Original Article

Immunohistochemistry biomarker TP53 expression predicts the survival of thymomas

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Background: Thymomas are rare malignancies. Thymectomy is the optimal therapy which could prolong the survival of patients. However, prognostic factors of thymomas are not clear.

Methods: Thymomas patients were enrolled from 2001 to 2016. Clinical and pathological prognostic factors of thymomas were evaluated by univariate and multivariate analyses.

Results: A total number of 98 patients was eligible for this study. All patients were received complete resection (CR). Diagnostic age [elder than the median 60 *vs.* younger than 60, hazard ratio (HR) =2.325, P=0.027], Masaoka stage (III *vs.* I, HR =10.756, P<0.001; IV *vs.* I, HR =6.558, P=0.014), and diabetes mellitus (DM) (with *vs.* without, HR =0.142, P=0.004) were independent prognostic factors for overall survival (OS). Immunohistochemistry (IHC) biomarker TP53 expression also influenced OS significantly (positive *vs.* negative, HR =5.157, P=0.018). Furthermore, age (elder than 60 *vs.* younger than 60, HR =2.980, P=0.022) was independent prognostic factors for recurrence free survival (RFS).

Conclusions: We found that diagnostic age, clinical stages, DM, TP53 expression in IHC, and quality perioperative nursing are prognostic factors in thymomas.

Keywords: Thymomas; surgery; TP53

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Introduction

Thymomas are rare oncologic diseases with an incidence of 0.15 case per 100,000 people and the most common tumors in anterior mediastinum (1). The optimization for the therapeutic strategies of thymomas is crucial. The extremely low incidence precludes the extensive understanding and treatment of thymomas. In this work, we focused on thymomas patients with type A to B3 based on WHO pathologic classification who received complete resection (CR).

Previously researchers found that age at diagnosis, Masaoka stage, WHO pathological grade, tumor size, resected marginal status, and postoperative radiotherapy (PORT) were prognostic factors for thymomas (2-6). Unfortunately, the usage of other parameters for survival is unclear, such as molecular signatures, adjuvant chemotherapeutic strategies, quality of perioperative nursing, and immunohistochemistry (IHC) markers. Recent years, molecular targeted-therapy and immunotherapy

have applied to clinical work to treat solid malignancies such as lung cancer, which could prolong patients' survival significantly. Unfortunately, neither chemotherapy nor targeted-therapy/immunotherapy could improve the outcome of thymoma patients especially for patients could not receive surgery (6-12). Therefore, searching for therapeutic targets is a crucial part of the further research work.

Biomarkers detected by IHC are often used as prognostics factors and guide for adjuvant treatment parameters in malignances. *TP53* is a tumor suppressor gene and the most commonly mutated gene in human carcinomas (13). Mutant *TP53* could be used as a prognostic marker of thymic carcinoma with aggressive behaviors (8). However, the correlation between *TP53* expression in IHC and the survival of thymomas is unknown.

In this study, we investigated the clinical prognostic factors, and the contribute of *TP53* status in IHC to the survival of thymomas.

Methods

Data collection and follow-up

In this retrospective analysis, we reviewed 113 consecutive thymomas (type A to B3) patients who were enrolled into Fudan University Affiliated Huadong Hospital from January 2001 to December 2016.

The inclusion criteria were: (I) patients were received complete surgical resection, (II) patients were diagnosed as thymomas with type A to B3 pathologically, (III) demography, characteristics, therapeutic regimens, follow-up information of patients were recorded. The exclusion criteria were: (I) patients had malignant oncologic history, (II) patients received palliative surgery, (III) patients received neoadjuvant therapies including radiotherapy and/or chemotherapy, (IV) patients did not abide by the prescriptions from surgeons postoperatively, such as adjuvant therapies or follow-up. The parameters were obtained from medical records including: age at diagnosis, gender, pathological grade, clinical stage (Masaoka stage), surgical approach (SA), adjuvant therapies, expression of biomarkers by IHC, recurrence was defined by cytologic or pathologic confirmation via biopsy or surgery, time from surgery to last contact, time from surgery to recurrence, and cause of death.

We performed the first CT follow-up 3 months after surgery, and then yearly CT follow-up at the outpatient clinic. In addition, the patients were followed up every 6 months by telephone. Follow-up information was updated until death or last contact (June 2018); median follow-up time was 54 (range, 0–195) months. All 98 patients finished the procedure of follow-up and all information was recorded. The study was approved by our institutional ethics committee, and all patients provided written informed consent for therapies and inclusion of personal data in our scientific database.

Statistical analyses

Statistical analyses were performed by SPSS software, version 23.0 (SPSS Inc., Chicago, IL, USA). Categorical and continuous variables were compared by χ^2 test and Student *t*-test respectively. Kaplan-Meier analysis and log-rank test were performed to evaluate overall survival (OS) and recurrence free survival (RFS). Cox's proportional hazards regression analysis was performed to confirm predictors of OS and RFS. OS or RFS time were measured from surgery to death or recurrence, respectively. Patients alive until last contact were censored at that date. A two-tailed P value <0.05 was considered statistically significant. The hazard ratio (HR) were presented with 95% confidence interval (CI).

Results

Baseline characteristics

A total number of 98 patients met the inclusion and exclusion criteria. According to Masaoka stage, patients were divided into I, II, III and IV stage groups, which had 54, 17, 22 and 5 patients, respectively. The median age at diagnosis was 60 (range, 23–85) years, and male/female gender ratio was approximately 0.85. Myasthenia gravis (MG) occurred in 13 patients. Besides, 23 patients had diabetes mellitus (DM). Patients were divided into type A–B1 and B2–B3 based on WHO classification with 54 and 44 patients, respectively. Open surgery was performed in 53 patients and minimal invasive surgery was 45. During surgery, 14 patients had mediastinal lymph nodes dissection (LND).

Based on Chi-square test, with the advancement of clinical stage, the pathological grade was significantly upgrading, the proportion of open surgery and adjuvant therapies (P<0.001 for all) were increasing significantly (*Table 1*). The distribution of diagnostic age and proportion

Table 1 The characters of patients

Variables	No.	Masaoka stage				P value
		I	II	III	IV	
Number		54	17	22	5	
Age (year)						0.074
≤60	47	20	11	12	4	
>60	51	34	6	10	1	
Gender						0.134
Male	45	19	10	13	3	
Female	53	35	7	9	2	
MG						0.638
Without	85	49	14	18	4	
With	13	5	3	4	1	
DM						0.087
Without	75	38	17	16	4	
With	23	16	0	6	1	
WHO grade						<0.001
A–B1	54	39	9	6	0	
B2–B3	44	15	8	16	5	
Surgery						<0.001
Open	53	40	6	4	3	
Minimal	45	14	11	18	2	
LND						0.178
Without	84	47	16	16	5	
With	14	7	1	6	0	
PORT						<0.001
Without	57	41	10	5	1	
With	41	13	7	17	4	

MG, myasthenia gravis; DM, diabetes mellitus; LND, lymph nodes dissection; PORT, postoperative radiotherapy; No, number.

of gender had no significant difference in each clinical stage. The distribution of variables had no significant difference in P53 positive and negative groups (*Table 2*).

Survival analyses

To evaluate the prognostic factors of thymomas, OS and RFS were analyzed. Univariate analysis revealed that recurrence (P=0.049) influenced OS. While, pathologic grade (P<0.001), Masaoka stage (P=0.001), and PORT (P=0.007) influenced RFS but no OS (*Table 3*).

According to the clinical routine in IHC test of thymomas, all detective biomarkers including CD1, CD3, CD5, CD30, P63, TP53, TdT, and Ki-67, only the *TP53* expression could predict OS. Distribution of patient characteristics between *TP53* positive and negative expression groups had no significant difference. *TP53* negative patients had significantly better OS (OS rate: 96.9% *vs.* 84.8%; OS time: 214.0 *vs.* 74.2 months, P=0.044) (*Table 4*).

All variables were analyzed by multivariate analysis. HR of age at diagnosis (elder than 60 *vs.* younger than 60 years: HR =2.325; 95% CI, 1.099–4.918, P=0.027), stage (III *vs.* I: HR =10.756; 95% CI, 2.340–25.352, P<0.001; IV *vs.* I: HR =6.558; 95% CI, 1.262–23.460, P=0.014), and *TP53* expression (positive *vs.* negative: HR =5.157; 95% CI, 1.658–40.400, P=0.018) for OS indicated significant differences. Age at diagnosis, clinical stage, and *TP53* expression in IHC were independent prognostic factors for OS. Meanwhile, age at diagnosis (elder than 60 *vs.* younger than 60 years: HR =2.980; 95% CI, 1.169–7.600, P=0.022) were independent prognostic factors for RFS (*Table 5*).

According to multivariate analysis, HR of DM (with *vs.* without: HR =0.142; 95% CI, 0.037–0.545, P=0.004) for OS indicated significant differences. DM were independent prognostic factor for OS. All information of DM patients was listed in *Table S1*. For thymomas patients with DM, our hospital adopts a continuation of endocrine treatment program for the management, and monitors blood glucose level 4 times per day perioperatively. For a small number of patients with postoperative stress-induced hyperglycemia, short-acting insulin injection was used. Blood glucose level was monitored to adjust insulin dosage. To strengthen perioperative nursing, especially monitoring blood glucose level, significantly reduces the risk of occurrence of immediate and long-term complications, influences OS and RFS (*Table S1*).

Discussion

Thymomas patients have scarce metastasis (9,14), so surgery is cornerstone for treatment (3,15,16). In the present study, the prognostic factors for surgical treated thymomas were analyzed. Besides, the contribution of biomarkers to survival in thymomas was also assessed.

The prognostic factors of surgical treated thymomas are

Table 2 The distribution between P53 negative and positive patients

Variables	P53 negative	P53 positive	P value
Age			0.271
≤60	25	9	
>60	40	24	
Gender			0.948
Male	30	15	
Female	35	18	
MG			0.695
Without	57	28	
With	8	5	
WHO grade			0.226
A–B1	33	21	
B2–B3	32	12	
Stage			0.986
I	36	18	
II	11	6	
III	15	7	
IV	3	2	
SA			0.716
Minimal	36	17	
Open	29	16	
Sum	65	33	

MG, myasthenia gravis; SA, surgical approach.

identified. Elder age, advanced clinical stage, and without DM indicate significantly worse OS. Also, elder age is correlated with worse RFS. Age at diagnosis influences patient survival in multivariate analysis, but not in univariate analysis. With the growth of age, pathological grade and clinical stage advance significantly. This could be due to elders have longer developmental procedure of malignancies. Together, age at diagnosis, Masaoka stage, pathologic classifications and adjuvant therapies influence survival, which is consistent with a previous report that elder patients have relatively worse survival (17,18). It is worth noting that thoracic surgeons ignore the LND before, which influences the accuracy of TNM staging. For this reason, the utility value and credibility of TNM staging system are decreased. The prognostic value of TNM stage needs further investigation (19).

Thymomas patients accompanied with DM have significantly better OS than patients without DM. DM is a negative prognostic factor and leads to significantly worse outcome in lung cancer (20). However, TZDs treatment for DM could significantly reduce the risk of lung cancer and metformin was associated with better prognosis in lung carcinoma patients with DM (21,22). Metformin, a common anti-diabetic drug, could inhibit tumor growth (23). Common anti-diabetic drugs could reduce blood glucose concentration to suppress malignancies, which may improve thymomas patients' OS. We speculate that reducing blood glucose concentration may moderately benefit thymomas patients. However, anti-diabetic drugs did not affect patients' RFS.

In previous studies, the role of chemotherapy for thymoma was accessed. The first-line chemotherapeutic regimen for thymomas is platinum (cisplatin or carboplatin) combined with gemcitabine, docetaxel or paclitaxel (24). However, previous studies showed that chemotherapy is not effective in thymomas (25). In this study, adjuvant chemotherapy was used in a small part of patients, and no significant difference of survival was found between with and without chemotherapy groups (the data was not shown). This suggests that specific targets have not been identified in thymomas.

PORT has different efficacy for thymomas at different clinical stages. Some researchers reported that CR is a sufficient treatment for earlier stage tumors, while PORT should be performed in thymomas at advanced stages or resected lesion with positive margins. However, some scholars have suggested that surgical treated patients do not need further treatment including PORT (6). Based on our previous work, PORT could significantly prolong the OS of Masaoka stage II–IV patients (5). Resected marginal status did not significantly affect patients' survival, and surgical treatment is the optimal choice for thymomas, even thymomas invade surrounding tissues or metastasis has occurred.

Biomarkers are tested by IHC method in resected samples. *TP53* expression decreases thymomas patients' OS. *TP53* could be used as a prognostic factor for thymomas. Thymomas with *TP53* mutation have more aggressive behaviors, and worse prognosis (8). Normal *TP53* protein has a short half-life that could not be detected by IHC test.

Table 3 Univariate analysis for OS and RFS of patients according to clinical outcome

Variables	OS			RFS		
	Rate (%)	Time (month)	P value	Rate (%)	Time (month)	P value
Age			0.200			0.355
≤60	95.7	168.5		90.4	171.6	
>60	90.2	134.6		87.0	148.1	
Gender			0.371			0.761
Male	95.6	162.9		88.3	162.2	
Female	90.6	142.1		88.9	163.8	
MG			0.171			0.623
Without	94.1	138.6		89.0	158.7	
With	84.6	163.8		85.7	146.0	
DM			0.104			0.185
Without	90.7	136.7		87.6	161.4	
With	100.0	197.2		92.3	170.7	
WHO grade			0.942			<0.001
A–B1	92.6	157.8		97.2	186.3	
B2–B3	93.2	165.9		90.3	167.4	
Masaoka stage			0.226			0.001
I	96.3	159.3		97.1	166.4	
II	94.1	171.3		88.5	169.9	
III	81.8	103.1		76.8	137.6	
IV	100.0	95.1		75.0	94.4	
LND			0.406			0.361
Without	94.0	171.4		89.4	166.2	
With	85.7	98.5		84.2	100.4	
PORT			0.417			0.007
Without	91.2	142.3		94.3	177.3	
With	95.1	161.2		82.5	147.2	
Recurrence			0.049			–
Without	93.7	175.6		–	–	
With	66.7	95.1		–	–	

MG, myasthenia gravis; DM, diabetes mellitus; LND, lymph nodes dissection; PORT, postoperative radiotherapy; OS, overall survival; RFS, recurrence free survival.

Table 4 Univariate analysis for OS and RFS of patients according to pathological outcome

Variables	Number	OS			RFS		
		Rate (%)	Time (month)	P value	Rate (%)	Time (month)	P value
P53				0.044			0.747
Negative	65	96.9	214.0		96.9	212.1	
Positive	33	84.8	74.2		97.0	83.9	
P63				0.894			0.508
Negative	18	88.9	93.0		94.4	99.4	
Positive	80	93.8	207.7		97.5	215.2	
Ki67				0.574			0.227
Negative	42	95.2	98.1		95.2	97.1	
Positive	56	91.1	163.4		98.2	220.0	
TdT				0.800			0.187
Negative	33	90.9	202.3		100	–	
Positive	65	93.8	79.8		95.4	–	
CK				0.197			0.574
Negative	58	96.6	85.2		96.6	84.1	
Positive	40	87.5	157.6		97.5	217.7	
CD1				0.945			0.955
Negative	61	93.4	206.6		96.7	212.4	
Positive	37	91.9	93.6		97.3	101.7	
CD3				0.491			0.656
Negative	35	94.3	211.3		97.1	215.6	
Positive	63	92.1	79.3		96.8	84.8	
CD5				0.620			0.104
Negative	76	93.4	183.3		98.7	221.4	
Positive	22	90.9	56.7		90.9	58.0	
CD20				0.370			0.381
Negative	64	90.6	161.8		95.3	–	
Positive	34	97.1	85.9		100.0	–	

OS, overall survival; RFS, recurrence free survival.

While mutant *TP53* could have long half-time which could be detected by IHC (8). Positive *TP53* expression in IHC indicates *TP53* mutation cause significantly worse OS.

Limitation

One limitation of this study is that it is a retrospective analysis based on a single institute database. This may cause selection bias and limit the generalization of the findings. The other limitation is that sample size is relatively small. This causes the statistical error inevitably. However, the results concerning the rare disease are ensured reliable and credible according to the corrective, rigorous, and scientific statistical analysis in this study. Besides, since

Table 5 Multivariate analysis for OS and RFS of patients

Variables	OS			RFS		
	HR	95% CI	P value	HR	95% CI	P value
Age (≤60)						
>60	2.325	1.099–4.918	0.027	2.980	1.169–7.600	0.022
Gender (male)						
Female	0.828	0.375–1.825	0.639	1.503	0.630–3.589	0.359
MG (without)						
With	2.065	0.753–5.665	0.159	2.915	0.890–7.550	0.077
DM (without)						
With	0.142	0.037–0.545	0.004	0.604	0.179–2.033	0.415
WHO grade (A–B1)						
B2–3	0.833	0.305–2.277	0.722	3.511	0.668–18.438	0.138
Masaoka stage (I)						
II	1.284	0.349–4.725	0.706	1.236	0.275–5.555	0.782
III	10.756	2.340–25.352	<0.001	3.016	0.628–14.493	0.168
IV	6.558	1.262–23.460	0.014	1.201	0.190–7.601	0.845
Recurrence (without)						
With	1.966	0.706–5.476	0.196	–	–	–
P53 (negative)						
Positive	5.157	1.658–40.400	0.018	1.336	0.063–28.523	0.853
P63 (negative)						
Positive	0.157	0.009–2.750	0.205	0.219	0.005–10.556	0.443
Ki67 (negative)						
Positive	1.856	0.078–9.336	0.898	1.069	0.001–3.804	0.191
TdT (negative)						
Positive	0.993	0.161–6.128	0.994	–	–	–
CK (negative)						
Positive	4.286	0.465–39.535	0.199	0.410	0.004–37.560	0.699
CD1 (negative)						
Positive	1.391	0.212–9.134	1.391	0.947	0.023–38.891	0.977
CD3 (negative)						
Positive	1.551	0.240–10.034	0.645	28.258	0.93–8631.5	0.252
CD5 (negative)						
Positive	1.028	0.122–8.635	0.979	5.988	0.047–770.69	0.470
CD20 (negative)						
Positive	1.087	0.090–13.156	0.948	–	–	–

OS, overall survival; RFS, recurrence free survival; HR, hazard ratio; CI, confidence interval; MG, myasthenia gravis; DM, diabetes mellitus.

different surgeons have different attitudes concerning the importance of LND, the assessment of lymph nodes involvement should be treated scientifically. The credibility of TNM staging system needs to be improved in clinical and scientific researches in the future.

Conclusions

Elder patients, advanced Masaoka stage, without DM, and *TP53* positive expression in IHC indicate significant worse OS in thymomas. While, elder age could shorten RFS of patients. Together, we found that age at diagnosis, clinic stages, DM, *TP53* expression, and quality perioperative nursing are factors could predict prognosis in thymomas.

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Footnote

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at http://dx.doi.org/10.21037/gs.2020.03.01). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was approved by our institutional ethics committee. Written Informed consent was obtained from each participant included in the study.

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Supplementary

Table S1 The characters of patients with DM

Patients	P53	Age	Gender	Size (cm)	Grade	Stage	SA	CR	LN	AT	Survival
1	Negative	36	Male	6.0	B3	IV	Mini	Yes	No	No	57
2	Negative	39	Female	3.0	B3	III	Mini	No	No	R	192
3	Positive	45	Male	3.0	AB	I	Mini	Yes	No	No	60
4	Negative	52	Male	3.0	AB	I	Mini	Yes	Yes	R	22
5	Negative	52	Male	8.0	B3	III	Open	Yes	No	No	47
6	Positive	57	Male	2.0	B1	I	Mini	Yes	No	No	47
7	Positive	57	Male	5.0	B2	III	Open	Yes	Yes	R + C	59
8	Negative	58	Female	7.5	B1	I	Mini	Yes	No	No	36
9	Negative	62	Male	7.0	B3	I	Mini	Yes	No	R	41
10	Negative	64	Male	5.5	AB	I	Mini	Yes	No	No	50
11	Positive	66	Male	5.0	AB	I	Mini	Yes	No	No	59
12	Negative	66	Female	4.0	AB	I	Open	Yes	No	No	48
13	Negative	67	Male	4.5	B1	I	Mini	Yes	No	No	40
14	Negative	67	Male	3.5	B3	III	Open	Yes	No	R	52
15	Positive	68	Male	8.0	AB	III	Open	Yes	Yes	No	60
16	Negative	68	Female	10.0	B1	III	Open	Yes	Yes	R	57
17	Negative	69	Female	4.0	AB	I	Mini	Yes	No	No	41
18	Negative	70	Male	10.0	AB	I	Open	Yes	No	No	59
19	Positive	73	Male	3.0	B1	I	Mini	Yes	No	No	40
20	Positive	73	Female	4.0	B3	I	Mini	Yes	No	No	49
21	Negative	74	Male	9.0	B3	I	Open	Yes	No	No	29
22	Positive	75	Male	7.0	AB	I	Mini	Yes	No	R	40
23	Positive	76	Male	5.5	A	I	Mini	Yes	No	No	31

SA, surgical approach; CR, complete resection; LN, lymph nodes; AT, adjuvant therapy.