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Head and neck squamous cell carcinoma of unknown primary: Outcomes of a pre-defined institutional treatment policy in a region with a high prevalence of skin cancer

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ABSTRACT

Objectives: To determine the rate of subsequent primary site failure in patients with head and neck squamous cell carcinoma of unknown primary (UKP HNSCC) in a region with a high prevalence of cutaneous squamous cell carcinoma, according to a pre-determined institutional policy. Secondary aims included regional and distant control, and overall survival.

Material and methods: Patients presenting between April 2005 and June 2016 to the Princess Alexandra Hospital Head and Neck Multidisciplinary Meeting with UKP HNSCC from either presumed mucosal or cutaneous sites treated with curative intent were eligible. Patients with presumed mucosal origin were treated with radiation therapy (RT) with or without chemotherapy, while patients with presumed cutaneous SCC were treated with surgery and post-operative RT with or without chemotherapy.

Results: A total of 63 patients met the inclusion criteria. Median follow up duration was 3.9 years (IQR 2.07-5.14). There were no subsequent primary site failures. The rate of nodal failure among presumed mucosal patients was 11.5%, and 8.1% among presumed cutaneous patients. The rate of distant metastatic failure was 11.1% among all patients. The estimated 5 year overall survival was 71.2% (95% CI 59.2–85.7%).

Conclusion: Treatment according to our pre-defined institutional policy for UKP HNSCC in a region with a high prevalence of cutaneous SCC appears to be safe and effective with low rates of mucosal primary emergence and nodal failure.

Introduction

Head and neck squamous cell carcinoma of unknown primary (UKP HNSCC) comprises up to 7% of all HNSCC metastatic to regional lymph nodes in the absence of distant metastatic disease [1].

Inherent to UKP HNSCC is a degree of diagnostic uncertainty regarding the primary site, which classically refers to mucosal tumours of the upper aerodigestive tract. Retrospective data suggest up to 90% of UKP HNSCC arise from the oropharynx [2]. The literature to date has focused on mucosal UKP HNSCC, showing high rates of locoregional control with combinations of surgery and radiotherapy, with or without chemotherapy [3].

A clinical dilemma arises when managing patients in regions with a high prevalence of skin cancer, as cutaneous SCCs can also cause metastatic regional neck adenopathy. The estimated nodal metastasis rate is around 5% for cutaneous primaries of the head and neck region [4]. The index skin lesion cannot always be determined. There may be no history of prior skin cancers, pathological uncertainty, long intervals between primary excision and nodal recurrence, or an absence of primary lesions in the corresponding region of lymphatic drainage. While cutaneous SCCs commonly metastasize to intra-parotid nodes, they can also spread to other cervical nodal stations typically associated with mucosal primaries. Specifically, when metastatic SCC is contained within high cervical nodes with no primary lesion, it can be difficult to differentiate between a cutaneous and mucosal malignancy. Similarly, high neck nodes from mucosal disease can be peri-parotid, and be difficult to distinguish from intra-parotid nodes arising from a skin primary.

In the clinical setting, over-expression of p16 may be used as a surrogate marker to identify HPV-associated oropharyngeal HNSCC [5].

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However, p16 over-expression is seen in up to 31% of cutaneous SCCs, rendering this test alone insufficient in differentiating mucosal from cutaneous primary sites [6]. This further complicates the clinical dilemma when managing patients with UKP HNSCC – particularly in Queensland, Australia, the region with the highest prevalence of cutaneous SCC in the world [7].

Differences exist in the optimal management of node-positive cutaneous and mucosal HNSCC. The treatment of mucosal UKP HNSCC comprises definitive radiation therapy (RT) with or without chemotherapy, or upfront surgery with or without adjuvant RT/chemotherapy [3]. Elective mucosal irradiation of potential primary sites can be considered, though considerable variation exists in practice and there is no high quality evidence to suggest superiority of any one approach, particularly in regions with a high prevalence of cutaneous SCC. For node-positive cutaneous SCC, standard treatment comprises upfront surgery with or without adjuvant RT [8]. A recently presented Trans-Tasman Radiation Oncology Group (TROG) trial revealed no benefit to concurrent chemotherapy in the cutaneous setting [9].

At our centre, patients with risk factors for both mucosal and cutaneous primaries are common, resulting in a clinical dilemma with regards to optimal management. This has led to the development of an institutional risk-stratification algorithm incorporating assessment of multiple clinico-pathologic features. Herein, we present the outcomes of our treatment algorithm for UKP HNSCC utilised by our head and neck tumour board.

Material and methods

Study population

The study was a retrospective analysis of patients diagnosed with UKP HNSCC localised to the head and neck, treated with curative intent at the Princess Alexandra Hospital, Brisbane, Australia between 1st April 2005 and 1st June 2016. Institutional ethics approval was received.

All patients underwent assessment by the head and neck multidisciplinary tumour board, which included at a minimum, a head and neck surgeon, radiation and medical oncologist, pathologist and radiologist. Following clinical examination, investigations included panendoscopy and biopsies, computerised tomography (CT) and 18-fluorine fluoro-deoxy-glucose (FDG) positron emission tomography (PET)/CT if a mucosal primary was suspected. PET/CT was not performed routinely where a cutaneous primary site was suspected. MRI was not routinely performed. When determining potential primary site, an evaluation of clinico-pathological risk factors was undertaken, as per Table 1. Testing of p16 became routinely available in 2010 at our centre. Prior to this, patients were assessed on the basis of smoking and alcohol status, presence of cutaneous risk factors, and nodal distribution. Tonsillectomies were performed where a mucosal primary was suspected, as well as biopsies of the base of tongue. Base of tongue mucosectomy was not performed.

Table 1
Clinico-pathologic risk factor profile.

Cutaneous primary category 1	Mucosal non-HPV associated category 2	Oropharyngeal HPV-associated category 3
• Significant sun damaged skin • Previous head and neck skin cancer • Typically p16 negative – but may be positive in a minority	• Older age • Smoking history > 10 pack-years • p16 negative • History of heavy alcohol intake	• Younger age • Smoking history < 10 pack-years • p16 positive • Bulky, necrotic adenopathy • Basaloid histology

Treatment

Patients were managed according to a pre-defined institutional treatment policy as per Table 2. Patients with a presumed mucosal primary underwent definitive RT comprising 66–70 Gy to gross nodal disease, plus elective irradiation of the neck and potential primary mucosal sites as per institutional protocol. This has been described in detail in a previous study from our institution validating the ICON-S staging system for HPV-associated oropharyngeal HNSCC [10]. RT was given bilaterally in N2c and N3 disease. In N2a and N2b disease, the laterality of elective neck irradiation was determined by gross disease volume, patient age/performance status/comorbidities and the location of the suspected primary site. The presumed primary site to be irradiated was based on a combination of clinico-pathologic features, including p16 status, age, race, nodal distribution and smoking/alcohol status. Total mucosal irradiation was not undertaken.

In the presumed mucosal setting, elective nodal irradiation encompassed levels II–IV as a minimum. Retropharyngeal nodes were included if an oropharyngeal primary was suspected and there was bulky upper level II nodal disease, increasing the risk of retrograde spread. They were also included if a hypopharyngeal or nasopharyngeal primary was suspected, in which case level V was included as well. In the presumed cutaneous setting, ipsilateral neck irradiation encompassed levels I–V.

Patients with a presumed cutaneous primary received upfront surgery followed by adjuvant RT. Patients presenting with intra-parotid lymph nodes alone were treated as presumed cutaneous primaries. Patients who underwent surgery alone were not included. Patients enrolled on the TROG 05.01 Post-Operative Concurrent Chemo-Radiotherapy Versus Post-Operative Radiotherapy in High-Risk Cutaneous Squamous Cell Carcinoma of the Head and Neck (POST) (NCT 00193895) trial were randomised to receive either RT alone, or chemoradiotherapy with concurrent weekly carboplatin [9]. RT was given unilaterally in all presumed cutaneous patients, as all had unilateral nodal disease.

Patients with significant risk factors for both mucosal and cutaneous primaries were classified as presumed mucosal patients, and treated via upfront neck dissection followed by post-operative radiotherapy which encompassed potential mucosal primary sites.

Treatment was delivered via Intensity Modulated RT (IMRT), Volumetric Modulated Arc Therapy (VMAT), or 3D Conformal Radiation Therapy (3D CRT).

Statistical analysis

Descriptive statistics were reported as mean and standard deviation (SD) for normally distributed continuous data, or median and interquartile range (IQR) for non-normally distributed data. Frequencies (raw counts and percentages) were presented for categorical data.

Survival was calculated from date of presentation to the date of death from any cause, or the closeout date. Estimated overall survival (OS) was calculated using the Kaplan-Meier method with 95% confidence intervals (CI) and presented using Kaplan-Meier curves. Survival distributions were compared between presumed mucosal and cutaneous primary sites using the log-rank test. The 5 year OS were also calculated and reported with 95% CI. All analyses were performed using the R statistical software and p-values with $p < .05$ were considered statistically significant [11].

Results

Patient and tumour characteristics

A total of 63 patients with UKP HNSCC were included. The close-out date for analysis was 1st of March 2017. Median follow up duration was 3.9 years (IQR 2.07-5.14). One patient was lost to follow up as their