Subclassification of non-solid-type papillary thyroid carcinoma identification of high-risk group in common type

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Two hundred and sixty-three cases of primary human papillary thyroid carcinoma (PTC) were analyzed. All cases met the following parameters: tumor size ≥ 10 mm, no distant metastasis at presentation, and no coexistence of other histological type. The histological features of the solid/trabecular component, encapsulation, tall/columnar cell component and loss of polarity/cohesiveness were utilized to subclassify the 263 cases of PTC into five groups: solid type (15.6%), encapsulated group (9.5%), tall/columnar cell group (7.2%), micropapillary/discohesive group (19.8%) and not-otherwise-specified group (47.9%). We focused on the latter four non-solid groups and compared their prognosis with the solid type. The tall/columnar cell group showed the worst disease-free survival rate (DFS) analyzed by the Kaplan–Meier method, followed by the micropapillary/discohesive group. The not-otherwise-specified group and encapsulated group showed a better DFS rate than the solid type. Cancer-related death was noted in the tall/columnar cell group (21.1%) and micropapillary/discohesive group (3.8%), but not in the other groups. The four non-solid histological groups were further categorized into two prognostic groups: high-risk group (including tall/columnar cell group and micropapillary/discohesive group); and low-risk group (including encapsulated group and not-otherwise-specified group). Their 10-year disease-free survival rates were 78.7% and 93.1%, respectively. In the present study, histological grouping was significantly correlated with prognosis in the multivariate analysis according to the Cox proportional hazards regression model in addition to clinical parameters of extrathyroid invasion and gross lymph node metastasis, which predicts the patient outcome in terms of tumor recurrence and cancer-related death more precisely. (*Cancer Sci* 2008; 99: 1908–1915)

To predict the survival of patients with thyroid carcinoma, some prognostic factors (age, sex, stage of tumor, histological type of tumor, extrathyroid extension, distant metastasis, gross lymph node metastasis, completeness of resection, etc.) and scoring systems (European Organization for Research on Treatment of Cancer [EORTC]; patient age, tumor grade, extent and size [AGES]; metastasis, age, completeness of resection, invasion and tumor size [MACIS]; primary tumor, regional lymph nodes and distant metastasis [TNM]; and existing age of patient, presence of distant metastasis, extent and size of tumor [AMES]) have been reported as useful.[1–7] One of the useful histopathologic prognostic factors is the histological grade of the tumor and it is used in several scoring systems to identify patients in various risk groups.[8,9] Akslem and LiVolsi reported that the subclassification of papillary thyroid carcinoma (PTC) had only a minor prognostic impact, whereas histological grade was a strong and independent prognostic marker, and they recommended that all papillary thyroid carcinoma be given a histologic grade based on the combined examination of nuclear atypia, tumor necrosis and vascular invasion.[9] However, recent modification of the classification of thyroid tumors by the World Health Organization (WHO) did not include histological grade but maintained the traditional diagnosis for thyroid carcinoma. It states that 'a problem in using grade is that the vast majority of institutions do not grade papillary carcinoma since most are well differentiated'.[10] Our group has pointed out that subclassification of common (usual, conventional or classic) types of papillary thyroid carcinoma or non-solid-type differentiated thyroid carcinoma is possible based on histological characteristics, and this distinction, low-risk group and low-grade malignant tumors, has proved to be useful to predict tumor recurrence after surgical treatment.[11] Our low-grade malignant tumors were defined by pure histological characteristics of an invasive growth pattern and having two characteristic histological patterns, namely, loss of cellular cohesiveness and cellular polarity.[11] These new histological parameters, loss of cellular polarity and cohesiveness, were first introduced in our previous study and are seen more in cases of loss of retinoid receptor expression and high proliferation index in common types of differentiated papillary carcinoma of the thyroid.[12]

This paper subclassifies in detail non-solid-type PTC into four groups based on the histological characters of tall/columnar cell components besides loss of polarity/cohesiveness and encapsulation,[11] revealing various risk groups and identifying more useful parameters to predict patient outcome.

Materials and Methods

Patient profiles. We reviewed patients with primary papillary thyroid carcinoma who underwent primary surgical treatment in 1990 and 1991, at Kuma Hospital, Kobe, Japan. In total, 263 cases were submitted to our study. Patients with tumors less than 10 mm, or with distant metastasis at presentation were excluded from the study. Pure oxyphilic variant was excluded from our study, since it may harbor totally different genetic alterations from common type of PTC,[13] and also because of the fact that it involved a very small number of cases in our series that could not reach statistical significance. Well-differentiated tumors of uncertain malignant potential and well-differentiated carcinoma not otherwise specified, as proposed by Williams, were excluded because of diagnostic difficulty and inter-observer variation in diagnosis.[14] PTC with anaplastic transformation was also

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excluded from our study, because it is well known to have a much poorer prognosis than the common type of PTC, with overall 5-year survival ranging from 0 to 14% and median survival of 2.5–6 months.[15–17] Medullary thyroid carcinoma, malignant lymphoma, squamous cell carcinoma and intrathyroid epithelial thymoma were also excluded because of different histogenesis. Solid/trabecular/insular carcinoma with increased numbers of mitoses (≥ 3/10 per high power field [HPF]) or necrosis showing an absence of nuclear features of thyroid papillary carcinomas was also excluded from our study, since this group of carcinoma was defined as poorly differentiated carcinoma in the new modification of the WHO classification,[18] and has a relatively poor disease-free survival rate and overall survival rate. Twenty-eight (10.6%) men and 235 (89.4%) women were enrolled in this study, and their age at surgery was 46 ± 14 years (mean ± SD; median = 46). Clinically palpable lymph node metastasis (gross lymph node metastasis) before operation was found in 51 (19.4%) patients but not in 209 (79.5%) patients; details were unknown for three (1.1%) patients. Metastasis to the lymph node was histologically identified in 219 (83.3%) cases, but absent in 44 (16.7%) cases. All patients had complete follow-up data. Patients with less than 5-year follow-up were excluded. The average follow-up period was 150.09 ± 30.308 (mean ± SD) months. Recurrence (including local recurrence, lymph node metastasis and distant metastasis) during the follow-up period was examined by routine chest radiography, bone scintigraphy or computed tomography if the patients displayed symptoms or signs of recurrence. Recurrence was evident in 38 (14.4%) patients; four of 38 patients had lung metastasis, 22 of 38 patients had lymph node metastasis, five of 38 patients had recurrence in the residual thyroid, one patient had metastasis in the trachea, one patient had bone, brain and lung metastases, one patient had bone, subcutaneous tissue and muscle metastases, two patients had bone and lymph node/lung metastases, and the other two patients had subcutaneous fat and/or muscle metastases. During the follow-up period, 15 (5.7%) patients died, including six (2.3%) patients who died of cancer and nine (3.4%) who died of other causes.

Surgery was either lobectomy plus isthmectomy (LI), lobectomy only (LO), subtotal thyroidectomy (ST), or total thyroidectomy (TT). Eighty-eight patients received LI (33.5%), four LO (1.5%), 14 ST (5.3%) and 157 TT (59.7%). Lymph node dissection was performed in all patients in our analysis. In the 263 cases, five were positive for thyroid carcinoma at the surgical margin. No postoperative chemotherapy, radiation or I^{131} treatment was applied in this series of patients.

Histological examination. Histological sections from the primary tumors and their metastases were reviewed by two pathologists (K.K. and Y.B.). PTC were first categorized into two groups, solid-type and non-solid-type PTC. As in Materials and Methods, poorly differentiated carcinoma, in other words, solid/trabecular/insular carcinoma with necrosis or marked mitotic figures (≥3/10 per HPF) was excluded.[16] Non-solid-type PTC was reclassified into four groups according to the histological features of encapsulation, presence of tall cell or columnar cell components and loss of cellular polarity or cohesiveness. They were named: (1) encapsulated group; (2) tall/columnar cell group; (3) micropapillary/discohesive group; and (4) not-otherwise-specified (NOS) group. In non-solid-type PTC, there was well-encapsulated PTC with no or only minimal invasion, classified as the encapsulated group regardless of the features of tall/columnar cell component or loss of polarity/cohesiveness. Non-solid-type PTC with invasion was classified into three groups: if it contained 10% or more tall/columnar cell component, it was classified as the tall/columnar cell group; if it contained less than 10% tall/columnar cell component but with 20% or more loss of cellular polarity/cohesiveness, it was classified as the micropapillary/discohesive group; if neither the tall/columnar component nor carcinoma component occurring with loss of polarity/cohesiveness reached the above-described percentage, it was categorized into the not-otherwise-specified (NOS) group of PTC. The diagnosis procedure of our new classification is shown in Table 1. In this new classification, encapsulated follicular variant (FV) of PTC with or without minimal capsular invasion was categorized into the encapsulated group; FV of PTC with wide invasion was classified into the NOS group, since it seldom showed components with loss of cellular polarity/cohesiveness or tall/columnar cell components. The typical histological features of the five groups are shown in Fig. 1.

Statistical analysis. Time-independent, categorical and continuous data were evaluated using the χ^2 test, Fisher's exact test or Student's *t*-test as appropriate. The disease-free survival rate (DFS) was calculated from the time of primary surgery to the final contact day or the day on which recurrence was identified. DFS analysis was performed using the Kaplan–Meier method and log rank tests were used to determine prognostic factors. Univariate analyses were performed on the following parameters: histological grouping, age, sex, tumor diameter, extrathyroid invasion (Ex), pT (TNM category of UICC), gross lymph node metastasis, histological lymph node metastasis, stage grouping (TNM category of UICC) and surgical margin. All factors found to be significant by univariate analyses were subjected to multivariate analyses using the Cox proportional hazards regression model. Differences were considered significant when the *P*-value was less than 0.05. Data analysis was performed using StatView-J, version 5.0 statistical software (SAS Institute, Cary, NC, USA).

Results

Correlation between histological grouping and clinical parameters. All 25 patients classified into the encapsulated group showed no extrathyroid invasion or gross lymph node metastasis (Table 2). Patients in this group showed a tendency to have less metastatic carcinoma in the lymph nodes at surgery than any other group. This group contained four cases with tall/columnar features and three cases with micropapillary/discohesive features, and none of them recurred during the observation period. Patients in the tall/columnar cell group (average age 49.0) and solid type (average age 49.3) showed a tendency toward older age than any other group (average age of encapsulated group, NOS group and micropapillary/discohesive group: 47.1, 45.7 and 42.2, respectively), though this did not reach statistical significance. No significant correlation between histological grouping and other clinical parameter (age, sex, tumor size, Ex, pT, gross lymph node metastasis and stage grouping) was identified.

Histological grouping and recurrence or survival analyses. The postoperative recurrence rate and survival rate of patients were compared among the five groups (Table 3). The mean follow-up period using recurrence as the end point was more than 113 months in all groups. No recurrence was noted in the encapsulated group. The tall/columnar cell group and solid type showed more cases of positive recurrence than the NOS group. There was a significant difference in the recurrence rate between the NOS group and the tall/columnar cell group ($P = 0.001$), NOS group and micropapillary/discohesive group ($P = 0.0054$). No significant difference was identified between tall/columnar cell and micropapillary/discohesive groups, tall/columnar cell group and solid type, NOS group and solid type, and micropapillary/discohesive group and solid type.

The mean follow-up period for survival, using death as the end point, was more than 143 months in all groups. There was no case of cause-specific death in the encapsulated group, NOS group and solid type. Cancer-related death was identified in 21.1% (4 in 19) of tall/columnar cell group cases and 3.8% (2

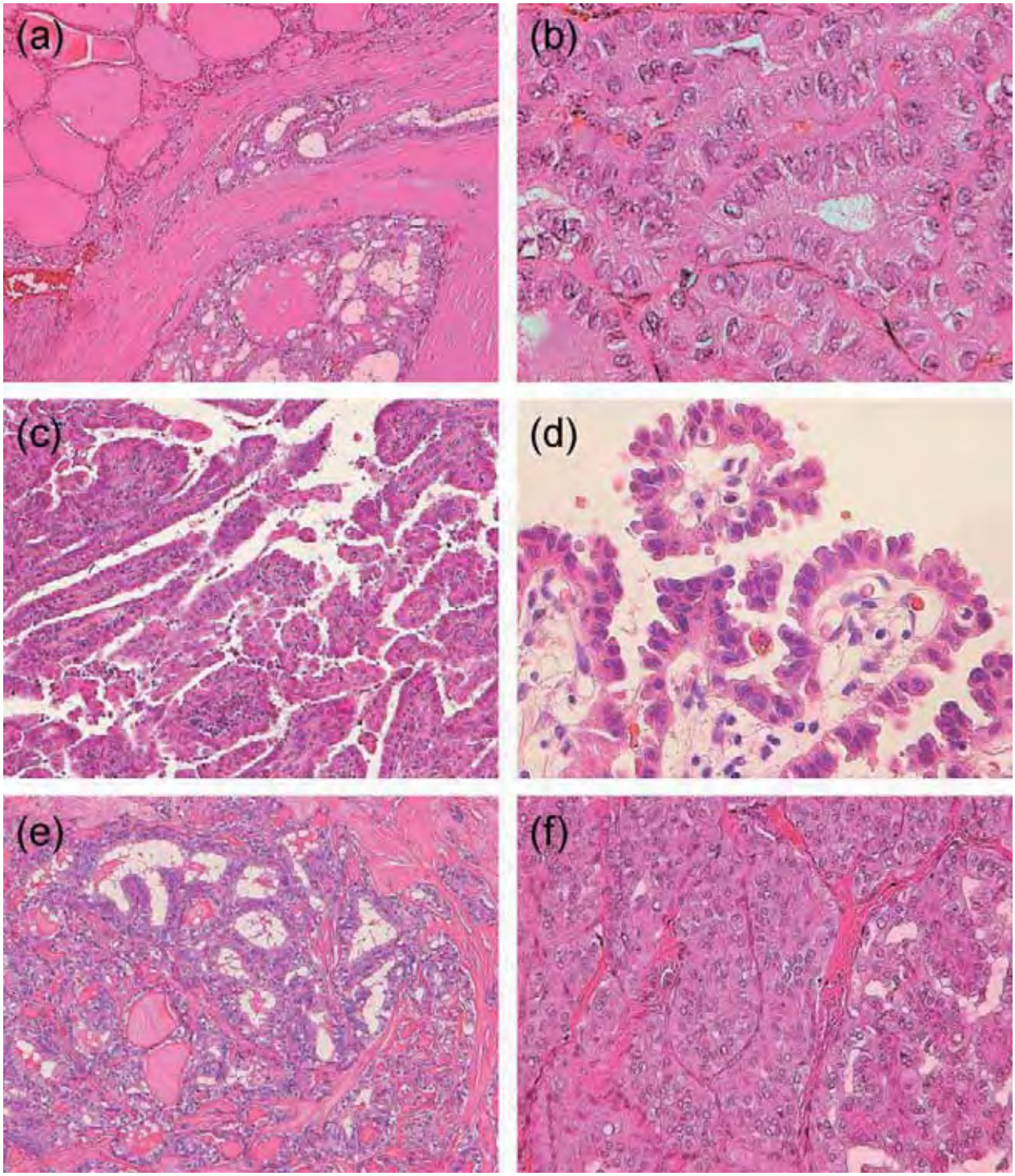

Fig. 1. Five histological subgroups of papillary thyroid carcinoma (PTC) in hematoxylin and eosin staining sections. (a) Encapsulated group. The PTC component is well capsulated by fibrous tissue showing pushing margin to the surrounding thyroid parenchyma. It may be defined as follicular variant of papillary thyroid carcinoma by some pathologists because of its prominent follicular structure, but in our category, it belongs to encapsulated group. Magnification ×20. (b) Tall/columnar cell group. The carcinoma cells show clear and abundant cytoplasm with heights at least twice their widths. Magnification ×40. (c) Micropapillary/discohesive group. Irregular micropapillary structures are covered by cuboidal or flat epithelium which is an indication of loss of polarity for PTC firstly described by Tang *et al*. in our group. In the middle part of this picture, loss of cellular cohesiveness was identified with carcinoma cells loosely or individually arranged without tubular or papillary formation. Magnification ×20. (d) Micropapillary/discohesive group. The predominant hobnail pattern of the covering epithelium in the micropapillary structure indicates loss of polarity. Magnification ×40. (e) Not-otherwise-specified group. Invasive growth of follicular epithelium shows typical nuclear features of papillary thyroid carcinoma arranged in follicular or papillary structures. No tall/columnar cell component or loss of polarity/cohesiveness is noted. It may be defined as follicular variant of papillary thyroid carcinoma by some pathologists because of its' prominent follicular structure, but in our category, it belongs to not-other-wise specified group. Magnification ×20. (f) Solid type. Notice two different growth patterns of the left (solid component) and right (papillary structure) halves, although the cytological features, overlapping of nuclei and ground grass nuclei, are same between them. Magnification ×20.

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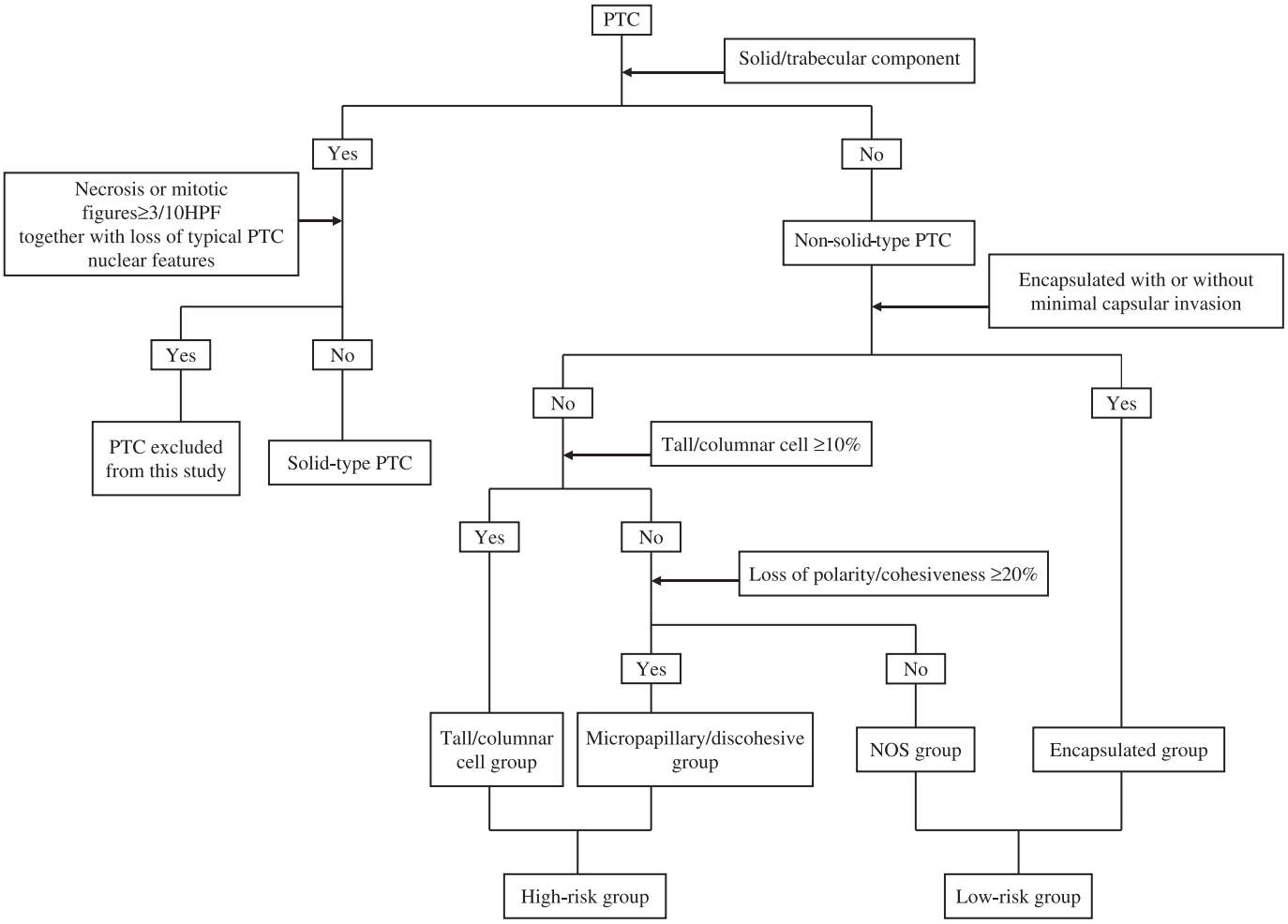
Table 1. Our suggested procedure for subclassifying papillary thyroid carcinoma (PTC; excluding those mentioned in the patient profiles)



PTC: papillary thyroid carcinoma; NOS: not-otherwise-specified. PTC was primarily divided into two types, solid type and non-solid type. The latter was further subclassified into four groups: tall/columnar cell group, micropapillary/discohesive group, NOS group and encapsulated group. The first two groups were placed in the high-risk group and the latter two groups in the low-risk group.

in 52) of micropapillary/discohesive group cases. More cancer-related death was detected in the tall/columnar cell group than in the micropapillary/discohesive group, and the difference was significant ($P = 0.0447$).

Disease-free survival rate and histological grouping. The disease-free survival (DFS) rate in the tall/columnar cell group, micropapillary/discohesive group, NOS group and solid type was analyzed using the Kaplan–Meier method with the log rank test (Fig. 2). The encapsulated group was omitted from this analysis and the subsequent univariate and multivariate analyses since no recurrence was observed. The difference in DFS between two groups was also analyzed using the Kaplan–Meier method with the log rank test. The tall/columnar cell group and micropapillary/discohesive group showed significantly poorer prognosis than the NOS group ($P = 0.0004$ and 0.0254, respectively). The solid type also showed poorer prognosis than the NOS group, although it did not reach significance ($P = 0.0576$). No significant difference in DFS was identified between the tall/columnar cell group and micropapillary/discohesive group ($P = 0.1829$), tall/columnar cell group and solid type ($P = 0.2146$) or micropapillary/discohesive group and solid type ($P = 0.9406$).

Identification of low-risk and high-risk groups. According to cancer-related death, combining DFS curves by Kaplan–Meier

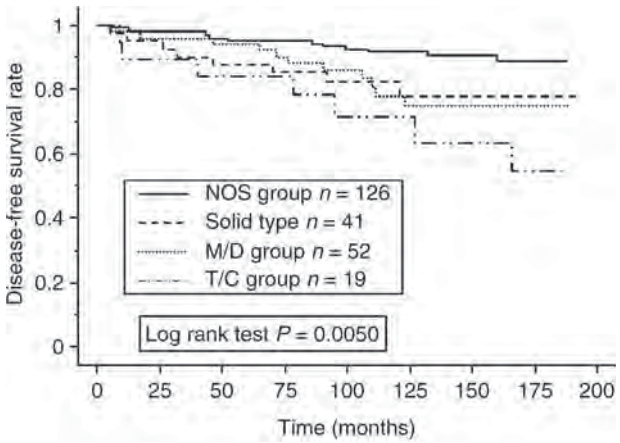


Fig. 2. Disease-free survival curve of patients in four histological subgroups using Kaplan–Meier method and log rank test. NOS: not-otherwise-specified; M/D: micropapillary/discohesive; T/C: tall/columnar cell.

Table 2. The correlation between different histological types of thyroid carcinoma and clinicopathological parameters

Group	Encap (*n* = 25)	NOS (*n* = 126)	M/D (*n* = 52)	T/C (*n* = 19)	Solid (*n* = 41)	*P*-value
Age						0.0710
<60 years	22	106	46	14	28	
≥60 years	3	20	6	5	13	
Sex						0.8518
Male	3	15	6	1	3	
Female	22	111	46	18	38	
Tumor size						0.4486
<2 cm	11	48	14	7	10	
≥2 and ≤4 cm	10	57	27	11	25	
>4 cm	4	21	11	1	6	
Ex						0.4092*
0	25	75	34	10	23	
1	0	28	10	2	7	
2	0	23	8	7	11	
pT						0.3548*
pT1	13	32	11	5	8	
pT2	8	31	19	4	12	
pT3	4	40	14	3	9	
pT4a	0	23	8	7	12	
Gross LN meta						0.4526**
Negative	25	99	36	15	34	
Positive	0	26	15	3	7	
Unknown	0	1	1	1	0	–
Histological LN meta					0.0793	
N0	10	18	6	3	7	
N1a	4	13	5	1	5	
N1b	11	95	41	15	29	
Stage grouping						0.4919***
I	13	60	30	8	19	
II	2	1	2	0	1	
III	3	12	3	0	4	
IVa	7	53	17	11	17	
Operation method					–	
LI	14	34	18	8	14	
LO	2	2	0	0	0	
ST	2	6	4	2	0	
TT	7	84	30	9	27	

Encap: encapsulated; NOS: not-otherwise-specified; T/C: tall/columnar cell; M/D: micropapillary/discohesive; Ex: extrathyroid invasion, according to the 6th Edition of General Rule for the Description of Thyroid Cancer. LN: lymph node; meta: metastasis; pT, N0 and N1ab are according to the TNM category of AJCC/UICC; LI: lobectomy and isthmectomy; LO: lobectomy only; ST: subtotal thyroidectomy; TT: total thyroidectomy; –: statistical analysis was not performed. **P*-value was evaluated using *x-square* test for all groups, except the encapsulated group. ***P*-value was evaluated using the *x-square* test for all groups with negative or positive LN metastasis, except the encapsulated group. ****P*-value was evaluated using the *x-square* test for all groups, except the tall/columnar cell group.

Table 3. Prognosis among five different histological subtypes using recurrence or death as the end point

Group	Encap (*n* = 25)	NOS (*n* = 126)	M/D (*n* = 52)	T/C (*n* = 19)	Solid (*n* = 41)	*P*-value
Recurrence						
Mean follow-up period (month ± SD)	141.7 ± 42.3	135.7 ± 37.4	126.9 ± 47.6	113.5 ± 58.7	119.7 ± 52.6	–
Positive	0	12 (9.5%)	11 (21.2%)	7 (36.8%)	8 (19.5%)	0.0093*
Negative	25 (100%)	114 (90.5%)	41 (78.8%)	12 (63.2%)	33 (80.5%)	
Death						
Mean follow-up period (month ± SD)	160.4 ± 22.8	150.1 ± 26.9	151.8 ± 34.0	143.6 ± 37.9	143.5 ± 33.7	–
Alive	23 (92.0%)	123 (97.6%)	48 (92.4%)	15 (78.9%)	39 (95.1%)	–
Died of cancer	0	0	2 (3.8%)	4 (21.1%)	0	
Died of other causes	2 (8.0%)	3 (2.4%)	2 (3.8%)	0	2 (4.9%)	

Encap: encapsulated; NOS: Not-otherwise-specified; M/D: Micropapillary/discohesive; T/C: Tall/columnar cell; –: statistical analysis was not performed. **P*-value was evaluated using the *x-square* test for all groups, except the encapsulated group.

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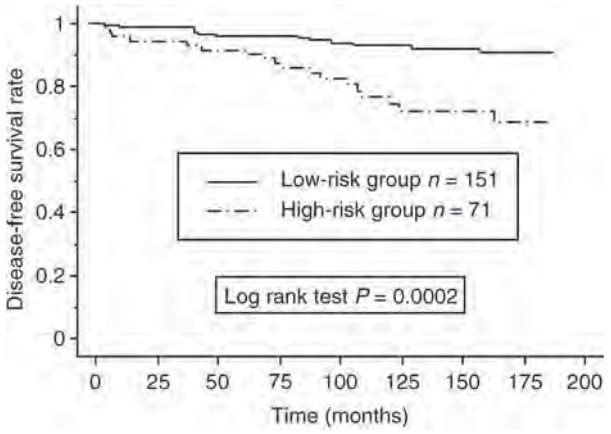

Fig. 3. Disease-free survival curve of patients in the low-risk and high-risk groups of papillary thyroid carcinoma using Kaplan–Meier method and log rank test. The 10-year disease-free survival rate of patients in high-risk group is 78.7%, which is significantly different from it in low-risk group (93.1%).

analysis, we further divided the non-solid type of PTC into two prognostic groups: high-risk group (including tall/columnar cell group and micropapillary/discohesive group); and low-risk group (encapsulated group and NOS group). The PTC cases with cancer-related death were only found in the high-risk group in our study. The efficiency of high- and low-risk group classification was confirmed by the Kaplan–Meier method with $P = 0.0002$ (Fig. 3). The 10-year DFS rate of the high-risk and low-risk groups was 78.7% and 93.1%, respectively.

Univariate analysis of prognostic factors and tumor recurrence. We evaluated histological grouping, age, sex, tumor diameter, extrathyroid invasion (Ex), pT, gross lymph node metastasis, histological lymph node metastasis, stage grouping and surgical margin as risk factors for recurrence. Cox univariate analysis was performed and the results are shown in Table 4. Histological grouping, age, Ex, pT, gross lymph node metastasis and surgical margin were significant prognostic factors for recurrence, whereas sex, tumor diameter, histological lymph node metastasis and stage grouping were not significant prognostic factors in the Cox univariate analysis.

Multivariate analysis of prognostic factors. Multivariate analysis was carried out for the prognostic factors shown as significant by univariate analysis. The results revealed that histological grouping, age and gross lymph node metastasis were independent factors predicting more chance of recurrence (Table 5). In histological grouping, the NOS group showed the best prognosis with a relative risk (RR) of 0.580 compared with the solid type (RR 1), whereas the tall/columnar cell group showed the worst prognosis with an RR of 2.706. The micropapillary/discohesive group showed slightly worse prognosis (RR 1.233) than the solid type. Gross negative lymph node metastasis significantly and negatively correlated with recurrence ($P < 0.0001$, RR 0.173). Patient age less than 60 years was also a favorable prognostic factor ($P = 0.0024$, RR 0.280).

Table 4. Univariate analysis of clinical and histological parameters, using recurrence as the end point by log rank test

Parameters	Univariate analysis	
	Cases with recurrence/ total cases	*P*-value
Histological grouping		*0.0050*
Not otherwise specified	12/126	
Micropapillary/discohesive	11/52	
Tall/columnar cell	7/19	
Solid	8/41	
Age		*0.0039*
<60 years	26/194	
≥60 years	12/44	
Sex		0.4136
Female	33/213	
Male	5/25	
Tumor diameter		0.0675
≤4 cm	28/199	
>4 cm	10/39	
Extrathyroid invasion		*<0.0001*
0	15/142	
1	6/47	
2	17/49	
pT		*<0.0001*
1	6/68	
2	9/82	
3	8/52	
4a	15/36	
Gross LN metastasis		*<0.0001*
Negative	19/184	
Positive	19/51	
Unknown	0/3	
Histological LN metastasis		0.4169
N0	3/34	
N1a	4/24	
N1b	31/180	
Stage grouping		0.1269
I + II	14/121	
III	4/19	
IVa	20/98	
Surgical margin		*0.0015*
Positive	3/5	
Negative	35/233	

Italics: Statistic significance was identified. Extrathyroid invasion (0, 1, 2) was defined according to the 6th Edition of General Rule for the Description of Thyroid Cancer. LN: lymph node metastasis. pT, N0, N1ab and stage grouping are based on the TNM category of ACJJ/UICC.

Discussion

In general opinion, papillary carcinoma represents a group of low-grade malignancies with 10-year DFS of more than 90%; however, this malignancy demonstrates distant metastasis or recurrence after surgery in a small number of patients and cancer-related death in rare cases.[19–21] How to predict prognosis using histological features and clinical parameters, and how to effectively inform clinicians about the probability of recurrence is a big challenge for pathologists. New diagnostic terminology, poorly differentiated carcinoma (PDC) of the thyroid, was first introduced by Sakamoto[22,23] for aggressive carcinoma of both PTC and follicular thyroid carcinoma background that showed a solid/trabecular/scirrhous growth pattern. Carcangiu later introduced the terminology 'poorly differentiated (insular) thyroid carcinoma'.[24] Recently, it was listed as diagnostic terminology in the new edition of the Histological Classification of Thyroid Tumors by WHO, and detailed diagnostic criteria were proposed by Hiltzik and Volante.[18,25] The diagnosis includes solid/trabecular/insular growth with necrosis or increased mitoses together with the absence of typical PTC nuclear features. Even excluding Sakamoto PDC or WHO PDC from the common type of PTC, PTC patients still have a heterogeneous prognosis. Although Akslen and LiVolsi reported that subclassification of papillary thyroid carcinoma had only a minor prognostic impact,[9] in our study,

Table 5. Multivariate analysis of clinical and histological parameters, using Cox proportional regression model

Parameters	95% CI	*P*-value	RR (relative risk)
Histological grouping		*0.0420*	
Not otherwise specified	0.221–1.525	0.2696	0.580
Micropapillary/discohesive	0.466–3.263	0.6729	1.233
Tall/columnar cell	0.907–8.071	0.0741	2.706
Solid	–	–	1
Age		*0.0024*	
<60 years	0.123–0.637	–	0.280
≥60 years	–	–	1
Extrathyroid invasion		0.5985	
0	0.203–4.815	0.9878	0.988
1	0.103–2.899	0.4776	0.546
2	–	–	1
pT		0.7052	
1	0.076–3.092	0.4440	0.485
2	0.101–2.710	0.4392	0.522
3	0.172–4.753	0.9061	0.905
4a			1
Gross lymph node metastasis		*<0.0001*	
Negative	0.079–0.380	–	0.173
Positive	–	–	1
Surgical margin		0.9772	
Negative	0.261–3.680	–	0.981
Positive	–	–	1

Italics: Statistic significance was identified. 95% CI: 95% confidence interval. Extrathyroid invasion was defined according to the 6th Edition of General Rule for the Description of Thyroid Cancer. pT was categorized according to the TNM category of AJCC/UICC.

when we used subclassification applying the histological features of encapsulation, loss of cellular cohesiveness/polarity and the presence of tall/columnar cell components as useful, we found statistic parameters that allowed us to identify certain groups of PTC with poor disease-free survival rate and more cancer-related death, and the difference was statistically significant.

The encapsulated group is a group of PTC characterized by capsulated and expansive growth and no extrathyroid invasion. No gross lymph node metastasis at surgery was found in 25 cases in this group. We used the encapsulation parameter before the parameter of tall/columnar cell components and loss of polarity/cohesiveness in subclassfying PTC because some aggressive variants of PTC, such as the columnar cell variant, demonstrated similar prognosis with well-differentiated thyroid carcinoma when it is encapsulated,[26] and it was true in our series even if the cut off value decreased to 10% for tall/columnar component and 20% for micropapillary/discohesive component. The encapsulated group is classed as malignant with 60% lymph node metastasis at operation, but this PTC group acted almost benign after surgical resection, showing no recurrence and no cause-specific death after a mean follow-up period of more than 141 months.

Loss of cellular polarity/cohesiveness proved to be effective as a reliable parameter in subgrouping PTC. Loss of polarity/cohesiveness is usually used in the diagnosis of epithelial malignancy, but is seldom used in the diagnosis of PTC. In 2003, it was first used as histological terminology to describe PTC by Tang from our group, and then developed by Kakudo.[11,12] We used the terminology 'Micropapillary/discohesive group' to define the group of non-solid PTC that showed loss of polarity/cohesiveness in 20% or more carcinoma cells, since loss of polarity is usually seen in micropapillary structures in PTC, where the covering carcinoma cells show a 'hobnail pattern'. This phenomenon was also shown in serous borderline tumors and carcinoma of the ovary. The histological feature of loss of cellular polarity/cohesiveness has been described at the molecular level that loss of cohesiveness was positively correlated with loss of retinoid receptor mRNA expression.[12] Loss of cohesiveness/polarity was showed to be significant in univariate analysis, but did not reach a significant level in multivariate analysis in predicting DFS.[11] During decades of diagnosing PTC, we found that carcinoma cells demonstrating loss of polarity/cohesiveness usually existed at the invasive front of carcinoma (interface between carcinoma and thyroid parenchyma), indicating that carcinoma cells with loss of polarity/cohesiveness represent a more invasive entity; therefore, it is reasonable to utilize the terminology of loss of cellular polarity/cohesiveness as a meaningful prognostic factor. Loss of cellular polarity/cohesiveness was not usually seen in the solid variant of PTC, PDC of Sakamoto and PDC of WHO definition; therefore, these parameters can be applied to only non-solid-type PTC, as in this paper.

Tall cell and columnar cell variants tend to show more aggressive clinical behavior than conventional papillary carcinoma.[27–29] Furthermore, the columnar cell variant with an aggressive growth pattern showed higher metastatic potential than tumors of columnar cell variant that are encapsulated or partially encapsulated.[26] The utilization of tall/columnar cell components as a category criterion was first applied in this study and confirmed to be practical. The tall or columnar cell variant of PTC has been widely accepted as diagnostic terminology and listed in the WHO category as an independent variant, in which the tall or columnar cell component should be in the majority. In the present study, among the 263 cases of PTC, we identified only two cases of pure (more than 50%) tall cell variant and one case of pure columnar cell variant. Among them, one case of tall cell variant and the case of columnar cell variant developed postoperative recurrence. Various proportions of tall/columnar cell component were found in many cases, which were divided into two groups of more than 10% (tall/columnar cell group) and less than 10% with loss of polarity/cohesiveness ≥20% (micropapillary/discohesive group) or without (NOS group) in this study. Our results confirmed that the tall/columnar cell component is a good indicator of recurrence even if it occupies only 10% of the tumor area. As far as we know, 10% is the lowest threshold in the literature, but it did not affect the significantly higher recurrence rate of tall/columnar cell PTC. Four patients of 11 in the tall/columnar cell group who died of cancer were ≥58 years at surgery. They possessed both Ex2 (according to the 6th Edition of General Rule for the Description of Thyroid Cancer) and N1b (according to the TNM [tumor, node, metastases] category of AJCC/UICC). They died 52–133 months after surgery owing to the metastasis to either lung or brain. Our tall/columnar group represented the highest aggressive variant of non-solid-type PTC since it had the worst DFS and showed most cases of cancer-related death in all four non-solid groups analyzed. The prognosis of the tall/columnar cell (T/C) group does not show obvious correlation with the proportion of this component in our study. We believe that this lower cutoff value (10%) may be the best way to evaluate the aggressive type of carcinoma in the early stage of disease, which makes our study unique.

In this article, two prognostic groups, low-risk and high-risk groups, were well correlated with the pure histological features. There was no cancer-related death in the low-risk group. We did not define the previously reported PTC variants as a special entity (whereas in Sywak's article they were placed in the category of thyroid cancer with intermediate differentiation[30]) since in our 263 cases of PTC they were a minor proportion, with two cases of tall cell variant, one case of columnar cell variant and six cases of solid variant, and they did not behave more aggressively or show poorer prognosis than the common type of PTC.

Histological grouping using pure histological features applied to PTC was shown to be an independently significant factor in multivariate analysis. To the best of our knowledge, this is the

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first instance of confirming significance and feasibility by multivariate analysis. Besides histological grouping, age and gross lymph node metastasis were also independently significant factors in multivariate analysis, coincident with Noguchi's findings from Japan.[5]

In summary, we applied the histological features of encapsulation, presence of tall/columnar cell component and loss of polarity/cohesiveness to subclassify non-solid-type PTC into four groups. This histological grouping was markedly significant by the Kaplan–Meier method and multivariate analysis. We further divided non-solid-type PTC into two prognostic groups, high-risk and low-risk groups, based on the DFS and cancer-related death. In this study, histological grouping and the identification of two risk groups were significantly correlated with prognosis, which predicts patient outcome in terms of tumor recurrence and cancer-related death more precisely and additionally informs clinicians how to treat patients suffering from PTC.

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