Do Histologically Aggressive Subtypes of Papillary Thyroid Microcarcinoma have Worse Clinical Outcome than Non-Aggressive Papillary Thyroid Microcarcinoma Subtypes? A Multicenter Cohort Study

Authors

Sayid Shafi Zuhur[1], Hunkar Aggul[1], Ugur Avci[2], Selvinaz Erol[3], Mazhar Müslüm Tuna[4], Serhat Uysal[5], Gulhan Akbaba[6], Faruk Kilinç[7], Merve Catak[8], Sakin Tekin[9], Ogun Irem Bilen[1], Beyza Olcay Öztürk[1], Ecem Bilgehan Erden[1], Gulsah Elbuken[1], Halise Cinar Yavuz[4], Pinar Kadioglu[5], Nese Cinar[6], Faruk Kutluturk[8], Taner Bayraktaroglu[9], Birol Topçu[10], Aysegul Isal Arslan[11], Hasan Gucer[12], Gulcin Cihangiroglu[13], Cumhur Selcuk Topal[14], Tulin Ozturk[15], Leyla Tekin[16], Gokhan Artas[17], Elif Akcay[18], Banu Dogan Gun[19], Yuksel Altuntas[3]

Affiliations

1 Department of Endocrinology and Metabolism, Faculty of Medicine, Tekirdag Namik Kemal University, Tekirdag, Turkey
2 Department of Endocrinology and Metabolism, Faculty of Medicine, Recep Tayyip Erdogan University, Rize, Turkey
3 Department of Endocrinology and Metabolism, University of Health Sciences, Sisli Hamidiye Etfal Training and Research Hospital, Istanbul, Turkey
4 Department of Endocrinology and Metabolism, University of Health Sciences, Umraniye Training and Research Hospital, Istanbul, Turkey
5 Department of Endocrinology and Metabolism, Cerrahpasa Medical Faculty, Istanbul University-Cerrahpasa, Istanbul, Turkey
6 Department of Endocrinology and Metabolism, Faculty of Medicine, Mugla Sitki Kocman University, Mugla, Turkey
7 Department of Endocrinology and Metabolism, Faculty of Medicine, Elazig Firat University, Elazig, Turkey
8 Department of Endocrinology and Metabolism, Faculty of Medicine, Tokat Gaziosmanpasa University, Tokat, Turkey
9 Department of Endocrinology and Metabolism, Faculty of Medicine, Bulent Ecevit University, Zonguldak, Turkey
10 Department of Biostatistics, Faculty of Medicine, Tekirdag Namik Kemal University, Tekirdag, Turkey
11 Department of Pathology, Faculty of Medicine, Tekirdag Namik Kemal University, Tekirdag, Turkey
12 Department of Pathology, Faculty of Medicine, Recep Tayyip Erdogan University, Rize, Turkey
13 Department of Pathology, University of Health Sciences, Sisli Hamidiye Etfal Training and Research Hospital, Istanbul, Turkey
14 Department of Pathology, University of Health Sciences, Umraniye Training and Research Hospital, Istanbul, Turkey
15 Department of Pathology, Cerrahpasa Faculty of Medicine, Istanbul University-Cerrahpasa, Istanbul, Turkey
16 Department of Pathology, Faculty of Medicine, Mugla Sitki Kocman University, Mugla, Turkey
17 Department of Pathology, Faculty of Medicine, Elazig Firat University, Elazig, Turkey
18 Department of Pathology, Faculty of Medicine, Tokat Gaziosmanpasa University, Tokat, Turkey
19 Department of Pathology, Faculty of Medicine, Bulent Ecevit University, Zonguldak, Turkey

Key words

papillary microcarcinoma, aggressive subtype, clinical outcome

received 01.12.2022
accepted after revision 10.02.2023
accepted manuscript online 10.02.2023
published online 06.04.2023

Bibliography

Horm Metab Res 2023; 55: 323–332
DOI 10.1055/a-2032-5810
ISSN 0018-5043

Georg Thieme Verlag, Rüdigerstraße 14,
70469 Stuttgart, Germany

Correspondence

Dr. Sayid Shafi Zuhur
Namik Kemal University, Faculty of Medicine
Endocrinology and Metabolism
Köseilyas mah. Suleymanpasa
59100 Tekirdag
Turkey
Tel.: +905071044480, Fax: +90282 250 9950
zuhur744@gmail.com

ABSTRACT

Histologically aggressive micropapillary thyroid carcinomas (PTMC) subtypes are thought to be associated with an aggressive clinical course. However, evidence for unfavorable clinical outcomes in patients with aggressive PTMC subtypes is not clear. In this study, we intended to determine the difference in clinical outcomes between patients with aggressive and non-aggressive PTMC subtypes. In this multicenter cohort study, the computer-recorded clinical and histopathological data of patients who underwent thyroid surgery between January 2000 - January 2021 in 9 referral centers and were diagnosed as PTMC were analyzed. A total of 1585 patients [female 1340 (84.5 %), male 245 (15.5 %), mean age 47.9 ± 11.63 years), with a mean follow-up time of 66.55 ± 37.16 months], were included in the study. Ninety-eight cases were diagnosed as aggressive and 1487 as non-aggressive subtypes. Persistent/recurrent disease was observed in 33 (33.7 %)and 41 (2.8 %) patients with aggressive and non-aggressive subtypes ($p < 0.001$). Diseases-free survival rates were markedly lower in patients with aggressive than in those with non-aggressive PTMC subtypes (66.3 vs. 94.8 %, log-rank $p < 0.001$). Moreover, in multivariate analysis, aggressive histology was an independent predictor of persistent/recurrent disease, after controlling for other contributing factors (HR 5.78, 95 % CI 3.32–10, $p < 0.001$). Patients with aggressive PTMC subtypes had higher rates of incomplete biochemical and structural response than patients with non-aggressive subtypes as well ($p < 0.001$). Aggressive PTMC subtypes share many characteristics with histologically identical tumors > 1 cm in size. Therefore, the histopathological subtype of PTMC should be taken into consideration to tailor a personalized management plan.

Introduction

Papillary thyroid microcarcinoma (PTMC) is defined as papillary thyroid carcinomas (PTC) measuring ≤ 1 cm in size [1]. The clinical importance of PTMCs is controversial with many reports suggesting that it may represent a subclinical disease that is non-progressive and has no significant effect on morbidity or survival [2]. However, even though the clinical course of PTMCs is generally indolent, a small number of PTMCs, particularly those with histologically aggressive subtypes may be associated with an aggressive clinical course [3].

The histologically aggressive subtypes of PTC are the diffuse sclerosing, tall cell, columnar cell, solid, and hobnail subtypes [3, 4]. Studies suggest higher rates of bilateral disease, multifocality, extrathyroidal extension [ETE, either microscopic (mETE) or macroscopic], locoregional recurrence, neck lymph-node (LN)/distant metastasis, decreased survival, and in some cases, absence of avidity to radioiodine (RAI) in patients with aggressive subtypes of PTC [3, 5–11]. Therefore, the aggressive subtypes of PTC have been classified as "intermediate risk" for recurrence in the latest American Thyroid Association (ATA) guidelines, irrespective of their size [5]. Unfortunately, despite total thyroidectomy and central LN dissection have been recommended for the treatment of aggressive subtypes of PTMC, subtyping of PTC by cytopathological evaluation of the fine needle aspiration (FNA) specimens is challenging, even for the most experienced cytopathologists [6, 12]. Therefore, most of the cases are diagnosed after the histopathological evaluation of surgical specimens [6, 12].

To date, only a few studies have evaluated the clinical outcomes of histologically aggressive PTMC subtypes. In a population-level analysis, aggressive PTMC subtypes were suggested to exhibit more aggressive pathologic characteristics than classic PTMCs, but the overall and disease-specific survival rates were similar [6]. Considering the recent rising trend towards active surveillance as well as thermal ablation rather than surgical treatment, and challenges in the cytological diagnosis of aggressive subtypes in FNA specimens, determining the differences in clinical outcomes such as persistent/recurrent disease, disease-free survival (DFS) rate, and dynamic risk stratification between histologically aggressive and non-aggressive PTMC subtypes is of paramount importance [13, 14]. However, although several studies were carried out to compare the clinical outcomes between histologically aggressive and classic subtypes of larger PTCs, the difference in clinical outcomes between patients with histologically aggressive and non-aggressive PTMC subtypes have not been exclusively studied [3, 15, 16]. Therefore, in this multicenter cohort study, we intended to find answers to certain questions such as: do histologically aggressive subtypes of PTMC have worse clinical outcomes than non-aggressive subtypes? If so, should patients receive a more aggressive treatment based on the presence of aggressive histology? We also aimed to evaluate whether aggressive histology is an independent predictor of persistent/recurrent disease when controlling for other contributing risk factors.

Materials and Methods

Patient selection and study design

The computer-recorded data collected from 9 referral hospitals were analyzed. The patients included in this study consisted of consecutive individuals who underwent hemithyroidectomy or total thyroidectomy for toxic nodular thyroid disease, nodular thyroid disease with suspicious FNAC results, or Graves' disease, between January 2000-January 2021, and were diagnosed as PTMC by histopathological analysis. The primary objectives of this study were to determine the differences in structural persistent/recurrent disease and DFS rates, and the secondary objective was to assess the dynamic risk stratification results, between patients with histologically aggressive and non-aggressive PTMC subtypes. The following data were recorded for each patient: Patient and tumor characteristics, the extent of surgery, ETE, central or lateral neck LN in-

volvement or distant metastasis at diagnosis, radioactive iodine (RAI) ablation, persistent disease, and development of locoregional recurrence or distant metastasis during the follow-up period. To assess whether the diagnosis was compatible with the recent WHO classification of tumors [17], the tissue sections of the patients with a histopathological diagnosis of aggressive subtypes were re-examined by experienced cytopathologists in each center. All patients were classified according to the 8th edition of the American Joint Committee on Cancer (AJCC)/Union for International Cancer Control TNM staging system and the 2009 revised ATA management guidelines for thyroid nodules [18, 19]. However, due to the lack of information regarding the size of metastasis in resected neck LNs, the patients could not be stratified according to the 2015 ATA guidelines for thyroid nodules [5]. For those patients with more than one PTMC, the largest tumor was recorded and considered for analysis, unless the histopathological analysis results were consistent with one of the aggressive subtypes. Patients with < 1 year of follow-up data, patients with any missing data, patients with concomitant thyroid carcinomas larger than 1 cm, patients < 18 years old, and patients who were diagnosed as non-invasive follicular thyroid neoplasm with papillary-like nuclear features (NIFTP) after 2016, were not included in the study. This study was performed in line with the principles of the Declaration of Helsinki. Approval was granted by the Ethics Committee of Tekirdag Namık Kemal University, School of Medicine.

Treatment and follow-up for clinical outcomes

The treatment and follow-up protocols of the patients were carried out as previously reported [20]. All patients had undergone total thyroidectomy or hemithyroidectomy. Decisions for the extent of surgery, completion of thyroidectomy, central or lateral cervical LN dissection, and RAI treatment were made based on the institutional guidelines at the time of the initial surgery. All patients were followed with serum TSH, free T4, thyroglobulin (Tg), and anti-Tg antibody levels at 3- to 6-month intervals as well as ultrasonographic examinations of the neck at least once a year. Stimulated Tg level assessment and other imaging studies including diagnostic iodine 131 (^{131}I) whole-body scans (WBS), 18-FDG PET/CT, computed tomography, magnetic resonance imaging, and bone scan were also performed as needed. During the follow-up period, neck LNs with any suspicious or indeterminate appearance on ultrasonography underwent fine-needle aspiration cytology and/or measurement of Tg in needle washout fluid. Patients were accepted as "disease free" if they had no cytopathologic and imaging evidence of disease, undetectable suppressed Tg, and anti-Tg antibody levels in those who had undergone total thyroidectomy with or without RAI treatment. A cut-off value of ≤ 30 ng/dl for Tg was used to define "disease-free status" in patients who underwent hemithyroidectomy. For the assessment of dynamic risk stratification, patients were classified into four response groups, according to the dynamic risk stratification system (excellent, indeterminate, biochemical incomplete, and structural incomplete responses) [5].

Statistical analysis

Predictive Analytics Software Statistics 18 (International Business Machines Corporation) for Windows was used for data input and statistical analysis. An independent sample *t*-test or Mann–Whitney U-test was used to compare 2 groups, whereas an analysis of variance was used to compare ≥ 3 groups, followed by a Tukey (or Tamhane T2) test for subgroup comparisons. A chi-square test was used for categorical data comparison. DFS was estimated using the Kaplan–Meier method. Cox's proportional hazards model was used to evaluate the effect of age, sex, tumor size, neck LN involvement, multifocality, tumor stage, mETE, and aggressive histology on persistent/recurrent disease. All tests used were two-sided and A p-value of < 0.05 was considered statistically significant.

Results

After excluding 131 patients with insufficient follow-up data, a total of 1585 patients with PTMC [female 1340 (84.5 %), male 245 (15.5 %)], mean age 47.9 ± 11.63 years, min. 18, max. 80 years) with a mean follow-up time of 66.55 ± 37.16 months (min. 13, max. 240 months) were included in the study. The baseline clinical and histopathological characteristics and follow-up outcomes of the cohort according to the extent of surgery are presented in ▶**Table 1**. In this study, 98 (6.2 %) cases with PTMCs were histopathologically diagnosed as aggressive (diffuse sclerosing 2.8 %, tall cell 2.6 %, columnar cell 0.4 %, and solid subtype 0.3 %), and 1487 cases (93.8 %) as non-aggressive subtypes (▶**Table 1**). Patients with aggressive PTMC subtypes tended to be younger compared to patients with non-aggressive subtypes (42.6 ± 12.4 vs. 48.24 ± 11.5 years, p < 0.001), while no significant difference was found in terms of sex between both groups (p = 0.50) (▶**Table 2**). On the other hand, patients with aggressive PTMC subtypes tended to have larger tumor sizes, bilateral and multifocal disease, mETE, as well as higher rates of central and lateral neck LN involvement than patients with non-aggressive subtypes (p < 0.001 for all comparisons) (▶**Table 2**). Furthermore, more patients with aggressive PTMC subtypes had undergone completion thyroidectomy, central and lateral neck LN dissection as well as RAI ablation than patients with non-aggressive PTMC subtypes (p = 0.005, p < 0.001, p = < 0.001, and p < 0.001, respectively). Likewise, more patients with aggressive PTMC subtypes had stage II disease than patients with non-aggressive subtypes (p = 0.005) (▶**Table 2**). Persistent/recurrent disease was observed in 33 (33.6 %) and 41 (2.8 %) patients with aggressive and non-aggressive PTMC subtypes, respectively (p < 0.001) (▶**Table 2**). Patients with aggressive PTMC subtypes also tended to have lower rates of excellent response and higher rates of incomplete biochemical and structural response rates than patients with non-aggressive subtypes (p < 0.001) (▶**Table 2**). Distant metastasis at the initial diagnosis was present in one patient with a non-aggressive subtype and one patient with a tall cell subtype, while one patient with a non-aggressive and one with a tall cell subtype developed distant metastasis during follow-up. On the other hand, 5 (0.3 %) patients with non-aggressive subtypes had a macroscopic ETE, while no patient with an aggressive subtype had macroscopic ETE. Considering patients with aggressive PTMC subtypes, no marked difference was observed between patients with tall cell and diffuse sclerosing subtypes in terms of age, sex, type of surgery, bilateral and multifocal disease, neck LN involvement, mETE, tumor stage, and initial ATA risk stratification (p > 0.05 for all comparisons) (▶**Table 3**). However, more patients with the tall cell subtype had a tumor size of ≥ 5 mm than patients with the diffuse sclerosing subtype (p = 0.039), and although statistically only marginally signifi-

▶ **Table 1** Baseline clinical and histopathological characteristics of 1585 patients with PTMC according to the extent of surgery.

Variables	Hemithyroidectomy n = 160 (10%)	Total Thyroidectomy n = 1425 (90%)	Total Cohort n = 1585 (100%)
Age (years)	46 .03 ± 11.44	48.1 ± 11.64	47.9 ± 11.63
< 55	127 (79.4)	1024(71.9)	1151 (72.6)
> 55	33 (20.6)	401(28.1)	434 (27.4)
Sex			
Female	133 (83.1)	1207(84.7)	(84.5)
Male	27 (16.9)	218(15.3)	245 (15.5)
Completion thyroidectomy	65 (4.1)	–	–
Neck LN Dissection			
Central	–	145(10.1)	145 (9.1)
Lateral	–	11(0.77)	11 (0.7)
Central and Lateral	–	96(6.7)	96 (6.1)
Histopathologic subtype			
Classic	109 (68.1)	916(64.3)	1025(64.7)
Follicular	32 (20)	341(23.9)	373(23.5)
Oncocytic	5 (3.1)	73(5,1)	78 (4.9)
Diffuse sclerosing	3 (1.9)	42(2.9)	45 (2.8)
Tall cell	7 (4.4)	35(2.5)	42 (2.6)
Columnar cell	1 (0.6)	5(0.4)	6 (0.4)
Solid subtype	1 (0.6)	4 (0.3)	5 (0.3)
Clear cell	1 (0.6)	3 (0.2)	4(0.2)
Warthin-like	1 (0.6)	6(0.4)	7(0.4)
Tumor diameter (mm)	5.75 ± 2.91	5.81 ± 2.79	5.8 ± 2.8
< 5 mm	82 (51.2)	653(45.8)	735(46.4)
≥ 5 mm	78 (48.8)	772(54.2)	850(53.6)
Tumor foci and location			
Unilateral	160 (100	1044(73.3)	1204 (76)
Bilateral	–	381(26.7)	381 (24)
Multifocal	41(25.6)	630(44.2)	671 (42.3)
Unifocal	119(74.4)	795(55.8)	914 (57.7)
Microscopic ETE	15(9.4)	115(8.1)	130 (8.2)
Neck LN involvement at diagnosis	–	107 (7.5)	107 (6.8)
Central (N1a)	–	71(5)	71 (4.5)
Lateral (N1b)	–	36(2.5)	36 (2.3)
RAI treatment TNM Staging#	–	562(39.4)	562 (35.5)
Stage I	160(100)	1406(98.7)	1566 (98.8)
Stage II	–	19(1.3)	19 (1.2)
Initial ATA risk stratification			
Low	134(83.7)	1225(86)	1359 (85.7)
Intermediate	26(16.3)	197(13.8)	223 (14.1)
High	–	3 (0.2)	3 (0.2)
Follow-up time	65.03(42.61)	66.72(36.51)	66.5 ± 37.16
Persistent/recurrent disease	13(8.1)	61(4.3)	74 (4.7%)
ATA Dynamic risk stratification			
Excellent response	145(90.6)	1146(80.4)	1291(81.5)
Indeterminate response	9(5.6)	227(15.9)	236(14.9)
Incomplete biochemical response	6(3.8)	41(2.9)	47(3)
Incomplet structural response	–	11(0.8)	11(0.7)

PTMC: Papillary thyroid microcarcinoma; LN: Lymph node.; # No patient in the cohort was classified as stage III or IV; ATA: American Thyroid Association.

▶ **Table 2** Clinical and histopathological characteristics of 1585 patients with histologically aggressive and non-aggressive PTMC subtypes.

Variables	Aggressive subtype n = 98 (6.1 %)	Non-aggressive subtype n = 1487 (93.9 %)	p-Value
Age (years)	42.6 ± 12.4	48.2 ± 11.5	< 0.001
< 55	83(84.7)	1068(71.8)	
> 55	15(15.3)	419(28.2)	0.005
Sex			
Female	83 (84.7)	1257 (84.5)	
Male	15 (15.3)	230 (14.5)	0.5
Type of surgery			
Total thyroidectomy	86 (87.8)	1139 (90)	
Hemithyroidectomy	12 (12.2)	148 (10)	0.48
Completion thyroidectomy	10 (10.2)	55 (3.7)	0.005
Neck LN Dissection	49 (50)	203 (13.6)	< 0.001
Central	35(35.7)	110 (7.4)	< 0.001
Lateral	2 (2)	9 (0.6)	< 0.001
Central + Lateral	12 (12.2)	84 (5.6)	< 0.001
Tumor size (mm)	7.16 ± 2.26	5.71 ± 2.81	< 0.001
< 5	25(25.5)	710(47.7)	
≥ 5	73(74.5)	777(52.3)	< 0.001
Tumor foci and location			
Unilateral	52(53.1)	1151 (77.4)	
Bilateral	46(46.9)	335 (22.6)	< 0.001
Multifocal	58(59.2)	613(41.2)	
Unifocal	40(40.8)	874(58.8)	< 0.001
Microscopic ETE	27 (27.6)	103 (6.9)	< 0.001
Neck LN involvement at diagnosis			
Central (N1a)	18 (18.4)	53 (3.6)	< 0.001
Lateral (N1b)	10 (10.2)	26 (1.7)	< 0.001
RAI treatment	85 (86.7)	477 (32.1)	< 0.001
TNM Staging[#]			
Stage I	93(94.9)	1473 (99.1)	
Stage II	5 (5.1)	14 (0.9)	0.005
Initial ATA risk stratification			
Low	–	1359 (91.4)	
Intermediate	96 (98)	127 (8.5)	
High	2 (2)	1 (0.1)	< 0.001
Persistent/recurrent disease	33 (33.7)	41(2.8)	< 0.001
ATA dynamic risk stratification			
Excellent response	65 (66.3)	1226 (82.4)	
Indeterminate response	13 (13.4)	223 (15)	
Incomplete biochemical response	11 (11.2)	36 (2.4)	
Incomplete structural response	9 (9.2)	2 (0.1)	< 0.001

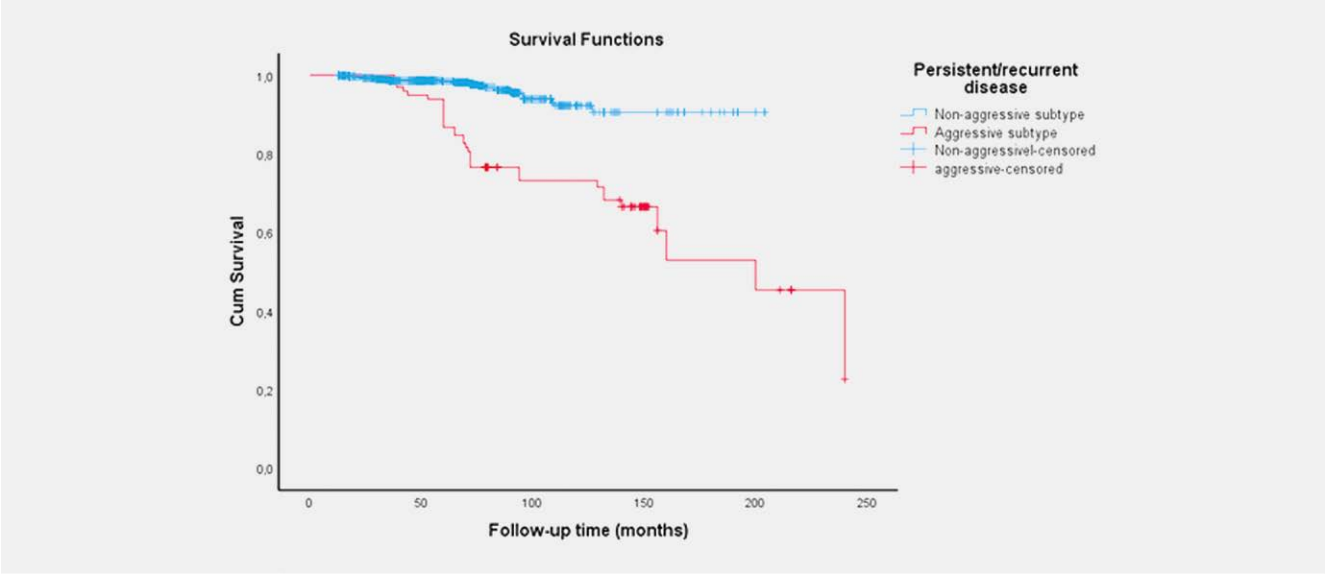
PTMC: Papillary thyroid microcarcinoma; LN: Lymph node; ETE: Extrathyroidal extension.; [#] No patient in the cohort classified as stage III or IV; ATA: American Thyroid Association.

cant, persistent/recurrent disease and incomplete structural response rates were more common in patients with tall cell than in patients with diffuse sclerosing subtype (p = 0.05, and p = 0.07, respectively) (▶ **Table 3**). Although the number of patients with columnar and solid PTMC subtypes was not adequate for within-group analysis, persistent/recurrent diseases were observed in 2 patients with a solid subtype, while no patient with a columnar subtype had persistent/recurrent disease.

▶ **Table 3** The differences in histopathological characteristics and clinical outcomes of the 98 patients with aggressive PTMC subtypes.

Variables	Diffuse Sclerosing n = 45 (45.9 %)	Tall Cell n = 42 (42.8 %)	p-Value	Solid subtype n = 5 (5.1 %)	Columnar cell n = 6 (6.1 %)
Age (years)	43.20 ± 11.84	41.81 ± 12.93	0.6	42.80 ± 18.8	43.33 ± 9.24
< 55	37(82.2)	36(85.7)		4(80)	6(100)
> 55	8(17.8)	6(14.3)	0.44	1(20)	–
Sex					
Female	41 (91.1)	33(78.6)		4(80)	5(83.3)
Male	4(8.9)	9(21.4)	0.09	1(20)	1(16.7)
Type of surgery					
Total Thyroidctomy	42 (93.3)	35(83.3)		4(80)	5(83.3)
Hemithyroidectomy	3 (6.7)	7 (16.7)	0.13	1(20)	1(16.7)
Completion thyroidectomy	3(6.7)	6 (14.2)	0.2	1(20)	–
Neck LN Dissection					
Central	14(31.1)	17(40.5)		1(20)	3(50)
Lateral	2(4.4)	–		–	–
Central and Lateral	6(13.3)	5(11.9)	0.47	1(20)	–
Tumor diameter (mm)	6.8 ± 2.5	7.5 ± 1.9	0.136	7.4 ± 3.4	7.1 ± 1.4
< 5 mm	16(35.6)	7(16.7)		1(20)	1(16.7)
≥ 5 mm	29(64.4)	35(83.3)	0.039	4(80)	5(83.3)
Tumor foci and location					
Unilateral	22(48.9)	22(52.4)		4(80)	4(66.7)
Bilateral	23(51.1)	20(47.6)	0.45	1(20)	2(33.3)
Multifocal	26 (57.8)	28(66.7)		1(20)	3(50)
Unifocal	19 (42.2)	14(33.3)	0.26	4(80)	3(50)
Microscopic ETE	15 (33.3)	12 (28.6)	0.4	–	–
TNM Staging#					
Stage I	41(91.1)	41(97.6)		5(100)	6(100)
Stage II	4 (8.9)	1(2.4)	0.2	–	–
Neck LN involvement at diagnosis					
Central (N1a)	7 (15.6)	8 (19)		2(40)	–
Lateral (N1b)	7 (15.6)	3 (7.1)	0.45	–	–
RAI treatment	38(84.4)	37(88.1)	0.42	5(100)	6(100)
Initial ATA risk stratification					
Low	–	–		–	–
Intermediate	44(97.8)	41(97.6)		5(100)	6(100)
High	1 (2.2)	1(2.4)	0.73	–	–
Persistent/recurrent disease	12 (26.7)	19(45.2)	0.05	2(40)	–
ATA Dynamic risk stratification					
Excellent response	33(73.3)	25(59.5)		4(80)	3(50)
Indeterminate response	7(15.6)	5(11.9)		1(20	–
Incomplete biochemical					
Response	4(8.9)	4(9.5)		–	3(50)
Incomplete structural					
response	1(2.2)	8(19)	0.07	–	–

The number of patients with columnar and solid subtypes was not eligible for statistical analysis.; PTMC: Papillary thyroid microcarcinoma; ETE: Extrathyroidal extension; LN: Lymph node.; # No patient in the cohort classified as stage III or IV.



▶ **Fig. 1** Kaplan–Meier curves displaying the estimated persistent/recurrent disease-free survival probability in patients with histologically aggressive and non-aggressive PTMC subtypes.

Kaplan–Meier and Cox regression analysis

In the Kaplan–Meier analysis, the overall DFS rate was 95.4 %. However, DFS was markedly lower in patients with aggressive than in those with non-aggressive PTMC subtypes [66.3 %, estimated median DFS 171.5 months (95 % CI: 151–191.9) vs 94.8 %, estimated median DFS 193 months (95 % CI: 188.7–197.27), respectively (Log-Rank $p < 0.001$) (▶ **Fig. 1**). Considering Cox's model, in univariate analysis, male sex, tumor size ≥ 5 mm, mETE, neck LN involvement, tumor stage, and multifocality as well as aggressive histology were all independent predictors of persistent/recurrent disease, while age > 55 was not an independent predictor of persistent/recurrent disease. However, in multivariate analysis, male sex, neck LN involvement, tumor stage, as well as aggressive histology were independent predictors of persistent/recurrent disease while tumor size ≥ 5 mm, mETE, and multifocality were not independent predictors of persistent/recurrent disease (▶ **Table 4**).

Discussion

In the present study, persistent/recurrent disease as well as incomplete biochemical and structural response rates were more common in patients with aggressive than in patients with non-aggressive PTMC subtypes (▶ **Table 2**). The DFS rate was markedly lower in patients with aggressive PTMC subtypes compared to patients with non-aggressive PTMC subtypes as well. Moreover, in multivariate analysis, aggressive histology was an independent predictor of persistent/recurrent disease, after controlling for other contributing factors (▶ **Table 2,4**).

In recent years, an increase in the frequency of PTMC has been observed [21]. Generally, studies report excellent clinical outcomes and DFS rates in patients with PTMC. In a recent meta-analysis comparing DFS among patients with PTMC who underwent thyroidectomy, the 10-year DFS rates were found as 95 % and 92 % after total thyroidectomy and hemithyroidectomy, respectively [22]. However, a recurrence rate as high as 19 % has been reported as well [23]. To the best of our knowledge, no study has evaluated the impact of aggressive histology on the clinical outcomes of PTMC so far. As in prior studies [22], the overall persistent/recurrent disease and DFS rates in our study were 4.7 and 95.3 %, respectively. However, when persistent/recurrent disease and DFS rates were analyzed according to the histopathological subtypes, persistent/recurrent diseases were significantly more common and DFS rates were markedly lower in patients with histologically aggressive than in those with non-aggressive PTMC subtypes (2.8 vs. 33.7 %, $p < 0.001$, and 97.3 vs 66.3 %, $p < 0.001$, respectively).

Since most of the PTMCs have an indolent clinical course, it has raised the question of which treatment method is a more appropriate option for these patients [24]. Nowadays, active surveillance is being recommended over immediate surgery in patients with low-risk PTMC [21]. In a recent systematic review, Chou et al. suggested that in patients with small low-risk DTC, active surveillance and immediate surgery may have a similar mortality rate and risk of recurrence [25]. In a study by Kudo et al., no significant difference was observed in disease-specific and overall survival among patients with classic, tall cell, and diffuse sclerosing PTMC subtypes, but patients with tall cell and diffuse sclerosing subtypes tended to have more frequent mETE, nodal metastasis, and multifocality than patients with classic PTMC [6]. However, they haven't analyzed DFS rates and dynamic risk stratification results between classic and aggressive PTMC subtypes [6]. Our study results were in line with that reported by Kudo et al. Neck LN involvement, mETE, multifocal and bilateral disease were all more common in patients with aggressive PTMC subtypes (▶ **Table 2**). Furthermore, patients with aggressive PTMC subtypes tended to have larger tumor sizes, more common stage–II disease, as well as higher rates of completion thyroidectomy and RAI treatment than patients with non-aggressive subtypes (▶ **Table 2**). In addition to the findings of Kudo et al., our study results suggest a markedly lower DFS and higher persistent/

▶ **Table 4** The effect of aggressive histology as well as age, sex, tumor size, neck lymph node involvement, microscopic extrathyroidal extension, multifocality, and stage on persistent/recurrent disease in patients with PTMC according to Cox's proportional hazard model.

Variables	HR (95 % CI)	p-Value
Univariate analysis		
Age (years)	Ref.	
> 55	1.07 (0.62–1.85)	0.78
Sex	Ref.	
Male	2 (1.14–3.57)	0.015
Tumor size	Ref.	
≥ 5 mm	3.2 (1.84–5.55)	< 0.001
Neck LN involvement at diagnosis	Ref.	
	12.78 (8.0–20.3)	< 0.001
Microscopic ETE	Ref	
	5.18 (3.2–8.3)	< 0.001
Multifocal tumor	Ref	
	3.1 (1.94–5.14)	< 0.001
Stage	Ref	
II	10.4 (4.7–22.7)	< 0.001
Aggressive histology	Ref.	
	12.3 (7.77–19.6)	< 0.001
Multivariate analysis		
Sex	Ref.	
Male	1.86 (1.04–3.33)	0.037
Tumor size	Ref.	
≥ 5 mm	1.72(1.06–3.22)	0.079
Neck LN involvement at diagnosis	Ref.	
	4.4 (2.31–8.47)	< 0.001
Microscopic ETE	Ref	
	1.27 (0.72–2.26)	0.4
Multifocal tumor	Ref	
	1.3 (0.75–2.24)	0.34
Stage	Ref	
II	3.12 (1.13–8.3)	0.028
Aggressive histology	Ref.	
	5.78 (3.32–10)	< 0.001

PTMC: Papillary thyroid microcarcinoma; ETE: Extrathyroidal extension.

recurrent diseases in patients with aggressive PTMC subtypes [6]. Therefore, aggressive PTMC subtypes share many clinical and histopathological characteristics with their identical tumors > 1 cm in size and may not be appropriate for active surveillance and should be treated as histologically identical tumors > 1 cm in size.

Tall cell and diffuse sclerosing subtypes are the most frequently observed aggressive subtypes of PTMC [6]. Studies indicated that angiolymphatic and parenchymal invasion, ETE, neck LN involvement, locoregional recurrence, and distant metastasis are more frequent in patients with tall cell than in non-aggressive PTC subtypes [26]. Furthermore, tall cell histology was suggested to be an independent predictor of neck LN involvement in patients with PTMC [27]. In a recent meta-analysis, comparing the tall cell subtype and classic PTC, multifocality, ETE, neck LN involvement, distant metastasis, and cancer-related mortality were all significantly more common in patients with tall cell subtype than in patients with classic PTC [28]. Moreover, tumor recurrence was more common in patients with the tall cell than in those with classic PTC as well (OR 5.12, 95 % CI 1.7–15.44, p = 0.004) [24]. The diffuse sclerosing subtype is consisting about %6 of PTCs. In a recent meta-analysis including 732 patients with diffuse sclerosing subtype, vascular invasion, ETE, neck LN involvement, and distant metastasis were all more common in patients with diffuse sclerosing than patients with classic PTC [29]. Moreover, persistent/recurrent disease was observed in 22 % of the patients with diffuse sclerosing and 10.7 % of patients with classic PTC (OR 2.83; 95 % CI 1.59–5.05). In our study, persistent/recurrent disease and incomplete structural response rates were observed in 45.2 %, 19 %, 26.7, and 2.2 % of the patients with tall cell and diffuse sclerosing subtypes, respectively (p = 0.05 and p = 0.07). Therefore, the presence of tall cell histology, even in patients with PTMC is associated with higher rates of persistent/recurrent diseases and structural incomplete response and should be taken into consideration when deciding on surgical treatment or active surveillance.

Solid and columnar subtypes of PTC are the other rare subtypes of PTC. The solid subtype is associated with a markedly higher risk for vascular invasion, tumor recurrence, and cancer mortality than classic PTC [30]. On the other hand, the columnar subtype is variable in biological behavior, some are clinically aggressive, whereas others are more clinically indolent [31]. In our study, only 5 patients had solid and 6 had columnar PTMC subtypes. Persistent/recurrent disease was observed in 2 patients with a solid PTMC subtype and non of the patients with a columnar subtype. However, the number of patients with solid and columnar PTMC subtypes was not adequate to make a within-group analysis.

Neck LN involvement is an independent predictor of recurrence in patients with PTMC [32]. PTMC with lateral LN involvement is more likely to have biochemical or structural persistence or recurrence compared with PTMC without LN involvement [33]. On the other hand, male sex, age < 55 years, multifocality, tumor size > 5 mm, and ETE are all found to be independent risk factors of central and lateral neck LN metastasis [34, 35]. On the contrary, bilateral multifocality was also suggested to be only an indicator of aggressiveness but not an independent predictor of worse clinical outcomes [36]. Although in the recent ATA guidelines, aggressive histology and mETE have been classified as "intermediate risk" for persistent/recurrent disease [5], a recent study suggested that mETE in small PTCs is not an independent risk factor for persistent/recurrent disease, and therefore, could be classified and treated as "low risk" tumors [37]. In our study, male sex, neck LN involvement, tumor stage as well as aggressive histology were independent predictors of persistent/recurrent disease, while age at diagnosis, multifocality, mETE, and size ≥ 5 mm were not independent predictors of persistent/recurrent disease. Therefore, according to our study

results too, PTMCs with mETE could be classified as "low-risk" tumors.

Unfortunately, despite aggressive PTC subtypes having unique cytopathologic characteristics, preoperative diagnosis of aggressive PTMC subtypes is difficult, and it is more common for patients to be diagnosed postoperatively after the histopathologic examination [6, 8, 38]. Nevertheless, multiple mutations could be present in aggressive subtypes of PTC [21, 39], and the molecular and genetic analysis of the FNAC may provide some clues regarding the histopathological subtype and aggressive clinical behavior [40]. For instance, $BRAF^{V600E}$, TERT promoter, and TP53 mutations are highly prevalent in the tall cell, columnar cell, and solid subtypes. On the other hand, RET/PTC rearrangements appear to predominate, while $BRAF^{V600}$ mutation may be present in only 20 % of the cases with diffuse sclerosing subtype [17]. Therefore, further molecular analysis may help to identify them before surgery.

Our study has several limitations. First of all, the retrospective nature of our study makes it subject to bias. In addition, because the FNAs of the patients with non-incidentally identified PTMCs were performed in different centers, we could not analyze the FNAC results. Furthermore, only patients with sufficient follow-up data were included in the study. Therefore, a significant number of patients, even those with a proven persistent/recurrent disease had to be excluded. And finally, molecular and genetic analysis had not been performed in any of the cases. However, the strength of our study derives from the inclusion of a relatively large number of patients with aggressive PTMC subtypes defined based on the newly published WHO criteria. Therefore, we believe that our study is an obvious example of daily practice.

Conclusions

Our study results suggest that histologically aggressive PTMC subtypes are associated with a markedly lower DFS rate as well as a higher frequency of persistent/recurrent disease than non-aggressive subtypes. Aggressive histology is an independent predictor of persistent/recurrent diseases as well. Moreover, incomplete biochemical and structural response rates are more common in patients with aggressive PTMC subtypes than in those with non-aggressive subtypes. Aggressive PTMC subtypes share many characteristics with histologically identical tumors > 1 cm in size. Therefore, the histopathological subtype of PTMC must be taken into serious consideration to tailor a personalized management plan. Further studies are needed to improve our understanding of the clinical outcomes of aggressive PTMC subtypes.

Conflict of Interest

The authors declare that they have no conflict of interest.

References

[1] Hughes DT, Haymart MR, Miller BS et al. The most commonly occurring papillary thyroid cancer in the United States is now a microcarcinoma in a patient older than 45 years. Thyroid 2011; 21: 231–236

[2] Wartofsky L. Management of papillary microcarcinoma: primum non nocere? J Clin Endocrinol Metab 2012; 97: 1169–1172

[3] Coca-Pelaz A, Shah JP, Hernandez-Prera JC et al. Papillary thyroid cancer – aggressive variants and impact on management: a narrative review. Adv Ther 2020; 37: 3112–3128

[4] Lloyd R, Osamura R, Klöppel G et al. WHO classification of tumours of endocrine organs. 4. Lyon: International Agency for Research on Cancer; 2017

[5] Haugen BR, Alexander EK, Bible KC et al. 2015; American thyroid association management guidelines for adult patients with thyroid nodules and differentiated thyroid cancer: the American thyroid association guidelines task force on thyroid nodules and differentiated thyroid cancer. Thyroid 2016: 1–133

[6] Kuo EJ, Goffredo P, Sosa JA et al. Aggressive variants of papillary thyroid microcarcinoma are associated with extrathyroidal spread and lymph-node metastases: a population-level analysis. Thyroid 2013; 23: 1305–1311

[7] Carcangiu ML, Bianchi S. Diffuse sclerosing variant of papillary thyroid carcinoma. Clinicopathologic study of 15 cases. Am J Surg Pathol 1989; 13: 1041–1049

[8] Carling T, Ocal IT, Udelsman R. Special variants of differentiated thyroid cancer: does it alter the extent of surgery versus well-differentiated thyroid cancer? World J Surg 2007; 31: 916–923

[9] Albareda M, Puig-Domingo M, Wengrowicz S et al. Clinical forms of presentation and evolution of diffuse sclerosing variant of papillary carcinoma and insular variant of follicular carcinoma of the thyroid. Thyroid 1998; 8: 385–391

[10] Fukushima M, Ito Y, Hirokawa M, Akasu H et al. Clinicopathologic characteristics and prognosis of diffuse sclerosing variant of papillary thyroid carcinoma in Japan: an 18-year experience at a single institution. World J Surg 2009; 33: 958–962

[11] Kazaure HS, Roman SA, Sosa JA. Aggressive variants of papillary thyroid cancer: incidence, characteristics and predictors of survival among 43,738 patients. Annals Surg Oncol 2012; 19: 1874–1880

[12] Canberk S, Montezuma D, Ince U et al. Variants of papillary thyroid carcinoma: an algorithmic cytomorphology-based approach to cytology specimens. Acta Cytol 2020; 64: 288–298

[13] Van Dijk SPJ, Coerts HI, Gunput STG et al. Assessment of radiofrequency ablation for papillary microcarcinoma of the thyroid: a systematic review and meta-analysis. JAMA Otolaryngol Head Neck Surg 2022; 148: 317–325

[14] Miyauchi A. Clinical trials of active surveillance of papillary microcarcinoma of the thyroid. World J Surg 2016; 40: 516–522

[15] Song E, Jeon MJ, Oh HS et al. Do aggressive variants of papillary thyroid carcinoma have worse clinical outcome than classic papillary thyroid carcinoma? Eur J Endocrinol 2018; 179: 135–142

[16] Kim M, Cho SW, Park YJ et al. Clinicopathological characteristics and recurrence-free survival of rare variants of papillary thyroid carcinomas in Korea: a retrospective study. Endocrinol Metab (Seoul) 2021; 36: 619–627

[17] Baloch ZW, Asa SL, Barletta JA et al. Overview of the 2022 WHO Classification of Thyroid Neoplasms. Endocr Pathol 2022; 33: 27–63

[18] Amin MB, Edge S, Greene F et al. AJCC Cancer Staging Manual. 8th ed. Berlin: Springer Verlag; 2017

[19] Cooper DS, Doherty GM et al. Revised American thyroid association management guidelines for patients with thyroid nodules and differentiated thyroid cancer. Thyroid 2009; 19: 1167e1214

[20] Zuhur SS, Aggul H, Çelik M et al. Can age at diagnosis and sex improve the performance of the American thyroid association risk stratification system for prediction of structural persistent and recurrent disease in patients with differentiated thyroid carcinoma? A multicenter study. Endocr Pract 2022; 28: 30–35

[21] Haymart MR. Progress and challenges in thyroid cancer management. Endocr Pract 2021; 27: 1260–1263

[22] Van Gerwen M, Alsen M, Lee E et al. Recurrence-free survival after total thyroidectomy and lobectomy in patients with papillary thyroid microcarcinoma. J Endocrinol Invest 2021; 44: 725–736

[23] Ardito G, Revelli L, Giustozzi E et al. Aggressive papillary thyroid microcarcinoma: prognostic factors and therapeutic strategy. Clin Nucl Med 2013; 38: 25–28

[24] Mehanna H, Al-Maqbili T, Carter B et al. Differences in the recurrence and mortality outcomes rates of incidental and nonincidental papillary thyroid microcarcinoma: a systematic review and meta-analysis of 21329 person-years of follow-up. J Clin Endocrinol Metab 2014; 99: 2834–2843

[25] Chou R, Dana T, Haymart M et al. Active surveillance versus thyroid surgery for differentiated thyroid cancer: a systematic review. Thyroid 2022; 4: 351–367

[26] Longheu A, Canu GL, Cappellacci F et al. Tall cell variant versus conventional papillary thyroid carcinoma: a retrospective analysis in 351 consecutive patients. J Clin Med 2020; 10: 70

[27] Medas F, Canu GL, Cappellacci F et al. Predictive factors of lymph node metastasis in patients with papillary microcarcinoma of the thyroid: retrospective analysis on 293 cases. Front Endocrinol (Lausanne) 2020; 11: 551

[28] Vuong HG, Long NP, Anh NH et al. Papillary thyroid carcinoma with tall cell features is as aggressive as tall cell variant: a meta-analysis. Endocr Connect 2018; 7: R286–R293

[29] Vuong HG, Kondo T, Pham TQ et al. Prognostic significance of diffuse sclerosing variant papillary thyroid carcinoma: a systematic review and meta-analysis. Eur J Endocrinol 2017; 176: 433–441

[30] Vuong HG, Odate T, Duong UNP et al. Prognostic importance of solid variant papillary thyroid carcinoma: A systematic review and meta-analysis. Head Neck 7 2018; 40: 1588–1597

[31] Chen JH, Faquin WC, Lloyd RV, Nosé V. Clinicopathological and molecular characterization of nine cases of columnar cell variant of papillary thyroid carcinoma. Mod Pathol 2011; 24: 739–749

[32] Usluogullari CA, Onal ED, Ozdemir E et al. A retrospective analysis of prognostic factors predictive of lymph-node metastasis and recurrence in thyroid papillary microcarcinoma. Minerva Endocrinol 2015; 40: 15–22

[33] Papachristos A, Do K, Tsang VH et al. Outcomes of papillary thyroid microcarcinoma presenting with palpable lateral lymphadenopathy. Thyroid 2022; 32: 1086–1093

[34] Carvalho AY, Kohler HF, Gomes CC et al. Predictive factors of recurrence of papillary thyroid microcarcinomas: analysis of 2,538 patients. Int Arch Otorhinolaryngol 2021; 25: e585–e593

[35] Wen X, Jin Q, Cen X et al. Clinicopathologic predictors of central lymph node metastases in clinically node-negative papillary thyroid microcarcinoma: a systematic review and meta-analysis. World J Surg Oncol 2022; 20: 106

[36] Yan T, Qiu W, Song J et al. Bilateral multifocality, a marker for aggressive disease, is not an independent prognostic factor for papillary thyroid microcarcinoma: A propensity score matching analysis. Clin Endocrinol (Oxf) 2021; 95: 209–216

[37] Castagna MG, Forleo R, Maino F, Fralassi N et al. Small papillary thyroid carcinoma with minimal extrathyroidal extension should be managed as ATA low-risk tumor. J Endocrinol Invest 2018; 41: 1029–1035

[38] Silver CE, Owen RP, Rodrigo JP et al. Aggressive variants of papillary thyroid carcinoma. Head Neck 2011; 33: 1052–1059

[39] Fahiminiya S, de Kock L, Foulkes WD. Biologic and Clinical Perspectives on Thyroid Cancer. N Engl J Med 2016; 375: 2306–2307

[40] Pappa T, Ahmadi S, Marqusee E et al. Oncogenic mutations in PI3K/AKT/mTOR pathway effectors associate with worse prognosis in BRAFV600E-driven papillary thyroid cancer patients. Clin Cancer Res 2021; 27: 4256–4264