

Implementation of diffusion-weighted magnetic resonance imaging in target delineation of central lung cancer accompanied with atelectasis in precision radiotherapy

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Abstract. Radiotherapy, particularly the target delineation of cancer based on scanned images, plays a key role in the planning of cancer treatment. Recently, diffusion-weighted magnetic resonance imaging (DW-MRI) has emerged as a prospective superior procedure compared with intensified computed tomography (CT) and positron emission tomography (PET) in the target delineation of cancer. However, the implication of DW-MRI in lung cancer, the leading cause of cancer-associated mortality worldwide, has not been extensively evaluated. In the present study, the gross target volumes of lung cancer masses delineated using the DW-MRI, CT and PET procedures were compared in a pairwise manner in a group of 27 lung cancer patients accompanied with atelectasis of various levels. The data showed that compared with CT and PET procedures, DW-MRI has a more precise delineation of lung cancer while exhibiting higher reproducibility. Together with the fact that it is non-invasive and cost-effective, these data demonstrate the great application potential of the DW-MRI procedure in cancer precision radiotherapy.

Introduction

Lung cancer is the leading cause of cancer-associated mortality worldwide (1). Radiotherapy, alone or in combination with either surgery or systematic therapies, is a key treatment modality in the curative treatment of lung cancer patients,

particularly those with advanced-stage disease (2). With the advance of radiotherapy technologies, precision radiotherapy has greatly improved the outcome for patients with lung cancer, while reducing the toxicity of an increased dose and alleviating the risk to adjacent organs. Notably, the precision delineation of the gross target volume (GTV) based on image data serves an essential role in precision radiotherapy. Several non-invasive procedures, including intensified computed tomography (CT) and positron emission tomography (PET), have been widely used for the target volume delineation of lung cancer (3). Precision radiotherapy based on CT imaging generates a risk to the organs due to its poor soft tissue contrast, particularly for central lung cancer accompanied with pulmonary atelectasis or mediastinal node metastasis (4).

Although a number of studies have demonstrated that PET outperforms CT in diagnosing nodal involvement in lung cancer (3,5,6), PET could inevitably yield false-positive results (7). Recently, the combination of PET and CT (PET/CT) has significantly improved the accuracy and sensitivity of the lung cancer diagnosis (3,8) and has become a routine aspect of the contemporary radiotherapy treatment planning process (9). However, the target delineation criteria have not yet been fully optimized (10) due to low image resolution and the difficulty in fusing the PET and CT images.

Diffusion-weighted magnetic resonance imaging (DW-MRI) can detect the restricted diffusion of water molecules through exploiting the random motion of water protons in biological tissue (11). Compared with normal tissues, malignant tumors exhibit a significantly decreased diffusion of water molecules. The difference in the diffusion of water molecules among tissues enables DW-MRI to detect malignant tumors and differentiate them from benign masses (12). Previous studies have shown that DW-MRI is comparable with PET/CT in detecting malignant lesions (13-15). Numerous studies reported that DW-MRI provided more accurate delineation for a number of cancer types, including prostate, head and neck, and cranial tumors (16-18). Compared with PET/CT, DW-MRI has demonstrated the same level of sensitivity or higher in detecting the nodal and primary malignancies in

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lung cancer (12). Nevertheless, the implication of DW-MRI in lung cancer, particularly lung cancer with pulmonary atelectasis, has not yet been intensively investigated. In the present study, the potential implication of DW-MRI in assessing central lung cancer with pulmonary atelectasis was evaluated and the successful implementation of DW-MRI in precision radiotherapy treatment planning was demonstrated.

Patients and methods

Patient selection. The patients recruited in the present study were histologically diagnosed with central lung cancer accompanied with pulmonary atelectasis. In general, all patients exhibited a good health condition with a Karnofsky performance status of ≥ 70 (19) and with no contraindications to MRI examination. The images from CT, PET/CT and MRI scans for each individual patient were collected within 1 week. The results from the PET/CT scan were used as the standard for diagnosis. All patients provided written informed consent prior to enrolling in the study. The study was approved by the Institutional Review Board and the Ethics Committee of Shandong Cancer Hospital and Institute (Jinan, China).

Population. A total of 27 patients with central lung cancer without any antitumor therapy scheduled to receive precision radiotherapy were enrolled in the present study between October 2014 and June 2015. The cohort included 23 males and 4 females. The patient ages ranged from 37 to 79 years, with a median of 61 years. All patients were histologically confirmed with central lung cancer via biopsy. The cohort included 12 cases of squamous cell carcinoma, 6 cases of adenocarcinoma, 6 cases of small cell carcinoma, 2 cases of atypical carcinoid and 1 case of adenoid cystic carcinoma. The tumors were located in the upper left lung in 8 cases, the lower left lung in 4 cases, the upper right lung in 5 cases, the middle right lung in 4 cases and the lower right lung in 6 cases.

CT scan and image acquisition. Prior to radiotherapy, all patients underwent CT simulation using immobilization by an evacuated vacuum-bag in the supine position and a CT scanner (Brilliance CT Big Bore; Philips Healthcare, DA Best, The Netherlands), with a 3-mm slice thickness from the circular cartilage to the upper pole of the kidney. Following the scan, each patient was injected with 90 ml ioversol (320 mg/ml) for enhancement scanning.

PET/CT scans and image acquisition. The PET/CT scan was performed with the GE Discovery LS PET/CT scanning system (GE Healthcare Life Sciences, Shanghai, China). All patients were requested to fast at least 6 h and it was necessary that their blood glucose should be within the normal range prior to the PET/CT examination. Between 40 and 60 min after the intravenous injection of fluorodeoxyglucose (^{18}F -FDG; 5.55–7.40 MBq/kg), the CT scan was performed and emission images were acquired. The patient was immobilized by evacuated vacuum-bag in the supine position using the fixed-field parameters based on the CT. The PET images were reconstructed using the Ordered-Subset Expectation Maximization (OSEM) with the built-in software on the

scanning machine, and the PET images were attenuation corrected with CT.

DW-MRI scan and image acquisition. The DW-MRI scan was performed by the Achieva 3.0T MR PHILIPS scanner (Philips Healthcare). Patients were kept in the same supine position as for the CT scan. The scanning parameters were as follows: i) Cross sectional T1-weighted image (T1WI): Repetition time/echo time TR/TE 10 sec/2 msec; slice thickness/inter-slice gap, 3/0 mm; field of view (FOV), 375 mm; matrix, 352x160; ii) cross-sectional T2WI: TR/TE 1.5 sec/80 msec; slice thickness/interslice gap, 3/0 mm; FOV, 375 mm; matrix, 352x160; iii) coronal T2WI: TR/TE, 1.8 sec/80 msec; slice thickness/interslice gap, 3/0 mm; FOV, 375 mm; matrix, 352x160; and iv) DWI: TR/TE, 2.6 sec/52 msec; slice thickness/interslice gap, 3/0 mm; FOV, 375 mm; matrix, 352x160; diffusion-weighted sequence ($b=600 \text{ sec/mm}^2$) was added in the axial plane.

Image fusion. To delineate GTVs, all CT, PET and DW-MRI images were transferred to a treatment planning system (TPS, Eclipse V11.5; Varian Medical Systems, Palo Alto, CA, USA). The PET and DW-MRI images from each patient were fused with the corresponding CT images. The accuracy of registration was visually inspected using the software provided by the TPS.

Using the large aperture static image as the reference, the rigid registration of the gray scale image method, together with the correction based on the skeletal signs, was used to locate the PET and DW-MRI images in the coordinate system.

GTV delineation on CT, PET/CT and DW-MRI images. In total, 10 radiotherapists independently reviewed the CT, PET and DW-MRI images, and delineated the contours of the tumor following the standard procedure. The lung cancer usually shows a heterogeneous and lobulated mass with rough edges in CT image and the tumor edges were used as the reference on GTV_{CT} delineation.

The ^{18}F -FDG concentration and characteristics of the lung lesions were used to determine the tumor tissue and the lung tissue on the PET/CT images. Using Eclipse V11.5, the contour of the primary tumor target zone in GTV_{PET} was first automatically outlined if the standardized uptake value was ≥ 2.5 , while the non-tumor regions could manually be removed by referencing the CT image. On DW-MRI images, the solid region of the tumor appeared to have high signal intensity. By contrast, the pulmonary atelectasis and the obstructive inflammation had relatively low signal intensity. Only the area with a high signal was used in contouring GTV_{MRI}. The volumes of the target area were automatically provided using Eclipse V11.5 software.

Distance between centroids of GTVs. The three directional coordinates of the GTV_{CT}, GTV_{PET} and GTV_{MRI} centroids were determined using the Eclipse V11.5 software and were denoted as (x, y, z). The relative coordinates between two GTV centroids were denoted as (Δx , Δy , Δz), with Δx the distance in the left/right (LR) direction, Δy the distance in the superior/inferior direction and Δz the distance in the anterior/posterior direction. The formula $V = \sqrt{(\Delta x^2 + \Delta y^2 + \Delta z^2)}$ was used to

Table I. GTV measurements using CT, PET/CT and diffusion-weighted MRI (n=27).

GTV measurements, cm ³	Mean (standard error of the mean)	P-value ^a
GTV _{CT}	109.45 (14.90)	N/A
GTV _{PET}	85.23 (13.10)	N/A
GTV _{MRI}	83.10 (14.26)	N/A
GTV _{CT} -GTV _{MRI}	26.34 (6.39)	<0.001
GTV _{CT} -GTV _{PET}	24.22 (5.84)	0.003
GTV _{PET} -GTV _{MRI}	2.12 (2.46)	0.395

^aGTV measurements were compared by Student's t-test. CT, computed tomography; PET, positron emission tomography; MRI, diffusion-weighted magnetic resonance imaging; GTV, gross target volume; N/A, not applicable.

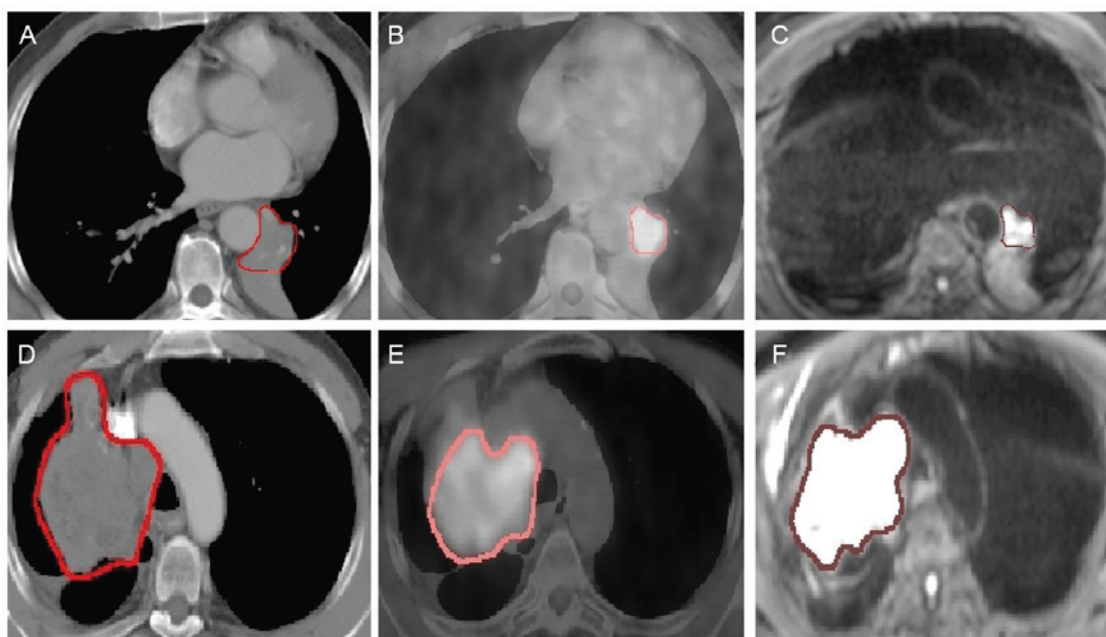


Figure 1. Delineation of CT, PET/CT and DW-MRI images. (A-C) Images of central lung cancer (squamous cell carcinoma) in a 74-year-old male patient. (D-F) Images of central lung cancer (small cell tumor) in a 61-year-old male patient. (A) The lower left lung tumor was accompanied with atelectasis, which results in blurry tumor edges. The GTV_{CT} is outlined in red. (B) PET/CT image of the concentrated radioactive tracers in the left lower lung. The GTV_{PET} is outlined in pink. (C) DW-MRI of the lung tumor with clear edges. The signal from the atelectasis is relatively low, which can be easily differentiated from the real tumor tissues. The GTV_{MRI} is outlined in brown. (D) CT image of the lung tumor. The GTV_{CT} is outlined in red. (E) PE/CT image of the concentrated radioactive tracers in the lung tumor. The GTV_{PET} is outlined in pink. (F) DW-MRI of the lung tumor. The GTV_{MRI} is outlined in brown. CT, computed tomography; PET, positron emission tomography; DW-MRI, diffusion-weighted magnetic resonance imaging; GTV, gross target volume.

calculate the distance between centroids of GTVs (i.e., GTV_{CT} vs. GTV_{PET}; GTV_{PET} vs. GTV_{MRI}; and GTV_{PET} vs. GTV_{MRI}).

Statistical analysis. Statistical analysis was performed using the SAS 9.3 software (SAS Institute Inc., Cary, NC, USA). All the parameters were descriptively summarized, including the mean and standard deviation. The differences between the GTVs and the distance to the centroids of the GTVs are presented as the mean and standard error of the mean, and were assessed using Student's t-test. The difference was considered as statistically significant if $P < 0.05$. Pearson's correlation coefficient values were summarized for the GTVs measured by three different approaches. The comparison between the group means was performed using one-way analysis of variance. The variation in the target volume of the tumors measured by different radiotherapists was assessed by

the variation coefficient (CV) as follows: $CV = \text{standard deviation} / \text{mean} \times 100$.

Results

Collection of CT, PET/CT and DW-MRI images. To implement DW-MRI as a preferred lung cancer radiotherapy procedure that is reproducible, non-invasive and cost-effective, the present study evaluated and compared CT, PET/CT and DW-MRI images of lung cancer. A total of 27 patients were diagnosed with lung cancer and images were collected according to the aforementioned methods. Using image fusions, GTVs for CT, PET/CT and DW-MRI images were delineated. Images from 2 individual patients are presented as examples in Fig. 1.

The delineated tumors among the 27 subjects varied in shape and size. Noticeably and as expected, atelectasis

compromised the precise delineation of the tumors in the majority of cases, as demonstrated by the blurry boundary in Fig. 1A and D. It is also worth noting that compared with the GTVs of the CT and PET/CT images, the delineated GTV of the DW-MRI images was often smaller in size with clear edges (Fig. 1C and F).

Pairwise comparison between GTV_{CT} , GTV_{PET} and GTV_{MRI} . A total of 27 GTV measurements were obtained for all patients based on CT, PET/CT and DW-MRI images, respectively. GTV_{CT} values ranged from 13.48 to 258.75 cm³, with a mean of 109.45 cm³, whereas GTV_{PET} values ranged from 2.48 to 219.97 cm³, with a mean of 85.23 cm³, and GTV_{MRI} values ranged from 3.88 to 246.95 cm³, with a mean of 83.10 cm³ (Table I). Among the 27 subjects analyzed, 23 subjects presented with a larger mean GTV_{CT} than mean GTV_{MRI} value, 22 subjects with a larger mean GTV_{CT} than GTV_{PET} value, and 21 subjects with a larger mean GTV_{PET} than mean GTV_{MRI} value (data not shown).

The mean GTV_{CT} was larger than the mean GTV_{MRI} and GTV_{PET} by a value of 26.34 cm³ and 24.22 cm³, respectively (Table I). Student's t-test showed that the differences in the mean GTV between CT and MRI, and between CT and PET, were statistically significant (Table I), suggesting that CT contouring is statistically different from PET and MRI contouring. By contrast, the difference in the mean GTV between PET and MRI was negligible and not significantly different (Table I).

Correlations of GTV_{CT} , GTV_{PET} and GTV_{MRI} . The correlations among GTVs were also examined by measuring the Pearson's correlation coefficient in a pairwise manner. Pearson's correlation values of the three comparisons were all greater than 0.8 (Fig. 2), suggesting that all three contour methods are coherently related. However, Pearson's correlation between GTV_{PET} and GTV_{MRI} (Fig. 2A, $r=0.9546$) was significantly higher than those between GTV_{CT} and GTV_{PET} (Fig. 2B, $r=0.8056$), and between GTV_{CT} and GTV_{MRI} (Fig. 2C, $r=0.8443$). This demonstrates a direct dependency between PET and MRI contouring, and a divergence of CT from the other contouring methods.

Pairwise comparison between CV of GTV_{CT} , GTV_{PET} and GTV_{MRI} . To evaluate the robustness and the reproducibility of the DW-MRI procedure, cancer images of the 27 subjects were randomly collected by 10 individual medical doctors and the CV was calculated for CT, PET/CT and DW-MRI procedures, respectively. CV is a standardized measure of dispersion in a distribution. The CV among doctors for the GTV_{MRI} procedure was 26.60%, which is markedly smaller than the CVs for the GTV_{PET} (32.00%) and GTV_{CT} (33.76%) procedures. These data suggested that DW-MRI is the most robust and reproducible procedure in lung cancer radiotherapy.

Distance between centroids of GTVs. The mean distance between the centroids of GTV_{CT} and GTV_{PET} was 0.87 cm (SD, 0.54 cm). The mean distance between the centroids of GTV_{MRI} and GTV_{PET} was 0.72 cm (SD, 0.34 cm). No statistically significant differences in the distances were observed.

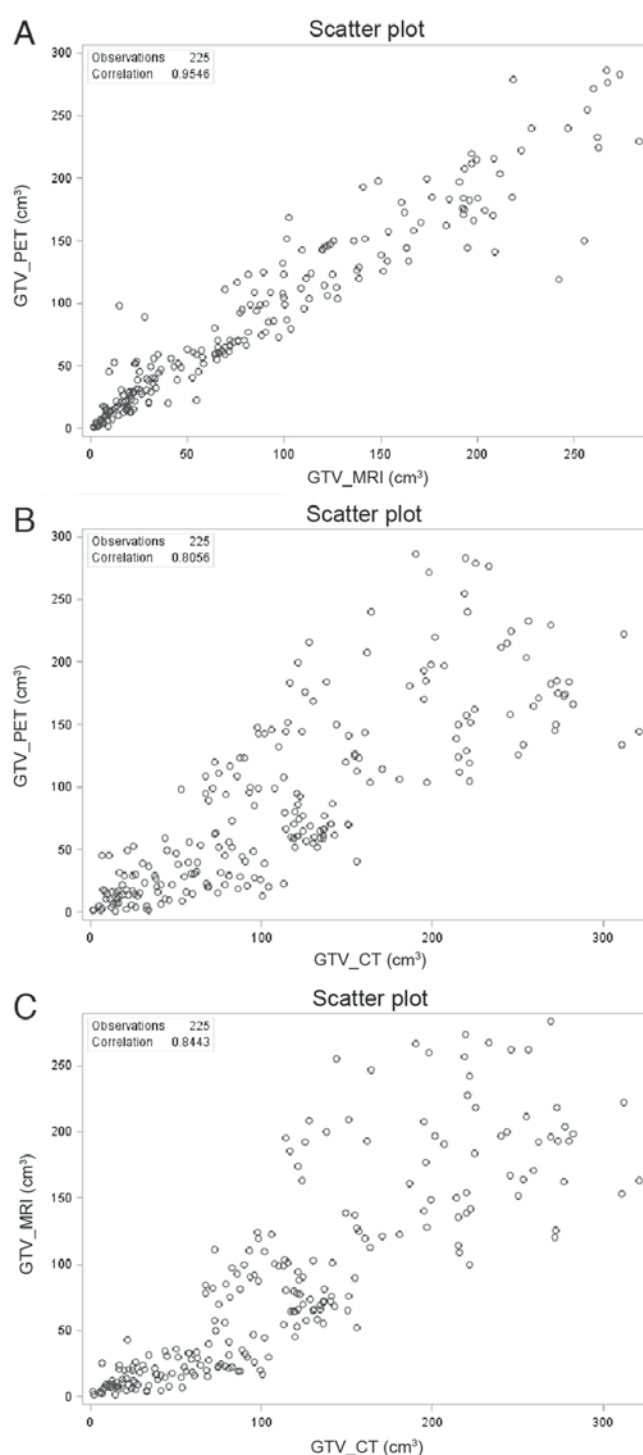


Figure 2. Scatter plots of GTV measurements using CT, PET/CT and DW-MRI procedures. (A) Pairwise comparison between GTV_{MRI} and GTV_{PET} . (B) Pairwise comparison between GTV_{CT} and GTV_{PET} . (C) Pairwise comparison between GTV_{CT} and GTV_{MRI} . CT, computed tomography; PET, positron emission tomography; DW-MRI, diffusion-weighted magnetic resonance imaging; GTV, gross target volume.

Discussion

It is not uncommon that central lung cancer occurs with obstructive pulmonary atelectasis (20). Conceivably, accompanying atelectasis often obscures the accuracy of a central lung cancer diagnosis (21,22). The present study observed the confounding effect of atelectasis on delineating the lung

cancer (Fig. 1). Distinguishing central lung cancer from obstructive pulmonary atelectasis is critical in clinical staging and target delineation. An incorrect delineation of GTV could lead to decreased survival rates and increased side effects from radiotherapy (2).

A hallmark feature of an intensified CT scan is the superior spatial resolution of lung cancer. However, it is fairly challenging to distinguish lung cancer from pulmonary atelectasis due to inflammation and effusion (23,24). Relatively low soft-tissue contrast prevents CT from providing precise information on the GTV extension in the vast majority of tissues. It has been widely recognized that this limitation of CT has led to inter- and intra-observer variations in GTV delineation in lung cancer (25,26).

PET/CT is an extremely important innovation in lung cancer imaging, which is capable of explicitly differentiating between the normal tissues and cancer tissues. PET/CT has been proven to significantly enhance the accuracy of conventional imaging in estimating the full spectrum of a number of tumors, including lung cancer (27). Numerous studies have reported that PET/CT has an influential contribution on the radiotherapy of lung cancer patients (24,28), as it can easily distinguish the central lung cancer from atelectasis.

MRI has been rapidly and widely deployed in radiotherapy planning due to its exquisite high contrast, high resolution soft tissue visualization and functional imaging modalities, which outperform PET/CT in terms of tumor visualization capability (26). It has been suggested that DWI combined with MRI can provide important information in differentiating lung cancer and atelectasis (20).

In the present study, the mean GTV measurements based on DW-MRI were significantly smaller than the mean GTV based on CT, and these were indistinguishable from the mean GTV based on PET/CT (Table I), which is consistent with previous studies (17,29-32). DW-MRI is an excellent technique in differentiating the central lung cancer from obstructive pulmonary atelectasis and can provide accurate information for target delineation. In addition, it was shown that the distance between the centroids of CT and PET images was similar to that between the centroids of MRI and PET images, suggesting that the difference in GTVs using different procedures is largely attributable to the shape of the target delineation, but not the location of the target centers. Notably, delineation based on DW-MRI achieves similar clinical results with PET/CT, while it can avoid the radiation for patients during the PET/CT scan, as well as lowering the treatment cost.

The large variation among radiotherapists, and even for the same doctor over a period of time, is not uncommon in the target delineation (33,34). The methodology defects and poor differentiation between normal tissues and tumors account for the inter-observer variations (26). In the present study, the variation based on DW-MRI was noticeably lower than that based on PET/CT and CT. Overall, DW-MRI is much more robust and reproducible compared with CT and PET/CT procedures. Due to relatively poor soft-tissue contrast of the CT image, it can only provide limited information for target delineation. GTV based on CT varied enormously between radiotherapists, although it was prophetically suggested that the variation could be decreased via rigid training. By contrast,

the variations in estimating GTV using DW-MRI and PET/CT are much smaller and more stable among radiotherapists than that in CT. In other words, compared with PET/CT, DW-MRI has the highest target delineation precision and lowest variation to the same extent, thus significantly decreasing the toxicity of unintentional dosing and impairment of adjacent tissues during the radiotherapy. DW-MRI is highly recommended as it radiation-free and cost-effective, which is of particular benefit in developing countries.

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