

Analysis of prognostic factors for the indication of central lymphadenectomy in papillary thyroid carcinomas

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SUMMARY: Analysis of prognostic factors for the indication of central lymphadenectomy in papillary thyroid carcinomas.

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Background. *In this study we examined whether it was possible following preoperative parameters statistically significant correlation with the presence of metastatic lymphnodes in the papillary thyroid carcinoma. We conducted a retrospective study in a group of patients with a preoperative diagnosis of papillary carcinoma who underwent total thyroidectomy associated with routine lymphadenectomy of the central compartment (level VI).*

Patients and Methods. *The study group consisted of patients whose definitive histological lymph node examination was positive for metastasis (N1), and the control group comprised patients found negative for metastasis (N0).*

Results. *Tumour diameter had a significance at 10% level [$Pr(>|z|)$: 0.056], thus indicating that increased tumour size results in a higher probability of being in group N1. The logistic regression revealed that variables with a significance at 5% level for the presence of metastatic lymph nodes in the central compartment (N1) were: sex [$Pr(>|z|)$: 0.019], overall patient age [$Pr(>|z|)$: 0.012] and age >45 [$Pr(>|z|)$: 0.022]. We performed a statistical analysis with the association of three preoperative variables (presence of ultrasound-revealed microcalcifications, presence of solid hypoechoic nodule and type III vascularisation on echocolor-Doppler); this was found to result in a highly significant probability of entering into group N1.*

Conclusions. *We found variables statistically significant for the presence of metastatic central compartment lymph nodes, including female sex, age >45 yrs and tumour diameter >1.5 cm. The association of papillary carcinoma with microcalcifications, solid hypoechoic nodule structure and type III vascularisation on echocolor-Doppler also resulted in a statistically significant increase in the probability of positive level VI lymph nodes.*

RIASSUNTO: Analisi di fattori prognostici per la valutazione dell'indicazione alla linfodectomia centrale nei carcinomi papilliferi della tiroide.

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Obiettivo. *In questo studio retrospettivo abbiamo analizzato, in pazienti con diagnosi preoperatoria di carcinoma papillifero della tiroide, i fattori prognostici preoperatori statisticamente significativi per la presenza di metastasi linfonodali. Tutti i pazienti sono stati sottoposti a tiroidectomia totale associata con linfodectomia del comparto centrale ipsilaterale di principio (livello VI).*

Pazienti e metodi. *Il gruppo di studio è risultato composto da pazienti nei quali la diagnosi istologica definitiva confermava la presenza di metastasi linfonodali (N1), il gruppo di controllo è risultato composto dai pazienti con linfonodi negativi (N0).*

Risultati. *Il diametro del tumore è risultato significativo ad un livello del 10% [$Pr(>|z|)$: 0.056], per cui al crescere del diametro della neoplasia aumenta la probabilità che il paziente si trovi nel gruppo N1. La regressione logistica ha dimostrato che variabili con una significatività al livello del 5% per la presenza di metastasi linfonodali nel compartimento centrale (N1) sono il sesso ($Pr(>|z|)$: 0.019), l'età [$Pr(>|z|)$: 0.012] e l'età >45 [$Pr(>|z|)$: 0.022]. Inoltre, l'analisi statistica per valutare l'associazione con tre variabili preoperatorie (presenza di microcalcificazioni ecograficamente dimostrate, presenza di noduli solidi ipoecogeni e vascolarizzazione di tipo III all'ecocolor-Doppler), ha dimostrato una correlazione statisticamente significativa con la presenza di metastasi linfonodali.*

Conclusioni. *Abbiamo evidenziato che le variabili sesso femminile, età >45 anni e diametro del tumore >1.5 cm sono statisticamente significative per la presenza di metastasi linfonodali. L'associazione di carcinoma papillifero con nodulo solido ipoecogeno/microcalcificazioni e vascolarizzazione tipo III all'ecocolor-Doppler è statisticamente significativa la presenza di metastasi linfonodali al VI livello.*

KEY WORDS: Carcinoma thyroid - Lymphadenectomy of the central compartment - Papillary thyroid carcinoma metastasis - Total thyroidectomy.
Carcinoma della tiroide - Linfodectomia del compartimento centrale - Metastasi di carcinoma papillifero della tiroide - Tiroidectomia totale.

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Introduction

Papillary thyroid carcinoma (PTC) is the most common cancer of the thyroid and endocrine glands. Its unique behaviour is unanimously demonstrated in the literature: its prognosis is significantly influenced by the patient's age and the presence of metastatic lymph nodes is common, although they do not affect survival.

Metastasis of a malignant differentiated thyroid tumour to the cervical lymph nodes will theoretically extend bilaterally, as it can easily spread through the lymphatic drainage system arranged around the gland, consisting of the Delphian/prelaryngeal, pretracheal and paratracheal lymph nodes, located in the anatomical/surgical region delimited laterally by the carotid arteries, above by the hyoid bone and below by the mediastinal vessels – the so-called central compartment (level VI). Lymphadenectomy incorporates the level VI lymph nodes, the upper, mid and lower jugular lymph nodes (levels II, III and IV), the supraclavicular lymph nodes and those around the spinal accessory nerve (level V). Level I, consisting of submandibular and submental lymph nodes, is only exceptionally affected by thyroid cancer and is not normally included in the dissection (1-4).

When treating differentiated papillary thyroid carcinoma (PTC), different experiences and indications for the choice of lymph node dissection are reported in the literature and there is still international debate on this matter today. Some authors prefer to always perform a regulated, complete lymphadenectomy, while others argue that this is necessary only in the presence of macroscopic lymph node metastases. A few others still reduce it to the excision of the lymph nodes clinically affected (5, 6).

The aim of this retrospective study is to look for preoperative prognostic factors and assess histological features leading to the indication for routine lymphadenectomy of the central compartment during total thyroidectomy.

Patients and methods

We retrospectively studied a group of patients observed from January 2000 to December 2003 with a preoperative fine-needle aspiration biopsy (FNAB) of papillary carcinoma who underwent total thyroidectomy associated with routine lymphadenectomy of the central compartment.

In this study, only two surgeons performed total thyroidectomy associated with routine lymphadenectomy of the central compartment (level VI), where we considered the lymph nodes and lymphatic structures found within the two triangles delimited by the hyoid bone above, the tracheal margins inside, the carotid sheath outside, and the upper edge of the anonymous vein below. The lymphatic cell tissue extends down into the superior anterior mediastinum. The lymph nodes in this compartment are located in the tracheoesophageal groove (paratracheal lymph nodes), in front of the trachea (pretracheal nodes), around the thyroid gland (prethyroidal nodes) and on

the cricothyroid membrane (Delphian or precricoid node) (7).

Our study consisted of two groups of patients with a preoperative diagnosis of PTC who underwent total thyroidectomy and routine level VI lymphadenectomy. The study group consisted of patients whose definitive histological lymph node examination was positive for metastasis (N+), and the control group of patients found negative for metastasis (N0).

The following preoperative parameters were examined: sex, overall age of patients, patient age (< or >45), tumour diameter as ascertained by ultrasound (< or >1.5 cm), preoperative ultrasound findings (solid, solid hypoechoic, solid hyperechoic, solid non-uniform, solid isoechoic, mixed structure), presence of nodule with microcalcifications visible by ultrasound, nodule vascularisation with EchoColour-Doppler (ECD) classified as follows: Type I (no vascularisation), Type II (peripheral vascularisation), Type III (peri- and intranodular vascularisation) (8-10), preoperative scintigraphy (intense or weak uptake with I^{131} scintigraphy), thyroglobulin level (RIA method, normal range 0.20-50.0 ng/ml), calcitonin level (RIA method, normal range 0.00-30.0 pg/ml), anti-TG and anti-TPO antibody positivity (IEMA method, normal range 0.00-70.0 U/ml).

The following parameters were considered during the definitive histological examination, based on the 2002 UICC classification (VI edition) (11): pT, infiltration and/or overrun of the thyroid capsule, infiltration of pre-thyroidal soft tissues, infiltration of pre-thyroid muscles, presence of multiple foci and cancer stage.

The histological sub-type (pure papillary, diffuse sclerosing variant, follicular variant, tall cell variant, papillary with insular component) and presence of histological vascular invasion were also analysed.

We evaluated statistically if a variable - or the association of a number of variables - enabled the identification of neoplastic features determining a greater risk of patients having metastatic lymph nodes in the central compartment (N1).

The correlation of individual parameters was therefore analysed statistically to find out which had the greatest influence in determining the presence of metastatic lymph nodes in the level VI compartment (N+), in order to demonstrate whether a single factor or set of factors was statistically significant for the indication to routine central lymphadenectomy.

A logistic regression model (12) was used to establish which factors affected the likelihood of being in the study group, indicating the variable concerned as Y , with a value of 1 for study group patients (N1) and 0 for control group patients (N0).

The model has the form $\Pr(y=1)=\text{logit}^{-1}(X\beta)$, where logit is defined as $\text{logit}(x) = \log(x/(1-x))$. This model enables analysis of binary-type dependent variables.

The model's coefficients were estimated through a Bayesian procedure, postulating an a priori Cauchy distribution (13). This avoided various problems of non-identification which arise with logistic regression, especially due to dichotomic variables among the independent variables.

The explanatory (or independent) variables considered in the analysis were: sex, overall age of patients, age >45, ultrasound findings (solid, solid hypoechoic, solid hyperechoic, solid non-uniform, solid isoechoic, mixed structure), ECD (types I, II and III), microcalcifications (positive or negative), scintigraphy (intense uptake, weak uptake), thyroglobulin (positive or negative), calcitonin (positive or negative), anti-TG and anti-TPO antibodies (positive or negative), preoperative diameter on ultrasound (< or >1.5 cm), pT (pT1, pT2, pT3, pT4), cancer stage (I, II, III, IV), multiple foci (present or absent), capsule infiltration, infiltration of pre-thyroidal soft tissues, infiltration of muscles and presence of histological vascular invasion, and histological sub-type (pure papillary, diffuse sclerosing variant, follicular variant, tall cell variant, papillary with insular component) were evaluated from the definitive histological examination.

The variables, coefficients of the “complete” logistical regression and the relative standard errors were calculated and the less statistically significant variables were eliminated, to examine whether any variables had a greater statistical effect on the presence of metastatic lymph nodes in the central compartment (N1). In the Table n.2 and n.3, the first column reports the estimated coefficient of each variable considered (Estimate), the second reports the standard error (Std. Error), the third reports the ratio of the two values (z) and the fourth gives the corresponding p -value, to assess the coefficient’s significance [$\text{Pr}(> |z|)$]. An approximative test of the significance of each variable was conducted by dividing the coefficient estimate by its standard error. The result was then compared with the standardised normal distribution. The analysis was conducted using the statistical package R (version 2.4.1, 2006; The R Foundation for Statistical Computing).

Where indicated, the Chi-Square test was used for univariate analysis of individual parameters with univariate analysis. Significance for this test was considered at $P < 0.05$ and $P < 0.001$. $P > 0.05$ was considered as not significant (NS).

Results

A total of 51 patients with no preoperative evidence of lymphadenopathy and undergoing total thyroidectomy and level VI lymphadenectomy, between January 2000 and December 2003, were thus included in the study. Of these, 27 were found to have positive lymph nodes after level VI lymphadenectomy (N+) (group N1) and 24 were negative at the definitive histological examination (N-) (group N0) (Table 1).

The female to male ratio was 5.7:1 in group N1 and 2:1 in group N0. The percentage of female patients was 85.2% (4 M, 23 F) in group N1 and 66.6% (16 F, 8 M) in group N0.

The mean overall age of the studied patients was 41.4 (range 16-71); for group N1 it was 43.7 (range 17-71) and for group N0 38.8 (range 16-69).

The “complete” logistic regression (Table 2) revealed that variables with a significance at 5% level for the presence of metastatic lymph nodes in the central compartment (N1) were: sex [$\text{Pr}(> |z|)$: 0.019], overall patient age [$\text{Pr}(> |z|)$: 0.012] and age > 45 [$\text{Pr}(> |z|)$: 0.022].

The negative value of the coefficient “sex” (Estimate column) indicates that female patients have a higher probability of being in the N1 group.

Overall age also had a negative coefficient, therefore the probability of being in the N1 group increases with age, although not by much (coefficient = -0.14). The estimate coefficient is positive for age > 45 (= 4.0856), indicating that patients aged over 45 have a higher probability of being in group N1 [$\text{Pr}(> |z|)$: 0.022] (Table 2).

Tumour diameter had a significance at 10% level [$\text{Pr}(> |z|)$: 0.056], with a positive coefficient (estimate 1.1745), thus indicating that increased tumour size results in a higher probability of being in group N1 (Table 2).

The following variables had positive coefficients and are therefore probably determining factors for the presence of N1: ultrasound variables solid hypoechoic (estimate coefficient: 2.1307), solid isoechoic (estimate coefficient: 1.5073), mixed structure (estimate coefficient: 1.7483), multiple foci (estimate coefficient: 1.2837) and histological vascular invasion (estimate coefficient: 1.2704), although these were not statistically significant, due to the low number of samples examined (Table 2).

The “restricted” logistical regression (Table n.3), obtained by removing some variables, essentially confirmed the greater significance of the following variables: female sex [$\text{Pr}(> |z|)$: 0.027] with significance at 5% level and age [$\text{Pr}(> |z|)$: 0.059] with significance at 10% level, and also revealed the significance at 10% level of the variable diameter > 1.5 cm [$\text{Pr}(> |z|)$: 0.067], which in the complete logistic regression assumed significance at 10% level (Table 2).

We performed a further statistical analysis with the association of three preoperative variables (presence of ultrasound-revealed microcalcifications, presence of solid hypoechoic nodule and type III vascularisation on ECD). This was found to result in a highly significant probability of entering into group N1 [$\text{Pr}(> |z|)$: 0.051] (the three variables are expressed together as “preoperative diagnosis” in Table 3).

The chi-square test revealed significance for the presence of nodules with type III vascularisation in the N1 group ($P = 0.038$) (Table 1).

With respect to postoperative variables, pT was significant when passing from pT1 to pT2, pT3 and pT4 for the N1 study group, with $P = 0.026$ for the pT3 and pT4 forms. The tumour stage, although presenting a greater incidence of stage III and IV forms in the N1 group, was not statistically significant due to the small sample size (Table 1).

Capsule infiltration was statistically significant, resulting in a greater incidence of N1 forms ($P = 0.026$) (Table 1).

The definitive histological examination variable, comprising the histological subtypes (pure papillary = 1, sclerosing variant = 2, follicular variant = 3, tall cell variant = 4, insular component = 5) is an index of severity correlated with the increasing value of the variable. However, the caseload examined does not enable a severity index for the various histological subtypes to be established (due to the low number of cases analysed), although increasing severity does increase the likelihood of being in group N1. Furthermore, considering the various histological subtypes as a whole, with the exception of pure papillary carcinoma, the probability of being in group N1 is almost statistically significant for the other histological subtypes ($P = 0.07$) (Table 1).

TABLE 1 - CLINICAL CHARACTERISTICS OF GROUP N1 AND N0 PATIENTS.

Group	Group N1 27 cases	Group N0 24 cases	P value
Sex			
Female	23/27 (85.2%)	16/24 (66.6%)	Pr(> z): 0.019
Male	4/27 (14.8%)	8/24 (33.3%)	
Age, yrs (range)	43.7 (17-71)	38.8 (range 16-69 anni)	Pr(> z): 0.012
Tumour diameter, cm (range)	1.7 (0.5-3.5)	1.2 (range 0.5-3)	Pr(> z): 0.056
Weak uptake with I ¹³¹ scintigraphy	55.55% (15/27)	10/24 (41.66%)	
Intense uptake with I ¹³¹ scintigraphy	18.5% (5/27)	2/24 (8.33 %)	
Ultrasound			
Solid structure	74.07% (20/27)	16/24 (66.6%)	
Solid hypoechogenic structure	77.7% (21/27)	12/24 (50%)	
Solid non-uniform structure	25.9% (7/27)	3/24 (12.5%)	
Solid isoechogenic structure	7.4% (2/27)	0	0.038
Solid hyperechogenic structure	25.9% (7/27)	5/24 (20.8%)	
Mixed structure	11.1% (3/27)	4/24 (16.6%)	
Vascularisation with echocolour-Doppler			
Type I	1/27 (3.7%)	3/24 (12.5%)	
Type II	5/27 (18.5%)	9/24 (37.5%)	
Type III	21/27 (77.7%)	12/24 (50%)	0.038
Microcalcifications	16/27 (59.2%)	10/24 (44.6 %)	
Thyroglobulin level	17/27 (62.9%)	10/24 (41.6%)	
Calcitonin level	6/27 (22.2 %)	4/24 (16.6%)	
Anti-TG and anti-TPO antibody positive	8/27 (29.6%)	6/24 (25%)	
Residual thyroid			
Normal tissue	8/27 (29.6%)	12/24 (50%)	
Nodular hyperplasia	3/27 (11.1%)	1/24 (4.1%)	
Thyroiditis	16/27 (59.2%)	11/24 (45.8%)	
Tumor pT			
pT1	2/27 (7.4%)	13/24 (54.1%)	
pT2	10/27 (37%)	5/24 (20.8 %)	
pT3	7/27 (25.9%)	0	0.026
pT4	8/27 (29.6%)	6/24 (25%)	
Tumor stage			
Stage I	11/27 (40.7%)	15/24 (62.5%)	
Stage II	4/27 (14.8%)	3/24 (12.5%)	
Stage III	8/27 (29.6%)	4/24 (16.6%)	
Stage IV	4/27 (14.8%)	2/24 (8.3%)	
Presence of multiple foci	15/27 (55.5%)	5/24 (20.8%)	
Infiltration and/or overrun of the thyroid capsule	15/27 (55.5 %)	6/24 (25%)	0.026
Infiltration of pre-thyroidal soft tissues	8/27 (29.6%)	3/24 (12.5%)	
Infiltration of pre-thyroid muscles	4/27 (14.8%)	1/24 (4.1%)	
Histological vascular invasion	9/27 (33.3%)	3/24 (12.5%)	0.038
Tumor right lobe	10/27 (37%)	10/24 (41.6%)	
Tumor left lobe	10/27 (37%)	12/24 (50%)	
Tumor isthmus	4/27 (14.8%)	5/24 (20.8%)	

Discussion

Locoregional lymph node metastases are a common finding in papillary thyroid carcinomas, ranging from 20% to 50% depending on the surgical studied (2, 14, 15).

The central compartment of the neck, also known as level VI, is the first level region for papillary carcinoma metastasis, and is therefore often the most affected area (16, 17), although in a recent study by Bian (4) lymph nodes were affected at several levels in 81.4% of cases,

TABLE 2 - COEFFICIENTS OF "COMPLETE" LOGISTIC REGRESSION AND STANDARD ERRORS.

	Estimate	Std. Error	z	Pr(> z)
Sex	-2.4386	1.0392	-2.35	0.019 **
Age	-0.1405	0.0561	-2.5	0.012 **
Age >45	4.0856	1.781	2.29	0.022 **
Histology [§]	-0.3316	0.5022	-0.66	0.509
Weak uptake with I ¹³¹ scintigraphy	0.7621	0.9851	0.77	0.439
Intense uptake with I ¹³¹ scintigraphy	0.5513	1.2658	0.44	0.663
Solid structure US	0.2032	1.3586	0.15	0.881
Solid hypoechogenic US	2.1307	1.3359	1.59	0.111
Solid non-uniform structure US	0.694	1.0427	0.67	0.506
Solid isoechogenic US	1.5073	1.78	0.85	0.397
Mixed structure US	1.7483	1.5111	1.16	0.247
Solid hyperechogenic US	-0.4523	1.2724	-0.36	0.722
Vascularisation echocolour-Doppler (ECD) [°]	0.1962	0.6977	0.28	0.779
Microcalcifications	0.3929	0.7947	0.49	0.621
Thyroglobulin level	0.4272	1.0514	0.41	0.685
Calcitonin level	0.756	1.121	0.67	0.5
Anti-TG and anti-TPO antibody	-0.891	0.954	-0.93	0.35
Tumour diameter	1.1745	0.6142	1.91	0.056 *
Residual thyroid [#]	0.6527	0.5517	1.18	0.237
pT [•]	-0.3098	0.5936	-0.52	0.602
Tumor stage[^]	-0.2343	0.7831	-0.3	0.765
Multiple foci	1.2837	1.6691	0.77	0.442
Infiltration				
thyroid capsule	0.4866	1.6511	0.29	0.768
pre-thyroidal soft tissues	-0.452	1.3098	-0.35	0.73
pre-thyroid muscles	0.1861	1.4329	0.13	0.897
Histological vascular invasion	1.2704	1.0991	1.16	0.248
Tumor right and left lobes	0.6728	1.1197	0.6	0.548
Tumor right lobe	-1.2344	0.9309	-1.33	0.185
Tumor left lobe	-1.0358	2.0098	-0.52	0.606

Legend: **significance at 5% level; *significance at 10% level; [§] includes: pure papillary, diffuse sclerosing variant, follicular variant, tall cell papillary, papillary with insular component; [°] includes: ECD type I, II and III; [#] includes: normal thyroid, nodular hyperplasia, chronic thyroiditis; [•] includes: pT1, pT2, pT3, pT4; [^] includes: stage I, II, III, IV.

and in 70.8% the first PTC metastasis was found in level III.

The level VI lymph nodes are located in the tracheoesophageal groove (paratracheal nodes), in front of the trachea (pretracheal nodes), around the thyroid gland (prethyroid nodes) and on the cricothyroid membrane (Delphian or precricoid node) (7).

When lymph nodes in this area are clinically or instrumentally evident, so-called "central" lymphadenectomy is generally proposed by most authors, due to its greater radicality (18). However, other authors (14) have proposed a surgical protocol in which central lymphadenectomy is indicated as routine in aggressive PTC (diffuse sclerosing carcinoma, tall cell carcinoma, strongly invasive follicular carcinoma, Hürtle cell carcinoma, insular carcinoma) (19) and in AMES high-risk differentiated cancers (20). The literature contains conflicting opinions on the "preventive" role of lymphadenectomy

of this district if there is no evidence of lymphadenopathy (21, 22).

The potential benefit in terms of disease recurrence or persistence offered by routine level VI lymphadenectomy is therefore a matter of debate; most authors affirm that it is not indicated as routine, due to the greater incidence of the recurrent nerve lesions and high incidence of temporary or persistent hypoparathyroidism (21, 22).

Various authors have recently studied the progressive change in both the techniques and indications for lymphadenectomy (from 1958 to 2002), also revealing that the levels most affected and thus treated are level VI (80.5%), level IV (67.5%) and level II (35%) (23).

The incidence of metastatic lymphadenopathy found with preoperative ultrasound examinations (US) varies from 38% to over 60% (17, 24, 25).

In this study, preoperative clinical and instrumental

evidence of metastatic lymphadenopathy was found in 16.3% of patients, rising to 24.3% when also considering those in whom a level VI lymphadenectomy was performed.

Some authors affirm that intraoperative macroscopic evaluation of the central lymph nodes is not a parameter for surgical excision, as they may sometimes be enlarged due to a reactive process or a previous thyroiditis (25).

In this study we examined whether it was possible to evaluate preoperative PTC parameters diagnosed by FNAB which have a statistically significant correlation with the presence of metastatic lymph nodes (N1), to enable the indication for level VI lymphadenectomy in the absence of preoperative clinical and instrumental evidence of lymph node involvement to be proposed as routine.

There are no literature studies to this effect. Individual prognostic factors and some "guidelines" have been analysed (26, 27) with respect to indications on when to perform a routine central lymphadenectomy.

A negative prognostic factor reported in the literature in the past was male sex; Kjellman (28) recently studied this in association with other variables, perhaps due to the disease's high incidence in women.

In our study, women made up 85.2% of the N1 group (4 M/23 F) and 66.6% of the N0 group (8 M/16 F). The variable "female sex" had significance at 5% level for the presence of metastatic lymph nodes in the central compartment [$\text{Pr}(> |z |): 0.019$]. Tumour diameter – a widely studied prognostic factor – was found to have positive significance at 10% level [$\text{Pr}(> |z |): 0.056$], so that increased tumour size was associated with a higher probability of entering in the N1 group.

Kjellman's univariate analysis (28) found that male sex, increased tumour size, presence of lymph node metastasis, multiple foci and poorly differentiated tumours were always associated with a greater risk of metastasis. Of these factors, increased tumour size was the independent variable mainly associated with metastasis ($P=0.0004$), especially in men ($P=0.02$).

In our study, the presence of a solid hypoechoic nodule on ultrasound indicated a greater degree of malignancy/aggressiveness ($P=0.038$); above all, the combined analysis with other variables (ultrasound microcalcifications and type III vascularisation on Echo Colour Doppler) revealed a highly significant risk for the probability of entering in Group N1 [$\text{Pr}(> |z |): 0.0096$].

Grey-scale ultrasound (US) is a highly sensitive method for the diagnosis of thyroid nodules, but is neither sensitive nor specific for diagnosis of malignancy, although for some authors nodules with a solid component are in themselves an indication for a cytological examination of the nodules (29-31). Others affirm that preoperative ultrasound can reveal lymph node meta-

stases previously undetected in 43.4% of clinical examinations (4).

In consideration of the abnormal cell proliferation of malignant nodules and their consequent increased vascularisation, various classifications have been proposed (32, 33) to use ECD to evaluate the flow pattern associated with a higher incidence of malignant tumours (34-36).

In our study, we found that type III vascularisation on ECD in association with other parameters was an unfavourable prognostic index, with a statistically significant probability that the nodule was already in a metastatic (N1) form ($P=0.038$).

Cappelli (37,38) recently evaluated the importance of measuring the nodule's anteroposterior and transverse diameter with ultrasound (A:T ratio ≥ 1), considering this a good predictive index for malignancy independently of diameter. He also demonstrated that diameter was not significantly correlated with extracapsular invasion or the presence of lymph node metastasis. An A:T diameter ratio ≥ 1 , margin irregularities ($P < 0.001$), a solid hypoechoic structure ($P < 0.001$), an intranodular pattern (type II) ($P < 0.001$) and the presence of microcalcifications were significantly more common in malignant than in benign tumours, further confirming that the association of these factors is an indication for FNAC.

We found that the tumour diameter had significance at 10% level in PTC cases [$\text{Pr}(> |z |): 0.056$], i.e. increasing diameter resulted in a higher probability of level VI metastatic lymph nodes (N1).

Analysis of the diameter of the most aggressive forms did not produce any statistically significant findings, due to the low number of samples analysed. However, the most aggressive forms did have a smaller diameter, and there is therefore a correlation between the presence of more aggressive forms and the probability of N1 forms.

In a previous study (39), we found that the mean tumour diameter in diffuse sclerosing variant carcinomas (DSV) was 0.9 cm (range 0.2-4.5 cm), in comparison with pure papillary (PC) carcinomas whose mean diameter was 1.2 cm (range 0.1-1.8 cm). The mean diameter was therefore smaller in DSV patients. Multivariate analysis demonstrated that in DSV patients, a tumour diameter lower than the median was associated with a more than 33% increase in mortality. Metastatic laterocervical lymph nodes diagnosed and subsequently confirmed by postoperative histological examination were found in 13.3% of DSV patients and 5.9% of PTC patients. The incidence of metastatic laterocervical lymph nodes on diagnosis was significantly higher in DSV carcinomas ($p < 0.05$). Level VI lymphadenectomy was performed in 34.9% of DSV patients and 10.1% of PC patients; this difference was statistically significant ($p < 0.001$).

Microcalcifications were revealed by ultrasound in

TABLE 3 - COEFFICIENTS OF "RESTRICTED" LOGISTIC REGRESSION AND STANDARD ERRORS.

	Estimate	Std. Error	z	Pr(> z)
Sex (female)	-2,37	1,072	-2,21	0,027 **
Age	-0,106	0,056	-1,89	0,059 *
Age >45 yrs	3,046	1,707	1,78	0,074 *
Histology [§]	-0,365	0,535	-0,68	0,495
Weak uptake with I ¹³¹ scintigraphy	1,112	1,055	1,05	0,292
Intense uptake with I ¹³¹ scintigraphy	0,883	1,31	0,67	0,5
Solid structure US	0,152	1,359	0,11	0,911
Solid hypoechoic US	1,254	1,301	0,96	0,335
Solid non-uniform structure US	0,572	1,108	0,52	0,605
Solid isoechoic US	1,512	1,844	0,82	0,412
Mixed structure US	1,559	1,484	1,05	0,293
Solid hyperechoic structure US	-0,223	1,304	-0,17	0,864
Vascularisation echocolour-Doppler (ECD) [°]	-0,315	0,748	-0,42	0,674
Microcalcifications	-0,335	0,9	-0,37	0,71
Thyroglobulin level	0,402	1,119	0,36	0,719
Calcitonin level	1,267	1,187	1,07	0,286
AntiTG and anti-TPO antibody	-0,803	1,003	-0,8	0,423
Diameter 1.5 cm	1,152	0,629	1,83	0,067 *
Residual thyroid [#]	0,547	0,555	0,99	0,324
pT [•]	-0,15	0,618	-0,24	0,809
Tumor stage [^]	-0,179	0,783	-0,23	0,819
Microcalcifications	1,22	1,722	0,71	0,479
Infiltration of thyroid capsule	0,648	1,719	0,38	0,706
Infiltration of pre-thyroidal soft tissues	-0,406	1,369	-0,3	0,767
Infiltration pre-thyroid muscles	-0,408	1,572	-0,26	0,795
Histological vascular invasion	1,76	1,193	1,48	0,14
Tumor right and left lobes	0,936	1,17	0,8	0,424
Tumor right lobe	-0,948	0,955	-0,99	0,321
Tumor left lobe	-0,681	2,037	-0,33	0,738
Preoperative diagnosis ^{&}	2,917	1,492	1,95	0,051 *

Legend: **significance at 5% level; *significance at 10% level; § includes: pure papillary, diffuse sclerosing variant, follicular variant, tall cell papillary, papillary with insular component; ° includes: ECD type I, II and III; • includes: normal thyroid, nodular hyperplasia, chronic thyroiditis; # includes: pT1, pT2, pT3, pT4; ^ includes: stage I, II, III, IV; & preoperative diagnosis: presence of ultrasound-revealed microcalcifications, presence of solid hypoechoic nodule and type III vascularisation on ECD.

51% of the carcinoma cases studied; in itself this is not a determining factor for greater tumour malignity (N1) but if not associated with a nodule with a solid structure on US and type III vascularisation on ECD [Pr(>|z|): =0.051], it has a positive coefficient estimate of 2.917 (Table n. 3).

US microcalcifications have been considered by various authors as an index for the differential diagnosis of nodule malignity and benignity (37). Iannuccilli (40) found that the presence of microcalcifications with a snowstorm pattern is 100% specific for malignity.

Numerous studies have found that US examination of the central compartment is not highly disease-sensitive. Ito (41) demonstrated that US has high specificity (99.1%) but low sensitivity (10.1%), thus not affecting the disease-free duration.

Although there are currently few studies, Ito (42) recommends lateral prophylactic lymphadenectomy for aggressive PTCs, such as larger sizes and massive extrathyroidal extension, while central compartment lymphadenectomy is recommended as routine, as it is

the district alongside the thyroid gland. He does not recommend mediastinal lymphadenectomy by sternotomy. The same author (42) asserts that lateral and central compartment lymphadenectomy must be performed "aggressively" in order to radically impede the disease's recurrence in previously dissected regions.

In another study of microcarcinomas (PMCT), Ito (43) states that if the PMCT has a 3.0 mm diameter but is associated with lymph node metastases and distant metastasis, this has a worse prognosis and is an indication for routine total thyroidectomy and therapeutic lymphadenectomy.

In a recent study, Bian (4) analysed the distribution of cervical metastases of PTC in two patient groups; the first showing preoperative clinical evidence of lymphadenopathy, and the second without clinically evident lymph nodes which were revealed by ultrasound. He found that 21.5% of patients presented bilateral metastases, in 81.4% at more than one level. The distribution of metastatic lymph nodes was as follows: level II in 60.2%, level III in 70.8%, level IV in 61.9%, level

VI in 58.4%, level V in 22.5%. Preoperative ultrasound revealed metastatic lymph nodes in 43.4% of cases in which they were not found on palpation.

The traditional opinion that central compartment lymphadenectomy changes the disease-free interval without improving the prognosis for PTC patients is today under challenge from recent studies of large case-loads, which demonstrate a significantly higher incidence of mortality for PTCs with the presence of metastatic lymph nodes at this level (44).

Sywak (25) reports that systematic ipsilateral level VI prophylactic lymphadenectomy enables more radical/complete tissue removal from the region, reducing the incidence of metastasis. He also evaluates the effect of this dissection on serum TG concentration, as this has considerable importance in follow-up and adjuvant treatment. In particular, in low-risk PTC classes with a very low probability of disease-related mortality, serum TG concentration enables the disease's evolution to be followed closely (45).

Sywak (25) found that the systematic removal of the central compartment lymph nodes resulted in a significant reduction in thyroglobulin levels and thus in ablative radioiodine therapy. In the same study, he found a higher incidence of temporary hypocalcaemia in patients

undergoing level VI dissection (as this interferes with the vascularisation of the parathyroid glands, especially the ipsilateral inferior gland), but with respect to long term data on permanent hypoparathyroidism and recurrent lesions following routine compartment VI lymphadenectomy, he found no difference to international global data (46).

Our study of a selected but limited number of cases revealed that it is possible to identify a group of PTC patients for whom routine ipsilateral level VI lymphadenectomy is advisable.

We found a number of variables to be statistically significant for the presence of metastatic central compartment lymph nodes, including female sex, age >45 and tumour diameter >1.5 cm. The association of PTC with US microcalcifications/solid hypoechoic nodule structure and type III vascularisation on ECD also resulted in a statistically significant increase in the probability of positive level VI lymph nodes. Other variables were found to be determining factors but were not statistically significant, and thus require further study.

Recent studies of molecular genetics and molecular biology are of fundamental importance in the correlation of PTC with lymph node metastases.

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