Peer Review File

Article information: https://dx.doi.org/10.21037/med-22-53

Reviewer A Comments:

Comment 1

This article is insufficiently comprehensive, given its title and the expectation it creates, and, aside from discussing the new ITMIG mediastinal compartment classification, does not offer any updated information regarding mediastinal mass evaluation and how to arrive at specific diagnoses.

The 2020 ACR Appropriateness Criteria for mediastinal mass evaluation now consider both CT and MRI first line modalities for evaluation of mediastinal masses, with MRI in some cases supplanting CT. The repeated statement that CT remains the first line modality for this purpose, with MRI primarily reserved as a problem-solving tool, reflects old thinking and, unfortunately at many sites, current practice but does not reflect the true relative value of each modality for this purpose. Please modernize/correct these repeated statements (Abstract, Lines 40-42, Introduction Lines 99-100, and Conclusion, Lines 305-6) to acknowledge the lack of inferiority, if not superiority, of MRI for mediastinal mass evaluation. Underutilization of MRI for mediastinal mass evaluation has repeatedly led to unnecessary thymectomy, for benign entities, including thymic cysts and hyperplasia. Please see PMID 25575742: This clinically significant issue is insufficiently addressed.

Cystic vs solid and hyperplasia vs tumor are common mediastinal mass quandaries, both of which are more definitively addressed and answered by MRI than CT. Would emphasize that benign mediastinal cysts can have attenuation values up to 100 HU and therefore mimic solid lesions on CT, leading to unnecessary surgical resection, including thymectomy.

Bronchogenic cysts and other mediastinal cysts can occasionally be T2-hypointense secondary to certain blood products. Please incorporate this information.

Reply 1

We appreciate the invaluable feedback and have included the references from the JACR and the European Journal of Radiology in our revision. As suggested, the following has been modified throughout the text:

"**Abstract**

CT and MRI are useful to characterize mediastinal lesions detected on radiography. MRI is superior to CT in the differentiation of cystic from solid lesions and in detection of fat to differentiate thymic hyperplasia from thymic malignancy.

Imaging Evaluation

Chest radiography can detect a mediastinal mass with the loss of normal mediastinal borders (referred to as the silhouette sign) (Fig 2). The American College of Radiology Appropriateness Criteria Imaging of Mediastinal Masses recommends either CT or MRI as the next imaging study of patients with

indeterminate mediastinal mass detected on radiography 3. CT and MRI can characterize size, location, morphology, margins, density/intensity, enhancement, and invasion of neighboring structures 4. Advantages of CT include its widespread availability, fast acquisition time, relatively low cost, and detection of calcium 5. Advantages of MRI include lack of radiation exposure, superior soft tissue contrast resolution to detect invasion of the mass across tissue planes, including the chest wall and diaphragm, involvement of neurovascular structures, and potential for dynamic sequences during free-breathing or cinematic cardiac gating to assess motion of the mass relative to adjacent structures 3. MRI is superior to CT in the differentiation of cystic from solid lesions and in detection of fat to differentiate thymic hyperplasia from thymic malignancy.

Cystic Lesions

However, some benign mediastinal cysts can have attenuation values of up to 100 HU and therefore mimic solid lesions on CT, leading to unnecessary surgical resection, including thymectomy 8.

When CT features are indeterminate, further imaging evaluation with MRI can provide diagnostic information 9. Cysts on MRI typically are hypointense on T1 weighted images, hyperintense on T2 weighted images and do not show contrast enhancement. However, cysts with blood products can be hypointense on T2 weighted MRI.

Conclusion

Cross-sectional imaging with CT and MRI is indispensable in the evaluation of mediastinal pathologies. Localization of a mediastinal lesion to a compartment and characterization of morphology, density/intensity, enhancement, and mass effect on neighboring structures can help narrow differentials."

Comment 2

In the Fat-Containing Lesions section, please offer some information about CSR/SII calculation, because it is not always possible to appreciate small but diagnostically significant signal suppression with the naked eye.

Reply 2

As suggested, the following has been added to the text:

"When fat and soft tissue are present in the same voxel, as typically present with thymic hyperplasia or the normal thymus, there is a homogeneous decrease in signal intensity on opposed-phase images compared to in-phase images. When this signal drop is not clearly visible to the naked eye, quantitative calculation of signal drop in chemical shift MRI can be useful. This can be measured with the Chemical Shift Ratio (CSR) or the more recent Signal Intensity Index (SII) 14. The CSR is dependent on the signal intensity of paraspinal musculature and its formula is: CSR = (tSIop/mSIop)/(tSIin/mSIin) On the other hand, SII does not depend on muscle signal intensity and is calculated as: SIIthy = [(tSIin – tSIop)/(tSIin)] X 100% 15."

Comment 3

In the hemangioma section, please acknowledge that the discontinuous peripheral nodular enhancement pattern with progressive fill-in is only one of several enhancement patterns of mediastinal hemangiomas, just as in the liver.

Reply 3

As suggested, we have modified the text.

"Similar to extramediastinal hemangiomas, one pattern of enhancement is the discontinuous peripheral nodular enhancement with progressive fill-in on delayed phases on both CT and MRI 24."

Comment 4

The Esophageal Leiomyoma section reports esophageal leiomyomas to be T2-hyperintense. Is this a typo? More typically, leiomyomas are T2-hypointense because of their closely packed smooth muscle fibers. Please correct/modify as needed.

Reply 4

This is not a typographical error. As reported by Yang et al., esophageal leiomyoma has slightly high signal intensity on T2 weighted MRI images. This reference has been added to the manuscript.

Comment 5

In the paraganglioma section, please acknowledge that many paragangliomas, especially small ones, may not exhibit the "salt and pepper pattern" on MRI. Also, please provide the most typical/classic locations for paragangliomas in the thorax (e.g. along the necks of ribs and the aortopulmonary space).

Reply 5

The following has been added to the text:

"Tumors originating from chromaffin cells are located in 90% of cases in the adrenal gland and called pheochromocytomas, while in the remaining 10% of cases have an extra-adrenal origin (paraganglionic cells scattered throughout the body) and are termed paragangliomas. Paragangliomas are neuroendocrine tumors that can occur in all three mediastinal compartments 31. Mediastinal paragangliomas have indistinguishable imaging characteristics to paragangliomas elsewhere in the body. In the anterior mediastinum, paragangliomas arise from the parasympathetic paraganglia, usually the aortic body chemoreceptors located in the aorticopulmonary window, and are termed aorticopulmonary paragangliomas or aortic body tumors. In the posterior mediastinum, paragangliomas arise from the sympathetic chain along the neck of the ribs in the paravertebral sulci…. On MRI, paragangliomas are typically hyperintense on T2-weighted sequences and have a characteristic "salt-and-pepper" pattern cause by areas of signal void related to high velocity flow in intratumoral vessels 31. However, many paragangliomas, especially small ones, may not exhibit the "salt and pepper pattern" on MRI."

Comment 6

In the GIST section, please make clear that leiomyomas are far more common than GISTS in the esophagus.

Reply 6

As suggested, we have the following:

“In the esophagus, the most common benign neoplasm is leiomyoma, far more common than GISTs.”

Comment 7

Lines 253-255: The statement about pulmonary chondromas initially seems out of place in this mediastinal mass paper, though part of Carney’s triad. Please incorporate it into the text better.

Reply 7

We have modified the incorporation of pulmonary chondroma.

“The final component of Carney’s triad is pulmonary chondromas, are composed of hyaline cartilage surrounded by a thin fibrous pseudocapsule 38. On CT, pulmonary chondromas typically appears as round nodules with smooth margins, and a variable amount of calcification 39. On MRI, calcifications within the lesions appear as foci of low signal intensity 40.”

Comment 8

In the parathyroid adenoma section, consider mentioning that DCE imaging evaluation could be performed by MRI as well, to assist in making this diagnosis without subjecting the patient to multiple passes of ionizing radiation exposure. Also, occasionally parathyroid adenomas are cystic.

Reply 8

As suggested, we have added the following to the text:

“High-temporal-resolution dynamic contrast enhanced (DCE) MR imaging allows differentiation of the parathyroid glands from lymph nodes and thyroid tissue due to their faster arterial enhancement and earlier contrast washout, with a mean parathyroid maximal enhancement of 13 seconds earlier than thyroid tissue and 29 seconds earlier than lymph nodes using this technique 46. MRI has the benefit of making the diagnosis without subjecting the patient to ionizing radiation exposure.”

Comment 9

No paravertebral masses are discussed. Please add some discussion about masses most commonly occurring in this space.

Reply 9

As suggested, we have added the following to the text:

“Paravertebral Lesions

The paravertebral compartment of the mediastinum includes the spine and paravertebral soft tissues. When a mass is detected in the paravertebral region on CT, the most likely diagnosis is a neurogenic lesion. There are two broad categories of neurogenic neoplasms: peripheral nerve sheath tumors such as schwannoma or neurofibroma which present as round or dumbbell lesions and the sympathetic ganglion neoplasms such as ganglioneuroma (Figure 11), ganglioneuroblastoma and neuroblastoma which present as elongated masses involving 3 or more vertebral levels. Other less common neoplasms in the differential include lymphoma, bone tumors, and metastases. Nonneoplastic entities include spinal infections, cystic lesions (meningocele and neurenteric cyst), pancreatic pseudocyst and extramedullary hematopoiesis.

Accounting for 70% of mediastinal neurogenic tumors, peripheral nerve sheath tumors arise from spinal or proximal intercostal nerves, less commonly from the vagus, recurrent laryngeal, or phrenic nerves 48. Peripheral nerve sheath neoplasms can show communication with the spinal canal. Areas of heterogeneity may be due to cystic changes or hemorrhage and are more common in schwannomas than in neurofibromas (Figure 12) 48. Neurogenic tumors can erode adjacent ribs or vertebrae and enlarge the neural foramina. MRI is useful to show the extent of intraspinal/extradural extension. The “fascicular sign” is seen in some schwannomas and refers to multiple hypointense, small, ring-like structures corresponding to fascicular bundles. The “target sign” is more commonly seen in neurofibromas than in schwannomas and refers to the central low signal intensity surrounded by peripheral high signal intensity. FDG PET/CT is useful to differentiate malignant peripheral nerve sheath tumors from benign neurofibromas, with sensitivity of 95% and specificity of 72% 49. It is important to be aware that some schwannomas may demonstrate intense FDG avidity 50.”

Comment 10

Figures—The figures could be a bit more comprehensive. There is a paucity of MR imaging.

Reply 10

We have added 2 MRI cases, schwannoma and ganglioneuroma.

Comment 11

Figure 3. The fat-saturated T2WI suggests septations within the cyst, though these may be artifactual. Please either show an image without these apparent septations and/or show pre/post-contrast imaging that shows no septations. You may wish to find a more classic case.

Reply 11

As suggested, we have submitted a new figure 3B at a different level.

Comment 12

Figure 4b. Please improve windowing/contrast and brightness.

Reply 12

As suggested, figure 4b has been modified.

Reviewer B Comments:

Comment 1

1. Line 231-238

It would be better to explain FDG-PET findings of paragangliomas. FDG PET/CT in Figure 8B shows increased FDG uptake.

Reply 1

The following has been added to the text:

"PET/CT with 68-Ga DOTATATE is increasingly used for the diagnosis and follow-up of paragangliomas. PET/CT with 18-F Fluorodeoxyglucose (FDG) has been shown to better detect metastatic disease/recurrent disease in comparison to 123-Iodine MIBG and CT/MRI. 32"

Comment 2

2. Line 240-251

What about the typical MRI findings of GISTs?

Reply 2

The following has been added to the text:

"On MRI, small GISTs (≤ 5 cm) appeared as round tumors with strong and homogeneous arterial enhancement and a persistent enhancement pattern. Large GISTs (> 5 cm) appeared as lobulated tumors with mild heterogeneous gradual enhancement, and they frequently exhibited intratumoral cystic change. The presence of intratumoral cysts or a low ADC value is suggestive of a high-risk GIST. 36"

Comment 3

3. Line 253-255

What about the MRI findings of pulmonary chondromas?

Reply 3

The following has been added to the text:

"On MRI, calcifications within the lesions appear as foci of low signal intensity.39"