14. Levenback C, Burke TW, Gershenson DM, Morris M, Malpica A, Ross MI. Intraoperative lymphatic mapping for vulvar cancer. *Obstet Gynecol* 1994;84:163–167.
15. Levenback C, Burke TW, Morris M, Malpica A, Lucas KR, Gershenson DM. Potential applications of intraoperative lymphatic mapping in vulvar cancer. *Gynecol Oncol* 1995;59:216–220.
16. Kapteijn BA, Nieweg OE, Liem IH, et al. Localizing the sentinel node in cutaneous melanoma: gamma probe detection versus blue dye. *Ann Surg Oncol* 1997;4:156–160.
17. Stehman FB, Bundy BN, Dvoretsky PM, Creasman WT. Early stage I carcinoma of the vulva treated with ipsilateral superficial inguinal lymphadenectomy and modified radical hemivulvectomy: a prospective study of the gynecologic oncology group. *Obstet Gynecol* 1992;79:490–497.
18. McCarthy WH, Thompson JF, Uren RF. Invited commentary. *Arch Surg* 1995;130:659–660.
19. Brady MS, Coit DG. Sentinel lymph node evaluation in melanoma. *Arch Dermatol* 1997;133:1014–1020.

Fluorine-18-FDG Detection of Laryngeal Cancer Postradiotherapy Using Dual-Head Coincidence Imaging

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The aim of this study was to investigate whether, in patients treated for laryngeal carcinoma, a differentiation was possible between local recurrence or local control using a dual-head SPECT camera with PET capability. **Methods:** Eleven male patients (age range 51–71 yr; mean age 62 yr) who had previously undergone radiotherapy for laryngeal carcinoma were studied using 5 mCi (185 MBq) ^{18}F-fluorodeoxyglucose (FDG). The mean interval between initial treatment and ^{18}F-FDG PET was 21.9 mo (range 6–65 mo). Six patients had histologically proven local recurrence and five patients showed local control clinically. The mean follow-up in the local control group was 5.2 mo. **Results:** Fluorine-18-FDG PET scans were positive in all six local relapses. Histopathological examination of the laryngectomy specimen revealed a mean tumor size of 2.6 cm (range 1.4–5.0 cm). In one patient, false-positive uptake was seen in an inflammatory lymph node. Fluorine-18-FDG PET scans were negative in all five patients with local control. **Conclusion:** It is possible to differentiate between local recurrence and local control in patients previously treated for laryngeal carcinoma with a dual-head SPECT scanner with PET capability.

Key Words: PET; SPECT; laryngeal carcinoma; local recurrence; fluorine-18-fluorodeoxyglucose

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With an incidence of about 600 cases per year, laryngeal carcinomas represent 2% of the newly diagnosed cancers in the Netherlands (*1*). Modern treatment of these tumors consists of high-dose radiation therapy, either as a single therapy or in combination with surgical intervention. These procedures may cause a variety of acute and late post-treatment changes such as edema, fibrosis and scarring (*2*). In these patients, recurrent disease, which can occur in as many as 50% of patients with advanced primary disease (*3*), may be difficult to distinguish from post-treatment reactions. CT or MRI frequently do not accurately predict disease recurrence (*4,5*). In addition, post-treatment biopsies may reveal false-negative results and should be performed with caution, since the capacity of the irradiated tissue to recover is diminished.

Tumor imaging with ^{18}F-2-fluoro-2-deoxy-D-glucose (FDG) has yielded promising results for detecting a variety of primary tumors (*6–9*). The mechanism of FDG uptake is well documented and is based on the increased glycolysis that is associated with malignancy compared with most normal tissues (*10,11*). However, because of the high cost and limited availability of dedicated PET scanners, alternative methods of imaging the 511-keV photons of positron emitters have been sought. With a dual-head SPECT scanner with a coincidence module, PET scanning with FDG is possible.

The aim of this study was to investigate if a differentiation could be made in patients being treated for laryngeal carcinoma between malignant and benign lesions using a dual-head SPECT scanner with a coincidence module.

MATERIALS AND METHODS

Patients

Eleven male patients (mean age 62 yr) who had previously undergone radiotherapy for laryngeal carcinoma underwent ^{18}F-FDG PET. Six patients had proven recurrent disease with a mean interval of 20 mo (range 6–65 mo) after initial treatment. Direct laryngoscopy and biopsy under general anesthesia were performed 13 times in these patients with an interval between biopsy and ^{18}F-FDG PET of at least 4 wk. Three out of six patients underwent a contrast-enhanced CT study (two glottic and one supraglottic laryngeal carcinoma). Five patients without clinical suspicion of tumor recurrence were used as control subjects. In this group, the average time from the completion of the initial treatment was 23.8 mo (range 12–45 mo). Mean follow-up after ^{18}F-FDG PET was 5.2 mo. Diabetes mellitus was an exclusion criterion. All six patients with proven recurrent disease underwent laryngectomy. Age, primary site, primary tumor, regional nodes and metastasis (TNM)-stage, previous treatment, time since last treatment and pathologic findings of the laryngectomy specimens are summarized in Table 1.

Imaging Study

All patients were studied after fasting overnight. Preceding the PET studies, the patients' plasma glucose levels were measured with a standard clinical test. At 60 min after the intravenous administration of 5 mCi (185 MBq) ^{18}F-FDG imaging of the neck was performed using a dual-head SPECT scanner with a coincidence module (Vertex-MCD; ADAC, Milpitas, CA). The spatial resolution of 5 mm of this scanner is comparable with a dedicated PET scanner. Acquisition involved a rotation of each detector 180° with 32 stops at 45 sec per stop. PET images were generated using

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TABLE 1
Patient Characteristics, Imaging Findings and Histopatholgic Results

Patient no.	Age (yr)	TNM stage	Site	Radiation therapy (Gy)	Interval (mo)*	FDG PET	Tumor size (cm)†
1	56	T2N3M0	Supraglottis	70	7	TP	5.0
2	53	T2N0M0	Supraglottis	70	14	TP	1.4
3	66	T1N0M0	Glottis	66	6	TP	3.2
4	59	T2N0M0	Supraglottis	70	24	TP	1.5
						FP	LN
5	71	T1N0M0	Glottis	66	65	TP	2.0
6	51	T2N0M0	Glottis	60	6	TP	2.5
7	68	T2N0M0	Glottis	70	30	TN	NA
8	67	T1bN0M0	Glottis	66	45	TN	NA
9	62	T2N0M0	Glottis	70	12	TN	NA
10	63	T1N0M0	Glottis	66	17	TN	NA
11	66	T1bN0M0	Glottis	66	15	TN	NA

*Interval between initial treatment and FDG PET study.
†Histopathologic finding of laryngectomy specimen.
TP = true positive; FP = false positive; LN = lymph node; TN = true negative; TNM = primary tumor, regional nodes and metastasis; NA = not applicable.

filtered backprojection with a Weiner filter (cutoff frequency 0.8). All images were analyzed visually.

RESULTS

The mean plasma glucose level in this study was 4.6 mmol/liter (range 4.2–6.2 mmol/liter). Fluorine-18-FDG PET scans were positive in all six patients with local relapse as shown in Table 1. Histopathological examination of the laryngectomy specimens of these patients demonstrated a mean tumor size of 2.6 cm (range 1.4–5.0 cm). The site of increased uptake corresponded with the location of the local recurrence found in the histologic specimen (Fig. 1). CT showed local edema, ulceration of the left vocal cord and a frayed right vocal cord, respectively, in three out of six patients with local recurrence and this was consistent with the endoscopic findings. In one patient, ^{18}F-FDG uptake was false-positive in a lymph node. Histologic examination of this lymph node revealed an inflammatory response but no malignancy. Fluorine-18-FDG PET scans were negative in all five locally controlled patients. During a mean follow-up period of 5.2 mo, no signs of recurrent disease were seen.

DISCUSSION

PET is a promising complementary diagnostic tool for managing and following up patients with cancer. Using ^{18}F-FDG, it is possible to look at physiological processes and perform metabolic imaging. Fluorine-18-FDG is transported like glucose into the cell and trapped in phosphorylated form without further significant metabolism (*12*). In this respect, ^{18}F-FDG PET has been applied successfully to a variety of malignant human tumors such as brain, pancreatic and musculoskelatal tumors (*6–9*). Several articles have reported on the value of ^{18}F-FDG PET for detecting and staging primary tumors of the head and neck (*13–15*). A sensitivity has been described ranging between 88% and 100%, including detecting metastases in the lymph nodes. One of the major deficiencies of PET scanning, however, is its lack of anatomic definition of the lesion site and extent. In contrast, MRI and CT provide detailed structural information such as destruction of normal fascial planes and tumor infiltration into deep structures, thus helping clinical staging and therapeutic planning. However, these anatomically based imaging modalities have a sensitivity varying with the location and type of tumor at between 60% and 88% (*16,17*).

PET is clearly superior to clinical examination and superior to either CT or MRI for the postirradiation patient who exhibits a spectrum of marked soft-tissue changes ranging from persistent or excessive laryngeal edema through ulcerated or granular endolaryngeal soft-tissue change, to perilaryngeal neck erythema, edema and tenderness. Biopsy, although usually required for diagnosis, is frequently equivocal. The surgeon is often reluctant to obtain multiple or deep biopsy specimens in such cases for fear of initiating or aggravating radionecrosis. The accuracy of ^{18}F-FDG PET in differentiating a tumor from postirradiation tissue changes is in the range of 82% to 88%, compared with 45% for CT or MRI (*18,19*).

Because of the high cost and limited availability of ^{18}F-FDG PET, alternative methods of imaging the 511-keV photons of positron emitters have been sought. Fluorine-18-FDG SPECT imaging can be performed on a dual-head gamma camera used routinely. This substantial reduction in cost would allow for more general use of ^{18}F-FDG imaging. The obvious cost savings, however, needs to be balanced against data comparing the relative accuracy of 511-keV PET and the SPECT method. SPECT cameras have a resolution of 1.7–1.8 cm (FWHM) (*20*) compared with 4–6 mm for dedicated PET scanners. With a dual-head camera and high-energy collimators, Drane et al. (*21*) reported detecting primary and nodal metastases in 91% of their patients. Martin et al. (*22*) reported detecting 78% of all hypermetabolic lesions with ^{18}F-FDG PET. In this study, the

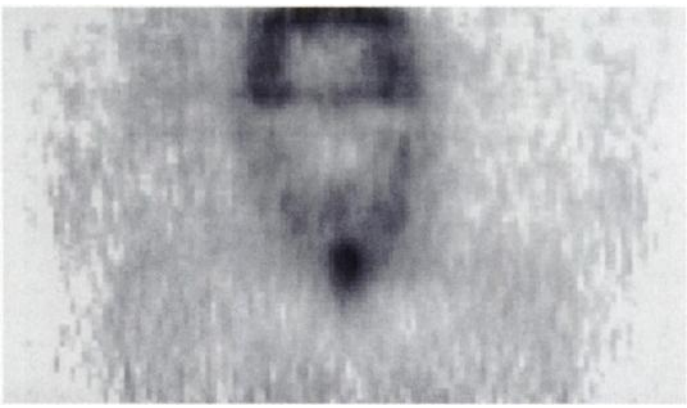

FIGURE 1. A 51-yr-old man (Patient 6) who had previously undergone radiotherapy for a T2N0M0 glottis carcinoma was suspected of having local recurrence. Coronal ^{18}F-FDG image of neck with dual-head SPECT scanner with coincidence module demonstrates focally increased uptake of left paramedian in larynx. Pathologic examination of laryngectomy specimen revealed tumor in left vocal cord with diameter of 2.5 cm.

sensitivity of ^{18}F-FDG SPECT was 92% for detecting malignancies 1.8 cm or more in diameter, showing the inferior spatial resolution of SPECT compared with PET.

This study was performed using a dual-head SPECT camera with PET capability with a spatial resolution of 5 mm (FWHM). In all six patients, histologically proven recurrences ranging from 1.4 to 5.0 cm were detected accurately, whereas in one patient a false-positive uptake was seen in a lymph node. Histologic examination of this node revealed an inflammatory response but no malignancy. Activated inflammatory cells have a markedly increased glycolysis and the hexose monophosphate shunt is stimulated by phagocytosis with increases of 20–30 times baseline being common in these stimulated cells (*23*). Although tissue types may differ with regard to the absolute uptake of ^{18}F-FDG, tumor uptake is usually greater than the uptake in most types of inflammation.

None of the five patients with local control showed increased uptake of ^{18}F-FDG. A mean follow-up of 5.2 mo may, however, provide insufficient time in which to assess the value of these scans. False-negative results have been described in patients with scans performed within 4 mo of radiation therapy (*18*). Higashi et al. (*24*) reported that there appears to be a period immediately after radiation therapy during which ^{18}F-FDG incorporation into tumor cells is decreased, although a viable tumor remains. It is possible that this effect is time limited. It has been suggested that ^{18}F-FDG studies at 4 mo after completing treatment may more accurately reflect disease status. The shortest post-treatment interval in patients with a negative ^{18}F-FDG scan in this study was 12 mo, thus excluding the immediate radiation therapy effect as a cause of the scan result.

CONCLUSION

Measurement of ^{18}F-FDG with a dual-head SPECT scanner with PET capability is very sensitive for detecting local recurrence of laryngeal carcinoma. In this study, detecting malignant neoplasms was possible for a tumor of 1.4 cm in diameter compared with tumors $>$ 2 cm in diameter detected by ^{18}F-FDG-SPECT with 511-keV collimation. These results justify a prospective study on early detection of local relapses using this technique.

REFERENCES

1. Statistics Netherlands. Diagnosis in curative health care. In: Statistics Netherlands and ministry of health, welfare and sports. *Vademecum of health statistics of the Netherlands 1996*. Heerlen: CBS; 1996:212–215.
2. Bronstein AD, Nyberg DA, Schwartz AN, Schuman WP, Griffin BR. Soft tissue changes after head and neck radiation: CT findings. *Am J Neuroradiol* 1989;10:171–175.
3. Million RR, Cassisi NJ. Oral cavity. In: Million RR, Cassisi NJ, eds. *Management of head and neck cancer: a multidisciplinary approach*, 2nd ed. Philadelphia: Lippincott; 1994:239–298.
4. Gussack GS, Hudgin PA. Imaging modalities in recurrent head and neck tumors. *Laryngoscope* 1991;101:119–124.
5. Harnsberger H, Mancuso A, Muraki A, Parkin J. The upper aerodigestive tract and neck: CT evaluation of recurrent tumors. *Radiology* 1983;149:403–409.
6. Rigo P, Paulus P, Kachen BJ, et al. Oncological applications of positron emission tomography with ^{18}F-fluorodeoxyglucose. *Eur J Nucl Med* 1996;23:1641–1674.
7. Strauss LG, Conti PS. The applications of PET in clinical oncology. *J Nucl Med* 1991;32:623–648.
8. Coleman RE, Hoffman JM, Hanson MW, et al. Clinical application of PET for the evaluation of brain tumors. *J Nucl Med* 1991;32:616–622.
9. Adler LP, Blair HF, Makley JT, et al. Noninvasive grading of musculoskeletal tumors using PET. *J Nucl Med* 1991;32:1508–1512.
10. Minn H, Joensuu H, Ahonen A, Klempi P. FDG imaging: a method to assess the proliferative activity of human cancer in vivo. *Cancer* 1988;61:1776–1781.
11. Wahl RL, Hutchins GD, Buchsbaum DJ, Liebert M, Grossman HB, Fisher S. Fluorine-18-2-fluoro-2-deoxy-D-glucose uptake into human tumor xenografts: feasibility studies for cancer imaging with PET. *Cancer* 1991;67:1544–1550.
12. Gallagher BM, Fowler JS, Gutterson NI, et al. Metabolic trapping as a principle of radiopharmaceutical design: some factors responsible for the biodistribution of Fluorine-18-FDG. *J Nucl Med* 1978;19:1154–1161.
13. McGuirt WF, Greven KM, Keyes JW, et al. PET in the evaluation of laryngeal carcinoma. *Ann Otol Rhinol Laryngol* 1995;104:274–278.
14. Bailet JW, Abemayor E, Jabour BA, Hawkins RA, Ho C, Ward PH. PET: a new, precise imaging modality for detection of primary head and neck tumors and assessment of cervical adenopathy. *Laryngoscope* 1992;102:281–289.
15. Braams JW, Pruim J, Freling NJM, et al. Detection of lymph node metastases of squamous-cell cancer of the head and neck with FDG-PET and MRI. *J Nucl Med* 1995;36:211–216.
16. Laubenbacher C, Saumweber D, Wagner-Manslau C, et al. Comparison of fluorine-18-fluorodeoxyglucose PET, MRI and endoscopy for staging head and neck squamous-cell carcinomas. *J Nucl Med* 1995;36:1747–1757.
17. Steinkamp HJ, Heim T, Zwicker C, et al. The value of nuclear magnetic resonance tomography in tumor staging of laryngeal/hypopharyngeal cancer. *HNO* 1992;40:339–345.
18. Greven KM, Williams DW, Keyes JW, et al. PET of patients with head and neck carcinoma before and after high-dose irradiation. *Cancer* 1994;74:1355–1359.
19. 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 MRI diagnosis. *Radiology* 1996;200:135–141.
20. van Lingen A, Huijgens PC, Visser FC, et al. Performance characteristics of a 511-keV collimator for imaging positron emitters with a standard gamma-camera. *Eur J Nucl Med* 1992;19:315–321.
21. Drane WE, Nicole MW, Mastin ST, Kuperus JH. SPECT with 2-[fluorine-18]fluoro-2-deoxy-D-glucose (FDG). *Radiology* 1995;197:341–343.
22. Martin WH, Delbeke D, Patton JA, Sandler MP. Detection of malignancies with SPECT versus PET, with 2-[fluorine-18]-fluoro-2-deoxy-D-glucose. *Radiology* 1996; 198:225–231.
23. Amrein PC, Larson SM, Wagner HN. An automated system for measurement of leukocyte metabolism. *J Nucl Med* 1975;15:352–355.
24. Higashi K, Clavo AC, Wahl RL. In vitro assessment of 2-fluoro-2-deoxy-D-glucose, L-methionine and thymidine as agents to monitor the early response of a human adenocarcinoma cell line to radiotherapy. *J Nucl Med* 1993;34:773–779.