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# Preoperative ultrasonography for evaluation of clinically N0 neck in oral cavity carcinoma

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ABSTRACT

The aim of this study was to evaluate preoperative ultrasound criteria to detect lymph node (LN) cervical metastasis in patients with clinically node-negative neck (cN0) oral cavity squamous cell carcinoma (OCSCC). A prospective, single-center, observational study was conducted in 90 patients undergoing cancer excision with or without elective neck dissection (END) between 2005 and 2012. A surgeon and an experienced radiologist performed preoperative cervical ultrasonography in all cases. The primary objective was to obtain an a priori sensitivity of 90% and specificity >50% in cN0 OCSCC staging. The sonographic criteria for LN assessment were as follows: number; neck levels; clusters; aspect; heterogeneity; longitudinal diameter (L); transverse diameter (T); L/T ratio; and combination in series or in parallel of T and L/T ratio. The gold standard for comparison was the LN histological identification of metastasis after END or the occurrence in the follow-up at least 36 months. Statistically significant sonographic criteria in univariate analysis ($P < 0.05$) were as follows: multilevel lymph nodes, T diameter >6.5 mm, and the combination T > 6.5 mm or L/T < 1.3 ratio; and in multivariate logistic regression analysis were ($P < 0.05$): combination T > 6.5 mm and L/T < 1.3 ratio, LN in level II, and moderately-poorly differentiated OCSCC. By using selected sonographic criteria, ultrasound can be a valid preoperative diagnostic method to optimize staging cervical metastasis and to help decide about neck dissection.



## 1. Introduction

Cervical metastasis is the most important prognostic factor in patients with oral cavity squamous cell carcinoma (OCSCC) and one of the major aspects in treatment decisions (Iype et al., 2008; Kaneoya et al., 2009; Mark Taylor et al., 2010; de Bree and van den Brekel, 2015). Staging procedures commonly used in OCSCC often cannot detect subclinical lymph node metastasis (LNM) in the neck. The incidence of unnoticed metastasis in initial examination ranges between 20% and 35%, reaching even up to 50% (Thomsen et al., 2005; Kowalski and Sanabria, 2007). Because of this high rate of occult metastasis, most authors choose to perform an elective neck dissection (END) in the clinically node-negative neck (cN0) instead of a wait-and-see strategy. As consequence, a high percentage of cN0 OCSCC patients are theoretically overtreated. The advantages and disadvantages of both options in terms of survival, morbidity and costs are still a matter of debate. Recently two studies have favored the benefit of END in cN0 OCSCC based on the specific mortality and overall survival rate of patients (Fasunla et al., 2011; D'Cruz et al., 2015).

For preoperative evaluation of LNM, ultrasonography (US), US-guided fine-needle aspiration (US-FNA), computed tomography (CT), magnetic resonance imaging (MRI), fluorodeoxyglucose-positron emission tomography (FDG-PET), and PET/MRI are available (van den Brekel, 2000; Nieuwenhuis et al., 2002; Haberal et al., 2004; Wensing et al., 2006; Hodges et al., 2010; Loeffelbein et al., 2012; Souren et al., 2016). In a meta-analysis in which different diagnostic methods for cervical LNM assessment were compared (de Bondt et al., 2007), the sensitivity (87%) and specificity (86%) were higher with US than with CT and MRI, although the range of

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sensitivity (60–97%) and specificity (70–100%) were quite wide (Takeuchi et al., 1999; Yusa et al., 1999; Stuckensen et al., 2000; Hayashi et al., 2003; Dangore-Khasbage et al., 2009). Studies concerning on the use of US for LNM assessment show great variability in relation to characteristics of enrolled patients, sonographic criteria, and diagnostic efficacy variables, thus limiting external validity and applicability of results. The aim of this prospective study was to evaluate the diagnostic efficacy of preoperative US for identifying cervical LNM using different sonographic criteria in cN0 OCSCC to optimize the staging method in the truly negative neck and to help to decide which patients would benefit from the END.

## 2. Material and methods

### 2.1. Patients

This prospective, single-center, observational study was conducted at the Virgen Macarena University Hospital, Seville (Spain), in patients undergoing surgical treatment for cN0 OCSCC. The study period was from January 2005 until May 2012 (maximum follow-up of 10 years and minimum of 3 years). The study was approved by the ethics committee, and all patients gave informed consent. Inclusion criteria were primary OCSCC newly diagnosed, safety margin tumoral excision with or without END, and a minimum of 3 years of follow-up. END comprised at least the I–II–III neck levels. The choice of performing an isolated excision or an excision plus END were discussed at the multidisciplinary head and neck cancer committee, and treatment decisions were based on clinical and imaging findings according to the recommendations of National Comprehensive Cancer Network Head and neck cancers guidelines (Pfister et al., 2013). Exclusion criteria were postoperative radiation therapy administration to tumor bed or neck levels, loco-regional recurrence, or second tumor appearance in the follow-up.

### 2.2. Diagnostic techniques

All patients underwent a bilateral cervical US before the primary surgery performed by the main observer (A.R.M.) and an experienced radiologist in head and neck US (Y.M.L.). Philips ATL HDI 4000 (Philips Ultrasound, Bothell, WA, USA) ultrasound system version with a 6- to 12-MHZ linear transducer was used. With the patient in the supine position and the neck in hyperextension, scanning was performed from level I to V on the homolateral neck to the tumor except when the primary OCSCC affected the middle line in which both necks were included, aiming to generate the same metastasis pre-test probability of having LNM. Postoperative monitoring was carried out once a month in the first year, once each 2 months in the second year, and once each 3 months in the third and successive years. FNA and CT were requested in case of appearance of cervical metastasis in the follow-up.

### 2.3. Variable analysis

Each cervical level was examined for LN presence and absence, and the information was recorded. If LN were present, they were critically examined using the following objective criteria: number, neck level affected, clusters (at least 3 in contact), aspect (peripheral vascularization and/or heterogeneity with inner hypo- and hyperechoic areas) (Reid et al., 1995; Yusa et al., 2000), largest or longitudinal (L) diameter (mm), smallest or transverse (T) diameter (mm), ratio between L and T diameters (L/T), and combinations in series or in parallel of T diameters and L/T ratios when the two criteria or a single criterion was needed to confirm the diagnosis, respectively. The gold standard for comparison of sonographic criteria was the LNM histological identification after END or the occurrence in the follow-up for at least 36 months.

### 2.4. Statistical analysis

The primary study objective was to obtain an a priori sensitivity of 90% and specificity >50% in cN0 OCSCC staging. The sample size was calculated for a 90% sensitivity and 10% accuracy by unilateral asymptotic 95% range, for which 25 metastatic necks would be required to be included. If the likelihood of finding metastasis is 30%, the sample necessary would be of 83 cN0 necks. Assuming an exclusion likelihood of 15%, a recruitment of 96 cases was estimated.

The diagnostic efficacy variables evaluated were as follows: sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), positive likelihood ratio (PLR), negative likelihood ratio (NLR), total successes ratio (true positive + true negative/total), non-operated metastatic neck ratio (1-sensitivity), non-metastatic operated neck ratio (1-specificity), and total END avoided ratio (true negative + false negative/total). A Fagan nomogram was applied to find the likelihood change of having or not having metastasis from pretest to posttest. PLR reported the likelihood of occult metastasis if the test was positive, and NLR reported the likelihood of not having occult metastasis if the test was negative. A receiver operating characteristic (ROC) curve was plotted to select the best cutoff value for the sensitivity and specificity objective, and to compare diagnostic performance of criteria with the area under the curve.

The association between the histological confirmation of metastasis (dichotomous qualitative variable) and the qualitative diagnostic criteria was studied by $\chi^2$ test and Fisher test. The association between the histological confirmation of metastasis and the quantitative diagnostic criteria was studied by Student t test or Mann–Whitney U test. In the qualitative variables of heterogeneity and vascularization, analysis of concordance was performed using the $\kappa$ test, for which 20 cases randomly selected were assessed by an experienced radiologist in head and neck US and compared with the results of the main observer.

Multivariate analysis was performed using logistic regression. All of the statistical significant criteria in univariate analysis were included to determine the contribution of each variable to the overall statistical model, without any a priori selection. Taking the predicted likelihood obtained in the logical progression as diagnostic criteria, an ROC curve was performed, and the most appropriate cutoff values were selected according to the primary objective. Statistical analysis was performed using the SPSS version 22.0 program (SPSS Inc., Chicago, IL, USA). Values of $P < 0.05$ were considered significant.

## 3. Results

Of 96 consecutive patients who initially met the inclusion criteria, 6 cases were excluded during follow-up, 3 patients due to 3 secondary tumors and 3 due to local tumoral recurrence. Of the 90 remaining patients enrolled, 65 were men and 25 women (mean age 60 years, SD = 12.46 years). The patient distribution by clinical and therapeutic characteristics is shown in Table 1. Tumor size was grouped into T1–T2 and T3, and differentiation grade in well and moderately-poorly differentiated, to select those cases with maximal risk to facilitate interpretation of results in a contingency table. A supraomohyoid END (including levels I–III) was performed in 10 patients and a comprehensive END (including levels I–V) in 52. Four patients with tumors located in the midline underwent a bilateral END. The mean follow-up for END cases was 41.6 months (SD = 23.1 months) and for non-END cases was 50.1 months