What Additional Treatment Is Indicated for Oral Cavity Cancer With Isolated Perineural Invasion?

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BACKGROUND

Oral cavity squamous cell carcinoma (OCSCC) is primarily treated with surgical excision, which allows a comprehensive histopathologic assessment of the cancer. Microscopic findings of high-risk features influence patient prognosis as well as additional treatment recommendations, including neck dissection, radiation therapy, or chemotheraphy. Perineural invasion (PNI) is recognized as an unfavorable pathologic finding. Additional treatment is widely recommended based on the identification of PNI in OCSCC.

The purpose of this review is to evaluate the oncologic evidence supporting treatment recommendations for patients with early-stage OCSCC, with isolated PNI and no additional risk factors.

LITERATURE REVIEW

Perineural invasion is a microscopic finding of neoplastic spread along neuronal structures that can result in metastatic spread beyond the confines of the local cancer. Perineural invasion has emerged as a key pathologic feature, but the absence of a consistent definition may contribute to varying reports of the incidence and prognostic value. The definition of PNI ranges from tumor cells abutting the perineurium to cancer cells present within every layer of the peripheral nerve sheath. Liebig et al. proposed one of the more widely accepted descriptions: perineural invasion is defined by the presence of tumors cells in any of the three layers of the nerve sheath or surrounding 33% of the circumference of the nerve.1

Historically, PNI has been identified as a pathologic finding associated with a poor prognosis, despite the absence of randomized prospective trials directly comparing treatment options for patients with OCSCC and isolated PNI. The high-risk nature of PNI was confirmed by Tai et al., who retrospectively reviewed pathologic findings of 190 patients with early-stage oral tongue squamous cell carcinoma. In this study, PNI was defined as the presence of the tumor infiltrating in “any layer of the nerve sheath,” and predicted a worse 5-year disease-specific survival compared to patients presenting without PNI (76% vs. 92%, P < .003).2 In addition, PNI, similar to tumor thickness, was found to independently predict regional lymph node metastasis on multivariate analysis (55% vs. 21%; P = 0.017). The association between PNI and depth of tumor invasion was confirmed with the presence of PNI in 10.2% of tumors between 2 mm to 5 mm in depth, and 69% of primary tumors > 10 mm. Importantly, performing elective neck dissection(s) in patients with PNI was found to significantly reduce the rate of neck recurrence from 85.7% to 16.2% (P = 0.001). The validity of this observation was limited by a small sample size. Collectively, these findings confirm the negative prognostic value of PNI and suggest that elective neck dissection for patients with early stage OCSCC with PNI might reduce the risk of locoregional recurrence.

In additional to the risk of regional spread, PNI at the site of the primary cancer also is postulated to reflect an infiltrative pattern of local tumor spread and serves as a potential path for tumor cell migration along neuronal tissue. However, whether PNI represents an independent risk factor for local recurrence is controversial. In Tai et al.’s multivariate analysis of clinicopathologic features associated with local recurrence, only tumor thickness above 5 mm was predictive of local recurrence.2 This finding contrasts with a retrospective review of 88 patients with OCSCC by Chinn et al., who reported worse locoregional control in patients with PNI(+) cancers at 3-years follow-up compared to their PNI(−) counterparts (52% vs. 82%, P = 0.005).3 Furthermore, Chin et al.’s analysis assessed the benefit of radiation therapy in PNI(+) patients, which found the adjuvant treatment extends the disease-free interval (1.7 years vs. 6.5 years, P = 0.012). However, this study did not characterize the pathologic...
criteria for PNI but rather defined the extent of PNI based on the number of foci of nerve invasion. Of note, their study population was limited to only 20 patients with PNI(+) disease and included various tumor (T)-stages (1–4) of OCSCC. Although Chinn et al. suggests an oncologic benefit of adjuvant radiation therapy to reduce the risk of recurrence, the small sample size and heterogeneity of T-stages limit the strength of their conclusion.

The role of adjuvant radiation therapy for early stage OCSCC with PNI was further investigated by Chatzistefanou et al., who performed a retrospective review of 78 patients that included two matched groups of 39 patients with and without PNI. This study adopted pathologic criteria for PNI that was congruent with those of Liebig et al., including tumor cells in any layer of the nerve sheath and/or tumor involving more than a third of a nerve’s circumference. Their analysis revealed that, despite PNI(+) OCSCC having a higher rate of regional lymph node spread and regional recurrence warranting a neck dissection, adjuvant radiation therapy did not significantly reduce the incidence of local recurrence ($P = 0.763$, odds ratio [OR] = 3.387) or regional recurrence ($P = 0.319$, OR 4.741).4

Bur et al., in a systematic review of 13 studies, provided additional evidence for the limited value of adjuvant radiation therapy based on the identification of isolated PNI. Specifically, they noted that “preponderance of evidence” shows limited benefit of adjuvant radiation therapy and does not endorse a universal recommendation of adjuvant radiation therapy to improve locoregional control and/or survival in patients with isolated PNI. Importantly, this study also contributed to what might constitute a future consensus definition of PNI, noting that studies specifically investigating large nerve PNI ($\geq 1$ mm in diameter) reported a significantly worse local control and overall survival that may warrant adjuvant therapy.5 Future studies investigating PNI would benefit from characterizing the definition based on the size of the nerve, as well as patterns of tumor spread similar to Liebeg et al., which will offer consistent histologic details to clarify the benefit of adjuvant radiation in case-specific conditions.

**BEST PRACTICE**

Perineural invasion has been validated an important pathologic diagnosis in OCSCC that should be carefully examined because it significantly contributes to prognosis and oncologic management. Perineural invasion independently predicts occult cervical lymph node metastasis as well as neck recurrence. Based on the available data, an elective neck dissection is recommended in patients with PNI. However, the use of adjuvant radiotherapy for OCSCC with isolated PNI remains controversial. There is no conclusive evidence that radiation therapy improves local control in the absence of other adverse pathologic features. Therefore, the use of adjuvant radiation therapy should not be universally recommended for patients with PNI and no additional adverse histologic findings.

**LEVEL OF EVIDENCE**

Liebig and Bur: level 2a, systematic review of retrospective cohort studies. Tai, Chinn, and Chatzistefanou: level 2b, individual retrospective cohort study.

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