Role of Diagnostic ^{131}I SPECT/CT in Long-Term Follow-up of Patients with Papillary Thyroid Microcarcinoma

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Papillary thyroid microcarcinoma (PTMC) usually has a favorable prognosis but can also be aggressive, with neck and distant metastases. We evaluated the diagnostic role of ^{131}I SPECT/CT in detecting metastases in PTMC patients during long-term follow-up and whether the procedure should be included in the current diagnostic protocol. **Methods:** We retrospectively studied 351 consecutive PTMC patients who had undergone thyroidectomy and radioiodine therapy; 21 were at high risk, 94 at low risk, and 236 at very low risk. During follow-up, the patients underwent diagnostic ^{131}I whole-body scanning (WBS) followed by SPECT/CT. **Results:** WBS found 248 radioiodine-avid foci in 126 patients, and SPECT/CT found 298 in 139 patients, confirming all foci found on WBS. SPECT/CT also correctly classified 76 of the avid foci as unclear or wrongly classified on WBS. Globally, SPECT/CT detected and correctly classified 64 neoplastic lesions in 27 of 30 patients with metastases, and WBS evidenced 39 of 64 lesions, 28 of which were unclear or wrongly classified, in 16 of the 30 patients. Nineteen of 27 patients, including 13 at very low risk, had only neck metastases, 9 of 19 being T1aN0M0 with an undetectable thyroglobulin level. Three of 27 patients, including 1 at very low risk, had only distant metastases with an undetectable or very low thyroglobulin level. Five of 27 patients had neck and distant metastases with a thyroglobulin level $<$2.5 ng/mL in 1 case, between 2.5 and 10 in 3 cases, and $>$10 in the remaining case. SPECT/CT also reduced WBS false-positive results in 15 of 139 patients (10.8%). SPECT/CT had an incremental value over WBS in 38.1% of patients with positive findings and changed the classification and therapeutic management in 21.6%. **Conclusion:** Metastases occurred in 8.5% of patients during long-term follow-up. SPECT/CT performed better than WBS, particularly in patients at very low risk with inconclusive WBS results, a TNM stage of T1aN0M0, and an undetectable or very low level of thyroglobulin. Prolonged surveillance is justified in PTMC patients, and wider use of ^{131}I SPECT/CT in the diagnostic protocol is suggested.

Key Words: papillary thyroid microcarcinoma (PTMC); long-term follow-up; neck and distant metastases; ^{131}I planar whole-body scan; ^{131}I SPECT/CT

J Nucl Med 2018; 59:1510–1515
DOI: 10.2967/jnumed.117.204636

Papillary thyroid microcarcinoma (PTMC) is a small thyroid cancer with a 10-mm maximum diameter, as defined by the World Health Organization (*1*), and usually has an excellent long-term prognosis in younger patients (*2*) but worse outcomes in male patients and patients older than 45 y. Generally, the patients experience complete remission after surgery, and aggressive therapy with radioiodine cannot be recommended because it has not been shown to benefit survival (*3*). However, PTMC can be multifocal and bilateral and can include extracapsular extension, extrathyroidal spread, neck lymph-node metastases, both macrometastases and micrometastases (*2,4*), and distant metastases with worse disease-free survival, especially when there is multifocal involvement (*2,5,6*), suggesting the need for aggressive treatment. Thus, prolonged surveillance is justified, particularly in multifocal cases and in those with locoregional and distant metastases at the time of surgery, considering that recurrence is possible for many years (*4*).

Conventional ^{131}I planar whole-body scanning (WBS), in association with serum thyroglobulin measurement and radiologic imaging procedures, has long been considered the diagnostic procedure of reference in patients thyroidectomized because of differentiated thyroid carcinoma: for detection of thyroid residues and local and distant metastases, for restaging after radioiodine therapy, and for long-term follow-up. However, WBS is characterized by low sensitivity, particularly for detecting small lesions, and by false-positive results due to low specificity because physiologic uptake is not always easily differentiable from pathologic uptake (*7*).

More recently, the hybrid imaging technology SPECT/CT, obtaining cross-sectional, functional, and anatomic fusion images, has proved capable of improving WBS performance in detecting radioiodine-avid foci of differentiated thyroid carcinoma, increasing sensitivity and accuracy, and allowing precise anatomic localization and characterization of lesions (*8–11*).

Moreover, SPECT/CT has demonstrated higher performance than WBS in PTMC patients both in the preablation phase and after therapeutic radioiodine doses, particularly in detecting lymph node metastases for more accurate staging and better therapeutic decisions (*12–14*). However, to our knowledge, no study has reported on the use of SPECT/CT in PTMC patients during long-term follow-up.

The aim of the present retrospective study was to investigate the role of diagnostic ^{131}I SPECT/CT in detecting metastases during long-term follow-up of PTMC patients who underwent thyroidectomy and radioiodine therapy at initial diagnosis. Moreover, we evaluated whether the procedure has an incremental value over WBS and should be included in the current PTMC diagnostic protocol for better patient management.

MATERIALS AND METHODS

Patients

The present study was of the long-term follow-up of the 351 PTMC patients who were referred to our nuclear medicine facility between

Received Nov. 3, 2017; revision accepted Feb. 26, 2018.
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Published online Mar. 1, 2018.

September 2008 and December 2015 to undergo a diagnostic radioiodine scan for disease surveillance.

We retrospectively enrolled consecutive patients, 77 of whom were male and 274 female, and 98 of whom were younger than 45 y and 253 older (Table 1). All patients had undergone total thyroidectomy. The tumors were 5 mm or smaller in 157 patients and larger than 5 mm in 194 (maximum diameter, 10 mm), thus being classified as PTMC in accordance with the histologic thyroid tumor classification of the World Health Organization. The tumors were diagnosed incidentally in 248 patients and nonincidentally in 103. Seventy-five patients had multiple foci involving only a single lobe, whereas 24 had bilateral, multifocal disease. Fourteen had extrathyroidal extension. The lymph node status was evaluated in all patients, 12 of whom were positive for metastases. Four of these 12 were T1aN1aM0 and 8 were T1aN1bM0, the latter also having palpable lymph nodes suggestive of malignancy on ultrasound (focal or diffuse hyperechogenicity, intranodular microcalcifications, a microlobulated margin, a round shape, a low-echo hilum, an intranodular cystic component, and mixed or central vascularity). Six of these 12 also had multifocal, unilateral carcinomas; 2 had multifocal, bilateral carcinomas; and 1 had extrathyroidal extension and distant metastasis (T4N0M1). At surgery, in accord with the classification of the European Thyroid Cancer Taskforce (*15*), the patients were classified as being at very low risk (unifocal T1 [≤1 cm] N0M0 and no extension beyond the thyroid), at low risk (T1 [>1 cm] N0M0, T2N0M0, or multifocal T1N0M0), or at high risk (any T3 or T4 or T4N1M1). Thus, 20 were at high risk, 96 at low risk, and 235 at very low risk.

TABLE 1
Characteristics of PTMC Patients at Surgery

Characteristic	Patients (*n*)
Sex	
Male	77
Female	274
Age (range, 18–81 y)	
≤45 y	98
45 y	253
Histology	
Papillary microcarcinoma	351
Size	
≤5 mm	157
5 mm	194
Structural characteristics	
Unifocal	252
Multifocal, unilateral	75
Multifocal, bilateral	24
Extrathyroidal extension	14
Neck lymph node status	
Level VI lymph node metastases (N_{1a})	20
Cervical metastases (N_{1b})	13
Distant metastases	1
Risk stratification	
High risk	20
Low risk	96
Very low risk	235

All patients had undergone radioiodine therapy after thyroidectomy, including those with uncomplicated PTMC who assented to this type of treatment (2,970–3,700 MBq in all patients except one with distant metastases at diagnosis, who received 5,550 MBq).

Subsequent to 2 wk of a low-iodine diet and avoidance of iodine-containing medications, all patients underwent diagnostic WBS (5 cm/min) followed by SPECT/CT, 48–72 h after an oral 185-MBq ^{131}I dose. One hundred eighty patients were hypothyroidal after 4–6 wk of thyroid hormone therapy withdrawal, and 171 patients had received an increment of exogenous thyroid-stimulating hormone (TSH) after recombinant human TSH stimulation according to standard procedures. The total number of scintigraphic examinations was 625 (323 in hypothyroidal patients and 302 in patients after recombinant human TSH). Preablation diagnostic ^{131}I imaging was excluded from the present study.

Before scintigraphy, all patients underwent laboratory tests such as urinary iodine excretion (ioduria), serum TSH, and thyroglobulin during a hypothyroidal state and or after recombinant human TSH stimulation and antithyroglobulin antibodies. At scintigraphy, TSH levels were always more than the arbitrary level of 50 μU/mL, and those of ioduria were less than 300 μg/L; the thyroglobulin cutoff was 0.2 ng/mL.

The institutional review board approved this retrospective study, and the requirement to obtain informed consent was waived. Before scintigraphy, written informed consent is routinely obtained from all patients, whose data are treated in accordance with the local privacy rules and regulations.

Scintigraphy Protocol

Both WBS and SPECT/CT were performed on a hybrid variable-angle dual-head γ-camera, the Infinia Hawkeye 4 (GE Healthcare), equipped with high-energy, parallel-hole collimators with 20% energy windows centered on the ^{131}I photon peak (364 keV) and integrated with an x-ray transmission system (low-dose CT) to provide anatomic maps for attenuation correction and image fusion.

Planar ^{131}I WBS was performed in both anterior and posterior projections using a matrix size of 1,024 × 256 pixels. Spot views of selected body areas in anterior, posterior, and lateral projections (600 s/view) were also acquired on the basis of the planar WBS findings.

In all cases, planar images were followed by SPECT/CT, including in the field of view the neck (cervical regions and thyroid bed) and chest. SPECT/CT was also used to image any other suspected areas of increased uptake as seen on planar imaging.

First, emission SPECT images were acquired over 360° (180° per head) using a 128 × 128 matrix size, a 3° angular step, an acquisition time of 30 s per frame (30 min total), and a zoom factor ranging from 1 to 1.2 according to the individual patient. The body-contouring system was used to minimize the distance between the patient and the collimator. The SPECT examination was followed by CT, with an x-ray tube and detector array rotating together in a fixed geometry at 2.0 rpm for a 90° L-mode scan. Multiple CT slices were obtained in helical mode (four 5-mm-thick slices obtained simultaneously, with beam coverage of 2 cm in each gantry rotation, and reconstructed online to a 512 × 512 image matrix). The CT scan was acquired within 4.5 min. Cross-sectional attenuation images (128 × 128 image matrix), in which each pixel represents imaged tissue attenuation, were generated in all cases. SPECT was always acquired first, followed by CT, and the SPECT images were reconstructed with the iterative method (ordered-subsets expectation maximization) and fused with the CT images using a dedicated software package (Xeleris workstation; GE Healthcare).

Data Analysis

SPECT/CT images were independently interpreted by 3 experienced nuclear medicine physicians who were informed of the clinical

reason for the scintigraphy but were unaware of any investigational results. Disagreements were resolved by consensus. SPECT/CT data were classified as normal if there was only physiologic tracer distribution or as positive if there was evidence of neoplastic lesions. The SPECT/CT results were compared with those of WBS.

Any focal or diffuse uptake higher than the surrounding background and incompatible with physiologic activity was defined as ^{131}I tumor uptake. Radioiodine foci in the salivary glands, urinary collecting system, and gastrointestinal tract was considered physiologic except for small focal, circumscribed areas that could not be clearly distinguished and had been considered suggestive of lesions on WBS.

WBS data were considered unclear when the anatomic site of a lesion was difficult to specify and when foci were difficult to characterize. An incremental value over WBS was assigned to SPECT/CT when it increased diagnostic accuracy by providing better identification and interpretation of radioiodine-avid foci (e.g., cervical metastases vs. benign residual tissue), more correct anatomic localization and characterization (e.g., distant small metastases in bone, soft tissue, lung, or mediastinum), and more precise differentiation between tumors and physiologic uptake than could be obtained from WBS.

Metastasis diagnosis was also confirmed by histologic examination or, when that was not available, by clinical examinations showing changes in thyroglobulin level and by radiologic follow-up for at least 12 mo but no more than 84 mo. In patients with positive planar and SPECT/CT findings who underwent radioiodine therapy, posttherapeutic scan data were also considered.

Statistical Analysis

The McNemar test was used to assess the statistical significance of differences in per-patient and per-lesion sensitivity between SPECT/CT and planar WBS in the detection of radioiodine-avid malignant foci. The results were considered significant when the *P* value was less than 0.05.

RESULTS

Both ^{131}I WBS and SPECT/CT were negative for suspected radioiodine-avid foci in 209 patients classified as having no evidence of disease, whereas each of 3 patients in whom both procedures were negative for radioiodine-avid foci had one neck metastasis ascertained 24–36 mo after surgery.

WBS showed 248 radioiodine-avid foci in 126 patients, and SPECT/CT showed 298 in 139 patients (Table 2), confirming all WBS-positive foci. Both procedures concordantly classified 172 foci, whereas SPECT/CT correctly characterized 73 foci unclear on WBS and identified 50 foci occult on WBS. Moreover, SPECT/CT changed the classification of 3 further foci wrongly considered to be residue on WBS: 2 were changed to neck lymph node metastases, and the third was changed to physiologic uptake in the cervical esophagus. Including the latter case, in 15 patients classified as unclear on WBS, SPECT/CT globally characterized 14 cases of physiologic foci (1 in the rhinopharynx, 5 in the cervical esophagus, 5 in the thoracic esophagus, 2 in the thymus [residue], and 1 in menstruating uterus) and 4 cases of benign disease (2 cases of fibrocystic breast disease and 2 cases of vertebral arthrosis in the inflammatory phase, with a herniated disk also being present in 1 of the 2 latter cases). Nine of these 15 patients had only 1 radioiodine-avid focus each.

Globally, SPECT/CT correctly classified 64 malignant foci in 27 of 30 patients (90%) with ascertained metastases (5 at high risk, 8 at low risk, and 14 at very low risk), 7 of whom were under 45 y old and 20 of whom were over. WBS evidenced 39 metastases in 16 of these 30 patients (53.3%) (6 at high risk, 5 at low risk, and 5 at very low risk), but 28 of 39 foci (71.8%) were considered unclear or wrongly classified. The time at which metastasis appeared after the initial PTMC diagnosis ranged from 8 to 57 mo, excluding 1 patient who already had distant metastases at diagnosis.

TABLE 2
Planar WBS and SPECT/CT Classification of Radioiodine-Avid Foci

Site	Classification	
	Planar WBS*	SPECT/CT†
In neck	220 radioiodine-avid foci	263 radioiodine-avid foci
	162 residues	159 residues
		2 metastases
		1 physiologic focus
	58 unclear	30 residues
		23 metastases
		5 physiologic foci
		Planar WBS occult foci
		25 residues
		18 metastases
Outside neck	28 radioiodine-avid foci	35 radioiodine-avid foci
	11 metastases	11 metastases
	2 cutaneous contaminations	2 cutaneous contaminations
	15 unclear	3 metastases
		4 benign disease
		8 physiologic foci
		Planar WBS occult foci
		7 metastases

*248 foci in 126/351 patients.
†298 foci in 139/351 patients.

As shown in Table 3, metastases involved 43 lymph nodes in the neck (18 laterocervical, 11 submandibular adjacent to salivary glands, 9 paratracheal, and 5 supraclavicular) well evidenced and characterized on SPECT/CT; 22 of these 43 were occult, 19 unclear, and 2 wrongly classified as residue on WBS. Moreover, 21 metastases were identified and characterized only on SPECT/CT outside the neck, including 4 in the lungs, 9 in the lymph nodes (3 mediastinal, 1 hilar pulmonary, 1 abdominal, and 4 inguinocrural), 3 in bone (ischium, rib, and spine), and 5 in pelvic soft tissue, 7 of which were occult and 3 unclear on WBS. In particular, the 19 of 27 patients (4 at high risk, 2 at low risk, and 13 at very low risk) who had been correctly classified on SPECT/CT had lymph node metastases in the neck only, and 13 of these were at very low risk and had T1aN0M0 disease with undetectable or very low thyroglobulin serum levels. In addition, in 13 of these 19 patients, neck lymph node metastases were single, and 7 of these were occult on WBS. One of these latter cases (patient 22) is illustrated in Supplemental Figure 1 (supplemental materials are available at http://jnm.snmjournals.org).

TABLE 3
Characteristics of Patients with Metastatic PTMC at Surgery and During Follow-up

Patient no.	Age (y)	Sex	Clinical diagnosis	At surgery						During follow-up					
										Thyroglobulin (ng/mL)		Lesions, planar WBS (*n*)		Lesions, SPECT/CT (*n*)	
				Size (mm)	Focality	TNM	LN	M	Risk	Hypo	rh TSH	In neck	Outside neck	In neck	Outside neck
1	59	F	STN-i	5	UF	T1aN0M0			VL	<2.5		1U		1LCL	
2	50	F	MNG-i	5	UF	T1aN0M0			VL		Und			2LCL, 1SCL	
3	68	M	MNG-ni	10	UF	T4N0M1		Bone	H		>10	1U	1PM, 5STM, 4ICL, 1U	1 LCL	1PM, 5STM, 4ICL, 1bone*, 1ABL
4	61	F	MNG-i	10	UF	T1aN0M0			VL		Und			1SML	
5	65	F	MNG-i	2	UF	T1aN0M0			VL	Und				1SML	
6	43	M	STN-ni	10+microfoci	MF BL	T1aN1bM0	N_1b		H			3U		3LCL	
7	73	F	MNG-HD-i	9+2	MF BL	T1aN1bM0			L	<2.5		1U		1PTL	1ML
8	49	F	STN-ni	10+microfoci	MF UL	T1aN1bM0			L	2.5–5		3U		2SML, 1PTL	1PM (NSCLC)
9	49	F	MNG-i	10	UF	T1aN0M0			VL	<2.5				1SML	
10	66	F	STN-ni	10		T1aN0M0			L	<2.5					1bone*
11	69	F	MNG-ni	6+4	MF BL	T1aN1bM0			L	5–10		5U	1U	2SML, 2PTL, 1SCL	1bone*
12	60	F	MNG-HD-i	4	UF	T1aN0M0			VL	Und				1LCL	
13	35	F	GD-i	10	UF	T1aN0M0			VL	Und				1PTL	
14	49	F	MNG-ni	10+7	MF BL	T1aN0M0			L	Und		2U		1SML, 1SCL	
15	72	F	STN-ni	10	UF	T1aN0M0			VL	Und		1U		1SCL	
16	47	M	GD-i	8	UF	T1aN0M0			VL		<2.5			1LCL, 1SML	
17	38	F	STN-ni	6	UF	T1aN0M0			VL	<2.5				2 PTL	
18	66	F	MNG-ni	4	UF	T1aN1bM0	N_1b		H	2.5–5		2U		4LCL, 1SCL	1ML, 1PM
19	60	F	MNG-HD-ni	10+5	MF BL	T1aN0M0			L		<2.5		1PM		1PM, 1HPL
20	40	M	MNG-i	7+3	MF UL	T1aN0M0			L	Und				1PTL	
21	54	F	MNG-i	5	UF	T1aN0M0			VL	Und		1U		1SML	
22	47	F	GD-i	6	UF	T1aN0M0			VL	Und				1LCL	
23	40	F	STN-ni	2.5+microfoci	MF UL	T1aN1bM0	N_1b		H	5–10		2†		1LCL, 1PTL	
24	43	F	MNG-HD-i	6	UF	T1aN0M0			VL	Und		1U		1SML	
25	43	M	STN-HD-ni	9+3	MF, UL	T1aN1aM0	N_1a		H	Und		1U		1LCL	
26	31	F	STN-HD-ni	10	UF	T1aN1bM0	N_1b		H	>10		1U		2LCL	
27	54	F	MNG-i	7	UF	T1aN0M0			VL	Und			1U		1ML

*Ischium in patient 3, rib in patient 10, and spine in patient 11.

†Wrongly classified as residues.

Clinical diagnosis: HD = Hashimoto thyroiditis; GD = Graves disease; i = incidental; MNG = multinodular goiter; ni = not incidental; STN = solitary thyroid nodule.

Focality: BL = bilateral; MF = multifocal; UF = unifocal; UL = unilateral.

LN = lymph node metastases; M = distant metastases.

Risk: H = at high risk; L = at low risk; VL = at very low risk.

Hypothyroidal (hypo) and recombinant human (rh) TSH: und = undetectable.

Lesions: ABL = abdominal LN; HPL = hilar pulmonary LN; ICL = inguinocrural LN; LCL = laterocervical LN; ML = mediastinal LN; NSCLC = non–small cell lung cancer; PM = pulmonary metastases; PTL = paratracheal LN; SCL = supraclavicular LN; SML = submandibular LN; STM = soft-tissue metastases; U = unclear.

Three of the 27 patients (2 at low risk and 1 at very low risk), all with T1aN0M0 disease, had metastases only outside the neck, and thyroglobulin was undetectable or very low. One of the low-risk cases, with 1 pulmonary metastasis and 1 hilar pulmonary lymph node metastasis, is illustrated in Supplemental Figure 2.

The remaining 5 of the 27 patients (2 at high risk and 3 at low risk) had metastases both in the neck and outside the neck with thyroglobulin levels <2.5 ng/mL in 1 case, between 2.5 and 10 in 3 cases, and >10 in the remaining case.

Moreover, during follow-up, 7 of the 27 patients (patients 2, 3, 11, 13, 16, 18, and 26) experienced disease progression despite treatment, and 3 of these were at very low risk (patients 2, 13, and 16). In those 3 and in patients 11 and 26, further neck laterocervical lymph node metastases occurred. Moreover, a spine metastasis initially present in patient 11 remained unmodified, another pulmonary metastasis was evidenced in patient 18, and patient 3, who had distant metastases at diagnosis, experienced disease progression despite 3 high doses of radioiodine and died 40 mo after the initial tumor diagnosis.

In patient 8, SPECT/CT 39 mo after the initial diagnosis detected 3 neck foci that had been classified as unclear for lymph node metastasis on WBS, as well as identifying a further focus of weak right-hilar-pulmonary radioiodine uptake that had been occult on planar imaging (thyroglobulin levels in hypothyroidism: 2.5–5 ng/mL). At this last site, diagnostic CT of the thorax evidenced an 11-mm lesion that proved to be a primary pulmonary adenocarcinoma at surgery and was positive for cytokeratin 3D3 (CAM 5.2) but negative for thyroglobulin at immunohistochemical analysis.

DISCUSSION

This retrospective study was of 351 PTMC patients who underwent thyroidectomy and radioiodine therapy with long-term follow-up using diagnostic ^{131}I WBS and SPECT/CT for disease surveillance.

No evidence of neoplastic disease was found in 91.5% of patients, thus confirming that most PTMC patients are at little clinical risk. However, not always did the patients prove risk-free, since 30 of the 351 (8.5%) developed metastases, 70% of whom were younger than 45 y and 73.3% of whom had a tumor size of 5–10 mm.

SPECT/CT identified metastases in 27 of the 30 affected patients (90%), whereas WBS identified metastases in 16 of the 30 (53.3%), ascertaining a statistically significant higher number of lesions (95.5% vs. 58.2%, $P < 0.00001$); however, 71.8% of the WBS-positive lesions were unclear or wrongly classified. SPECT/CT had an incremental value over WBS in 38.1% of positive patients considering the identification of thyroid residue or neoplastic lesions and changed WBS classification and therapeutic management in 21.6% of patients. SPECT/CT also avoided unnecessary treatments by correctly characterizing benign lesions or physiologically avid foci, thus reducing false-positive results on WBS, in 10.8% of patients. This aspect can assume greater significance when these foci are single and when classification based on WBS can lead to inappropriate treatments. Regarding false-positive results, SPECT/CT, but not WBS, caused an incorrect initial diagnosis of pulmonary radioiodine-avid metastasis from PTMC in a patient who also had neck metastases of thyroid cancer origin, whereas a primary pulmonary adenocarcinoma was ascertained only at histology. No valid explanation seems available for radioiodine uptake by this type of tumor, which was also thyroglobulin-negative at immunohistologic analysis, although some authors have tried to formulate hypotheses in similar cases of rare PTC (*16*).

All 6 of the 27 patients who already had metastases at surgery experienced recurrence during follow-up, underlining that the presence of metastases at the initial diagnosis can represent an important risk factor for recurrence or even, in rare cases, death (*14*). However, only 1 patient who had already shown clinically significant symptoms of extensive involvement at initial diagnosis died, due to thyroid cancer. Other authors have described some PTMC cases with extensive distant metastases (bone and lung) either as the initial symptoms of disease (*17*) or just after surgery at the first radioiodine ablation (*6*), presenting disease progression and even death due to metastatic disease.

Among 27 of the 30 patients with metastases on SPECT/CT, 6 also had Hashimoto thyroiditis and 3 had Graves disease. Some studies (*18,19*) have reported good tumor prognosis in patients with coexistence of these 2 diseases, whereas other studies (*20*) have observed that the tumor is more aggressive in patients with Graves disease, also suggesting that the thyroid-stimulating antibodies may be responsible for greater aggressiveness of thyroid malignancy. In the present study, 3 of 9 metastatic PTMC patients with coexistence of Graves disease or Hashimoto thyroiditis also experienced disease progression, thus suggesting that these diseases may contribute to a worse tumor prognosis. Although in the 27 cases identified by SPECT/CT most metastases were detected within the first 5 y after surgery, with a range of 8–57 mo, the surveillance should be prolonged because some of the patients, even if at very low risk or with a tumor smaller than 5 mm, experienced disease progression during follow-up, with further lesions appearing on SPECT/CT despite treatment; in addition, it is not possible to predict when an occult metastasis will become clinically evident—even more so in PTMC patients with aggressive forms of PTMC that behave similarly to PTC.

We maintain that SPECT/CT is certainly preferable to WBS in evidencing and characterizing malignant PTMC lesions during follow-up, since SPECT/CT proved to have a global incremental value over WBS, correctly changing classification and patient management. This result is particularly significant in patients who have inconclusive WBS results, are at very low risk, have tumors classified as T1aN0M0, and have undetectable or very low thyroglobulin levels, particularly when there is only a single neoplastic lesion. Moreover, only SPECT/CT was able to characterize single lymph node metastases adjacent to submandibular glands, which are difficult to differentiate from residue or physiologic uptake on WBS alone. In most patients pulmonary and bone metastases were detectable only on SPECT/CT, being too small to be identified—and too difficult to be characterized—on WBS.

Even if thyroglobulin could be considered a reliable marker for recurrent or residual disease during postsurgical follow-up in this study (since total thyroidectomy and radioiodine therapy were performed on all patients in this study), positive SPECT/CT findings can be accompanied by an undetectable or very low thyroglobulin serum level when there is a lymph node metastasis (particularly if single). Our results seem to confirm the data of some authors who found low or even undetectable thyroglobulin serum levels in PTMC patients—whether on or off thyroxin—with isolated lymph node neck metastases or with small or diffuse pulmonary metastases but positive ^{131}I WBS results (*21,22*). Thyroglobulin can also be elevated when there are negative ^{131}I WBS results but the patient has poorly differentiated thyroid carcinoma. In such cases, nuclear medicine imaging procedures other than ^{131}I scanning can been used (*23,24*).

On the basis of the present data—on a long-term follow-up of a large series of PTMC patients—^{131}I SPECT/CT seems to add an important contribution to WBS imaging interpretation. This finding agrees with the favorable results reported by other authors for preablation phases and for phases after ablation by therapeutic doses (*12–14*).

Finally, in the present study SPECT/CT proved to be a useful diagnostic noninvasive imaging procedure despite its limitations (a spatial resolution limited in small lesions by the partial-volume effect; the longer examination typical of the method, with the associated possible patient discomfort [but only a slight radiation exposure from the low-energy CT component, with effective doses averaging 1 mSv for a neck/chest scan and 1.5 mSv for an abdomen/pelvis scan]) (*25*). The SPECT/CT procedure is simple to perform and provides excellent images that, with adequate training, are easy to read. SPECT/CT could clearly define the

anatomic site of radioiodine-avid lesions both in the neck and outside the neck, helping with their characterization and thus clarifying planar image interpretation, reducing equivocal and false-positive results, and revealing more neoplastic lesions. Thus, we recommended wider use of SPECT/CT in the long-term follow-up of PTMC patients for surveillance after thyroidectomy and radioiodine therapy, particularly for the most aggressive tumor variants. However, our results demonstrated that metastases also occur in less aggressive PTMCs, thus suggesting that SPECT/CT would have value in those as well.

The limitations of this study were due to its retrospective nature: the patients were followed up by only one department, and the experienced nuclear medicine physicians who independently interpreted the SPECT/CT images belonged to that same department. Thus, the results may not be generalizable; planar WBS and SPECT/CT were performed on some patients who were hypothyroidal and on others who had undergone recombinant human TSH stimulation. For practical and ethical reasons, histopathologic examinations were not performed on all metastases, some lesions being validated only by the data on clinical and thyroglobulin variations or by the results of radiologic and nuclear medicine procedures.

CONCLUSION

^{131}I SPECT/CT plays an important role in the long-term follow-up of PTMC, providing more information than WBS in detecting and characterizing radioiodine-avid metastases. Moreover, SPECT/CT can clarify the interpretation of radioiodine-avid foci that are unclear on WBS, differentiating malignant lesions from physiologic or benign uptake and thus reducing false-positive results on planar imaging. Significant diagnostic importance can be ascribed to ^{131}I SPECT/CT because of its ability to detect metastases in very-low-risk patients with inconclusive WBS results, T1aN0M0 disease, undetectable or very low thyroglobulin levels, and, particularly, single lesions. Thus, wider use of ^{131}I SPECT/CT in the diagnostic PTMC protocol during long-term follow-up is recommended to ascertain recurrence early and to guide decisions on the best treatment for a given patient.

DISCLOSURE

No potential conflict of interest relevant to this article was reported.

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