More Evidence From a US Nationwide Cohort Study for the Survival Benefit of END in Early Mouth Cancer: Time for a Change in Guidelines

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Mouth cancer, or oral squamous cell carcinoma (OSCC), is the 11th most common malignancy. It can be the most socially disabling cancer, affecting appearance, speech, and eating, yet clinical research to improve treatment is very poorly funded.

Therefore, the research by Wushou et al1 on early mouth cancer, reported elsewhere in this issue, in combination with reports from 2 rare prospective randomised research studies—one from Tata Memorial Centre in Mumbai in 20152 and a nationwide study from Britain with a meta-analysis in 2019 (the SEND trial)3—merit an opportunity to modify guidelines regarding the treatment of early mouth cancer.

The article by Wushou et al1 concentrates on clinical stage T1N0M0 (cT1N0M0) OSCC. They identified and analyzed data on 5,752 patients from the NCI SEER database, comparing overall survival (OS) and disease-specific survival (DSS) in patients who underwent tumor resection with or without elective neck dissection (END). They found only one previous prospective randomised trial (SEND) that specifically quantified the benefit of END in cT1N0 OSCC.3 The paper on this trial showed that END was beneficial for small tumors (pt1 stage) or tumor diameter ≤10 mm, with corresponding disease-free survival (DFS) hazard ratios (HRs) of 0.49 and 0.63, respectively.3 In fact, the Tata Memorial trial also reported an OS benefit for END with T1N0 tumors, with HRs of approximately 0.75.2 Therefore, the British paper concluded that together, it and the Tata Memorial study provided evidence of the benefit for END regardless of tumor size.3

Zhan et al4 in 2018 reported on patients with cT1N0 OSCC who were treated with surgical resection and END. Their data was abstracted from the National Cancer Database. They identified 2,623 (15%) patients with occult neck disease and studied the relationship between tumor differentiation and the presence of occult neck disease. They concluded that END should be recommended for all moderately (17.4% occult neck disease) and poorly differentiated (28.5% occult neck disease) cT1N0 OSCC, regardless of the depth of invasion. They suggested that clinicians could consider not performing END in well-differentiated tumors, for which they found only 5.9% of patients had occult neck disease.4 Yet in the SEND trial, the DFS HR for this subgroup of patients with well-differentiated OSCC was 0.54, suggesting benefit for END even in those with pt1 stage tumors that are well-differentiated.3

This discrepancy between pathologic findings of only 5.9% of occult disease but clinical benefit for END suggested by the SEND trial could be explained by the presence of micrometastases and isolated tumor cells that are not identified on routine pathologic examination.5 The detection of these, which are reported to be present in 8.8% of pathologically node-negative necks, would upstage disease in these patients. It suggests that standard pathologic examination may underestimate the percentage of patients with...

See page 385 for related article.
Elective Neck Dissection in Early Mouth Cancer

occult neck disease that, if left untreated, will manifest later and require therapeutic neck dissection. And it lends further support to the concept of offering END in early mouth cancer, as the surgery clears this previously undetected “super” occult neck disease.3

Wushou et al1 “aimed to gather sufficient evidence to make strong well-supported recommendations to either support or refute the findings of [this] single published study,” specifically evaluating whether performing END at the same time as local tumor resection confers benefit for OS and DSS in patients with cT1N0M0 OSCC. They also studied certain prognostic factors, such as age, sex, marital status, tumor differentiation, and tumor site.

Of incidental interest was their finding that being married had a significantly protective effect, associated with improved OS and DSS. They did not report whether unmarried women fared better, worse, or the same as unmarried men. This finding regarding the association of marital status and increased survival was also reported in another study in 2017 using SEER data from 11,022 patients.6 The investigators found that married patients were more likely to be diagnosed at an earlier stage, and postulated that family support was valuable.6

Wushou et al1 reported some limitations with their study. In the British meta-analysis, the findings of the Mumbai2 and British studies3 complemented each other, generating even more valuable information. As Wushou et al point out, their study now complements the Mumbai and British studies. Similarly, the findings from these 2 studies can address and resolve Wushou et al’s limitations.

First, they did not report depth of invasion.1 The SEND paper conducted analyses according to the 8th edition of the AJCC Cancer Staging Manual.7 The per-protocol OS HRs were 0.76 for T1, 0.64 for T2, and 0.73 for T3, respectively, with corresponding DFS HRs of 0.51, 0.75, and 0.75, confirming that even patients with favourable staging still benefit from END.3

Second, Wushou et al1 are concerned that research data bias may potentially exist due to surgeon bias and patient choice. The British paper recognised this and gained ethical approval at an early stage to include eligible patients who were not approached or declined randomization but agreed to follow up. They were analysed separately to the randomised group as a form of real-world cohort. Their results mirrored the results of the main trial and are reported in the paper.3

Finally, Wushou et al1 were concerned that they did not evaluate the long-term complications of neck dissection or lymph node metastasis after surgery. The British paper followed patients for 5 years, reporting on survival, recurrences, and new tumors, as well as complications, adverse effects, quality-of-life outcomes, and resource use, and therefore captured all these events.3 In that study, the investigators reported that more patients experienced an adverse effect of any grade in the END group, but there was no significant difference in serious events. Although neck sensory and motor nerve effects and swallowing problems were more common in patients who underwent END, the procedure had minimal impact on most quality-of-life components.3 END increased the length of hospital stay from a median of 2 days for tumor resection only to 6 days for END. Up to 2 years postoperatively the resource use was the same for END.

Wushou et al1 state that their “findings showed that END significantly improved both OS and DSS in these patients, which is consistent with the findings of 2 large-scale prospective randomized studies and a meta-analysis of all prospective randomized studies. Our retrospective analysis using the SEER database to analyze 5,752 patients with only cT1N0M0 OSCC complements those studies, and together with the meta-analysis provides evidence supporting a review of head and neck cancer guidelines.”

The President of The Union for International Cancer Control submitted a comment on the paper by Hutchison et al8 to the British Journal of Cancer, stating that “despite the highest form of evidence by way of 2 large randomised trials in favour of an [END]… We stand the risk of subjecting our patients to poorer disease control by observing the neck in spite of having irrefutable evidence in favour of END.”8

In light of these 2 comments,10 I reviewed the current NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines) for Head and Neck Cancers (Version 1.2021).9 In the Principles of Surgery [SURG-A, available at NCCN.org] section, there are 11 references dating from 1978 to 2016, including 7 references on sentinel lymph node (SLN) biopsy. The guidelines state that “SLN biopsy is an alternative to [END] for identifying an occult cervical metastasis in patients with early (T1 or T2) oral cavity carcinoma in centers where expertise for this procedure is available.”

A Cochrane review from 201810 states, “The evidence is insufficient to draw conclusions about [END] of clinically negative neck nodes.” This 2018 review precedes the 2019 SEND trial,2 which resolves a second issue raised in the Cochrane review: “Reporting of adverse events in all trials was poor and it was not possible to compare the quality of life… ”10

Although this Cochrane systematic review10 was the most recent reference cited in the “Cancer of the Oral Cavity” section of the NCCN Guidelines, there are now 3 papers, 2 of which were published after 2018, showing OS, DFS, and DSS benefit for END in patients with cT1N0 and cT2N0 OSCC: a prospective randomised study (PRS) from a renowned Indian tertiary centre; a European nationwide PRS with 5-year follow-up, real-world cohort, and meta-analysis; and now big data from a renowned database of American patients.1
In the face of this new, powerful evidence from diverse sources across 3 continents, all ethics committees would probably regard it as unethical to conduct another PRS on this topic, so it is unlikely that any further, new, high-level research evidence will be produced. Therefore, isn’t it time to modify the guidelines and provide unequivocal support for the survival benefit of END in early mouth cancer?

There is now quantifiable information on the benefits for survival with END and also the complications and resource implications of selecting either END or local resection only. This knowledge enables surgeons to inform patients and their families about the benefits and drawbacks of opting for or against END, and thereby allows them to participate in treatment decision-making. Now that the age of the paternalistic doctor is over, the guidelines should also recommend that doctors offering END to all N0 patients should do so explaining all this quantifiable evidence about relative benefits for their disease stage and the percentage risk of complications. Armed with good evidence, we can help our patients make the best choice for themselves and their family.

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