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# Sentinel Node Biopsy in Larynx Cancer: 5 Years Follow-up

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## ABSTRACT

**Background:** The management of the clinically and radiologically negative neck in patients with early Head and Neck Squamous Cell Carcinoma (HNSCC) is still controversial. As approximately 20 to 30% of these patients harbor occult disease in the neck, most of them have to undergo elective neck dissection with no great benefit to majority of them. Sentinel Lymph Node Biopsy (SLNB) is emerging as a potential method for staging of lymphatic metastasis in HNSCC. It has been demonstrated that the status of the sentinel node predicts the presence of metastasis in the remainder of the nodes within the nodal basin.

**Objective:** To evaluate the accuracy of method in squamous cell carcinoma of larynx and compare neck status between Sentinel Node Biopsy (SNB) followed by Elective Neck Dissection (END) and SLNB alone.

**Results:** Eighteen patients, 12 at glottis and in 6 supraglottis with a mean age of 63 years (49-83) were evaluated. The follow-up was 64 months (48-87), sentinel node was identified in all the patients and it was positive in four patients (22%). Five patients (27%) received postoperative radiotherapy because of local factors such as: positive margin, vascular invasion, perineural invasion or extra-capsular spread. During the follow-up period none of the patients had local or neck recurrence (0%). In the last evaluation none of the patients had local or neck recurrence.

**Conclusion:** Sentinel Node Biopsy (SNB) in larynx cancer shows negative predictive value of 100%, accuracy of 100% and recurrence rate of 0%. It is important to note that no randomized study of sufficient sample size and sensitivity exists in the literature, but preliminary studies shows a new perspective in head and neck cancer.

**KEYWORDS:** Head and neck cancer; Sentinel node biopsy; larynx.

**ABBREVIATIONS:** HNSCC: Head and Neck Squamous Cell Carcinoma; SLB: Sentinel lymph node biopsy; SNB: Sentinel Node Biopsy; END: Elective Neck Dissection; US: Ultrasound; AJCC: American Joint Committee of Cancer; H&E: Hematoxilin-Eosin; IHC: Immunohistochemical; SSS: Step Serial Section; SPEC-CT: Single photon emission computed tomography; CT: Computed Tomography.

## INTRODUCTION

The management of the clinically and radiologically negative neck in patients with early head and neck squamous cell carcinoma (HNSCC) is still controversial. As only approximately 30% of patients harbor occult disease in the neck, most of the patients have to undergo elective neck dissection with no benefit.[1] As in several other solid tumors, sentinel lymph node biopsy (SLNB) is emerging as a potential method for staging lymphatic metastasis in HNSCC.[2,3]

It has been demonstrated that the status of the sentinel node predicts the presence of

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metastasis in the remainder of the nodes within the nodal basin.[4] Multiple validation studies revealed that sentinel node detection rates in HNSCC are above 95% and negative predictive values for negative sentinel nodes of 95%.[5]

HNSCC had a high metastatic potential because of rich lymphatic network in head and neck area, therefore with a high propensity to lymph nodes metastasis.[6-8] Lymph node status is the most important prognostic factor in patients with HNSCC.[9] Evaluation of the neck is still largely based on palpation only.[10]

However, it is widely accepted that palpation is unreliable for assessment of the neck nodes. The sensitivity of palpation is generally around 75% and specificity varies from 73% to 97%.[11,12] Ultrasound (US) can detect a high number of non palpable enlarged lymph nodes, but some studies shows that when the sensitivity is about 90%, the specificity is as low as 30%.[13,14]

Other studies shows that combined evaluation (palpation, US and CT-scan) has average 30% of false negative and false positive.[15] Even in patients with no clinical evidence of lymph node metastasis (N0), there is a high incidence of occult metastasis. This ranges from 10 to 50% depending on the primary tumor characteristics, which include tumor subsite in head and neck area, T-stage and depth of invasion.[6,8]

Therefore, a strategy to identify patients at risk of metastasis in clinically negative necks allows accurate staging and implementation of appropriate adjuvant treatment, avoiding unnecessary elective neck dissection (END) for remaining 70 to 80% of patients and therefore minimizes morbidity associated with the treatment.[16]

The sentinel lymph node biopsy (SLNB) concept has been adopted from the treatment of melanoma and breast cancer to early oral and oropharyngeal squamous cell carcinoma during the last decade with great success.[17-19] Multiple validation studies in the context of elective neck dissections revealed sentinel node detection rates above 95% and negative predictive values for negative sentinel nodes of 95%.[5] The purpose of SLNB mapping is to detect the lymph node echelon that first drained from the primary lesion by using dye or radioactive tracer. This concept has the potential to become the new standard of care in the near future.

The aim of this study is to evaluate patients with Squamous Cell Carcinoma (SCC) of larynx without evidence of neck metastasis submitted to sentinel node biopsy instead of elective neck dissection and describe the neck recurrence rate.

## METHODS

Consecutive patients with SCC of larynx that would need END as part of their surgical treatment and without clinically and radiologically lymphatic metastasis and without previous treatment, were included in the study between June 2006 to November 2013. All patients were staged according to 2002 American Joint Committee of Cancer (AJCC) Staging.[14]

The local Institutional Review Board (IRB) approved the study protocol. Informed consent was obtained from all the patients submitted to this study. All the patients had histopathological confirmation of SCC.

Then the patients were staged at the neck and primary site with computer tomography scan before the treatment. Each side of the neck was considered separately when END was indicated bilaterally, due to bilateral lymphatic drainage of lesion.

Each patient was then submitted to direct laryngoscopy and injection of radiolabeled colloid at the periphery of the tumor, with special needles for microlaryngoscopic surgery in paraglottic space. The radiotracer ($^{99m}$Tc dextran) transit time to the lymph node is less than 1 h and may be retained in the lymph node for an additional 3-6 h.

The dose of radioisotope was 0.2 mCi. Intraoperative detection of sentinel node was performed with handheld gamma probe after resection of larynx tumor with partial external laryngectomy or endoscopic transoral laryngectomy. In case of external approach for partial laryngectomy, the same incision is used for detection and removal of sentinel nodes. Otherwise, in case of transoral endoscopic approach, nn incision is made at the regions with higher levels of radiations than background and they were excised.

The primary resection of tumor is always performed for easier detection of sentinel nodes without the high radiation energy in primary tumor site, very close to the nodal echelons, which usually trespass the radiation of sentinel node that could be undetectable in presence of radiation of primary tumor. After removal of sentinel node, it was checked for radioactivity in *ex-vivo* out of the surgical field.

Standard pathological evaluation consisted of examining a three longitudinal section of lymph nodes by Hematoxilin-Eosin (H&E) staining in order to find metastatic deposits. If H&E was negative for metastasis, Immunohistochemical (IHC) evaluation with Step Serial Section (SSS) was performed. Patient was referred to postoperative radiation therapy in presence of positive margins, perineural invasion, presence of vascular or lymphatic embolus, presence of extracapsular spread or multiple lymphatic metastasis.

When only a single metastasis without extracapsular spread was detected, no adjuvant treatment was delivered. In case of positive margins or extracapsular spread was detected, besides radiation therapy, concomitant postoperative chemotherapy was delivered with cisplatin and 5-fluorouracil.

Post-operative evaluation with clinical examination was performed monthly in first six months, bi monthly until the

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first year, and every three months after. Radiologic evaluation was performed every six months with CT scan.

### SNLB Technique

SLNB was performed *via* peritumoral injection of technetium. Lymphoscintigraphy and Single photon emission computed tomography (SPEC-CT) was performed in all cases. The skin of neck was marked accordingly and a gamma probe was used for identification of sentinel lymph node. Step serial sections of the sentinel lymph node were stained with hematoxylin-eosin and immunohistochemistry was performed.

All patients were followed postoperatively with a computed tomography (CT) scan every six months. Adjuvant treatment was indicated in patients with positive margins, extracapsular spread, presence of perineural invasion, or vascular emboli.

### Statistical Analysis

Statistical analysis were performed *via* SPSS Statistics 17 (Windows & Mac) software, and comparisons were made *via* Odds Ratio. The disease free survival between the two groups was also calculated for the two populations. A confidence interval of 95% was employed.

For the evaluation of recurrence rate during the estimated interval time, the Cox regression model was employed. For comparisons between groups by age, stage, histopathological status and follow-up length, a T-test was employed. P-values <0.05 were considered statistically significant.

### Ethics

The current study was approved by the Institutional Review Board (IRB). Informed consent was obtained from all the subjects.

## RESULTS

Eighteen patients were evaluated. Average age was 63 years (range 49-83 years). In 12 patients the primary site was glottis and in 6 patients, supraglottis.

The average follow-up of 64 months (48-87) was achieved. The sentinel node was not found in only one patient who was excluded from the study. This patient was treated by END. Sentinel node was positive in four patients (22%). Five patients (27%) received post-operative radiotherapy because of local factors such as: positive margin, vascular invasion, perineural invasion or extra-capsular spread. During the follow-up period none of patients had local or neck recurrence (i.e. neck recurrence rate was 0%).

| Variables | Patients | Obs1 |
|---|---|---|
| Gender | Male | 18(100%) |
| | Female | 0(0%) |
| Age | 63 years old | Min 49 - max 83 |
| Follow-up | 64 months | Min 48 - max 87 |
| Tumor | Glottis | 12 cases |
| | Supraglottis | 6 patients |
| Tumor stage | T3NOM0 | 15 patients |
| | T2N0M0 | 03 patients |
| SNB + | 4 patients | 22% |
| RT post op | 5 patients | 27% |
| Neck recurrence | 0 patients | 0% |

SNB: Sentinela Node Biopsy; RT: Radiotherapy.

**Table 1:** Subject's data.

## DISCUSSION

The status of metastasis to the cervical lymph node is the single most important prognostic factor in HNSCC.[9,20] Peritumoral lymphatics provide the primary access for tumor cells to enter the lymphatic system. Tumor cell motility and rich lymph vessel density are the key factors that determine this initial lymphatic permeation.[21]

The diagnostic ability of US, CT-scan and Magnetic Resonance Imaging (MRI) is primarily based on node morphology and size criteria, with nodes smaller than 10 mm generally not considered to be harboring metastasis, thus radiologic features shows even 30% of false-negative and false-positive.[22,23] It has been observed that the status of sentinel node predicts presence of metastasis in the remainder of the nodes within the nodal basin, which forms the basis of SLNB.

The concept of SLNB for HNSCC attracted significant interest in the recent past for the mere fact that there are no reliable methods to detect occult metastasis in clinically N0 necks.[13,24,25] Literature review shows sentinel node detection rates above 95% and negative predictive values for negative sentinel nodes of 95%.[5]

There is a critical point when the lymph node is fully occupied by carcinoma cells at which the tracer could not flow into the lymph node and therefore would show no accumulation of radiotracer. Another consideration is about 'skip metastasis' reported in until 16% of patients with SCC of the oral tongue.[26] Our casuistic do not permit evaluate these points.

The SLNB technique initially was described with injection of isosulphan blue dye around the tumor. As the technique needs visualization, it is necessary to expose the entire nodal basin, thereby increasing the invasiveness of the procedure. Moreover, isosulphan blue dye has apparent lower reliability than radiotracer localization with hand held gamma probe. For localization of sentinel node.[27]

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Different radiolabeled materials have been developed for lymphoscintigraphy, and $^{99m}$Tc is now the most widely used material for lymphoscintigraphy with intraoperative detection on sentinel node. The main advantages of $^{99m}$Tc colloids are: emission of only gamma rays and low radiation exposure to the patients and physicians, half-life of six hours and it has a peak energy. The dose of radiotracer used are ranged from 0.5 to 0.8 mCi.[27] These tumors traditionally are considered difficult to access for the injection of isotope, but an experienced surgeon may easily do the procedure.

Standard pathological evaluation consists of examining a longitudinal section by H&E staining in order to find metastatic deposits.[28] Studies have shown that routine evaluation misses up to 21% of disease nodes. It is suggested that SSS with H&E and IHC, and molecular methods may help to identify smaller metastatic deposits.[29]

Our results observes similar results on neck recurrence in both groups and despite the difficultness of access to larynx tumor it could be performed without Lymphoscintigraphy with intra-operative injection of radiotracer of $^{99m}$Tc dextran which has a higher flow rate through lymphatic channels than $^{99m}$Tc phytate and allows intra-operative evaluation after performance of partial laryngectomy through an external or endoscopic approach.

With microlaryngoscopic needless and small syringe of 1 ml, it is easy to inject radiotracer around the tumor in larynx, glottic or supraglottic area. The number of patients of our randomized study was not large and this could be a bias, even the follow-up could be longer, but until now no one recurred in the neck. The technique on SLNB could be promising in neck staging for HNSCC of larynx with high accuracy for selection of adjuvant treatment.

The objective of SLNB is to decrease the morbidity of pathologic neck staging. In addition to oncologic safety, an improvement in the quality of life of patients undergoing SLNB needs to be demonstrated. Prospective randomized studies are necessary to standardize the method and hopefully avoid some controversies surrounding the technique. The ultimate question to be answered is, if this technique can improve survival and reduce morbidity in long term follow-up.

## CONCLUSION

This data gives, besides the studies limitations, support to continue evaluating patients committed by larynx cancer with sentinel node biopsy without elective neck dissection. The neck recurrence rate in those patients was 0%.

## CONFLICTS OF INTEREST

The authors declare that they have no conflicts of interests.

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