Gene Expression Analysis As a Tool in Early-Stage Oral Cancer Management

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Elective neck dissection for clinically stage N0 (cN0) disease has been called the gold standard in the management of early-stage oral squamous cell cancer (OSCC), despite advances in imaging technologies and the recent application of sentinel lymph node mapping.¹ Approximately 30% of patients with cN0 disease have nodal metastasis found by pathology (pN+),¹⁻⁵ with poor prognosis, particularly if there is extracapsular spread.⁶ To avoid the substantial risk of delayed detection and treatment,^{7,8} elective neck dissection has been recommended for cN0 patients with a tumor invasion depth of 4 mm or greater.⁹ Neck dissection provides nearly definitive information about nodal metastasis. If no positive nodes are found, there is little risk of regional recurrence.⁵⁻¹⁰ Elective neck dissection alone can often represent sufficient treatment for early-stage disease, while guiding the use of adjuvant radiation and chemotherapy when indicated. Nevertheless, with approximately 70% of cN0 cases also pN0, elective neck dissection raises concern over unnecessary surgery and its associated morbidity.¹¹ Thus, some clinicians instead recommend watchful waiting, hoping to detect and treat any nodal metastasis quickly,² whereas others argue that the potential therapeutic benefit of neck dissection outweighs the risk of morbidity.¹ Consequently, interest in solving this clinical treatment dilemma has prompted continued investigation into novel ways to improve the management of the cN0 neck in early-stage OSCC.

In the article that accompanies this editorial, van Hooff et al¹² report major advances toward a primary-tumor RNA expression signature to help in this choice. With a laboratory-made microarray, this group had previously identified genes whose expression levels in primary oral-cavity tumors were related to nodal metastasis.^{13,14} They now have moved their analysis platform to a commercial microarray in a Clinical Laboratory Improvement Amendments/International Organization for Standardization–approved laboratory, finding a gene-expression signature-score cutoff in a “platform transition” cohort that provided 92% negative predictive value in cT1-T2N0 cases (ie, 92% of cases with negative expression signatures were actually metastasis free, based on pathologic evaluation of the neck dissection). They then used that signature cutoff to classify a “validation” cohort of 222 specimens from eight institutions, finding 89% negative predictive value and 86% assay sensitivity for detecting pN+ cases. Major challenges, however, remain in incorporating these promising technical results into clinical practice.

A major reason for Van Hooff et al’s successful extension of earlier findings to the more clinically relevant setting of their study is the large number of diagnostic genes—696 genes, with a total of 732 microarray probe sequences—whose primary-tumor expression levels were used quantitatively. The risk of nodal metastasis for each patient was gauged by how closely each of its 732 expression values matched the corresponding average expression value over the 54 pN+ patients in the “platform transition” cohort. This type of signature avoids the risk of relying on a small set of genes or on yes/no categorization of expression. Using quantitative expression of a large number of genes is expected to provide more reliability from study to study,¹⁴ an expectation supported by the results of Van Hooff et al.

This technical success, however, means that we now must face the difficulties that remain in translating microarray analysis into clinical practice. Even if future prospective studies support the present estimates of assay performance, and even if the practical difficulties of disseminating this technology widely can be overcome, there are significant clinical issues with regard to whether or how patients and physicians should use this information in the way that these authors propose.

Table 1. Hypothetical Over- and Undertreatment With Different Management Strategies For cN0 OSCC

cN0 Management	No. of Surgical Procedures	Per 100 cN0 Patients	
		pN0 Undergoing Neck Dissection	pN+ Without Neck Dissection
Watchful waiting	One	0	30
Elective neck dissection	One	70	0
Sentinel mapping (IHC) ^{17*}	Two (if N+)	0	3
Sentinel mapping (PCR) ^{18†}	One	5	4
Microarray ^{12‡}	Two	41	4

NOTE. Based on 30% of cN0 as pN+.

Abbreviations: cN0, clinical stage N0; IHC, immunohistochemistry; OSCC, oral squamous cell cancer; N+, node positive; NPV, negative predictive value; PCR, polymerase chain reaction; pN+, nodal metastasis found by pathology.

*Based on 96% NPV for step-sectioning and IHC, and assuming no false-positive pathology reports.

†Based on 86% sensitivity and 93.3% specificity for PCR compared with consensus pathology.

‡Based on Figure 3B; only one surgery would be required if microarray technology can be adapted to biopsy specimens.

One issue is the change in timing of the course of care as a result of waiting for microarray results, which are not available for several days at best after a tumor sample is obtained. One approach would be to excise the tumor, wait for microarray results, then perform neck dissection on patients whose microarray results predict pN+, resulting in two surgeries in close succession.

Alternatively, microarray results could potentially be obtained from the initial diagnostic tumor biopsy, and thus be available to guide the choice of neck dissection at the time of primary tumor excision. In this scheme, the wait for microarray results would not add substantially to the usual delay between initial diagnosis and definitive surgery. It remains to be determined, however, whether standard biopsy specimens could be analyzed as reliably as the whole frozen tumor specimens used in the present study. In addition to technical issues of sample size and preservation, the intratumor heterogeneity that is increasingly recognized as characteristic of solid epithelial tumors,^{15,16} including head and neck tumors,^{16a} means that any one biopsy specimen might not be representative of the entire tumor.

A second issue is the low specificity of the microarray-based classification, which erroneously labels nearly 60% of pN0 patients as being at risk of nodal metastasis and thus recommended for neck dissection. These patients would still be overtreated, as they would be if all patients underwent neck dissection, but with the added psychological and practical disadvantages of two surgical procedures. Third, 86% sensitivity means that the 14% of true pN+ patients who are misclassified would now face the risks of a delayed diagnosis during watchful waiting. Fourth, the 30% of patients correctly classified as pN0, while avoiding surgery, would still face the psychological uncertainty of watchful waiting. Consequently, the types of tradeoffs would be changed under the approach these authors propose, but much uncertainty would remain.

Other clinical approaches to cN0 oral cancer may provide similar or better results. Sentinel lymph-node biopsy (SLB) with immunohistochemistry (IHC) had a negative predictive value for OSCC nodal metastasis of 96% in a recent multicenter prospective trial.¹⁷ Like the proposed microarray approach, SLB with IHC also requires separate management of the primary and neck with two surgical procedures, as a result of the wait for final pathology. This problem has been addressed directly by Ferris et al,¹⁸ who proposed adding rapid polymerase chain reaction (PCR) analysis of tumor-specific RNA expression, in sentinel nodes, to inform intraoperative decisions about the need for neck dissection. The sensitivity and specificity of their PCR assay would provide a negative predictive value of 94% if 30% of cN0 cases are pN+.¹⁸ Table 1 shows estimates of over- and undertreatment arising from clinical management strategies based on these evolving technologies.

Also, the risks of neck dissection used to justify interest in these approaches may be less than feared for cN0 patients. Radical neck dissection, used therapeutically for advanced disease, has well-known morbidity, often with permanent functional impairment of the shoulder and neck.¹¹ In patients with cN0 OSCC, however, neck dissection is now typically a selective neck dissection (SND), limited to nodes most likely to be involved in spread.^{19,20} SND can minimize morbidity,²¹ and a type of SND often performed for oral-cavity primary tumors (removing nodes at levels I to III¹⁹) provided the best quality of life of all neck dissections.²² Meticulous attention to technique and better perioperative care and postoperative physical therapy might reduce this risk even further.^{23,24}

Ultimately, the choice of whether to perform a neck dissection in early-stage OSCC depends on the balance of risks and benefits judged by a patient with a physician. Not all patients will make the same choices regarding the risk of morbidity from neck dissection and risk of late detection of nodal metastasis. Thus, prospective studies of this or of any similar use of microarray results to guide clinical decisions must not be limited to evaluating the technical reliability of the classification scheme. Studies must also evaluate how the entire treatment approach based on microarray results affects patient outcome. The measures of outcome must incorporate detailed analysis of morbidity and changes in psychological status over time,²⁰ not just cancer recurrence and death, and the microarray-guided approach should be compared against a comparable clinical approach like SLB or upfront SND. Such studies will not be easy to design or carry out, but only such studies will provide the information needed to decide whether and how to incorporate microarray results into the clinical care of individual patients with early-stage oral cancer.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

The author(s) indicated no potential conflicts of interest.

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