Endocrine (2021) 72:727–734
https://doi.org/10.1007/s12020-020-02510-2

ORIGINAL ARTICLE

Ultrasound features value in the diagnosis and prognosis of medullary thyroid carcinoma

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Received: 13 March 2020 / Accepted: 23 September 2020 / Published online: 4 October 2020

Abstract

Purpose Ultrasound (US) is the most important imaging in the preoperative diagnosis of medullary thyroid carcinoma (MTC). MTC are easy to be misdiagnosed due to lacking typical malignant US features. This study investigated US features, clinical characteristics, prognosis, and detection methods, aimed to explore the association between US features and biological behavior, and improve early diagnosis of MTC.

Methods A total of 189 MTC patients were enrolled in the study. Based on US features, 29 MTC were categorized as "indeterminate" (i-MTC) and 160 MTC were categorized as "malignant" (m-MTC) according to Thyroid Imaging, Reporting and Data System published by America College of Radiology (ACR TI-RADS). We compared US features, clinical characteristics and prognosis between both groups. We analyzed cytological categories of fine needle aspiration (FNA) within each i-MTC and m-MTC group according to the 2017 Bethesda System for Reporting Thyroid Cytopathology (TBSRTC). We assessed the positive rate of FNA, frozen pathological examination, and preoperative serum calcitonin (Ctn) level in i-MTC and m-MTC groups.

Results Preoperative US features were significantly different in shape, margin, composition, echogenicity, and calcifications between i-MTC and m-MTC ($p < 0.05$). I-MTC showed a hypoechoic solid or solid-cystic nodule lacking malignant US features. While m-MTC was presented as a solid nodule with obviously malignant US features. There were significant differences in lymph node dissection, extent of tumor, lymph node metastasis, and TNM stage and prognosis between i-MTC and m-MTC ($p < 0.05$). Compared to m-MTC, i-MTC underwent central neck dissection more frequently rather than lateral neck dissection at the time of the initial operation; i-MTC had less extrathyroidal invasion and lymph node metastasis, earlier stage, higher rate of biochemical cure, and lower rate of structural persistence/recurrence ($p < 0.05$). The 2017 TBSRTC of i-MTC and m-MTC was significantly different ($p < 0.05$). Preoperative serum Ctn level had a higher diagnostic sensitivity for both i-MTC and m-MTC when comparing to FNA and frozen pathological examination ($p < 0.05$).

Conclusions US features were associated with biological characteristics and prognosis of MTC. I-MTC lack malignant US features, preformed less aggressiveness, and better prognosis. TBSRTC according to FNA combined with serum Ctn were helpful for the detection of i-MTC.

Keywords Medullary · Thyroid · Carcinoma · Ultrasound · Biology · Calcitonin

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Introduction

Medullary thyroid carcinoma (MTC) is an endocrine malignancy arising from the parafollicular thyroid C cells. It accounts for 1–2% of thyroid carcinomas due to the marked increased incidence of papillary thyroid carcinoma (PTC) over the last three decades according to the recent Surveillance, Epidemiology, and End Results data, but it leads to 8–13% of all thyroid cancer-related death [1, 2].

Age, tumor size, extrathyroid invasion, lymph node metastases, distant metastases, serum calcitonin (Ctn) level, and tumor-node-metastases (TNM) stage are the significantly prognostic factors in patients with MTC. As MTC is not responsive to radioiodine or TSH suppressive therapy, early diagnosis and complete surgical resection are needed to potentially achieve biochemical cure [3, 4]. The most frequently used diagnostic tools in MTC are ultrasound (US), fine needle aspiration (FNA), serum Ctn, and frozen pathological examination. US is the most important imaging in the preoperative diagnosis and staging of MTC. Previous studies reported that malignant US features including irregular shape, ill-defined margin are risk factors for lateral lymph node metastasis [5–7]. All these studies suggested the US features of MTC are associated with its biological behavior. But the inference is based on limited evidence. We also found that a considerable number of MTC cases are easily missed or delayed diagnosis due to lacking malignant US features. Whether these i-MTC and m-MTC are not only different in US features but also in biologic behavior remains to be elucidated.

Thyroid Imaging, Reporting and Data System published by America College of Radiology (ACR TI-RADS) and Bethesda System for Reporting Thyroid Cytopathology (TBSRTC) have been widely applied in the management of thyroid nodules and proved to be useful when applied to diagnosis of MTC [8–10]. The former is aimed to predict the probability of thyroid malignancy using a scoring system based on multiple US parameters and provide guidance for FNA. The latter is applied to assess risk of malignancy of thyroid nodules based on cytologic categories of FNA. In this study, we investigated difference in US features, clinical characteristics, and prognosis between i-MTC and m-MTC. Furthermore, we analyzed categories of FNA within each group according to the 2017 TBSRTC. Finally, we assessed the diagnostic performance of FNA, preoperative serum Ctn levels and frozen pathological examination in the detection of MTC aiming to achieve the early diagnosis of i-MTC

Materials and methods

Patients and grouping

The retrospective study included MTC patients who underwent initial thyroid surgical treatment in our institution from 2010 to 2015. Exclusion criteria: (1) Patients who did not have sufficient ultrasonic, clinical, pathological or follow up data. (2) Patients with concomitant diagnosis of PTC.

US examinations were performed for every thyroid gland before undergoing thyroid surgery with an iU22 system (Philips Healthcare, Bothell, WA) equipped with an available 12-5-MHz linear transducer. All ultrasonic images were evaluated and recorded by two independent sonologists, each of them was blinded to each other´s diagnosis and pathology result. If the diagnosis were discordant, the third sonologist served to achieve consensus. Based on ACR TI-RADS, lesions were scored as 0, 2, 3, 4–6, and ≥7 points with a probability of thyroid cancer 0%, 0%, <5%, 5–20%, and ≥20%, respectively. In this study, all lesions with MTC were scored and categorized by ACR TI-RADS. Nodules scored 3–6 points were categorized as "indeterminate" (i-MTC) with a probability of MTC < 20%. Nodules scored ≥ 7 points were categorized as "malignant" (m-MTC) with a probability of MTC ≥ 20%. In case of multifocal MTC, only the most prominent focus was analyzed in the study.

Procedures

Ultrasonic and clinicopathological data

Ultrasonic and clinicopathological data of i-MTC and m-MTC were analyzed. US findings included shape, margin, composition, echogenicity, calcifications, and vascularity. Vascularity was assessed into four types on color Doppler sonography: I-type: absence of intranodular or perinodular vascular flow; II-type: a mild intranodular vascular flow; III-type: diffuse intranodular vascular flow; and IV-type: perinodular vascular flow [11]. Clinicopathological data included age at diagnosis, sex, thyroid surgery, complete thyroid tumor excision, number of lesions, tumor size, extent of tumor, lymph node metastasis, distant metastasis, and the American Joint Committee on Cancer eighth TNM stage [12].

FNA, frozen pathological examination, and preoperative serum Ctn level in the detection of MTC

FNA reports according to TBSRTC were analyzed. The TBSRTC is divided into 6 categories including I, II, III, IV, V, and VI. I: nondiagnostic or unsatisfactory; II: benign; III: atypia of undetermined significance or follicular lesion of undetermined significance; IV: follicular neoplasm or

suspicious for a follicular neoplasm; V: suspicious for malignancy; and VI: malignancy. The positivity rate of FNA, frozen pathological examination, and preoperative serum Ctn level in the detection of i-MTC and m-MTC were also compared. Positive was defined as patients with MTC or suspicious MTC by cytologic or histologic detection. Negative was defined as patients with benign, indeterminate, nondiagnostic, or other types of thyroid cancer by cytologic or histologic detection. Serum Ctn was measured using immunochemiluminometric assays in our hospital. Preoperative serum Ctn level ≥ 10 pg/mL is defined as "positive" and <10 pg/mL as "negative."

Follow up

Patients were followed for more than 5 years after the initial thyroid surgery. The mean follow-up time was shown in Table 3. Postoperative serum Ctn level was measured 3 months after thyroidectomy, then every 6–12 months, simultaneously with neck US. Chest CT, contrast-enhanced MRI or contrast-enhanced CT of the liver, bone scintigraphy, and PET/CT wound be considered depending on the status of patients. The normal basal serum Ctn level was <10 pg/mL for both pre operation and post operation. Based on the last follow-up, postoperative disease status was classified into biochemical cure, biochemical recurrence, or tumor recurrence. Biochemical cure was defined as serum Ctn level <10 pg/mL and no lesions evidenced via neck US or other imaging. Biochemical recurrence was defined as serum Ctn level≥10 pg/mL with no evidence of a lesion. Structural recurrence was confirmed by identification cervical lesions or distant metastases on US or other imaging during follow-up time.

Statistical analysis

Data were analyzed with a statistical software program (IBM SPSS Statistics 23). US features, clinicopathological characteristics, follow-up results, and diagnostic methods were compared between i-MTC and m-MTC. The $\chi 2$ test was used for categorical variable analysis. Statistical analysis in tumor size and follow-up times were performed with *t*-test. A value of $p < 0.05$ was considered statistically significant.

Results

Between 2010 and 2015, 221 patients with MTC underwent initial thyroid surgery at our institution. Overall, 3 patients accompanied with PTC elements, and 29 patients who did not have sufficient ultrasonic, clinical, pathological, or follow-up data were excluded from the study. Ultimately, the retaining 189 patients were enrolled in the study.

Table 1 The preoperative US features of i-MTC and m-MTC

	i-MTC $n = 29$ (%)	m-MTC $n = 160$ (%)	$\chi 2$	p
Shape			29.289	0.000
Round to oval	20 (69.0)	30 (18.8)		
Irregular	9 (31.0)	130 (81.2)		
Margin			24.937	0.000
Smooth	25 (86.2)	55 (34.4)		
Ill-defined margin	4 (13.8)	105 (65.6)		
Composition			8.152	0.004
Solid	24 (86.2)	154 (96.2)		
Solid and cystic	5 (13.8)	6 (3.8)		
Echogenicity			6.719	0.035
Hyperechoic or isoechoic	1 (3.4)	0 (0)		
Hypoechoic	25 (86.2)	121 (75.6)		
Markedly hypoechoic	3 (10.3)	39 (24.4)		
Calcifications			80.166	0.000
Absent	26 (89.7)	18 (11.3)		
Present	3 (10.3)	142 (88.7)		
Vascularity			4.577	0.206
I-type	10 (34.5)	79 (49.4)		
II-type	4 (13.8)	17 (10.6)		
III-type	12 (41.4)	60 (37.5)		
IV-type	3 (10.3)	4 (2.5)		

I-MTC and m-MTC by ACR TI-RADS

In the study, 26 nodules were scored as 4–6 points and 3 nodules as 3 points, 160 nodules as ≥7 points. There were no nodules scored as 0 and 2 points. Finally, 29 i-MTC and 160 m-MTC were enrolled in the study.

Preoperative US characteristics of MTC

Preoperative US features of i-MTC and m-MTC were summarized in Table 1. There were significant differences in shape, margin, composition, echogenicity, and calcifications between i-MTC and m-MTC ($p < 0.05$). i-MTC had higher frequency of round tumor shape, smooth margin, solid or solid and cystic composition, hypoecho, and absence of calcifications (shown in Fig. 1). M-MTC showed obviously malignant features, including higher frequency of irregular tumor shape, ill-defined margin, solid composition, hypoecho or markedly hypoecho, and calcifications (shown in Fig. 2). There was no significant difference in vascularity between i-MTC or m-MTC groups ($p \geq 0.05$).

Clinicopathologic characteristics of MTC

Clinicopathological characteristics of i-MTC and m-MTC are described in Table 2. There were significant differences in lymph node dissection, extent of tumor, lymph node metastasis, and TNM stage between i-MTC and m-MTC ($p < 0.05$). Compared to m-MTC, i-MTC underwent central

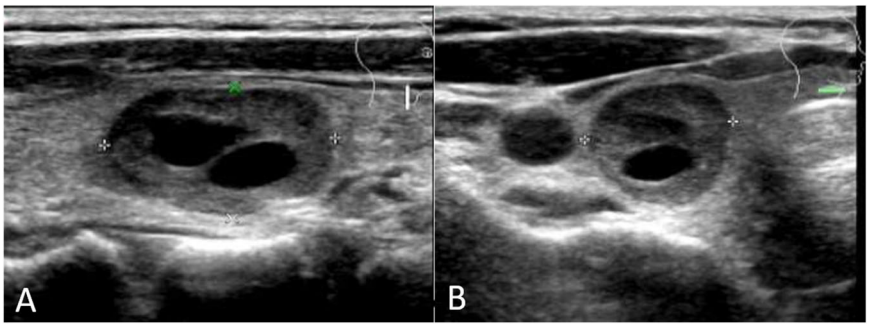

Fig. 1 US features of i-MTC. **a**, **b** A thyroid nodule with a round tumor shape, smooth margin, solid and cystic composition, hypoechoic, and absence of calcifications

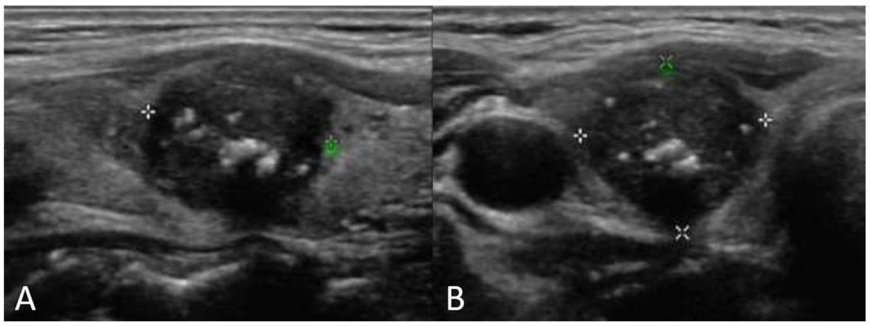

Fig. 2 US features of m-MTC. **a**, **b** A thyroid nodule with an irregular tumor shape, ill-defined margin, solid composition, hypoechoic, and presence of calcifications

neck dissection more frequently rather than lateral neck dissection, displayed extrathyroidal invasion, and lymph node metastasis less frequently. 7(24.1%), 17(58.6%), 5(17.2%), and 0(0%) i-MTC were treated by ipsilateral central neck dissection, bilateral central neck dissection, central neck dissection plus ipsilateral lateral neck dissection, or bilateral lateral neck dissection, respectively, while 20(12.5%), 51(31.9%), 64(40.0%), and 25(15.6%) for m-MTC, respectively.

22 (75.9%) i-MTC and 88 (55.0%) m-MTC had intrathyroidal invasion, while 7 (24.1%) i-MTC and 72 (45.0%) m-MTC had extrathyroidal invasion. I-MTC was at earlier TNM stage than m-MTC. I-MTC at N0, N1a, and N1b were 22 (75.9%), 4 (13.8%), and 3 (10.3%) respectively, while m-MTC at N0, N1a, and N1b were 66 (41.2%), 18 (11.3%), and 76 (47.5%). I-MTC at stage I, II, III, and IV were 9 (31.0%), 13 (44.8%), 4 (13.8%), and 3 (10.3%), respectively, while m-MTC at stage I, II, III, and IV were 41 (25.6%), 27 (16.9%), 16 (10.0%), and 76 (47.5%), respectively. There were no significant differences in age at diagnosis, sex, thyroidectomy, complete tumor resection, tumor size, and multifocality between two groups ($p \geq 0.05$).

Follow up results of MTC

Follow up results of i-MTC and m-MTC are summarized in Table 3. There was no significant difference in follow-up time between i-MTC and m-MTC ($p \geq 0.05$). Compared to m-MTC, i-MTC had higher rate of biochemical cure and lower structural persistence/recurrence ($p < 0.05$). By the end of the follow-up period, i-MTC with biochemical cure, biochemical recurrence, structural persistence/recurrence were 23 (79.3%), 5 (17.2%), and 1 (3.4%) vs 78 (48.8%), 42 (26.2%), and 40 (25.0%) in m-MTC. Only one i-MTC was diagnosed with neck tumor recurrence. No cases of i-MTC had distant metastasis. Among 40 structural persistence/recurrence of m-MTC, 29 cases were diagnosed with neck structural persistence/recurrence, 3 cases with both neck structural persistence/recurrence and distant metastasis, and 8 cases with distant metastasis. The difference in frequency of distant metastasis between i-MTC and m-MTC was not statistically significant.

FNA, frozen pathological examination, and preoperative serum Ctn level in the detection of MTC

The results of FNA according to TBSRTC between i-MTC and m-MTC were compared in Table 4. The categories of the 2017 TBSRTC were significantly different between i-MTC and m-MTC ($p < 0.05$). I-MTC with Bethesda categories I, II, III, IV, V, and VI were 0, 0, 2 (6.9%), 3 (10.3%), 14 (48.3%), and 10 (34.5%), respectively. M-MTC with Bethesda categories I, II, III, IV, V, and VI were 0, 1 (0.6%), 6 (3.8%), 1 (0.6%), 78 (48.8%), and 74 (46.2%), respectively. FNA, frozen pathological examination, and preoperative serum Ctn level in diagnosis of i-MTC and m-MTC were described in Table 5. The positive rate of FNA, frozen pathological examination, and preoperative serum Ctn level in diagnosis of MTC were

Table 2 Clinicopathological characteristics of i-MTC and m-MTC

	i-MTC $n = 29$(%)	m-MTC $n = 160$(%)	$\chi 2$	p
Age at diagnosis (year, mean)	49.8	48.6	−0.453	0.652
Sex			0.589	0.443
Male	11 (37.9)	73 (45.6)		
Female	18 (62.1)	87 (54.4)		
Thyroid surgery			1.973	0.160
Total thyroidectomy	23 (79.3)	142 (88.7)		
Unilateral lobectomy	6 (20.7)	18 (11.3)		
Lymph node dissection			15.223	0.002
Ipsilateral central neck dissection	7 (24.1)	20 (12.5)		
Bilateral central neck dissection	17 (58.6)	51 (31.9)		
+Ipsilateral lateral neck dissection	5 (17.2)	64 (40.0)		
+Bilateral lateral neck dissection	0 (0)	25 (15.6)		
Complete thyroid tumor excision			0.234	0.593
Complete surgery	29 (100)	154 (96.2)		
Incomplete surgery	0 (0)	6 (3.8)		
Tumor size (cm, mean)	1.93	2.04	−0.430	0.668
Multifocality			2.095	0.553
Solitary	23 (79.3)	119 (74.4)		
Satellite in the ipsilateral lobe	4 (13.8)	23 (14.4)		
Satellite in the contralateral lobe	2 (6.9)	12 (7.5)		
Satellite in both lobes	0 (0)	6 (3.7)		
Extent of tumor			4.329	0.041
Intrathyroidal	22 (75.9)	88 (55.0)		
Extrathyroidal	7 (24.1)	72 (45.0)		
Lymph node metastasis			16.679	0.000
N0	22 (75.9)	66 (41.3)		
N1a	4 (13.8)	18 (11.2)		
N1b	3 (10.3)	76 (47.5)		
Distant metastasis			/	/
Absence	29 (100)	159 (99.4)		
Presence	0 (0)	1 (0.6)		
TNM stage			17.777	0.000
I	9 (31.0)	41 (25.6)		
II	13 (44.8)	27 (16.9)		
III	4 (13.8)	16 (10.0)		
IV	3 (10.3)	76 (47.5)		

N0 patients without any cervical lymph node metastasis, *N1a* patients with central lymph node metastasis, *N1b* patients with lateral cervical lymph node metastasis at initial thyroid surgery

Table 3 Follow up results of i-MTC and m-MTC

	i-MTC $n = 29$(%)	m-MTC $n = 160$(%)	$\chi 2$	p
Follow up time (month mean)	60.5	64.8	0.236	0.814
Follow up result			12.389	0.02
Biochemical cured	23 (79.3)	78 (48.8)		
Biochemical recurrence	5 (17.2)	42 (26.2)		
Structural persistence/ recurrence	1 (3.4)	40 (25.0)		
Cervical persistence/ recurrence			3.589	0.032
Yes	1 (3.4)	32 (20.0)		
No	28 (96.6)	128 (80.0)		
Distant metastasis			1.048	0.220
Yes	0 (0)	11 (6.9)		
No	29 (100.0)	149 (93.1)		

Table 4 The 2017 TBSRTC of i-MTC and m-MTC

	I	II	III	IV	V	VI
i-MTC $n = 29$(%)	0	0	2 (6.9)	3 (10.3)	14 (48.3)	10 (34.5)
m-MTC $n = 160$(%)	0	1 (0.6)	6 (3.8)	1 (0.6)	78 (48.8)	74 (46.2)
$\chi 2$	12.481					
p	0.014					

significantly different ($p < 0.05$). Compared to FNA and frozen pathological examination, preoperative serum Ctn had the highest positive rate for both i-MTC and m-MTC ($p < 0.05$). The positive rates of FNA in the diagnosis of i-MTC and m-MTC were 48.3% and 54.4%, respectively. The positive rates of frozen pathology for i-MTC and m-MTC were 62.1 and 65.6%. The positive rate of preoperative serum Ctn for i-MTC and m-MTC were 93.1 and 95.6%. There were no significant differences for FNA, frozen pathological examination, or preoperative serum Ctn in the diagnosis of i-MTC and m-MTC ($p \geq 0.05$).

Discussion

US features of MTC were closely related to clinicopathological characteristics and prognosis. In Fukushima's study, extrathyroid extension and lateral cervical lymph node metastasis were detected in 6 (11%) and 9 (17%) of 54 MTC patients diagnosed as thyroid carcinoma on US, but 23 MTC patients diagnosed as benign nodule on US had not displayed any of these features [6]. Similarly, in

Table 5 FNA, frozen pathological examination, and preoperative serum Ctn level in the detection of i-MTC and m-MTC

	i-MTC		m-MTC		$\chi2$	p
	$n = 29(\%)$		$n = 160(\%)$			
	Positive	Negative	Positive	Negative		
FNA	14 (48.3)	15 (51.7)	87 (54.4)	73 (45.6)	0.376	0.552
Frozen pathology	18 (62.1)	11 (37.9)	105 (65.6)	55 (34.4)	0.137	0.833
Preoperative Ctn level	27 (93.1)	2 (6.9)	153 (95.6)	7 (4.4)	0.344	0.630
$\chi2$	14.008	71.977				
p	0.001	0.000				

Kim's study, extrathyroid extension and lateral cervical lymph node metastasis were found in 19 (23.2%) and 32 (39.0%) of 82 MTC patients with malignant US findings, while only 2 (4.9%) and 7 (17.1%) of 41 MTC patients with benign US findings [7]. Oh et al. also found 16 (61.5%) and 17 (65.4%) of 26 MTC patients with lateral cervical lymph node metastasis at initial surgery showed irregular shape and spiculated margin. 7 (14.9%) and 9 (19.1%) of 47 MTC patients without lymph node metastasis or recurrence of disease displayed irregular shape and spiculated margin [5]. In this study, MTC lesions were assessed comprehensively on a mix of such US features as tumor shape, margin, composition, echogenicity, and calcifications by ACR TI-RADS. I-MTC scored as 3–6 points showed round tumor shape, smooth margin, solid or solid and cystic composition, hypoecho, and absent of calcifications. M-MTC scored as ≥7 points showed irregular tumor shape, ill-defined margin, solid composition, hypoechoic or markedly hypoechoic, and presence of calcifications. Compared to m-MTC, i-MTC was associated with less frequent extrathyroidal invasion and lymph node metastasis, earlier TNM stage and higher tendency of biochemical cure and lower structural persistence/recurrence. Extrathyroidal invasion, lymph node metastases, and TNM stage at the diagnosis are significant prognostic factors in patients with MTC [3, 4]. Extrathyroidal invasion has been established as a vital assessment of disease progression and is associated with lymph node metastasis [13, 14]. The location and number of metastatic lymph node are essential indicators for biochemical cure and structural persistence/recurrence [5, 15, 16]. Structural persistence/recurrence is the main leading cause for disease-specific mortality of MTC [17]. In the study, lymph node surgery on i-MTC and m-MTC is significantly different. 24 (82.8%) and 5 (17.2%) i-MTC were treated by central neck dissection and lateral neck dissection respectively, which account for 71 (44.4 %) and 89 (55.6%) in m-MTC. According to follow up results, only 6 (20.6%) i-MTC did not achieve biochemical cure and 1(3.4%) i-MTC developed structural recurrence which were far below 82 (51.2%) and 40 (25.0%) for m-MTC, respectively. The initial surgical approach on i-MTC is appropriate in this study. I-MTC was associated with less aggressive behavior and better prognosis.

Disease stage is an independent prognostic factor for MTC. However, MTC is usually occult in onset leading to more than half of the MTC presenting at an advanced stage at the time of diagnosis [18, 19]. Our study demonstrated that more than half of m-MTC presented with stage III or IV disease at the time of diagnosis. I-MTC with stage I, II, III, and IV disease were 9 (31.0%), 13 (44.8%), 4 (13.8%), and 3 (10.3%), respectively. More than three-quarters of i-MTC were diagnosed at an early stage. Therefore, the early diagnosis of i-MTC can provide an appropriate opportunity for treatment to improve prognosis. US combined with FNA is the standard preoperative diagnostic procedure for thyroid nodules. FNA report according to TBSRTC of i-MTC and m-MTC were analyzed in the study. There were 2 (6.9%) FNA reports corresponding to category III, 3 (10.3%) to category IV, 14 (48.3%) to category V, and 10 (34.5%) to category VI in the i-MTC group. There were 1 (0.6%) FNA reports corresponding to category II, 6 (3.8%) to category III, 1 (0.6%) to category IV, 78 (48.8%) to category V, and 74 (46.2%) to category VI in the m-MTC group. The result indicated that 27 (93.1%) i-MTC and 153 (95.6%) m-MTC would undergo surgery based on the result of FNA. The 2015 guidelines from the American Thyroid Association recommend total thyroidectomy and central neck dissection for MTC in the initial surgery. Compartment-oriented lymph node dissection should be considered if lymph node metastasis is clinically suspected [2]. As a more extensive surgical approach for MTC than other types of thyroid cancer [2, 17], it is essential to get the diagnosis of MTC or suspicious MTC to avoid the consequent risk of an incomplete therapeutic approach after initial thyroid surgery. The variable appearance on aspiration cytology and lack of amyloid in MTC lead to a high false-negative rate of FNA in the diagnosis of MTC [20, 21]. In this study, 48.3% (14/29) i-MTC and 54.4% (87/160) m-MTC were diagnosed with MTC or were suspicious of MTC by FNA. The remaining cases were misdiagnosed with benign, indeterminate, PTC, or poorly differentiated carcinoma. Ctn is a main and reliable biochemical marker for MTC. Measurement of serum Ctn in suspicious MTC has been beneficial

to improve the diagnosis of MTC [22, 23]. In this study, we found that preoperative serum Ctn level had a higher diagnostic accuracy than FNA and frozen pathology for both i-MTC and m-MTC. Serum Ctn measurement was beneficial to avoid false-negative results for MTC. However, the routine measurement of serum Ctn in all patients with thyroid nodules is controversial [21]. In the study, we found all thyroid nodules with MTC were scored as ≥3 points by ACR TI-RADS and 99.5% (188/189) thyroid nodules with MTC were diagnosed with Bethesda categories III, IV, V, and VI. In view of the above, we suggested to exam serum Ctn in patients with thyroid nodules diagnosed with Bethesda categories III, IV, V, and VI.

The study has some limitations. It is a retrospective design and presents a possibility of selection bias. Prospective studies are needed in order to clarify this. The widespread use of US contributes to detect a large number of thyroid nodules. As routine Ctn measurement in thyroid nodules is not recommended, MTC diagnosis may be missed or delayed. There could be a relatively smaller number of i-MTC patients enrolled in the study. Further studies in a larger cohort are necessary to validate our findings.

In conclusion, US features were associated with biological characteristics and prognosis of MTC. I-MTC showed lack of US malignant features and predicted less aggressiveness and better prognosis. TBSRTC according to FNA combined with serum Ctn measure are helpful for the diagnosis of MTC.

Author contributions J.Z. and F.Y. participated in the study conception and design. L.H.Z., Y.M., and J.M. analyzed and interpreted the patient clinical data. X.J.X. analyzed the ultrasonographs. J.H.W. analyzed histological examination. S.Z. checked for statistical consistency. X.W. was the operator of FNA and reviewed the paper critically. J.Z. was a major contributor in writing the manuscript. X.W., J.Z., and J.T. were guarantors of the study, had full access to all data, and took responsibility for the integrity and accuracy of the data analysis. X.W. analyzed cytological categories of FNA according to TBSRTC in revision. All authors read and approved the final manuscript.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Ethics This research project was approved by the Ethics Committee of Tianjin Cancer Institute and Hospital. Written consents were obtained from each patient.

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