transplant. Veness *et al.* [16] has clearly demonstrated in a group of cardiothoracic transplant patients that the development of metastatic cSCC is associated with a universally poor disease-specific outcome. Similarly, Palme *et al.* [13] also confirmed that the presence of immunosuppression was an independent poor prognostic factor for disease-specific survival. Other tumour factors that may be significant and warrant further investigation include the presence of skin involvement, and overexpression of molecular markers such as EGFR or VGFR [17]. Any future consideration of a change to the current staging system may need to include assessment of these factors.

## Conclusion

The lack of a standard and accurate staging system in metastatic head and neck cSCC prevents meaningful prognostication. The ultimate goal of an appropriate staging system is to achieve better patient prognostication and treatment allocation. A revision of the current TNM staging system may allow the better allocation of treatment and also a more meaningful comparison of outcomes. In addition, a common system allows standardized communication among treating clinicians and institutions, as well as multi-institutional research, and better distribution of potentially novel therapies in the future.

## References and recommended reading

Papers of particular interest, published within the annual period of review, have been highlighted as:

- • of special interest
- •• of outstanding interest

Additional references related to this topic can also be found in the Current World Literature section in this issue (p. 136).


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