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Clinical Behavior and Outcome of Papillary Thyroid Cancers Smaller than 1.5 cm in Diameter: Study of 299 Cases

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To investigate predictors of relapse in small (≤1.5 cm) papillary thyroid cancers, we performed a retrospective chart review study of patients treated and followed up in our institution according a standard prospective protocol. Between 1975 and 2001, 299 patients were operated for a differentiated papillary thyroid cancer no larger than 1.5 cm in size. Near-total or total thyroidectomy was performed in 292 patients, and lobectomy in seven patients.

Persistent/recurrent disease was observed in 77 patients; in 37 of these patients, the only sign was increased TSH-stimulated serum thyroglobulin (Tg). Ten patients developed distant metastases, and 68 locoregional metastases. At multivariate analysis, persistent/recurrent disease was associated with: 1) nonincidental thyroid cancer; 2) lymph node metastases at presentation; and 3) bilateral tumor. Development of distant metastases was associated with the sclerosant variant and the presence of lymph node metastases at presentation. Tumor size (≤1.0 cm *vs.* 1.1–1.5 cm) was not predictive of relapse. No patient died because of the disease, but 14.4% had evidence of disease at their last follow-up visit.

Serum Tg level below 1.0 ng/ml at the first postsurgical evaluation during L-T_4 withdrawal was an accurate predictor of no relapse.

In conclusion, approximately one of four patients with a papillary thyroid cancer no more than 1.5 cm in size develops relapsing/persisting disease after surgery. Baseline histopathological characteristics and serum Tg levels off L-T_4 at first postsurgical evaluation can accurately predict the risk of relapse. (*J Clin Endocrinol Metab* 89: 3713–3720, 2004)

PAPILLARY THYROID CARCINOMAS (PTCs) represent 85–90% of all thyroid carcinomas. PTCs usually have a good prognosis and a mortality rate of less than 10% (1–3). With the increasing use of high-resolution sonography and fine needle aspiration biopsy, thyroid cancer tends to be diagnosed at an early stage (4–6). Therefore, an increasing proportion of newly diagnosed thyroid carcinomas has a small size: when no larger than 1.0 cm in diameter, they are classified as microcarcinomas. The great majority of them are PTCs. A number of studies have shown that microcarcinomas of the thyroid have a more favorable prognosis than larger tumors (7–10). Many microcarcinomas may remain occult and become diagnosed as an incidental finding during surgery for goiter or other benign thyroid disorders ("incidental" microcarcinomas) (9–11). However, some microcarcinomas may have a negative outcome, including distant metastases and patient death (7–11). It would be clinically important, therefore, to identify those microcarcinomas that have the potential to spread and cause relapse and even patient death. These aggressive microcarcinomas require close follow-up and intensive treatment, whereas the follow-up of the low-risk microcarcinomas, which represent the large majority of microcarcinomas, doesn't require costly and complex medical procedures and should be simplified.

Many questions on this issue remain unanswered. First, it is not entirely clear whether 1.0-cm tumor size should be considered a threshold for risk evaluation or whether cancers larger than 1.0 cm but still small (no larger than 1.5 cm in diameter) can also be expected to have a similar favorable clinical behavior as tumors no larger than 1.0 cm (2, 12). This issue is particularly interesting because a new prognostic TNM (Tumor, Node, Metastases) staging of thyroid tumors has been adopted recently (13). According to this new staging, thyroid tumors no larger than 2.0 cm in size but limited to the thyroid gland are classified T1, whereas, according to the previous TNM staging, only tumors no larger than 1.0 cm were classified as T1 (14). Furthermore, in relation to tumor size also, the clinical impact of incidental *vs.* nonincidental carcinomas should be better assessed.

Second, although predictors of relapse or persisting disease are quite well established in large PTCs (1–3, 15), they have not been consistently identified in small PTCs. This is due in part to the fact that lobectomy, rather than near-total thyroidectomy, is usually considered a sufficient treatment for these cancers. When lobectomy is performed, much information is lost [*i.e.* presence of bilateral foci and locoregional lymph nodes, relevance of postsurgery thyroglobulin (Tg) levels].

Finally, familial microcarcinomas have been suggested to

Abbreviations: AbTg, Anti-Tg antibodies; CT, computed tomography; DTC, differentiated thyroid carcinoma; PTC, papillary thyroid carcinoma; Tg, thyroglobulin; TNM, Tumor, Node, Metastases; WBS, whole body scan.

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have an aggressive behavior that requires a more aggressive treatment (16). However, this observation has not yet been confirmed.

To address these questions we have performed a retrospective chart review study of patients with small PTCs (≤1.5 cm) treated and followed up in our institution according a standard prospective protocol and have studied possible prognostic factors that may address the best therapeutic strategy.

Patients and Methods

Patients

We reviewed the clinical records of a consecutive series of 299 patients who were operated for a PTC no larger than 1.5 cm between 1975 and 2001 and followed up at our Thyroid Clinic including Endocrinology and Nuclear Medicine facilities. This retrospective study was performed in accordance with the ethical roles of our institution. In 148 cases, clinical signs were present (clinical or nonincidental carcinomas), whereas in the remaining 151 cases the tumor was an incidental finding after thyroidectomy performed for other diseases (incidental carcinomas) (Table 1).

Patients with nonincidental cancer underwent near-total or total thyroidectomy in 141 cases and lobectomy in seven cases; patients with incidental cancer underwent near-total thyroidectomy in 128 cases and lobectomy in 23 cases (Table 1). However, in 15 patients (seven in the first group and eight in the second group), lobectomy was followed by completion thyroidectomy within 8 months. Therefore, 284 of 299 (95.0%) patients were treated with near-total or total thyroidectomy either as first choice or within 8 months of diagnosis. Furthermore, eight additional patients, initially treated with lobectomy, underwent completion thyroidectomy after a period ranging from 15 months to 14 yr (median, 54 months) for a suspect of relapse (confirmed in three of them at histology). Therefore, only seven patients initially treated with lobectomy did not undergo completion thyroidectomy. All of them had an incidental cancer.

Patients with nonincidental PTC, in addition to near-total or total thyroidectomy, also underwent paratracheal lymph node dissection. Laterocervical lymph nodes were dissected when macroscopically involved or in the presence of extensive invasion of central nodes.

Histopathological evaluation and tumor staging

For each case, all histological slides were reviewed by a pathologist unaware of the clinical data, and diagnoses were graded according to the thyroid malignancy World Health Organization classification (17).

TABLE 1. Mode of diagnosis and surgical treatment of 299 small PTCs

Mode of diagnosis	N	Surgical treatment	
		Near-total Tx	Lobectomy
Nonincidental carcinomas			
FNAB[a]	103	96	7
Lymph node[b]	43	43	
Bone metastases	1	1	
Laryngeal carcinoma	1	1	
Total	148	141	7
Incidental carcinomas			
Multinodular goiter	111	95	16
Graves' disease	25	24	1
Toxic adenoma	10	8	2
Toxic multinodular goiter	1	1	
Cyst	4		4
Total	151	128	23

Tx, Thyroidectomy; FNAB, fine-needle aspiration biopsy.

[a] Seven patients had Graves' disease; one patient had a toxic multinodular goiter.

[b] FNAB was performed in 10 patients and nodal biopsy in five. Four patients had concomitant Graves' disease.

Tumors were staged according to both the fifth and sixth editions of TNM staging (13, 14), where T (extent of the primary tumor) and N (regional lymph node metastases) were determined on the basis of pathological data and M (evidence of distant metastases) was based on the findings at the first postsurgical ^{131}I-whole-body scan (WBS).

Postoperative follow-up

All 284 patients subjected to near-total or total thyroidectomy were examined while in hypothyroidism, after L-T_4 withdrawal, as previously described (18, 19). In patients with low residual (<3%) neck ^{131}I uptake and with tumors at low risk according to TNM staging, sonography of the neck and WBS were performed after a diagnostic dose of 5 mCi (185 MBq) ^{131}I. Patients (n = 43) with residual cervical uptake greater than 3% but negative neck sonography (performed to exclude the presence of nodules in the remaining thyroid tissue or enlarged/suspicious lymph nodes) were treated with an ablative dose of radioactive iodine [30 mCi (1110 MBq) ^{131}I]. Finally, 91 patients with a T4 and /or N1 tumor (as defined in the fifth edition TNM system) underwent postsurgical treatment with radioiodine at a dose of 100 mCi (3,700 MBq). Residual or metastatic malignant tissue due to recurrent disease (in patients free of disease for at least 12 months after first postsurgical evaluation) or due to persistent disease was considered present when ^{131}I-WBS was positive and/or serum Tg levels were detectable. Serum Tg was measured by RIA with a functional sensitivity (lowest concentration measured with an interassay coefficient of variation ≤ 20%) of 3 ng/ml up until 1989. After that date, serum Tg was measured by an immunoradiometric assay (ILMA Nichols Institute Diagnostics, Diasorin, Saluggia, Italy) with a functional sensitivity of 0.5 ng/ml. Anti-Tg antibodies (AbTg) were measured in all patients by an immunoradiometric assay (ILMA Nichols Institute Diagnostics, Diasorin). The presence of distant metastases at ^{131}I-WBS was always confirmed by at least one additional imaging test [standard x-rays, computed tomography (CT) scan or magnetic resonance imaging]. Nonsurgically removable distant metastases were treated with therapeutic doses of ^{131}I every 8–12 months. Diagnosis of regional lymph node involvement was made when either radioiodine uptake or the finding of high Tg levels and/or malignant cells in the fine needle aspirates confirmed ultrasound evidence of suspicious lymph nodes. Local (in the thyroid bed) recurrences were also diagnosed by radioiodine uptake and confirmed by ultrasound or CT imaging plus cytological examination. Disease progression was defined as enlargement of metastases or tumor masses in the neck (as evaluated by ^{131}I-WBS and/or CT imaging plus serum Tg increase) and/or appearance of new metastatic foci.

Statistical analysis

Time to local and distant metastases occurrence was calculated from the date of surgery. The cumulative rates of local and distant metastases were compared using Kaplan-Meier plots. The log-rank test was used to evaluate the differences between curves. The following clinical and histopathological variables were analyzed for correlation with the occurrence of metastases: patient age (<45 *vs.* ≥45 yr), gender, familial thyroid disease, living in an iodine-deficient area, nonincidental tumor, tumor size (≤1.0 cm *vs.* 1.1–1.5 cm), multifocal or bilateral disease, extrathyroidal invasion, vascular invasion, and lymph node metastases at surgery. The same variables plus the presence of distant metastases at presentation were analyzed for correlation with persistent disease. Univariate and multivariate analysis of prognostic variables was carried out according to the Cox proportional hazard model. Only variables identified to be potentially significant at univariate analysis were included in the multivariate model to evaluate their independent effect. A P value below 0.05 was considered significant. Data analysis was performed using the SPSS 8.0 statistical package for Windows (SPSS, Inc., Chicago, IL).

Results

Patients

The study included 299 patients operated for differentiated small carcinomas of the thyroid at our Thyroid Clinic between 1975 and 2001. Near-total or total thyroidectomy

was carried out in 284 patients and lobectomy in 15 patients. Patient age ranged from 13–79 yr, and there was a strong predominance of female patients (Table 2). All patients were coming from geographical areas previously characterized for iodine intake. The large majority was coming from the city of Catania and other areas of Sicily that are iodine sufficient; less than 10% of patients were coming from areas with mild iodine-deficient intake. It is noteworthy that approximately 41% of patients had a family history of thyroid disease, and 6% had a first-degree relative with thyroid cancer. In 12% of patients, thyroid cancer was concomitant with Graves' disease (Table 2).

Tumor features at presentation

At presentation, tumor size was no larger than 1.0 cm in 187 cases and was 1.1–1.5 cm in 112 cases. Baseline histopathological characteristics are shown in subgroups classified either for tumor size or as incidental and nonincidental (Tables 3 and 4). Relapsing/persisting disease occurred in only 6 of 115 (5.2%) patients with an incidental tumor and no other risk factor and in 7 of 67 (10.4%) patients with a nonincidental tumor and no other risk factor.

Approximately one third of tumors were multifocal, and nearly one fifth of tumors were bilateral. Extrathyroidal invasion was also surprisingly frequent (20.0%), as well as locoregional metastases (30.1%). Nine tumors belonged to the sclerosant variant of PTC; one tumor belonged to the tall cell variant. All the others belonged to the classical PTC variant. Distant metastases were present in only eight cases (2.7%) (Tables 3 and 4). In only one case the presence of a distant metastasis led to the discovery of the tumor.

At multivariate logistic regression analysis, bilateral foci were marginally associated with tumor size larger than 1.0 cm ($P = 0.032$). Extrathyroidal invasion was significantly associated with male sex ($P = 0.01$), vascular invasion ($P = 0.01$), lymph node metastases ($P = 0.0001$), and tumor size larger than 1.0 cm ($P = 0.004$). Lymph node metastases at presentation were associated with patient age above 45 yr ($P < 0.0001$), extrathyroidal invasion ($P = 0.0006$), and nonincidental cancer ($P < 0.0001$), but not tumor size.

TABLE 2. Clinical characteristics of 299 small PTCs

	No. (%)
Patient age (yr)	
Range	13–79
Median	41.9
Gender (F/M)	257/42
% F	86.0%
From iodine-deficient area	25 (8.4)
Familial thyroid disease	122 (40.8)
Familial thyroid cancer	18 (6.0)
Concurrent Graves' disease	36 (12.0)

F, Female; M, male.

Clinical evolution and follow-up

Follow-up ranged from 12.2 to 252.4 months, with a median of 45.2 months. Median time for the first postoperative follow-up was 4.17 months. A total of 10 patients (3.3%) developed distant metastases, eight at presentation and two after 87.2 and 73.0 months from diagnosis, respectively. Metastases occurred in lungs in nine patients and in bone in one patient. All patients with distant metastases were treated with radioiodine [200–900 mCi (7.4–33.3 GBq); mean dose 380 mCi (10.4 GBq)]. At the last follow-up visit, four of these patients were disease-free, four had progressive reduction of

TABLE 3. Histopathological characteristics of 299 small PTCs at presentation, classified in two subgroups according to the tumor size

	All cases	Tumor size		
		≤1.0 cm	1.1–1.5 cm	
No.	299	187	112	*P* value[a]
Multifocal	95 (31.7)	50 (26.7)	45 (40.2)	0.030
Bilateral	55 (18.4)	28 (15.0)	27 (24.1)	0.023
Extrathyroidal	60 (20.0)	26 (13.9)	34 (30.3)	0.000
Vascular invasion	14 (4.7)	8 (4.3)	6 (5.3)	0.456
Lymph node	90 (30.1)	46 (24.6)	44 (39.3)	0.009
Sclerosant variant	9 (3.0)	9 (4.8)	0	0.015
Distant metastases	8 (2.7)	5 (2.7)	3 (2.7)	0.746

Data represent number (%).
[a] ≤1.0 cm *vs.* 1.1–1.5 cm, Fisher's exact test.

TABLE 4. Histopathological characteristics of 299 small PTCs at presentation, classified on the basis of the presence (nonincidental) and the absence (incidental) of clinical/cytopathological signs of cancer before surgery

	All cases	Incidental	Nonincidental	*P* value[a]
No.	299	151	148	
Multifocal	95 (31.7)	37 (24.5)	58 (39.2)	0.009
Bilateral	55 (18.4)	22 (14.6)	33 (22.3)	0.101
Extrathyroidal	54 (20.1)	16 (10.6)	38 (25.7)	0.001
Vascular invasion	14 (4.7)	4 (2.6)	10 (6.7)	0.107
Lymph node	90 (30.1)	24 (15.9)	66 (44.6)	0.000
Sclerosant variant	9 (3.0)	5 (3.3)	4 (2.7)	0.513
Distant metastases	8 (2.7)	1 (0.7)	7 (4.7)	0.060

Data represent number (%).
[a] Incidental *vs.* nonincidental, Fisher's exact test.

serum Tg levels and radioiodine uptake at ^{131}I-WBS, and two had progressive disease. Overall, 77 patients (25.7%) showed evidence of relapsing or persisting disease during the follow-up. Causes of tumor persistence/relapse were locoregional lymph nodes in 30 patients and distant metastases in 10. In 37 patients, elevation of serum Tg after L-T_4 withdrawal was the only indicator of the disease (follow-up ranged from 12.2 to 194.5 months; median, 45.9 months). At the time of the last follow-up visit, 256 patients were disease-free, whereas 43 patients had persisting disease (Table 5). No patient in this cohort died from the disease.

Predictors of distant metastases and of persisting/relapsing disease

At univariate Cox analysis, the development of distant metastases was associated with the presence of lymph node metastases at presentation and with the sclerosant variant of papillary cancer (odd ratios, 4.97 and 9.38, respectively; Table 6). Other variables, such as nonincidental cancer, extrathyroid invasion, and bilateral foci were also associated with a higher risk, but the association did not reach statistical significance (Table 6). Tumor size (≤1.0 *vs.* >1.0 cm) was not a factor ($P = 0.479$). Multivariate analysis confirmed that both lymph node metastases and the sclerosant variant are independent risk factors for distant metastases ($P = 0.014$ and $P = 0.002$, respectively). Odd ratios and 95% confidence intervals are given in Table 6.

At univariate Cox analysis, several patient or tumor characteristics were identified as predictors of persisting/relapsing disease: age above 45 yr, nonincidental cancer, extrathyroidal invasion, lymph node metastases, and bilateral foci. Tumor size did not reach statistical significance (Table 7). Interestingly, patients from an endemic goiter area carried a reduced risk of persisting/relapsing disease (Table 7), although the difference reached statistical significance only in nonincidental cancers ($P = 0.047$, log-rank test).

Patients with a cancer concomitant with Graves' disease had an increased risk of relapsing/persisting lymph nodes at follow-up when corrected for incidental cancer ($P = 0.0123$, log-rank test).

Multivariate analysis indicated that metastatic lymph nodes at thyroidectomy are the most important predictors of relapse/persisting disease (odd ratio, 4.09). Significantly associated with persistent/recurrent disease, although less predictive, were bilateral foci and nonincidental cancer (Table 7).

Outcome of familial small carcinomas

Familial microcarcinomas have been suggested to have an increased aggressiveness (16). Eighteen patients (6.0% of to-

TABLE 5. Outcome of 299 small PTCs

Patient follow-up status	N (%)
Disease free	256 (85.6)
With disease	43 (14.4)
Lymph node	17 (5.7)
Distant and local	2 (0.7)
Distant	4 (1.3)
Elevated Tg	20 (6.7)

TABLE 6. Univariate and multivariate analysis of clinical and histopathological characteristics in patients with a small PTC, using distant metastases as end point

Variable	Hazard ratio	95% Confidence interval	*P* value
Univariate analysis			
Lymph node metastases			
No	1.00		
Yes	4.97	1.28–19.32	0.020
Sclerosant variant			
No	1.00		
Yes	9.38	1.98–44.30	0.005
Extrathyroid invasion			
No	1.00		
Yes	4.53	0.95–21.58	0.058
Nonincidental cancer			
No	1.00		
Yes	4.06	0.86–19.14	0.076
Bilateral foci			
No	1.00		
Yes	2.87	0.81–10.9	0.079
Multivariate analysis			
Lymph node metastases			
No	1.00		
Yes	5.51	1.41–21.49	0.014
Sclerosant variant			
No	1.00		
Yes	11.76	2.43–56.93	0.002

TABLE 7. Univariate and multivariate analysis of clinical and histopathological characteristics in patients with a small PTC, using persisting/relapsing disease as end point

Variable	Hazard ratio	95% Confidence interval	*P* value
Univariate analysis			
Age			
<45 yr	1.00		
≥45 yr	1.73	1.05–2.82	0.028
Nonincidental cancer			
No	1.00		
Yes	2.59	1.60–4.18	0.000
Extrathyroidal invasion			
No	1.00		
Yes	2.60	1.60–4.23	0.000
Lymph node metastases			
No	1.00		
Yes	5.51	3.44–8.83	0.000
Bilateral foci			
No	1.00		
Yes	2.41	1.49–3.89	0.000
Tumor size			
≤1.0 cm	1.00		
>1.0 cm	1.54	0.98–2.42	0.059
Endemic area			
No	1.00		
Yes	0.28	0.07–1.17	0.082
Multivariate analysis			
Lymph node metastases			
No	1.00		
Yes	4.09	2.47–6.77	0.000
Bilateral foci			
No	1.00		
Yes	2.04	1.26–3.32	0.004
Nonincidental cancer			
No	1.00		
Yes	1.66	1.01–2.74	0.041
Extrathyroidal invasion			
No	1.00		
Yes	1.56	0.94–2.60	0.080

tal) in the present series had one or more first-degree relatives with a thyroid cancer and were classified as familial PTCs (Table 2). Twelve of them were incidental and 6 nonincidental. Fifteen were microcarcinomas (≤1.0 cm). Distant metastases occurred in one patient out of 18 (5.5%) in the familial group and in nine of 281 (3.2%) in the nonfamilial group (not significant), respectively. Corresponding values of lymph node metastases were 4 of 18 (22.2%) *vs.* 86 of 281 (30.6%). The proportion of bilateral and extrathyroid cancers was also very similar between the two groups. Persistent/recurrent disease was observed in 4 of 18 (22.2%) *vs.* 73 of 281 (26.0%) patients in the familial and nonfamilial groups, respectively.

TNM staging as cancer relapse predictor: fifth vs. sixth edition TNM

Because the TNM staging has been recently revised, we have classified the present series of small PTCs according to both the new TNM staging (sixth edition) and the previous one (fifth edition). Table 8 compares the two classifications. According to the new TNM, tumors no larger than 2.0 cm are now classified as T1 instead than T2. As a consequence, 13 cancers in the present series would be classified as stage II according to the fifth edition of TNM staging, whereas they are now classified as stage I according to the sixth edition (Table 8). The outcome of these 13 cases was very similar to the 206 classified as stage I with both classifications.

On the other hand, 12 cancers previously classified as stage III are now classified as stage IV according to the new TNM (Table 8). All of them had metastases to cervical lymph nodes, and all relapsed and showed persisting disease at the last follow-up visit. Therefore, the distinction between N1a (pretracheal, paratracheal, and prelaryngeal/Delphian lymph nodes) and N1b (cervical or superior mediastinal lymph nodes) that are differently responsible for the classification (stage III and stage IVA, respectively), seems appropriate according to these data. Five cancers previously classified as stage IV are now classified as stage IVC according to the new TNM. All of them relapsed (Table 8).

Clinical relevance of Tg measurement at first postsurgical evaluation

Tg level at the first postsurgical evaluation, after L-T_4 withdrawal, was very predictive of the outcome (Table 9). Data were available from 292 patients (284 patients who had undergone near-total or total thyroidectomy at first surgery or in the first 8 months after first surgery, and eight who were initially treated with lobectomy and had undergone completion thyroidectomy in the course of follow-up). Of these 292 patients, 269 had negative AbTg antibodies. On the basis of serum Tg levels, these 269 patients could be classified in three groups: 1) 86 patients with Tg below 1.0 ng/ml; 2) 100 patients with Tg 1.0–10.0 ng/ml; and 3) 83 patients with Tg above 10.0 ng/ml. In the first group, only one patient (1.1%) showed cancer relapse (at locoregional lymph nodes) during follow-up and remained disease-free after therapy. In the

TABLE 8. TNM staging, fifth *vs.* sixth edition, in 248[a] small PTCs

	Stage	Fifth edition				Sixth edition			
		T	N	M	No.	T	N	M	No.
Under 45 yr					176				176
	I	Any T	Any N	M0	172	Any T	Any N	M0	172
	II	Any T	Any N	M1	4	Any T	Any N	M1	4
45 yr and older					72				72
	I	T1	N0	M0	34	T1	N0	M0	47
	II	T2	N0	M0	13	T2	N0	M0	—
		T3	N0	M0	—				
	III	T4	N0	M0	6	T3	N0	M0	6
		Any T	N1	M0	14	T1	N1a	M0	1
						T2	N1a	M0	—
						T3	N1a	M0	1
	IV	Any T	Any N	M1	5				
	IVA					T4a	N0	M0	—
						T4a	N1a	M0	—
						T1	N1b	M0	8
						T2	N1b	M0	—
						T3	N1b	M0	3
						T4a	N1b	M0	1
	IVB					T4b	Any N	M0	—
	IVC					Any T	Any N	M1	5

Fifth edition TNM staging: Primary tumor (T)—T1, tumor ≤1 cm, limited to the thyroid; T2, tumor >1 to ≤4 cm, limited to the thyroid; T3, tumor >4 cm, limited to the thyroid; T4, tumor of any size extending beyond the thyroid capsule. Regional lymph nodes (N)—N0, no regional lymph node metastasis; N1, regional lymph node metastasis.

Sixth edition TNM staging: Primary tumor (T)—T1, tumor ≤2 cm; T2, tumor >2 cm to ≤4 cm, limited to the thyroid; T3, tumor >4 cm or of any size with minimal extrathyroid extension; T4a, tumor of any size extending beyond the thyroid capsule to invade sc soft tissues, larynx, trachea, esophagus, or recurrent laryngeal nerve; T4b, tumor invades prevertebral fascia or encases carotid artery or mediastinals vessels. Regional lymph nodes (N)—N0, no regional lymph node metastasis; N1, regional lymph node metastasis.

[a] As mentioned in *Patients and Methods*, lymph nodes were not excised in incidental carcinomas. Patients under 45 yr (n = 176) could be appropriately staged (N state has no impact on staging in patients younger than 45 yr). However, the 51 patients ≥45 yr could not be staged appropriately because Nx. Therefore, only 248 patients were reported in this table.

TABLE 9. Predictive value of serum Tg levels, off L-T_4, at first postsurgical evaluation on the outcome of small PTCs

Tg (ng/ml)	Patients (n)	Mean follow-up (months)	Persisting/relapsing disease			
			Total relapses	Lymph nodes	Distant metastases	Elevated serum Tg
<1.0	86	62.5	1	1	0	0
1.0–10	100	52.8	16	5	1	10
>10.0	83	67.7	57	20	9	28

TABLE 10. Prognostic value of the combination of serum Tg levels, off L-T_4, at first postsurgical evaluation and histopathological risk factors (lymph node metastases, sclerosant variant, bilateral foci, nonincidental cancer, extrathyroidal invasion)

Tg (ng/ml)	Patients (n)	Persisting/relapsing disease			
		None	One factor	Two factors	Three or more factors
<1.0	86	0/28 (–)	1/30 (3.3%)	0/23 (–)	0/5 (–)
≥1.0	183	10/57 (17.5%)	8/44 (18.2%)	27/49 (55.1%)	28/33 (84.8%)

second group, 16 (16.0%) patients presented a relapse (10 of these patients remained disease-free after treatment). In the third group, 57 patients (68.7%) showed evidence of relapse (19 of them remained disease-free after therapy).

AbTg were positive in 23 patients. Three of them had serum Tg levels above 10 ng/ml after L-T_4 withdrawal, and all of them had a relapse (two with lymph node metastases and one with persistent elevated Tg levels). None of the remaining 20 patients, having Tg levels below 1.0 ng/ml, had evidence of relapse at neck sonography or at ^{131}I-WBS.

We then evaluated whether a combination of histopathological risk factors and serum Tg measurement at first postsurgical evaluation could provide a better predictive index (Table 10). Twenty-eight patients had a Tg below 1.0 ng/ml and no risk factor at presentation; none of them relapsed. In 58 patients with Tg below 1.0 ng/ml and one or more risk factors, only one relapse occurred (Table 10). Patients with Tg of at least 1.0 ng/ml had a relapse rate ranging from 18.2 to 84.8%. In these patients, the highest relapse rate was associated with the presence of two or more risk factors at tumor presentation (Table 10).

These data suggest that in most cases clinical relapse of small thyroid cancer is related to distant or local cancer spreading, already present at the time of surgical treatment, and that the Tg measurement is a sensitive marker of this condition and a good predictor of outcome.

We evaluated whether residue ablation improved the accuracy of serum Tg as a predictor of relapse. Forty-three patients had a postoperative residue with a radioiodine uptake of at least 3% and were, therefore, ablated with 30 mCi radioiodine. In these 43 patients, median serum Tg decreased from 12.0 to 2.5 ng/ml after ablation of postsurgical thyroid residue. Patients with a serum Tg below 1.0 ng/ml increased from 86 to 119 ng/ml (Table 11). The negative and positive predictive values of serum Tg were 98.8 and 39.9%, respectively, before residue ablation and increased to 99.2 and 48.7%, respectively, after residue ablation.

TABLE 11. Predictive accuracy of serum Tg in 269 patients with a small PTC before and after residue ablation

Tg (ng/ml)	Before residue ablation	After residue ablation
<1.0	1/86 (1.2)	1/119 (0.8)
1.1–10.0	16/100 (16.0)	16/86 (18.6)
≥10.0	57/83 (68.7)	57/64 (89.1)

Data represent relapses/patients (%). Radioiodine ablation (30 mCi) was performed in 43 patients. Predictive value of serum Tg < 1.0 ng/ml: negative predictive value = 98.8% *vs.* 99.2%, before and after ablation, respectively; positive predictive value = 39.9% *vs.* 48.7%, before and after ablation, respectively.

Discussion

In this study, we evaluated the characteristics and the outcome of a large series of small PTCs (up to 1.5 cm in diameter). The great majority of our patients (97.7%) were treated by near-total thyroidectomy; this allowed us to identify multifocal or bilateral cancer foci with high accuracy and to maximize sensitivity of ^{131}I-WBS and serum Tg measurement to detect persisting/relapsing disease. This is an important point because multifocal thyroid cancers have a relapse rate higher than unifocal cancers (2, 12), a characteristic that is true also for microcarcinomas (8.6 *vs.* 1.2%, respectively) (9). We found that approximately 20% of small (≤1.5 cm) PTCs had extrathyroid invasion and/or bilateral foci, which might have been overlooked in most previous studies where microcarcinoma patients were treated with lobectomy or with nonuniform surgical approaches.

Our study confirms that small PTCs have a favorable outcome in most cases. The disease, however, may present with signs of aggressiveness including multifocality (~30%), lymph node metastases (~30%), vascular invasion (4.7%), and even distant metastases (2.7%). Moreover, 77 of 299 (25.7%) patients showed evidence of persisting/relapsing disease during follow-up. Increased serum Tg off L-T_4 was the only sign of disease in 37 of them.

Cause-specific patient death must be considered exceptional when PTCs are smaller than 1.5 cm because none of the 299 patients in our series died of the disease. However, 43 (14.4%) patients still had persisting/relapsing disease at the last follow-up visit. This proportion is higher than values reported by other authors (7–11), and we cannot exclude that, with a longer follow-up, some of these 43 patients may suffer an unfavorable outcome.

Different potential predictors of cancer behavior were investigated, first of all those for distant metastases, the most serious complication. At multivariate analysis, only two cancer characteristics were predictive of the development of distant metastases: the presence of initial lymph node metastases and the sclerosant variant of papillary cancer. Other

authors have previously recognized the adverse prognostic value of lymph node involvement at microcarcinoma presentation. Hay *et al.* (7) analyzed 535 microcarcinomas and found that local relapse was related to the presence of metastatic lymph nodes and to the extension of initial surgery. Baudin *et al.* (9) observed that the most effective predictor of local relapse is the presence of multiple foci, which was correlated with the presence of metastatic lymph nodes at presentation. Our work extends the negative prognostic significance of lymph node involvement at presentation to the development of distant metastases in PTCs up to 1.5 cm.

The association between sclerosant variant and distant metastases in small PTCs, to our knowledge, has never been reported before.

At multivariate analysis, lymph node metastases at presentation were the strongest predictors of persisting/relapsing disease (odd ratio, 4.49) when considering all disease events. Nonincidental cancer and presence of bilateral foci were also predictors (odd ratios, 1.73 and 2.03, respectively).

One major issue with thyroid microcarcinomas is the threshold value of tumor diameter and whether slightly larger tumors (*i.e.* 1.1–1.5 cm in diameter) can be assimilated to microcarcinomas in terms of outcome. When we subdivided small PTCs into three groups according to their size (diameter, <0.5, 0.6–1.0, and 1.1–1.5 cm; Table 3), we observed a progressively increasing frequency of signs of tumor aggressiveness (multifocality, bilaterality, extrathyroidal invasion, and lymph node involvement) with increasing tumor size at presentation. This is particularly evident for tumors larger than 1.0 cm with respect to tumors no larger than 1.0 cm in diameter. Only vascular invasion and distant metastases at presentation were not more frequent in larger tumors, probably because they depend on tumor biology more than on tumor size.

Tumor size, however, was not a predictor of persistent/recurrent disease at both univariate and multivariate analysis. The contrast between these observations may be explained by the fact that these tumors, both the smaller ones and the slightly larger ones, have a very indolent and slow progression. Therefore, differences in terms of outcome can be seen only after a much longer period of time.

At present, however, data from the present study indicate that the new TNM staging (sixth edition) (13) seems to perform better that the previous TNM (14), at least as far as small differentiated thyroid carcinomas (DTCs) are concerned. According to the new TNM, tumors no larger than 2.0 cm are now classified as T1 and no more as T2. This classification is in agreement with our finding that size larger than 1.0 cm is not a predictor of unfavorable outcome. According to the new TNM staging, 13 cancers previously classified stage II could now be classified as stage I. The outcome of these 13 cases was not different from that of other stage I cancers. Conversely, the new TNM staging allows distinguishing tumors with cervical or superior mediastinal lymph nodes (N1b, stage IVA) from tumors with pretracheal, paratracheal, and prelaryngeal/Delphian lymph nodes (N1a, stage III) that are all classified as stage II according to the fifth edition of TNM staging. Twelve N1b cancers occurred in our series, and follow-up of these cancers showed a high relapse rate.

Two additional prognostic factors should be taken into account: concomitant Graves' disease and endemic goiter area. The former was positively associated with relapse, whereas the latter was negatively associated with relapse. In both cases, the effect was observed only in the subgroup of nonincidental carcinomas. These findings confirm our previous reports suggesting that Graves' disease negatively affects the outcome of clinical DTCs (19, 20). The negative relation between cancer relapse and endemic goiter area has never been previously reported and is, at present, unexplained.

One important observation from our study is that, when considering persistence/relapsing disease, strong prognostic information comes from serum Tg levels at the first postsurgical evaluation after L-T_4 withdrawal. Patients considered disease-free at that time, because of having a Tg serum level below 1.0 ng/ml, had approximately 1% probability to develop a local recurrence, and, most important, none of them developed distant metastases. Our diagnostic protocol included measurement of Tg serum levels after L-T_4 withdrawal, ^{131}I-WBS, and neck sonography. However, all patients that were not cured by surgery could be identified by the combination of serum Tg measurement plus neck sonography. ^{131}I-WBS did not add further information. In these patients, therefore, follow-up can be simplified as already suggested by others for low-risk DTCs (21). Remarkably, in patients with serum Tg of at least 1.0 ng/ml at first postsurgical evaluation, the probability of tumor relapse can be accurately predicted by considering the presence or the absence of a variety of histopathological risk factors (metastatic lymph nodes, sclerosant variant, bilateral foci, nonincidental cancer, and extrathyroid invasion).

Furthermore, thyroid residue ablation increased the accuracy of serum Tg as a predictor of relapsing/persisting disease.

Finally, we could not confirm previous findings of an increased aggressiveness of familial microcarcinomas (16). In our series, 18 patients had a family history of thyroid cancer, as documented by at least one first-degree relative affected. These 18 patients did not differ from the remaining patients by histopathological characteristics associated with aggressiveness. The outcome of these 18 carcinomas was also unremarkable. The reason for the discrepancy between these observations and a previous report (16) is unclear. Familial thyroid cancer is a heterogeneous disorder that is associated with known but also unknown genetic syndromes (22). Familial small carcinomas originated from different genetic defects may, therefore, have different aggressiveness and clinical outcome. Because the genetic defect of familial cancer was not investigated, it can be hypothesized that the two studies include a different proportion of patients with various genetic syndromes. Further studies with genetic characterization are therefore required to address this issue.

We conclude that, although distant metastases and cause-specific deaths are infrequent in small PTCs, persisting/relapsing disease occurs in 25.7% of cases. Although larger cancers (diameter, 1.1–1.5 cm) in this series had a higher prevalence of signs of aggressiveness at presentation, we found no significant difference in the outcome in respect to microcarcinomas (diameter, <1.0 cm) at multivariate analysis. These data support the appropriateness of the new TNM

staging. In this regard, the difference between incidental and nonincidental was more important than tumor size. The strongest predictors of distant cancer relapse were lymph node metastases at presentation and the sclerosant variant. The presence of lymph node metastases at presentation was also the strongest predictor of total adverse events. In contrast, patient age, male sex, and family history for thyroid cancer had no prognostic value. Apart from tumor characteristics, serum Tg measurement at the first postsurgical evaluation was the strongest prognostic indicator.

This study does not address the issue of whether or not near-total thyroidectomy or lobectomy should be used to treat small PTCs. However, it indicates that a high proportion of these small cancers carry one or more risk factors at presentation, including bilateral foci. It also indicates that the measurement of serum Tg at first postsurgical examination off L-T_4, combined with the evaluation of histopathological risk factors, provides a powerful predictive index of cancer relapse. Patients with Tg below 1.0 ng/ml can be considered cured and need only minimal follow-up, whereas in patients with Tg of at least 1.0 ng/ml, the presence of histopathological risk factors can accurately predict the risk of relapse. These findings suggest considering near-total thyroidectomy as first-choice surgical treatment.

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