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Differentiated thyroid carcinomas: the relevance of various pathological features for tumour classification and prediction of tumour progress

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Summary. In this series of 263 surgically treated cases of thyroid cancer, 12% were finally classified as benign lesions after histopathological review. Difficulty in the assessment of tumour capsule invasion in follicular neoplasms was the most frequent cause of diagnostic error. Squamous metaplasia, clusters of ground glass nuclei and psammoma bodies were found to be the most specific discriminators between papillary and follicular carcinomas. Among papillary carcinomas, tumour diameter above 30 mm, thyroid capsular invasion and regional lymph node metastases were found to be significant prognostic factors according to survival analyses. Of additional practical importance, our results indicate that tumour infiltration in the thyroid capsule should be reported as a marker of early extra-thyroidal extension.

Key words: Thyroid cancer – Classification – Thyroid capsular invasion – Lymph node metastasis – Prognosis

Introduction

The histopathological characteristics of differentiated thyroid carcinomas have been described in several studies (LiVolsi 1990), and various features are important for a correct tumour classification. Some characteristic may also be predictors of tumour progression (Tscholl-Ducommun and Hedinger 1982; Carcangiu et al. 1985; Tennvall et al. 1985). The purpose of the present study was to review the prevalence and specificity of some pathological features which are commonly used criteria in tumour description and classification, and to investigate the statistical associations between these features and the presence of thyroid capsular invasion (TCI) and co-existing lymph node metastases in papillary carcinomas (PCs). The prognostic significance of TCI as a marker of early extra-thyroidal extension was of particular interest.

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Materials and methods

A total of 263 consecutive patients were treated surgically for thyroid cancer at the Department of Surgery, Haukeland Hospital, University of Bergen in the period 1971–1985. All patients in our series were reported to the Cancer Registry of Norway and account for 10% of thyroid cancers in Norway during 1970–1985 (Akslen et al. 1990).

There were no substantial differences in the distribution of sex, age and histological types when compared to the Registry cases (Table 1). However, our patients tended to be somewhat younger. In addition, the frequency of PC was slightly higher. Since only surgically treated cases have been included in our series, only 2.2%

Table 1. Thyroid cancer patients from Haukeland Hospital 1971–1985 compared with all Norwegian cases 1970–1985 (figures after histopathological revision in parentheses)[a]

Variables	Patient series		
	Haukeland Hospital		Norwegian cases
Sex (%)			
Males	25.9	(27.2)	24.7
Females	74.1	(72.8)	75.3
Age			
Mean (years)	48.2	(48.0)	55.0
Histology (%)			
Papillary	71.4	(78.6)	62.6
Follicular	20.1	(13.4)	18.9
Medullary	3.5	(4.5)	3.8
Undifferentiated	1.9	(3.1)	2.1
Others	3.1	(0.4)	12.6
Tumour stage (%)			
Stage 1	62.9	(54.8)	59.8
Stage 2A+2B	32.0	(36.2)	24.8
Stage 2C	1.5	(6.8)	4.1
Stage 3	3.5	(2.3)	11.3
Number of cases	259	(224)	2625

[a] Cases of malignant lymphoma are not included in this table

Table 2. Variables examined in the present study

Variables	Categories
Standard variables	
Sex	Males, females
Age	0–29, 30–49, 50–74, 75+ years
Histological type	Papillary, follicular, medullary, anaplastic, others
Tumour stage	Stage 1: intra-thyroidal tumours; stage 2A: regional lymph node metastases, without extra-thyroidal extension; stage 2B: regional lymph node metastases plus extra-thyroidal extension; stage 2C: extra-thyroidal extension only; stage 3: distant metastases
Macroscopic features	
Tumour diameter[a]	Continous (mm)
Macroscopic appearance	Solid demarcated tumour, cystic, diffuse growth, multiple, no tumour, unknown
Microscopic features	
Localization	Right, left, isthmus, bilateral, ectopic, unknown
Tumour capsule	+ −
Papillary structure	+ −
Follicular structure	+ −
Cribriform structure	+ −
Trabecular structure	+ −
Solid structure	+ −
Squamous metaplasia	+ −
Main growth pattern[b]	Papillary, follicular, trabecular, cribriform, solid, squamous
Differentiation grade[c]	high, moderate, poorly
Ordinary cells	+ −
Oxyphil cells	+ −
Clear cells	+ −
Spindle-shaped cells	+ −
Large pleomorphic cells	+ −
Small tumour cells	+ −
Main cell type[b]	Ordinary, oxyphil, clear, spindle-formed, large, small
Hyperchromatic nuclei	+ −
Ground glass nuclei	+ −
Main nuclear type[b]	Hyperchromatic, ground glass
Grade of nuclear atypia[d]	Slight, moderate, marked
Cystic degeneration	+ −
Tumour necrosis	+ −
Inflammation	None, slight, moderate, marked
Germinal centres	+ −
Multinucleated cells	+ −
Fibrosis	+ −
Hyalinization	+ −
Psammoma bodies	+ −
Tumour extension[e]	No invasion, invasion of tumour capsule/border, thyroid tissue invasion, thyroid capsular invasion, major extra-thyroidal invasion
Vascular invasion[f]	+ −
Multifocal growth[g]	+ −
Bilateral growth[g]	+ −
Lymph node metastases	+ −

[a] Tumour diameter could not be determined in 9 cases
[b] >50% of the tumour area

of the cases had distant metastases at the time of presentation, compared to 11.3% of the national material.

Table 2 summarizes the variables which were studied. The histology was reviewed using routine slides and immunohistochemical examination in selected cases. The tumours were classified according to the WHO criteria (Hedinger 1988). Tumour stage was based on clinical data and pathology reports, using a modification of the categories applied by the Cancer Registry of Norway. The primary tumour extension was studied in detail by examination of infiltration of the tumour capsule, surrounding thyroid tissue, thyroid capsule, vascular channels, nerves, striated muscle and extra-thyroidal lipomatous tissue. TCI was recorded as being present in cases with tumour cells in the connective tissue at the level of the capsular vessels, including the cases where early extra-thyroidal infiltration was suspected. Major extra-thyroidal invasion, i.e. the pT4 category of the UICC classification (UICC 1987), was recorded as present when tumour infiltration of skeletal muscle, large nerves or lipomatous tissue was evident.

Deaths of thyroid cancer were recorded until 1 July 1989 (maximum follow-up 18.3 years, median 7.3 years). No patient was lost to follow-up.

The statistical package BMDP was used for tabulation and analysis (Dixon 1985). Associations between different variables were assessed by Pearson's chi-square test, and Cramer's v was used as a measure of association. Differences in age distribution were tested by Student's t-test. The Mann-Whitney test was used for variables without normality. The simultaneous influence of multiple pathological features on the presence/absence of co-existing lymph node metastases was tested by logistic regression analysis. Survival analysis was performed by the life-table method (BMDP-1L), using deaths of thyroid cancer as the end-point.

Results

After exclusion of 32 cases (27 females, 5 males) with the final diagnosis of a benign lesion (12%), 231 cases (including 7 malignant lymphomas) remained for further analyses (Table 1), and 86% of these had been treated with near-total/total thyroidectomy. Of the malignant tumours, 18 cases (8%) had their diagnosis changed to another type.

There were no significant differences between males and females with respect to age, histological type and tumour stage. Of the PCs, 87 (50%) were stage 1, compared to 26 (87%) of the follicular carcinomas (FCs). Lymph node metastases were present in only one case of FC, and 1 FC and 3 PCs had distant metastases (stage 3) at the time of diagnosis. Ten percent of the PCs were incidentally found during surgery for benign lesions, and 11% of all PCs presented with regional lymph node metastases as the initial clinical manifestation. Four cases of PC were considered to be ectopic carcinomas, probably originating in the thyroglossal duct, and in 3 cases

[c] According to the criteria of Tscholl-Ducommun and Hedinger (1982); Harach and Franssila (1988)
[d] According to Tennvall et al. (1985)
[e] See Materials and methods; tumour capsule invasion was evaluated according to Franssila et al. (1985) and Hedinger (1988); major extra-thyroidal infiltration was recorded as present when tumour invasion of skeletal muscle, large nerves or lipomatous tissue was clearly evident (category pT4 according to UICC 1987)
[f] Vascular invasion was evaluated according to Franssila et al. (1985)
[g] After microscopical examination

Table 3. Differences between papillary and follicular carcinomas with respect to pathological features of the primary tumour, extent of infiltration and lymph node metastases[a]

Variables	Papillary Carcinoma		Follicular carcinoma		
	n	%	*n*	%	P^b
Main growth pattern					<0.0005
Papillary	127	73.4	0	0.0	
Follicular	41	23.7	25	83.3	
Trabecular/solid	5	2.9	5	16.7	
Differentiation grade					<0.0005
Highly differentiated	65	37.6	9	30.0	
Moderately differentiated	100	57.8	14	46.7	
Poorly differentiated	8	4.6	7	23.3	
Main cell type					<0.0005
Ordinary cell type	166	96.0	21	70.0	
Oxyphilic cells	3	1.7	7	23.3	
Clear cells	3	1.7	2	6.7	
Others	1	0.6	0	–	
Main nuclear type					0.001
Hyperchromatic nuclei	113	65.3	30	100.0	
Ground glass nuclei	60	34.7	0	–	
Grade of nuclear atypia					<0.0005
Slight/moderate atypia	161	93.1	20	66.7	
Marked atypia	12	6.9	10	33.3	
Additional features					
Squamous metaplasia +	29	16.8	0	–	0.02
Cystic degeneration +	76	43.9	6	20.0	0.01
Tumour necrosis +	11	6.4	6	20.0	0.01
Multinucleated cells +	107	61.8	3	10.0	<0.0005
Psammoma bodies +	104	60.1	2	6.7	<0.0005
Primary tumour extension					0.001
No invasion	7	4.0	0	0.0	
Tumour capsule/border	42	24.3	18	60.0	
Thyroid parenchyma	37	21.4	6	20.0	
Thyroid capsule	58	33.5	3	10.0	
Major extra-thyroidal infiltration (pT4)	29	16.8	3	10.0	
Vascular invasion					<0.0005
Present	24	13.9	13	43.3	
Absent	149	86.1	17	56.7	
Regional lymph node metastases					<0.0005
Present	74	42.8	1	3.3	
Absent	99	57.2	29	96.7	
Total	173		30		

[a] Three cases of papillary carcinoma with unknown primary tumour have been excluded
[b] Papillary versus follicular carcinomas (Pearson's chi-square)

with lymph node involvement, no primary tumour could be found.

The number of cancer cases (after review) increased significantly during the period (linear regression: $P<0.001$). The proportion of benign lesions decreased from 17% (1971–1978) to 9% (1979–1985) (chi-square: $P<0.05$), and the frequency of benign cases initially diagnosed as FC also decreased (62% to 28%, chi-square: $P<0.025$). The patients' age, the frequency of PC and the proportion of stage 1 tumours did not change significantly throughout the period. Among PCs, the frequency of incidental findings tended to increase during the period (8% in 1971–1978 to 12% in 1979–1985, not significant).

Tumour diameter did not differ between clinically detected PC and FC (median 22 mm versus 20 mm). The median diameter of incidentally found PCs was 6.0 mm (range 2–10 mm; $n=17$). PCs occurring in patients below 50 years of age were smaller than in patients 50 years or above (18.0 mm versus 25.0 mm, Mann-Whit-

ney test: $P=0.03$). No significant change in tumour diameter was observed for PC or FC during the study period. Forty-six percent of the PCs had a defined tumour capsule, compared with 80% of the FCs ($P=0.02$).

Papillary structures were not accepted in FCs, but pseudopapillary formations were present in 11 cases (37%). Thirteen cases of PC (8%) lacked papillary structures but showed distinct ground glass nuclei (6 of these were microcarcinomas ≤ 10 mm in diameter). A higher frequency of FCs were predominantly trabecular/solid when compared with PCs (17% versus 3%, $P<0.005$) (Table 3). Squamous differentiation was present in 17% of PCs, compared with none of the FCs ($P<0.025$). FC was more frequently considered to be poorly differentiated than PC according to the growth pattern (23% versus 5%, $P<0.0005$). Ground glass nuclei were present in clusters in 87% of PCs, whereas 35% of the cases were dominated by this nuclear type, in contrast to none of the FC cases ($P=0.001$). However, scattered ground glass nuclei were found in 47% of FCs. Marked nuclear atypia was more frequent in FC than in PC (33% versus 7%, $P<0.0005$). Tumour necrosis was about three times as frequent in FC, and was found in only 6% of PCs ($P=0.01$). Psammoma bodies were identified in 60% of the PCs and in two cases of FC ($P<0.0005$). Vascular invasion was noted in 43% of FCs, and this proportion tended to increase from 20% (1971–1978) to 55% in 1979–1985 (chi-square: $P=0.07$). The number of sections from each tumour increased from 3.1 (1971–1978) to 5.8 (1979–1985) (Mann-Whitney test: $P=0.025$). Definite vascular invasion was recorded in 14% of PCs. Multifocal tumour growth was significantly more frequent in PC than in FC, 24% versus 3% ($P=0.01$). Other differences are shown in Table 3.

All cases of FC showed either definite infiltration through the tumour capsule or extensive infiltration (Table 3). PCs infiltrated the surrounding thyroid parenchyma and thyroid capsule about twice as often as FCs in the present study. Major extra-thyroidal invasion (pT4) was found in 17% of PCs, compared with 10% of FCs.

Table 3 shows that 74 cases of PC had tumour spread to one or more regional lymph nodes (43%). Bilateral nodal spread was found in 27% of PCs.

Males had significantly larger PCs than females (Table 4). Larger tumours showed a higher frequency of marked nuclear atypia, tumour necrosis, TCI, major extra-thyroidal extension (pT4) and lymph node metastases. Both squamous metaplasia ($P=0.01$) and psammoma bodies ($P=0.01$) were significantly associated with a solid growth pattern. TCI was more frequently found in large tumours and especially in those lacking a distinct tumour capsule. In tumours less than or equal to 30 mm in diameter, TCI was present in 42% of the cases, compared to 70% in tumours over 30 mm ($P=0.004$). Tumours with marked nuclear atypia, tumour necrosis and psammoma bodies also showed an increased tendency for TCI (Table 4). The frequency of co-existing lymph node spread was increased in tumours larger than 30 mm in diameter and in those lacking a distinct capsule (Table 5). Metastases were also associated with the presence of psammoma bodies and TCI. Multifocal tumour growth and bilateral involvement at the time of diagnosis were not correlated to nodal spread. Multivariate analysis (logistic regression) showed that increasing tumour diameter, lack of tumour capsule, presence of psammoma bodies and TCI each showed a significant and independent association with co-existing lymph node spread at the time of diagnosis (Table 6).

Table 4. Papillary thyroid carcinoma: statistical associations between some clinical and pathological features (for detailed explanations, see Table 2 and Materials and methods)

	Sex	Age	Diameter	Capsule	Nuclei	Atypia	Necrosis	Psammoma	TCI	pT4
Age	−0.17 *									
Diameter	−0.17 *	0.25 **								
Capsule	−0.03	0.08	0.02							
Nuclei	0.00	−0.21 **	−0.13	0.10						
Atypia	−0.11	0.17 *	0.22 **	0.03	−0.01					
Necrosis	−0.02	0.15 *	0.16 *	0.06	−0.19 **	0.21 **				
Psammoma	0.00	−0.15 *	0.10	0.18 *	0.12	−0.06	−0.03			
TCI	−0.12	0.10	0.18 *	0.40 ***	0.00	0.18 *	0.17 *	0.20 **		
pT4	−0.03	0.23 **	0.16 *	0.17 *	−0.07	0.12	0.14	−0.01	0.42 ***	
LNM+	−0.13	0.08	0.17 *	0.32 ***	0.03	−0.01	0.11	0.28 ***	0.36 ***	0.14

In each cell: Cramer's v, * $P<0.05$, ** $P<0.01$, *** $P<0.001$
TCI, Thyroid capsular invasion; pT4, major extra-thyroidal tumour growth; LNM, lymph node metastases

Table 5. Papillary thyroid carcinoma: tumour diameter, tumour capsule formation, psammoma bodies and thyroid capsular invasion in the primary tumour of lymph node negative and lymph node positive cases of papillary carcinoma ($n=173$)[a]

Variables	Node negative		Node positive		
	n	%	*n*	%	*P*[b]
Tumour diameter					0.0006
0–10 mm	31	67.4	15	32.6	
11–20 mm	35	66.0	18	34.0	
21–30 mm	23	71.9	9	28.1	
31–40 mm	2	22.2	7	77.8	
41–50 mm	3	33.3	6	66.7	
51+ mm	3	20.0	12	80.0	
Tumour capsule					<0.00005
Present	60	74.1	21	25.9	
Absent	39	42.4	53	57.6	
Psammoma bodies					0.0003
Present	48	46.2	56	53.8	
Absent	51	73.9	18	26.1	
Thyroid capsular invasion					<0.00005
Present	34	39.5	52	60.5	
Absent	65	74.7	22	25.3	

[a] Three cases of papillary carcinoma with unknown primary tumour were excluded
[b] Node negative versus node positive cases (Pearson's chi-square)

Table 6. Papillary thyroid carcinoma: multivariate analysis (logistic regression) of tumour diameter, tumour capsule formation, presence of psammoma bodies and thyroid capsular invasion of the primary tumour with respect to the presence of co-existing lymph node metastasis ($n=173$)[a]

Variables	Regression coefficient	*P*-value
Tumour diameter[b]	0.89	0.0005
Tumour capsule[c]	0.54	0.009
Psammoma bodies[d]	0.44	0.03
Thyroid capsular invasion[d]	0.46	0.02

[a] Three cases of papillary carcinoma with unknown primary tumour were excluded
[b] >30 mm versus ≤30 mm
[c] Absent versus present
[d] Present versus absent

Table 7. Survival analysis (life-table method) of patients with papillary thyroid carcinoma; only deaths from thyroid cancer have been considered ($n=173$)[a]

Variables	*P*-value[b]
Tumour diameter[c]	0.001
Tumour capsule[d]	ns (<0.10)
Psammoma bodies[d]	ns
Tumour extension[e]	0.004
Lymph node metastasis[d]	0.03

[a] Three cases of papillary carcinoma with unknown primary tumour were excluded
[b] Mantel-Cox' test of differences between the groups
[c] >30 mm versus ≤30 mm
[d] Absent versus present
[e] Categories: intra-thyroidal, thyroid capsular invasion, major extra-thyroidal invasion

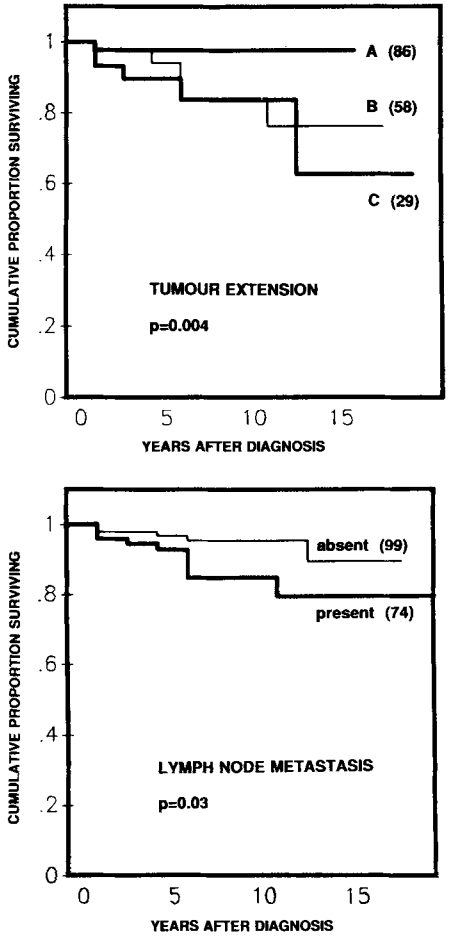

Fig. 1. Survival analysis (life-table method) of patients with papillary thyroid carcinoma ($n=173$), with respect to primary tumour extension and lymph node metastases: *A*, intra-thyroidal; *B*, thyroid capsular invasion (TCI); *C*, major extra-thyroidal invasion, pT4

The frequency of marked nuclear atypia and necrosis increased with age, whereas ground glass nuclei and psammoma bodies were significantly more frequent among the younger patients (Table 4). Necrosis was more often found in large tumours with marked nuclear atypia. Associations between the other variables were not strong.

There were few cases of FC and the results should therefore be interpreted cautiously. Like PCs, increasing tumour diameter was associated with tumour necrosis ($v=0.35$, $P<0.05$). The presence of TCI ($v=0.45$, $P<0.01$) or major extra-thyroidal extension ($v=0.39$, $P<0.05$) was more frequent in tumours without a distinct capsule. Necrosis was more frequent among the elderly ($v=0.35$, $P<0.05$), and was furthermore significantly correlated to the presence of marked nuclear atypia ($v=0.35$, $P<0.05$), as in the PCs.

In PCs, decreased survival was significantly associated with increasing tumour diameter, presence of TCI and lymph node metastases (Table 7, Fig. 1). There was no significant difference between cases with tumour tissue in the thyroid capsule and those with major extra-thyroidal invasion. The difference with respect to lymph node spread was small but statistically significant.

Discussion

In some cases, the distinction between benign and malignant thyroid neoplasms may be difficult. The proportion of mis-classified tumours was found to be 12% in the present series, and this figure compares well with the studies of others (Franssila and Saxén 1972; Holm et al. 1980). Assessment of capsular invasion in follicular neoplasms was found to be the major problem. Only 50% of the cases originally described as FCs could be verified using the WHO criteria (Hedinger 1988), compared to 34% and 62% in two other studies (Franssila and Saxen 1972; Holm et al. 1980).

Our study describes a wide range of pathological features in both PCs and FCs. Several criteria should therefore be used to discriminate between the two types, especially in difficult cases such as the follicular variant of PC or predominantly solid tumours. Squamous metaplasia, which was identified in 17% of the PCs, did not appear in any of the tumours that were otherwise accepted as FCs. Ground glass nuclei were common in PCs, but scattered nuclei of this type were also found in as many as 47% of the FCs, as others have noted (Kahn and Perzin 1983). Only large clusters should therefore be regarded as a sign of PC (Kahn and Perzin 1983). Psammoma bodies were present in more than half of the papillary tumours and were more frequent in the solid subtype, but they were also found in two cases of FC. In difficult cases with an ambiguous growth pattern, we believe that squamous metaplasia, clustered ground glass nuclei and psammoma bodies are the most specific and useful discriminators between PC and FC. Although some differences in other features were noted, most other variables did not contribute.

The extension of the primary tumour is considered to be prognostically important in papillary thyroid carcinomas (Byar et al. 1979; Akslen et al. 1991). In contrast to most other studies where major extra-thyroidal invasion has been emphasized, the present results focus on the importance of TCI. This feature may be regarded as an indicator of early extra-thyroidal growth, and it was present in about 50% of PCs, about three times as frequent as major extra-thyroidal extension. The frequency of TCI was high in tumours above 30 mm in diameter and was also correlated to features of the primary tumour such as lack of tumour capsule, marked nuclear atypia, tumour necrosis and the presence of psammoma bodies. These characters may thus reflect a subgroup of more aggressive tumours.

Survival analyses of PCs indicate that TCI may be a significant step in the process of extra-thyroidal infiltration, since there was no significant difference in survival between cases with tumour tissue in the thyroid capsule and those with extensive extra-thyroidal growth. As a practical consequence, we therefore believe that TCI should be recorded and reported as a prognostic factor. In addition, our results suggest that the pTNM criteria (UICC 1987) should be modified to include TCI positive cases among those with major extra-thyroidal extension, i.e. in the pT4 category.

The prognostic significance of lymph node metastases has been a matter of discussion (Byar et al. 1979; Tennvall et al. 1985; Tubiana et al. 1985; Akslen et al. 1991). Since the frequency of lymph node spread in part depends on the surgical procedure and sampling of histological sections, this study has also focused on features of the primary tumour that correlate with the presence of nodal metastases. Large tumours, absence of tumour capsule and presence of psammoma bodies were found to be significantly associated with both TCI and the presence of lymph node metastases. In addition, TCI itself was significantly associated with nodal tumour spread. When these variables were examined with respect to patient survival, only tumour diameter, TCI and lymph node metastases proved to be of significant importance as prognostic indicators.

Age is a major prognostic factor in thyroid cancer (Byar et al. 1979; Akslen et al. 1991). In the present group of PCs, increasing age was associated with a higher frequency of large tumours, marked nuclear atypia and tumour necrosis. These features may therefore explain in part the marked age effect found in prognostic studies.

Our study suggests that the following histological features should be systematically studied in order to discriminate between PCs and FCs: squamous metaplasia, clusters of ground glass nuclei and psammoma bodies. In PCs, tumour diameter above 30 mm, lack of tumour capsule, presence of psammoma bodies and TCI were all found to correlate strongly with the presence of lymph node metastases. Preliminary analyses of patient survival indicate that large tumours (above 30 mm), presence of tumour tissue in the thyroid capsule and lymph node spread increase the risk of thyroid cancer deaths. These features should therefore be recorded in histopathological reports.

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