The Feasibility of ^{18}F-FDG PET Scans 1 Month After Completing Radiotherapy of Squamous Cell Carcinoma of the Head and Neck

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Our purpose was to prospectively evaluate the efficacy of PET with ^{18}F-FDG 1 mo after the completion of radiotherapy in patients with squamous cell carcinoma of the head and neck (SCCHN). **Methods:** Ninety-seven patients underwent ^{18}F-FDG PET scans before and after radiotherapy for nondisseminated SCCHN. The first scans were obtained no more than 4 wk before the start of radiotherapy, and follow-up scans were obtained 1 mo after the completion of radiotherapy. ^{18}F-FDG PET images were analyzed using standardized uptake values (SUVs). All patients were followed for at least 6 mo or until death. **Results:** The median SUVs of preradiotherapy primary sites and nodes were 6.5 (range, 2.3–23.0) and 5.6 (range, 1.2–16.8), respectively. The median SUVs of postradiotherapy primary sites and nodes were 1.8 (range, basal status value to 9.7) and 1.8 (range, basal status value to 8.6), respectively. Evaluation of the postradiotherapy status of tumors in these SCCHN patients showed the sensitivity of ^{18}F-FDG PET to be 88%, the specificity to be 95%, and the overall diagnostic accuracy to be 94.9%. **Conclusion:** Our results indicate that ^{18}F-FDG PET might be a valuable imaging method for evaluating the response to radiotherapy in patients with SCCHN. One month after the completion of radiotherapy is not too early for follow-up ^{18}F-FDG PET to be performed to evaluate the response to radiotherapy.

Key Words: ^{18}F-FDG PET; radiotherapy; head and neck cancer; standardized uptake value; squamous cell carcinoma

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The use of CT and MRI scans has improved the planning of radiation treatment (*1–3*) and the evaluation of radiotherapy responses. These methods are limited, however, in assessing residual viable tumors treated with radiotherapy. For example, when one is evaluating the response to radiotherapy, confusion can arise because of loss of normal tissue planes and because of tissue edema, fibrosis, granulation, necrosis, and scarring after radiotherapy (*4,5*). These limitations can be overcome with PET, a functional imaging technique that can provide biologic information about tissue metabolism.

Although biopsy of the remaining tissue can provide an unambiguous evaluation of whether the patient has residual disease, biopsy is invasive and associated with the risks of bleeding, infection, delayed wound healing, and necrosis. In addition, differentiating between residual viable tumor cells and nonviable tumor cells is difficult because of changes in cell morphology due to radiation. A method that accurately evaluates the treatment response to definitive radiotherapy but reduces the need for invasive techniques is therefore needed. Because ^{18}F-FDG uptake is likely to correlate with the number of viable tumor cells and their metabolic activity, ^{18}F-FDG PET may be particularly helpful for differentiating between recurrent and residual tumors early after radiotherapy, for deciding if salvage treatment is necessary, and for detecting postradiation changes (*6–13*). The other method—to wait and see—is associated with the risks of disease progression and salvage treatment delay. Early discrimination is important because it can enable prompt salvage treatment when the size of the residual tumor volume has been reduced. When used to evaluate the response to radiotherapy, ^{18}F-FDG PET is usually performed 3–4 mo after the end of radiotherapy to avoid false-positive findings (*14,15*). It has also been suggested that a scan obtained at the time of the first clinical follow-up examination can provide reliable and relevant information (*16*). We found, however, that in 22 patients with squamous cell carcinoma of the head and neck (SCCHN), ^{18}F-FDG PET performed earlier may be able to identify more patients with residual disease who can benefit from salvage surgery (*17*). There are no guidelines for the optimal timing of posttreatment ^{18}F-FDG PET in patients with head and neck cancer.

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Therefore, we prospectively evaluated the clinical efficacy of ^{18}F-FDG PET performed 1 mo after the completion of radiotherapy for determining the response to radiotherapy in patients with SCCHN.

MATERIALS AND METHODS

Patients

Between August 2001 and September 2004, 97 SCCHN patients were diagnosed and treated with definitive radiotherapy at the Asan Medical Center, Ulsan University College of Medicine, Seoul, Korea. Eligible patients included those with poorly differentiated or undifferentiated carcinomas and no distant metastases. This clinical study was approved by the institutional review board of our hospital, and all patients provided oral or written informed consent.

The staging work-up consisted of taking a medical history and performing a physical examination, panendoscopy with tumor measurements, a biopsy, a dental evaluation, a bone scan, chest radiography, a complete blood count, liver function testing, and contrast-enhanced CT or MRI of the head and neck. At the time of the second ^{18}F-FDG PET scan, CT or MRI was not routinely performed, but all patients underwent a routine examination including fiberoptic endoscopy of the nasopharynx or larynx. CT or MRI of the nasopharynx, including the neck, was performed if the primary tumor invaded the parapharyngeal or intracranial space.

PET

All patients fasted for at least 8 h before undergoing ^{18}F-FDG PET and, to stimulate ^{18}F-FDG excretion from the renal calyces and subsequent voiding, drank 1 L of water just before the scan began. In each patient, including those with diabetes mellitus, the serum glucose concentration had to be under control and less than 120 mg/dL; the average blood glucose concentration before intravenous injection of ^{18}F-FDG was 99 $\pm$ 12 mg/dL. All patients rested for at least 1 h before undergoing PET. About 555 MBq (15 mCi) of ^{18}F-FDG, of radiochemical purity greater than 99%, were injected into a peripheral vein of the anterior upper arm. Sixty minutes later, PET studies from the skull base to the pelvis were obtained with septa (2-dimensional mode) on a full-ring scanner—88 on an ECAT Exact HR+ PET scanner (CPS/Siemens) and 9 on a Biograph Sensation PET/CT scanner (CPS/Siemens). These scanners have an axial field of view of 15.5 cm and a full width at half maximum of 4.6 mm at the center of the field of view. The PET scans were obtained at 4 and 6 min per bed position for transmission and emission scanning, respectively. PET images were reconstructed on a 128 $\times$ 128 matrix using an ordered-subsets expectation maximization algorithm for 8 subsets and 2 iterations, with a 6-mm gaussian filter. A segmented attenuation-correction algorithm was used with ordered-subsets expectation maximization. Attenuation correction was performed using 2 different methods. The ECAT Exact HR+ was used for attenuation correction of the PET images obtained on that scanner, and the CT data from the Biograph Sensation were used for attenuation correction of the PET images obtained on that scanner. The maximal standardized uptake value (SUV_{max}) (*18*) was measured for 1 pixel of each region of interest, and the SUV was determined using the whole-body attenuation-corrected image according to the following equation: SUV = maximum regional activity (Bq/mL)/(injected activity [Bq]/lean body weight [g]). The region of interest was defined by visual interpretation on the workstation computer. No correction was made for glucose or partial volume. All PET images were interpreted by a professor of nuclear medicine. An SUV_{max} reading of 3.0 was used to distinguish between malignancy and normal tissue. If the SUV was 2.5–3.5, a biopsy was performed whenever possible. If a biopsy could not be performed, the clinical outcome was determined by follow-up status.

Response Evaluation and Follow-up

Immediately after and 1 mo after the completion of radiotherapy, patient response was evaluated by physical examination and fiberoptic endoscopy. If residual disease was suspected or abnormal uptake of ^{18}F-FDG was seen, a biopsy was performed for confirmation. All patients were followed up for at least 6 mo or until death. In this study, the period of response evaluation was 6 mo after the completion of radiotherapy. Recurrence was defined as evidence of disease after 6 mo. However, if the neck node was palpable, or if there was a residual mass in the nasopharynx, larynx, or hypopharynx as shown by fiberoptic endoscopy, we performed further studies such as CT, MRI, or neck sonography 2 mo after radiotherapy.

Study Design and Statistical Analysis

The baseline ^{18}F-FDG PET scan of each patient was obtained no more than 4 wk before the initiation of radiotherapy. All patients also underwent whole-body ^{18}F-FDG PET within 4–6 wk of the completion of radiotherapy, as described previously (*17*). CT or MRI was not routinely performed at the same time as the postradiotherapy ^{18}F-FDG PET scan. If a residual mass was observed in the primary tumor site and the residual node was palpable, CT or MRI was performed 1 mo later with strict clinical follow-up. The cutoff SUV was 3.0, with SUVs of less than 3.0 defined as negative and SUVs of 3.0 or more defined as positive, the same value as that used in a previous study (*19*). However, because SUVs are semiquantitative, it is not possible to determine the specific value for reference. The results for primary sites and lymph nodes were separately evaluated to determine the sensitivity, specificity, and accuracy of ^{18}F-FDG PET. If a patient had 2 or more metastatic lymph nodes, only the one with the highest SUV was measured. *P* values of less than 0.05 were considered statistically significant. Categorizations of continuous variables used medians as cutoff values. The distributions of continuous outcome variables were compared among subgroups, with the Mann–Whitney *U* test used for binary outcomes.

RESULTS

Demographic Data

Of the 97 patients, 85 were men and 12 were women, with a median age of 57 y (range 17–83 y). The patient characteristics are summarized in Table 1. The follow-up period ranged from 6 to 39 mo (median, 20 mo). Fifty patients had nasopharyngeal cancer, 16 had hypopharyngeal cancer, 16 had carcinoma of the larynx, 8 had carcinoma of the oropharynx, 4 had oral cavity cancer, and 3 had carcinoma of the paranasal sinus. After radiotherapy, 86 patients (89%) showed locoregional complete responses. Partial responses to radiotherapy were confirmed by biopsy or salvage surgery. Of the 86 patients who had locoregional complete responses, 14 had locoregional recurrent tumors and 8 had distant metastases. Of the 14 cases of locoregional

TABLE 1
Patient Characteristics at Baseline (n = 97)

Characteristic	Value
Sex (n)	
Male	85 (87.6%)
Female	12 (12.4%)
Age (y)	
Range	17–83
Median	57
Primary site (n)	
Nasopharyngeal	50 (51.5%)
Hypopharyngeal	16 (16.5%)
Glottic	11 (11.3%)
Oropharyngeal	8 (8.2%)
Supraglottic	5 (5.2%)
Oral cavity	4 (4.1%)
Paranasal sinus	3 (3.1%)
Concurrent chemoradiotherapy (n)	
Yes	49 (50.5%)
No	48 (49.5%)
Radiation dose (Gy)	
Range	64.2−80.0
Median	72.0

failure, 7 occurred at the primary site, 5 at the regional nodes, and 2 at both sites.

^{18}F-FDG PET Findings

Using ^{18}F-FDG PET, we evaluated a total of 388 SUV sites before and after radiotherapy in 97 patients. Before radiotherapy, the median SUV at the primary sites was 6.5 (range, 2.3–23.0), and the median SUV at the neck nodes was 5.6 (range, 1.2–16.8). One month after the completion of radiotherapy, the median SUV at the primary sites was 1.8 (range, basal status value to 9.7), and the medium SUV at the neck nodes was 1.8 (range, basal status value to 8.6) (Table 2). Basal status is classed as a level of ^{18}F-FDG uptake that is similar to the background ^{18}F-FDG uptake level of normal tissue and is usually an SUV of about 1.0. This term was used because physiologic ^{18}F-FDG uptake of normal tissue varies. At the primary sites and neck nodes, the SUVs for true- and false-positive lesions ranged from 3.1 to 9.7 at primary sites and from 3.2 to 4.4 at neck nodes. A positive PET result was defined as an SUV of at least 3. The mean SUV of true-positive lesions was significantly higher than that of false-positive lesions (3.7 ± 0.41 vs. 6.0 ± 2.02; P = 0.003, t test).

Postradiotherapy PET image analysis showed that 23 sites were positive for uptake and 171 were negative (Table 3). Of the 23 positive sites, 15 (65.2%) were true-positive, as shown by biopsy results or evidence of recurrence after at least 6 mo. Of the 171 negative sites, 2 (1.2%) were considered to be false-negative. Thus, the sensitivity of ^{18}F-FDG PET in evaluating the postradiotherapy status of these SCCHNs was 88.2% and the specificity was 95.5%. The overall diagnostic accuracy of this method was 94.9%. The lack of false-negative findings for neck nodal disease is particularly interesting, making the sensitivity of this method for neck nodes 100%. The diagnostic accuracy was 90.7% at primary sites and 99.0% at the neck nodes (P = 0.002, χ^2 test). Figure 1 shows a typical example of ^{18}F-FDG PET scans of a patient with tumors that had a complete metabolic response as shown by ^{18}F-FDG PET but that were classed as morphologically nonresponsive on CT.

The nonspecific inflammation resulting from radiotherapy of the primary tumor site did not reduce ^{18}F-FDG uptake below the basal level, although there were no residual tumor cells. However, reductions of less then 50% in initial gross tumor volume were observed in 9 patients, 8 of whom were pathologically positive and 1 of whom was pathologically negative. The SUVs of the pathologically positive cases ranged from 4.1 to 9.7 (mean, 6.3), whereas the SUV of the pathologically negative patient was 1.9. These 9 patients, who were diagnosed with clinically residual disease, were found to have residual tumor tissue on biopsy or

TABLE 3
Results of ^{18}F-FDG PET for SCCHN (n = 97)

Parameter	Primary site	Neck node	Total
TP (n)	10	5	15
FN (n)	2	0	2
FP (n)	7	1	8
TN (n)	78	91	169
Sensitivity* (%)	83.3	100.0	88.2
Specificity† (%)	91.8	98.9	95.5
Positive predictive value (%)	58.8	83.3	65.2
Negative predictive value (%)	97.5	100.0	98.8
Overall diagnostic accuracy‡ (%)	90.7	99.0	94.9

*[TP/(TP + FN)] × 100.
†[TN/(TN + FP)] × 100.
‡[F × AP + (1 − F) × AN] × 100.
TP = true-positive; FN = false-negative; FP = false-positive; TN = true-negative; F (fraction of patients with positive test) = [TP + FP]/[TP + FN + FP + TN]; AP (accuracy of positive test) = TP/[TP + FP]; AN (accuracy of negative test) = TN/[TN + FN].

TABLE 2
SUV of 97 Tumors Before and 1 Month After Radiotherapy

Timing	SUV range, with median in parentheses	
	Primary site	Lymph node
Before radiotherapy	2.3–23.0 (6.5)	1.2–16.8 (5.6)
After radiotherapy	Basal status value to 9.7 (1.8)	Basal status value to 8.6 (1.8)

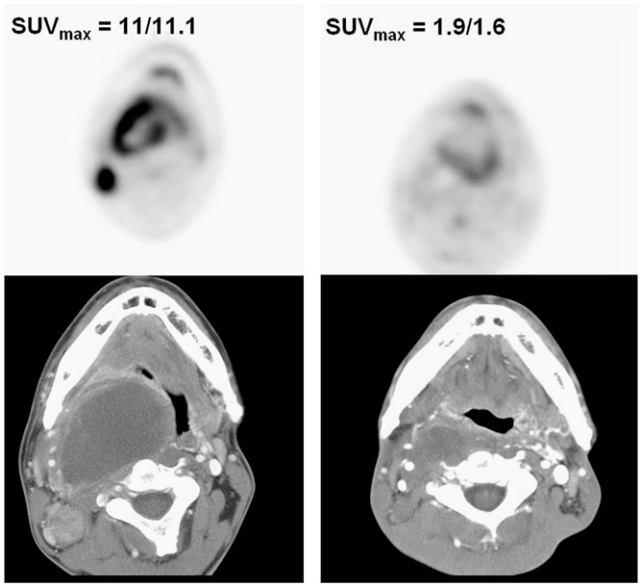

FIGURE 1. Example of complete metabolic response. CT images after radiation therapy showed residual disease (bottom right panel), but no pathologic evidence of disease was observed.

fine-needle aspiration. With the exception of 1 case, all PET-negative nodes were less than 1.5 cm as measured by neck sonography.

The ^{18}F-FDG PET–negative and CT-positive case is presented in Figure 1. This patient was a 29-y-old man who presented with a swollen right neck node, dysphagia, and odynophagia. Panendoscopy showed a large, bulky tumor occupying the entire nasopharyngeal cavity and extending into the right lateral pharyngeal wall. The clinical stage according to the 5th edition of the staging manual (*20*) of the American Joint Committee on Cancer was T2b N2 M0. The residual primary tumor and neck node were observed on CT 1 mo after the completion of radiotherapy, although ^{18}F-FDG PET showed a complete metabolic response (SUV, 1.9). Three months after radiotherapy, salvage surgery was performed to remove the residual tumor. The pathologic finding was total necrosis. The patient is in a locoregional control state at present.

DISCUSSION

Among the methods available for evaluating residual abnormalities, including fibrosis, necrosis, inflammation, and viable tumor after radiotherapy, there is no easy discriminative and objective method for measuring the response to radiotherapy in patients with head and neck cancer. However, such a diagnostic method is needed to enable oncologists to more easily explain outcomes to patients. In clinical practice, most of the conventional follow-up diagnostic methods have often been nonspecific and unsatisfactory for detecting early recurrent cancer in asymptomatic patients (*21*). CT or MRI scans have been used mainly for tumor diagnosis and evaluation of treatment response, but these methods reflect only morphologic tumor changes. In particular, these methods are not specific for the detection of viable residual tumors after radiotherapy. By contrast, ^{18}F-FDG PET scans are constantly being improved and can now be used for initial diagnosis, staging work-up, and detection of residual or recurrent disease (*22–28*). In this study, we used ^{18}F-FDG PET to evaluate the response 4 wk after the completion of radiotherapy. Theoretically, metabolic imaging with ^{18}F-FDG PET can differentiate between viable residual tumors and postradiotherapy nonmalignant conditions, and ^{18}F-FDG PET is an increasingly popular oncology-imaging method. It is particularly useful for radiation oncologists because it can distinguish tumor recurrence from radiation fibrosis and necrosis (*28–32*). The results reported here indicate that, when a residual mass is observed on CT scans, ^{18}F-FDG PET may be the most accurate and earliest noninvasive technique to differentiate recurrence from postradiotherapy changes. That is, an ^{18}F-FDG uptake level of greater than 3 SUVs for the residual mass indicates a high probability of persistent disease, and salvage therapy should strongly be considered (*19*). We previously reported that a maximum SUV of 2.5 is the cutoff value for negative PET findings (*17*). We have shown here that ^{18}F-FDG PET performed as early as 4 wk after the completion of radiotherapy can be used to evaluate the response to radiotherapy in patients with SCCHN. The optimal timing of postradiotherapy ^{18}F-FDG PET in cases of head and neck cancer is a subject of debate. The hypothesis is that metabolic change is faster than morphologic change. If residual disease was suspected, CT/MRI scans were performed 2 mo after radiotherapy. Therefore, CT or MRI findings did not affect interpretation of the ^{18}F-FDG PET findings in this study. The response evaluations were not affected by CT or MRI results but were determined only by the results of ^{18}F-FDG PET.

Previous studies have reported that the sensitivity of ^{18}F-FDG PET is higher than the specificity when ^{18}F-FDG PET is used to evaluate the response to radiotherapy (*28,30,33–35*). In our study, however, the specificity of ^{18}F-FDG PET was higher than its sensitivity. The cutoff value of SUV may be subjective, however, which would affect the sensitivity and specificity of this method. Although the presence of viable tumor cells would be expected to increase the ^{18}F-FDG uptake level, this method could not detect a very small volume of residual disease (a tumor of $<$5-mm diameter). When used to diagnose malignant tumors, ^{8}F-FDG PET would be expected to be lower in sensitivity than in specificity. A reduction in ^{18}F-FDG uptake would indicate a decrease in the number of viable tumor cells. According to previous reports of PET performed 12 wk after therapy, the negative predictive value of PET is high but the positive predictive value is low (*19,36*), and similar results were reported in this study. Therefore, it is possible that patients with negative ^{18}F-FDG PET results achieved a complete response after radiotherapy. According to previous reports, when ^{18}F-FDG PET is performed earlier, the positive

predictive value is higher than the negative predictive value (*23,37,38*). Moreover, the authors of these papers concluded that performing ^{18}F-FDG PET too early can give inaccurate results. By contrast, the present study and similar results show that the negative predictive value was much higher than the positive predictive value (*19,36*). We cannot clearly explain the reason for the discrepancy between previous reports and these findings.

In addition to being seen in malignant tumors, ^{18}F-FDG uptake is also seen in various noncancerous conditions. For example, ^{18}F-FDG uptake is increased in inflammatory conditions—a fact that limits the use of ^{18}F-FDG PET in the diagnosis of early-stage tumors and after radiotherapy. Although the level of ^{18}F-FDG uptake by malignant tumors is higher than the level seen in inflammatory conditions, the borderline between malignant and inflammatory conditions is not clear. Therefore, determination of the cutoff value for a negative PET result was of practical importance. Several previous studies have used SUVs for analysis of ^{18}F-FDG uptake (*11,15,19,39,40*). Although there are various diagnostic methods, additional clinical findings such as initial disease status, treatment method, and patient status are essential when final clinical decisions are made.

The timing of ^{18}F-FDG PET after radiotherapy is important when one is evaluating the response of both the primary tumor and the neck nodes; however, the optimal timing of ^{18}F-FDG PET after radiotherapy remains controversial. Most studies have reported that an interval of 3–4 mo after completion of radiotherapy is required to avoid false-negative results (*23,37*). In addition, these reports suggest that ^{18}F-FDG PET should be performed more than 3 mo after the completion of radiotherapy to reduce the probability of false-positive results (*11,41*). We think that clinical decision making should not be delayed for that length of time, in view of the anxiety of a patient who has to wait to learn the outcome of radiotherapy. Rogers et al. studied 12 patients with stage III or IV cancer of the head and neck (according to the classification of the American Joint Committee on Cancer) who underwent PET 1 mo after the completion of definitive radiation, and unfortunately, only 14% showed true-negative results (*37*). We argue that the recommendation to wait 3–4 mo is contraindicated by our results (*17*). Another problem associated with delaying ^{18}F-FDG PET is that delay may lead to inappropriate salvage times or loss of patients to follow-up. We think that the purpose of diagnosis is to provide appropriate treatment and to improve the patients' satisfaction. Imaging methods for evaluating the response to radiotherapy should provide information as early as possible because of the need to rapidly decide on the necessity of salvage treatment. Although the optimal timing of ^{18}F-FDG PET to evaluate radiotherapy response has not been established, in our practice we aim to get information on the residual tumor as soon as possible and to reduce the time between completion of radiotherapy and ^{18}F-FDG PET. Our data indicate that a 1-mo interval between the end of radiotherapy and ^{18}F-FDG PET is reliable and that ^{18}F-FDG PET can reliably and accurately identify recurrent or residual disease. In addition, early ^{18}F-FDG PET scans can be useful for neck node evaluation. Moreover, scans performed after 3–4 mo increase the risk of regional progression or distant spread and of radiation-induced fibrosis. Thus, we believe that delaying ^{18}F-FDG PET does not provide any further information to aid clinical decision making.

CONCLUSION

We have shown here that ^{18}F-FDG PET performed 1 mo after the end of radiotherapy is a valuable diagnostic method for evaluating the response to radiotherapy in patients with SCCHN. These findings indicate that follow-up ^{18}F-FDG PET 1 mo after completion of radiotherapy is not too early for evaluating the response to radiotherapy. If patients have negative ^{18}F-FDG PET findings, we recommend only 1 mo of follow-up; however, when positive ^{18}F-FDG PET findings are observed, further evaluation is needed.

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REFERENCES

1. Goitein M, Abrams M. Multi-dimensional treatment planning: I. Delineation of anatomy. *Int J Radiat Oncol Biol Phys.* 1983;9:777–787.
2. Nagata Y, Nishidai T, Abe M, et al. CT simulator: a new 3-D planning and simulating system for radiotherapy: Part 2. Clinical application. *Int J Radiat Oncol Biol Phys.* 1990;18:505–513.
3. Nishidai T, Nagata Y, Takahashi M, et al. CT simulator: a new 3-D planning and simulating system for radiotherapy: Part 1. Description of system. *Int J Radiat Oncol Biol Phys.* 1990;18:499–504.
4. Bronstein AD, Nyberg DA, Schwartz AN, Shuman WP, Griffin BR. Soft-tissue changes after head and neck radiation: CT findings. *AJNR.* 1989;10:171–175.
5. Glazer HS, Niemeyer JH, Balfe DM, et al. Neck neoplasms: MR imaging. Part II. Posttreatment evaluation. *Radiology.* 1986;160:349–354.
6. Larson SM, Weiden PL, Grunbaum Z, et al. Positron imaging feasibility studies. II: Characteristics of 2-deoxyglucose uptake in rodent and canine neoplasms—concise communication. *J Nucl Med.* 1981;22:875–879.
7. Wahl RL, Hutchins GD, Buchsbaum DJ, Liebert M, Grossman HB, Fisher S. ^{18}F-2-deoxy-2-fluoro-D-glucose uptake into human tumor xenografts. Feasibility studies for cancer imaging with positron-emission tomography. *Cancer.* 1991;67:1544–1550.
8. Abe Y, Matsuzawa T, Fujiwara T, et al. Assessment of radiotherapeutic effects on experimental tumors using ^{18}F-2-fluoro-2-deoxy-D-glucose. *Eur J Nucl Med.* 1986;12:325–328.
9. Di Chiro G, Oldfield E, Wright DC, et al. Cerebral necrosis after radiotherapy and/or intraarterial chemotherapy for brain tumors: PET and neuropathologic studies. *AJR.* 1988;150:189–197.
10. Patronas NJ, Di Chiro G, Brooks RA, et al. Work in progress: [^{18}F] fluorodeoxyglucose and positron emission tomography in the evaluation of radiation necrosis of the brain. *Radiology.* 1982;144:885–889.
11. Greven KM, Williams DW III, Keyes JW Jr, et al. Distinguishing tumor recurrence from irradiation sequelae with positron emission tomography in patients treated for larynx cancer. *Int J Radiat Oncol Biol Phys.* 1994;29:841–845.
12. Hawkins RA, Hoh C, Dahlbom M, et al. PET cancer evaluations with FDG. *J Nucl Med.* 1991;32:1555–1558.

13. Sigurdson ER, Cohen AM. Commentary on "the applications of PET in clinical oncology." *J Nucl Med.* 1991;32:649–650.
14. Greven KM, Williams DW III, Keyes JW Jr, et al. Positron emission tomography of patients with head and neck carcinoma before and after high dose irradiation. *Cancer.* 1994;74:1355–1359.
15. Kitagawa Y, Sadato N, Azuma H, et al. FDG PET to evaluate combined intra-arterial chemotherapy and radiotherapy of head and neck neoplasms. *J Nucl Med.* 1999;40:1132–1137.
16. Goerres GW, Schmid DT, Bandhauer F, et al. Positron emission tomography in the early follow-up of advanced head and neck cancer. *Arch Otolaryngol Head Neck Surg.* 2004;130:105–109.
17. Nam SY, Lee S, Im KC, et al. Early evaluation of the response to radiotherapy of patients with squamous cell carcinoma of the head and neck using ^{18}FDG-PET. *Oral Oncol.* 2005;41:390–395.
18. Strauss LG, Conti PS. The applications of PET in clinical oncology. *J Nucl Med.* 1991;32:623–648.
19. Yao M, Smith RB, Graham MM, et al. The role of FDG PET in management of neck metastasis from head-and-neck cancer after definitive radiation treatment. *Int J Radiat Oncol Biol Phys.* 2005;63:991–999.
20. Fleming I, Cooper J, Henson D. *AJCC Cancer Staging Manual.* 5th ed. Philadelphia, PA: Lippincott-Raven; 1997.
21. Grigsby PW, Siegel BA, Dehdashti F, Mutch DG. Posttherapy surveillance monitoring of cervical cancer by FDG-PET. *Int J Radiat Oncol Biol Phys.* 2003;55:907–913.
22. Farber LA, Benard F, Machtay M, et al. Detection of recurrent head and neck squamous cell carcinomas after radiation therapy with 2-^{18}F-fluoro-2-deoxy-D-glucose positron emission tomography. *Laryngoscope.* 1999;109:970–975.
23. Greven KM, Williams DW III, McGuirt WF Sr, et al. Serial positron emission tomography scans following radiation therapy of patients with head and neck cancer. *Head Neck.* 2001;23:942–946.
24. Lapela M, Eigtved A, Jyrkkio S, et al. Experience in qualitative and quantitative FDG PET in follow-up of patients with suspected recurrence from head and neck cancer. *Eur J Cancer.* 2000;36:858–867.
25. Stokkel MP, Terhaard CH, Hordijk GJ, van Rijk PP. The detection of local recurrent head and neck cancer with fluorine-18 fluorodeoxyglucose dual-head positron emission tomography. *Eur J Nucl Med.* 1999;26:767–773.
26. Kresnik E, Mikosch P, Gallowitsch HJ, et al. Evaluation of head and neck cancer with ^{18}F-FDG PET: a comparison with conventional methods. *Eur J Nucl Med.* 2001;28:816–821.
27. Teknos TN, Rosenthal EL, Lee D, Taylor R, Marn CS. Positron emission tomography in the evaluation of stage III and IV head and neck cancer. *Head Neck.* 2001;23:1056–1060.
28. Anzai Y, Carroll WR, Quint DJ, et al. Recurrence of head and neck cancer after surgery or irradiation: prospective comparison of 2-deoxy-2-[F-18]fluoro-D-glucose PET and MR imaging diagnoses. *Radiology.* 1996;200:135–141.
29. Chaiken L, Rege S, Hoh C, et al. Positron emission tomography with fluorodeoxyglucose to evaluate tumor response and control after radiation therapy. *Int J Radiat Oncol Biol Phys.* 1993;27:455–464.
30. Lapela M, Grenman R, Kurki T, et al. Head and neck cancer: detection of recurrence with PET and 2-[F-18]fluoro-2-deoxy-D-glucose. *Radiology.* 1995; 197:205–211.
31. Bailet JW, Sercarz JA, Abemayor E, Anzai Y, Lufkin RB, Hoh CK. The use of positron emission tomography for early detection of recurrent head and neck squamous cell carcinoma in postradiotherapy patients. *Laryngoscope.* 1995;105: 135–139.
32. Wong RJ, Lin DT, Schoder H, et al. Diagnostic and prognostic value of [(18)F]fluorodeoxyglucose positron emission tomography for recurrent head and neck squamous cell carcinoma. *J Clin Oncol.* 2002;20:4199–4208.
33. Fischbein NJ, OS AA, Caputo GR, et al. Clinical utility of positron emission tomography with ^{18}F-fluorodeoxyglucose in detecting residual/recurrent squamous cell carcinoma of the head and neck. *AJNR.* 1998;19:1189–1196.
34. Kao CH, Shiau YC, Shen YY, Yen RF. Detection of recurrent or persistent nasopharyngeal carcinomas after radiotherapy with technetium-99m methoxyisobutylisonitrile single photon emission computed tomography and computed tomography: comparison with 18-fluoro-2-deoxyglucose positron emission tomography. *Cancer.* 2002;94:1981–1986.
35. Ng SH, Joseph CT, Chan SC, et al. Clinical usefulness of ^{18}F-FDG PET in nasopharyngeal carcinoma patients with questionable MRI findings for recurrence. *J Nucl Med.* 2004;45:1669–1676.
36. Porceddu SV, Jarmolowski E, Hicks RJ, et al. Utility of positron emission tomography for the detection of disease in residual neck nodes after (chemo)-radiotherapy in head and neck cancer. *Head Neck.* 2005;27:175–181.
37. Rogers JW, Greven KM, McGuirt WF, et al. Can post-RT neck dissection be omitted for patients with head-and-neck cancer who have a negative PET scan after definitive radiation therapy? *Int J Radiat Oncol Biol Phys.* 2004;58: 694–697.
38. Kubota K, Yokoyama J, Yamaguchi K, et al. FDG-PET delayed imaging for the detection of head and neck cancer recurrence after radio-chemotherapy: comparison with MRI/CT. *Eur J Nucl Med Mol Imaging.* 2004;31:590–595.
39. Ahuja V, Coleman RE, Herndon J, Patz EF Jr. The prognostic significance of fluorodeoxyglucose positron emission tomography imaging for patients with nonsmall cell lung carcinoma. *Cancer.* 1998;83:918–924.
40. Choi NC, Fischman AJ, Niemierko A, et al. Dose-response relationship between probability of pathologic tumor control and glucose metabolic rate measured with FDG PET after preoperative chemoradiotherapy in locally advanced non-small-cell lung cancer. *Int J Radiat Oncol Biol Phys.* 2002;54:1024–1035.
41. Eichhorn T, Schroeder HG, Glanz H, Schwerk WB. Histologically controlled comparison of palpation and sonography in the diagnosis of cervical lymph node metastases [in German]. *Laryngol Rhinol Otol (Stuttg).* 1987;66:266–274.