A comparison of computed tomography with magnetic resonance imaging for the diagnosis of thoracic extramedullary hemopoiesis in patients with leukemia: A non-inferiority retrospective diagnostic study

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Abstract. At present, MRI is the primary choice of examination for the diagnosis of thoracic extramedullary hemopoiesis. When thoracic extramedullary hemopoiesis presents as posterior mediastinum masses in specific clinical contexts, the diagnosis is not challenging. Other radiological presentations may be more difficult for diagnosis and require biopsy. Needle biopsy is typically preferred for the diagnosis of extramedullary hemopoiesis however, the high vascularization of tissues is one of the complications of this method thus, it is avoided. The aim of the present study was to compare the diagnostic parameters of CT with MRI for the diagnosis of thoracic extramedullary hemopoiesis in patients with leukemia, with an open lung biopsy as a reference standard. Chest CT, chest MRI and open lung biopsy data from a total of 912 patients with leukemia with a sign(s) and symptoms of suspected paravertebral and/or pulmonary extramedullary hemopoiesis were reviewed. In the present study, thoracic extramedullary hemopoiesis was defined as diffusivity of both lung fields being increased compared with the blood pool and no other abnormal focal of lungs being increased compared with the blood pool. The beneficial score was calculated for CT and MRI and plotted for the decision making of irradiation. With respect to open lung biopsy, MRI had a higher sensitivity compared with CT (0.865 vs. 0.809; P<0.0001; q=1691) however, CT had a higher accuracy compared with MRI (0.833 vs. 0.733; P<0.0001; q=3020). The low rate of overdiagnosis was observed for both methods for the detection of thoracic extramedullary hemopoiesis however, the working area for detecting thoracic extramedullary hemopoiesis at least once in images was higher for MRI compared with CT. CT and MRI both have diagnostic importance in the detection of thoracic extramedullary hemopoiesis in patients with leukemia however, chest MRI misdiagnoses the condition while CT can confirm it (level of evidence, 3).

Introduction

In extramedullary hemopoiesis, normal blood cells are formed outside of the bone marrow when the bone marrow is functioning normally (1). Extramedullary hemopoiesis is associated with congenital hemoglobinopathies, such as spherocytosis, sickle cell anemia and thalassemia or with bone marrow replacement conditions, such as myelofibrosis, lymphoma, leukemia and myelodysplasia (2). Extramedullary hemopoiesis is primarily observed in the spleen and liver, but is less common in the thoracic region and it is important to diagnose, as it can lead to pulmonary hemorrhage (3,4). In radiography, extramedullary hemopoiesis is identified as a bilateral lobulated fatty dense mass (5). The spleen and liver are the most common sites for involvement of extramedullary hemopoiesis; however, the whole body is affected, whereby ~5% of all cases are reported as thoracic extramedullary hemopoiesis (3). Cytopathological diagnosis lacks efficiency (6), thus novel strategies for accurate diagnosis are required for effective treatment.

Thoracic extramedullary hemopoiesis is located in the pulmonary parenchyma, pleural spaces, pulmonary arteries and the lower paravertebral area (7). It is diagnosed using chest X-ray, CT and MRI (8). Currently, MRI is the gold standard used to diagnosis patients with thoracic extramedullary hemopoiesis (9). When thoracic extramedullary hemopoiesis presents as posterior mediastinum masses in specific clinical contexts, it is easy to diagnose by MRI (10). The other radiological presentations, such as those observed in intrathoracic mass, may be more difficult to diagnose by MRI and CT as they are not associated with adjacent bone destruction and require biopsy (11). Needle biopsy is typically preferred as

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Abbreviations: CT, computed tomography; MRI, magnetic resonance imaging

a reference standard for the diagnosis of extramedullary hemopoiesis however, high vascularization of tissues is one of the complications of this method thus, it is avoided and in addition improved imaging techniques are required for effective diagnosis (2). Antitumor therapy is essential for the survival of patients with leukemia (12) and in the management of extramedullary hemopoiesis; of which, irradiation is the primary treatment of choice (13). The diffuse pattern, such as infiltration and fleeting in densities of thoracic extramedullary hemopoiesis is uncommon for X-ray, MRI and CT images (4) compared with biopsy.

The objective of the present study was to compare the diagnostic parameters of chest CT with MRI for the diagnosis of thoracic extramedullary hemopoiesis in patients with leukemia, with an open lung biopsy as a reference standard. Open lung biopsy has high diagnostic yields and an acceptable level of safety for respiratory distress disease (14).

Materials and methods

Subjects. A total of 987 patients with leukemia with the sign(s) and symptoms of suspected paravertebral and/or pulmonary extramedullary hemopoiesis at the First People's Hospital of Yongkang (Yongkang, Zhejiang, China) and Tongji Medical College Huazhong University of Science and Technology (Wuhan, Hubei, China) were recruited between 3rd January 2015 and 1st March 2019. Among them, 75 patients were excluded from the analysis, as their data in their respective medical records was incomplete. Thus, chest CT, MRI and open lung biopsy data of a total of 912 patients with leukemia were included in the analysis of the present study. The present study was approved by the review board of the First People's Hospital of Yongkang (Yongkang, Zhejiang, China) and written informed consent was provided from all the patients. Details of patient recruitment and workflow are demonstrated in Fig. 1.

Inclusion criteria. Patients with leukemia aged ≥18 years old with epistaxis, hemoptysis, pulmonary hypertension, severe tricuspid regurgitation, complaints of chest pain, enlargement of the chest, abdominal bloating, shortness of breath and/or the other sign(s) and symptoms of suspected paravertebral and/or pulmonary extramedullary hemopoiesis (suspected of having extramedullary hemopoiesis) who required diagnosis at admission were included in the study.

Chest CT. Static anterior and posterior CT images of the chest were obtained by shielding the liver and spleen (as per protocol) using the Light speed VCT CT 96 (GE Healthcare) at 120 kVp and 240 mA/sec (radiation exposure factors). The images were obtained from the apices to the lung bases under a deep inspiration (2) by three radiologists (minimum 3 years of experience) at The First People's Hospital of Yongkang and The Tongji Medical College Huazhong University of Science and Technology. The reconstructed image thickness was 1.5-mm.

Chest MRI. Chest MRIs were performed using a 1.5-T SIGNA™ Artist (GE Healthcare) by three radiologists with full parallel imaging capabilities and a minimum of 3-years

of experience. The breath-hold imaging protocol was utilized. MRI workstation SIGNA™ Artist (GE Healthcare) was used as the imaging platform. Coronal and axial T2 and T1-weighted images with a 2-mm slice thickness, 192x256 matrix size and 44 cm field of view were evaluated for image analysis (8). Apparent transverse relaxation time was 2 msec.

Open lung biopsy. The open lung biopsies (not video-assisted thoracoscopic biopsy) were performed when the patients were arranged in the supine position by three physicians (minimum 3 years of experience). The samples were collected and sent to the laboratory for examination purposes. All laboratory analyses were performed as previously described (15) by pathologists (minimum 3 years of experience) at The First People's Hospital of Yongkang and The Tongji Medical College Huazhong University of Science and Technology. Atypical cellular infiltration and presence of megakaryocyte was considered as thoracic extramedullary hemopoiesis.

Image analysis. All the images were analyzed by a total of 5 radiologists (minimum 5-years of experience in cancer imaging analysis) of the aforementioned hospitals. The differences of opinion in diagnosis were solved by consensus of all radiologists. Thoracic extramedullary hemopoiesis was defined as diffusivity of both lung fields being increased compared with the blood pool and no other abnormal focal being increased compared with the blood pool (5). If the microscopic septa were below the resolution of images, then it was considered as normal (16). Image analysis was included in the evaluation of the distribution, location and density of masses (the adipose tissue; Table I) (8).

Decision making of irradiation. The beneficial score was calculated for CT and MRI scans, for each patient, as per the equation below (1) and plotted for decision making of irradiation.

$$
\begin{aligned}
&\text{Beneficial score} \\
&= \frac{\text{True thoracic extramedullary hemopoiesis detected}}{\text{Data of leukemia patients included}} \\
&\quad - \left(\frac{\text{False thoracic extramedullary hemopoiesis detected}}{\text{Data of leukemia patients included}} \right. \\
&\quad \left. \times \frac{\text{Level of diagnostic confidence above which decision of irradiation was taken}}{1 - \text{level of diagnostic confidence above which decision of irradiation was taken}} \right)
\end{aligned}
$$

Statistical analysis. InStat v.Window 3.0.1 (GraphPad Software, Inc.) was used for statistical analysis. Categorial parameters are presented as the frequency (%) and continuous parameters are presented as the mean ± standard deviation. Categorial parameters were analyzed using χ^2 independence test and continuous parameters (accuracy and sensitivity) were analyzed using the Wilcoxon sum rank test following Tukey-Kramer multiple comparisons tests (considering critical value q>3.14 as significant) for sensitivity and accuracy. Multivariate regression analyses were performed for predictive features of thoracic extramedullary hemopoiesis. Sensitivity was determined as the ratio of numbers of true thoracic extramedullary hemopoiesis detected by imaging modality to those detected by the open lung biopsy. Accuracy was determined as the ratio of numbers of true thoracic extramedullary hemopoiesis absent detected by imaging modality to those detected by the open lung biopsy. P<0.05 and a 95% confidence interval were considered to indicate a statistically significant difference.

Table I. Image analysis of thoracic extramedullary hemopoiesis.

	Observations	
Chest CT	Chest MRI	Prediction
Hypodense tissue	T1 weighted images: homogeneous/heterogeneous hypointense signals	Suspicious for thoracic extramedullary hemopoiesis
Dense soft parts	T2 weighted images: homogeneous/heterogeneous hyperintense signals, hyperintense foci	
Septal thickening		
Ground-glass opacities		
[a]Alveolar/ground-glass consolidation	-	-

[a]Partial collapse of lung. CT, computed tomography; MRI, magnetic resonance imaging.
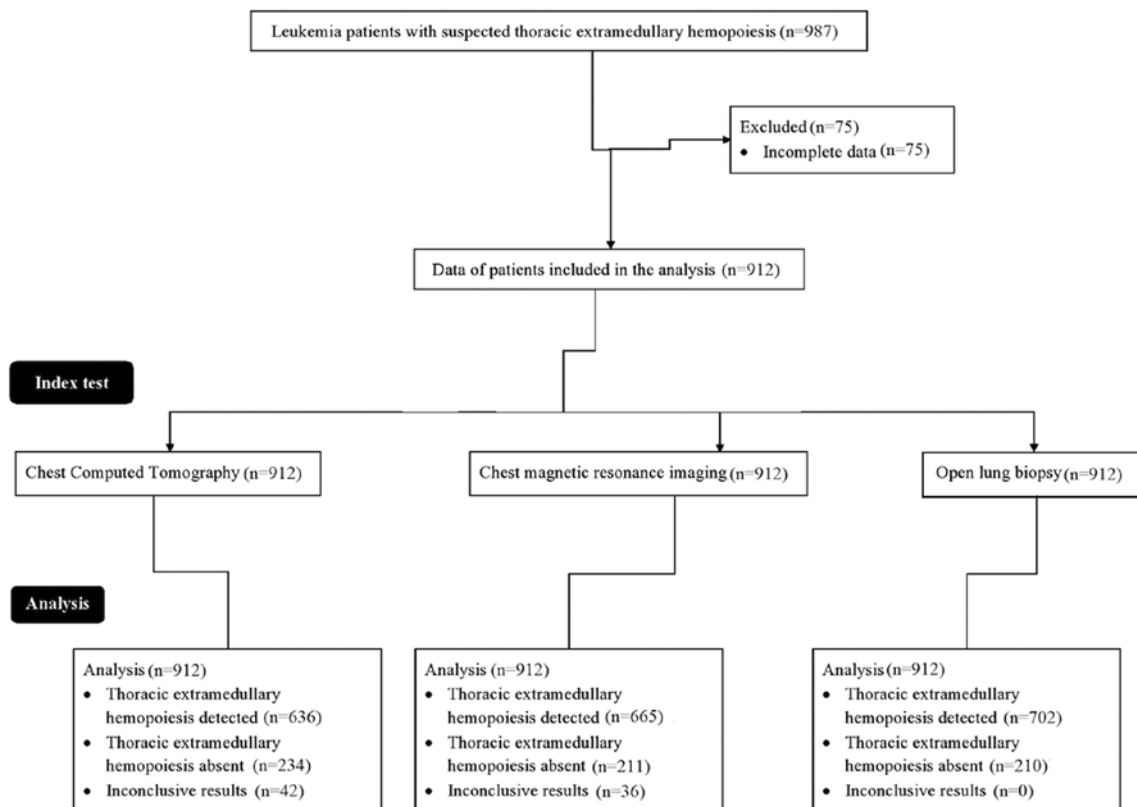
Figure 1. Workflow of the study detailing the number of patients that were enrolled, excluded and divided into the different imaging groups.

Results

Demographic and clinical characteristics in patients with leukemia. The demographic and clinical characteristics of patients, at the time of admission are presented in Table II. Chest pain was the most frequently recorded sign/symptom of suspected paravertebral and/or pulmonary extramedullary hemopoiesis in the hospitalized patients. The patient cohort consisted of more male patients compared with female patients (77 vs. 23%) and the majority of the patients had a 4-6-year history of leukemia (78%). All of the patients were treated with hydroxyurea to control splenomegaly and a raised total white cell count.

Characteristics of the masses observed using chest CT. A total of 568 patients had lower paravertebral masses, 68 patients had septal thickening and 276 patients had decreased diffusivity of both lung fields compared with the blood pool. An example of a lower paravertebral mass is presented in Fig. 2, which had the bilateral masses (adipose tissue) in the paravertebral regions. In 455 patients, the masses were relatively symmetrical and bilateral. In 62 patients, the mass was unilateral on the right side and in 51 patients the mass was unilateral on the left side. A representative image of a unilateral homogeneous mass in the left side is presented in Fig. 3. Of the 568 patients with detected masses; the presence of adipose tissue was confirmed

Table II. Demographic and clinical characteristics of the patients with leukemia at the time of admission.

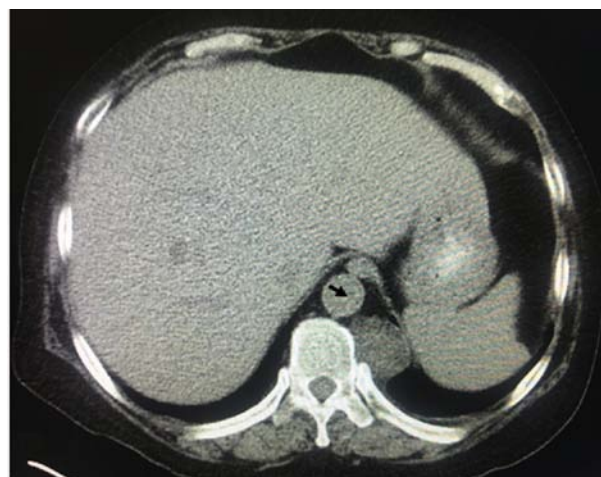| Characteristic	Number
Patients with leukemia included in study, n	912
Age, years	
Minimum	18
Maximum	65
Mean ± SD	48.5400±11.1300
Sex, n (%)	
Male	699 (77)
Female	213 (23)
Ethnicity	
Han Chinese	837 (92)
Mongolian	65 (7)
Tibetan	10 (1)
History of leukemia, n (%)	
≤3 years	102 (11)
4-6 years	712 (78)
>6 years	98 (11)
Mean hemoglobin content ± SD, mg/dl	10.1200±2.1500
Epistaxis, n (%)	312 (34)
Chest pain, n (%)	445 (49)
Enlargement of chest, n (%)	245 (27)
Mean cardiac output ± SD, l/min	4.5100±1.2100
Mean pulmonary vascular resistance ± SD, WU	3.6100±0.5200
Mean pulmonary arterial pressure ± SD, mmHg	76.1200±8.8900
Mean tricuspid regurgitation ± SD, cm	2.7200±0.2100
Mean white cell count, cell/litre	$40.09 \times 10^9 \pm 1.12 \times 10^9$
Mean platelet count, cell/litre	$369.76 \pm \times 10^9 \pm 1.01 \times 10^9$
Diabetes mellitus, n (%)	255 (28)
Chronic renal failure, n (%)	45 (5)
Mechanically ventilated, n (%)	2 (0.2)
Mean airway pressure ± SD, cm H_2O	16.8900±2.8100

WU, Wood units.

Figure 2. A scan of a 49-year-old female patient with leukemia presenting with lower paravertebral masses using chest computed tomography (mediastinal window; an axial view of the chest with emphasis on the mediastinum). The arrow indicates the aorta. The bilateral masses (adipose tissue) present in the paravertebral regions.
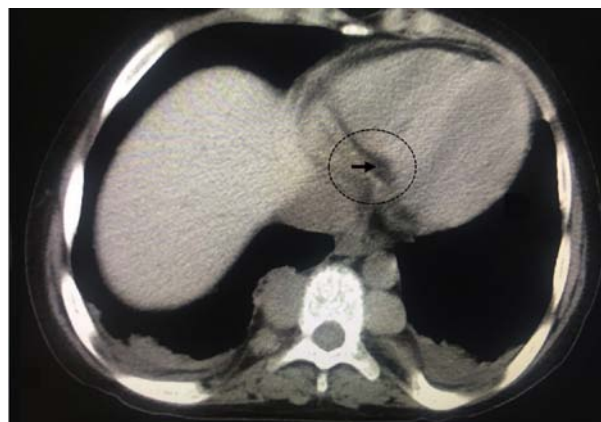

Figure 3. A scan of a 58-year-old male patient with leukemia presenting with a homogeneous mass (arrow) on the left side using chest computed tomography (mediastinal window; an axial view of the chest with emphasis on the mediastinum).
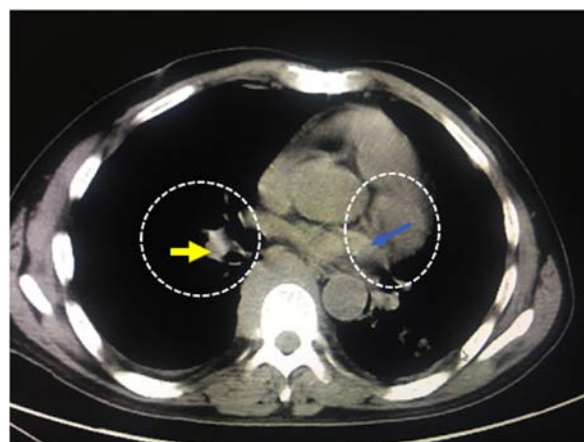

Figure 4. Representative scan of a 52-year-old male patient with leukemia presenting with paravertebral extramedullary hemopoiesis using chest CT (mediastinal window; an axial view of the chest with emphasis on the mediastinum). Homogeneous masses, with iso dense/iso attenuating soft parts can be observed (blue arrow). CT reveals a small right paravertebral soft tissue mass (yellow arrow). CT, computed tomography.

in 445 patients, significant masses were found in 71 patients and homogeneous masses, with iso dense/iso attenuating soft parts were found in 52 patients (Fig. 4).

Characteristics of images in patients with leukemia using MRI. Extramedullary hemopoiesis was observed in 607 of patients with leukemia, while 305 patients exhibited no heterogenous and/or mixed type signals (Table III). Of those, 231 patients had hyperintense foci within the lung lesion, 131 patients had homogeneous hyperintense signals and 245 had heterogeneous hyperintense signals in lung lesions (Fig. 5).

Table III. Diagnostic parameters of adopted imaging modalities.

Parameters	Open lung biopsy	Chest CT	P-value[a]	Chest MRI	P-value[a]
Number of patients with leukemia, n	912	912		912	
True thoracic extramedullary hemopoiesis detected, n (%)	702 (77)	568 (62)	<0.0001	607 (67)	<0.0001
True thoracic extramedullary hemopoiesis absent, n (%)	210 (23)	175 (19)	0.051	154 (17)	0.001
False thoracic extramedullary hemopoiesis detected, n (%)	0 (0)	68 (7)	<0.0001	58 (6)	<0.0001
False thoracic extramedullary hemopoiesis absent, n (%)	0 (0)	59 (7)	<0.0001	57 (6)	<0.0001
Inconclusive results, n (%)	0 (0)	42 (5)	<0.0001	36 (4)	<0.0001
Mean sensitivity	1	0.8090	<0.0001	0.8650	<0.0001
Mean accuracy	1	0.8330	<0.0001	0.7330	<0.0001

Data were analyzed using the χ^2 independence test. [a]With respect to open lung biopsy. CT, computed tomography; MRI, magnetic resonance imaging.
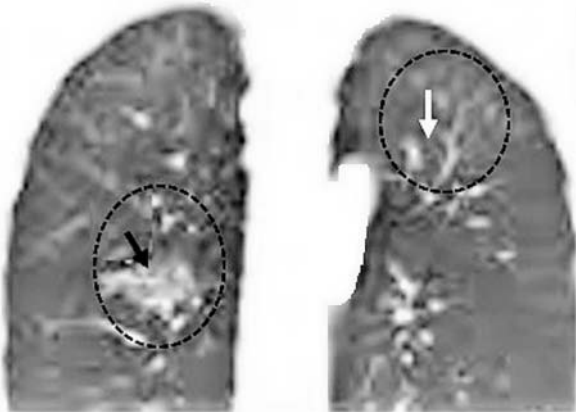

Figure 5. Representative chest magnetic resonance imaging (axial T1-weighted) scan. A 42-year-old male patient with leukemia presenting with multiple masses. The white arrow indicates the homogeneous hypointense signal to a bright area while the black arrow indicates the heterogeneous hypointense signal in the bronchus.
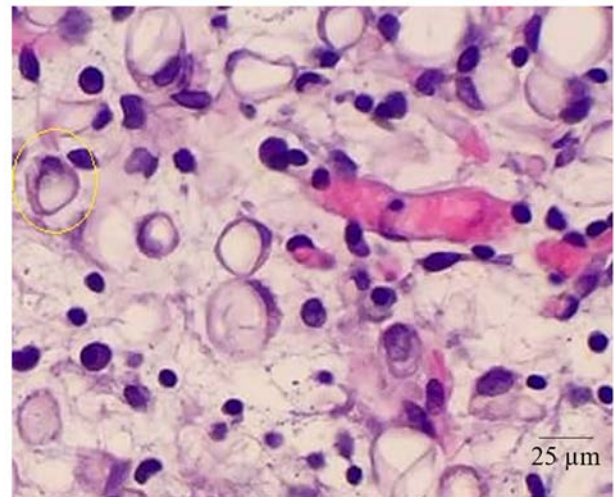

Figure 6. Histopathology result of an open lung biopsy of a 49-year-old male patient with leukemia. Atypical cellular infiltrates showing features of myeloid origin. The yellow circle indicates a megakaryocyte. Histopathology was performed by pathologists (minimum 3 years' experience) of the participating institutes.

Thoracic extramedullary hemopoiesis detection in patients with leukemia. Open lung biopsies detected features of thoracic extramedullary hemopoiesis in 702 patients, and absence in 210 patients (Table III; Fig. 6).

MRI has greater sensitivity and CT higher accuracy compared with open lung biopsy. With respect to open lung biopsy, chest MRI had a higher sensitivity compared with that in chest CT (0.865 vs. 0.809; P<0.0001; q=1691; Fig. 7A). However, chest CT had a higher accuracy compared with that in MRI (0.833 vs. 0.733; P<0.0001; q=3020, Fig. 7B). The other diagnostic parameters of imaging modalities are presented in Table III. A total of 68 and 58 scans of false positive thoracic extramedullary hemopoiesis were reported by chest CT and MRI, respectively. Furthermore, 59 and 57 cases of absent false thoracic extramedullary hemopoiesis were reported by chest CT and MRI, respectively.

Predictive factors for extramedullary hemopoiesis in patients with leukemia. Univariate regression analysis was performed prior to multivariate to identify independent factors. Age (P=0.041), history of leukemia (P<0.05), hemoglobin content (P=0.038), enlargement of chest (P=0.028),

tricuspid regurgitation (P=0.049), white cell count (P=0.048) and platelet count (P=0.047) were associated with thoracic extramedullary hemopoiesis (Table IV).

Decision making of irradiation in patients with leukemia. There was a low rate of overdiagnosis using chest CT and MRI for the detection of thoracic extramedullary hemopoiesis in patients with leukemia, compared with open lung biopsy (except for a high rate of overdiagnosis in the lungs). However, the working area that detects thoracic extramedullary hemopoiesis at least once in images was higher for the chest MRI compared with CT (0-0.905 vs. 0.430-0.900; Fig. 8).

Discussion

In the present study with respect to open lung biopsies, chest MRI had a greater sensitivity compared with CT, which is inconsistent with previous case reports (8,17). The absence

Table IV. Multivariate regression analyses for predictive features of thoracic extramedullary hemopoiesis in patients with leukemia (n=702).

Characteristics	Risk ratio	95% CI	P-value
Age, years	1.5000	2.2000-3.5000	0.0410[a]
Sex (male)	1.3000	1.5100-1.7000	0.0520
Ethnicity (Han Chinese)	0.9000	1.3000-1.9000	0.1230
History of leukemia			
≤3 years	1.1000	1.5000-2.1000	0.0520
4-6 years	1.5000	1.3000-2.5000	0.0420[a]
>6 years	1.9000	1.2000-4.8000	0.0210[a]
Hemoglobin content, mg/dl	1.5000	1.3000-2.3000	0.0380[a]
Epistaxis	1.3000	1.4000-2.2000	0.0530
Chest pain	0.8500	0.0900-1.0100	0.0900
Enlargement of chest	1.7000	1.1000-2.3000	0.0280[a]
Cardiac output, l/min	1.1000	1.2000-2.2000	0.0520
Pulmonary vascular resistance, WU	1.2100	1.3700-2.2300	0.0530
Pulmonary arterial pressure, mmHg	1.3000	1.3800-2.2500	0.0590
Tricuspid regurgitation, cm	1.4000	1.1100-2.3300	0.0490[a]
White cell count, cell/litre	1.7000	1.1200-2.2400	0.0480[a]
The platelet count, cell/litre	1.6000	1.2300-2.5200	0.0470[a]
Diabetes mellitus (% HbA1C)	1.6000	1.1000-1.9500	0.0850
Chronic renal failure (serum creatinine content)	1.5000	1.2200-1.8200	0.0790
Mechanically ventilated (presence of support)	1.7000	1.1300-1.7500	0.0560
Mean airway pressure, cm H_2O	1.2000	1.2200-1.3500	0.1560

True thoracic extramedullary hemopoiesis absent was considered as the reference standard (n=210). [a]A risk ratio >1 and P<0.05 was considered significant. WU, Wood units.
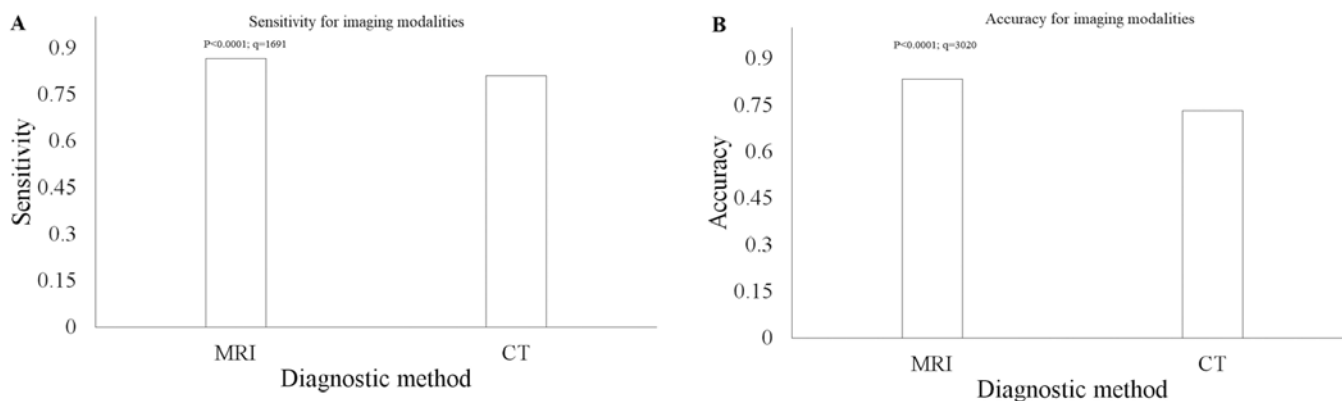

Figure 7. Diagnostic parameters (sensitivity and accuracy) of imaging modalities with respect to open lung biopsy. (A) Sensitivity and (B) accuracy for imaging modalities. The Wilcoxon sum rank test, following Tukey-Kramer multiple comparisons tests were performed to determine statistical significance. P<0.05 and q>3.14 were considered significant. MRI, magnetic resonance imaging; CT, computed tomography.

of diffusion restriction on MRI favors diagnosis (17). The diagnostic differences are not large between open lung biopsy and chest MRI (T1- or T2-weighted images) or the chest CT, as lesions possess dense soft parts on the CT scans and signal intensities on MRI (2). No definitive imaging pattern is pathognomonic and a biopsy is required for the diagnosis of thoracic extramedullary hemopoiesis (8). Open lung biopsy has the risk of persistent air leakage and hemorrhagic complications due to pulmonary hypertension (2,18,19). The results of the present study demonstrated that the chest MRI or the CT is a non-invasive and reliable method for the diagnosis of thoracic extramedullary hemopoiesis in patients with leukemia.

The results from the present study demonstrated that chest CT had a higher accuracy compared with that in chest MRI, which is inconsistent with previous case reports (8,13,16,20-22). These case reports had inadequate sample sizes, thus introduced statistical errors. The chest CT is the main imaging modality for the diagnosis of thoracic extramedullary hemopoiesis as it provides
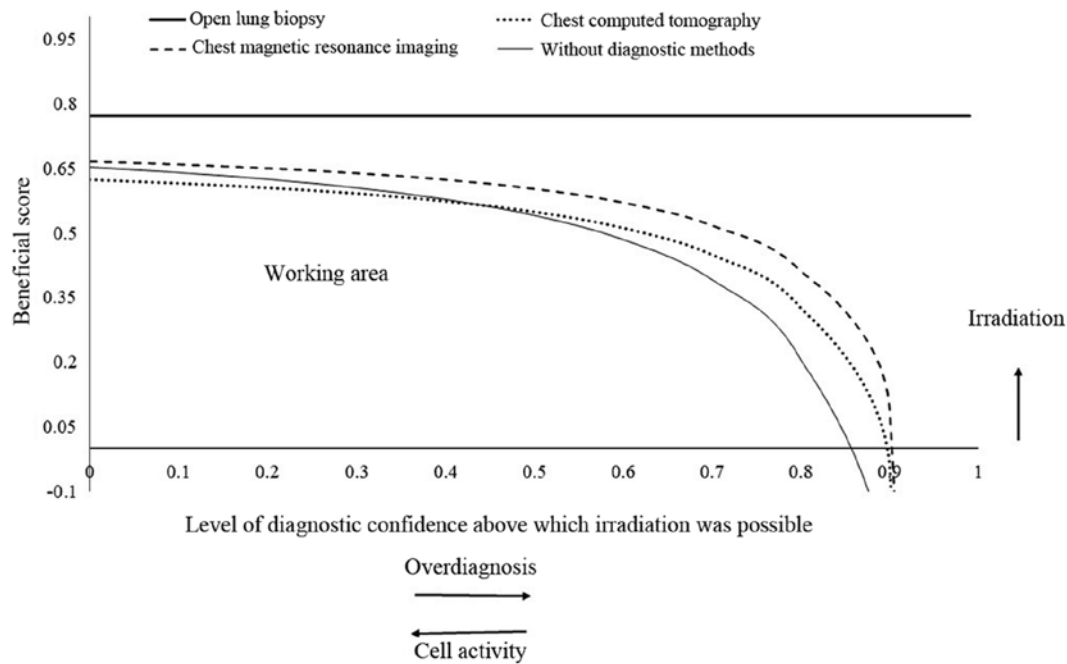
Figure 8. Decision of irradiation making. All images were analyzed by 5 radiologists (minimum 5 years of experience) of the participating institutes. Thoracic extramedullary hemopoiesis was defined as diffusivity of both lung fields being increased compared with the blood pool and no other abnormal focal being increased compared to the blood pool. The working area is defined as the space available to implement the imaging method, in order to identify extramedullary hemopoiesis.

a specific finding for nodules and masses (16). For scattered foci of internal fat, CT reveals a low-density mass whereas MRI demonstrates variable enhancements (23). MRI is the examination of choice and provides valuable diagnostic information (9) however, it can be variable and influenced by fibrous structure, fatty components and iron deposition on the cellular surface of the hematopoietic tissue (8). MRI signals for thoracic extramedullary hemopoiesis appear with higher signal intensity similar to those of tumors (13,24). Therefore, MRI misdiagnoses thoracic extramedullary hemopoiesis. The results of the present study indicated that unlike the chest MRI, the chest CT can confirm thoracic extramedullary hemopoiesis with/without adipose tissue.

In the present study, there were 68 and 58 scans of false positive thoracic extramedullary hemopoiesis, using chest CT and MRI, respectively. CT detects thoracic extramedullary hemopoiesis by septal thickening and ground-glass opacities, however lung infections and congestive cardiac failure also demonstrate ground-glass opacities under the chest CT (19,21,25). In addition, CT scans detect pleural metastases, which are originally pleural soft tissues (13). Chest MRI detects intense signals due to iron deposition on adipose tissues (1) and patients with leukemia are regularly treated with blood transfusions (26), which leads to higher iron deposition on lung medullary stroma and to false thoracic extramedullary hemopoiesis detection using chest MRI (1).

The present study reported that there were 59 and 57 cases of absent false thoracic extramedullary hemopoiesis using chest CT and MRI, respectively. Low cellular activity or little medullary stroma present in the lungs may not be detected by chest CT (16). In addition, older lesions with iron deposition or fatty infiltration may not be present as a hypointense signal on T1-weighted images or as a hyperintense signal on T2-weighted images (2,8).

There are several limitations to the present study, for example it is a retrospective in design and not a prospective study. Diffusion-weighted imaging has a diagnostic role in the detection of thoracic extramedullary hemopoiesis, as it does not demonstrate diffusion restriction in the images (17). Diffusion-weighted images was not performed in the present study despite previous recommendation to do so over T1- or T2-weighted images of the chest MRI, in order to decrease inconclusive and false positive results. In the present study, follow-up conditions and treatment were not described for the enrolled patients, which may have affected the validity of the results as treatment is affected by the diagnosis accuracy of the respective disease. Sensitivities, accuracies and the decision making of irradiation for paravertebral and pulmonary extramedullary hemopoiesis evaluation were not provided separately.

In conclusion, the present non-inferiority retrospective diagnostic study revealed that chest CT and MRI both have diagnostic importance in the detection of thoracic extramedullary hemopoiesis in patients with leukemia with manageable complications. The chest CT could confirm thoracic extramedullary hemopoiesis with/without fat involvement. The chest MRI had high sensitivity due to the absence of diffusion restriction. MRI misdiagnoses thoracic extramedullary hemopoiesis and CT confirmed thoracic extramedullary hemopoiesis. The chest CT is recommended for the diagnosis of suspected paravertebral and/or pulmonary extramedullary hemopoiesis in patients with leukemia.

Acknowledgements

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