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ORIGINAL SCIENTIFIC REPORT

Prognostic Impact of the Turin Criteria in Poorly Differentiated Thyroid Carcinoma

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Abstract

Background The Turin criteria including solid, trabecular, and/or insular architecture, lack of typical nuclear features of papillary carcinoma, and mitoses, necrosis, or convoluted nuclei were adopted in the recent 4th edition of the World Health Organization classification published in 2017.

Materials and methods Between 2006 and 2017, 11,001 cases underwent initial surgery for primary malignant thyroid tumor derived from follicular cells. A total of 75 (0.7%) cases were diagnosed with PDTC according to the 2004 WHO classification. Based on the Turin criteria, 30 (40%) cases were re-classified as PDTC-Turin (+) and 45 (60%) cases were PDTC-Turin (−). Clinicopathological features and prognosis were compared between PDTC-Turin (+) and PDTC-Turin (−).

Results Seventy-five patients (48 females and 27 males) had a median age at the time of surgery of 57 years. Preoperative diagnosis was benign in 16 (21%), follicular tumor in 40 (53%), and malignant in 19 (25%). The 5-year cause-specific survival (CSS) and disease-free survival (DFS) rates were 97% and 44% for PDTC-Turin (+) and 100% and 88% for PDTC-Turin (−). On univariate analysis, CSS and DFS rates were significantly worse in the PDTC-Turin (+) than in the PDTC-Turin (−) ($p = 0.0096$, and $p = 0.0016$). Multivariate analysis showed that Turin criteria status, Ki-67 labeling index $\geq$ 10%, and age 55 $\geq$ years were the independent prognostic factors for recurrence.

Conclusions The prevalence of PDTC diagnosed with the Turin criteria was low, but it showed more aggressive behavior. The 2017 WHO classification reflects the prognosis more accurately than the 2004 WHO classification.

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Introduction

Poorly differentiated thyroid carcinoma (PDTC) is a tumor of follicular cell origin with morphological and biological attributes intermediate between well-differentiated (follicular or papillary) thyroid carcinoma (WDTC) and anaplastic thyroid carcinoma (ATC). In 1983, Sakamoto et al. [1] proposed the new clinicopathological entity, PDTC, whose characteristic histology was the presence of solid, trabecular, and/or scirrhous patterns. Conversely, in 1984, Carcangiu et al. [2] reported the initial pathological description of the discrete category of PDTC; it required an insular pattern of growth, consistently presence of mitotic activity, capsular and blood vessel invasion, and frequent necrotic foci, sometimes leading to the formation of "peritheliomatous" structures. However, these authors used different characteristics to define this entity, resulting in a long-standing dispute regarding the appropriate pathological definition of PDTC. In 2004, the 3rd edition of the World Health organization (WHO) tumor classification defined it as a specific entity, stating that it is characterized by solid, trabecular, or insular architecture (so-called STI patterns), infiltrative growth, necrosis, and vascular invasion of follicular cell origin, with morphological and biological attributes intermediate between differentiated and anaplastic carcinoma of the thyroid [3]. In the WHO classification, STI patterns constitute a major part of the tumors. This 3rd WHO classification has been adopted by the Japanese Society of Thyroid Cancer (7th edition) [4], and STI patterns were observed histologically in ≥50% of tumors. In 2007, the Turin criteria attempted to universally define PDTC by pathologists and investigators; the criteria included: (1) the presence of a solid/trabecular/insular pattern of growth; (2) the absence of the conventional nuclear features of papillary carcinoma; and (3) the presence of at least one of the following features: convoluted nuclei, mitotic activity of ≥ 3 per 10 high-power fields (HPFs), and tumor necrosis [5].

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Recently, the Turin criteria have become widely accepted as a useful diagnostic algorithm [6–8], and they were adopted in the more recent 4th edition of the WHO classification published in 2017 [9], but the prevalence and prognosis of PDTC diagnosed with the Turin criteria are uncertain.

Materials and methods

Patient selection

A total of 11,001 cases underwent initial surgery for primary malignant thyroid tumor derived from follicular cells at Ito Hospital in Tokyo between 2006 and 2017. Of these, 676 cases were histologically diagnosed as FTC excluding Hurthle cell carcinoma and 75 (0.7%) cases were diagnosed with PDTC according to the 2004 WHO classification. At the beginning of this study, all PDTCs were reviewed by an experienced endocrine pathologist (T. K.), a co-author of this study, blinded to patients' outcomes. The following parameters were evaluated: percentage of STI patterns, presence of tumor necrosis, mitoses, and convoluted nuclei according to the Turin criteria (Fig. 1). Based on the Turin criteria (2017 WHO classification), 30 cases were re-classified as PDTC-Turin (+) and 45 cases were PDTC-Turin (−). All PDTC cases according to the 2004 WHO classification showed histologically major (≥50%) STI patterns. In 676 FTC cases, 54 cases showed histologically minor (≥10% and <50%) STI patterns. We further subcategorized FTC into two groups: pure FTC and FTC with minor STI patterns. All patients were retrospectively staged according to the 8th TNM classification [10].

Ultrasonographic evaluation and fine-needle aspiration biopsy cytology (FNABC)

The ultrasound scanners used were HDI 5000 7–15-MHz liner probe (Philips Medical Systems, Bothell, Wash. USA), LOGIQ9 7–15-MHz linear probe (GE Medical Systems), Voluson 730 and E8 (GE Medical Systems), and Toshiba Aplio and Xario (Canon Medical System). All patients underwent ultrasonography preoperatively. The ultrasonographic (US) features of the thyroid nodules were evaluated based on shape, margin, echotexture, echogenicity, cystic features, and calcification. The US diagnosis of the thyroid nodules was classified into three categories: benign (hyperplastic nodule), indeterminate (follicular adenoma or follicular tumor), and malignant (follicular thyroid carcinoma or poorly thyroid carcinoma) using original criteria in our hospital [11]. The FNABC was performed under US guidance. FNABC was diagnosed by the Bethesda System for

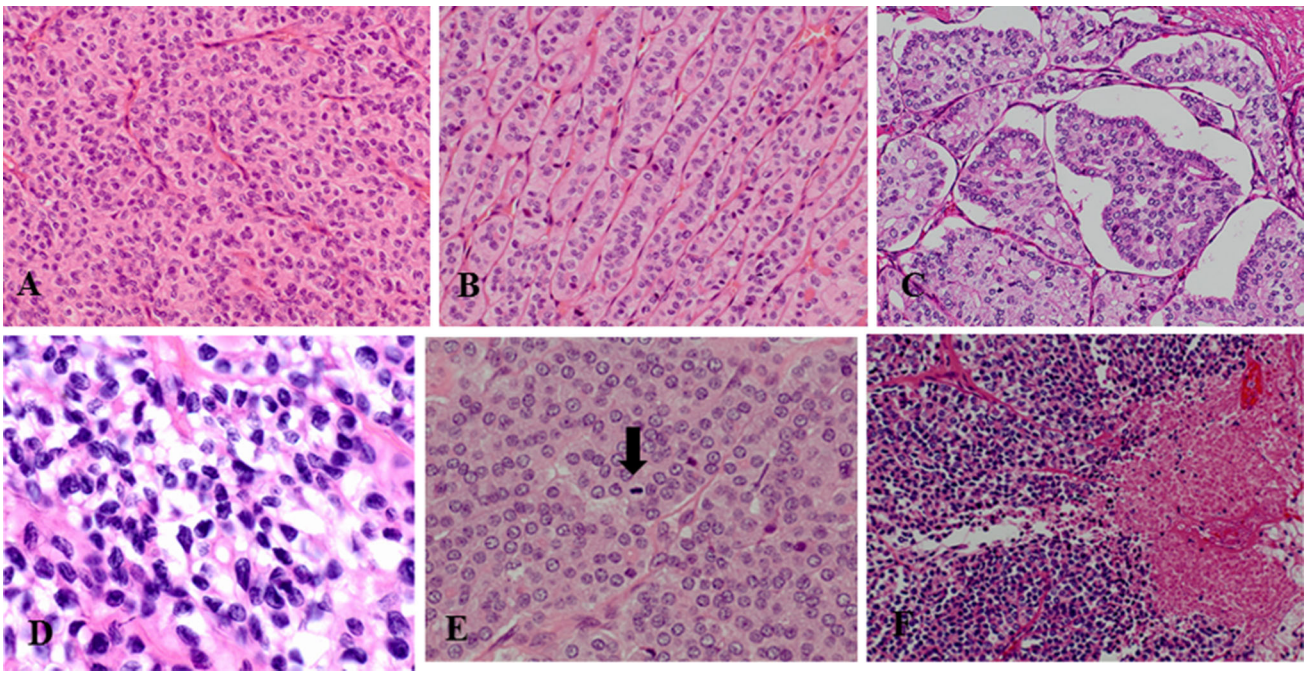

Fig. 1 Poorly differentiated thyroid carcinoma. **a** Solid growth pattern. **b** Trabecular growth pattern. **c** Insular growth pattern. **d** Convoluted nuclei. **e** Mitoses. **f** Tumor necrosis

Reporting Thyroid Cytopathology. The thyroid nodule was classified into six categories: benign, atypia of undetermined significance (AUS) or follicular lesion of undetermined significance (FLUS), follicular neoplasm (FN) or suspicious for a follicular neoplasm (SFN), suspicious of malignancy, and malignant [12].

Statistical analysis

The Kaplan–Meier method was used to calculate the cumulative survival rate of patients from the date of diagnosis to the date of recurrence, death, or the most recent follow-up examination. Disease-free survival (DFS) rates were calculated in patients who underwent curative surgery without distant metastases at diagnosis. The impact of various factors on survival was analyzed by the log-rank test. Multivariate analyses of prognostic factors were based on the Cox proportional hazards model. A p value less than 0.05 was considered significant. All statistical analyses were performed with computer software (JMP ver. 12.0; SAS Institute Inc, Cary, NC).

Immunohistochemical (IHC) analysis

Immunohistochemical analysis was performed on 3-μm-thick sections of formalin-fixed and paraffin-embedded tissues. Deparaffinized sections were incubated with a mouse monoclonal antibody against Ki-67 (MIB-1, Dako, Glostrup, Denmark) at room temperature for 2 h. Inhibiting endogenous peroxidase and antigen retrieval by autoclaving (120 °C, 10 min in citrate buffer) was performed before each primary antibody reaction. To visualize the reaction, the labeled polymer method (Histofine Simple Stain MAX PO, Nichirei, Japan) was used according to the manufacturer's instructions. The Ki-67 labeling index (LI) was evaluated in the 57 PDTCs. Other 18 patients with strong calcification could not be evaluated. To estimate the Ki-67 LI, the hot area was examined under 400 × magnification, and the percentage of cancer cell nuclei stained positively was calculated.

Results

Patients' clinical characteristics

The clinical characteristics of the 547 FTC cases, the 54 FTC with minor STI patterns, the 45 PDTC-Turin (−), and the 30 PDTC-Turin (+) cases are shown in Table 1. Distant metastases (M1) were diagnosed by CT scan and whole-body scintigraphy after total thyroidectomy. In 75 PDTC cases, the locations of distant metastases were lung in 6 (67%) cases and lung and bone in 3 (33%) cases. During a median follow-up of 5 years, 18 (24%) patients developed distant recurrence. Preoperative diagnosis was benign in 16 (21%), follicular tumor in 40 (53%), and malignant in 19 (25%). At initial surgery, 36 (48%) of the PDTC cases

Table 1 Clinical characteristics in patients with FTC and PDTC

Clinical characteristics	Category	Histopathological diagnosis by 2004 WHO classification *n* (%)			
		FTC		FTC	
		Others	Minor STT (+)	Turin (−)	Turin (+)
Sex ratio	Male/female	131/416 (24/76)	19/35 (35/65)	17/28 (38/62)	10/20 (33/67)
Age at diagnosis	Median (range)	50 (10–85)	63 (30–88)	54 (19–83)	62 (29–80)
	55 ≥	223 (41)	37 (69)	22 (49)	19 (63)
Maximum tumor size (mm)	Median (range)	41 (2–130)	48 (14–123)	50 (20–125)	53 (12–130)
	40 ≥	304 (56)	40 (74)	34 (76)	20 (67)
Distant metastasis at diagnosis (M1)	Present	21 (4)	19 (35)	2 (4)	7 (23)
Extra-thyroidal invasion	Present	4 (1)	3 (6)	0 (0)	10 (33)
Complete resection	Present	546 (99.8)	54 (100)	45 (100)	29 (97)
Total thyroidectomy	Present	320 (59)	49 (91)	33 (73)	28 (93)
RAI (after TT)	Present	264 (83)	44 (90)	29 (85)	25 (89)
Local recurrence	Present/absent	13/532 (2/98)	5/47 (10/90)	2/43 (4/96)	6/21 (22/78)
Recurrence and/or distant metastasis	Present/absent	43/482 (8/92)	8/27 (23/77)	6/37 (14/86)	11/10 (52/47)

underwent total thyroidectomy and 39 (52%) underwent lobectomy. After pathological diagnosis, 25 cases underwent completion total thyroidectomy; all 61 (81%) cases underwent total thyroidectomy. In 74 (99%) of the PDTC cases, complete resection (R0) was performed, and only one patient underwent incomplete resection (R2) because of massive invasion of the trachea and larynx. Lymph node dissection was performed in 15 (20%) cases because they had preoperatively detectable lymph node metastases. Central lymph node dissection and unilateral modified lymph node dissection were performed for 8 and 7 cases, respectively.

In our institution, RAI therapy was usually recommended after total thyroidectomy when the postoperative diagnosis was PDTC. Fifty-four (89%) cases that underwent total thyroidectomy received RAI after initial surgery. The remaining 7 (11%) cases did not receive RAI therapy because of their older age or refusing the therapy. High-dose RAI treatment was conducted in 15 cases with uptake of ^{131}I for distant metastases. Of 74 cases who underwent complete resection, 8 (11%) cases had lymph node recurrences, and all cases underwent re-operation. In Japan, molecular target drugs were approved in 2014. Of 7(9%) PDTC cases treated with them for progressive distant metastases, 3 had stable disease (SD), 3 had partial response (PR), and one had progressive disease (PD). Four (6%) of the 75 PDTC cases died of thyroid carcinoma after a median follow-up of 63 (range 0.1–157) months. Death was related to PDTC in three cases with distant metastases and one case with local progression of anaplastic transformation. The prevalence and prognosis of other large series of PDTC are summarized in Table 2 [6, 8, 13–15].

US findings

The results of US findings in four groups are shown in Table 3. The common US findings of PDTC were irregular shape (73%), indistinct margin (60%), heterogeneous echogenicity (77%), and hypoechogenicity (97%). The US diagnosis of indeterminate or malignant was significantly more frequent in PDTC (87%) than in FTC (69%) ($p = 0.03$, Fisher's test), as shown in Table 4.

Results of fine-needle aspiration biopsy cytology

In 676 cases, 674 (99.7%) underwent FNABC. The results of FNABC compared between four groups are shown in Table 5. In 28 PDTC-Turin (+) cases, 14 (50%) cases were diagnosed as suspicious of malignancy and malignant, and 5 (18%) cases were diagnosed with PDTC. The presence of diagnosed follicular neoplasm or malignancy was significantly higher in PDTC-Turin (+) (82%) than in FTC (40%) cases ($p = 0.04$, Fisher's test), as shown in Table 6.

CSS and DFS of cases with FTC and PDTC

With a median follow-up of 5 years, four cases of PDTC-Turin (+) and eight cases of FTC (of two cases with minor STI patterns) died due to the disease. The CSS and DFS rates were compared with four groups: pure FTC, FTC with

Table 2 Comparison among different published series in PDTC

Study (year)	Criteria	Number of patients	Period	Prevalence (%)	Median age (range)	Gender (M/F)	M1 (%)	5-year CSS	10-year CSS	5-year DFS	10-year DFS	Median follow-up (mo)
Hiltzik [13] (2006)	HHG	58	1992–2004	N/A	57 (6–93)	28/30	38 (66)	60%	N/A	25%	N/A	43 (4–205)
Ito [14] (2008)	2004 WHO (PTC)	15	1987–1995	0.8	N/A	2/13	1 (7)	N/A	80%	N/A	54%	160 (6–228)
	2017 WHO (Turin)	5		03		1/4	1 (20)		60%		25%	
Asioli [6] (2010)	Mayo Clinic (Turin)	56	1995–2000	1 8	61 (14–90)	27/29	N/A	69%	46%	N/A	N/A	N/A
	University of Turin	96	1974–2008	67		31/65		74%	46%			
	Total	152	1974–2008	2 7		58/94		72%	46%			
Ibrahimpasic [15] (2014)	HHG	91	1986–2009	N/A	59 (16–93)	35/56	24 (26)	66%	N/A	N/A	N/A	50 (1–215)
Gnemmi [8] (2013)	2017 WHO (Turin)	46	2000–2010	N/A	56 (47–69)	20/26	N/A	73%	N/A	59%	N/A	68 (39–101)
	HHG	50	2000–2010		55 (45–67)	19/31		72%		62%		
This study	2004 WHO	75	2006–2017	0.6	57 (19–83)	27/48	12	99%	88%	75%	66%	63 (0.1–157)
	2017 WHO (Turin)	30		0 2	62 (29–80)	10/20	23	97%	69%	44%	44%	

HHG Hiltzik' histological grade, *N/A* not available

minor STI patterns, PDTC-Turin (−), and PDTC-Turin (+), as shown in Fig. 2. The CSS rates at 5 and 10 years for these groups were 99% and 97% for pure FTC and 97% and 94% for FTC with minor STI and 100% and 100% for PDTC-Turin (−) and 97% and 69% for PDTC-Turin (+), respectively. The CSS of PDTC-Turin (+) was poorer than pure FTC and FTC with minor STI, although the difference was not significant (Fig. 2a). The DFS rates at 5 and 10 years for these groups were 92% and 86% for pure FTC and 72% and 67% for FTC with minor STI and 89% and 78% for PDTC-Turin (−) and 44% and 44% for PDTC-Turin (+), respectively. The DFS of PDTC-Turin (+) was significantly poorer than that of pure FTC ($p < 0.0001$) and that of FTC with STI ($p = 0.0048$) (Fig. 2b).

CSS and DFS of cases with PDTC

As for PDTC, 30 cases were re-classified as PDTC-Turin (+) and 40 cases were PDTC-Turin (−). On univariate analysis, CSS rates were significantly worse in the PDTC-Turin (+) cases than in the PDTC-Turin (−) cases ($p = 0.0096$; Fig. 3a). CSS rates were significantly worse in the group with Ki-67 labeling index (LI) $\geq$ 10% than in the group with Ki-67 LI < 10% ($p = 0.0003$; Fig. 3b). CSS rates were significantly worse in the group with mitotic count $\geq$ 3 per 10 HPFs than in the group with mitotic count <3 per 10 HPFs ($p = 0.0001$; Fig. 3c). Multivariate analysis for CSS showed that there was no significant difference, because there were only four deaths.

DFS rates were significantly worse for PDTC-Turin (+) than for PDTC-Turin (−) cases ($p = 0.0016$; Fig. 4a). As for the Ki-67 LI, the risk of recurrence was higher for Ki-67 LI $\geq$ 10% than for Ki-67 LI < 10% ($p < 0.0001$; Fig. 4b). DFS rates were significantly worse in the group with mitotic count $\geq$ 3 per 10 HPFs than in the group with mitotic count <3 per 10 HPFs ($p < 0.0001$; Fig. 4c). DFS rates were significantly worse in the presence of tumor necrosis than in the absence of tumor necrosis ($p = 0.0001$; Fig. 4c). The group with age at diagnosis ≥55 years was at higher risk of recurrence than the group with age <55 years ($p = 0.0321$; Fig. 4f). Univariate analyses showed that sex, tumor size, presence of convoluted nuclei, and vascular invasion were not significantly related to CSS and DFS. Multivariate analysis was performed to study which factors (age, Turin criteria, and Ki-67 LI) were related to the prognosis of PDTC cases. Mitotic activity and tumor necrosis are the elements of the Turin criteria; therefore, these factors were excluded in the multivariate analysis, showing that Turin criteria (hazard ratio (HR) 3.9, $p = 0.0245$, CI 1.2–14.9) and Ki-67 LI $\geq$ 10% (HR 3.4, $p = 0.0385$, CI 1.1–11.1) and age $\geq$ 5 years (HR 3.6, $p = 0.0418$, CI 1.0–16.7) were the independent prognostic factors for recurrence (Table 7).

Table 3 US findings in patients with FTC and PDTC

Features	Category	Histopathological diagnosis by 2004 WHO classification *n* (%)			
		FTC		PDTC	
		Others	Minor STI (+)	Turin (−)	Turin (+)
Shape	Regular/irregular	412/135 (75/25)	27/27 (50/50)	22/23 (49/51)	8/22 (27/73)
Margin	Clear/indistinct	440/107 (80/20)	29/25 (54/46)	26/19 (58/42)	12/18 (40/60)
Echotexture	Homogeneous/heterogeneous	214/333 (39/61)	7/47 (13/87)	8/37 (18/82)	7/23 (23/77)
Echogenicity	Isoechoic/hypoechoic	179/368 (33/67)	9/45 (17/83)	5/40 (11/89)	1/29 (3/97)
Cystic features	Solid/cystic	465/82 (85/15)	48/6 (89/11)	41/4 (91/9)	28/2 (93/7)
Calcification	Presence/absence	85/462 (15/85)	12/42 (22/78)	14/31 (31/69)	12/18 (40/60)
Diagnosis	Benign/indeterminate/malignant	183/48/316 (33/9/58)	5/10/39 (9/19/72)	14/9/22 (31/20/49)	4/13/13 (14/43/43)
		547	54	45	30

Table 4 Comparison of US diagnosis between FTC and PDTC

Diagnosis of US	Histopathological diagnosis by 2017 WHO classification *n* (%)	
	FTC	PDTC
Benign	202 (31)	4 (13)
Indeterminate or malignant	444 (69)	26 (87)
	646	30

$p = 0.03$ (Fisher's test)

Discussion

The prevalence of PDTC among primary thyroid carcinomas derived from follicular cells in the USA has been reported to be 1.8% (56 of 3128), and that in northern Italy was 6.7% (96 of 1442) [6]. In other Japanese series, the prevalence of PDTC by the 2004 WHO classification and by the 2017 WHO classification was 0.8% and 0.3% [13]. In the present study, PDTC had a low prevalence of 0.7% (75 of 11,001) by the 2004 WHO classification and 0.3% (30 of 11,001) by the 2017 WHO classification (Turin criteria). In some previous reports, the mean age of cases was between 56 and 61 years, with a female predilection ranging from 1.1 to 4 [6, 8, 12–15]. In the present series, the mean age of PDTC cases was 58 years, with a female-to-male ratio of 2:1. This result was the same as previous reports.

Although the diagnosis of PDTC is made postoperative histopathology, US and FNABC have been useful for preoperative evaluation of thyroid nodule. We have demonstrated that both of US and FNABC played complementary role in diagnosing FTC [11]. Several reports have described the US findings of PDTC [16, 17]. In our series, irregular shape, indistinct margin, heterogeneous echogenicity, and hypoechogenicity were common US findings of PDTC. To our knowledge, there have been no published reports comparing US findings and FNABC of a large series of FTCs and PDTCs.

The treatment strategies for PDTC have not been standardized. Multimodal therapies including surgery, RAI

Table 5 Results of fine-needle aspiration biopsy in patients with FTC and PDTC

FNABC	Histopathological diagnosis by 2004 WHO classification *n* (%)			
	FTC		PDTC	
	Others	Minor STI (+)	Turin (−)	Turin (+)
Non-diagnostic or unsatisfactory	2 (0.4)	0 (0)	0 (0)	0 (0)
Benign	184 (34)	13 (26)	16 (35)	5 (18)
Atypia of undetermined significance or follicular lesion of undetermined significance	27 (5)	2 (4)	5 (11)	0 (0)
Follicular neoplasm or suspicious for a follicular neoplasm	296 (55)	27 (54)	21 (47)	9 (32)
Suspicious for malignancy	21 (4)	4 (8)	3 (7)	7 (25)
Malignant	7 (1)	4 (8)	0 (0)	7 (25)
	547	54	45	28

Table 6 Comparison of US diagnosis between FTC and PDTC

FNABC	Histopathological diagnosis by 2017 WHO classification *n* (%)	
	FTC	PDTC
Benign, AUS, FLUS	383 (60)	5 (18)
FN, SFN, suspicious for malignancy, malignant	247 (40)	23 (82)
	630	28

$p = 0.04$ (Fisher's test)

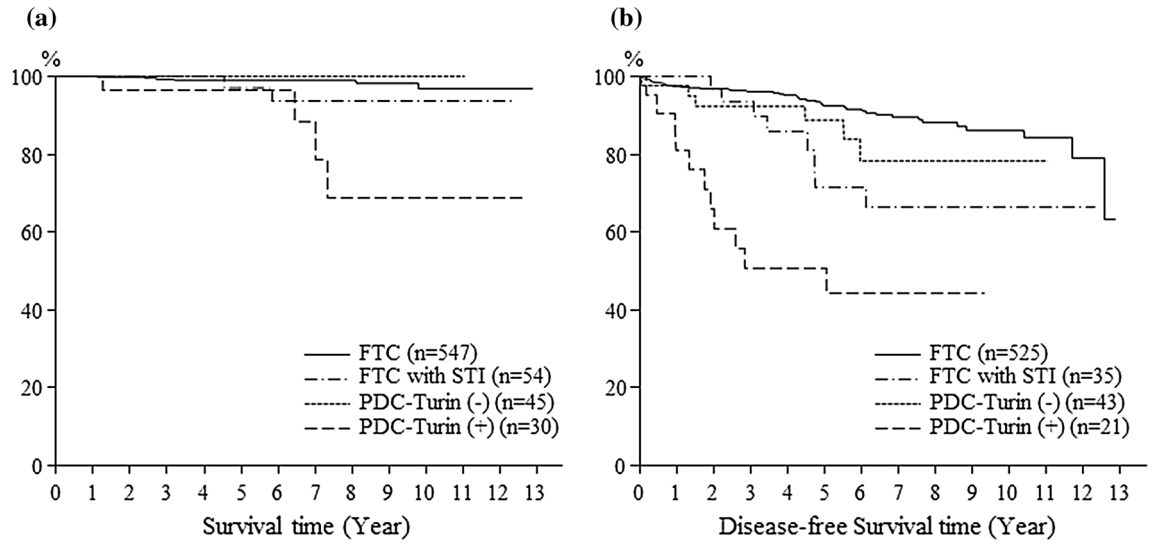

Fig. 2 **a** Kaplan–Meier survival curves of CSS for four groups: pure FTC, FTC with minor STI patterns, PDTC-Turin (−), and PDTC-Turin (+). **b** DFS for four groups: pure FTC, FTC with minor STI patterns, PDTC-Turin (−), and PDTC-Turin (+)

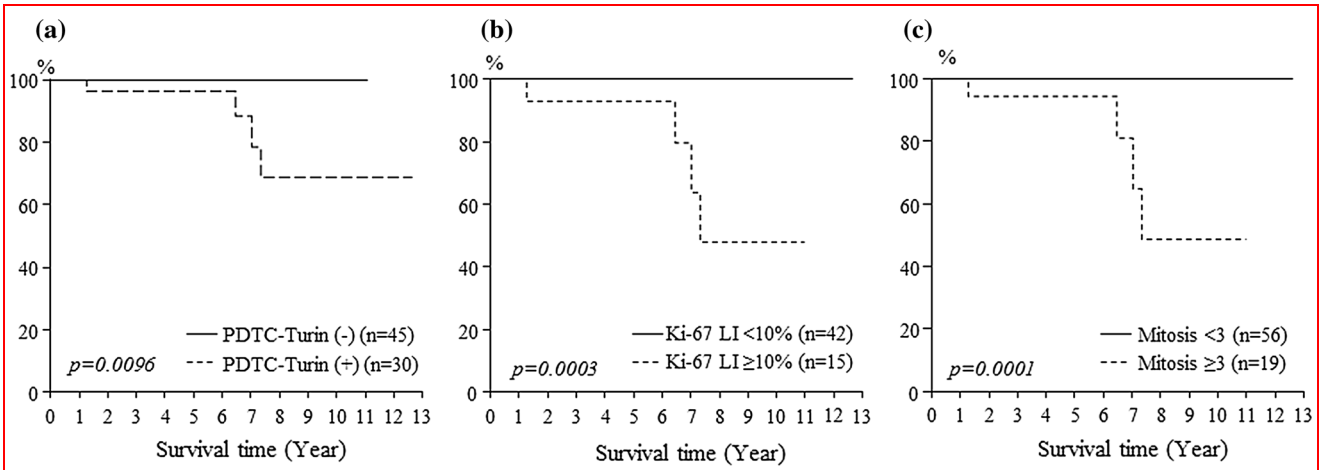

Fig. 3 Kaplan–Meier survival curves of CSS for the 75 PDTC cases. **a** Comparison between PDTC-Turin (+) and PDTC-Turin (−). **b** Comparison between the group with Ki-67 LI ≥ 10% and the group with Ki-67 LI < 10%. **c** Comparison between the group with mitotic count ≥ 3 per 10 HPFs and the group with mitotic count <3 per 10 HPFs

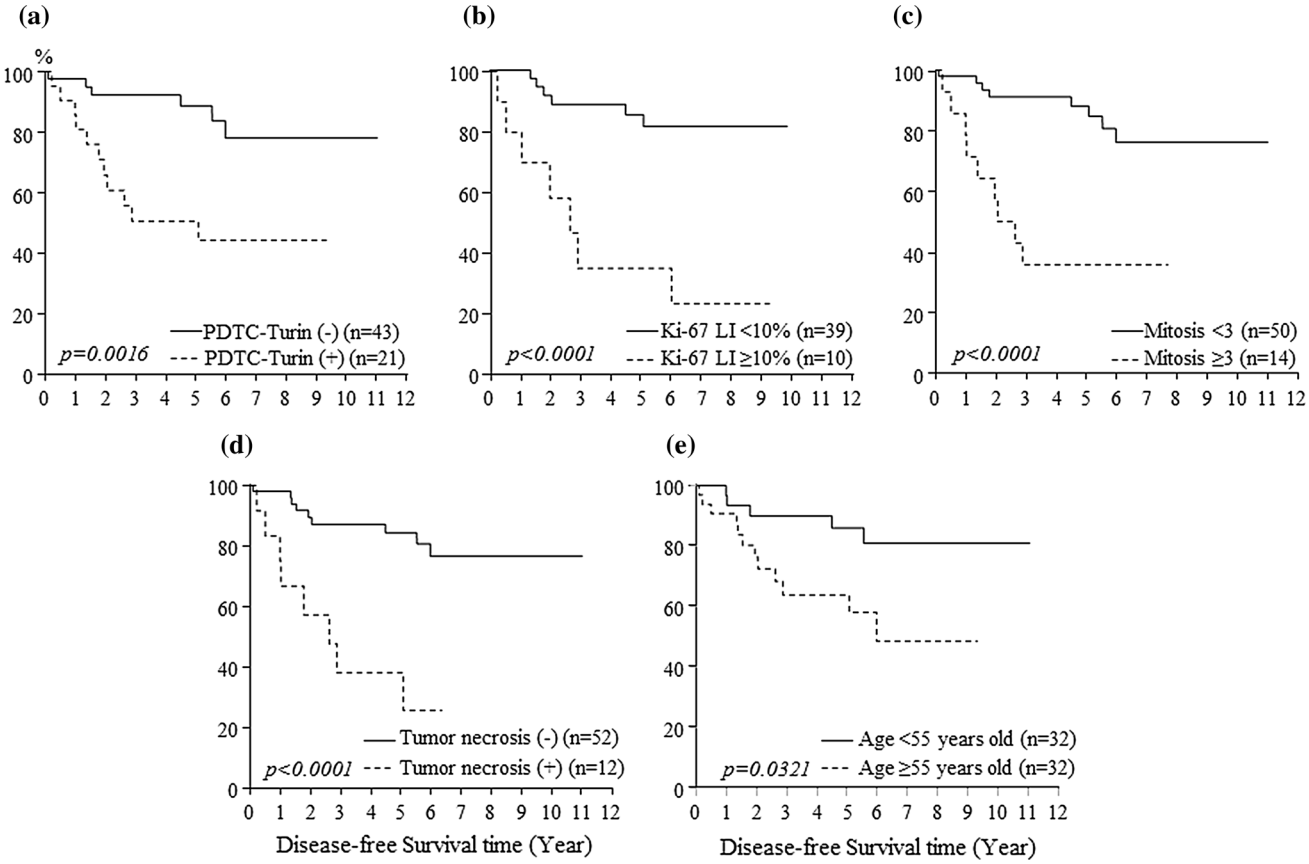

Fig. 4 Kaplan–Meier survival curves of DFS for PDTC. **a** Comparison between PDTC-Turin (+) and PDTC-Turin (−). **b** Comparison between the group with Ki-67 LI ≥ 10% and the group with Ki-67 LI < 10%. **c** Comparison between the group with mitotic count ≥3 per 10 HPFs and the group with mitotic count <3 per 10 HPFs. **d** Comparison between the group with tumor necrosis and the group without tumor necrosis. **e** Comparison between the age at diagnosis ≥55 years and age <55 years

therapy, and external beam radiotherapy have been performed. Total thyroidectomy and RAI therapy are usually recommended in cases with PDTC [18, 19]. Volante et al. [20] reported that the survival rate of cases with PDTC who were treated with high-dose RAI tended to be higher than that of cases treated without RAI. Kazarue et al. [21] reported that for patients who had insular thyroid carcinoma with distant metastasis, thyroidectomy and RAI independently improved the survival. Recently, new systemic therapies such as sorafenib [19, 22] and lenvatinib [23] were approved for the treatment of ^{131}I-refractory thyroid carcinoma. In Japan, these molecular target drugs were approved in 2014, and only seven PDTC cases received them for progressive disease. Since the follow-up periods were short, it will be necessary to accumulate clinical data and to follow up PDTC cases for a long time to observe their results. PDTC is generally considered in the middle of the spectrum between well-differentiated thyroid carcinoma and anaplastic thyroid carcinoma [20]. The prognosis of PDTC varies between the pathological criteria of PDTC. In the published series of PDTC, 5- and 10-year CSS rates were almost 70% and 46%, respectively [6, 8, 13–15]. In the present PDTC series, 5- and 10-year CSS rates were 99% and 88% for the PDTC (2004 WHO) cases and 97% and 69% for the PDTC (2017 WHO) cases, respectively. The present result showed better outcomes than previous series. In another Japanese report, the prognosis of PDTC was good [24, 25]. One possible reason may be related to dietary factors.

Volante et al. [20] reported that univariate and multivariate statistical analyses demonstrated that age >45 years, presence of necrosis, irrespective its extent, and mitotic count >3/10HPFs were associated with poor outcome. Tumor necrosis and increased mitotic activity of the Turin criteria were important histological features related to prognosis [8]. The finding of necrosis or increased mitotic activity also identifies thyroid carcinomas with poor outcomes, with considerable overlap with the Turin criteria. In the present study, univariate analysis showed that the risk of death was higher for PDTC-Turin (+), increased mitotic activity ≥3 per 10 HPFs, and Ki-67 LI ≥ 10%. Univariate analysis showed that the risk of

Table 7 Univariate and multivariate analysis of prognostic factor for recurrence

Prognostic factor for recurrence	*P* value		Risk ratio	95% CI	
	Univariate	Multivariate		Lower	Upper
Age at diagnosis ≥ 55 years	<0.0001	0.0418	3.6	1.0	16.7
Ki-67 LI ≥ 10%	0.0001	0.0385	3.4	1.1	11.1
Turin criteria	0.0016	0.0245	3.9	1.2	14.9

recurrence was higher for age ≥55 years, PDTC-Turin (+), tumor necrosis, increased mitoses, and Ki-67 LI ≥ 10%. Multivariate analysis demonstrated that the Turin criteria, Ki-67 LI ≥ 10%, and age ≥ 55 years were the independent prognostic factors for recurrence. Some studies have shown that the focal presence (≥10%) of PDTC in an otherwise well-differentiated carcinoma may be associated with aggressive features and/or may unfavorably affect prognosis [1, 26, 27]. The clinical characteristic of FTC with minor STI patterns was similar to that of PDTC-Turin (+), especially for high-risk features including age and distant metastasis. In the 54 FTC with minor STI cases, 12 (22%) cases satisfied the Turin criteria for the presence of high mitotic activity and/or tumor necrosis. The US diagnosis as indeterminate or malignant was high in FTC with minor STI (91%) as well as in PDTC-Turin (+) (86%). Interestingly, some patients with minor STI patterns showed aggressive behavior, and two fatal cases showed high mitotic activity and tumor necrosis histologically. When FTC with minor STI cases satisfies the Turin criteria, careful follow-up is necessary.

Some PDTCs arise from preexisting, well-differentiated, follicular or papillary carcinoma, whereas others are likely to arise de novo. The results of a recent large genomic study provide support for the hypothesis that PDTCs and ATCs arise from WDTC through the accumulation of genetic abnormalities [28, 29]. Previous molecular biological studies suggested that some genetic alterations involving the *RET-Ras-BRAF* signaling cascade were identified in PDTCs, and they were associated with tumor dedifferentiation [30–32]. A higher prevalence of *CTNNB1* mutation has been reported in PDTC and ATC cases [33], and mutations in other WNT pathway genes (*AX1N1* and *APC*) have been reported in <5% of PDTC cases [28]. Telomerase reverse transcriptase (*TERT*) promoter mutations have a significantly higher prevalence in aggressive thyroid tumors, including PDTC and ATC [34–37]. *AKT1* mutations have been reported in 19% of PDTC, nearly always in combination with *BRAF* mutation [38]. Further studies should be performed to assess the molecular mechanism involved in PDTC.

Immunohistochemistry (IHC) is not usually necessary to make the diagnosis, but it can be helpful to confirm follicular cell derivation. We previously reported that the highest growth activity (GA) was observed in undifferentiated carcinomas (33%), and FTCs (3%) showed a higher GA than PTCs (2%) on Ki-67 IHC analysis [39]. Ki-67 LI in WDTC and PDTC was significantly lower than in ATC [40]. A Ki-67 LI > 10% seems to be a good indicator of high risk of anaplastic transformation [41]. In the present series, univariate analysis demonstrated that Ki-67 LI ≥ 10% was a prognostic factor for death and recurrence. Moreover, multivariate analysis showed that Ki-67 LI ≥ 10% was the independent prognostic factor for recurrence. This suggests that Ki-67 expression might reflect cell proliferation and be associated with a poorer prognosis in thyroid carcinoma.

Several limitations of this study should be acknowledged. First, this study was a retrospective study, and the follow-up period was short. Further accumulation of patients' clinical data is needed. Next, patients were treated various therapies, including surgery, RAI therapy, external beam of radiotherapy, chemotherapy, and tyrosine kinase inhibitor. Therefore, it is difficult to determine which therapy is most appropriate. We usually recommend a total thyroidectomy and RAI therapy in cases with PDTC.

Conclusions

The prevalence of PDTC diagnosed with the Turin criteria was low, but it showed more aggressive behavior. The 2017 WHO classification reflects the prognosis more accurately than the 2004 WHO classification.

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