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Tumour thickness as a predictor of nodal metastases in oral cancer: Comparison between tongue and floor of mouth subsites

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SUMMARY

Objectives: To identify whether tumour thickness as a predictor of nodal metastases in oral squamous cell carcinoma differs between tongue and floor of mouth (FOM) subsites.
Materials and methods: Retrospective review of 343 patients treated between 1987 and 2012. The neck was considered positive in the presence of pathologically proven nodal metastases on neck dissection or during follow-up.
Results: There were 222 oral tongue and 121 FOM tumours. In patients with FOM tumours 2.1–4 mm thick, the rate of nodal metastases was 41.7%. In contrast, for tongue cancers of a similar thickness the rate was only 11.2%. This increased to 38.5% in patients with tongue cancers that were 4.1–6 mm thick. Comparing these two subsites, FOM cancers cross the critical 20% threshold of probability for nodal metastases between 1 and 2 mm whereas tongue cancers cross the 20% threshold just under 4 mm thickness. On logistic regression adjusting for relevant covariates, there was a significant difference in the propensity for nodal metastases based on tumour thickness according to subsite ($p = 0.028$).
Conclusion: Thin FOM tumours (2.1–4 mm) have a high rate of nodal metastases. Elective neck dissection is appropriate in FOM tumours $\geqslant$2 mm thick and in tongue tumours $\geqslant$4 mm thick.

Introduction

Oral squamous cell carcinomas (OSCC) have a propensity for nodal metastases, which in turn impart important prognostic significance [1,2]. Elective neck dissection in the clinically negative neck has shown to improve survival [3], however neck dissection is not without complications [4]. In order to identify patients who are likely to have nodal metastases, several primary tumour factors like tumour differentiation, perineural invasion, lymphovascular invasion and tumour thickness have been studied [5–7]. Presently it is well recognized that tumour thickness or depth of invasion is an important predictor of nodal metastases in oral cancer [8]. Several reports suggest that the rate of nodal metastases based on tumour thickness differs according to the oral cavity subsite. But the literature varies as to what should be considered the 'critical tumour thickness' to prompt a neck dissection in such cases. This critical value represents the thickness at which the probability of nodal metastases exceeds 20% [9] and varies from 2–8 mm in most studies, with a recent meta-analysis suggesting that 4 mm is most reproducible [8]. This is supported by data from the Sydney Head and Neck Cancer Institute (SHNCI) published over 10 years ago and has formed the basis of elective treatment of the neck in our unit for the last decade [10].

It is important to note that most studies have grouped all oral subsites together. However, earlier reports from Spiro and Mohit-Tabatabai suggest that even thin floor of mouth (FOM) cancers have a high propensity for nodal metastases [11,12] compared to tongue primaries. To date, single institution comparisons between tongue and FOM lesions are lacking. The primary aim of this study is to determine the rates of nodal metastases based on tumour thickness in the two subsites (tongue and FOM) and whether the critical tumour thickness for neck dissection should differ for each subsite thereby individualizing the need for neck dissection based on the subsite.

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Materials and methods

Since October 1987, the clinical and pathologic data of all patients treated in the Department of Head and Neck Surgery, Royal Prince Alfred Hospital (RPAH), have been prospectively entered into a comprehensive computerized database. Clinical outcome data were collected at the time of clinical review and entered by the database manager. Clinico-pathological data for all patients with oral tongue or FOM squamous cell carcinoma (SCC) treated between October 1987 and October 2012 was extracted from the database. Patients previously treated for head and neck SCC were excluded. Tumour thickness was measured on formalin fixed paraffin embedded sections stained with haematoxylin and eosin to the nearest 0.1 mm using an ocular micrometer. Multiple sections of the tumour were studied to identify the area with maximum thickness. The tumour thickness was measured from the level of adjacent normal mucosa to the deepest point of tumour invasion as described by Moore et al. [13]. The tumour thickness was measured without superficial keratin or inflammatory debris if present [14].

The department has routinely performed an elective neck dissection in patients with tumours $\geqslant$4 mm thick or when a free flap reconstruction was required, with the remaining patients undergoing observation. Therefore in order to reduce bias from exclusion of thin tumours that were observed or thick tumours with detectable neck disease, a neck was considered positive if either nodal metastases were proven on elective or therapeutic neck dissection or pathologically proven nodal recurrence occurred during follow-up. Institutional ethics committee approval has been obtained for this study.

Statistical analysis was performed using Stata version 11.0 SE (StataCorp LP, College Station, TX). All statistics were 2-sided and a value of $p < 0.05$ was considered statistically significant. Categorical data were compared using the chi-square test or Fisher's exact test when appropriate. Multivariable analysis was performed using a two stage mixed-effects logistic regression model allowing for random baseline and coefficients for the oral cavity subsites (FOM and tongue). After adjusting for the effect of tumour size, an interaction term was introduced to the model to determine whether the rate of nodal metastases varied significantly between oral tongue and FOM cancers according to tumour thickness. Tumour thickness and size were right skewed and hence a log-transformation was performed to normalise the residuals.

Results

A total of 343 patients were included in this study and median follow up was 2.3 years. There were 227 males and 116 females with a median age of 60 years (range 22–97 years). There were 222 oral tongue tumours and 121 FOM tumours. The number and proportion of patients in each subsite is summarized according to T category in Table 1. All patients underwent wide excision of the primary with curative intent and 262 (76.4%) patients had a neck dissection as part of their initial treatment. Out of the 262 patients who underwent neck dissections, 188 had an elective neck dissection whereas 74 had a therapeutic neck dissection. In the FOM group 73 patients had elective neck dissections, 34 patients had therapeutic neck dissections and 14 patients had their neck observed. In patients with tongue primaries, 115 patients had elective neck dissections, 40 patients had therapeutic neck dissections and 67 patients had their neck observed. Of the 81 patients who had their neck observed, three received elective neck irradiation. In total, 143 patients had radiotherapy as part of their adjuvant treatment based on adverse pathological features. The proportion of patients receiving radiotherapy was higher in patients with FOM tumours (52.1% vs. 36.0%, $p = 0.004$). Of the 262 patients who had a neck dissection, 135 had at least one pathologically positive node. In those patients who had their necks observed and received no adjuvant radiotherapy, there were 13 patients who developed neck recurrence (FOM = 2 and tongue = 11). In the patients who had no neck dissection but radiotherapy to the neck, there was one patient in the FOM group who had nodal recurrence.

The number and proportion of patients with nodal metastases according to subsite and tumour thickness is summarized in Table 2. In patients with FOM tumours 2.1–4 mm thick, the rate of nodal metastases was 41.7%. In contrast, for tongue cancers of a similar thickness the rate was only 11.2%. This increased to 38.5% in patients with tongue cancers that were 4.1–6 mm thick.

On univariable analysis, at a population (marginal) level, tumour thickness was associated with an 8% increase in the odds of nodal metastases for each 1 mm increase in tumour thickness (OR 1.08, 95% CI 1.043–1.114, $p < 0.001$) and tumour size was associated with a 5% increase in the odds of nodal metastases for each 1 mm increase in tumour size (OR 1.05, 95% CI 1.028–1.067, $p < 0.001$). The overall proportion of patients with nodal metastases in the FOM group was not significantly greater than the tongue group (44% vs. 37%, $p = 0.21$). Adjusting for the effect of tumour size and subsite, increasing tumour thickness was significantly associated with an increased rate of nodal metastases ($p < 0.001$) as shown in Table 3 (mixed effects model 1), however tumour size was no longer significant ($p = 0.24$). Introduction of an interaction term between tumour thickness and oral cavity subsite (mixed effects model 2 – Table 4) demonstrates that the baseline odds of nodal metastases in an individual with FOM cancer is 5.9 times that of an individual with tongue cancer ($p = 0.016$). However for an individual with tongue cancer, every 2.7 mm (log 1 mm) increase in tumour thickness increases the odds of nodal metastases 2.1 times more than an individual with FOM cancer ($p = 0.028$). This is illustrated in Fig. 1, where patients with FOM cancer have a higher rate of nodal metastases than patients with tongue cancer, particularly in patients with thin tumours. Comparing these two subsites, FOM cancers cross the critical 20% threshold of probability for nodal metastases between 1.1 and 2 mm whereas tongue cancers cross the 20% threshold just under 4 mm thickness.

Table 1
Tumour site and pathological T stage.

T category	FOM (%)	Tongue (%)	Total
1	40 (33.0)	97 (43.7)	137
2	50 (41.3)	89 (40.1)	139
3	4 (3.3)	28 (12.6)	32
4	27 (22.3)	8 (3.6)	35
Total	121	222	343

Abbreviations: FOM, floor of mouth.

Table 2
Tumour thickness and nodal metastasis.

Site	Thickness * (mm)	*n*	N0 (%)	N+ (%)
Tongue	0–2	17	17 (100.0)	0 (0.0)
	2.1–4	27	24 (88.8)	3 (11.2)
	4.1–6	26	16 (61.5)	10 (38.5)
	6.1–8	34	26 (76.4)	8 (23.6)
	>8	118	57 (48.3)	61 (51.7)
Floor of mouth	0–2	7	6 (85.7)	1 (14.3)
	2.1–4	12	7 (58.3)	5 (41.7)
	4.1–6	25	18 (72.0)	7 (28.0)
	6.1–8	18	6 (33.3)	12 (66.7)
	>8	59	31 (52.5)	28 (47.5)