

# The Benefit of Early PET/CT Surveillance in HPV-Associated Head and Neck Squamous Cell Carcinoma

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**Objective:** To evaluate the ability of posttreatment positron emission tomography and computed tomography (PET/CT) to predict ultimate disease status in patients with head and neck squamous cell carcinoma and known human papillomavirus (HPV) status.

**Design:** Retrospective.

**Setting:** Single tertiary academic referral center.

**Patients:** Clinical and radiographic data, including HPV status, were available for 62 patients with head and neck squamous cell carcinoma who underwent treatment from 2005 to 2010.

**Main Outcome Measures:** The first posttreatment PET/CT scan, performed between 4 and 16 weeks (median, 9 weeks) after treatment, was categorized as negative, probably negative, or positive for residual disease. The PET/CT and clinical follow-up results, including disease status, were obtained every 3 months thereafter.

**Results:** Among the 62 patients, 35 results (56%) were

negative, 15 (24%) were probably negative, and 12 (19%) were positive. Eight of the 27 HPV-negative patients were PET/CT positive compared with 4 of the 35 HPV-positive patients (Cochran-Armitage trend test,  $P = .11$ ). The median follow-up for disease-free patients was 21 months from the completion of the treatment. Disease-free survival was associated with PET/CT outcome (log-rank  $P < .001$ ) and HPV status (log-rank  $P = .01$ ). Using recurrence at 2 years as a reference standard, the early PET/CT scans had a specificity of 69% (95% confidence interval [CI], 46%-91%) and a negative predictive value of 79% (95% CI, 57%-99%). All PET/CT-negative HPV-positive patients ( $n = 6$ ) were free of disease at 2 years, although this proportion was not statistically different from the PET/CT-negative HPV-positive patients in this small cohort.

**Conclusions:** A negative posttreatment PET/CT result may have the potential to identify patients who are at very low risk of recurrence. The HPV status may augment the predictive utility of an initial negative PET/CT result.

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**D**ESPITE MANY RECENT ADVANCES in the diagnosis and treatment of head and neck squamous cell carcinoma (HNSCC), the rate of locoregional or distant recurrence remains high (up to 40% in patients with high-risk clinical and pathologic features).<sup>1</sup> Among such cases, 90% of recurrences occur within the first 2 years after treatment.<sup>2,3</sup> Tissue distortion due to surgery and/or irradiation makes posttreatment surveillance of HNSCC challenging by conventional follow-up methods such as clinical examinations, computed tomography (CT), or magnetic resonance imaging (MRI).

In recent years, several studies have shown that combined positron emission tomography (PET) and CT offers advantages in the early detection of persistent or recurrent disease.<sup>4-7</sup> In a prospective

study from our institution, combined PET/CT demonstrated more sensitivity and specificity in the detection of HNSCC than either PET or CT alone in patients known to have or suspected of having active head and neck cancer.<sup>8</sup> Moreover, the high negative predictive value (NPV) of PET/CT (97%-99%) provides valuable information that can potentially spare patients from unnecessary neck dissection.<sup>5,6</sup> The National Comprehensive Cancer Network Clinical Practice Guidelines in Oncology for Head and Neck Cancers have been updated to include PET/CT as an option for posttreatment evaluation to assist in selecting patients with lip, oropharyngeal, hypopharyngeal, occult primary, or glottic and supraglottic laryngeal cancers who would benefit from a neck dissection.

Human papillomavirus (HPV) plays a role in the pathogenesis of a subgroup of

patients with HNSCC.<sup>9</sup> The causal association between HPV and oropharyngeal carcinoma has been established.<sup>10</sup> Human papillomavirus-positive oropharyngeal carcinoma is a clinically and biologically distinct entity. Patients with HPV-positive oropharyngeal carcinoma have better 3-year overall and progression-free survival, better response to chemoradiation therapy (CRT), and a lower locoregional recurrence rate than patients with HPV-negative oropharyngeal carcinoma.<sup>9-11</sup> In a recent study, PET/CT demonstrated a high positive predictive value in detecting recurrence specifically in those patients with HPV-negative, nonoropharyngeal primary cancers and a history of alcohol and tobacco use.<sup>12</sup>

Although PET/CT is now routinely used for HNSCC surveillance, the clinical utility of the first posttreatment PET/CT scan for predicting tumor recurrence and whether HPV status plays a role in this trend have not been evaluated. The purpose of this study was to assess the use of a first PET/CT scan in predicting early disease recurrence as well as the added value of HPV status for prediction.

## METHODS

### PATIENTS

We conducted a retrospective study that was approved by the institutional review board of the University of Pittsburgh, Pittsburgh, Pennsylvania, and was compliant with the Health Information Portability and Accountability Act (HIPAA). Data from patients with biopsy-proven HNSCC who presented to our institute between December 2005 and July 2010 were extracted from our tumor registry. Adult patients were included if they had known HPV status (tested at the University of Pittsburgh Medical Center), were treated with curative intent at our institution, and had combined PET/CT imaging for posttreatment tumor surveillance within 16 weeks of completing treatment. Exclusion criteria were (1) distant metastatic disease, (2) a previous history of head and neck cancer, (3) a history of previous radiation to the head and neck region, (4) diagnosis at our institution but treatment elsewhere, and (5) PET/CT performed for confirmation of clinical evidence of recurrences rather than routine posttreatment surveillance.

### FLUDEOXYGLUCOSE F18 PET/CT IMAGING

All patients underwent pretreatment PET/CT for staging purposes and baseline imaging for comparison to posttreatment scans. According to the posttreatment PET/CT surveillance protocol at the University of Pittsburgh Medical Center, first posttreatment PET/CT was performed 8 to 10 weeks after completion of treatment. Actual PET/CT occurred between 4 and 16 weeks after treatment. Combined PET/CT fusion imaging was performed with a dual-channel CT scanner (Reveal; CTI Medical System, Knoxville, Tennessee) combined with lutetium oxyorthosilicate PET (LSO Allegra; CTI Medical Systems). Patients were instructed to fast for 4 to 6 hours before undergoing PET/CT, and their blood glucose levels were measured before fludeoxyglucose F18 (FDG) injections. Those with blood glucose levels higher than 200 mg/dL (to convert to millimoles per liter, multiply by 0.0555) were rescheduled. The PET/CT imaging was performed from the head through the abdomen 60 minutes after an intravenous injection of 8 to 15 mCi FDG. Helical CT (pitch, 1.0; 120-140 mA; 130 kilovolt [peak]) was performed immediately before PET. The CT was performed with

intravenous contrast (120 mL ioversol [Optiray 350; Mallinckrodt Inc, Loma Linda, California]) in all patients. The PET images were then reconstructed with CT-based attenuation correction.

### IMAGING INTERPRETATION

The axial CT images were reviewed on a conventional Picture Archiving and Communication System workstation (Philips iSite). The PET/CT fusion scans, including multiplanar reformatted images, were reviewed on a dedicated workstation (Vital Images). All images were interpreted by 1 of 2 dedicated head and neck radiologists with 8 and 6 years of experience in PET/CT imaging of HNSCC. Interpretation was performed as a normal part of clinical care, with all clinical information available to the interpreting physicians.

The PET/CT results were classified into 1 of 3 categories: (1) negative, (2) probably negative, or (3) positive. A negative PET/CT result showed no evidence of disease on either the CT or the PET portion of the examination. A probably negative designation was given when either the PET or the CT portion of the examination showed persistent disease but the other portion showed complete resolution. Probably negative was also used when there was a dramatic response of bulky disease to therapy but small amounts of FDG avidity remained. Asymmetrical FDG uptake in a region of prior tumor, which was considered likely to be physiologic uptake, would also be considered probably negative. The PET/CT result was defined as positive if there was a definite increase in standardized uptake value at the site of tumor, a new site of tumor spread, or a failure to respond to treatment. These designations were based on the subjective interpretations of the radiologists. Strict standardized uptake value thresholds were not used, in keeping with the usual practice pattern at our institution.

### POSTTREATMENT SURVEILLANCE

The patients were evaluated clinically 1 month after completion of their treatment, and the first posttreatment PET/CT examination was performed 4 to 16 weeks after treatment completion according to the University of Pittsburgh Medical Center HNSCC PET/CT surveillance protocol, allowing for deviation of PET/CT timing. Patients were then followed up every 3 months with clinical examinations, supplemented by additional PET/CT examinations when clinically appropriate.

The PET/CT results were categorized into 1 of 3 categories by the attending radiologist: positive, probably negative, and negative. If a patient had any suspicious findings on routine clinical examinations, PET/CT imaging was ordered to evaluate the primary site and neck. If the PET/CT scans demonstrated any lesions that were suspicious for recurrent or residual disease, tissue sampling with fine-needle biopsy or open biopsy was performed, except in the setting of clear progressive disease as mentioned above. In the cases of discordance between the clinical and radiologic evaluations, clinical evaluation was given preference in guiding the diagnosis or therapy. Pathologic confirmation of tumor presence was considered the reference standard for recurrence. Negative clinical and radiographic follow-up results for at least 6 months were considered evidence of absence of residual disease.

### HPV DETECTION

For each patient, paraffin-embedded specimens were obtained from diagnostic biopsy of the primary site. The HPV DNA status was then evaluated using *in situ* hybridization to detect the presence or absence of HPV. Tumor p16 status was also evaluated by im-

**Table 1. Demographic and Clinical Characteristics of 62 Study Patients**

Characteristic	Total, No. (%) <sup>a</sup>	PET/CT Result			3-Group Comparison P Value
		Negative (n = 35)	Probably Negative (n = 15)	Positive (n = 12)	
Age, median, y		62	50	53	.02
Sex					
Male	53 (85)	11	13	29	.52
Female	9 (15)	1	2	6	
T stage					.09 <sup>b</sup>
0	3 (5)	3	0	0	
1	12 (19)	7	4	1	
2	26 (42)	14	9	3	
3	13 (21)	6	2	5	
4	7 (11)	4	0	3	
X	1 (2)	1	0	0	
N stage					.13
0	11 (18)	4	4	3	
1	11 (18)	7	2	2	
2	35 (56)	19	9	7	
3	5 (8)	5	0	0	
Disease site					.32
Oral cavity	6 (10)	2	1	3	
Oropharynx	45 (74)	25	14	6	
Hypopharynx	2 (3)	1	0	1	
Larynx	5 (8)	3	0	2	
Other/unknown	3 (5)	3	0	0	
HPV status					.11
Positive	35 (56)	22	9	4	
Negative	27 (44)	13	6	8	

Abbreviations: HPV, human papillomavirus; PET/CT, positron emission tomography and computed tomography.

<sup>a</sup>Percentage of nonmissing data.

<sup>b</sup>Excludes 1 case with stage X.

munohistochemical analysis. Positive p16 expression was defined as strong and diffuse nuclear and cytoplasm staining in 70% or more of the tumor cells.<sup>13</sup> Discrepancy between the 2 methods is rare (only 1 case in our study). This discrepancy was resolved by reviewing the results of HPV in situ hybridization and identifying several positive cells along with extremely strong p16 expression (>70% tumor cells homogeneously positive); the patient was then considered HPV positive.

### STATISTICAL ANALYSIS

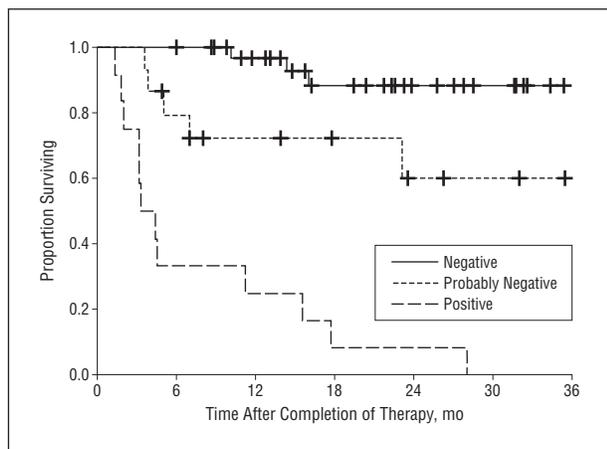
Patients were classified into 1 of 3 categories according to the results of their PET/CT scan: negative, possibly negative, or positive. Clinical and demographic data were compared among these 3 groups by assuming an implicit order among the 3 classes. Age, T stage, and N stage were compared with the Jonckheere-Terpstra test; sex and HPV status were compared with the Cochran-Armitage trend test. The primary objective of this study was to evaluate the predictive accuracy of the initial PET/CT scan. The reference standard for evaluation was defined as the presence or absence of disease at 2 years after therapy. Emphasis was placed on the NPV for predicting no evidence of disease at 2 years. A negative PET/CT result was unequivocally negative and excluded the middle category of cases deemed probably negative. The specificity and NPV were estimated with 95% confidence intervals (CIs). The HPV status was assessed for independence of disease site with an exact  $\chi^2$  test and by computing the odds ratio of HPV infection given tumor location (oropharynx vs all others). The predictive value of HPV status, as well as other clinical covariates, was tested with the Fisher exact test or an exact  $\chi^2$  test of negative scans only. Positive scans were not amenable to sta-

tistical analysis because 5 positive scans led to a contemporaneous diagnosis of recurrence, thereby violating the assumption of variable independence. Disease-free survival and length of follow-up were calculated from the date of completion of treatment, first evidence of recurrence, or last date of follow-up. Disease-free survival was estimated for the entire cohort and by PET/CT status by the Kaplan-Meier method with Greenwood confidence intervals. A 1-sided confidence interval for an observed frequency of 100% was calculated by the principle of duality between tests and confidence intervals.<sup>14</sup>

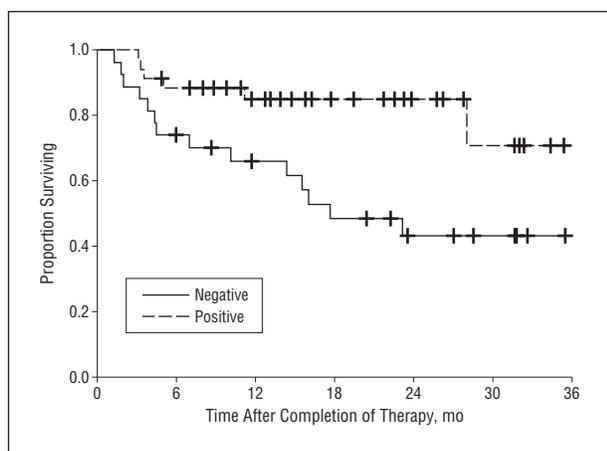
## RESULTS

### PATIENT CHARACTERISTICS

From April 2006 to December 2009, 116 biopsy-proven HNSCC cases with known HPV status were identified from our tumor registry. According to our inclusion and exclusion criteria, 54 patients were excluded; therefore, data for 62 patients were included in this analysis. Of these 62 patients, 35 (56%) were HPV positive and 27 (44%) were HPV negative. The median follow-up time for patients with no evidence of disease was 22 months after treatment (range, 5-35 months). The median time from completion of the treatment to the first posttreatment PET/CT scan was 9 weeks, with an interquartile range between 8 and 12 weeks and a range of 4 to 16 weeks. Patient characteristics are summarized in **Table 1**.



**Figure 1.** Kaplan-Meier estimates of disease-free survival by initial positron emission tomography and computed tomography outcome. Vertical tick marks indicate censoring times.



**Figure 2.** Kaplan-Meier estimates of disease-free survival by human papillomavirus (HPV) status. Patients who were HPV negative had a median survival of 18 months, whereas the median survival for HPV-positive patients has not been reached (log-rank  $P = .02$ ).

### DISEASE-FREE SURVIVAL

Of the 62 patients investigated, 20 developed disease recurrence. The median disease-free survival was not reached, and the probability of 2-year disease-free survival was 0.64 (95% CI, 0.48-0.76). Among 35 patients with a negative PET/CT result, there were 3 recurrences at 10, 14, and 16 months (**Figure 1**). All 12 patients with a positive PET/CT result had a recurrence, with 5 recurrences detected on PET/CT scans (log-rank  $P < .001$ ). The HPV-positive patients had fewer recurrences and greater disease-free survival than the HPV-negative patients (**Figure 2**) (log-rank  $P = .01$ ).

### PREDICTIVE UTILITY OF PET/CT

We defined disease recurrence at 2 years as the reference standard for predictive accuracy of PET/CT. This definition is based on the observation that at our institution 90% of recurrences occur within 24 to 30 months after definitive therapy. In the study cohort, we observed 20 recurrences, 19 of which (95%) occurred within

**Table 2. Predictive Accuracy of Positron Emission Tomography and Computed Tomography (PET/CT)**

PET/CT Outcome	Disease Status at 2 y		Total
	No Evidence of Disease	Recurrence	
Negative	11	3	14
Possible negative	4	5	9
Positive	1	11	12
<b>Total</b>	<b>16</b>	<b>19</b>	<b>35</b>

24 months. One patient experienced a recurrence at 28 months. Eleven of these 19 patients had a positive PET/CT result, and 5 of the 11 patients were diagnosed as having a recurrence at the time of their PET/CT examination (**Table 2**). Of the 16 patients who survived disease free for 2 years, 11 had a negative PET/CT result, for a specificity of 69% (95% CI, 46%-91%) and a NPV of 79% (95% CI, 57%-99%).

### ADDED BENEFIT OF HPV STATUS TO THE UTILITY OF PET CT IMAGING

Positive HPV status was associated with both improved clinical outcome and a negative initial PET/CT result. We sought to ascertain whether HPV status augmented the predictive utility of PET/CT scans. We observed that HPV status was primarily site dependent (exact  $\chi^2 P = .009$ ), with 89% of HPV-positive tumors found in the oropharynx (**Table 3**). The odds ratio of HPV infection among oropharyngeal tumors was 7.2 (95% CI, 1.7-34.6). **Table 4** shows the distribution of PET/CT results (divided into negative vs probably negative plus positive) by HPV status and 2-year outcome. After stratifying the PET/CT outcome by patient HPV status, we found that all 6 patients who were PET/CT negative and HPV positive were recurrence free at 2 years (Table 3). Conversely, of the 8 HPV-negative patients with a negative PET/CT result, 3 had a recurrence by 2 years (Fisher exact  $P = .21$ ). Although a statistically significant difference in outcome was not found based on HPV status, the numbers of patients are very small. The best estimate of the NPV for HPV-positive patients is between 61% and 100%. No HPV-positive patient with a negative, first post-treatment PET/CT result manifested recurrence in this cohort. The 3 patients with a negative PET/CT result and a recurrence at 2 years had American Joint Committee on Cancer stages T2N0M0, T2N2M0, and T4N2M0, an outcome that does not provide enough information to eliminate T and N stages as confounding variables.

### COMMENT

Many recent studies have proposed that combined PET/CT imaging may improve the accuracy of posttreatment evaluation for HNSCC.<sup>15-19</sup> A negative PET or PET/CT result is considered a powerful predictor of outcome and has played a role in the decision making for posttreatment management of HNSCC.<sup>6,15,16,19</sup> In the situation of a complete clinical response after definitive head

**Table 3. Human Papillomavirus (HPV) Status by Disease Site**

HPV status	Hypopharynx	Larynx	Nasopharynx	Oral Cavity	Oropharynx	Unknown	Total
Negative	2	3	1	4	14	3	27
Positive	0	2	0	2	31	0	35

**Table 4. Predictive Accuracy of Positron Emission Tomography and Computed Tomography (PET/CT) Stratified by Human Papillomavirus (HPV) Status**

PET/CT Outcome	Disease Status at 2 y	
	No Evidence of Disease	Recurrence
Negative		
HPV+	6	0
HPV-	5	3
Possibly negative or positive		
HPV+	3	5
HPV-	2	11

and neck cancer treatment, methods of posttreatment tumor surveillance are evolving. The National Comprehensive Cancer Network Clinical Practice Guidelines in Oncology for Head and Neck Cancers now include PET/CT as an option for posttreatment surveillance.<sup>20</sup>

In our study, we divided all patients with a negative first posttreatment PET/CT result into 2 groups: HPV positive and HPV negative. We attempted to evaluate the utility of PET/CT imaging as a tumor surveillance tool according to the HPV status. Our data reveal that in the HPV-positive group a negative first posttreatment PET/CT result is highly predictive of disease-free survival. However, in the HPV-negative group, the NPV was reduced to 62% (5 of 8 patients) (95% CI, 29%-96%). These findings might be of value in individualizing the PET/CT surveillance plan based on HPV status of the primary tumor. Because the negative first posttreatment PET/CT results may predict good treatment outcomes for selected patient subpopulations, these patients may require less frequent serial PET/CT scanning for surveillance in the setting of continued negative clinical examination results on follow-up. Not only can HPV status increase prediction accuracy but also because 89% of cases of HPV infection were in oropharyngeal tumors, tumor site may serve as a surrogate predictor in the absence of HPV infection status. We also suspect that tumor stage may improve predictive ability but could not verify this because of the small sample size. Serial PET/CT scans with clinical evaluations at follow-up visits might be warranted to detect recurrences in HPV-negative patients. Combined PET/CT imaging remains an effective and noninvasive, yet expensive, surveillance tool for patients with head and neck cancer. With HPV testing for HNSCC becoming more available, the ability to individualize PET/CT surveillance plans based on HPV status is of clinical value and might decrease the financial burden for many patients with HNSCC without compromising the quality of tumor surveillance.

Several other recent studies have supported the findings of a high NPV of PET/CT and its role in posttreat-

ment management.<sup>6,15,16,19</sup> Yao et al<sup>19</sup> suggested that patients with a negative first posttreatment PET/CT result could be seen less frequently for surveillance owing to excellent treatment outcome. However, none of these studies analyzed HPV status. In a recent prospective study, Moeller et al<sup>12</sup> used HPV status in their subgroup analysis. In 98 patients with advanced HNSCC, HPV phenotyping was available in one-third of their patient cohort. They concluded that PET/CT scans improved posttreatment response assessment for patients with HPV-negative tumors, patients with nonoropharyngeal primary cancers, and patients with a history of alcohol and tobacco use, who are at high risk of treatment failure.<sup>12</sup> They do not recommend routine use of serial PET/CT scans in low-risk patients (HPV positive, oropharyngeal primary cancers, and no history of alcohol and tobacco use). To our knowledge, this is the only prospective study to risk stratify patients with HNSCC using PET/CT scanning and HPV status as tumor surveillance. Our study results are similar to those of the above-mentioned 2 studies.

The preferred timing of PET/CT scanning to assess treatment response is between 8 and 10 weeks at our institution. This timing is based on a previous retrospective study of HNSCC at our institution in which the predictive accuracy of PET/CT scans was 100% when they were obtained later than 8 weeks vs 76.5% between 4 and 8 weeks.<sup>7</sup> Similarly, other studies have demonstrated 8 weeks posttreatment as an appropriate time to maximize accuracy.<sup>12,21</sup> Although some authors might suggest 8 to 12 weeks to maximize accuracy, we think that the detection of residual disease is clinically valuable when the scans are obtained earlier in time to facilitate timely salvage treatment.<sup>5,21</sup>

Some limitations of this retrospective study merit attention. First, the referral pattern at our institution is different from other settings because of its nature as a high-volume tertiary care center. The results might not be applicable to general populations. Second, there was no standardization of radiologic evaluation, and there was only haphazard adherence to a PET/CT surveillance program. Third, patients were evaluated for clinical management without regard to research use of data, and data were collected retrospectively rather than as a designed study. While we attempted to enhance the predictive ability of PET/CT scans via HPV status, we cannot rule out that other clinical and pathologic factors, such as disease site or stage, may provide equal or even superior stratification compared with HPV status. Finally, the follow-up period for this study is limited at 19 months after the first posttreatment PET/CT scan and at 21.5 months after completion of treatment. The longest follow-up period in the literature for a similar study was 29.2 months after completion of treatment in a long-term outcome re-

port.<sup>19</sup> Other studies<sup>6,12,16,18</sup> have had median follow-up periods ranging from 10 to 28 months (10, 18, 23, and 28 months) from the completion of treatment. Although the clinical follow-up period in our study is similar to that in the study by Moeller et al<sup>12</sup> (92 weeks), an ideal period in this setting would be 24 months, with 25 negative first posttreatment PET/CT results in HPV-positive patients.

In conclusion, a negative posttreatment PET/CT result has the potential to identify patients who are at low risk of early recurrence. The HPV status may add benefit to a PET/CT surveillance plan for oropharyngeal and/or HPV-positive carcinoma. Further investigation is warranted to determine whether a negative first posttreatment PET/CT result in HPV-positive patients with HNSCC may obviate the need for additional PET/CT scans.

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**Author Contributions:** Drs Zhang, Branstetter, and Ferris had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. *Study concept and design:* Zhang and Ferris. *Acquisition of data:* Zhang, Branstetter, Beswick, and Maxwell. *Analysis and interpretation of data:* Zhang, Branstetter, Gooding, and Ferris. *Drafting of the manuscript:* Zhang, Beswick, Maxwell, and Ferris. *Critical revision of the manuscript for important intellectual content:* Zhang, Branstetter, Beswick, Gooding, and Ferris. *Statistical analysis:* Branstetter and Gooding. *Obtained funding:* Ferris. *Administrative, technical, and material support:* Zhang, Maxwell, and Ferris. *Study supervision:* Branstetter and Ferris.

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**Additional Contributions:** Jennifer Hetrick, RHIA, CRT, assisted in extracting extract data from the head and neck cancer database at the University of Pittsburgh Medical Center Network Cancer Registry.

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