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When will RNA-based tests similar to Oncotype DX be used for oral cancer?

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Abstract

Methods for detection, diagnosis and predicting treatment outcomes for oral squamous cell carcinoma (OSCC) have not changed in decades. Information from studies about molecular changes that occur with these tumors are not useful in the clinic. This is in contrast to breast cancer where global gene expression analysis in the form of the Oncotype DX and Mammaprint tests are used routinely to determine ideal treatment for a large subset of breast tumors. While the first large scale studies of gene expression in both cancer types were done over a dozen years ago, research on OSCC has not led to gene expression profiles that are useful in the clinic. Global gene expression data for well over a thousand breast tumors linked to clinical outcomes has been available online for nearly ten years. This accelerated the development and validation of multiple RNA classifiers used to predict breast cancer treatment outcomes. Molecular characterization of oral and head and neck cancer research has been handicapped primarily due to low sample numbers. The recent release from The Cancer Genome Atlas of global gene expression analyses of over 500 head and neck tumors, including 308 oral tumor samples, obtained by standardized methods, along with linked clinical outcome data, should change this. It makes the vision of including gene expression analysis in OSCC treatment planning an obvious and attainable goal that could occur in the next five years.

Key words: Treatment outcome; Oral squamous cell carcinoma; Gene expression classifier

Core tip: Methods for characterizing oral squamous

cell carcinoma have not changed in decades. This is in contrast to breast cancer where global gene expression analysis is often used to determine ideal treatment. Studies focusing on molecular changes in oral cancer have suffered from lack of uniformity and small size. The recent release from The Cancer Genome Atlas of global gene expression analyses of over 500 head and neck tumors, including 308 oral tumors, should bring to the clinic in the next few years gene and gene expression analysis, and improved outcomes.

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INTRODUCTION

Detection and diagnosis of oral cancer is done today largely the same way it was done 30 years ago. White light is used to visually scan the oral cavity for unexplained lesions, followed by cervical lymph node visual examination and palpation. Suspicious oral lesions are then surgically biopsied and, after sectioning and staining, the pathologist provides a diagnosis based on tumor cell nuclear size and stain intensity, cell morphology and an examination of the mucosal architecture. While vital stains such as Toluidene blue can be used to stain the oral cavity, making lesions more easily detectable, and brush cytology is available to noninvasively assay cell and nuclear size and shape, these adjunct methods themselves are decades old and have not gained widespread usage[1]. Unlike detection, diagnosis, and even treatment planning with other cancers, measurement of molecular changes are seldom done with oral cancer.

In 2002, just two years after the original global gene expression analysis of breast tumors was published[2,3], one of the first relatively large scale studies of global gene expression in 26 head and neck tumors was revealed[4] (Table 1). At that time there was great optimism that those types of studies would provide gene expression signatures that could be used to diagnose and type oral tumors. However, there were problems early on including the usage of non-ideal statistical methods for studies with low sample numbers that often resulted in over-fitted data. The inclusion of multiple tumor subtypes compounded the problem of insufficient sample numbers and also made interpretation complex[5]. Finally, comparisons were often done between RNA from tumor and healthy mucosa; and not tumor *vs* benign lesions that can be mistaken for oral squamous cell carcinoma (OSCC)[6]. One way to rectify these problems is to study a subgroup of tumors in a single high risk group, such as tobacco or betel nut users, and to compare these tumors to benign pathology[5]. Until these factors are considered, improved detection of head and neck cancer using gene expression based methods will not move to the clinic and even then there is unlikely to be a single genetic classifier for all OSCCs.

Another potential role for gene expression analysis of OSCC is in the prediction of treatment outcomes. Currently OSCC staging is based on the universally used TNM system of the Union International Contre Ie cancer and the American committee on cancer. TNM staging is based on anatomic extent of the tumor only. Specifically T stands for tumor size, N indicates nodal involvement and M indicates presence or not of distant metastasis. The shortcomings of the currently used TNM staging system for head and neck and OSCC are elegantly discussed by Takes *et al*[7]. It is unfortunate that despite these limitations OSCC staging plays a key role in treatment decisions that ultimately impact survival. Studies have indicated that tumor specific histopathologic characteristics impact on outcomes and survival, such as depth of invasion, tumor volume and thickness, presence of extracapsular extension, perineural invasion, pattern of invasion, lymphovascular invasion, but these research findings are not routinely included in staging or treatment decision-making for multiple reasons[8-14]. Typically, early stage tumor patients are treated with single modality therapy, surgery alone or, rarely, radiotherapy alone, while more advanced stage tumors receive multimodality treatment with surgery and adjuvant therapy such as radiation with or without chemotherapy. The rationale is that stage Ⅰ or Ⅱ tumors, which are by definition without lymph node involvement, can be reasonably controlled with surgery or localized irradiation. Systemic genotoxic treatment provides no advantage and has potentially more toxic side effects. While this approach has spared patients unnecessary adjunctive treatment, it would be better to know which tumors have a propensity to progress and need multimodality treatment. Much effort has been made to develop a gene expression-based classifier for OSCC that does not just stage the tumor but also predicts aggressiveness. For example, this was attempted by recording changes in gene expression pattern in tumor tissue that correlate with lymph node invasion and/or tumor recurrence[15-19]. A problem in these studies may have been insufficient sample numbers. A second lesser problem was the seeming paradox that there was very little overlap between marker RNAs identified by one group and that of another, the latter creating a level of doubt about the methodology (needs a period).

ORAL CANCERS LIKE BREAST CANCERS ARE NOT ALL ALIKE

The state of the gene expression-based staging of breast cancer offers a contrast in clinical value[20,21]. The Oncotype DX treatment response predictor has been used over one-half million times for breast cancer

Table 1 Major events in global gene expression analysis of breast and head and neck cancer

Breast cancer	Events	HNSCC
2000 (Perou *et al*[2])	First large scale global gene expression analysis	2002 (Méndez *et al*[4])
2001 (Sørlie *et al*[3])	First identification of tumor subtypes based on global gene expression analysis	2004 (Chung *et al*[22])
2002 (van de Vijver *et al*[35])	First published classifier to advise treatment based on global gene expression analysis	2005 (Roepman *et al*[18])
2003 (Sorlie *et al*[34])	First confirmation of tumor subtypes based on global gene expression analysis	2013 (Walter *et al*[23])
2006 (Paik *et al*[28])	First validated classifier to advise treatment based on global gene expression analysis	Still waiting
2006 (1200 samples)	More than 1000 samples global gene expression analysis data available	2013 (1200 samples)

HNSCC: Head and neck squamous cell carcinoma.

staging. This gene expression-based test fills a void left by the uncertainty over which stage Ⅰ and Ⅱ breast cancers require chemotherapy after surgery. It was known early on that a subset of early-stage estrogen receptor positive breast tumors tended to progress if chemotherapy was withheld[20,21]. In 2000 and 2001, it was first noted that breast cancer could be divided into more than 4 subtypes based on gene expression analysis[2,3]. These groups roughly coincided with the older histological classifications. The realization that breast tumors were a heterogeneous group made it clear in the beginning that studies of gene expression in breast tumors would require large numbers of samples or a focus on one subtype, or both, to produce meaningful results. An effort was made to maximize the number of cases in studies and to make data available to multiple groups *via* the web. By contrast, in 2004 Chung *et al*[22] made the observation that head and neck tumors fell into 4 groups, but there was no clear association with etiology or histology. Attempts to link gene expression with targeted treatment were unsuccessful[23]. And the only accepted subgroup of head and neck cancers, oral pharyngeal cancers with transforming human papillomavirus (HPV) was not linked to a specific gene expression subtype till years later[23-25]. In short, it was difficult to discern how real the subgroups were and what the gene expression similarities meant until two gene expression studies done about a decade later on 138 and 279 head and neck tumors respectively showed the same head and neck squamous cell carcinoma (HNSCC) subtypes based on gene expression and/or DNA alterations[23,24]. A meta-analysis published in 2015 after 9 years and over 20 studies totaled 1300 samples and revealed a further subdivision of two of the subtypes[26]. This evidence shows that HPV-negative HNSCC and OSCC are not homogenous cancers but fall into separate subtypes.

Starting in the early 2000s, several groups sought to design a gene expression-based classifier that could aid in diagnosis and treatment decisions for breast cancer (Table 1). The group that ended up producing the Oncotype DX gene expression-based classifier made several decisions that probably facilitated their dominance in the United States market for breast cancer analysis[27]. First, they largely focused on genes already shown to be important for cancer, thus reducing the number of samples required for a statistically valid analysis. Next, they optimized analysis of RNA from fixed tumor tissue in paraffin blocks, already the standard method for storage of biopsy material. Finally, they used large numbers of samples and focused on one subset of breast tumor patients, those with estrogen receptor enriched but lymph node negative breast cancer. Finally, their test answered an important clinical question: Which patients with node negative tumors that were estrogen receptor positive would best be helped by being treated with genotoxic chemotherapy after surgery[28]? Research on head and neck and oral cancer did none of these things. Typically, frozen tissue was required and low numbers of samples were used so while classifiers for head and neck and oral cancer were produced they were not validated for clinical usage. For example, early work suggested a role for the epidermal growth factor receptor in the oral cancer process and treatments that target this protein have been tested but there has been little success[29]. The lack of targeted therapies for oral cancer is likely due to the lack of sufficient numbers of molecularly well characterized oral cancer tumor samples.

WHAT NEED DO THE ONCOTYPE DX, MAMMAPRINT AND OTHER SIMILAR GENE EXPRESSION-BASED TESTS FILL?

Breast cancer diagnosis routinely entails histology, histochemistry to measure estrogen, progesterone and estrogen receptors, and finally the FISH assay to directly measure *HER2* gene amplification. In addition, immunohistochemistry measures the Ki-67 level, which is proportional to tumor proliferation and correlates with responsiveness to genotoxic chemotherapy[20,21]. By contrast, tumors that show low proliferation rates seldom recur and do not respond to genotoxic chemotherapy. This makes measuring cell proliferation rates in tumors crucial, but Ki-67 immunohistochemistry is prone to variation depending on tissue preparation, antibody staining, and pathologist quantification. As a result, Ki-67 protein is a poor marker. Tumor grade, which is a measure of how differentiated the tumor cells appear and correlates with Ki-67 levels and is also a predictor of recurrence, is also difficult to quantify accurately and consistently between laboratories. As is now well understood, Oncotype DX and the 16 cancer genes it measures[27], Mammaprint with the 70 genes it measures[30], and the Genomic Grade Index

that originally measured 96 genes[31], include a large percentage of genes that vary with cell proliferation rates. Because so many genes change in expression levels with changes in proliferation rates, it is possible to have 3 different working gene expression tests-Oncotype DX, Mammaprint, and the Genomic Grade Index - for prediction of treatment response of node negative estrogen receptor positive tumors, with little overlap in the markers that are measured. Remarkably, the markers for the different tests were selected based on different criteria such as their ability to predict survival or differentiate early *vs* late stage tumors among different subsets of breast cancer groups, yet they all contain a large percentage of markers for cell proliferation[27,30,31]. While they also can predict estrogen receptor status, it is now recognized that their ability to more accurately and reproducibly quantify tumor cell proliferation than Ki-67 immunohistochemistry and tissue grade is what makes them valuable in the clinic.

CONCLUSION

The Oncotype DX and other tests all address an important and frequent question about treatment in a common cancer: When to use conventional chemotherapy in early breast cancer? While there are newer gene expression-based tests that better address questions of optimal treatment for longer survival (10 years *vs* 5 years) and that may help more patients, the current tests now help many patients and that is why they exist[20,21]. There is a similar clinical question for OSCC patients, in that clinicians have to make decisions about which patients will get adjuvant therapy with radiotherapy or chemoradiotherapy after surgery. Recent work by The Cancer Genome Atlas (TCGA) will help to address this. TCGA has characterized over 500 head and neck tumors in regard to genomic changes, miRNA and mRNA expression changes, along with large amounts of clinical information including treatment follow up and cancer recurrence[32]. Genetic studies from TCGA allow the identification of pathways that are altered with OSCC[24]. For example there is a subgroup of tumors that lack HPV but have an intact *p53* gene and have long recurrence-free survival times. TCGA work also confirms the 4 gene expression based subgroups of head and neck cancer and for oral cancer. This will make easier the identification of targeted and conventional genotoxic-based chemotherapies that will show efficacy with individual subgroups of tumors but not all OSCCs. It is not hard to believe that a validated classifier for OSCCs that respond best to treatment will be in the clinic before long, simply because the numbers to begin these studies in earnest are beginning to be available to researchers[26,33]. While the heterogeneity of OSCC makes the development of a single classifier for OSCC difficult, it makes the vision of including gene expression analysis in OSCC treatment planning an obvious and attainable goal that could occur in the next five years if enough tumor samples are characterized using standardized methods.

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