Elective neck dissection versus observation in the clinically node negative neck in early oral cancer: Do we have the answer yet?

de Bree, R.; van den Brekel, M.W.M.

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Editorial

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In principle, the indication of neck dissection in oral squamous cell carcinoma (OSCC) is a problem of risk-benefit evaluation between probability of neck metastases, the problem of complications associated with neck dissection and the prognostic influence of delayed diagnosis of metastasis during follow-up [1]. Although elective neck dissection (END) results in early treatment of occult lymph node metastases, the vast majority of these neck dissections harbors no metastases and was unnecessary. Moreover, these patients are subjected to morbidity such as shoulder morbidity, pain and sensibility disorders, which may have major impact on health related quality of life. Furthermore, neck dissection may remove a barrier to cancer spread in case of local recurrence or second primary tumor.

Unfortunately, there is no consensus on the elective treatment of the neck in early oral cancer patients with a clinically N0 (cN0) neck. Many retrospective studies on OSCC patients with cN0 neck were considered not helpful in resolving this problem. Therefore, Fasunla et al. [2] systematically reviewed the in 2010 available literature and performed a meta-analysis on the existing randomized controlled clinical trials which compared END with observation (and therapeutic neck dissection only when lymph node metastasis were detected) in early OSCC patients. Only four randomized clinical trials with a total of 283 patients were eligible for inclusion in this meta-analysis. Although the data used in that meta-analysis were from different parts of the world, between-study heterogeneity of the relative risk of disease specific death in the trials were tested and no statistically significant difference were found. This meta-analysis showed that END significantly reduced the risk of disease specific death: fixed-effects model RR = 0.57 (95% confidence interval (CI) 0.36–0.89; $p = 0.014$) and random-effects model RR = 0.59 (0.37–0.96; $p = 0.034$) [2].

D'Cruz and Dandekar from Tata Memorial Center (Mumbai, India) performed a critical appraisal of this meta-analysis which revealed 'some caveats that need careful consideration before the findings can be accepted' [3]. They pointed on the poor follow-up in one of the included studies that resulted in a large number of patients with advanced neck recurrences and low salvage rates. The relatively wide confidence intervals, due to the wide variation in the estimates of effect in the constituent studies, may hamper clinical significance and practice change. As the authors of the meta-analysis already discussed, the risk of heterogeneity is still present although a statistical test failed to demonstrate this. An important concern was the long time span in which the studies were conducted, in which various aspects of patient care may change. Finally, they emphasized the need for meticulous follow-up of patients on the observation arm [3]. The same group analyzed their series of 359 patients with early oral cancer, found no difference in disease specific survival between END and observation and elaborated the need for a large randomized controlled clinical trial (RCT) [4]. The Head and Neck Disease Management group of Tata Memorial Centre performed such a trial, enrolled 596 patients and reported very recently the results of the first 500 patients [5]. The conclusion was that among patients with early stage OSCC, END results in higher rates of overall and disease free survival than observation with therapeutic neck dissection in patients in whom lymph node metastases are detected during follow-up [5]. Now the question arises if this RCT really answers the question on how to manage the cN0 neck in early OSCC patients?

Key eligibility criteria in this RCT were lateralized T1 or T2 previously untreated OSCC amenable to undergo transoral excision. In the observation group, in 45% a neck metastasis became apparent, whereas in 30% in the END group neck metastases were diagnosed at histopathology [5]. It is well known that routine histopathological examination overlooks a considerable percentage of micrometastases [6]. As a consequence, histopathology underestimates the number of tumor-positive neck dissection specimens, which explains this difference. In the observation group the gold (reference) standard is the conversion rate of the neck during follow-up, which is the most reliable measure for the incidence of metastases.

In studies investigating outcome of patients with a cN0 neck a clear definition of 'clinically N0' is mandatory. In other words, which examinations were performed to come to this diagnosis? However, in this study, the cN0 was not clearly defined. To examine the role of ultrasound (US), the authors included even some patients with suspicious findings. Further, the US scoring criteria were not described. It is clear that the incidence of delayed metastases and neck recurrences will be higher if the neck was staged only by palpation compared to staging by advanced diagnostic techniques. When the nodal status was assessed by palpation of the neck in combination of CT or MRI imaging and if indicated FDG-PET or USgFNAC, the incidence of lymph node metastasis in OSCC patients during observation (watchful waiting) was 18% in a study of Melchers et al. [7]. Nieuwenhuis et al. [8] and Flach et al. [9] reported a neck conversion in cN0 patients assessed by USgFNAC of 21% and 28%. These figures are much lower than the 45% reported in the RCT, suggesting a less accurate diagnostic work-up and a different target group which may hamper

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generalizability of their results. In patients with a higher incidence of occult lymph node metastases the calculated risk of a poorer survival after observation of the neck as compared to END will be higher.

Fasunla et al. [2] discussed that the observed pooled effect in their meta-analysis between END and observation might have been largely influenced by older studies. The included trials took place over four decades. The observation that the oldest study in the meta-analysis have the highest incidence of occult lymph node metastases suggests the availability of more sophisticated investigational tools for early detection of lymph node metastasis with better staging of the neck in recent times [10]. They suggested that if similar studies from their meta-analysis were conducted later with better investigational tools available, the observed difference might have been absent. Not only availability, but also the use of diagnostic techniques and expertise of the involved physicians is important. The accuracy rates of USgFNAC for nonspecialist radiologists are significantly less than subspecialist radiologists [11]. Borgemeester et al. [12] found a variation in sensitivity from 9% to 53% between different radiologists who performed more than 20 USgFNAC examinations.

The group of Tata Memorial Centre had chosen overall survival as primary endpoint and disease free survival as secondary endpoint for their RCT. END resulted in an improved 3-yrears overall survival rate (80%; 95% CI 74–86) as compared with observation and therapeutic neck dissection (68%; 95% CI 61–74): hazard ratio of death 0.64 (95% CI 0.45–0.92; $p = 0.01$). Patients in the END group had a higher disease free survival than those in the observation group (79% vs 46%, $p < 0.001$) [5]. It is not surprising that END improves the regional control rate because development of lymph node metastases during observation of the neck should be taken into account as an inevitable consequence of the adopted strategy. Therefore, this disease free survival is a useful outcome measure of diagnostic work-up but not a reliable outcome measure in comparing END and observation of the neck. Ganly et al. [13] reported on a series on 216 cT1-T2N0 patients treated with or without END and found a 5-years disease specific, overall and disease free survival of 86%, 79% and 70%, respectively [13]. Disease specific survival is probably the most clinically meaningful endpoint for measuring an eventual benefit of END, but unfortunately is not reported in the RCT. As mentioned above, in the meta-analysis of Fasunla et al. [2], END significantly reduces the risk of disease specific deaths.

During follow-up all patients received physical examination and half of them also had ultrasonography. Again, scoring criteria were not defined and ultrasonography was not combined with fine needle aspiration cytology, which is capable to increase the accuracy of ultrasonography. Despite the fact that the protocol of this RCT mandated close and meticulous follow-up, less than 50% of the patients with a relapse in the neck were eventually salvaged and the 3-years overall survival of 68% in the observation group is disappointing. Moreover, during this 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% extranodal spread and 18% unresectable neck disease [5]. When occult lymph node metastasis can grow to such sizes during surveillance, the meticulousness of the follow-up can be questioned.

Borgemeester et al. [12] compared the overall survival in head and neck squamous cell carcinoma patients with a clinically N0 neck who underwent END or close observation using regular USgFNAC during follow-up. Survival in the OSCC patients of the close observation group was not different from the END group: 90% and 81% after 3 years and 79% and 75% after 5 years, respectively. Yuen et al. [14] performed a randomized clinical trial comparing END and close observation (USgFNAC every 3 months for the first 3 years) in 71 cT1-T2N0 OSCC patients and reported in the observation group a 100% salvage rate. The actuarial 5-year disease specific survival rates were 87% for observation and 89% for END patients [14]. Nieuwenhuis et al. [8] showed that by using USgFNAC pretreatment and during follow-up 79% of the delayed metastases could be salvaged resulting in a regional control rate of 88%. Flach et al. [9] analyzed the outcome of patients with early OSCC managed by an observation strategy towards the cN0 neck using USgFNAC and found no disease specific survival difference as compared to END: 5-years disease specific survival for patients with delayed metastases in the observation group 80% and for the patients with lymph node metastases in the END 81%. After curative intent treatment (99%) for delayed metastases 91% of the patients were regionally controlled. It was concluded that using this 'wait and scan' policy using strict surveillance with regular USgFNAC is justified in OSCC patients staged cN0 by USgFNAC. While unnecessary neck dissections could be avoided in the vast majority of patients, a small proportion of patients with delayed metastases needed probably more extensive surgery with adjuvant radiotherapy [9].

Many pretreatment imaging techniques to diminish the incidence of occult metastases haven been studied, and comparative studies have shown USgFNAC to be the most accurate. However, the sensitivity is only in the range of 50–65% and whether imaging should change the current management of the cN0 neck remains controversial. In early OSCC, sentinel node biopsy has a sensitivity of 93% for the detection of occult lymph node metastases [15]. This figure is probably even higher in the more experienced centers. Thus, sentinel node biopsy has a much higher sensitivity and can be used to better select candidates for neck dissection. Although the long-term follow-up results of the large European SENT study are not yet reported, several centers have already adopted sentinel node biopsy as an alternative to elective neck dissection. In the American NCCN guidelines as well as the guidelines of the Dutch Head and Neck Society, sentinel node biopsy is already mentioned as an alternative for elective neck dissection. However, this technique does require experience and is currently recommended only for centers with the necessary facilities and expertise. The group of Tata Memorial Centre recently reported their experience in 51 early OSCC patients and found a sensitivity of only 71%. In spite of this low percentage, they concluded that SNB is a reliable method to detect occult metastasis which has potential to replace END [16].

The Head and Neck Disease Management group of Tata Memorial Centre has to be commended for performing this important RCT [5]. Unfortunately, not all caveats of the meta-analysis as pointed out by authors of this RCT [3] have been solved yet. The confidence interval for hazard ratio of disease related death was still relatively wide. There seems to be a substantial difference in pretreatment work-up and follow-up between head and neck centers in the world. Although the patients included in the meta-analysis were accrued over a prolonged time period spanning four decades, the RCT took still more than 10 years to include enough patients. However, it is likely that clinical practice between 2004 and 2014 changed less than between 1966 and 2004. Within this period of 10 years they screened 1281 patients and included 596 patients, whereas in their retrospective study they included 359 cases in 5 years (1997–2001). It is not clear if all suitable patients were included and if some bias may be introduced. Since the main carcinogens to which patients in this RCT were exposed were chewed tobacco and areca nut, the distribution among subsites (e.g. buccal mucosa) and their clinical behavior may differ from other centers over the world. As shown and discussed previously [3] heterogeneity may be problem to implement study results worldwide, even from a successful RCT. However, this RCT clearly shows a prognostic benefit of elective neck treatment in the population in India, using the quite strict follow-up without routine USgFNAC. A few non-randomized studies from Europe have shown

no advantages of END when strict USgFNAC follow-up was employed. In these studies, the salvage rates were much higher and relapses were diagnosed earlier. So, if routine very strict follow-up using USgFNAC by a well trained ultrasonographer cannot be assured, END is the safest strategy. The next step in refinement of the choice to manage the cN0 neck with END or observation is to perform a RCT comparing END with close observation in OSCC patients with a cN0 neck based on sentinel node biopsy.

Conflict of interest statement

None declared.

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R. de Bree *

Department of Head and Neck Surgical Oncology, UMC Utrecht Cancer Center, University Medical Center Utrecht, Utrecht, P.O. Box 85500, 3508 GA Utrecht, The Netherlands

Department of Otolaryngology–Head and Neck Surgery, VU University Medical Center, Amsterdam, The Netherlands

* Tel.: +31 88 75 508 19.

E-mail address: r.debree@umcutrecht.nl

M.W.M. van den Brekel

Department of Head and Neck Oncology and Surgery, The Netherlands Cancer Institute, Antoni van Leeuwenhoek Hospital, Amsterdam, The Netherlands.

Amsterdam Center for Language and Communication, University of Amsterdam, Amsterdam, The Netherlands

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