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Original Article

Sonographic predictors of aggressive behavior in medullary thyroid carcinomas

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ABSTRACT

Objective: To identify the clinical and sonographic risk factors for aggressive behavior of Medullary Thyroid Carcinomas (MTCs).
Material and methods: This is a retrospective analysis. The informed consents were waived. Totally, 127 patients were selected from the database. Two radiologists were invited to review the clinical records and ultrasonic images and scored all the cases according to ACR TI-RADS, retrospectively. Kappa test was used to evaluate the consistency between the two reviewers. Logistic regression analysis was carried to identify the risk factors for aggressive behaviors of MTCs. Comparison of survival proportions between different groups were calculated by Kaplan–Meier method and log-rank test.
Results: Female patients with MTCs were more commonly seen than male (1.7:1), male sex was a risk factor for both metastasis (OR: 4.471, P = 0.001) and perithyroidal invasion (OR = 4.674, P = 0.004). Consistency between the two reviewers were quite high (K value, 0.797–0.988). On sonograms, typical MTCs manifest as hypoechoic (96.9%) solid nodules (94.5%). Sex of patients (P = 0.001), margin (P = 0.003) and focality (P = 0.01) of the nodule were independent risk factors for metastasis, whereas sex of the patients (P = 0.004) and margin (P = 0.000) were independent risk factors for perithyroidal invasion. By Kaplan–Meier analysis, survival proportions different between groups with/without perithyroidal extension (P = 0.000) but not between groups with/without metastasis (P = 0.473).
Conclusion: High frequency ultrasound and TI-RADS were effective methods for preoperative diagnosis of MTC. Sex of the patients and margin of the nodule are common risk factors for both metastasis and perithyroidal invasion. Focality of the tumor is another independent risk factor for metastasis.

1. Introduction

Originating from parafollicular C-cells, medullary thyroid carcinoma (MTC), a malignant tumor, is rarely encountered in clinical practice.[1,2] According to the NIH SEER (National Cancer Institute Surveillance, Epidemiology, and End Results Program) reports, in the last three decades, along with a markedly increased incidence of papillary thyroid carcinomas (PTCs), the proportion of MTCs has decreased, from 3–10% to 1–2%.[3] However, the incidence of MTC-related death is still high, about 13.4%.[4,5] MTC is widely considered to be more malignant than other differentiated thyroid cancers, being extremely aggressive and having a poor prognosis. Evidence that MTCs are aggressive includes perithyroidal invasion, lymphatic metastases, distant metastases, and recurrence. Early diagnosis and thorough preoperative evaluation is vital for optimizing the prognosis of patients with MTC because this cancer is characteristically unresponsive to conventional chemotherapy or radiotherapy.

The American Thyroid Association (ATA) guidelines strongly recommend performing thyroid sonography and assessment of the cervical lymph nodes in patients with known or suspected thyroid nodules.[6] There are many published studies concerning the ultrasonic features of MTCs,[7–9] however, most of them were designed to compare the sonographic findings with those of PTCs.[10–12] Yet there are few published data about the association between sonographic findings and aggressive behavior of MTCs.[13,14]

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Abbreviations

Medullary thyroid carcinoma MTC
American College of Radiology ACR
Thyroid imaging reporting and data system TI-RADS
Odds ratio OR
Inter-quartile range IQR
Tumor-node-metastasis TNM
Papillary thyroid carcinomas PTCs
American Thyroid Association ATA
Area under the curve AUC
Receiver Operating Characteristic Curve ROC
National Cancer Institute Surveillance, Epidemiology, and End Results Program NIH SEER

The aim of this study was to identify the clinical and sonographic risk factors for aggressive behavior of MTCs. Here, three aggressive behaviors were studied, namely metastasis (both lymph nodular and distant metastasis) and perithyroidal invasion.

2. Materials and methods

This was a retrospective analysis, thus, the requirement for informed consent was waived. The protocol was approved by the Institutional Review Board of the Severance Hospital of Yonsei University.

2.1. Patients and clinical data

Patients who had been diagnosed as having MTC between February 2006 and October 2018 were selected from the database of our hospital. All diagnoses had been confirmed by surgeries and pathological examinations. All patients had undergone thyroid and neck ultrasound examination preoperatively to detect suspicious thyroid nodules and abnormally large lymph nodes. Two radiologists extracted the clinical data, including age, sex, date, surgical procedure, and distant metastases (present/absent). During follow-up, the patients' outcomes (recurrence and death) were recorded. TNM and stage of the disease were determined according to the staging system updated by AJCC/UICC in 2009.[15]

2.2. Review of ultrasonic images

Two radiologists with 11- and 26-years' experience in ultrasonic diagnosing reviewed the sonographic images of the enrolled patients. When there were inconsistencies, decisions were made in consensus. Ultrasonic findings, including composition (cystic/almost cystic, spongiform, mixed cystic and solid, solid or almost complete solid), echogenicity (anechoic, hyperechoic or isoechoic, hypoechoic, very hypoechoic), shape (wider-than-tall, taller-than-wide), margin (smooth/ill-defined, lobulated or irregular, extra-thyroidal extension), and echogenic foci (none or large comet-tail artifacts, macrocalcifications, peripheral calcifications, punctate echogenic foci) were scored according to the American College of Radiology (ACR) thyroid imaging, reporting and data system (TI-RADS).[16] The final category was determined on the basis of the sum of the allocated scores, ranging from TR1 (benign) to TR5 (high suspicion of malignancy). Sizes of nodules were determined by the largest diameter in all sonographic views. In patients with multifocal MTCs, only the most prominent focus (biggest or with the most suspicious findings) was analyzed in this study, and the largest diameter of that focus was recorded.

2.3. Pathological results

All patients had undergone surgery. Pathological diagnoses were made according to the World Health Organization (WHO) histological classification.[17] A single radiologist collected and reviewed all the pathological reports and extracted information associated with the patient's prognosis, including focality of the MTCs (unifocal/multifocal), lymphatic invasion (present/absent, and the locations of all involved lymph nodes), and extrathyroidal extension (present/absent). If there was any doubt or uncertainty, immunohistochemistry staining with antibodies to calcitonin and thyroglobulin was performed.

2.4. Statistical analysis

Statistical analysis was performed with SPSS 18.0 (SPSS, Chicago, IL, USA). Measurement data with normal and non-normal distribution are presented as mean ± standard diversion and median with inter-quartile ranges (IQR), respectively. Enumeration data are illustrated as number with percentage. Consistency between the two reviewers were evaluated by Kappa test. The kappa values were interpreted as follows: <0.2, slight agreement; 0.21–0.40, fair agreement; 0.41–0.60, moderate agreement; 0.61–0.80, substantial agreement; and 0.81–1.0, perfect agreement. Comparisons between groups were performed with Student's *t*-test (for measurement data with normal distribution), the Mann–Whitney U test (for measurement data with non-normal distribution), the χ^2 and Fisher's exact tests (for enumeration data). Statistically significant variables found in univariate analysis were entered into a binary logistic regression analysis to identify the independent risk factors for aggressive behavior of MTCs through forward elimination method. Results were presented as odds ratio (OR) with 95% confidence interval (CI) and *p* value. Comparison of survival rate between different groups were calculated by Kaplan–Meier method and log-rank test. All *P* values are two-sided. Differences were statistically significant at $P < 0.05$.

3. Results

3.1. Patient's clinical characteristics

The enrolled patients' clinical characteristics are listed in Table 1. The study cohort comprised 127 patients with MTC and preoperative sonographic images, including 47 male and 80 female patients (mean age, 51.8 ± 15.4 years old, range, 6–82 years). As to surgical procedures, 105 (82.7%) patients underwent total thyroidectomy and 22 (17.3%) underwent subtotal thyroidectomy. Central/lateral neck dissection was performed in 88 (62.3%) patients. The mean size of the primary tumors was 1.9 ± 1.4 (0.3–8.0) cm. About half (64/127, 50.4%) of the tumors were smaller than 2 cm. Regional lymph nodes were involved in 42 patients, including 12 with only central lymph node metastases and 30 with both central and lateral neck node metastases.

3.2. Ultrasonic findings of the MTCs

The nodules' sonographic features were classified according to the TI-RADS criteria and are summarized in Table 2. Two radiologists reviewed the images and the kappa test showed high consistency between them (0.797–0.988; Table 2). Among the descriptive ultrasonic factors, the greatest consistency was achieved for margin and the lowest for echogenicity. The kappa value for TI-RADS grades between the two reviewers was 0.909. All tumors scored 3 or more and were classified as suspicious (TR3 to TR5), 61.4% being considered highly suspicious (TR5). As to the

Table 1
Clinical characteristics of the enrolled patients with MTCs.

Clinical Information	Patients (n = 127)
Mean Age (years old)	51.8 ± 15.4 (6–82)
Sex, n (%)	
Male	47 (37.0%)
Female	80 (63.0%)
Size of the nodule (cm)	1.9 ± 1.4 (0.3–8.0)
TNM Classification	
Primary Tumor, n (%)	
T1	64 (50.4%)
T2	25 (19.7)
T3	31 (24.4%)
T4	7 (5.5%)
Regional Lymph Nodes, n (%)	
N0	85 (66.9%)
N1a	12 (9.4%)
N1b	30 (23.6%)
Distant Metastasis, n (%)	
M0	121 (95.3%)
M1	6 (4.7%)
Anatomic Stage, n (%)	
Stage I	54 (42.5%)
Stage II	28 (22.0%)
Stage III	12 (9.4%)
Stage Iva	28 (22.0%)
Stage IVb	0 (0%)
Stage IVc	5 (3.9%)
Median and IQR of Follow-up time (days)	1813, 2451
Results of follow-up, n (%)	
Lost	1 (0.8%)
Distant Metastasis, n (%)	6 (4.7%)
Dead	7 (5.5%)
Survive	113 (89.0%)

Note: MTC medullary thyroid carcinoma, IQR inter-quartile range, TNM tumor-node-metastasis.

Table 2
Summary of sonographic characteristics of the MTCs.

Sonographic Information	Number (Percentage)	Kappa Value
Composition, n (%)		0.849
Cystic/almost complete cystic	0 (0%)	
Spongiform	0 (0%)	
Mixed cystic and solid	7 (5.5%)	
Solid or almost complete solid	120 (94.5%)	
Echogenicity, n (%)		0.797
Anechoic	0 (%)	
Hyperechoic or isoechoic	4 (3.1%)	
Hypoechoic	52 (40.9%)	
Very hypoechoic	71 (55.9%)	
Shape, n (%)		0.879
Wider-than-tall	80 (66.0%)	
Taller-than-wide	47 (37.0%)	
Margin, n (%)		0.988
Smooth/ill-defined	57 (44.9%)	
Lobulated or irregular	42 (33.1%)	
Extra-thyroidal extension	28 (22.0%)	
Echogenic foci, n (%)		0.971
None or large comet-tail artifacts	74 (58.3%)	
Macrocalcifications	7 (5.5%)	
Peripheral calcifications	4 (3.1%)	
Punctate echogenic foci	42 (33.1%)	
TI-RADS level, n (%)		0.909
TR1	0 (0%)	
TR2	0 (0%)	
TR3	8 (6.3%)	
TR4	41 (32.3%)	
TR5	78 (61.4%)	

Note: MTC medullary thyroid carcinoma, TI-RADS thyroid imaging reporting and data system.

composition of the nodules, most (94.5%) were solid or almost completely solid, only seven nodules having a mixed cystic and solid composition. No nodules were classified as cystic or spongiform. The MTCs were commonly hypoechoic (40.9%; 52/127) or extremely hypoechoic (55.9%; 71/127). As to shape, 80 tumors (66.0%) were found to be wider-than-tall. Peripheral calcifications were found in four (3.1%) patients. No echogenic foci and punctate echogenic foci were identified in 74 (58.3%) and 42 (33.1%) of tumors, respectively. In summary, on sonograms, MTC nodules usually present as hypoechoic/very hypoechoic solid nodules with smooth margins (see Fig 1 and 2).

3.3. Pathological findings and follow-up

Pathological examination of the resected specimens revealed that 37 (29.1%) patients had more than one focus of MTCs in their thyroid. Extra-thyroid extension was identified in 36 patients and lymph node metastases in 42. The median duration and IQR of follow-up was 1813 days and 2451 days, respectively, with a range of 17–4635 days. By the end of follow-up, one patient was lost, six patients had been found to have distant metastases (all had lymph node metastases), including one with liver metastasis, one with liver and mediastinal metastases, and the other four with lung metastases. Seven patients died during follow-up, the minimum post-operative survival time being 17 days.

3.4. Univariable and multivariable analysis of aggressive behavior of MTCs

The patients were classified according to metastasis status: the group with lymphatic metastases comprised 42 patients, whereas the group with no metastases comprised 85 patients. Result of univariable analysis are shown in Table 3. There were significant differences in sex and size of nodule between the two groups. As to sonographic findings, focality, shape, margin, echogenic foci, and TI-RADS grade differed significantly between the groups. Multivariate logistic regression using these factors was then performed and showed that only sex of the patient (OR: 4.471, P = 0.001, B = 1.498), margin (P = 0.003) and focality (OR: 7.192, P = 0.01, B = 1.214) of the nodules were independent risk factors for metastasis of MTCs (see Table 4).

Table 3 also shows a comparison of clinical and sonographic indexes between patients with and without perithyroidal invasion (comprising 36 and 91 patients, respectively). Perithyroidal invasion was more frequently seen in male patients with larger nodules ($P < 0.001$). As to sonographic characteristics, shape, margin, echogenic foci, and TI-RADS grade of the nodules differed significantly between these two groups. Multivariable analysis showed that, two factors, sex of the patients (P = 0.004, OR = 4.674, 95% CI: 1.623–13.464) and margin (P = 0.000) of the nodules were risk factors for perithyroidal invasion (Table 5). On Kaplan–Meier analysis (Fig. 3), survival proportion curves different between groups with/without perithyroidal extension ($P = 0.002$) but not between groups with/without metastasis ($P = 0.473$). However, analysis of the distant metastasis free survival proportion was significant in both comparisons ($P = 0.000$).

4. Discussion

To the best of our knowledge, this is the first study to determine sonographic risk factors associated with aggressive behavior in MTCs, using TI-RADS as the main system for evaluation of sonographic features.

In this study, there were many more female patients with MTCs than male patients; however, male sex was a risk factor for metastasis and perithyroidal invasion. On sonograms, typical MTCs manifest as hypoechoic/very hypoechoic solid nodules with

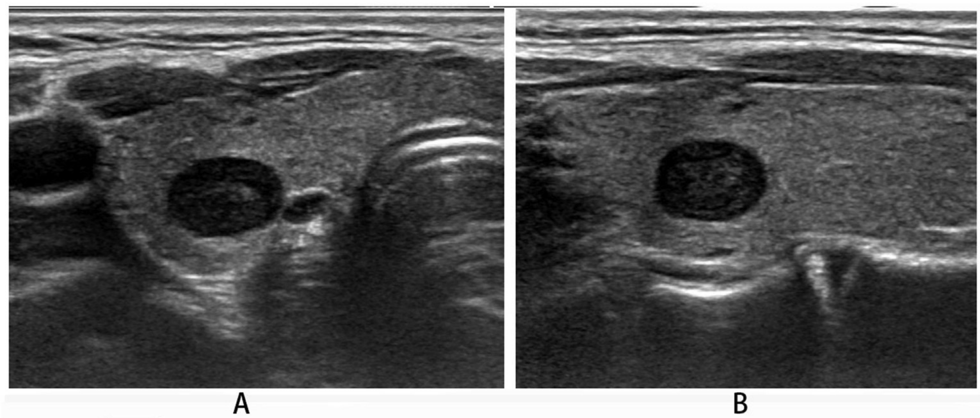

Fig. 1. A small oval nodule was found in the thyroid of a 43-year-old woman. Transverse and longitudinal sonograms are shown. The nodule was solid and extremely hypoechoic. The margin was smooth and no calcification was detected inside the nodule. No cervical or distant metastases were found and the tumor was staged as T1N0M0. After surgery, the patient was followed for 232 days, and no recurrence was detected.

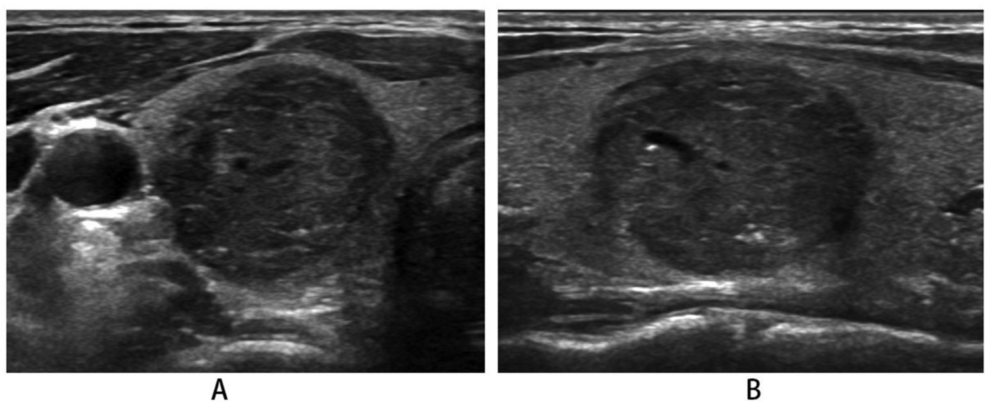

Fig. 2. Transverse and longitudinal views of an aggressive medullary thyroid carcinoma in a 32-year-old man. The nodule was hypoechoic and solid with several punctate echoic foci. Metastases were found in 12 of 46 lymph nodes with perithyroidal soft tissue extension. No distant metastases were identified. The TNM stage was TIVaN1bM0. The patient was followed for about 6 years after surgery and no recurrence was detected.

smooth margins. Echogenic foci were found in 41.7% patients with MTCs. Multifocal nodules were seen in 37 patients, accounting for 29.1% of our cohort. Margin and focality of the nodules were independent risk factors for metastasis of MTCs, whereas margin of the nodule was the only risk factor for perithyroidal invasion (Fig. 4).

MTC, the third most common thyroid malignancy after papillary and follicular thyroid carcinomas, is well known because of its unfavorable prognosis. Sporadic MTCs usually occur between the fourth and sixth decades of life.[18] In our cohort, the mean age of the patients was 51.8 ± 15.4 years. However, the age of the patients was not significantly associated with aggressive behavior. The sex ratio of patients with MTC in our study (male: female, 1:1.7) is consistent with a previous report (1:1.3)[19] which found that MTCs occur more frequently seen in female patients. According to multivariable analysis, male sex was an independent risk factor for both metastasis and perithyroidal invasion, the OR value being quite high (OR = 4.471 for metastasis and 4.674 for perithyroidal invasion). We therefore believe that male patients with MTCs are more apt to develop advanced disease and adverse outcomes than are female patients. Several previous studies have found that old age and male sex are associated with poor prognosis,[20,21] however, another study published in 2018 concluded that neither age nor sex are associated with lateral cervical lymphatic metastasis of MTCs.[22]

High frequency ultrasound examination is the imaging modality of choice among for evaluating MTCs. Many articles about sonographic findings of MTCs have been published; however, there are some discrepancies between them, especially regarding shape, margin, and microcalcifications. In a study published by Choi et al, 47% of MTCs had ill-defined or spiculate margins and 39% had microcalcifications. Fukushima et al reported that one in three MTC nodules are identified as benign by ultrasonography.[23] A systemic review and meta-analysis found that irregular margins are presented in 38.0% of patients and a “taller-than-wide” shape in 14.4% of patients.[24] In our cohort, more than 80% nodules were very hypoechoic, solid, and “wider-than-tall” in shape. The proportion of punctate echogenic foci found in the present study is in line with the meta-analysis published by Valderrabano et al[25] Zhou et al speculated that differences in sonographic features may be related to differences stage of growth of the tumor and proved their point by evaluating differences in sonographic features of MTCs of different size.[26] We completely agree with this conclusion. Additionally, we believe that inconsistencies in terminology and definitions of features have also contributed to the reported diversity. In 2017, TI-RADS was proposed by the ACR committee. To the best of our knowledge, only one study has evaluated the efficacy of TI-RADS in assessing sonographic features and lymph node metastasis in MTCs.[14] Similar with our study, their 57 enrolled patients were all classified into groups according to severity of suspicious findings (TR3 to TR5). In our study, two radiologists reviewed the

Table 3
Results of univariable analysis of aggressive behavior of MTCs.

	Metastasis			Perithyroidal extension		
	Non-metastatic Group	Metastatic Group	P	With	Without	P
Mean Age (years old)	50.4 ± 15.9	54.5 ± 14.1	0.167	55.3 ± 14.7	50.3 ± 15.5	0.1
Sex, n (%)			0.000**			0.001**
Male	22 (25.9%)	25 (59.5%)		22 (61.1%)	25 (27.5%)	
Female	63 (74.1%)	17 (40.5%)		14 (38.9%)	66 (72.5%)	
Size of the nodule (cm)	1.7 ± 1.2	2.6 ± 1.7	0.001**	2.7 ± 1.8	1.7 ± 1.1	0.000**
Focality of the nodules, n (%)			0.015*			0.522
Unifocal	66 (77.6%)	24 (57.1%)		24 (66.7%)	66 (72.5%)	
Multifocal	19 (22.4)	18 (42.9%)		12 (33.3%)	25 (27.5%)	
Composition, n (%)			0.056			0.641
Cystic/almost complete cystic	0 (0%)	0 (0%)		0 (0%)	0 (0%)	
Spongiform	0 (0%)	0 (0%)		0 (0%)	0 (0%)	
Mixed cystic and solid	7 (8.2%)	0 (0%)		2 (5.6%)	5 (5.5%)	
Solid or almost complete solid	78 (91.8%)	42 (100%)		34 (94.4%)	86 (94.5%)	
Echogenicity, n (%)			0.345			0.664
Anechoic	0 (0%)	0 (0%)		0 (0%)	0 (0%)	
Hyperechoic or isoechoic	4 (4.7%)	0 (0%)		1 (2.8%)	3 (3.3%)	
Hypoechoic	35 (41.2%)	17 (40.5%)		17 (47.2%)	35 (38.5%)	
Very hypoechoic	46 (54.1%)	25 (59.5%)		18 (50.0%)	53 (58.2%)	
Shape, n (%)			0.004**			0.002**
Wider-than-tall	61 (71.8%)	19 (45.2%)		15 (41.7%)	65 (71.4%)	
Taller-than-wide	24 (28.2%)	23 (54.8%)		21 (58.3%)	26 (28.6%)	
Margin, n (%)			0.000*			0.000**
Smooth/ill-defined	47 (55.3%)	10 (23.8%)		8 (22.2%)	49 (42.9%)	
Lobulated or irregular	27 (31.8%)	15 (35.7%)		7 (19.4%)	35 (35.2%)	
Extra-thyroidal extension	11 (12.9%)	17 (40.5%)		21 (58.3%)	7 (22.0%)	
Echogenic foci, n (%)			0.004*			0.000**
None or large comet-tail artifacts	58 (68.2%)	16 (38.1%)		16 (44.4%)	58 (63.7%)	
Macrocalcifications	5 (5.9%)	2 (4.8%)		2 (5.6%)	5 (5.5%)	
Peripheral calcifications	3 (3.5%)	1 (2.4%)		0 (0%)	4 (4.4%)	
Punctate echogenic foci	19 (22.4%)	23 (54.8%)		18 (50%)	24 (26.4%)	
TI-RADS level, n (%)			0.000*			0.001**
TR1	0 (0%)	0 (0%)		0 (0%)	0 (0%)	
TR2	0 (0%)	0 (0%)		0 (0%)	0 (0%)	
TR3	8 (9.4%)	0 (0%)		3 (8.3%)	5 (5.5%)	
TR4	35 (41.2%)	6 (14.3%)		3 (8.3%)	38 (41.8%)	
TR5	42 (49.4%)	36 (85.7%)		30 (83.3%)	48 (52.7%)	
TNM Stage, n (%)						
T, n (%)			0.000*			0.000**
T1	54 (64.5%)	10 (23.8%)		3 (8.3%)	61 (67.0%)	
T2	17 (20.0%)	8 (19.0%)		0 (0%)	25 (27.5%)	
T3	12 (14.1%)	19 (45.2%)		26 (72.2%)	5 (5.5%)	
T4	2 (2.4%)	5 (11.9%)		7 (19.4%)	0 (0%)	
N, n (%)						0.000**
N0	85 (100%)	0 (0%)		12 (33.3%)	73 (80.2%)	
N1a	0 (0%)	12 (28.6%)		5 (13.9%)	7 (7.7%)	
N1b	0 (0%)	30 (71.4%)		19 (52.8%)	11 (12.1%)	
M, n (%)						0.007**
M0	85 (100%)	36 (85.7%)		31 (86.1%)	90 (98.9%)	
M1	0 (0%)	6 (14.3%)		5 (13.9%)	1 (1.1%)	
Stage, n (%)			0.000*			0.000**
Stage I	54 (63.5%)	0 (0%)		2 (5.6%)	52 (57.1%)	
Stage II	28 (32.9%)	0 (0%)		7 (19.4%)	21 (23.1%)	
Stage III	0 (0%)	12 (28.6%)		5 (13.9%)	7 (7.7%)	
Stage Iva	3 (3.5%)	25 (59.5%)		17 (47.2%)	11 (12.1%)	
Stage IVb	0 (0%)	0 (0%)		0 (0%)	0 (0%)	
Stage IVc	0 (0%)	5 (11.9%)		5 (13.9%)	0 (0%)	

Note: *significant at P < 0.05, ** significant at P < 0.01, MTC medullary thyroid carcinoma, TI-RADS thyroid imaging reporting and data system, TNM tumor-node-metastasis.

Table 4
Risk factors for metastasis of MTCs.

	B	SE	P	OR	95%CI
Male Sex (vs. Female)	1.498	0.447	0.001**	4.471	1.860–10.743
Margin (vs. smooth/ill-defined margin)			0.003**		1.015–11.47
Lobulated or irregular	0.859	0.51	0.029	2.727	1.111–6.693
Extra-thyroidal extension	1.973	0.57	0.001**	7.192	2.352–21.995
Multifocal (vs. unifocal)	1.214	0.472	0.01	3.367	1.334–8.499
Constant	−2.539	0.489	0.000**	0.079	

Note: MTC medullary thyroid carcinoma, SE standard error, CI confidence interval, OR odds ratio, *significant at P < 0.05, ** significant at P < 0.01.

Table 5
Risk factors for perithyroidal invasion of MTCs.

	B	SE	P	OR	95%CI
Male Sex (vs. Female)	1.542	0.54	0.004**	4.674	1.623–13.464
Margin (vs. smooth/ill-defined margin)			0.000**		
Lobulated or irregular	0.638	0.646	0.323	1.893	0.533–6.715
Extra-thyroidal extension	3.299	0.668	0.000**	27.098	7.315–100.38
Constant	−3.024	0.577	0.000**	0.049	

Note: MTC medullary thyroid carcinoma, SE standard error, CI confidence interval, OR odds ratio, *significant at $P < 0.05$, ** significant at $P < 0.01$.

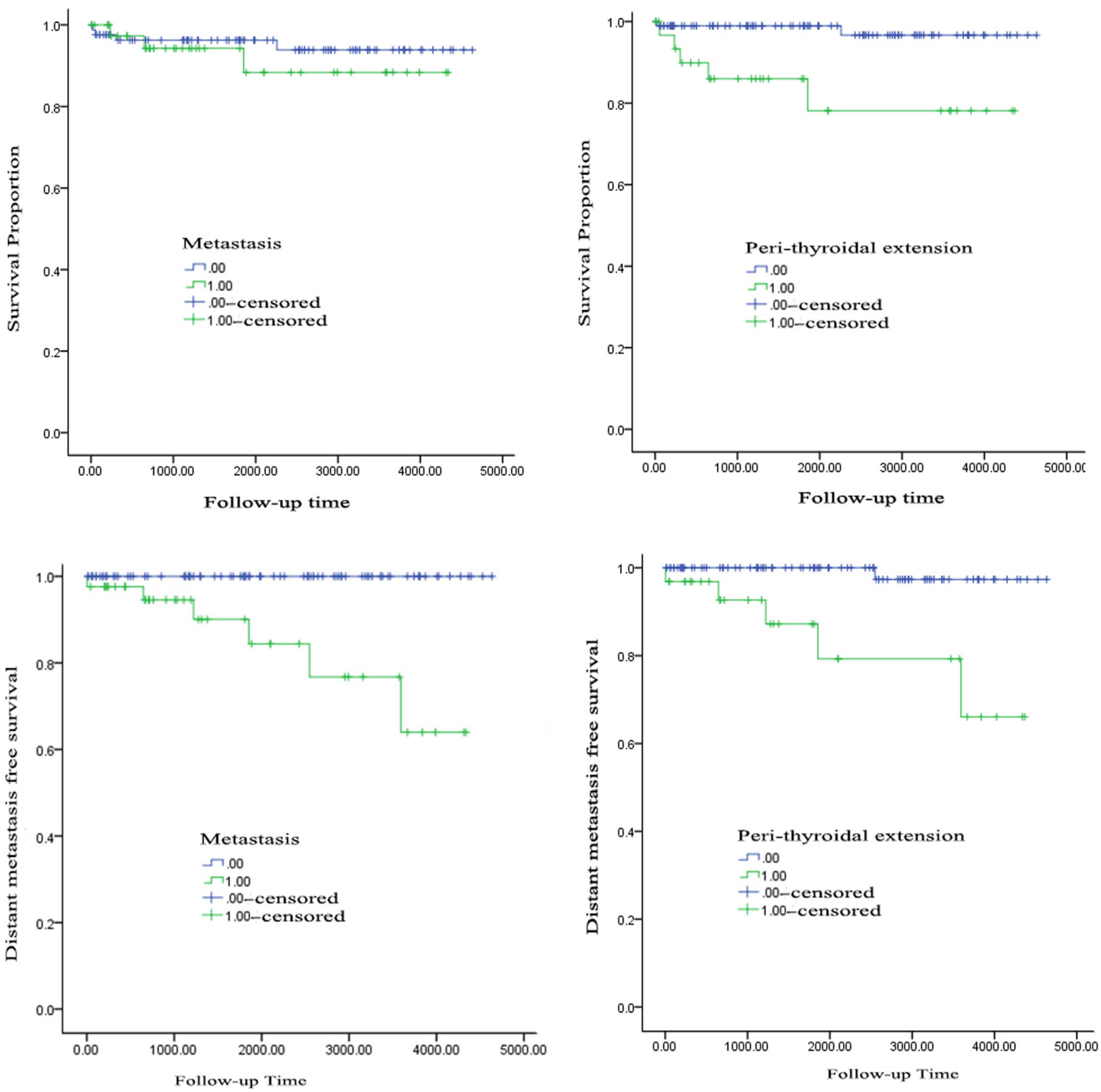

Fig. 3. Kaplan–Meier curves showed comparisons between groups with/without perithyroidal extension and groups with/without metastasis.

ultrasound images. Results of a kappa test confirmed high consistency between the two reviewers. Thus, we believe that TI-RADS provides useful and objective information for evaluation of MTCs.

The prognosis of patients with MTCs is relatively poor, the ten-year mortality rate being 13.5%–38%.[4] Metastasis and perithyroidal invasion are the most important aggressive behaviors of MTCs. Forty-two of the 127 patients in this study had lymphatic metastases and six had distant metastases. In one study[14] that investigated the association between sonographic characteristics and lymph node metastasis in patients with MTCs, irregular shape and presence of microcalcification were found to be independent risk factors. In our study, we found margin and focality of the nodule to be independent risk factors for metastasis. The multicenter study conducted by Trimboli et al[13] is the largest study to

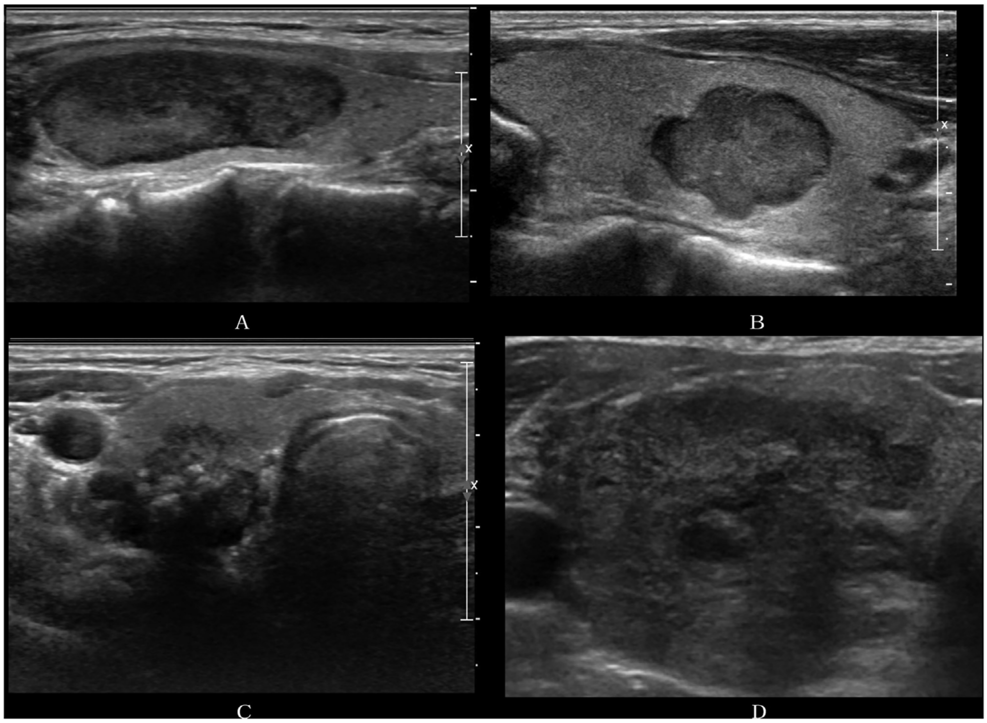

Fig. 4. Shows sonograms of patients diagnosed as MTCs with different margins: A, smooth; B, lobulated; C, irregular; D, extra-thyroid extension. The first three patients were followed for 1979 days, 2521 days, and 435 days, respectively. No recurrence/distant metastasis was found. The fourth patient was 52 years old, he died of distant metastasis (to liver) 305 days after surgery.

investigate the association between ultrasound features and cancer aggressiveness. In contrast with our study, in which we analyzed each sonographic characteristic individually, they used an ultrasound risk stratification method to divide the enrolled 134 MTCs into two groups, "M-type" MTC (with suspicious ultrasonic findings) and "B-Type" MTCs (with indeterminant or benign ultrasonic findings), and concluded that sonographically suspicious MTCs are frequently associated with features of aggressiveness. In our study, in addition to metastasis, we also analyzed the risk factors for perithyroidal invasion and found only sex of the patient and margin of the nodule to be risk factors for perithyroidal invasion. In the preoperative sonographic examinations, perithyroidal invasion were correctly diagnosed in 22 cases and missed in seven. Besides, the consistency between the two reviewers for margin was very high. We therefore concluded that high frequency ultrasound is an effective modality for predicting perithyroidal invasion of MTCs.

In our study, the follow-up was calculated by days. The median duration and IQR of follow-up was 1813 days and 2451 days, respectively, with a range of 17–4635 days. Seven patients died during follow-up. The patient who died 17 days after surgery because of post-operative complications was male, 71 years old. The lesion was 6 cm on ultrasound. The pathological result was "medullary carcinoma, anaplastic variant, over anaplastic carcinoma". On Kaplan–Meier analysis (Fig. 3), survival proportion curves different between groups with/without perithyroidal extension ($P = 0.000$) but not between groups with/without metastasis ($P = 0.473$). About the distant metastasis free survival analysis, comparison between both the groups were significant ($P = 0.000$). Further study with larger sample was expected to confirm this result.

The strengths of our study are the large sample and the thorough analysis of sonographic characteristics. However, it also had several limitations. First, it was a retrospective study conducted in a single hospital. Thus, though the size of the study cohort was relatively large, selective bias was inevitable. A prospective multicenter study is required to verify our findings. Second, we did not consider possible inherited factors in our study because 70 patients in our cohort had not been tested for *RET* gene mutation. It is therefore possible that not all of our patients had sporadic MTCs, some may have had hereditary MTCs.

In conclusion, both clinical and sonographic examination are important in assessing patients with MTCs. Sex of the patient and margin of the nodule are risk factors for both metastasis and perithyroidal invasion. Focality of the tumor is another independent risk factor for metastasis. Therefore, in clinical practice, we should pay more attention to male patients, especially those with multifocal tumors and irregular margins.

5. Key points

1. On sonograms, typical MTCs manifest as hypoechoic/very hypoechoic solid nodules with smooth margins.
2. Male sex of the patient was the common risk factor for both metastasis and perithyroidal invasion. Irregular margin/extra-thyroidal extension and multifocal of the nodules were independent risk factors for metastasis. And margin of the nodule was the only enrolled independent ultrasonic risk factor for perithyroidal invasion.
3. In clinical practice, male patients with multifocal tumors should be closely followed-up, especially when the margin of the tumor was irregular or perithyroidal invasion.

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