Predictive value of tumor thickness for cervical lymph-node involvement in squamous cell carcinoma of the oral cavity: a meta-analysis of reported studies

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CRD summary
The authors found an association between tumour thickness and cervical lymph node involvement. The optimum cut-off point for the consideration of neck management was 4mm. There was some discrepancy in the authors' interpretation of the strength of the evidence. Given that the included studies were probably of poor quality, a cautious interpretation is likely to be reliable.

Authors' objectives
To assess the relationship between tumour thickness and the risk of cervical lymph-node involvement, and to determine the optimal thickness cut-off point for prompting prophylactic neck management.

Searching
MEDLINE and EMBASE were searched to identify relevant English-language studies, published from 1966 to January 2007. Search terms were reported and the bibliographies of relevant articles were cross-checked.

Study selection
Studies of tumour thickness in patients with all clinical tumour and node categories, treated with primary surgery for squamous cell carcinoma of the oral cavity, and with at least two-years of follow-up for those with untreated necks, were eligible for inclusion in the review. Tumour thickness had to be described in relation to the risk of cervical lymph-node involvement. The term positive lymph-node declaration was used to describe different methods of detection of cervical lymph-node involvement at immediate or delayed time points.

The included patients had various disease sub-sites, including oral cavity, tongue, buccal mucosa, floor of mouth, and lower lip. Most patients were classified as tumour (T)1, T2 or both cases. Tumour thickness was clearly defined in the majority of studies, and (where reported) it was measured using an ocular micrometer. All studies used formalin-fixed, paraffin-embedded tissue samples from primary surgery. Excluded studies were of patients with non-oral cavity cancers or histologies other than squamous cell carcinoma; those treated primarily with nonsurgical therapies; those with adjuvant or neoadjuvant treatment (other than surgery) for the untreated neck; those with tumour thickness measurement other than upon pathologic examination; or where absolute numbers were not reported.

Two independent reviewers selected studies for inclusion, and disagreements were resolved by reassessing the article.

Assessment of study quality
The authors stated that the methodological quality of included studies was assessed, but there were no details of the criteria used.

Two independent reviewers carried out the quality assessment.

Data extraction
Data were extracted to enable the calculation of odd ratios (ORs) and 95% confidence intervals (CIs) in relation to the absolute number of cases with or without positive lymph-node declaration.

Two independent reviewers carried out the data extraction.

Methods of synthesis
ORs and 95% CIs were pooled in a random-effects meta-analysis (DerSimonian and Laird) and using Peto estimates to
detect heterogeneity. Tumour thickness cut-off points of 3mm, 4mm, 5mm, and 6mm were assessed using negative predictive values and these were compared, using logistic regression, with generalised estimating equations to account for study clusters. Positive predictive values were not compared due to variable data.

**Results of the review**
Sixteen studies (n=1,136 patients) were included in the meta-analysis. There were 15 retrospective studies and one prospective study.

The pooled odds ratio of positive lymph-node declaration overall was 7.3 (95% CI 5.3 to 10.1; 16 studies). For the T1 to T2 group the ratio was 6.2 (95% CI 4.1 to 9.3; nine studies). For the node zero (N0) group it was 8.8 (95% CI 5.3 to 14.7; 10 studies) and for the stage I and II subgroups (T1-T2 N0) it was 7.1 (95% CI 4.3 to 11.8; seven studies).

There was a statistically significant increase in false negative positive lymph-node declarations with increasing tumour thickness cut-off points (4mm 4.5%, 95% CI 2.6 to 7.2; nine studies; and 5mm 16.6%, 95% CI 11.5 to 22.8; six studies).

**Authors' conclusions**
There was an association between tumour thickness and cervical lymph node involvement. The authors also stated that tumour thickness was a strong predictor of outcome. The optimum tumour thickness cut-off point for consideration of neck management was 4mm.

**CRD commentary**
The review question was clear and the inclusion criteria appeared to be sufficiently detailed to enable replication. The search strategy included some relevant sources, but the potential for language and publication biases could not be ruled out. The review process was carried out with adequate attempts to minimise errors and bias. The results of the methodological quality assessment were not reported, but, as the authors acknowledged, the reliance on retrospective studies was likely to limit the overall reliability of the findings. The apparent clinical heterogeneity amongst the included studies means that the choice of synthesis was likely to be justified.

The authors' conclusions reflected the evidence presented, but there was some discrepancy in the authors' interpretation of the strength of the evidence in the paper. Given that the included studies were probably of poor quality, their more cautious interpretation is likely to be valid.

**Implications of the review for practice and research**
**Practice:** The authors stated that the standardisation of tumour thickness measurement was needed before it can become a valid predictor in planning neck treatment.

**Research:** The authors did not state any implications for research.

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Record Status
This is a critical abstract of a systematic review that meets the criteria for inclusion on DARE. Each critical abstract contains a brief summary of the review methods, results and conclusions followed by a detailed critical assessment on the reliability of the review and the conclusions drawn.