Original Article

Incidence and clinical variable inter-relationships of thymic epithelial tumors in northwest China

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Background: Thymic epithelial tumors (TETs) are the most common primary thymus tumors, but neither the possible ethnical/regional differences in the incidence of TETs nor the inter-relationships among the clinical variables has been revealed in northwest China.

Methods: A retrospective chart review was performed among pathologically confirmed TET patients from January 2004 to December 2015 in a tertiary general hospital of northwest China and the incidence, clinical features and the inter-relationships among clinical variables were analyzed.

Results: A total of 603 pathologically confirmed TETs patients (age range, 5–78 years; 308 males) were enrolled and the most common lesion location was anterior mediastinum (98.5%), among them, 192 (31.8%) had myasthenia gravis (MG). Twenty-six (5.7%), 112 (24.6%), 83 (18.2%), 137 (30.1%), 74 (16.3%), and 23 (5.1%) patients fell into the World Health Organization (WHO) type A, AB, B1, B2, B3 and thymic carcinoma (TC), respectively. The incidence of TETs was slightly higher in the female population and the age group of 40–60 years old. In addition, MG predominantly coexisted with WHO types A–B3 TETs and the TETs with MG were smaller than those without MG. The correct diagnosis rates were 42.3% (77 out of 182), 61.1% (127 out of 208), 89.3% (250 out of 280) and 75.0% (3 out of 4) for chest X-ray, non-contrast computed tomography (CT), contrast CT scan and magnetic resonance imaging (MRI), respectively.

Conclusions: Distinct gender and age differences exist in the incidence of TETs and the A–B3 TETs are closely related with MG. Contrast CT scan plays more important role in diagnosing TETs.

Keywords: Thymic epithelial tumor (TET); incidence; World Health Organization (WHO) classification; myasthenia gravis (MG)

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Introduction

Thymus is a primary lymphoid organ where the positive and negative selections of T cells take place, ensuring the acquisition of central T cell tolerance (1,2). Thymic epithelial tumors (TETs), including thymomas and thymic carcinomas (TCs), are the most common form of the primary thymus tumor. TETs are overall rare tumors (3,4) with reported incidence of 0.13 per 100,000 person-years in USA (3) and 0.32 per 100,000 person-years in Netherlands (4). On the contrary, the incidence of TETs is higher in Asia, accounting for 0.50 per 100,000 person-years in South Korea (5) and 0.393 per 100,000 person-years in China (6). TETs have been reported to occur at any age but mostly at the age of 40-60 years old, without sex predilection (3,7-9). However, the incidence of TETs and its features in China have not been intensively investigated.

Based on 18 tertiary referral centers in 14 provinces, the Chinese Alliance for Research in Thymomas (ChART) has built up the first national database for thymic malignancies, now containing more than 2,500 treated cases during 1994–2012 (10). However, northwest China was not covered with ChART, despite the potential influence of weather, longitude, ethnic difference on the incidence of TETs. Most large sample thymoma studies have been reported in south China (11-14) and the feature of TETs in northwest China remains unclear.

Because thymus is the site for T cell maturation, most thymomas present a thymopoietic activity, accounting for the possible onset of autoimmune disorders, of which myasthenia gravis (MG) is by far the most common to affect 30–50% of thymoma patients (15,16). The possible inter-relationships between clinical variables in thymoma patients were investigated in a single-center (17) study and a multi-center (18) study in European countries but not China.

We hereby reported the results of a single-center study from a high-volume northwest China institution for TETs surgery, with the aim of revealing the epidemiological features of TETs, evaluating how the most important variables may influence the others and investigating the diagnostic efficacy of multiple imaging modalities for TETs.

Methods

Data sources

This retrospective single-center study was approved by the ethics committee of Tangdu Hospital of the Fourth Military Medical University (TDLL201608-13), and informed consent was waived. Between January 2004 and December 2015, a total of 603 TETs (including 23 TCs) patients received thymectomy in our hospital. Patients with primary neuroendocrine tumors of the thymus, with an inoperable lesion or receiving tumor biopsy only were excluded. Preoperative standard work-up included routine blood tests, electrocardiography (ECG), echocardiography if required (in case of invasive lesions or high-risk patients), pulmonary function tests with diffusion capacity (diffusion lung capacity for carbon monoxide) and arterial blood gas analysis, neurological consultation to rule out MG according to the clinical status, and total body computed tomography (CT) scan. Histology was assessed according to the 2004 World Health Organization (WHO) classification. TETs were classified as type A, AB, B1, B2, B3 or TC (19).

For the inter-relationship evaluations, the following clinical variables were assessed: WHO histology, MG, tumor size, age and gender. For the statistical analysis, we dichotomized WHO histology [(I) A + AB + B1; (II) B2 + B3 + TC], tumor size [(I) maximal tumor diameter <4 cm; (II) maximal tumor diameter ≥4 cm] and age [(I) age <40 years; (II) age ≥40 years] into two categories, as we did in our previous publication (20). Because the Masaoka-Koga staging system was not introduced in our hospital until 2014, we could not define the TETs staging in the current study and thus Masaoka-Koga stage was not included for the inter-relationship analysis.

Incidence

The hospital-based incidence was calculated by dividing the number of confirmed TETs patients with the number of the corresponding annual in-patients (2004–2015). The age distribution of TETs cases was analyzed using a 5-year age group. To describe the geographic distribution of TETs patients in northwest China, the region where the patients came from were collected.

Diagnostic power of varied imaging modalities for TETs

To investigate the diagnostic efficacy of varied imaging modalities for TETs, a retrospective chart review was performed at the Picture Archiving and Communications Systems (PACS) containing all medical images for pathologically confirmed TETs patients from January 2004 to December 2015. Three radiologists (Xiu-Long Feng, Yong-Kang Xin and Sha-Sha Zhao) reviewed all images and diagnostic reports on the PACS. The diagnostic accuracy

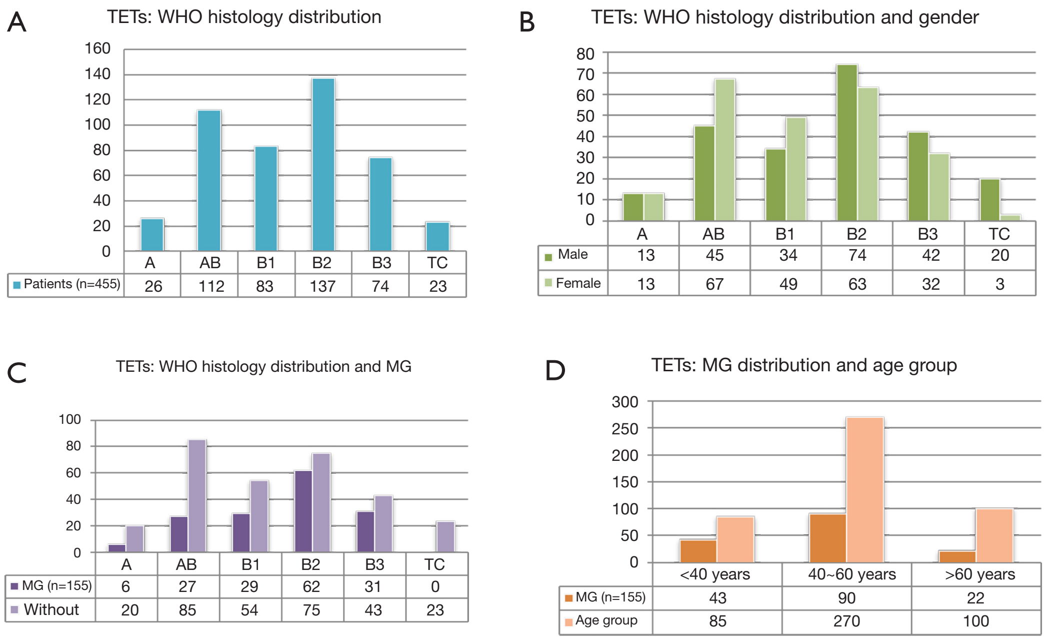

Figure 1 Patient characteristics and distribution of clinical variables according to TETs WHO subtypes. TETs, thymic epithelial tumors; WHO, World Health Organization; MG, myasthenia gravis.

was analyzed by comparing the image diagnosis and pathology results as correct diagnosis and misdiagnosis.

Inter-relationships analysis among clinical variables and statistical analysis

Univariate and multivariate analyses were performed to reveal the factors affecting the incidence of TETs. For the inter-relationship evaluations, we considered the following 5 variables: WHO histology subtypes (WHO A/AB/B1 *vs.* B2/B3/TC), MG status (yes *vs.* no), gender (male *vs.* female), maximal tumor diameter (<4 *vs.* ≥4 cm) and age (<40 *vs.* ≥40 years). Odds ratio (OR) and corresponding 95% confidence intervals (95% CIs) were provided for each model.

Categorical variables were summarized as frequency counts and percentages. Continuous variables were reported as means and standard deviations (SD). Comparisons between 2 or more groups of variables were performed using Fisher's exact test. A P value of <0.05 was considered as statistically significant. All statistical analyses were performed using SPSS 20.0 software (SPSS Inc, Chicago, IL, USA). Statistical graphs were generated using GraphPad Prism 6 software.

Results

General data

A total of 603 pathologically confirmed TETs patients (308 males) with a mean age of 49 (±12, range, 5–78) year were enrolled in this study. Among them, 192 (31.8%) comorbidity with MG, 16 patients (2.7%) had another autoimmune disease (11 hyperthyroidism, 3 pure red cell aplasia 1 hypogammaglobulinemia and 1 nephritic syndrome), cough, chest tightness, chest pain, shortness of breath, dyspnea, and so on were other major comorbidity symptoms. A small number of patients with no obvious self-feeling symptom were recruited during physical examination. Pathological classifications of 455 participants during 2009–2015 were obtained, and 26 (5.7%), 112 (24.6%), 83 (18.2%), 137 (30.1%), 74 (16.3%), and 23 (5.1%) patients fell into the WHO type A, AB, B1, B2, B3 and TC, respectively. Patient characteristics and distribution of clinical variables according to TETs WHO subtypes are presented in *Figure 1*.

According to the 3-compartment model of the mediastinum, the most common location of TETs was in the anterior mediastinum (98.51%). One (0.17%) was

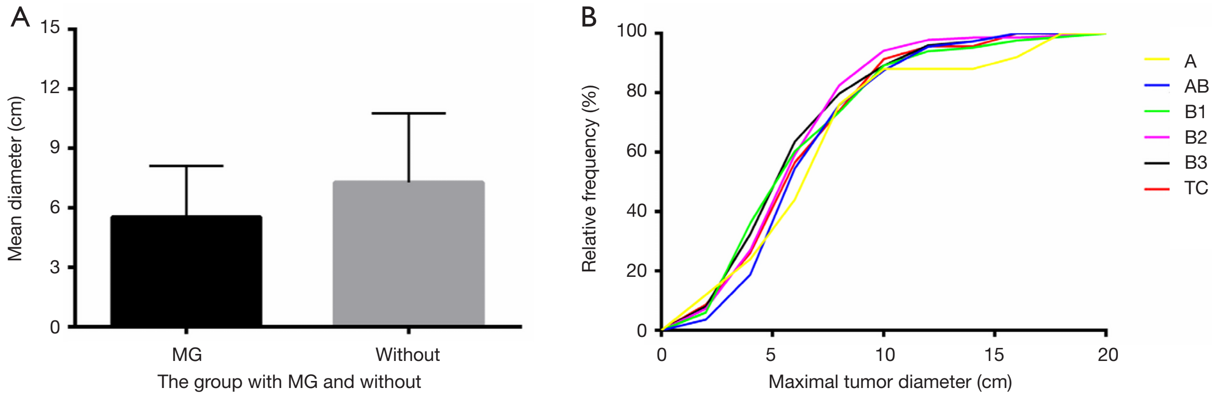

Figure 2 Differences in tumor diameter of TETs between groups (MG status and WHO pathological classification). (A) The mean of maximal tumor diameter of all TETs between the group with MG and without; (B) the average maximal tumor diameter and cumulative relative curve of TETs from WHO pathological classification perspective. TETs, thymic epithelial tumors; WHO, World Health Organization; MG, myasthenia gravis.

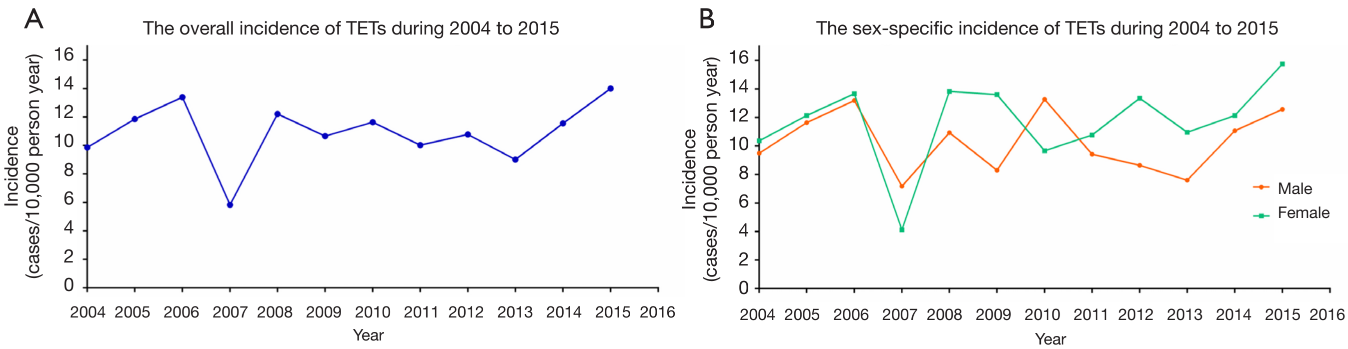

Figure 3 The annual incidence (including sex-specific incidence) based on hospital patient population. (A) The overall incidence (per 10,000 person year) of TETs during the past decade (2004–2015); (B) the female and male incidences (per 10,000 person year) of TETs during the past decade (2004–2015). TETs, thymic epithelial tumors.

in the middle mediastinum, 4 (0.66%) in the posterior mediastinum, and the other 4 (0.66%) in the heterotopic locations (2 in pleural cavity and 2 inside the lungs).

MG predominantly existed with WHO types A–B3 TETs and the maximal tumor diameters of TETs with MG (5.6±2.6 cm) were smaller than those without MG (7.5±3.6 cm, $P<0.0001$). We then analyzed the size difference among different subtypes of TETs using the cumulative curves of Kruskal-Wallis test and no significant difference was revealed among these subtypes (*Figure 2*).

Incidence: estimation of the incidence of TETs based on the hospital database

A total of 603 TETs patients during 2004–2015 were collected and the annual incidence (including sex-specific incidence) based on hospital patient population was analyzed. It should be noted that the "incidence" used in the current study is different from the one based on the general population in the epidemiological study.

The overall incidence of TETs was generally stable during the past decade (2004–2015), with 2 peaks in 2006 and 2015, 1 fall in 2007 as well as a gradual increase during 2014 to 2015. The highest incidence was 1.4 cases per 100,000 patients in 2015. The female incidences were slightly higher than those in the male during 2011 to 2015. Pooling all the data together, a male-to-female incidence ratio of 1:1.19 was revealed (*Figure 3*).

The age onset of TETs fell in a normal distribution, with a high incidence in the age group of 40–60 years old. The median age at diagnosis was 49 years, with an age range of 5 to 78 years. There was no significant

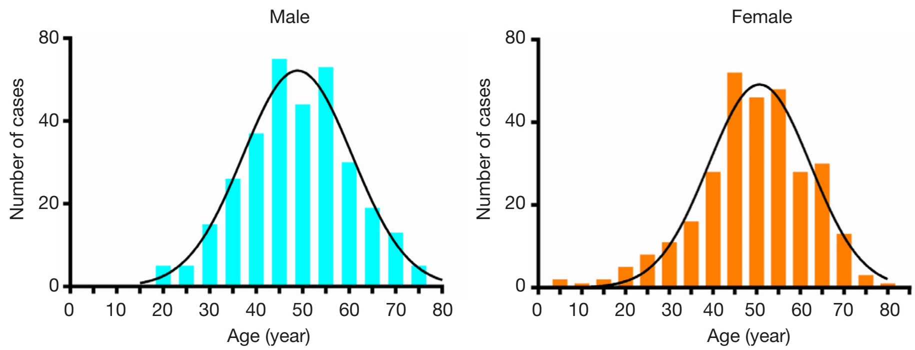

Figure 4 The age distribution of TETs between male and female population. TETs, thymic epithelial tumors.

603	Shaanxi	Gansu	Ningxia	Shanxi	Qinghai	Xinjiang	Other provinces
Patients	427	72	15	50	2	2	35
Percentage (%)	70.81	11.94	2.49	8.29	0.33	0.33	5.80

Figure 5 The regional distribution of 603 TET patients. Chinese map was cited from the software of Adobe Illustrator CS6. TETs, thymic epithelial tumors.

difference in the age distribution of TETs between male and female (P=0.4880) (*Figure 4*).

The geographical distribution of 603 TETs patients

The geographical distribution of 603 patients is presented in *Figure 5*. Most TETs patients were from Shaanxi Province (70.81%), followed by Gansu (11.94%) and Ningxia (2.49%). All of these provinces are within northwest China. TETs patients from Shanxi province were 8.29%, and those from other provinces were 5.80% of the total patients.

Interrelationships among clinical variables of TETs

Regression analyses were performed to evaluate the

Table 1 Logistic regression analysis with four variables of interest (outcome variable: WHO histology subtypes; clinical variables: gender, maximal tumor diameter, myasthenia gravis)

Logistic regression	OR	Standard error	95% CI	P value
Outcome variable: WHO histology subtypes (WHO A/AB/B1 *vs.* B2/B3/TC)				
MG status (yes *vs.* no)	1.546	0.209	1.027-2.327	0.037
Gender (male *vs.* female)	0.536	0.192	0.368–0.782	0.001
Maximal tumor diameter (<4 *vs.* ≥4 cm)	0.763	0.286	0.435–1.338	0.346
Age (<40 *vs.* ≥40 years)	0.922	0.250	0.564–1.507	0.746
Outcome variable: MG status (yes *vs.* no)				
WHO histology subtypes (WHO A/AB/B1 *vs.* B2/B3/TC)	1.545	0.209	1.027-2.326	0.037
Gender (male *vs.* female)	0.750	0.208	0.499-1.127	0.166
Maximal tumor diameter (<4 *vs.* ≥4 cm)	0.410	0.284	0.235-0.717	0.002
Age (<40 *vs.* ≥40 years)	0.405	0.251	0.248-0.663	0.000
Outcome variable: gender (male *vs.* female)				
WHO histology subtypes (WHO A/AB/B1 *vs.* B2/B3/TC)	0.536	0.192	0.368–0.781	0.001
MG status (yes *vs.* no)	0.750	0.208	0.499–1.126	0.165
Maximal tumor diameter (<4 *vs.* ≥4 cm)	1.218	0.284	0.699–2.125	0.486
Age (<40 *vs.* ≥40 years)	1.203	0.250	0.738–1.963	0.459
Outcome variable: maximal tumor diameter (<4 *vs.* ≥4 cm)				
WHO histology subtypes (WHO A/AB/B1 *vs.* B2/B3/TC)	0.763	0.287	0.435–1.339	0.346
MG status (yes *vs.* no)	0.412	0.284	0.236–0.719	0.002
Gender (male *vs.* female)	1.204	0.284	0.691–2.100	0.512
Age (<40 *vs.* ≥40 years)	0.491	0.409	0.220–1.093	0.082
Outcome variable: age (<40 *vs.* ≥40 years)				
WHO histology subtypes (WHO A/AB/B1 *vs.* B2/B3/TC)	0.916	0.250	0.561–1.495	0.725
MG status (yes *vs.* no)	0.406	0.251	0.248–0.664	0.000
Gender (male *vs.* female)	1.199	0.249	0.736–1.954	0.466
Maximal tumor diameter (<4 *vs.* ≥4 cm)	0.486	0.410	0.218–1.084	0.078

WHO, World Health Organization; OR, odds ratio; CI, confidence interval; MG, myasthenia gravis.

interrelationships among the clinical variables of TETs, as reported in *Table 1*.

WHO histology

When WHO histology was considered as the outcome variable, B2/3 subtypes were associated with MG (OR: 1.546; 95% CI: 1.027–2.327, P=0.037). A/AB/B1 subtypes were associated with female (OR: 0.536; 95% CI: 0.368–0.782, P=0.001).

MG

When MG was considered as the outcome variable, it was associated with <40 years group (OR: 0.405; 95% CI: 0.248–0.663, P<0.001), maximum tumor diameter of <4 cm (OR: 0.410; 95% CI: 0.235–0.717, P=0.002) as well as B2/3 subtypes of TETs (OR: 1.545; 95% CI: 1.027–2.326, P=0.037).

Gender

When considering gender as the outcome variable, female gender was associated with A/AB/B1 subtypes of TETs (OR: 0.536; 95% CI: 0.368–0.781, P=0.001) only.

Tumor size

When considering maximum tumor diameter as the outcome variable, maximum tumor diameter (<4 cm) was associated with MG (OR: 0.412; 95% CI: 0.236–0.719, P=0.002) only.

Age

When considering age as the outcome variable, <40 years was associated with MG (OR: 0.406; 95% CI: 0.248–0.664, P<0.000) only.

Diagnostic power of varied imaging modalities for TETs

A total of 455 pathologically confirmed TETs patients with available medical imaging recordings were retrieved from 2009 to 2015. These patients received different modalities of chest imaging, including chest X-ray, CT and/or magnetic resonance imaging (MRI) before thymectomy. Among them, 182 patients underwent chest X-ray, 182 underwent non-contrast CT scan, 280 underwent contrast CT scan, and only 4 underwent MRI. A number of patients underwent more than one modality of imaging examination. The correct diagnosis rates were 42.3% (77 out of 182), 61.1% (127 out of 208), 89.3% (250 out of 280) and 75.0% (3 out of 4) for chest X-ray, non-contrast CT, contrast CT scan and MRI, respectively. Thirty-seven TETs patients were misdiagnosed as teratoma (21), lymphoma (8) and lung cancer (8) based on their images.

Discussion

In the current study, we retrospectively investigated the clinical scenarios of 603 TETs patients. The overall incidence of TETs was stable and gradually increased during 2014 to 2015. The highest incidence was 1.4 cases per 100,000 in 2015. During 2011 to 2015 the female incidence was slightly higher than that in the male population. The age onset of TETs showed a normal distribution, with the peak incidence in the age of 40–60 years. There was no significant difference in the age distribution of TETs between genders. For the inter-relationship analysis of clinical variables, our study has the strength due to the large number of patients collected in a high-volume thoracic surgery institution, as well as a quite uniformed protocol for pre-, intra- and postoperative management of patients. However, the intrinsic bias due to its retrospective design should also be kept in mind. Our study indicates that MG correlates with B2/B3-type tumor, smaller tumor size (<4 cm) and younger age (<40 years). The contrast CT was with the highest diagnostic efficacy for TETs.

The 2004 WHO classification is the most widely used system for the histological classification of TETs. It provides important diagnostic and therapeutic basis for clinical, pathological and immunological research (21). According to an American study, thymoma incidence is higher in Asians/Pacific Islanders and blacks than in whites, suggesting that race, geographic or weather may affect the occurrence of TETs (22). In the current study, we could not reveal the real the incidence of TETs because only the hospital-based database was used, but we did offer some information of TETs in northwest China. Our study suggested that the highest proportion of TETs in northwest China was subtype B2, which is in accordance with the previous studies (23,24). Inconsistent with previous studies (3,7-9), we revealed significant gender differences in TETs especially AB/B1 subtypes in northwest China, which may be explained by the different ethnic difference, geography or weather.

According to the general understanding, the larger the tumor, the more malignant it is. It seems true that TCs are always observed with a maximal diameter of larger than 8 cm (20). However, we revealed no tumor size difference among the varied TETs types, suggesting that tumor size may not serve as a reliable biomarker for malignancy. We did observe that TETs without MG were larger than those with MG. This fact may not reflect the influence of MG on TETs, but rather that TETs patients with MG symptoms are more likely looking for early diagnosis and treatment. Therefore, thoracic CT scan was required for all MG patients in the clinic to screen for the simultaneous thymic lesions.

Most thymomas indicate a thymopoietic activity, with MG being the most common comorbidity. According to previous studies, approximately 30–50% of thymomas are with MG, otherwise, 15% of patients presenting with MG are identified as having thymoma (25,26). In the current study, the morbidity of MG in TET patients was 31.84% (192/603), especially among B2/3-types TETs, but not TCs. Furthermore, our results indicated that MG correlates with smaller tumor (<4 cm) and younger age (<40 years). These findings are consistent with the previous ones (27,28). However, a small portion (1%) of TCs were also associated with MG in a previous Japanese study (29) and TC was shown to be accompanied with MG based on another case study (30).

In summary, we reported that in northwest China, TETs favor female gender and 40–60 years old population and the most common TETs fall into the WHO B2 type. In addition, MG exists in over 30% TETs, and correlates with B2/3-type tumor, smaller tumor (<4 cm) and younger age (<40 years). The contrast CT was observed with the highest diagnostic efficacy for TETs.

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Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

Ethical Statement: This retrospective single-center study was approved by the ethics committee of Tangdu Hospital of the Fourth Military Medical University (TDLL201608-13), and informed consent was waived.

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