Margin Analysis—Has Free Tissue Transfer Improved Oncologic Outcomes for Oral Squamous Cell Carcinoma?

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KEYWORDS

• Microvascular tissue transfer • Free flaps • Surgical margins • Oncologic outcomes
• Oral squamous cell carcinoma

KEY POINTS

- Free tissue transfer is a reliable, safe method of reconstruction of defects of the head and neck.
- Negative surgical margins improve locoregional tumor control.
- Despite trends for improved oncologic outcomes with free tissue transfer, there are no conclusive data within the published literature to validate this statement.

A former tenet of head and neck surgery was that the ablative procedure should never be dictated by a surgeon's reconstructive skills. Taken a step further, some units divided the ablative and reconstructive teams to avoid compromising a resection in an effort to match a given reconstructive plan. When a reconstructive armamentarium is limited to local and regional flaps, tissue volume and component options are limited. Simple human nature dictates being more conservative with the margins that are sought to be achieved. Free tissue transfer offers myriad options in terms of volume and character of tissue that may be used to reconstruct virtually any head and neck defect. Without a doubt, most surgeons admit taking wider margins when a decision has been made to proceed with a free tissue reconstruction.

Surgical margin status is frequently reported to be a strong predictor of outcome and this remains, at least to some degree, partly under the control of the surgeon as a technical exercise.[1,2] When attempting to examine whether the use of free tissue transfer has a relationship with oncologic outcome investigators have approached this question from this angle: Freed from reconstructive constraints to take any surgical margin desired, will oncologic outcomes improve? That said, when reviewing the potential impact of free tissue transfer on oncologic outcomes, the following elements should be considered.

First, regarding margins, does free tissue transfer result in wider margins? This seems not always to be the case. Ellis and colleagues[3] examined the records of 250 patients treated for oral cavity cancer that were not able to show that surgeons achieved wider margins when free flaps were used. By contrast, Hanosono and colleagues[4] found their rate of positive margins dropped from

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18% to 7% with the introduction of free tissue transfer to their unit. It is hard to imagine that surgeons are not more liberal with margins when reliable free tissue transfer options are at their disposal but it is also likely true that margin status is a reflection of tumor biology and, in this regard, something beyond the control of the surgeon.

Second, it should be considered that given the overall reliability of free tissue transfer, with success rates routinely in excess of 90%, it is possible that these patients will more reliably receive on-time adjuvant therapy and thereby enjoy a survival benefit. It is also possible that the functional gains achieved with free tissue transfer lead to better health and nutrition of patients that may also have an impact on survival. This is a complex issue.

How then would this question ideally be studied? Because of the indisputable benefits of free tissue transfer on reconstructive grounds, it is unethical to design a study where patients are randomized to an inferior reconstructive option. As such, most efforts in this regard rely on historical data, making robust comparisons challenging. This introduces significant potential for bias. If modern era outcomes were compared with those of the past, any changes seen would be the aggregate of improved patient selection, medical care, and adjuvant care in addition to frank changes in disease patterns, such as the rise in prevalence of human papillomavirus–related disease. Surrogate lines of inquiry could instead focus on factors believed associated with better oncologic outcomes, such as the frequency of on-time delivery of adjuvant chemoradiotherapy.

Consider an indirect comparison. Marchetti and colleagues[5] compared a retrospective series of 42 consecutively treated oral cavity cancers to 3 historical series from the pre–free flap era spanning the late 1950s to the early 1980s. The investigators' series include T2 through T4 tumors all treated with resection and microvascular reconstruction. They offer few operative data from this patient population other than oral cavity subsite and TNM staging. Unfortunately, the investigators did not include margin status from their resections. As discussed previously, such a comparison is weak at best with significant potential for bias and errors in the comparison. With that in mind, the investigators were not able to demonstrate a difference in survival for patients in their study compared with the historical samples.

Direct comparisons reduce some of the potential for bias because the patient populations are potentially more similar. The investigators (discussed later) conducted single-institution reviews of their patient populations and used a variety of methods to attempt to glean useful information from the differences in treatment therein.

Rogers and colleagues[6] conducted a retrospective review of a consecutive series of 489 oral cavity cancer patients treated over a 10-year period; 65% of their patients received a free flap as part of their treatment. On a univariate analysis, free flap surgery was associated with a worse overall (72% vs 51%) and disease-specific (88% vs 70%) 5-year survival. Importantly there was no effort to match patients by factors known to affect outcome, so it is likely this is a reflection of higher-stage disease. In support of this, free flap surgery was not found an independent predictor of disease-specific survival when analyzed as part of a multivariable Cox regression analysis (hazard ratio 0.9). In further support of this assertion, the same pattern was seen for radiotherapy in this study in that it was associated with worse survival on univariate analysis but not when analyzed as part of a multivariable Cox regression analysis (hazard ratio 0.8).

Hsieh and colleagues[7] sought to be more selective when studying this question and focused on patients with late-stage disease. Specifically, this group analyzed the impact of free tissue transfer in a cohort of patients from a single Taiwanese institution treated between 2002 and 2008 with stage IV oral squamous cell carcinoma. No patient had evidence of distant disease. In their sample, 93 patients underwent free flap reconstruction and 149 patients did not due to limited defects, poor-quality recipient vessels, and/or significant medical comorbidities. The medical exclusions in the non–free flap group accounted for only 3% of the patients (n = 4/149). All patients were followed for at least 18 months or until death. When comparing the 2 groups, they were similar in most features except that the free flap group presented with larger tumors, more buccal lesions, fewer tongue cancers, and more T4 tumors (66% vs 50%) than the non–free flap group. When analyzing outcomes between the 2 groups, the investigators found a nonsignificant trend to a lower incidence of positive margins of 17.2% versus 12.1% (P = .213). Further comparisons did not find any significant differences in recurrence rates, local recurrence rates, 5-year overall survival, and 5 year disease-specific survival. Although the investigators highlight that the free flap group had similar survival despite more advanced T stage, it is hard to draw a definitive conclusion about oncologically superior outcomes with free flaps in this study.

Hanasono and colleagues[4] completed a 25-year retrospective review of all patients with T3 and T4 disease surgically resected at the MD Anderson Cancer Center. At this center, microsurgical techniques were incorporated after 1989. This allowed

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