Abstract: Background. Stage migration occurs when new diagnostic modalities provide additional information, leading to reclassification of disease stage. Our objective was to examine whether stage migration occurs with inclusion of positron emission tomography (PET) scans in staging head and neck squamous cell carcinoma (HNSCC).

Methods. In a retrospective cohort study, subjects were identified through university hospital and Veterans Affairs Medical Center cancer registries with incident HNSCC from 2000 to 2003. American Joint Committee on Cancer (AJCC 6th edition) criteria were used for TNM staging with and without PET scan results. Five-year survival data were acquired from medical records and the Social Security Death Index.

Results. Addition of PET changed TNM classification in 13/65 patients (20%) with stage reclassification in 5/65 patients (8%, p = .03). Apparent stage-specific 5-year survival was altered, although these changes were not statistically significant.

Conclusions. Although stage migration was documented by inclusion of PET scan information in this series, stage-specific survival was not significantly changed. Prospective investigation of this phenomenon is necessary. © 2010 Wiley Periodicals, Inc. Head Neck 32: 1283–1287, 2010

Keywords: staging; head and neck cancer; PET scan; survival; stage migration

Classifying the stage of a neoplastic lesion is important to help determine optimal individualized therapy and to predict survival. In 1984 Alvin Feinstein described the “Will Rogers Phenomenon” and coined the term “stage migration.” Will Rogers said, “When the Okies left Oklahoma and went to California, they raised the average intelligence level of both states.” When dealing with cancer, improvements in diagnostic imaging allow clinicians to diagnose asymptomatic malignancies and metastatic lesions that would normally go undetected by standard diagnostic methods. This detection could shift patients with these subclinical findings into more advanced stages. As a result, the apparent survival in the localized stages would be improved by the removal of these patients with occult but significant oncologic findings. Concurrently, apparent survival in the advanced stages might also be improved by the addition of patients whose oncologic findings were not yet overt. This process of reclassifying “better” patients into ‘worse’ stages can improve survival rates in all morphologic stages without affecting overall [survival].”
In 2004, Drs. Champion and Piccirillo published a retrospective review of 90 patients with laryngeal cancer. They staged each patient twice, once with CT information and once without. They found that adding the CT data led to upstaging, or stage migration, in 17% of patients because the CT scans were finding occult lesions or nodes not detectable by physical examination alone. They then compared 2-year survival data based on the type of staging system used (both with and without CT information). The results showed that stages I, III, and IV groups all appear to have improved stage-specific 2-year survival, although none of the differences was statistically significant. Overall survival for all groups in aggregate remained unchanged, suggesting the stage-specific improvement may be secondary to stage migration.

Positron emission tomography (PET) scans have been used for nearly 2 decades to help diagnose head and neck malignancies. Recently, the use of PET scans has improved staging of head and neck squamous cell carcinoma (HNSCC). The purpose of this study was to determine whether the addition of PET scan information leads to stage migration in HNSCC. A secondary goal was to evaluate the impact of PET scan information on apparent stage-specific survival.

MATERIALS AND METHODS
This study was approved by the University of Washington institutional review board for human subjects research (#27512) and Department of Veterans Affairs Research and Development Committee (Yueh #0024). Individual written informed consent was not required by these review boards because of the retrospective nature of the study as well as minimal risk to subjects. Patient confidentiality was maintained throughout the study. A retrospective chart review was performed. Subjects were identified through the University of Washington and Seattle Veteran Affairs cancer registries with incident HNSCC diagnosed between 2000 and early 2003. Patients with recurrent cancers were excluded. Inclusion criteria required that a PET scan was performed preceding treatment, that treatment (or the decision for no treatment) be commenced during the study period, and that treatment data were available in the medical record. PET scans were performed on the Advance (GE Medical Systems, Waukesha, WI) PET scanner located at the University of Washington Medical Center. This scanner does not have an integrated CT scanner.

Patient characteristics including date of birth, age, and sex were abstracted from the records. Data collected on the tumor included information required for TNM classification from the physical examination, endoscopic findings, and imaging modalities including the PET scan. Treatment data collected included the dates for the therapeutic surgery and chemotherapy or radiation treatment. Using American Joint Committee on Cancer (AJCC 6th edition) criteria, all subjects were staged twice: once without PET information and another time including PET information. “Time zero” was defined as the date of first antineoplastic therapy or the date corresponding to a decision for no treatment. Five-year survival data were then calculated. Death status was determined by reviewing the medical records as well as the Social Security Death Index.

All data were entered into a Microsoft Access (Microsoft, Redlands, WA) database and then transferred to Stata 10.0 (Stata Corp., College Station, TX) for statistical analysis. Descriptive statistics were used to characterize the overall sample and subjects according to cancer stage. The 1-sided sign test (used for nonparametric, discrete data) was used to compare the distribution of stages without and with the inclusion of PET information to determine whether any upstaging seen was statistically significant.

Fisher’s exact test was used to compare survival between stages.

RESULTS
Between 2000 and 2003, 133 patients underwent PET scans for head and neck carcinomas. Of these patients, 23 were excluded because they had neoplasms other than SCC. Thirty-two were removed because the PET scans were performed to evaluate recurrent lesions or were for surveillance, as this study evaluated only incident neoplasms. Six patients were treated after the end of the enrollment period and therefore were excluded for lack of complete 5-year survival data. Finally, 7 patients did not have treatment data available in the medical record. This left 65 subjects that met all inclusion criteria.
The majority of the subjects were male, and there was a skew toward an older population (Table 1). The most common site of tumor was the oropharynx, followed by the oral cavity and lip, then the larynx (Table 1). The remaining sites of tumor were distributed among the neck (equivalent to unknown primary tumor) and salivary glands.

The outcomes of the PET scans are summarized in Table 2. Sixty-three percent of the time, no change was found between staging information obtained from the PET scan and staging information obtained from traditional methods (including physical exam, chest radiography, CT, and laboratory studies). Upstaging in terms of TNM classification (for example, from N1 to N2) occurred in 20% of subjects, whereas true stage reclassification (eg, from stage 3 to stage 4) occurred in 8%. Of those, about 2/3 were attributed to the discovery of metastatic lesions, whereas 1/3 was attributed to finding additional lymph node involvement (either contralateral or multiple ipsilateral nodes). Interestingly, PET scans did reveal a second primary lesion in 4 of the subjects. Among 5 subjects with unknown primary tumors, the PET scan was able to detect the primary lesion in 2 of these patients (40%). One subject was “falsely upstaged,” meaning that the PET scan identified a contralateral node that was ultimately found to be negative for disease. Theoretical downstaging occurred in 4 subjects when a questionable mass on physical exam or CT was found to be likely nonmalignant on PET scan, although this information was not used to change the patients’ clinical stage.

The TNM classification was then used to categorize patients into stages I through IV (Table 3). The distribution was skewed toward advanced stages regardless of PET data inclusion. Comparison of the distribution of stages with and without PET data demonstrated the migration of patients from the lower staged lesions to the most advanced stage. Two patients migrated from stage II to stage IV, and 3 patients migrated from stage III to stage IV. The distribution of this upstaging was found to be statistically significant.

The 5-year survival rates within each stage were then calculated with and without PET data inclusion (Table 4). Small changes in stage-specific survival were demonstrated; however, the direction of change was not consistent between stages and did not meet statistical significance. As illustrated, with the inclusion of PET data stage II and stage III stage-specific
survival decreased, whereas stage IV stage-specific survival increased. When these patterns were compared with our preliminary findings using 2-year survival data, the survival trends were found to be consistent over time (data not shown). Despite the changes in stage-specific survival, overall survival did not change.

DISCUSSION
Comparison of staging of HNSCC with and without the inclusion of PET scan data demonstrated a 20% rate of TNM reclassification. This rate is similar to the TNM upstaging of 17% noted when CT scan data were included in the staging of laryngeal SCCs. In this study, the rate of actual stage migration was 8% because not all TNM reclassification resulted in a change in stage. The findings described herein illustrate another example in which a new technology can influence the staging of neoplasms.

Despite several cases of upstaging in this population with predominantly advanced HNSCC, the data did not demonstrate a statistically significant Will Rogers phenomenon. Specifically, in this phenomenon we would have expected to see an apparent improvement in stage-specific 5-year survival, but a stable overall 5-year survival. A likely explanation is that we simply did not have enough patients in this population with lower-staged (I or II) tumors that would have a greater potential to be upstaged with a PET scan. Between 2000 and 2003 when this study screened for subjects, PET scans constituted a relatively new diagnostic tool, and in general were reserved for patients with higher-staged or most concerning lesions. Since having had a PET scan was a requirement for inclusion, the lack of a PET scan likely excluded most of the stage I and stage II subjects. Because of limitations on access to this type of data, we are unable to ascertain how many new patients with head and neck cancer were ineligible for inclusion during this time as the result of a lack of PET scan information. Furthermore, this population reflects a tertiary medical center that serves a 5-state population, and tends to be referred patients with advanced head and neck cancer.

A key advantage of using PET scans was demonstrated in our finding of 40% detection among unknown primary lesions, although the number of patients in this group was small. This finding is similar to that reported by Dr. Miller and colleagues with an unknown primary detection rate of 30.1%.

One limitation of this study is the potential for misclassification error of death status. Even though we used 3 independent sources to acquire these data and allowed 6 months for death data to be recorded, it is possible that some death records were not accurate. Another limitation is the lack of use of a combined PET/CT scanner for the imaging. Use of PET/CT is an even more recent advancement in imaging and may improve the sensitivity of detecting upstaging with PET technology. A recent paper by Connell and colleagues showed a 34% change in TNM classification as a result of PET/CT scan information. Their study was designed to evaluate PET/CT scan utility in determining treatment responsiveness and assist with post-treatment management, as opposed to our study that was designed to evaluate survival and the effects of upstaging.

CONCLUSIONS
The inclusion of fluorine-18 fluorodeoxyglucose (18F-FDG) PET scan data led to TNM reclassification of 20% in this population of patients with incident HNSCC. This supports earlier findings that the TNM staging system can be unstable over time as a consequence of technological improvements. Though the data did not demonstrate a statistically significant Will Rogers phenomenon, upstaging by PET scan and any other new diagnostic instrument can appear to improve stage-specific survival while overall survival remains stable.

Acknowledgments. The authors acknowledge Bevan Yueh, MD, MPH, for advice and insight during project planning and manuscript preparation.

REFERENCES