

Profile and Factors Associated with Mortality in Mediastinal Mass During Hospitalization at Cipto Mangunkusumo Hospital, Jakarta

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ABSTRAK

Tujuan: untuk mendapatkan karakteristik, variasi jenis massa dan tindakan penunjang diagnostik, serta faktor-faktor mortalitas saat perawatan pada pasien dengan massa mediastinum yang telah didiagnosis dan tatalaksana di RSCM dalam kurun waktu 10 tahun. **Metode:** penelitian ini merupakan studi kasus kontrol, dengan menelusuri rekam medik 113 pasien dengan massa mediastinum selama bulan Januari 2000-Desember 2009 di RSCM, Jakarta. Pada analisis faktor-faktor mortalitas; sepsis, syok, pneumonia, tuberkulosis paru, sindrom vena cava superior, efusi pelura masif, efusi perikard dan gagal napas digunakan regresi logistik analisis multivariat. **Hasil:** terdapat 201 pasien dengan massa mediastinum selama kurun waktu sepuluh tahun, dan 113 pasien memenuhi kriteria penelitian (69 pria dan 44 wanita dengan usia rerata 47 tahun). Massa mediastinum terbanyak terdapat pada kisaran usia 18-60 tahun. Pasien yang memberikan keluhan saat awal diagnosis sebanyak 107 kasus. Lokasi massa terbanyak pada kompartemen anterosuperior. Foto toraks dapat mendeteksi 61 kasus massa mediastinum. Empat puluh dua pasien menjalani tindakan torakotomi untuk mendapatkan hasil jenis massa secara histopatologi. Mortalitas saat perawatan di rumah sakit mencapai 39,8%. Regresi logistik analisis multivariat mendapatkan faktor sepsis ($p=0,000$), sindrom vena kava superior ($p=0,000$), dan efusi pleura masif ($p=0,047$), sebagai faktor bermakna yang berhubungan dengan mortalitas saat perawatan. **Kesimpulan:** gambaran klinis dan radiologis pada studi ini menunjukkan bahwa massa mediastinum dapat menyerupai gejala penyakit lain. Jenis dan modalitas diagnostik pada studi ini berbeda dibandingkan studi lainnya (baik di dalam maupun luar negeri) yang pernah dilaporkan dengan proporsi mortalitas yang tinggi saat perawatan.

Kata kunci: massa mediastinum, sepsis, sindrom vena kava superior, efusi pleura masif.

ABSTRACT

Aim: to obtain characteristics, variations of the type of mass, diagnostic modalities, and mortality factors during hospitalization in patients with mediastinal mass at our institute during a 10-year period. **Methods:** a case-control study was conducted, by browsing through the medical records of 113 mediastinal mass patients who were treated at Cipto Mangunkusumo Hospital, Jakarta, during a 10-year period (January 2000-December 2009). Factors associated with mortality, i.e; sepsis, septic shock, pneumonia, lung tuberculosis, superior vena cava syndrome, massive pleural effusion, pericard effusion, and respiratory failure were analyzed by logistic regression multivariate analysis. **Results:** two hundred and one mediastinal mass patients were diagnosed and treated at our institute, 113 medical records were available to be included in this study. There were 69 males and 44 females with the age range of 18-60 years. One-hundred and seven patients were symptomatic at presentation. Mediastinal tumor was the most common mediastinal mass found among the subjects. The most frequent mass location was in the

anteriosuperior compartement. Chest X-ray imaging were able to detect 61 cases of mediastinal mass, while 42 patients underwent thoracotomy (open biopsy) to acquire histopathology diagnosis. The proportion of mortality during hospitalization reached 39.8%. Logistic regression multivariate analysis found sepsis ($p=0.000$), superior vena cava syndrome ($p = 0.000$), and massive pleural effusion ($p=0.047$), were significant factors associated with mortality during hospitalization. **Conclusion:** the clinical and radiologic features of mediastinal mass patients in our institute showed that mediastinal mass may resemble the symptoms of other diseases. Types and diagnostic modalities performed in our study differs from other studies previously reported in other countries with a high proportion of mortality during hospitalization.

Key words: mediastinal mass, sepsis, superior vena cava syndrome, massive pleural effusion.

INTRODUCTION

Various diseases may emerge in or involve the mediastinum. These diseases may include primary tumors, metastatic tumors, cysts or acute and chronic infections. Mediastinal mass is a term for mass(es) in the mediastinum, i.e. the space between right and left lungs. The mediastinal space is narrow and cannot be expanded, thus a growth in this space will compress adjacent organs and cause a life-threatening emergency. Most mediastinal masses grow slowly, and thus patients often seek medical attention as the mass gets large enough, accompanied by signs of symptoms due to the compression of the mass to adjacent organs. Factors known to be associated with increased morbidity rate are infection, pulmonary emergency, cardiovascular emergency, and neurologic emergency. Infection include sepsis, septic shock, pneumonia, and pulmonary tuberculosis; pulmonary emergency-massive pleural effusion and respiratory failure; cardiovascular emergency-superior vena cava syndrome and massive pericardial effusion, while neurologic emergency-myasthenia crisis.¹⁻³ A prompt and appropriate evaluation on those factors is very important in the management of patients with mediastinal masses, particularly as a guide to determine useful diagnostic modalities, treatment options and to facilitate appropriate evaluation on various levels of diagnostic process and treatment. Increased patient's risks will determine when the treatment should be conducted aggressively to provide better result, ease the patient's suffering, and to reduce the mortality rate.⁴

In comparison with reports from abroad, data regarding mediastinal mass in Indonesia is still scarce. In view of the broad clinical and radiologic manifestations of mediastinal mass and how they

often resemble other diseases, hence study of mediastinal mass patients in Indonesia, especially at our institute (Cipto Mangkunkusumo hospital, which is a major general public hospital and the national referral hospital in Central Jakarta, Indonesia) is needed. Results obtained from this study will give important epidemiology data (10 years) regarding mediastinal mass, treatment, outcome of treatment in Indonesia, especially at our institute and could guide clinicians to establish the diagnosis of patients with mediastinal mass and to stratify patients with high mortality factors in order to conduct more optimal patient management.

METHODS

Sample

We conducted a case control study to analyze factors associated with mortality during hospitalization. Data were obtained from patients' medical records. Study was conducted between April 2010-July 2010 by browsing medical records of mediastinal mass patients treated in our institute from January 2000-December 2009. Samples were collected by browsing and documenting all outpatient and inpatient medical records who had been diagnosed (based on chest x-ray and or histopathology) with mediastinal masses in Cipto Mangunkusumo Hospital of the within the aforementioned period.

Subjects

In the analysis on factors associated with mortality during hospitalization, all mediastinal mass patients who died during hospitalization within January 2000-December 2009 were included in the case group. In the other hand, we conducted simple random sampling to include the control group, i.e.; patients who survived during

hospitalization. A ratio of case:control = 1:1 was utilized. Study has been approved by the Ethical Committee of University of Indonesia (approval number 135/PT02.FK/ETIK2010) and patients' confidentiality was maintained throughout the study.

Statistical Analysis

Data collected were subsequently processed using SPSS version 16.0. Both descriptive and analytic data were presented in text, tables, or diagrams as necessary. Factors associated with mortality (sepsis, septic shock, pneumonia, lung tuberculosis, superior vena cava syndrome, massive pleural effusion, pericard effusion, and respiratory failure) were analyzed by logistic regression multivariate analysis.

RESULTS

Two hundred and one mediastinal mass cases were recorded in the hospital data registry within the 10-year period (January 2000-Desember 2009). We successfully collected 113 medical records of those patients while the remaining 88 patients were excluded from our study since their medical records were not found. Most of the patients were males, with a ratio of 3:2 and mostly within the range of 18-60 years, as seen in **Table 1**. Seven (6.2%) of the cases were found in pediatric, while 106 (93.8%) in adults patients, with a ratio of 15:1. The youngest patient was 6 years and the oldest was 85 years of age.

Table 1. Demographic profile

Variables	n (%)
Gender	
- Male	69 (61.1)
- Female	44 (38.9)
Age	
- <18 years	7 (6.2)
- 18-60 years	77 (68.1)
- >60 years	29 (25.7)

One hundred and seven patients (94.2%) were symptomatic, while six patients (5.2%) were asymptomatic at presentation. Respiratory symptoms were the most common initial symptoms, whereas fine crackles in 51 (45.1%) patients and SVCS in 33 (29.2%) patients were the most common physical examination findings and complications. Majority of the mass located in the

anterosuperior compartment, were symptomatic at presentation. (**Table 2 and 3**)

Table 2. Clinical manifestations

Symptoms	n (%)	Physical findings & complication	n (%)
Cough	82 (72.6)	Lymphadenopathy	21 (18.6)
Dyspnea	81 (71.7)	Rales	51 (45.1)
Chest pain	23 (20.4)	Wheezing	2 (1.8)
Wheezing	2 (1.8)	SVCS	33 (29.2)
		Pleural effusion	28 (24.8)
		Myasthenia gravis	21 (18.6)
Non-respiratory symptoms			
Weight loss	60 (53.1)		
Fever	35 (31.0)		
Fatigue/ Weakness	33 (29.2)		
Night sweat	23 (20.4)		
Husky voice	12 (10.6)		

Table 3. The presence of clinical symptoms based on mass location in thoracic cavity

Location	Symptomatic	Asymptomatic
	n (%)	n (%)
Anterosuperior	56 (47.1)	4 (66.7)
Anteroinferior	2 (1.7)	0 (0.0)
Media	20 (16.8)	0 (0.0)
Posterosuperior	7 (5.9)	0 (0.0)
No CT scan	34 (28.5)	2 (33.0)

All 113 patients had chest X-ray while thoracic CT scans were performed in 77 (68.1%) subjects. Thirty six (31.9%) subjects without thoracic CT scan were still included in the study since their clinical and histopathologic data were available in their medical records. Chest X-ray could detect 61 (79.2%) mediastinal masses while the remaining were either normal in 10 (8.8%) subjects or had some forms of abnormalities other than mediastinal masses in 14 (12.4%) cases. Based on the location found from chest X-ray examination, the most common location was superior mediastinal found in 27 (23.9%) cases followed by right mediastinal in 21 (18.6%) cases. Apart from chest X-ray findings, thoracic CT scans found that in 60 (48.0%) subjects the mass were located at anterosuperior mediastinal and in 20 (16.0%) cases in medial mediastinal compartment. Various kinds of mediastinal mass based on histopathological examination is shown

in **Table 4**. Mediastinal tumor (44.2%) was the most common mass found, with thymoma (25.0%) as the most common mediastinal tumors and 51 (45.1%) mediastinal mass were undiagnosed by histopathologic examinations. Fifty one subjects in whom histopathological diagnosis were not confirmed was due to mortality in 27 (52.9%), while the materials were not available in another 17 (33.3%), and in the remaining 7 (13.8%) subjects, histopathology results were inconclusive.

Table 4. Types of mediastinal masses

	N	%
Tumor	50	44.2
- Thymoma	27	25.0
- Lymphoma	3	2.8
- Seminoma	2	1.8
- Teratoma	1	0.9
- Neurogenic Tumor	1	0.9
- Other Tumors:		
- Thymic carcinoma	7	6.5
- Carcinoma	9	8.3
- Miscellaneous	6	5.6
Thyroid	6	5.3
Cyst	2	1.8
Lymphadenopathy	1	0.9
Other Mass	3	2.7
Undiagnosed	51	45.1

Forty-two patients (37.2%) underwent surgery/open biopsy to obtain the histopathologic diagnosis. In the remaining 71 patients, trans thoracic biopsy (TTB) (14 cases; 12.4%), CT guided trans thoracic aspiration (4 cases; 3.5%), pleural fluid cytology (4 cases; 3.5%), fine needle aspiration cytology (FNAC) of the lymph nodes (LN) (4 cases; 3.5%), sputum cytology (3 cases; 2.7%), bronchial lavage cytology (2 cases, 1.8%) while the rest (40 cases; 35.4%) did not undergo any diagnostic procedures due to poor performance status or severe concomitant disease. In patients with surgery/open biopsy procedure, diagnosis was acquired in 42 patients (67.7%), TTB in 12 (19.4%), and LN FNAC in 3 patients (4.8%), while sputum cytology and bronchial lavage cytology were undiagnostic. Thirty-six out of 42 patients who underwent surgery successfully had their mediastinal mass

removed and three patients died after surgery.

Among 113 patients with mediastinal mass, 45 (39.8%) patients died during hospitalization. Highest mortality occurred in patients with respiratory failure, which occurred in 25 patients (100%), septic shock in 11 patients (11%) and the lowest mortality was obtained from pulmonary tuberculosis in 5 patients (50%). Logistic regression multivariate analysis was conducted on the variables with p value of <0.25 to get adjusted OR value. Sepsis, superior vena cava syndrome (SVCS), and massive pleural effusion were statistically significant factors found to be associated with mortality during hospitalization. (**Table 5**)

Table 5. Multivariate analysis of factors associated with mortality during hospitalization

Variables	Odds Ratio (95% CI)	P
Sepsis	36.243 (7.201 – 182.418)	0.000
SVCS	19.649 (4.541 – 85.021)	0.000
Massive pleural effusion	7.828 (1.025 – 59.793)	0.047

DISCUSSION

In the present study, more male subjects with mediastinal masses were observed, i.e. 69 (61.1%) subjects with ratio of 3:2. This result is similar to that of Vaziri M et al.⁵ which found 62% of 105 cases were male subjects. On the other hand, a study conducted by Junior RS et al.⁴ reported 53.5% of 114 cases were female, implying no sex predilection for mediastinal masses. Moreover, the most common range of age group was 18-60 years, which was found in 77 (68.1%) subjects. Similar result was also found by Nelson TG et al.⁶ who found the most common age range of 18-45 years in 75% subjects and the study results by Júnior RS et al.⁴ demonstrating age range between 20-49 years in 57 subjects of 114 patients with mediastinal masses.

In the present study, majority of subjects were symptomatic at presentation, i.e. in 107 (94.7%). It is similar to observations reported by Nelson TG et al.⁶ (97% of 141 patients) and Dubashi et al.⁸ (97% of 91 patients). Meanwhile, several studies also reported comparable findings in a fewer proportion ranging from 61–88%. These includes study by Blegvad S et al.¹⁰ (61% of 129 patients), Davis et al.⁷ (62% of 400 subjects),

Bastos P et al.⁹ (68% of 171 patients), Júnior RS et al.⁴ (68% of 114 patients), Adegboye VO et al.¹¹ (77.1% of 105 patients), and Vaziri et al.⁵ (88% of 105 patients). Most presenting symptoms during the diagnosis were associated with malignant lesions.^{7,4,11}

On the other hand, 6 (5.3%) subjects in the present study were asymptomatic at presentation. The observed proportion of asymptomatic patients is much less than reports from Vaziri et al.⁵ (12%), Adegboye VO et al.¹¹ (22.9%), Júnior RS et al.⁴ (30.8%), Bastos P et al.⁹ (32%), Davis et al.⁷ (38%), and Blegvad S et al.¹⁰ (39%). This observation may be due to the fact that a large proportion of patients in Indonesia visit hospital because of their symptoms rather than due to routine examination results. This is contrary from other countries where most of mediastinal mass is found through a routine examination.¹²

Based on the location within the thoracic cavity, 56 (47.1%) subjects with anterosuperior mass were symptomatic at presentation. Similar findings with higher proportions was reported by Davis et al.⁷ (75%) and Adegboye VO et al.¹¹ (86.6%) with anterosuperior location as the most common compartment in subjects who had symptoms at the time of diagnosis. The presence of mass in the anterosuperior mediastinal is more likely to cause symptoms due to compression or invasion of the mass to the adjacent airway that may lead to airway obstruction.¹³

Rales was the most common physical finding; found in 50 (45.1%) subjects. However, no data of rales percentage in patients with mediastinal mass was reported from other studies. Lymphadenopathy was found in 21 (18.6%) subjects with supraclavicular lymphadenopathy being the most common findings in 14 (12.4%) subjects. A higher proportion of similar results was observed in a study conducted by Adegboye VO et al.¹¹ which reported lymphadenopathy in 33.3% subjects and also in study by Dubashi et al.⁸ that reported 21.9% subjects with supraclavicular lymphadenopathy. The occurrence of lymphadenopathy is associated with malignancy.⁸

Various complications may accompany a mediastinal mass, known as complication because it is correlated with compression and/or invasion of the mass (mostly tumor) to the adjacent organs or resulting from systemic reaction due to tumor.¹² In the present study, SVCS was the most common

complication in 33 (29.2%) subjects. Such result is similar to the study conducted by Dubashi et al.⁸ (28% subjects) and by Adegboye VO et al.¹¹ (23.5% subjects), which are higher compared to studies by Bastos P et al.⁹ (7% subjects) and by Vaziri et al.⁵ (10% subjects). The presence of SVCS is associated with malignancy or mediastinal tumor.¹¹ Supporting this observation, study by Chen JC et al.¹⁴ demonstrated that pulmonary cancer (75%), mediastinal tumor (20%), metastases of solid tumor (5%) was the cause of SVCS. In addition, Pratama S¹² reported that mediastinal tumor was the cause in 27.1% patients with SVCS.

Thoracic CT scans in these patients revealed the most common location of mediastinal mass to be in the anterosuperior compartment as found in 60 (48.0%) subjects. Several studies also observed that anterosuperior compartment were the most common location but with various proportions. The presence of a mediastinal mass in the anterosuperior compartment was reported by Davis et al.⁷ (54%), Júnior RS et al.⁴ (57.8%), Bastos et al.⁹ (58%), Adegboye VO et al.¹¹ (63.8%), Vaziri et al.⁵ (65%), Shrivastava C.P et al.¹⁵ (72%), and Dubashi et al.⁸ (93.6%). Chest X-rays showed that 10 (8.8%) subjects had normal imaging and 14 (12.4%) subjects had no detectable masses. This may occur since CT scan has more advantage compared to chest X-ray in detecting mediastinal mass, determining the location and characteristics of such masses.

In the present study, chest x-ray detected 61 (79.2%) cases of mediastinal masses. Such result is similar to a study in 90 subjects indicating that chest X-ray may only detect 62 (69%) cases of mediastinal masses.¹⁷ Some literatures demonstrate that the accuracy of detection depends on mediastinal compartment, i.e. 48% (10/21) visualization of medial mediastinal mass, 67% (20/30) of anterior compartment, and 100% (4/4) of posterior mediastinal mass. Although chest X-ray has some limitation and there are various superior radiological modalities (CT scan, magnetic resonance imaging, positron emission tomography scan, etc), but it still has important role as initial diagnostic procedure to establish the diagnosis for mediastinal mass.¹⁷

Mediastinal tumor found in 50 (44.2%) subjects was the most common type of mediastinal mass in this study. Similarly, at least 10 other studies reported that mediastinal tumor as the

most common type of mediastinal mass.^{4-9,11,15,18,19} Of all mediastinal tumor, thymoma was the most common type of mediastinal tumor (in 27 (25.0%) subjects). The same observations are also demonstrated by Davis et al.⁷ (17% subjects), Júnior RS et al.⁴ (40% subjects), Pratama S¹² (37.8% subjects), Dubashi et al.⁸ (39% subjects), Bastos et al.⁹ (31% subjects) and Shrivastava C.P. et al.¹⁵ (31% subjects). Vaziri et al.⁵ observed mediastinal lymphoma as the common findings (31.5% subjects) while Nelson TG et al.⁶ reported the same observation in 20.5% subjects. Similarly, Adegboye VO et al.¹¹ found mediastinal lymphoma in 21.9% subjects. On the other hand, Kim KR et al.¹⁹ reported germinal cell tumor as the most common types of mediastinal tumor (28.4% subjects). While dealing with patients who had mediastinal mass, mediastinal tumor may be considered as the initial diagnosis.

Open biopsy was the most common procedure in this study. Forty two (67.7%) subjects underwent open biopsy either as diagnostic procedures to determine the type of mediastinal tumor histopathologically or as treatment modalities, with a low mortality rate (9.8%). This finding is similar to the study conducted by Lam et al.²⁰ reporting 26 subjects of 29 patients who had open biopsy in establishing diagnosis of mediastinal mass; however, greater number was reported by Dubashi et al.,⁸ i.e. 28% of 91 patients. Procedure or modalities to obtain the type of mediastinal mass depends on some factors; if the mediastinal mass is assumed to be benign, capsulated, resectable, and non-lymphatous lesion based on radiological imaging and or difficult to establish diagnosis after various examinations, then open biopsy is the procedure of choice to obtain definitive etiology or treatment.²¹ In contrast, if the mass seems to be invasive and not resectable then biopsy could be performed through imaging or surgical assistance.²²

The incidence of mortality in patients with mediastinal mass is associated with some factors, namely infection, pulmonary, cardiovascular and neurologic emergency.¹⁻³ In the present study, the proportion of mortality during hospitalization was found in 45 (39.8%) subjects, of whom 16 (35.6%) subjects were diagnosed with mediastinal tumor. In addition, another 27 (52.9%) subjects who died with mediastinal masses in whom the definite type of mediastinal mass had not

been identified. This is likely to occur since the subjects had come in a very late stage and having other concomitant disease as well as having financial constraints thus delaying optimal diagnostic procedure and appropriate treatment. Investigators of the present study did not find data of other studies (both local and overseas studies) on mortality proportion of subjects with mediastinal mass during hospitalization.

In the present study, bivariate and multivariate analysis were performed on factors that may be associated with mortality during hospitalization. By logistic regression multivariate analysis, significant factors include sepsis (OR 36.243; 95% CI 7.201-182.418; $p=0.000$), SVCS (OR 19.649; 95% CI 4.541-85.021; $p=0.000$) and massive pleural effusion (OR 19.649; 95% CI 4.541-85.021; $p=0.047$).

Having significantly high OR found from this study, sepsis represents a systemic inflammation and extensive tissue damage resulting in vascular endothelial necrosis which lead to multiple organ damage or even death. This was supported by Cohen who stated that multiple organ disorder is caused by thrombosis and coagulation in small blood vessel resulting in septic shock and consequently causing death.²³ Mortality due to sepsis during hospitalization ranges between 25%-80%. Risk factors associated with bad prognosis include organ dysfunction, underlying disease, source of infection and microorganisms.²⁴

As a medical emergency, SVCS frequently manifests in patients with malignant process of the thoracic cavity. Patients with SVCS need an immediate diagnostic evaluation and treatment. Their survival rate depends on the underlying disease. This study showed that 25.6% of patients with mediastinal masses present with SVCS and 82.7% of them died during hospitalization. A study by Wilson et al.²⁵ showed that around 10% patients with bronchogenic carcinoma and 45% patients with lymphoma who had radiation may survive for approximately 30 months; while patients with SVCS due to malignancy who had not had any treatment will die in 30 days. Superior vena cava syndrome occurs due to obstruction of circulation through superior vena cava resulting in increased vein pressure. The increased vein pressure of the upper part of the body will cause edema of the head, neck and arms. In severe condition, SVCS may cause

laryngeal and brain edema leading to symptoms of headache, impaired consciousness and sudden death.²⁵

Accumulation of pleural fluid occurs when production speed exceeds the reduced lymphatic clearance due to malignant infiltration. Malignancy is the most common cause of massive pleural effusion.²⁶ Jiménez et al.²⁶ found that 53.7% etiology of malignancy in 121 patients with massive pleural effusion. The survival rate of patients with massive pleural effusion is about 5 months. Park et al.²⁷ reported that among 298 subjects with pleural effusion, 41 (13.8%) subjects had massive pleural effusion with malignancy (46.3%) as the most common cause, followed by tuberculosis (36.6%), parapneumonia effusion (9.8%), and transudate (7.3%). This study found high mortality rate in patients with massive pleural effusion in whom malignant masses were present (66.7%).

This study also found other variables that are likely to have association with mortality during hospitalization such as pneumonia, pulmonary tuberculosis, respiratory failure, and myasthenia crisis but failed to demonstrate significant correlation in multivariate analysis. This may occur due to small sample size to obtain statistically significant correlation.

The present study was retrospective in nature by analyzing secondary data from medical records. Completeness and reliability of data largely depends on the records which were completed by different physicians. Some history, physical findings and other supporting tests were not documented in the medical records. In addition, despite being conducted in the largest tertiary hospital in the country, the results are based from a single centre with internal validation and therefore, the results should be confirmed and validated by a multicentre study to be generalized beyond our institution.

CONCLUSION

The clinical and radiologic features of mediastinal mass patients in our institute showed that mediastinal mass may resemble the symptoms of other diseases. Types and diagnostic modalities performed in our study differ from other studies previously reported with a high proportion of mortality during hospitalization. Factors statistically significant

associated with mortality during hospitalizations were sepsis, superior vena cava syndrome, and massive pleural effusion. Factors known to be associated with mortality should be identified in the comprehensive and integrated management of patients with mediastinal mass.

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