The Journal of Laryngology & Otology (2016), ***130*** (Suppl. S1), *S32–S37*.

doi:10.1017/S0022215115002212

MAIN ARTICLE

Squamous cell carcinoma of the lip: depth of invasion, local recurrence and regional metastases. Experience of a rural multidisciplinary head and neck unit

A PASTUSZEK, M HANSON, R GRIGG

Ear, Nose and Throat Surgical Department, Toowoomba General Hospital, Queensland, Australia

Abstract

Background: The internationally recognised American Joint Committee on Cancer (tumour–node–metastasis) staging system utilises tumour size to determine stage. Other factors (i.e. tumour depth) may provide additional prognostic information.

Method: A thorough retrospective analysis was performed of 68 patients with primary lip squamous cell carcinoma operated on or discussed by the Darling Downs Health Service between 2005 and 2013.

Results: Twelve patients developed lymphatic spread. There was a statistically significant increased risk of nodal metastasis in: patients with tumours of increased thickness (U = 103.50; degrees of freedom = 68; $p < 0.001$), those with a larger overall tumour size (U = 163.50; degrees of freedom = 68; $p = 0.005$) and patients living further from the treatment centre (U = 199.00; degrees of freedom = 68; $p = 0.018$).

Conclusion: It may be reasonable that other factors are considered for staging of lip squamous cell carcinomas, in combination with tumour–node–metastasis staging. Depth of invasion may have utility in prognosis and treatment; however, larger prospective analysis needs to be performed. Patients living in a more rural setting presented with more advanced disease, suggesting an ongoing rural–metropolitan gap in healthcare.

Key words: Lip; Carcinoma, Epidermoid; Carcinoma, Planocellular; Carcinoma, Squamous; Squamous Cell Carcinoma; Prognosis

Introduction

Squamous cell carcinoma (SCC) of the lip is the most common lip malignancy. The main risk factor is ultraviolent radiation.[1] The cancer has a predilection for the lower lip.[2]

The prognostic factor most affecting long-term survival and disease-free time is the presence or absence of neck or distant metastases, which has been shown to decrease survival to around 50 per cent.[3]

The American Joint Committee on Cancer (tumour–node–metastasis (TNM)) staging system is the current system used for staging lip SCCs.[4] This staging system groups lip with oral cavity cancers, and utilises maximal tumour size when assessing the prognosis of T_{1-3} staged tumours (Table I). There have been few studies investigating factors other than those included in TNM staging for assessing the prognosis of such cancers.

Previous research has investigated tumour depth of invasion and tumour grade in relation to the likelihood for recurrence or local spread.[2,5,6] These studies have suggested that alternative factors are helpful, in addition to TNM staging, in providing valuable prognostic information.

There is no apparent consensus on how to manage an N_0 neck in a patient with a lip SCC. Onerci *et al.* suggest that the risk of nodal spread for tumours greater than 5 mm is sufficient to undergo suprahyoid neck dissection.[2] Najim *et al.* found that tumours with a thickness of greater than 4 mm had a threefold increased risk of nodal spread, and therefore required close follow up or prophylactic neck dissection.[7] Further studies have suggested close clinical follow up or elective neck dissection for T_{2a} tumours (larger than 3 cm), or only undergoing surgery in the presence of known nodal spread.[7–9]

Presented at the Australian Society of Otolaryngology Head and Neck Surgery 64th Annual Scientific Meeting, 1 April 2014, Brisbane, Queensland, Australia.
Accepted for publication 24 July 2015 First published online 25 August 2015

TABLE I
AJCC STAGING OF LIP AND ORAL CAVITY SQUAMOUS CELL CARCINOMA[4]

Tumour (T) stage	Description
T_{IS}	Carcinoma in situ
T_1	Tumour ≤2 cm in greatest dimension
T_2	Tumour >2 cm but ≤4 cm in greatest dimension
T_3	Tumour >4 cm in greatest dimension
T_{4a}	Moderately advanced local disease Lip: invasion of cortical bone, inferior alveolar nerve, mouth floor or face skin (chin or nose) Oral cavity: invades adjacent structures only (e.g. through cortical bone (mandible or maxilla) into deep (extrinsic) tongue muscle (genioglossus, hyoglossus, palatoglossus or styloglossus), maxillary sinus or face skin)
T_{4b}	Very advanced local disease; tumour invades masticator space, pterygoid plates, or skull base &/or encases internal carotid artery

AJCC = American Joint Committee on Cancer

This study aimed to review whether other features (histological or demographical) could identify those patients at risk of developing locoregional spread of SCC. We hypothesised that increased maximal tumour thickness is a risk factor for nodal spread and may identify patients at risk, some of whom would otherwise have early staged disease (T_1 or T_2). In addition, patients who live further from treatment centres may present for treatment with more advanced disease and may even have a higher risk of nodal spread because of delayed treatment.

Based on our salvage neck dissection experience, the five-year survival rate in metastatic SCC patients is approximately 78 per cent. Therefore, identifying those patients most at risk of nodal spread is essential for close monitoring to ensure early intervention. The identification of patients at risk will help encourage those living far from medical services, who may access medical services infrequently, to seek regular follow up.

The Darling Downs district covers a vastly expansive area (over 77 388 km^2). Government incentives that bring doctors to more rural and remote regions of Queensland attempt to ensure that the healthcare standards of rural communities and access to care resembles metropolitan counterparts.

Materials and methods

A retrospective review of all patients with lip SCC discussed at the Darling Downs regional head and neck unit multidisciplinary meeting and operated on at the Toowoomba General Hospital was undertaken. Data for the years 2005 to 2013 were obtained.

Inclusion criteria included: an histological appearance consistent with SCC; the lip identified as the primary site of disease; data for excision or biopsy performed to determine the thickness of tumour invasion; histological data (tumour thickness, differentiation, stage and so on) based on original excision or biopsy, and not re-excision data; and the availability of adequate documentation indicating the site of SCC, the presence of a pathology report, and noted follow up for at least 12 months post-surgical excision or a return to the care of the referring physician without noted prior recurrence.

A chart review of the patients was undertaken. Relevant information was obtained regarding tumour depth, initial staging, perineural invasion, tumour differentiation, maximal tumour size (largest size of the tumour in any dimension), smoking status, treatment undertaken, location at the time of diagnosis and signs of recurrence.

Smoking status categories were: current smoker (including daily smokers and occasional smokers), ex-smoker (smoker previously for more than 1 pack year, or more than 100 cigarettes smoked but not currently a smoker) and non-smoker (patient who has never smoked or smoked less than 100 cigarettes in their lifetime, or has smoked less than 1 pack year and is not currently smoking).

Tumour thickness was defined as the distance between the surface and the deepest level of invasion.

The dataset was collected and collated. A statistical analysis was performed to provide a demographic summary of the patient group and identify statistically significant risk factors for nodal spread.

A Kolmogorov–Smirnov test of normality was conducted to establish whether the continuous variables (age, tumour size, tumour thickness and distance from the treatment centre) could be assumed to be from a normally distributed population. The null hypothesis for the Kolmogorov–Smirnov test was that the data had been sampled from a normally distributed population. The null hypothesis was assessed at alpha = 0.001.

Parametric statistics (mean and standard deviation (SD)) were used to describe the data variables found to be normally distributed; alternatively, non-parametric statistics were used. The choice of parametric or non-parametric statistical hypothesis testing techniques to address the research questions was made in a similar manner.

The difference between mean tumour thickness in patients with nodal metastasis versus those without spread was calculated and analysed utilising the Mann–Whitney U test.

Results

A total of 72 patients with SCC of the lip were discussed at the Darling Downs head and neck multidisciplinary meeting or operated on at the Toowoomba General Hospital between the years 2005 and 2013. Sixty-eight of these patients met the inclusion criteria, with adequate documentation and clinical information available.

From this group of 68 patients, 12 had evidence of lymphatic spread (3 at the time of initial diagnosis

https://doi.org/10.1017/S0022215115002212 Published online by Cambridge University Press

TABLE II
TEST OF NORMALITY FINDINGS

Variable	Kolmogorov–Smirnov test value		
	Statistic	df	*p*
Age (years)	0.075	68	0.200
Tumour size (mm)	0.290	68	<0.001
Tumour thickness (mm)	0.173	68	<0.001
Distance from treatment centre (km)	0.272	68	<0.001

Df = degrees of freedom

and 9 diagnosed during follow up). Of the 9 patients with nodal metastasis diagnosed during follow up, the mean time was 11 months (SD ± 3.2 months) following initial excision of SCC. Four of these patients underwent initial surgery at other centres. One case of nodal metastasis was to the parotid region from upper lip SCC.

Test of normality

A Kolmogorov–Smirnov test of normality was conducted to establish whether the continuous variables in the study (age, tumour size, tumour thickness and distance from the treatment centre) could be assumed to be from a normally distributed population. The test results, shown in Table II, indicated that, except for age, none of the continuous variables could be assumed to be from a normally distributed population at a 0.001 level of significance. Therefore, the subsequent use of non-parametric statistics and techniques is justified for the analysis of tumour size, tumour thickness and distance from the treatment centre.

Demographic and clinical characteristics

The demographic and clinical characteristics of the patients are shown in Tables III and IV. There were 68 patients in total. The average age of the patients at the time of the examination was 61.09 years (SD = 16.43 years), with a range of 17–89 years. The vast majority of patients ($n = 56$, 82.35 per cent) were male. Over half of the patients were smokers or ex-smokers ($n = 37$, 54.41 per cent).

The median tumour size was 8.65 mm (interquartile range = 11.72 mm) and median tumour thickness was 3.68 mm (interquartile range = 4.00 mm).

For most patients, the tumour stage was T_1 ($n = 56$, 83.5 per cent). Eight patients (11.76 per cent) had stage T_2 tumours, one patient (1.47 per cent) had a stage T_3 tumour and three patients (4.41 per cent) had stage T_4 tumours. The tumour classification was T_1N_0 for all T_1 patients, T_2N_0 for all T_2 patients and T_3N_{2C} for all T_3 patients. For the three patients with a stage T_4 tumour, the tumour classifications were $T_{4a}N_2$, T_4N_0 and T_4N_1.

The largest cohort of patients had a tumour differentiation classification of well differentiated SCC ($n = 31$, 45.59 per cent). This was followed by a classification of moderately differentiated SCC ($n = 24$, 35.29 per cent). Two patients (2.94 per cent) had moderately to poorly differentiated SCC. Six patients (8.82 per cent) had moderately to well differentiated SCC. One patient (1.47 per cent) had poorly differentiated SCC. Four patients (5.88 per cent) had well to moderately differentiated SCC.

The vast majority of patients had no perineural invasion ($n = 59$, 86.76 per cent) and no nodal disease ($n = 56$, 82.35 per cent). Most patients lived very close to the treatment centre (median = 0 km (approximately equal), interquartile range = 139 km).

TABLE III
PATIENTS' DEMOGRAPHIC AND CLINICAL CHARACTERISTICS

Characteristic	Frequency (*n* (%))*
Gender	
– Male	56 (82.35)
– Female	12 (17.65)
Smoking status	
– Ex-smoker	31 (45.59)
– Smoker	37 (54.41)
Tumour (T) stage	
– T_1	56 (82.35)
– T_2	8 (11.76)
– T_3	1 (1.47)
– T_4	3 (4.41)
Tumour differentiation	
– Moderately differentiated SCC	24 (35.29)
– Moderately to poorly differentiated SCC	2 (2.94)
– Moderately to well differentiated SCC	6 (8.82)
– Poorly differentiated SCC	1 (1.47)
– Well differentiated SCC	31 (45.59)
– Well to moderately differentiated SCC	4 (5.88)
Perineural invasion?	
– No	59 (86.76)
– Yes	9 (13.24)
Nodal disease?	
– No	56 (82.35)
– Yes	12 (17.65)

*Total $n = 68$. SCC = squamous cell carcinoma

TABLE IV
PATIENT AGE, TUMOUR SIZE, TUMOUR THICKNESS AND DISTANCE FROM TREATMENT CENTRE

Variable	Mean	Median	SD	IQR
Age (years)	61.09	62.00	16.43	23.75
Tumour size (mm)	12.93	8.65	11.72	6.65
Tumour thickness (mm)	4.49	3.68	3.54	4.00
Distance from treatment centre (km)	68.00	0.00*	106.13	139.00

*Approximately equal. SD = standard deviation; IQR = interquartile range

Hypotheses testing

The data for tumour size, tumour thickness and distance from the treatment centre were compared between patients with and without nodal metastasis using a Mann–Whitney U test (Table V). The results indicated that the median tumour size (U (68) = 163.50, $p = 0.005$), median tumour thickness

https://doi.org/10.1017/S0022215115002212 Published online by Cambridge University Press

TABLE V
TUMOUR SIZE, TUMOUR THICKNESS AND DISTANCE FROM TREATMENT CENTRE BY NODAL METASTASIS

Variable	Nodal metastasis?						Statistical test value		
	No		Yes		Total		U	df	*p*
	Median	IQR	Median	IQR	Median	IQR			
Tumour size (mm)	8.50	6.50	24.00	36.50	8.65	6.65	163.50	68	0.005
Tumour thickness (mm)	3.00	3.00	7.00	4.88	3.68	4.00	103.50	68	<0.001
Distance from treatment centre (km)	0.00	83.00	142.00	230.75	0.00	139.00	199.00	68	0.018

Df = degrees of freedom; IQR = interquartile range

(U (68) = 103.50, $p < 0.001$) and median distance from the treatment centre (U (68) = 199.00, $p = 0.018$) were significantly greater for patients with nodal metastasis compared to the patients without nodal metastasis, at a 0.05 level of significance.

Spearman's rank non-parametric correlation co-efficient was used to test for a statistically significant association between tumour size and distance from the treatment centre. The results indicated that this correlation was not significant at the 0.05 level of significance (r = 0.095, $p = 0.44$).

The joint frequency distribution of various pairs of categorical variables from this study was analysed with the chi-square test, to check for a statistically significant association. A chi-square test of independence was performed to examine the association between smoking status and nodal metastasis. The relation between these variables was not significant (chi-square = 0.114; $n = 68$; $p = 0.735$). The chi-square test of independence could not be performed to examine the associations between perineural invasion and nodal metastasis, between tumour differentiation and nodal metastasis, or between tumour stage and nodal metastasis, as the assumption of large expected frequencies was violated. The cross-tabulations for these pairs are summarised in Tables VI–VIII.

The mean tumour thickness in the patients with nodal spread was 8.3 mm (SD = 3.19), with a range from 3.5 mm (T_1) to 20 mm (T_4) (Table IX). The mean tumour thickness in patients without nodal spread was 3.72 mm (SD = 1.69), with a range from 0.5 mm (T_1) to 15 mm (T_2). Using the Mann–Whitney U test, the difference in mean tumour thickness was found to be statistically significant (U (68) = 572, $p = 0.001$).

TABLE VI
PERINEURAL INVASION BY NODAL METASTASIS

Perineural invasion?	Nodal metastasis?		
	No	Yes	Total
No	50 (84.7)	9 (15.3)	59 (100.0)
Yes	6 (66.7)	3 (33.3)	9 (100.0)
Total	56 (82.4)	12 (17.6)	68 (100.0)

Data represent numbers (and percentages) of cases within the dataset.

TABLE VII
TUMOUR DIFFERENTIATION BY NODAL METASTASIS

Tumour differentiation	Nodal metastasis?		
	No	Yes	Total
Moderately differentiated SCC	18 (75.0)	6 (25.0)	24 (100.0)
Moderately to poorly differentiated & poorly differentiated SCC	3 (100.0)	0 (0.0)	3 (100.0)
Moderately to well differentiated SCC	6 (100.0)	0 (0.0)	6 (100.0)
Well differentiated SCC	27 (87.1)	4 (12.9)	31 (100.0)
Well to moderately differentiated SCC	2 (50.0)	2 (50.0)	4 (100.0)
Total	56 (82.4)	12 (17.6)	68 (100.0)

Data represent numbers (and percentages) of cases within the dataset. SCC = squamous cell carcinoma

TABLE VIII
TUMOUR STAGE BY NODAL METASTASIS

Tumour (T) stage	Nodal metastasis?		
	No	Yes	Total
T_1	51 (91.1)	5 (8.9)	56 (100.0)
T_2	5 (62.5)	3 (37.5)	8 (100.0)
T_3 & T_4*	0 (0.0)	4 (100.0)	4 (100.0)
Total	56 (82.4)	12 (17.6)	68 (100.0)

Data represent numbers (and percentages) of cases within the dataset. *Locally advanced tumours

Discussion

Squamous cell carcinoma of the lip usually presents early and follows an indolent clinical course, with a five-year survival rate between 85 and 95 per cent.[10] Our study findings are consistent with those of most patients presenting at an early stage of disease.

Currently, most centres advocate neck dissection or radiotherapy when nodal disease is detected either at the time of diagnosis or during follow up. For the N_0 neck, there is no consensus regarding management; multiple studies have attempted to formulate criteria for prophylactic neck dissection.

Studies have recently indicated that tumour thickness is an important prognostic indicator for predicting nodal spread. Onerci *et al*. indicated that prophylactic

https://doi.org/10.1017/S0022215115002212 Published online by Cambridge University Press

TABLE IX
DEPTH OF INVASION IN LIP SCC CASES WITH NODAL METASTASIS

Initial staging (tumour–node (TN))	Tumour thickness (mm)
T_1N_0	6.8
T_4N_1	13.5
T_2N_0	10
T_2N_0	12
T_1N_0	7
T_2N_0	4
T_1N_0	7
T_3N_{2c}	3.6
T_1N_0	2.9
T_4N_0	20
$T_{4a}N_2$	6
T_1N_0	3.5

SCC = squamous cell carcinoma

neck dissection should be considered for tumours over 5 mm.[2] Najim *et al.* found that the risk of lymphatic metastasis was significantly increased for tumours over 4 mm thick, warranting close observation or consideration of further treatment (e.g. radiotherapy and/or prophylactic neck dissection).[7] Vanderlei *et al.* focused on current TNM staging, and suggested that tumours larger than 3 cm in their greatest dimension also be considered for prophylactic neck dissection.[8]

The statistical analysis in the current study indicated an increased risk of nodal spread from lip SCC in those with a larger median tumour size (U = 163.50; degrees of freedom = 68; $p = 0.005$) or increased median tumour thickness (U = 103.50; degrees of freedom = 68; $p < 0.001$), and in those who live further from the specialist treatment centre (U = 199.00; degrees of freedom = 68; $p = 0.018$). This analysis suggests that tumour depth of invasion, overall tumour size and distance from treatment centre may be helpful in predicting which patients have tumours that are at higher risk of nodal spread; these patients should receive closer review or be considered for further treatment. Larger prospective studies are needed in this area.

The risk of nodal disease was not associated with smoking status, presence of perineural invasion or degree of tumour differentiation. However, the analysis of perineural invasion as a risk factor for nodal metastasis was underpowered because of low numbers.

In our experience, patients with metastatic lip SCC have a five-year survival rate of approximately 78 per cent. Therefore, we prefer an approach focused on close clinical and radiological observation.

With regard to our current approach to the N_0 neck, for those with tumours less than 4 mm, wide local excision alone is recommended. For patients with tumours larger than 4 mm (known pre-operatively), a neck ultrasound should be conducted prior to excision, with fine needle aspiration if indicated. For patients with tumours larger than 4 mm (identified post-operatively), management should entail close clinical follow up, with a low threshold for neck ultrasound. For patients with aggressive tumours greater than 6 mm thick or larger than 3 cm in size, or for patients unreliable for follow up, consider discussion of levels I–III neck dissection, or recommend close clinical follow up with ultrasound, with fine needle aspiration if indicated.

- **Lip squamous cell carcinoma (SCC) usually presents at an early stage**
- **It has a low five-year mortality rate, which decreases to around 50 per cent in the presence of nodal metastasis**
- **It is currently staged using the tumour–node–metastasis system, but alternative prognostic indicators may be helpful in identifying patients at risk**
- **Patients with lesions over 4 mm deep have an increased risk of nodal metastasis, highlighting the need for close follow up**
- **The relationship between distance from specialist care and likelihood for nodal disease from lip SCC indicates an ongoing gap in healthcare equality**

The finding that patients who live further from treatment centres have a higher risk of nodal spread suggests that, despite attempted advancement in rural and regional access to healthcare, a rural–metropolitan gap is still present. Increased attention to rural healthcare, particularly from specialist departments, is suggested.

References

1 Ariyawardana A, Johnson NW. Trends of lip, oral cavity and oropharyngeal cancers in Australia 1982–2008: overall good news but with rising rates in the oropharynx. *BMC Cancer* 2013;**13**:333
2 Onerci M, Yilmaz T, Gedikoglu G. Tumour thickness as a predictor of cervical lymph node metastasis in squamous cell carcinoma of the lower lip. *Otolaryngol Head Neck Surg* 2000; **122**:139–42
3 Zitsch RP 3rd, Park CW, Renner GJ, Rea JL. Outcome analysis for lip carcinoma. *Otolaryngol Head Neck Surg* 1995;**113**: 589–96
4 American Joint Committee on Cancer. Lip and oral cavity. In: Edge SB, Byrd DR, Compton CC *et al.*, eds. *AJCC Cancer Staging Manual*, 7th edn. New York: Springer, 2010;29–40
5 Frierson HF Jr, Cooper PH. Prognostic factors in squamous cell carcinoma of the lower lip. *Hum Pathol* 1986;**17**:346–54
6 Onerci TM. Indications for neck dissection in lower lip carcinoma. In: American Society of Head & Neck Surgery, Pittsburgh. *Proceedings of the 4th International Conference on Head and Neck Cancer*. Toronto: American Journal of Otolaryngology, 1996;472–7
7 Najim M, Cross S, Gebski V, Palme CE, Morgan GJ, Veness MJ. Early-stage squamous cell carcinoma of the lip: the Australian experience and the benefits of radiotherapy in improving outcome in high-risk patients after resection. *Head Neck* 2013;**35**:1426–30
8 Vanderlei JP, Pereira-Filho FJ, da Cruz FA, de Mello FL, Kruschewsky Lde S, de Freitas LC *et al.* Management of neck metastases in T2N0 lip squamous cell carcinoma. *Am J Otolaryngol* 2013;**34**:103–6
9 Yilmaz S, Ercocen AR. Is elective neck dissection in T1-2, N0 patients with lower lip cancer necessary? *Ann Plast Surg* 2009; **62**:381–3
10 Hosal IN, Onerci M, Kaya S, Turan E. Squamous cell carcinoma of the lower lip. *Am J Otolaryngol* 1992;**13**:363–5

https://doi.org/10.1017/S0022215115002212 Published online by Cambridge University Press

Address for correspondence:
Dr Andrew Pastuszek,
8 Long Island Court,
Mermaid Waters,
QLD 4218, Australia

Fax: +61 (0)746 165 122
E-mail: atpastuszek@gmail.com

Dr A Pastuszek takes responsibility for the integrity of the content of the paper
Competing interests: None declared

https://doi.org/10.1017/S0022215115002212 Published online by Cambridge University Press