

Peer Review File

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Reviewer A

In this small retrospective study, the authors sought to determine the nature of giant middle mediastinal lesions. While the authors' conclusions are intriguing, the study could be improved. I hope the authors consider the following points:

1. The authors set a cutoff of 73 mm to define a giant lesion. They state in the discussion that all lesions above 73 mm were mesenchymal in origin, and none of the lesions 73mm were mesenchymal, there are mesenchymal lesions in the <73 mm group according to the results section. Other mesenchymal lesions in the middle mediastinum included hemangiomas and lymphangioma. While technically ectodermally derived, ganglioneuroma, and schwannoma would often be considered mesenchymal.

You are right. The text has been changed accordingly (page 13, line 262).

2. The study could be strengthened by including cases that only had a biopsy and no resection. I would assume that these biopsies exist and that imaging characterizes could also be reviewed.

Patients who received surgical biopsy were included in the study. Since this study was performed at a thoracic surgery department, we did not have access to data of patients who received CT-guided or transbronchial biopsy only and were not presented to our department. We modified the text according to your comment (page 5, line 111).

3. It is unclear from the conclusions what is the significance of labeling a lesion as a "giant" mediastinal lesion. The majority of these lesions will be biopsied, so does the size even matter?

This is a very good point that could be debated (see special series on management of "giant mediastinal tumors" in MEDIASTINUM, Vol 6 – December 2022. Link: Management of Giant Mediastinal Tumors (Ongoing) - Mediastinum (amegroups.com))

4. In general, how was metastatic disease excluded. A leiomyosarcoma in an unusual site in a female (case 3), is always concerning for metastatic disease from the gyn tract.

Thank you for your comment. It is true, it is a very rare tumor site, but primary leiomyosarcomas of the mediastinum do exist¹. The patient received PET-CT and gynecological evaluation to rule out metastasis. We have added this detail to the text (page 9, line 199).

1. Iwata T, Miura T, Inoue K, Hanada S, Inoue H, Miyamoto Y. Primary leiomyosarcoma of the anterior mediastinum encasing the aortic arch, left common carotid and left subclavian arteries. *Ann Thorac Cardiovasc Surg* 2012;18:140-3.

5. What was the sarcoma in case 4? Were genetic tests done to determine what type of sarcoma this represents?

The patient had round cell sarcoma as mentioned in the text (page 11, line 228). In patients with suspected sarcoma, histology examination was routinely performed

by a dedicated sarcoma pathologist. We added this to the materials and methods section (page 5, line 123- 124).

Reviewer B

General Comments:

This paper is an interesting small study/case series with a simple goal of defining the term “giant,” apparently for the purpose of narrowing differential diagnosis of visceral mediastinal masses.

Why was the 90th percentile selected as the definition for “Giant”? Are there precedents for this choice? Please justify the choice of $\geq 90\%$.

This is a very good question. We selected the $>90^{\text{th}}$ percentile to define the outliers of our cohort as other did in different contexts such as diagnostic impact of tumor volume and size^{2,3} or obesity in children⁴. The text was modified accordingly (page 5, line 99-100).

2. Ho JC, Fang P, Cardenas CE, et al. Volumetric assessment of apparent diffusion coefficient predicts outcome following chemoradiation for cervical cancer. *Radiother Oncol* 2019;135:58-64.
3. Li C, Oh SJ, Kim S, et al. Risk factors of survival and surgical treatment for advanced gastric cancer with large tumor size. *J Gastrointest Surg* 2009;13:881-5.
4. Gamliel A, Ziv-Baran T, Siegel RM, Fogelman Y, Dubnov-Raz G. Using weight-for-age percentiles to screen for overweight and obese children and adolescents. *Prev Med* 2015;81:174- 9.

Small study—the 90% cutoff yielding exclusively mesenchymal tumors for this small cohort might be different than that of a larger cohort. This should be acknowledged in the limitations section, with the suggestion that the 90% cutoff serve as a guideline put forward gingerly.

Thank you for your comment. The limitations have been changed accordingly (page 15, line 310).

Please spell out all acronyms at first use throughout the manuscript.

Writing/grammar need some improvement.

The text was again read with caution.

Methods:

Please indicate the specialty/qualifications of the 3rd author/reader—that is 2 senior surgeons (with ?# years of experience after training) and 1 ? specialist (with ? # years of experience after training). Was a radiologist included as a reviewer of the CT studies or were all 3 reviewers surgeons?

For this study, all CTs were reviewed by surgeons. Relation of the tumor according to the mediastinal compartments was performed by a resident and then reviewed by two senior surgeons, one with 6 years' experience and one with 19 years.

Results:

Case 3. Please clarify. Did the MRT not demonstrate the left ventricular myocardial invasion by tumor?

Assuming you are talking about case 4, unfortunately MRI did not demonstrate left ventricular myocardial invasion. (page 11, line 184) mentioned in the text.

Discussion:

The discussion meanders a bit. Please organize it better and be a bit more

succinct. In the conclusion, consider suggesting that a study with a much larger sample size be done to validate results of this very small study.

The result section has been changed according to your suggestions.

Figures: Please crop the figures, excluding unnecessary anatomy that does not assist in diagnosis. For example, in Figure 3a, the image could be cropped down to the bone/muscular chest wall, excluding most of the chest wall fat. Please also brighten the image and improve the contrast a bit.

All figures have been changed accordingly.

Figure 2 nicely illustrates compression of the right main PA by the mass, but it does not, on the single image, demonstrate the left atrial compression well.

Please either delete the latter description or add an image showing left atrial compression more convincingly/overtly.

Thank you for your comment. The description has been changed accordingly (page 8, line 142).

Figure 4—The left atrial compression can be easily deduced. The left ventricular compression might be better shown on another image. Consider showing an orthogonal image.

Unfortunately, it was difficult to show compression of all three structures on a single image. We changed the description of the figure accordingly (page 11, line 196).

Reviewer C

This is a retrospective chart review study, and the authors defined the term "giant" and describe their surgical experience in treating patients with giant lesions of the middle mediastinum. It is thought to be a well-documented study of a rare disease.

I would like to address a few concerns.

Comment 1.

Page 3, Line 111-114, The authors describe the 90th percentile as giant because of its normal distribution. Since it shows a normal distribution, it is not probable to define the 90th percentile equal or above of the cohort as "large" or "giant". Please add a statistical or mathematical basis reference.

We are not sure we understand this comment. Since there is a normal distribution, we decided to use the 90th percentile as a cut-off value. This has been used in different contexts to define outliers (see comment 1, reviewer B)

Comment 2.

Page 3, Line 117-119, One hundred and fifty-seven patients with mediastinal lesions were operated on between January 2016 and August 2021. Thirty-six patients (23%) had lesions located in the middle mediastinal compartment. ; If so, patients with middle mediastinum mass who did not undergo surgery would not have been included in the study. This can cause a type 1 error and serious error in the authors' assertion of a giant mass or mesenchymal origin mass. These should be added to the limitation section.

Thank you very much for your comment. You are right, patients who did not undergo surgery were not included as the study was performed at a thoracic surgery department. We have added this limitation to the text accordingly (see comment 2 reviewer A) (page 15, line 317-318).

Comment 3.

Are the researchers in charge of CT images, those in charge of histopathologic data, and researchers in charge of patients' data identical or overlapping?

Even considering that it is a retrospective design study if blinding is not performed during the research quality investigation, this can reduce the quality of the result analysis bias.

It is recommended to add the content and revise the content to the limitation.

You are fully correct. Not being blinded can lead to bias. Here the CT imaging were assessed without any clinical data. The text was modified (page 5 line 87/88).