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Techniques

Radio-guided Surgery for Non-^{131}I-avid Thyroid Cancer

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Objective: In this paper we report in a larger series the use of radio-probe-guided surgery (RGS) in nonradioiodine-avid, well-differentiated thyroid cancer (DTC). *Design:* Thirty-seven patients with locoregional recurrent, nonradioiodine avid DTC were studied with ^{99m}Tc-sestamibi directed RGS using a handheld gamma probe as an intraoperative detector. *Outcome:* Twenty-three women and 14 men were followed after RGS for 35.4 ± 12.5 months (range 9–57). There were 33 papillary (one "tall" cell variant), 2 follicular, and 2 Hürthle cell cancers. In 7 patients, thyroid cancer recurred in the neck while cervical lymph node metastases were found in 31 patients (one patient had papillary cancer in both the thyroid bed and cervical lymph nodes). Sixty-six discrete nodules ranging from 6 to 45 mm (mean tumor diameter, 18.4 ± 8.5 mm) were identified by both high-resolution ultrasound and ^{99m}Tc-sestamibi probe-guided RGS. After RGS, Tg (thyroglobulin) fell in 33 of 37 patients and mean target/nontarget sestamibi uptake ratios decreased in all 37 patients ($p < 0.0001$). *Conclusion:* These data confirm our earlier observations that a ^{99m}Tc-sestamibi intraoperative gamma probe can be used to identify and guide resection of recurrent tumor and involved lymph nodes in locoregional metastases of nonradioiodine-avid thyroid cancer.

Introduction

The loss of radioiodine-concentrating ability by differentiated thyroid cancer (DTC) is seen in as many as 30% of cases, which increases to approximately 40% in patients over 65 years old (1–5). In addition, loss of radioiodine avidity has been seen after radioiodine therapy and as a result of progressive tumor dedifferentiation (6,7). Elevated cellular metabolic activity, thyroglobulin (Tg) secretion, and the distribution of potential sites of metastases to cervical and mediastinal lymph nodes are preserved; however, this functional change adversely affects prognosis and limits the approach to therapy in patients with suspected metastatic disease (8–10). Anatomic imaging with high-resolution ultrasound has proven useful in the identification of small lymph nodes, but it alone cannot discern the presence of metastases (11). Scintigraphy with radiopharmaceuticals with avidity for thyroid cancer has been demonstrated to be useful in this regard. Technetium-99m (^{99m}Tc) labeled methoxyisobutyl-isonitrile (^{99m}Tc-MIBI), ^{99m}Tc-tetrafosmin, ^{201}Thallium, ^{18}F-fluorodeoxyglucose, and others have been used to depict nonradioiodine-avid metastases of differentiated thyroid cancer with high sensitivity and accuracy (11–19). When combined with high-resolution ultrasound, ^{99m}Tc-MIBI scintigraphy can be used to diagnostic advantage in patients with locoregional metastases of nonradioiodine-avid thyroid cancer (20,21). Further, surgical intervention can be facilitated with the ability to positively identify involved lymph nodes with an intraoperative gamma probe technique. In this report, we expand our previous experience in the use of ^{99m}Tc-MIBI radio-guided surgery for locoregional recurrence of nonradioiodine avid, differentiated thyroid cancer (22).

Materials and Methods

Thirty-seven patients with locoregional recurrent, nonradioiodine-avid, well-differentiated thyroid cancer were studied with ^{99m}Tc-MIBI directed radio-guided surgery (RGS) using a handheld gamma probe as an intraoperative detector. Selection criteria for RGS were previously described and included: (1) prior treatment for DTC by total thyroidectomy and ^{131}iodine therapy, (2) negative radioiodine-131 scan with increasing serum Tg levels at follow-up, (3) locoregional recurrence on both ^{99m}Tc-MIBI and high-resolution ultrasound

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of the neck, and (4) discernable accumulation of ^{99m}Tc-MIBI uptake in tumor foci without distant metastases (22).

Technetium-99m MIBI scans were performed as described previously (20–22). A 550–740 MBq dose of ^{99m}Tc-MIBI was injected intravenously, and whole-body and spot views of the neck and chest were acquired for 20 to 30 min and at 2 h after injection. A large field-of-view gamma camera (Orbiter 7500 or E-CAM, Siemens, Hoffman Estates, IL, USA) was equipped with a parallel-hole, low-energy, high-resolution collimator. Neck ultrasound was performed at the same time with a small-port, high-resolution 10-MHz transducer (Technos, Esaote, Italy).

Serum Tg was measured by immunoradiometric assay (Nycomed, Milan, Italy) in patients both on and off L-thyroxine. Patients with a Tg level of < 2 ng/mL were considered athyrotic (21–24). Serum anti-Tg antibody (TgAb) levels were measured by a radioimmunoassay method (Biodata, Milan, Italy) (21,22).

An 11 mm handheld, commercially available gamma probe (Scintiprobe 100, Pol.hi.tech, Carsoli-Aquila, Italy) was used. The intraoperative procedure for RGS has been previously described (22) and consisted of the following:

1. In the operating suite, 10 min before starting the procedure, a low dose of ^{99m}Tc-sestamibi 1 mCi (37 MBq) was injected in a peripheral vein, followed by a flushing dose of saline (30 mL).
2. Using the earlier obtained scans of the neck as a guide, the neck was surveyed using the gamma probe to identify foci of ^{99m}Tc-sestamibi accumulation.
3. Through a wide neck incision the gamma probe was again used to scan the operative field for foci of ^{99m}Tc-sestamibi uptake.
4. Radioactivity was measured using the gamma probe over foci of ^{99m}Tc-sestamibi accumulation (T), over nonthyroid areas for background activity (B), directly over resected tumor tissue, and over the tumor bed to assess the success of the procedure. Tumor (T)/bed (B) and tumor bed (TB)/B ratios were calculated.
5. The operating surgeon was queried as to the usefulness of RGS in each patient using a 4-point scale: 1, very useful; 2, useful; 3, moderately useful; 4, not useful.

Verbal and written, institutionally approved informed consent was obtained from each patient. In the case of minors, permission was obtained from parents. Pregnant operating personnel were excluded from participation in the study.

Follow-up ranged from 9 to 57 months and all patients underwent detailed investigation (at 1 and 2 months, and then at 6-month intervals au: change ok? from 6 monthly $>$ 6 month intervals) by means of clinical examination, serum Tg and TgAb measurements, neck US, and other imaging modalities as necessary.

Data were expressed as mean $\pm$ standard deviation (SD). Linear regression analysis was used to compare tumor size with tumor ^{99m}Tc-sestamibi uptake. *P* values of less than 0.05 were considered significant.

Results

Thirty-seven consecutive patients with recurrent locoregional, nonradioiodine-avid well-differentiated thyroid cancer underwent RGS with ^{99m}Tc-sestamibi and a handheld gamma probe. Eight of the 37 patients in this series were previously reported in the literature (22). Table 1 reviews the clinical, laboratory, imaging, and pathology findings in this group. There were 23 women and 14 men with an average age of 45.6 years (range 17–65 years) followed for a mean time of 34.5 ± 12.5 months (range 9–57 months). All patients underwent total thyroidectomy and radioiodine therapy and were maintained on L-thyroxine at a dose titrated to achieve suppressed thyroid-stimulating hormone (TSH) levels. Radioiodine doses ranged from 100 mCi (370 MBq) to 300 mCi (1110 MBq) (Table 1). Nineteen patients received a single dose (minimum dose 150 mCi [555 mBq]; maximum dose 300 mCi [1110 Mbq]); 15 patients received two doses (cumulative dose between 250 mCi [925 MBq] and 400 mCi [1480 MBq]), and 3 patients received three doses (cumulative dose of 300 mCi [1110 MBq], 500 mCi [1850 MBq], and 800 mCi [2960 MBq], respectively). There were 33 papillary cancers (one tall cell variant), 2 follicular cancers, and 2 Hürthle cell carcinomas. In 7 patients, thyroid cancer recurred in the neck while cervical lymph node metastases were found in 31 patients (one patient had papillary cancer in the thyroid bed and cervical lymph node metastases).

Preoperative mean target/nontarget MIBI uptake ratio was 2.52 ± 0.89 (range 1.0–5.4) and fell postoperatively in the operative field in all 37 patients ($p < 0.0001$) (Fig. 1). Thyroglobulin levels were elevated in 33 patients, with 4 patients expressing anti-Tg antibody preoperatively. Postoperatively Tg fell in all 33 patients (23 had postoperative Tg levels $<$2.0 ng/mL) and was $<$1 ng/mL in 2 of the 4 patients with the preoperative presence of anti-Tg antibodies, which became negative postoperatively (Fig. 2). In 2 patients (see Table 1, patients 4 and 34) with markedly elevated preoperative Tg levels of 980 ng/mL and 1833 ng/mL, initial postoperative declines of Tg (275 ng/mL and 720 ng/mL, respectively) were temporary, with marked increases at follow-up intervals of 6 and 8 months to 1320 ng/mL and 1125 ng/mL, respectively, with the development of lung metastases. Neither the size nor the number of tumor foci correlated with preoperative Tg levels.

Sixty-six discrete nodules were identified by both high-resolution ultrasound and ^{99m}Tc-sestamibi probe RGS (Fig. 3) and were resected. Mean tumor nodule diameter was 18.4 ± 8.5 mm (range 6–45 mm). In 23 patients, a solitary focus of thyroid cancer was located in the thyroid bed (6 patients) or in a cervical lymph node (17 patients); in 7 patients, two foci were located in the thyroid bed (2 patients) and in cervical lymph nodes (5 patients); in 6 patients, three cervical lymph nodes were identified, and in 2 patients, four and six cervical lymph nodes containing thyroid cancer, respectively, were identified (Table 1). There were no complications (postoperative hypoparathyroidism or recurrent laryngeal nerve palsy) after RGS. Estimated radiation exposure to operating room personnel, including the operating surgeon, to the low dose (1 mCi) of administered ^{99m}Tc-sestamibi was ~1 μSi/h. The operating surgeon assessed RGS as *very useful* in 8 patients in whom metastatic foci were embedded in fibrotic tissues or located behind blood vessels, *useful* in 17 patients, *moderately useful* in 10 patients, and *not useful* in 2 patients.

Discussion

Radioiodine-negative thyroid cancer presents a challenge in diagnosis and localization. Loss of radioiodine avidity by

Table 1. Clinical, Pathological, Laboratory, Imaging, and Operative Results

Patient	Sex	Age at dx	Tx	TNM stage	Ca type	Age at relapse (yr)	Site(s) of relapse	US	MIBI	Lesion(s) (mm)	T/B pre-op	TB/B post-op	Pre-opTg (ng/mL)	Post-opTg (ng/ml)	Follow-up (mo)	Status
1	F	58	TTx, 250 mCi ^{131}I	$T_4N_{1a}M_0$	Papillary	63	Thyroid bed	Positive	Positive	30	3.0	0.9	22	0.2	57	LDF
2	F	23	TTx, 200 mCi^{131}I	$T_4N_{1b}M_0$	Papillary	25	Cervical LN	Positive	Positive	20 14 18	3.2 2.2 3.2	1.0 1.0 0.9	39	2.0	53	LWD
3	F	25	TTx, 100, 100, 150 mCi^{131}I	$T_1N_{1b}M_0$	Papillary	43	Cervical LN	Positive	Positive	17 22	4.0 3.7	0.9 0.9	44	0.5	51	LDF
4	F	65	TTx, 200 mCi^{131}I	$T_4N_0M_0$	Hurtle Ca	67	Thyroid bed ↓ Lung mets	Positive	Positive	35	4.5	2.0	980	275 ↓ 1320	44 ↓ 51	LWD
5	F	57	TTx, 150 mCi^{131}I	$T_4N_{1a}M_0$	Papillary (TC)	58	Thyroid bed	Positive	Positive	30	2.2	1.0	93	0.2	50	LDF
6	F	46	TTx, 100, 150 mCi^{131}I	$T_4N_{1a}M_0$	Papillary	59	Cervical LN	Positive	Positive	25 16	2.3 2.5	0.8 1.0	18	0.7	49	LDF
7	M	72	TTx, 200 mCi^{131}I	$T_4N_0M_0$	Papillary	76	Cervical LN	Positive	Positive	40 30	3.0 2.5	1.0 1.0	70	0.4	48	LDF
8	M	72	TTx, 100, 100 mCi^{131}I	$T_4N_0M_0$	Follicular	67	Thyroid bed	Positive	Positive	13	3.4	0.8	95	5.3	48	LWD
9	F	42	TTx, 200 mCi^{131}I	$T_4N_0M_0$	Papillary	51	Cervical LN	Positive	Positive	20 14	2.6 2.8	1.0 1.0	36	<0.1	43	LDF
10	F	27	TTx, 200 mCi^{131}I	$T_4N_1M_0$	Papillary	32	Cervical LN	Positive	Positive	25	2.2	0.7	43	2.8	43	LWD
11	F	56	TTx, 200,300, 300 mCi^{131}I	$T_4N_1M_0$	Papillary	60	Cervical LN	Positive	Positive	12	2.0	1.0	40 TgAb positive	Tg <0.1 TgAb positive	42	LWD
12	F	30	TTx, 200 mCi^{131}I	$T_4N_1M_0$	Papillary	37	Cervical LN	Positive	Positive	12 10 12	2.3 2.5 2.3	0.8 0.9 0.8	22	0.1	41	LDF
13	F	51	TTx, 200 mCi^{131}I	$T_4N_{1b}\ M_0$	Papillary	52	Cervical LN	Positive	Positive	8 10 13	2.2 2.0 1.8	1.0	9.2	0.3	43	LDF
14	F	51	TTx, 200 mCi^{131}I	$T_2N_xM_0$	Papillary	53	Cervical LN	Positive	Positive	22	4.1	0.8	270	<0.1	43	LDF
15	F	17	TTx, 150, 100 mCi ^{131}I	$T_2N_1M_0$	Papillary	18	Cervical LN	Positive	Positive	19 15 6	3.0 2.0 2.0	0.8 1.0 1.0	112	0.1	42	LDF
16	M	72	TTx, 200, 200 mCi^{131}I	$T_4N_0M_0$	Papillary	76	Cervical LN	Positive	Positive	14	4.6	1.1	35	0.4	40	LDF
17	M	26	TTx, 200 mCi^{131}I	$T_4N_1M_0$	Papillary	28	Thyroid bed	Positive	Positive	45	3.0	0.8	78	<0.1	40	LDF
18	M	20	TTx, 200, 300 mCi^{131}I	$T_4N_1M_0$	Papillary	36	Cervical LN	Positive	Positive	20 20	2.0 1.7	0.7 1.0	65	0.2	39	LDF
19	M	33	TTx, 150 mCi^{131}I	$T_1N_{1b}M_0$	Papillary	33	Cervical LN	Positive	Positive	10 20 23	2.3 2.0 2.3	1.0 1.0 1.0	50	0.2	38	LDF
20	M	21	TTx, 150 mCi^{131}I	$T_4N_1M_0$	Papillary	23	Cervical LN	Positive	Positive	15 5 8	2.0 1.0 1.0	1.0 1.0 1.0	2	<0.1	38	LDF

(*continued*)

TABLE 1. (*continued*)

Patient	*Sex*	*Age at dx*	*Tx*	*TNM stage*	*Ca type*	*Age at relapse (yr)*	*Site(s) of relapse*	*US*	*MIBI*	*Lesion(s) (mm)*	*T/B pre-op*	*TB/B post-op*	*Pre-opTg (ng/mL)*	*Post-opTg (ng/ml)*	*Follow-up (mo)*	*Status*
21	M	54	TTx, 100, 300 mCi ^{131}I	$T_4N_1M_0$	Follicular	68	Cervical LN	Positive	Positive	23 28 17 20 20 30	1.3 1.4 1.0 2.3 1.3 1.8	1.0 1.0 1.0 1.0 1.0 1.0	112	4.8	35	LWD
22	F	36	TTx, 150, 100 mCi ^{131}I	$T_{2b}N_1M_0$	Papillary	38	Cervical LN	Positive	Positive	16 10	1.7 1.0	1.0 1.0	Tg < 0.1 TgAb positive	Tg <0.1 TgAb negative	33	LDF
23	F	25	TTx, 150, 300 mCi ^{131}I	$T_4N_0M_0$	Papillary	27	Cervical LN	Positive	Positive	10 17 10 19	2.3 2.3 2.3 2.3	1.0 1.0 1.0 1.0	163	< 0.1	32	LDF
24	F	35	TTx, 300 mCi ^{131}I	$T_{1b}N_1M_0$	Papillary	37	Cervical LN	Positive	Positive	20	2.5	1.0	19	0.1	31	LDF
25	M	50	TTx, 200 mCi ^{131}I	$T_4N_1M_0$	Papillary	63	Thyroid bed	Positive	Positive	17	5.4	0.8	88	7.6	30	LWD
26	F	17	TTx, 300 mCi ^{131}I	$T_4N_1M_0$	Papillary	30	Cervical LN	Positive	Positive	27 22	2.5 2.7	1.0	46	0.2	29	LDF
27	M	54	TTx, 200, 200 mCi ^{131}I	$T_4N_0M_0$	Hurtle Ca	62	Cervical LN	Positive	Positive	30	2.3	1.0	17	< 0.1	27	LDF
28	F	28	TTx, 100, 200 mCi ^{131}I	$T_2N_0M_0$	Papillary	34	Cervical LN	Positive	Positive	7.9	3.5	0.9	5.29 (0-0.13)	< 0.1	27	LDF
29	M	58	TTx, 150, 150 mCi ^{131}I	$T_4N_1M_0$	Papillary	60	Cervical LN	Positive	Positive	20	1.7	1.0	5.9	0.3	26	LDF
30	F	34	TTx, 200, 200 mCi ^{131}I	$T_4N_1M_0$	Papillary	42	Cervical LN	Positive	Positive	40	2.5	1.0	Tg< 0.1 TgAb positive	Tg < 0.1 TgAb negative	25	LDF
31	F	35	TTx, 200 mCi ^{131}I	$T_4N_1M_0$	Papillary	44	Cervical LN	Positive	Positive	12	3.4	0.9	3.8	<0.1	24	LDF
32	F	38	TTx, 100, 150 mCi ^{131}I	$T_{1b}N_0M_0$	Papillary	61	Cervical LN	Positive	Positive	23	2.5	1.0	Tg <0.1 TgAb positive	Tg <0.1 TgAb negative	20	LDF
33	F	59	TTx, 150 mCi ^{131}I	$T_{1b}N_0M_0$	Papillary	63	Cervical LN	Positive	Positive	9	2.0	1.0	582	4.7	20	LWD
34	F	16	TTx, 100, 200 mCi ^{131}I	$T_4N_1M_0$	Papillary	16	Thyroid bed, Cervical LN ↓ Lung mets	Positive	Positive	9 11 15	3.6 2.8 3.2	 1.0 0.9	1833	720 ↓ 1125	9 ↓ 16	LWD
35	M	46	TTx, 100, 200 mCi ^{131}I	$T_1N_1M_0$	Papillary	69	Cervical LN	Positive	Positive	20	4.1	1.0	18.6	<0.1	13	LDF
36	M	27	TTx, 200 mCi ^{131}I	$T_3N_1M_0$	Papillary	30	Cervical LN	Positive	Positive	14	3.1	1.0	4.9	0.4	12	LDF
37	M	26	TTx, 100, 200, 200 mCi ^{131}I	$T_4N_1M_0$	Papillary	29	Cervical LN	Positive	Positive	11	2.4	0.0	244	2.0	12	LWD

Status (LDF, LWD) established by measuring serum Tg both under L-thyroxine and after TSH stimulation withdrawal in 21 patients and recombinant human TSH in 14 patients. Ttx (total thyroidectomy); ^{131}I, ^{131}I therapy; LN, lymph nodes; T/B, tumor to background ratio measured intraoperatively by gamma probe; TB/B, tumor bed to background ratio measured intraoperatively by gamma probe after lesion extirpation; Tg, thyroglobulin; LDF, living disease-free (Tg levels < 1.0 ng/mL); LWD, living with disease.

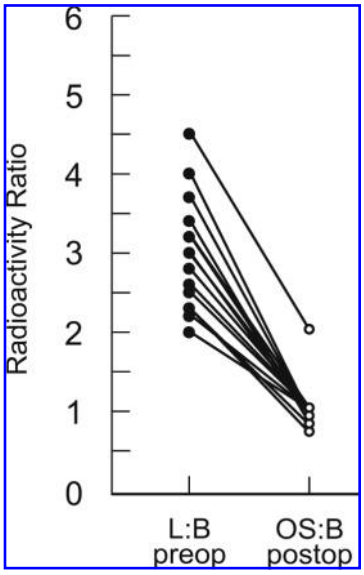

FIG. 1. Pre- and post-RGS radioactivity ratios. L, lesion; B, background; OS, operative site.

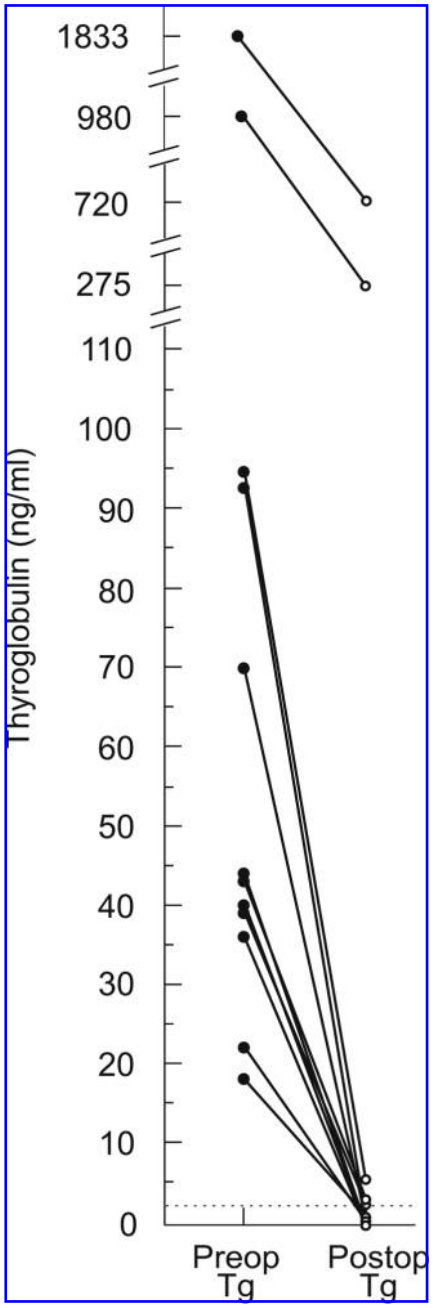

FIG. 2. Pre- and post-RGS thyroglobulin levels. Dotted line, thyroglobulin level of 2 ng/mL.

DTC is seen in older patients and more-aggressive and less-differentiated cell types (5). Thyroglobulin levels are elevated despite the loss of the ability to accumulate radioiodine (21). Accurate localization of recurrent thyroid cancer is important, especially in patients whose tumors have lost the ability to accumulate radioiodine since effective therapy becomes dependent on a surgical approach (21). Ultrasound alone or in combination with ^{99m}Tc-sestamibi has been shown to be sensitive in localizing recurrent thyroid cancer (21,22,25,26). The incorporation of intraoperative probe-guided surgery is based on the success of this technique in the treatment of parathyroid adenomas (27–29).

Radiopharmaceuticals available for imaging non-radioiodine-avid thyroid cancer include ^{201}Thallium, ^{99m}Tc-tetrafosmin, ^{99m}Tc-sestamibi, ^{111}In-pentetreotide, and ^{18}F-fluorodeoxyglucose (30). The mechanisms responsible for ^{99m}Tc-MIBI and ^{99m}Tc-tetrafosmin uptake by thyroid cancer are probably due to cellular mitochondrial content, but other factors such as cellular desmoplasia, membrane potentials, and active transport may also play a role (31–33). In a comparison study by Nishyama and colleagues, ^{201}Thallium and ^{99m}Tc-tetrafosmin demonstrated equal sensitivity in the detection of locoregional metastases of well-differentiated thyroid cancer (12). ^{99m}Tc-sestamibi was used by Alam and coworkers to localize locoregional metastases of well-differentiated thyroid cancer with sensitivity and positive predictive and negative predictive values of 94.4, 96.3, and 97.7%, respectively (13).

Pentetreotide is a somatostain analog that has been shown to localize thyroid neoplasms to include medullary thyroid cancer, but it has not been applied to the identification of locally recurrent disease in the neck. Fluorodeoxyglucose, a glucose analog, has been used to localize a wide variety of neoplasms using positron emission tomography and has been specifically useful in localizing radioiodine negative thyroid cancers (34,35). The recent availability of handheld probes designed to detect positron emissions is now being applied in the localization of metastatic disease and may allow studies of this type in thyroid cancer.

In a preliminary report we presented 8 patients with recurrent, ^{131}I-negative, well-differentiated thyroid cancer in which locoregional metastases were identified at surgery with probe-directed, low-dose ^{99m}Tc-sestamibi (22). The present study expands and confirms our earlier experience, now with 37 patients, all of whom had their recurrent thyroid cancer successfully localized and extirpated using this technique. Thyroglobulin levels fell postoperatively in all patients: based on a postoperative Tg level of <2 ng/mL (6 weeks after thyroid hormone withdrawal or after recombinant TSH administration, with follow-up intervals

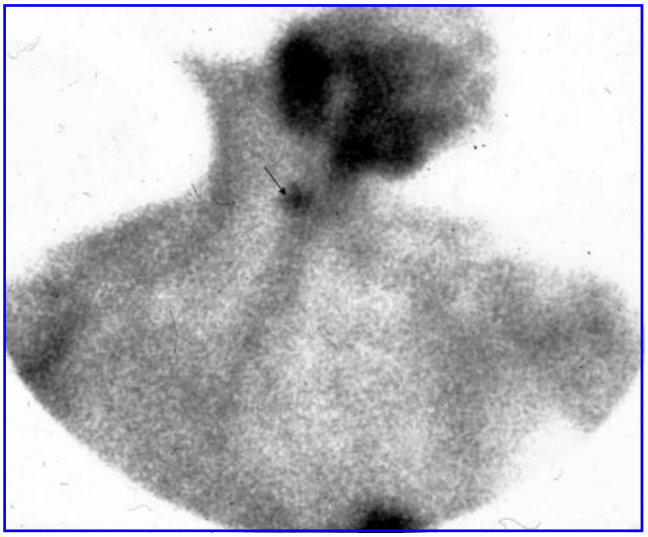

FIG. 3. ^{99m}Tc-sestamibi scan of a patient with recurrent thyroid cancer in a right cervical lymph node (arrow).

from 12 to 57 months), 28 patients are considered to be disease-free, while the remaining 9 with postoperative Tg levels >2 ng/mL (range 2.8–1320 ng/mL, done 6 weeks after thyroid hormone withdrawal or after recombinant TSH administration) are living with disease (LWD) from between 12 and 53 months duration of observation. Two patients in the latter group, both with high preoperative Tg levels, have had the late development of demonstrable tumor outside of the neck (Table 1). These patients may have harbored metastatic disease that became clinically apparent only after an additional interval of observation. Despite a lack of correlation between the size or number of tumor foci to Tg levels, it is apparent that patients presenting with markedly elevated Tg levels may not be optimal candidates for RGS if the goal of the procedure is cure (Tg <2 ng/mL). However, partial responses (Tg >2 ng/mL; <5.3 ng/mL) can be achieved in some patients with a follow-up interval of observation in our series that now exceeds 53 months. The present study does not allow an assessment of the efficacy of RGS in the treatment of thyroid cancer, nor will it allow us to make a comparison of RGS with other modalities for the intraoperative localization of thyroid cancer. Furthermore, we are unable to determine the effect of this approach upon mortality in nonradioiodine–avid thyroid cancer, but it appears in this small series that RGS may alter morbidity and subsequent thyroid cancer recurrence with an improvement in the quality of life of these patients.

Our technique allows injection of ^{99m}Tc-sestamibi and scanning prior to operation to take advantage of the more rapid washout of the tracer from DTC metastases and to limit the dose of ^{99m}Tc-sestamibi necessary for adequate counts for probe localization (22). Thus, the low-dose (1 mCi), single injection of ^{99m}Tc-sestamibi approach also allows for less radiation exposure (~1 μSi/h) to surgical personnel and maximizes the target to nontarget radioactivity levels necessary to identify tumor foci and assess the success of the procedure by using the probe to survey for residual collections of radioactivity (22). In contrast to other modalities for thyroid cancer localization, ^{99m}Tc-sestamibi and ultrasound are readily available, inexpensive, and within the scope of the diagnostic capabilities of virtually all laboratories. Furthermore, the addition of intraoperative probe guidance is not technically demanding.

This work builds upon our experience and the reports of others in the localization and probe-guided extirpation of thyroid cancer and parathyroid adenomas using ^{99m}Tc-sestamibi and demonstrates the applicability of this approach in the treatment of locoregional recurrence of radioiodine-negative thyroid cancer.

References

1. Schlumberger M, Tubiana M, De Vethaire F, Hill G, Gardet P, Travagli J, *et al.* (au: provide all authors please) 1986 Long-term results of treatment of 283 patients with lung and bone metastases from differentiated thyroid carcinoma. J Clin Endocrinol Metab **63**:960–970.
2. Rubello D, Salvatori M, Pelizzo MR, Rampin L, Fanti S, Mariani G 2005 Radio-guided surgery of differentiated thyroid cancer using ^{131}I or ^{99m}Tc-Sestamibi (editorial). Nucl Med Commun **27**:1–4.
3. Casara D, Rubello D, Saladini G, Gallo V, Massarotto G, Busnardo B 1991 Distant metastases in differentiated thyroid cancer: long-term results of radioiodine treatment and statistical analysis of prognostic factors. Tumori **77**:432–436.
4. Casara D, Rubello D, Saladini G, Massarotto G, Favero A, Busnardo B 1993 Different features of pulmonary metastases in differentiated thyroid cancer: natural history and multivariate statistical analysis of prognostic variables. J Nucl Med **34**:1621–1631.
5. Casara D, Rubello D, Saldini G, De Besi P, Fassina A, Busnardo B 1992 Differentiated thyroid carcinoma in the elderly. Clin Exp **4**:333–339.
6. Casara D, Rubello D, Tomasella G, Saladini G, Ferlin G, Busnardo B 1997 Importance of 99mTc-methoxy-isobutyl-isonitrile (MIBI) scintigraphy in differentiated thyroid carcinoma patients with elevated serum thyroglobulin levels and negative ^{131}I scan. Thyroid Clin Exp **9**:95–100.
7. Casara D, Rubello D, Saladini G, Mazzarotto R, Sotti G, Tomasella G, Pelizzo, MR 1999 Clinical approach in patients with metastatic differentiated thyroid carcinoma and negative ^{131}I whole body scintigraphy: importance of 99mTc-MIBI scan combined with high resolution neck ultrasonography. Tumori **85**:120–125.
8. Girelli M, Busnardo B, Amerio R, Nacamulli D, Casara D, Pelizzo M 1985 Serum thyroglobulin levels in patients with well-differentiated thyroid cancer during suppressive therapy: study on 429 patients. Eur J Nucl Med **10**:252–256.
9. Rubello D, Gireli M, Casara D, Piccolo M, Perin A, Busnardo B 1990 Usefulness of combined antithyroglobulin and thyroglobulin assay in the follow-up of patients with differentiated thyroid cancer. J Endocrinol Invest **13**:737–742.
10. Rubello D, Casara D, Girelli M, Picolo M, Busnardo B 1991 Clinical meaning of anti-thyroglobulin antibodies in differentiated thyroid cancer: a prospective study. J Nucl Med **33**:1478–1480.
11. Rubello D, Saladini G, Capri A, Casara D 2000 Nuclear medicine imaging procedures in differentiated thyroid carcinoma patients with negative iodine scan. Biomed Pharmacother **54**:337–344.
12. Nishiyama Y, Yamamato Y, Ono Y, Takahashi K, Nakano S, Satoh K, Ohkawa M, Tanabe M 2000 Comparison of ^{99m}Tc-tetrafrosmin with ^{201}Tl and ^{131}I in the detection of differ-

entiated thyroid cancer metastases. Nucl Med Commun **21**:917–923.
13. Alam MS, Kasagi K, Misaki T, Miyamato S, Iwata M, Iida Y, Konishi J 1998 Diagnostic value of technetium-99m methoxyisobutyl isonitrile (99mTc-MIBI) scintigraphy in detecting thyroid cancer metastases: a critical evaluation. Thyroid **8**:1091–1100.
14. Mansberg R, Crawford B, Uren RF, Thompson JF 2005 Minimally invasive radio-guided surgery for recurrent thyroid cancer using iodine-123. Clin Nucl Med **30**:43.
15. Wu H-S, Liu F-Y, Huang W-S, Liu Y-C, Chang C-T, Kao C-H 2003 Technetium-99m tetrofosmin single photon emission computed tomography to detect metastatic papillary thyroid carcinoma in patients with elevated human serum thyroglobulin levels but negative I-131 whole body scan. Clin Radiol **58**:787–790.
16. Chen Y-K, Liu F-Y, Yen R-F, Kao C-H 2003 Compare FDG-PET and Tc-99m tetrofosmin SPECT to detect metastatic thyroid carcinoma. Acad Radiol **10**:835–839.
17. Hurtado-Lopez LM, Arellano-Montano S, Torres-Acosta EM, Zaldivar-Ramirez FR, Duarte-Torres RM, Alonso-de-Ruiz P, Martinez-Duncker I, Martinez-Duncker C 2004 Combined use of fine-needle aspiration biopsy, MIBI scans and frozen section biopsy offers the best diagnostic accuracy in the assessment of the hypofunctioning solitary thyroid nodule. Eur J Nucl Med Mol Imaging **31**:1273–1279.
18. Fujie S, Okumura Y, Sato S, Akaki S, Katsui K, Himei K, Takemoto M, Kanazawa S 2005 Diagnostic capabilities of I-131, Tl-201, and Tc-99m-MIBI scintigraphy for metastatic differentiated thyroid carcinoma after total thyroidectomy. Acta Med Okayama **59**:99–107.
19. Dietlein M, Moka D, Scheidhauer K, Schmidt M, Theissen P, Voth E, Eschner W, Schicha H 2000 Follow-up of differentiated thyroid cancer; comparison of multiple diagnostic tests. Nucl Med Commun **21**:991–1000.
20. Hsu C, Liu F, Yen R, Kao C 2003 Tc-99m MIBI SPECT in detecting metastatic papillary thyroid carcinoma in patients with elevated human serum thyroglobulin levels but negative I-131 whole body scan. Endo Res **29**:9–15.
21. Rubello D, Mazzarotto R, Casara D 1999 The role of technetium 99m methoxyisobutylisonitrile scintigraphy in the planning of therapy and follow-up of patients with differentiated thyroid carcinoma after surgery. Eur J Nucl Med **27**:431–440.
22. Rubello D, Piotto A, Pagetta C, Pelizzo M-R, Casara D 2002 99mTc-MIBI radio-guided surgery for recurrent thyroid carcinoma: technical feasibility and procedure and preliminary results. Eur J Nucl Med **29**:1201–1205.
23. Schlumberger M, Berg G, Cohen O, Duntas L, Jmar F, Jarzab B, Limbert E, Lind P, Pacini F, Reiners C, Sanchez Franco F, Toft A, Weirsinga WM 2003 Follow-up of low risk patients with differentiated thyroid carcinoma: a European perspective. Eur J Endocrinol **150**:105–112.
24. Mazzaferri EL, Robbins RJ, Spenser CA, Braverman LE, Pacini F, Wartofsky L, Haugen BR, Sherman SJ, Cooper DS, Braunstein GD, Lee S, Davies TF, Arafah BM, Ladenson PW, Pinchera A 2003 A consensus report of the role of serum thyroglobulin as a monitoring method for low-risk patients with papillary thyroid carcinoma. J Clin Endocrinol Metab **88**:1433–1441.
25. Elser H, Henze M, Herman C, Eckert W, Mende U 1997 ^{99m}Tc-MIBI for recurrent and metastatic differentiated thyroid carcinoma. Nuckearmedizin **37**:7–12.
26. Franceschi M, Kusic Z, Fransceschi D, Luiniac L, Roncevic S 1996 Thyroglobulin determination, neck ultrasonography and iodine-131 whole body scintigraphy in differentiated thyroid carcinoma. J Nucl Med **37**:446–451.
27. Casara D, Rubello D, Piotto A, Pelizzo M 2000 ^{99m}Tc-MIBI radioguided minimally invasive parathyroid surgery planned on the basis of a preoperative combined ^{99m}Tc-pertechnetate/^{99m}Tc-MIBI and ultrasound imaging protocol. Eur J Nucl Med **27**:1300–1304.
28. Casara D, Rubello D, Pelizzo M, Shapiro B 2001 Clinical role of ^{99m}Tc-MIBI scan, ultrasound and intra-operative gamma probe in the performance of unilateral and minimally invasive surgery in primary hyperparathyroidism. Eur J Nucl Med **28**:1351–1359.
29. Meller B, Sahlmann C, Horstmann O, Gerl J, Baehre M, Meller J 2005 Conventional gamma and high energy probe for radioguided dissection of metastases in a patient with recurrent thyroid carcinoma with (99m)Tc-MIBI and (18)F-FDG. Nucl Med **44**:N23–25.
30. Rubello D, Saladini G, Carpi A, Casara D 2000 Nuclear medicine imaging procedures in differentiated thyroid carcinoma patients with negative iodine scan. Biomed Pharmacother **54**:337–344.
31. Boz A, Arici C, Güngör F, Yildiz A, Colak T, Karayalcin B 2001 Gamma-probe-guided resection and scanning with Tc-99m MIBI of a local recurrence of follicular thyroid carcinoma. Clin Nucl Med **26**:820–822.
32. Sarikaya A, Huseyinova G, Irfanoglu ME, Erkmen N, Cermik TF, Berkarada S 2001 The relationship between 99Tcm-sestamibi uptake and ultrastructural cell types of thyroid tumors. Nucl Med Commun **22**:39–44.
33. Songdale J, Younes A, Maublant J, Veyre A, Platts EA, Pickett RD 1994 Uptake of Tc-99m-Tetrafosmin in isolated mitochondria: evidence for an active mechanism. J Nucl Med **35**:46P–47P.
34. Iwata M, Kasagi K, Misaki T, Matsumoto K, Iida Y, Ishimori T, Nakamoto Y, Higashi T, Saga T, Konishi J 2004 Comparison of whole-body ^{18}F-FDG PET, ^{99m}Tc-MIBI SPET and post-therapeutic ^{131}I-Na scintigraphy in the detection of metastatic thyroid cancer. Eur J Nucl Med Mol Imaging **31**:491–498.
35. Wu HS, Huang WS, Liu YC, Yen RF, Shen YY, Kao CH 2003 Comparison of FDG-PET and technetium-99m MIBI SPECT to detect metastatic cervical lymph nodes in well-differentiated thyroid carcinoma with elevated serum hTg, but negative I-131 whole body scan. Anticancer Res **23**:4235–4238.

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2. Meryem Kaya, Tevfik Fikret Çermik. 2008. Tc-99m MIBI Scintigraphy in Tall Cell Variant of Papillary Thyroid Carcinoma With Negative Radioiodine Scan. *Clinical Nuclear Medicine* **33**:9, 615-618. [CrossRef]