Outcome predictors and impact of central node dissection and radiometabolic treatments in papillary thyroid cancers $\leq$2 cm

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Abstract

The incidence of papillary thyroid cancer (PTC) is rapidly growing, the recorded increase being mainly related to tumors $\leq$2 cm. The re-classification of tumors $>$1 and $\leq$2 cm limited to the thyroid from the T2 to the T1 category triggered some concerns about their best management. In order to identify possible predictors of disease outcome, several clinico-pathological features were analyzed by uni- and multivariate analyses in a retrospective consecutive series of 251 PTCs $\leq$2 cm. Moreover, since 37% of cases were submitted to prophylactic central compartment node dissection (CLND, VI–VII levels) and radioiodine ablation was performed only when the tumor had an extrathyroidal extension, the impact of these therapeutic tools on the final outcome was evaluated. Among all outcome predictors analyzed, only lymph node metastases and extracapsular invasion were strongly associated with persistence/recurrence. It is worth noting that neither age nor tumor size was a significant indicator of the outcome. Interestingly, as far as the therapeutic interventions are concerned, CLND was strongly associated with remission, whereas radioiodine ablation did not influence the outcome. In conclusion, present results confirm the prognostic influence of node metastases and extra-thyroidal invasion, indicating the need for aggressive treatment in tumors extending beyond the capsule. On the contrary, all pT1N0 tumors, regardless of the diameter, the number of intrathyroidal foci, and the age can be effectively treated only by surgery. The major impact of prophylactic CLND on prognosis suggests to routinely associate it to total thyroidectomy in cases with a preoperative diagnosis of malignancy.

Endocrine-Related Cancer (2009) **16** 201–210

Introduction

The incidence of papillary thyroid cancer (PTC) is rapidly growing (Hodgson *et al*. 2004), only partially due to an actual increase in disease occurrence and mainly to the improvement of diagnostic methods, such as ultrasonographic evaluation and fine-needle aspiration cytology. Indeed, the recorded increase is mainly related to tumors $\leq$2 cm and in particular to those measuring 1 cm or smaller, defined as micro-carcinomas (PTM; Davies & Welch 2006). PTMs account for up to 30% of all differentiated thyroid cancers (Bramley & Harrison 1996) and are frequently diagnosed during surgery for benign thyroid diseases, being classified as 'incidental PTM' (Baudin *et al*. 1998, Sugitani & Fujimoto 1999). Several studies demonstrated that PTMs have a more favorable prognosis than larger tumors (Hay *et al*. 1992, Noguchi *et al*. 1996, Baudin *et al*. 1998, Sugitani & Fujimoto 1999) and the high prevalence of these tumors in autoptic series (5–35%; Sampson *et al*. 1974,

DOI: 10.1677/ERC-08-0119

Online version via http://www.endocrinology-journals.org

Harach *et al*. 1985) favored the idea that PTMs can become clinically evident in a minority of cases. Nevertheless, locoregional recurrences (0–11% of patients with PTM; Grant *et al*. 1988, Hay *et al*. 1992) and, in rare cases, distant metastases, have been reported (Strate *et al*. 1984, Mazzaferri & Jhiang 1994), indicating the need to distinguish between low- and high-risk tumors even in the microcarcinoma category. Indeed, PTMs limited to the thyroid gland are considered low-risk tumors and can be effectively treated with total thyroidectomy alone, while PTMs with extrathyroidal extension deserve a more aggressive treatment (Pacini *et al*. 2006). However, while a consensus has been reached for small tumors below 1 cm, some concerns exist about the treatment of tumors of the size between 1 and 2 cm limited to the thyroid, previously staged as pT2 and recently reclassified as pT1 (AJCC, 6th edition). Another matter of discussion regarding PTC management is the opportunity to perform the prophylactic central neck dissection (CLND), as recently proposed by some authors (Sywak *et al*. 2006, White *et al*. 2007) based on the fact that thyroid tumor cells are spread through the lymphatic system in a sequential fashion, the first involved being the central compartment. Indeed, cervical lymph node metastases at diagnosis are quite common in PTC (20–50% of patients) (Cooper *et al*. 2006), and micrometastases are even more frequent, found in nearly 90% of cases (Arturi *et al*. 1997).

Some studies evaluated the clinical features and prognostic factors of small tumors. Among PTMs, tumor size was found to be associated with a more aggressive disease, but not to affect the final outcome (Chow *et al*. 2003, Roti *et al*. 2006). Accordingly, the risk to develop extrathyroidal extension and locoregional metastases increases with size starting from a diameter of 5 mm, while the risk for distant metastatization begins to increase in tumors >20 mm (Machens *et al*. 2005). As far as tumors below 2 cm are concerned, the retrospective analysis of patients with PTC smaller than 1.5 cm showed that tumor size was not a predictor of persistent/recurrent disease (Pellegriti *et al*. 2004). More recently, it has been reported in a large series that tumors of the size 11–20 mm have more aggressive features than those ≤ 1 cm (Rossi *et al*. 2008). However, in that descriptive study, outcome predictors were not assessed.

The aim of the present study was to retrospectively evaluate clinical features of small PTCs, dividing them into two groups according to the diameter ≤ 1 and $>1 \leq 2$ cm. Moreover, in order to define the better therapeutic approach and follow-up for these tumors, outcome predictors of persisting or relapsing disease were analyzed by appropriate statistical analyses. Finally, the impact of both radioiodine ablation and prophylactic CLND (VI–VII levels) on the final outcome was studied.

Materials and methods

Patients and methods

Among 2166 consecutive patients submitted to total thyroidectomy at the Endocrine Surgery Unit from 1995 to 2006, 438 patients (93 M, 345 F, mean age $\pm$ S.D. 45 ± 15.4) had a diagnosis of PTC. For the purpose of the present study, 251 sequential patients (57.3%) with tumors ≤ 2 cm were considered. All the patients received the same treatment. In particular, they were all operated by the same surgeon, were treated with radioiodine at the same center and followed up by the same endocrine equipe. All the patients underwent total thyroidectomy, while prophylactic central lymph node dissection (CLND) was performed, starting from September 1998, in all cases ($n=92$) with a previous diagnosis of malignancy. In particular, CLND consisted in the removal of all soft tissue-containing lymph nodes from the hyoid bone superiorly to the innominate vessels inferiorly, the lateral borders being the common carotid arteries. This compartment (VI–VII levels) comprises the precricoid (Delphian), pretracheal, and paratracheal nodes, including nodes along the recurrent laryngeal nerves. Paratracheal dissection was ipsilateral in 82 patients, and bilateral in those cases ($n=10$) in whom the tumor had an isthmic localization or bilateral foci were known preoperatively. Patients with a preoperative ultrasonographic or clinical suspicion of laterocervical lymph node metastases were submitted to ipsilateral ($n=32$) or bilateral ($n=3$) laterocervical dissection. Tumors were classified according to the thyroid malignancy World Health Organization classification (Hedinger 1988) and staged according to the sixth edition of TNM staging (AJCC 2002). A direct laryngoscopy was performed preoperatively in all the patients, and post-operatively in patients presenting with any phonation disorder 5 days after surgery. As far as radioiodine ablation is concerned, among all cases operated before January 2004, 61.3% (103/168) was treated with 50–100 mCi of ^{131}I. The non-treated patients all had tumors ≤ 1 cm limited to the thyroid. Starting from January 2004, following the publication of the sixth TNM edition, all pT1N0 and pT1mN0 patients were treated only by surgery. Thus, the percentage of radioiodine ablation decreased to 44.6% (37/83 patients).

All the patients were followed up according to the European guidelines for thyroid cancer (Pacini *et al.* 2006). In particular, thyroid residue ablation was assessed by recombinant human TSH test (Thyrogen, Genzyme Corp., Cambridge, MA, USA) 10–12 months after radioiodine therapy. The patients were maintained on TSH suppressive L-T4 treatment unless disease remission was documented and were then shifted to lower doses, aimed to reach TSH levels between 0.5 and 1.0 mU/l. Patients in remission were yearly monitored by neck ultrasound and Tg/Ab-Tg evaluation, during L-T4 treatment. TgAb were measured by Liaison Kit (Byk-Sangtec Diagnostica, Dietzenbach, Germany), while Tg levels were measured by means of a highly sensitive (minimal detectable concentration = 0.18 μg/l) immunometric assay (Delfia hTg; Wallac, Turku, Finland). Patients with persistent or relapsing disease were treated by surgery and/or radioiodine treatment.

Patients with tumors ≤ 2 cm were divided into two groups according to tumor size: group A = tumor ≤ 1 cm (156 patients, 120F/36M), and group B = tumor $> 1 \leq 2$ cm (95 patients, 78F/17M).

Criteria for the identification of disease status

Criteria used to identify remission or persistent/recurrent disease were drawn on the bases of the European and American guidelines for the management of differentiated thyroid cancer (Cooper *et al.* 2006, Pacini *et al.* 2006). Moreover, cut-off values for both basal (during thyroid hormone therapy) and rhTSH-stimulated Tg levels have also been established based on the experience derived by the use of the same Tg assay on a long-term basis.

Patients with differentiated thyroid cancer treated with total thyroidectomy ± lymphoadenectomy and radioiodine ablation

Remission: undetectable (< 0.2 μg/l) basal and stimulated Tg levels at the rhTSH test performed 10–12 months after initial treatments with negative anti-thyroglobulin autoantibodies and neck ultrasound.
Persistent or recurrent disease: presence of at least one of the following: a) basal Tg levels > 2 μg/l on consecutive determinations; b) Tg response to rhTSH higher than 2 ng/ml or higher than 1 ng/ml in 2 rhTSH test performed with 10–12 months interval; c) presence of neck or body masses with a cytology and/or Tg washout levels positive for metastasis of thyroid cancer; d) presence of radioiodine uptake; and e) persistence of anti-Tg antibodies for more than 4 years with a trend to increase or sudden rise of autoantibodies.

Patients with differentiated thyroid cancer treated with total thyroidectomy ± lymphoadenectomy

Remission: a) undetectable basal Tg levels or basal Tg levels comprised between 0.2 and 1 ng/ml but with a reduction trend between Tg levels after surgery and at 10–12 months control, in association with negative anti-thyroglobulin autoantibodies and neck ultrasound; and b) basal Tg levels ≤ 1 μg/l not responsive or with a response to rhTSH ≤ 2 μg/l without significant variations in two determinations performed with 10–12 months interval with negative neck ultrasound.
Persistent or recurrent disease: presence of at least one of the following: a) basal Tg levels > 2 μg/l on consecutive determinations; b) Tg response to rhTSH higher than 2 ng/ml or with a trend to increase in 2 rhTSH test performed with 10–12 months interval; c) presence of neck or body masses with a cytology and/or Tg washout levels positive for metastasis of thyroid cancer; d) presence of radioiodine uptake; and e) persistence of anti-Tg antibodies for more than 4 years with a trend to increase or sudden rise of autoantibodies.

In patients with a poorly differentiated histotype, other procedures such as CT scan, MRI, and FDG-PET were also used to identify persistent or recurrent disease.

Statistical analysis

The following clinical, histopathological, and therapeutic variables were analyzed and compared in the two groups: age at diagnosis, gender, incidentality, mode of diagnosis, pTNM, multifocality, lymph nodal metastases at histology, stage, central node dissection, laterocervical dissection, radioiodine ablation, radioiodine uptake, Tg levels at the last follow-up visit, and outcome. Relations between discrete variables were evaluated by means of χ^2 test or *t*-test, as appropriate. The following outcome predictors were evaluated by uni- and multivariate analysis: gender, age, multicentricity, lymph node metastases and extrathyroidal extension at histology, central neck dissection and radioiodine ablation. Univariate analyses between covariates and risk of recurrence were performed using χ^2 test. Multivariate analysis of prognostic variables was carried out by stepwise logistic regression. Statistical significance was defined as $P < 0.05$. All statistical analyses were performed using

SPSS 8.0 statistical package for Windows (SPSS Inc., Chicago, IL, USA).

Results

Clinical, pathological, and therapeutic features

Clinical and pathological features of groups A and B are reported in Table 1. The mean age at diagnosis was of 46.5±23.3 years (range 12–78) and the female/male ratio was 4:1, without significant differences between groups A and B. A significantly higher number of incidental tumors, i.e. diagnosed following thyroidectomy for benign disease, was found in group A compared with group B (52.6 vs 24.2%, $P<0.0001$), while the cytological diagnosis on the nodule was more frequent in group B (41 vs 72.6%, $P<0.0001$). Interestingly, in about 5% of cases the diagnosis was done on a metastatic lymph node. Among the 251 patients with tumor ≤2 cm, 185 (73.7%) have been classified as pT1. A significantly higher rate of pT1 cases was found in group A (85.9 vs 53.7%, $P<0.0001$), while most pT3 cases were found in group B (41 vs 12.2%, $P<0.0001$). No significant differences were noted in multifocality (41.7% in group A and 47.4% in group B), whereas lymph node metastases found at histology were more frequent in group B (38.9 vs 23%, $P=0.009$). Among patients submitted to laterocervical dissection, due to the preoperative suspicion of metastatic disease, 77.7% (group A) and 74% (group B) had at least one

Table 1 Clinical, histopathological, and therapeutic data of patients according to tumor size

		Tumor size		
	All cases	**≤1 cm**	**>1≤2 cm**	***P***
Patients (*n*)	251	156	95	
Age (mean±S.D.)	46.5±23.3	47.5±13.7	44.7±16.2	NS
Gender F/M	198/53	120/36	78/17	NS
Incidentality	105	82 (52.6%)	23 (24.2%)	<0.0001
Diagnosis of malignancy				
Cytology on nodule	133	64 (41%)	69 (72.6%)	<0.0001
Cytology on lymph node	13	10 (6.4%)	3 (3.2%)	NS
Tx for goiter	74	72 (46.2%)	23 (24.2%)	0.0005
Tx for Graves'	8	10 (6.4%)	0	0.01
PTNM				
pT1	185	134 (85.9%)	51 (53.7%)	<0.0001
pT3	58	19 (12.2%)	39 (41%)	<0.0001
pT4	8	3 (1.9%)	5 (52.6%)	NS
Multifocality	110	65 (41.7%)	45 (47.4%)	NS
Lymph node metastases[a] (pN1)	73	36 (23%)	37 (38.9%)	0.009
Stage <45 years				
Stage I	108	62 (39.7%)	46 (48.4%)	NS
Stage II	0	0	0	–
Stage ≥45 years				
Stage I	93	72 (46.2%)	21 (22.1%)	0.0001
Stage II	0	0	0	–
Stage III	38	17 (10.9%)	21 (22.1%)	NS
Stage IVA	12	5 (3.2%)	7 (7.4%)	NS
Stage IVB	0	0	0	–
Central node dissection	92	41 (26.3%)	51 (53.7%)	0.01
Laterocervical dissection	35	20 (12.8%)	15 (15.8%)	NS
^{131}I residue ablation	140	67 (42.9%)	73 (76.8%)	<0.0001
^{131}I uptake levels (mean±S.D.)	1.37±0.81	1.56±0.71	1.16±0.86	NS
^{131}I mean dose (mCi)	104.7	95.9	133.8	NS
Follow-up (months)	69.2±57.6	70±44.2	66±44.2	NS
Tg levels (mean±S.D.)[b]	0.32±0.72	0.31±0.58	0.33±0.93	NS
Remission (any pT)	224	144 (92.3%)	80 (84.2%)	NS
Remission (only pT1)	175	128 (82%)	47 (49.5%)	NS

Data on follow-up and outcome are also reported. Tx, total thyroidectomy; NS: not significant.
[a]Lymph node metastases at histology.
[b]Tg (thyroglobulin) levels at the last follow-up visit during L-T4 therapy; Tg levels (250 μg/l) of the only patient (group B) with distant metastases have been excluded.

metastatic laterocervical lymph node at histology. On the other hand, 33.3% (group A) and 51.5% (group B) of patients submitted to prophylactic CLND, had at histology at least one metastasis in pretracheal or paratracheal lymph nodes. Coexisting central neck compartment and laterocervical nodal metastases were found in 22 out of 29 cases (75.8%).

According to the staging system that consider TNM and age, no differences in stages were found between the two groups in patients below 45 years, while stage I was significantly more represented in group A when considering patients older than 45 years. As expected, due to the high frequency of incidentality in PTM, CLND was more frequently performed in patients of group B, for the majority of them a preoperative diagnosis being available. Patients of group B were more frequently ablated with radioiodine ($P<0.0001$) and were given a slightly higher total dose of radioiodine, considering ablating and therapeutic doses ($P=$NS).

The mean follow-up was of 69.2 months (median: 60 months, range 3–144), not different from groups A and B. Tg levels at the last follow-up visit during L-thyroxine treatment were 0.31 ± 0.58 in group A and 0.33 ± 0.93 in group B ($P=$NS). No differences in the outcome were observed, neither considering all tumors (any pT) nor examining only pT1 tumors. Persistent or recurrent disease was recorded in 27 patients (10.7%). In particular, 22 of them have not been submitted to CLND and had the following diagnosis of recurrence/persistence: Tg levels indicating persistence without evidence of disease (72.7%); Tg levels indicating persistence and ipsilateral paratracheal metastatic nodes (20.6%); Tg levels indicating persistence and bilateral paratracheal metastatic nodes (5%) and Tg levels indicating persistence and ipsilateral laterocervical metastatic nodes (1.7%). The remaining recurrent/persistent patients have been submitted to ipsilateral central dissection in three cases and to bilateral central dissection in two cases; they all displayed Tg levels indicating persistence, associated with clinical evidence of laterocervical metastatic nodes in one case and to distant metastases to lungs, liver, and bone, already present at diagnosis, in another patient.

Thus, persistence/recurrence was diagnosed in 22 out of 159 (37.3%) patients not having CLND, in 3 out of 82 (3.6%) cases treated with ipsilateral CLND and in 2 out of 10 (20%) patients submitted to bilateral dissection.

The rate of complications did not increase in the group of patients who underwent CLND (Fig. 1). In particular, a transient hypoparathyroidism was recorded in 7.2% of patients submitted to total thyroidectomy alone and in 8.8% of cases treated with total thyroidectomy and CLND, while a permanent hypoparathyroidism was found in 3.6 and 1.5% of patients. A temporary laryngeal nerve paralysis was observed in 3.1% of patients treated by thyroidectomy alone and in 2.7% of cases with CLND associated,

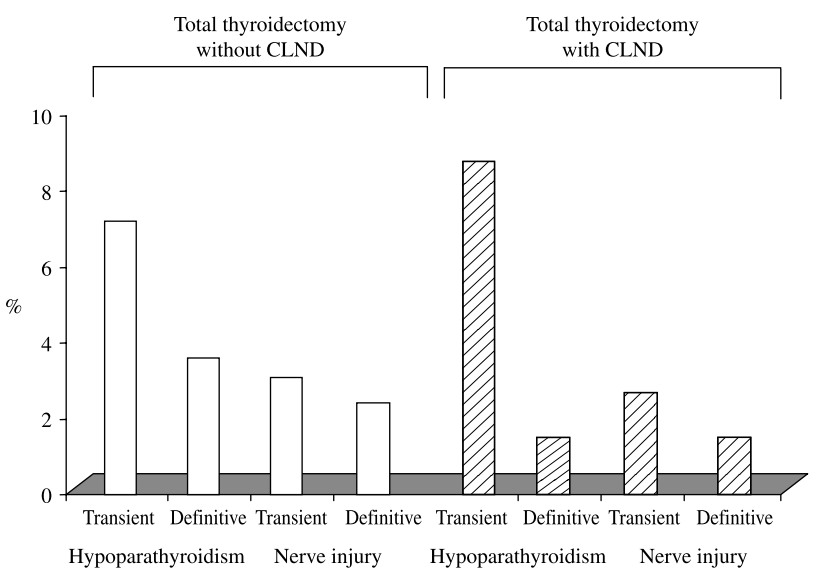

Figure 1 Rate of temporary and persistent surgical complications (hypoparathyroidism and recurrent laryngeal nerve injury). No statistically significant differences were found between patients who underwent total thyroidectomy associated or not with central node dissection.

whereas accidental permanent nerve injury was recorded in 2.4 and 1.5%. In two patients recurrent laryngeal nerves were removed as a result of carcinoma extension. No other complications were observed, with the exception of a wound infection in one patient.

Prognostic factors associated with persistence/recurrence (outcome predictors)

Univariate and multivariate analyses were carried out to identify clinical, pathological, and therapeutic features associated with persistent/recurrent disease. Patients who underwent laterocervical dissection ($n=35$) had a preoperative diagnosis of lymph nodal metastases and were thus excluded from these analyses. Considering groups A ($n=136$) and B ($n=80$) separately (Tables 2 and 3), univariate and multivariate analyses showed that in both the groups the most important predictors of persistent/relapsing disease were lymph nodal metastases and extrathyroidal invasion at histology. In group B, multicentricity was associated with disease persistence/relapse at uni- and multivariate analyses. CLND was found to be significantly associated with a better outcome both at univariate and multivariate analyses in group B, whereas no significance was found in group A. This discrepancy is likely due to the low number of patients submitted to CLND in group A, in which most tumors were incidentally found. In group A, radioiodine ablation was weakly associated with remission only at univariate analysis, whereas in group B it was not associated with outcome.

Other variables, such as gender and age were not predictors of relapsing/persisting disease neither in group A nor in group B.

Considering the two groups together (Table 4), thus including all tumors ≤ 2 cm, univariate analysis showed that multicentricity, tumor size, lymph node metastases at histology and extrathyroidal invasion were associated with persistent or recurrent disease. The significance of these outcome predictors was confirmed at multivariate analysis only for lymph node metastases at histology ($P<0.0001$) and extrathyroidal invasion ($P=0.001$). As far as the therapeutic interventions are concerned, radioiodine ablation was an indicator of remission only at univariate analysis, whereas CLND was found to be associated with a better outcome at uni- and multivariate analyses.

Discussion

The re-classification of tumors >1 and ≤ 2 cm limited to the thyroid from the pT2 to the pT1 category (AJCC 2002) triggered some questions about their best management. Indeed, indications for treatment and follow-up of PTM are included in both European and American guidelines (Cooper *et al*. 2006, Pacini *et al*. 2006), whereas no consensus exists for tumors with a diameter between 1 and 2 cm. Thus, in the present study, clinico-pathological features of two groups of small PTCs divided according to their diameter (≤ 1 and $>1 \leq 2$ cm), have been reported. Moreover, in order to identify potential predictors of disease outcome in these tumors, several clinical, pathological,

Table 2 Univariate analysis using persisting/relapsing disease as end-point, and multivariate analysis of clinical, histopathological, and therapeutic features of patients with papillary thyroid cancers ≤ 1 cm, excluding those submitted to latero-cervical dissection ($n=136$)

	Univariate analysis			Multivariate analysis		
Variable	**Odds ratio**	**95% CI**	***P* value**	**Odds ratio**	**95% CI**	***P* value**
Gender						
M vs F	1.24	0.23–6.53	0.673	2.51	0.21–29.10	0.459
Age						
<45 vs ≥ 45 years	2.87	0.65–12.57	0.253	0.57	0.057–5.86	0.641
Multicentricity						
No/yes	0.68	0.16–2.86	0.703	0.87	0.09–7.77	0.901
Lymph node metastases[a]						
No/yes	0.01	0.00–0.15	<0.0001	57.78	3.70–809.75	0.004
Extrathyroidal invasion						
No/yes	0.06	0.01–0.29	0.0001	23.81	1.72–329.23	0.018
LND (central compartment)						
No/yes	0.38	0.08–1.72	0.193	0.13	0.00–3.76	0.240
Radioiodine ablation						
No/yes	5.93	1.14–30.64	0.020	1.86	0.19–18.30	0.591

[a]Lymph node metastases in the central compartment at histology. LND, lymph node dissection.

Table 3 Univariate analysis using persisting/relapsing disease as end-point and multivariate analysis of clinical, histopathological, and therapeutic features of patients with papillary thyroid cancers $>1\leq 2$ cm ($n=80$)

	Univariate analysis			Multivariate analysis		
Variable	**Odds ratio**	**95% CI**	***P* value**	**Odds ratio**	**95% CI**	***P* value**
Gender						
M vs F	0.43	0.05–3.67	0.676	1.91	0.11–31.29	0.649
Age						
<45 vs ≥ 45 years	1.85	0.54–6.22	0.375	0.56	0.05–5.33	0.614
Multicentricity						
No/yes	0.05	0.00–0.43	<0.0001	10.50	1.14–96.84	0.038
Lymph node metastases[a]						
No/yes	0.09	0.02–0.39	<0.0001	28.09	2.61–301.69	0.006
Extrathyroidal invasion						
No/yes	0.12	0.02–0.60	0.005	19.15	1.21–303.26	0.036
LND (central compartment)						
No/yes	0.13	0.01–1.09	0.031	0.02	0.00–0.33	0.006
Radioiodine ablation						
No/yes	0.85	0.21–3.44	1.000	0.15	0.01–2.23	0.171

[a]Patients submitted to latero-cervical dissection are not included. LND, lymph node dissection.
[b]Lymph node metastases in the central compartment at histology.

and therapeutic parameters were analyzed by appropriate statistical analyses. The present cohort of patients is homogeneous since all the patients were submitted to total thyroidectomy by the same surgeon and followed up by the same endocrine equipe.

In the present series 41.8% of cases were incidental tumors, in accordance with literature data (Pellegriti *et al*. 2004, Roti *et al*. 2006, Besic *et al*. 2008) and as expected were more frequent in group A. Multifocal lesions were found with a frequency higher (44%) than that in other cohorts (20–40%; Baudin *et al*. 1998, Pellegriti *et al*. 2004, Roti *et al*. 2006, Besic *et al*. 2008, Rossi *et al*. 2008). This could be due to epidemiological reasons, genetic background, or to a more accurate pathological evaluation of samples. In PTCs ≤ 2 cm, the impact of multicentricity on tumor outcome is still debated. Indeed, in some studies it has been significantly correlated with disease relapse

Table 4 Univariate analysis using persisting/relapsing disease as end-point and multivariate analysis of clinical, histopathological, and therapeutic features of all patients with papillary thyroid cancers $>1\leq 2$ cm, excluding those submitted to latero-cervical dissection ($n=216$)

	Univariate analysis			Multivariate analysis		
Variable	**Odds ratio**	**95% CI**	***P* value**	**Odds ratio**	**95% CI**	***P* value**
Gender						
M/F	0.90	0.31–3.09	1.00	1.71	0.34–8.58	0.501
Age						
<45 years/≥ 45 years	2.42	0.96–6.12	0.06	0.43	0.08–2.18	0.309
Multicentricity						
No/yes	4.78	1.68–13.58	0.002	4.56	0.79–26.09	0.088
Tumor size						
$\leq 1/>1\leq 2$	3.01	1.19–7.62	0.01	2.11	0.33–13.55	0.429
Lymph node metastases[a]						
No/yes	0.04	0.01–0.13	<0.0001	30.52	5.62–165.70	<0.0001
Extrathyrodal invasion						
No/yes	0.07	0.02–0.23	<0.0001	33.62	4.42–255.48	0.001
LND (central compartment)						
No/yes	0.14	0.01–1.12	0.033	0.01	0.001–0.16	0.001
Radioiodine ablation						
No/yes	3.53	1.23–9.94	0.014	0.88	0.14–5.58	0.898

[a]Lymph node metastases in the central compartment at histology. LND, lymph node dissection.

(Baudin *et al*. 1998, Chow *et al*. 2003, Pellegriti *et al*. 2004), whereas in other series the association with the outcome has been found to be marginal, indicating that a more aggressive treatment is not required in case of multiple foci (Kato *et al*. 1992, Mazzaferri & Jhiang 1994). In the present series, multicentricity was associated with a worst outcome in tumors of group B, whereas no significance was found at the multivariate analysis performed on all tumors ≤ 2 cm. In PTCs, tumor size has been always considered an important prognostic factor, PTM being generally regarded as indolent and larger tumors being more frequently associated with metastatic spread (Hay *et al*. 1992, Chow *et al*. 2003, Leboulleux *et al*. 2005, Roti *et al*. 2006). Accordingly, the risk of extrathyroidal invasion and lymph node metastatization was found to increase starting from a diameter of 5 mm (Machens *et al*. 2005, Besic *et al*. 2008), while an increased risk of distant metastases was reported for a diameter ≥ 8 mm (Roti *et al*. 2006) or >20 mm (Machens *et al*. 2005), though no significant differences in the outcome were observed. As far as small tumors are concerned, in the retrospective analysis of a large series of patients with PTC smaller than 15 mm, tumor size was not a predictor of persistent/recurrent disease (Pellegriti *et al*. 2004). Differently, another study showed that cancers 11–20 mm had more aggressive features than those ≤ 10 mm, though those data were not evaluated with respect to the outcome (Rossi *et al*. 2008). The present study first shows that primary tumor size is not a predictor of relapse/persistence in tumors ≤ 2 cm. This argues in favor of the validity of the last TNM staging system, which includes all tumors ≤ 2 cm limited to the thyroid in the T1 category. Extrathyroidal invasion and lymph nodal metastases at diagnosis were significantly more represented in group B and were highly correlated with a worst outcome both at uni- and multivariate analyses, in accordance with previous studies (Hay *et al*. 1992, Chow *et al*. 2003, Pellegriti *et al*. 2004, Besic *et al*. 2008).

As far as outcome predictors related to treatment procedures are concerned, the role of post-surgical radioiodine ablation in small PTC is controversial, since either a positive effect (Chow *et al*. 2003) or any impact (Baudin *et al*. 1998, Sawka *et al*. 2004) on the outcome has been reported. In the present series, radioiodine ablation was not associated with the outcome at multivariate analysis. However, it must be highlight that in group B a higher percentage of patients was treated with radioiodine (77 vs 43%). This could represent a bias, and the evaluation of a larger number of cases with tumors $>1 \leq 2$ cm not treated with radioiodine is needed. Nevertheless, though PTM were significantly less treated either by radioiodine ablation or by CLND, the rate of remission was not different between the two groups considering only pT1 or even any pT cases. In the present study, ipsilateral or bilateral laterocervical dissection was performed only in patients with a preoperative clinical or ultrasonographic suspicion of laterocervical lymph node metastases, representing 24% of patients with a non-incidental tumor. Interestingly, in about 5% of cases the diagnosis was done on a metastatic lymph node, with a higher frequency in PTM. These data, consistent with previously reported results (Chow *et al*. 2003), suggest that in some tumors the earlier carcinogenic drive is toward metastatization instead of growth.

Interestingly, prophylactic pretracheal/paratracheal lymph node dissection (CLND, level VI–VII) was highly associated with remission. In particular, 33.3% (group A) and 51.5% (group B) of patients who submitted to this surgical procedure were found to have at histology at least one metastasis in pretracheal or paratracheal lymph nodes. In none of them tumor recurrence was observed, in accordance with a previous report (Besic *et al*. 2008). It is also worth to note that this prophylactic procedure leads to a precise identification of the lymph nodal involvement at disease presentation, leading to a better definition of the follow-up. Finally, if performed by skilled surgeons, CLND is not associated with an increased risk of complications, as demonstrated in the present study and in other series (Ito *et al*. 2007). However, while the management of clinically apparent lymph nodes is generally agreed upon in most centers, controversy exists about the role of prophylactic CLND, though the frequent involvement of the central compartment is well known (Gimm *et al*. 1998, Machens *et al*. 2002, Qubain *et al*. 2002) and reoperation in that region is quite difficult due to the higher risk of recurrent nerve injury (Ito *et al*. 2007, White *et al*. 2007). Nevertheless, the topic remains controversial both due to the evidence that node metastases in PTC can increase local recurrence rates, but do not ultimately affect survival (Hughes *et al*. 1996) and due to the absence of prospective, randomized data studying the impact of CLND on recurrence or disease-specific mortality in PTC. Present data are concordant with previous results obtained in surgical series (Sywak *et al*. 2006, Ito & Miyauchi 2007, White *et al*. 2007) and seem to indicate a major role of prophylactic CLND in PTC outcome. Although this surgical procedure will not likely alter disease-related survival rates, it can be argued that, particularly in low-risk PTC cases for which the likelihood of death from cancer is very low, a prompt

complete remission has a great significance for both the patient and the treating physician.

In conclusion, present results confirm the prognostic influence of node metastases and extrathyroidal extension, indicating the need for an aggressive treatment including total thyroidectomy, lymphadenectomy, and radioiodine ablation in all tumors extending beyond the thyroid capsule (pT3, pT4) and in the presence of locoregional or distant metastases (any-pT with N1 and/or M1), in accordance with European and American guidelines (Cooper *et al*. 2006, Pacini *et al*. 2006). At variance, since in the present series neither tumor size, multicentricity, age, nor radioiodine ablation has been shown to affect outcome, all pT1N0 tumors, regardless of the tumor diameter, the number of intrathyroidal foci and the age, can be effectively treated only by surgery. The major impact of prophylactic CLND on prognosis recommends to routinely associate it to total thyroidectomy in cases with a preoperative diagnosis of malignancy.

Declaration of interest

Authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of the research reported.

Funding

Authors declare that this research did not receive any specific grant from any funding agency in the public, commercial, or not-for-profit sector.

References

American Joint Committee of Cancer 2002 Cancer staging manual. In *AJCC Cancer Staging Handbook*, Eds FL Greene, DL Page, ID Fleming, AG Fritz, CM Baclch, DG Heller & M Morrow, edn 6, New York: Springer-Berlag.

Arturi F, Russo D, Giuffrida D, Ippolito A, Perrotti N, Vigneri R & Filetti S 1997 Early diagnosis by genetic analysis of differentiated thyroid cancer metastases in small lymph nodes. *Journal of Clinical Endocrinology and Metabolism* **82** 1638–1641.

Baudin E, Travagli JP, Ropers J, Mancusi F, Bruno-Bossio G, Caillou B, Cailleux AF, Lumbroso JD, Parmentier C & Schlumberger M 1998 Microcarcinoma of the thyroid gland: the Gustave-Roussy Institute Experience. *Cancer* **83** 553–559.

Besic N, Pilko G, Petric R, Hocevar M & Zgajnar J 2008 Papillary thyroid microcarcinoma: prognostic factors and treatment. *Journal of Surgical Oncology* **97** 221–225.

Bramley MD & Harrison BJ 1996 Papillary microcarcinoma of the thyroid gland. *British Journal of Surgery* **83** 1674–1683.

Chow SM, Law SC, Chan JK, Au SK, Yau S & Lau WH 2003 Papillary microcarcinoma of the thyroid. Prognostic significance of lymph node metastasis and multifocality. *Cancer* **98** 31–40.

Cooper DS, Doherty GM, Haugen BR, Kloos RT, Lee SL, Mandel SJ, Mazzaferri EL, McIver B, Sherman SI, Tuttle RM *et al.* 2006 Management guidelines for patients with thyroid nodules and differentiated thyroid cancer. *Thyroid* **16** 109–142.

Davies L & Welch HG 2006 Increasing incidence of thyroid cancer in the United States, 1973–2002. *Journal of the American Medical Association* **295** 2164–2167.

Gimm O, Rath FW & Dralle H 1998 Pattern of lymph node metastases in papillary thyroid carcinoma. *British Journal of Surgery* **85** 252–254.

Grant CS, Hay ID, Gough IR, Bergstralh EJ, Goellner JR & McConahey WM 1988 Local recurrence in papillary thyroid carcinoma: is extent of surgical resection important? *Surgery* **104** 954–962.

Harach HR, Franssila KO & Wasenius VM 1985 Occult thyroid carcinoma of the thyroid. A 'normal' finding in Finland. A systematic autopsy study. *Cancer* **56** 531–538.

Hay ID, Grant CS, van Heerden JA, Goellner JR, Ebersold JR & Bergstralh EJ 1992 Papillary thyroid microcarcinoma: a study of 535 cases observed in a 50-year period. *Surgery* **112** 1139–1146.

Hedinger C 1988 *Histological Typing of Thyroid Tumors: WHO International Histological Classification of Tumors*. edn 2, Berlin, Heidelberg, New York: Springer-Verlag.

Hodgson NC, Button J & Solorzano CC 2004 Thyroid cancer: is the incidence still increasing? *Annals of Surgical Oncology* **11** 1093–1097.

Hughes CJ, Shaha AR, Shaha JP & Loree TR 1996 Impact of lymph node metastasis in differentiated carcinoma of the thyroid: a matched-pair analysis. *Head & Neck* **18** 127–132.

Ito Y & Miyauchi A 2007 Lateral and mediastinal lymph node dissection in differentiated thyroid carcinoma: indications, benefits and risks. *World Journal of Surgery* **31** 905–915.

Ito Y, Higashiyama T, Takamura Y, Miya A, Kobayashi K, Matsuzuka F, Kuma K & Miyauchi A 2007 Risk factors for recurrence to the lymph node in papillary thyroid carcinoma patients without preoperatively detectable lateral node metastasis: validity of prophylactic modified radical neck dissection. *World Journal of Surgery* **31** 2085–2091.

Kato R, Sasaki J, Kurihara H, Suzuki K, Iida Y & Kawaoi A 1992 Multiple thyroid involvement (intraglandular metastases) in papillary thyroid carcinoma: a clinicopathologic study of 105 consecutive patients. *Cancer* **70** 1585–1590.

Leboulleux S, Rubino C, Baudin E, Caillou B, Hartl DM, Bidart JM, Travagli JP & Schlumberger M 2005 Prognostic factors for persistent or recurrent disease of papillary thyroid carcinoma with neck lymph node metastases and/or tumor extension beyond the thyroid capsule at initial diagnosis. *Journal of Clinical Endocrinology and Metabolism* **90** 5723–5729.

Machens A, Hinze R, Thomusch O & Dralle H 2002 Pattern of nodal metastasis for primary and reoperative thyroid cancer. *World Journal of Surgery* **26** 22–28.

Machens A, Holzhausen HJ & Dralle H 2005 The prognostic value of primary tumor size in papillary and follicular thyroid carcinoma. A comparative analysis. *Cancer* **103** 2269–2273.

Mazzaferri EL & Jhiang SM 1994 Long-term impact of initial surgical and medical therapy on papillary and follicular thyroid cancer. *American Journal of Medicine* **97** 418–428.

Noguchi S, Yamashita H, Murakami N, Nakayama I, Toda M & Kawamoto H 1996 Small carcinomas of the thyroid. A long-term follow-up of 867 patients. *Archives of Surgery* **131** 187–191.

Pacini F, Schlumberger M, Dralle H, Elisei R, Smit JWA, Wiersinga W & the European Thyroid Cancer Taskforce 2006 European consensus for the managmenet of patients with differentiated thyroid carcinoma of the follicular epithelium. *European Journal of Endocrinology* **154** 787–803.

Pellegriti G, Scollo C, Lumera G, Regalbuto C, Vigneri R & Belfiore A 2004 Clinical behavior and outcome of papillary thyroid cancers smaller than 1.5 cm in diameter: study of 299 cases. *Journal of Clinical Endocrinology and Metabolism* **89** 3713–3720.

Qubain SW, Nakano S, Baba M, Takao S & Aikou T 2002 Distribution of lymph node micrometastasis in pN0 well-differentiated thyroid carcinoma. *Surgery* **131** 249–256.

Rossi R, Roti E, Trasforini G, Pansini G, Cavazzini L, Zatelli MC, Pearce EN, Braverman LE & Degli Uberti EC 2008 Differentiated thyroid cancers 11–20 mm in diameter have clinical and histopathologic characteristics suggesting higher aggressiveness than those $\leq$10 mm. *Thyroid* **18** 309–315.

Roti E, Rossi R, Trasforini G, Bertelli F, Ambrosio MR, Busutti L, Pearce EN, Braverman LE & Degli Uberti EC 2006 Clinical and histological characteristics of papillary thyroid microcarcinoma: results of a retrospective study in 243 patients. *Journal of Clinical Endocrinology and Metabolism* **91** 2171–2178.

Sampson RJ, Woolner LB, Bahn RC & Kurland LT 1974 Occult thyroid carcinoma in Olmsted Country, Minnesota: prevalence at autopsy compared with that in Hiroshima and Nagasaki, Japan. *Cancer* **34** 2072–2076.

Sawka AM, Thephamongkhol KT, Brouwers M, Thabane L, Browman G & Gerstein HC 2004 A systematic review and metaanalysis of the effectiveness of radio-active iodine remnant ablation for well-differentited thyroid cancer. *Journal of Clinical Endocrinology and Metabolism* **89** 3668–3676.

Strate SM, Lee EL & Childers JH 1984 Occult papillary carcinoma of the thyroid with distant metastases. *Cancer* **54** 1093–1100.

Sugitani I & Fujimoto Y 1999 Symptomatic versus asymptomatic papillary thyroid microcarcinoma: a retrospective analyses. *Endocrine Journal* **46** 209–216.

Sywak M, Cornford L, Roach P, Stalberg P, Sidhu S & Delbridge L 2006 Routine ipsilateral level VI lymphadenectomy reduces postoperative thyroglobulin levels in papillary thyroid cancer. *Surgery* **140** 1000–1007.

White ML, Gauger PG & Doherty GM 2007 Central lymph node dissection in differentiated thyroid cancer. *World Journal of Surgery* **31** 895–904.