Available online at www.sciencedirect.com

ScienceDirect

Biomedical Journal

journal homepage: www.elsevier.com/locate/bj

Original Article

Diagnostic pitfalls and therapeutic outcomes of the macrofollicular variant of papillary thyroid carcinoma

Soh-Ching Ng [a,e], Bie-Yu Huang [a,e], Sheng-Fong Kuo [a,e], Chuen Hsueh [b,e], Kun-Chun Chiang [c,e], Chih-Hung Chen [a,e,*], Jen-Der Lin [d,e,**]

[a] Division of Endocrinology and Metabolism, Department of Internal Medicine, Chang Gung Memorial Hospital at Keelung, Keelung, Taiwan
[b] Department of Pathology, Chang Gung Memorial Hospital at Linkou, Taoyuan, Taiwan
[c] Department of General Surgery, Chang Gung Memorial Hospital at Keelung, Keelung, Taiwan
[d] Division of Endocrinology and Metabolism, Department of Internal Medicine, Chang Gung Memorial Hospital at Linkou, Taoyuan, Taiwan
[e] College of Medicine, Chang Gung University, Gueishan, Taoyuan, Taiwan

ARTICLE INFO

Article history:
Received 19 April 2017
Accepted 18 December 2018
Available online 20 March 2019

Keywords:
Total thyroidectomy
Thyroglobulin
Radioactive iodide
Cancer-specific mortality

ABSTRACT

Background: The macrofollicular variant of papillary thyroid cancer (MFVPTC) is a rare histological variant of papillary thyroid cancer (PTC), with only 71 cases reported through 2014. This study analyzed the clinical, preoperative thyroid ultrasonography (US), and fine needle aspiration cytology (FNAC) features; and therapeutic outcomes of 11 patients with MFVPTC.

Methods: The records of 393 patients with histologically diagnosed follicular variant of papillary thyroid carcinoma (FVPTC), including 11 with MFVPTC, were retrospectively reviewed. Preoperative thyroid US findings, clinical presentation, treatment outcomes, and survival rates were analyzed.

Result: Mean tumor size was significantly greater in patients with MFVPTC than that in those with FVPTC (4.2 ± 2.1 cm vs. 2.9 ± 1.7 cm; $p = 0.016$). No patient with MFVPTC had lymph node involvement, but one had a micrometastasis to the lung, which responded well to therapeutic radioiodine. All MFVPTC lesions were isoechoic on US. Eight nodules had calcifications and eight had irregular margins. FNAC showed that these tumors had low cellularity, absence or focal presence of enlarged clear nuclei, and subtle or focal nuclear features of PTC. Cells were, arranged in microfollicular pattern, with abundant colloid background. Multifocal PTCs were detected in the opposite lobe of two patients. All 11 patients with MFVPTC had excellent outcomes. No patient experienced recurrence, and survival rates were high.

* *Corresponding author*. Division of Endocrinology and Metabolism, Chang Gung Memorial Hospital at Keelung, 222, Maijin Rd., Keelung 204, Taiwan.
** *Corresponding author*. Division of Endocrinology and Metabolism, Chang Gung Memorial Hospital at Linkou, 5, Fusing St., Gueishan, Taoyuan 333, Taiwan.
E-mail addresses: yh1008@cgmh.org.tw (C.-H. Chen), einjd@adm.cgmh.org.tw (J.-D. Lin).
Peer review under responsibility of Chang Gung University.
https://doi.org/10.1016/j.bj.2018.12.006

Conclusions: Malignant US criteria combined with FNAC features have a low preoperative diagnostic rate for MFVPTC. Surgery is recommended for patients with thyroid nodules larger than 4 cm and those with subtle and focal atypical nuclei in FNAC.

At a glance of commentary

Scientific background on the subject

The macrofollicular variant of papillary thyroid cancer (MFVPTC) is a rare histological variant of PTC, only 71 cases reported through 2014. MFVPTC were under-diagnosed because they may mimic benign lesions on cytopathology. Insufficient information was available in their ultrasonography (US) and fine needle aspiration cytology (FNAC) features.

What this study adds to the field

The clinical presentation, treatment outcomes, and survival rates of 382 FVPTC (382 non-MFVPTC and 11 MFVPTC) were analyzed. Malignant US criteria combined with FNAC features had a low diagnostic rate for MFVPTC. Surgery is recommended for nodules larger than 4 cm and those with subtle and focal atypical nuclei in FNAC.

The macrofollicular variant of papillary thyroid cancer (MFVPTC) is a rare histological variant of papillary thyroid cancer (PTC), with only 71 patients described through 2014 [1]. The categorization of MFVPTC as PTC, follicular thyroid carcinoma, or follicular variant of papillary thyroid cancer (FVPTC), remains unclear [2–4].

Thyroid ultrasonography (US) and fine needle aspiration cytology (FNAC) are first-line diagnostic tools for thyroid nodules [5]. These modalities, however, have demonstrated reduced sensitivity and specificity in the preoperative diagnosis of FVPTC [6]. Moreover, insufficient information is available about the thyroid US and FNAC characteristics of MFVPTCs. MFVPTCs may be under-diagnosed because they may mimic adenomatous goiter or benign thyroid lesions on cytopathology.

The purpose of this study was to retrospectively review the thyroid cancer database of our institution to assess the characteristics of MFVPTC on preoperative US and FNAC. In addition, clinical features and therapeutic outcomes of patients with these tumors were analyzed.

Material and methods

Participants

Between 1993 and 2013, 3404 patients with thyroid cancer, including 2783 (81.8%) with PTC, underwent regular follow-up care at Chang Gung Medical Center in Linkou, Taiwan. Of these 2783 patients, 437 (15.7%) who were lost to follow-up after one year and 246 (8.8%) who underwent initial thyroidectomy at another hospital were excluded.

Of the remaining 2100 patients with PTC, 393 (18.7%) were diagnosed with histologically proven FVPTC, including 11 (0.5%) with MFVPTC. The 393 patients included 303 (77.1%) women and 90 (22.9%) men, of mean age 45.1 ± 13.4 years (range: 10–82 years, median: 46 years). Of the 393 patients, 317 (80.7%) underwent total thyroidectomy (TT) or complete thyroidectomies (CTT, with a second surgical intervention performed after pathological diagnosis of carcinoma).

All thyroid carcinoma tissues were pathologically classified according to World Health Organization criteria [7]. Patients were staged in accordance with the tumor-node-metastasis (TNM) staging criteria of the American Joint Committee on Cancer (AJCC) 7th edition [8].

This study was approved by the Institutional Review Board of Chang Gung Medical Center (Approval No. 102-3433B). Because of the retrospective nature of this study, the requirement for informed consent was waived.

Preoperative examinations and postoperative evaluation and management

Thyroid US in most patients was performed by an endocrinologist or radiologist using a real-time US machine (GE Voluson 730 Expert) and a 10-MHz transducer. Factors evaluated included the composition of the nodules, echogenicity, texture, margins, shape, and the presence or absence of halos. Microcalcifications were defined as calcifications ≤1 mm in diameter, which were visualized as tiny, punctate hyperechoic foci, with or without acoustic shadows; and macrocalcifications were defined as hyperechoic foci >1 mm in diameter. FNAC was performed on suspected thyroid nodules using a 24-gauge needle. The aspirates were stained with Papanicolaou stain or by the Romanowsky-based method [9]. Ten of the 11 patients with MFVPTC underwent preoperative FNAC. FNAC results were interpreted as described [10].

Surgery was recommended to patients cytologically diagnose Bethesda category IV to VI disease and to patients with enlarged nodules and an inadequate number of cells for interpretation during follow-up. Some patients with initial cytological diagnoses of benign masses were requested to undergo repeat US and FNAC 3 and 6 months later.

This study enrolled patients who underwent TT or less than TT and had a final histopathologic diagnosis of MFVPTC. Five of these patients underwent a second surgical intervention, resulting in CTT, with the bilateral thyroidectomy specimens undergoing further histopathological analyses.

Patients underwent remnant radioiodine ablation with 1.11–3.7 GBq (30–100 mCi) 4–6 weeks after thyroidectomy. If a

Table 1 Clinical features of total FVPTC, MFVPTC and Non-MFVPTC.

Clinical Characteristic	Total FVPTC	MFVPTC vs. Non-MFVPTC		p value
		MFVPTC	Non-MFVPTC	
Number (%)	393 (100.0)	11 (2.8)	382 (97.2)	
Sex, Female (%)	303 (77.1)	7 (63.6)	296 (77.5)	0.281[b]
Age at diagnosis (year) [range/median]	45.1 ± 13.4 [10–82/46]	44.0 ± 18.2 [10–65/47]	45.1 ± 13.2 [11–84/46]	0.788[a]
Tumor size (cm), histology [range/median]	3.0 ± 1.7 [0.2–10.0/2.8]	4.2 ± 2.1 [1.7–7.8/4.0]	2.9 ± 1.7 [0.2–10.0/2.7]	0.016[a]
Post-operative 1 month Tg (ng/mL) [range/median]	624.8 ± 4863.7 [0.0–65320/4.2]	10.8 ± 6.0 [0.0–20.5/9.9]	643.4 ± 4935.6 [0.0–65320/3.9]	0.672[a]
Multifocality (%)	101 (25.7)	2 (18.2)	99 (25.9)	0.563[b]
Operative method				0.147[b]
TT or CTT (%)	317 (80.7)	7 (63.6)	310 (81.2)	
Less than TT (%)	76 (19.3)	4 (36.6)	72 (18.8)	
Clinical stage				0.476[b]
Stage I (%)	326 (83.0)	10 (90.9)	316 (82.7)	
Stage II–IV (%)	67 (17.0)	1 (9.1)	66 (17.3)	
TNM stage				
Stage I (%)	239 (60.8)	7 (63.6)	232 (60.7)	0.846[b]
Stage II–IV (%)	154 (39.2)	4 (36.4)	150 (39.3)	
Non-remission (%)	55 (14.0)	1 (9.1)	54 (14.1)	0.634[b]
Follow-up period (year) [range/median]	6.9 ± 5.1 [0.1–20.2/5.8]	4.2 ± 2.5 [2.2–9.5/2.9]	7.0 ± 5.1 [0.1–20.2/5.8]	0.064[a]
Post-operative ^{131}I accumulative dose (mCi) [range/median]	116.8 ± 196.3 [0.0–1640/60.0]	65.5 ± 52.1 [0.0–200/60.0]	118.2 ± 198.7 [0.0–1640/60.0]	0.380[a]
Radiation therapy (%)	13 (3.3)	0	13 (3.4)	0.534[b]
2nd primary cancer (%)	24 (6.1)	0	24 (6.3)	0.391[b]
Diabetes mellitus (%)	39 (9.9)	2 (18.2)	37 (9.7)	0.353[b]
Total mortality (%)	24 (6.1)	0	24 (6.3)	0.391[b]
TCA mortality (%)	15 (3.8)	0	15 (3.9)	0.503[b]
Disease free (%)	179 (45.5)	8 (72.7)	171 (44.8)	0.066[b]

Abbreviations: TT: Total thyroidectomy; CTT: complete thyroidectomy; TCA: thyroid cancer.
Data are presented as mean ± S.D. where applicable.
[a] Student's t-test analyses.
[b] Chi-square test.

distant metastasis was diagnosed on a radioiodine scan, patients were administered an additional of 3.7–7.4 GBq (100–200 mCi) ^{131}I radioiodine 6 months later. Through the end of 2014, serum Tg levels were measured using an immunoradiometric assay kit (CIS Bio International, Gif-sur-Yvette, France), with a detection limit of 0.5 ng/mL and a functional sensitivity, as determined in our laboratory, of 1.2 ng/mL. Concentrations of anti-Tg antibody were measured by competitive radioimmunoassay (Biocode, Liège, Belgium), with an analytical sensitivity of 6 IU/mL.

Table 2 Morphologic and cytologic features of the 11 patients with MFVPTC.

No	Age (yr)	Sex	Ultrasound Characteristics							FNAC[a]
			Size (cm)	Halo	Margin	Calcification	Internal component	Shape	Goiter	
1	47	Female	6.0	Incomplete	Poor/IR	Micro	Spongiform	W	M	II
2	32	Male	4.5	Incomplete	Well/R	Micro	Solid, MC	W	M	II
3	10	Female	4.3	incomplete	Well/R	None	Solid	W	S	IV
4	53	Female	3.8	incomplete	Poor/IR	None	Solid, MC	T	M	VI
5	59	Female	1.8	None	Interrupted calcified rim/IR	Macro	Solid	W	M	II
6	65	Male	1.7	None	Poor/Infiltrated	Micro	Solid	W	M	IV
7[b]	16	Male	7.5	Complete	Well/R	Macro	Cystic	W	S	NA
8	39	Male	7.8	Incomplete	Well/IR	None	Spongiform	W	S	II
9	62	Female	8.0	None	Poor/IR	Micro	Solid, MC	W	M	II
10	64	Female	5.0	None	Poor/IR	Micro, macro	Solid	W	M	II
11	38	Female	1.7	Incomplete	Well/IR	Micro, macro	Solid, MC	W	M	IV
mean			4.7 ± 2.4							

Abbreviations: R: regular; IR: irregular; W: wider than tall; T: taller than wide (transverse view); M: multiple nodules; S: single nodule; Cystic predominant (>50% cystic tissue); Solid predominant (<50% cystic tissue); Solid/MC (microcystic<5% cystic).
[a] Cytology categorized by Bethesda system: II Benign, IV Follicular Neoplasm, V Suspicious for malignancy, VI Malignant; NA: not available.
[b] Computerized Tomography features.

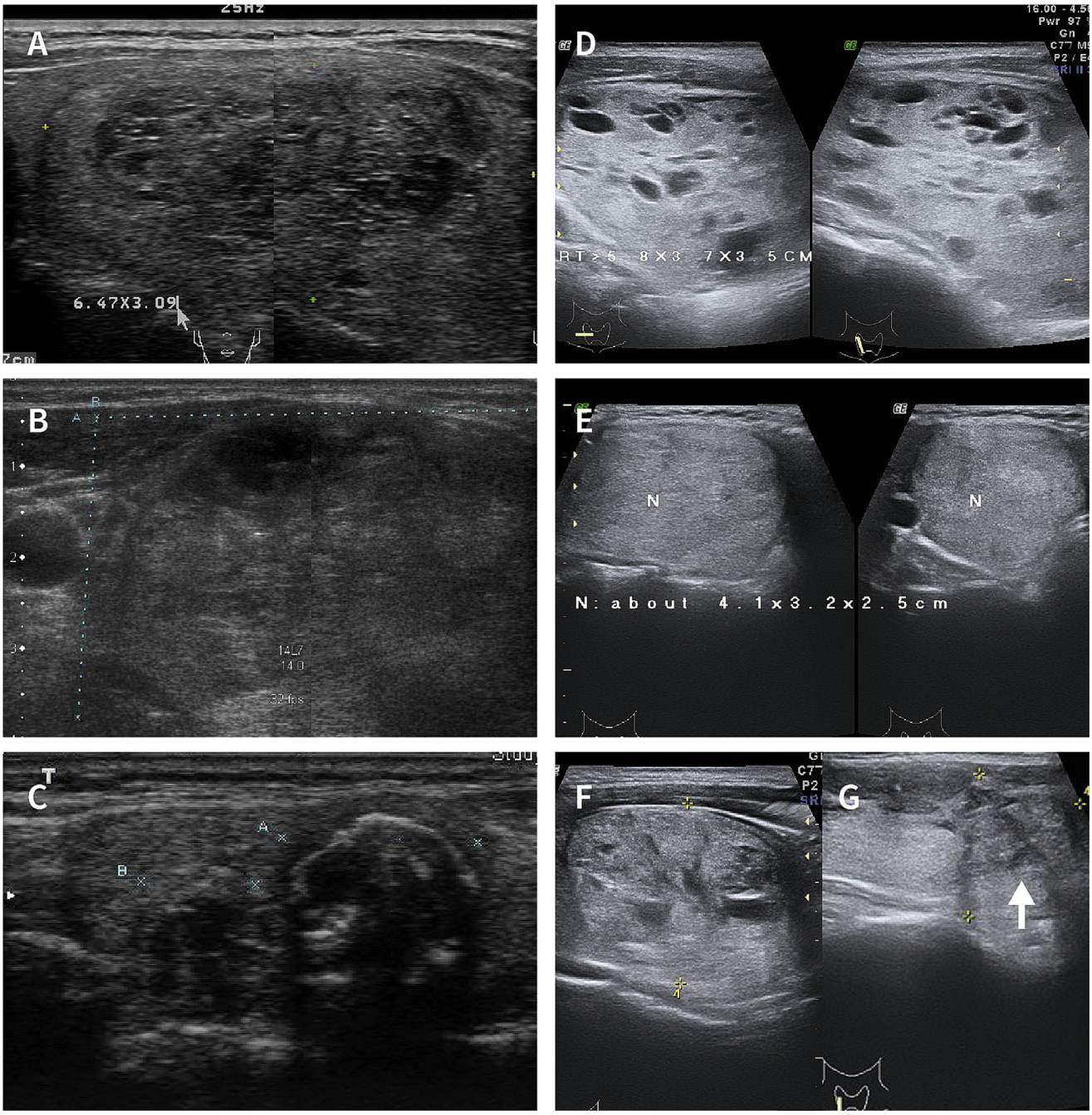

Fig. 1 Ultrasonography characteristics of the macrofollicular variant of papillary carcinoma. (A) A tumor with poorly-defined, irregular margins, incomplete halo and cystic degeneration (Patient 1). (B) Transverse US section of an isoechoic mass with poorly-defined, irregular margins, incomplete halo with micro- and macro-calcifications and cystic degeneration (Patient 10). (C) Longitudinal US view of a tumor with interrupted calcified rim, poorly-defined, irregular margins, and macrocalcifications with an acoustic shadow (Patient 5). (D) Transverse/longitudinal images of a tumor occupying the entire lobe with spongiform microcysts (Patient 8). (E) Longitudinal/transverse images of a large single isoechoic tumor with well-defined and regular margins, without calcification (Patient 3). (F) Longitudinal view of an isoechoic mass with well-defined, regular margins and halo (Patient 2). (G) Multinodular goiter with a tumor having infiltrative margins and microcalcifications (Patient 6) (arrow).

Patients with undetectable serum Tg levels, defined as <1.2 ng/mL, were evaluated by noninvasive methods, including neck US, with or without chest radiography, once or twice a year. Patients with detectable Tg levels were evaluated by neck US, with or without chest radiography, more frequently, and received additional radioiodine doses. Based on clinical indications, selected patients underwent ^{131}I scans annually or biannually during follow-up, with thyroid hormone withdrawn or recombinant human thyroid stimulating hormone (rhTSH) administered. Patients showing a 24-h ^{131}I

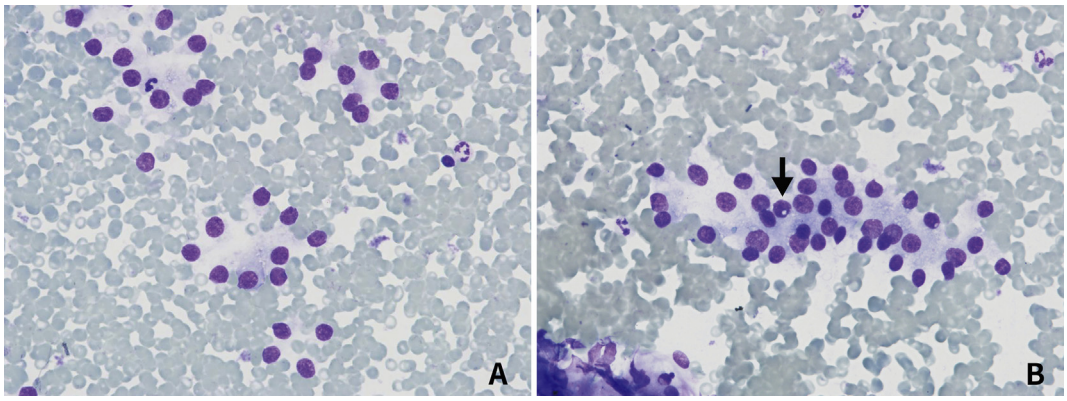

Fig. 2 Cytological characteristics of the macrofollicular variant of papillary thyroid carcinoma. (A) Low cellularity, microfollicular pattern, and mild anisonucleosis. (B) Enlarged, pale nuclei, anisonucleosis, and coarse chromatin are subtle and focally displayed. Tiny inclusion body (arrow) and colloid particles (Riu Quick staining, ×400) were observed.

uptake >0.5% underwent further therapeutic ablation with 30 mCi ^{131}I. Remission was defined as a negative result on ^{131}I whole-body scans, absence of visible tumor outside the neck area, and absence of local or distant metastases on noninvasive examinations. Patients in remission with undetectable Tg in the absence of levothyroxine treatment and undetectable anti-Tg antibodies at final follow-up were defined as being disease-free.

Factors recorded included patient age, sex, primary tumor size, US findings, FNAC results, surgical methods, histopathological variables (size, encapsulation, tumor capsule invasion, extrathyroidal extension, neck regional lymph nodes, or distant metastasis), and TNM stage [8]. Clinical stage was categorized as Class I (single or multiple intrathyroidal foci); Class II (lymph node metastasis); Class III (tumor invasion outside the thyroid gland or unresectable lymph nodes) or Class IV (distant metastasis) [11]. Other factors evaluated included post-operative serum Tg concentrations, titers of serum anti-Tg antibody 4–6 weeks after surgery, regular therapeutic ^{131}I scanning results, cumulative dose of ^{131}I, findings on post-operative US and chest radiography, clinical determination of distant metastases by noninvasive radiologic and/or nuclear medical modalities, and treatment outcomes. Cytology findings and diagnoses were compared with the final histological diagnosis.

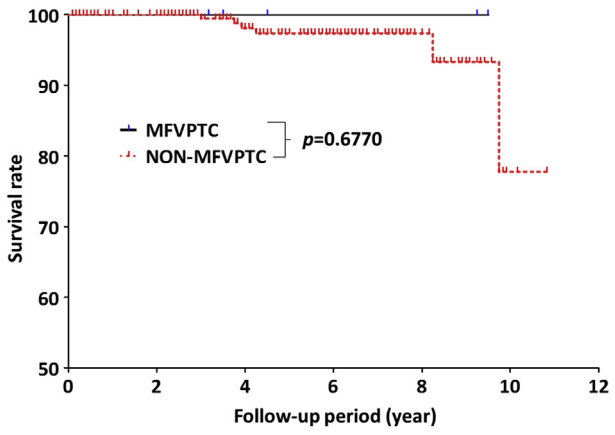

Fig. 3 Kaplan–Meier survival curves of patients diagnosed with the macrofollicular variant of papillary thyroid carcinoma (MFVPTC) and with the follicular variant of papillary thyroid carcinoma not including MFVPTC (NON-MFVPTC).

Statistical analysis

Survival rates were calculated using the Kaplan–Meier method and compared using the log-rank test [12]. All statistical analyses were performed using Statistical Product and Service Solutions version 17.0 (SPSS Inc., Chicago, IL, USA). p-values < 0.05 were considered statistically significant in all tests.

Result

Of the 393 patients diagnosed with FVPTC in our institution, 11 (2.8%) were diagnosed with MFVPTC [Table 1]. Age and sex did not differ significantly between the 382 patients with non-MFVPTC and the 11 MFVPTC. MFVPTCs were significantly larger in size histologically than non-MFVPTCs (4.2 ± 2.1 cm vs. 2.9 ± 1.7 cm; $p = 0.016$). Although a lower percentage of patients with MFVPTC underwent TT or CTT (63.6% vs. 81.2%; $p = 0.147$), there were no significant differences in surgical methods or post-operative ^{131}I doses [Table 1].

Of the 11 patients with MFVPTC, one patient (Patient 1 in Table 2), a 47-year-old woman with a post-operative serum Tg level of 20 ng/mL 1 month after total thyroidectomy, presented with a distant (lung) metastasis detected on a 3.7 GBq (100 mCi ^{131}I) therapeutic scan evaluating remnant ablation. After treatment with 7.4 GBq (200 mCi) ^{131}I, the patient was disease-free, with an undetectable Tg level. She showed no evidence of recurrence after 5.7 years of follow-up.

Table 2 shows the age, sex, thyroid US and FNAC results of the 11 patients with MFVPTC, as well as the computed tomography results of one MFVPTC patient. The US images of all MFVPTC lesions were heterogeneous and isoechogenic. Eight of the 11 nodules had calcifications, and eight had irregular margin. Seven presented with halo signs, including 6 with incomplete halos, and seven demonstrated intranodular

cystic degeneration. [Fig. 1] displays the thyroid US features of the seven surgically proven MFVPTCs.

Of the 10 FNAC specimens, six (60%) were benign lesions, three (30%) were follicular neoplasms, and one (10%) was a malignant tumor, according to the Bethesda System. FNAC samples were characterized by 1) low cellularity; 2) absence or focal presence of enlarged clear nuclei, with a few having coarse chromatin intermixed among fine chromatin; 3) abundant colloid fragments; and 4) cells in dissociated distributions or microfollicular patterns, rather than in typical papillary structures. Enlarged clear nuclei, anisonucleosis, and intranuclear inclusion bodies were typical nuclear features, but they could be subtle and focal [Fig. 2]. Histologically, multifocal PTCs (microPTC and PTC), with characteristics similar to those of classic PTC, were observed in the opposite lobe of two patients.

After thyroidectomy, 10 of the 11 MFVPTC patients (all except patient 7) were treated with 30–100 mCi ^{131}I for remnant ablation. After a mean follow-up of 6.9 ± 5.1 years, disease-specific survival did not differ significantly in patients with MFVPTC and those with Non-MFVPTC [Fig. 3], with 5-year survival rates of 100% and 97.4%, respectively, and 10-year survival rates of 100% and 77.8%, respectively. .

Discussion

This study found that the mean age of the patients with MFVPTC was 44.0 ± 18.2 years, with a female predominance (63.6%). These numbers are similar to the mean age (44.37 ± 13.77 years) and female predominance (78.7%) we observed in patients with FVPTC [13]. In addition, our results are consistent with a cross-sectional population analysis of a US national cancer database, in which patients had a mean age of 47.9 years and showed female predominance (79.3%) [14].

MFVPTC was first described in 1991 as usually encapsulated and was regarded as a well-differentiated carcinoma [15]. These tumors were histologically defined as tumors with macrofollicles (>200 μm in diameter) occupying more than 50% of the cross-sectional area of tumor follicles [15]. They are characterized by a predominant follicular architecture [16], in contrast to the well-formed papillary structures observed in conventional PTCs [10,15,16].

Over the last 3 decades, nuclear histological features, such as enlarged nuclei, pale ground glass opacity, intranuclear cytoplasmic inclusions, and nuclear grooves, have become of paramount importance in the diagnosis of PTC and its variants [16]. Most MFVPTCs have an indolent behavior, but multiple bone and lung metastases may occur [15,17,18]. Hence, careful cytopathological interpretations of any nuclear features suggesting malignant potential and a thorough review of previous, seemingly benign thyroid lesions in thyroidectomy specimens are important, because MFVPTCs may show delayed recurrence and/or distant metastases.

FNAC is a widely accessible preoperative diagnostic procedure with high accuracy, especially for PTC. However, FNAC is less accurate in diagnosing FVPTC and MFVPTC than conventional PTC. The nuclear features of MFVPTC are often more subtle on FNAC than observed histologically. MFVPTCs usually present with focal nuclear atypia, as well as lower cellularity, and more abundant colloid than conventional PTC and FVPTC. Assessments of cytological features may be unable to distinguish MFVPTC from benign lesions [1]. Cytology can also be affected by interobserver variability [19–21], which reduces the possibility of surgical intervention for a definite pathological diagnosis.

Our rate of MFVPTC diagnosis using preoperative FNAC was slightly lower than previously reported [1]. The earlier study found that using FNAC often resulted in MFVPTCs being diagnosed as benign lesions. Of the MFVPTCs in the earlier study, 29% were diagnosed as macrofollicular adenomas/adenomatous goiter; 14% as follicular neoplasms, 37% as PTC, and 20% as atypia of undetermined significance. Our rate of MFVPTC diagnosis using FNAC was even lower than the rate we previously reported for FVPTC [13]. Of the 75 FVPTCs in that study, 22 (29%) were diagnosed as benign thyroid lesions, 42 (56%) as follicular neoplasms, and 11 (15%) as PTC.

US can also easily evaluate patients pre-operatively. Thyroid US may help identify tumors with malignant potential, may indicate the need for FNAC, and may facilitate the detection of malignancy. US features indicative of malignancy include irregular margins, including microlobulated, spiculated and infiltrative margins; solid consistency; marked hypoechogenicity; micro- and/or macro-calcifications, shape taller than wide measured on a transverse view; and absence of halo [22–25]. These features, however, may be absent from FVPTC and MFVPTC specimens. In our study, all MFVPTC specimens exhibited isoechogenecity. Thus far, no characteristic US features of MFVPTC have been described.

In conclusion, preoperative diagnosis of MFVPTC by US plus FNAC poses more challenges than diagnosis of conventional PTC and FVPTC. This results in fewer patients with MFVPTC undergoing total thyroidectomy as initial surgical intervention. Although MFVPTC has a good survival rate, distant metastases may occur.

Conflicts of interest

The authors have no conflicts of interest relevant to this article.

Acknowledgement

This work was supported in part by grants from the Chang Gung Memorial Hospital (CMRPG3E1901) awarded to J.D. Lin.

REFERENCES

[1] Yeo MK, Bae JS, Oh WJ, Park GS, Jung CK. Macrofollicular variant of papillary thyroid carcinoma with extensive lymph node metastases. Endocr Pathol 2014;25:265–72.

[2] Pusztaszeri M, Pache JC, Karenovics W, Kohler R, Triponez F, Bongiovanni M. A noninvasive encapsulated macrofollicular variant of papillary thyroid carcinoma presenting with gross

lymph node metastasis: a case report and literature review. Thyroid 2013;23:1178–9.
[3] Lin JD, Hsueh C, Huang BY. Papillary thyroid carcinoma with different histological patterns. Chang Gung Med J 2011;34:23–4.
[4] Lloyd RV, Buehler D, Khanafshar E. Papillary thyroid carcinoma variants. Head Neck Pathol 2011;5:51–6.
[5] Lin JD, Chao TC, Huang BY, Chen ST, Chang HY, Hsueh C. Thyroid cancer in the thyroid nodules evaluated by ultrasonography and fine-needle aspiration cytology. Thyroid 2005;15:708–17.
[6] Liu J, Singh B, Tallini G, Carlson DL, Katabi N, Shaha A, et al. Follicular variant of papillary thyroid carcinoma: a clinicopathologic study of a problematic entity. Cancer 2006;107:1255–64.
[7] DeLellis RA. Pathology and genetics of tumors of endocrine organs. J Surg Oncol 2006;94:662–9.
[8] Edge SB, Byrd DR. The American Joint Committee on Cancer: the 7th edition of the AJCC cancer staging manual and the future of TNM. Ann Surg Oncol 2010;17:1471–4.
[9] Riu CH. On the studies of the methods of staining blood film (Romanosky's system). J Niigata Med Assoc 1956;70:635.
[10] Cibas ES, Ali SZ. The Bethesda system for reporting thyroid cytopathology. Thyroid 2009;19:1159–65.
[11] DeGroot LJ, Kaplan EL, McCormick M, Straus FH. Natural-history, treatment, and course of papillary thyroid-carcinoma. J Clin Endocrinol Metab 1990;71:414–24.
[12] Zhang DD, Zhou XH, Freeman DH, Freeman JL. A non-parametric method for the comparison of partial areas under ROC curves and its application to large health care data sets. Stat Med 2002;21:701–15.
[13] Chang HY, Lin JD, Chou SC, Chao TC, Hsueh C. Clinical presentations and outcomes of surgical treatment of follicular variant of the papillary thyroid carcinomas. Jpn J Clin Oncol 2006;36:688–93.
[14] Lin HW, Bhattacharyya N. Clinical behavior of follicular variant of papillary thyroid carcinoma: presentation and survival. Laryngoscope 2010;120:712–6.
[15] Albores-Saavedra J, Gould E, Vardaman C, Vuitch F. The macrofollicular variant of papillary thyroid carcinoma: a study of 17 cases. Hum Pathol 1991;22:1195–205.
[16] Albores-Saavedra J, Wu J. The many faces and mimics of papillary thyroid carcinoma. Endocr Pathol 2006;17:1–18.
[17] Cardenas MG, Kini S, Wisgerhof M. Two patients with highly aggressive macrofollicular variant of papillary thyroid carcinoma. Thyroid 2009;19:413–6.
[18] Marques P, Leite V, Bugalho MJ. Remarkable response to radioiodine therapy in a case of metastatic macrofollicular variant of papillary thyroid carcinoma. Clin Nucl Med 2014;39:219–21.
[19] Hirokawa M, Shimizu M, Terayama K, Kanahara T, Sonoo H, Manabe T. Macrofollicular variant of papillary thyroid carcinoma. Report of a case with fine needle aspiration biopsy findings. Acta Cytol 1998;42:1441–3.
[20] Chung D, Ghossein RA, Lin O. Macrofollicular variant of papillary carcinoma: a potential thyroid FNA pitfall. Diagn Cytopathol 2007;35:560–4.
[21] Policarpio-Nicolas MC, Sirohi D. Macrofollicular variant of papillary carcinoma, a potential diagnostic pitfall: a report of two cases including a review of literature. Cyto J 2013;10:16.
[22] Haugen BR, Alexander EK, Bible KC, Doherty GM, Mandel SJ, Nikiforov YE, 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;26:1–133.
[23] Seo H, Na DG, Kim JH, Kim KW, Yoon JW. Ultrasound-based risk stratification for malignancy in thyroid nodules: a four-tier categorization system. Eur Radiol 2015;25:2153–62.
[24] Russ G. Risk stratification of thyroid nodules on ultrasonography with the French TI-RADS: description and reflections. Ultrasonography 2016;35:25–38.
[25] Gharib H, Papini E, Garber JR, Duick DS, Harrell RM, Hegedus L, et al. American association of clinical endocrinologists, American college of endocrinology, and associazione medici endocrinologi medical guidelines for clinical practice for the diagnosis and management of thyroid nodules-2016 update. Endocr Pract 2016;22:622–39.