How Does Depth of Invasion Influence the Decision to Do a Neck Dissection in Clinically N0 Oral Cavity Cancer?

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BACKGROUND

Oral cavity squamous cell carcinoma (OCSCC) has an especially high propensity for occult cervical metastasis, with early reports estimating this risk to be more than 40%. Although early-stage (cT1-2) OCSCC can often be cured with surgery, metastasis to cervical lymph nodes portends a poor prognosis. Nodal metastasis has a profound effect on mortality; the 5-year survival rate is reduced by approximately 50% in these patients. Traditional therapy for early-stage OCSCC involves surgical resection or irradiation of the primary tumor, with treatment of the clinically positive neck. However, until recently, there have been no large-scale, prospective studies evaluating optimal management of the clinically negative (cN0) neck. This is particularly concerning given the increased rate of regional recurrence in a previously cN0 neck and the relatively poorer outcomes among patients undergoing salvage therapy. As such, multiple prior studies have attempted to improve outcomes in the management of early-stage OCSCC by identifying predictors of cervical nodal metastases, or by determining the impact of elective treatment of the cN0 neck—usually through elective neck dissection (END).

Substantial histopathologic evidence has identified depth of invasion (DOI) of the primary tumor as a possible predictor of regional metastasis in OCSCC. However, DOI is broadly defined as the extent of cancer growth beneath an epithelial surface, resulting in a wide range of measurement techniques and threshold values, although more sophisticated histopathologic imaging and analytical tools will likely eliminate these discrepancies in the future. Furthermore, many studies in the literature combine all subsites (oral tongue, floor of mouth, buccal mucosa, lips, alveolar ridge, retromolar trigone) of the oral cavity when determining treatment outcomes without stratification. This is problematic because the clinical behavior manifest in each of these subsites differs based on lymphatic drainage patterns. Finally, accurate determination of DOI is limited to measurements performed on permanent pathologic analysis (as opposed to frozen sections), which precludes decision making for management of the cN0 neck until after primary tumor resection. In light of this growing evidence, is it appropriate to utilize depth of primary tumor invasion as a predictor of regional disease for early-stage OCSCC?

LITERATURE REVIEW

The MEDLINE database was comprehensively searched using the key words “tumor thickness,” “depth of invasion,” and “oral squamous cell carcinoma” between time of database inception and June 1, 2015. A vast number of reports have been published on this topic, and efforts have been made to include those articles of historic importance as well as landmark studies.

The earliest report of DOI being a risk factor for occult cervical metastases in OCSCC was published by Spiro in 1986. In a retrospective review of 99 patients with cT1-3N0 OCSCC (oral tongue and floor of mouth), the authors found that 26 of 57 patients (46%) with thicker tumors (>2-mm DOI) developed locoregional recurrence as compared to only five of 42 patients (2%) with thin tumors (<2-mm DOI). Although this study demonstrated a statistically significant survival benefit among patients with thin tumors, the technique by which DOI was determined on histologic analysis was not described.

A retrospective histopathologic review of 72 cases of cT1-2N0 OCSCC of the oral tongue further affirmed the prognostic value of DOI, which was measured as the greatest distance from “the surface of the tumor of the deepest point of invasion.” Among patients with thin tumors (<3-mm DOI), one of 12 (8%) had or developed occult nodal disease, compared to 30 of 60 (50%) patients with thicker tumors (>3-mm DOI). On analysis of all tumor characteristics, including tumor stage, histologic grade, lymphovascular and perineural invasion, and...
tumor shape, DOI was the only statistically significant predictor of occult cervical metastases, local recurrence, and survival.

Kligerman et al. reported the first prospective, randomized study involving the relationship between DOI and nodal metastases. Sixty-seven patients with cT1-2N0 OCSCC of the oral tongue and floor of mouth were randomized to receive primary resection with or without END. One of 14 (7%) patients with thin tumors (≤ 4-mm DOI) had or developed nodal metastases, as compared to six of 20 (30%) patients with thicker tumors (> 4-mm DOI). Though the study sample size is small, the findings reinforce what has been suggested from retrospective studies.

More recently, a detailed literature review by Pentenero et al. reinforced the link between DOI and cervical metastases in OCSCC. Specifically, the authors reviewed 55 articles encompassing nearly 6,000 patients. Despite this impressive number of patients, there was ultimately no consensus cutoff above which DOI should be considered a reliable prognosticator for END—and the majority of studies focused on oral tongue primaries. Furthermore, DOI and tumor thickness were used interchangeably in various studies, and different studies employed different techniques to report these measurements. Of note, however, the median and mode DOI of these studies were both 4 mm (range, 1.5 –10 mm). Consequently, DOI of 4 mm or more is the most common threshold used for performing END for a cN0 neck.

In a landmark study, D’Cruz et al. sought to definitively answer the question of whether END conferred a survival benefit in early-stage, lateral OCSCC through a prospective, randomized controlled study. A total of 496 patients with cT1-2N0 OCSCC (oral tongue, buccal mucosa, floor of mouth) were randomized to receive primary tumor resection with or without END. In the therapeutic neck dissection group, a salvage neck dissection was performed when nodal relapse became evident. At a median follow-up of 39 months, the overall survival and disease-free survival rates for the END group were 80% and 69.5%, respectively, as compared to 67.5% and 45.9% in the therapeutic neck dissection group, respectively. Interestingly, on post hoc analysis, there was no survival benefit in END for patients whose primary tumors had < 3-mm DOI, although the sample size for this analysis was small (71 patients). However, the only significant predictor of node positivity in patients who underwent END was DOI, wherein patients with ≤ 3-mm and > 3-mm DOI had 5.6% and 16.9% occult cervical metastases, respectively.

**BEST PRACTICE**

Although the subsites of interest, study design, and techniques for measuring DOI vary significantly, all reported literature supports a relationship between DOI and occult cervical metastases, especially in oral tongue cancer. This, taken in conjunction with results of the only large-scale, prospective, randomized controlled study on this topic, has caused a paradigm shift toward advocating for END for thicker tumors when this information is available. Thus, patients with cT1-2 N0 oral tongue squamous cell carcinomas with known > 3-mm DOI should be counseled on the possible survival benefit of END with primary tumor resection. There currently is no evidence to support END in patients with primary tumors having ≤ 3-mm DOI.

**LEVEL OF EVIDENCE**

Recommendations for using DOI in guiding treatment of the N0 neck in OCSCC are based on a large-scale, prospective, randomized controlled trial (level 1 evidence); a prospective cohort study (level 2 evidence); a systematic review of cohort studies (level 2 evidence); and retrospective reviews (level 3 evidence).

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