ONCOLOGY

Role of prophylactic central neck dissection in cN0 papillary thyroid cancer

Il ruolo dello svuotamento profilattico del compartimento centrale del collo nel carcinoma papillare tiroideo cN0

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SUMMARY

Prophylactic central neck dissection in papillary thyroid cancer is controversial. In this retrospective cohort study, the aim was to assess possible advantages of prophylactic central neck dissection with total thyroidectomy in cN0 papillary thyroid cancer. A total of 244 consecutive patients with papillary thyroid cancer, without clinical and ultrasound nodal metastases (cN0), were evaluated out of 1373 patients operated for a thyroid disease at the Istituto Europeo di Oncologia, Milan, Italy from 1994 to 2006. Of these 244 patients, 126 (Group A) underwent thyroidectomy with central neck dissection, while 118 (Group B) underwent thyroidectomy alone. Demographic, clinical and pathological features were analysed. Overall recurrence rate was 6.3% (8/126) in Group A and 7.7% (9/118) in Group B, with a mean follow-up of 47 (Group A) and 64 (Group B) months. In Group A patients, 47% were pN1a and all patients with recurrence had nodal involvement ($p = 0.002$). Survival rate did not differ in the two groups. Nine patients were lost to follow-up. Group A patients were older and their tumours were larger in size; according to the pT distribution, a higher extra-capsular invasion rate was observed. The two groups were equivalent as far as concerns histological high risk variants and multifocality. Nodal metastases correlated with stage: pT1-2 vs. pT3-T4a, $p = 0.0036$. A lower risk of nodal metastases was related to thyroiditis ($p = 0.0034$). In conclusion, central neck metastases were predictive of recurrence without influencing prognosis. From data obtained, possible greatest efficacy of central neck dissection in pT3-4 papillary thyroid cancer without thyroiditis is suggested.

KEY WORDS: Thyroid • Papillary thyroid cancer • Nodal metastases • Central neck dissection

RIASSUNTO

Il ruolo della linfoadenectomia del compartimento centrale del collo nel trattamento del carcinoma papillare della tiroide è controverso. Obiettivo di questo nostro studio retrospettivo è stato quello di valutare i possibili vantaggi della linfoadenectomia del compartimento centrale associata a tiroidectomia totale in caso di carcinoma papillare della tiroide cN0. Abbiamo analizzato 244 pazienti operati consecutivamente per carcinoma papillare della tiroide senza metastasi linfonodali alla valutazione clinica ed ecografica (cN0) fra i 1373 pazienti operati per patologia tiroidea presso l'Istituto Europeo di Oncologia, Milano, Italia dal 1994 al 2006. 126 pazienti (gruppo A) sono stati sottoposti a tiroidectomia con linfoadenectomia del compartimento centrale, 118 (gruppo B) alla sola tiroidectomia totale. Sono state analizzate le caratteristiche anatomopatologiche, cliniche e demografiche dei due gruppi. Il tasso di recidiva è stato del 6,3% (8/126) nel gruppo A e 7,7% (9/118) nel gruppo B, con una media di follow-up di 47 (gruppo A) e 64 (gruppo B) mesi. Il 47% dei pazienti del gruppo A si sono dimostrati pN1a e tutti i pazienti recidivati in questo gruppo avevano presentato un coinvolgimento linfonodale ($p = 0,002$). La sopravvivenza non differiva nei due gruppi. Nove pazienti sono stati persi al follow-up. Nel gruppo A, i pazienti erano più anziani ed i tumori presentavano dimensioni maggiori; come per la distribuzione di pT, si è osservata in questo gruppo una maggiore percentuale di tumori con invasione extra-capsulare. I due gruppi erano sovrapponibili per quanto concerne le varianti istologiche ad alto rischio e la multifocalità. La presenza di metastasi linfonodali era correlata con lo stadio: pT1-2 vs pT3-T4a, $p = 0,0036$. La presenza di tiroidite è stata messa in relazione ad un basso rischio di metastasi ($p = 0,0034$). In conclusione la presenza di metastasi nel compartimento centrale è predittiva di recidiva senza influenzare la prognosi. Sulla base dei nostri dati suggeriamo una maggiore efficacia della linfoadenectomia del compartimento centrale in caso di carcinoma papillare della tiroide pT3-4 senza tiroidite.

PAROLE CHIAVE: *Tiroide • Carcinoma papillare della tiroide • Metastasi linfonodali • Svuotamento centrale del collo*

Introduction

Papillary Thyroid Carcinoma (PTC) accounts for about 80% of all thyroid malignancies. Ten-year survival is more than 90% [1]. Nodal metastases in PTCs are frequent (20-50%) [2], and up to 15% of patients who undergo total thyroidectomy will develop a nodal recurrence [3]. The prognostic value of nodal metastases is controversial; according to some Authors they are predictive of disease recurrence [4-11]. The central compartment (level VI) is considered to be the first echelon of nodal metastases in thyroid carcinomas, except for those located in the upper part of the gland [12]. The VI level is defined as the anatomical area between hyoid and sternum bones, and the bilateral carotid arteries and includes paralaryngeal, paratracheal and prelaryngeal (or Delphian) nodes [13].

There is a general consensus concerning the treatment of neck metastases (cN1) in PTC: central compartment dissection (CND) in cN1a patients and CND + neck dissection in cN1b [2].

The role of prophylactic CND in patients without clinical metastatic nodes (cN0) is a debated point [14-24]. The advantages are: careful staging of the disease in order to plan the best treatment; less complicated surgical technique than in cases of re-operation for removing metastatic nodes which may have developed following total thyroidectomy, and possible improvement of overall survival [15 16]. The disadvantages are: possible side-effects of dissection and possible overtreatment in cN0 pN0 patients.

The aim of this retrospective study was to evaluate possible advantages of prophylactic CND in cN0 PTCs in terms of overall survival (OS), and disease-free survival (DFS).

Materials and methods

From January 1994 to December 2006, 1373 patients underwent thyroid surgery at the Head and Neck Department of the Istituto Europeo di Oncologia, Milan, Italy (IEO). Of these 578 had thyroid cancer with or without nodal metastases. In this study, 244 consecutive patients with a cN0 PTC that had undergone total thyroidectomy were considered. Diagnostic pre-operative work-up included: clinical examination, fiber-optic laryngoscopy, chest X-ray, neck and thyroid ultrasonography (US), and fine needle aspiration biopsy (FNAB) when the US imaging showed a nodule suspicious for malignancy. The operations were performed by various surgeons including senior surgeons and residents.

IEO guidelines for total thyroidectomy

cT2 – cT4 PTC; multi-nodular goitre with compression signs and symptoms; multi-nodular goitre with hypo- and hyperthyroidism; diffuse thyroiditis with disthyroidism; thyroid nodule(s) with a history of exposure to ionizing radiation or a positive family history; patients with a single thyroid nodule emphatically requesting total thyroidectomy instead of more conservative surgery.

In the study were also included those patients for whom a completion thyroidectomy had been performed because of a diagnosis of high risk PTC after hemi-thyroidectomy. The completion thyroidectomy was performed within one month of the first operation.

Prophylactic CND at IEO

Given the treatment protocols during the time period January 1994-December 2001, all patients who were submitted to thyroidectomy did not receive routine CND. Towards the end of 2001, as a result of an internal audit of all thyroidectomy patients with nodal disease recurrence, and whilst awaiting changes in the TNM classification, it was decided to submit all patients with pre-operative diagnosis of PTC to prophylactic CND. Patients with a single lateral node underwent ipsilateral CND; those with bilateral and isthmic or para-isthmic nodes underwent bilateral CND. No prophylactic neck dissection (levels II-V) was performed. The patients were subdivided as follows:

– Group A: total thyroidectomy and prophylactic CND, in patients with a pre-operative diagnosis of PTC (starting from 2002);
– Group B: total thyroidectomy without CND, in patients with a non-neoplastic pre-operative diagnosis, and those with a pre-operative diagnosis of PTC treated before 2002.

CND was performed according to the surgical technique described by Shah and Patel [25 26].

Post-operative treatment was planned in the weekly multidisciplinary (surgery, endocrinology, nuclear medicine, pathology and radiology) meetings.

Indications for post-operative radio-iodine therapy

pN1, pT3-4, and pT2 patients >45 years, and multifocal tumours.

All patients received suppressive TSH treatment with L-Thyroxine.

Post-operative follow-up

High risk patients (> 45 years of age, pT3-4, pN1, high risk histological variants) were examined every 4 months in the first and second year and every 6 months from the third post-operative year; patients at low risk were evaluated every 6 months. Examination included clinical assessment and video-laryngoscopy, functional assessment (fT3, fT4, TSH, HTG, Ab-anti HTG), neck and thyroid US. Chest X-ray was performed on a yearly basis. After radio-iodine treatment, high risk patients underwent whole body scintigraphy scan in the immediate post-operative period and at 6 months, 1, 2, 3, 5, 7 and 10 years, thereafter. Possible need for other examinations depends on clinical signs and symptoms.

We reviewed each patient chart and recorded risk factors (history of exposure to radiation), patient demographics

(sex, age) and nodule characteristics (cT, histological variant, pT, size (mm), multifocality, concomitant thyroiditis, extra-capsular, and extra-thyroid invasion). The largest nodule size determined the pT classification in multifocal cancers. PTC was classified according to the AJCC/UICC TMN, VI Edition [27].
Number and doses of post-operative radio-iodine treatment were recorded.
Those patients whose last evaluation interval exceeded 6 months were recalled. Clinical reports and examinations of patients evaluated elsewhere were collected and obtained, all other patients were followed at the IEO. Recurrences were recorded according to time elapsing after operation, site (local, nodal or distant metastases), staging, and treatment performed.

Statistical analysis

Baseline characteristics of study patients were summarized in terms of mean ± standard deviation (SD) and median, minimum and maximum values for continuous variables and frequencies and percentages for categorical variables. Continuous variables were classified to be evaluated for the association with dissection (Group A). With regard to categorical variables, the differences between Group A and Group B were evaluated using the Pearson Chi-square test.
Disease-free survival (DFS) was calculated from surgery to last follow-up visit or recurrence. Survival probabilities over time were estimated by the Kaplan-Meier approach and differences over subset of patients were evaluated by the Log-Rank test.
To guarantee stable estimates from the multivariate analyses, the number of possible predictors for each multivariable model was related to the number of reported events. The general rule of a minimum of 5 events per predictor was adopted. Accordingly, for the 10-year DFS analysis, the CND impact was evaluated by a multivariate proportional hazard Cox regression model, by adjusting for T-stage and total (complete) resection margins.
Statistical analyses were performed using the SAS statistical software (version 8.02 for Windows™).

Results

With regard to the 244 patients studied, 126 were included in Group A and 118 in Group B. Clinical and demographic characteristics of the two groups are outlined in Table I. They are comparable as far as concerns sex, exposure to radiation, and surgery; for 6% of Group A (7/126) and 8% (9/118) of Group B patients, completion thyroidectomy was performed. In 14 out of 16, both operations were performed at IEO, while 2 had hemi-thyroidectomy elsewhere and completion thyroidectomy at IEO.
Age distribution was different in the two groups: 64 patients in Group A and 86 in Group B were > 45 years old ($p = 0.0004$). The groups were different in cT classification: PTC was diagnosed on the specimen in 42% of Group B patients ($p \leq 0.0001$).
Pathological features are outlined in Table II: pT3-4 are significantly larger in Group A (36.5%) than in Group B (17.8%), $p = 0.0011$. Likewise, PTC micro-carcinomas were more frequent in Group B (47%) than in Group A (29%), $p = 0.0024$. Histological variant, thyroiditis, multi-

Table I. Demographic and clinical characteristics of patient cohort.

	Total n = 244 (%)	Group A n = 126 (%)	Group B n = 118 (%)	Univariate p value*
Sex				
Male	50 (20)	26 (21)	24 (20)	
Female	194 (80)	100 (79)	94 (80)	0.95
Age (years)				
Mean (range)		46 (16-75)	52 (17-82)	
< 45	94 (39)	62 (49)	32 (27)	
≥ 45	150 (61)	64 (51)	86 (73)	0.0004
Radiation exposure				
Yes	6 (2.5)	2 (1.6)	4 (3)	
No	238 (97.5)	124 (98.4)	114 (97)	0.36
cT				
0	56 (23)	6 (5)	50 (42)	
1	108 (44)	76 (60)	32 (27)	
2	67 (27)	38 (30)	29 (25)	
3	11 (5)	6 (5)	5 (4)	
4	2 (1)	0	2 (2)	< 0.0001
Thyroidectomy				
Total	228 (93)	119 (94)	109 (92)	
Completion	16 (7)	7 (6)	9 (8)	0.51

* *Chi-Square.*

Table II. Pathological features of PTCs.

	Total n = 244 (%)	Group A n = 126 (%)	Group B n = 118 (%)	Univariate p value*
pT				
1-2	177 (73)	80 (63.5)	97 (82.2)	
3-4	67 (27)	46 (36.5)	21 (17.8)	0.0011
pN				
0		67 (53)	26 (22)	
1a		59 (47)	7 (6)	
X		0	85 (72)	
Size (mm)				
Mean (range)		17 (1-60)	15 (0,12-100)	
≤ 10 mm	92 (38)	36 (29)	56 (47)	0.0024
Histologic variants				
Low risk	230 (94)	119 (94.5)	111 (94)	
– Classic		88 (70)	79 (67)	
– Follicular		30 (24)	32 (27)	
– Warthin-like		1 (0.5)	0	
High risk	14 (6)	7 (5.5)	7 (6)	
– Tall cell		4 (3)	2 (2)	
– Desmoplastic		0	1 (0.75)	
– Sclerosant		2 (2)	3 (2.5)	
– Anaplastic spot		0	1 (0.75)	
– Insular		1 (0.5)	0	0.90
Multifocality				
Yes	105 (43)	57 (45)	48 (41)	
No	139 (57)	69 (55)	70 (59)	0.47
Thyroiditis				
Yes	52 (21)	32 (25)	20 (17)	
No	192 (79)	94 (75)	98 (83)	0.11

** Chi-Square.*

Table III. Follow-up and post-operative treatment.

	Total n = 244 (%)	Group A n = 126 (%)	Group B n = 118 (%)	Univariate p value*
I^{131}				
Yes	149 (60)	87 (69)	62 (53)	
No	79 (33)	28 (22)	51 (43)	
n.a.	16 (7)	11 (9)	5 (4)	0.0016
FU (months)				
Mean (range)		47 (0-159)	64 (0-144)	
Recurrence				
Yes	17 (7)	8 (6.3)	9 (7.7)	
No	218 (89)	114 (90.5)	104 (88.1)	
n.a.	9 (4)	4 (3.2)	5 (4.2)	0.83
Site of recurrence				
HTG		1	1	
Central**		4	4	
Regional**		5	5	
Distant**		1	2	
DFS (months)				
Mean (range)		45 (0-159)	60 (0-143)	
Status				
Awod	226 (92.5)	118 (93.5)	108 (91)	
Awd	4 (2)	2 (1.5)	2 (2)	
Dfd	2 (1)	1 (1)	1 (1)	
Dfod	3 (1)	1 (1)	2 (2)	
n.a.	9 (3.5)	4 (3)	5 (4)	0.96

*n.a. = data not available; FU = follow-up; HTG = human thyroglobulin; Awod = alive without disease; Awd = alive with disease; Dfd = died from disease; Dfod = died from other disease. * Chi-square; ** Group A: one patient had central and lateral neck metastases and one had central, lateral neck and distant metastases; Group B: one patient had central and lateral neck metastases and one had central, lateral neck and distant metastases.*

focality and extra-capsular spread were evenly distributed between the two groups.

In Group A, 59 out of 126 patients (47%) had nodal metastases (pN1a). In Group B, 7 patients (6%) were pN1a due to positivity of the Delphian node, removed en bloc with the thyroid; these patients were included in Group B according to the intention-to-treat analysis.

Post-operative radioiodine treatment is outlined in Table III: 87 (69%) Group A patients and 62 (53%) Group B patients received this treatment. Mean follow-up was 47 and 64 months in Groups A and B, respectively; 9 patients were lost to follow-up (4 in Group A, and 5 in Group B).

Group A patients developed 8 recurrences (6.3%), and Group B patients 9 (7.7%). The disease-free period was 45 months in Group A and 60 months in Group B (Table III). One Group B patient developed recurrence 11 years after thyroidectomy and was excluded from the 10-year analysis (Table IV). Two patients had a diagnosis of recurrence based only on a post-operative HTG increase that returned to baseline after radioiodine treatment.

Multivariate analysis did not show any difference in DFS between the two groups according to pT and completeness of resection.

In Group A, comparison of the patients with (55) and without (67) lymph node metastases, evaluated in the follow-up period (122), showed a correlation between the presence of metastases and extra-capsular invasion ($p = 0.0233$), as well as the presence of metastases and pT3-4 staging ($p = 0.0036$), as non-independent variables (Table V). Thyroiditis is inversely correlated to the presence of lymph node metastases ($p = 0.0034$).

Of the 122 patients (Group A), 8 had disease recurrence and all of these were pN1a at the time of initial surgery, p=0.002 (long rank test, Table VI). All these patients

Table IV. 10-year (post-thyroidectomy) disease-free survival (DFS).

Variables	Total n = 235	Events* n = 16 (%)	Estimated DFS %	Univariate p value**	Multivariate p value†
CND					
No	113	8 (7.1)	90.7		
Yes	122	8 (6.6)	64.7	0.69	0.43
Sex					
F	187	13 (6.9)	89.0		
M	48	3 (6.2)	62.6	0.99	
Age (years)					
< 45	90	4 (4.4)	94.6		
≥ 45	145	12 (8.3)	81.7	0.25	
cT					
0-1	159	6 (3.8)	93.7		
2	64	6 (9.4)	85.6		
3-4	12	4 (33.3)	45.4	0.002	
Total resection					
No (positive margins)	15	4 (26.7)	51.9		
Yes	220	12 (5.4)	88.9	< 0.0001	
Histologic risk variants					
Low	222	15 (6.8)	85.5		
High	13	1 (7.7)	91.7	0.96	
Tumour size					
≤ 10 mm	90	3 (3.3)	96.3		
> 10 mm	145	13 (9.0)	81.3	0.14	
Multifocality					
No	131	8 (6.1)	87.1		
Yes	104	8 (7.7)	84.4	0.50	
Extracapsular extension					
No	150	3 (2.0)	97.5		
Yes	85	13 (15.3)	70.1	0.0003	
Thyroiditis					
No	187	16 (8.5)	82.2		
Yes	48	0 (–)	100	0.034	
pT					
1-2	170	3 (1.8)	97.7		
3-4	65	13 (20.0)	59.1	< 0.0001	

** One recurrence occurred 11 years after thyroidectomy in a patient without CND. In this statistical analysis, only events occurring in the 10-year follow-up period were considered; ** log-rank test; † Wald's test. Adjusted by pT and total (complete) resection.*

Table V. Risk factors according to histology of N (VI level) in Group A*.

Variables	Total n = 122	pN0 n = 67 (%)	pN1a n = 55 (%)	Univariate p value**
Sex				
Female	97	55 (82.1)	42 (76.4)	
Male	25	12 (17.9)	13 (23.6)	0.4356
Age				
< 45 yrs	59	28 (41.8)	31 (56.4)	
≥ 45 yrs	63	39 (58.2)	24 (43.6)	0.1090
cT				
1	80	45 (67.2)	35 (63.6)	
2	36	20 (29.8)	16 (29.1)	
3	6	2 (3)	4 (7.3)	0.5509
Total resection				
No (positive margins)	11	3 (4.5)	8 (14.5)	
Yes	111	64 (95.5)	47 (85.5)	0.0534
Histologic risk				
Low	115	63 (94)	52 (94.5)	
High	7	4 (6)	3 (5.5)	0.9030
Tumour size				
≤ 10 mm	36	20 (30)	16 (29)	
> 10 mm	86	47 (70)	39 (71)	0.9270
Multifocality				
No	66	39 (58.2)	27 (49)	
Yes	56	28 (41.8)	28 (51)	0.3146
Extracapsularity				
No	67	43 (64.2)	24 (43.6)	
Yes	55	24 (35.8)	31 (56.4)	0.0233
Thyroiditis				
No	91	43 (64.2)	48 (87.3)	
Yes	31	24 (35.8)	7 (12.7)	0.0034
pT				
1-2	77	50 (74.6)	27 (49.1)	
3-4	45	17 (25.4)	28 (50.9)	0.0036

** 4 patients without follow-up were excluded; ** Chi-square.*

Table VI. 10-year (post-thyrodectomy) disease-free survival (DFS) within the subset of patients who received CND (n = 122)*.

Variables**	Total n = 122	Events n = 8 (%)	Estimated % DFS	Univariate p value†
pN				
0	67	0 (–)	100.0	
1a	55	8 (14.6)	36.9	0.002
Total resection				
No (positive margins)	11	2 (18.2)	44.4	
Yes	111	6 (5.4)	70.4	0.048
Multifocality				
No	66	3 (4.5)	72.7	
Yes	56	5 (8.9)	44.7	0.10
Extracapsular extension				
No	67	0 (-)	100.0	
Yes	55	8 (14.6)	51.0	0.005
Thyroiditis				
No	91	8 (8.8)	41.0	
Yes	31	0 (–)	100.0	0.064
pT				
1-2	77	0 (–)	100.0	
3-4	45	8 (17.8)	46.8	0.0006

** 4 patients without follow-up were excluded; ** only those significantly associated with 10-year local recurrence; † log-rank test. Due to small number of events, no multivariate analysis was performed.*

had pT3-4 tumour (p = 0.0006), extra-capsular invasion (p = 0.005), none of these patients had thyroiditis (p = 0.064) and an association was found with incomplete resection (p = 0.048). Given the small number of unfavourable events, a multivariate analysis was not performed.

Discussion

We analysed the results of central neck dissection in patients with papillary thyroid carcinoma, without clinical or US evidence of lymph node metastases. Disease-free rates of the two groups (Group A – with and Group B – without CND) were correlated with the clinico-pathological characteristics of each group. Comparison of the two groups studied is in keeping with other studies on prophylactic CND [17-20]: no significant advantages were demonstrated in terms of survival rates and disease recurrence even adjusting for differences in risk factors presence in the two groups (pT and complete resection). Few Authors showed an improvement in survival rates of cN0 patients achieved by CND [15,16]; others suggested CND only on a speculative basis [22]. A real improvement in survival rates remains difficult to prove, given the characteristics of the disease process (PTC), which has a low prevalence, an indolent clinical course and requires long-term follow-up.

The evaluation of OS is clearly limited, in this study, by the short-term follow-up, but unlike other published studies, the groups presented were fairly homogeneous in size and characteristics. With regard to recurrences, the present follow-up is sufficient for a reliable evaluation: several studies showed that loco-regional recurrences are more likely to occur within the first 4 years [28]. Similarly to Sywak et al. [20], in the present study, only patients without pre-operative diagnosis of lymph node metastases, undergone total thyroidectomy or completion thyroidectomy were included. Furthermore, while other Authors excluded tumours < 1 cm in size [20], these were included in the present study, as recent evidence shows that even microcarcinomas must be treated in a manner consistent with larger tumours, in the same stage [19]. In agreement with the findings of Shah et al. [17], no difference was observed in the site of disease recurrence between the two groups and CND does not appear to have any influence on the local or regional spread of disease. Some Authors have suggested the absence of local recurrences after CND [21] or a decrease in lateral neck metastases as a result of hypothetical interruption of lymphatic flow. However, although the central compartment represents the first theoretical site of metastasis, lateral neck metastases can still occur in the absence of central compartment disease, mainly when the tumour is located in the upper lobe [12].

Re-operation in the thyroid surgical field, although not frequent, is associated with a higher rate of complications, compared to those of initial surgery [23] and a recent review of the literature suggests that more aggressive initial surgical treatment may be warranted [14]. However, other Authors showed that with a careful surgical technique, re-operations, in the same field, are possible without an increase in post-operative complications [24]. It should not be forgotten that in case of lateral neck metastases, when CND has not been previously performed, the re-operative approach should include CND, and similar post-operative complications might be expected such as those encountered in re-operation for local disease recurrence in the thyroid bed [23].

In the patients that received CND, the presence of metastatic disease was demonstrated in 47% of patients, a finding in agreement with data previously reported in the literature [20 22 23], further corroborating the difficulty of pre-operative staging of level VI lymph nodes by means of US.

In the CND group, all patients with disease recurrence presented pathological lymph node involvement at initial surgery, thus suggesting a predictive value of pN1 for disease recurrence; however given the small sample size and low incidence, it was not possible to perform a multivariate analysis with other factors associated with disease recurrence (extra-capsular extension and pathologic tumour size).

The significance of the presence of lymph node metastases, in PTC, is controversial: historically, it has not been considered to be an influential factor for survival rates [4-6] and it has also been shown to have a potential predictive value of recurrence without influencing the survival rate [6-8]. However, there is also evidence showing that the presence of metastases does, indeed, affect survival rates [10,21]. Ito et al. [9] did not consider central compartment metastases as a prognostic factor and according to Beasley et al. [11], only lateral neck metastases are of prognostic value for disease recurrence.

In the present study, a correlation was found between the presence of lymph node disease in the central compartment with stage pT3-4 and then extracapsular invasion of the tumour. Metastatic potential remained for patients with initial disease (pT1-2) or microcarcinoma. The presence of thyroiditis seems to prevent the occurrence of lymph node metastases (p = 0.0034) and is inversely related with risk of disease recurrence, although not statistically significant; this confirms the results reported by other Authors[10,28]. We can, therefore, identify, at high risk of metastases, those patients with advanced disease (pT3-4) without histological evidence of thyroiditis. Comparable results, in terms of recurrence between our two groups, could be related to CND and radioiodine therapy in Group A, given the presence of a larger number of advanced disease in this group.

Clearly, there are many factors to be considered in the evaluation of the usefulness of CND, particularly, as suggested by Shindo et al. [22], as a tool for staging and its potential implications on treatment and follow-up. In posi-

tive CND patients pT1-2 aged > 45 years (Stage I-II) the tumour becomes Stage III. In this study, a larger number of patients in Group A received radio-metabolic therapy compared to those in Group B.

On the basis of these data, even though there is no evidence of beneficial effects on survival, in our opinion, whenever it is possible to maintain low levels of morbidity, prophylactic CND should be an integral part of the initial surgical management of PTC, mainly on account of its potential predictive value for disease recurrence, as demonstrated in the present series. Moreover, this should allow better staging and optimization of post-operative treatment and follow-up regimens. The potential risks associated with re-operation are a further indication for prophylactic CND. Based on these data, patients with T3-T4 PTC, without thyroiditis, are at high risk of developing central metastases: they could benefit more from CND, considering that a positive CND is a potential predictive factor for disease recurrence. Further studies are necessary to better define the role of prophylactic CND in the initial treatment of thyroid carcinoma and to establish better diagnostic modalities to identify the specific subsets of patients in whom prophylactic CND may have positive effects on long-term survival rates.

References

[1] Hundahl SA, Fleming ID, Fremgen AM, Menck HR. *A national cancer data base report on 53,856 cases of thyroid carcinoma treated in the US, 1985-1995.* Cancer 1998;83:2638-48.

[2] Cooper DS, Doherty GM, Haugen BR, Kloos RT, Lee SL, Mandel SJ, et al. *Management guidelines for patients with thyroid nodules and differentiated thyroid cancer.* Thyroid 2006;16:109-42.

[3] McConahey WM, Hay ID, Woolner LB, van Heerden JA, Taylor WF. *Papillary thyroid cancer treated at the Mayo Clinic, 1946 through 1970: initial manifestations, pathologic findings, therapy, and outcome.* Mayo Clin Proc 1986;61:978-96.

[4] Mazzaferri EL, Jhiang SM. *Long-term impact of initial surgical and medical therapy on papillary and follicular thyroid cancer.* Am J Med 1994;97:418-28.

[5] Sato N, Oyamatsu M, Koyama Y, Emura I, Tamiya Y, Hatakeyama K. *Do the level of nodal disease according to the TNM classification and the number of involved cervical nodes reflect prognosis in patients with differentiated carcinoma of the thyroid gland?* J Surg Oncol 1998;69:151-5.

[6] Grebe SK, Hay ID. *Thyroid cancer nodal metastases: biological significance and therapeutic considerations*. Surg Oncol Clinc N Am 1996;5:43-63.

[7] Wada N, Suganuma N, Nakayama H, Masudo K, Rino Y, Masuda M, et al. *Microscopic regional lymph node status in papillary thyroid carcinoma with and without lymphadenopathy and its relation to outcomes*. Langenbeck's Arch Surg 2007;392:417-22.

[8] Hughes CJ, Shaha AR, Shah JP, Loree TR. *Impact of lymph node metastasis in differentiated carcinoma of the thyroid: a matched-pair analysis.* Head Neck 1996;18:127-32.

[9] Ito Y, Tomoda C, Uruno T, Takamura Y, Mija A, Kobayashi K, et al. *Clinical significance of metastasis to the central compartment from papillary microcarcinoma of the thyroid.* World J Surg 2006;30:91-9.

[10] Lundgren CI, Hall P, Dickman PW, Zedenius J. *Clinically significant prognostic factors for differentiated thyroid carcinoma: a population-based, nested case-control study.* Cancer 2006;106:524-31.

[11] Beasley NJP, Lee J, Eski S, Walfish P, Witterick I, Freeman JL. *Impact of nodal metastases on prognosis in patients with well-differentiated thyroid cancer.* Arch Otolaryngol Head Neck Surg 2002;128:825-8

[12] Qubain SW, Nakano S, Baba M, Takao S, Aikou T. *Distribution of lymph node micrometastasis in pN0 well-differentiated thyroid carcinoma.* Surgery 2002;131:249-56.

[13] Robbins KT, Clayman G, Levine PA, Medina J, Sessions R, Shaha A, et al. *American Head and Neck Society; American Academy of Otolaryngology-Head and Neck Surgery. Neck dissection classification update: revisions proposed by the American Head and Neck Society and the American Academy of Otolaryngology -Head and Neck Surgery.* Arch Otolaryngol Head Neck Surg 2002;128:751-8.

[14] White ML, Gauger PG, Doherty GM. *Central lymph node dissection in differentiated thyroid cancer.* World J Surg 2007;31:895-904.

[15] Tisell LE, Nilsson B, Molne J, Hansson G, Fjalling M, Jansson S, et al. *Improved survival of patients with papillary thyroid cancer after surgical microdissection.* World J Surg 1996;20:854-9.

[16] Scheumann GFW, Gimm O, Wegener G, Hundeshagen H, Dralle H. *Prognostic significance and surgical management of locoregional lymph node metastases in papillary thyroid cancer.* World J Surg 1994;18:559-68.

[17] Shah MD, Hall FT, Eski SJ, Witterik IJ, Walfish PG, Freeman JL. *Clinical course of thyroid carcinoma after neck dissection.* Laryngoscope 2003;113:2102-7.

[18] Steinmuller T, Klupp J, Rayes N, Ulrich F, Jonas S, Graf KJ, et al. *Prognostic factors in patients with differentiated thyroid carcinoma.* Eur J Surg 2000;166:29-33.

[19] Wada N, Duh QY, Sugino K, Iwasaki H, Kameyama K, Mimura T, et al. *Lymph node metastasis from 259 papillary thyroid microcarcinomas: frequency, pattern of occurrence and recurrence, and optimal strategy for neck dissection.* Ann Surg 2003;237:399-407.

[20] Sywak M, Cornford L, Roach P, Stalberg P, Sidhu S, Delbridge L. *Routine ipsilateral level VI lymphadenectomy reduces postoperative thyroglobulin levels in papillary thyroid cancer.* Surgery 2006;140:1000-7.

[21] Pereira JA, Jimeno J, Miquel J, Iglesias M, Munné A, Sancho JJ, et al. *Nodal yield, morbidity, and recurrence after cen-*

tral neck dissection for papillary thyroid carcinoma. Surgery 2005;138:1095-100.

[22] Shindo M, Wu JC, Park EE, Tanzella NP. *The importance of central compartment elective lymph node excision in the staging and treatment of papillary thyroid cancer.* Arch Otolaryngol Head Neck Surg 2006;132:650-4.

[23] Roh JL, Park JY, Rha KS, Park CI. *Is central neck dissection necessary for the treatment of lateral cervical nodal recurrence of papillary thyroid carcinoma?* Head Neck 2007;29:901-6.

[24] Kim MK, Mandel SH, Baloch Z, Livolsi VA, Langer JE, Didonato L, et al. *Morbidity following central compartment reoperation for recurrent or persistent thyroid cancer.* Arch Otolaryngol Head Neck Surg 2004;130:1214-6.

[25] Shah JP. *Indications, rationale, and techniques in neck dissection*. In: Najarian JS, Delaney JP, editors. Progress in cancer surgery. St Louis: Mosby – Year Book; 1991. p. 262-73.

[26] Shah JP, Patel SG. *Central Neck Dissection.* In: Shah JP, Patel SG, editors. *Head and Neck Surgery and Oncology.* Third Edition. St Louis: Mosby; 2003. p. 373-4.

[27] AJCC. *TNM Classification of Malignant Tumors*. Sixth Edition. New York: Springer; 2002.

[28] Gupta S, Patel A, Folstad A, Fenton C, Dinauer CA, Tuttle RM, et al. *Infiltration of differentiated thyroid carcinoma by proliferating lymphocytes is associated with improved disease-free survival for children and young adults.* J Clin Endocrinol Metab 2001;86:346-54.

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