# *Selected Summaries*

## Neck dissection in lymph node-negative oral cancer

D'Cruz AK, Vaish R, Kapre N, Dandekar M, Gupta S, Hawaldar R, Agarwal JP, Pantvaidya G, Chaukar D, Deshmukh A, Kane S, Arya S, Ghosh-Laskar S, Chaturvedi P, Pai P, Nair S, Nair D, Badwe R; Head and Neck Disease Management Group. (Head Neck Services, Department of Medical Oncology, Advanced Center for Treatment, Research and Education in Cancer, Clinical Research Secretariat, and the Departments of Radiation Oncology, Head Cytology, Radio-diagnosis, and Surgical Oncology, Tata Memorial Centre, Mumbai, Maharashtra, India.) Elective versus therapeutic neck dissection in node-negative oral cancer. *N Engl J Med* 2015;**373:**521–9.


### SUMMARY

The Head and Neck Disease Management Group at the Tata Memorial Centre, Mumbai, did a prospective, randomized trial to resolve the long-standing controversy on optimal treatment of lymph nodes in the clinically negative (N0) neck with early oral squamous cell carcinoma (OSCC). This single-institution trial was designed to answer two important issues. First, the survival difference between patients undergoing elective neck dissection (END) or a 'wait and watch' followed by therapeutic neck dissection (TND) in those with a relapse of the disease in the lymph nodes; and second, the role of ultrasound in the early detection of nodal metastasis during follow-up. Data analysis of the first 500 patients enrolled between 2004 and 2014 and completing a minimum of 9 months' follow-up has been reported.

Patients with lateralized cT1 or T2, cN0 OSCC involving the tongue, floor of mouth or buccal mucosa were stratified on the basis of findings of ultrasound of the neck and thereafter randomly assigned in the ratio of 1:1 to undergo either END or TND. In the END group, 105 of 243 patients had T1 stage and 138 of 243 patients had T2 stage disease, and the majority had a primary (207/243) in the tongue. In the TND group, 114/253 had T1, 139/253 had T2 stage disease and the tongue was the most common site (216/253).

In the END group, 174 patients underwent supra-omohyoid dissection (level I to III) and 60 underwent modified neck dissection (level I to V) depending on the operative findings or frozen section. Among these, 72 of 243 (29.6%) patients had node-positive disease, i.e. 38 had N1 and 34 had N2b/c stage. Both groups received adjuvant radiotherapy (RT) for primary tumour, 49 of 243 patients in END and 80 of 253 patients in TND; inferring that the TND group had more 'high-risk' features.

All the patients in the trial were followed up with a physical examination while the secondarily randomized patients had an ultrasound of the neck too. There were 81 recurrences in the END group and 146 in the TND group. In the END group, 25 of 81 had only lymph nodal recurrence, while 4 of 81 had lymph nodal and local/distant recurrence. In contrast, in the TND group, 108 of 146 patients had lymph nodal relapse, while 8 of 146 had lymph nodal and local/distant relapse. The data regarding previous RT in both groups with recurrence are not available.

In the TND arm, 114 of 253 (45%) patients had lymph nodal relapse and 94 of 114 (82.5%) were surgically salvageable. The clinical stage of patients ($n$=114) with lymph nodal relapse in the TND arm was N1 in 36, N2a in 11 N2b/c in 45 and N3 in 21 patients (it was not known in 1 patient). Eighty-six patients underwent neck dissection; of these, 80 had extracapsular extension (ECE), which is almost double than that in the END arm (37 of 72). At 3 years, the OS rates were 80% and 67.5% in the END and TND groups, respectively (p=0.01). The corresponding DFS rates were 69.5% and 45.9%, respectively (p<0.001). The END group had higher OS and DFS rates after adjustment for covariates, including stratification factors along with tumour grade, presence or absence of lymphovascular or perineural invasion, resection margin status, and depth of tumour invasion.

OS was significantly high in the 'true node-positive' patients, i.e. positive lymph nodes on pathology, in the END group as compared with patients with lymph nodal relapse in the TND group. This was because of the advanced lymph nodal stage and the high incidence of ECE in the latter group. Ultrasound of the neck was not a sensitive tool to identify early lymph nodal relapse. The authors concluded that END is an appropriate management strategy in patients with early OSCC.


### COMMENT

This timely study has the potential for changing current practice. Oral cancer is emerging as a major public health problem in Southeast Asian countries and is largely attributable to tobacco abuse.[1] The majority of patients present at an advanced stage due to lack of screening, awareness and access to healthcare. Unlike other solid tumours, distant spread is rare in oral cancers. Most tumours metastasize to cervical lymph nodes, which is the most important prognostic factor affecting survival in OSCC.

Currently, the management of lymph nodes in the neck is based on clinical assessment of the neck and characteristics of the primary tumour including sub-site, T-stage, grade and depth of invasion. The clinical assessment of the neck has a low accuracy.[2] Various imaging modalities including ultrasound and CT, MRI and PET scans as well as fine-needle aspiration cytology (FNAC) have been evaluated with variable outcomes.[3,4] Unlike in melanoma and breast cancer, sentinel lymph node biopsy has failed as a minimally invasive staging tool for assessment of the neck in oral cancers.[5]

The present management guidelines recommend neck dissection for patients with clinically positive lymph nodes, and END or a 'wait and watch' policy followed by TND in patients with relapse in the lymph nodes in the neck.[6]

These guidelines are based on evidence generated from previous studies with a limited number of patients. In addition, the majority of studies included entire head and neck SCC with a heterogeneous biological behaviour. A meta-analysis by Fasunla *et al.* in 2011 included four randomized controlled trials done between 1966 and 2004. They analysed data of 283 patients and concluded that END may be justified due to a statistically significant reduction in disease-specific death rates and lymph node recurrences in the neck. However, the study did not show any significant survival benefit of END over the policy of observation.[7]

Due to the prevailing policies and lack of clarity in the management of clinically negative neck in early stage oral cancers, many of these patients are offered a 'wait and watch' policy followed by TND in patients with a relapse. Two major drawbacks of this policy are the need for an intensive clinical follow-up and imaging expertise. In the absence of high-quality follow-up, these

patients can present with advanced neck disease not amenable for salvage, impacting OS.

This trial provides level IB evidence and has the potential to change practice globally and impact the survival of patients with oral cancer. The policy of END seems to be appropriate in the management of the neck in a subset of patients with cancers of the tongue, floor of mouth and buccal area, which constitute 75% of oral cancers. A 'wait and watch' policy can be reserved for selected patients with low-risk clinicopathological characteristics and sub-sites such as the palate, alveolus and lip, which have a low propensity for lymphatic spread.

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# Community-based management of neonatal infections: New field trials

African Neonatal Sepsis Trial (AFRINEST) group, Tshefu A, Lokangaka A, Ngaima S, Engmann C, Esamai F, Gisore P, Ayede AI, Falade AG, Adejuyigbe EA, Anyabolu CH, Wammanda RD, Ejembi CL, Ogala WN, Gram L, Cousens S. (Department of Community Health, Kinshasa School of Public Health, Kinshasa, DR Congo; Departments of Pediatrics and Maternal Child Health, Schools of Medicine and Public Health, University of North Carolina, Chapel Hill, NC, USA; Department of Child Health and Paediatrics, School of Medicine, Moi University, Eldoret, Kenya; Department of Paediatrics, College of Medicine, University of Ibadan, and University College Hospital, Ibadan, Nigeria; Department of Paediatrics and Child Health, Obafemi Awolowo University, Ile-Ife; Department of Paediatrics and Child Health, Obafemi Awolowo University, Ile-Ife; Department of Paediatrics and Department of Community Medicine, Ahmadu Bello University Teaching Hospital, Ahmadu Bello University, Zaria, Nigeria; Department of Infectious Disease Epidemiology, Faculty of Epidemiology and Population Health, London School of Hygiene and Tropical Medicine, London, United Kingdom.) Oral amoxicillin compared with injectable procaine benzylpenicillin plus gentamicin for treatment of neonates and young infants with fast breathing when referral is not possible: A randomised, open-label, equivalence trial. *Lancet* 2015;**385:**1758–66.

African Neonatal Sepsis Trial (AFRINEST) group, Tshefu A, Lokangaka A, Ngaima S, Engmann C, Esamai F, Gisore P, Ayede AI, Falade AG, Adejuyigbe EA, Anyabolu CH, Wammanda RD, Ejembi CL, Ogala WN, Gram L, Cousens S. (Department of Community Health, Kinshasa School of Public Health, Kinshasa, DR Congo; Departments of Pediatrics and Maternal Child Health, Schools of Medicine and Public Health, University of North Carolina, Chapel Hill, NC, USA; Department of Child Health and Paediatrics, School of Medicine; Moi University, Eldoret, Kenya; Department of Paediatrics, College of Medicine, University of Ibadan, and University College Hospital, Ibadan, Nigeria; Department of Paediatrics and Child Health, Obafemi Awolowo University, Ile-Ife; Department of Paediatrics, Ahmadu Bello University Teaching Hospital, Ahmadu Bello University, Zaria; Department of Community Medicine, Ahmadu Bello University Teaching Hospital, Ahmadu Bello University, Zaria, Nigeria; Department of Infectious Disease Epidemiology, Faculty of Epidemiology and Population Health, London School of Hygiene and Tropical Medicine, London, United Kingdom.) Simplified antibiotic regimens compared with injectable procaine benzylpenicillin plus gentamicin for treatment of neonates and young infants with clinical signs of possible serious bacterial infection when referral is not possible: A randomised, open-label, equivalence trial. *Lancet* 2015;**385:**1767–76.

## SUMMARY

These two field trials compared the efficacy of different antibiotic regimens to treat possible severe bacterial infection (PSBI) among neonates and young infants (0–59 days) in the community. They also tested the feasibility and safety of screening for and management of these infections by trained community health workers (CHWs) and nurses. These multisite, open-label, equivalence trials were conducted at five field sites in three countries—Democratic Republic of Congo, Kenya and Nigeria from April 2011 to June 2013. Trained CHWs recorded pregnancies and births in the area and, by home visiting, followed up 85 592 babies to identify those with signs of illness. After referring to hospital those with the signs of serious illness, the remaining 'ill' babies and several self-referrals were seen by the study nurses who either excluded those with no illness or referred to hospital the critically ill. Of the remaining, those with only fast breathing were eligible for inclusion in the first trial and those who had one or more signs of PSBI were eligible for the second trial.

After a further round of exclusion, referral or refusal, finally 2333 babies with only fast breathing were randomly assigned to receive either injectable procaine penicillin and gentamicin once a day or oral amoxicillin twice a day each for 7 days. Another 3564 babies with