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Molecular Biology and Clinical Behavior of Oral Cancer

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Our understanding of the molecular biology of oral squamous cell carcinoma (SCC) has progressed significantly over the past decade. The profound increase in basic science knowledge, however, has not affected our ability as clinicians to control oral SCC or provided us with tools to improve patient outcome. The challenges we face as oral and maxillofacial surgeons providing comprehensive surgical management for patients with oral cancer have remained the same: difficulty in predicting the capricious clinical behavior of oral cancer, recurrence at the primary site after resection, cervical and distant metastasis, and the development of second primary oral cancers. The causes and the solutions of these clinical challenges have a molecular basis. As molecular technologies advance, genetic and proteomic approaches are likely to be integrated into clinical practice. Molecular approaches are clearly going to be used to predict clinical behavior, determine prognosis, guide surgical treatment, and assist with tumor surveillance. In this article, I first review the traditional histopathologic features that have been used to treat patients with oral cancer. I then present some of the more recent molecular studies and technologies that we, as surgeons, might be using in the future to tip the balance in our patients' favor.

Traditional histopathologic features used to manage oral cancer

Histopathologic evaluation of margins

In discussing the impact of histologic margins on outcome, one of the primary difficulties is the lack of a clear definition among clinicians, pathologists, and investigators regarding what is meant by "clear" and "close" margins as well as the distinction between mucosal and deep margins [1–5]. Although surgeons typically try to resect oral cancer with a 1-cm margin of clinically normal tissue, pathologic evaluation of the specimen almost always demonstrates significantly less normal tissue surrounding the cancer. This reduced margin can partially be explained by the tissue shrinkage that occurs with specimen processing. A study in dogs demonstrated that 30% to 50% tissue shrinkage (from the clinical to histologic margin) occurs with specimen processing [6]. Another issue that can compound the interpretation of margins and studies evaluating margins in oral cancer is the site of the primary cancer. Woolgar and Triantafyllou [5] have demonstrated that the oral cancer subsite significantly influences the status of the margins. Using the definition of a 1-mm margin as an involved margin, these authors showed that the percentage of involved margins was highest in maxillary alveolar (45%), retromolar (38%), buccal mucosa (33%), mandibular alveolus (17%), and tongue (11%) SCC [5]. Not surprisingly, the incidence of involved margins increased with the tumor T stage in this study [5]. Even when histologic margins are clear, recurrences occur and are most likely secondary to retained histologically normal but genetically

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altered mucosa [7]. As molecular technology advances in terms of efficiency and sensitivity, it is anticipated that molecular margin analysis should significantly improve surgeons' ability to obtain histologically and genetically clear margins.

Tumor grading

Although Broders' tumor grading system [8] of well, moderately, and poorly differentiated carcinomas is commonly used in pathology reports, the value of tumor grading in the management of oral SCC remains equivocal. Tumor grade has been investigated to determine whether higher grade correlates with an increased cervical metastasis rate. Byers and colleagues [9] looked at oral tongue SCCs and demonstrated a significant association between tumor grade and metastasis. It is important to note in this report, however, that the clinically negative nodes in the patients with T1 and T2 lesions were not analyzed. A more recent study demonstrated no association between tumor grade and subclinical nodal metastasis [10]. Tumor grade is currently not used in clinical practice to predict metastasis or to guide treatment of oral SCC.

Tumor size

Tumor size (T in the tumor node metastasis [TNM] staging system) [11] has not been particularly effective in predicting cervical metastasis. Multiple studies have demonstrated that even T1 tongue SCCs are associated with a significant rate (greater than 20%) of cervical metastasis (Table 1). It is generally agreed that if the risk of cervical metastasis is greater than 20%, treatment of the neck is indicated. Weiss and coworkers [12] used a computer model and decision analysis to determine the optimal strategy for the treatment of the N0 neck as a function of the probability of occult cervical metastasis. The data analyzed included studies with large numbers of patients and contained a minimum 2-year follow-up, with results analyzed in terms of outcome as a function of stage of neck disease. A sensitivity analysis was performed to determine the optimal threshold for treatment of the neck. The authors concluded that for patients with head and neck SCC and stage N0 neck status, treatment of the neck is indicated if the probability of occult cervical metastasis is greater than 20%. Based on this prediction model [12] and the available studies (see Table 1), surgical treatment of the neck is often indicated for patients with T1N0 oral SCC lesions. A possible exception would be in lesions demonstrating only superficial invasion (ie, less than 2 mm of invasion). If this decision is based on an incisional biopsy, however, sampling error must be considered.

Table 1
Studies on occult metastases in T1 tongue squamous cell carcinomas: occult neck metastases (%)

Author	Date	Site	T1
Spiro and Strong	1971–1974	Tongue	29.4
Lee and Litton	1972	Tongue	24
Whitehurst and Droulias	1977	Tongue	24
Johnson et al	1980	Tongue	36
Ho et al	1992	Tongue	46
Yuen et al	1999	Tongue	21

Tumor thickness

Tumor thickness has been proposed to provide more predictive information regarding metastasis than tumor size. Similar to Breslow's work [13] showing that malignant melanoma thickness is a primary predictive variable, work in the area of oral SCC has also demonstrated the importance of tumor thickness in predicting cervical metastasis. In oral SCC, the critical thickness has not been determined and studies have varied considerably regarding the thickness that suggests the cervical metastasis rate is high. In 1986, Mohit-Tabatabai and colleagues [14] and Spiro and coworkers [15] looked at the predictive value of tumor thickness with SSC of the floor of the mouth. Mohit-Tabatabai and colleagues [14] retrospectively reviewed 84 cases of patients with early floor of the mouth SCC and found that when patients had a tumor thickness less than 1.5 mm, the incidence of cervical metastasis was 1.8%; however, a tumor thickness greater than 1.5 mm carried with it a cervical metastasis rate of 48%. Spiro and coworkers [15] retrospectively evaluated 105 patients with tongue or floor of the mouth SCC and found that a tumor thickness of 2 mm or less carried a metastasis rate of 7.5% and a tumor thickness greater than 2 mm carried a metastasis rate of 38%. Byers and colleagues [9] evaluated 91 patients with tongue SCC and attempted to correlate lymph node metastasis with multiple preoperative and intraoperative factors, including thickness of the specimen; depth of muscle invasion; frozen margin status; perineural, vascular, or lymphatic invasion; histologic differentiation; and DNA ploidy. In this study,