To Prof. Norihiro Sadato with best wishes.
From. Y. Kitagawa

Whole-body ^{18}F-fluorodeoxyglucose positron emission tomography in patients with head and neck cancer

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Objective. Because of the high risk of secondary primary malignancies in addition to possible distant metastases, whole-body evaluation is critically important in patients with head and neck cancer. We evaluated the clinical usefulness of whole-body ^{18}F-fluorodeoxyglucose (FDG) positron emission tomography (PET) before initial treatment.
Study design. We performed whole-body FDG PET in 26 patients with head and neck cancer (squamous cell carcinoma, n = 20; salivary gland carcinoma, n = 6) before initial treatment. FDG images were prospectively evaluated, and further imaging studies were performed if required. Final diagnosis for the presence or absence of distant lesions was made by analysis of the pathologic findings of surgical specimens or by analysis of the clinical follow-up data for more than 1 year.
Results. PET images showed FDG avid lesions distant from the head and neck area in 3 of 26 patients (11.5%). Two patients were confirmed to have secondary primary cancer (one with colon cancer in the early stage and another with small lung metastasis from postoperative colon cancer). They were diagnosed and treated properly both for the head and neck cancer and the secondary primary cancer. One patient was confirmed to have large lung metastasis from head and neck cancer, and appropriate treatment was selected.
Conclusions. Whole-body FDG PET has a clinical impact on the management of patients with head and neck cancer by detecting secondary primary malignancies as well as distant metastases.
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The pathologic stage of most head and neck malignancies is closely associated with patient prognosis and also serves to help us select appropriate treatment for each patient. Therefore, complete physical examinations as well as appropriate imaging studies are critically important for the accurate staging before initial treatment. In addition to tumor staging evaluation, whole-body evaluation appears to also be important because of a high risk for secondary primary malignancies in patients with head and neck cancer (4% per year).[1,2] However, there was no single diagnostic tool that could reliably detect unknown malignancies in any part of the body.

Positron emission tomography (PET) with ^{18}F-fluorodeoxyglucose (FDG) has been confirmed to be a noninvasive, reliable diagnostic imaging tool for various kinds of malignancies.[2] FDG is a glucose analog, and accumulation of FDG in the cells is proportional to glucose consumption. Increased uptake of FDG, associated with increased glycolytic activity in cancer cells, can be imaged and quantified by means of PET.[3,4] Recent technical advancement enables whole-body PET imaging in a short period of time.

This study was performed to evaluate the clinical usefulness of whole-body FDG PET in the detection of distant metastases and secondary primary cancer before initial treatment in patients with head and neck cancer.

MATERIAL AND METHODS

Patients

The study was prospectively carried out and included 26 consecutive patients with head and neck cancer who underwent a whole-body FDG PET study before initial treatment (18 men and 8 women; mean age, 67 years; range, 31-80 years). The clinical staging was based on the International Union Against Cancer[5] and the American Joint Committee on Cancer[6] tumor staging classification. The FDG PET study was performed before biopsy in all patients to eliminate the influence of biopsy on PET results.[7] Twenty patients had squamous cell carcinoma (SCC; well differentiated, n = 15; moderately differentiated, n = 5), and the remaining 6 patients had salivary gland carcinomas (adenoid cystic

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carcinoma, n = 3; adenocarcinoma, n = 1; mucoepidermoid carcinoma, n = 1; undifferentiated carcinoma, n = 1). The study protocol was approved by the Ethical Committee of Fukui Medical University, and all patients gave written informed consent.

FDG PET imaging

FDG was produced by the method of Hamacher et al[8] with an automated FDG synthesis system (NKK, Tokyo, Japan), with ^{18}F being generated by a small cyclotron (OSCAR3, Oxford Instruments, Oxford, United Kingdom). PET scanning was performed with a GE Advance System (GE, Milwaukee, Wis). This system permits the simultaneous acquisition of 35 transverse slices with interslice spacing of 4.25 mm with septa (2-dimensional mode). Coronal and sagittal whole-body images were reconstructed to a full width at half maximum of approximately 10 mm. In 13 patients, 3-dimensional data acquisition was performed without correction for attenuation. Emission data of 7 to 10 axial field of views (AFOVs; 1- to 3-minute data acquisition for each AFOV) were obtained. Data were acquired 2 dimensionally in the other 13 patients (6 to 7 AFOVs with 2- to 4-minute data acquisition for each AFOV). In 3 of 13 patients, transmission scans using 2 standard rod sources of $^{68}Ge/^{68}Ga$ (1 minute for each AFOV) were obtained for attenuation correction after completion of the emission scans. The subjects received 244 to 488 MBq of FDG in a fasting state from the cubital vein over 10 seconds. Whole-body imaging was started at approximately 60 minutes after an injection of FDG. The plasma glucose levels were measured for all patients to confirm that they were in a fasting state.

Image interpretation and final diagnosis

Experienced nuclear medicine physicians and oral surgeons interpreted FDG PET images qualitatively. At the time of image interpretation, relevant correlative information concerning the physiologic findings was available.[9] Quantitative analysis was not performed. If there was an area with increased FDG uptake other than that of the known primary lesion, further diagnostic procedures, including magnetic resonance imaging, computed tomography, and an endoscopy with biopsy, were performed. Whole-body gallium images were also available for 13 patients. Final diagnosis for the presence or absence of distant lesions was obtained by analysis of the pathologic findings from surgical specimens or by analysis of the follow-up data of the clinical course for more than 1 year.

RESULTS

PET images demonstrated a focus of FDG accumulation corresponding to the known primary site of the head and neck cancer in all patients. In 6 of 13 patients (46%), primary tumors were also visualized on gallium images. Increased FDG uptake in an area distant from the head and neck region was demonstrated in 13 patients. In 10 of 13 patients, foci of slight to moderate spotty FDG uptake were visualized in the pulmonary hilum and mediastinum. However, they did not have enlarged lymph nodes on computed tomographs or magnetic resonance images and did not develop lymph nodes metastasis during the follow-up period of 2 years.

Three of the other patients (11.5%) had a focus of increased FDG uptake in the lung field or in the abdomen. Two of 3 patients were confirmed to have secondary primary cancer (one with colon cancer at an early stage and another with small lung metastasis from postoperative colon cancer). Because they were diagnosed and treated properly at a relatively early stage, they remained free of recurrence for 2 years after treatment. There was no visualization of these tumors on the gallium image. One patient was confirmed to have large lung metastasis from the head and neck cancer, and surgical treatment was avoided.

Although 1 patient developed gastric cancer 2.5 years after the initial diagnosis and another developed esophageal cancer 3 years after the diagnosis, there was no lesion with increased FDG uptake on the initial PET images.

CASE REPORTS

Patient 1

A 63-year-old man with carcinoma of the oral floor (moderately differentiated SCC) showed a large lung tumor in the left upper lung field on the chest x-ray film (Fig 1, *A*), which was visible on the whole-body FDG PET image (Fig 1, *B*) as well as on the gallium image (Fig 1, *C*). The tumor was confirmed histopathologically to be metastasis from the carcinoma of the oral floor. Surgical treatment was not performed for this patient after chemoradiotherapy. He died of metastatic tumor of the lung 1 year later.

Patient 2

A 64-year-old man with carcinoma of the mandibular gingiva (well differentiated SCC, T4N0M0) had a focus of increased FDG accumulation in the lower abdomen (Fig 2), which was not visible on the gallium image. The patient was confirmed to have secondary primary cancer of the sigmoid colon by means of endoscopic biopsy (well-differentiated adenocarcinoma). After successful intra-arterial chemotherapy with radiation therapy to the head and neck region, 2 surgeries were performed for colon cancer and gingival cancer. He remained tumor-free for more than 2 years after surgery.

Patient 3

A 71-year-old man with carcinoma of the oral floor (moderately differentiated SCC, T4N0M0) demonstrated a small

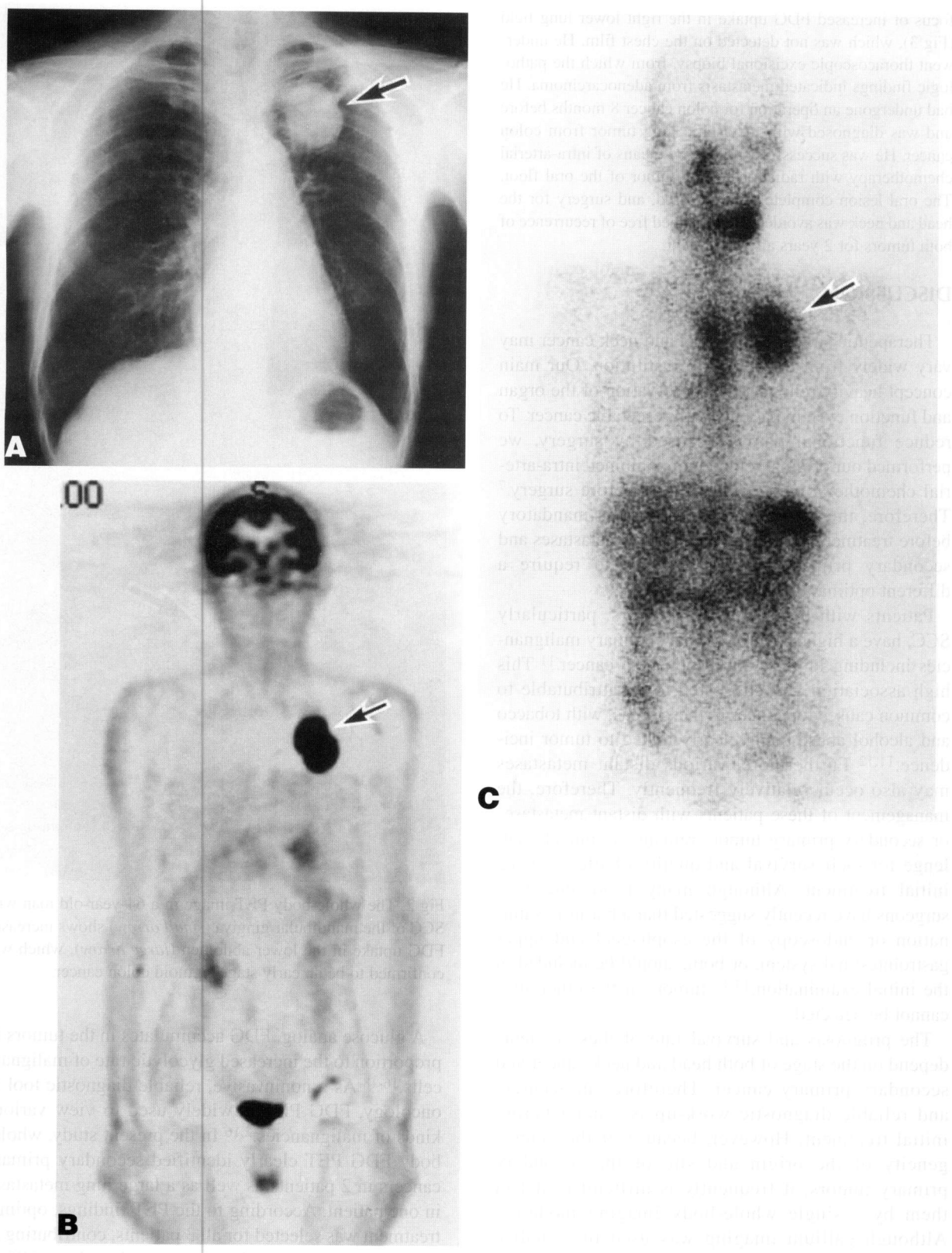

Fig 1. **A**, The chest radiograph of a 63-year-old man with SCC of the oral floor reveals a large tumor (*arrow*) in the left upper lung field. **B,** The PET image shows intense accumulation of FDG in the tumor (*arrow*), which was confirmed to be metastasis from cancer of the oral floor. **C,** The tumor in the lung was also visualized on the gallium image (*arrow*).

focus of increased FDG uptake in the right lower lung field (Fig 3), which was not detected on the chest film. He underwent thoracoscopic excisional biopsy, from which the pathologic findings indicated metastasis from adenocarcinoma. He had undergone an operation for colon cancer 8 months before and was diagnosed with metastatic lung tumor from colon cancer. He was successfully treated by means of intra-arterial chemotherapy with radiation for the tumor of the oral floor. The oral lesion completely disappeared, and surgery for the head and neck was avoided. He remained free of recurrence of both tumors for 2 years after treatment.

DISCUSSION

Therapeutic strategies for head and neck cancer may vary widely from institution to institution. Our main concept heavily relies on the preservation of the organ and function even in patients with resectable cancer. To reduce functional damage caused by surgery, we performed our original regimen of combined intra-arterial chemotherapy and radiotherapy before surgery.[7] Therefore, the whole-body evaluation is mandatory before treatment to exclude any distant metastases and secondary primary cancers that would require a different optimal therapy.

Patients with head and neck tumors, particularly SCC, have a high risk of secondary primary malignancies including lung[4,10] and esophageal cancer.[11] This high association was suggested to be attributable to common causes for cancer in these areas, with tobacco and alcohol abuse being clearly linked to tumor incidence.[11,12] Furthermore, various distant metastases may also occur relatively frequently. Therefore, the management of these patients with distant metastases or secondary primary tumors remains a clinical challenge for their survival and quality of life after the initial treatment. Although many head and neck surgeons have recently suggested that a barium examination or endoscopy of the esophageal and upper gastrointestinal system, or both, should be included in the initial examination,[13-15] tumors at the other sites cannot be detected.

The prognosis and survival rate of these patients depend on the stage of both head and neck cancer and secondary primary cancer. Therefore, an accurate and reliable diagnostic work-up is crucial before initial treatment. However, because of the heterogeneity of the origin and site of the secondary primary tumors, it frequently is difficult to detect them by a single whole-body imaging modality. Although gallium imaging was used to visualize tumors, it could detect primary head and neck tumors in less than 50% of the patients and could not visualize distant lesions—except the large lung metastasis—in our study.

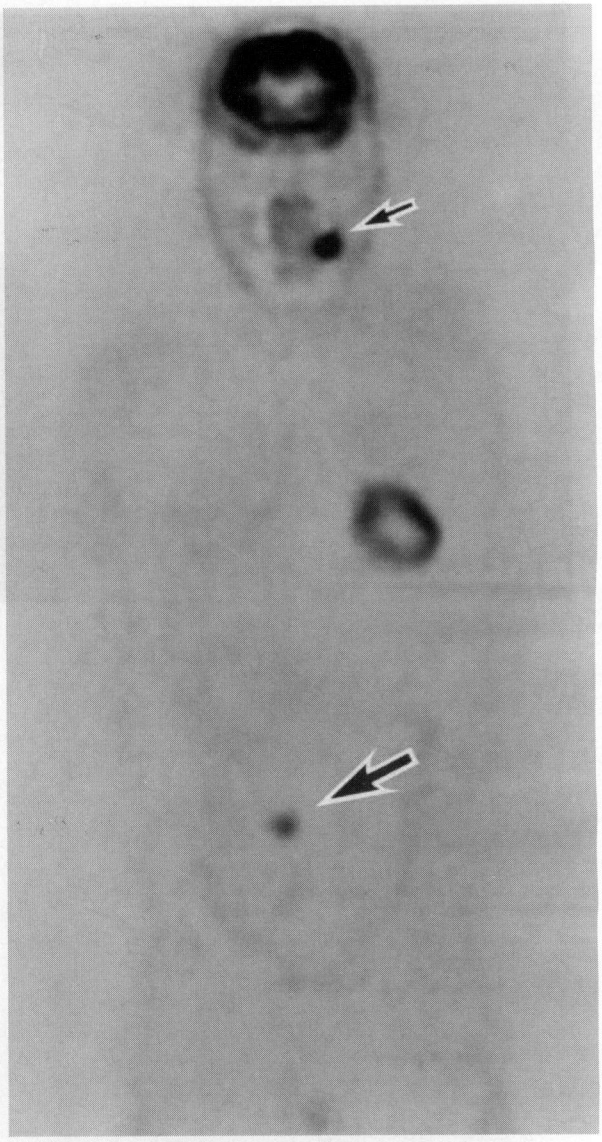

Fig 2. The whole-body PET image in a 64-year-old man with SCC of the mandibular gingiva (*small arrow*) shows increased FDG uptake in the lower abdomen (*large arrow*), which was confirmed to be an early stage sigmoid colon cancer.

A glucose analog, FDG accumulates in the tumors in proportion to the increased glycolytic rate of malignant cells.[16-18] As a noninvasive, reliable diagnostic tool in oncology, FDG PET is widely used to view various kinds of malignancies.[2,16] In the present study, whole-body FDG PET clearly identified secondary primary cancers in 2 patients as well as a large lung metastasis in one patient. According to the PET findings, optimal treatment was selected for all 3 patients, contributing to their prolonged survival and improved quality of life.

In 10 patients, foci of slight to moderate spotty FDG uptake were noted in the pulmonary hilum or mediastinum, or both. However, these foci appeared to be

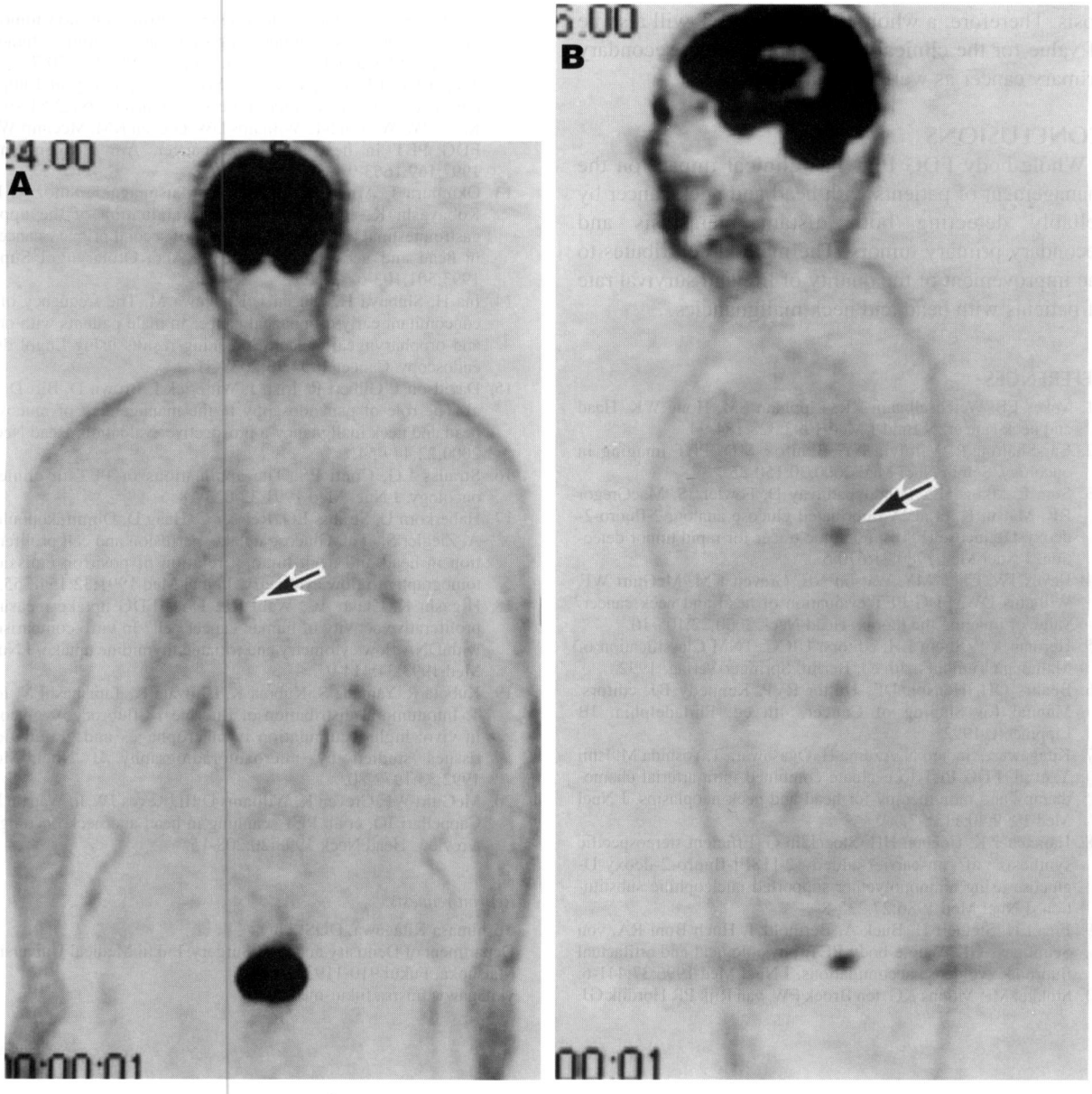

Fig 3. A focus of increased accumulation of FDG (coronal view, **A,** sagittal view, **B)** is seen in the right lower lung field (*arrow*) of a 71-year-old man with SCC of the oral floor. The lesion was confirmed to be metastatic adenocarcinoma from colon cancer operated on 8 months before.

nonspecific and were negative for metastasis. It was known that the inflammatory process also accumulated FDG.[19] In this situation, however, a computed tomography or magnetic resonance imaging examination would be required to rule out possible metastasis to the hilar or mediastinal lymph node.

Among the known malignancies, FDG PET was useful to detect carcinomas of the lung and the esophagus,[20] which are frequently seen in patients with head and neck cancer. Although primary colon cancer is not commonly associated with head and neck cancer, 2 of 26 patients had colon cancer in the present study. Barium or endoscopic examination of the colon routinely cannot be included in the initial evaluation. Because whole-body FDG PET has a high capability to detect most malignancies at any site in the body, it can be used as a reliable diagnostic modality in the initial evaluation of the staging and for the detection of secondary primary cancers in patients with head and neck neoplasms. In addition, 2 patients developed secondary primary cancer during the follow-up period, that probably did not exist at the time of initial diag-

nosis. Therefore, a whole-body FDG PET will also be of value for the clinical follow-up to detect secondary primary cancer as well as recurrence.

CONCLUSIONS

Whole-body FDG PET has clinical impact on the management of patients with head and neck cancer by reliably detecting both distant metastasis and secondary primary tumors. The method contributes to the improvement of the quality of life and survival rate of patients with head and neck malignancies.

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