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Diagnostic capabilities of I-131, TI-201, and Tc-99m-MIBI scintigraphy for metastatic differentiated thyroid carcinoma after total thyroidectomy.

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Abstract

We investigated the diagnostic capabilities of I-131, Tl-201, and Tc-99m-MIBI (hexakis-2-methoxyisobutyl- isonitrile) scintigraphy for thyroid cancer metastases after total thyroidectomy over the entire body and for every locus before and after thyroid bed ablation. After total thyroidectomy of thyroid cancer, 36 cases were subjected to I-131 treatment 64 times. They consisted of 17 men and 19 women with 31 papillary carcinomas and 5 follicular carcinomas. Their ages were 22–75(an average of 60.5+/-12.3) years. I-131 scintigraphy(I-131), Tl-201 scintigraphy(Tl-201), and Tc-99m- MIBI scintigraphy (Tc-99m-MIBI) were performed. We defined the metastases as those cases in which serum thyroglobulin (Tg)increased significantly or in which we were able to prove the lesions on CT (computed tomography), MRI (magnetic resonance imaging) or bone scintigram. Three radiology medical specialists visually evaluated each scintigram and calculated the sensitivity, specificity, and likelihood ratio. For whole-body sensitivity, both Tl-201 and Tc-99m-MIBI were high before ablation and I-131 was high after ablation. Before ablation, the negative likelihood ratio was less than 0.1 for Tl-201 and Tc-99m-MIBI, while the positive likelihood ratio was more than 10 for Tl-201. After ablation, the positive likelihood ratio for I-131, Tl-201, and Tc-99m-MIBI was more than 10. The sensitivity of the mediastinum was appropriate, except for I-131 before ablation, and the sensitivity of the lung before and after ablation was inferior for either tracer. The specificity of the cervix for I-131 before ablation was markedly deteriorated, but it increased after ablation.

KEYWORDS: I-131scintigraphy, Tl-201 scintigraphy, Tc-99m-MIBI scintigraphy, thyroid cancer metastases

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Original Article

Diagnostic Capabilities of I-131, Tl-201, and Tc-99m-MIBI Scintigraphy for Metastatic Differentiated Thyroid Carcinoma after Total Thyroidectomy

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We investigated the diagnostic capabilities of I-131, Tl-201, and Tc-99m-MIBI (hexakis-2-methoxy-isobutyl-isonitrile) scintigraphy for thyroid cancer metastases after total thyroidectomy over the entire body and for every locus before and after thyroid bed ablation. After total thyroidectomy of thyroid cancer, 36 cases were subjected to I-131 treatment 64 times. They consisted of 17 men and 19 women with 31 papillary carcinomas and 5 follicular carcinomas. Their ages were 22–75 (an average of 60.5 ± 12.3) years. I-131 scintigraphy (I-131), Tl-201 scintigraphy (Tl-201), and Tc-99m-MIBI scintigraphy (Tc-99m-MIBI) were performed. We defined the metastases as those cases in which serum thyroglobulin (Tg) increased significantly or in which we were able to prove the lesions on CT (computed tomography), MRI (magnetic resonance imaging) or bone scintigram. Three radiology medical specialists visually evaluated each scintigram and calculated the sensitivity, specificity, and likelihood ratio. For whole-body sensitivity, both Tl-201 and Tc-99m-MIBI were high before ablation and I-131 was high after ablation. Before ablation, the negative likelihood ratio was less than 0.1 for Tl-201 and Tc-99m-MIBI, while the positive likelihood ratio was more than 10 for Tl-201. After ablation, the positive likelihood ratio for I-131, Tl-201, and Tc-99m-MIBI was more than 10. The sensitivity of the mediastinum was appropriate, except for I-131 before ablation, and the sensitivity of the lung before and after ablation was inferior for either tracer. The specificity of the cervix for I-131 before ablation was markedly deteriorated, but it increased after ablation.

Key words: I-131 scintigraphy, Tl-201 scintigraphy, Tc-99m-MIBI scintigraphy, thyroid cancer metastases

The standard therapy for differentiated thyroid cancer is surgical resection followed by radioiodine (I-131) ablation [1]. Despite this effective treatment, the overall recurrence rate of thyroid cancer is 20% [2]. Apart from the growth of metastases from differentiated thyroid cancer, which is comparatively slow and passes without symptom, discovery is often late and thus therapeutic time is lost [3].

Conventional imaging modalities used for surveillance include CT (computed tomography) for detecting lung metastases, MRI (magnetic resonance imaging) for brain lesions, and ultrasonography for cervical nodal metastases. However, radioisotopic examination is comparable [1], and I-131 scanning (I-131) is indispensable for the

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management of patients with differentiated thyroid cancer [4].

Serum thyroglobulin (Tg) is a glycoprotein 660,000 Daltons in size that is normally sequestrated in the follicles of the thyroid gland and plays a central role in the synthesis and storage of thyroid hormones [5]. Patients with differentiated thyroid cancer are followed up after thyroidectomy by serial Tg estimation and I-131 whole body scanning [6, 7]. Even if their Tg level increases, I-131 does not accumulate, and therefore the other diagnostic method is indispensable [8].

The accumulation of Tl -201 in lung cancer, malignant lymphoma, and parathyroid tumor other than differentiated thyroid cancer as a tracer for oncoscintigraphy as well as myocardial scintigraphy depends on blood flow and Na^{+}-K^{+}-ATPase [9-11]. On the other hand, the accumulation of Tc-99m-MIBI (hexakis-2-methoxy-isobutyl-isonitrile) reflects mitochondrial metabolism [12], but Tc-99m MIBI atypically accumulates in the metastatic lesions of thyroid cancer [9]. In the case of a high level of Tg and negative I-131, Tl-201 and Tc-99m-MIBI scintigraphy is better [13]. More than 50% of cases for which I-131 was normal are positive for Tl-201 and Tc-99m-MIBI [14]. However, they confused before ablation cases with after ablation cases for I-131.

A consensus has not yet been obtained regarding the detectability of systemic metastatic lesions of differentiated thyroid cancer by I-131, Tl-201, and Tc-99m-MIBI before and after ablation, as reported by Dadparvar [15]. Furthermore, the diagnostic capability for all sites before and after ablation of I-131 has not been reported on. Therefore, we compared the diagnostic capabilities of I-131, Tl-201, and Tc-99m-MIBI scintigrams of the entire body and all loci before and after ablation.

Materials and Methods

Our subjects were patients with differentiated thyroid cancer after total thyroidectomy and I-131 therapy had been performed in our institute from August, 1999 to June, 2003. There were 36 patients treated a total of 64 times. They consisted of 17 men and 19 women. Their ages ranged from 22 to 75 years, with an average of 60.5 ± 12.3 years. The histopathological examinations performed were as follows: 31 papillary carcinomas with 52 samples taken and 5 follicular carcinomas with 12 samples taken. We measured Tg before I-131 therapy during 3 weeks of iodine limitation. In addition, Tl-201, Tc-99m-MIBI, and bone scintigraphy were performed during this period.

Based on several reports [3, 9, 16, 17], we defined the cases as metastatic when TSH (thyroid stimulating hormone) was greater than or equal to 50 μU/ml and Tg (immunoradiometric assay, less than 35 ng/ml) was more than 30 ng/ml, or when TSH was less than 50 μU/ml and Tg was more than 10 ng/ml, or we were able to prove the lesions on CT, MRI or bone scintigram.

The number of metastatic regions totaled 69, including 12 regions in the cervix, 41 regions in the lung, 6 regions in the mediastinum, 7 regions in the bone, and 3 regions in the meninx.

Imaging Method. Tl-201 and Tc-99m-MIBI scintigraphy was performed using a double-headed gamma camera (7200A/DI, 9300A/DI, Toshiba, Tokyo, Japan) fitted with a low-energy parallel hole collimator. Briefly, planar images were obtained 5 min after intravenous administration of 74 MBq of Tl-201 or 555 MBq of Tc-99m-MIBI. SPECT (single photon emission computed tomography) images were then obtained 20 min later. The energy setting was 70 keV $\pm$ 10% for Tl-201 and 140 keV $\pm$ 10% for Tc-99m-MIBI. Images were acquired on a 64×64 pixel matrix with 60 angular steps over 360 degrees at 30 sec per step. The data was reconstructed utilizing a Butterworth prefilter and filtered backprojection with a Ramp filter.

For I-131 scintigraphy, the patients orally received 3.7-5.55 GBq ^{131}I-Na, and most scintigraphy was performed 48 h later, except for 1 case for whom scintigraphy was performed 7 days later. Planar images were obtained by means of a double-headed gamma camera (7200A/DI, 9300A/DI, Toshiba, Tokyo, Japan) with a medium-energy parallel hole collimator, where the energy setting was at 364 keV $\pm$ 10%.

We defined ablation for the first time as before ablation and ablation after the second time as after ablation. We also divided the body into 5 areas: cervix, lung, mediastinum, bone, and other. If there was a definite accumulation in one place in each part, as with metastasis or recurrence, we defined it as being increased accumulation. Regarding accumulation in the 64 cases, 3 kinds of scintigram, I-131, Tl-201, and Tc-99m-MIBI, were visually interpreted. We defined the case for accumulation being equal or lower than the background as no accumulation, and accumulation being higher than the background as increased accumulation. All images were interpreted by 3 consultants, including 2 nuclear specialists, by consensus.

Diagnostic capability. To evaluate diagnostic capabilities, we calculated the sensitivity, specificity, and positive and negative likelihood ratios.

Statistical analysis. The positive and negative likelihood ratios were the index for which the number of metastatic cases was taken to be the numerator and the number of non-metastatic cases the denominator, among positive or negative cases, respectively. The positive likelihood ratio was considered to be significant for values above 10, and the negative likelihood ratio was considered to be significant for values under 0.1. We used χ^2 analysis for diagnostic capabilities of each tracer for the entire body before and after ablation. A P value of less than 0.05 was considered statistically significant.

Results

For the entire body before ablation, the sensitivity and specificity were slightly high for Tl-201 and Tc-99m-MIBI in comparison with I-131. Tl-201 was the highest for the positive likelihood ratio, with a value of 14. For the negative likelihood ratio, Tl-201 and Tc-99m-MIBI were less than 0.1, but I-131 was 0.14 (Table 1).

For the entire body after ablation, the sensitivity of I-131 increased and the sensitivity of Tl-201 and Tc-99m-MIBI decreased. The specificity of both tracers was high, and no differences were observed. The positive likelihood ratio was found to be more than 10 for both tracers. However, the negative likelihood ratio was not less than 0.1 for either of them (Table 2).

The specificity of I-131 was statistically significant ($P < 0.05$) before and after ablation (Table 3).

The sensitivity and specificity before and after ablation

Table 1 Results of postoperative diagnostic studies before I-131 ablation for patients with thyroid carcinoma

	I-131	TI-201	Tc-99m-MIBI	
TP	9	14	14	
TN	106	124	122	
FP	20	1	3	
FN	15	11	11	(region)**
Sensitivity (%)	38	56	56	
Specificity (%)	84	99	98	
LR (+)	0.45	14.00	4.67	
LR (−)	0.14	0.09	0.09	

TP, true-positive; TN, true-negative; FP, false-positive; FN, false-negative; LR (+), positive likelihood ratio; LR (−), negative likelihood ratio.
*LR+ values of 10 or greater and LR- values of 0.1 or smaller are consistent with a test with considerable diagnostic value.
**metastatic regions were divided into 5 areas: neck, lung, mediastinum, bone, and other.

Table 2 Results of diagnostic studies after I-131 ablation for patients with thyroid carcinoma

	I-131	TI-201	Tc-99m-MIBI	
TP	28	21	20	
TN	122	124	124	
FP	2	1	1	
FN	18	24	25	(region)**
Sensitivity (%)	61	47	44	
Specificity (%)	98	99	99	
LR (+)	14.0	21.0	20.0	
LR (−)	0.14	0.19	0.20	

TP, true-positive; TN, true-negative; FP, false-positive; FN, false-negative; LR (+), positive likelihood ratio; LR (−), negative likelihood ratio.
*LR+ values of 10 or greater and LR- values of 0.1 or smaller are consistent with a test with considerable diagnostic value.
**metastatic regions were divided into 5 areas: neck, lung, mediastinum, bone, and other.

Table 3 Results of diagnostic studies before and after I-131 ablation for patients with thyroid carcinoma

	Sensitivity (%)			Specificity (%)		
	I-131	TI-201	Tc-99m-MIBI	I-131	TI-201	Tc-99m-MIBI
before ablation	38	56	56	84	99	98
after ablation	61	47	44	98	99	99
P	0.108	0.285	0.212	0.0000313*	0.478	0.614

*$P < 0.05$, χ^2 test

for the scintigram of each region are shown in Table 4.

For the cervical region, lymph node metastasis before ablation occurred in 5 cases (local recurrence: 1 case), and lymph node metastasis after ablation occurred in 7 (local recurrence: 1 case). The sensitivity decreased slightly for both tracers before and after ablation. For Tl-201 and Tc-99m-MIBI, the sensitivity was appropriate in comparison with I-131 before and after ablation, while the specificity was appropriate except for I-131 before ablation.

For the lung, the sensitivity of each scintigram was less than 50%, but the specificity was 100% for all scintigrams.

For the mediastinum, there was no accumulation of I-131 for 2 cases before ablation. However, for all 4 cases after ablation, the accumulation was present. The sensitivity levels of Tl-201 and Tc-99m-MIBI were 100 %, but the specificity was not. For before ablation, a false-positive was observed for one Tl-201 case and two Tc-99m-MIBI cases, and for after ablation one Tl-201 case and one Tc-99m-MIBI case were observed. In all cases the tracer seemed to be accumulated in the blood pool.

For the bones, the sensitivity of I-131 was 100% before and after ablation, but the sensitivity of Tl-201 and Tc-99m-MIBI was 40% after ablation and decreased before and after ablation. The specificity was appropriate before and after ablation. For I-131, 1 false-positive case was observed after ablation.

For meningeal metastases, all tracers were observed before ablation. For 2 cases I-131 was observed after ablation, but for Tl-201 and Tc-99m-MIBI the sensitivity decreased. The specificity was appropriate for all tracers.

There was almost complete agreement between the results with Tl-201 and Tc-99m-MIBI before and after ablation. However, for Tc-99m-MIBI there were many false-positives in comparison with Tl-201, and the positive likelihood ratio was low before ablation.

Among the cases examined, 1 was a 66-year-old woman with a tumor diagnosed as local recurrent papillary cancer before ablation, where her Tg was 470 ng/ml (Fig. 1A). The accumulation of I-131 was not observable in the tumor because of its accumulation in the thyroid bed (Fig. 1B). However, we did observe increased accumulation of Tl-201 (Fig. 1 C) and Tc-99m-MIBI (Fig. 1D).

Another case was that of a 67-year-old woman with right 8th rib metastasis from follicular carcinoma after ablation, for whom the Tg was 13.2 ng/ml (Fig. 2A). A Tc-99m-HMDP (hydroxymethylene diphosphonate) bone scintigram showed decreased accumulation in her right 8th

Table 4 Sensitivity and specificity before and after ablation of scintigraphy for various sites

Position	Nuclide	Sensitivity (%)		Specificity (%)	
		Before (n = 30)	After (n = 34)	Before (n = 30)	After (n = 34)
Cervix	I-131	60.0 (3/ 5)	57.1 (4/ 7)	20.8 (5/24)	100 (27/27)
	Tl-201	100 (5/ 5)	85.7 (6/ 7)	100 (24/24)	100 (27/27)
	MIBI	80.0 (4/ 5)	71.4 (5/ 7)	95.8 (23/24)	100 (27/27)
Lung	I-131	21.4 (3/14)	44.4 (12/27)	100 (16/16)	100 (7/ 7)
	Tl-201	35.7 (5/14)	33.3 (9/27)	100 (16/16)	100 (7/ 7)
	MIBI	35.7 (5/14)	29.6 (8/27)	100 (16/16)	100 (7/ 7)
Mediastinum	I-131	0 (0/ 2)	100 (4/ 4)	100 (28/28)	100 (30/30)
	Tl-201	100 (2/ 2)	100 (4/ 4)	96.4 (27/28)	96.7 (29/30)
	MIBI	100 (2/ 2)	100 (4/ 4)	92.9 (26/28)	96.7 (29/30)
Bone	I-131	100 (2/ 2)	100 (5/ 5)	100 (28/28)	96.6 (28/29)
	Tl-201	50 (1/ 2)	40 (2/ 5)	100 (28/28)	100 (29/29)
	MIBI	100 (2/ 2)	40 (2/ 5)	100 (28/28)	100 (29/29)
Others	I-131	100 (1/ 1)	100 (2/ 2)	100 (29/29)	100 (32/32)
	Tl-201	100 (1/ 1)	0 (0/ 2)	100 (29/29)	100 (32/32)
	MIBI	100 (1/ 1)	50 (1/ 2)	100 (29/29)	100 (32/32)

*The number of metastatic regions totaled 69.

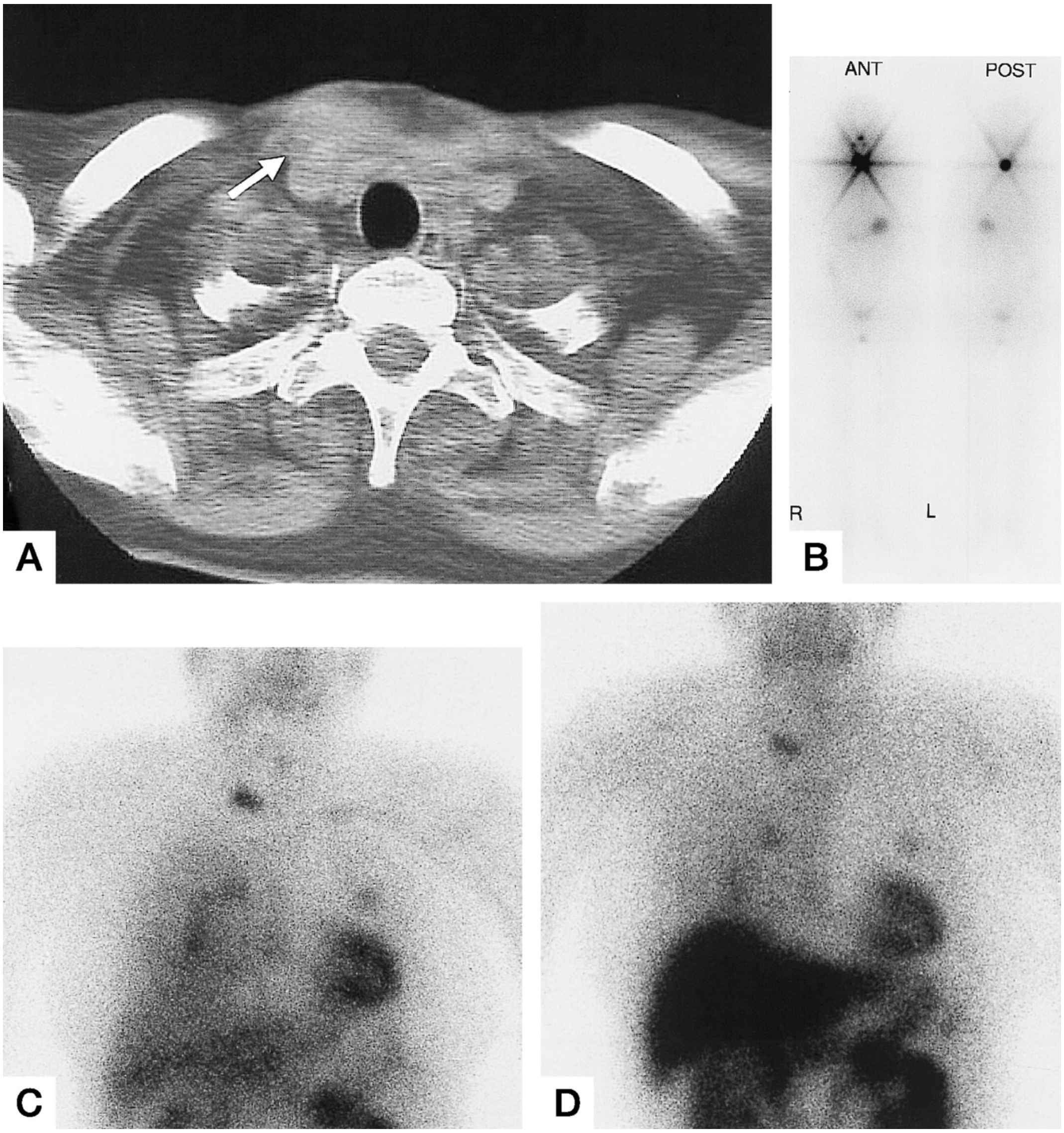

Fig. 1 Images from Case 1, a 66-year-old woman who had a tumor diagnosed as papillary carcinoma with local recurrence and multiple lung metastases. A local recurrent mass was noted by CT (arrow) A. ^{131}I accumulated in the thyroid bed B, but a ^{201}Tl scintigram C and a ^{99m}Tc-MIBI scintigram D showed more prominent and extensive uptake in accordance with a local recurrent mass.

rib, and this was diagnosed as bone metastasis (Fig. 2B). Tl-201 and Tc-99m-MIBI showed no accumulation in the right 8th rib (Fig. 2D, Fig. 2E), but I-131 showed increased accumulation in the rib (Fig. 2 C).

Discussion

We studied the diagnostic capabilities of nuclear medicine examinations with respect to metastatic foci for differentiated thyroid carcinoma of the entire body and all sites before and after ablation. For the entire body, Tl-201 and Tc-99m-MIBI were found to be appropriate diagnostic tracers before ablation, and I-131 was found to be appropriate after ablation. This is because I-131 has lower sensitivity and specificity and positive likelihood ratio than Tl-201 and Tc-99m-MIBI, and because Tl-201 and Tc-99m-MIBI are superior to I-131 regarding their negative and positive likelihood ratios. For Tl-201, the

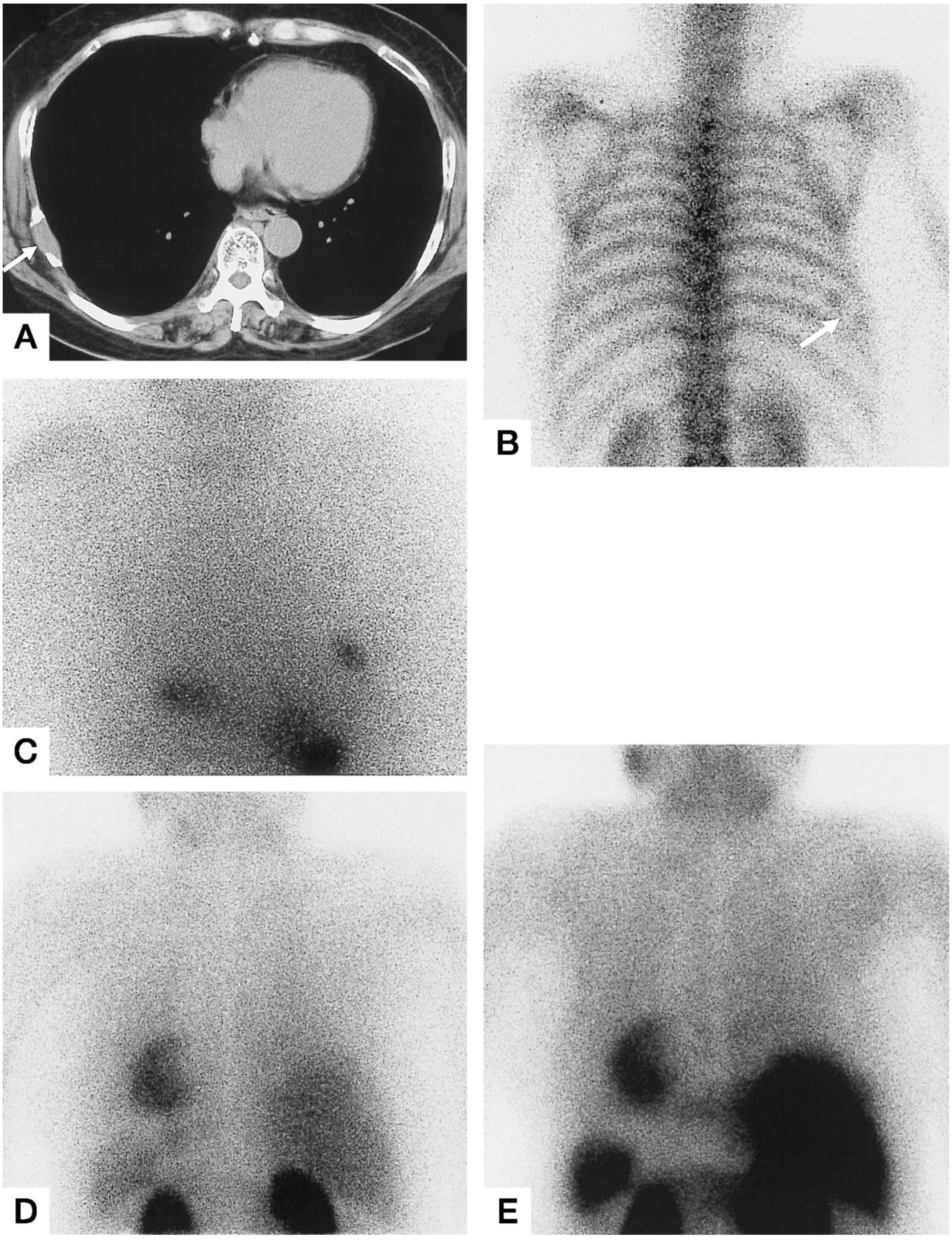

Fig. 2 Images from Case 2, a 67-year-old woman with rt. 8th rib metastasis from follicular carcinoma. An osteolytic lesion was noted by CT (arrow) **A**. A ^{99m}Tc- HMDP bone scintigram showed a bone lesion at the rt. 8th rib (arrow) **B**. A ^{131}I scintigram showed extensive uptake in accordance with rt. 8th rib metastasis **C**. A ^{201}Tl scintigram **D** and a ^{99m}Tc-MIBI scintigram **E** showed no uptake by the rt. 8th rib.

positive likelihood ratio is at its highest at 14.

With regard to why the sensitivity of I-131 is low before ablation accumulating in the thyroid bed [18], we believe that accumulation in the residual tumor and recurrent lesion is relatively decreased and can be overlooked.

On the other hand, although the sensitivity of I-131 increases for the entire body after ablation, the sensitivity of Tl-201 and Tc-99m-MIBI deteriorates. Our results differed from a report by Dadparvar in which the sensitivity of I-131 rose after ablation [15].

It has been reported that the sensitivity of I-131 is 47–84% and its specificity is 96–99% [5, 9], but all reports show mixed results for before and after ablation. We found good specificity similar to that described in previous reports, but the sensitivity before ablation was low at 38%, and the sensitivity after ablation also tended to be low at 61%. The reason why the sensitivity after ablation rose appears to be that the accumulation for residual tumors or recurrent lesions is relatively increased. Regarding the reason why the sensitivity before and after ablation was low, in most cases there is a period of 2 days before imaging by I-131 administration, as reported by Okuyama *et al*. [18], to allow for insufficient washing of the background. It is possible that we could not confirm I-131 accumulation in small lesions.

In our study, both before and after ablation, the sensitivity and specificity of Tl-201 and Tc-99m-MIBI were observed to be within the ranges noted on previous studies, which reported that the sensitivity of Tl-201 is 45–94% [16] and its specificity is 82–97% [19], while the sensitivity of Tc-99m-MIBI is 36–100% [5, 9, 20] and its specificity is 89–94% [5, 9, 20]. However, compared with before ablation, the sensitivity after ablation deteriorated. We thought that the causes were the degradation of metabolism, blood flow degradation, and a disorder of the cell membrane due to thyroid gland tissue dysfunction. The reason is that the accumulation of Tc-99m-MIBI reflects mitochondrial metabolism [12], and the accumulation of Tl-201 depends on blood flow and Na^+-K^+-ATPase [9].

We could not find a report that divided every section into before and after ablation for I-131, over the range that we examined. In our study, the sensitivity was observed to be less than 50% for all tracers and the positive rate of lung metastases was lower in comparison with a report which found that is 82% for I-131, 55% for Tl-201, and 46% for Tc-99m-MIBI [9]. The lungs are the most common site for distant metastases of differentiated thyroid carcinoma [21]. The low sensitivity of I-131 and Tl-201 in lung metastases for identifying lesions of 1 mm by CT in comparison with bone metastases and lymph node metastases probably occurs because it is hard to detect aberrant accumulation by radioisotope examination for which the spatial resolution is inferior [18]. It was difficult to find lung metastases for Tl-201, due to the low energy and degradation of the imaging and contrast due to scattered radiation [22].

It is desirable to use both I-131 and Tl-201 for the metastatic foci, except in the case of lung metastases, instead of only using I-131 [23]. These techniques are effective for searching before ablation for metastatic lesions other than lung metastases. We investigated the diagnostic capabilities for the cervical region and mediastinal lymph nodes and found that Tl-201 and Tc-99m-MIBI were superior tracers. For the cervical region, in our study the specificity before ablation for I-131 was poor, because I-131 accumulates in the thyroid bed even in cases without metastases or recurrence. In the cervical region, the cervical echo examination [1] or combination Tl-201 scintigraphy can be used jointly to check for cervical metastases.

It was reported that the positive rate of metastatic lymph node detection including for the cervix and mediastinum is 78% by I-131, 39% by Tl-201, and 56% by Tc-99m-MIBI [9], and Tc-99m-MIBI is superior for detection in comparison with I-131 [17, 24]. We believe there were false-positive cases in Tl-201 and Tc-99m-MIBI for mediastinal lymph nodes because of atypical accumulation (so-called blood pooling) in the mediastinum due to a secretion, a leakage, or an inflammation.

For thyroid cancer with bone metastasis, the prognosis is poor and the 10-year survival rate is less than 20% [25]. In addition, the sensitivity of bone scintigraphy to bone metastatic lesions is low, and the retrieval of bone metastasis by the optimum nuclide is generally required. There is a bulletin assuming that Tl-201 and Tc-99m-MIBI may be better than I-131 for detecting bone metastasis [18, 26], but we found that the detection capabilities of I-131 are appropriate.

With respect to the diagnostic capability of Tl-201 and Tc-99m-MIBI in comparison with detectability, better performance is achieved using Tc-99m-MIBI than Tl-201 [27–29]. However, in our study, Tl-201 performed well, although large discrepancies were noted as mentioned in reports by Reynolds and Seabold [14, 30]. Tc-99m-MIBI was inferior to Tl-201 due to the high occurrence of false-positive results. We expect improvements in diagnostic capabilities when Tl-201 is used before ablation.

Our study had some limitations. The first limitation is that because before and after ablation there is little cases to examine every site, we cannot conclusively comment about the utility of this examination. The second limitation is that we could only make a confirmation of lung metastasis by CT examination and not by nuclear medicine examination. However, it seems that there are few cases such as ours reported in the literature. The third limitation is that this was not a complete prospective study. The cases after the second therapy for which ablation was performed more than twice were included in our report. Thus, we cannot make a comparison before and after ablation purely using threshold values that we found.

In the future, PET (positron emission tomography) systems may be prevalent. However, at institutions without access to PET, we can expect improvements in the detection of recurrence and metastasis after total thyroidectomy using I-131 and Tl-201 as complements to each other.

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