Margin Analysis
Squamous Cell Carcinoma of the Oral Cavity

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KEYWORDS

• Surgical margin • Oral squamous cell carcinoma • Margin shrinkage • Frozen sections

KEY POINTS

- There is a relationship between locoregional control and margin status. A minimum of 5 mm of tumor-free tissue is considered a clear margin.
- The utility of frozen sections in oral squamous cell carcinoma is controversial; however, frozen sections may give the surgeon an additional opportunity to prevent an ultimately positive margin.
- Specimen-driven margins appear to be more predictive of actual margin status than defect-driven margins.
- There is a role for adjuvant chemo-radiotherapy in patients with close or positive margin status.

Oral squamous cell carcinoma (OSCC) is the most common oral malignancy, accounting for more than 90% of oral cancers. In the United States, OSCC represents nearly 4% of all annually diagnosed malignancies, and nearly 32,000 new cases of OSCC are anticipated in 2016, with more than 6000 cancer-related deaths.[1] A primary management principle for most oral cavity cancers is complete surgical excision, and a "negative margin" on final pathology. This article primarily focuses on defining terms, including negative margin, close margin, and positive margin, and, furthermore, delineates the current role of frozen section analysis and adjuvant therapy in treating OSCC with respect to surgical margin status.

Initial assessment of OSCC begins with a thorough clinical evaluation. Of paramount importance is a complete evaluation of all anatomic structures in the oral cavity by both visual examination and palpation. The examination may be aided by the use of pan-endoscopy under anesthesia if the tumor is located in an area that is painful or difficult to evaluate. In addition to a scrupulous evaluation of the oral cavity, a careful examination of the cervical lymph nodes is a vital aspect of the initial assessment of OSCC. Manual palpation, computed tomography (CT) scan and PET/CT scan are routinely used to assess both regional and distant metastases. A fat-suppressed, contrast-enhanced neck MRI is useful in select cases, as it may allow the clinician to view the neck in planes not available by CT. After a comprehensive workup is completed and the patient is staged, the decision to proceed with surgical resection is usually determined by a multidisciplinary group of treating specialists. The prognosis of OSCC is influenced by many factors, including tumor size and stage, depth of invasion, tumor grade, lymphovascular and perineural invasion, extranodal extension, and patient age and distant metastases.[2–5] Although these factors are predetermined and cannot be influenced by the surgeon, the surgeon has the greatest capacity to influence the surgical margin, which is an important independent prognosticator.[6–11]

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Clear surgical margins are an important prognosticator for local control and disease-specific survival. A recent meta-analysis investigated the relationship between surgical margins and local recurrence in OSCC. A 21% absolute risk reduction in local recurrence was associated with clear surgical margins.[11] The importance of a clear surgical margin and local control was further emphasized in a study by Kurita and colleagues,[7] who found that the 5-year local control rate was 91.0% for a clear margin, 80.4% for a close margin, and just 43.8% for a positive margin.

In the contemporary literature, Looser and colleagues[12] were among the first to opine that a clear surgical margin required a defined distance past the invasive tumor, and suggested a distance of 5 mm. Since then, multiple studies have attempted to elucidate exactly what constitutes a "clear" margin. The most common consensus distance for a clear margin in OSCC is a minimum of 5 mm or more of healthy tissue around the tumor[8–10]; however, some investigators have suggested that 3 mm of surrounding healthy tissue suffices as a clear margin.[13,14] Yamada and colleagues[10] performed a systematic evaluation of the impact of the width of the free margin on surgical outcomes, and found that a tumor with a free margin of 4 mm was associated with an increased risk of local recurrence, whereas a free margin of 5 mm was not associated with a significant risk of local recurrence. This appears to confirm that 5 mm of healthy tissue around the tumor is indeed the minimum acceptable amount for a clear margin.

There is consensus among the Royal college of Pathologists (RCP), the American College of Pathologists (ACP), and the National Comprehensive Cancer Network (NCCN) that to be considered a "negative" margin, the minimal acceptable amount of disease-free tissue is 5 mm. The definition of a "positive" margin is slightly variable, as the ACP defines a positive margin as invasive carcinoma less than 1 mm from the surgical margin, whereas both the RCP and the NCCN define a positive margin as invasive carcinoma or carcinoma-in-situ/high-grade dysplasia present at margins (microscopic cut-through of tumor).

According to the NCCN:

Clear margin: The distance from the invasive tumor front that is *5 mm or more* from the resected margin

Close margin: The distance from the invasive tumor front to the resected margin that is less than 5 mm

Positive margin: Carcinoma-in-situ or invasive carcinoma at the margin of resection

Although the consensus classification of a negative margin is invasive tumor 5 mm or more from the surgical margin, recent evidence suggests that small tumors may not require 5-mm margins, and large tumors may require greater than 5-mm margins to be considered truly negative. Heiduschka and colleagues[15] investigated whether small OSCCs require the same margin clearance as large tumors. They evaluated the association between the ratio of the closest margin to tumor thickness, and correlated their findings with local control and survival. They found that the ratio of margin to tumor thickness was an independent predictor for local recurrence and disease-specific death, and that the minimum safe margin could be calculated by multiplying the tumor thickness by a factor of 0.3 (**Fig. 1**).

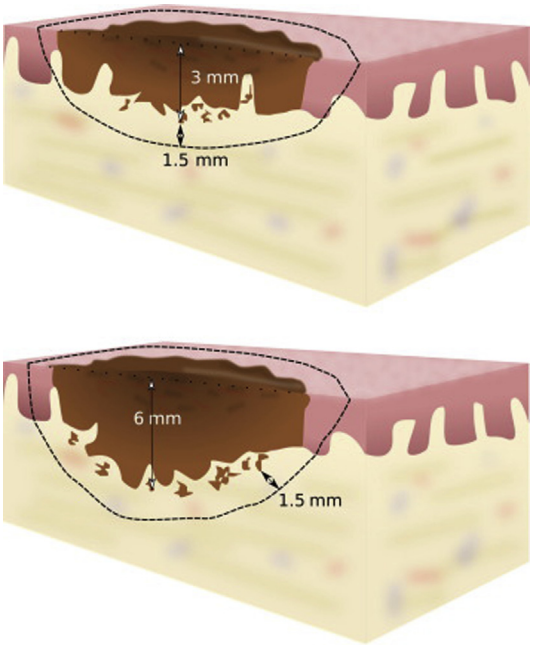

Fig. 1. Two schematized cross-sections of OSCC tumors; tumor thickness was measured as the distance from the level of the mucosa (*dotted line*) to the deepest extent of the tumor. The closest margin in this assumption is between the tumor and the resection (*dashed line*). In the first example, the margin-to–tumor thickness ratio (MTR) is 1.5 mm/3.0 mm = 0.5; in the second example the MTR is 1.5 mm/6.0 mm = 0.25. Hence, a safe margin for a tumor with a thickness of 4 mm requires 1.2 mm, a safe margin for a tumor with 8-mm thickness would be 2.4 mm and a tumor with a thickness of 15 mm would require the traditional margin of 5 mm. (*From* Heiduschka G, Virk SA, Palme CE, et al. Margin to tumor thickness ratio - A predictor of local recurrence and survival in oral squamous cell carcinoma. Oral Oncol 2016;55:49–54; with permission.)