Sentinel lymph node biopsy versus elective neck dissection in evaluation of cN0 neck in patients with oral and oropharyngeal squamous cell carcinoma. Systematic review and meta-analysis study

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Abstract  Background: The sentinel node biopsy concept has been gaining popularity in the head and neck cancer literature and several pilot studies have been published.

  Purpose: This study aimed to systematically evaluate the diagnostic accuracy of sentinel lymph node biopsy in cN0 patients with squamous cell carcinoma of the oral cavity and oropharynx.

  Methods: A systematic literature review was performed using MEDLINE from 1980 to 2014 by combining oral cavity and oropharyngeal SCC keywords with sentinel node biopsy keywords. We included diagnostic accuracy studies which used neck dissection as a reference test for the sentinel node biopsy. Study characteristics and measures of accuracy were extracted. Diagnostic accuracy was calculated from 2×2 tables.

  Results: A total of 35 studies (1121 patients) were included. The pooled sensitivity, specificity, positive likelihood ratio (LR+), negative likelihood ratio, diagnostic odds ratio, positive predictive value, negative predictive value and accuracy were 93%, 100%, 35.89%, .12%, 282.7%, 100%, 97% and 97.8%, respectively.

  Conclusions: High sensitivity, negative predictive value and accuracy of SLNB support its role as a valid diagnostic technique to correctly stage cN0 patients with OCSCC and OPSCC.

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1. Introduction

Oral cavity and oropharyngeal squamous cell carcinoma (OCSCC and OPSCC) are considered an important part of the global burden of cancer, mainly due to the widespread use of tobacco and alcohol.1
The most important prognostic factor is the presence of cervical lymph node metastases, which can decrease the 5-year survival rates to lower than 50%.

Staging of the neck by palpation and imaging techniques (e.g. MRI, CT, ultrasound-guided fine needle aspiration cytology (USgFNAC)) are not sensitive enough in detecting micrometastases resulting in a high incidence of occult metastases in the neck. These techniques are based primarily on size criteria, with nodes smaller than 10 mm not generally considered suspicious. However, nodes as small as 2.0 mm can contain micrometastatic disease and therefore there is still a 20–30% incidence of occult nodal metastasis in necks categorized as N0. Exact staging of the N0 neck is therefore crucial in managing this type of cancer.

In SCC of the oral cavity and oropharynx, the main options for the treatment of the N0 neck are elective neck dissection, radiation therapy, or a combination of the two. Currently accepted management policies are that patients with greater than 20% chance of subclinical metastases, based on the anatomic site and the size of the primary tumor, should undergo elective neck dissection (END). However, such a policy might still over treat up to 80% of patients, and ENDS carry with them an associated morbidity.

Because of the need to accurately stage the neck and to treat only those most likely to benefit from therapy, much interest has arisen in sentinel lymph node biopsy (SLNB). The validity of the concept of SLNB is based on the fact that tumor cells will spread from the primary site to a single node or group of nodes (the sentinel nodes), before progressing to the remainder of the lymph nodes i.e. if the sentinel node is positive for the disease, the patient’s neck is considered to harbor disease whether any further deposits are found on histological examination subsequently and therefore there are no false-positive cases in this scenario.

The systematic review and meta-analysis were conducted to assess the diagnostic accuracy of SLNB in evaluation of N0 neck in patients with oral and oropharyngeal squamous cell carcinoma.

2. Methods

2.1. Search for relevant studies

Using MEDLINE database (http://www.pubmed.com), we conducted a systematic literature search to identify relevant studies published within the last 34 years (from 1980 up to 25/1/2014). Disease-specific search terms (cN0 neck, Clinically negative neck, oral cavity SCC, oropharyngeal SCC) were combined with diagnostic modality specific search terms (SLNB and END) in addition to methodological search term (meta analysis) in all our searches. The electronic searches were supplemented by scanning the reference lists from retrieved articles to identify additional studies that may have been missed during the initial search. It was decided to include only those studies which are published in English language or translated to English language; dealing with human subjects, including patients who had a concurrent END performed at the time of SLNB in evaluation of cN0 neck in patients with OSCC & OPSCC in order to acquire pathological validation of the SLNB technique. Also patients in the included studies did not receive any treatment before being evaluated by these operative techniques. In studies that included patients with different diseases,
only those patients with OCSCC and OPSCC with cN0 were included. Lymph nodes that demonstrated any evidence of carcinoma, including micro metastasis and tumor islet cells, were considered positive. Excluded articles: are those articles which miss one or more of the above mentioned inclusion criteria, duplicated studies or those outdated by subsequent ones. Studies that provided insufficient data to construct a $2 \times 2$ contingency table were also excluded.

2.2. Study selection and data abstraction

In order to obtain $2 \times 2$ contingency tables from the included studies, we extracted or calculated TP, FN and TN. In sentinel node biopsies, FP results are not possible. For the evaluation, the number of neck sides, not the number of patients, was used.

To calculate sensitivity and specificity, true-positive (TP) was considered when histopathology of SLNB proved the presence of the metastatic cervical lymph node. When histopathology of SLNB did not reveal the presence of the metastatic cervical lymph node and was subsequently confirmed by histopathology of END, it was considered to be true-negative (TN). It was considered false-negative (FN) if the metastatic cervical lymph node was confirmed in END subsequently to negative SLNB.

2.3. Quality assessment of primary studies

For each included study, the methodological quality was assessed by using the Quality Assessment of Studies of Diagnostic Accuracy Included in Systematic Reviews (QUADAS) criteria, which is a 14-item instrument. The questions in this checklist are aimed at establishing the validity of the study under review – that is, making sure that it has been carried out carefully, and that the conclusions represent an unbiased assessment of the accuracy and reliability of the test being evaluated. Each question covers an aspect of methodology that is thought to make a difference to the reliability of a study.

If the quality item was achieved, we give it (+), and (−) for the quality item not achieved or data not available. Fulfillment of the methodological quality criteria for the included articles was considered high, acceptable, or low, when the percentage of the mean (sum/total) of adherence for all included article was >70%, 50–70%, or <50%, respectively.
2.4. Statistical methods

The primary outcome for analysis is the diagnostic performance of SLNB that detected the neck lymph node metastasis compared with the reference standard of END specimens. For each individual study we have calculated the following diagnostic values: sensitivity, specificity, positive likelihood ratio (LR+), negative likelihood ratio (LR−) and diagnostic odds ratio with a confidence interval of 95%. The sum of the ROC curve was used to estimate the general accuracy of SLNB. Data were pooled using random or fixed effect model according to the presence or absence of a significant heterogeneity. The random effect model incorporated the heterogeneity of the studies into the analysis of the overall efficacy. The fixed effect model assumed that data came from a single study that is, assuming no inter-study heterogeneity. Statistical heterogeneity among studies was evaluated by the Cochran Q statistic (considered significant for p values <0.10) and the I² test. Likelihood ratios are metrics that are calculated using a combination of sensitivity and specificity values. The positive likelihood ratio (LR+) is defined as the ratio of specificity/(1 – sensitivity). When a diagnostic test has absolutely no discriminating ability, both likelihood ratios equal 1. Meta analysis of the collected data was conducted using the software: Meta-Disc© version 1.4.  

3. Result

3.1. Study identification and eligibility

Our search identified 525 potentially relevant studies in MEDLINE (Table 1). Out of them, there were 284 potentially eligible studies. We excluded 103 out of the 284 studies because they miss one or more of the above mentioned inclusion criteria or were duplicated or were outdated by other more recent ones. Thus, 181 studies remained for possible inclusion and were retrieved in full text version. After reviewing the full article, 146 studies were excluded for the following reasons: some of them were essay studies while others were containing non cN0 neck or the primary was non OCSCC and OPSCC. Still other studies were containing neither SLNB nor END or a 2 x 2 table could not be constructed. This process left 35 original articles which fulfilled all inclusion criteria and thus were
included and used for further analyses. The overall cohort totaled 1121 patients (no of neck sides = 1121).

3.2. Methodological quality assessment of the included studies

Systematic review of the included studies using QUADAS tool revealed that the total methodological quality score, expressed as a fraction of the maximum score, ranged from 9/14 (64%) to 13/14 (93%) with mean (83.3%) (High).

3.3. Analysis of included articles

Our searching of the Medline database revealed 35 studies which contained 1121 cases in total comparing the roles of SLN versus END in evaluation of cN0 neck in patients with OCSCC and OPSCC with the histopathological analysis of the SLNB and neck dissection specimens as the gold standard.

Most studies mentioned the detection rate of sentinel nodes. In these studies at least one sentinel node was detected in almost all patients and a sentinel node biopsy could thus be performed in all patients. Fifteen studies only included T1-2 N0 oral cavity patients whereas another 4 studies included as well T3-4 N0. Thirteen studies included T1-2 N0 OCSCC and OPSCC whereas another 3 studies included as well T3-4 NO OCSCC and OPSCC.

The detection rate (true positive) of SLNB versus END was 301 (26.85%) out of 1121 neck sides, false-negative results were 24 (2.14%) out of 1121 neck sides and the true negative results were 796 (71%) out of 1121 neck sides (Table 2).

The most common method to preoperatively localize SLN included injecting a radioactive sentinel node tracer followed by lymphoscintigraphy (in 34 studies). Blue dye was used alone for localization of SLN in only one study and in addition to radioactive tracer in 12 studies. 33 studies utilized a gamma probe intraoperatively in addition to lymphoscintigraphy. In all studies, the histopathologic examination consisted of serial sectioning with hematoxylin and eosin (H&E) staining, followed by immunohistochemistry staining for negative SLN in only 21 studies.

The pooled sensitivity of SLNB versus END is 93%. There is a significant heterogeneity between the sensitivities of SLNB versus END in evaluation of cN0 neck in patients with OCSCC & OPSCC in included studies as the p value of chi-square test was 0.06 (<0.1) and I² index was 28.1% (25–50%) (Fig. 1).

The pooled specificity is 100%. There is no significant heterogeneity between the specificities of SLNB versus END in evaluation of cN0 neck in patients with OCSCC & OPSCC in included studies as the p value of chi square test was 1.0000 (> 0.1) and I² index was 0.0% (0–25%) (Fig. 2).
The pooled Positive Likelihood Ratio is 35.89. There is no significant heterogeneity between the Positive Likelihood Ratios of SLNB versus END in evaluation of cN0 neck in patients with OCSCC & OPSCC in included studies as the p value of chi-square test was 0.999 (>0.1) and $I^2$ index was 0.0% (0–25%) (Fig. 3).

The pooled Negative Likelihood Ratio is 0.12. There is no significant heterogeneity between the Negative Likelihood Ratio of SLNB versus END in evaluation of cN0 neck in patients with OCSCC & OPSCC in included studies as the p value of chi-square test was 0.433 (>0.1) and $I^2$ index was 2.1% (0–25%) (Fig. 4).

The pooled Diagnostic Odds Ratio is 282.73 (denoting high validity of the test). There is no significant heterogeneity of SLNB versus END in evaluation of cN0 neck in patients with OCSCC & OPSCC in included studies as the p value of chi-square test was 0.433 (>0.1) and $I^2$ index was 0.0% (0–25%) (Fig. 5).

The area under the ROC Curve (AUC) = 0.985 (Fig. 6).

### 3.4. Diagnostic accuracy

The overall sensitivity (0.93), specificity (1.00), LR+ (35.89), LR– (0.12), DOR (282.7), AUC (0.985), PPV (1.00), NPV (0.97) and the accuracy (0.978) of SLNB versus END in evaluation of N0 neck in patients with OCSCC & OPSCC are reported in Table 3.

### 4. Discussion

Although diagnostic tools have developed significantly, we have no effective procedures available to identify hidden metastatic disease in the cervical lymph nodes of patients with OSCC and OPSCC. The incidence is situated at around 30%, a high percentage, and the presence of regional disease is the cause of the death of one of every two patients.50

The application of SNB has been demonstrated to be very useful in melanoma and breast cancer51,52 and for this reason we have studied its application in primary OCSCC and OPSCC, through Meta analysis of 35 studies, in an attempt to determine if SLNB is a useful technique in the diagnosis of regional metastasis.

It must be noted that all articles in this study have 100% specificity (Fig. 2) and positive predictive value because there are no false-positive cases in this scenario. However, false negative results can have several causes including uneven radionuclide injection, obscuring of sentinel lymph nodes by the radioactive signal of the primary tumor, and lymphatic
obstruction by gross tumor, resulting in redirection or unpredictable lymphatic flow and were defined as skip metastases or jump metastases.\textsuperscript{8}

In our meta-analysis, 1121 patients with OSCC and OPSCC underwent SLNB followed by immediate END. A positive sentinel lymph node biopsy confirmed occult metastasis in 301 neck sides out of 1121 neck sides considered clinically to be free of disease, equal to 26.85\% of our series, which appropriately correlates with the 30\% occult metastatic rate, reported by Don et al.\textsuperscript{50}

Overall, the sensitivity of SLNB in OSCC and OPSCC was 93\% (Fig. 1), with a NPV of 97\% (Table 3). This result
translates to only 3% of necks with negative results actually being metastatic. Our data demonstrates quite clearly that OCSCC and OPSCC patients with negative SLNBs can be assured of a very high degree of certainty that subsequent ENs will also be negative.

Our results were concordant with the diagnostic metaanalysis of Govers et al. 2013 (21 studies comprising 847 patients of cT1/T2N0 oral cavity and oropharyngeal squamous cell carcinoma) and Paleri et al. 2005 (19 studies comprising 301 patients of oral cavity and oropharyngeal squamous cell carcinoma) who reported a pooled sensitivity of 0.94 (0.90–0.97) and 92.6 (85.2–96.4), respectively.

In the present study, the pooled Positive Likelihood Ratio of SLNB is 35.89 (Fig. 3). This means that a person with cN0 neck having metastatic lymphadenopathy is about 36 times more likely to have a positive test than a person with cN0 neck who has not got metastatic lymphadenopathy in cases of OCSCC and OPSCC. On the other hand, the pooled Negative Likelihood Ratio of SLNB is 0.12 (Fig. 4), indicating that the probability of having a negative test for individuals with metastatic lymphadenopathy in cN0 neck is 0.12 times of that of those without metastatic lymphadenopathy in cN0 neck of patients with OCSCC and OPSCC.

In the present study, the pooled Diagnostic Odds Ratio of SLNB is 282.73 (>1) (Fig. 5). This means that for the SLNB the odds for positivity among cN0 neck of subjects with metastatic lymphadenopathy is nearly 283 times higher than the odds for positivity among cN0 neck of subjects without metastatic lymphadenopathy.

In the present study, Area Under Curve (AUC) is equal to 0.985 (Fig. 6) denoting excellent diagnostic value of SLNB versus END in evaluation of cN0 neck in patients with OCSCC & OPSCC in included studies.

The present study revealed generally high quality scores of the included studies; suggesting that most of included studies presented enough information overall and satisfied most of the requirements established. However most of studies had a suboptimal design in regard to the blinding method (Item 11) as the interpretation of the histopathological examination results of the neck dissection specimen was done with the knowledge of the SLNB histopathological results.

There is no significant heterogeneity between the specificity, Positive Likelihood Ratio, Negative Likelihood Ratio and Diagnostic Odds Ratio in the included studies (Figs. 2–5), while there was a significant heterogeneity between the sensitivity in the included studies (Fig. 1) and this was the reason to adapt a random effect model for data pooling.

To the best of our knowledge, this is the largest metaanalysis of SLNB in patients with oral cavity and oropharyngeal SCC.

5. Conclusions

The results of this diagnostic meta-analysis demonstrate that sentinel node biopsy appears to be a sensitive method in the detection of neck metastases in cN0 neck of OCSCC and OPSCC that could suggest its utility in the management process.

6. Recommendations

Multi-center prospective randomized double blind controlled trials comprising larger patient cohorts comparing the roles of SLNB versus END in evaluation of cN0 neck in patients with OCSCC and OPSCC are required. Long-term follow-up will also be critical to better assess disease free and disease specific survival of SLNB patients.

Researchers should pay attention to fulfill QUADAS items specially the blinding.

References


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Table 3  Diagnostic performance of SLNB versus END in evaluation of cN0 neck in patients with OCSCC & OPSCC in included studies.


