Background:

Elective neck dissection (END) in patients with squamous cell carcinoma (SCC) of oral cavity and oropharynx with clinically N0(cN0) necks is considered when risk of lymphatic metastasis is higher than 20%. However, with this criteria, up to 80% of surgical specimens will be negative histopathologically. No accurate technique could predict which patient really presents with occult lymphatic metastasis. Therefore in high risk patients END should be performed. The sentinel lymph node biopsy (SLNB) seems to be clinically safe as a staging procedure of cN0 according to several articles and meta-analysis. Controversy is related to positive sentinel lymph node(SLN) as usually it requires re-approaching the neck for subsequent neck dissection in a previous operated field with the inconvenience of two stage surgery. Frozen section is not reliable for micrometastases. Some primary tumors presents with aggressive patterns that warrants adjuvant treatment including the neck in the radiation field and in these situation neck dissection could be postponed. The objective of this study is to calculate the rate of neck recurrence after SLNB technique with limphoscintigraphy and gamma probe in patients with T1/T2 SCC of oral cavity and oropharynx, without END in cN0 necks when sentinel lymph nodes(SLN) was histopathologically positive.

Methods

Prospective clinical study was accomplished with consecutive patients with SCC of oral cavity and oropharynx, staged as T1 or T2 from may 2005 to october 2011. All of them were clinically and radiologically negative necks at CT scan, without previous treatment, with infiltrative lesions. SLN was localized and dissected off with handheld gamma probe after resection of primary tumor. SLN was evaluated with hematoxilin-eosin and immunohistochemistry with step serial section. In the presence of adverse prognostic factors in the primary tumor or lymphatic disease, patient was submitted to adjuvant treatment. Subjects were followed after surgery monthly with clinical exam in the first year and every two months at the second year. CT scan was required every six months for the first two years. Then the surveillance was as usual

Results

Forty eight consecutive patients were included in this study. The follow up ranged from two years to eight years with mean value of 4,8 years. Forty-one were SLN negative and seven were positive(15%). Of theses seven positive SLN cases, five(71%) received adjuvant treatment: chemoradiation for positive margins(2) and presence of extracapsular spread(2) and one only radiation therapy for perineural invasion. One patient with positive SLN with extracapsular spread recurred despite adjuvant treatment salvaged with radical neck dissection(14%). All patients are alive without disease. The rate of neck recurrence was 14% in this cohort of patients with positive SLN during the follow-up.
Conclusion

Neck recurrence rate in positive SLN cases is not higher than observed in other cohorts of patients treated with END with positive neck specimens for T1/T2 oral cavity or oropharynx cancer. This perspective of SLNB could avoid two stage surgery in this small cohort of patients. SLNB could be reliable as staging procedure and is a useful tool for selection of patients for multimodality treatment.
PROSPECTIVE STUDY OF FEASIBILITY OF SENTINEL LYMPH NODE BIOPSY WITHOUT NECK DISSECTION IN LOCALLY ADVANCED ORAL CAVITY AND OROPHARYNX CANCER

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Background

Elective neck dissection (END) in patients with squamous cell carcinoma (SCC) of oral cavity and oropharynx with clinically N0(cN0) necks must be considered in advanced stage disease. However, no accurate technique could predict which patient really presents with occult lymphatic metastasis. Therefore in these patients END should be performed. The sentinel lymph node biopsy (SLNB) seems to be clinically safe as a staging procedure of cN0 according to several articles and meta-analysis for T1/T2 disease. The outcomes of these procedure was not well established in advanced local disease with cN0 necks. The objective of this study is to evaluate the rate of neck control after SLNB technique with lymphoscintigraphy and gamma probe in patients with T3/T4 SCC of oral cavity and oropharynx, without END in cN0 necks.

Methods

Prospective clinical study was accomplished with consecutive patients with SCC of oral cavity and oropharynx, staged as T3 or T4 from may 2005 to october 2011. All of them were clinically and radiologically negative necks at CT scan, without previous treatment. SLN was localized and dissected off with handheld gamma probe after resection of primary tumor transorally. SLN was evaluated with hematoxilin-eosin and immunohistochemistry with step serial section. In the presence of adverse prognostic factors in the primary tumor( positive margin) or lymphatic disease(extracapsular spread), patient was submitted to adjuvant treatment chemoradiation. All patients received postoperative radiation therapy. Subjects were followed after surgery monthly with clinical exam in the first year and every two months at the second year. CT scan was required every six months for the first two years. Then the surveillance was as usual

Results

Sixteen consecutive patients were enrolled in this study. The follow up ranged from two years to eight years with mean value of 3,7 years. Eleven patients presented with negative SLN(70%) and during follow-up neither recurred. One received chemoradiation and ten radiation as adjuvant treatment. Five patients were positive SLN(30%) and four received adjuvant chemoradiation and one radiation treatment. Two patients among positive SLN recurred in neck(40%). One died of recurrent disease in neck and other were salvaged with radical neck dissection and is alive without disease.

Conclusion
SLNB is feasible even in locally advanced stage oral cavity and oropharynx SCC. This technique could avoid neck dissection in these patients when SLN is histopathologically negative. Positive SLN may warrant further neck dissection.

Key words: head and neck, sentinel node, squamous cell carcinoma, lymphatic metastases.
**Introduction:** The optimal management of node negative neck in early (T1T2) oral tongue cancer is controversial. Selective neck dissection (SND) is commonly done. To "wait and watch" is the other approach that may carry an increased risk of nodal recurrence. Sentinel lymph node biopsy (SNB) is an approach in between. The sentinel node is the first node reached by the lymphatics, assuming a sequential drainage from the tumor, and should be predictive of the nodal stage.

**Methods:** This is a randomized, controlled, single center, two-arm trial. All patients were clinically node negative. In the latter part of the study, ultrasonogram of the neck was included as the imaging modality. All patients underwent surgical resection of the tumor. The patients in Arm 1(SNB Arm): underwent lymphoscintigraphy and SNB. SND was done in patients in whom a frozen section of the sentinel node was positive, and in whom the histopathology of the node was positive. Radiolabelled sulphur colloid was used for lymphoscintigraphy. The patients in Arm 2 (Neck Dissection Arm) underwent SND. 121 patients were randomized, 60 in Arm 1 and 61 in Arm 2. In Arm 1, 55 patients were included in the final analysis; 5 patients were excluded, one had T3 disease on table, four other patients due to protocol violation. In arm B, 55 patients were included in the final analysis; 6 patients were excluded, 2 had advanced disease on table, in 2 patients sentinel lymph nodes were not identified, 2 patients had protocol violation. The study period was between January 2004 and May 2011. The mean follow up period was 53 months. Chi Square test and Kaplan Meir Survival curves were used for statistical analysis.

**Results:**

1. The efficacy of Frozen section:Sensitivity: 76.5%, Specificity: 100%, Positive predictive value: 100%, Negative predictive value: 96.07%.

2. The efficacy of SNB to detect a positive node (as a staging procedure): Sensitivity: 81.8%, Specificity: 100%, Positive predictive value: 100%, Negative predictive value: 91.4%.

3. Oncological results: 24 patients developed recurrences. 89 patients are alive and disease free at the end of follow up.

4. Nodal recurrence without local recurrence

   Arm 1(SNB Arm): 12/ 55 (21.8%)

   Arm 2 (Neck Dissection Arm): 2 /55 (3.6%)

   p =0.01

   Survival:
5 Year Overall survival: Arm 1: 79.8%, Arm 2: 90.2%, (p= 0.315).

5 Year Disease free survival: Arm 1: 65.8%, Arm 2: 80.2% (p= 0.101)

**Conclusions:** This is the first randomized controlled trial comparing sentinel lymph node biopsy with selective neck dissection. The nodal recurrence rate in the SNB arm was significantly lower. The survival rates were higher in the neck dissection arm, though not statistically significant. The small sample size is a limitation of this study and this may be the reason for the survival differences not reaching significance. This study shows that sentinel node biopsy is not an effective procedure in managing the neck in T1T2 tongue cancers.
ANALYSIS OF SENTINEL NODE BIOPSY COMBINED WITH OTHER DIAGNOSTIC TOOLS IN STAGING CN0 HEAD & NECK CANCER

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Importance:

To avoid the unnecessary treatment of cN0 necks, a staging strategy must be sensitive enough to reduce the risk of occult metastases to less than 15~20%.

Objective:

The aim of this study was to complete a systematic review and meta-analysis for CT, MRI, PET, US, US-guided fine needle aspiration (US-FNA), sentinel node biopsy (SNB) in the evaluation of cN0 neck. Analysis of combined diagnostic tools in staging non-palpable cN0 HN cancer can be simulated.

Data Sources:

PubMed & (up to Aug 2013) and CENTRAL (via the Cochrane database up to Aug 2013) were searched using the following keywords: (a) (Head and Neck Neoplasms[MH]) NOT (Thyroid Neoplasms[MH] OR Esophageal Neoplasms[MH] OR Nasopharyngeal Neoplasms[MH] OR Salivary Gland Neoplasms[MH] OR Melanoma[MH] OR Parathyroid Neoplasms[MH]); (b) Diagnostic imaging[MH]; (c) lymph node[TW] OR neck node[TW]; and (d) sensitivity[TW] OR accuracy[TW].

Study Selection:

Sufficient data were presented to construct a 2x2 contingency table (sensitivity and/or specificity with absolute numbers of false positive (FP), false negative (FN), true positive (TP) and true negative (TN) findings) for the modalities compared using the reference standard.

Data Extraction:

The Quality Assessment of Diagnostic Accuracy Studies (QUADAS) quality assessment tool was used to evaluate the relevant study design characteristics of each study. Each study that met the inclusion criteria will be analyzed by two independent reviewers. Univariate meta-analyses were performed to calculate the combined sensitivities of US-FNA and SNB. Bivariate /Hierarchical SROC models are performed to calculate the combined sensitivities and specificity of CT, MRI, US & PET. Based on Bayesian theory and collected data with different pre-examination probabilities, the post examination negative neck nodal probability will be calculated.

Results:

A total of 73 articles were selected based on agreement between the two reviewers. The pooled estimates for sensitivity are 56.4% (95% confidence interval [CI], 44.7%~67.4%) and 84.9% (82.0~87.5%) for US-FNA and SNB respectively. The pooled estimates for sensitivity were 47.0% (95% confidence interval [CI], 38.2%~56.0%), 56.6% (39.8~71.9%), 48.3% (30.9~66.1%), and 63.3% (54.0~71.7%) for CT, MRI, PET and US respectively. The pooled estimates for specificity were 88.9% (82.0%~93.3%), 82.5%
(39.8~71.9%), 86.2% (76.9~92.1%) and 79.1% (73.4~83.8%) for CT, MRI, PET and US respectively. Even with 60% pre-test prevalence rate of occult metastasis, CT then SNB or MRI then SNB strategies still have very high NPV as 88%; which means final occult metastatic rate will be 12%.

Conclusions:

The SNB procedure seems has the best diagnostic performance. Combined of CT/MRI and SNB for the non-palpable clinical NO HN cancer is preferred.
LESSONS LEARNED AND RECOMMENDATIONS FOR MINIMIZING RECURRENT AFTER SENTINEL NODE BIOPSY

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Introduction:

The Sentinel European Node Trial (SENT) provides the largest single cohort of patients with oral cancer that have undergone Sentinel Node Biopsy (SNB). Although reports of sensitivity and negative predictive value are good (sensitivity 87% and negative predictive value 95%), the false negative rate remains high enough (13%) to be a barrier to wide adoption of the technique. The purpose of this presentation is to identify how false negative results and recurrences come about and how they can be reduced in the future.

Methods:

Data from 420 patients enrolled in the SENT trial were examined to identify differences between the recurrence group compared to the whole trial population. In the trial group there were 54 recurrences of which 15 were false negative results. The possible factors influencing a recurrence were divided into technical and biological factors. Possible technical sources of error included imaging errors, incorrect pathological diagnosis, and surgical technique. Biological factors which could influence recurrence were also examined such patient and tumour characteristics. A pathology QA review was undertaken by a panel of pathologists as part of this analysis.

Results:

Recurrences were local (15/54, 28%) loco-regional (9/54, 17%) regional (29/54, 54 %) and regional/distant (1/54, 2%).

With regard to technical factors, only the use of blue dye intraoperatively seemed to reduce the chance of a false negative result (p=0.05) however associations were shown with operator frequency and type of lymphoscintigraphy performed (13% false negative rate with static imaging alone compared to 4% with SPECT/CT, p=0.06)

In all types of recurrence the most significant correlation was depth of tumour>4mm, which was also predictive of cervical metastasis (p=0.02). Other biological factors such as the presence of perineural or sarcolemal spread and poorly differentiated tumours gave a higher chance of recurrence at the tumour site (p=0.005,.P=0.003 and p=0.03 respectively)

Panel pathology review did not upgrade any false negative cases to SNB positive.

Discussion:

Extensive pathological review of the sentinel nodes has confirmed that pathological errors are not likely to be the cause of false negative results. We therefore have to look at each step of the radiology and surgical process to identify where accuracy can be improved. Case selection may be one of the most important factors in minimizing poorer outcomes and newer technologies such as 3D navigation and
fluorescence guided SNB should help in reducing errors further.
EVALUATION OF THE USE OF FREEHAND SPECT FOR SENTINEL NODE BIOPSY IN EARLY STAGE ORAL CARCINOMA
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Rationale. Inadequate intraoperative visualization of the sentinel node can hamper its biopsy. Freehand SPECT is a 3D tomographic imaging modality based on the concepts of SPECT, which can be used for intraoperative visualization and navigation towards the sentinel node in order to improve its localization and removal during surgery.

Methods. The use of freehand SPECT was evaluated during 29 sentinel node biopsy procedures in early stage oral cancer patients. Intraoperative detection of sentinel nodes was compared with preoperative identified sentinel nodes on lymphoscintigraphic examination. Additional value of freehand SPECT was subjectively scored by the surgeon directly following the biopsy procedure.

Results. Freehand SPECT was able to detect 95% of sentinel nodes intraoperatively. Most sentinel nodes not detected (3 out of 4) were located in level Ib of the neck. Freehand SPECT appeared to be of additional value for facilitating the intraoperative detection of sentinel node in 38% of procedures.

Conclusion. The use of the freehand SPECT system is feasible in the intraoperative detection of sentinel nodes in early stage oral cancer. Freehand SPECT provides helpful information facilitating the SN biopsy procedure in a percentage of cases. However, freehand SPECT cannot always detect SNs which are located close to the injection site site.
Objective: The presence of cervical lymph node metastasis has been shown to be the most important adverse prognostic factor in oral and oropharyngeal cancer. Therefore, elective neck dissection (END) is widely performed for in those without clinical and radiological neck metastasis (cN0), although it would cause morbidity and only 25-30% of patients actually bear occult lymphatic disease. Sentinel lymph node (SLN) biopsy provides better staging than preoperative imaging modalities and less morbidity than END, so that it would be an alternative to END. However, the practice of SLN biopsy is still limited because standard SLN procedure using a radioisotope requires rigid control and costly equipment. Easily-used and cost-effective indocyanine green (ICG), producing near-infrared (NIR) fluorescence, has recently been used for SLN biopsy in various cancers. The aim of this study is to investigate the feasibility of the technique in patients with oral and oropharyngeal squamous cell carcinoma.

Methods: A total of five patients with cN0 oral (n=4) and oropharyngeal (n=1) squamous cell carcinoma who were scheduled for primary tumor resection and END were selected. One or two milliliter of ICG solution (5 mg/ml) was injected submucosally at four adjacent point around the tumor under general anesthesia. A scheduled skin incision for END was made and a sub-platysmal flap raised. Cervical tissues were detected using NIR video camera system and all first fluorescing lymph nodes were biopsied as SLNs. Subsequently END was performed to compare the SLNs and regional lymph nodes histologically.

Results: SLNs were easily obtained (average 3.8, range 2-7) in all five patients with NIR fluorescence imaging because fluorescing lymph nodes were clearly visualized and distinguished from surrounding tissues. Two patients showed a positive SLN and the both of them harbored regional lymph node metastases. Three patients showed a negative SLN and no regional metastasis. No adverse effect occurred.

Conclusion: This study demonstrated feasibility to detect SLNs in oral and oropharyngeal cancer patients using ICG and NIR fluorescence imaging. This is a prospective technique for SLN detection by direct visualization and further investigation is warranted to supersede END.
ROLE OF SENTINEL NODE BIOPSY FOR INTERMEDIATE-THICKNESS MELANOMA OF THE SCALP

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INTRODUCTION: Melanoma of the scalp remains a complex disease due to the erratic lymphatic drainage and a propensity for distant failure. Thus, the utility of sentinel lymph node biopsy (SLNB) in this population remains undefined. We report the outcomes of patients with intermediate thickness melanoma of the scalp who underwent SLNB to determine the recurrence and survival rates.

METHODS: The charts of 60 patients with intermediate thickness melanoma (1.01-4 mm) of the scalp who underwent SLNB from 2000-2012 were reviewed. Demographic, clinical and pathological data were reviewed.

RESULTS: We identified 60 patients who were eligible for the study, and SLNB was successfully performed in all patients. The mean tumor thickness was 2.21 mm. An average of 3.8 LN were harvested at the time of SLNB, and a positive SLN was identified in 40% of patients. A completion neck dissection was performed in 70.8% of patients with positive sentinel nodes, and 11.7% of the specimens harbored non-sentinel nodal metastases. The regional failure rate after SLNB was 13%, and distant failure occurred in 40% of patients. The mean time to death was 46 months.

CONCLUSIONS: We report a high rate of SLN positivity among patients with intermediate thickness melanoma of the scalp. SLNB in this group of patients is highly predictive of distant metastasis. For this group of patients, SLNB provides accurate staging of the regional node basin and important prognostic information.
**S463 SENTINEL NODE BIOPSY IN ORAL CAVITY SQUAMOUS CELL CARCINOMA: TEN YEARS EXPERIENCE**

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**Introduction**: Sentinel node Biopsy (SNB) is now becoming an established investigative tool in the management of T1-T2 oral cavity SCC. Multiple validation studies report 93% sensitivity and negative predicting value of 95% after 5yrs follow-up. Critical observations regarding the clinical use of the SNB protocol are based on the elevated number of SN detected (>2.5) and on their localisation in multiple and distant levels of the neck.

**Material and Methods**: From Dec 2001 to Dec 2012, 52 patients (26m, 26f, mean age 62.3 yrs) affected by cT1-T2N0 oral cavity SCC were submitted to dynamic and static planar lymphoscitigraphy using a dose of 30-50 MBq Nanocolinjected superficially in the subepithelial stroma of the peritumoral area. Surgical excision of the tumour and radioguided SNB, using a hand held gamma probe, was performed within 3hrs after Lymphoscintigraphy (same day protocol). The mean follow up was more than 9 years.

**Results**: Sentinel Nodes (SN) were found in all cases and in 78.8% of them they were localised in the ipsilateral neck levels I-II only. The mean number of SNs detected was 2.2. Metastases were found in 16 out of 52 cases (30.7%) at level I, II and III, all identified by step serial sectioning on routine H&E staining. Other metastatic nodes were found in neck specimen of 5/16 SNB+ patients after neck dissection. No one of the 36 SNB-patients had node metastases in the ipsilateral neck in the follow up.

**Conclusions**: This study confirms the accuracy of SNB to predict the presence of occult metastases and the validity of same day protocol in detecting SN really close to the tumour site (level I and II).