ORIGINAL ARTICLE

Thymoma Profile at Dr. Moewardi General Hospital: Does Thymoma Size Really Affect Distant Metastasis?

Novita Silvana Thomas[1*], Fahlevie Fahlevie[1], Ana Rima Setijadi[1], Widiastuti Widiastuti[2], Sastia Rakhma[3]

[1]Department of Pulmonology and Respiratory Medicine, Faculty of Medicine, Universitas Sebelas Maret/Dr. Moewardi General Hospital, Surakarta, Indonesia.
[2]Department of Radiology, Faculty of Medicine, Universitas Sebelas Maret/Dr. Moewardi General Hospital, Surakarta, Indonesia.
[3]Institute of Clinical Medicine, National Cheng Kung University, Tainan, Taiwan.

ARTICLE INFO

Article history:
Received 16 October 2023
Received in revised form
27 November 2023
Accepted 19 December 2023
Available online 30 January 2024

Keywords:
Cancer,
Mediastinal mass,
Metastasis,
Profile,
Thymoma.

Cite this as:
Thomas NS, Fahlevie F, Setijadi A, *et al*. Thymoma Profile at Dr. Moewardi General Hospital: Does Thymoma Size Really Affect Distant Metastasis?. *J Respi* 2024; 10: 30-35.

ABSTRACT

Introduction: Size is a predictor factor of a patient's prognosis and metastasis in solid tumors. This study determined the relationship between thymoma size and distant metastasis.

Methods: A cohort retrospective study using medical record data was conducted at Dr. Moewardi General Hospital, Surakarta, from January 2019 to August 2021. Of 1,430 thoracic oncology patients, 150 (10%) had mediastinal mass with thymoma as the majority (48.6%). About 73 thymoma patients were included. The size of the thymoma was the dependent variable, and the metastasis (distant and non-distant) was the independent variable. The cut-off point of thymoma size was determined with receiver operating characteristic (ROC) analysis. The correlation of thymoma size with distant metastasis was analyzed with the Chi-Square test, and $p < 0.05$ was considered significant.

Results: Thymoma was predominated by males (53.4%), the mean age was 43 ± 16 years old, and dyspnea was the most common symptom. Metastatic lesions were found in 87.7% of the patients, and the most common metastatic sites were intrathoracic (79.5%), followed by axillary lymph nodes (49.3%), bone (21.9%), liver (20.5%), and brain (1.4%). The cut-off value of thymoma size was 8.25 cm, indicating that ≥8.25 cm was categorized as large thymoma. Distant metastasis was found in 86.0% of large thymoma patients. The large tumors tend to spread into various sites (OR = 5.39; 95% CI 2.8-32.6; p = 0.002).

Conclusion: Thymoma must be taken into account when there are male patients in their forties presented with dyspnea and mediastinal mass. The cut-off point of 8.25 cm for the thymoma size can predict distant metastasis.

INTRODUCTION

Thymic epithelial tumors are classified as thymoma, thymic carcinoma, and thymic neuroendocrine tumors (NETs), with thymoma being the most common.[1,2] According to the United States Cancer Statistics and Surveillance, Epidemiology, and End Results databases, thymoma accounts for 66.3% of all thymic tumors, thymic carcinoma for 20.4%, and thymic NETs for 3.5%.[3] Thymoma represents only 0.2–1.5% of all malignancies and has an estimated incidence of between 0.13 and 0.32/100,000/year.[4] The incidence of thymoma in Indonesia is still unknown. A study by Vianney and Rachmadi in 2021 found 32 cases of thymoma over five years (2014-2018) based on archival data from the Department of Anatomical Pathology, Faculty of Medicine, Universitas Indonesia/Dr. Cipto Mangunkusumo Hospital.[5] The epidemiology of thymoma has limited information because the majority of data come from relatively small, retrospective, single-center cohort reviews with a small number of population-based studies.[4,6,7]

Despite being slow-growing, about 50% of malignant epithelial tumors in the anterior mediastinum are thymomas.[1,8] Approximately 30% of thymoma patients were asymptomatic.[9] Thymoma is often detected by incidental findings on chest radiography or computed tomography (CT) scan upon routine physical

*Corresponding author: novsiltho@gmail.com

Jurnal Respirasi (Journal of Respirology), p-ISSN: 2407-0831; e-ISSN: 2621-8372.
Accredited No. 200/M/KPT/2020; Available at https://e-journal.unair.ac.id/JR. DOI: 10.20473/jr.v10-I.1.2024.30-35

examination on medical check-ups or when patients present with shortness of breath and chest pain.[8,9] Another disadvantage caused by thymoma is the possibility of recurrence after treatment.[10–12] Even after a radical thymectomy has been conducted, recurrent thymoma can be found and follow-up should be performed for long enough to find its recurrence.[13]

Thymomas can be locally invade to surrounding structures, including the adjacent pericardium, mediastinal pleura, lungs, and major vessels.[1,14] Distant metastasis to regional lymph nodes or extra thoracic sites was uncommon.[14] The recognition of thymic metastasis were challenging because of extra thoracic metastasis incidence is around 3-6%.[10,14,15]

Tumor size is a predictor factor of patient's prognosis in various type of solid tumors.[16] Some studies found that tumor size in thymoma has a significant prognostic factors like survival, recurrence, or even metastasis rate.[11,16–19] Although the tumor size has been widely used in thoracic oncology staging system, this criterion is not applied in thymoma staging.[16,20] Hence, this study was conducted to describe thymoma profile of patients treated at Dr. Moewardi General Hospital, Surakarta, and investigate the relationship between the tumor size and distant metastasis in thymoma patients.

METHODS

A cohort retrospective study was conducted using medical record data of patients diagnosed with thoracic oncology at Dr. Moewardi General Hospital, Surakarta. There were 1,430 thoracic oncologic patients from January 2019 to August 2021. Of these, 150 patients (10%) were diagnosed with mediastinal mass, 73 patients (48.6%) with comprising thymoma, 11 patients (7.3%) with thymic carcinoma, 23 patients (15.3%) with Hodgkin/non-Hodgkin lymphoma, one patient with germ cell carcinoma (0.6%), and 42 patients (28%) on diagnostic examination. Patients suffering from thymoma whose baseline information, characteristics of tumor, and follow-up information were recorded in detail were included. Patients with incomplete information were excluded from the study.

Thymoma patients were divided into two groups based on the tumor size with the cut-off point of 8.25 cm (<8.25 cm and ≥8.25 cm). Patients with thymoma size ≥8.25 cm was categorized as large thymoma. The metastasis was classified into distant and non-distant. In this study, distant metastasis is an extra thoracic organ or lymph node metastasis and is diagnosed by radiographic findings using a CT scan before getting any treatment. To evaluate the significance relationship between thymoma size and the distance of metastasis, univariate and bivariate analyses were performed using the odds ratio analysis and Chi-Square test. The result was significant at $p < 0.05$ with a 95% confidence interval.

RESULTS

A total of 73 thymoma patients were included in this study. Gender, age, clinical symptoms, occupation, origin, tumors size before getting any treatment, metastasis, treatment, and mortality data were gained from each patient's medical record (Table 1).

Table 1. Characteristics of thymoma patients

Variable		N	%
Gender			
	Male	39	53.4
	Female	34	46.6
Age			
	<40	33	45.2
	40-60	29	39.7
	>60	11	15.1
Clinical Symptom			
	Dyspnea	47	64.4
	Chest pain	15	20.5
	Cough	11	15.1
Occupation			
	Entrerpreneur	28	38.4
	Housewife	19	26.0
	Farmers	17	23.3
	Students	6	8.2
	Laborer	3	4.1
Origin			
	Surakarta	43	58.9
	Others	30	41.1
Size at First			
	≥91 mm	41	56.2
	51-90 mm	25	34.2
	0-50 mm	7	9.6
Metastasis			
	Intrathoracic	58	79.5
	Axilla	36	49.3
	Bone	16	21.9
	Liver	15	20.5
	Brain	1	1.4
Treatment			
	Chemotherapy	33	45.2
	Chemotherapy and surgery	12	16.4
	Chemotherapy and radiation	9	12.3
	Chemotherapy, radiation and surgery	2	2.7
	Surgery	3	4.1
	No treatment	14	19.2
Outcome			
	Alive	69	94.5
	Dead	4	5.5

Thymoma was predominated by males (53.4%) rather than females (46.6%). Most of thymoma patients were less than 40 years old (45.2%), with the mean age was 43 ± 16 years old. At the time of diagnosis, dyspnea was the most common symptom (64.4%), followed by chest pain (20.5%) and cough (15.11%). These patients presented with the tumor size of ≥91 mm (56.2%), 51-90 mm (34.2%), and 0-50 mm (9.6%) with mean tumor size was 9.98 cm (SD ± 4.25).

Metastatic lesions were found in 87.7% of the patient, and the most common metastatic sites were intra thoracic (79.5%), followed by axillary lymph nodes (49.3%), bone (21.9%), liver (20.5%), and brain (1.4%). Most of these patients had chemotherapy (45.2%), followed by combination of chemotherapy and surgery (16.4%), chemotherapy and radiation therapy (12.3%), surgery only (4.1%), and combination of chemotherapy, radiation, and surgery (2.7%). There were 19.2% patients that who did not want to get any treatment. The most common chemotherapy agent administered to thymoma patients was the combination of cyclophosphamide, doxorubicin, platinum-based, and vincristine about 38 patients (52.1%), followed by ten patients (13.7%) received combination cisplatin and etoposide, and six patients (8.2%) received chemotherapy cisplatin and paclitaxel. This study found 5.5% death on the observation.

Of 73 thymoma patients, 53 patients (72.6%) had distant metastasis. The cut-off points of thymoma size evaluated by receiver operating characteristic (ROC) analysis obtained that the size of ≥8.25 cm was considered as a large size of thymoma. Most patients with distant metastasis had the thymoma size of ≥8.25 cm (n = 37; 86.0%). Large tumor had a tendency to spread into various sites (OR = 5.39; 95% CI 1.8-16.6; p < 0.002). This indicated that distant metastasis of thymoma was significantly related to the tumor size (Table 2).

. The relationship of tumor size with distant metastasis

		Metastasis				p-value	OR 95% CI
		Distant		Non-distant			
		n	%	n	%		
Thymoma size	≥8.25 cm	37	86.0	6	14.0	<0.002	5.39 (1.8-16.6)
	<8.25 cm	16	53.3	14	46.7		
		53	72.6	20	27.4		

DISCUSSION

This study found that most common thymoma was mediastinal mass (48.6%). The National Comprehensive Cancer Network (NCCN) 2023 and Han's study in 2019 support that thymoma accounts for 20% to 50% malignancies in the anterior mediastinum.[1,8] This study also showed that thymoma was predominated by males (53.4%), similar to studies conducted in Indonesia by Singh, *et al*. (2013) and Nikita, *et al*. (2021).[21,22] Another studies showed that females were dominated in thymoma.[7,16] In general, other evidences showed gender has no influence on the development of the disease.[3,4,6] Most of the patients in this study were entrepreneur and live in Surakarta with the majority was Javanese ethnic. Incidence of thymoma varied in terms of race, as shown by Engels, *et al*. (2010) who stated that black people have a higher incidence than white people (0.20/100,000 vs. 0.12/ 100,000).[4] NCCN 2023 showed that the incidence of thymomas is higher in African Americans as well as Asians and Pacific Islanders, which indicates that genetics plays a role.[1,3] This study could not be compared to other studies because specific ethnic patterns were not reported.

Thymoma patients were mostly aged less than 40 years old (45.2%), with the mean age was 43 ± 16 years old ranging from 16 to 86 years old. Bian, *et al*. (2018) reported the mean age of subjects with thymoma was 56 years old (12–90 years old).[16] Hsu, *et al*. (2019) showed that the 70-79 years old age group was the age-specific peak incidence of thymoma and is consistent with Engels' study.[3,4] Suryaman, *et al*. (2022) reported two thymoma cases that showed thymoma occur at 30 years old.[23] There were variations in the incidence of thymoma, but usually occurred in adults aged 35 to 70 years old.[1,6,24]

Most of this study subjects had prior symptoms such as dyspnea, chest pain, and cough. Approximately ⅓ of thymoma patients will not report significant symptoms and an additional ⅓ will report symptoms.[9,24] Cough, dyspnea, and/or chest pain are usually associated with mass effects including compression and invasion of surrounding structures.[9] The size and density of the thymus decrease with age. Hussein, *et al*. (2022) showed normal thymus size was about 3 cm with homogenous soft tissue in children less than 10 years old.[25] It will decrease until 1.5 cm in patients older than 20 years old with fatty infiltration, and after 35 years old, it could not be seen.[25] In Indonesia, most patients visit hospital because of their symptoms rather than due to routine examination results.[21] Similar with this study, most of these patients presented with the tumor size of more than 9 cm that could be associated with the symptoms caused by mass effect.[9] Most presenting symptoms during the diagnosis were associated with malignant lesions.[21]

Metastatic lesions were found in 87.7% of the patients, and the most common metastatic sites were intra thorax (79.5%), followed by axillary lymph nodes (49.3%), bone (21.9%), liver (20.5%), and brain (1.4%). Metastasis was common in thymic carcinomas, followed by high risk thymomas.[10] A study by Khandelwal, *et al*. (2016) was in line with this study that showed the most common locations for metastasis were pleura, lungs, and thoracic nodes.[10] Extra thorax metastasis incidence is rare (3-6%).[10,14,15] Some studies showed the most common sites of thymoma metastasis are lymph nodes, liver, bone, brain, spleen, kidneys, pancreas, gastrointestinal tract, ovary, and other soft tissues.[14,15] Generally, thymomas are indolent tumors, but malignancy should be considered because of the ability to local invasion, pleural dissemination, and systemic metastasis.[26]

In this study, the patients presented with the tumor size of ≥91 mm (56.2%) with mean tumor size was 9.98 cm (SD ± 4.25). Meanwhile, Yun, *et al*. (2021) found mean tumor size according to the CT scan was 5.6 ± 2.4 cm, and in the study by Fukui, *et al*. (2016) was 4.9 cm, respectively.[17,18] Tseng, *et al*. (2022) found that the mean tumor size was 5.7 cm.[7] The mean tumor size can vary due to stage of the thymoma. The majority of the population were at an earlier stage, while in this study, most of the patients came with end-stage metastasis.

The size of thymoma has been underestimated and has hindered meaningful comparisons.[16] Yun, *et al*. (2021) showed that tumor size has a significant prognostic effect.[17] The optimal cut-off value was 5.4 cm for overall survival (OS) and 5.5 cm for recurrence free survival (RFS).[17] Fukui, *et al*. (2016) suggested that tumors larger than 40 mm showed significantly worse outcomes in survival.[18] Hwang, *et al*. (2016) showed the node metastasis rate was 17.6% at tumor size larger than 60 mm.[19] Bian, *et al*. (2018) found that patients with tumor size larger than 90 mm had worse outcomes and increase the rate of metastasis.[16] Their studies showed that patients with a tumor larger than 50 mm had an increase metastasis at a rate of 1.958 times and tumor larger than 90 mm had metastasis rate of 3.845 times.[16] Okumura, *et al*. (2019) found a significantly higher incidence of recurrence in cases with a thymoma larger than 50 mm in size and of tumor death in cases with a thymoma larger than 80 mm.[11] This study found that patients with tumor size larger than 8.25 cm had an increase metastatic rate about 5.39 times higher. These studies support this study that increased thymoma size influenced distant metastatic rate.[16,19]

Most of the patients in this study had chemotherapy (45.2%) because the population in this study were stage IV and chemotherapy was the primary therapeutic approach in the case of metastasis.[1,15] NCCN Guidelines 2023 recommended surgery such as total thymectomy and complete excision of tumor for all resectable thymoma patients who can tolerate the surgery.[1] Surgical resection plays an important role in survival and recurrence rate.[24,27] For patients with advanced disease (stage III or IV thymoma), chemotherapy is recommended and is often followed by radiation for patients with incompletely resected disease. For thymoma that is initially considered unresectable, induction chemotherapy followed by surgical resection can result in favorable rates of overall and disease-free survival.[1,24] The variation treatment in this study was already based on the newest NCCN recommendation and local guideline consent with patients preference.

Chemotherapy agent administered to thymoma patients was the combination of cyclophosphamide, doxorubicin, platinum-based, and vincristine for 38 patients (52.1%), followed by the combination of cisplatin and etoposide for 10 patients (13.7%), and chemotherapy cisplatin and paclitaxel for six patients (8.2%). There were six first-line recommendation chemotherapy regimens, and all of the patients in this study had been treated according to the NCCN guidelines.[1] The mortality rate in Tseng's (2017) study is relatively similar to that of this study, 5.56% and 5.5%, respectively.[7] Factors associated with mortality included increasing patient's age, larger tumor size, and presence of metastasis.[28]

This study has several limitations. This was a cohort retrospective and single-centered study. Therefore, the sample size was relatively small with a lack of ethnic variation. This study also did not include risk factors and comorbidity of patients which can be investigated further in future studies. Large number of thymoma cases in multiple centers with longer duration will be needed to get the incidence, risk factors, and thymoma size for scientific research conclusions.

CONCLUSION

Thymoma must be taken into account when there are male patients in their forties presented with dyspnea and mediastinal mass. This study could be an additional baseline research to evaluate the relationship of thymoma tumor size and the distance of metastasis.

Acknowledgments
None declared.

Conflict of Interest
The authors declared there is no conflict of interest.

Funding
None declared.

Authors' Contributions
Conceived the study, designed the experiment, gathered, analyzed and interpreted the data, made tables and figures, wrote the manuscript: NST, FF. Reviewed and revised: ARS, WW, SR. All authors contributed and approved the final version of the manuscript.

REFERENCES
1. Network NCC. *Thymomas and Thymic Carcinomas*. Philadelphia, https://www.nccn.org/professionals/physician_gls/pdf/thymic.pdf (2023).
2. Marx A, Chan JKC, Chalabreysse L, *et al*. The 2021 WHO Classification of Tumors of the Thymus and Mediastinum: What is New in Thymic Epithelial, Germ Cell, and Mesenchymal Tumors? *J Thorac Oncol* 2022; 17: 200–213. [PubMed]
3. Hsu C-H, Chan JK, Yin C-H, *et al*. Trends in the Incidence of Thymoma, Thymic Carcinoma, and Thymic Neuroendocrine Tumor in the United States. *PLoS One* 2019; 14: e0227197. [PubMed]
4. Engels EA. Epidemiology of Thymoma and Associated Malignancies. *J Thorac Oncol* 2010; 5: S260-5. [PubMed]
5. Rachmadi MMVL. Aspek Klinik dan Karakteristik Tipe Histopatologik Timoma. *Maj Patol Indones* 2021; 30: 172–179. [Journal]
6. Rich AL. Epidemiology of Thymoma. *J Thorac Dis* 2020; 12: 7531–7535. [PubMed]
7. Tseng Y-C, Hsu H-S, Lin Y-H, *et al*. Does Size Affect the Prognosis of Resectable Thymoma beyond the Eighth Edition TNM? *Thorac Cancer* 2022; 13: 346–352. [PubMed]
8. Han X, Gao W, Chen Y, *et al*. Relationship between Computed Tomography Imaging Features and Clinical Characteristics, Masaoka-Koga Stages, and World Health Organization Histological Classifications of Thymoma. *Front Oncol* 2019; 9: 1041. [PubMed]
9. Minervini F, Kocher GJ. When to Suspect a Thymoma: Clinical Point of View. *J Thorac Dis* 2020; 12: 7613–7618. [PubMed]
10. Khandelwal A, Sholl LM, Araki T, *et al*. Patterns of Metastasis and Recurrence in Thymic Epithelial Tumours: Longitudinal Imaging Review in Correlation with Histological Subtypes. *Clin Radiol* 2016; 71: 1010–1017. [PubMed]
11. Okumura M, Yoshino I, Yano M, *et al*. Tumour Size Determines both Recurrence-Free Survival and Disease-Specific Survival after Surgical Treatment for Thymoma. *Eur J Cardiothorac Surg* 2019; 56: 174–181. [PubMed]
12. Abdel Jalil R, Abdallah FA, Obeid Z, *et al*. Locally Advanced Thymoma; Does Neoadjuvant Chemotherapy Make a Difference? *J Cardiothorac Surg* 2023; 18: 245. [PubMed]
13. Xu J, Ding X, Wang L, *et al*. The Clinicopathologic Features and Management of Recurrent Thymoma. *Clin Surg* 2022; 7: 1–4. [Journal]
14. Otsuka S, Hiraoka K, Kimura N, *et al*. Invasive Thymoma Metastases to the Pancreas: A Case Report. *International Journal of Surgery Case Reports* 2023; 105: 108004. [PubMed]
15. Wu C-W, Yang T-L. Spleen Metastasis of Recurrent Malignant Thymoma. *Journal of Surgical Case Reports* 2022; 2022: rjac375. [PubMed]
16. Bian D, Zhou F, Yang W, *et al*. Thymoma Size Significantly Affects the Survival, Metastasis and Effectiveness of Adjuvant Therapies: A Population Based Study. *Oncotarget* 2018; 9: 12273–12283. [PubMed]
17. Yun JK, Kim HR, Kim DK, *et al*. Tumor Size as a Prognostic Factor in Limited-Stage Thymic Epithelial Tumors: A Multicenter Analysis. *J Thorac Cardiovasc Surg* 2021; 162: 309-317.e9. [PubMed]
18. Fukui T, Fukumoto K, Okasaka T, *et al*. Prognostic Impact of Tumour Size in Completely Resected Thymic Epithelial Tumours. *Eur J Cardiothorac Surg* 2016; 50: 1068–1074. [PubMed]
19. Hwang Y, Park IK, Park S, *et al*. Lymph Node Dissection in Thymic Malignancies: Implication of the ITMIG Lymph Node Map, TNM Stage Classification, and Recommendations. *J Thorac Oncol* 2016; 11: 108–114. [PubMed]
20. Amini A, Rusthoven CG. Thymoma: Does Tumor Size Matter? *Journal of Thoracic Disease* 2019; 11: S2005–S2007. [PubMed]
21. Singh G, Amin Z, Wuryantoro, *et al*. Profile and Factors Associated with Mortality in Mediastinal Mass during Hospitalization at Cipto Mangunkusumo Hospital, Jakarta. *Acta Med Indones* 2013; 45: 3–10. [PubMed]
22. Nikita SMO, Widiastuti W, Rima A, *et al*. The Relationship between CT Scan and Incidence of Intrathoracic Thymoma Metastases in Dr. Moewardi General Hospital, Surakarta. *Bali Med J* 2021; 10: 741–745. [Journal]
23. Suryaman R, Djajalaksana S, Setyawan U, *et al*. Thymoma (Case Report): Importance of Comorbidity, Lifestyle, and Thymoma Size in Treatment Success. *Malang Respir J* 2022; 4: 251–264. [Journal]
24. Burt BM, Shrager JB. Benign and Malignant Neoplasms of the Mediastinum. In: Grippi MA, Elias JA, Fishman JA, *et al*. (eds) *Fishman's Pulmonary Diseases and Disorders*. New York, NY: McGraw-Hill Education, http://accessmedicine.mhmedical.com/content.aspx?aid=1122363861 (2015).
25. Hussein SA, Sabri YY, Fouad MA, *et al*. Role of Different Imaging Modalities in the Evaluation of Normal and Diseased Thymus. *Egypt J Bronchol* 2020; 14: 5. [Journal]
26. Liou DZ, Ramakrishnan D, Lui NS, *et al*. Does Size Matter? A National Analysis of the Utility of Induction Therapy for Large Thymomas. *J Thorac Dis* 2020; 12: 1329–1341. [PubMed]
27. Zhang Y, Lin D, Aramini B, *et al*. Thymoma and Thymic Carcinoma: Surgical Resection and

Multidisciplinary Treatment. *Cancers (Basel)*; 15. Epub ahead of print March 2023. [PubMed]
28. Khorfan R, Bharat A, Odell DD. Management and Long-Term Outcomes of Advanced Stage Thymoma in the United States. *Ann Thorac Surg* 2021; 111: 223–230. [PubMed]