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ORIGINAL ARTICLE

The tumor doubling time is a useful parameter for predicting the histological type of thymic epithelial tumors

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Abstract

Purpose We assessed the utility of the tumor doubling time (TDT) for predicting the histological type of thymic epithelial tumors.

Methods We retrospectively reviewed 130 patients with thymic epithelial tumors who underwent computed tomography two or more times before surgery. The patients were divided into low-risk thymoma (types A, AB and B1), high-risk thymoma (types B2 and B3) and thymic carcinoma (thymic carcinoma and thymic neuroendocrine tumor) groups. In the 96 patients who showed tumor enlargement, the relationship between the histological type and the TDT of the tumor was investigated.

Results The study population included 55 men and 41 women from 26 to 82 years of age. The TDT of the thymic carcinoma group (median 205 days) was significantly shorter in comparison to the low-risk thymoma (median 607 days) and high-risk thymoma (median 459 days) groups. No significant differences were observed between the low-risk thymoma and high-risk thymoma groups. When we set the cutoff time for differentiating thymic carcinoma group from thymoma at 313 days, the sensitivity and specificity were 83.8% and 82.1%, respectively.

Conclusions The TDT is a useful parameter for differentiating between thymoma and thymic carcinoma group.

Keywords Tumor doubling time · Thymic epithelial tumors · Histological type · Computed tomography

Introduction

With an incidence of approximately 1.3/1,000,000, thymic epithelial tumors are the most common type of neoplasm arising in the anterior mediastinum [1, 2]. According to the latest classification, which was updated in 2015, thymic epithelial tumors are classified into three major categories: thymoma (including types A, AB, B1, B2, and B3), thymic carcinoma and thymic neuroendocrine tumors [3]. The WHO histological classification has been reported to reflect the oncological behavior and prognostic factors of thymic epithelial tumors [4]. The prognosis of patients with thymoma is favorable in comparison to patients with thymic carcinoma or thymic neuroendocrine tumor. Thus, predicting the histological type of thymic epithelial tumors before treatment is considered valuable for planning treatment strategies.

The tumor doubling time (TDT), originally described by Schwartz in 1961 [5], is considered to reflect the natural growth rate and biological nature of some types of malignant solid tumors. In lung cancer patients, the TDT is reported to be associated with the histological subtype, genetic features and prognosis [6, 7]. The TDT is also reported to be associated with the histological subtype of breast cancer [8] and renal cell carcinoma [9]. However, few reports have examined the clinical significance of the TDT in patients with thymic epithelial tumors [10, 11].

In this study, we retrospectively analyzed 130 patients with thymic epithelial tumors who underwent computed tomography (CT) two or more times before surgery. The relationship between the TDT and the histological type of the tumor was investigated in the 96 patients who showed

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tumor growth. We also analyzed the relationship between the TDT and the tumor stage according to the Masaoka–Koga staging system [12].

Methods

Approval for this retrospective study was obtained from the institutional review board of Nagoya University Hospital, which waived the requirement for individual patient consent (approval number: 2014-0100). From April 2007 to December 2016, 160 patients with thymic epithelial tumors underwent initial treatment, including surgery, at Nagoya University Hospital. Of these 160, a total of 30 patients were excluded because they underwent induction therapy including steroid pulse therapy ($n=11$), or failed to undergo serial CT at least twice with an interval exceeding 20 days before surgery ($n=19$). The largest diameter on axial CT images was recorded for each tumor. The slice thicknesses for the former CT scans were ≤ 1 mm (22 scans), 1.1–2.0 mm (8 scans), 2.1–3.0 mm (5 scans), 5 mm (87 scans) and 7 mm (8 scans). The slice thicknesses for the latter CT scans were ≤ 1 mm (120 scans) and 5 mm (10 scans). Clinicopathological data were collected by reviewing electronic medical records and databases in our department.

The TDT was calculated for each tumor using the equation originally developed by Schwartz in 1961:

$$\mathrm{Td} = t \times \log 2/\left[3 \times \log \mathrm{Dt}/\mathrm{D0}\right],$$

where t is the interval between two CT sessions, Dt is the final tumor diameter and D0 is the initial tumor diameter. Serial CT images of a 66-year-old man with Masaoka–Koga stage III thymic squamous cell carcinoma are shown in Fig. 1a, b. The maximum tumor size increased from 4.1 to 4.4 cm over 86 days. The TDT of this tumor was thus calculated as 213 days.

Tumors were reviewed by an experienced pathologist (H.T.) and diagnosed according to the World Health Organization (WHO) classification [3] as follows: type A, type AB, type B1, type B2, type B3, thymic carcinoma and thymic neuroendocrine tumor. The patients were divided into low-risk thymoma (types A, AB and B1), high-risk thymoma (types B2 and B3) and thymic carcinoma (thymic carcinoma and thymic neuroendocrine tumors) groups according to a simplified histological classification. All tumors were staged using the Masaoka–Koga staging system.

The Mann–Whitney *U* test for unpaired observations was used to compare the TDT of each group. p values of < 0.05 were considered to indicate a statistically significant difference in comparisons between two groups. p values of < 0.016 were considered to indicate a statistically significant difference in comparisons among three groups, which were performed according to the Bonferroni method. All statistical analyses were performed using the STATA software program (Ver. 12, College Station, TX, USA).

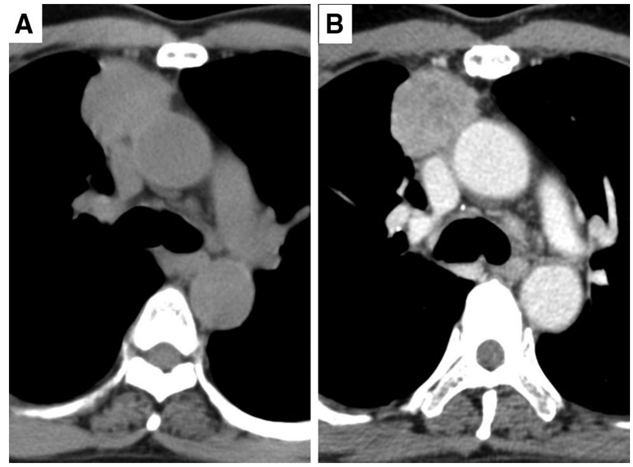

Fig. 1 **a**, **b** Serial computed tomography images of a 66-year-old man with Masaoka–Koga stage III thymic squamous cell carcinoma. The maximum tumor size increased from 4.1 to 4.4 cm over 86 days. The tumor doubling time of this tumor was therefore determined to be 213 days

Results

Table 1 shows the characteristics of the 130 patients. This study included 74 men and 56 women from 26 to 82 years of age (median 62 years of age). The median preoperative tumor size was 4.5 cm, with 99 tumors diagnosed as thymoma and 31 as thymic carcinoma, including 23 squamous cell carcinomas, 6 carcinoid tumors and 2 large-cell neuroendocrine carcinomas. The median interval of the serial CT studies was 64 days (range 21–3188 days). The distribution of the Masaoka–Koga stage and WHO histological classifications are shown in Table 2.

During the follow-up period, 96 patients showed an increase in tumor size (low-risk thymoma, $n=43$; high-risk thymoma, $n=25$; thymic carcinoma group, $n=28$). Tumor regression was observed in nine patients (low-risk thymoma, $n=3$; high-risk thymoma, $n=3$; thymic carcinoma group, $n=3$), while 25 patients showed no change in tumor size (low-risk thymoma, $n=19$; high-risk thymoma, $n=6$) (Table 3). The TDT was ultimately calculated in the 96 patients who showed tumor growth.

The TDTs of the tumors in each group are shown in Fig. 2. The TDT in the thymic carcinoma group (median 205 days; range 43–725 days) was significantly shorter than that in those with low-risk thymoma (median 607 days; range 170–6188 days) and high-risk thymoma (median 459 days; range 116–3005 days) ($p < 0.0001$ and $p = 0.0001$,

Table 1 Patient characteristics

	Total $n=130$
Age (years)	
Median (range)	62 (26–82)
Sex	
Male	74
Female	56
Histological type	
Thymoma ($n=99$)	
A	9
AB	38
B1	18
B2	27
B3	7
Thymic carcinoma ($n=31$)	
SCC	23
Carcinoid	6
LCNEC	2
Preoperative tumor size (cm)	
Median (range)	4.5 (1.1–10)
Interval of CT studies (days)	
Median (range)	64 (21–3188)

SCC squamous cell carcinoma, *LCNEC* large-cell neuroendocrine carcinoma, *CT* computed tomography

respectively). No significant difference was observed between the low-risk and high-risk thymoma groups ($p=0.1435$).

Figure 3 shows the receiver operating characteristic (ROC) curve for the differential diagnosis between thymoma and thymic carcinoma group. When we set the cutoff time at 313 days, the sensitivity and specificity were 83.8% and 82.1%, respectively, and the area under the curve (AUC) was 0.866, which was considered quite high.

Table 4 shows the TDT stratified by the Masaoka–Koga stage. No significant difference was observed between patients with stage I/II thymoma (median 518 days; range 116–6168 days) and those with stage III/IV disease (median 484 days; range 186–1441 days) ($p=0.7132$). Similarly, no significant difference was observed between those with stage I/II thymic carcinoma group (median 228 days; range 69–725 days) and those with stage III/IV disease (median 205 days; range 43–653 days) ($p=0.534$).

Discussion

The oncological behavior differs markedly among thymomas, thymic carcinomas and thymic neuroendocrine tumors. In comparison to thymoma, thymic carcinoma and thymic neuroendocrine tumor are aggressive tumors with a higher incidence of lymph node and distant metastasis [13]. Due to the higher incidence of nodal metastasis, lymph node dissection around the thymus should be performed during surgery for accurate pathological staging. According to the latest European Society of Medical Oncology (ESMO) guidelines, systematic lymphadenectomy is recommended for thymic carcinoma [14]. When considering induction therapy for advanced-stage cases, it should be noted that chemotherapy regimens differ according to the histological type. Thus, predicting the histological type and stage of thymic epithelial tumors is extremely important for planning the treatment strategy.

However, predicting the histological subtype of thymic epithelial tumors without reviewing biopsied or surgical

Table 2 The Masaoka–Koga stage and WHO histological classifications

	A	AB	B1	B2	B3	C	Total
Stage I	3	15	5	2		2	27
Stage II	5	23	12	15	3	10	68
Stage III			1	8	1	13	23
Stage IV	1			2	3	6	12
Total	9	38	18	27	7	31	130

WHO World Health Organization

Table 3 Change in the tumor size

	Interval of CT studies (day) median (range)	Low-risk thymoma	High-risk thymoma	Thymic carcinoma	Total
Growth	72 (24–3188)	43	25	28	96
No change	43 (21–363)	19	6		25
Regression	41 (22–830)	3	3	3	9
Total	64 (21–3188)	65	34	31	130

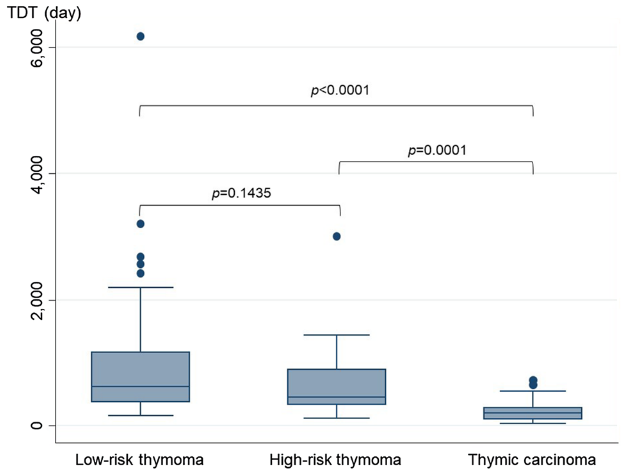

Fig. 2 The tumor doubling times (TDTs) in the subgroups according to the simplified WHO histological classification. The TDT in the thymic carcinoma group (median 205 days; range 43–725 days) was significantly shorter than that in the low-risk thymoma (median 607 days; range 170–6188) and high-risk thymoma (median 459 days; range 116–3005 days) groups ($p < 0.0001$ and $p = 0.0001$, respectively). No significant difference was observed between the low-risk and high-risk thymoma groups ($p = 0.1435$)

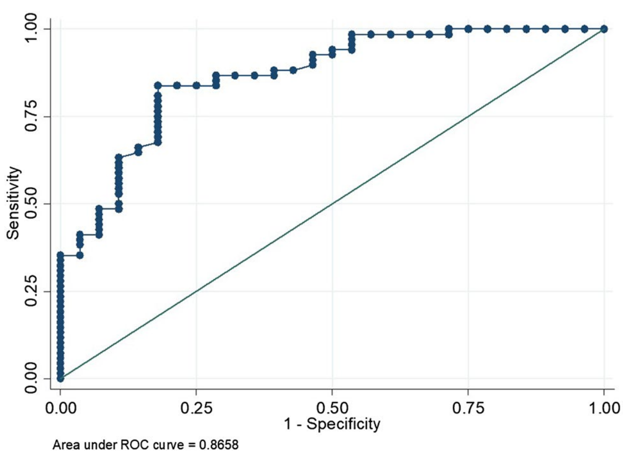

Fig. 3 The receiver operating characteristic (ROC) curve for differentiating thymic carcinoma group from thymoma. When we set the cutoff time at 313 days, the sensitivity and specificity were 83.8% and 82.1%, respectively. The area under the curve (AUC) was 0.866

resected specimens is quite difficult. Thus far, the only modality that may be able to differentiate between thymoma and thymic carcinoma is positron emission tomography (PET)-CT [15, 16]. The standardized uptake value (SUV) in thymic carcinoma is reported to be significantly higher than that of thymoma, as the SUV on PET-CT reflects the oncological aggressiveness of thymic epithelial tumors. The TDT is considered to reflect the oncological behavior of some types of malignant solid tumors [6–9]. Our clinical question was whether there is a significant difference in the TDT between low-risk thymoma, high-risk thymoma and thymic carcinoma groups, as reported in previous studies using the SUV on PET-CT.

In patients with lung cancer, the TDT has been reported to be associated with the histological subtype, genetic features and prognosis. Usuda et al. analyzed the clinicopathological data of 174 patients with primary lung cancer [6]. They reported that the TDT differed according to the histological type and that it was a prognostic factor in patients with primary lung cancer. Nakamura et al. reported that the TDT in patients with epidermal growth factor receptor (EGFR) mutation-negative lung cancer was significantly shorter than in those with EGFR mutation-positive lung cancer [7]. A few reports have described the association of the TDT and the histological type among thymic epithelial tumors. Choe et al. calculated the TDT in 42 patients with histologically proven thymic epithelial tumors (low-risk thymoma, $n = 24$; high-risk thymoma, $n = 14$; and thymic carcinoma, $n = 4$) [10]. They concluded that the TDT was significantly different among the three groups (median TDT: 436, 381 and 189 days for low-risk thymoma, high-risk thymoma and thymic carcinoma, respectively). Jeong et al. retrospectively evaluated the correlation of the volume doubling time (VDT) and the histological type of thymic epithelial tumors in 50 patients (low-risk thymoma, $n = 15$; high-risk thymoma, $n = 26$; and thymic carcinoma, $n = 9$) [11]. The authors established two methods for calculating the VDT: the first used 3D volumetry (3D-VDT); the second used the longest diameter (LD-VDT). According to their analysis, in thymic carcinoma, both the 3D-VDT and LD-VDT were significantly shorter in comparison to low-risk and high-risk

Table 4 TDT stratified by stage

	TDT in stage I/II median (range)	TDT in stage III/IV median (range)	*p* value
Thymoma ($n = 68$)	518 (116–6168) $n = 62$	484 (186–1441) $n = 6$	0.7132
Thymic carcinoma ($n = 28$)	228 (69–725) $n = 13$	205 (43–653) $n = 15$	0.534

TDT tumor doubling time

thymoma. These results derived from two previous studies [10, 11] are consistent with our own observations.

The findings from our retrospective study suggest the TDT may be useful for predicting the histological type of thymic epithelial tumors, especially for the differential diagnosis between thymoma and thymic carcinoma group. A strength of our study was its high sensitivity and specificity, derived from analyzing a relatively large study cohort. However, patients with thymic epithelial tumors who showed spontaneous regression had the possibility of being included in either the thymoma or thymic carcinoma group [17]. Nine (thymoma, $n=6$; thymic carcinoma, $n=3$) of the 130 patients (6.9%) in our study showed spontaneous tumor regression. Although the spontaneous regression of thymic epithelial tumors is relatively rare, this phenomenon must be recognized. In addition, the histological classification of thymic epithelial tumors that showed no change in tumor size in the present study was thymoma in all cases. A lack of change in the tumor size over a relatively long period may suggest the possibility of thymoma.

The present retrospective analysis was associated with several limitations. First, the study population was not very large, although—to the best of our knowledge—this is the largest of such studies performed to date. Second, the CT slice thickness and interval of serial CT scanning varied among the patients. Comparing data from CT scans performed under different conditions might lead to inaccurate measurement of the axial tumor size.

In conclusion, the TDT is a useful parameter for differentiating between thymoma and thymic carcinoma group. A prospective, multi-institutional study is needed to confirm our findings.

Compliance with ethical standards

Conflict of interest The authors declare no conflicts of interest in association with the present study.

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