Shifting Paradigm of the Management of Node-Negative Neck in Early Oral Cancers: Where do we Stand Today?

Richa Vaish[1,2]

[1] Department of Head and Neck Surgical Oncology, Tata Memorial Centre, Homi Bhabha National Institute, Mumbai, Maharashtra, India
[2] Homi Bhabha National Institute, Tata Memorial Centre, Homi Bhabha National Institute, Mumbai, Maharashtra, India

Address for correspondence Richa Vaish, MS, M Ch (Head Neck Oncology), Associate Professor and Surgeon, Department of Head and Neck Oncology Room no 1224 HBB, Tata Memorial Centre, Homi Bhabha National Institute, Dr E Borges Road, Parel, Mumbai 400012, India (e-mail: drmahajanricha@gmail.com).

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The long-standing debate of watchful waiting versus elective neck dissection (END) in clinically node-negative early oral cancers came to an end with the publication of a large randomized controlled trial (RCT) that showed absolute overall survival (OS) benefit of 12.5%[1,2] in favor of END. The findings of this trial were corroborated by another large trial which showed a significant improvement in the disease-free survival with 34% reduction in the risk of recurrence[3] with END. This benefit was present across the whole cohort including the small and thinner tumors as well.[3,4] There has been a deluge of meta-analyses since then which further reinforce the importance of END in this set of patients making it the standard of care.[5–7] In addition to the survival benefits reported by these trials, another important point that became apparent was that nearly 55 to 70% of these patients were not harboring any occult metastasis.[1,3] Neck dissection is mangled with the associated morbidity predominantly of shoulder dysfunction secondary to dissection in the proximity of spinal accessory nerve. Both these facts garnered interest to find an alternative which could either spare the neck dissection in these patients or limit the morbidity.

Attempts have been made to identify the patients who are truly node negative for occult metastasis. Various imaging modalities have been studied to identify metastatic nodes. While they seem to have good diagnostic accuracy in clinically manifest neck, the sensitivity is extremely low when it comes to clinically node-negative neck.[8] The meta-analysis comparing the conventional imaging modalities namely computed tomography (CT), magnetic resonance imaging, positron emission tomography (PET), and ultrasonography showed the sensitivity to be 52, 65, 66, and 66%, respectively, making these poor tools to screen the node-negative neck.[9] Recently, a published meta-analysis comprising of 18 studies showed that the pooled sensitivity of F-18 FDG PET or PET/CT for the detection of lymph node metastasis in clinically node-negative neck for patient-based analysis was merely 58%.[10] So, sparing the neck dissection based on imaging is flawed with the danger of missing the occult neck metastasis. These metastases, if undetected and not addressed at the time of index surgery, lead to neck recurrences of which nearly 50% succumb to disease,[1] a price too high to pay to spare the neck or limit the morbidity.

Efforts have also been directed to identify the novel molecular marker that could predict the occult metastasis in the neck but having low sensitivity no marker alone is foolproof. Various markers have been identified that show some association with occult metastasis but none can predict the probability with diagnostic accuracy high enough so as to enable sparing neck dissection in all true node-negative cases.[11,12] DNA microarray gene-expression profiling in 82 tumor training set identified 102 predictor genes to detect lymph node metastasis in oral and oropharyngeal tumors.[13] However, external validation of this multigene signature on a cohort spanning across all T categories (T1-4) showed the negative predictive value (NPV) of merely 72% which improved to 89% in T1-2N0 cohort,[14] which was still unacceptably low.

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For more than a decade, the role of sentinel lymph-node biopsy (SLNB) in this scenario has enthralled the researchers. An initial study showed that the SLNB performed in 106 patients who were clinically and found pathologically NO 100 of these patients were also pathologically node negative on neck dissection amounting to the NPV of 94% which improved to 96% with additional sections and immunohistochemistry.[15] Various meta-analyses reported high NPV of SLNB making it the ideal diagnostic tool in clinically node-negative early oral cancers.[16] However, the therapeutic value of SLNB was unreported. Sentinel European Node Trial (SENT) reported 3-year survival outcomes in a large multicentric trial with 415 patients which established SLNB as an oncologically safe procedure.[17] More than a quinquennium has elapsed since this publication, but SLNB failed to gain popularity and replace END on a wide scale.

The literature was still lacking an RCT comparing SLNB with the gold standard of END. Recent back-to-back publication of large RCTs comparing the outcomes of SLNB versus END has provided a fillip to the interest in SLNB.[18,19] French trial was a phase III equivalent trial which randomly assigned the node-negative early oral and oropharyngeal cancer patients to END and SLNB arms.[18] Primary endpoint of the trial was 2-year neck node recurrence-free survival (NNRFS), and the other endpoint was neck and shoulder morbidity. The trial analyzed 279 patients, 139 in neck dissection and 140 in the SLNB arm. Two-year NNRFS was 89.6% in the neck dissection and 90.7% in the SLNB arm, which established the equivalence of the procedure. The shoulder function outcome as assessed by using a self-reported questionnaire and arm abduction test showed a better function with SLNB as compared to END, apparent till the end of 6 months. The SLNB also decreased the median hospital stay by 1 day compared to END. Hot on the heels of this trial the Japanese trial was published which confirmed and reinforced the finding of the French trial.[19] This was a multicentric non-inferiority RCT comprising of oral cancers T1/T1N0 $\geq$4 mm having a 3-year OS as the primary endpoint and postoperative neck functionality as the secondary endpoint. Analysis was performed on 271 patients, 137 in END and 134 in the SLNB arm. The results showed that the 3-year OS in the SLNB arm was non-inferior to END, 87.9% (lower limit of one-sided 95% confidence interval [CI], 82.4) and 86.6% (lower limit 95% CI, 80.9), respectively. The authors also reported better shoulder function in the SLNB arm based on functionality test scores. Both these trials, however, were criticized due to their wide non-inferiority margins.[20] It is clear from these trials that SLNB limits the morbidity which albeit evens out at the end of 1 year. Also, both these trials have not reported cost-effectiveness of the procedure till date.

So, at the end of all these publications where do we stand today? We know from the literature that it is important to address the neck in clinically node-negative early oral cancers. END is time tested and a widely followed standard of surgery. There is evidence that SLNB is an oncologically safe procedure which also limits the morbidity. Both END and SLNB are recommended as treatment options in node-negative neck in early oral cancers in standard guidelines.[21] Despite this, SLNB has its own limitations which would hinder its applicability globally. The infrastructure, logistics, and cost-effectiveness are the biggest constraints of this procedure. It is a two-staged procedure, both the French and Japanese groups performed frozen section to avert the second procedure but even with a more extensive protocol of 2-mm-thick blocks of rapid frozen specimen (FS) in the Japanese trial, the sensitivity of the frozen section at the best improved to only 68.5%.[18,19] Serial step sectioning and immunohistochemistry improve the diagnostic accuracy of SLNB which is time and resource consuming. Early tongue cancers are being treated across various fraternities, even at non-oncologic centers. SLNB needs an infrastructure consisting of dedicated nuclear medicine and pathology departments, lacking at many of these centers. With such protocols, it will be a huge challenge to implement this procedure in resource constraint settings and high-volume centers. Therefore, the need of the hour is a surgical procedure which is easy to carry out, cost-effective, has fast turnover, and limits the morbidity of neck dissection or a cost-effective diagnostic test/molecular marker with high accuracy that can spare the neck dissection without compromising the oncologic outcomes.

Conflict of Interest
None declared.

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