Review

Elective neck dissection in oral squamous cell carcinoma: Past, present and future☆

Remco de Bree[a,*], Robert P. Takes[b], Jatin P. Shah[c], Marc Hamoir[d], Luiz P. Kowalski[e], K. Thomas Robbins[f], Juan P. Rodrigo[g,h], Alvaro Sanabria[i], Jesus E. Medina[j], Alessandra Rinaldo[k], Ashok R. Shaha[c], Carl Silver[l], Carlos Suárez[h,m], Manuel Bernal-Sprekelsen[n], Alfio Ferlito[o]

[a] Department of Head and Neck Surgical Oncology, UMC Utrecht Cancer Center, University Medical Center Utrecht, Utrecht, the Netherlands
[b] Department of Otolaryngology-Head and Neck Surgery, Radboud University Medical Center, Nijmegen, the Netherlands
[c] Head and Neck Service, Memorial Sloan Kettering Cancer Center, New York, NY, USA
[d] Department of Head and Neck Surgery, Head and Neck Oncology Program, St Luc University Hospital and Cancer Center, Brussels, Belgium
[e] Department Otorhinolaryngology-Head and Neck Surgery, Centro de Tratamento e Pesquisa Hospital do Cancer A.C. Camargo, São Paulo, Brazil
[f] Division of Otolaryngology-Head and Neck Surgery, Southern Illinois University School of Medicine, Springfield, USA
[g] Instituto Universitario de Oncología del Principado de Asturias, University of Oviedo, Oviedo, Spain
[h] Department of Otolaryngology, Hospital Universitario Central de Asturias, Oviedo, Spain
[i] Department of Surgery, School of Medicine, Universidad de Antioquia, Clínica Vida/Instituto de Cancerología Las Américas, Medellín, Colombia
[j] Department of Otorhinolaryngology, The University of Oklahoma Health Sciences Center, Oklahoma City, OK, USA
[k] University of Udine School of Medicine, Udine, Italy
[l] Department of Surgery, University of Arizona College of Medicine, Phoenix, AZ, USA
[m] Fundación de Investigación e Innovación Biosanitaria del Principado de Asturias, Oviedo, Spain
[n] Department of Otorhinolaryngology, Hospital Clinic, University of Barcelona Medical School, Barcelona, Spain
[o] Coordinator of the International Head and Neck Scientific Group, Italy

ARTICLE INFO

ABSTRACT

In 1994 a decision analysis, based on the literature and utility ratings for outcome by a panel of experienced head and neck physicians, was presented which showed a threshold probability of occult metastases of 20% to recommend elective treatment of the neck. It was stated that recommendations for the management of the cN0 neck are not immutable and should be reconfigured to determine the optimal management based on different sets of underlying assumptions. Although much has changed and is published in the almost 25 years after its publication, up to date this figure is still mentioned in the context of decisions on treatment of the clinically negative (cN0) neck. Therefore, we critically reviewed the developments in diagnostics and therapy and modeling approaches in the context of decisions on treatment of the cN0 neck. However, the results of studies on treatment of the cN0 neck cannot be translated to other settings due to significant differences in relevant variables such as population, culture, diagnostic work-up, follow-up, costs, institutional preferences and other factors. Moreover, patients may have personal preferences and may weigh oncologic outcomes versus morbidity and quality of life differently. Therefore, instead of trying to establish "the" best strategy for the cN0 neck or "the" optimal cut-off point for elective neck treatment, the approach to optimize the management of the cN0 neck would be to develop and implement models and decision support systems that can serve to optimize choices depending on individual, institutional, population and other relevant variables.

Introduction

Oral squamous cell carcinomas (OSCC) have a proclivity to metastasize through lymphatics to regional lymph nodes first rather than to spread hematogeneously. Therefore, management of the neck has to be included in the treatment planning in most of the patients with OSCC. Moreover, the presence of clinically apparent cervical lymph node metastases is one of the most important prognostic factors in OSCC

since it roughly reduces survival by half. Whereas in the treatment of the overt metastatic lymph nodes in the neck there may be debate on how best to treat the neck [1], the management of clinically negative (cN0) neck remains a much more controversial issue. There is general agreement that elective treatment of the neck is indicated when there is a high likelihood of occult, clinically undetectable, lymph node metastases, when the neck needs to be entered for surgical treatment of the primary tumor, or when the patient will be unavailable for regular follow-up. When there is lower likelihood of occult lymph node metastases, the choice is between elective treatment and watchful waiting. This question certainly arises in the smaller (T1 and T2) OSCCs, because these tumors usually can be excised transorally and the neck is not entered surgically. The dilemma of elective treatment or watchful waiting was addressed by Lefebvre et al. where they found no clear advantages of an elective neck dissection (END) in a series of 579 patients treated for early stage oral cancer between 1974 and 1983 [2].

The rationale for elective treatment is based on the premise that occult metastases will inevitably progress into clinically manifest disease and that treatment at an earlier N-stage implies better oncological outcome [3]. The main arguments against elective treatment of the neck are that a large proportion of patients are subjected to treatment that they do not need and elective dissection of the neck is associated with morbidity, i.e. shoulder morbidity.

However, the question remains, as to which patients should undergo elective neck dissection and who should not. To answer this question, the paper of Weiss et al. [4] has been referred to numerous times since its publication in 1994. The decision analysis in this study concluded that if the probability of occult metastasis in the neck is greater than 20%, elective treatment of the neck is warranted [4]. Although much has changed and is published in almost 25 years after its publication, this figure is still mentioned in the context of decisions on treatment of the cN0 neck. Therefore, we critically reviewed the developments in diagnostics and therapy and modeling approaches in the context of decisions on treatment of the cN0 neck in OSCC patients.

Decision analyses

Decision analysis is a method by which the effect of different variables concerning the outcome of a treatment can be rigorously analyzed. Choices of treatments and probabilities of various outcomes are arranged in a decision tree with the intent of identifying the probability of certain results given the decision options available. In 1990 Velanovich [5] was probably the first to perform a decision analysis for treatment of head and neck squamous cell carcinoma (HNSCC). The quality-adjusted life expectancies were determined using best estimates of survival, recurrence, short-term morbidity and quality of life after radiotherapy and surgical resection of stage I floor of mouth cancer from available literature at that time. The quality-adjusted life expectancies for surgical resection with neck dissection (18.50 years) was higher than for surgical resection without neck dissection (14.48 years) and that for primary radiotherapy (7.95 years). However, sensitivity analysis showed that these results varied with quality of life assumptions and survival data. Therefore, it was recommended that each institution needs to review its survival data and question patients about quality of life to determine how treatment options fit into the decision analysis [5].

Weiss et al. [4] reported in 1994 on the use of decision analysis to determine the optimal strategy for neck treatment as a function of the probability of occult cervical lymph node metastasis. To determine the optimal threshold for treatment, they constructed a decision tree with the use of a computer model to compare the three major strategies in the treatment of HNSCC patients with a cN0 neck: END, elective neck irradiation and observation. Probabilities of each of the possible events depicted in the trees were gleaned from the available literature at that time and inserted into the tree structure. Then a sensitivity analysis on the variable of the probability of occult metastasis was performed to

determine the optimal threshold for treatment of the neck. They concluded that a HNSCC patient with a cN0 neck should be observed if the probability of occult lymph node metastasis is less than 20%. If the probability is greater than 20%, treatment of the neck (either END or elective radiation therapy) is warranted. In the introduction of their article they state that suggested thresholds in the past were problematic because they were intuitive, but also because several factors had changed at the time of their analysis. They mentioned that modern imaging techniques staged the neck more accurately than ever before and the likelihood and severity of morbidity associated with neck dissection was considerably less as modified radical neck dissection was performed at that time instead of the classical radical neck dissection. Since their study, the means to more accurately assess the status of the neck have improved considerably (e.g. better imaging and sentinel node biopsy procedure) and *selective* END has been popularized based on the patterns of metastasis. This was also pointed out by Weiss et al. [4] stating that the conclusions of the analysis are only as good as the data that are fed into the model. Data that were used in the analysis were probability of recurrence, successful salvage rate and quality of life outcome. Salvage therapy was expected to be successful in only 50% of the patients in the observation group, in whom metastatic lymph nodes appear in the neck at a later time. However, it can be anticipated that improved follow-up strategies, e.g. watchful waiting and wait and scan, will increase the success rate of salvage neck dissections. In their study the utility (desirability) ratings for outcome were established by a panel of three experienced head and neck physicians and use of the time trade off method in which the question should be answered how much time of life one would give up to have a better function (quality of life). It was argued that patients had difficulties in separating out the morbidity of neck treatment from treatment morbidity in general [4]. However, patient's preferences may differ from expectations of treating physicians.

Others [6–9] have also performed studies on decision analysis for the management of the cN0 neck Using different probability assumptions of occult lymph node disease, recurrence rate, salvage rate survival and morbidities (shoulder disability and scar), recommendations vary from the END for all patients, thresholds of 20–44.4% to perform END, to careful observation for all patients (Table 1). Methods to perform decision analysis have improved. Former studies used a deterministic approach where probabilities are fixed in the model. These studies, did not consider the expected variations in probabilities and outcomes that commonly occurs in medical practice. Recent methodological improvements such as probabilistic approach and discrete event simulation, where distributions of probabilities are used, are more realistic. These new models, more than establish a threshold, describe a cloud of points in a decision quadrant and define a spectrum of values where each therapeutic strategy can be chosen.

In fact, as also Weiss et al. [4] stated, recommendations for the management of the cN0 neck are not immutable and should be reconfigured to determine the optimal management based on different sets of underlying assumptions. Pitman [10] recommended in 2000 to lower the threshold to perform END from 20% to 15%, because of the risk-benefit ratio has changed. However, no decision analysis was performed. In the present paper we will discuss the different factors which may affect the threshold for performing an END.

Imaging workup for cN0 determination

When reviewing the literature on the management of the cN0 neck it is important to realize that the staging of the cN0 neck has not been uniformly done, since different diagnostic techniques have been used in different studies. Thus the reported risk of occult metastases is dependent on the diagnostic techniques used. Modern imaging techniques, such as computed tomography (CT), magnetic resonance imaging (MRI), positron emission tomography (PET) and ultrasound are more reliable than palpation. However, these techniques do not detect

Table 1
Studies on decision analysis on management of clinically negative neck.

Authors	Year	Factors included in model	Major conclusion	Comments
Velanovich [5]	1990	Recurrence, survival, short-term morbidity, quality of life	Quality-adjusted life expectancies with neck dissection (18.50 years) higher without neck dissection (14.48 years)	Standard radical neck dissection
Weiss et al. [4]	1994	Recurrence, successful salvage rate, survival and quality of life	Observation if probability of occult lymph node metastasis is less than 20%	Standard modified radical neck dissection, low salvage rate, utility ratings for outcome by physicians
Davidson et al. [6]	1995	Probability of occult nodal disease, salvage rate, recurrence rate after END, dying from intercurrent disease and morbidities of having surgery, scars and spinal accessory nerve dysfunction, survival	END had the highest expected utility outcome, patients with early oral cancer should undergo an END	Based on evidence in literature until 1990, dependent on accepted assumptions and probabilities for patient (population)
Kaneko et al. [7]	2002	Prognosis and survival, probability of subclinical nodal metastasis, probability of complete removal of subclinical metastases by END and negative impact on quality of life caused by END	Careful observation strategy preferable for all oral cancer with no clinical metastases	Low rate of subclinical nodal metastasis, standardized systematic postoperative screening, possibility of recurrence after therapeutic neck dissection not taken into account
Song et al. [8]	2008	Recurrence, successful salvage rate, survival	END strategy should be applied for cN0 patients with early stage tongue cancer, if occult lymph node metastatic rate < 0.17 and/or salvage rate > 0.73 watchful waiting preferable strategy	Occult metastatic rate and salvage rate likely to be improved with pre- and posttreatment modern diagnostic imaging techniques
Okura et al. [9]	2009	Recurrence, successful salvage rate, survival and quality of life	Threshold of occult lymph node metastasis to perform END 44.4%	Used decision tree of Weiss et al., probabilities of recurrence, successful salvage rates and survival adjusted but not utilities

micrometastases [11]. In a meta-analysis of 73 articles comparing different imaging modalities for the detection of lymph node metastasis in HNSCC patients with a cN0 neck on palpation for CT, MRI, PET, ultrasound and ultrasound-guided fine-needle aspiration (USgFNAC), pooled estimates for sensitivity of 47.0%, 56.6%, 48.3%, 63.3% and 56.4% were found, respectively. The specificity for these imaging techniques was 88.9%, 82.5%, 86.2%, 79.1% and 100%, respectively [12]. A recent study on FDG-PET/CT in cN0 OSCC patients revealed for the detection of occult lymph node metastasis a sensitivity of 21.4% and a specificity 98.4%. With a low overall rate of occult metastasis a negative predictive value of 99.1% was reported [13]. A study in 49 oropharyngeal squamous cell carcinoma patients with a palpably negative neck showed that the addition of PET-CT to CT/MRI did not provide better diagnostic accuracy for detecting nodal metastasis: on a level-by-level analysis a sensitivity of PET-CT, CT/MRI, and a combination of PET-CT and CT/MRI of 54.6%, 54.6%, and 60.6%, respectively [14]. USgFNAC was reported to be superior to other imaging techniques, with reported sensitivity of up to 73% and a specificity approaching 100% [15]. However, the accuracy is very dependent on the experience of the sonographer [16] and has been reported to be much lower in a multicenter clinical setting [17].

In an attempt to improve the detection of occult lymph node metastases the sentinel lymph node (SLN) concept was introduced in early oral cancer [18]. The most recent meta-analyses showed a pooled sensitivity of 87–92% and a negative predictive value of 94–96% for the detection of occult lymph node metastases by SLN biopsy in early oral squamous cell carcinoma [19,20]. Using SLN biopsy in these patients the risk of occult lymph node metastases was 4–6%, which is far below the thresholds to perform an elective neck dissection found in aforementioned decision analyses [4,8].

Predictors for occult nodal involvement in cN0 neck

Prediction profiles may be useful in clinical decision making on treatment of the cN0 neck. If the risk of occult metastases can be assessed reliably, personalized cancer treatment can improve. Depth of invasion (DOI) of the primary tumor is the most promising pathological predictive factor for nodal metastases [21,22]. However, the two recent meta-analyses on this topic involved different study groups, measurement techniques and cut-off values, which hampers good comparison between studies. Both studies found a wide range for cut-off values of 1.5–10 mm, with a most optimal cut-off value of 4 mm in the meta-analysis of Huang et al. [22]. Brockhoff et al. [23] found different DOI cut-off values for a 20% or greater risk of having nodal metastasis in different tumor locations. They suggested to offer a neck dissection in case of > 2 mm DOI in tongue tumors, > 2–3 mm DOI in floor of mouth tumors and > 3–4 mm DOI for the retromolar trigone and alveolus/hard palate tumors [23]. A recent large study of Liu et al. [24] using a cut-off value of 4 mm DOI reported poor sensitivity, specificity, and positive and negative predictive values for prediction of nodal metastasis (54.2%, 67.3%, 45.0%, and 74.8%, respectively) [24]. Similarly, in a recent study, Goerkem et al. [25] were not able to find an optimal cut-off value and reported an area under the curve of 0.54 in an ROC analysis. They concluded that DOI should not be used to decide on elective treatment of the neck [25]. The recent publication of the randomized controlled trial on elective neck dissection versus watchful waiting by D́Cruz et al. [24] defined a threshold for END of 3 mm. Using this threshold the rate of lymph node metastases was 28% in their series [26]. As a consequence, if all patients with a DOI larger than this would undergo an END 72% of patients would receive an unnecessary treatment. With the introduction of DOI in the 8th TNM staging system there is probably some reduction in occult lymph node metastasis for cT1-2N0 OSCC as compared to the 7th edition of the TNM staging system.

Another option to overcome the clinical dilemma whether or not to treat a cN0 neck without invasive diagnostic techniques is tumor profiling with biomarkers. Biomarkers may supply additional information

on the metastatic potential of a tumor. Through the years numerous biomarkers have been studied and identified as potentially relevant for the prediction of regional metastasis. However, due to the complexity of the metastatic process it is unlikely that a single marker for metastasis can be identified. Therefore, techniques allowing the study of many factors simultaneously seem to be the most promising [27]. In 2005, the first gene expression profile to predict nodal metastasis was developed and recently validated in a Dutch multicenter study with a negative predictive value of 89%. Although this seems to be a figure that has not been surpassed by other validated profiles, its use in clinical practice is currently still not considered cost-effective [28,29]. Nevertheless, a combination of both tumor profiling and SLN biopsy could further improve the diagnostic accuracy of staging the neck with limited invasive diagnostic techniques [30].

Follow-up

If cN0 neck is not treated electively a wait and see policy with close follow-up with or without diagnostic techniques such as USgFNAC is an option in carefully selected patients. Using such a wait and scan approach salvage rates of 75–100% have been reported [16,31–33]. These salvage rates are higher than the salvage rate of 73%, mentioned in the previously discussed decision analysis of Song et al. as a threshold to perform an END [8]. Thus, in such strategies futile END can be avoided in the majority of patients and neck disease control and survival did not seem to be compromised [34]. However, in the few patients who need a (salvage) neck dissection for delayed metastases, treatment of the neck will probably be more extensive, e.g. modified radical neck dissection with or without (chemo-)radiotherapy as compared to upfront elective treatment, by a selective END followed by (chemo-)radiotherapy based on indication from pathology reports [33].

Morbidity

It is well established that neck dissection is associated with esthetic (scar) and functional (shoulder) morbidity. This morbidity is characterized by shoulder pain, limitations of abduction and scapular winging. Shoulder function is an important aspect of health-related quality of life as it is related to various activities of daily living [35]. Therefore it is an important factor in the considerations whether or not to treat the neck electively. Modifications of the radical neck dissection were fashioned to limit the extent and frequency of shoulder dysfunction [36]. Eventually, the concept of selective neck dissection (SND) evolved as a strategy to remove lymph node groups at greatest risk, but was also intended to reduce morbidity [37]. Spinal accessory nerve sparing neck dissections are associated with better preservation of shoulder function as compared to nerve-sacrificing neck dissections. Nevertheless, significant shoulder dysfunction continues to arise, in a fair number of patients, even when the spinal accessory nerve is spared during the neck dissection procedure [38,39]. A recent systematic review indeed showed that the prevalence and incidence of shoulder and neck dysfunction varies by type of neck dissection. Prevalence rates of pain after (modified) radical neck dissection (0–100%) were markedly higher compared to SND (9–25%). Reduction in shoulder abduction was reported in 92–100% of radical neck dissections, in 23% of modified radical neck dissections and in 5% of SNDs [40]. Furthermore, considering the low risk of sublevel IIB lymph node metastasis, this level can be spared in END and a significant reduction on the morbidity can be expected [41,42]. Giordano et al. [43] reported a higher impact on the motor action potentials of the spinal accessory nerve in SND including sublevel IIB compared to patients in whom only sublevel IIA was dissected [43]. Nevertheless, despite the use of nerve-sparing surgical techniques during neck dissections, the rate of postoperative paralysis of the trapezius muscle is still high because in almost 40% of the patients an active motor branch from the cervical plexus is distributed to all functional parts of the trapezius muscle [44]. The evolution of the

concept for more limited surgery as with SND may impact the clinical decision making paradigm on whether or not to electively treat the neck.

Although shoulder morbidity is probably the most important sequelae of an END, other morbidities may also appear. Impairment in the sensitivity of the neck, ear and supraclavicular area is a common complaint of patients. As expected, early oral cancer patients who underwent SLN biopsy experienced significantly less impairment from cervical scars, and had less sensory dysfunction as compared to patients who underwent selective END [45]. In modern times, esthetic considerations are also important in the decision making of END. Potential injury of the marginal branch of the facial nerve is expected in 4–7% of cases [46]. The scar after dissection can be a reason of concern in some patients although with the application of minimally invasive surgery in the neck, these concerns can be surpassed [47].

Costs

Strategies in which not all patients undergo a neck dissection may save costs. However, before implementing such a strategy it must be clear that the oncological results are similar. Acevedo et al. [48] performed cost-effectiveness analysis of END in the initial surgical management of early-stage OSCC using a Markov model to simulate primary, adjuvant, and salvage therapy, disease recurrence, and survival in patients with cN0 early stage OSCC patients. They concluded that compared to watchful waiting of the neck, END reduces costs ($6,000) and improves health outcomes (0.42 QALYs), making this a cost-effective treatment strategy for patients with early stage OSCC [48]. Kosuda et al. [49] designed a decision tree sensitivity analysis based on the two competing strategies: ipsilateral (not further specified) END versus SLN biopsy. They found that the introduction of SLN biopsy instead of ipsilateral END would yield cost savings of $1218 per cN0 classified patient in Japan and avoid 7 surgical deaths per 1000 patients who would undergo END [49]. Using a treatment model derived from data of the European Sentinel Node Trial (SENT), O'Conner et al. [50] produced estimates of relative treatment costs between patients managed through a traditional selective END or SNLB pathway for units from Spain, United Kingdom and The Netherlands. The SLN biopsy pathway appears to be cheaper relative to the traditional selective END approach in all centers [50]. In the Netherlands, Govers et al. [51] performed a cost-effectiveness study on the management of the cN0 neck in early stage OSCC. In a decision analytic model the cost-effectiveness was evaluated for selective END, watchful waiting, gene expression profiling followed by neck dissection or watchful waiting, SLN biopsy followed by neck dissection or watchful waiting, and gene expression profiling and SLN biopsy (for positive gene expression profiling) followed by neck dissection or watchful waiting. SLN biopsy followed by neck dissection or watchful waiting appeared to be the most effective and most cost effective strategy. Compared with END the incremental cost effectiveness ratio was €3356 per quality-adjusted life year (QALY) gained [51]. Van der Linden et al. [52] calculated the cost-utility of different strategies for the detection of occult lymph node metastases in cT1-T2N0 OSCC: USgFNAC, SLN biopsy, USgFNAC with if negative SLN biopsy and selective END. With a 5- or 10-year time horizon, the SLNB strategy results in the highest number of additional quality adjusted life years for the smallest additional costs (€56 and €74, respectively) compared to USgFNAC [52].

Real costs and reimbursements by national reimbursement systems may vary. Moreover, willingness to pay for a quality adjusted life year (QALY) may differ from country to country, although no formal threshold for cost-per-QALY values is yet defined in all countries.

Variations in clinical practice

Variations in clinical practice may result in different ways of management of the cN0 neck. In 2006 a questionnaire on neck management

in case of early oral and oropharyngeal cancer was sent out to all eight head and neck cancer centers of the Dutch Head and Neck Society [53]. The questionnaire consisted of two parts: the first concerning the factors influencing the decision of whether or not to perform an END, and the second concerning case examples (as used previously by Dünne et al. [54]. This study [53] found, similar to Dünne et al. [54] for German centers, no uniformity amongst Dutch head and neck cancer centers regarding management of the cN0 neck in early stage oral and oropharyngeal carcinoma. Besides, there was a difference between Dutch and German centers concerning the same case examples [53,54]. More recently Govers et al. [55] performed an international comparison of the management of the neck in early OSCC in the Netherlands, UK, and USA using questionnaire sent to representatives of head and neck cancer centers and observed a high variation both within and between countries [55].

An example of differences in clinical practice is shown by the randomized clinical trial of the Head and Neck Disease Management group of Tata Memorial Centre from India on elective versus therapeutic neck dissection in cN0 oral cancer in patients with lateralized T1 or T2 previously untreated OSCC amenable to undergo transoral excision [26]. In the observation group in 45% a neck metastasis became apparent, which is much higher than for example in several Dutch studies using ultrasound guided fine needle aspiration cytology in the pretreatment diagnostic work-up (delayed metastasis rate 18–28%) [31,32,56]. This difference suggests a less accurate diagnostic work-up and a different target group which may hamper generalizability of their results. During follow-up all patients in this randomized clinical trial received physical examination and half of them also had ultrasonography. Unfortunately, less than 50% of the patients with a relapse in the neck were eventually salvaged. Other studies from different countries reported on salvage rates of 75–100% [16,31–33]. In this trial a 3-years overall survival rate of 68% in the observation group was found, whereas using a wait and scan follow-up including regular USgFNAC a 3-year overall survival rate of 90% and a 5-year overall survival rates of 79%-82% have been reported [16,33]. Moreover, using their follow-up protocol, 28% of the patients with a relapse in the neck had metastasis larger than 3 cm (18% larger than 6 cm), 93% extracapsular spread and 18% unresectable neck disease. Given the size distribution of lymph node metastasis detected during surveillance, it is likely that the follow-up differs from other centers. These data suggest that there is a substantial difference in pretreatment work-up and follow-up between head and neck centers in the world. Since the carcinogens (chewed tobacco and areca nut) to which patients in this randomized clinical trial were exposed, the distribution among subsites (e.g. buccal mucosa) and their clinical behavior may differ from other centers over the world [57]. This heterogeneity is a problem to implement study results worldwide [58], even from a successful randomized clinical trial. Nevertheless, this trial clearly shows a prognostic benefit of END in OSCC in the population in India, where follow-up without routine USgFNAC is used. Although in this setting END was the best strategy, this may change after introduction of the SLN biopsy procedure in the diagnostic work-up [59].

Patient's preference

For individualized treatment, patients participation is extremely important. In the decision analysis of Weiss et al. [4] utility (desirability) ratings were generated by consultation with a panel of three experienced head and neck physicians instead of patients. The authors clarify that attempts to perform time trade-off with patients were unrewarding, because patients were assumed to have difficulty in separating the morbidity of neck treatment from treatment morbidity in general [4]. However, physicians may rate morbidity different from patients. Flach et al. [60] performed an evaluation of the patients' perspective on neck management strategies using semi-structured interviews of early OSCC patients who were treated according a SLN

biopsy strategy with neck dissection in case of a positive SLN. Depending on the neck level of the positive SLN and on the preference of the institute, patients underwent a selective or modified radical neck dissection. Twenty-two patients were asked to choose between two strategies for the neck: an END strategy, which combines staging and treatment of the neck but which may turn out to be unnecessary, or a stepwise strategy in which they undergo SLN biopsy to stage the neck and only in case of a positive SLN biopsy undergo subsequent neck dissection. In the stepwise SLN biopsy strategy they receive individualized treatment with the risk of undergoing two operations. Of these patients, 19 (86%) preferred the SLN biopsy strategy. The 3 (14%) other patients preferred the END strategy. Of notice, all these 3 patients were SLN biopsy positive and these 3 patients were 37.5% of all interviewed SLN biopsy positive patients [50]. Therefore, this finding may be biased by the fact that all patients had undergone SLN biopsy and there was no control group in whom patients had undergone END. Govers et al. [54] calculated health utilities from the EQ-5D-3L questionnaire outcomes and adjusted for potential confounding by age, gender and time since treatment. They included four subgroups of cN0 classified early OSCC patients who underwent different diagnostic and treatment modalities for the neck between 2001 and 2013: watchful waiting, SLN biopsy, selective neck dissection and modified radical neck dissection. The adjusted mean utility scores were 0.804, 0.863, 0.834 and 0.794, respectively [54]. Van der Linden et al. [51] calculated also health utilities from the EQ-5D questionnaire outcomes in early OSCC patients treated between 2007 and 2010 and found a score associated with health status of watchful waiting without regional failure of 0.84, of watchful waiting with regional failure of 0.79 and of receiving treatment of the neck of 0.77 [51]. These figures were different from the study of Weiss et al., in which head and neck physicians at that time rated utilities of patients in the group of observation without delayed metastases 1.0, in case of salvaged delayed metastases 0.94 and END 0.97 [4].

Decision aids

Identifying and making a decision on the best treatment can be difficult for patients. Decision aids can be used when there is more than one reasonable option, when no option has a clear advantage in terms of health outcomes, and when each option has benefits and harms that patients may value differently. Decision aids describe the options available and help people to understand these options as well as the possible benefits and harms. This allows patients to consider the options from a personal view (e.g. how important the possible benefits and harms are to them) and prepares them to participate with their health practitioner in making a decision. The ultimate goal of patient decision aids is to improve decision making in order to reach a high-quality decision. Decision aids differ from usual health education materials, because they make the decision options explicit being considered and provide a detailed, specific, and personalized focus on options and outcomes for the purpose of preparing people for decision making [61].

Patient decision aids supplement (rather than replace) clinicians' counseling about options. The specific aims of decision aids and the type of decision support they provide may vary slightly, but in general they: (1) provide evidence-based information about a health condition, the options, associated benefits, harms, probabilities, and scientific uncertainties; (2) help patients to recognize the values-sensitive nature of the decision and to clarify, either implicitly or explicitly, the value they place on the benefits, harms, and scientific uncertainties (to accomplish this, strategies that may be included in the decision aid are: describing the options in enough detail that patients can imagine what it is like to experience the physical, emotional, and social effects; and guiding patients to consider which benefits and harms are most important to them); and (3) provide structured guidance in the steps of decision making and communication of their informed values with others involved in the decision (e.g. clinician, family, friends) [61]. In a

Table 2
Overall and disease specific survival data from large series of sentinel lymph node biopsy, elective neck dissection and watchful waiting management in early oral squamous cell carcinoma patients.

	SLN biopsy		END		Watchful waiting	
	n	survival	n	survival	n	survival
Overall survival						
3-year OS						
D'Cruz et al. [26]			245	80.0%*	255	67.5%*
Schilling et al. [64]	415	88%				
5-year OS						
Moya-Plana et al. [65]	179	76.4%^	50	78.7%^		
Patel et al. [66]			2720	74.7%*	3279	64.9%*
Disease specific survival						
3-year DSS						
Schilling et al. [64]	415	94%				
5-year DSS						
Patel et al. [66]			2720	84.1%*	3279	76.3%*

SLN: sentinel lymph node; END: elective neck dissection; n: number of patients; OS: overall survival; DSS: disease specific survival; * significant difference; ^non-significant difference.

Cochrane review, Stacey et al. [61] found that decision aids have a variable effect on actual choices but they reduce the choice of elective surgery.

Clinical decision support systems, which link patient data with an electronic knowledge base in order to improve decision-making, should be developed in order to individualize the treatment of the cN0 neck in early OSCC patients based on all relevant data of the patient and outcome parameters of diagnostics and treatment of the treating center. However, the development process for patient decision aids is complex [62].

Comparison between elective neck dissection and other strategies

During the past 25 years selective END of levels I-III has been the standard approach for the cN0 neck in OSCC. Alternative approaches have emerged and have been compared with this procedure. However, comparison is very complex and the above review is to give an overview of the dilemmas. A recent systematic review and meta-analysis of prospective studies on END versus observation in squamous cell carcinoma of cN0 OSCC patients showed a lower specific death rate related to regional recurrences in the END group [63]. A large single center randomized clinical trial found an improved rate of overall survival for END as compared to observation [26]. Overall and disease specific survival data from large series of SLN biopsy, END and watchful waiting management in early oral squamous cell carcinoma patients are summarized in Table 2.

Based on the literature up to date, the main strategies are selective END and SLN biopsy. Head to head comparison in a randomized clinical trial has not been performed and based on the available literature, the current debate remains unresolved, in many national guidelines END and SLN biopsy based strategies are both options in the management of early stage OSCC. Even if a randomized trial would be performed it would be the question whether it would provide definitive and universally applicable results given the multiple factors that have been reviewed and discussed above.

Conclusion

In summary, the results of studies on treatment of the cN0 neck cannot be translated to other settings due to significant differences in relevant variables such as population, culture, diagnostic work-up, follow-up, costs and others. Moreover, patients may have personal preferences and may weigh oncologic outcomes versus morbidity and quality of life differently. Given this complexity, we support the conclusion of Weiss et al. that "decision analysis is useful in complex clinical situations."

In fact much of this has already been acknowledged already in the 1990's. Weiss et al. [4] in 1994 stated that their analysis may be reconfigured to determine the optimal management based on a different set of underlying assumptions. Velanovich [5] suggested already in 1990 that each institute needs to review its own survival data and question patients about quality of life to determine how treatment options fits into decision analysis and also Davidson et al. [6] stated that their conclusion is very dependent on whether or not their assumptions and probabilities apply to the particular patient being managed at any given time. Unfortunately, the 20% risk of occult lymph node metastasis threshold to perform observation or END, suggested by Weiss et al. [4] in 1994, is still used today by many physicians and should be adapted to the present time.

Therefore, instead of trying to establish "the" best strategy for the cN0 neck or "the" optimal cut-off point for elective neck treatment, the approach to optimize the management of the cN0 neck would be to develop and implement models and decision support systems that can serve to optimize choices depending on individual, institutional, population and other relevant variables such as those discussed above.

Conflict of interest statement

None declared.

References

[1] Rodrigo JP, Grilli G, Shah JP, et al. Selective neck dissection in surgically treated head and neck squamous cell carcinoma patients with a clinically positive neck: Systematic review. Eur J Surg Oncol 2018;44:395–403.

[2] Lefebvre JL, Coche-Dequeant B, Buisset E, Mirabel X, Van JT, Prevost B. Management of early oral cavity cancer. Experience of Centre Oscar Lambret. Eur J Cancer B Oral Oncol 1994;30B:216–20.

[3] Ogura JH, Biller HF, Wette R. Elective neck dissection for pharyngeal and laryngeal cancers. An evaluation. Ann Otol Rhinol Laryngol 1971;80:646–50.

[4] Weiss MH, Harrison LB, Isaacs RS. Use of decision analysis in planning a management strategy for the stage N0 neck. Arch Otolaryngol Head Neck Surg 1994;120:699–702.

[5] Velanovich V. Choice of treatment for stage I floor-of-mouth cancer. A decision analysis. Arch Otolaryngol Head Neck Surg 1990;116:951–6.

[6] Davidson J, Biem J, Detsky A. The clinically negative neck in patients with early oral cavity carcinoma: a decision-analysis approach to management. J Otolaryngol 1995;24:323–9.

[7] Kaneko S, Yoshimura T, Ikemura K, et al. Primary neck management among patients with cancer of the oral cavity without clinical nodal metastases: A decision and sensitivity analysis. Head Neck 2002;24:582–90.

[8] Song T, Bi N, Gui L, Peng Z. Elective neck dissection or "watchful waiting": optimal management strategy for early stage N0 tongue carcinoma using decision analysis techniques. Chin Med J (Engl) 2008;121:1646–50.

[9] Okura M, Aikawa T, Sawai NY, Iida S, Kogo M. Decision analysis and treatment threshold in a management for the N0 neck of the oral cavity carcinoma. Oral Oncol 2009;45:908–11.

[10] Pitman KT. Rationale for elective neck dissection. Am J Otolaryngol 2000;21:31–7.

[11] de Bree R, Takes RP, Castelijns JA, et al. Advances in diagnostic modalities to detect occult lymph node metastases in head and neck squamous cell carcinoma. Head Neck 2015;37:1829–39.

[12] Liao LJ, Hsu WL, Wang CT, Lo WC, Lai MS. Analysis of sentinel node biopsy combined with other diagnostic tools in staging cN0 head and neck cancer: A diagnostic meta-analysis. Head Neck 2016;38:628–34.

[13] van den Brekel MW, Castelijns JA, Stel HV, Golding RP, Meyer CJ, Snow GB. Modern imaging techniques and ultrasound-guided aspiration cytology for the assessment of neck node metastases: a prospective comparative study. Eur Arch Otorhinolaryngol 1993;250:11–7.

[14] Zhang H, Seikaly H, Biron VL, Jeffery CC. Utility of PET-CT in detecting nodal metastasis in cN0 early stage oral cavity squamous cell carcinoma. Oral Oncol 2018;80:89–92.

[15] Sohn B, Koh YW, Kang WJ, Lee JH, Shin NY, Kim J. Is there an additive value of 18 F-FDG PET-CT to CT/MRI for detecting nodal metastasis in oropharyngeal squamous cell carcinoma patients with palpably negative neck? Acta Radiol 2016;57:1352–9.

[16] Borgemeester MC, van den Brekel MWM, van Tinteren H, et al. Ultrasound-guided aspiration cytology for the assessment of the clinically N0 neck: factors influencing its accuracy. Head Neck 2008;30:1505–13.

[17] Takes RP, Righi P, Meeuwis CA, et al. The value of ultrasound with ultrasound-guided fine-needle aspiration biopsy compared to computed tomography in the detection of regional metastases in the clinically negative neck. Int J Radiat Oncol Biol Phys 1998;40:1027–32.

[18] Alkureishi LW, Burak Z, Alvarez JA, et al. Joint practice guidelines for radionuclide lymphoscintigraphy for sentinel node localization in oral/oropharyngeal squamous cell carcinoma. Ann Surg Oncol 2009;16:3190–210.

[19] Liu M, Wang SJ, Yang X, Peng H. Diagnostic efficacy of sentinel lymph node biopsy in early oral squamous cell carcinoma: a meta-analysis of 66 studies. PLoS ONE 2017;12:e0170322.

[20] Yang Y, Zhou J, Wu H. Diagnostic value of sentinel lymph node biopsy for cT1/T2N0 oral squamous cell carcinoma: a meta-analysis. Eur Arch Otorhinolaryngol 2017;274:3843–52.

[21] Pentenero M, Gandolfo S, Carrozzo M. Importance of tumor thickness and depth of invasion in nodal involvement and prognosis of oral squamous cell carcinoma: a review of the literature. Head Neck 2005;27:1080–91.

[22] Huang SH, Hwang D, Lockwood G, Goldstein DP, O'Sullivan B. Predictive value of tumor thickness for cervical lymph-node involvement in squamous cell carcinoma of the oral cavity: a meta-analysis of reported studies. Cancer 2009;115:1489–97.

[23] Brockhoff 2nd HC, Kim RY, Braun TM, Skouteris C, Helman JI, Ward BB. Correlating the depth of invasion at specific anatomic locations with the risk for regional metastatic disease to lymph nodes in the neck for oral squamous cell carcinoma. Head Neck 2017;39:974–9.

[24] Liu KY, Durham JS, Wu J, Anderson DW, Prisman E, Poh CF. Nodal disease burden for early-stage oral cancer. JAMA Otolaryngol Head Neck Surg 2016;142:1111–9.

[25] Goerkem M, Braun J, Stoeckli SJ. Evaluation of clinical and histomorphological parameters as potential predictors of occult metastases in sentinel lymph nodes of early squamous cell carcinoma of the oral cavity. Ann Surg Oncol 2010;17:527–35.

[26] D'Cruz AK, Vaish R, Kapre N, et al. Elective versus therapeutic neck dissection in node-negative oral cancer. N Engl J Med 2015;373:521–9.

[27] Takes RP, Rinaldo A, Rodrigo JP, Devaney KO, Fagan JJ, Ferlito A. Can biomarkers play a role in the decision about treatment of the clinically negative neck in patients with head and neck cancer? Head Neck 2008;30:525–38.

[28] Roepman P, Kemmeren P, Wessels LF, Slootweg PJ, Holstege FC. Multiple robust signatures for detecting lymph node metastasis in head and neck cancer. Cancer Res 2006;66:2361–6.

[29] van Hooff SR, Leusink FK, Roepman P, et al. Validation of a gene expression signature for assessment of lymph node metastasis in oral squamous cell carcinoma. J Clin Oncol 2012;30:4104–10.

[30] Leusink FK, van Es RJ, de Bree R, et al. Novel diagnostic modalities for assessment of the clinically node-negative neck in oral squamous-cell carcinoma. Lancet Oncol 2012;13:e554–61.

[31] Nieuwenhuis EJ, Castelijns JA, Pijpers R, et al. Wait-and-see policy for the N0 neck in early-stage oral and oropharyngeal squamous cell carcinoma using ultrasonography-guided cytology: is there a role for identification of the sentinel node? Head Neck 2002;24:282–9.

[32] Yuen AP, Ho CM, Chow TL, et al. Prospective randomized study of selective neck dissection versus observation for N0 neck of early tongue carcinoma. Head Neck 2009;31:765–72.

[33] Flach GB, Tenhagen M, de Bree R, et al. Outcome of patients with early stage oral cancer managed by an observation strategy towards the N0 neck using ultrasound guided fine needle aspiration cytology: No survival difference as compared to elective neck dissection. Oral Oncol 2013;49:157–64.

[34] Rodrigo JP, Shah JP, Silver CE, et al. Management of the clinically negative neck in early-stage head and neck cancers after transoral resection. Head Neck 2011;33:1210–9.

[35] Remmler D, Byers R, Scheetz J. A study of shoulder disability resulting from radical and modified neck dissections. Head Neck Surg 1986;8:280–6.

[36] Bocca E. Functional neck dissection: An evaluation and review of 843 cases. Laryngoscope 1984;94:942–5.

[37] El Ghani F, van den Brekel MWM, de Goede CJT, et al. Shoulder function and patient well-being after various types of neck dissections. Clin Otolaryngol 2002;27:403–8.

[38] Erisen L, Basel B, Irdesei J, et al. Shoulder function after accessory nerve-sparing neck dissections. Head Neck 2004;26:967–71.

[39] Medina J. Supraomohyoid neck dissection: Rational, indications and surgical technique. Head Neck 1989;11:111–22.

[40] Gane EM, Michaleff ZA, Cottrell MA, McPhail SM, Hatton AL, Panizza BJ, et al. Prevalence, incidence, and risk factors for shoulder and neck dysfunction after neck dissection: A systematic review. Eur J Surg Oncol 2017;43:1199–218.

[41] Kraus DH, Rosenberg DB, Davidson BJ, et al. Supraspinal accessory lymph node metastasis in supraomohyoid neck dissection. Am J Surg 1996;172:646–9.

[42] Kou Y, Zhao T, Huang S, et al. Cervical level IIb metastases in squamous cell carcinoma of the oral cavity: a systematic review and meta-analysis. Onco Targets Ther 2017;10:4475–83.

[43] Giordano L, Sarandria D, Fabiano B, Del Carro U, Bussi M. Shoulder function after selective and superselective neck dissections: clinical and functional outcomes. Acta Otorhinolaryngol Ital 2012;32:376–9.

[44] Svenberg Lind C, Lundberg B, Hammarstedt Nordenvall L, Heiwe S, Persson JK, Hydman J. Quantification of trapezius muscle innervation during neck dissections: cervical plexus versus the spinal accessory nerve. Ann Otol Rhinol Laryngol 2015;124:881–5.

[45] Schiefke F, Akdemir M, Weber A, Akdemir D, Singer S, Frerich B. Function, postoperative morbidity, and quality of life after cervical sentinel node biopsy and after selective neck dissection. Head Neck 2009;31:503–12.

[46] Møller MN, Sørensen CH. Risk of marginal mandibular nerve injury in neck dissection. Eur Arch Otorhinolaryngol 2012;269:601–5.

[47] Raj R, Lotwala V, Anajwala P. Minimally invasive supraomohyoid neck dissection by total endoscopic technique for oral squamous carcinoma. Surg Endosc 2016;30:2315–20.

[48] Acevedo JR, Fero KE, Wilson B, et al. Cost-effectiveness analysis of elective neck dissection in patients with clinically node-negative oral cavity cancer. J Clin Oncol 2016;34:3886–91.

[49] Kosuda S, Kusano S, Kohno N, et al. Feasibility and cost-effectiveness of sentinel lymph node radiolocalization in stage N0 head and neck cancer. Arch Otolaryngol Head Neck Surg 2003;129:1105–9.

[50] O'Connor R, Pezier T, Schilling C, McGurk M. The relative cost of sentinel lymph node biopsy in early oral cancer. J Craniomaxillofac Surg 2013;41:721–7.

[51] Govers TM, Takes RP, Karakullukcu BM, et al. Management of the N0 neck in early stage oral squamous cell cancer: a modeling study of the cost-effectiveness. Oral Oncol 2013;49:771–7.

[52] van der Linden N, Flach GB, de Bree R, Uyl-de Groot CA. Cost-utility of sentinel lymph node biopsy in cT1-T2N0 oral cancer. Oral Oncol 2016;53:20–6.

[53] de Bree R, van der Waal I, Doornaert P, Werner JA, Castelijns JA, Leemans CR. Indications and extent of elective neck dissection in patients with early stage oral and oropharyngeal carcinoma: nationwide survey in The Netherlands. J Laryngol Otol 2009;123:889–98.

[54] Dünne AA, Folz BJ, Kuropkat C, Werner JA. Extent of surgical intervention in case of N0 neck in head and neck cancer patients: an analysis of data collection of 39 hospitals. Eur Arch Otorhinolaryngol 2004;261:295–303.

[55] Govers TM, de Kort TB, Merkx MA, et al. An international comparison of the management of the neck in early oral squamous cell carcinoma in the Netherlands, UK, and USA. J Craniomaxillofac Surg 2016;44:62–9.

[56] Melchers LJ, Schuuring E, van Dijk BA, et al. Tumour infiltration depth ≥4 mm is an indication for an elective neck dissection in pT1cN0 oral squamous cell carcinoma. Oral Oncol 2012;48:337–42.

[57] de Bree R, van den Brekel MWM. Elective neck dissection versus observation in the clinically node negative neck in early oral cancer: Do we have the answer yet? Oral Oncol 2015;51:963–5.

[58] D'Cruz AK, Dandekar MR. Elective versus therapeutic neck dissection in the clinically node negative neck in early oral cavity cancers: do we have the answer yet? Oral Oncol 2011;47:780–2.

[59] Chaturvedi P, Datta S, Arya S, Rangarajan V, et al. Prospective study of ultrasound-guided fine-needle aspiration cytology and sentinel node biopsy in the staging of clinically negative T1 and T2 oral cancer. Head Neck 2015;37:1504–8.

[60] Flach GB, Verdonck-de Leeuw IM, Witte BI, et al. Patients' perspective on the impact of sentinel node biopsy in oral cancer treatment. Oral Surg Oral Med Oral Pathol Oral Radiol 2016;122:279–86.

[61] Stacey D, Légaré F, Lewis K, et al. Decision aids for people facing health treatment or screening decisions. Cochrane Database Syst Rev 2017;4:CD001431.

[62] Coulter A, Stilwell D, Kryworuchko J, Mullen PD, Ng CJ, van der Weijden T. A systematic development process for patient decision aids. BMC Med Inform Decis Mak 2013;13(Suppl 2):S2.

[63] Ding Z, Xiao T, Huang J, et al. Elective neck dissection versus observation in squamous cell carcinoma of oral cavity with clinically n0 neck: a systematic review and meta-analysis of prospective studies. J Oral Maxillofac Surg 2018 August 22. [Epub ahead of print].

[64] Schilling C, Stoeckli SJ, Haerle SK, et al. Sentinel European Node Trial (SENT): 3-year results of sentinel node biopsy in oral cancer. Eur J Cancer. 2015;51:2777–84.

[65] Moya-Plana A, Aupérin A, Guerlain J, et al. Sentinel node biopsy in early oral squamous cell carcinomas: Long-term follow-up and nodal failure analysis. Oral Oncol 2018;82:187–94.

[66] Patel TD, Vázquez A, Marchiano E, et al. Efficacy of elective neck dissection in T1/T2N0M0 oral tongue squamous cell carcinoma: a population-based analysis. Otolaryngol Head Neck Surg 2016;155:588–97.