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# Cost–utility of sentinel lymph node biopsy in cT1–T2N0 oral cancer

Naomi van der Linden [a,d,*], Géke B. Flach [b], Remco de Bree [b,c], Carin A. Uyl-de Groot [a]

[a] Institute for Medical Technology Assessment, Erasmus University Rotterdam, PO Box 1738, 3000 DR Rotterdam, The Netherlands
[b] Department of Otolaryngology-Head and Neck Surgery, VU University Medical Center, PO Box 7057, 1007 MB Amsterdam, The Netherlands
[c] Department of Head and Neck Surgical Oncology, UMC Utrecht Cancer Center, UMC Utrecht, PO Box 85500, 3508 GA Utrecht, The Netherlands
[d] CHERE, University of Technology Sydney, PO Box 123, Broadway NSW 2007, Sydney, Australia

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SUMMARY

*Objectives:* To calculate the cost–utility of different strategies for the detection of occult lymph node metastases in cT1–T2N0 oral cancer.
*Methods:* A decision tree followed by a Markov model was designed to compare the cost–utility of the following strategies: (a) USgFNAC (ultrasound guided fine needle aspiration cytology), (b) SLNB (sentinel lymph node biopsy), (c) USgFNAC and, if negative, SLNB (d) END (elective neck dissection). Data was collected from 62 patients in four Dutch head and neck centres. Utilities were measured with the EQ5D questionnaire and resource use was recorded from patient charts. Costs were calculated from a hospital perspective. Uncertainty was explored with scenario analyses and probabilistic sensitivity analyses.
*Results:* With a 5- or 10-year time horizon, SLNB results in the highest number of additional quality-adjusted life years (QALYs, 0.12 and 0.26, respectively) for the smallest additional costs (€56 and €74, respectively) compared to USgFNAC. With a lifetime horizon END results in the highest number of additional QALYs (0.55) for an additional €1.626 per QALY gained compared to USgFNAC. When we make different assumptions regarding the duration of disutilities ($\geqslant$5 years) or the improvement ($\geqslant$3%) of sensitivity of SLNB, SLNB is the most favourable strategy from all time horizons.
*Conclusion:* SLNB is a good diagnostic strategy to evaluate cT1–T2N0 oral cancer. SLNB is the preferred strategy in a 5- or 10-year time horizon. From a lifetime horizon, END may be preferred. SLNB may become the optimal strategy from all time horizons if its sensitivity can be slightly improved.


## Introduction

The management of the clinically N0 (cN0) neck in T1–T2 oral cancer patients is controversial. Either elective neck dissection (END) or watchful waiting (WW) is performed, depending on the perceived chance of occult lymph node metastases. Nowadays, more and more evidence supports the use of diagnostic tools to stage the clinically negative neck more reliable, in addition to palpation and/or imaging techniques (ultrasound, CT, MRI and/or PET). When uncertainty about the existence of occult lymph node metastases decreases, undertreatment and overtreatment (unnecessary surgery) can be reduced. Diagnostic tools to do so include ultrasound guided fine needle aspiration cytology (USgFNAC), sentinel lymph node biopsy (SLNB) and molecular markers. Currently, the diagnostic performance of SLNB seems most promising [1,2].

Introducing SLNB in the routine management of cT1–T2N0 oral cancer impacts costs as well as clinical outcomes. Three previous studies were published about the cost-effectiveness of SLNB compared to other approaches. In 2003, Kosuda et al. showed SLNB to save $1.218 per stage cN0 patient and avoid 7 surgical deaths per 1.000 patients, as compared to neck dissection [3]. In 2013, O'Connor et al. used multi-centre trial data on 481 cT1–T2N0 oral cancer patients to calculate the relative cost ratio for treatment with traditional surgery (including END) as compared to SLNB, followed by either surgery (following positive SNLB) or WW [4]. Costs of the SLNB approach were only 48% of the costs of the traditional surgical approach.

In 2013, Govers et al. published a Markov decision analytic model to evaluate the cost-effectiveness of five strategies: END, WW, gene expression profiling (GEP) followed by neck dissection or WW, SLNB followed by neck dissection or WW, and GEP and SLNB (for positive GEP) followed by neck dissection or WW [5]. Over a 5-year time horizon, SLNB was the most cost-effective

* Corresponding author at: CHERE, University of Technology Sydney, PO Box 123, Broadway NSW 2007, Sydney, Australia.
*E-mail addresses:* naomi.vanderlinden@chere.uts.edu.au (N. van der Linden), gb.flach@vumc.nl (G.B. Flach), R.deBree@umcutrecht.nl (R. de Bree), uyl@bmg.eur.nl (C.A. Uyl-de Groot).

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strategy, costing €3.356 per QALY (quality-adjusted life year) gained as compared to END. Outcomes were sensitive for utility values, which were taken from expert opinion. Analysis on the expected value of perfect information showed further information on quality of life to be valuable.

The current study expands on the evidence from Govers et al.. Information from a different, prospective, multicentre clinical trial ("SNUS trial") is used to compare four strategies for the detection of occult lymph node metastases and treatment choice: (A) USgFNAC followed by neck dissection or radiotherapy when positive and WW when negative, (B) SLNB followed by neck dissection or radiotherapy when positive and WW when negative, (C) USgFNAC and, if negative, SLNB followed by neck dissection or radiotherapy when positive and WW when negative and (D) END. As opposed to the study from Govers et al., clinical outcomes, economic outcomes and quality of life estimates were obtained from the trial. In this article, the cost–utility of the various diagnostic and treatment strategies will be presented, with the aim to inform routine clinical practice.

DFS = disease free survival, DSS = disease-specific survival, END = elective neck dissection, GEP = gene expression profiling, HNSCC = head and neck squamous cell carcinoma, ICUR = incremental cost–utility ratio, OS = overall survival, QALY = quality-adjusted life year, SLNB = sentinel lymph node biopsy, USgFNAC = ultrasound guided fine needle aspiration cytology, WW = watchful waiting.

## Methods

In order to calculate cost–utility of the various strategies, a decision model was designed and informed with data from the SNUS trial.

### *The SNUS trial*

Sixty-two patients with T1–T2 oral cancer and cN0 neck based on palpation and USgFNAC were enrolled from four centres of the Dutch Head and Neck Society [6]. SLNB negative patients were carefully observed. Positive patients were treated by neck dissection, radiotherapy or a combination of both (see Fig. 1). Endpoints of the study were risk of occult lymph node metastases, neck control, accuracy, 5-year disease free survival (DFS), overall survival (OS) and disease-specific survival (DSS).

Twenty of 62 patients (32%) had positive SLNBs. Macrometastases were found in 9 patients, micrometastases in 8, and isolated tumour cells in 3 patients. Median follow-up was 52.5 months. Of the 42 SLNB negative patients, 5 developed a regional recurrence of whom 4 patients could be successfully salvaged. DFS, OS and DSS of SLNB negative patients were 72.0%, 92.7% and 97.4%, and for SLNB positive patients these numbers were 73.7%, 79.7%, 85.0%, respectively (DFS: $p = 0.916$, OS: $p = 0.134$, DSS: $p = 0.059$). Neck control rate was 97% in SLNB negative and 95% in SLNB positive patients. Sensitivity was 80% and negative predictive value 88% [6].

### *Model structure and transition probabilities*

Using patient level data from the SNUS trial and additional literature, four different diagnostic and treatment strategies were compared. In Microsoft Excel 2010, a decision tree was designed to model the diagnostic pathways (see Fig. 2). A Markov model represented the subsequent follow-up (see Fig. 3), with a cycle length of one year. Transition probabilities for the four strategies were obtained from Dutch studies. The probabilities as well as the data sources are presented in Fig. 2. The probability of neck recurrence after treatment of the neck was assumed to be 0.05 [6] for all strategies, independent of the diagnostic method.

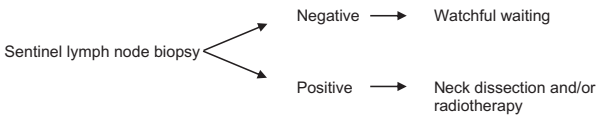


**Fig. 1.** Study design of the trial.

Overall survival rates in the first five years were obtained from Flach et al. [7] and were 95%, 78%, 71%, 66% and 63% for years 1 to 5, respectively. Overall survival after five years was based on Dutch life tables from Statistics Netherlands (2015), combined with 20% excess mortality since the conditional long-term survival of Dutch head and neck squamous cell carcinoma (HNSCC) patients remains poorer compared to the general population [8].

The time horizons of the model were five years, ten years and lifetime.

### *Model input – health state utilities*

Patient health related quality of life was measured in SNUS trial patients [9], using various instruments including the EQ5D. Since the utility associated with undergoing USgFNAC and SLNB was similar, equal utility was assumed for all patients in strategy A, B, and C who did not need treatment. This utility was 0.84, which was calculated by averaging the utility for all SNUS trial patients without regional failure ($n = 49$).

The average outcome for SNUS trial patients with regional failure was 0.79 ($n = 2$). The disutility of regional failure therefore is (0.84–0.79=) 0.05. Since only two patients experienced regional failure in the SNUS trial, the uncertainty associated with this estimate is high. However, the estimate seems reasonable in the light of available literature. For example, Weiss et al. report a disutility of regional failure of 0.06 [10].

For patients who received treatment of the neck (without regional failure), average utility was 0.77 ($n = 18$). This utility is applied to all patients in strategy D, and those patients in strategy A, B and C who were tested positive (and were therefore treated with ND or RT). The disutility after ND or RT is therefore (0.84–0.77=) 0.07. This is relatively high compared to the disutility of ND reported by Weiss et al. (0.03) [10]. Also, it is 0.01 higher than the disutility of regional failure. However, the differences are small and non-significant.

Since quality of life losses usually resolve over time [11], in the base-case we assume the utility to return to 0.84 after one year, for all patients. In the base-case, the discount rate for effects was 1.5%, consistent with Dutch pharmacoeconomic guidelines.

### *Model input – costs*

Resource use was recorded from hospital databases and patient charts and included inpatient hospital stays and consultations, day-care treatments, outpatient visits, surgery, radiotherapy, diagnostic imaging and laboratory testing including pathological and microbiological diagnostics. Costs were calculated from a hospital perspective and included direct medical costs only, in 2015 Euros. Unit costs were preferably obtained from the Dutch cost manual 2015, alternatively from the VU University Medical Center or, in case both were unavailable, from Dutch tariffs. Follow-up costs were calculated per year and are presented in Table 1. In the base-case, the discount rate for costs was 4%, consistent with Dutch pharmacoeconomic guidelines.

### *Data analyses*

Costs, effects and cost-effectiveness were calculated per diagnostic strategy. Incremental cost–utility ratios (ICURs) were