

# Commentary on Elective versus therapeutic neck dissection in node-negative oral cancer

## BACKGROUND

Lymph node metastasis is the single most important prognostic factor in oral squamous cell carcinoma.<sup>[1]</sup> With the reported incidence of occult metastasis in early stage (T1, T2) oral cancer of 30%, there are opposing clinical practices. There are proponents for elective neck dissection (END) and others for watchful-wait, and to undertake therapeutic neck dissection (TND) for those who are found to have developed nodal metastasis during follow-up. Though there were four previous randomized trials and a meta-analysis, comparing these two clinical practices, being underpowered and due to methodological errors the issue remains unresolved.

In this practice-changing prospective randomized clinical trial comparing END and TND, D'Cruz *et al.*<sup>[2]</sup> has categorically demonstrated the superiority of END in patients with T1, T2, and N0 squamous cell carcinoma of oral cavity in terms of overall survival and disease-specific survival.

## TRIAL DESIGN

The study was designed to accrue 710 patients with clinical T1, T2, and N0 oral squamous cell carcinoma. The neck was deemed N0 by physical examination and ultrasound scan. In the END group, the neck was managed by selective neck dissection involving levels 1-3 and if the nodes prove to be positive by pathology, they were converted to modified radical neck dissection (MRND) covering levels 1-5. In the TND group, those patients who develop nodal relapse were managed by either MRND or radical neck dissection. The decision for adjuvant radiation was left to the discretion of the treating physicians. The post-treatment follow-up was randomized either into physical examination alone or physical examination and ultrasound scan. The study had a stringent follow-up regimen with 4 weeks for first 6 months, followed by 6 weeks for next 6 months, then every 8 weeks for next 12 months, and every 12 weeks thereafter. Between 2004 and 2014, 596 patients were enrolled. A planned interim analysis was carried out on the first 500 patients who have completed at least 9 months of follow-up (median follow-up 39 months). Based on the results of the analysis of the first 500 patients (245 in the END and 255 in the TND) demonstrating superiority of END, the

data safety monitoring committee stopped the accrual of patients in June 2014. The present article reports the result of this patient group.

## PRINCIPAL FINDINGS

1. END resulted in improvement in overall survival (80% vs. 67.5%;  $P = 0.01$ ) and disease-specific survival (69.5% vs. 45.9%;  $P < 0.001$ ).
2. There were 81 (33.3%) recurrences in the END and 146 (57.7%) in the TND group.
3. Adjuvant radiation after primary surgery was given in 118 (48.6%) patients in the END and 86 (34%) patients in the TND group. After salvage surgery, 25 (10.3%) patients in the END and 71 patients (28.1%) in the TND group received adjuvant radiation.
4. 25/81 (30%) recurrences in the END was in the neck nodes, while that of TND group was 108/146 (74%). The local recurrence was significantly higher in the END, 23 (28%) compared to 7 (4.8%) in the TND group.
5. 72/243 (29.6%) in the END and 114/253 (45.05%) in the TND group developed node failures. These were 52.8% N1, 47.2% N2b/c in the END and 31.5% N1, 9.6% N2a, 39.4% N2b/c, and 18.4% N3 in the TND group.
6. While extracapsular spread was observed only in 51.4% in END, 93.02% had extracapsular spread in the TND group. 20 (17.5%) neck recurrences in the TND group were deemed to be unresectable at the time of diagnosis.
7. *Post-hoc* sub-group analysis showed lack of benefit for END in patients with tumor depth of invasion measuring  $< 3$  mm ( $n = 71$ ).
8. Addition of ultrasound scan to physical examination did not improve early detection of neck failures (data not provided). 21 (18.4%) of the neck recurrences were detected with advanced N3 disease. Of which, 20 (17.5%) were considered unresectable.

## STRENGTHS OF THE STUDY

1. Well-powered and well-designed trial.
2. Single center trial ensuring consistency in imaging, pathology, surgery, and adjuvant radiation.

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3. Despite the fact that the study was carried out in India, where buccal mucosal cancer is the predominant sub-site, the design of the study ensured weightage to tongue and floor of mouth making the result of study applicable to a global patient population.
4. Large study population allowed sub-group analysis that helped to generate hypothesis for further studies.
5. Undertaking prospective randomized surgical trials are a daunting task. The authors to be congratulated for carrying out a clinically relevant and stringent surgical clinical trial.

### DRAWBACKS OF THE STUDY

1. As demonstrated by the present trial and several previous studies,<sup>[3]</sup> subjective nature of ultrasound scan offer questionable value in the evaluation of neck. In addition, the study also included patients with indeterminate and suspicious node by ultrasound scan in the trial. The latter patients should not have been considered as N0.
2. The high incidence of node relapse of 114/253 (45%) in the TND group as opposed to 72/243 (29.6%) in the END group cannot be readily explained. This may have been contributed by the lack of sensitivity of initial neck evaluation by ultrasound scan. As computed tomography scan is now routinely used for both primary and neck evaluation, use of this modality could have avoided this error. Higher proportion of patients in the END group receiving adjuvant radiation could have lowered the neck failure rate.
3. Despite rather stringent follow-up regimen, 21 subjects in the TND group were diagnosed at N3 and 20 of which were deemed inoperable. This further attests the limitation of physical examination for evaluation of neck after radiotherapy and poor sensitivity of ultrasound scan.
4. In the present trial, subjects who were found to have pathological positive node in the END group and those with clinical node relapse in the TND group underwent MRND or RND. As level V is rarely involved in oral cavity cancers and these patients would require adjuvant radiotherapy, a more conservative approach of selective neck dissection would have been equally effective.<sup>[4]</sup>
5. A higher percentage of patients in the END group receiving adjuvant radiotherapy on the basis of nodal disease may have skewed the oncological outcome in favor of the END group.
6. Despite the fact that 93% of the patients in the TND had extracapsular extension, these patients were denied chemo-radiotherapy as adjuvant treatment, which is now considered as a standard of care.<sup>[5]</sup>

### CLINICAL IMPLICATIONS

The result from this study has established END as a standard of care for the management of occult metastasis in patients with early stage oral squamous cell carcinoma. The sub-group analysis suggests that END will have beneficial effect only in those tumors with a depth of invasion over 3 mm. Though 3 mm depth is determined by histopathologic examination, one can consider any clinically palpable oral cavity tumors to have depth over 3 mm.

### FUTURE PERSPECTIVES

The management of neck has evolved over the years from radical neck dissection to MRND and the selective neck dissection in an attempt to preserve function without compromising oncological outcome. Dr. D'Cruz trial has clearly demonstrated the need for END to manage N0 neck. Though this trial demonstrated superior oncological outcome compared to watchful-wait policy, one should accept that this is over treatment in about 70% of the patients who do not have metastatic nodal disease. There are emerging data to suggest that sentinel node biopsy *in lieu* of END to manage N0 neck disease is equally effective.<sup>[6]</sup> However, it requires larger prospective trial demonstrating oncologic equivalence to END.

Currently depth of invasion is the only clinically useful marker that can predict risk of node metastasis. With the improved understanding from tumor biology, one may identify more precise molecular markers that could better delineate metastatic markers of primary tumors.<sup>[7]</sup>

### CONCLUSION

The results from this study have established END as a standard of care for T1, T2, and N0 oral squamous cell carcinoma.

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