Sentinel lymph node biopsy in squamous cell carcinoma of the tongue

Marta Mariano • Luís Castelhano • Marta Melo • Susana Pereira • Luís Oliveira • Pedro Montalvão • Miguel Magalhães

ABSTRACT
Objective: Reporting the performance of sentinel lymph node biopsy (SLNB) in patients with squamous cell carcinoma (SCC) of the tongue.
Study design: Retrospective observational study.
Material and Methods: Clinical records from patients with SCC of the tongue cT1-2N0 submitted to SLNB were analysed. A sample of 23 patients was obtained. The gold standard for diagnosing lymph node metastasis was the histology of neck dissection specimens. The average follow up was 29.7 months.
Results: Forty-seven sentinel lymph nodes were obtained, 17% with SCC metastasis, from 26.1% of patients. Neck dissection was performed in 18 patients and 22.2% were positive for SCC metastasis. In this sample, SLNB had a sensitivity of 75% and a negative predictive value (NPV) of 83.3%.
Conclusion: SLNB showed high sensitivity and NPV in this sample. Increasing use of this technique will improve its performance and avoid unnecessary elective neck dissections.
Keywords: sentinel lymph node biopsy, squamous cell carcinoma, tongue

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INTRODUCTION

Sentinel lymph node biopsy (SLNB) is described in the guidelines of the National Comprehensive Cancer Network as an alternative to elective neck dissection (END) for identifying occult neck metastases in patients with cT1-2N0 squamous cell carcinoma (SCC) of the oral cavity.[1] This technique is used for tumor staging, whereas END also ensures the treatment of patients with anatomopathological findings of SCC metastases.[2] The latter are found in 20–30% of patients; therefore, objective examination and imaging assessment do not allow reliable staging. However, the systematic use of END means that 70–80% of patients needlessly undergo this procedure.[3-5] SLNBs have reduced the application of END on such patients because only those without SLNs or which are histologically positive for SCC metastases now undergo END.[1] SLNBs reduce surgical duration, intra- and postoperative complications, the morbidity and functional incapacity of patients, and improves esthetic outcomes.[1,3,4,6] It also has the advantage of identifying anomalous patterns of lymphatic drainage when SLNs are identified in areas of the neck not encompassed by supraomohyoid END, which is typically applied as elective surgery for cN0 lesions of the oral cavity.[3,7] However, SLNB also has a few disadvantages associated with potential false negatives as a result of heterogeneous perilesional injection of radiopharmaceuticals, tumoral obstruction of lymphatic drainage, and difficulty in detecting SLNs by lymphoscintigraphy due to high activity in the region of the primary tumor, which is particularly important for lesions of the floor of the mouth associated with SLN in area I.[4] Nevertheless, the reported 5-year survival rates and of neck disease control by SLNBs do not significantly differ from those of elective END.[1,2-4]

SLNBs are usually obtained by lymphoscintigraphy after radiopharmaceuticals are submucosally injected into the periphery of the primary tumor. This allows preoperative lymphatic mapping and intraoperative detection of the SLN using a handheld gamma probe.[3,4] Visual detection of the SLN can be combined with this technique after dyes are injected into the periphery of a primary tumor.[3,4] An alternative is lymphography using injected iopamidol and computed tomography (CT) that avoids the need for radiopharmaceuticals.[8,9]

The tongue is the most common site of SCC of the oral cavity.[7,10] The present study aimed to determine the outcomes of SLNB of SCC of the tongue at the

Otorhinolaryngology (ORL) department of the Instituto Português de Oncologia de Lisboa Francisco Gentil (IPOLFG).

MATERIAL AND METHODS

This retrospective study analyzed the clinical records of 23 consecutive patients diagnosed with cT1-2N0 SCC of the tongue, and from whom SLNBs were obtained over the preceding five years in the ORL department of the IPOLFG. The diagnoses were confirmed by incisional biopsy and tumors were clinically staged based on objective examinations and CT and/or magnetic resonance imaging (MRI). All patients with a primary tumor that predominantly involved the tongue were included, regardless of extension to other regions of the oral cavity. All patients underwent simultaneous transoral excision of the primary tumor and SLNB. Thirteen patients underwent elective simultaneous END and SLNB during the initial validation of the technique. Exclusive SLNBs were obtained during the subsequent phase of END, followed by therapeutic END in a second surgery only if indicated. In this context, five therapeutic ENDs proceeded; three were due to positive SLNB findings, one was due to palpable neck metastases that appeared during the early postoperative period, and one due to pT3 restaging based on pathological findings of the primary tumor. Histology of the surgical specimen from the END was considered the gold standard for diagnosing of lymph node metastases in these 18 patients, and we also calculated the sensitivity and negative predictive value (NPV) of the SLNBs. The mean follow-up was 29.7 (1–58) months.

The patients received subcutaneous perilesional injections of albumin nanocolloids (n = 20) or rhenium nanocolloids (n = 3) labeled with metastable Technetium-99 (99mTc), then preoperative lymphatic maps of all patients were created using SPECT-CT lymphoscintigraphic images (Figure 1). Sentinel lymph nodes were intraoperatively detected using a handheld gamma probe. After the SLNs were identified and excised, the background activity in the operative field was < 10% of the initial activity, thus confirming that the excised lymph nodes were SLNs.

Data were statistically analyzed using IBM SPSS Statistics 25 (IBM Corp., Armonk, NY, USA). Survival was analyzed using Kaplan-Meier curves for categorical variables and Cox models were used for continuous variables and multivariate analyses. Estimated survival is presented with standard errors (SE). The level of statistical significance was set at 0.05.

RESULTS

Radiographically-guided SLNBs were obtained from 23 patients diagnosed with cT1-2N0 SCC of the tongue during the study period. Twelve (52.2%) were men and 11 (47.8%) were women. The mean age at clinical presentation was 65.5 (44–85) years. Seventeen (73.9%) had primary tumors exclusively located on the tongue, whereas six (26.1%) had tumors of the tongue that extended to the floor of the mouth. The clinical stage after the objective examination and complementary CT (74.0%), MRI (13%), or both (13%) was cT1N0 in 14 (60.9%) patients and cT2N0 in nine (39.1%).

The rate of intraoperative SLN detection was 100%. The median number of excised SLNs per patient was 2 (1–4). Eight (17.0%) SLNs from six patients were positive for SCC metastases, indicating that 26.1% of the patients had occult lymph node metastases.

Among the 17 patients with negative SLNBs, 10 underwent simultaneous elective END and two underwent subsequent therapeutic END (one each because of palpable neck metastases appearing during the early postoperative period and pT3 restaging of the primary tumor according to pathological findings). The pathological findings confirmed N0 stage in all elective ENDs and revealed SCC metastases in both subsequent ENDs. All patients with positive SLNBs underwent elective and therapeutic END (n = 3 each). The pathological findings did not reveal SCC metastases in the remaining lymph nodes after all elective and one of three therapeutic ENDs. The remaining lymph nodes obtained in the other two therapeutic ENDs were positive for SCC metastases. The sensitivity of detection was 75% and the NPV was 83.3% for SLNBs.

Two patients had relapsed cervical lymph node disease; one had early postoperative cervical metastases and the other had a locoregional relapse at nine months of follow-up. Both of these patients died. Two isolated local relapses occurred, of which one was extensive at 10 months of follow-up and led to death. The other had

FIGURE 1
SPECT-CT lymphoscintigraphy image
Patient diagnosed with cT1N0 SCC of the tongue received perilesional injection of albumin 99mTc-nanocolloids. Right margin, sentinel lymph node.

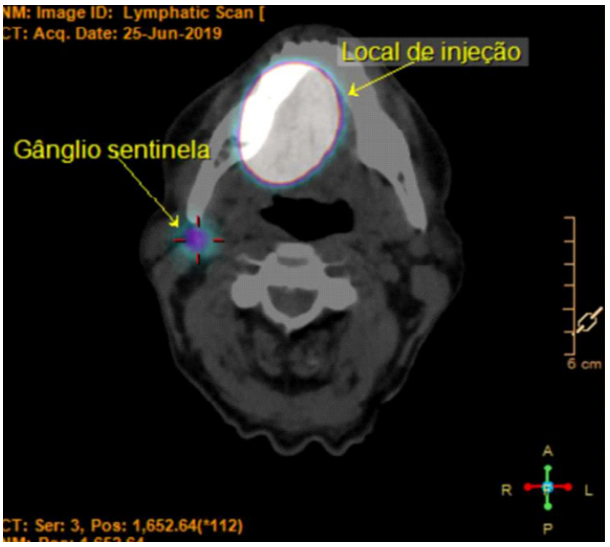


FIGURE 2
Kaplan-Meier curve of overall survival.

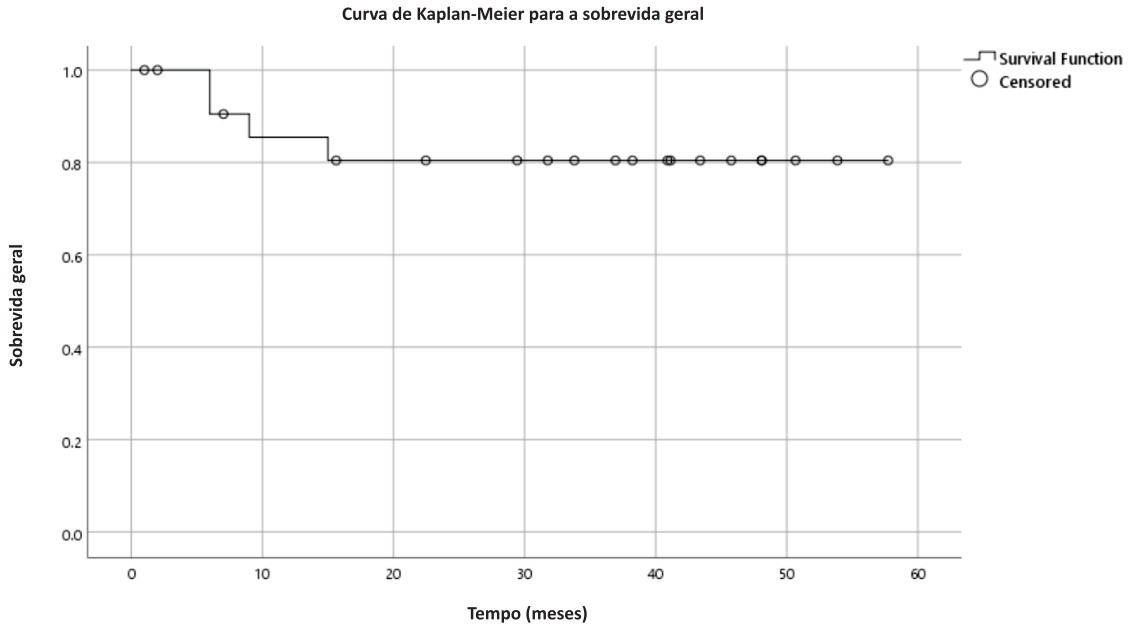
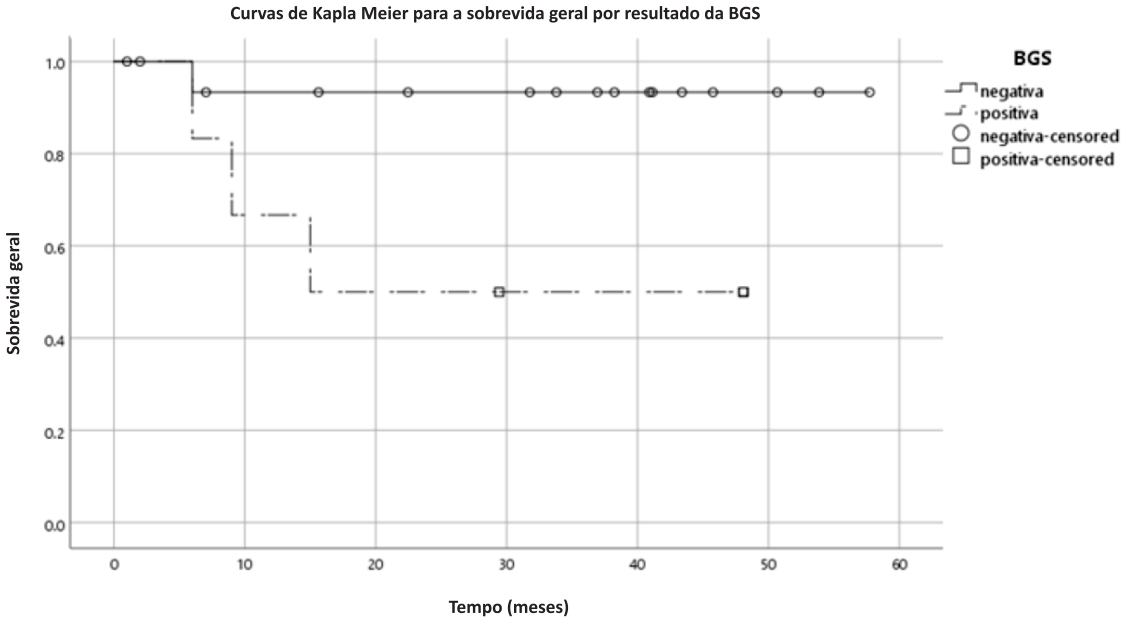


FIGURE 2
Kaplan-Meier curves of overall survival according to sentinel lymph node biopsy results (p = 0.029)



a relapse at four months of follow-up that was surgically treated and this patient remains alive. Another patient died as a result of complications from adjuvant treatments. These accounted for a death rate of 17.4% among the cohort. All patients who died had pN+ tumors, three of whom had positive SLNBs and one had a false negative SLNB. The estimated survival rates at 12 and 24 months were 85.4% (SE 7.8%) at and 80.4% (SE 8.8%), respectively (Figure 2). The estimated median survival duration was not reached. The estimated survival at 12 months was significantly lower among the patients with positive, than negative SLNB in the univariate analysis (50.0% [SE 20.4%] vs. 93.3% [SE 6.4%], p = 0.029; Figure 3). Estimated survival did not significantly differ based on the other risk factors of age (p = 0.556), sex (p = 0.147), T1/T2 stage (p = 0.109), alcohol consumption (p = 0.919), and smoking (p = 0.930; Table I). The results of the multivariate analysis using the remaining factors as covariables showed that the effect of the SLNB result on estimated survival was no longer statistically significant (p = 0.121).

DISCUSSION

SLNBs are considered appropriate for managing patients with cT1-2N0 SCC of the oral cavity. From a technical perspective, the rate of intraoperative SLN detection in SLNBs obtained from the study cohort was 100% with a median of two SLNs excised per patient. These results conform with those reported (98–100% rate of intraoperative SLN detection[10-13]; mean, 2.4–3.2 SLNs excised per patient)[13,17]. The sensitivity and NPV of SLNBs in the sample were 75% and 83.3%, respectively. Several studies that have assessed the performance of SLNBs in carcinoma of the oral cavity found sensitivity and NPV ranges of 78–91% and 90–96%, respectively.[2,4,5,7,11-15] Many of these authors evaluated

TABLE 1
Influence of various factors on overall survival

Factor	p
Alcohol consumption	0.919
SLNB	0.029*
Stage T1/T2	0.109
Age	0.556
Sex	0.147
Smoking	0.930

Univariate analysis of categorical variables using Kaplan-Meier curves and of continuous variables using Cox models.
SLNB, sentinel lymph node biopsy.
*Statistically significant.

SLNBs to define the presence or absence of cervical lymph node metastases during follow-up periods of 19–60 months as the gold standard.2,4,11,12 The largest of these studies focusing on the application of SLNBs was a European multicenter prospective trial involving 14 institutions and 145 patients. That study found 86% sensitivity and an NPV of 95% after follow-up for three years.13 Moreover, the largest trial of SLNB validation, which prospectively used simultaneous END as the gold standard, was developed by the American College of Surgeons Oncology Group and included 140 patients from 25 North American hospitals. They found that the sensitivity and NPV were 90% and 96%, respectively.5 Two more recent meta-analyses of 66 studies of 3,566 patients with cT1-2N0 SCC of the oral cavity and 35 with 1,084 patients with cT1-2N0 SCC of the tongue showed grouped sensitivity of 87% and 92% and NPVs of 94% and 96%, respectively.10,16 The 75% sensitivity and NPV of 83.3% obtained herein are close to those reported in the literature, albeit slightly lower. However, they do mean that at this point and considering the 26% rate of occult lymph node metastases in this cohort, SLNB avoided the need for unnecessary END and its associated morbidity in 61 of 100 treated patients. This advantage was offset by the risk of seven patients in the same cohort of 100 patients being undertreated due to false negatives obtained in SLNB. The lower performance of SLNB has been associated with a lower volume of procedures and to some locations of the primary tumor, such as the floor of the mouth.[2,5] Sagheb et al. conducted a prospective study of 10 patients diagnosed with cT1-2N0 SCC of the tongue compared SLNB with systematic elective END. The sensitivity was 75%, with which our findings concurred.[17] In fact, the small sample size was a limitation of the present study, as was the inclusion of patients with primary tumors extending to the floor of the mouth. However, we believe that analyzing and reporting the results of this technique is important. Moreover, its validity has been shown in other studies of the oral cavity and not only specific sites.[5]

Interest in less invasive therapeutic approaches is increasing, and the present sensitivity and NPV were similar to previous findings. Therefore, we believe that our findings support the notion that more patients should undergo SLNB, with the aim of it becoming a routine and standardized procedure. The reliability should be improved by monitoring outcomes and defining strategies to avoid the disadvantages of false negative results. These strategies may include a closer clinical follow-up of patients with negative SLNB, and monitoring patients using imaging to detect lymph node metastases early enough to deliver timely salvage treatment.[4,13,18] Lymphatic mapping with radiopharmaceuticals can be combined with dyes injected in the periphery of the primary tumors, thus adding visual detection of SLNs to activity detection.[3,4,7] Although a direct comparison is not always possible because of the heterogeneity of samples and follow-up periods, the estimated overall survival of 85.4% at 12 months and 80.4% at 24 months obtained herein was similar to that reported by others (87%[4], 88%[11], and 80%[13] at two, three, and five years, respectively). The significantly different survival between the groups with positive and negative SLNBs indicates that risk in these patients can be stratified, and in fact expected, considering that cervical lymph node metastases comprise the main prognostic factor in SCC of the oral cavity.[7,11,12,17] The fact that the significance of this difference disappeared in our multivariate analysis is probably due to the size of the sample and the few patients who died. Therefore, studies of larger and more representative samples are needed to confirm our findings.

CONCLUSION

In the present study, SLNBs were useful for analyzing cT1-2N0 SCC of the tongue, with a sensitivity of 75% and an NPV of 83.3%. The avoidance of unnecessary END in 83.3% of patients without cervical lymph node metastases suggested that SLNBs confer a benefit for patients with SCC. An increased number of patients treated after SLNBs will help to improve accuracy. Systematic clinical monitoring of patients after obtaining SLNBs is fundamental for the timely detection

of cervical lymph node metastases in patients with false negative results.

Conflict of Interest

The authors declare no conflict of interest regarding this article.

Data confidentiality

The authors declare having followed the protocols in use at their working center regarding patients' data publication.

Human and animal protection

The authors declare that the followed procedures complied with regulations established by the Ethics and Clinical Research Committee and according to the Helsinki declaration of the World Medical Association.

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Availability of scientific data

There are no publicly available datasets related to this study

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