BASIC SCIENCE

Human papillomavirus (HPV) positivity has proven to correlate with an improved treatment response and improved survival in oropharyngeal squamous cell carcinoma. The exact mechanism of this is not well understood but may be explained by HPV-positive cells having an increased sensitivity to ionizing radiation. One proposed mechanism would be alterations in the DNA damage response (DDR) of cells to ionizing radiation. SMG-1 (suppressor with morphogenic effect on genitalia) is a tumor suppressor gene known to play a role in cells DDR ability. The goal of this project was to see whether alterations in SMG-1 expression could play a role in the DDR of oropharyngeal squamous cell carcinoma.

The authors looked at 3 HPV-negative and 2 HPV-positive cell lines. Owing to promoter hypermethylation, HPV-positive cells express SMG-1 at lower levels than HPV-negative tumors. In the HPV-negative cell lines, they transfected the cells with an E6/E7 construct, which resulted in decreased SMG-1 expression (similar to what is seen in HPV-positive cell lines) and an increased sensitivity to ionizing radiation. In HPV-positive cells in which SMG-1 expression was increased, an increased resistance to ionizing radiation was demonstrated.

The authors demonstrated that SMG-1 expression negatively correlated with HPV status. They also feel that the lower level of SMG-1 expression of HPV tumor cells may play a role in the enhanced response to therapy that is seen in HPV-positive oropharyngeal squamous cell carcinoma.

Chad Zender, MD

NEOPLASMS, MALIGNANT

The goal of this very interesting and important study was to identify molecular tumor markers in biopsied lymph nodes of patients with clinically N0 disease that can help improve the accuracy of rapid intraoperative determination of the presence of occult metastasis. By doing so, the authors express their desire to use such a technique to reduce the number of unnecessary selective neck dissections and the associated morbidity in early-stage squamous cell carcinoma (SCC) of the head and neck. The authors did extensive molecular screening analysis on primary tumor, metastatic tumor, and benign lymph node tissue to determine the presence of expressed genes in lymph node tissue that are highly correlated with the presence of metastatic tumor within an involved node. Once a series of candidate genes were identified, their usefulness was further tested using a novel reverse transcriptase–polymerase chain reaction (RT-PCR) analysis of sections from sampled lymph nodes of 442 specimens of known pathologic status developed to determine the correlation of candidate gene expression to permanent section hematoxylin-eosin, and immunohistochemical evaluation of these nodes.

Two candidate genes emerged from these analyses as being useful to detect occult metastasis in sampled nodes: one was the Pemphigus vulgaris antigen (PVA); the other, a tumor-associated calcium channel receptor known as TACSTD1. A multiplex quantitative RT-PCR (qRT-PCR) assay that could be used to detect the presence of these genes in a tissue sample in approximately 35 minutes was developed. This correlated with the time it took to get frozen section analysis in an intraoperative setting. After determining target marker genes, setting up the rapid qRT-PCR assay, and testing the accuracy of this assay against permanent section analysis, the assay was used on prospectively harvested benign and tumor involved nodal tissue to determine accuracy. qRT-PCR was found to be highly accurate at detecting metastatic disease within nodal tissue with a determined accuracy of 94.2%. The negative predictive value was 95.5%, and positive predictive value (PPV) was 91.7%. In the end the authors were able to demonstrate the utility of using the qRT-PCR assay to detect the presence of occult metastatic tissue in biopsied lymph node specimens with a high degree of correlation to permanent section analysis. Also, they showed that this could be done in a short overall time frame.

This article is worth a reading primarily because it may be an example of applied molecular analysis that is clinically applicable and may have a major impact on the routine management of the neck in patients with SCC of the head and neck and a clinically N0 neck status.

Salvatore Caruana, MD

NEOPLASMS, MALIGNANT

Human papillomavirus (HPV)-related head and neck squamous cell carcinoma (SCC) is increasing in incidence, involves younger patients, and is associated with improved survival. The authors of this paper analyzed the relationship between HPV status in oral cavity and oropharyngeal cancers and quality of life (QOL).

HPV and subtype analysis was performed for 240 patients. The specimens were classified as HPV-negative, low-risk HPV, and high-risk HPV. QOL was assessed using the University of Washington QOL questionnaire, and the scores were categorized as pretreatment, immediate posttreatment (3–8 months after treatment), and 1-year posttreatment (9–15 months after treatment). Pretreatment, immediate posttreatment, and 1-year posttreatment QOL data were available for 209, 89, and 84 patients, respectively.

There were 158 HPV-negative, 4 low-risk HPV, and 66 high-risk HPV tumors. The low-risk HPV patients were included with the HPV-negative patients for analysis and comparison with the high-risk HPV patients. Multimodality therapy, chemotherapy, and radiation therapy were associated with QOL score change between pretreatment and 1-yr posttreatment, though not significant on multivariate analysis. Pretreatment QOL scores were significantly higher in patients with high-risk HPV tumors (86 vs 79, p = .015). These patients also experienced a significantly greater decrease in QOL score from pretreatment to the immediate posttreatment period (-18 vs -6, p = .041). QOL scores for the 1-yr posttreatment period and the change from the pretreatment score were similar in both groups. When accounting for tumor site, high-risk HPV status was no longer significant with higher pretreatment QOL scores and greater change between pre-treatment and immediate posttreatment QOL scores.

This study did not find patients with high-risk HPV tumors to have better 1-year QOL scores. The authors suggest that these patients had oropharyngeal tumors with advanced disease and therefore were treated with multimodality therapy which was associated with lower QOL scores. This highlights the importance of ongoing QOL assessment in a younger patient population with likely better survival outcomes, in the setting of trials investigating de-intensified treatment protocols.

Rahmatullah Rahmati, MD
NEOPLASMS, MALIGNANT

Human papillomavirus outcomes in an access-to-care laryngeal cancer cohort.

Human papillomavirus (HPV) status has been associated with improved survival in oropharyngeal squamous cell carcinoma (SCC), but its significance in laryngeal SCC is unclear. Also from oropharyngeal SCC data, HPV-positive tumors are more prevalent in white Americans than in African Americans, resulting in racial survival disparity. This study looked at the overall prevalence, race-based prevalence, and survival outcomes based on HPV status of patients with laryngeal cancer. Clinicopathologic factors, HPV status, insurance status, and treatment modality were evaluated in 79 patients. HPV16 was detected with real-time quantitative polymerase chain reaction.

Overall, HPV16 prevalence was 27%. White Americans had higher HPV prevalence than did African Americans (33% vs 16%, p = .058). HPV and insurance type were significantly correlated (p = .001) with most HPV-negative patients having Medicare (28/56). There was no significant associated between overall survival, HPV status, race, or clinical stage. There was no survival difference between surgical and nonsurgical treatment groups. Finally, patients with private insurance had better survival than did Medicare and health maintenance organization (HMO) groups.

Unlike patients treated for oropharyngeal SCC, patients in this study cohort with HPV-positive laryngeal SCC did not have a survival advantage.

Rahmatullah Rahmati, MD

NEOPLASMS, MALIGNANT

Intraoral metal contact allergy as a possible risk factor for oral squamous cell carcinoma.

The authors of this study looked at the possibility of oral squamous cell carcinogenesis induced by contact allergy to dental restoration metals. This was a prospective study in which 65 patients with oral SCC and 48 control patients underwent patch testing to dental restoration metals. Patients with a history of oral SCC were tested against 28 metal allergens used in dental repairs, whereas patients in the control group were tested with 8 “common” metals (chosen from pilot study demonstrating association with contact allergy and oral SCC). Overall, 34% of the patients with SCC were allergic to at least 1 metal that was in a restoration immediately adjacent to the cancer site. Contact allergy to at least 1 metal of the “common” metals was detected in 29% of patients with SCC and 21% of the control group. Patients with oral SCC were 3 times more likely to have a mercury contact allergy than the control group. Of the patients with SCC allergic to at least 1 “common” metal, 76% were women. Of those allergic to mercury and gold, 60% and 84% were women, respectively. Finally, when analyzing based on traditional risk factors of tobacco and alcohol use, patients at high risk for SCC had significant metal contact allergy compared with that of low-risk patients.

Further investigation is necessary to determine the relationship between contact allergy to dental restoration metals and oral carcinogenesis. The authors suggest patch testing for patients with oral SCC and adjacent metal dental restoration and possible extraction of those repairs when testing is positive.

Rahmatullah Rahmati, MD

PATHOLOGY

EGFR, HER2, survivin, and loss of pSTAT3 characterize high-grade malignancy in salivary gland cancer with impact on prognosis.

There is a growing focus on personalized medicine and development of targeted therapies. In this context, the authors analyzed protein overexpression and gene amplification of human epidermal growth factor receptor 2 (HER2) and epidermal growth factor receptor (EGFR) in 286 archival major and minor salivary gland carcinomas, using immunohistochemistry and fluorescence in situ hybridization (FISH). Expression of pSTAT3 and survivin was also assessed.

EGFR overexpression was most frequent in mucoepidermoid carcinoma (MEC), salivary duct carcinoma (SDC), and squamous cell carcinoma (SCC). Increased EGFR gene copy (high polysomy or gene amplification) was most frequent in SDC, SCC, and adenocarcinoma not otherwise specified (NOS). HER2 overexpression was most frequent in SDC and adenocarcinoma NOS. High gene copy number of HER2 was most frequent in SDC, SCC, and adenocarcinoma NOS.

EGFR overexpression, increased EGFR gene copy, increased HER2 gene copy, strong nuclear staining for survivin, and weak or loss of expression of pSTAT3 were all correlated with worse disease-specific survival. Increased gene copy number of EGFR and HER2 were associated with loss of pSTAT3 expression. Whereas activated STAT3 has been found to be a negative risk factor in a number of carcinomas at other sites, strong nuclear expression of pSTAT3 correlates with favorable survival in salivary gland carcinomas. Strong nuclear pSTAT3 immunostaining correlates with low survivin expression and may play a role as a tumor suppressor in the absence of EGFR, HER2, and survivin. While these molecular markers provide prognostic information, histologic grade remains the strongest predictor of survival. While the molecular markers correlate with prognosis, results of initial phase II clinical trials looking at targeted therapy for salivary gland carcinomas have not been promising.

Mary R. Schwartz, MD