Original paper

Comparison of clinicopathological features in incidental and nonincidental papillary thyroid carcinomas in 308 patients

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Incidental papillary thyroid carcinomas (IPTCs) consist of a significant portion of increasing incidence in papillary thyroid carcinomas. This study investigated the clinicopathological features of IPTCs from different perspectives and by comparing nonincidental PTCs (NIPTCs) in patients who underwent total thyroidectomy and lymph node dissection. Basic results were as follows. IPTC was present in 27.9% of 308 patients. IPTCs were significantly accompanied by lymphocytic thyroiditis (LT), particularly, multinodular hyperplasia (MNH). IPTCs were more common in older patients (51.3 years vs. 47.2 years) and in female patients. IPTCs significantly differed from NIPTCs in terms of smaller tumour size, lymphatic vessel invasion (2.6% vs. 97.4%), extrathyroidal extension (4.3% vs. 95.7%), lymph node metastasis (3.6% vs. 96.4%), multifocality (21.2% vs. 78.8%), bilaterality (5.3% vs. 94.7%), and BRAFV600 mutation (6.7% vs. 93.3%). Older age, bilaterality, encapsulation, and radioactive iodine (RAI) were significantly more common in IPTCs > 5 mm than in those ≤ 5 mm. In conclusion, IPTCs are more commonly associated with LT and MNH. IPTCs may have a more favourable prognosis than NIPTCs, and tumour size > 5 mm may predict bilaterality and need for RAI. Nevertheless, the patient-based clinical approach in IPTCs may have benefits in the management of IPTCs.

Key words: incidental papillary thyroid carcinoma, nonincidental papillary thyroid carcinoma, clinicopathological feature.

Introduction

One of the malignancies with the largest increases in incidence in the past decades is papillary thyroid carcinoma (PTC). This increase is associated with the improvement of imaging procedures, including ultrasound (US) [1] and ultrasound-guided fine-needle aspiration (USFNA) [2], and clinical management of thyroid nodules [1, 3, 4]. However, preoperatively unsuspected PTCs – namely, incidental PTCs (IPTCs), and particularly, microcarcinomas – comprise a significant portion of this increased incidence, with reported percentages between 3% and 75.5% [3, 5, 6, 7, 8, 9, 10, 11, 12]. IPTCs can be defined as

PTCs that are identified on pathological examination [via fine-needle aspiration (FNA) or histopathological evaluation] without any clinical or radiological suspicion for malignancy [3, 13]. However, because FNA is generally performed for the radiological evaluation of a suspected nodule, PTCs determined via histopathological examination may better correspond to the term "incidental" than those determined via FNA.

Arguments about the factors preventing preoperative diagnosis of IPTCs have been evaluated in several previous investigations. Many of these studies have investigated the background of thyroid disease associated with IPTCs [11, 14, 15, 16]. Some of these reports have stated that lymphocytic thyroiditis (LT) in the background is a major risk factor for IPTCs [15, 16], whereas multinodular hyperplasia (MNH) in the background has been reported to be a risk factor for development of IPTCs [17, 18] or to be a risk factor for multifocality of these tumours [14] in some of these studies. Some authors have investigated the relationship between surgical procedures and the detection of IPTCs, reporting that the rates of IPTCs are higher in patients with total thyroidectomy or near-total thyroidectomy [19]. Tumour size of IPTCs has also been the topic of some studies. Although the current guidelines for management of thyroid nodules recommend FNA for nodules 10 mm or larger [20], Pagni *et al*. [17] suggested that FNA should be performed for nodules 5 mm or larger in ultrasonography, and they also mentioned the false-negative results arising in nodules larger than 20 mm due to the heterogeneity of the nodule. Vasileiadis *et al*. [11] reported the association of nonincidental diagnosis with tumour size larger than 5 mm.

The prognosis of IPTCs has been the subject of several papers, particularly in terms of the presence or absence of a difference between IPTCs and nonincidental PTCs (NIPTCs). Accumulated data from the results of these studies revealed that IPTCs, in particular incidental microcarcinomas, have a more favourable prognosis than NIPTCs [11, 19, 21, 22, 23, 24]. In addition, the molecular basis of IPTCs has been investigated in previous studies. One of these studies examined the molecular features of IPTCs larger than 10 mm and reported that almost 70% of these tumours share the same molecular basis with nonincidental ones [3].

The present study mainly aims to answer three questions in a study group of patients who have undergone preoperative FNA of a nodule or nodules (not including the index tumour nodule), who have undergone total thyroidectomy, and who have undergone at least palpable lymph node dissection (at initial surgery or completion of surgery). The authors want to evaluate whether these tumours are being prevented from detection in preoperative imaging procedures. They also want to investigate whether the prognosis of these tumours, including BRAF V600 mutation as a prognostic parameter, differs from nonincidental tumours. Finally, the authors examine whether a cut-off value of 5 mm is associated with clinicopathological features in IPTCs.

Material and methods

Patient selection

Patients diagnosed with PTC in the Department of Pathology were reviewed retrospectively (between August 2007 and February 2016). The study design was approved by the local ethics committee of the university hospital. Patients were selected according to the following criteria: 1) patients who had been diagnosed with PTC, 2) patients who had undergone preoperative FNA, and/or 3) patients who had undergone total thyroidectomy with central/cervical lymph node dissection. Tumours which fulfil the criteria for diagnosis of "noninvasive follicular thyroid neoplasm with papillary-like nuclear features" [25] were excluded. There were 308 cases that met these criteria. Medical records and histopathological reports based on the hospital's database system were reviewed. BRAF V600 mutation status of the patients was obtained from records at the Laboratory of Molecular Pathology in the Department of Pathology.

Definitions of clinicopathological criteria

Ultrasonography, FNA, and histopathological reports were reviewed. The patients with inconsistent localisation of FNA and tumour localisation were grouped as "unsampled in FNA/incidental PTC (IPTC)" and patients with consistent localisation of FNA and tumour localisation were grouped as "sampled in FNA/nonincidental PTC (NIPTC)". Initially, clinicopathological features were compared between the IPTC and NIPTC groups. Then, clinicopathological features were compared between the IPTC groups by tumour size (≤ 5 mm and > 5 mm) [11, 17]. Clinical features considered for statistical analyses were as follows (Table I):

- age at time of diagnosis (< 45 years and ≥ 45 years),
- gender (male or female),
- serum levels of antithyroglobulin antibodies (anti-TG) (absent, present),
- serum levels of antithyroperoxidase antibodies (anti-TPO) (absent, present),
- postoperative radioactive iodine (RAI) therapy (absent, present),
- distant metastasis (absent, present),
- recurrence (absent, present).

Diagnosis of FNA was grouped according to the Bethesda System for Reporting Thyroid Cytopathology [4]: nondiagnostic, benign, atypia of unknown

significance/follicular lesion of unknown significance (AUS/FLUS), suspicious for follicular neoplasm (SFN), follicular neoplasm (FN), suspicious for malignancy (SFM), and malignant. Histopathological features considered for statistical analyses were as follows (Table II):

- diagnosis of FNA (nondiagnostic, benign, AUS/FLUS, SFN, FN, SFM, malignant),
- tumour surrounding LT (absent, present),
- MNH (absent, present),
- histological diagnosis (only PTC, PTC with LT, PTC with MNH),
- primary tumour diameter (PTD) (≤ 5 mm, 6-10 mm, 11-20 mm, 21-40 mm, > 40 mm) (diameter of the largest tumour focus in multifocal tumours) [26],
- status of surgical margin (tumour negative, tumour close to margin, tumour positive),
- encapsulated tumour border (absent, present),
- lymphatic vessel invasion (LVI) (absent, present),
- blood vessel invasion (BVI) (absent, present),
- perineural invasion (PNI) (absent, present),
- extrathyroidal extension (ETE) (according to the American Joint Committee on Cancer) (absent, present) [26],
- lymph node metastasis (LNM) (absent, metastasis in ≤ 5 lymph nodes, metastasis in >5 lymph nodes),
- histological variant [conventional variant PTC (CVPTC), follicular variant PTC (FVPTC), tall cell variant PTC (TCVPTC), other variants],
- tumour focality (unifocal, multifocal),
- number of samples per lobe (≤ 4 samples, 5-10 samples, 11-15 samples, totally sampled),
- laterality (unilateral, bilateral),
- BRAF V600 mutation status (wild-type, mutated).

Definition of focality and laterality

Patients with two or more foci of tumours were grouped into a multifocal group. Laterality was defined as the presence of tumours in both thyroid lobes. Multifocal tumours located in one thyroid lobe and in the isthmus were grouped as unilateral tumours.

BRAF V600 mutation analysis

Tumour tissue containing at least 30% tumour cells was isolated from the sections of 220 patients for BRAF analysis. Then, DNA purification was performed using the nucleic acid isolation kit for paraffin-embedded tissue [QIAamp DNA FFPE Tissue Kit (50), QIAGEN Catalogue No. 56404, EZ1 DNA Tissue Kit (48), QIAGEN 953034, PAXgene Tissue Containers (10), QIAGEN Catalogue No. 765112, PAXgene Tissue DNA Kit (50), QIAGEN Catalogue No. 767134]. Following the polymerase chain reaction procedures, pyrosequencing analysis was performed on PyroMarkQ24 using sequencing primers, including the Seq Primer BRAF 600 or Seq Primer BRAF 464–469 (QIAGEN Catalogue No. 970470) for BRAF.

Table I. Clinical features of patients in the study group

Clinical features		N (%) (n = 308)
Age	<45 years	110 (35.7)
	≥45 years	198 (64.3)
Mean age		48.4
Gender	Female	263 (85.4)
	Male	45 (14.6)
Preoperative diagnosis	Absent (Incidental)	86 (27.9)
	Present (Non-incidental)	222 (72.1)
Anti-thyroglobulin antibodies (n = 234)	Absent	165 (70.5)
	Present	69 (29.5)
Anti-thyroperoxidase antibodies (n = 229)	Absent	154 (67.2)
	Present	75 (32.8)
Radioactive iodine therapy	Absent	144 (46.8)
	Present	164 (53.2)
Distant metastasis	Absent	307 (99.7)
	Present	1 (0.3)
Recurrence	Absent	301 (97.7)
	Present	7 (2.3)

Statistical analyses

Results are shown as number and percentage. Both the chi-squared test (Pearson, Yates, or Fisher) and Kruskal-Wallis test (for continuous variables) were used for comparison of clinicopathological features in IPTC and NIPTC groups. These tests were also used for comparison of clinicopathological features according to the tumour size with a cut-off value of 5 mm in IPTCs. A p value < 0.05 was considered as statistically significant. IBM SPSS Statistics 20.0 (IBM Corporation, Armonk, NY, USA) was used for statistical analysis.

Results

Clinical and histopathological features of study group patients

The median age of patients was 48.4 years. The number of patients younger than 45 years was 110 (35.7%) and the number aged 45 or older was 198 (64.3%). Of the 308 patients, 263 (85.4%) were female and 45 (14.6%) were male. Antibodies for anti-TG were present in 69 (29.5%) of 234 pa-

Table II. Histopathological features of patients in the study group

Histopathological features		N (%) (n = 308)
Fine needle aspiration	Nondiagnostic	29 (9.4)
	Benign	15 (4.9)
	AUS/FLUS	47 (15.2)
	SFN	78 (25.3)
	FN	39 (12.7)
	SFM	56 (18.2)
	Malignant	44 (14.3)
Lymphocytic thyroiditis	Absent	275 (89.3)
	Present	33 (10.7)
Multinodular hyperplasia	Absent	254 (82.5)
	Present	54 (17.5)
Histological diagnosis	PTC	221 (71.8)
	PTC and LT	33 (10.7)
	PTC and MNH	54 (17.5)
Primary tumour diameter	≤ 5 mm	113 (36.7)
	6-10 mm	87 (28.2)
	11-20 mm	70 (22.7)
	21-40 mm	28 (9.1)
	> 40 mm	10 (3.2)
Surgical margin	Negative	231 (75.0)
	Close to	22 (7.1)
	Positive	55 (17.9)
Encapsulated tumour border	Absent	174 (56.5)
	Present	134 (43.5)
Lymphatic vessel invasion	Absent	269 (87.3)
	Present	39 (12.7)
Blood vessel invasion	Absent	300 (97.4)
	Present	8 (2.6)
Perineural invasion	Absent	304 (98.7)
	Present	4 (1.3)
Extrathyroidal extension	Absent	239 (77.6)
	Present	69 (22.4)
Lymph node metastasis	Absent	273 (88.6)
	Present (≤ 5)	28 (9.1)
	Present (>5)	7 (2.3)
Histological variant	CVPTC	148 (48.1)
	FVPTC	155 (50.3)
	TCVPTC	4 (1.3)
	Others (WLVPTC)	1 (0.3)
Tumour focality	Unifocal	176 (57.1)
	Multifocal	132 (42.9)
Number of samples (per lobe)	≤4	41 (13.3)
	5-10	141 (45.8)
	11-15	19 (6.2)
	Total	107 (34.7)
Laterality	Unilateral	270 (87.7)
	Bilateral	38 (12.3)
BRAF V600 (n = 220)	Wild-type	175 (79.5)
	Mutated	45 (20.5)

AUS/FLUS – atypia of unknown significance/ follicular lesion of unknown significance; SFN – suspicious for follicular neoplasia; FN – follicular neoplasia; SFM: – suspicious for malignancy; PTC – papillary thyroid carcinoma; LT – lymphocytic thyroiditis; MNH – multinodular hyperplasia; CVPTC – conventional variant of papillary thyroid carcinoma; FVPTC – follicular variant of papillary thyroid carcinoma; TCVPTC – tall cell variant of papillary thyroid carcinoma; WLVPTC – Warthin-like variant of papillary thyroid carcinoma

tients, and antibodies for anti-TPO were present in 75 (32.8%) of 229 patients. Cytological diagnosis of FNA was nondiagnostic in 29 (9.4%) of the patients, benign in 15 (4.9%), AUS/FLUS in 47 (15.2%), FNS in 78 (25.3%) (Fig. 1A, B), FN in 39 (12.7%), SFM in 56 (18.2%) (Fig. 1C, D), and malignant in 44 (14.3%). Incidental diagnosis of PTC was present in 86 (27.9%) of the patients, and the tumour was suspected preoperatively in 222 (72.1%). LT was present in 33 (11.7%) of the patients, whereas MNH was present in 54 (17.5%). PTC was not associated with either MNH or LT in 221 (71.8%) of the patients. LT was defined in tumour surrounding the thyroid in 33 (10.7%) of the patients (Fig. 2). PTC was accompanied by MNH in 54 (17.5%) of the patients. Tumour size was 5 mm or less in 113 (36.7%), 6 mm to 10 mm in 87 (28.2%), 11 mm to 20 mm in 70 (22.7%), 21 mm to 40 mm in 28 (9.1%), and greater than 40 mm in 10 (3.2%) of the patients. The surgical margin was tumour negative in 231 (75.0%) of the patients. The tumour was close to the surgical margin in 22 (7.1%) of the patients, and the tumour was present at the surgical margin in 55 (17.9%). The tumour was encapsulated in 134 (43.5%) of the patients. LVI was detected in 39 (12.7%) of the patients, whereas 8 (2.6%) revealed BVI. Invasion of perineural spaces was observed in 4 (1.3%) of the patients. ETE was present in 69 (22.4%) of the patients. LNM was detected in 35 (11.4%) of 308 patients. Metastases were present in ≤ 5 lymph nodes in 28 (9.1%) of the patients, whereas 7 (2.3%) had metastases in more than five lymph nodes. The histological variant of the tumour was CVPTC in 148 (48.1%) of the patients, FVPTC in 155 (50.3%), and TCVPTC in 4 (1.3%). One (0.3%) of the patients had a tumour revealing Warthin-like variant. Multifocality of the

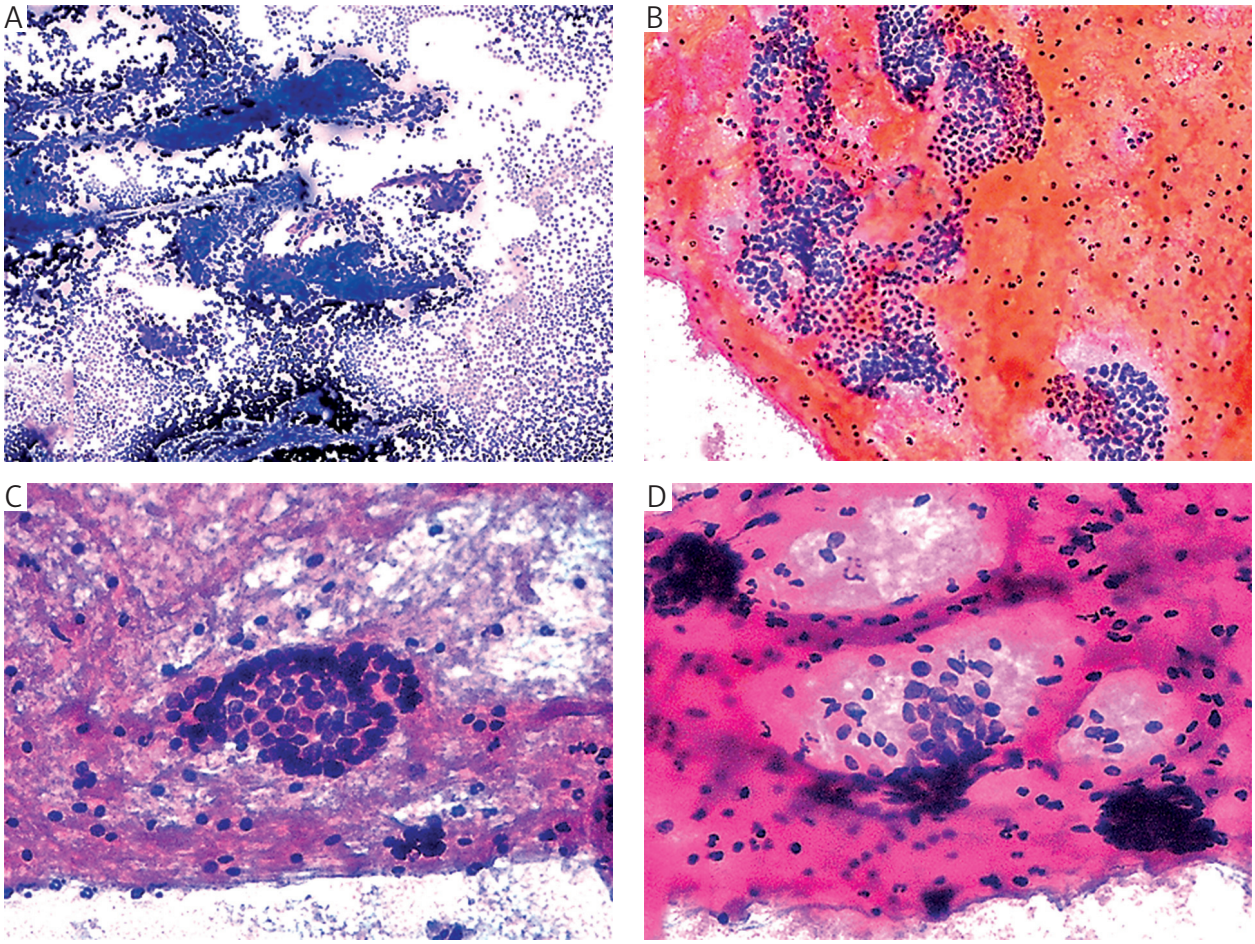

Fig. 1. Suspicious for follicular neoplasia [A) May-Grünwald Giemsa, original magnification 100×, B) Papanicolaou, original magnification 200×] and suspicious for malignancy [C, D) Papanicolaou, original magnification 400×]

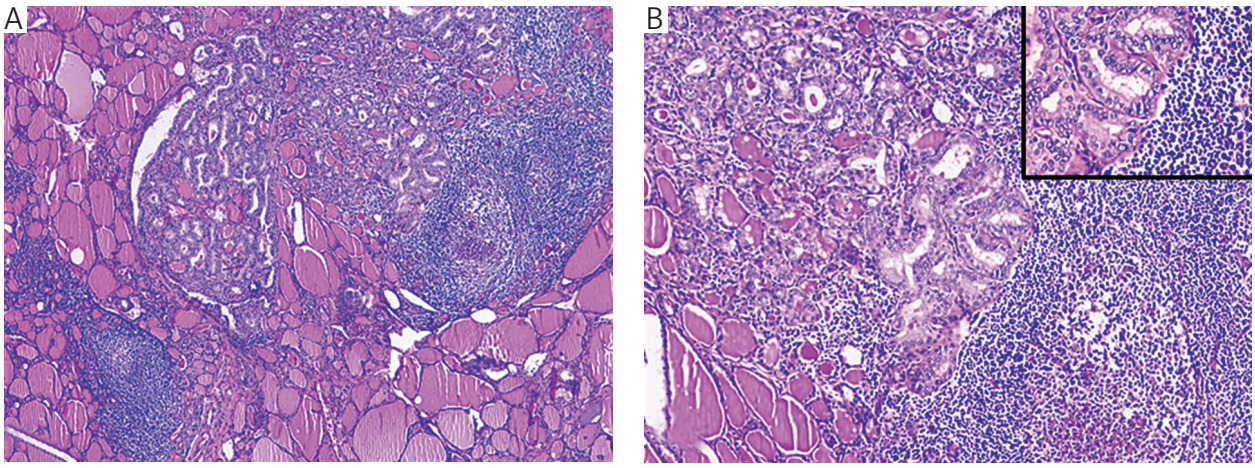

Fig. 2. Incidental papillary thyroid carcinoma in the background of lymphocytic thyroiditis [HE: A) original magnification 20×, B) original magnification 100×, insert: original magnification 400×]

tumour was defined in 132 (42.9%) of the patients. Bilateral tumours were present in 38 (12.3%) of the patients. The number of samples per lobe was 4 or less in 41 (13.3%) of the patients, 5 to 10 in 141 (45.8%), and 11 to 15 in 19 (6.2%), and all of the specimens were sampled in 107 (34.7%) of the patients (Fig. 3). BRAF V600 mutation was detected in 45 (20.5%) of the 220 patients analysed for mutation. RAI therapy was present in 164 (53.2%) of the patients. One (0.3%) of the patients had distant metastasis, whereas 7 (2.3%) of them recurred during follow-up (Tables I and II).

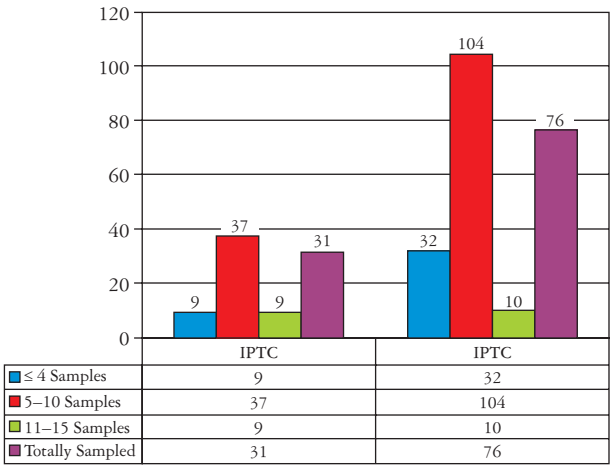

Fig. 3. Relationship between number of samples and incidental and nonincidental diagnosis of papillary thyroid carcinoma (IPTC – incidental papillary thyroid carcinoma, NIPTC – nonincidental papillary thyroid carcinoma)

Comparisons of clinicopathological and molecular features between IPTC and NIPTC

Clinicopathological features were compared between groups consisting of IPTC and NIPTC (Table III). Older age ($p = 0.014$), female gender ($p = 0.029$), presence of LT in tumour surrounding thyroid ($p < 0.001$), presence of MNH in tumour surrounding the thyroid ($p < 0.001$), smaller tumour size ($p < 0.001$), absence of tumour at surgical margin ($p < 0.001$), and lack of a tumour capsule ($p < 0.001$) were more commonly described in IPTCs. Histological diagnosis of PTC associated with MNH was more common than the diagnosis of solely PTC or the diagnosis of PTC associated with LT ($p < 0.001$). The most common cytological diagnosis was SFN in IPTCs, and the most common cytological diagnosis was SFM in NIPTCs ($p < 0.001$). The cytological diagnosis as nondiagnostic, benign cytology,

Table III. Comparisons of clinicopathological and molecular features between IPTCs and NIPTCs

Clinicopathological feature		Incidental PTC	Non-incidental PTC	Total (n = 308)	p
Age		51.34±10.29	47.26±12.80		0.014
Gender	Female	80 (30.4)	183 (69.6)	263	0.029
	Male	6 (13.3)	39 (86.7)	45	
Anti-thyroglobulin antibodies	Absent	51 (30.9)	114 (69.1)	165	0.302
	Present	16 (23.2)	53 (76.8)	69	
Anti-thyroperoxidase antibodies	Absent	44 (28.6)	110 (71.4)	154	1.000
	Present	22 (29.3)	53 (70.7)	75	
Fine needle aspiration	Nondiagnostic	11 (12.8)	18 (8.1)	29	<0.001
	Benign	7 (8.2)	8 (3.6)	15	
	AUS/FLUS	17 (20.0)	30 (13.5)	47	
	SFN	34 (40.0)	44 (19.8)	78	
	FN	9 (10.6)	30 (13.5)	39	
	SFM	7 (8.2)	49 (22.1)	56	
	Malignant	1 (1.2)	43 (19.4)	44	
Lymphocytic thyroiditis	Absent	65 (23.6)	210 (76.4)	275	<0.001
	Present	21 (63.6)	12 (36.4)	33	
Multinodular hyperplasia	Absent	38 (15.0)	216 (85.0)	254	<0.001
	Present	48 (88.9)	6 (11.1)	54	
Histological diagnosis	PTC	17 (7.7)	204 (92.3)	221	<0.001
	PTC and LT	21 (63.6)	12 (36.4)	33	
	PTC and MNH	48 (88.9)	6 (11.1)	54	
Primary tumour diameter	≤5 mm	72 (63.7)	41 (36.3)	113	<0.001
	6-10 mm	9 (10.3)	78 (89.7)	87	
	11-20 mm	3 (4.3)	67 (95.7)	70	
	21-40 mm	2 (7.1)	26 (92.9)	28	
	>40 mm	0 (0.0)	10 (100.0)	10	

Table III. Cont.

Clinicopathological feature		Incidental PTC	Non-incidental PTC	Total (n = 308)	p
Surgical margin	Negative	81 (35.1)	150 (64.9)	231	<0.001
	Close to	5 (22.7)	17 (77.3)	22	
	Positive	0 (0.0)	55 (100.0)	55	
Encapsulated tumour border	Absent	63 (36.2)	111 (63.8)	174	<0.001
	Present	23 (17.2)	111 (82.8)	134	
Lymphatic vessel invasion	Absent	85 (31.6)	184 (68.4)	269	<0.001
	Present	1 (2.6)	38 (97.4)	39	
Blood vessel invasion	Absent	86 (28.7)	214 (71.3)	300	0.070
	Present	0 (0.0)	8 (100.0)	8	
Perineural invasion	Absent	86 (28.3)	218 (71.7)	304	0.268
	Present	0 (0.0)	4 (100.0)	4	
Extrathyroidal extension	Absent	83 (34.7)	156 (65.3)	239	<0.001
	Present	3 (4.3)	66 (95.7)	69	
Lymph node metastasis	Absent	85 (31.1)	188 (68.9)	273	0.002
	Present (≤5)	1 (3.6)	27 (96.4)	28	
	Present (>5)	0 (0.0)	7 (100.0)	7	
Histological variant	CVPTC	46 (31.1)	102 (68.9)	148	0.249
	FVPTC	40 (25.8)	115 (74.2)	155	
	TCVPTC	0 (0.0)	4 (100.0)	4	
	Others (WLVPTC)	0 (0.0)	1 (100.0)	1	
Tumour focality	Unifocal	58 (33.0)	118 (67.0)	176	0.023
	Multifocal	28 (21.2)	104 (78.8)	132	
Number of samples (per lobe)	≤4	9 (22.0)	32 (78.0)	41	0.208
	5-10	37 (26.2)	104 (73.8)	141	
	11-15	9 (47.4)	10 (52.6)	19	
	Total	31 (29.0)	76 (71.0)	107	
Laterality	Unilateral	84 (31.1)	186 (68.9)	270	0.002
	Bilateral	2 (5.3)	36 (94.7)	38	
BRAF V600	Wild-type	66 (37.7)	109 (62.3)	175	<0.001
	Mutated	3 (6.7)	42 (93.3)	45	
Radioactive iodine therapy	Absent	70 (48.6)	74 (51.4)	144	<0.001
	Present	16 (9.8)	148 (90.2)	164	
Distant metastasis	Absent	86 (28.0)	221 (72.0)	307	0.721
	Present	0 (0.0)	1 (100.0)	1	
Recurrence	Absent	86 (28.6)	215 (96.8)	301	0.098
	Present	0 (0.0)	7 (100.0)	7	
Tumour foci	Numeric	1.53 ±0.95	1.98 ±1.50		0.010

IPTC – incidental papillary thyroid carcinoma; NIPTC – non-incidental papillary thyroid carcinoma; PTC – papillary thyroid carcinoma; LT – lymphocytic thyroiditis; MNH – multinodular hyperplasia; AUS/FLUS – atypia of unknown significance/follicular lesion of unknown significance; SFN – suspicious for follicular neoplasia; FN – follicular neoplasia; SFM – suspicious for malignancy; CVPTC – conventional variant of papillary thyroid carcinoma; FVPTC – follicular variant of papillary thyroid carcinoma; TCVPTC – tall cell variant of papillary thyroid carcinoma; WLVPTC – Warthin-like variant of papillary thyroid carcinoma

AUS/FLUS, and SFN was more common in IPTCs than NIPTCs, whereas diagnosis as FN, SFM, and malignant cytology was more common in NIPTCs than IPTCs. Tumour size was 5 mm or less in most IPTCs (72/86, 63.7%), whereas it was larger than 40 mm in most NIPTCs ($p < 0.001$). Presence of LVI ($p < 0.001$), LNM ($p = 0.002$), ETE ($p < 0.001$), multifocality ($p = 0.023$), bilaterality ($p = 0.002$), BRAF mutation ($p < 0.001$), and RAI ($p < 0.001$) was significantly associated with nonincidental diagnosis. The mean number of tumour foci was higher in NIPTCs than in IPTCs (1.98 ±1.50 vs. 1.53 ±0.95) ($p = 0.010$). The rate of recurrence was higher in NIPTCs without significance ($p = 0.098$). Namely, all seven patients with recurrence during follow-up were in the NIPTC group.

Comparisons of clinicopathological and molecular features in IPTCs by tumour size (PTD ≤ 5 mm and PTD > 5 mm)

Clinicopathological features were compared by tumour size with a cut-off value of 5 mm in IPTCs (Table IV). Younger age ($p = 0.05$), infiltrative tumour border ($p = 0.002$), unilateral disease ($p = 0.025$), and absence of RAI ($p < 0.001$) were significantly more common in IPTCs with a tumour size of 5 mm or less. BRAF V600 mutation was detected in three

Table IV. Comparisons of clinicopathological and molecular features in IPTCs by tumour size (PTD ≤ 5 mm and PTD > 5 mm)

Clinicopathological features		PTD ≤ 5 mm	PTD > 5 mm	Total (n = 86)	p
Age		50.16 ±9.80	56.28 ±11.22		0.050
Gender	Female	68 (85.0)	12 (15.0)	80	0.256
	Male	4 (66.7)	2 (33.3)	6	
Anti-thyroglobulin antibodies (n = 66)	Absent	40 (78.4)	11 (21.6)	51	0.146
	Present	15 (93.8)	1 (6.3)	16	
Anti-thyroperoxidase antibodies (n = 65)	Absent	36 (81.8)	8 (18.2)	44	0.624
	Present	18 (81.8)	4 (18.2)	22	
Fine needle aspiration	Nondiagnostic	8 (72.7)	3 (27.3)	11	0.625
	Benign	6 (85.7)	1 (14.3)	7	
	AUS/FLUS	16 (94.1)	1 (5.9)	17	
	SFN	27 (79.4)	7 (20.6)	34	
	FN	7 (77.8)	2 (22.2)	9	
	SFM	7 (100.0)	0 (0.0)	7	
	Malignant	1 (100.0)	0 (0.0)	1	
Lymphocytic thyroiditis	Absent	53 (81.5)	12 (18.5)	65	0.501
	Present	19 (90.5)	2 (9.5)	21	
Multinodular hyperplasia	Absent	31 (81.6)	7 (18.4)	38	0.887
	Present	41 (85.4)	7 (14.6)	48	
Histological diagnosis	PTC	12 (70.6)	5 (29.4)	17	0.236
	PTC and LT	19 (90.5)	2 (9.5)	21	
	PTC and MNH	41 (85.4)	7 (14.6)	48	
Surgical margin	Negative	69 (85.2)	12 (14.8)	81	0.188
	Close to	3 (60.0)	2 (40.0)	5	
Encapsulated tumour border	Absent	58 (92.1)	5 (7.9)	63	0.002
	Present	14 (60.9)	9 (39.1)	23	
Lymphatic vessel invasion	Absent	71 (83.5)	14 (16.5)	85	0.835
	Present	1 (100.0)	0 (0.0)	1	
Blood vessel invasion	Absent	72 (83.7)	14 (16.3)	86	Not calculated
	Present	–	–	–	

Table IV. Cont.

Clinicopathological features		PTD ≤ 5 mm	PTD > 5 mm	Total (n = 86)	p
Perineural invasion	Absent	72 (83.7)	14 (16.3)	86	Not calculated
	Present	–	–	–	
Extrathyroidal extension	Absent	69 (83.1)	14 (16.9)	83	0.579
	Present	3 (100.0)	0 (0.0)	3	
Lymph node metastasis	Absent	71 (83.5)	14 (16.5)	85	0.835
	Present	1 (100.0)	0 (0.0)	1	
Histological variant	CVPTC	42 (91.3)	4 (8.7)	46	0.107
	FVPTC	30 (75.0)	10 (25.0)	40	
	TCVPTC	–	–	–	
	Others (WLVPTC)	–	–	–	
Tumour focality	Unifocal	51 (87.9)	7 (12.1)	58	0.121
	Multifocal	21 (75.0)	7 (25.0)	28	
Number of samples (per lobe)	≤ 4	9 (100.0)	0 (0.0)	9	0.479
	5-10	29 (78.4)	8 (21.6)	37	
	11-15	8 (88.9)	1 (11.1)	9	
	Total	26 (83.9)	5 (16.1)	31	
Laterality	Unilateral	72 (85.7)	12 (14.3)	84	0.025
	Bilateral	0 (0.0)	2 (100.0)	2	
BRAF V600 (n = 68)	Wild-type	56 (84.8)	10 (15.2)	66	0.078
	Mutated	1 (33.3)	2 (66.7)	3	
Radioactive iodine therapy	Absent	64 (91.4)	6 (8.6)	70	< 0.001
	Present	8 (50.0)	8 (50.0)	16	
Distant metastasis	Absent	72 (83.7)	14 (16.3)	86	Not calculated
	Present	–	–	–	
Recurrence	Absent	72 (83.7)	14 (16.3)	86	Not calculated
	Present	–	–	–	
Tumour foci	Numeric	1.50 ±0.98	1.71 ±0.82		0.164

IPTC – incidental papillary thyroid carcinoma; PTD – primary tumour diameter; LT – lymphocytic thyroiditis; MNH – multinodular hyperplasia; AUS/FLUS – atypia of unknown significance/follicular lesion of unknown significance; SFN – suspicious for follicular neoplasia; FN – follicular neoplasia; SFM – suspicious for malignancy; PTC – papillary thyroid carcinoma; CVPTC – conventional variant of papillary thyroid carcinoma; FVPTC – follicular variant of papillary thyroid carcinoma; TCVPTC – tall cell variant of papillary thyroid carcinoma; WLVPTC – Warthin-like variant of papillary thyroid carcinoma.

of the patients, and two of the three had tumours larger than 5 mm (p = 0.078).

Discussion

IPTCs have an important impact on the increasing incidence of PTCs. The present study focused on IPTCs with different perspectives, including the features protecting these tumours from detection in preoperative imaging procedures, the prognosis of these tumours, and the effect of tumour size on clinicopathological features in IPTCs. The basic results of this study are outlined as follows: First, LT and MNH may either conceal or cause IPTCs. Second, IPTCs may have a more favourable prognosis than nonincidental ones (in terms of tumour size, LVI, ETE, LNM, multifocality, bilaterality, and BRAF V600 mutation), and they are more common in older patients and female patients. Finally, IPTCs 5 mm or smaller may present as unilateral tumours with infiltrative borders, particularly in younger patients, and they may not require postoperative RAI.

The incidence of IPTCs has been examined in surgical specimens and in autopsy series in several previous studies. The reported rates of IPTCs, either microcarcinomas or carcinomas larger than 10 mm, ranged between 2.3% and 75.5% in different series from various geographic regions [5, 6, 7, 10, 12, 18,

27, 28]. The informed incidence of IPTCs in autopsy series ranged between 1% and 35.6% [29, 30, 31, 32]. Two of these series included only microcarcinomas [30, 31], whereas the others consisted of both microcarcinomas and IPTCs larger than 10 mm [29, 32]. In the present study, the rate of IPTCs was determined as 27.9% in a study group consisting of patients who underwent total thyroidectomy with preoperative US and USFNA, as suggested in previous studies [14, 16]. The broad range of the incidence rates of IPTCs may be related to geographic features, radiation exposure, presence/absence or type of background thyroid disease, surgical procedure and number or procedure of sampling in macroscopy [19]. In this issue, the studies which have been performed on autopsy thyroids – one of them in our department – revealed that sampling and histological examination of whole thyroid may increase the incidence of IPTCs (partially sampled specimens vs. sampling of whole thyroid, Martinez-Tello *et al*. [31]; 4.6% vs. 22% for incidental microcarcinomas, Azatcam [32]; 11.1% vs. 28% for IPTCs, including microcarcinomas and PTCs larger than 10 mm). Neuhold *et al.* [33] reported the correlation between the number of samples per specimen and the rate of diagnosis of incidental microcarcinomas in their study. Thus, in the present study, we investigated whether the number of samples had an effect on the incidence of IPTCs. Although there was no significance in comparisons, we could detect the IPTCs more commonly in totally sampled specimens or in specimens with 5 to 10 samples per lobe. Thus, prospective studies in surgical specimens targeting detailed gross examination on the basis of detailed clinical data may reveal more appropriate information on this subject.

In terms of the background thyroid disease related to IPTCs, according to previously reported data [11, 14, 15, 16, 17], MNH and LT seemed to be the most common diseases associated with IPTCs. However, most of these studies have generally investigated only one background disease per group. In the present study, we investigated the relationship of IPTCs between LT and MNH together. The results of the study revealed that either LT-accompanied PTCs or MNH-accompanied IPTCs were more common than solely IPTCs. Yet, IPTCs with MNH were more common than IPTCs with LT [14, 34]. In the present study, LT was defined as the presence of lymphocytic infiltrate with lymphoid follicles and oncocytic metaplasia in follicular epithelial cells regardless of the status of serum antibodies, and we ignored focally lymphocytic infiltrates during the assessment. We also evaluated the relationship of incidental diagnosis with the status of autoantibodies as a separate parameter, and we documented the lack of relationship between serum autoantibodies and the incidental diagnosis. In addition, all patients underwent USFNA of a nodule other than the tumour nodule. The cytological diagnosis in FNA significantly differed between IPTCs and NIPTCs. The most common cytological diagnosis was SFN in IPTCs, and it was SFM in NIPTCs. The higher rates of SFN in IPTCs may be a reflection of the frequency of MNH as the most common background thyroid disorder in IPTCs. The multinodular appearance in MNH and the pseudonodular appearance in LT may be the reasons these tumours are concealed in US, or these diseases may be the cause of these tumours.

Pagni *et al*. [17] stated that primary tumour size may be the cause of incidental diagnosis in histopathological examination and reported that primary tumour size of 5 mm or less and tumours larger than 20 mm may hinder the preoperative diagnosis of malignancy. Vasileiadis *et al.* [11] reported the association between tumour size larger than 5 mm and nonincidental diagnosis. In the present study, 72 of 86 patients with IPTCs had tumours of 5 mm or less, as suggested in previous studies. Also, the comparisons of clinicopathological features in IPTCs according to primary tumour size with a cut-off value of 5 mm exhibited additional results in this issue. In the present study, IPTCs 5 mm or smaller were significantly associated with unilateral disease, infiltrative tumour border, younger age, and inexpediency of RAI. Thus, lack of a tumour capsule and primary tumour diameter of 5 mm or less may be other masking features of IPTCs and may prevent these tumours from being detected in preoperative radiological examinations. The presence of an IPTC larger than 5 mm in a thyroid lobectomy specimen, particularly in older patients, may require completion surgery due to the risk of bilateral disease and may also require additional sections due to the risk of indications for RAI, namely ETE.

Prognosis of IPTCs has been reported to be more favourable than NIPTCs [11, 21, 22, 24, 35]. In the present study, clinicopathological features and the BRAF V600 mutation status as a probable prognostic factor were compared between IPTCs and NIPTCs, as well as in IPTCS according to primary tumour size with a cut-off value of 5 mm. In a recent meta-analysis, it was found that the mean age for IPTCs is 47.2 years and that there is no difference between IPTCs and NIPTCs according to the patient's age [24]. The same report stated that IPTCs are more common in female patients, but without significance. In our study, IPTCs were more common in female patients and the mean age of patients was 51.3 years, which was similar to the data reported in the meta-analysis. Some studies have stated that FVPTC was the most common histological variant in IPTCs [7, 10, 17, 21], whereas other studies indicated that CVPTC was the most common variant in IPTCs [15, 18], as in our study. One of the studies

Table V. Overview of studies presenting data about incidental papillary thyroid carcinomas

Study	Year/ Country	IPTC/ PTC n (%)	Mean age	Female/ male	FNA	Surgical procedure	Predominant background disease	Predominant histological tumour type	Mean PTD (mm)	LNM (%)	ETE (%)	Multifocality (%)	Bilaterality (%)	RAI (%)	Recurrence (%)
Barbaro *et al.* [28]	2005/ Italy	12/392 (3.06)	34-72	7/5	Present	TT	NE	NE	NE	0	0	8.3	NE	NE	NE
Gulben *et al.* [18][a]	2008/ Turkey	81/475 (17)	37.0	66/15	NE	TT/PT	NE	CVPTC	6 ±2	12.3	9.9	11.1	10	37	1.2
Braddly *et al.* [27]	2009/ USA	81/678 (12)	52.0	68/13	Presentb	TT/PT	MNH	NE	2.8 ±1.7	NE	NE	27	22	27	0
Xu and Wang [37][a]	2010/ China	54/177 (30.5)	49.6	43/11	NE	PT	NE	NE	0.3 ±0.2	NE	NE	7.4	NE	NE	0
Dunki-Jacobs *et al.* [5][a]	2012/ USA	55/194 (28.4)	48.2	46/9	Present	TT/PT	NE	NE	NE	5.5	3.6	32.7	35.3	NE	NE
Nanjappa *et al.* [10]	2013/ India	37/187 (19.8)	NE	NE	Present	TT/NT/PT	STN	FVPTC	4.2 ±1.9	NE	NE	NE	NE	NE	NE
Wang *et al.* [38]	2013/ China	147/709 (20.7)	47.6	126/21	NE	TT/NT/PT	NE	NE	4.4 ±2.2	6.1	0.7	12.9	6.8	NE	5.4
Ergin *et al.* [39]	2014/ USA	134/248 (54.0)	53.0	118/16	Present[b]	TT	MNH	NE	5	6.8	NE	37.5	NE	NE	NE
Pagni *et al.* [17]	2014/ Italy	45.2 127/281	NE	NE	Present	TT/PT	HT	FVPTC	NE	NE	NE	NE	NE	NE	NE
Vasileiadis *et al.* [11][a]	2014/ Greece	258/339 (76.1)	50.8	216/42	Present	TT	NE	NE	3.1 ±2.2	4.7	2.3	29.5	19.4	NE	0.4
Slijepcevic *et al.* [16]	2015/ Serbia	403/2466 (16.3)	NE	345/58	Present[b]	PT/TT	MNH	NE	NE	NE	NE	NE	NE	NE	NE
Can *et al.* (present study)	2017/ Turkey	86/308 (27.9)	48.4	80/6	Present	TT	MNH	CVPTC	1.5 ±0.9	1.2	4.3	21.2	5.3	9.8	0

[a]Studies included only papillary microcarcinomas
[b]For some of the patients in the group
IPTC – incidental papillary thyroid carcinoma; PTC – papillary thyroid carcinoma; NE – not evaluated for incidental papillary thyroid carcinoma; FNA – fine needle aspiration; PTD – primary tumour diameter; LNM – lymph node metastasis; ETE – extrathyroidal extension, RAI – radioactive iodine therapy; TT – total thyroidectomy, NT – near-total thyroidectomy; PT – partial thyroidectomy; MNH – multinodular hyperplasia; STN – solitary thyroid nodule; HT – Hashimoto's thyroiditis; CVPTC – conventional variant of papillary thyroid carcinoma; FVPTC – follicular variant of papillary thyroid carcinoma

was performed in a nearby geographic region and reported similar results to our study by declaring the most common histology as CVPTC in IPTCs [18]. The occurrence of such a difference may be associated with geographic features and/or with the properties of the study groups. Poor prognostic features such as larger tumour size, ETE, LNM, LVI, multifocality, bilaterality, BRAF V600 mutation, and requirement of RAI were significantly more common in NIPTCs, as reported in previous studies [5, 11, 22, 24, 36]. All patients in the group had undergone at least palpable lymph node dissection, and only one patient with IPTC (1/86) had exhibited metastasis in a central lymph node. This patient was a 36-year-old woman, and total thyroidectomy was performed due to the FNA diagnosis (diagnosis of another nodule located in a contralateral lobe rather than in the tumour) as AUS/FLUS with compatible image of MNH in US. The tumour was defined by histopathological examination of 15 samples per lobe. Histological diagnosis was unifocal, unilateral CVPTC smaller than 5 mm. The tumour did not have a capsule and exhibited ETE and LVI. Molecular analysis revealed wild-type BRAF V600. ETE was present in 3 of 86 patients with IPTC, one of whom was the patient with LNM. All were female with a diagnosis of unilateral CVPTC smaller than 5 mm with infiltrative borders. One of these tumours revealed BRAF V600 mutation in molecular analysis. Seven patients with recurrence had been diagnosed as NIPTCs in the group presented in the meta-analysis reported by Mehanna *et al.* [24]. Although none of the patients in the group had undergone lymph node dissection, Gulben *et al.* [18] reported that multifocality and thyroid capsule invasion were predictors of LNM for IPTCs in their study. The presence of ETE in the only patient with LNM in our study group – consisting of patients with total thyroidectomy and at least palpable lymph node dissection – may support the results of the authors in terms of prediction of ETE for LNM. Thus, in terms of the most significant prognostic markers, including LNM and ETE, the results of the present study may reveal that female patients with a diagnosis of IPTC smaller than 5 mm with conventional histology and infiltrative tumour borders should be managed very carefully for the possibility of LNM.

An overview of some of the previous studies, including IPTCs (not all incidental thyroid carcinomas), and of the present study is given in Table V [5, 10, 11, 17, 18, 27, 28, 37, 38, 39]. Based on the profile documented in Table V, IPTCs may constitute 3% to 54% of PTCs, and they may occur more commonly in female patients older than 45 years with a background of MNH. Papillary microcarcinomas, particularly those smaller than 5 mm with either conventional or follicular variant histology, may emerge as IPTCs. Although they do not generally have aggressive clinical behaviour, they may reveal poor prognostic features, including LNM and ETE; present as multifocal and bilateral disease; and/or indicate RAI. Thus, this overview may underline the significance of patient-based clinical management in IPTCs.

The present study has some limitations such as lack of data about preoperative detailed radiological examination and the tests of thyroid functions. In addition, the retrospective design of the study may prove restrictive.

In conclusion, the present study investigated clinicopathological features of IPTCs in a study group of patients who underwent preoperative FNA of a nodule or nodules (not the index tumour nodule), total thyroidectomy, and lymph node dissection. These patients underwent all evaluation steps in the diagnostic process, and the tumours were diagnosed in the final step, namely, histopathological evaluation. The results of the present study may be more accurate for defining the term "incidental carcinoma". The main results of the present study can be summarised as follows: 1) LT and MNH may either conceal or cause IPTCs; 2) IPTCs may have a more favourable prognosis than nonincidental ones (in terms of tumour size, LVI, ETE, LNM, multifocality, bilaterality, and BRAF V600 mutation), and they are more common in older patients and female patients; and 3) IPTCs of 5 mm or less may present as unilateral tumours with infiltrative borders, particularly in younger patients, and they may not require postoperative RAI. Thus, diagnosis of IPTCs larger than 5 mm in lobectomy specimens of older patients requires awareness of bilateral disease and indications for RAI. However, aggressive features such as LNM and ETE and indication of RAI, as well as probable poor prognostic features, including multifocal and bilateral disease, may be more uncommon in IPTCs than NIPTCs, yet there is a possibility of emergence of aggressive features in IPTCs. Thus, patient-based clinical management in IPTCs may have benefits. Further studies with a larger series of patients and with complete data about the diagnostic process may provide more objective information about incidental papillary carcinomas.

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