
POSITRON EMISSION TOMOGRAPHY WITH ¹⁸F-FLUORODEOXYGLUCOSE TO PREDICT PATHOLOGIC RESPONSE AFTER INDUCTION CHEMOTHERAPY AND DEFINITIVE CHEMORADIOTHERAPY IN HEAD AND NECK CANCER

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Abstract: *Background.* Conventional imaging is limited in identifying persistent disease after organ-preserving therapy for patients with advanced squamous cell carcinoma of the head and neck (SCCHN). We studied the accuracy of positron emission tomography (PET) with ¹⁸F-fluoro-2-deoxy-D-glucose (FDG-PET) in restaging disease in patients with SCCHN after they had undergone induction chemotherapy (ICT) followed by chemoradiotherapy (CRT).

Methods. Forty patients with advanced SCCHN were treated with ICT followed by CRT. FDG-PET imaging was performed to

assess for residual cancer at the primary site and in nodal metastases. Two nuclear medicine physicians interpreted PET scans in random sequence. Test characteristics were calculated with pathologic analysis or clinical recurrence as the standard.

Results. After induction chemotherapy, PET imaging had a sensitivity of 100% and specificity of 65% for detecting persistent disease at the primary tumor site. After ICT and CRT were completed, the sensitivity and specificity of PET imaging were 67% and 53%, respectively, for detecting occult disease in cervical lymph nodes.

Conclusions. FDG-PET imaging showed some correlation with pathologic response after ICT and CRT in patients with advanced SCCHN. The use of FDG-PET warrants further investigation in this setting. © 2004 Wiley Periodicals, Inc. *Head Neck* **26**: 890–896, 2004

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Squamous cell carcinoma of the head and neck (SCCHN) is a common cause of cancer-related morbidity and mortality in the United States. It is

estimated that 38,530 new cases will be diagnosed in the United States in 2004.¹ Potentially curative therapy exists for many patients seen with locally advanced SCCHN and frequently includes combined-modality treatment with chemotherapy, radiotherapy, and surgery. In recent years, research has focused on preserving organ structure and function by combining chemotherapy and radiotherapy as definitive treatment for patients with locally advanced SCCHN in lieu of primary surgery.²⁻⁶ In addition to preserving the organ, sequential therapy with induction chemotherapy followed by chemoradiotherapy allows for adjustments during treatment, attempting to optimally balance long-term benefits with treatment-related toxicities.⁷

After organ-preserving therapy is completed, patients are monitored for persistent or recurrent disease with physical examinations, conventional imaging techniques, and, at times, repeat biopsy. However, these tools have limitations because of the difficulty in differentiating tumor from edema, inflammation, and tissue reaction after chemoradiotherapy. Moreover, with postradiotherapy biopsy, the risk of significant morbidity is increased.⁸⁻¹⁰ Improved methods of detecting persistent tumor are needed.

Unlike conventional imaging studies that rely on structural means of detecting malignancy, positron emission tomography (PET) with ¹⁸F-fluoro-2-deoxy-D-glucose (FDG-PET) is a functional imaging modality that relies on the increased uptake and metabolism of glucose within tumor cells. Previous studies have demonstrated the value of FDG-PET in the diagnosis and staging of patients with SCCHN, as well as the confirmation of clinically suspected tumor recurrence.¹¹⁻¹⁹ The role of this functional imaging modality in detecting persistent disease after completion of treatment with induction chemotherapy (ICT) followed by definitive chemoradiotherapy (CRT) has not been evaluated. In this single-institution study, we studied the ability of FDG-PET to detect residual disease after organ-sparing therapy.

PATIENTS AND METHODS

Patient Selection. Forty patients with stage III or IV SCCHN (American Joint Committee on Cancer [AJCC] staging) were studied. All patients were treated at the Dana-Farber Cancer Institute between December 1999 and April 2002. Patients had histologically proven SCCHN of the oral

cavity, oropharynx, hypopharynx, larynx, or malignant cervical lymphadenopathy without an identifiable primary site of disease.

All patients were treated with ICT followed by CRT. Patients underwent PET scanning after induction chemotherapy and 4 to 12 weeks after completion of CRT. After ICT and PET imaging were completed, patients underwent repeat examination under anesthesia to assess response and to biopsy the primary tumor site. After all planned therapy, patients at high risk for persistent disease in cervical lymph nodes underwent scheduled unilateral neck dissection. Other patients were monitored by conventional means for tumor recurrence.

Induction Chemotherapy and Chemoradiotherapy.

ICT consisted of either cisplatin (100 mg/m² on day 1) and 5-fluorouracil (5-FU; 1000 mg/m²/day by intravenous continuous infusion [IVCI] on days 1-5) or cisplatin (100 mg/m² on day 1), docetaxel (75 mg/m² on day 1), and 5-FU (1000 mg/m²/day by IVCI on days 1-4). Carboplatin (dosed to area under the time-concentration curve [AUC] of 5.5) was substituted for cisplatin in some patients. Treatment was given every 3 weeks for a total of three cycles, with delays or dose modifications for toxicity. Induction therapy was followed by one of two CRT protocols. Patients received either standard fraction radiotherapy of 2 Gy per fraction over 7 weeks and concurrent carboplatin weekly (AUC of 1.5) throughout the course of radiotherapy or daily single-fraction radiotherapy followed by twice-daily concomitant boost radiotherapy. The latter group received weekly docetaxel (20-25 mg/m²) during the 4 weeks of once-daily radiotherapy.

¹⁸F-Fluoro-2-Deoxy-D-Glucose-Positron Emission Tomography Imaging.

Patients underwent PET imaging after induction chemotherapy and again 4 to 12 weeks after the completion of chemoradiotherapy. Patients fasted for 4 hours before the scan; FDG (approximately 740 MBq) was administered intravenously followed by an uptake period of 50 minutes. Most patients were given diazepam (5 mg orally) before FDG injection, and all patients were instructed not to talk or chew during uptake and imaging. Imaging was performed from the skull base to upper thorax in two bed positions. Emission data were acquired for 15 minutes at each bed position, and transmission data were acquired for 5 minutes at each bed position. Data were reconstructed

by means of segmented attenuation correction and an attenuation-weighted, ordered-subsets, expectation-maximization (OSEM-AW) reconstruction algorithm based on the work of Hudson and Cutler.^{20,21}

Two nuclear medicine physicians visually interpreted the PET images independently in a random sequence, blinded to all clinical information, including anatomic imaging data. The results were reported as either positive or negative at the primary site of disease and cervical lymph node regions. In cases of disagreement, the observers jointly reviewed the PET images until consensus was reached.

Statistical Considerations. The primary objective of the study was to define the accuracy of PET imaging in detecting persistent malignant disease after induction chemotherapy and definitive chemoradiotherapy. The standard for calculating test characteristics was pathologic assessment or overt clinical recurrence. The sensitivity, speci-

ficity, and positive and negative predictive values for PET imaging were calculated by means of standard formulas. The overall accuracy was calculated as follows: (true-positive + true-negative)/total number of scans. Results are reported with 95% confidence intervals (CIs) when available.

RESULTS

Patients. The baseline characteristics of the cohort are displayed in Table 1. The median age of the patients was 54 years (range, 29–78 years), and most of the patients were men (78%). The location of the primary tumor included the pharynx (58%), larynx (20%), oral cavity (10%), and unknown primary site (12%). Most of the patients (88%) had stage IV disease, and 38 patients (95%) had clinical evidence of malignant cervical lymphadenopathy at diagnosis. At the time of analysis, patients had been followed for a median of 20 months (range, 9.7–30 months).

Assessment of Primary Site after Induction Chemotherapy. All patients completed ICT. Thirty-three patients had a PET scan after completing ICT; seven patients did not undergo PET imaging after ICT (physician preference in five patients and patient refusal in two patients). Twenty-six of these patients had a repeat biopsy of the primary tumor site after PET imaging. Six patients did not undergo repeat biopsy (four patients with unknown primary tumor, physician discretion in one patient, and patient refusal in one patient),

Table 1. Baseline characteristics of patients with advanced squamous cell carcinoma of the head and neck treated with induction chemotherapy followed by chemoradiotherapy.

Characteristic	No. patients (%) (N = 40)
Age, median (range)	54 (29–78)
Sex	
Male	31 (78%)
Female	9 (22%)
Race	
Caucasian	39 (98%)
African-American	1 (2%)
Location of primary tumor	
Pharynx	23 (58%)
Larynx	8 (20%)
Oral cavity	4 (10%)
Unknown	5 (12%)
Tumor stage	
III	5 (12%)
IV	35 (88%)
T classification	
1	3 (8%)
2	9 (22%)
3	12 (30%)
4	11 (28%)
Unknown	5 (12%)
N classification	
0	2 (5%)
1	3 (8%)
2	22 (55%)
3	13 (32%)

Note. T and N classifications according to the American Joint Committee on Cancer. Percentages may not equal 100 owing to rounding.

Table 2. Test characteristics of ¹⁸F-fluoro-2-deoxy-D-glucose-positron emission tomography imaging for detecting residual disease in patients with advanced squamous cell carcinoma of the head and neck after induction chemotherapy and chemoradiotherapy.

Test characteristic	Value (95% CI)	
	After ICT (n = 26)	After CRT (n = 24)
Sensitivity	100% (29%–100%)	67% (36%–97%)
Specificity	65% (46%–85%)	53% (28%–79%)
Overall accuracy	69% (51%–87%)	58% (39%–78%)
Positive predictive value	27% (6%–61%)	46% (19%–73%)
Negative predictive value	100% (78%–100%)	73% (46%–99%)

Abbreviations: ICT, induction chemotherapy; CRT, chemoradiotherapy; CI, confidence interval.

Note. Sensitivity, specificity, and positive and negative predictive values were calculated with standard formulas. Overall accuracy = true-positive + true-negative/total number of scans.



FIGURE 1. Coronal (A) and sagittal (B) ^{18}F -fluoro-2-deoxy-D-glucose–positron emission tomography (FDG-PET) images of a patient with persistent FDG uptake in the primary tumor in the left base of tongue after induction chemotherapy. The repeat biopsy confirmed the presence of persistent viable tumor.

and one patient underwent biopsy before repeat PET scanning and was excluded from this analysis. Test characteristics for FDG-PET imaging were estimated with data obtained from these 26 patients, and the results are shown in Table 2. Three patients had persistent disease at the primary site on repeat biopsy, and all three had abnormal uptake on PET (sensitivity, 100%; 95% CI, 29%–100%). PET images from a patient with persistent tumor at the base of tongue can be seen in Figure 1. Twenty-three patients had negative biopsies, and 15 of these patients had negative PET scans (specificity, 65%; 95% CI, 46%–85%). The overall accuracy of PET for predicting persistent tumor at the primary site after ICT was 69% (95% CI, 51%–87%). The negative predictive value of PET imaging after ICT was 100% (95% CI, 78%–100%).

Assessment of Cervical Lymph Nodes after Chemoradiotherapy. All 40 patients completed combined chemoradiotherapy, and 37 patients underwent

PET imaging after CRT. Three patients refused further PET scanning. Twenty-four patients had a planned unilateral neck dissection, and the remaining 13 patients were followed with conventional surveillance methods for evidence of recurrence. The test characteristics for PET imaging after CRT were estimated by use of data from the 24 patients with pathologic correlation from neck dissection and are summarized in Table 2.

Nine patients had residual cancer in the resected cervical nodes, and six of these had a positive PET scan (sensitivity, 67%; 95% CI, 36%–97%). PET images from a patient with persistent viable tumor in the left cervical lymph nodes can be seen in Figure 2. Of the 15 patients with no residual disease in the cervical nodes on pathologic evaluation, eight had a negative PET scan (specificity, 53%; 95% CI, 28%–79%). The overall accuracy of PET imaging for detecting occult residual disease in cervical lymph nodes after CRT was 58% (14 of 24; 95% CI, 39%–78%). The negative predictive value for PET after

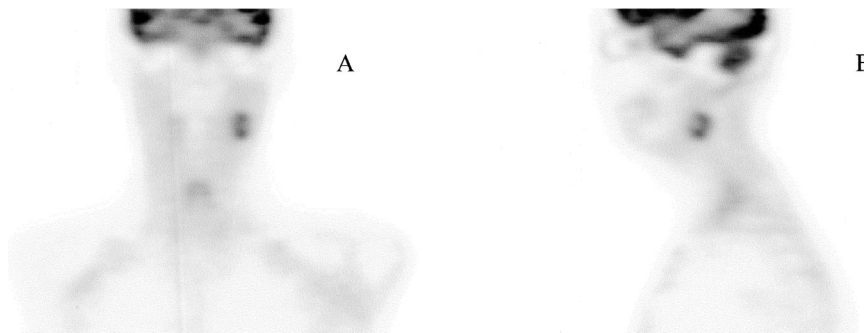


FIGURE 2. Coronal (A) and sagittal (B) ^{18}F -fluoro-2-deoxy-D-glucose–positron emission tomography (FDG-PET) images of a patient with persistent FDG uptake in the left upper cervical lymph nodes after completion of induction chemotherapy and chemoradiotherapy. Elective lymph node dissection confirmed the presence of viable tumor in the left neck.

definitive chemoradiotherapy was 73% (eight of 11; 95% CI, 46%–99%).

Thirteen patients were followed with surveillance for tumor recurrence after completing all planned therapy and undergoing PET imaging. The median follow-up after completion of CRT for this group of patients was 20.5 months (range, 16.4–30.7 months). Eight patients had a negative PET scan, and five patients had a positive PET scan after completion of CRT. All 13 patients were alive without evidence of recurrent disease at last follow-up.

DISCUSSION

We studied the ability of FDG-PET imaging to detect persistent malignant disease in patients with advanced SCCHN treated with a sequential, organ-sparing regimen of induction chemotherapy followed by chemoradiotherapy. PET imaging correlated with primary site pathologic findings after induction chemotherapy and to a lesser degree with nodal pathology at the time of neck dissection after completion of all therapy. These findings help to define the role of FDG-PET in the ongoing efforts to improve treatment planning and assessment of response to organ-sparing sequential therapy in patients with head and neck cancer.

During treatment with sequential ICT and CRT, patients undergo repeated, phased assessments of response to therapy. After induction chemotherapy is completed, the primary site of disease and the neck are re-evaluated with anatomic imaging studies and clinical examination. The primary site is often evaluated pathologically with repeat biopsies during panendoscopy. These results can provide prognostic information and aid in clinical decision making, including whether to pursue early salvage therapy or more aggressive chemoradiotherapy.^{22,23} However, this reassessment requires an examination under anesthesia (EUA) and repeat biopsies with the associated costs, risks, and discomforts. Moreover, scheduling and performing the repeat EUA can delay the initiation of definitive chemoradiotherapy, which has been shown to adversely affect outcomes.^{24,25}

No previous studies have evaluated the accuracy of PET imaging in assessing response at the primary tumor after ICT in patients with SCCHN. Our study suggests that PET scanning is predictive of pathologic response of the primary tumor after ICT with a sensitivity of 100%.

Importantly, the high negative predictive value (100%) may make this imaging modality particularly helpful in defining a favorable risk subgroup. If early PET scanning provides the same prognostic information as assessment with repeat EUA, this invasive procedure could potentially be omitted, reducing costs and expediting the delivery of planned therapy.

Managing patients after the completion of organ-sparing locoregional therapy for advanced SCCHN also poses difficulties. Patients can be surveyed longitudinally for disease recurrence with clinical examinations and conventional imaging techniques. With this strategy, if disease recurrence is detected, salvage therapy with surgical resection or repeat radiotherapy can be considered. Alternatively, neck dissection can be electively pursued after the completion of CRT in patients at clinical high risk for occult persistent disease on the basis of initial nodal status or response to ICT.

Both of these approaches have shortcomings. Because of difficulties differentiating recurrent tumor from postradiation tissue changes with physical examination and anatomic imaging, watchful waiting can be associated with delays in the detection of disease recurrence. Moreover, surgical salvage in a previously irradiated neck is difficult and has been associated with poor long-term outcomes.^{26,27} Some investigators have suggested that initial planned neck dissection might improve local disease control and ultimate survival of patients treated with organ-preserving therapy.²⁸ However, this approach is associated with unnecessary surgery in most patients who are found to have no residual occult malignancy. Also, increased morbidity such as chronic pain, facial edema, and cranial nerve dysfunction may result.

We found suggestive evidence that FDG-PET imaging is predictive of occult persistent disease after completion of chemoradiotherapy. A high percentage of patients in this study (nine of 24, 38%) were found to have persistent cancer in cervical lymph nodes at the completion of CRT. In these patients, PET scanning detected abnormal FDG uptake in six patients, resulting in a sensitivity of 67%. Because of the limited numbers of patients, test results for clinical subgroups are not available. Of the 15 patients without persistent disease, eight had a positive PET scan (specificity, 53%). A clear explanation of the high false-positive rate is unavailable. However, increased FDG uptake in tissues recovering from

the inflammation associated with CRT may have confounded the interpretation of the PET images, resulting in false-positive interpretations. The negative predictive value of PET imaging after CRT is encouraging (73%) and may further define a group of patients with a favorable prognosis.

Few studies have evaluated the use of FDG-PET imaging after the completion of definitive organ-sparing therapy. In 2000, Lowe et al²⁹ reported the results of a prospective study evaluating PET imaging in the surveillance of patients treated with an organ-sparing approach. In this study, 30 patients completed radiotherapy and were imaged at scheduled times (2 and 10 months). Sixteen patients had disease recurrence within the first year of follow-up. The sensitivity and specificity of PET imaging were 100% and 93%, respectively, for detecting subclinical disease recurrence. This was statistically superior to physical examination ($p = .002$) but not to conventional imaging.

Several differences exist between our study and that of Lowe et al. First, the timing of initial PET scanning was delayed until 2 months after completion of radiotherapy in the study by Lowe et al. In our study, several patients underwent PET scanning between 4 and 8 weeks after completion of CRT. Ongoing tissue inflammation in the radiation field may have resulted in increased FDG uptake and contributed to the higher false-positive rate seen in our study. Also, the treatment regimen in the previous report was heterogeneous. Some of the patients were treated with surgical salvage after induction chemotherapy followed by postoperative radiotherapy. These patients received only 60 Gy of radiation. In our study, all of the patients were treated with ICT followed by full-dose definitive radiotherapy with concurrent chemotherapy. This more aggressive form of local therapy will increase local toxicity and tissue reaction, potentially confounding the interpretation of PET images.

Consideration should be given to some particular aspects of our study. First, baseline FDG-PET imaging was not obtained before therapy was initiated. However, previous reports have demonstrated that SCCHN is overwhelmingly FDG-avid on PET imaging, with 92% to 100% of tumors detected with FDG-PET imaging.^{16,30,31} Second, the timing of PET scanning in this setting may affect its accuracy. Most patients in this trial underwent FDG-PET scanning soon after completing ICT and CRT. Delaying PET imaging after the completion of chemoradiotherapy may

allow for the repair of tissue injury and resolution of inflammation, possibly reducing the false-positive rate and improving the accuracy of PET imaging. The optimal timing of PET imaging warrants further study. Third, our study gives a conservative estimate of the accuracy of PET scanning because of the stringent method used during the interpretation of the PET images. The scans were independently read in a random sequence without any clinical or radiographic correlation. In clinical practice, the patients' clinical history and correlation with anatomic imaging would almost certainly improve the accuracy of PET scanning. This should be evaluated further in future studies. Last, this study evaluated a relatively small number of patients, and the findings should be confirmed in the context of future prospective trials.

In summary, our study found that PET imaging correlates with pathologic findings at the primary tumor site and to a lesser degree in cervical lymph nodes in patients with advanced SCCHN treated with an organ-preserving strategy of ICT and CRT. Additional follow-up of this patient cohort will help define the long-term prognostic significance of PET imaging in this setting. As more patients are offered organ-sparing therapy, the task of evaluating response to treatment becomes increasingly more important. If PET imaging provides accurate and timely information, it may be a helpful component of the management of such patients. Specific details about the timing and technique of PET imaging and interpretation warrant further investigation to improve on the accuracy of the test before it is considered a standard means of assessing initial response to organ-sparing therapy.

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