Papillary Thyroid Cancer with Chest Metastases Only Detected Using Radioactive Iodine

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Background: Insufficient information exists on the prognostic factors of papillary thyroid cancer (PTC) with chest metastases, which is detected only using a radioactive iodide (^{131}I) whole body scan (WBS) but could not be detected using radiographic findings. The aim of this study was to analyze the clinical features and treatment results of patients with PTC.

Methods: This retrospective study includes 17 patients diagnosed from 1985 through 2002. The clinical features and responses to treatment were compared between patients with diffuse lung metastases and those with focal lung or mediastinal metastases, and at the end of follow up the results were also compared between disease-free patients and those with persistent chest metastases.

Results: The mean age of the 17 patients was 32.2±19.1 years. After a mean follow up of 89.6±51.3 months, all 17 patients survived except for one who died of a non-thyroid-related disease. Six of the 17 patients were disease-free at the end of follow up, and eight of the 17 patients became free of chest metastases. The dose of ^{131}I required to cure chest metastases was higher in the patients with diffuse lung uptake than those with focal chest uptake. The primary tumor size and serum thyroglobulin (Tg) level on the first finding of chest metastases differed markedly between disease-free patients and patients with persistent chest metastases.

Conclusions: ^{131}I scans can effectively demonstrate early chest metastases, which are difficult to detect from chest X-ray or computed tomography (CT). The prognosis for patients with papillary thyroid carcinoma with chest metastases detectable only using ^{131}I is favorable. Additionally, the low serum Tg level on the first finding of chest metastases and the small size of the primary tumor may have favorable therapeutic outcomes.

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Key words: papillary thyroid cancer, chest metastases, ^{131}I scintigraphy.

Papillary thyroid cancer (PTC) is the most common thyroid cancer treated in endocrine clinics and has a mortality rate lower than other cancers.[1-5] Distant metastases at the time of diagnosis has been reported in 1% to 7.5% of patients with PTC.[5-7] In a previous study by the authors, the results showed a corresponding figure of 5.8%.[3] Most of the information on treatment is derived from large cohort studies, since no prospective randomized trials of treatment have been conducted. The use of radioactive

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iodine (^{131}I) to treat papillary and follicular thyroid cancer and detect distant metastases has been well established.[8] In most of the patients with PTC, the chest metastases can be detected using both chest X-ray and ^{131}I scan.[9,10] Clinically, a minority of patients have been found for whom ^{131}I uptake showed lung or mediastinal metastases from PTC while traditional chest X-ray films did not. In these patients, Schlumberger et al.[9] reported of a 91% and Casara et al.[10] reported of a 96% 10-year survival, and both also reported excellent response to ^{131}I treatment.[10,11] Even so, limited information is available regarding the clinical characteristics and therapeutic outcomes of PTC patients with chest metastases detectable only by ^{131}I scans. Therefore, in this retrospective study we attempted to determine the clinical features and results of treatment and the prognosis of such patients at our hospital.

METHODS

From January 1985 through December 2002, 17 patients with PTC with chest metastases detectable only using ^{131}I were admitted to our hospital. At this medical center, all patients with differentiated thyroid carcinoma underwent operation after the tumors were found to be malignant by preoperative thyroid ultrasonography and fine needle aspiration cytology (FNAC). In most cases, frozen sections were taken during surgery. Total or near-total thyroidectomies were performed with lateral neck or central neck lymph node dissection. Four to 6 weeks following surgery, cancer studies were performed, including serum thyroglobulin (Tg), thyroid-stimulating hormone (TSH), thyroxine (T4) or free T4. In our study, 11 patients underwent whole body ^{131}I image scans 72 hours after 74 MBq or 185 MBq ^{131}I diagnostic scans, but the other six patients, including two patients whose serum Tg levels were more than 2500 ng/mL, underwent therapeutic scans of higher ^{131}I dose (ranged from 1110 to 5550 MBq) instead of diagnostic scans from the beginning of the ^{131}I therapy. When the patients received diagnostic scans, they were asked to return 24 hours later for us to measure the uptake of ^{131}I in the neck region using a single probe thyroid uptake system (AP 187-295; Atomic Product Corporation, Oak Ridge, Tenn, USA). Generally, when the ^{131}I uptake of the neck exceeded 0.5% of the dose at 24 hours, thyroid remnants were ablated with 1111-3700 MBq ^{131}I. When a diagnostic scan revealed chest metastases, then 3700-5550 MBq ^{131}I was used for treatment. Hospitalization for isolation was arranged when the dose of the ^{131}I scan exceeded 1111 MBq. Regular examinations, including chest X-ray, measurement of serum Tg levels, and diagnostic or therapeutic scans were performed on all patients every 6 months thereafter according to their physicians' policies. ^{131}I treatments were continued until there was less than 0.5% ^{131}I uptake over the neck region in the diagnostic scan and no evidence of distant metastases. Patients then underwent the aforementioned examinations annually, at 2-year intervals and finally at 5-year intervals, unless clinical or laboratory test results displayed recurrent cancer. All patients received thyroxine (T_4) replacement, except during the diagnostic or therapeutic scans. The dose of T_4 replacement was titrated by the patient's thyroid function to keep the patient serum TSH level below the normal range.

In this study we retrospectively analyzed all of the patients with PTC treated in our hospital from 1985 through 2002; ^{131}I whole body scans of these patients were reviewed. Chest metastases were observed in 20 patients with PTC only found using ^{131}I scan, but not on chest X-ray films. Chest metastases are defined here as positive findings in the lung or mediastinum on the diagnostic or therapeutic ^{131}I scan. Three patients with involvement of organs other than the chest were excluded later, including two with either vertebral or rib metastasis, as verified using results of 99mTc-methylene diphosphonate bone scans, and one with breast uptake of ^{131}I,[12] mimicking lung metastases. The follow-up period for these 17 patients continued for at least 1 year after surgery.

Chest CT and ^{201}Thalium (^{201}Tl) were performed in six and seven of the 17 patients with chest metastases, respectively. As described in our earlier study, ^{201}Tl imaging was conducted 20 min following an intravenous injection of 185 MBq of ^{201}Tl chloride in each patient.[13]

In this study we applied the following clinical classifications[5] owing to the varied age distribution of the sample patients. Stage I refers to a tumor with single or multiple intrathyroidal foci. Stage II refers to a tumor with cervical lymph node metastases. Stage III refers to a thyroid tumor with an extrathyroid extension including fixed cervical metastases.

Stage IV involves metastatic lesions outside the neck. At the end of the follow-up period, disease-free status was defined as the absence of distant metastases, no local recurrence by non-invasive examination, and a serum Tg level of below 10 ng/mL without T_4 treatment or serum Tg that was undetectable with T_4 treatment.[14] Data are presented as mean ± SD and statistical analysis, using the Wilcoxon rank sum test and the Fisher's exact test, was performed to determine the statistical significance ($p \leq 0.05$ was considered significant).

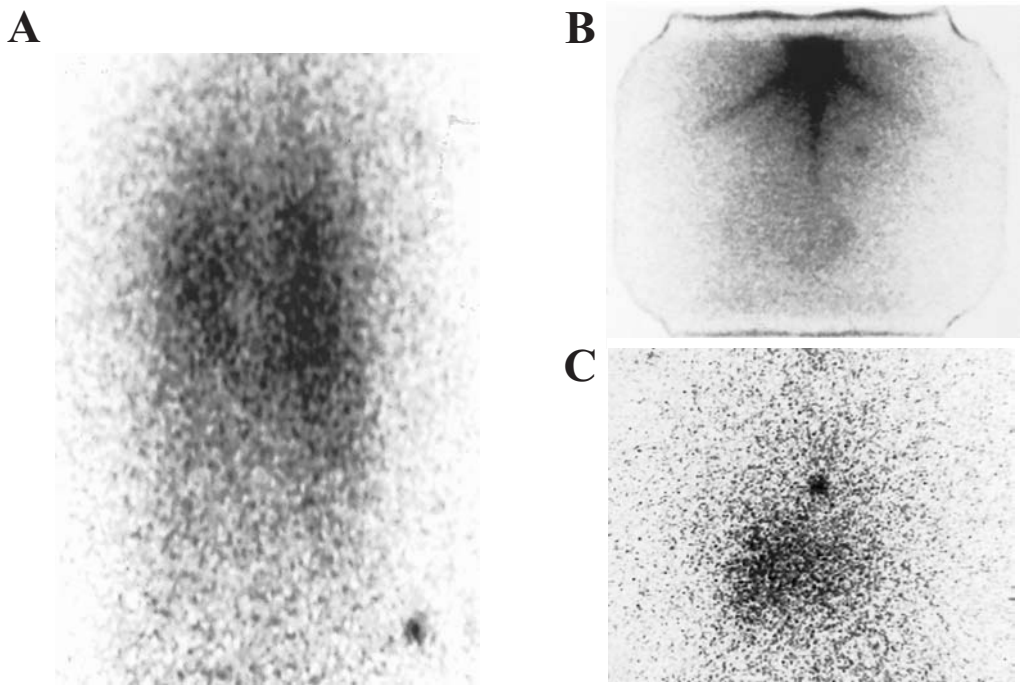
RESULTS

The mean age of the 17 patients was 32.2 ± 19.1 years (range, 6 to 72 years old). Table 1 shows the age distribution. Ten patients were female and seven were male. All patients presented with enlarged neck masses and one also presented with dyspnea and hoarseness.

Following the operations, the patients had hypothyroid status (TSH levels >30 mU/L except one with TSH=7.18 mU/L) with serum Tg levels ranging from 4.46 to 1720 ng/mL. Each patient underwent ^{131}I scans for evaluation and treatment. Among the 11 patients who received ^{131}I diagnostic scans, the chest metastases were not detected in four patients and were found later by therapeutic scans of higher ^{131}I dose. The 24-hr ^{131}I uptake of the neck in these 11 patients ranged from 1.31 to 26.2%. Figure 1 shows the different patterns of chest metastases obtained by ^{131}I scan. Among the 17 patients, six presented with diffuse lung uptake (Fig. 1A), four presented with focal lung uptake (F) (Fig. 1B) and seven presented with mediastinal uptake (M) (Fig. 1C). Table 2 lists the clinical characteristics of the diffuse

Table 1. Age Distribution of the 17 Patients with Papillary Thyroid Cancer Detected by ^{131}I Scan Only

Age (years)	<10	10-20	21-30	31-40	41-50	51-60	>60
Male	2	0	2	0	1	1	1
Female	0	5	0	1	3	1	0



Figs. 1 Patterns of chest metastases determined by ^{131}I scan. (A) Diffuse lung uptake (posterior view), (B) focal lung uptake (anterior view), (C) mediastinal uptake (anterior view).

Table 2. Clinical Presentations of 17 PTC Patients with Diffuse ^{131}I Lung Uptake or Focal ^{131}I Uptake

Patient	Tumor size (cm)	Tg* (ng/mL)	Total ^{131}I dosage to cure chest metastases (MBq)	F/U duration (months)	Age (years)	Gender	Persistent chest metastases (Y/N)
Diffuse uptake (n=6)							
1	5	NA	13505	84	51	M	N
2	NA	66.2	7955	204	17	F	N
3	2	102	9694	72	20	F	N
4	6	250	-	84	30	M	Y
5	3.5	488	31598	72	20	F	N
6	2	49.7	7326	216	7	M	N
Mean	3.7±1.8	191.2±183.8	13830.6±10119.5	122±68.5	24.2±15.1		
Focal uptake (n=11)							
7	2	48.1	4995	120	50	F	N
8	2	72.6	8732	96	22	M	N
9	4.5	14.8	4070	12	34	F	N
10	2	4.46	1850	60	43	F	N
11	NA	317	7770	84	17	F	N
12	3	16.9	14800	72	42	M	N
13	6	58.6	1480	60	48	F	N
14	NA	5.28	3700	96	6	M	N
15	4	2969	-	84	56	F	Y
16	6	2589	-	36	72	M	Y
17	2	208	4810	72	13	F	N
Mean	3.5±1.7	573.1±1098.2	5801.6±4136.6	72±29.9	36.6±20.3		
p value	0.834†	0.395†	0.038†	0.185†	0.290†	0.644‡	1.000‡

* Measured on the first finding of chest metastasis after discontinuing thyroxine therapy for 4-6 weeks

† By Wilcoxon rank sum test (comparison between diffuse uptake group and focal uptake group)

‡ By Fisher exact test (comparison between diffuse uptake group and focal uptake group)

NA: Data not available

lung uptake group and the focal chest uptake (F+M) groups. The pattern of ^{131}I scan correlated with the dosage of radioactive iodine required to ablate the metastatic lesions; that is, the dose of ^{131}I required to cure chest metastases for the diffuse lung uptake group exceeded that for the focal chest uptake group.

Fourteen of the 17 patients, including the one diagnosed with PTC mixed with insular carcinoma, became free of chest metastases after using a mean ^{131}I dose of 8736±7662 MBq. All patients except one who died of non-thyroid-related disease were alive at the end of the follow-up period. Six of the 17 patients were disease-free at the end of follow up, and eight of the 17 patients became free of chest metastases, but their serum Tg levels remained elevated (Table 3). Only three of the 17 (17.6%) patients exhibited persistent chest ^{131}I uptake following radioactive iodine therapy. Among these three patients, one presented with diffuse lung ^{131}I uptake, and two presented with focal mediastinal ^{131}I uptake. Serum Tg levels on the first finding of chest metastasis were 250, 2969, and 2569 ng/mL and the total ^{131}I accumulated doses were 21830, 32560 and 18574 MBq, respectively. Table 4 summarizes the clinical characteristics of the patients who were cured of chest metastases, and compares them with those of the patients whose chest persisted. Among the listed parameters (gender, age, tumor size, Tg level, and follow-up period), only tumor size and serum Tg level on the first finding of chest metastases differed

Table 3. Clinical Presentations of Disease-free Patients and Patients Free of Chest Metastasis after Mean Follow-Up of More Than 7 Years

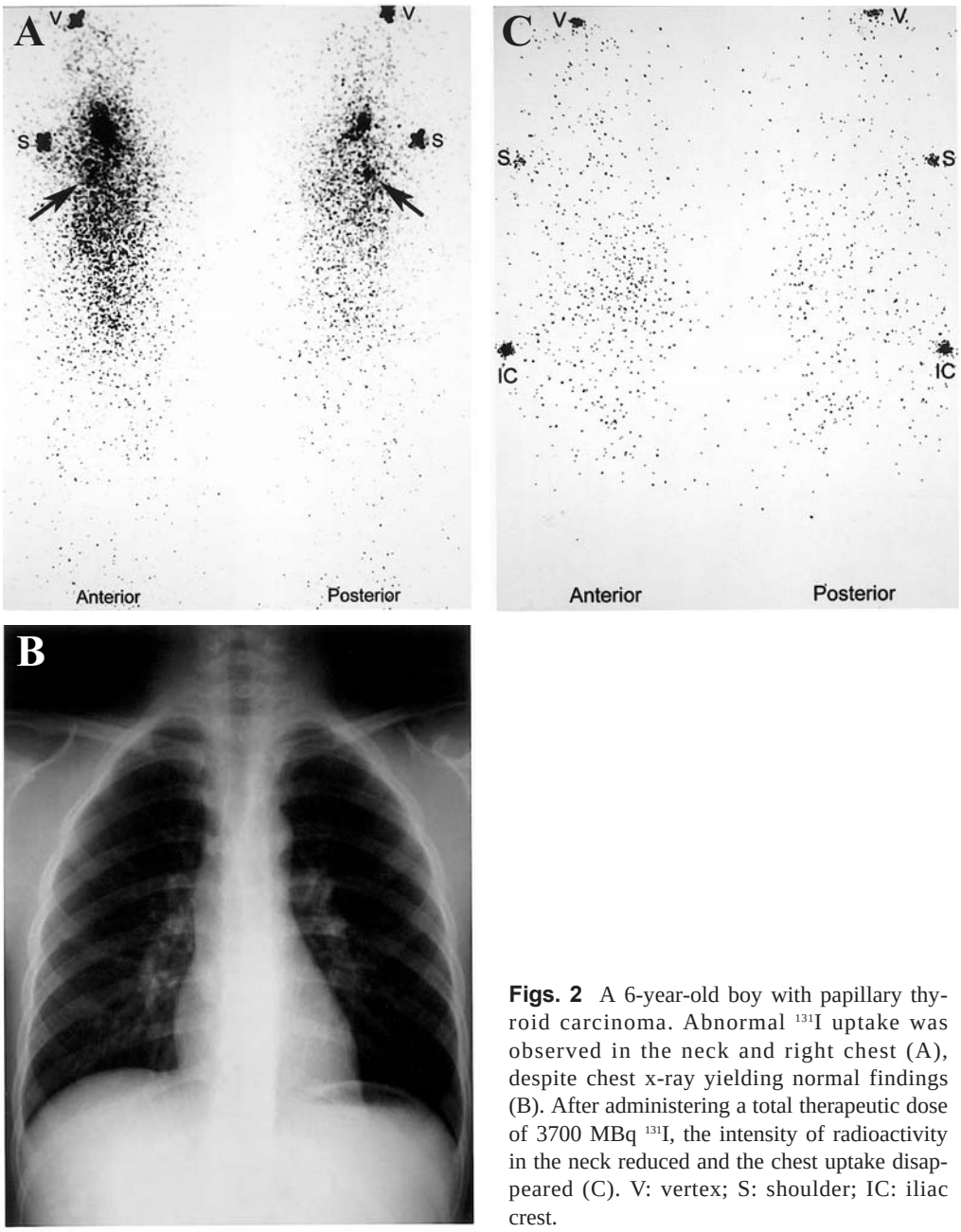
Patient	Gender	Age (years)	Primary tumor size (cm)	Tg* (ng/mL)	Post ^{131}I treatment Tg (ng/mL)	^{131}I uptake pattern	Total ^{131}I dosage for disappearance of chest uptake	Duration of follow up (mo)
Disease-free patients								
1	F	34	4.5	14.8	7.66 (off T4)	Focal†	4,070 MBq	12
2	F	43	2	4.46	<1 (off T4)	Focal†	1,850 MBq	60
3	M	42	3	16.9	7.3 (off T4)	Focal†	14,800 MBq	72
4	M	6	NA	5.28	<1 (on T4)	Focal‡	3,700 MBq	96
5	F	20	3.5	488	<1 (on T4)	Diffuse lung	31,598 MBq	72
6	M	7	2	49.7	<1 (on T4)	Diffuse lung	7,141 MBq	216
Patients free of chest metastasis								
1	M	51	5	NA	1.83 (on T4)	Diffuse lung	1,3505 MBq	84
2	F	50	2	48.1	6 (on T4)	Focal‡	4,995 MBq	120
3	M	22	2	72.6	13.2 (on T4)	Focal†	8,732 MBq	96
4	F	17	NA	66.2	3.68 (on T4)	Diffuse lung	7,955 MBq	204
5	F	17	NA	317	30.5 (on T4)	Focal†	7,770 MBq	84
6	F	48	6	58.6	5.2 (on T4)	Focal‡	1,480 MBq	60
7	F	20	2	102	1.08 (on T4)	Diffuse lung	9,694 MBq	72
8	F	13	2	208	21.1 (on T4)	Focal‡	4,810 MBq	72

* On the first finding of chest metastasis after discontinuing thyroxine therapy for 4-6 weeks
† Mediastinal metastases
‡ Focal lung metastases
NA: Data not available

Table 4. Clinical Features of Disease-Free and Persistent Chest Metastases Patients at the End of the Follow-up Period

Patient	Tumor size (cm)	Tg* (ng/mL)	F/U duration (months)	Age (years)	Gender (M/F)
Disease free					
1	4.5	14.8	12	34	F
2	2	4.46	60	43	F
3	3	16.9	72	42	M
4	NA	5.28	96	6	M
5	3.5	488	72	20	F
6	2	49.7	216	7	M
Mean	3±11.1	96.5±192.5	88±68.6	25.3±16.8	
Persistent chest metastases					
1	6	250	84	30	M
2	4	2969	84	56	F
3	6	2589	36	72	M
Mean	5.3±1.2	1936±1472.4	68±27.7	52.7±21.2	
p value	0.049†	0.038†	1.000†	0.121†	1.000‡

* On the first finding of chest metastasis after discontinuing thyroxine therapy for 4-6 weeks
† By Wilcoxon rank sum test (comparison between disease free group and persistent chest metastases group)
‡ By Fisher exact test (comparison between disease free group and persistent chest metastases group)
NA: Data not available



Figs. 2 A 6-year-old boy with papillary thyroid carcinoma. Abnormal ^{131}I uptake was observed in the neck and right chest (A), despite chest x-ray yielding normal findings (B). After administering a total therapeutic dose of 3700 MBq ^{131}I, the intensity of radioactivity in the neck reduced and the chest uptake disappeared (C). V: vertex; S: shoulder; IC: iliac crest.

significantly between those who were disease-free and those with persistent chest metastases. Additionally, the disease-free patients were noticeably younger than those with persistent chest metastases. However, for the sample size we had, we were unable to detect any statistical significance.

Seven of the 17 patients underwent chest CT studies, and no chest metastases were found. Moreover, six of the 17 patients received ^{201}Tl scans, and only one patient displayed definite chest uptake.

Two of the patients were younger than 10 years old on diagnosis. Figures 2 shows a ^{131}I scan of a 6-

year-old male patient. After the diagnosis of PTC, the patient underwent total thyroidectomy at the age of 6 years. Although under thyroxine suppression, chest metastasis was detected at 8 years old using regular ^{131}I scan. After a total dose of 3700 MBq ^{131}I (555-1,110 MBq each time), the radioactive uptake of the chest progressively declined and finally disappeared 18 months after beginning the initial treatment. The patient was disease free after a 6-year follow-up period. Another male patient was 7 years old at the time of diagnosis, and he presented with PTC with right neck masses in 1985.[15] A near total thyroidectomy was performed. Lung metastasis was suggested following a 740 MBq ^{131}I scan postsurgery. After being lost to follow-up for 4 years, the patient returned with diffuse lung ^{131}I uptake. The patient then underwent five consecutive treatments with 1110 MBq ^{131}I. After a total dose of 7326 MBq ^{131}I, the radioactive uptake disappeared from the lung at the age 13 years. The patient was 24 years old at the end of the study, and he was disease-free and had no known complications.

DISCUSSION

Although the prognosis of patients with PTC is generally favorable, distant metastases continue to cause death.[3,5,16] The 10-year survival rate in PTC patients with distant metastases is 27 % to 31%.[6,16,17] Though the mechanism through which cancer cells metastasize remains controversial, the lung is the most common site of distant metastases associated with PTC.[3,16]

The survival rate for patients below 40 years old at the time of distant metastases was more favorable (82%) than for those over 65 years old (18%).[16] In a series of 394 thyroid carcinoma patients with distant metastases, Schlumberger et al. found that most of the patients younger than 40 years old showed stronger capacity to take up iodine and better ^{131}I therapeutic outcomes.[18] Additionally, the patients with chest metastases detected by ^{131}I but not by chest X-ray were younger and had better prognosis.[10,11] In comparison, the patients with chest metastases detectable by both chest X-ray and ^{131}I scan were older with a mean age of 56.7 years and had poor prognosis.[10] Likewise, the 17 patients in this study were relatively young and none died of thyroid disease following a mean follow-up of 89.6$\pm$51.3 months. Compared with some studies about PTC with chest metastases in which the follow-up periods lasted more than 10 years,[16,19] the follow-up periods were shorter in our patients.

The mean serum Tg levels on the first finding of chest ^{131}I uptake in the focal lung and mediastinal uptake group exceeded that in the diffuse lung uptake group, possibly because of the disproportionately high Tg levels in two of the patients in the focal chest uptake group. Postoperative serum Tg levels have been used as tumor markers for predicting cancer recurrence in patients with well-differentiated thyroid cancer.[20-22] In this study, the low mean serum Tg level on the first finding of chest ^{131}I uptake also favors better therapeutic outcome. However, some patients in this study probable had incomplete thyroidectomy based on relatively high 24-hr neck ^{131}I uptake and low serum TSH level 4 to 6 weeks postoperatively, which may have interfered with the interpretation of the follow-up serum Tg levels.

A comparison between the patients with positive ^{131}I scans but negative chest X-ray films and those with negative ^{131}I scans but positive chest X-ray films was not performed because of insufficient data. Although Casara et al. reported that the therapeutic outcomes were much better in patients with positive ^{131}I scans but negative chest X-ray films than in patients with negative ^{131}I scans but positive chest X-ray films,[10] further work is needed to clarify the different clinical characteristics between these two groups of patients in our hospital.

In this study, the diagnostic scans failed to detect chest metastases in four patients which were later proved by the results of therapeutic scans. In fact, some pulmonary metastases are visualized only after large therapeutic dose of ^{131}I.[23] Chest CT scans were applied to detect lung metastases, which were suggested by an ^{131}I whole body scans with normal chest X-ray film results.[24] Nevertheless, all of the patients (n=7) who underwent chest CT in this study were negative for chest metastases. Since the ^{131}I treatment strategy was independent of chest CT findings, the role of CT in diagnosing chest metastases remains controversial.

^{201}Tl scans appear to be the most useful for detecting regional nodal disease but appear less reliable for visualizing bony and pulmonary metastases.[25] ^{201}Tl scans have been used in patients with negative ^{131}I scans together with elevated Tg lev-

els,[13,26,27] and in patients suggested of having false-positive ^{131}I WBS study results.[13,28,29] Additionally, ^{201}Tl scans have been especially useful in patients who were taking thyroid hormones.[30] Even so, ^{131}I scans have been reported to be more sensitive and specific than the ^{201}Tl scans for detecting distant metastases.[26,31] In this study, six patients received ^{201}Tl scans for correlation with ^{131}I scan results, and the findings were positive only in one case. Thus, the ^{201}Tl scan was of limited usefulness in diagnosing lung metastases.

Though ^{131}I therapy has been suggested in patients younger than 16 years old postoperatively,[24] little information is available regarding the appropriate frequency and dosage of ^{131}I treatment in children with PTC and lung metastases. Two of our patients, who had lung metastases at age 6 and 7 years old, received total doses of 3700 and 7326 MBq ^{131}I, respectively (by administering low doses of ^{131}I from 555-1110 MBq each time). The metastatic lung lesions subsided after the aforementioned ^{131}I treatment. In contrast to the report by Mazzaferri and Kloos,[19] none of our patients showed post ^{131}I therapeutic complications, such as pulmonary fibrosis or bone marrow damage, after 8 years and 18 years of follow-up, respectively.

In conclusion, chest metastases in PTC patients detectable only by radioactive iodine but not by roentgenograph might suggest early lesion detection, which may have favorable therapeutic outcomes. ^{131}I therapy is effective and should be a part of successful treatment. In addition, prognostic factors such as small primary tumor size and low serum Tg level on the first finding of chest metastases may be associated with better therapeutic outcomes.

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僅能以碘131掃描偵測到肺部轉移的甲狀腺乳突癌

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背 景： 有些甲狀腺乳突癌病人的肺部轉移能以碘131偵測到，但胸部X光檢查卻無變化，討論這類病人預後因子的相關文獻並不多，本研究試圖探討這些病人臨床表現的特徵及碘131之療效。

方 法： 此回顧性研究是針對1985年至2002年在本院治療的甲狀腺乳突癌病人。共有17位病人胸部X光檢查正常，卻能以碘131偵測到肺部轉移。若以碘131攝取的型態可進一步將這些病人分爲瀰漫性肺部轉移，以及局部性的肺部或縱膈腔轉移兩組。吾人以此比較其臨床特性及對碘131治療的反應，同時以最後一次追蹤的結果將病人分爲已治癒及持續檢出肺部轉移兩組，再從中分析影響其預後之因子。

結 果： 17位病人之平均年齡爲32.2±19.1歲。經過89.6±51.3個月的追蹤，除了1位病人死於非甲狀腺疾病，其餘16位病人均存活。這17位病人中，有6位病人已無疾病的跡象，另外有8位病人的肺部轉移消失。比較經碘131治療後肺部攝取消失者的臨床發現，呈現瀰漫性肺部轉移的病人，所需要的碘131治療劑量比呈現局部肺部或縱膈腔轉移的病人爲高。已治癒和持續肺部轉移兩組病人之血中甲狀腺球蛋白濃度及原發腫瘤的大小有顯著差異。

結 論： 碘131全身掃瞄能早期發現X光及電腦斷層偵測不出的肺部轉移。只能以碘131偵測到肺部或縱膈腔轉移的甲狀腺乳突癌病患，其預後佳。除此之外，血中甲狀腺球蛋白濃度較低以及原發腫瘤較小可能有較佳之預後。

(長庚醫誌 2004;27:663-72)

關鍵字： 甲狀腺乳突癌，肺部轉移，碘131核子掃瞄。

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