Differentiated Thyroid Carcinoma in Children and Adolescents: A 37-Year Experience in 85 Patients

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This study reports on 85 differentiated thyroid carcinoma (DTC) (72 papillary, 13 follicular) patients, younger than 18 yr of age at the time of diagnosis, consecutively treated during the period 1958–1995. **Methods:** Follow-up (median: 111 mo, range 1–324 mo) consisted of clinical examination, serum thyroglobulin (Tg), ^{131}I whole-body scintigraphy (whole-body scan) and other imaging procedures. **Results:** Forty-six patients had undergone total thyroidectomy, 38 partial thyroidectomy and 1 thyroid biopsy. In 47 patients, lymphadenectomy was also performed. Five patients were treated after surgery by external radiotherapy, 59 by ^{131}I therapy and 16 by both modalities. Iodine-131 therapy was successful in ablating thyroid remnants in 35/48 cases, lymph node metastases in 8/11 cases and lung metastases in 12/16 cases. Among the patients with scintigraphic-confirmed disappearance of lung metastases, serum Tg was still detectable in 10 cases, but continued to decrease spontaneously even without further therapeutic doses of ^{131}I. All patients were still alive after a median period of 137 mo (range 5–444 mo). Six patients experienced a recurrence of the disease in the neck. Sixty-seven patients were free of disease, 3 had lymph node metastases, 4 lung metastases and 11 had detectable levels of Tg without demonstrable metastases. No impairment of female fertility or untoward genetic effects were noticed. One male patient, treated with 3.33 GBq of ^{131}I, was infertile due to oligospermia. One case of gastric cancer and one of breast cancer occurred 8 and 19 yr, respectively, after ^{131}I therapy. **Conclusion:** Iodine-131 therapy is highly effective in reducing lung metastases, but undetectable levels of Tg are seldom achieved. Total thyroidectomy and ^{131}I therapy is an effective and safe treatment for the majority of patients with DTC diagnosed in childhood or adolescence.

Key Words: differentiated thyroid cancer; children; radioiodine therapy

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Differentiated thyroid carcinoma (DTC) is a rare disease in the general population and is also uncommon in childhood and adolescence (*1*).

Age is considered a significant independent prognostic factor in patients with DTC: the rates of both survival and recurrence are better in patients younger than 40 yr of age than in patients older than 40 yr of age (*2–5*). Nevertheless, lymph node and lung metastases are more frequent in patients in the first and second decades (*6*). For this reason there is disagreement in the literature about the optimal initial treatment and the type of follow-up needed (*6–8*).

The low incidence of the disease, particularly in childhood, and the need for very long periods of follow-up to establish risks in patients with a life span of many decades make it difficult to assemble a large and homogeneous series of such patients and makes effective prospective studies virtually impossible (*6–21*).

The data reported here are from 85 DTC patients younger than 18 yr of age at the time of diagnosis, who were treated and followed-up by our department in the period from 1958 to 1995.

MATERIALS AND METHODS

Between 1958 and 1995, 2870 patients with DTC were treated at the Nuclear Medicine Department of the "Ospedale di Circolo," Busto Arsizio, Italy. From this group, we selected 85 consecutive patients younger than 18 yr of age at the time of diagnosis and studied them retrospectively by evaluating the data previously collected in the database maintained in our department.

Thirteen patients (15.3%) were diagnosed in the period 1958–1970, 23 (27.1%) between 1971–1980, 31 (36.4%) between 1981–1990 and 18 (21.2%) between 1991–1995.

Surgical intervention was performed in our hospital in 34 cases (40.0%) and elsewhere in 51 cases.

All specimens of the patients operated on in our hospital and six of those operated on in other hospitals were reviewed at the same time, expressly for this study. Histotypes were defined by the World Health Organization classification (*22*) and the TNM staging used the 1987 UICC classification (*23*).

All patients underwent follow-up consisting of detailed clinical examinations performed in our department by a limited number of experienced physicians, using 180-MBq ^{131}I whole-body scan, serum thyroglobulin (Tg) assay and neck sonogram and chest radiograph. The intervals of the examinations depended on the estimated risk of the disease and ranged from 6 to 24 mo. The median follow-up was 111 mo (range 1–324 mo). Sixty patients (70.6%) underwent follow-up for more than 5 yr and 39 (45.9%) for more than 10 yr. Twenty-four patients who had not been directly evaluated in the last 24 mo were contacted by telephone. Information was also gathered when necessary from family or referring physicians.

The use of ^{131}I therapy changed over the period of the survey: in the 1960s, external radiotherapy was the therapy of first choice postoperatively, whereas ^{131}I therapy was added only occasionally, but with increasing frequency. Subsequently, external radiotherapy was added to ^{131}I therapy in patients at high risk of recurrence or in those in whom surgical excision was considered not to be complete. Since 1979, external beam radiation has not been performed in young patients. After 1980, all patients with papillary or follicular carcinoma were treated with ^{131}I after surgery except for those with papillary carcinoma $<$1 cm in diameter and without lymph node metastases and those with encapsulated follicular carcinomas $<$2 cm in diameter.

The period of time from surgical intervention to ^{131}I therapy depended on several factors, such as the time when the patient was referred to our department, the facilities available or factors related to the clinical course of the disease in individual patients. The median delay from pathological diagnosis of DTC and the first radiometabolic therapy was 2 mo (range 1–180 mo). Iodine-131 treatment was repeated at 6-mo intervals until complete ablation of the remnants was achieved.

Iodine-131 treatment of local recurrences and distant metastases

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was performed after demonstration of ^{131}I uptake on a ^{131}I whole-body scan performed 48 hr after the administration of 70–180 MBq of ^{131}I. Iodine-131 whole-body scans were performed using a rectilinear scanner in the period from 1958 to 1974 and with a gamma camera used thereafter. Scans were performed after a 20-day period of tri-iodothironine withdrawal and 35 days of levothyroxin withdrawal. A low-iodine diet was advised for at least 1 mo before the ^{131}I whole-body scan for the majority of the patients. Urinary iodine was never assayed.

Serum thyrotropin, Tg and anti-Tg antibodies were assayed on the same day as the diagnostic ^{131}I administration as well as during hormone therapy. Beginning in 1980, serum Tg was measured by several different commercial kits. Since 1992 Tg was assayed by an immunoradiometric test (Thyroglobuline IRMA Pasteur) with a limit of detection of 0.2 ng/ml, an intra-assay coefficient of variation ranging from 1.1% (at 387 ng/ml) to 14.2% (at 0.6 ng/ml) and an interassay coefficient of variation ranging from 4.5% (at 13.6 ng/ml) to 23.2% (at 0.8 ng/ml).

RESULTS

Details of clinical, therapeutic and follow-up data are reported in Table 1.

Sixty-three patients were female and 22 male (ratio, 2.86:1). The mean age was 14.7 yr (s.d. 3.0 yr), and the median age 15 yr (range 5–18 yr). Thyroid carcinoma in childhood is a very rare disease: 41 patients of this study were more than 15 yr of age and only 7 less than 10 yr of age. A comparison of the main clinical features for the patients $\leq$15 yr and $>$15 yr of age is reported in Table 2.

Previous irradiation of the neck region was documented in two patients (Patients 1 and 75). Both had been irradiated for angioma of the neck at 20 days and 3 mo of age. A papillary thyroid cancer developed in each case at 16 and 17 yr after the exposure.

The clinical manifestation that led to the diagnosis of DTC was known in 65/85 patients. It was a thyroid nodule in 38 patients (58.5%), cervical adenopathy in 17 (26.2%), both manifestations in 9 (13.8%) and hyperthyroidism in one (1.5%).

Fine-needle aspiration biopsy was performed before surgery in 16 of the patients operated on in our hospital. Cytological examination was consistent with papillary thyroid carcinoma, which was confirmed by histology in 13 patients. It was carcinoma with follicular neoplasm in two patients and with lymphocytic thyroiditis in one case, which were revealed to be encapsulated follicular carcinomas at histology. In 13 of 16 patients operated on in our hospital who lacked a presurgical cytological diagnosis, the operation occurred before 1976, when this procedure was not yet routinely performed.

Details of surgical interventions and complications are reported in Table 3. Permanent hypoparathyroidism was reported in seven patients (8.2%) and laryngeal nerve injury in three patients (3.5%). No case of laryngeal nerve injury and three cases of permanent hypoparathyroidism (operated on in 1968, 1978 and 1990) were reported among the patients operated on in our center.

Seventy-two patients (84.7%) had papillary thyroid carcinoma and 13 had follicular thyroid carcinoma (15.3%) [encapsulated follicular thyroid cancer (n = 11) and invasive follicular thyroid cancer (n = 2)].

The size of primary tumor and invasion beyond thyroid capsule was reported in 65/85 patients. The primary tumor was $<$1 cm in size (T1) in one patient (1.5%), between 1 and 4 cm (T2) in 34 patients (52.3%), $>$4 cm (T3) in 10 patients (15.4%) and extended beyond thyroid capsule (T4) in 20 patients (30.8%).

Cervical lymph node metastases were diagnosed within 1 yr of the initial diagnosis in 51 patients (60.0%): in 47 patients after surgical removal and in the other 4 patients by clinical examination (1 patient) or by ^{131}I whole-body scan (3 patients).

Lung metastases were diagnosed by ^{131}I whole-body scan in 16 patients (18.8%). They were present from the time of the first diagnosis of the disease in each case. In one case, lung metastases were revealed by ^{131}I whole-body scan only after thyroid remnant ablation, but it was probably already present from the time of the first diagnosis. The scintigraphic pattern of lung uptake was diffuse in nine patients, focal in five patients and both diffuse and focal in two patients. Lung metastases were also diagnosed by chest radiograph in only 2/13 patients. Other distant metastases of the disease were never observed.

Thyroid hormone replacement therapy consisted of the administration of desiccated thyroid in the first year of the survey.

Suppressive levothyroxin therapy was advised to most patients in the final 15 yr of the survey, when the assay of thyroid-stimulating hormone (TSH) was routinely performed in our department. In the last year levothyroxin therapy was designed to obtain a detectable, but low TSH in the patients at low risk of relapse and with a prolonged free-of-disease follow-up. Initial doses of levothyroxin were 4 μg/kg/day for children 6–10 yr of age, 3 μg/kg/day for those 11–15 yr of age and 2 μg/kg/day for those $\geq$16 yr of age. The dose for each patient was then individualized by administering the lowest dosage capable of suppressing serum TSH or maintaining it at detectable, but low levels. At the time of the final assay, serum TSH was actually undetectable in 63% of the patients, detectable but $<$0.2 μunit/ml in 17%, between 0.2 and 0.5 μunit/ml in 10% and $>$0.5 μunit/ml in 10%.

Postsurgical treatment consisted of external beam radiotherapy in 5 patients, ^{131}I therapy in 59 and on both modalities in 16. No postsurgical treatment was performed in five patients.

External beam radiotherapy was performed with fields encompassing the cervical region, with doses ranging from 50–65 Gy. Nine of 21 external beam radiation treatments were performed from 1958 to 1970 and 12/21 from 1971 to 1979. Fourteen patients were treated for incomplete surgical excision or suspect neoplastic tissue in the neck.

Seventy-five patients were treated by ^{131}I therapy. Details of the results of the ability of ^{131}I therapy to ablate thyroid remnants and to treat lymph node or lung metastases are reported in Table 4. Three of nine patients in whom thyroid remnant ablation was not obtained had undergone less than total thyroidectomy.

Iodine-131 treatment was still in progress at the time of the survey in the seven patients in whom lymph node or lung ^{131}I uptake had not yet been eliminated.

It is noteworthy that among the 12 patients in whom ^{131}I lung uptake was no longer evident on the ^{131}I whole-body scan, off-hormone treatment serum Tg was not detectable in only two, whereas it ranged from 6–333 ng/ml (median 20 ng/ml) in the other patients. Nevertheless, Tg continued to decrease spontaneously in this subgroup of patients even without further therapeutic administrations of ^{131}I. The most recent median Tg assayed was significantly lower than the median serum Tg assayed at least 6 mo after the last ^{131}I treatment (Wilcoxon test: $p < 0.01$) (Table 5).

The most frequent early complications were nausea, vomiting, gastrointestinal discomfort and transient sialadenitis. They were never serious nor did they require pharmacological treatment.

Thirteen of the 63 females treated with ^{131}I subsequently gave birth to 18 healthy children (11 girls and 7 boys). The

TABLE 1
Clinical, Therapeutic and Follow-Up Data of 85 DTC Patients <18 Years of Age at Diagnosis

Patient no.	Sex	Age (yr)	Clinical present-ation	First surgical interven-tion	Hysto-type	T	Lymph-node mets and local recurrence <1 yr	>1 yr	Lung mets	Second surgival interven-tion	Interval first–second surgical interven-tion (mo)	^{131}I (GBq)	No. of ^{131}I doses	Rx-therapy	Survival (mo)	Follow-up (mo)	Disease status
1	M	16	n	subtot	ef	T3						0			300	300	fr
2	F	14	mn	tt, bnd	p	T4	path					0			53	53	fr
3	F	15	mn	hemi	f	Tx	path			tt+ad	8	7.4	2		59	32	nm
4	F	16		hemi, mnd	p	Tx	path			tt	2	17.8	6		216	111	fr
5	F	18	n	lump	ef	T3	•					0		x	232	232	fr
6	M	10		lump	p	Tx	c			ad	1	2.1	1	x	396	102	fr
7	F	17	a	tt, ad	p	T2	path					7.4	5	x	312	166	fr
8	F	16		lump, ad	p	T2	path			ad	12	3.5	2	x	384	48	fr (r)
9	F	17	n	tt, ad	p	T4	path		d			7.4	2		78	78	Tg ↑
10	F	17	n	subtot	p	Tx						4.8	4	x	336	240	fr
11	M	13	a	subtot, mnd	p	Tx	path	c	d	tt+ad	24	31.1	7		122	122	lm
12	M	12	a	tt, ad	p	Tx	path					11.8	5	x	196	109	fr
13	M	12	a	tt, bnd	p	T3	path		d, fc			10.4	3		75	75	lm
14	F	17	n	tt, ad	p	T2	path					3.7	1		9	9	fr
15	F	13	n	subtot, ad	p	T4	path					5.5	3		140	140	fr
16	F	5	n	hemi	p	T2						2.8	2		119	107	fr
17	F	18		tt	p	Tx						0.7	1	x	444	312	fr
18	F	15		hemi	p	T4		c		ad	82	3.7	1		94	94	Tg ↑
19	F	9	n, a	tt, bnd	p	T3	path		d			3.5	1		10	10	Tg ↑
20	F	18	n	subtot	p	T2						6.7	2		20	10	fr (r)
21	F	13	n, a	tt, ad	p	T2	path			ad	2	0		x	232	232	fr
22	F	16	n	tt, ad	p	T4	s		d			17.0	6	x	290	290	lm
23	F	15	n	subtot	ef	T2						3.0	1		122	29	fr
24	F	14	n	hemi	p	T2						1.9	1		148	148	fr
25	F	16	mn	hemi	ef	T2						0			226	226	fr
26	F	11		subtot	p	Tx		c		bnd	27	8.5	3		167	167	fr
27	M	15	a	tt, ad	p	T4	path					11.1	3		18	18	fr
28	F	11		tt, ad	p	Tx	path			mnd	2	5.5	3		69	77	fr
29	F	16		subtot	p	Tx		c		rec	36	7.0	2		149	149	fr
30	M	8	n	lump	p	T3			d	tt	4	9.2	3		121	121	Tg ↑
31	M	6	a	tt, ad	p	T4	path		fc			9.6	5	x	207	207	fr
32	F	18	n	tt	p	T2						3.7	1		5	5	fr (r)
33	F	17	n	tt, ad	p	T2	path					6.7	4	x	242	242	fr (r)
34	F	13	mn, a	tt, bnd	p	T4	path					7.9	2		12	12	nm
35	F	13	a	tt, ad	p	Tx	path		d			12.2	4		137	137	Tg ↑
36	F	16	n	tt	p	T2						0		x	193	193	fr
37	M	11	n	hemi	ef	T3			fc	tt	3	7.4	2		109	109	fr
38	M	18	a	tt, bnd	p	T4	path		d	mnd	12	18.5	5		92	92	Tg ↑
39	F	13	a	tt, ad	p	Tx	path					2.6	2	x	293	155	fr
40	F	15	n	tt	ef	Tx			fc			11.1	4		252	252	Tg ↑
41	M	17	a	tt, mnd	p	Tx	path					3.3	2	x	324	204	fr
42	F	15	n	tt, ad	p	T2	path			ad	12	6.7	2		52	52	fr
43	F	15	n, a	tt, mnd	p	T2	path					3.7	1		141	141	fr
44	F	16		tt, ad	p	T2	path					7.4	2		10	10	fr (r)
45	F	18		hemi	p	T4		s		tt, bnd	31	9.9	3		228	168	fr
46	F	13	mn	tt	p	T2						7.4	4		154	154	fr
47	F	12	n	subtot, ad	p	T4	path		fc	tt, mnd	2	7.4	2		110	100	Tg ↑
48	F	17		tt, mnd	p	T4	path					7.4	2		25	25	fr
49	M	15	n	tt	p	T2	path			ad	4	11.1	3		224	224	fr
50	F	11	a	tt, ad	p	T4	path					6.7	2		84	84	fr
51	M	11	a	tt, ad	p	Tx	path					4.1	2		161	113	fr
52	F	18	a	tt, mnd	p	T2	path					7.4	2		22	22	fr
53	F	6	n, a	tt	p	T4	path		fc	mnd	2	14.1	4		24	24	lm
54	F	16	a	b	p	T4	path			tt, ad	1	6.3	2		152	147	fr
55	M	13		t, ad	p	T3	path					4.4	3	x	317	317	fr (r)
56	F	15	n	subtot	p	T3						0		x	84	84	fr
57	M	9	n	hemi	p	T2				tt	1	1.9	1		92	92	fr
58	F	18	n, a	hemi	p	Tx						3.3	4	x	312	240	fr (r)
59	M	15	n, a	tt, ad	p	T4	path					7.8	2		18	6	fr (r)
60	M	14		hemi	ef	Tx				tt	8	3.0	1		84	1	fr
61	F	18	n	subtot	p	T2						0		x	251	251	fr

TABLE 1
Continued

Patient no.	Sex	Age (yr)	Clinical present-ation	First surgical interven-tion	Hysto-type	T	Lymph-node mets and local recurrence <1 yr	>1 yr	Lung mets	Second surgival interven-tion	Interval first–second (GBq) surgical interven-tion (mo)	^{131}I (GBq)	No. of ^{131}I doses	Rx-therapy	Survival (mo)	Follow-up (mo)	Disease status
62	F	13	n	subtot, ad	p	T3	path					3.3	3	x	278	180	fr
63	F	14	n	tt	p	T2						0			144	144	fr
64	F	18	n	hemi	ef	T2				tt	2	1.9	1		60	60	fr
65	F	15		lump	ef	Tx				tt	168	7.4	2	x	252	228	fr
66	F	16	a	tt, ad	p	T2	path		d			9.6	3		152	152	Tg ↑
67	F	16	a	tt, ad	p	T4	path		d, fc			2.2	1		168	17	Tg ↑
68	M	17		tt, ad	p	T2	path					3.7	1		64	64	fr
69	F	16	n	tt, ad	p	T2	path					2.6	1		84	84	fr
70	F	18	hyper	subtot	p	T2						3.7	1		44	44	fr
71	M	18		tt, ad	p	Tx	path					6.7	3		144	144	nm
72	F	18		lump	p	T2				tt	2	5.9	2		126	126	fr
73	F	17		tt, ad	p	T2	path					3.7	1		34	34	fr
74	F	18	n	tt	p	T2						3.7	1		36	36	fr
75	F	18		tt, ad	p	T2	path					7.9	2		14	14	fr (r)
76	F	17	n	tt	p	T4	s					16.3	5		165	165	fr
77	M	13	a	tt, mnd	p	T2	path					3.7	1		21	21	fr
78	M	17	n	hemi	ef	T2						0			192	39	fr
79	M	13	n, a	subtot, ad	p	T4	path					10.4	5	x	350	184	fr
80	F	16	n	hemi	ef	T3				tt	4	3.7	1		34	34	fr
81	F	12	n	tt, bnd	p	T4	path		d	ad	2	9.2	2		70	70	Tg ↑
82	F	18	n, a	hemi, ad	p	Tx	path			tt	1	11.1	3		168	168	fr
83	F	14	n	lump	f	T2	s			tt	1	5.9	2		112	112	fr
84	F	18		subtot	p	T1		c		tt, ad	180	3.7	1		324	324	fr
85	F	12	n	lump	p	T2						2.6	1		111	111	fr

n = single thyroid nodule; mn = multinodular goiter; a = cervical adenopathy; hyper = hyperthyroidism; tt = total thyroidectomy; ad = adenectomy; mnd = monolateral neck dissection; subtot = subtotal thyroidectomy; bnd = bilateral neck dissection; hemi = hemithyroidectomy; lump = lumpectomy; b = biopsy; ef = encapsulated follicular carcinoma; p = papillary carcinoma; f = invasive follicular carcinoma; path = pathological diagnosis; c = clinical diagnosis; s = scintigraphic diagnosis; d = diffuse pattern; fc = focal pattern; fr = free of disease; (r) = thyroid remanant; nm = cervical lymph node metastases; lm = lung metastases; Tg ↑ = detectable thyroglobulin with no evidence of metastases.

median dose of ^{131}I administered had been 7.4 GBq (range 3.3–17.0 GBq). The median interval elapsed from the last ^{131}I treatment to conception was 72 mo (range 2–204 mo). One male patient (no. 41), previously treated with 3.3 GBq of ^{131}I, was infertile due to oligospermia.

One case of gastric cancer (Patient 22) and one of breast cancer (Patient 10) occurred 8 and 19 yr after the administration of 17.0 GBq (given in 6 doses) and 4.8 GBq of ^{131}I (4 doses), respectively. Both cancers were treated successfully by surgery and no relapses were registered after 7 and 6 yr, respectively, of follow-up.

Globally, six patients experienced a cervical recurrence of the disease more than 1 yr after initial diagnosis (median: 33.5 mo, range 24–180 mo). All of these patients had undergone less than total thyroidectomy. The diagnosis of the recurrence was made clinically in five patients and by ^{131}I whole-body scan in one.

TABLE 2
Comparison of Main Pathological and Clinical Features of DTC in Patients ≤15 Years and >15 Years of Age at Diagnosis

	Patients ≤15 yr	Patients >15 yr
Extracapsular invasion	12/32 (37.5%)	8/33 (24.2%)
Lymph node metastases	29/44 (65.9%)	22/41 (53.6%)
Lung metastases	11/44 (25.0%)	5/41 (12.2%)
Local recurrences	3/44 (6.8%)	3/41 (7.3%)

All of the patients were alive and in good health at the time of the survey, after a median period of 137 mo from the time of diagnosis (range 5–444 mo). Sixty-seven patients were free of disease as judged clinically and on the basis of serum Tg and imaging procedures. Twelve of the patients of this subgroup still had cervical ^{131}I uptake that was judged to be normal thyroid tissue remnants on the basis of the site of uptake and of subsequent follow-up. Three patients had ^{131}I avid node metastases and four had ^{131}I avid lung metastases. In these seven patients, treatment was still in progress at the time of the study. In 11 patients, serum Tg was detectable—off-hormonal treatment—but no metastases could be found by clinical examination or by imaging procedures in the course of follow-up.

DISCUSSION

Age is recognized as one of the most important prognostic factors for DTC (*2–5*). Patients <40 yr of age show longer periods of survival and a lower incidence of recurrence. Nevertheless, children show more advanced stages of the disease and higher recurrence rates (*5,6,14,17,19*), even if the rate of survival seems to be unaffected (*5–7*).

Childhood thyroid cancers are more often papillary and well differentiated. Lung metastases in these patients usually take up ^{131}I avidly (*19*), whereas bone metastases are very rare at this age. The phenomenon of loss-of-differentiation of the neoplastic thyroid cells might be absent or significantly delayed. All of

TABLE 3
Details on Surgical Therapy and Complications

First surgical intervention	n (%)	Number of reinterventions* To reduce thyroid remnant	To reduce thyroid remnant and for local metastases	For local metastases or recurrences	Permanent hypoparathyroidism	Laryngeal nerve injury
tt	10 (11.8)			2 (2)	1	
tt + ad	36 (42.3)			5 (5)	3	1
subtot	10 (11.8)			3 (0)	1	
subtot + ad	5 (5.9)		2 (1)		1	
hemi	13 (15.3)	5	3 (1)			1
hemi + ad	2 (2.3)	2				
lump	8 (9.4)	5		1 (1)	1	1
lump + ad	1 (1.2)			1 (1)		

*Number in parentheses is the number of reinterventions performed by the first year since diagnosis
tt = total thyroidectomy; tt + ad = total thyroidectomy and adenectomy or neck dissection; subtot = subtotal thyroidectomy; subtot + ad = subtotal thyrodectomy and adenectomy or neck dissection; hemi = hemithyroidectomy; hemi + ad = hemithyroidectomy and adenectomy or neck dissection; lump = lumpectomy or biopsy; lump + ad = lumpectomy and adenectomy.

these features may permit a greater chance of cure and control of the disease.

These data, although impressive, may be insufficient to propose less radical treatments. Deaths many years after first diagnosis have been reported (*11*), even after the complete scintigraphic clearing of lung metastases had been obtained (*8*). The long survival times observed could be the result of the more radical treatment performed by the majority of centers in the last 20 yr or a mere consequence of the indolent course of the disease.

Patients under the age of 18 accounted for 2.96% of the overall study from our department. DTC is particularly rare in the first decade (only seven cases), whereas it becomes progressively more frequent with advancing age.

The female-to-male ratio was similar to that of patients over 18 years of age in the second decade (3.33:1), whereas it was reversed in the first decade of life (0.75:1). This phenomenon could be related to the hormonal changes accompanying puberty (*1*).

The increasing number of patients observed in the different

TABLE 4
Results of Iodine-131 Therapy on 75 DTC Patients <18 Years of Age at Diagnosis

	Scintigraphic disappearance	^{131}I administered dose*	No scintigraphic disappearance	^{131}I administered dose*	Not ascertained
Thyroid remnants	35/48 (72.9%)	3.7 (1.8–11.1)	9/48 (18.7%)	6.7 (3.3–17.8)	4/48 (8.3%)
Lymph node metastases	8/11 (72.7%)	8.5 (6.7–16.3)	3/11 (27.3%)	7.4 (6.7–8.5)	—
Lung metastases	12/16 (75.0%)	9.2 (2.2–18.5)	4/16 (25.0%)	15.5 (10.4–31.1)	—

*Median (range) I-131 administered dose in GBq.

TABLE 5
Behavior of Serum Tg in 12 DTC Patients Treated Successfully with Iodine-131 for Lung Metastases

Patient no.	Tg after surgery and before ^{131}I (ng/ml)	TSH (μ units/ml)	Tg after the last ^{131}I treatment (ng/ml) (1)	TSH (μ units/ml)	Months elapsed from the last ^{131}I treatment	Most recent Tg off LT4-therapy (ng/ml) (2)	TSH (μ units/ml)	Months elapsed (Tg2-Tg1)	Most recent Tg on LT4-therapy (ng/ml)
9	350	>50	28	>50	12	6	>100	61	NA
19	204	>100	61	>100	6	NA	NA	—	6
30	290	>100	111	>50	10	19	>100	74	NA
31	NA	NA	95	>90	9	<1	>50	72	<1
35	763	50	110	>100	12	14	38	108	<1
37	37	85	27	>100	6	<1	50	86	NA
38	789	>50	48	>50	12	41	38	18	<1
40	NA	NA	41	>100	14	15	50	63	NA
47	873	16	152	>50	8	15	>50	62	NA
66	NA	NA	>1000	86	—	333	>50	48	11
67	NA	NA	NA	NA	—	8	>90	—	NA
81	1000	>50	118	>50	9	20	65	50	NA

NA = not ascertained

years of the survey could be related to the availability of better diagnostic tools and to the increasing number of patients referred to our center from other areas of the country over this period.

The long median follow-up period and the information on the current health status gathered for each patient reduce the possibility of selection bias.

This study confirms the good overall prognosis of DTC in children and adolescents. Nevertheless, relapses of the disease and cause-specific deaths are possible even after 2 or 3 decades from the time of initial diagnosis. Moreover, we do not know if the patients with no evidence of ^{131}I uptake at 185 MBq whole-body scan but detectable serum Tg off-hormonal therapy are already cured and if ^{131}I therapy could be halted (*24*). We have decided not to give further therapeutical doses of ^{131}I to these young patients to limit hazards from radiation exposure. Serum Tg continued to decline significantly even without further ^{131}I doses. This phenomenon may be linked to a delayed tumoricidal effect of the previous ^{131}I doses. If this phenomenon were to be confirmed in larger studies, the assumption that a reduction of serum Tg is proof of effective treatment in patients treated only on the basis of high serum Tg levels (*25*) may have to be critically revised.

Radioiodine therapy was performed in our department by administering empirically adjusted fixed doses, taking into account the fractional uptake of thyroid remnants and the site and extent of metastatic disease. Dosimetric evaluations were not performed to reduce the duration of hospitalization with important psychological and economic advantages. Quite low doses of ^{131}I (370–1850 Mbq)—often repeated—were frequently used in the very first year of the survey due to the scarcity of data about untoward effects and the lack of dosimetric evaluation. The administered doses became closer to those we use for adults (3–3.7 GBq for thyroid remnant ablation and 5.6 GBq for lung metastases) in the latter years of the study. With this policy, we have obtained an acceptable compromise between the effectiveness and hazards of radiometabolic therapy.

The incidences of lymph node and lung metastases were higher in patients less than 15 yr of age as compared with adults (65.9% versus 34.7% and 25.0% versus 7.0%), whereas they are closer in the patients over 15 yr of age.

The necessity of total thyroidectomy and radioiodine ablation of thyroid remnants to prevent local recurrences could be seriously questioned. The prognostic significance of cervical lymph node metastases is disputed in literature (*26,27*). Cervical lymph node metastases can be revealed by a sonogram of the neck (*28*) and effectively removed by surgery (*29*), whereas radioiodine was not always effective in treating lymph node metastases. Nevertheless, we believe that total thyroidectomy and ^{131}I ablation of thyroid remnants is a wise, cautious choice for the majority of children and adolescents with DTC for the following reasons: accidental injuries to recurrent laryngeal nerves and permanent hypoparathyroidism are serious consequences in young patients but are rare when the operation is performed by a skilled surgeon (*8*). Thyroid remnant ablation with ^{131}I improves subsequent whole-body scan and Tg sensitivity in diagnosing lung metastases, allowing earlier diagnoses and a greater effectiveness of radiometabolic therapy and reduces recurrences of the disease with beneficial psychological effects on the young patients and on their family and a possible—even if not sure—impact on survival.

A high percentage of lung metastases disappeared by ^{131}I whole-body scan after radioiodine therapy, but a completely undetectable serum Tg—off-hormone treatment—was reported in only a minority of patients. The tumors of this study were all well differentiated cancers. This might explain why all lung metastases were able to pick up ^{131}I and the subsequent good response to ^{131}I therapy.

This study confirms previous data showing that the risk of induction of second tumors and of untoward genetic effects in the offspring of exposed patients are low (*30*). Radioiodine treatment at a young age does not seem to impair subsequent fertility of women. Data on a possible reduction in fertility in men exposed to ^{131}I are scarce. A possible transient and permanent impairment of testicular germinal function were reported in a study of 103 patients treated with ^{131}I for DTC (*31*). In this study, one case of oligospermia in one patient treated with 3.33 GBq of ^{131}I was observed. No other serious complication from radioiodine therapy was observed.

Interest in childhood thyroid cancer has increased since the accident at the Chernobyl power station (*32*). Comparing this study with those from contaminated areas could be helpful in understanding some mechanisms of radiation-induced carcinogenesis. Thirty-one patients were diagnosed 1–8 yr after the accident. The level of contamination was low in Italy after the Chernobyl accident so no effect is expected (*33*). A true increase in the incidence of thyroid cancer has been reported in those children who were under 2 yr of age at the time of exposure and who lived in the most contaminated areas (*34*), as a consequence of the higher radiosensitivity of thyroid tissue and of the higher doses received (*35*). The mean age of the post-Chernobyl subgroup (15 $\pm$ 3.07 yr) was not different from that of patients diagnosed before 1986 (14.48 $\pm$ 3.0 yr), whereas the incidence of patients diagnosed between 5 and 12 yr of age was significantly less than that in a study from a contaminated area of Belarus (18.6% versus 76%). Our study confirms the prevalence of boys over girls diagnosed with thyroid cancer in the first decade of life (female-to-male ratio, 0.75:1), in accordance with other studies of unexposed patients and is different from a study of exposed children (female-to-male ratio, 0.75 versus 1.65). It also confirms that histological features of DTC of exposed children are those typical of aggressive tumors in a higher percentage than in the series of nonirradiated cases: penetration of thyroid capsule by tumor was present in 89% (Belarussian series) versus 30.8% in this series and moderately differentiated tumors in 75% versus 23.8%.

CONCLUSION

This study confirms the good overall prognosis of DTC in children and adolescents, despite the higher incidences of local and distant metastases with respect to adults. Iodine-131 therapy after total thyroidectomy was a safe treatment. It was highly effective in treating lung metastases and, probably, in reducing subsequent recurrences.

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Imaging Prostate Cancer with Technetium-99m-7E11-C5.3 (CYT-351)

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To evaluate the performance of the ^{99m}Tc-labeled monoclonal antibody CYT-351 in visualizing prostate cancer, radioimmunoscintigraphy (RIS) was performed in 35 patients. **Methods:** Antibody (0.5 mg) labeled with 600 MBq ^{99m}Tc was injected intravenously after obtaining informed consent. Planar and SPECT imaging was performed at 10 min and 6–8 and 22–24 hr postinjection. The scans were evaluated for visualization of the primary focus or local recurrence, extraprostatic invasion, lymph node involvement and uptake in bone and soft tissue metastases. **Results:** Thirty-six studies in 35 patients were performed. In 13/14 evaluable studies with clinically localized prostate cancer, RIS had a true-positive rate of 92% (12/13). In eight patients with previous incidental carcinoma detected during transurethral resection undertaken for clinically benign disease, there were 86% true-positive results (6/7) and one true-negative result, which were confirmed by systematic needle biopsies. In six patients with evidence of local recurrence after a previous radical prostatectomy, the true-positive rate was 100% (6/6), which was confirmed by raised or rising prostate-specific antigen levels (PSA) and/or by biopsy. In the eight patients with known metastases, the disease was visualized in 4/4 with progression but not in the 3/3 with regression; one patient demonstrated regressing disease as determined by PSA levels. The overall accuracy was 92%. **Conclusion:** RIS with ^{99m}Tc CYT-351 is capable of providing good quality images and yielding clinically useful information safely. It has a potentially important clinical role for patients with rising PSA levels but negative images by conventional modalities.

Key Words: prostate cancer; technetium-99m; monoclonal antibody; prostate-specific antigen

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Prostate cancer, one of the commonest malignancies in men, has large social consequences. The direct medical expenses and those of lost productivity and wages due to morbid complications from local extension and metastatic spread, or from the side effects of treatment, are estimated at four billion dollars annually in the U.S. (*1*). The death rate from prostate cancer increases rapidly with age, and since the population is aging steadily and mortality from other causes is decreasing, the number of deaths from prostate cancer is likely to continue to increase. With further development of current trends to use

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