Early Prediction of Response to Chemoradiotherapy for Head and Neck Cancer

Reliability of Restaging With Combined Positron Emission Tomography and Computed Tomography

James P. Malone, MD; Michael A. T. Gerberi, MD; Syam Vasireddy, MD; Larry F. Hughes, PhD; Krishna Rao, MD; Bruce Shevlin, MD; Matthew Kuhn, MD; Dean Collette, MD; Joel Tennenhouse, MD; K. Thomas Robbins, MD

Objective: To assess the role of combined positron emission tomography and computed tomography (PET-CT) in predicting early treatment response at the primary site and in the neck after chemoradiotherapy (CRT) for advanced squamous cell carcinoma of the head and neck (SCCHN).

Design: Retrospective analysis with a median follow-up of 24 months.

Setting: Academic, tertiary referral center.

Patients and Interventions: Thirty-one patients who were treated with concomitant intra-arterial CRT underwent PET-CT 6 to 8 weeks after the completion of treatment. Patients with findings on the physical examination, CT, or PET-CT indicative of persistent disease underwent appropriate surgical intervention for pathological assessment. Patients with a complete clinical response were observed with routine follow-up physical examination for disease recurrence. No evidence of disease at least 6 months after the completion of PET-CT was considered confirmation of complete clinical response.

Main Outcome Measures: Presence or absence of residual or recurrent disease during the follow-up period was used to calculate the sensitivity, specificity, and positive and negative predictive values of PET-CT for the primary site and the neck.

Results: Assessment of tumor response at the primary site with PET-CT had a sensitivity, specificity, and positive and negative predictive values of 83%, 54%, 31%, and 92%, respectively. In patients with pretreatment N1 to N3 disease, the sensitivity, specificity, and positive and negative predictive values of posttreatment PET-CT were 75%, more than 94%, more than 75%, and 94%, respectively, and the specificity and negative predictive value for patients with pretreatment N0 disease in the neck were 92% and more than 92%, respectively.

Conclusions: Negative PET-CT findings accurately determine early disease response at the primary site and in the neck. False-positive findings are common at the primary site. Patients with a negative PET-CT finding after the completion of intra-arterial CRT do not require surgical intervention.


During the past 2 decades, organ preservation strategies using chemoradiotherapy (CRT) have become important treatment modalities for patients with advanced-stage head and neck cancer. These nonsurgical approaches produce an excellent response at the primary tumor site and cervical lymph nodes resulting in high rates of locoregional disease control.1-3 Accurate and timely assessment of disease response at the primary tumor site and cervical lymph nodes after CRT is essential to detect residual disease, to direct surgical salvage, and to prevent tumor recurrence. In particular, assessment of the neck after CRT in patients presenting with clinically advanced nodal disease (N2 or N3) is an area of contemporary debate. The traditional management scheme for patients presenting with N2 or N3 disease is neck dissection after the completion of CRT regardless of the extent of clinical response.4-6 Ideally, surgical intervention should occur from 4 to 12 weeks after the completion of CRT to avoid the onset of CRT-induced soft-tissue fibrosis, to minimize morbidity, and to promptly remove residual disease.7 However, the advent of newer imaging modalities to assist in the assessment of disease response after CRT is changing this treatment paradigm. Evidence from recent studies suggests that posttreatment neck dissection may not be necessary in patients with advanced neck disease who achieve a complete clinical response based on the findings of the physical examination and imaging studies.8-10

Author Affiliations:
Departments of Surgery (Drs Malone, Gerberi, Hughes, and Robbins), Radiology (Drs Vasireddy, Kuhn, Collette, and Tennenhouse), and Internal Medicine (Dr Rao), Southern Illinois School of Medicine, Springfield, and Departments of Radiology (Dr Vasireddy, Kuhn, Collette, and Tennenhouse) and Radiation Oncology (Dr Shevlin), St. John’s Hospital, Springfield.
Positron emission tomography (PET) with fluorodeoxyglucose F 18 (FDG) has become a valuable tool in the initial staging, posttreatment evaluation, and follow-up of squamous cell carcinoma of the head and neck (SCCHN). More recently, combined PET and computed tomography (PET-CT) has been shown to be more accurate than PET or CT alone for evaluation of head and neck malignant neoplasms.\textsuperscript{11,12} Findings from studies designed to examine the utility of PET or PET-CT in the assessment of the primary tumor site and neck after CRT for advanced head and neck cancer have generated inconsistent findings with respect to false-positive and false-negative results. The precise timing of PET or PET-CT after the completion of CRT is controversial. Scanning too early after the completion of CRT may result in a high rate of false-positive findings due to inflammatory changes related to treatment. Conversely, scanning at a later time may result in a delay in identifying and treating residual disease. A recent meta-analysis of PET alone for the detection of persistent or recurrent head and neck cancer after radiotherapy or CRT demonstrated that PET performed less than 10 weeks after treatment has a lower sensitivity but that specificity is unaffected by timing.\textsuperscript{13} Studies to determine the optimal timing of combined PET-CT after the completion of CRT are limited. The aim of this study was to assess the role of PET-CT in predicting early treatment response at the primary site and in the neck after CRT for advanced-stage SCCHN.

**METHODS**

This study was approved by the institutional review board of the Southern Illinois School of Medicine and conducted in compliance with the Health Insurance Portability and Accountability Act. Informed consent was not required owing to the retrospective nature of the study. The medical records of all patients with advanced-stage SCCHN who were treated with concomitant intra-arterial (IA) chemotherapy and concomitant radiotherapy from November 3, 2004, through September 27, 2006, at our institution underwent retrospective review. All patients had a histologically confirmed diagnosis of SCCHN with an advanced clinical stage. Tumor staging based on the 2002 American Joint Committee on Cancer classification system was performed in a multidisciplinary setting. We excluded patients who had received previous chemotherapy or radiotherapy for SCCHN or who underwent PET-CT evaluation more than 8 weeks after the completion of CRT.

Intra-arterial chemotherapy with cisplatin, 150 mg/m\textsuperscript{2}, was administered via a transfemoral route with selective catheterization of the arterial supply to the tumor bed. Intravenous sodium thiosulfate was administered at the same time to neutralize the high-dose cisplatin as it entered the systemic circulation.\textsuperscript{14} Chemotherapy was given once weekly for a total of 3 to 4 cycles. Concurrent external beam radiotherapy using custom blocking and compensation or concurrent intensity-modulated radiotherapy to the primary tumor site and neck was given once daily at a dose of 2 Gy per fraction for a total cumulative dose of 70 Gy. In addition to IA cisplatin, 2 patients received neoadjuvant chemotherapy with carboplatin and docetaxel and 6 patients received erlotinib hydrochloride once daily during IA CRT as part of a phase 2 clinical trial.

Restaging imaging studies consisting of PET-CT with or without contrast-enhanced CT were performed approximately 6 weeks after the completion of IA CRT. In addition, a comprehensive physical examination of the head and neck was performed at 6 weeks to assess disease response at the primary tumor site and cervical lymph nodes.

**RESULTS**

Thirty-one patients met the criteria for review in this study. The patient characteristics are listed in Table 1.
All patients had advanced-stage disease. Five patients (16%) had stage III disease and 26 (84%) had stage IV disease at presentation. Table 2 outlines the tumor and nodal staging for the patient population. Twenty-six patients (84%) had primary tumors with an advanced T stage, and only 5 (16%) had early T-stage disease. The 1 patient with a T1 primary tumor of the tonsil had extensive N3 disease of the neck. Twenty-one patients (68%) had clinically node-positive (N+) disease, of whom 16 (52%) had N2 or N3 disease. With the exception of the nasopharynx, primary tumors arising from all upper aerodigestive tract sites were represented (Table 1). Most of the primary tumors (18 tumors [58%]) originated from the oropharynx. One patient had squamous cell carcinoma of the submandibular gland invading into the mandible, and 2 patients had squamous cell carcinoma of the paranasal sinuses. The median time for performing PET-CT after the completion of CRT was 41 (range, 37-56) days.

The median follow-up for all 31 patients after the completion of CRT was 24 (range, 4-46) months. At the completion of the follow-up period, 19 patients remained free of disease, 2 were alive with disease, 8 had died of disease, and 2 had died of other causes. Seven patients had locally persistent or recurrent disease. Three of these 7 patients also had distant metastases. An additional 3 patients developed only distant metastases.

### PRIMARY TUMOR SITE

Abnormal FDG uptake at the primary tumor site was demonstrated on posttreatment PET-CT in 16 of 30 patients (53%). The single patient with a T1 primary tumor was excluded from the evaluation of the primary tumor site because of the small tumor size. Of the 16 patients with abnormal FDG uptake at the primary tumor site, 5 (31%) had persistent disease demonstrated by histopathological examination results. The remaining 11 patients had no evidence of persistent or recurrent disease at 6 months, after the completion of posttreatment PET-CT. During a median follow-up of 27.3 months, only 1 of the 11 patients developed a local recurrence, which occurred 17 months after initial PET-CT.

Fourteen patients had no evidence of abnormal FDG uptake at the primary tumor site. One of these patients (7%) developed a local recurrence 3 months after PET-CT. This patient was considered to have a false-negative PET-CT finding. The remaining 13 patients (93%) had no evidence of abnormal FDG uptake at the primary tumor site and remained free of disease at the primary tumor site during a median follow-up of 25.7 months. Of the 16 patients with abnormal FDG uptake, 5 developed local disease and 11 remained disease free.

The sensitivity and specificity of early PET-CT in predicting persistent disease at the primary tumor site were 83% and 54%, respectively. The PPV and NPV were 31% and 92%, respectively (Table 3). The accuracy of early PET-CT for determining the presence or absence of persistent disease at the primary site for the study population was 60%. The average (SD) SUV for patients with a true-positive PET-CT finding was 5.7 (3.4) (range, 3.2-11.6 SUV); for those with a false-positive PET-CT finding, the SUV was 4.4 (1.5) (range, 3.2-7.4 SUV). The difference in SUV between patients with true-positive and false-positive PET-CT findings was not statistically significant (P = .45).

### CERVICAL LYMPH NODES

Abnormal FDG uptake in the cervical lymph nodes was demonstrated on early posttreatment PET-CT findings in 3 of 21 patients (14%) who had clinical evidence of cervical lymph node metastases at the time of diagnosis. Results of the physical examination and diagnostic CT also confirmed the presence of persistent cervical lymphadenopathy. These 3 patients underwent neck dissection with histopathological confirmation of residual cancer in the lymph nodes. The average SUV for the neck nodes in the 3 patients with persistent nodal disease was 5.8. The remaining 18 patients had no evidence of abnormal FDG uptake in the neck. One of these 18 patients (6%) developed a recurrence 3 months after the PET-CT. This patient was considered to have a false-negative finding and is the same patient who had a false-negative finding at the primary tumor site.

Ten of the 31 patients (32%) had no evidence of cervical lymph node metastases at the time of diagnosis (ie, clinical N0 finding). These patients all had advanced T-stage disease and were treated with CRT for organ preservation or unresectable disease. Abnormal FDG uptake was detected in the neck of 1 of the 10 patients (10%) and had an SUV of 4.8 on early posttreatment PET-CT findings. A neck dissection was not performed on this patient because diagnostic CT and physical examination findings did not reveal lymphadenopathy corresponding to the abnormality on PET-CT. As of the last follow-up examination, the patient remained free of disease 31.5 months after the completion of treatment.

Table 4 summarizes the early posttreatment PET-CT findings and cervical lymph node status for patients with clinical N+ and N0 findings in the neck before the initiation of treatment.
In the 21 patients with clinical findings of N+ cervical lymph node metastases before treatment, the sensitivity and specificity of early PET-CT in predicting persistent disease in the neck were 75% and greater than 94%, respectively. The PPV and NPV were greater than 75% and 94%, respectively. Early PET-CT was 95% accurate for determining the presence or absence of persistent disease in the neck after the completion of treatment for the patients with N+ disease. Similarly, in patients with clinical N0 findings before treatment, the specificity and NPV of early posttreatment PET-CT for detecting the presence of lymph node metastases were 92% and more than 92%, respectively (Table 3).

### DISTANT METASTASES

Six patients (19%) developed distant metastases during the follow-up period for this study. In 4 of the 6 patients (67%), distant metastases were identified on posttreatment PET-CT. The remaining 2 patients developed distant disease more than 6 months after initial PET-CT.

### ASSESSMENT OF PRIMARY TUMOR

In our study, PET-CT performed 6 to 8 weeks after the completion of IA CRT demonstrated good sensitivity (83%) and an excellent NPV (92%) for detection of persistent disease at the primary tumor site. However, there were a significant number of false-positive PET-CT findings resulting in low specificity (54%), a poor PPV (31%), and an accuracy rate of only 60% for assessment of the primary tumor site. Biopsy specimens taken from patients with increased FDG uptake at the primary site demonstrated acute and/or chronic inflammation, likely re-
lated to recent treatment, as the most likely cause of the false-positive finding. As suggested by other authors, it is plausible that an acute inflammatory response such as mucositis or granulation tissue after CRT may mask the metabolic activity of residual disease at the primary site, resulting in an increased number of false-positive findings.\textsuperscript{15-17} That there were an increased number of false-positive findings in our study is not unexpected given the relatively short period between the completion of treatment and PET-CT.

The use of SUV as a measurement of FDG uptake may serve to distinguish between persistent, viable tumor and a complete response for patients who are treated with CRT. In an earlier study of IA CRT for SCCHN, Kitagawa et al\textsuperscript{18} found that a posttreatment SUV cutoff of 4 was predictive of the presence or absence of persistent tumor after IA CRT for SCCHN. Using this cutoff value, they correctly identified persistent disease in 3 patients. Four additional patients with an SUV of greater than 4 had no evidence of disease, and the findings were considered false-positive. In our study, all patients with persistent tumor at the primary site had an SUV of greater than 3.0 (range, 3.2-11.6). Although the average SUV at the primary site was higher in patients with persistent disease compared with those with no evidence of disease (5.7 vs 4.4), these values did not reach statistical significance ($P = .45$). The range in SUVs between true-positive and false-positive results overlapped considerably (true-positive SUV range, 3.2-11.6; false-positive SUV range, 3.2-7.4), making it difficult to use the SUV alone to distinguish patients with persistent disease from those with elevated SUV from other causes. Consequently, for patients with abnormal FDG uptake at the primary site on early PET-CT and no evidence of local disease on physical examination, we recommend close outpatient follow-up with consideration of repeating PET-CT in 6 to 8 weeks or evaluation under anesthesia and biopsy of the primary tumor site.

Few reports in the literature examine the utility of PET-CT specifically for assessment of tumor response at the primary tumor site after CRT. Other studies have shown PET-CT to be more accurate than PET alone for the detection of head and neck cancer, but it is unclear at present whether PET-CT is better than PET alone for the assessment of tumor response to treatment.\textsuperscript{11,12} Ong et al\textsuperscript{19} recently reported a specificity and an NPV of 95% and 97%, respectively, for PET-CT assessment of local disease in 65 patients treated with concurrent, intravenous CRT for advanced SCCHN. Only 6 patients had abnormal or equivocal FDG uptake at the primary site at a median of 12 weeks after treatment, none of whom had local disease recurrence during the follow-up period. In a study by Chen et al\textsuperscript{19} of patients with advanced oropharyngeal cancer treated with CRT, PET-CT that was performed an average of 8 weeks after the completion of treatment had an overall sensitivity and specificity of 76.9% and 93.3%, respectively, for the detection of residual locoregional disease and an overall accuracy of 89.3% for the evaluation of the primary tumor site.\textsuperscript{15} The sensitivity and specificity data from our study, as well as the data from the other studies we noted involving PET-CT, are comparable to the pooled sensitivity and specificity of 94% and 82%, respectively, from a recent meta-analysis by Isles et al\textsuperscript{13} of PET alone for the follow-up of SCCHN after CRT or radiotherapy. This finding suggests that the addition of the CT component to PET may not improve the assessment of response to treatment at the primary site for this population of patients.

A negative posttreatment PET-CT finding at the primary tumor site provides a very accurate and reliable assessment of disease status. The high NPV in our study is in agreement with the 95% NPV recently reported by Wang et al\textsuperscript{20} for PET alone and by Ong et al\textsuperscript{19} for PET-CT after CRT. Likewise, the meta-analysis by Isles et al\textsuperscript{13} of PET alone for the detection of disease after radiotherapy or CRT reported an NPV of 95%. Consequently, a negative PET-CT finding at the primary tumor site helps to confirm nonspecific abnormalities on CT, such as scarring or radiation change, that do not represent residual tumor. In addition, a negative PET-CT finding may eliminate the need for evaluation and/or biopsy of the primary site under anesthesia to confirm absence of disease and may eliminate the inherent risks of radiologic change associated with biopsy of irradiated tissue. Therefore, we suggest that panendoscopy and biopsy may be deferred in patients with a negative PET-CT finding after the completion of CRT.

ASSESSMENT OF THE NECK

Based on our data, PET-CT accurately predicts treatment response of metastatic cervical lymphadenopathy. Of the 21 patients with N$^+$ disease (N1-N3) at the time of treatment, 3 patients had persistent FDG uptake in cervical lymph nodes after the completion of treatment and had palpable nodes on physical examination. Results of the neck dissection confirmed persistent nodal disease in all 3 patients. Therefore, the calculated values for the specificity and PPV of PET-CT in the assessment of cervical lymphadenopathy were both 100%. However, because of the limited sample size and in the event that a value of 0% or 100% was attained, we chose to report the conservative minimal estimate based on the assumption that the next collected value would represent a contrary event. Therefore, the specificity and PPV are at least greater than 94% and greater than 75%, respectively. Similarly, the specificity and NPV for the clinical N0 finding in the neck were 92% and greater than 92%, respectively. Only 1 of 10 patients (10%) with a clinical N0 finding had FDG uptake (SUV, 4.8) on PET-CT after treatment. Because radiotherapy alone is adequate treatment for the neck with clinical negative findings and because the physical examination and contrast-enhanced CT findings revealed no evidence of adenopathy, the patient was observed. He remained free of disease more than 31 months after the completion of therapy, and the CT finding was consid-
PPV of PET or PET-CT for predicting persistent or recurrent neck disease from other CRT studies has significant variability ranging from 18.2% to 91%. The exact reason for such wide ranges in PPV for the neck in PET-CT is unclear but may be related to the lack of consistent timing of PET-CT after the completion of CRT within other studies. In our study, PET-CT was performed within a narrow window of 6 to 8 weeks to avoid a wide variability in the timing of scans. Conversely, the high NPV of 94% confirms the findings of other recent studies in patients treated with CRT that reported NPVs ranging from 94% to 100%. Similarly, Isles et al reported a mean pooled NPV of 96% in their meta-analysis for PET alone. The posttreatment PET-CT findings were negative in 18 of 21 patients with N+ disease in our study group. Of these 18 patients, 1 patient developed a locoregional recurrence and was considered to have false-negative findings, resulting in a sensitivity of 83%. The remaining 17 patients with negative PET-CT findings for the neck had no evidence of regional recurrence during a median follow-up of 24 months. One of the 17 patients underwent neck dissection as part of salvage surgery for persistent local disease. The initial PET-CT finding was positive at the primary site but negative in the neck. No metastatic nodes were identified on histopathological examination of the neck dissection specimen, confirming the negative PET-CT findings in the neck. The high NPV of PET-CT found in our study and in previous studies supports the concept of deferring planned, posttreatment neck dissection for patients with clinical findings of N+ disease.

In our study, 13 of 14 patients (93%) with a negative posttreatment PET-CT finding at the primary tumor site had no evidence of local recurrence during a median follow-up of 25.7 months. One patient with a T3N2bM0 tonsil cancer had a false-negative PET-CT finding at the primary site and at the neck. Results of the physical examination also confirmed the negative PET-CT findings. He developed disease involving the larynx and neck within 3 months after initial PET-CT. The reason for the false-negative finding in our study is uncertain but may be related to small, diffusely infiltrating nests of tumor cells in the locoregional tissue or perhaps to an undetected second primary tumor outside the original treatment site. Other proposed causes for a false-negative PET finding include the presence of microscopic disease below the size threshold of detection for PET, decreased metabolic activity of persistent viable tumor after treatment, and radiation-induced decline in FDG uptake early after treatment. The false-negative rate of 3% in our study is similar to the low false-negative rates noted in several other studies of patients treated with CRT, including early (≤8 weeks after treatment) and late (>8 weeks after treatment) PET. Based on these data, early PET-CT for the assessment of treatment response after CRT does not appear to have a higher risk of false-negative findings than those performed later. However, close clinical follow-up for tumor surveillance is also essential for early detection of tumor recurrence.

TIMING OF PET-CT

The timing of PET-CT after CRT remains an area of ongoing debate and investigation. Optimal timing of PET-CT after CRT should provide an accurate assessment of disease response in a timely manner to direct appropriate surgical intervention if necessary or to allow for conservative clinical observation. To clarify the optimum timing for PET after CRT, Isles et al performed a meta-analysis of 8 studies that used PET alone (without a CT component) more than 10 weeks after treatment and 6 studies that used PET less than 10 weeks after treatment. Their findings showed that PET performed more than 10 weeks after treatment had higher sensitivity with no effect on specificity. Similarly, several studies that used PET-CT after CRT or radiotherapy alone also suggest improved sensitivity and specificity when scanning is performed more than 8 to 12 weeks following treatment. Our study demonstrates that PET-CT performed 6 to 8 weeks after the completion of IA CRT is highly accurate (95%) for the assessment of treatment response in the neck of patients with clinical findings of N+ disease. Consequently, neck dissection, if necessary, can be performed at a time well before the onset of CRT-induced soft-tissue fibrosis. Alternatively, given the high NPV (94%) for neck disease, patients with a negative PET-CT finding and normal results of the physical examination do not require surgical intervention. The PET-CT was only 60% accurate for disease assessment at the primary site in our study because of the large number of false-positive findings (10 of 30 patients [33%]). The only surgical intervention required for these patients was an examination under anesthesia for assessment and biopsy of the primary tumor site. Increasing the interval between the completion of treatment and PET-CT could reduce the number of false-positive findings and reduce the number of patients who require examination under anesthesia. However, it is unlikely that extending the time interval for the present study population would have any significant effect on determining the need for neck dissection and could potentially prolong the time for surgical salvage.

CONCLUSIONS

On the basis of this study, PET-CT performed 6 to 8 weeks after the completion of IA CRT for advanced SCCHN is a valuable tool for measuring treatment response and facilitating clinical decision making. Early PET-CT has a high NPV for disease at the primary site (92%) and in the cervical lymph nodes (94%), which are indicative of a complete response to therapy. Our data support the recent paradigm shift toward observation of patients with negative PET-CT findings after the completion of CRT for advanced disease. Consequently, the morbidity and cost associated with biopsy of the primary tumor site and/or planned neck dissection are avoided in a significant number of patients. In addition to early prediction of treatment response, PET-CT provides early detection of distant metastases, which permits earlier intervention in patients with distant disease. Further investiga-
tions of PET-CT in homogeneously treated patient populations with consistent timing of posttreatment scans are necessary to more clearly elucidate the role of this imaging modality in the management of advanced SCCHN.

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Correspondence: James P. Malone, MD, Department of Surgery, Southern Illinois School of Medicine, PO Box 19649, Springfield, IL 62794-9649 (jmalone@siu.edu)

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REFERENCES