Radioactive Iodine Treatment and External Radiotherapy for Lung and Bone Metastases from Thyroid Carcinoma

Martin Schlumberger, Cécile Challeton, Florent De Vathaire, Jean-Paul Travagli, Paule Gardet, Jean-Denis Lumbroso, Cecilia Francese, Françoise Fontaine, Marcel Ricard and Claude Parmentier

Institut Gustave-Roussy, Villejuif, France

We assessed the therapeutic benefits of ^{131}I treatment in patients with distant metastases of differentiated thyroid carcinoma. **Methods:** Of 2200 patients treated for differentiated thyroid carcinoma at our institution, 394 had lung and/or bone metastases. **Results:** Two-thirds of the patients had ^{131}I uptake in their metastases, but only 46% achieved a complete response. Prognostic factors for complete response were: younger age, presence of ^{131}I uptake in the metastases and small extent of disease. The survival rate was 33% at 15 yr. As shown by multivariate analysis, favorable prognostic factors for survival were: younger age and time of metastases detection, well-differentiated histologic type of the thyroid tumor, presence of ^{131}I uptake in the metastases, small extent of the disease and year of discovery of metastases. **Conclusion:** In terms of survival, the benefits of ^{131}I therapy cannot be demonstrated by prospective controlled studies. The present study clearly demonstrates, however, that treatment with ^{131}I is one of the factors which accounts for survival; patients whose metastases concentrated ^{131}I and who could be treated with radioiodine had higher survival rates. Patients who achieved complete response following treatment of distant metastases had a 15-yr survival rate of 89%, while those who did not achieve complete response had a survival rate of only 8%. The survival rate improved with the year of discovery of distant metastases, after ^{131}I total-body imaging and serum thyroglobulin measurements were routinely used.

Key Words: metastases; thyroid carcinoma; iodine-131; external radiotherapy

J Nucl Med 1996; 37:598–605

Distant metastases occur in 5%–23% of patients with differentiated thyroid carcinoma (*1–11*). Follow-up data of the few large patient groups reported to date, however, are far too limited to allow assessment of the long-term results of treatment and potential prognostic factors. These variables are closely interrelated, but multivariate analysis of such factors has been performed in only three studies (*7,9,11*). These obvious shortcomings account for the obscure picture of the natural history of metastatic disease in differentiated thyroid carcinoma and of the real benefits of radioiodine treatment and external radiotherapy.

In a previous report, (*7*) we showed how limited disease at the discovery of metastases affected remission and survival rates after radioiodine treatment, a finding which has been recently confirmed by an additional multivariate analysis (*11*). Notwithstanding, the benefits of radioiodine treatment have been questioned in the absence of visible metastases on plain radiographs, and it has been contended that prolonged survival in patients treated with radioiodine is actually a direct result of early detection of metastases (*9*). Unfortunately, prospective randomized studies addressing this question will not be completed in the near future, and the only evidence, although indirect, currently available, is that offered by retrospective studies.

Our own series now comprises 394 patients with lung and bone metastases and provides complementary data to previous reports (*7,12–14*) which show that radioiodine treatment has been clearly beneficial to a remarkable proportion of patients with lung metastases. It also suggests the need to investigate other treatment modalities for patients with massive metastatic dissemination.

Received Jan. 17, 1995; revision accepted Jul. 30, 1995.

For correspondence or reprints contact: Martin Schlumberger, MD, Institut Gustave-Roussy, 94805 Villejuif Cedex, France.

METHODS

Patients

From 1950 to 1992, 2200 patients with differentiated thyroid carcinoma were treated at our institution, 394 of whom had lung and/or bone metastases. Two patients with struma ovarii and 16 patients with unusual metastatic sites (brain in seven patients, liver in three, skin in three, brain and skin in one, adrenal in one and parotid gland in one) were not included in the study.

The study was terminated on July 31, 1992. Twenty-two patients were lost to follow-up before July 31, 1990. The median follow-up was 50 mo (range, 1–597 mo) after discovery of the metastases; 175 patients underwent follow-up for more than 5 yr, 91 for more than 10 yr and 45 for more than 15 yr.

Thyroid tumors were classified histologically as papillary in 172 patients, follicular well-differentiated (FWD) in 28 patients and follicular less-differentiated (FLD) in 173 patients, according to WHO recommendations (*15*). Patients with an anaplastic component as well as those with atypical histologic features and negative immunostaining for antibodies directed against thyroglobulin (Tg) were excluded from the study. No surgical specimens were available from 21 patients for microscopic examination; origin of the metastases in the thyroid was demonstrated by ^{131}I uptake in the metastases.

Thyroid Tumor Treatment

Thyroid surgery had been performed in 87% of the patients and lymph node dissection in 54% before treatment of the metastases (*16*). One-third of the patients treated surgically received postoperative external radiotherapy to the neck (*17*), while 36% without detectable metastases were given an ablative dose of 100 mCi ^{131}I. Thirteen percent of the patients, who had multiple and large distant metastases at presentation, did not have surgery but rather, were treated only with radioiodine and/or external radiotherapy to the neck.

Patient Follow-up

From 1960 on, all patients were given L-Thyroxine (LT4) treatment postoperatively to suppress TSH secretion; serum TSH levels were assessed by a radioimmunoassay and by sensitive TSH measurements. Whole-body ^{131}I imaging was performed once a year for the first 2 yr and then every 5 yr thereafter. To achieve optimal endogenous TSH stimulation (*18*), LT4 therapy was discontinued, T3 was given for 3 wk and then was withdrawn for 2 wk before performing the scan. Serum TSH and Tg levels were measured, and a TBS was performed 72 hr after the administration of 2–5 mCi ^{131}I on a whole-body double-probe rectilinear scanner, which has since been replaced by a homemade digitized whole-body scanner with two opposed heads equipped with an adapted collimator and a thick crystal (4″) that provides high detection rates for ^{131}I emitted photons. After the anterior and posterior views were acquired the geometrical mean of the two images was calculated to minimize the depth dependance of the pixel's content. The amount of radioactivity was then determined by drawing ROIs directly on the geometrical mean image. During calibration, patient thickness was taken into account. It appeared that the presence of bones did not significantly affect the counting rate. The sensitivity of this scanner is 1 μCi over the lungs and 0.1 μCi for point sources. A chest radiograph was obtained at the time of the ^{131}I whole-body scan. Bone radiographs were not performed routinely but rather, were limited to patients who had positive ^{131}I skeletal uptake and/or symptoms indicative of bone disease.

Patients without any evidence of disease after initial treatment of the thyroid tumor had an annual clinical examination and serum T4 and TSH measurements. Serum Tg determination was added to the annual follow-up from 1977 on (*19–21*). In five patients, interferences precluded serum Tg determination. In a previous study, serum Tg was measured during LT4 treatment in 349 patients who had no detectable disease after initial treatment. Tg was undetectable in 345 and ranged from 1 to 2 ng/ml in the other 4. After thyroid hormone withdrawal, the serum Tg level remained undetectable in 88% of these patients and was below 6 ng/ml in the other patients (*21*). Due to the high specificity of Tg measurement, a detectable Tg level during LT4 treatment led immediately to a ^{131}I whole-body scan.

Estimating Extent of Metastases

The extent of metastases was estimated by evaluating isotope scan and roentgenograms. Category 1 included patients with normal chest and bone radiographs whose metastases were visualized on ^{131}I whole-body scans. Patients in category 2 had micronodular lung metastases that were radiologically smaller than 1 cm (*22*) or a single bone metastasis identified by x-ray. Patients in category 3 had either macronodular lung metastases or multiple bone metastases.

Treatment of Patients with Metastases

Patients with radioiodine uptake in metastases were treated with radioactive iodine at a standard dose of 100 mCi in adults and 1 mCi/kg body weight in children. A whole-body scan was performed 5 days after each treatment, and LT4 treatment was resumed to achieve total suppression of TSH secretion. Patients with any radioiodine uptake in residual metastatic disease underwent another ^{131}I treatment 3–6 mo later. No diagnostic whole-body scans were obtained for patients with known metastases before ^{131}I therapy. A total of 348 patients were treated with ^{131}I for distant metastases, with a mean cumulative dose of 319 $\pm$ 239 mCi (range: 31–1425 mCi). There was no theoretical limit for the maximal cumulative dose of ^{131}I.

In patients who had abnormal bone or lung radiographs and high uptake in the thyroid region, 100 mCi ^{131}I were administered to ablate the thyroid remnant. Even in the absence of detectable metastatic uptake, another 100 mCi ^{131}I were given 3 mo after ablation to search for ^{131}I uptake in metastatic disease.

Patients with detectable Tg levels during LT4 treatment, or increasing serum Tg above 5 ng/ml following LT4 withdrawal and no other evidence of disease, were administered 100 mCi ^{131}I with a whole-body scan 5 days later (*23*). When patients with elevated Tg levels demonstrated no uptake on post-therapy ^{131}I whole-body scan, a complete work-up was performed, including neck and chest CT and bone scintigraphy.

Patients with radiographically visible bone metastases received external radiotherapy (*17*) [30 Gy (3000 rads) in 15 days or 45 Gy in 28 days], in association with ^{131}I therapy in 115 patients, or as the sole treatment in 22 patients whose metastases did not concentrate ^{131}I. Iodine-131 treatment was given before external irradiation and in case of ^{131}I uptake, therapy was repeated 3 mo or later after its completion.

Seventy-one patients with bone metastases had surgery because of orthopedic or neurological complications or because they had a high risk of such complications. Total excision was performed in only one patient with a single vertebral metastasis.

No response was found in 48 patients with progressive disease treated by chemotherapy using either a single agent, such as doxorubicin, cisplatinum, bleomycin, methotrexate, ellipticinum, etoposide or mitoxantrone, or a combined regimen (*24*).

Evaluation of Therapeutic Efficacy in Patients with Distant Metastases

Patients were followed every 2 mo with clinical examination, TSH and Tg measurements and radiographs of all metastatic sites. Iodine-131 whole-body scans were performed as previously described. Response to treatment was evaluated by radiographs and ^{131}I whole-body scans; for this study, serum Tg measurements CT and bone MR images were not taken into account when assessing tumor response to treatment but, rather, were studied separately. A complete response of metastatic lung disease was defined as the disappearance of lung ^{131}I uptake for more than 1 yr, as shown by post-therapy ^{131}I-TBS and verified 1 yr later by ^{131}I whole-body scanning with a diagnostic or a therapeutic dose of ^{131}I and a normal chest radiograph. A complete response to therapy for bone metastases was defined as the disappearance of ^{131}I bone uptake and clinical symptoms for more than 1 yr and recalcification of radiological lytic lesions.

Results of Tg determination and chest CT scans were then studied in each group of patients.

Patients who had achieved a complete response were followed every 6 mo with clinical examinations, TSH and Tg determinations and radiographs. No ^{131}I whole-body scans were obtained in these patients.

Statistical Analysis

The prognostic value of each variable was studied individually by log-rank testing and, taking the other variables into account, by Cox's model (*25*).

The expected number of leukemias in our cohort was estimated using incidence rates of leukemia by age and sex in France from 1978 to 1982 (*26*). No variation in the incidence of leukemia in Europe has been observed for more than 30 yr (*27*). This was not possible for solid tumors because there is no national cancer registry in France and because the incidence of solid tumors differs among countries (*11*).

RESULTS

The clinical characteristics of the 394 patients are summarized in Table 1. Metastases were present in 47% of the patients at initial treatment of the thyroid tumor, while they were discovered from 6 mo to 41 yr after the initial treatment in the other 53% (median 42 mo) (Fig. 1). Twenty-two percent of the latter patients experienced a neck relapse before the discovery of distant metastases.

Radiological Findings

Clinical symptoms such as thoracic pain and dyspnea were present in 21% of the 214 patients with isolated lung metastases. Chest radiographs revealed macronodules in 34% of these

TABLE 1
Univariate Analysis of Prognostic Factors

Factor	No. of patients	Remission (%)	10-yr survival rate (%)	No. of deaths	Relative risk of death	p value
Age (yr)						
4–19	37	78	100	3	1	
20–39	97	60	81	20	3.5	$<10^{-4}$
40–59	158	15	19	113	26.7	
60–82	102	13	13	83	40.4	
Sex						
Females	243	35	45	131	1	0.1
Males	151	26	33	88	2.1	
Histology*						
Pap	172	53	64	60	1	
FWD	28	14	40	19	2.1	$<10^{-4}$
FLD	173	13	19	124	3.3	
Radioiodine uptake						
Yes	263	46	57	108	1	$<10^{-4}$
No	120	2	8	102	5	
Site of metastases						
Lung	214	50	61	81	1	
Bone	108	10	21	82	2.5	$<10^{-4}$
Lung + bone	72	7	13	46	3.4	
Extent of metastases						
Category 1	84	82	91	9	1	
Category 2	99	40	63	37	3.5	$<10^{-4}$
Category 3	211	7	11	172	16.7	
Year of discovery						
Before 1960	34	15	21	32	2.3	
1960–1976	139	25	39	102	1.6	$<10^{-4}$
After 1976	221	38	49	85	1.0	
Discovery of metastases						
Early	183	30	39	102	1	
Late	203	34	44	109	1.1	0.4
Local relapse before metastases						
Yes	78	29	36	48	1.3	
No	313	32	42	168	1	0.1
Tg/T4†						
1–20	43	67	80	7	1	
21–100	59	39	54	23	2.0	$<10^{-4}$
>100	53	6	21	30	4.4	
Tg/TSH						
1–100	63	69	75	13	1	
101–1000	65	36	61	20	1.6	$<10^{-4}$
>1000	53	4	17	34	4.4	

*Pap = papillary; FWD = follicular well differentiated; FLD = follicular less differentiated.
†Tg level at the discovery of metastases. Tg/T4 = Tg level during LT4 treatment. Tg/TSH = Tg level following LT4 withdrawal (ng/ml).

214 patients and micronodules in 30%. Chest radiographs were normal in the other 36%; lung metastases were demonstrated by whole-body scans. Prior to 1977, 4% of the patients with lung metastases had normal chest radiographs. Once serum Tg measurements became an integral part of the follow-up protocol, however, the proportion of patients with normal radiographs at detection of metastases rose to 40%. This may be due to the fact that the discovery of an elevated serum Tg level immediately resulted in obtaining a whole-body ^{131}I scan.

One hundred eight patients had bone metastases only, while 72 patients had both bone and lung metastases. Pain, swelling or orthopedic complications occurred in 87% of these 180 patients. Thirty-three percent of these patients had a single bone metastasis (involving the base of the skull in 14), and 7% had no radiological abnormality.

The lungs were the only site of metastases in 75% of patients with papillary carcinoma and in the 41% with follicular carcinoma. Ninety-four percent of patients below 20 yr of age at the time of metastases discovery had only lung metastases; this percentage decreased to 33% in patients over 60.

Scintigraphic Findings

Iodine-131 whole-body scans demonstrated metastases in 67% of patients. The frequency of uptake was similar in patients with lung or with bone metastases. Uptake was observed in 79% of metastases from papillary carcinoma and in 54% of metastases from FLD carcinoma, in 90% of patients less than 40 yr and in 56% of patients over 40 yr. Among patients with lung metastases only, uptake was found in 95% of those with normal chest radiographs, in 88% of those with micronodules and in 37% of those with macronodules. In 15 patients with only lung metastases and a normal chest radiograph, ^{131}I uptake in the

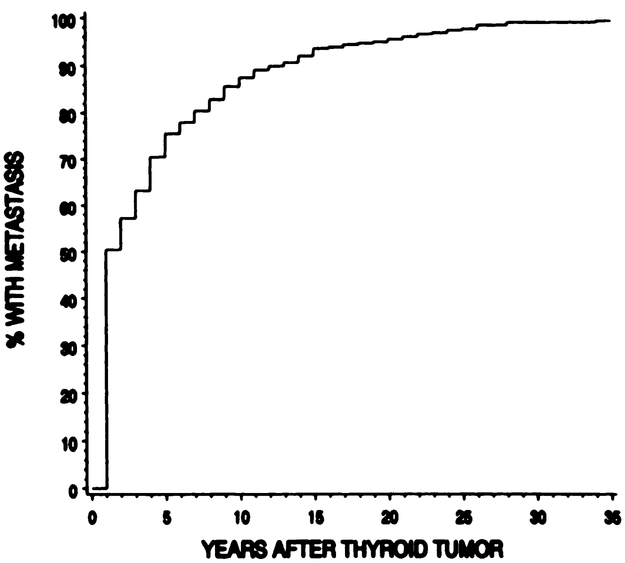

FIGURE 1. Cumulative incidence of distant metastases. Half of the distant metastases were present initially, and 15% were discovered more than 10 yr after initial treatment of the thyroid tumor.

lungs was documented only after the administration of 100 mCi ^{131}I. Lung CT performed in these 15 patients showed micronodules in eight.

Serum Tg Measurements

Serum Tg levels were measured in 155 patients upon detection of metastases during LT4 treatment. Tg levels were above 10 ng/ml in 130 and undetectable in three patients. Two of these three patients had normal chest radiographs and one had lung micronodules; a whole-body scan obtained with 2 mCi ^{131}I demonstrated lung uptake in all three patients.

After thyroid hormone withdrawal, the serum Tg level was above 5 ng/ml in all 181 patients in whom it was measured. It was above 10 ng/ml in 175 of these patients, above 40 ng/ml in 154 and above 100 ng/ml in 118.

Serum Tg levels, both on and off LT4 treatment, were higher in patients with FLD carcinoma than in those with papillary carcinoma, in those with bone metastases than in those with isolated lung involvement, and in those with lung macronodules than in patients with lung micronodules or with normal radiographs.

Clinical Course

Complete Response. One hundred twenty-four patients had complete response, as defined above, after treatment for distant metastases. Only two of 120 patients, whose bone metastases did not concentrate radioiodine, achieved complete response after external radiotherapy. Sixty-six percent of the 124 complete responses occurred within 5 yr after initiation of metastatic treatment. Follow-up after complete response lasted from 1 to 38 yr (mean ± s.d.: 8 ± 6 yr), and seven relapses occurred from 2 to 15 yr after complete response (two in the bones, three in the lungs, one in the brain and one in the neck). Thirteen patients who had achieved complete response died: five from thyroid carcinoma (after recurrence at distant sites), four from another carcinoma, one from an intercurrent disease and two from unknown causes.

One hundred eight of these 124 patients had lung metastases only and were treated with ^{131}I. The remaining 16 patients had bone metastases (11 had a single bone metastasis, localized at the base of the skull in nine; only three of these nine patients had radiological abnormalities). These patients were treated either with ^{131}I alone (n = 12), with external radiotherapy alone (n = 2) or with a combination of both modalities (n = 2).

TABLE 2
Multivariate Analysis of Prognostic Factors for Complete Response (Logistic Regression Analysis)

Factor	Relative risk of complete response (95% CI)	p value
Age (yr)*	0.96	$<10^{-4}$
Radioiodine uptake (Yes/No)	22.7 (5.0–100)	$<10^{-4}$
Extent of disease		
Category 1/Category 2	6.03 (2.7–13.2)	$<10^{-4}$
Category 1/Category 3	30.7 (12.9–73.4)	$<10^{-4}$

*Relative risk was estimated for the first group relative to the second except for age at discovery of metastases that was considered as a continuous variable.

Logistical regression analysis for complete response showed that age at the time of metastases discovery, ^{131}I uptake and extent of metastases had significant prognostic implications when all variables were considered (Table 2). Complete responses occurred in 46% of the patients with radioiodine uptake, in 82% of the 84 patients with a normal radiograph examination at discovery of metastases and in 15% of the 310 patients with metastases visible on the initial radiograph ($p < 0.001$).

Fourteen of the 15 patients whose lung metastases were documented only after administration of 100 mCi ^{131}I had complete response, since no uptake was seen after the last 100-mCi administration of ^{131}I. Serum Tg levels during LT4 treatment were detectable in all patients before treatment for the metastases and became undetectable in nine after treatment; it remained undetectable in six following LT4 withdrawal. A lung CT scan showed micronodules in eight patients before treatment and normalized in six after radioiodine treatment.

The mean cumulative dose of ^{131}I administered before complete response in the 124 patients was 293 mCi (±188 mCi). Patients who had only lung metastases received 253 mCi (±136 mCi) when chest radiographs were normal, 323 mCi (±202 mCi) when metastases were micronodular and 408 mCi (±244 mCi) when they were macronodular. Ninety-two percent of the 124 complete responses were observed after a cumulative dose equal to or less than 600 mCi (i.e., six treatment sessions). Among the 46 patients who received more than 600 mCi, only eight achieved complete response.

Serum Tg levels measured during LT4 treatment in 106 patients in whom complete response was obtained were undetectable in 54 patients, less than 10 ng/ml in 31 and above 10 ng/ml in 21. Serum Tg levels measured in 113 patients after LT4 withdrawal were undetectable in only 22%. A whole-body scan with 100 mCi was performed in 34 patients treated for lung metastases more than 1 yr after having achieved complete response: all these patients had detectable Tg levels following LT4 withdrawal, but no uptake was found. None of these 34 patients have relapsed.

Five recurrences were observed among patients whose Tg levels were measured at the time of complete response, two in patients with undetectable Tg levels and three in patients with detectable Tg levels at the time of complete response. Tg levels were detectable in all five patients at the time of recurrence.

Despite diffuse lung involvement, no clinical respiratory sequellae were observed. The functional respiratory tests, including CO diffusion studies, performed in 52 of these patients were normal in 49.

TABLE 3
Multivariate Analysis of Prognostic Factors of Survival (Cox's Model)*

Factor	Relative risk of death (95% CI)	p value
Age (yr)*	1.04 (1.0–1.1)	$<10^{-4}$
Histology		$<10^{-4}$
FLD/others	1.5 (1.1–2.0)	
Radioiodine uptake (Yes/No)	0.4 (0.3–0.5)	$<10^{-4}$
Extent of disease		
Category 2/Category 1	1.9 (0.9–4.0)	0.08
Category 3/Category 1	5.3 (2.7–10.5)	$<10^{-4}$
Year of discovery of metastases		
1960/After 1976	2.4 (1.5–3.8)	0.003
1960–1976/After 1976	1.3 (1–1.8)	0.07

*Relative risk was estimated for the first group relative to the second group except for age at discovery of metastases that was considered as a continuous variable.

Persistent Disease. Seventy-three patients alive at the end of the study had evidence of disease shown either by radiographs or ^{131}I whole-body scan. Serum Tg levels measured during LT4 treatment were undetectable in ten and detectable in the other 63 patients. They were detectable in all patients after LT4 withdrawal. Detectable Tg levels were significantly higher in these patients, both during LT4 treatment and after LT4 withdrawal, than in those who had achieved complete response ($p < 0.01$) (*7*). Of note, 78% of the patients have been treated for less than 5 yr. As previously stated, one-third of the complete responses occurred 5 yr or more after the initiation of treatment.

Survival

Two hundred nineteen patients died, 144 from thyroid cancer, 17 from intercurrent disease, nine from another malignancy and 49 from unknown causes. The overall survival rate from the time of metastases detection was 55% at 5 yr, 40% at 10 yr and 33% at 15 yr.

Prognostic Factors

The prognostic significance of each variable for survival, as evaluated by univariate analysis, is summarized in Table 1. Age at discovery of metastases, histologic type, ^{131}I uptake, the site (i.e., lung or bone), extent of metastases, year of discovery of metastases and Tg levels at discovery of metastases were all significant prognostic factors. Gender, the interval between treatment of the thyroid tumor and discovery of metastases and the occurrence of a local relapse before discovery of metastases were not considered significant.

Prognostic variables were strongly interrelated. Cox's regression analysis of survival showed that five variables were significant when all other factors were considered (Table 3) (Figs. 2–6). Patients who were older at the time of discovery of metastases had a higher risk of death due to cancer than younger patients. Patients with FLD had lower survival rates than patients with papillary or FWD tumors. No difference was observed between the latter two histologic types when all other factors were taken into account. Positive ^{131}I uptake indicated a favorable prognosis. The risk of death was highest in patients with macronodular lung metastases or multiple bone metastases; this risk was moderate for patients with micronodular lung metastases and a positive chest radiograph or with a single radiographically detectable bone metastasis. The lowest risk was observed for patients with lung metastases and normal

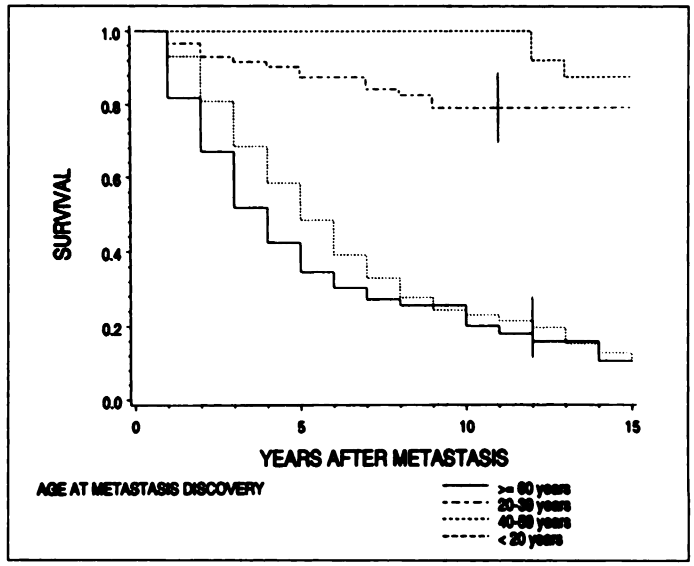

FIGURE 2. Survival after discovery of distant metastases as a function of age. Prognosis is favorable for patients younger than 40 yr and worsens above 40 yr.

chest radiograph or with a single bone metastasis not detectable radiologically. Patients whose metastases were discovered before 1960 (the year when ^{131}I whole-body scanning was introduced at our institution), had the highest risk of death, whereas those whose metastases were discovered from 1977 on (the year when Tg measurement became routinely available) had the lowest risk of dying from the disease.

Three groups of patients can be distinguished according to age at the discovery of metastases and to extent of disease. The survival rate at 10 yr was 96% in the 56 patients who were less than 40 yr of age and had normal radiographs and only 7% in the 156 patients over 40 yr of age with macronodular lung metastases or multiple bone metastases. The survival rate was 63% for the 182 other patients (Fig. 7).

Finally, the survival rate for the 124 patients who achieved complete response was 96% at 5 yr, 93% at 10 yr and 89% at 15 yr. This was significantly higher ($p < 0.001$) than the survival rate for the 270 patients who did not achieve complete response (37% at 5 yr, 14% at 10 yr and 8% at 15 yr) (Fig. 8). No difference in survival was observed among patients whose

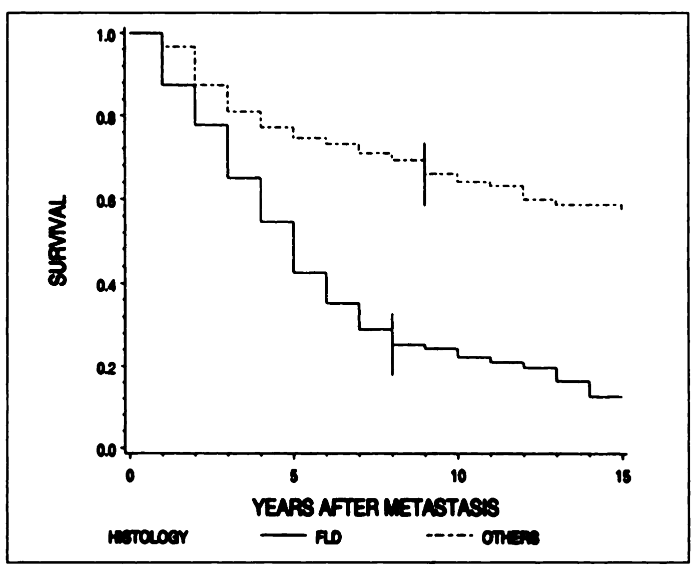

FIGURE 3. Survival after discovery of distant metastases as a function of histologic type of thyroid tumor (*15*).

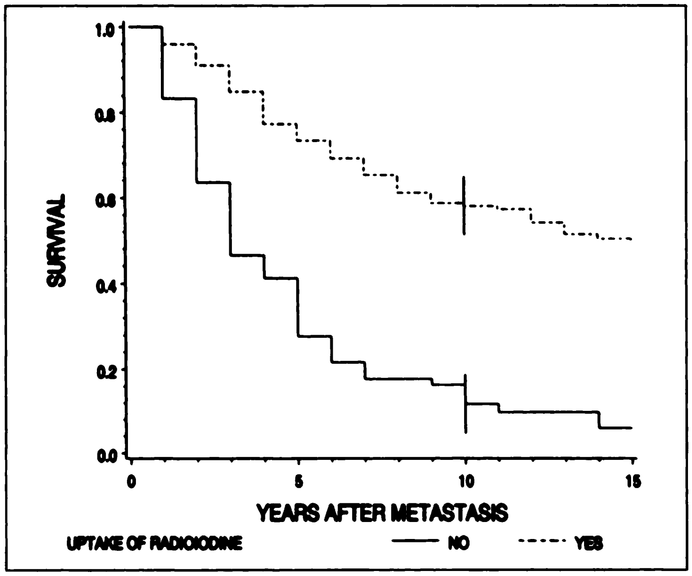

FIGURE 4. Survival after discovery of distant metastases as a function of radioiodine uptake.

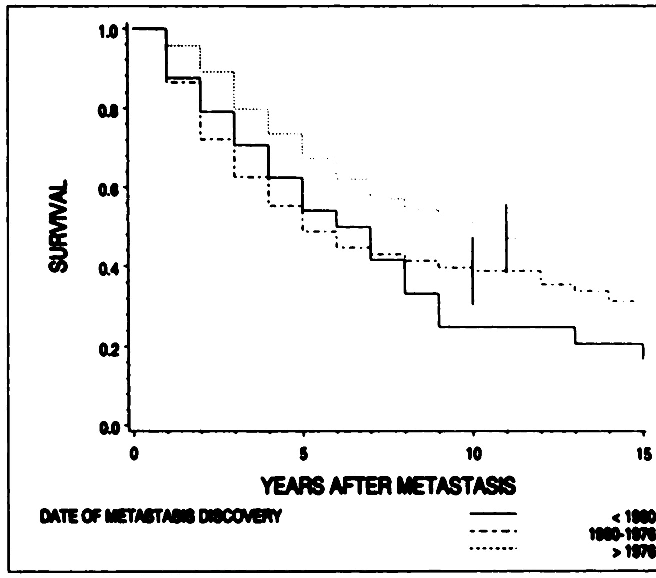

FIGURE 6. Survival after discovery of distant metastases as a function of the year of discovery. Iodine-131 whole-body scanning was introduced in 1960 and serum Tg measurement in 1977.

serum Tg levels were undetectable or detectable at the time of complete response.

Secondary Malignancies

A total of 19 secondary malignancies occurred in 16 patients treated for metastases of differentiated thyroid carcinoma. They included five cutaneous carcinomas, four colon carcinomas, three patients with acute nonlymphocytic leukemia (ANLL), two lung carcinomas and one of each of the following: breast, pancreas, tracheal, adrenal carcinoma and bone sarcoma. Four of the patients were men and 12 were women, with a mean age of 56 yr at discovery of the metastases (range: 21–81 yr) and a mean age of 65 yr at diagnosis of the second primary tumor (range 31–81 yr). All 19 secondary malignancies occurred in patients previously treated with ^{131}I, but 10 had external radiotherapy to the neck and 11 had external irradiation to bone metastases as well. The bone sarcoma occurred in an irradiated bone and the three patients with ANLL were also treated with external radiotherapy, one to the neck and two to distant metastases.

A total of 0.84 ANLL cases were expected, as compared to the three cases observed, leading to a standardized incidence ratio of 3.5 (IC 95%: 0.7–10.2). The cumulative probability of a secondary malignancy 10 yr after treatment of metastases was 6.5% ± 4.1%; it was 1.7% ± 2% for ANLL and 4.7% ± 3.6% for solid tumors.

Multivariate analysis for the occurrence of a second solid tumor indicated two prognostic factors: age of the patient at discovery of metastases (RR = 1.08 per year of age, 95% CI: 1.04–1.22, $p < 0.001$) and external radiotherapy (RR = 3.6, 95% CI: 0.8–16.7, $p = 0.1$). The cumulative dose of ^{131}I and gender were not significant.

Multivariate analysis for the occurrence of ANLL indicated three prognostic factors: age of the patient at discovery of

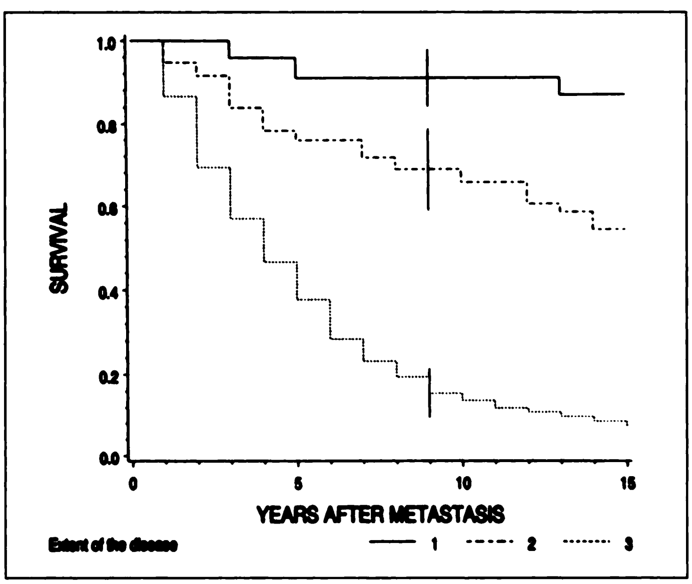

FIGURE 5. Survival after discovery of distant metastases as a function of the extent of the disease. Category 1 includes patients with normal chest and bone radiographs whose metastases were revealed by ^{131}I whole-body scanning. Category 2 includes micronodular lung metastases that were radiologically smaller than 1 cm (22) or a single bone metastasis identified by radiographs. Category 3 includes either macronodular lung metastases or multiple bone metastases.

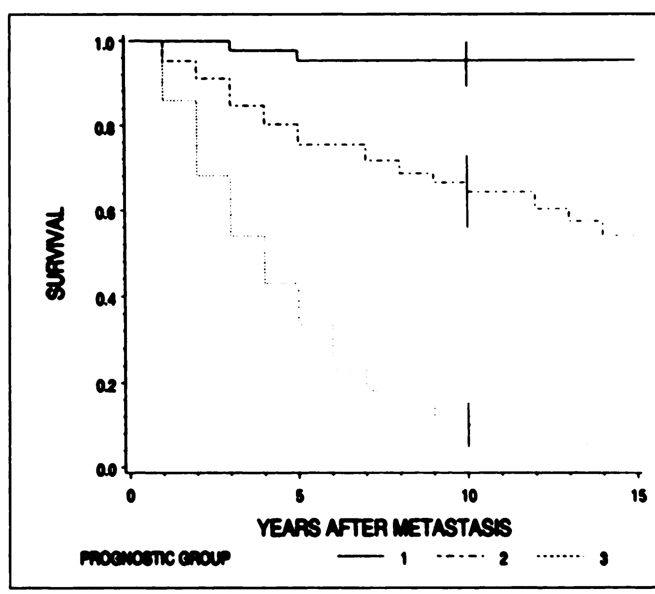

FIGURE 7. Survival after discovery of distant metastases as a function of the prognostic group. Group 1 includes the 56 patients younger than 40 yr of age with small metastases (Category 1); group 3 includes the 156 patients above age 40 with large metastases (Category 3); group 2 includes the other 182 patients.

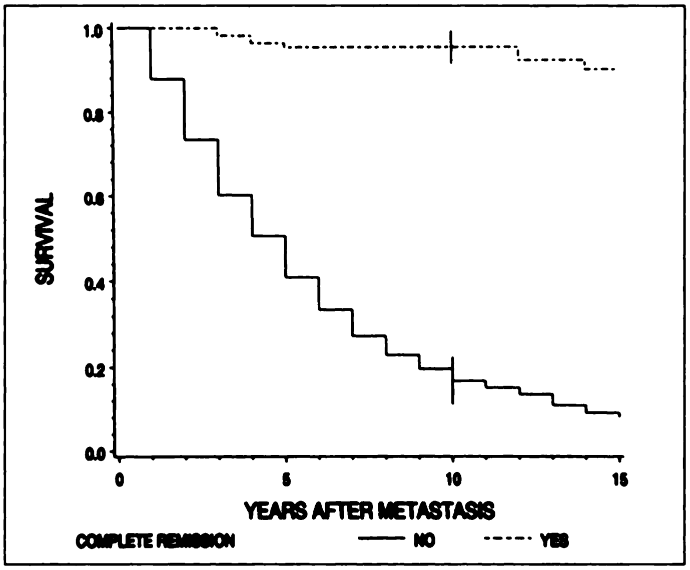

FIGURE 8. Survival after discovery of distant metastases as a function of complete response.

metastases (RR = 1.13, 95% CI: 1.0–12.7, $p < 0.06$), external radiotherapy (RR = 8.5, 95% CI: 0.7–94.1, p = 0.1) and a cumulative dose of ^{131}I exceeding 600 mCi (RR = 8.8, 95% CI = 0.7–111, p = 0.09). Because of the small number of ANLL patients, we were not able to test for an interaction between the effects of ^{131}I and external radiotherapy.

DISCUSSION

This study relates the long-term follow-up of 394 patients with distant metastases of differentiated thyroid carcinoma treated at a single institution. The large patient accrual is related to the referral pattern prevalent at our institution.

As previously reported, clinical signs, symptomatic of distant spread, appear late in the disease course. The early discovery of distant metastases is based on the combined use of serum Tg levels and ^{131}I whole-body scanning (*7,19,23,28*). Our data confirm that Tg measurement is a highly sensitive means of detecting metastases.

Response to treatment was assessed on the basis of radiological and scintigraphic criteria. The Tg level was not taken into account in the analysis of response, although it was detectable during LT4 treatment in 50% of the patients who had achieved complete response. The presence of detectable Tg levels in these patients was undoubtedly related to the persistence of microscopic foci of neoplastic tissue, but had no prognostic value regarding relapse, despite a mean follow-up of 8 yr. Long phases of dormancy and the long doubling time of most differentiated carcinomas could account for this lack of prognostic significance. In addition, clinical emergence of relapses is known to occur rapidly in patients with poorly differentiated carcinoma characterized by short doubling time and low Tg secretion. The low sensitivity of Tg measurement during LT4 treatment after radioiodine therapy is also shown by the 14% of patients with persistent disease, i.e., patients with uptake on radioiodine post-therapy scans, with undetectable Tg levels. These data confirm that the last negative post-therapy scan has to be checked 1–2 yr later by another post-therapy ^{131}I whole-body scan without performing a preceding diagnostic scan.

Overall survival at 15 yr from the time of metastases detection was 33%; this is in accordance with other series (*1–11*). Survival rate was 89% in patients who achieved complete response but only 8% in those who did not. This finding does not demonstrate that prolonged survival is due to treatment alone, since response to therapy was related to other favorable prognostic indicators (*29*). All patients who survived 15 yr or more after the discovery of the metastases, however, had been treated with radioiodine alone, or in combination with external radiotherapy in case of bone involvement. It is very unlikely that this large number of patients would be alive for such a long period of time after the discovery of the metastases without ^{131}I treatment.

In the absence of uptake, only two complete responses were observed. Patients treated with external radiotherapy to bone metastases, however, experienced rapid pain relief and recalcification of osteolytic abnormalities (*13,17*). Therefore, external radiotherapy should be the method of choice for bone metastases which cannot be readily excised surgically, even if they concentrate radioiodine, as it can deliver a uniform dose of 40 Gy with little additional toxicity. Indeed, external irradiation will decrease subsequent radioiodine uptake, but this is often related to its beneficial therapeutic effects (*13,17*). Furthermore, radioiodine treatment is still possible thereafter.

Radioiodine uptake was observed in 67% of patients, which is in accordance with other series (*1–11*), and yet only 46% of them achieved complete response. This underscores the role of other prognostic factors. Indeed, complete response was also found to be dependent on the age of the patient at discovery of metastases and on extent of metastatic disease. Younger patients and those with smaller metastases did respond better to radioiodine treatment, whereas low response rates were observed in patients with extensive metastatic dissemination. Bone metastases were associated with low response rates and with poor prognosis when they were visible on radiographs, which is generally the case. On the other hand, patients with metastases at the base of the skull achieved complete response far more frequently than patients with skeletal metastases elsewhere (*7,13*). This factor may be related, as implied above, to the limited extension of these metastases.

Although distant metastases, and in particular lung metastases with radioiodine uptake, may be stable for years or decades, the present data stress that all metastases should be treated at an early stage. Favorable responses to therapy have been observed in patients with small metastases, even if radioiodine uptake was low. It has been stated that if the calculated dose to the tumor is less than 35 Gy, it is unlikely to respond to ^{131}I treatment, and that the outcome of radioiodine therapy is related to the effective radiation dose (*30,31*). Although accurate dosimetry is not possible when metastases cannot be visualized on radiographs, these data suggest that neoplastic foci are more radiosensitive at an early stage. In fact, iodine uptake much lower than 0.1% of the administered activity can be easily detected by our scanner. This is in close agreement with previous data (*23,28*), which have been recently confirmed (*32*), on the effectiveness of ^{131}I therapy in patients with elevated Tg levels and negative diagnostic scans. The reasons why large metastases become radioresistant, however, is not clear. Radioresistance may be due to poor vascularization or the appearance of radioresistant subclones. Also, the cumulative dose of radioiodine necessary for cure can be reduced if metastases are treated early. Although the risk of secondary malignancies was not significantly increased for cumulative doses equal to or less than 600 mCi, which is consistent with previous data (*33*), the risk of acute leukemia was increased with limited benefits in terms of complete response for doses above 600 mCi when administered together with external radiotherapy.

Similarly, the decrease in radioiodine uptake with the patient's age suggests an accumulation of biochemical defects in tumors arising in older patients.

The present data, even in the presence of a negative whole-body scan following a diagnostic dose of radioiodine (*19,20,23,28,32*), argue for the administration of therapeutic doses of radioiodine to patients with elevated Tg levels and no other evidence of disease. They indicate that a whole-body scan is necessary for tumor detection after an ablative or therapeutic dose of radioiodine, because total radioiodine uptake in the lung is low in some of these patients. Similarly, ^{131}I whole-body scanning with 2 to 5 mCi appears to be of limited clinical value if it is to be followed by a 100-mCi treatment. Therapeutic ^{131}I will decrease the Tg level to an undetectable value, and uptake should disappear on the post-therapy whole-body scan, as should lung micronodules when detected on CT scans. We, like others (*1,3,4,5,11,23,28,32*), have found that a high proportion of patients with diffuse lung metastases and normal plain radiographs can undergo complete response with radioiodine alone for long periods of time without any apparent sequelae.

Other treatment modalities should be sought for patients with extensive metastatic disease, even if metastases show radioiodine uptake. Surgery may be beneficial, in that it will reduce the tumor mass.

Multivariate analysis of survival confirms previous data (*7,9,11*) and highlights the independent prognostic effect of age at discovery of metastases, histologic type of thyroid tumor, presence of radioiodine uptake, extent of metastases and the year of their discovery.

As previously reported (*9*), two factors (age and extent of tumor) establish three discrete groups of patients in whom the risk of death from thyroid cancer differs considerably. Iodine-131 uptake or its absence in metastases was not considered. It has been argued that ^{131}I treatment does not affect survival (*9*) and that the better survival rates found in patients with small metastases may be linked only to earlier detection of distant spread. Caution, however, must prevail because prognostic factors are closely interrelated, and in such subgroupings over 95% of younger patients with limited disease exhibited ^{131}I uptake and invariably responded to ^{131}I therapy, whereas 56% of patients over 40 yr of age had ^{131}I uptake and only 19% responded to therapy.

Further evidence of the effect of treatment is the 140% increase in survival when metastases were discovered after 1976 compared to those discovered before 1960 and the 30% survival increase compared to metastases discovered between 1960 and 1976. The independent prognostic effect of this factor (year of discovery of metastatic disease) may be related to the introduction of the routine use of ^{131}I whole-body scanning (in 1960) and serum Tg measurement (in 1977), as well as a more efficient application of radioiodine therapy, its association with external radiotherapy and a better assessment of LT4 treatment controlling TSH secretion.

CONCLUSION

The present study highlights the prognostic significance of the early discovery of distant metastases and demonstrates improvement in the survival of patients treated during recent years. With the combined use of Tg measurement and ^{131}I whole-body scanning, distant metatastic disease is detected earlier and can therefore be treated more efficiently.

ACKNOWLEDGMENTS

We thank M. Tubiana for helpful discussions, L. Saint-Ange and I. Kuchental for editing the manuscript and C. Logé for assistance in preparing the manuscript.

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