
Value of FDG PET in Papillary Thyroid Carcinoma with Negative ^{131}I Whole-Body Scan

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The management of metastatic thyroid carcinoma patients with a negative ^{131}I scan presents considerable problems. Fifty-four atrophic papillary thyroid carcinoma patients whose ^{131}I whole-body scans were negative underwent ^{18}F -fluorodeoxyglucose (FDG) PET; the purpose was to determine whether this procedure could localize metastatic sites. We also assessed its usefulness in the management of these patients. **Methods:** Whole-body emission scan was performed 60 min after the injection of 370–555 MBq ^{18}F -FDG, and additional regional attenuation-corrected scans were obtained. Metastasis was pathologically confirmed in 12 patients and was confirmed in other patients by overall clinical evaluation of the findings of other imaging studies and of the subsequent clinical course. **Results:** In 33 patients, tumor had metastasized, whereas 21 patients were in remission. FDG PET revealed metastases in 31 patients (sensitivity 93.9%), whereas thyroglobulin levels were elevated in 18 patients (sensitivity 54.5%). FDG PET was positive in 14 of 15 metastatic cancer patients with normal thyroglobulin levels. In 20 of 21 patients in remission, FDG PET was negative (specificity 95.2%), whereas thyroglobulin levels were normal in 16 patients (specificity 76.1%). The sensitivity and specificity of FDG PET were significantly higher than those of serum thyroglobulin. In patients with negative ^{131}I scans, FDG PET detected cervical lymph node metastasis in 87.9%, lung metastasis in 27.3%, mediastinal metastasis in 33.3% and bone metastasis in 9.1%. In contrast, among 117 patients with ^{131}I scan-positive functional metastases, ^{131}I scan detected cervical lymph node metastasis in 61.5%, lung metastasis in 56.4%, mediastinal metastasis in 22.2% and bone metastasis in 16.2%. In all 5 patients in whom thyroglobulin was false-negative with negative antithyroglobulin antibody, PET showed increased ^{18}F -FDG uptake in cervical lymph nodes, mediastinal lymph nodes, or both. Among patients with increased ^{18}F -FDG uptake only in the cervical lymph nodes, the nodes were dissected in 11. Metastasis was confirmed in all, even in normal-sized lymph nodes. **Conclusion:** FDG PET scan localized metastatic sites in ^{131}I scan-negative thyroid carcinoma patients with high accuracy. In particular, it was superior to ^{131}I whole-body scan and serum thyroglobulin measurement for detecting metastases to cervical lymph nodes. FDG PET was helpful for determining the surgical management of these patients.

Key Words: papillary thyroid carcinoma; PET; ^{18}F -fluorodeoxyglucose; ^{131}I whole-body scan; thyroglobulin

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Serum thyroglobulin measurement and ^{131}I whole-body scintigraphy are well-established methods for the detection of local tumor recurrence and metastases in the follow-up of patients with thyroid carcinoma (1). For the proper application of these methods, thyroid remnant ablation with ^{131}I is widely used for several reasons (2,3). It may destroy occult microscopic carcinoma in the remnant thyroid and, because no normal thyroid tissues remain, it eases later detection of metastatic carcinoma by ^{131}I scan, serum thyroglobulin measurement, or both. In one third to one half of patients, however, inconsistent results are observed, and these two methods are not always able to detect recurrence or metastasis (2,4). In such cases, anatomic imaging modalities such as ultrasonography, CT or MRI can be used. These methods are, however, of limited value, particularly when normal anatomy is altered by surgery. Functional imaging modalities such as ^{201}Tl , $^{99\text{m}}\text{Tc}$ -sestamibi and $^{99\text{m}}\text{Tc}$ -tetrofosmin are necessary and have been useful (5–8). PET using ^{18}F -fluorodeoxyglucose (FDG), an analog of glucose, has been used widely in oncology (9) and might be a suitable functional imaging modality for the evaluation of thyroid carcinoma.

Clinical experiences with FDG PET in patients with thyroid carcinoma have recently been reported (8,10–17). In the diagnosis of primary thyroid tumors, Adler and Bloom (11) and Uematsu et al. (17) reported that ^{18}F -FDG uptake successfully discriminated between malignant and benign tumors. The use of FDG PET in differential diagnosis of thyroid nodules is still controversial (18), however, and its use for their preoperative evaluation is not usually recommended (14). In the detection of recurrent or metastatic thyroid cancer, several investigators reported that FDG PET and ^{131}I whole-body scan played a complementary role (13–16). The most highly differentiated thyroid carcinoma is ^{131}I scan positive and FDG PET negative, whereas the least differentiated is ^{131}I scan negative and FDG PET positive. In

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addition, Grunwald et al. (8) reported that FDG PET was more sensitive than ^{99m}Tc -sestamibi, probably due to a better spatial resolution with respect to tomographic imaging but also due to differences in the tracer uptake mechanism.

Because of the alteration in ^{131}I and ^{18}F -FDG uptake in recurrent or metastatic tumors, ^{131}I scan-negative tumor masses might be identified by FDG PET; the selection of patients with ^{131}I scan-negative metastases will therefore lead to more favorable evaluation by this modality. The clinical usefulness of FDG PET in thyroid cancer patients whose ^{131}I scans were negative has not yet been reported, however. The purpose of this study was to determine whether FDG PET was able to localize recurrent or metastatic sites in athyrotic papillary thyroid cancer patients whose ^{131}I scans were negative and to assess its usefulness in the management of these patients.

MATERIALS AND METHODS

Study Population

Fifty-four thyroid cancer patients (12 men, 42 women; age range 24–72 y, mean 48.2 ± 12.2 y), who were suspected of having metastasis and whose prior ^{131}I whole-body scans were negative, underwent whole-body PET scan. Between 1995 and 1997, these patients participated in the postoperative care program of the Department of Nuclear Medicine, Seoul National University, and the Korea Cancer Research Center. Histological findings indicated that all patients had papillary carcinoma. All patients had undergone surgical thyroidectomy and subsequent ablation of the remnant thyroid with 1.11–3.7 GBq ^{131}I (19). PET scan was performed under thyroxine replacement therapy (thyroid-stimulating hormone [TSH] < 0.1 mIU/L). We compared FDG PET results with the findings of positive ^{131}I whole-body scans obtained in the aforementioned postoperative care program at the same time.

^{131}I Whole-Body Scan

^{131}I whole-body scan was performed 2 d after oral ingestion of 74–111 MBq ^{131}I . All patients had discontinued thyroid hormone replacement 4 wk earlier, and their serum TSH levels were elevated (>30 mIU/L). A large-field-of-view gamma camera (ON 410; Ohio Nuclear, Solon, OH) with a medium-energy parallel-hole collimator was used for imaging. A 20% symmetric window was centered at 364 keV. Anterior images of the neck, chest and abdomen were obtained, each accumulating 100,000 counts.

Images were evaluated by two experienced nuclear physicians for remnant thyroid uptake, diffuse liver uptake and presence of metastases.

FDG PET

Using an ECAT EXACT 47 (Siemens-CTI, Knoxville, TN), we performed PET scanning. Patients fasted overnight and 30 min before scanning and took 10 mg diazepam (Valium; Dong-Hwa, Seoul, Korea) orally to reduce ^{18}F -FDG uptake in the neck muscles. Patients were asked to stay in the supine position, resting with their eyes closed. Whole-body emission images were obtained 60 min after the injection of 370–555 MBq ^{18}F -FDG. All patients were asked to void just before scanning, which extended from the bottom of the pelvis to the bottom of the cerebellum. After the patient had been scanned for 6 min, the table position was increased by 16.5 cm and the acquisition process was started anew. Regional transmission images using a ^{68}Ge source and emission images were

also obtained for 30 min, after whole-body scan, according to the region of interest of each patient.

Images were visually interpreted by two experienced nuclear physicians, who reached a consensus. Standardized uptake value (SUV) was calculated in all lesions (20). The result of FDG PET was considered positive either when a lesion showed an SUV of more than 3.0 or when ^{18}F -FDG uptake had increased abnormally and was higher than in surrounding normal tissue.

Thyroglobulin and Antithyroglobulin Antibody Measurement

Blood samples for measuring serum thyroglobulin and antithyroglobulin antibody were drawn from patients during suspension of TSH suppression therapy at the time of ^{131}I whole-body scan. In 14 patients, thyroglobulin was measured during suppression therapy. Using commercial kits HTGK-2 (Sorin Diagnostics, Saluggia, Italy) and HENNINGtest antiTg (Brahms Diagnostica, GmbH, Berlin, Germany), thyroglobulin and antithyroglobulin levels were determined by radioimmunoassay, respectively.

Serum thyroglobulin levels were considered abnormal when their values were higher than 10 ng/mL on TSH stimulation (>30 mIU/L) or higher than 1.0 ng/mL on TSH suppression (<0.1 mIU/L). Serum antithyroglobulin antibody levels were considered abnormal when higher than 200 U/mL.

Confirmation of Metastasis

Metastasis was pathologically confirmed in 12 patients. Cervical lymph node dissection was performed in 11 patients, and a mediastinoscopic biopsy was performed in 1 patient. In other patients, metastatic disease was assessed clinically by radiography, sonography, CT or MRI. Finally, to allow cases to be defined as true-negative, true-positive, false-negative or false-positive, an overall clinical evaluation was made; this included pathologic findings, sonography, CT, MRI and appraisal of the subsequent clinical course.

Statistical Analysis

The sensitivity and specificity of FDG PET and serum thyroglobulin measurement were calculated. Statistical evaluation was performed using McNemar's test. The proportion of metastatic sites detected by FDG PET and ^{131}I whole-body scan was compared using the chi-square test. A *P* value < 0.05 was considered statistically significant.

RESULTS

Metastasis occurred in 33 of 54 patients (61.1%), and metastasis was not found in 21 patients (38.9%) (Table 1). FDG PET revealed metastases in 31 patients (sensitivity 93.9%), and thyroglobulin levels were elevated in 18 patients (sensitivity 54.5%). Fourteen of 15 metastatic cancer patients with normal thyroglobulin levels showed positive FDG PET. In 20 of 21 patients in remission, FDG PET was negative (specificity 95.2%). One false-positive was a case of active tuberculosis in the posterior mediastinal lymph node, which was confirmed on biopsy. Thyroglobulin levels were normal in 16 patients (specificity 76.1%). The sensitivity and specificity of FDG PET were significantly higher than those of serum thyroglobulin (*P* = 0.001 and 0.046, respectively).

Among 15 patients in whom metastasis occurred and in

TABLE 1

Comparison of Detectability Between FDG PET and Serum Thyroglobulin Measurement in Papillary Thyroid Carcinoma with Negative ¹³¹I Whole-Body Scan

Measurement*	Result	Metastasis	No metastasis
FDG PET	Positive	31	1†
	Negative	2	20
Thyroglobulin	Positive	18	5
	Negative	15‡	16

*FDG PET had sensitivity of 93.9% and specificity of 95.2%. Thyroglobulin test had sensitivity of 54.5% and specificity of 76.1%.

†Tuberculosis was found in posterior mediastinal lymph node.

‡FDG PET detected metastatic sites in 14 patients.

whom serum thyroglobulin levels were undetectable, 10 (66.7%) had elevated levels of serum antithyroglobulin antibody (Table 2). When patients with positive antithyroglobulin antibody were excluded, the sensitivity and specificity of serum thyroglobulin became 78.3% and 77.8%, respectively.

In 5 patients with negative antithyroglobulin antibody, serum thyroglobulin was false-negative. PET showed increased ¹⁸F-FDG uptake in the cervical lymph node of 4 of these patients and in the mediastinum of 2 (Table 3). In 18 patients, the serum thyroglobulin value increased. Fifteen patients showed increased ¹⁸F-FDG uptake in the cervical lymph nodes, 6 in the mediastinum, 7 in the lungs and 3 in the bone. In particular, a total of 12 patients showed increased ¹⁸F-FDG uptake in the lung or bone. In 10 of these patients, serum thyroglobulin levels were elevated; whereas in 2 of these patients, levels were normal with positive serum antithyroglobulin antibody. Serum thyroglobulin was more frequently false-negative in patients with regional lymph node metastasis than in those with distant metastasis.

¹³¹I whole-body scan revealed diffuse hepatic uptake in 13 patients (Fig. 1) (21). It was proved that in 11 of these patients, recurrent or metastatic carcinoma was present. Six patients had increased serum thyroglobulin levels; in 5

TABLE 2

Profiles of Serum Thyroglobulin and Antithyroglobulin Antibody According to Presence of Metastasis of Papillary Thyroid Carcinoma

Profile	Metastasis	No metastasis
Thyroglobulin positive		
Anti-Tg Ab positive	0	1
Anti-Tg Ab negative	18	4
Thyroglobulin negative		
Anti-Tg Ab positive	10	2
Anti-Tg Ab negative	5	14

Anti-Tg Ab = antithyroglobulin antibody.

TABLE 3

Relationship Between Profiles of Serum Thyroglobulin and Antithyroglobulin Antibody and Positive Sites on FDG PET

Profile	Cervical			
	lymph node	Mediastinum	Lung	Bone
Thyroglobulin positive				
Anti-Tg Ab positive	—	—	—	—
Anti-Tg Ab negative	15	6	7	3
Thyroglobulin negative				
Anti-Tg Ab positive	9	2	2	—
Anti-Tg Ab negative	4	2	—	—

Anti-Tg Ab = antithyroglobulin antibody.

patients, these levels were normal with positive antithyroglobulin antibody.

FDG PET detected cervical lymph node metastasis in 29 patients (87.9%), lung metastasis in 9 (27.3%), mediastinal metastasis in 11 (33.3%) and bone metastasis in 3 (9.1%). We compared these findings with those of patients who at the same time were ¹³¹I whole-body scan positive (Table 4). ¹³¹I scan detected cervical lymph node metastasis in 72 (61.5%) of 117 patients with functional metastases, lung metastasis in 66 (56.4%), mediastinal metastasis in 26 (22.2%) and bone metastasis in 19 (16.2%). The positive rate of FDG PET was higher than ¹³¹I whole-body scan in cervical lymph node metastasis ($P < 0.005$) and was lower in lung metastasis ($P < 0.005$).

Cervical lymph node dissection was performed in 11 patients who were FDG PET positive; metastatic papillary thyroid carcinoma was found in all of them (Table 5). Among 22 lymph nodes that showed metastatic lesions pathologically, 6 lymph nodes were normal size, which was 1.0 cm or less in diameter. FDG PET found metastatic lesions in 5 lymph nodes. A mediastinoscopic biopsy was performed in 1 patient in whom FDG PET showed increased ¹⁸F-FDG uptake in the posterior mediastinal lymph node; pathologic examination revealed active tuberculosis.

DISCUSSION

After total thyroid ablation, ¹³¹I whole-body scan and serum thyroglobulin measurement are used periodically to detect recurrence or metastasis of well-differentiated thyroid carcinoma. The sensitivity of this scan under these circumstances ranges from 45% to 87% (2,22,23), which is less than that of serum thyroglobulin. The latter is, however, of limited value, because it provides no localized information and is interfered with by antithyroglobulin antibody (1,16).

The results of the ¹³¹I scan and the serum thyroglobulin test agreed in only 40%–50% of patients with metastasis (2,24). In most patients, the scan was negative and the test was positive. In this study, serum thyroglobulin levels were elevated in 54.5% of metastatic cancer patients in whom the ¹³¹I scan was negative. Serum thyroglobulin sensitivity was low because of the high positive rate of antithyroglobulin

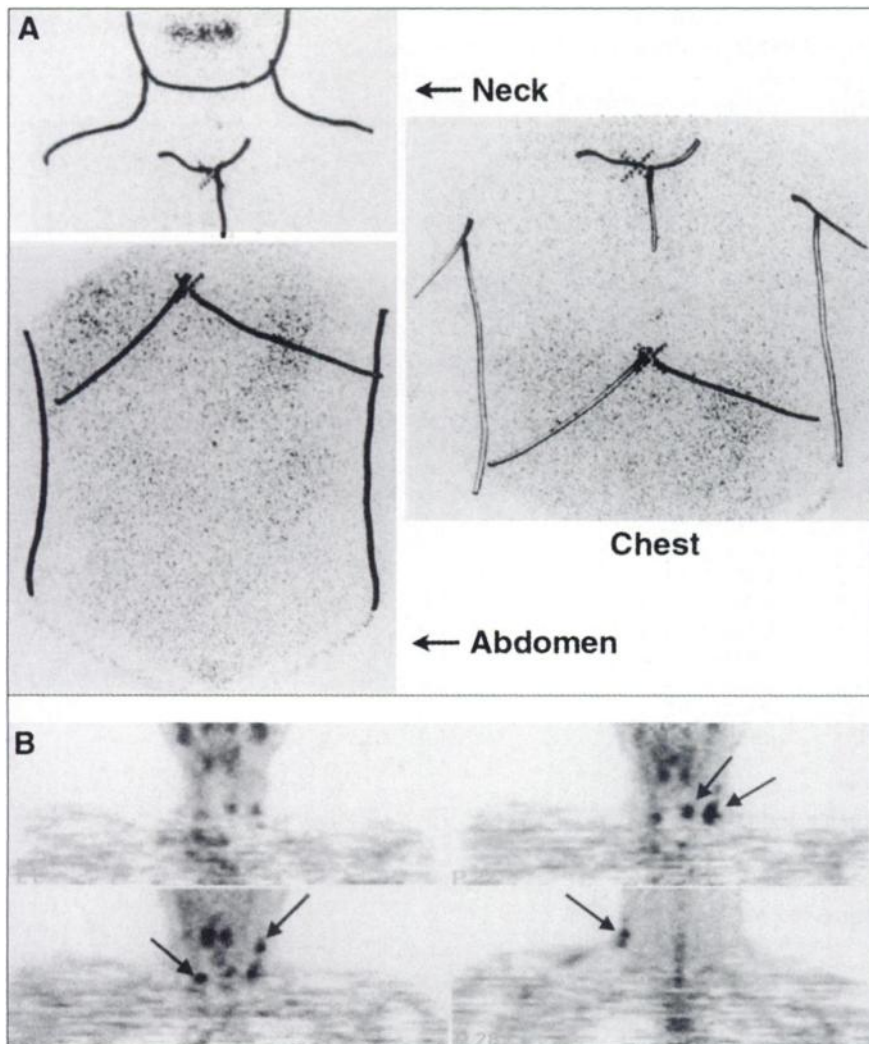


FIGURE 1. (A) Whole-body scan of patient 10 obtained 5 d after ingestion of 5.55 GBq ^{131}I shows no functioning metastatic sites; diffuse hepatic visualization was observed. Serum thyroglobulin level was 427 ng/mL. (B) FDG PET scan obtained 6 wk later shows abnormally increased ^{18}F -FDG uptake sites (arrows) on both sides of neck with normal ^{18}F -FDG uptakes in salivary gland, oral cavity, pharynx, larynx, bone marrow and others. Cervical lymph node dissection of both sides revealed metastatic papillary carcinoma in 13 of 17 lymph nodes.

antibody. Chung et al. (25) reported that among Koreans, the positive rate of antithyroglobulin was approximately 40%. This study showed that in patients in whom metastasis had occurred and who had normal levels of thyroglobulin, antithyroglobulin antibody was positive in 66.7% of patients

TABLE 4
Comparison of Metastatic Sites Detected by FDG PET and ^{131}I Whole-Body Scan

Site	^{131}I scan-positive group*	^{131}I scan-negative group, FDG PET finding
Cervical lymph node	72 patients (61.5%)†	29 patients (87.9%)†
Lung	66 patients (56.4%)†	9 patients (27.3%)†
Bone	19 patients (16.2%)	3 patients (9.1%)
Mediastinum	26 patients (22.2%)	11 patients (33.3%)
Total	117 patients	33 patients

*Data from patients with thyroid cancer registered at postoperative care program at same time.

†Significant difference between ^{131}I scan-positive group and ^{131}I scan-negative group ($P < 0.005$).

(Fig. 2). When patients with positive antithyroglobulin antibody were excluded, the sensitivity and specificity of serum thyroglobulin increased and were not statistically different from those of FDG PET.

Muller-Gartner and Schneider (26) reported that the false-negative serum thyroglobulin test results occurred in patients with small papillary carcinoma with cervical or mediastinal lymph node metastases and suggested that the small tumor mass might account for undetectable thyroglobulin production. The results of this study show that, in all 5 patients with false-negative serum thyroglobulin test results and with negative antithyroglobulin antibody, FDG PET revealed positive uptake in cervical or mediastinal lymph nodes. In contrast, 10 of 12 patients with distant metastasis showed elevated level of serum thyroglobulin levels and 2 showed normal levels with positive serum antithyroglobulin antibody. We found that in certain patients with negative ^{131}I scan and a normal thyroglobulin level, FDG PET was helpful for deciding whether to proceed with surgery.

In this study, FDG PET revealed metastases with a sensitivity of 93.9% in ^{131}I scan-negative patients. We know of no similar study, although Feine et al. (13) also found that

TABLE 5
FDG PET and Pathologic Findings in Postoperative Patients

Patient no.	Age	Sex	Tg/TgAb*	Lymph node location	Size† (cm)	FDG PET	Pathology
1	20	F	<1.0/1597	R superior IJC	3.0 × 1.5 × 1.0	–	–
				R mid IJC	7.0 × 2.2 × 2.0	+	+
				R inferior IJC	1.7 × 1.5 × 1.2	+	+
				L inferior IJC	1.3 × 1.7 × 0.5	+	+
2	33	F	<1.0/1056	R superior IJC	<1.0	–	–
				R mid IJC	1.0 × 1.0 × 1.0	+	+
				R supraclavicular	<1.0	+	–
3	37	F	<1.0/159	L perithyroid cartilage	1.5 × 1.0 × 1.0	+	+
				L peritracheal	2.5 × 1.5 × 1.5	+	+
4	47	F	47/<25	L supraclavicular	2.0 × 1.5 × 1.2	+	+
5	55	F	<1.0/772	R jugulodigastric	<1.0	–	–
				R mid IJC	1.5 × 1.5 × 1.5	+	+
				R inferior IJC	1.5 × 1.5 × 1.0	+	+
6	61	F	<1.0/5381	R mid IJC	1.0 × 1.0 × 1.0	+	+
				L mid IJC	1.7 × 1.5 × 1.5	+	+
7	62	F	257/<25	L mid IJC	1.2 × 1.0 × 1.0	–	–
				L inferior IJC	2.0 × 1.5 × 1.5	+	+
8	72	F	<1.0/2217	R mid IJC	2.0 × 2.0 × 2.0	+	+
				R supraclavicular	1.0 × 1.0 × 1.0	+	+
				L post-tracheal	2.0 × 1.5 × 1.0	+	+
9	59	F	<1.0/n.d.	L supraclavicular	1.5 × 1.5 × 1.0	+	+
10	36	M	427/<25	R superior IJC	<1.0	+	+
				L superior IJC	1.0 × 1.0 × 1.0	+	+
				L inferior IJC	3.0 × 1.5 × 1.5	+	+
11	47	M	51/<25	R superior IJC	<1.0	–	+
				R superior IJC	2.0 × 2.0 × 2.0	–	+
				R mid IJC	3.0 × 2.0 × 2.0	+	+

*Serum thyroglobulin level (ng/mL)/serum antithyroglobulin antibody level (U/mL).

†Conglomerated lymph nodes were considered as one lesion.

IJC = internal jugular chain; n.d. = not determined.

FDG PET detected non-¹³¹I-trapping metastases of thyroid carcinomas in about 95% of patients. Although ¹³¹I whole-body scans of these patients showed no metastatic uptake, 13 ¹³¹I scans showed diffuse hepatic uptake. We previously reported that liver uptake without uptake by thyroid remnant or metastasis suggested hidden metastases (21). In this study, 11 of these 13 patients were proven to have metastatic lesions. All these patients had an elevated level of serum thyroglobulin or antithyroglobulin antibody, which supports the hypothesis that hepatic uptake of ¹³¹I is due to hepatic clearance of ¹³¹I-labeled thyroglobulin or the thyroglobulin-antithyroglobulin immune complex.

FDG PET was performed in the TSH-suppressed state. Sisson et al. (10) reported an FDG PET case with and without TSH suppression and found higher ¹⁸F-FDG uptake under TSH stimulation. Grunwald et al. (8), however, found that when TSH levels were high, FDG PET was not significantly more sensitive.

It is generally accepted that glucose metabolism is increased, particularly in poorly differentiated carcinomas. FDG PET is therefore thought to be more effective for the detection of undifferentiated thyroid carcinoma, with a low sensitivity of ¹³¹I whole-body scan. Even in differentiated thyroid carcinoma, FDG PET was positive mainly in high-

grade carcinomas of the well-differentiated type (8,13). Hürthle cell carcinoma, an aggressive variant of follicular carcinoma, was usually positive on FDG PET and was often negative on ¹³¹I scan (8,13,27). In this study, we evaluated FDG PET only in papillary carcinoma, which is most common in Korea.

We observed ¹⁸F-FDG uptake in normal-sized lymph nodes, most of which were confirmed after surgery to be metastatic. Dietlein et al. (16) also reported similar findings, and this underlines the superiority of FDG PET over conventional anatomic imaging modalities. In addition, with regard to further ¹³¹I administration, CT evaluation is limited; imaging can be performed only without contrast enhancement (8).

The results of this study show that FDG PET more easily detected cervical and mediastinal lymph node metastasis than did ¹³¹I whole-body scan, a finding corroborated by Dietlein et al. (16). They found that FDG PET was beneficial when locoregional lymph nodes, the most frequent sites of metastasis, were involved. The therapeutic effect of ¹³¹I is lower in metastases in cervical lymph nodes than in those in the lung (28). In such cases, histological verification and subsequent lymph node dissection is mandatory. Anatomic imaging and the determination of thyroglobulin levels are

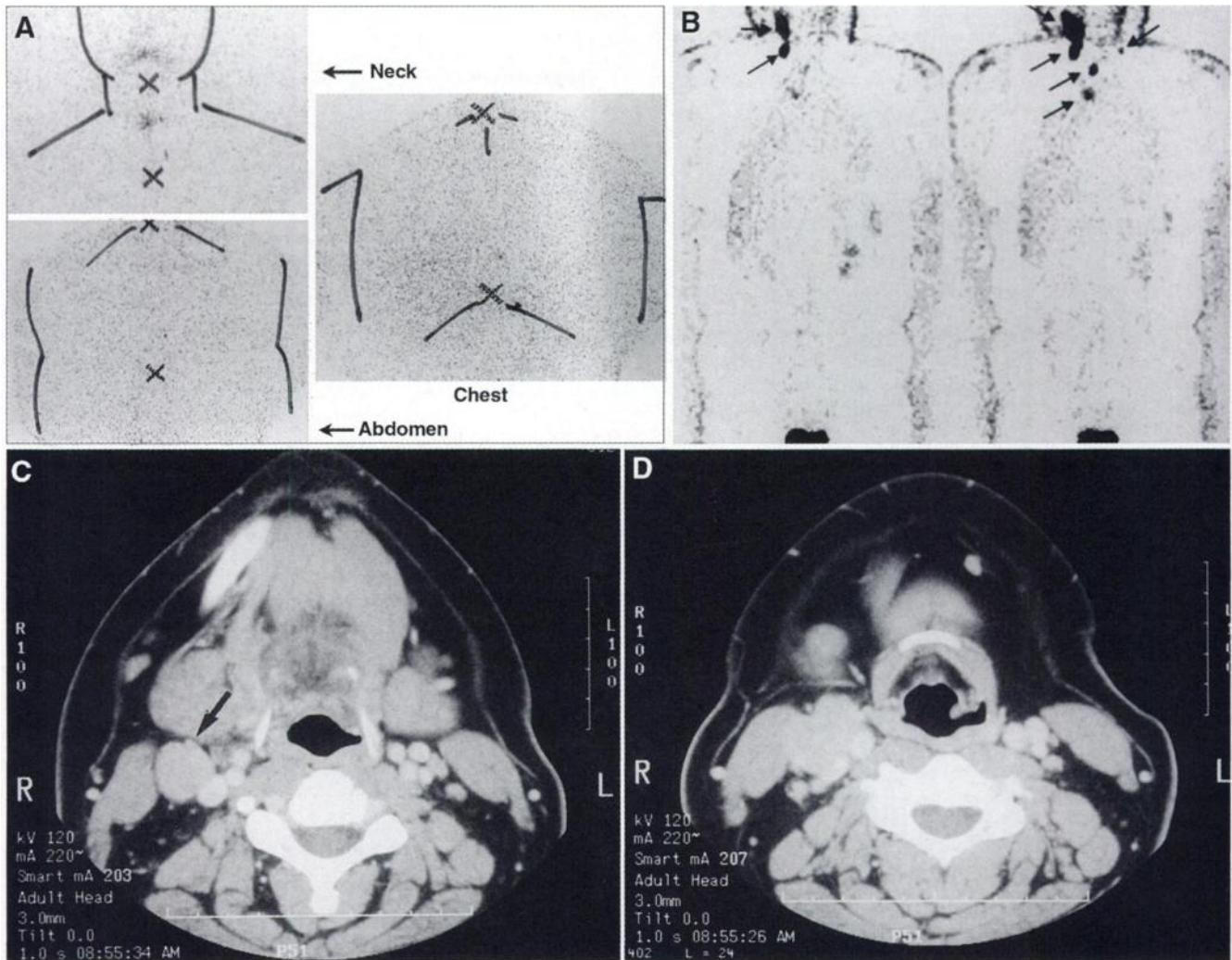


FIGURE 2. (A) Whole-body scan of patient 1 obtained 5 d after ingestion of 1.11 GBq ^{131}I shows no functioning metastatic sites. Serum thyroglobulin level was <1.0 ng/mL, although antithyroglobulin antibody level was 1597 U/mL. (B) FDG PET scan obtained 4 wk later shows abnormally increased ^{18}F -FDG uptake sites (arrows) on both sides of neck and mediastinum. (C) Neck CT shows enlarged lymph nodes in right internal jugular chain (arrow). (D) However, CT missed metastatic lymph node in left inferior internal jugular chain. Cervical lymph node dissection revealed metastatic papillary carcinoma on both sides of internal jugular chain (7 of 14 lymph nodes).

helpful. However, we found that metastasis could exist even in normal-sized lymph nodes, and 45.5% of metastatic patients showed normal serum thyroglobulin levels. On the basis of these findings, it can be said that FDG PET is helpful in determining the surgical management of patients with cervical and mediastinal lymph node metastasis.

CONCLUSION

FDG PET localized metastatic sites with high accuracy in papillary thyroid cancer patients who were ^{131}I whole-body scan negative. In particular, FDG PET was superior to ^{131}I whole-body scan and serum thyroglobulin measurement in detecting metastases in cervical lymph nodes. FDG PET was helpful in determining the surgical management of patients with metastases in cervical lymph nodes.

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