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Long-Term Outcome of 444 Patients with Distant Metastases from Papillary and Follicular Thyroid Carcinoma: Benefits and Limits of Radioiodine Therapy

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Aim: The goal of this study was to estimate the cumulative activity of ^{131}I to be administered to patients with distant metastases from thyroid carcinoma.

Methods: A total of 444 patients were treated from 1953–1994 for distant metastases from papillary and follicular thyroid carcinoma: 223 had lung metastases only, 115 had bone metastases only, 82 had both lung and bone metastases, and 24 had metastases at other sites. Treatment consisted of the administration of 3.7 GBq (100 mCi) ^{131}I after withdrawal of thyroid hormone treatment, every 3–9 months during the first 2 yr and then once a year until the disappearance of any metastatic uptake. Thyroxine treatment was given at suppressive doses between ^{131}I treatment courses.

Results: Negative imaging studies (negative total body ^{131}I scans and conventional radiographs) were attained in 43% of the 295 patients with ^{131}I uptake; more frequently in those who were younger, had well-differentiated tumors, and had a limited extent of disease. Most negative studies (96%) were obtained after the administration of 3.7–22 GBq (100–600 mCi). Almost half of negative studies were obtained more than 5 yr after the initiation of the treatment of metastases. Among patients who achieved a negative study, only 7% experienced a subsequent tumor recurrence. Overall survival at 10 yr after initiation of ^{131}I treatment was 92% in patients who achieved a negative study and 19% in those who did not.

Conclusion: ^{131}I treatment is highly effective in younger patients with ^{131}I uptake and with small metastases. They should be treated until the disappearance of any uptake or until a cumulative activity of 22 GBq has been administered. In the other patients, other treatment modalities should be used when tumor progression has been documented. (***J Clin Endocrinol Metab* 91: 2892–2899, 2006**)

DISTANT METASTASES OCCUR in less than 10% of patients with papillary and follicular thyroid carcinoma, but represent the most frequent cause of thyroid cancer-related death (1, 2). Radioiodine (^{131}I) is the main treatment modality in patients with ^{131}I uptake (3, 4) and may be associated with local treatments such as external beam radiation therapy or surgery (5–7).

In a previous analysis of patients with ^{131}I uptake in the metastases, negative imaging studies were obtained in 40%, and more frequently in younger patients with small lung metastases, demonstrating a beneficial effect of radioiodine treatment on tumor foci (8). In some other patients with ^{131}I uptake, partial response or symptomatic improvement was achieved, but was transient. These findings were confirmed by several smaller series of patients with metastases (9–15). We recently reported that cumulative activities of ^{131}I larger than 22 GBq (600 mCi) are associated with an increased risk of cancer and leukemia (16). Pulmonary fibrosis, xerostomia, and lacrimal complications have also been associated with a high cumulative activity of ^{131}I (17, 18).

In patients with disease progression, cytotoxic chemotherapy has little effect (19, 20). This led clinicians to repeatedly treat patients with ^{131}I, even when no objective response was achieved. However, the recently available molecular targeted therapies are promising, and patients who may benefit from ^{131}I treatment should be better defined, whereas trials with these new drugs should be proposed to the others (21).

The present retrospective study was performed on 444 patients with distant metastases treated between 1953 and 1994 at our institution. With a follow-up of at least 10 yr, it aimed to confirm the prognostic classification proposed in our previous reports and to focus on two incompletely resolved questions (22, 23): factors associated with tumor response to ^{131}I treatment and long-term outcome. From these data, we estimated the optimal cumulative activity of ^{131}I that should be administered.

Patients and Methods

Patients

From 1953–1994, 444 patients with differentiated thyroid carcinoma were treated for distant metastases at the Institut Gustave-Roussy (Villejuif, France). The study was completed on October 31, 2004, more than 10 yr after initiation of therapy for distant metastases. Fifty-three patients were lost to follow-up before October 2002. Distant metastases were discovered before 1973 in 155 patients, between 1974 and 1983 in 139 patients, and between 1984 and 1994 in 150 patients.

Thyroid tumors were histologically classified into three groups: papillary in 187 patients, follicular well-differentiated in 68 patients, and follicular poorly differentiated in 183 patients. This classification is easy to apply and was shown to have a high prognostic value (24, 25). Patients

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Abbreviations: CT, Computed tomography; ^{131}I-TBS, ^{131}I total-body scanning; Tg, thyroglobulin.

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with an anaplastic component and those with both atypical histological features and negative immunostaining for thyroglobulin (Tg) were not included in the study. No surgical specimens were available from six patients for microscopic examination; the thyroid origin of metastases was demonstrated by ^{131}I uptake in the metastases.

Thyroid tumor treatment

Thyroid surgery had been performed in 396 (90%) patients, with lymph node dissection in 145 patients (55%), and 403 patients were treated with ^{131}I [3.7 GBq (100 mCi)] for ablation of normal thyroid remnants or persistent disease in the neck or at distant sites. Postoperative external beam radiation therapy to the neck was delivered to 82 patients. Ten percent of the patients, mostly treated before 1975, did not undergo surgery due to older age, tumor extension to the trachea or esophagus, large neck and mediastinal lymph nodes, and/or large distant metastases at presentation, and were treated only with radioiodine and/or external beam radiation therapy to the neck.

Follow-up

All patients were treated with thyroid hormone to suppress TSH secretion (26). Before the availability of serum Tg measurement in routine practice, clinical examination, ^{131}I total-body scanning (^{131}I-TBS), and standard radiographs were used to detect persistent or recurrent thyroid carcinoma. A diagnostic ^{131}I-TBS with 74–185 MBq (2–5 mCi) was performed once a year for the first 2 yr and every 2–5 yr thereafter. High serum TSH concentrations were obtained by withdrawing L-T_4 for 5 wk, and T_3 for 2 wk. Since 1971, scanning was performed 72 h after ^{131}I administration with a whole-body double-probe rectilinear scanner, and since 1994, with a double-head γ camera equipped with high energy parallel collimators and thick crystals (Sopha Medical, Gif sur Yvette, France).

A chest x-ray was obtained at the time of ^{131}I-TBS. Bone x-rays were performed only in patients with abnormal ^{131}I skeletal uptake and/or symptoms indicative of bone disease.

Serum Tg assay became available in 1977. It was measured at the annual follow-up during L-T_4 treatment and after withdrawal at the time of ^{131}I administration. For 11 patients with detectable serum anti-Tg antibodies or interferences in the Tg assay, serum Tg concentration was not measured (27).

Estimating the extent of metastases

Patients were divided into three categories according to the extent of metastases evaluated by ^{131}I-TBS and radiographs: category 1 included patients with metastases on ^{131}I-TBS, but with normal chest and bone x-rays; category 2 included patients with micronodular lung metastases, defined radiologically as smaller than 1 cm in diameter, or with a single bone metastasis identified by x-rays; finally, category 3 included patients who had macronodular lung metastases or multiple bone metastases or both bone and lung metastases.

Treatment of metastatic disease

All patients with metastatic disease were treated with ^{131}I. ^{131}I therapy was also given to patients who, despite no other evidence of disease after thyroid tumor treatment, had serum Tg levels above 10 ng/ml after L-T_4 withdrawal and that increased over time (28). The activity was given after L-T_4 withdrawal and was 3.7 GBq (100 mCi) in adults and approximately 37 MBq (1 mCi)/kg of body weight in children. A posttherapy TBS was performed 3–5 d later, and L-T_4 treatment was resumed. In patients with metastatic uptake on posttherapy TBS, additional treatments with ^{131}I were given 3–9 months later for 2 yr and were then given annually; a longer interval of time was observed between two treatment courses in patients with minimal metastatic uptake. No diagnostic TBS was performed in patients with known metastatic disease before ^{131}I therapy (29). There was no fixed limit to the cumulative activity of ^{131}I.

External beam radiation therapy was delivered to patients with radiographically visible bone metastases. The usual radiation doses were 30 Gy (3000 rad) in 15 d or 40 Gy (4000 rad) in 28 d.

Surgery was performed in patients with bone metastases when there were orthopedic or neurological complications or a high risk of such complications.

Chemotherapy with cytotoxic agents was given to patients with progressive metastatic disease either refractory to radioiodine treatment or with no ^{131}I uptake, by using either a single agent (doxorubicin, cisplatinum, bleomycin, methotrexate, ellipticinum, etoposide, or mitoxantrone) or a combined regimen (30).

Evaluation of therapeutic efficacy

The efficacy of treatment was retrospectively evaluated by ^{131}I-TBS and radiographic findings. Four groups of patients were identified: patients with negative imaging studies who had no persistent uptake on posttherapy TBS and no radiological abnormalities (normal chest x-rays in cases of lung metastases and recalcification of bone lesions in case of bone metastases); patients who still had radiological abnormalities but no persistent uptake; patients with normal radiological examination who still had radioiodine uptake; and patients who had both radiological abnormalities and persistent uptake. In patients who had normal x-rays after the administration of more than 22 GBq (600 mCi) and who still had minimal metastatic uptake on the last posttherapy TBS, a diagnostic TBS with 185 MBq (5 mCi) was performed 1–2 yr later, and the absence of detectable uptake was then considered as negative study.

Serum Tg measurements, computed tomography (CT), and bone magnetic resonance imaging were not taken into account in the definition of negative studies. Nevertheless, lung CT scan was performed in 31 patients who had negative studies after treatment of lung metastases; the serum Tg levels were correlated with the clinical outcome after treatment.

Patients with negative studies after treatment of distant metastases were followed up every 6–12 months with clinical and laboratory examinations (TSH and Tg during thyroid hormone therapy) and radiographs. The absence of radioiodine uptake was verified 1–2 yr later by another ^{131}I-TBS performed with a diagnostic or a therapeutic activity. Then, patients did not undergo any other ^{131}I-TBS, unless they had evidence of progressive disease. In those patients with persistently detectable Tg, no further ^{131}I therapy was given until the serum Tg level increased over time.

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. Kruskal-Wallis test was used to compare median values.

Results

Characteristics of the patients at discovery of distant metastases

Clinical characteristics. The clinical characteristics of the 444 patients at discovery of distant metastases are summarized in Table 1. At discovery of distant metastases, 223 patients had only lung metastases, 115 had only bone metastases, 82 had both lung and bone metastases, and 24 had metastases at other sites (brain in 10 patients, liver in three patients, skin in eight patients, salivary glands in two patients, and eye in one patient).

The location of distant metastases was related to several factors: the lungs were the only site in 71% of patients with papillary carcinoma and in 35% of patients with follicular carcinoma, in 95% of patients aged less than 20 yr at the discovery of metastases and in only 29% of patients over 60 yr. In contrast, the bones were the only site in 12% of patients with papillary carcinoma and in 36% of patients with follicular carcinoma, in 22% of patients younger than 60 yr and in 34% of patients over 60 yr.

Scintigraphic findings. ^{131}I uptake in metastases was found in 68% of patients, with a similar frequency among patients

TABLE 1. Clinical characteristics of the 444 patients at diagnosis of distant metastases and univariate analysis of prognostic factors

Factor	No. of patients	Remission (%)	10-yr survival rate (%)	15-yr survival rate (%)	20-yr survival rate (%)	No. of deaths	Relative risk of death	*P*
Age (yr)								
4–19	37	79	100	90	87	7	1	
20–39	106	67	80	74	71	35	2.8	$<10^{-4}$
40–59	173	46	25	14	10	147	15	
60–90	128	30	14	6		118	23	
Gender								
Males	169	57	34	27	24	124	1	0.05
Females	275	63	46	36	32	183	0.8	
Histology								
Pap	187	78	64	55	53	93	1	
FWD	68	29	36	22	16	55	2.0	$<10^{-4}$
FPD	183	27	19	12	8	156	3.0	
Radioiodine uptake								
No	64	0	3			60	1	$<10^{-4}$
Yes	378	62	48	38	33	246	0.2	
Site of metastases								
Lung	223	74	63	54	49	113	1	
Bone	115	17	25	12	8	102	2.5	$<10^{-4}$
Lung and bone	82	30	13	11	9	70	3.3	
Extent of metastases								
Category 1	105	82	83	74	68	35	1	
Category 2	129	51	50	39	34	82	2.4	$<10^{-4}$
Category 3	207	24	15	8	6	188	7.3	
Year of discovery								
Before 1960	36		23	15	15	33	1.9	
1960–1976	142	72	35	28	25	111	1.4	0.001
After 1976	266	59	48	37	32	163	1	
Discovery of metastases								
Early	346	65	40	32	29	240	1	NS
Late	98	50	45	35	30	67	0.9	
Neck recurrence before metastases								
No	343	69	43	34	30	235	1	NS
Yes	87	53	35	31	27	60	1.1	
Tg/T_4								
1–20	45	92	69	55	48	21	1	
21–100	65	56	55	42	36	37	0.8	0.02
>100	59	13	23	15		47	1.4	
Tg/TSH								
1–100	70	80	70	58	49	31	1	
101–1000	74	66	60	46	41	39	0.6	0.001
>1000	62	12	20	15	15	49	1.4	

Pap, Papillary; FWD, follicular well differentiated; FPD, follicular poorly differentiated; NS, not significant. Tg level at the discovery of metastases: Tg/T_4, Tg level during L-T_4 treatment; Tg/TSH, Tg level following L-T_4 withdrawal (nanograms per milliliter).

with lung or bone localizations. Uptake was not assessed in 17 patients. It was found in 91% of patients less than 40 yr old, in 58% of patients over 40 yr, in 77% of patients with papillary carcinoma, in 92% with follicular well-differentiated, and in 53% with follicular poorly differentiated carcinoma. Among patients with pulmonary metastases only, ^{131}I uptake was found in all patients with normal x-rays (indeed, these metastases were demonstrated by ^{131}I-TBS), in 87% of those with micronodules and in 41% of those with macronodules.

Radiological findings. Among the 223 patients who had lung metastases only, chest radiographs showed macronodules in 34% and micronodules in 29%, and were normal in the other 37%. In the 115 patients who had only bone metastases, bone radiographs documented a single bone metastasis in 33 patients, and multiple bone metastases in 74 patients, and were normal in only eight patients.

Serum Tg measurements. At the discovery of metastases, serum Tg level obtained during L-T_4 treatment in 174 patients was detectable in 169 patients and undetectable in five patients. In four of these five patients, ^{131}I-TBS documented metastatic uptake (four with lung metastases, including three with a normal chest x-ray and one with macronodules, and one with both lung and bone metastases).

Serum Tg level obtained after L-T_4 withdrawal in 211 patients was detectable in all. It ranged from 5–9 ng/ml in six patients, 10–99 ng/ml in 61 patients, and was above 100 ng/ml in the other 144 patients.

Serum Tg levels, both during L-T_4 treatment and after L-T_4 withdrawal were higher in patients with follicular carcinoma than in those with papillary carcinoma, in patients with skeletal metastases than in those with only pulmonary localizations, and in patients with lung macronodules than in those with lung micronodules or with normal radiographs ($P < 0.001$).

TABLE 2. Clinical course according to ^{131}I uptake: characteristics of the patients

	^{131}I uptake + remission	^{131}I uptake + no remission	No ^{131}I uptake
Patients (n)	127	168	132
Age (yr; mean ± SD)	32 ± 16	51 ± 16	56 ± 13
Min-max	4–75	7–90	15–82
Initial sites of metastases (%)			
Lung	110 (87)	44 (26)	60 (45.5)
Bone	9 (7)	73 (43)	31 (23.5)
Lung and bone	7 (5)	40 (24)	34 (26)
Unusual sites	1 (1)	11 (7)	7 (5)
Extent of metastases (%)			
Category 1	80 (63)	17 (10)	7 (5)
Category 2	37 (29)	58 (35)	34 (26)
Category 3	10 (8)	93 (55)	91 (69)
Histology (%)			
Pap	96 (77)	41 (24.5)	41 (31.5)
FWD	11 (9)	50 (30)	5 (4)
FPD	18 (14)	77 (45.5)	84 (65)

Radioiodine uptake could not be assessed in 17 patients who were not included in the table. Pap, Papillary; FWD, follicular well differentiated; FPD, follicular poorly differentiated.

Clinical course

A total of 378 patients underwent ^{131}I therapy for distant metastases; they received a median cumulative activity of 13 GBq (355 mCi) [range: 0.6–55.3 GBq (18–1495 mCi)]. Additional treatments included surgery on bone metastases in 51 patients. External beam radiation therapy to bone metastases was given as the sole treatment in 12 patients with no ^{131}I uptake and in association with ^{131}I therapy in 86 patients with ^{131}I uptake. In the latter patients, ^{131}I treatment was administered before and again 3–6 months after radiation therapy. Systemic chemotherapy was given to 56 patients with progressive disease, and no tumor response was observed.

^{131}I could be effective only in metastatic patients with ^{131}I uptake (Tables 2 and 3), and for this reason outcome was studied according to the presence or absence of initial ^{131}I uptake in the metastases.

Patients with initial ^{131}I uptake (n = 295)

At the time of last treatment, among the 295 patients who had initial ^{131}I uptake in their metastases, 100 patients achieved negative imaging studies; the other 195 patients had persistent uptake (28 cases), radiological abnormalities (27 cases), or both persistent uptake and radiological abnormalities (140 cases).

Negative studies were ascertained during the subsequent follow-up in 27 patients by the disappearance of any radiological abnormality and of any uptake on a TBS performed with a diagnostic activity of ^{131}I. These patients had persistent uptake (n = 16), radiological abnormalities (n = 1), or both persistent uptake and radiological abnormalities (n = 10) at the time of last treatment. Thus, negative studies were obtained in 127 (43%) of these 295 patients.

Characteristics of the 127 patients who achieved negative imaging studies. Negative studies were obtained in 72% of the initial 129 patients younger than 40 yr at the discovery of distant metastases, and in 20% of the 166 patients aged above 40 yr ($P < 0.0001$). Seventy percent of the 137 patients with papillary thyroid carcinoma, 18% of the 61 patients with follicular well-differentiated, and 19% of the 94 patients with follicular poorly differentiated carcinoma ($P < 0.0001$) achieved negative studies. Seventy-one percent of the 154 patients with lung metastases, 12% of the 129 patients with either bone metastases alone or with both lung and bone metastases, and one of the 12 patients with metastases in other sites achieved negative studies ($P < 0.0001$). Finally, negative studies were obtained in 82% of the 97 patients in category 1, in 39% of the 95 patients in category 2, and in only 10% of the 103 patients in category 3 ($P < 0.0001$).

A median cumulative ^{131}I activity of 8.1 GBq (220 mCi) [range: 2.4–51.8 GBq (65–1400 mCi)] was administered to patients who achieved negative studies. Forty-eight percent of negative studies were observed after the administration of

TABLE 3. Clinical course according to ^{131}I uptake: cumulative ^{131}I activity and outcome

	^{131}I uptake + remission	^{131}I uptake + no remission	No ^{131}I uptake
Patients (n)	127	168	132
Cumulative ^{131}I activity administered			
Median (min-max): GBq	8.1 (2.4–51.8)	14.8 (2.2–55.3)	3.7 (0.7–36.2)
Median (min-max): mCi	220 (65–1400)	400 (60–1495)	100 (18–977.5)
Follow-up since last treatment (mean ± SD)	14 ± 8.8	2.6 ± 5.4	0.9 ± 2.5
Status at end of study, no. of deaths (%)	31 (24)	143 (85)	119 (92)
Causes of death, n (%)			
Thyroid cancer	9 (29)	101 (71)	94 (79)
Other causes	11 (35.5)	16 (11)	8 (7)
Unknown	11 (35.5)	26 (18)	17 (14)
10-yr survival rate (%)	92	29	10

Radioiodine uptake could not be assessed in 17 patients who were not included in the table.

a cumulative activity of less than 7.4 GBq (200 mCi), 36% with 7.4–14.8 GBq (201–400 mCi), 12% with 14.8–22.2 GBq (401–600 mCi), and only 4% with a cumulative activity higher than 22.2 GBq.

In patients with lung metastases only, the median cumulative activity administered to patients attaining negative studies was 8.1 GBq (220 mCi) [range: 2.4–26.0 GBq (65–700 mCi)], and was related to the extent of disease, being 7.4 GBq (200 mCi) in patients with a normal chest x-ray, 11.5 GBq (310 mCi) in patients with micronodular lung metastases, and 13.0 GBq (350 mCi) in those with macronodular lung metastases ($P = 0.02$). In patients with bone metastases only, the median cumulative activity administered to patients attaining negative studies was 9.2 GBq (250 mCi) [range: 3.7–22.2 GBq (100–600 mCi)].

These 127 patients were followed-up after achievement of negative studies for an average of 14 yr (±9 yr). Recurrences occurred in nine (7%) patients from 6 months up to 41 yr after achievement of negative studies, and were located at distant sites (seven in lungs and two in bones) and, in three patients, also in the neck. Thirty-one patients died during follow-up, including four patients from recurrent disease.

Chest CT scan obtained in 31 patients with lung metastases who had negative studies after treatment with radioiodine was normal in 22 patients and showed micronodules in nine patients. Abnormalities on CT scan were not related to serum Tg levels and had no prognostic influence on the outcome.

Serum Tg was measured during L-T_4 treatment in 80 of the 127 patients at the time when negative studies were attained, and was undetectable (<1 ng/ml) in 42 patients, detectable but less than 10 ng/ml in 26 patients, ranged from 10–20 ng/ml in five patients, and was above 20 ng/ml in the remaining seven patients. Among the 38 patients with detectable serum Tg during L-T_4 treatment at the time of negative studies, serum Tg level became undetectable during subsequent follow-up in 30 patients. Serum Tg was measured after withdrawal of L-T_4 therapy in 83 patients at the time of negative studies, and was undetectable in 22 patients, and detectable in the other 61 (2–4800 ng/ml).

Characteristics of the 168 patients who did not achieve negative studies. Among the 168 patients with initial ^{131}I uptake who did not achieve negative studies, 143 (85%) died (97 from thyroid cancer, 13 from intercurrent disease, and 33 from unknown causes), and the remaining 25 (15%) were still alive at the end of the study.

At the last follow-up examination, serum Tg measured on L-T_4 in 67 patients was detectable in 63 and ranged from 5 to over 10,000 ng/ml; serum Tg measured after L-T_4 withdrawal in 90 patients was detectable in 89 and ranged from 5 to over 10,000 ng/ml.

Patients with no ^{131}I uptake (n = 132)

A total of 132 patients had no demonstrable uptake at the time of the first treatment with ^{131}I. Two patients with a single bone metastasis had negative studies, one after surgery alone and the other one after external beam radiation therapy alone.

At the end of the follow-up, 119 had died (92%) (90 from thyroid cancer, five from intercurrent disease, and 24 from unknown causes), eight had persistent disease, and two had still negative studies.

Survival and prognostic factors

At the end of the study, 310 patients had died, including the 17 patients in whom radioiodine uptake could not be assessed (199 from thyroid cancer, 27 from intercurrent disease, and 84 from unknown causes), and 134 were alive.

The overall survival rate from the detection of metastases was 42% at 10 yr, 33% at 15 yr, and 29% at 20 yr. Survival rate in patients with ^{131}I uptake was 56% at 10 yr, 45% at 15 yr, and 40% at 20 yr; in patients without any ^{131}I uptake, it was 10% at 10 yr and 6% at 15 yr (Fig. 1).

After univariate analysis (Table 1), the significant prognostic factors for survival were: age at discovery of metastases, gender, pathology of the primary tumor, ^{131}I uptake, site and extent of metastases, year of discovery of metastatic disease, and Tg levels at discovery of metastases.

After multivariate analysis (Table 4), six variables remained significant for survival. In particular, female patients, patients who were younger at the time of the detection of metastases, those with papillary and follicular well-differentiated carcinoma, those with a limited extent of disease, and those with ^{131}I uptake in their metastases had a lower risk of death. Finally, the prognosis was better for patients in whom metastases were discovered after 1960 (the year when ^{131}I-TBS was introduced at our institution) and after 1976 (the year when serum Tg determination became routinely available). These tools permitted an earlier discovery of distant metastases and thus increased life expectancy after this discovery; this also improves the efficiency of radioiodine treatment in patients with radioiodine uptake and decreases the cumulative activity necessary for attaining negative studies.

According to the age at detection of metastases and to the initial extent of disease, it is possible to stratify patients into

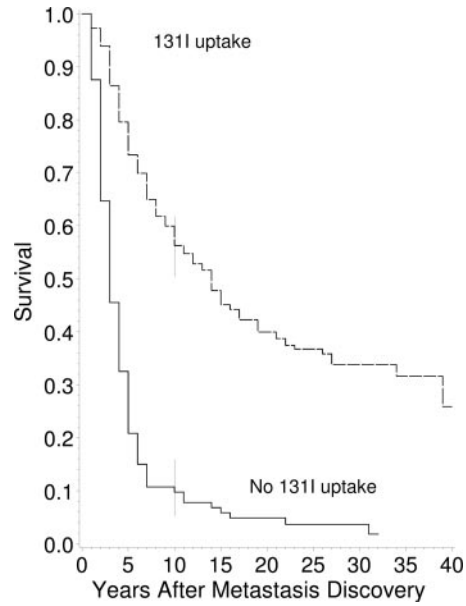

FIG. 1. Survival after the discovery of metastases according to the presence or absence of ^{131}I uptake in the metastases.

TABLE 4. Multivariate analysis of prognostic factors of survival (Cox's model)

Factor	Relative risk of death (95% CI)	*P* value
Age (yr)	1.0 (1.0–1.1)	$<10^{-4}$
Gender		
Females/males	0.7 (0.6–0.9)	0.008
Histology		
FWD/Pap	0.9 (0.63–1.3)	NS
FPD/Pap	1.5 (1.15–2.06)	0.004
^{131}I uptake	0.4 (0.3–0.6)	$<10^{-4}$
Extent of disease		
Category 2/category 1	1.9 (1.2–2.9)	0.007
Category 3/category 1	3.5 (2.3–5.3)	$<10^{-4}$
Year of discovery of metastases		
Before 1960/after 1976	1.8 (1.2–2.9)	0.009
1960–1976/after 1976	1.2 (0.9–1.7)	NS

95% CI, 95% Confidence interval; Pap, papillary; FWD, follicular well differentiated; FPD, follicular poorly differentiated; NS, not significant.

three groups for whom the survival rate was different. The survival rate at 10 yr was 95% in the 113 patients younger than 40 yr of age with metastases that were not visible on radiographs or that were micronodular. The 10-yr survival rate was 14% in the 266 patients older than 40 yr with macronodular lung metastases or multiple bone metastases. The 10-yr survival rate was 64% in the other 62 patients who were either older than 40 yr and had metastases that were not visible or were micronodular on radiographs or who were younger than 40 yr and had macronodular lung metastases (Fig. 2).

The 10-yr survival rate of 92% in patients with ^{131}I uptake who had negative studies after treatment was much better than the 29% survival rate observed in patients with ^{131}I uptake who had persistent abnormalities, and than the 10% survival rate observed in those without any initial ^{131}I uptake (Fig. 3). When compared with patients with ^{131}I uptake and who had persistent abnormalities, patients with no initial detectable ^{131}I uptake were older and had more frequent poorly differentiated follicular carcinoma, bone metastases, and extensive disease (Tables 2 and 3). Their relative risk of death was 2.0 (95% confidence interval, 1.6–2.6, $P < 0.0001$). This risk remained significant after adjustment for all prognostic indicators at 1.7 (95% confidence interval, 1.3–2.3, $P < 0.0001$).

Discussion

The present study confirms and expands previous reports concerning patients with distant metastases from papillary and follicular thyroid carcinoma (5–15).

Up to the present time, radioiodine was the only available systemic modality to treat patients with metastatic disease, and for this reason was repeatedly administered, even when it was not clearly effective. However, in the near future, new selective agents may prove to be effective. The present study was thus designed to select patients either for radioiodine treatment or for trials with these new agents.

A total of 127 patients (29% of all patients and 43% of those with ^{131}I uptake in the metastases) had negative studies after ^{131}I treatment, with no persistent uptake and no radiological abnormalities, demonstrating the efficiency of radioiodine

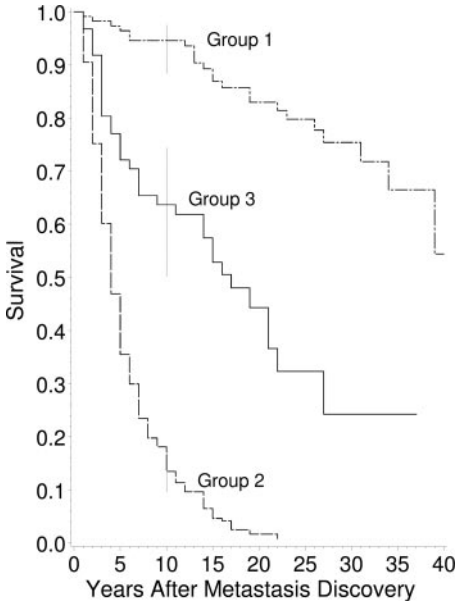

FIG. 2. Survival after the discovery of distant metastases according to the age at discovery and to the extent of disease. ^{131}I uptake was not taken into account, but was closely linked to the two other prognostic factors, and was invariably present in young patients with small metastases (group 1) and rarely present in older patients with large metastases (group 2). Group 1, Patients younger than 40 yr of age with metastases that were not visible on radiographs or that were micronodular (<1 cm in diameter). Group 2, Patients older than 40 yr with macronodular lung metastases or multiple bone metastases. Group 3, Patients older than 40 yr with normal x-rays or micronodular metastases and patients younger than 40 yr with macronodular lung metastases.

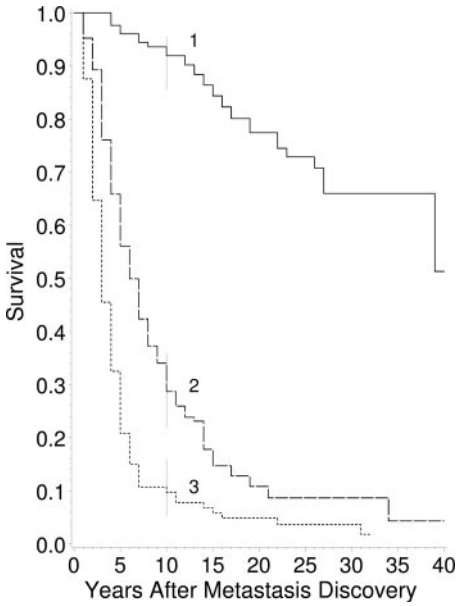

FIG. 3. Survival after the discovery of distant metastases. Group 1, Patients with ^{131}I uptake who attained negative imaging studies. Group 2, Patients with ^{131}I uptake who did not attain negative imaging studies. Group 3, Patients with no ^{131}I uptake.

treatment on tumor foci; only 7% had a recurrence during subsequent follow-up and the 10-yr survival rate was 92%. These patients who had ^{131}I uptake in their metastases were

younger than 40 yr, had papillary or follicular well-differentiated subtypes, and had a limited extent of disease. Clearly, any patient who meets these characteristics should be treated with radioiodine. In patients who did not achieve negative studies, beneficial effects of ^{131}I are difficult to quantify but probably contribute to the 10-yr survival rate of 29%. This is indeed significantly better than the 10-yr survival rate of 10% observed in patients without any detectable uptake, and may be related to different tumor biology and to the beneficial effects of radioiodine therapy. Indeed, in the absence of randomized studies it is not possible to distinguish survival benefits afforded by the presence of metastatic uptake that indicates a well-differentiated tumor tissue with a less aggressive behavior, from those of radioiodine treatment. However, it is unlikely that without radioiodine treatment such high long-term survival would have been observed in such a large number of metastatic patients.

Patients who are older than 40 yr, have large extent of metastases, and frequently have poorly differentiated carcinomas and low or no ^{131}I uptake may be candidates for therapeutic trials with new agents. However, some of these patients may have stable disease over years and had a good quality of life. Thus, patients should be offered these new treatment modalities only when disease progression has been documented. 2-[^{18}F]Fluoro-2-deoxy-D-glucose positron emission tomography scan may eventually confirm these ideas (23), but further studies are required to evaluate the role of this expensive tool for this purpose. Our classification is simple, validated, and easy to use.

Almost half of the negative studies were attained more than 5 yr after initiation of the treatment of distant metastases. These data are concordant with the delayed effect of ^{131}I treatment on thyroid cells in patients with thyrotoxicosis (31) or thyroid remnants after ablation for thyroid cancer (32, 33). Serum Tg became undetectable in the majority of the patients who had negative studies, either at the time of the last ^{131}I treatment or months later. These data suggest that residual neoplastic cells that have been irradiated can produce detectable amounts of Tg for long periods of time, but have limited proliferative capacity as suggested by the low recurrence rate. Thus, a single Tg level obtained after treatment may not have any reliable prognostic significance; on the contrary, a decreasing trend in Tg level will announce long-term remission and an increasing trend in clinical recurrence (32).

The large majority of negative studies were obtained with cumulative activities lower than or equal to 22 GBq (600 mCi). In previous studies, we have shown that the risk of cancer and leukemia becomes significant for cumulative activities higher than 22 GBq (16). The risk of lacrimal and salivary side effects increases with the cumulative activity, as well (17, 18). These data suggest that for patients who have already been treated with a cumulative activity of 22 GBq and who still have persistent uptake, the decision of administering further treatments should be made on an individual basis. Because beneficial effects may be delayed, another radioiodine treatment should be administered after an interval of at least 1 yr.

In conclusion, ^{131}I treatment is highly effective in a selected group of metastatic patients with ^{131}I uptake. These patients are younger than 40 yr and have small metastases from well-differentiated thyroid tumors. They should be treated until the disappearance of any uptake or until a cumulative activity of 22 GBq has been administered. In contrast, in the other patients when no response is attained after several ^{131}I treatment courses or who have no ^{131}I uptake, ^{131}I treatment should be abandoned and other treatment modalities used when tumor progression has been documented.

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The authors have nothing to declare.

References

1. **Mazzaferri EL, Kloos RT** 2001 Current approaches to primary therapy for papillary and follicular thyroid cancer. J Clin Endocrinol Metab 86:1447–1463
2. **Schlumberger MJ, Filetti S, Hay ID** 2003 Non toxic goiter and thyroid neoplasia. In: Larsen RP, Kronenberg HM, Melmed S, Polonsky KS, eds. Williams' textbook of endocrinology. 10th ed. Philadelphia: WB Saunders Company; 457–490
3. **Maxon HR, Smith HS** 1990 Radioiodine-131 in the diagnosis and treatment of metastatic well differentiated thyroid cancer. Endocrinol Metab Clin N Am 19:685–718
4. **Robbins RJ, Schlumberger MJ** 2005 The evolving role of ^{131}I for the treatment of differentiated thyroid carcinoma. J Nucl Med 46:28S–37S
5. **Bernier MO, Leenhardt L, Hoang C, Aurengo A, Mary JY, Menegaux F, Enkaoua E, Turpin G, Chiras J, Saillant G, Hejblum G** 2001 Survival and therapeutic modalities in patients with bone metastases of differentiated thyroid carcinomas. J Clin Endocrinol Metab 86:1568–1573
6. **Smit JWA, Vielvoye GJ, Goslings BM** 2000 Embolization for vertebral metastases of follicular thyroid carcinoma. J Clin Endocrinol Metab 85:989–994
7. **Tubiana M, Haddad E, Schlumberger M, Hill C, Rougier P, Sarrazin D** 1985 External radiotherapy in thyroid cancers. Cancer 55:2062–2071
8. **Schlumberger M, Challeton C, De Vathaire F, Travagli JP, Gardet P, Lumbroso JD, Francese C, Fontaine F, Ricard M, Parmentier C** 1996 Radioactive iodine treatment and external radiotherapy for lung and bone metastases from thyroid carcinoma. J Nucl Med 37:598–605
9. **Casara D, Rubello D, Saladini G, Masarotto G, Favero A, Girelli ME, Busnardo B** 1993 Different features of pulmonary metastases in differentiated thyroid cancer: natural history and multivariate statistical analysis of prognostic variables. J Nucl Med 34:1626–1631
10. **Dinneen SF, Valimaki MJ, Bergstralh EJ, Goellner JR, Gorman CA, Hay ID** 1995 Distant metastases in papillary thyroid carcinoma: 100 cases observed at one institution during 5 decades. J Clin Endocrinol Metab 80:2041–2045
11. **Hindie E, Mellière D, Lange F, Hallaj I, de Labriolle-Vaylet C, Jeanguillaume C, Lange J, Perlemuter L, Askienazy S** 2003 Functioning pulmonary metastases of thyroid cancer: does radioiodine influence the prognosis? Eur J Nucl Med Mol Imaging 30:974–981
12. **Lin JD, Chao TC, Chou SC, Hsueh C** 2004 Papillary thyroid carcinomas with lung metastases. Thyroid 14:1091–1096
13. **Nemec J, Zamrazil V, Pohunkova D, Rohling A** 1979 Radioiodine treatment of pulmonary metastases of differentiated thyroid cancer. Results and prognostic factors. Nuklearmedizin 18:86–90
14. **Pacini F, Cetani F, Miccoli P, Mancusi F, Ceccarelli C, Lippi F, Martino E, Pinchera A** 1994 Outcome of 309 patients with metastatic differentiated thyroid carcinoma treated with radioiodine. World J Surg 18:600–604
15. **Pittas AG, Adler M, Fazzari M, Tickoo S, Rosai J, Larson SM, Robbins RJ** 2000 Bone metastases from thyroid carcinoma: clinical characteristics and prognostic variables in one hundred forty-six patients. Thyroid 10:261–268
16. **Rubino C, De Vathaire F, Dottorini ME, Hall P, Schvartz C, Couette JE, Dondon MG, Abbas MT, Langlois C, Schlumberger M** 2003 Second primary malignancies in thyroid cancer patients. Br J Cancer 89:1638–1644
17. **Kloos RT, Duvuuri V, Jhiang SM, Cahill KV, Foster JA, Burns JA** 2002 Nasolacrimal drainage system obstruction from radioactive iodine therapy for thyroid carcinoma. J Clin Endocrinol Metab 87:5817–5820
18. **Mandel SJ, Mandel L** 2003 Radioactive iodine and the salivary glands. Thyroid 13:265–271
19. **Shimaoka K, Schoenfeld DA, De Wys WD, Creech RH, De Conti RA** 1985 Randomized trial of Doxorubicin versus Doxorubicin plus Cisplatin in patients with advanced thyroid carcinoma. Cancer 56:2155–2160

20. **Williams SD, Birch R, Einhorn LH** 1986 Phase II evaluation of Doxorubicin plus Cisplatin in advanced thyroid cancer: a Southeastern Cancer Study Group Trial. Cancer Treat Rep 70:405–407
21. **Braga-Brasaria M, Ringel MD** 2003 Beyond radioiodine: a review of potential new therapeutic approaches for thyroid cancer. J Clin Endocrinol Metab 88: 1947–1960
22. **Reiners C** 2003 Radioiodine therapy in patients with pulmonary metastases of thyroid cancer: when to treat, when not to treat? Eur J Nucl Med Mol Imaging 30:939–942
23. **Robbins RJ, Wan QW, Grewal RK, Reibke R, Gonen M, Strauss HW, Tuttle RM, Drucker W, Larson SM** 2006 Real-time prognosis for metastatic thyroid carcinoma based on 2-[^{18}F] fluoro-2-deoxy-D-glucose positron emission tomography. J Clin Endocrinol Metab 91:498–505
24. **Hedinger C, Williams ED, Sobin LH** 1988 Histological typing of thyroid tumours. In: International histological classification of tumours. World Health Organization. Vol 11. 2nd ed. Berlin: Springer-Verlag
25. **Rosai J** 1996 Ackerman's surgical pathology. 8th ed. St. Louis, MO: Mosby; 1318
26. **Biondi B, Filetti S, Schlumberger M** 2005 Thyroid-hormone therapy and thyroid cancer: a reassessment. Nat Clin Pract Endocrinol Metab 1:32–40
27. **Demers LM, Spencer CA** 2003 Laboratory medicine practice guidelines. Laboratory support for the diagnosis and monitoring of thyroid disease. Thyroid 13:4–126
28. **Schlumberger M, Mancusi F, Baudin E, Pacini F** 1997 ^{131}I therapy for elevated thyroglobulin levels. Thyroid 7:273–276
29. **Park HM, Perkins OW, Edmondson JW, Schnute RB, Manatunga A** 1994 Influence of diagnostic radioiodines on the uptake of ablative dose of iodine-131. Thyroid 4:49–54
30. **Droz JP, Schlumberger M, Rougier P, Ghosn M, Gardet P, Parmentier C** 1990 Chemotherapy in metastatic nonanaplastic thyroid cancer: experience at the Institut Gustave-Roussy. Tumori 76:480–483
31. **Becker DV, Hurley JR** 1982 Current status of radioiodine (^{131}I) treatment of hyperthyroidism. In: Freeman LM, Miller JM, eds. Nuclear medicine annual. New York: Raven Press; 265–290
32. **Baudin E, Do Cao C, Cailleux AF, Leboulleux S, Travagli JP, Schlumberger M** 2003 Positive predictive value of serum thyroglobulin levels, measured during the first year of follow up after thyroid hormone withdrawal, in thyroid cancer patients. J Clin Endocrinol Metab 88:1107–1111
33. **Pacini F, Agate L, Elisei R, Ceccarelli C, Lippi F, Molinaro E, Pinchera A** 2001 Outcome of differentiated thyroid cancer with detectable serum Tg and negative diagnostic ^{131}I whole body scan: comparison of patients treated with high ^{131}I activities versus untreated patients. J Clin Endocrinol Metab 86:4092–4097

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