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Clinical Features and Prognostic Factors for Survival in Patients with Poorly Differentiated Thyroid Carcinoma and Comparison to the Patients with the Aggressive Variants of Papillary Thyroid Carcinoma

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Abstract. We performed this study to compare the clinicopathologic features and outcomes between the patients with poorly differentiated thyroid carcinoma (PDTC) and the patients with the aggressive variants of papillary thyroid carcinoma (PTC). To evaluate the prognostic factors for survival of the patients with PDTC, we selected 49 patients with PDTC and 23 patients with the aggressive variants of PTC from three hospitals during the recent 15 years. The five-year survival rate and clinicopathologic features of the patients with PDTC were not different from those of the patients with the aggressive variants of PTC. Univariate analysis revealed the significant poor prognostic factors for survival of the patients with PDTC and the aggressive variants of PTC as follows: 1) an age more than 45 years, 2) a tumor size larger than 4 cm, 3) the presence of tumor invasion to extrathyroidal tissue or the trachea, 4) the presence of cervical lymph node invasion, 5) the presence of distant metastasis, 6) the absence of high-dose radioactive iodine (RAI) therapy, and 7) TNM stage II, III and IV. Distant metastasis and high-dose RAI therapy were independent significant predictors for survival of the patients with PDTC and the aggressive variants of PTC on multivariate analysis. However, distant metastasis was the only independent significant predictors for survival of the patients with PDTC excluding patients with the aggressive variants of PTC.

Key words: Poorly differentiated thyroid carcinoma, Papillary thyroid carcinoma, Survival
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SAKAMOTO *et al.* (1983) and Carcangiu *et al.* (1984) have described a distinctive thyroid carcinoma that is characterized by an insular, solid, trabecular and scirrhous pattern [1, 2]. They referred to this unique type of tumor as a poorly differentiated thyroid carcinoma (PDTC). Thereafter, some investigators have confirmed the presence of PDTC that had clinical and pathologic features that were considered intermediate between well-differentiated thyroid carcinoma (WDTC) and undifferentiated carcinoma [3–5]. Although PDTC loses the pathologic features of the WDTC, it produces thyroglobulin and contains colloids [5, 6]. It may respond to radioactive iodine (RAI) therapy [7].

Several histologic variants of papillary thyroid carcinoma (PTC) have been described. Some variants have an aggressive behavior with higher rates of morbidity and mortality. These variants with aggressive features

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include tall cell variant, columnar cell variant, diffuse sclerosing variant, and solid variant. Many investigators have tried to classify these aggressive variants of PTC into the PDTC [8–12]. Among the aggressive variants of PTC, we included the tall cell, columnar cell, solid and diffuse sclerosing variants of PTC in this study, and we defined them as the aggressive variants of PTC.

In the current study, we investigated the clinicopathologic features of a large cohort of patients with PDTC and compared them with those of aggressive variants of PTC.

Subjects and Methods

Patient study

We selected 49 patients with PDTC and 23 patients with the aggressive variants of PTC. All the patients underwent thyroidectomy at Asan Medical Center, Seoul National University Hospital or Samsung Medical Center between 1990 and 2004. We also included ten patients who were diagnosed with PDTC at the sites of recurrence and who primarily underwent thyroidectomy for WDTC. The median follow-up period of 72 patients with PDTC and the aggressive variants of PTC was 43 months with a range from one to 135 months.

Among the 49 patients with PDTC, 13 patients were men and 36 were women. Their mean age was 49 years with a range from 15 to 75 years. Thirty-one patients had non-insular PDTC including the trabecular or solid type, 17 had the insular carcinomas, and the other one had the mixed type of trabecular and insular carcinomas. Among the 23 patients with the aggressive variants of PTC, two patients were men and 21 were women. Their mean age was 44 years with a range from 19 to 73 years. Ten patients had the tall cell variant, five had the diffuse sclerosing variant, four had the columnar cell variant, three had the solid variant and the other one had the mixed type of the tall cell and columnar cell variants. Among the ten patients who recurred as PDTC after surgery for WDTC, four patients were men and six were women. Their mean age was 52 years with a range from 25 to 66 years at the time of recurrence. PDTC was frequently detected together with WDTC on the histopathologic findings. Follicular thyroid carcinoma (FTC) coexisted in 15 patients (31%) and PTC coexisted in 11 patients (22%). No other thyroid carcinoma was detected in 23 patients (47%) with PDTC. Among the 23 patients with the aggressive variants of PTC, the classical type of PTC was detected together in four patients.

Among 49 patients with PDTC, 37 patients (76%) visited the hospital for the palpable neck mass, eight (16%) visited the hospital for a thyroid mass that was incidentally detected by ultrasonography, and the other four visited the hospital for hoarseness, bone pain or dyspnea. Only 11 patients (22%) were diagnosed with PDTC by fine needle aspiration cytology (FNAC) prior to surgery. The other patients were diagnosed as follicular neoplasm (29%), PTC (24%), unknown carcinomas (18%), and benign thyroid tumors (6%) by FNAC. Among the 23 patients with the aggressive variants of PTC, 12 patients (52%) visited the hospital for the palpable neck mass, and two patients visited the hospital with complaints of hoarseness. Tumor was incidentally discovered by neck ultrasonography in the other nine patients. Twenty patients who underwent FNAC were diagnosed with PTC and the other three patients were diagnosed with the aggressive variants of PTC.

We retrospectively analyzed the medical records of 82 patients. We had the pathologic findings reviewed by one experienced pathologist. PDTC was defined as the presence of more than 10% of their unique cancer cell populations with three typical histopathologic features: trabecular or insular or solid growth pattern, necrosis and vascular invasion [13]. Tall cell variant, columnar cell variant, diffuse sclerosing variant and solid variant of PTC were defined as their unique cell populations having more than 30% of total cancer cells. We defined distant metastasis as histological confirmation of the tumor or as the presence of the typical features detected by radiological studies, RAI whole body scan or PET scan. The survival periods were calculated from the dates of pathologic confirmation to the dates of disease-specific death. We also calculated the survival periods from the dates of recurrence to the dates of disease-specific death for the patients diagnosed with PDTC at the sites of recurrence and who primarily underwent thyroidectomy for WDTC. We defined remission as the decrement of the serum thyroglobulin level (less than 10 ng/mL on discontinuation of levothyroxine) with no evidence of residual tumor or metastasis as determined by imaging scans. Because the staging system for the PDTC has not been established by the World Health Organization, we used the

staging system for WDTC to classify it [13].

Statistical analysis

Age, tumor size and follow-up periods were analyzed using the Mann-Whitney *U* test, and the other two-by-two tables were analyzed using Pearson's chi-square test or Fisher's exact test. Univariate analysis was based on the Kaplan-Meier method for disease-specific survival using the log-rank test. Comparison of the clinicopathologic parameters with the survival for the patients with PDTC was evaluated using Cox's proportional hazard regression analysis. All the data were analyzed using the SPSS software program (version 11.0 for Windows, Chicago, IL, USA). P values less than 0.05 were considered significant. Results were presented as means ± standard deviation or percentage. The follow-up periods and the accumulated RAI doses at remission were expressed as medians and ranges.

Results

1. Comparison of the clinicopathologic features of PDTC with those of the aggressive variants of PTC (Table 1)

The tumor size of the patients with PDTC was larger than that of the patients with the aggressive variants of PTC (4.7 ± 2.7 cm vs. 3.3 ± 2.7 cm, $p<0.05$). The distant metastasis of the patients with PDTC was more frequent than that of the patients with the aggressive variants of PTC (33% vs. 5%, $p<0.01$). Tumors were metastasized to the lungs and bones in six patients with PDTC, and the other four patients had multiple metastases to both lungs and bones. In contrast, only one (5%) of 23 patients with the aggressive variants of PTC had distant metastasis to the lung at the time of the initial diagnosis.

The median accumulated doses of ^{131}I to reach remission were 150 (75~780) mCi for the PDTC patients,

Table 1. Comparison of clinicopathologic parameters of PDTC with the aggressive variants of PTC

	PDTC (n = 49)	Aggressive variants of PTC (n = 23)	*P* value
Age (years)	49.3 ± 15.8 (15~75)	44.4 ± 16.6 (19~73)	NS
Gender (M : F)	13 : 36	2 : 21	NS
Tumor size (cm)	4.7 ± 2.7 (0.8~12.0)	3.3 ± 2.7 (0.4~13.0)	<0.05
Multifocal tumor	12% (6/49)	22% (5/23)	NS
Extrathyroidal invasion	59% (29/49)	65% (15/23)	NS
Tracheal invasion	10% (5/49)	4% (1/23)	NS
Cervical lymph node metastasis	29% (14/49)	48% (11/23)	NS
Distant metastasis	33% (16/49)	5% (1/23)	<0.01
TNM stage			
Stage I	33% (16/49)	61% (14/23)	<0.05
Stage II	6% (3/49)	0%	NS
Stage III	31% (15/49)	26% (6/23)	NS
Stage IV	31% (15/49)	13% (3/23)	NS
Treatment			
Total thyroidectomy	78% (38/49)	91% (21/23)	NS
RAI therapy	78% (38/49)	70% (16/23)	NS
External radiotherapy	18% (9/49)	9% (2/23)	NS
Follow-up periods (months)	46 (1~128)	43 (1~135)	NS
Clinical outcome			
Remission	45% (22/49)	70% (16/23)	NS
Persistence	10% (5/49)	4% (1/23)	NS
Recurrence	6% (3/49)	9% (2/23)	NS
Death	31% (15/49)	9% (2/23)	<0.05
Follow-up loss	10% (5/49)	9% (2/23)	NS

PDTC: poorly differentiated thyroid carcinoma, PTC: papillary thyroid carcinoma, RAI: radioactive iodine, NS: not significant. The TNM staging system was adopted from the WDTC system of the World Health Organization in 2004. We defined remission as the decrement of the serum thyroglobulin level (less than 10 ng/mL on withdrawal of T4) and no evidence of residual tumor or metastasis, as determined by imaging scans. Analyses of age, tumor size and the follow-up period were performed by Mann-Whitney *U* tests, and the other parameters were evaluated by Pearson's chi-square tests or Fisher's exact tests.

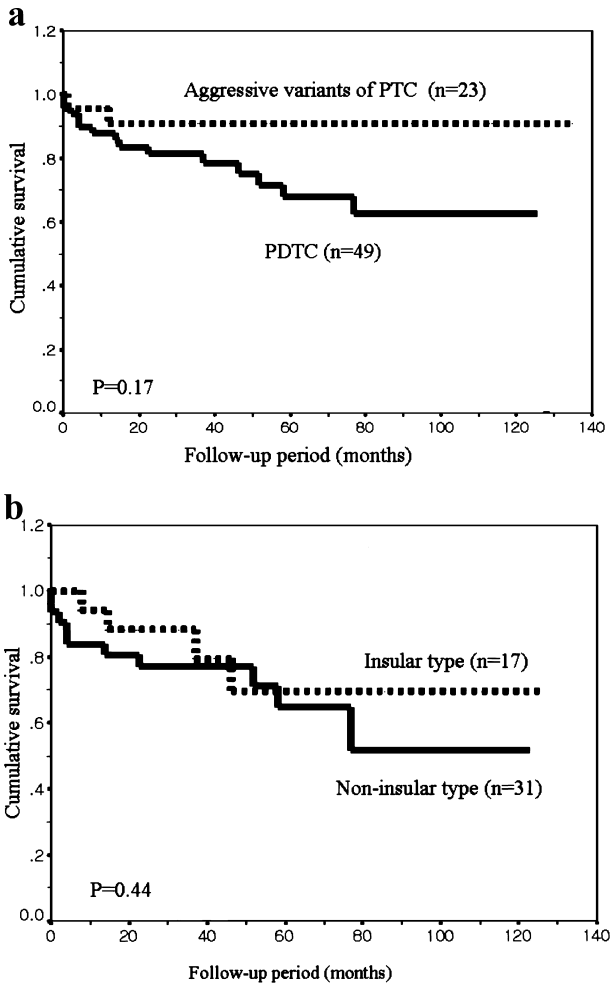

Fig. 1. Kaplan-Meier survival plots of the patients with thyroid cancer based on the pathologic types. (a) PDTC (poorly differentiated thyroid carcinoma) vs. aggressive variants of PTC (papillary thyroid carcinoma), (b) insular type vs. non-insular type of PDTC. There were no statistical differences between PDTC and the aggressive variants of PTC (p = 0.17), and between the insular type and non-insular type of PDTC (p = 0.44).

and 150 (100~550) mCi for the patients with the aggressive variants of PTC, respectively. Five-year survival rate of the patients with PDTC was not different from that of the patients with the aggressive variants of PTC on univariate analysis of the survival based on the Kaplan-Meier method (68% vs. 91%, p = 0.17; Fig. 1A).

2. Comparison of the clinicopathologic features of non-insular PDTC with those of insular PDTC (Table 2)

Other thyroid malignancies were more frequently detected in the patients with non-insular PDTC than in the patients with insular carcinoma (65% vs. 29%, $p<0.05$). Among the 20 patients with non-insular PDTC, FTC coexisted in 11 patients (55%), PTC coexisted in nine patients (45%). In contrast, FTC was detected together with insular carcinoma in three patients, and PTC was detected in the other two patients. Especially, the number of patients with persistent disease of the patients with non-insular PDTC was less than that of the patients with insular carcinoma (3% vs. 24%, $p<0.05$). However, the five-year survival rate of the patients with non-insular PDTC was not different from that of the patients with insular carcinoma when performing univariate analysis of the survival based on the Kaplan-Meier method (65% vs. 70%, p = 0.44; Fig. 1B).

3. Analysis of the survival and its related clinical factors in the patients with PDTC and the aggressive variants of PTC (Table 3)

We analyzed the survival and its related clinical factors in 49 patients with PDTC and 72 patients with PDTC including the aggressive variants of PTC, respectively. Gender, the pathologic types (*i.e.*, non-insular vs. insular; PDTC vs. the aggressive variants of PTC), the coexistence of other thyroid cancer, multifocality, the extent of thyroidectomy, and external radiation therapy did not have a significant influence upon the survival when these factors were analyzed by univariate analysis. However, univariate analysis for the survival revealed that the significant prognostic factors for poor survival in patients with PDTC and patients with PDTC including the aggressive variants of PTC as follows: 1) an age more than 45 years, 2) a tumor size larger than 4 cm, 3) the presence of tumor invasion to the extrathyroidal tissue or trachea, 4) the presence of cervical lymph node metastasis, 5) the presence of distant metastasis, 6) the absence of high-dose RAI therapy, and 7) TNM stage II, III and IV (Table 3, Fig. 2, 3).

When all the clinical factors including age, gender, coexistence of other thyroid cancer, pathologic differences between non-insular type and insular type, pathologic differences between PDTC and aggressive variants of PTC, tumor size, multifocality, extrathyroidal invasion, cervical lymph node invasion, distant metastasis, total thyroidectomy, external radiotherapy and RAI therapy were analyzed by multivariate analysis

Table 2. Comparison of the clinicopathologic parameters of non-insular PDTC with insular PDTC

	Non-insular carcinoma (n = 31)	Insular carcinoma (n = 17)	*P* value
Age (years)	47.4 ± 16.0 (19~75)	52.5 ± 15.6 (18~75)	NS
Gender (M : F)	8 : 23	5 : 12	NS
Association with other thyroid malignancy	65% (20/31)	29% (5/17)	<0.05
Tumor size (cm)	4.7 ± 2.8 (0.8~12.0)	4.6 ± 2.7 (0.8~11.0)	NS
Multifocal tumor	13% (4/31)	12% (2/17)	NS
Extrathyroidal invasion	52% (16/31)	71% (12/17)	NS
Tracheal invasion	16% (5/31)	0% (0/17)	NS
Cervical lymph node metastasis	29% (9/31)	29% (5/17)	NS
Distant metastasis	29% (9/31)	41% (7/17)	NS
Treatment			
Total thyroidectomy	71% (22/31)	94% (16/17)	NS
RAI therapy	71% (22/31)	77% (13/17)	NS
External radiotherapy	19% (6/31)	18% (3/17)	NS
Follow-up periods (months)	46 (1~123)	42 (1~128)	NS
Clinical outcome			
Remission	55% (17/31)	29% (5/17)	NS
Persistence	3% (1/31)	24% (4/17)	<0.05
Recurrence	3% (1/31)	12% (2/17)	NS
Death	32% (10/31)	29% (5/17)	NS
Follow up loss	7% (2/31)	12% (2/17)	NS

PDTC: poorly differentiated thyroid carcinoma, RAI: radioactive iodine, NS: not significant. A case with mixed type was excluded in this comparison. We defined remission as the decrement of the serum thyroglobulin level (less than 10 ng/mL on T4 withdrawal) and no evidence of residual tumor or metastasis, as determined by imaging scans. Analyses of age, tumor size and follow-up periods were performed by Mann-Whitney *U* test and other parameters were evaluated by Pearson's chi-square test or Fisher's exact test.

using Cox's proportional hazard regression model, the presence of distant metastasis (p = 0.039) and high-dose RAI therapy (p = 0.019) were independent significant factors for survival in the patients with PDTC including the aggressive variants of PTC (n = 72). However, the presence of distant metastasis was the only significant predictor for survival (p = 0.031), but high-dose RAI therapy was not a significant factor for survival in patients with PDTC (n = 49, p = 0.086).

4. Clinical features of the patients diagnosed with PDTC at the sites of recurrence and who primarily underwent thyroidectomy for WDTC

We analyzed 10 patients who were diagnosed with PDTC at the sites of recurrence and who primarily underwent thyroidectomy for WDTC. Prior to recurrence, seven patients were primarily diagnosed with PTC, and three patients had FTC. The median duration from the initial thyroidectomy to recurrence was 76 months with a range from 54 to 313 months.

The pathologic findings of recurred sites revealed insular carcinomas in five patients and non-insular PDTC in five patients. The average tumor size was 4.7 ± 2.8 cm with a range from 2.0 to 9.0 cm. At the time of recurrence, tumors were detected within the thyroid bed or in the cervical lymph nodes in eight patients, and tumor had invaded to the trachea in two patients. All the patients had distant metastases. Tumor had metastasized to the lung in four patients, to the bone in three patients, to the brain in one patient, to the chest wall in one patient, and to both the lung and bone in one patient.

After surgery, high-dose RAI therapy was done for three patients, external radiation therapy was done for two patients and both types of treatments were done in three patients. The one patient died immediately after surgery and the other one patient refused additional therapy. The median follow-up period was 25 months with a range from one to 162 months after removal of recurred tumor. Eight of ten patients died of thyroid carcinoma within 18 months. One of two survivors has been in remission until 80 months after surgery, while the other had persistent tumor.

Table 3. Correlation of the clinicopathologic parameters with survival in the patients with PDTC and the aggressive variants of PTC

	PDTC (n = 49)			PDTC + aggressive variants of PTC (n = 72)		
	Number	5-YSR(%)	*P* value	Number	5-YSR(%)	*P* value
Age			<0.005			<0.005
<45 years	19	95		32	97	
≥45 years	30	49		40	55	
Gender			NS			NS
Female	36	69		57	78	
Male	13	64		15	61	
Pathologic subtype-1			NS			
Non-insular	31	65				
Insular	17	70				
Pathologic subtype-2						NS
PDTC				49	68	
Aggressive variants*				23	91	
Coexistence with other thyroid cancer			NS			
No	23	54				
Yes	26	81				
Coexisted thyroid cancer type			NS			
PTC	10	100				
FTC	14	64				
Tumor size			<0.005			<0.001
<4 cm	21	100		36	100	
≥4 cm	28	48		36	52	
Multifocality			NS			NS
Single	43	73		61	73	
Multifocal	6	67		11	82	
Extrathyroidal invasion			<0.05			<0.01
Negative	20	95		28	96	
Positive	29	54		44	62	
Tracheal invasion			<0.0001			<0.0001
Negative	44	73		66	78	
Positive	5	20		6	33	
Cervical L/N metastasis			<0.05			<0.05
Negative	35	74		47	79	
Positive	14	54		25	65	
Distant metastasis			=0.0001			<0.0001
Negative	33	91		55	91	
Positive	16	31		17	31	
Thyroidectomy			NS			NS
Less than subtotal	7	71		9	78	
Total	38	74		59	78	
External radiotherapy			NS			NS
Not done	40	77		61	81	
Done	9	22		11	36	
RAI therapy			<0.05			<0.05
Not done	15	60		22	64	
Done	34	73		50	80	
TNM stage						<0.05
Stage I	16	100		30	100	
Stage II, III, and IV	33	53		42	58	

PDTC: poorly differentiated thyroid carcinoma, PTC: papillary thyroid carcinoma, Aggressive variants*: aggressive variants of PTC, RAI: radioactive iodine, L/N: lymph node, 5-YSR: 5-year survival rate, NS: not significant, Univariate analysis of the survival was based on the Kaplan-Meier method for disease-specific survival with log-rank test.

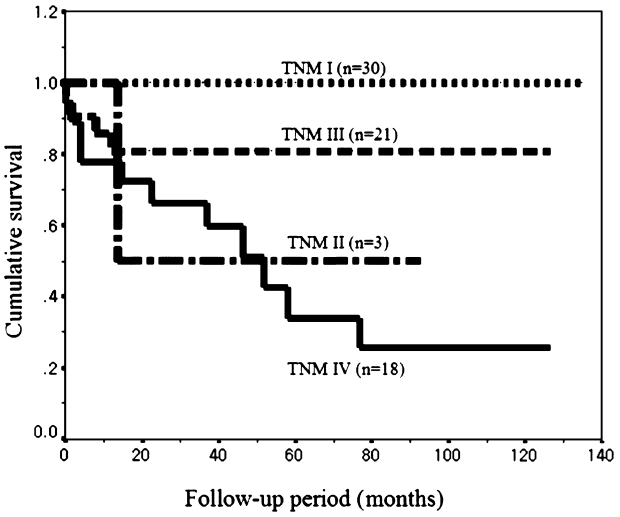

Fig. 2. Kaplan-Meier survival plots of patients with poorly differentiated thyroid carcinoma and aggressive variants of papillary thyroid carcinoma based on TNM staging. There were statistically significant differences between TNM stage I and stage II ($p<0.01$), stage I and stage III ($p<0.05$), and stage I and stage IV ($p<0.001$). However, there were no statistically significant differences between other TNM stages. The significance levels were adjusted by Bonferroni's correction to eliminate chance associations.

The survival rate of the patients diagnosed with PDTC at the sites of recurrence was significantly lower than that of the patients with primarily diagnosed as PDTC ($p<0.005$; Fig. 4).

Discussion

The clinical characteristics of the insular type of PDTC have been widely reported [2, 3, 14–18]. Some researchers have recently reported that the clinical features and survival rates of the non-insular type were not different from those of the insular type of PDTC, and they classified both types into the same disease entity [19, 20]. In this study, the clinical features and outcomes of the patients with the non-insular type were not different from those of the patients with the insular type of PDTC. The five-year survival rate of the patients with non-insular type was not different from that of the patients with insular type by univariate analysis of the survival based on the Kaplan-Meier method (65% vs. 70%, $p = 0.44$).

The tall cell and columnar cell variants of PTC are known to have more aggressive behavior and higher

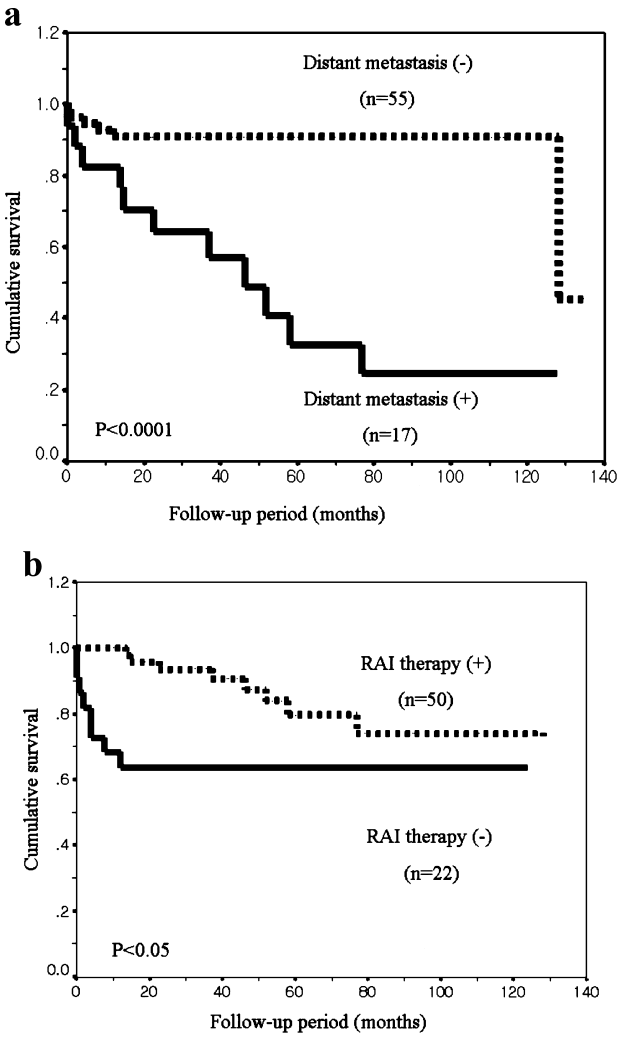

Fig. 3. Kaplan-Meier survival plots of the patients with thyroid cancer based on (a) distant metastasis, and (b) RAI (radioactive iodine) therapy. There was a good disease-specific survival for the patients without distant metastasis ($p<0.0001$) and the patients who were treated with postoperative RAI therapy ($p<0.05$).

mortality rate than the classical type of PTC [10–12, 21–23]. It has been widely accepted that these variants of PTC are classified with the PDTC [1, 4, 8, 9, 24]. With regard to clinical features, the diffuse sclerosing variant of PTC was more aggressive in tumor size, cervical lymph node invasion and recurrence rate than classic PTC [25–27]. However, its overall survival rate was not significantly different from that of classic PTC. The solid variant of PTC was known to have less favorable prognosis than classic PTC. However, Nikiforov *et al.* reported that survival rate of the solid variant was higher than that of PDTC [12]. Although the diffuse

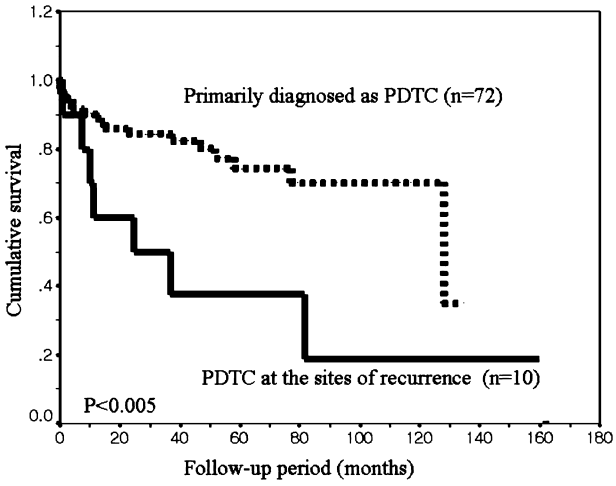

Fig. 4. Kaplan-Meier survival plot of the patients with thyroid cancer based on the patients who were primarily diagnosed as having PDTC (poorly differentiated thyroid carcinoma, n = 72) vs. the patients diagnosed as having PDTC at the sites of recurrence who primarily underwent thyroidectomy for well differentiated thyroid carcinoma (n = 10). The survival rate of the patients with PDTC at the sites of recurrence was significantly lower than that of the patients primarily diagnosed as PDTC ($p<0.005$).

sclerosing variant and solid variant of PTC seemed to have slightly superior prognosis than the tall cell variant and columnar cell variant of PTC, the clinical features of the former were different from those of classic PTC. Therefore, we speculated that these four variants might be classified into the same disease category.

This study is the first report to compare the clinical features and survival of these aggressive variants of PTC with those of classic PDTC. In this study, the clinical features and outcomes of the patients with the aggressive variants of PTC were not significantly different from those of the patients with PDTC. However, the tumor size was larger and distant metastasis was more frequent in the patients with PDTC than the patients with the aggressive variants of PTC ($p<0.05$). Mortality rate of the patients with PDTC was significantly higher than that of the aggressive variants of PTC (31% vs. 9%, $p<0.05$; Table 1). However, the five-year survival rate of the patients with PDTC was not different from that of the patients with the aggressive variants of PTC by univariate analysis (68% vs. 91%, $p = 0.17$). We assumed that these conflicting statistical results might be caused by the small number of enrolled patients and short follow-up period. We could not enroll sufficient number of patients because the incidence of PDTC and that of the aggressive variants of PTC were extremely low. Although the clinical features and outcomes of the aggressive variants of PTC might be intermediate between WDTC and PDTC, they seemed to be closer to PDTC rather than classic PTC (Table 1, Table 3, Fig. 1).

The ratio of PDTC cell population out of total cancer cell population has been debated in the diagnosis of PDTC. There have been two suggestions for the definition of PDTC. Some investigators suggested that PDTC should be defined as a cellular population greater than 75% of the total cancer cell population [1–4]. Other investigators suggested that its diagnosis was possible when the cellular population was more than 10% of the total cancer cell population [16, 28]. Recently, Volante *et al.* divided 183 patients with PDTC into three groups according to the extent of the PDTC component: 10~50%, 50~75% and more than 75% of total cancer cell population. They suggested that there was no significant difference in the prognosis among the three groups regardless of the extent of the PDTC component [20]. Nishida *et al.* reported that PDTC with an extent of more than 10% of the total cancer cell population had significantly worse recurrence rate (relative risk 4.04, $p<0.0001$) and survival rate ($p<0.0001$) than PDTC with an extent of less than 10% of the total cancer cell population [28]. Considering the previous reports, we concluded that it was appropriate for the extent of PDTC to be more than 10% of the cancer cell population.

Many investigators have emphasized the pathologic aspects of PDTC to analyze the prognostic factors for survival; however, we focused on its clinical aspects to analyze them. Nishida *et al.* suggested that age, gender, distant metastasis and extrathyroidal invasion were independent prognostic factors for survival in 38 patients with PDTC [28]. Volante *et al.* emphasized age, necrosis and the mitotic index as predictors for survival in 183 patients with PDTC [20]. In this study, age, tumor size, extrathyroidal invasion, cervical lymph node invasion, distant metastasis, RAI therapy and the TNM staging were the significant prognostic factors for survival by univariate analysis. However, gender was not a significant prognostic factor. Distant metastasis and RAI therapy were still independent significant predictors for survival of the patients with PDTC by multivariate analysis ($p<0.05$). The PDTC originated from thyroid follicular cells, and its clinical and pathologic features were intermediate between WDTC and un-

differentiated carcinoma [3–5]. Its uptake of RAI was dependent upon the degree of cellular differentiation. Volante *et al.* reported that the survival rate of patients with PDTC who were treated with high-dose RAI tended to be higher than that of the patients who were not treated with RAI therapy, although this was not statistically significant [20]. In this study, multivariate analysis revealed that high-dose RAI therapy was a significant predictor for survival of the patients with PDTC including the aggressive variants of PTC ($p = 0.019$), but its significance was reduced in the patients with PDTC excluding the aggressive variants of PTC ($p = 0.086$). We speculated that patients with the aggressive variants of PTC might have higher RAI uptake than patients with PDTC. If we could enroll a large enough number of patients with PDTC, RAI therapy might prove to be an independent prognostic factor for survival. In this study, the estimated five-year survival rate for the patients with PDTC was 67.9%, although follow-up period was relatively short (median 43 months). This survival rate was intermediate between the study of Sakamoto *et al.* (65.0%) and that of Volante *et al.* (85%) [1, 20].

There have been no reports to compare the clinical features and outcomes of the PDTC patients with those of patients diagnosed with PDTC at the recurred sites who primarily underwent thyroidectomy for WDTC. Although the number of these patients was limited, the median transition period from WDTC to PDTC was a relatively long duration (6.3 years with a range from 4.5 to 26.3 years). All the patients had distant metastases at the time of recurrence, and complete resection of the tumor was impossible in most patients. Their mortality rate was higher than that of the patients with primary PDTC and the aggressive variants of PTC (80% vs. 31% and 9%, respectively). From these findings, we concluded that the patients diagnosed with PDTC at the recurred sites who primarily underwent thyroidectomy for WDTC had extremely aggressive clinical features and poor outcomes.

Further, we concluded from these findings that there were no significant differences between the insular type and non-insular type of PDTC as well as PDTC and the aggressive variants of PTC for the overall clinical features and survival. Age, tumor size, extrathyroidal invasion, cervical lymph node invasion, distant metastasis, RAI therapy and the TNM stage were significant prognostic factors for survival of the patients with PDTC on univariate analysis. Distant metastasis was an independent predictor for survival on multivariate analysis. Follow-up of a greater number of patients for a longer period will be needed to establish the clinical data for the patients with PDTC and the aggressive variants of PTC.

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