Int J Clin Exp Med 2019;12(4):4361-4367
www.ijcem.com /ISSN:1940-5901/IJCEM0079577

Original Article

Mediastinal lymph node involvement predicts worse prognosis and lymph node dissection less than 3 during surgery benefits prognosis of Masaoka stage I thymoma

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Received May 14, 2018; Accepted February 11, 2019; Epub April 15, 2019; Published April 30, 2019

Abstract: Background: Thymoma size, stage, and postoperative therapies affect patient survival. First, the current study attempted to reveal the relationship between mediastinal lymph node involvement (LNI) and thymoma patient survival. Second, this study aimed to evaluate the efficacy of lymph node dissection (LND) during surgery. Methods: Thymoma patients with LND during surgery were enrolled in the Surveillance, Epidemiology, and End Results program database (SEER). Survival, based on age, tumor size, Masaoka stage, and LNI status, was analyzed via univariate and multivariate analysis. The efficacy of adjuvant therapies and LND was analyzed by stratification analysis in each WHO pathologic grade. Results: In all 399 patients, old age, advanced clinical stage, and positive LNI predicted significantly worse overall survival (OS) (P = 0.044, 0.012, 0.032). Postoperative radiotherapy and chemotherapy showed significant benefits for positive LNI patients (P = 0.003, 0.020), but adjuvant treatments did not affect the OS of negative LNI patients. Moreover, Masaoka Stage I patients receiving less than 2 lymph nodes removed with LND had significantly better OS than those with more than 3 (P = 0.038). However, in advanced stage, different numbers of LND did not affect patient OS. Conclusion: Diagnostic age, clinical stage, and LNI status were shown to be independent risk factors for OS. Compared with old age, advanced stage, and positive LNI patients, younger, local stage and negative LNI patients showed significantly better prognoses. Radiotherapy or chemotherapy significantly improved positive LNI patient OS. Stage I patients dissecting 1 or 2 lymph nodes manifested significantly better OS than those dissecting lymph nodes more than 3.

Keywords: Thymoma, surgery, lymph node dissection, postoperative treatment, survival

Introduction

Thymoma is a rare disease, with an incidence of 0.15 cases per 100,000 people, worldwide. However, in anterior mediastinal tumors, thymomas are most common and have a crucial status [1].

Guidelines of diagnosis and treatment have not been standardized. At least 14 classification systems have been used during the last four decades [2]. Recently, the Masaoka-Koga Staging system has been accepted, worldwide, as the standard clinical staging system for thymomas [3-5]. Histological diagnosis has been performed by the WHO classification system [6]. In 2014, the Tumor, Node, and Metastases (TNM) Staging System (8th edition) was updated for thymomas [7-11]. Radical surgery is a unique approach in treating thymomas completely [12-18]. However, in this indolent malignant disease, no systems have been able to clarify the relationship between mediastinal lymph node involvement (LNI) and patient prognoses [8, 19, 20]. Few studies have discussed the efficacy of lymph node dissection (LND) clearly. Moreover, the efficacy of adjuvant therapies used in treating patients in different LNI statuses has been controversial, especially in patients with lymph node metastasis [18, 21].

In this study, the Surveillance, Epidemiology, and End Results program database (SEER) was utilized to explore the relationship between LNI

Table 1. Patient characteristics divided by LNI

LNI	With	Without	Total	*P* value
Number	34	365	399	
Age (years)				0.482*
Median	54.2	56.1	55.9	
Range	12-85	15-90	12-90	
Gender				0.860#
Male	17	176	193	
Female	17	189	206	
Stage				< 0.001#
I	0	120	120	
II-III	25	195	220	
IV	9	50	59	
Size				0.934#
0-50	8	93	101	
51-90	16	160	176	
> 90	10	112	122	
PORT				0.018#
Without	8	164	172	
With	26	201	227	
POCT				< 0.001#
Without	15	284	299	
With	19	81	100	

LNI, lymph node involvement; PORT, postoperative radiotherapy; POCT, postoperative chemotherapy. *: *P* values calculated by Student's t-test. #: *P* values calculated by Chi-squared or Fisher's exact test.

and prognoses. In addition, this study compared the efficacy of different numbers of LND during surgical treatment. Based on different statuses of LNI, appropriate postoperative therapeutic regimens were discussed to prolong patient prognoses.

Patients and methods

Data from SEER was acquired in this study [1]. Inclusion criteria were applied to identify eligible patients: (1) Thymoma patients that received surgical treatment from 1988 to 2014; (2) Based on WHO histological grade system, thymomas were defined as type A to B3; (3) LND performed during surgery; and (4) Data was recorded completely, including baselines, tumor characters, therapeutic regimens, LND information, and follow-up information. Exclusion criteria were as follows: (1) Patients had tumor history; (2) Patients had preoperative adjuvant treatments; and (3) Patients had incomplete follow-up information. Parameters of the patients included diagnostic age, gender, clinical stage, tumor size, postoperative therapeutic regimens, number of LND, status of LNI, and time from diagnosis to last contact. According to SEER summary clinical stages, the patients were classified into stage L, R, and D. This classification was defined the same as the Masaoka-Koga Staging system. Stages L, R, and D were equivalent to Masaoka-Koga Stages I, II-III, and IV, respectively [22]. Performance conditions of patients, margin of surgical resection, dose, toxicity, and side-effects of adjuvant therapies were not included in SEER. These factors were not analyzed in the current study.

Statistical analysis was performed using SPSS software, version 23.0 (SPSS Inc., Chicago, USA). Student's *t*-test, Chi-squared test, or Fisher's exact test were performed to analyze continuous and nominal data variables. Kaplan-Meier method and Log-rank test were used to analyze patient overall survival (OS). Cox's proportional hazards regression model was employed to identify independent risk factors of OS. Time of OS is measured from diagnostic date to death. Patients living at last contact were censored at the date. Two-tailed *P* value < 0.05 indicates statistical significance. Hazard ratios (HR) are presented with 95% confidence intervals (CI).

Results

*Patient characteristics (**Table 1**)*

A total of 399 patients were enrolled. Median age of diagnosis was 55.9 years (range, 12-90 years). The number of males and females was 193 and 206, respectively. There were 227 patients with postoperative radiotherapy (PORT) and 100 patients with chemotherapy (POCT). All patients were divided into 2 LNI-groups (positive and negative), having 34 and 365 patients, respectively. Diagnostic age, ratio of gender, and distribution of tumor size between LNI-groups showed no differences. Moreover, 77% and 56% of positive LNI patients received PORT and POCT. However, a mere 55% and 22% of negative LNI patients received PORT and POCT. The proportion of patients with positive LNI receiving PORT and POCT was significantly higher than patients with negative LNI (*P* = 0.018, 0.000, respectively).

Table 2. Survival analysis for OS of patients

	No.	Univariate*			Multivariate#		
		Survival					
		Rate (%)	Time (Month)	*P* value	HR	95% CI	*P* value
Age				0.044			
≤ 55	177	81.4	155.0		1.000		
> 55	222	79.3	135.2		1.605	1.014-2.539	0.043
Gender				0.289			
Male	193	81.9	148.3				
Female	206	78.6	138.1				
Stage				0.012			
I	120	90.0	174.8		1.000		
II-III	220	76.8	133.3		2.264	1.207-4.249	0.011
IV	59	72.9	130.8		3.045	1.430-6.483	0.004
Size (mm)				0.064			
0-50	101	78.2	144.0				
51-90	176	85.8	157.0				
> 90	122	73.8	146.5				
LNI				0.032			
Negative	365	81.9	148.9		1.000		
Positive	34	61.8	122.2		1.753	1.065-3.183	0.035
PORT				0.848			
Without	172	82.0	154.8				
With	227	78.9	140.7				
POCT				0.990			
Without	299	80.3	146.6				
With	100	80.0	140.0				

OS, overall survival; HR, Hazard Ratio; CI, Confidence interval; LNI, lymph nodes involvement; No, number; PORT, postoperative radiotherapy; POCT, postoperative chemotherapy. *: Analysis was performed by Kaplan-Meier method and log-rank Test. #: Analysis was performed by Cox's proportional hazards regression model.

*Survival analysis of OS (**Table 2**)*

OS was analyzed to illustrate the predictive factors of OS. According to median diagnostic age, patients were divided into 2 age-groups (≤ 55 and > 55-year). Based on univariate analysis, gender, tumor size, and postoperative treatments showed no correlation with OS. Patient diagnostic ages younger than 55 had better OS than patients older than 55. Differences were significant (81.4% vs 79.5%, 155.0 months vs 135.2 months, $P = 0.044$). Compared with clinical local stage and negative LNI, advanced Masaoka-Koga stage and positive LNI could predict significantly worse OS ($P = 0.012$ and 0.032, respectively).

Variables in univariate analysis were enrolled into multivariate analysis. Based on Cox's proportional hazards regression model, diagnostic age (older vs younger, HR: 1.605, 95% CI: 1.014-2.539, $P = 0.043$), Masaoka stage (Stage II-III vs Stage I, HR: 2.264, 95% CI: 1.207-4.249, $P = 0.011$; Stage IV vs Stage I, HR: 3.045, 95% CI: 1.430-6.483, $P = 0.004$), and LNI (positive vs negative, HR: 1.753, 95% CI: 1.065-3.183, $P = 0.035$) were independent risk factors of OS. Variables that did not influence OS significantly are not listed. Patients older than 55-years, advanced clinical stage, and positive LNI status showed significantly worse OS.

*Efficacy of postoperative adjuvant therapy (**Table 3**)*

In the LNI negative-group, patients without PORT had better OS than patients with PORT. Differences showed no significance. However, for patients with positive LNI, OS of patients without PORT was significantly worse than in patients with PORT (OS rate: 25.0% vs 73.1%, OS time: 48.5 vs 141.9 months, $P = 0.003$). The same trend was observed in patients with POCT. In the LNI negative-group, OS showed no significant difference between patients with and without POCT. However, in positive LNI patients, the OS of patients without POCT was significantly worse than patients with POCT (OS rate: 40.0% vs 78.9%, OS time: 86.9 vs 136.5 months, $P = 0.020$). Results suggest that LNI status could guide postoperative therapeutic regimens reasonably. Evaluating LNI status during surgery showed significantly crucial effects in improving patient survival.

*Efficacy of LND in different dissected numbers (**Table 4**)*

The median dissected number of LND was 2. Patients were divided into 2 subgroups, accord-

Table 3. Stratification analysis for adjuvant therapeutic efficacy

Stratification	Adjuvant Therapy	No.	OS		*P* value
			Rate (%)	Time (month)	
LNI	PORT				
Negative					0.640
	Without	164	84.8	160.5	
	With	201	79.6	140.9	
Positive					0.003
	Without	8	25.0	48.5	
	With	26	73.1	141.9	
	POCT				
Negative					0.591
	Without	284	82.4	149.4	
	With	81	80.2	138.2	
Positive					0.020
	Without	15	40.0	86.9	
	With	19	78.9	136.5	

OS, overall survival; LNI, lymph node involvement; No, number; PORT, postoperative radiotherapy; POCT, postoperative chemotherapy.

Table 4. Stratification analysis for efficacy of dissected number of LND

Stratification (Stage)	No.		OS		*P* value
	LN	Patient	Rate (%)	Time (month)	
I	56	1-2	94.6	190.2	0.038
	64	3~	85.9	144.8	
II-III	114	1-2	77.2	132.8	0.485
	106	3~	76.4	137.5	
IV	29	1-2	69.0	129.4	0.962
	30	3~	72.9	141.2	
Total	199	1-2	80.9	149.0	0.158
	200	3~	79.5	140.7	

OS, overall survival; No, number; LND, lymph node dissection.

ing to the dissected number of lymph nodes (1 or 2 LND vs more than 3 LND). OS was compared between the 2 subgroups, evaluating the effectiveness of LND in each clinical stage. In the local stage, compared with less than 2 LND patients, more than 3 LND patients showed significantly worse OS (94.6% vs 85.9%, 190.2 vs 144.8 months, $P = 0.038$). However, differences in OS were not observed in advanced stages ($P > 0.05$).

Discussion

Prognostic factors of thymomas, such as patient baselines, tumor characteristics, and therapeutic regimens, have not been researched clearly because of rarity [18].

Survival of thymomas has a wide range. Surgery is the most important treatment of thymomas. Radical surgical treatment, especially, can significantly prolong patient survival [12-21, 23, 24]. If patients receive appropriate treatment, postoperatively, they have considerable survival, even with metastasis or recurrence [23, 25]. Therefore, LND during surgery has a crucial role in diagnosis of thymomas with real definition of N status [26]. Optimizing therapeutic regimens, postoperatively, based on N status is a reasonable approach in improving survival rates and prolonging survival times of patients [24].

Whether LND was received or not, previous studies have demonstrated that diagnostic age and gender of patients are predictive factors of patient OS [27, 28]. In this study, in LND patients, diagnostic age was a predictive factor of patient OS, according to univariate ($P = 0.044$) and multivariate analysis (HR: 1.605, 95% CI: 1.014-2.539, $P = 0.043$). Moreover, Masaoka-Koga stage and LNI status were shown to be independent risk factors of OS. With clinical stage upgrades, patient OS significantly decreased. Positive LNI patients manifested significantly poorer OS than negative LNI patients.

PORT showed an intensive correlation with prognosis, especially in advanced stage patients [25, 29]. PORT is an important postoperative therapeutic regimen. In this study, 76.5% of positive LNI patients received PORT. However, 55.1% of negative LNI patients received PORT. The proportion of patients receiving PORT in positive LNI was significantly higher than in negative LNI ($P = 0.018$). Some researchers believe that radical surgery is a good treatment for early stage thymomas, while advanced stage thymoma patients should receive PORT regardless of the status of resected margins and status of LNI. It could decrease the rate of relapse or metastasis [29-32]. On the other hand, some researchers have suggested that thymoma patients do not need to get further treatment, including PORT [13, 24, 32-34]. The current study found that patients with advanced

stage and positive LNI should receive PORT. Positive LNI patients receiving PORT significantly increased OS ($P = 0.003$). Differences in OS were not observed in negative LNI patients. LND during surgery is an important procedure, clarifying the real stage of thymomas and moderate postoperative therapies aimed at improving patient OS.

One previous study showed that chemotherapy had no association with survival and relapse of thymomas [28, 29]. The current study found that POCT could not promote OS for all patients. However, positive LNI patients receiving POCT significantly increased survival rates and prolonged survival times ($P = 0.020$). According to different LNI status, adjuvant therapies could be moderated to affiliate OS. Based on present analysis, it is recommended that positive LND patients receive PORT and POCT. These methods benefit survival rates and times, significantly.

Few studies have focused on the correlation between the number of LND and postoperative survival times of patients [35]. Park and his colleagues recommended that dissection of more than 10 lymph nodes could accurately predict OS of thymoma patients. OS and postoperative therapies have significant discrepancies between advanced stage and localized stage thymoma [36]. Extensive LND may decrease the rate of mistaken diagnosis of thymoma stage, but also assist in performing moderate adjuvant treatments. It could improve survival rates and prolong survival times [18]. This study, based on the median number of LND, divided patients into less than 2 (including 2) LND and more than 3 LND subgroups. Interestingly, it was found that the OS of patients with advanced Masaoka-Koga stage thymomas showed no differences between the two subgroups. However, patients in Masaoka-Koga Stage I and dissected more than 2 mediastinal lymph nodes predicted worse OS. Results suggest that thymomas with complete capsules should be performed LND to confirm pathological and clinical classification during surgery. Moreover, the number of LND should be less than 2 (including 2). Otherwise, it may decrease survival significantly ($P = 0.038$).

Limitations

OS has a significant relationship with postoperative treatment. However, SEER does not enroll data of doses and regimens of chemotherapy.

There was no data of the dose of postoperative radiotherapy in SEER. Thus, a limitation of this analysis is that it did not discuss these 2 factors in detail in the prognostic system. Fortunately, previous studies have shown that routine doses of chemotherapy and radiotherapy do not affect the efficacy of treatment, significantly [29].

Surgery is the most crucial treatment, but information about surgical resection margins was missed. This factor prevented this study from deeply discussing the efficacy of adjuvant therapy. Fortunately, previous studies have shown that, as an indolent disease, there are no significant differences in OS between patients undergoing radical and lesser resections for advanced thymomas [23].

Conclusion

According to different diagnostic ages, Masaoka-Koga stages, and LNI statuses, thymoma patients manifest broad ranges of survival rates and times. Positive LNI patients showed significantly worse postoperative prognosis than negative LNI patients. PORT and POCT have significant benefits for positive LNI patients. In addition, the number of LND significantly correlated with OS in Stage I patients. LND with less than 2 mediastinal lymph nodes manifests significantly better OS than patients dissecting more than 3 lymph nodes.

Disclosure of conflict of interest

None.

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