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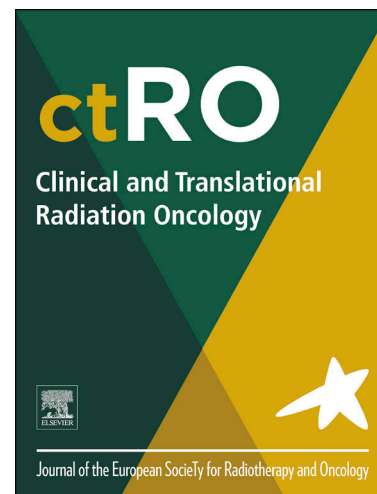
A Review of the Role of MRI in Diagnosis and Treatment of Early Stage Lung Cancer

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Abstract

   Despite magnetic resonance imaging (MRI) being a mainstay in the oncologic care for many disease sites, it has not routinely been used in early lung cancer diagnosis, staging, and treatment. While MRI provides improved soft tissue contrast compared to computed tomography (CT), an advantage in multiple organs, the physical properties of the lungs and mediastinum create unique challenges for lung MRI. Although multi-detector CT remains the gold standard for lung imaging, advances in MRI technology have led to its increased clinical relevance in evaluating early stage lung cancer. Even though positron emission tomography is used more frequently in this context, functional MR imaging, including diffusion-weighted MRI and dynamic contrast-enhanced MRI, are emerging as useful modalities for both diagnosis and evaluation of treatment response for lung cancer. In parallel with these advances, the development of combined MRI and linear accelerator devices (MR-linacs), has spurred the integration of MRI into radiation treatment delivery in the form of MR-guided radiotherapy (MRgRT). Despite challenges for MRgRT in early stage lung cancer radiotherapy, early data utilizing MR-linacs shows potential for the treatment of early lung cancer. In both diagnosis and treatment, MRI is a promising modality for imaging early lung cancer.

1. Introduction

Despite many recent advances in the diagnosis and treatment of lung cancer, it remains the most common cause of cancer death worldwide; accounting for 18% of cancer-related deaths [1]. Much work has been done to diagnose these malignancies early due to the wide discrepancy in survival between early stage and locally advanced lung cancer [2]. Low dose computed tomography (CT) is currently the standard of care in screening patients at high risk for lung cancer. Such programs have been implemented with moderate success, leading to adoption in the United States [3] and further consideration in Europe [4]. In addition to the refinement of CT technology, the acquisition of functional information in the form of positron emission tomography (PET) has become an indispensable adjunct to complete staging and diagnosis [5]. Despite the fact that magnetic resonance imaging (MRI) has become a mainstay in the imaging of other disease sites [6], MRI has not routinely been used as a part of the workflow in early lung cancer diagnosis, staging, treatment, or surveillance. In this paper, we will discuss the potential role of MRI in the diagnosis and treatment of early stage lung cancer.

2. Barriers to lung MRI

While in other body sites MRI provides excellent soft tissue contrast not achievable with computed tomography (CT), the physical properties of the lungs and mediastinum create unique challenges in the use of diagnostic MRI (Figure 1). First, the low tissue density and high air content of the lung drastically reduces the signal to noise ratio (SNR) because the MR signal is directly proportional to proton density [7]. Using a higher magnetic field (B_0) can theoretically improve SNR, but unfortunately it would exacerbate susceptibility artifacts due to magnetic field

inhomogeneities caused by omnipresent microscopic tissue-air interfaces smaller than standard voxel sizes [7].

In addition, motion from both the cardiac and respiratory cycles may cause ghosting artifacts on the MR images. Respiratory-induced image degradation can be ameliorated by breath-holding, however limiting acquisition time to encompass a breath-hold may compromise other parameters, such as spatial resolution. In addition, patients with lung cancer may have other comorbidities making breath-hold difficult. To provide adequate image quality, certain sequences require a longer acquisition time than would be practical for a patient to hold their breath (around 20s). The alternative of splitting such sequences into multiple breath-holds is also fraught with the addition of more artifacts from the need to combine potentially mismatching images from non-reproducible breath-holds [8]. Breath-hold reproducibility can be improved by using respiratory monitoring, patient coaching to achieve a displayed respiratory level, or active breathing control devices which can induce breath-holds at predetermined respiratory volumes. However, these devices may also require modifications for MR application [9]. Respiratory gating using bellows systems or navigator techniques can reduce breathing artifacts, while electrocardiogram (ECG) or pulse oximeter gating can reduce artifacts due to cardiac motion. Nevertheless, application of these techniques may substantially increase patient scanning time [10]. In addition to the physical limitations of MRI, many competing protocols exist without standardization, complicating both the acquisition and interpretation of lung MRIs [11]. Some patients may also not be eligible for MRIs due to the presence of non-compatible implants. Lastly, many patients also have difficulties with extended breath holds, the length of studies, and claustrophobia.

Because MRI utilizing lower static magnetic field strength presents theoretical advantages to lung imaging by reducing susceptibility artifacts despite theoretical reductions in SNR, some work has been done investigating lung MRI at lower magnetic fields [12]. With the evolution of image correction algorithms, open low-field MRIs have been shown to provide adequate images for radiation treatment planning in multiple disease sites, including in lung [13].

3. Advances in MRI technology

Despite the above barriers, MRI presents advantages over the current regimen of CT and PET/CT, including the ability to forgo the radioactive contrast agent administration necessary in PET/CT [14]. Advances in MRI technology have allowed for its increased clinical relevance in evaluating lung cancer. For example, turbo-spin echo (TSE) is a fast MRI sequence which is robust to susceptibility differences between air and lung tissues and allows for equivalent malignant nodule detection rate to MDCT [15]. A Half-Fourier single-shot TSE (HASTE) sequence, which improves scan times further by taking advantage of certain "mirror-image" properties of the raw MR data (k-space) reduces the influence of respiratory and cardiac motion artifact [16]. Although short-tau inversion recovery (STIR) sequences with TSE (turbo STIR) for fat signal suppression is typically used for better delineation of soft tissue and local tumor spread, it can be employed to enhance contrast for pulmonary lesions without unreasonably prolonging breath hold times. However, these sequences remain susceptible to flow artifact from significant blood flow throughout the lungs, which can additionally be mitigated by the use of black-blood sequences by using a double recovery sequence, especially when cardiac gating is inadequate [17]. Aside from TSE-based sequences, other groups have shown the viability of volumetric interpolated breath-hold examinations (VIBE), which is a radio-frequency spoiled 3D

gradient recall echo (GRE) sequences. Its application has presented less motion artifacts, but may miss smaller lesions [18].

Further MR sequences (e.g., ultra-short echo time (UTE) and balanced steady-state free precession (bSSFP)) address the challenge resulting from the very short T2* time of the lung parenchyma (1-2ms at 1.5T). UTE uses very short echo times, radial sampling of k-space and techniques to increase signals of tissues with very short T2/T2* times (e.g., lung parenchyma, cortical bone) for better visualization. bSSFP uses extremely short repetition times that prevent relaxation of magnetization, generating an almost constant "steady-state" signal, and "balanced" gradients which cause no net dephasing over a repetition time TR [19].

In a recent review, Biederer et al. explored MR data, including UTE and bSSFP, outlining the diagnostic challenges of using MRI for detection, primary or otherwise, of small malignant lesions [20]. The authors discussed potential scenarios in which MRI could play a role moving forward, from no contribution to an adjunct or replacement to CT, depending on further validation of diagnostic quality and cost. They ultimately concluded that while technical feasibility has been achieved, validation of better patient outcomes with MRI are still lacking [20]. Despite these limitations, for lesions near the chest wall, vertebral body, or near the mediastinum, MRI can provide more accurate staging due to its improved soft tissue contrast compared to CT and ability to identify local invasion of adjacent structures, including the mediastinum, ribs, nerve roots, pleura, which provide crucial information for staging [21] (Figure 2).

Lastly, other sequences and encoding algorithms may allow for free breathing image acquisition by overcoming image quality sensitivity to motion. In contrast to standard Cartesian

k-space acquisition, radial and spiral acquisitions can reduce ghosting and motion artifacts, at the cost of introducing streak artifacts and increasing the acquisition time. Kumar et al. demonstrated that such a sequence (StarVIBE) is feasible with free breathing and intermediate anatomic assessment between compliant breath hold VIBE and noncompliant breath hold VIBE [22]. StarVIBE was also successful in outperforming standard DCE for functional assessments in the setting of motion [22]. Although a full analysis of the utility of whole-body MRI to assess potential metastatic disease is beyond the scope of this review, significant motion artifacts have traditionally limited utility [23]. However, emerging data suggest the technological improvements noted above have improved the viability of whole-body MRI for initial staging [24].

4. Lung functional imaging

Drawing from data in other disease sites, functional MRI sequences are being applied to the lung. One example, diffusion-weighted imaging (DWI), detects restricted diffusion of water as signal attenuation, enabling hypercellular areas (tumors) to be distinguished from areas of higher diffusivity. In DWI, diffusion is quantified as an apparent diffusion coefficient (ADC) [25]. In lung cancer, DWI has been shown to more effectively delineate gross tumor volumes within atelectatic lung than CT or PET/CT, a commonly difficult clinical scenario [26]. DWI can also provide additional information over CT, including intratumor vasculature, lymph node involvement, and effusions (Figure 3). However, DWI may suffer from geometric distortions, mainly induced by susceptibility differences between air and tissue interfaces in the lungs, which may require additional technical solutions [27]. Aside from DWI, dynamic contrast-enhanced MRI (DCE) also provides functional information in the form of blood flow and vascular

permeability, further elucidating patterns of tumor vascularity [28]. This has been successfully

investigated in other disease sites, including the prostate (differentiating between malignant

tissue and benign hyperplastic tissue) [29] and the brain (differentiating between primary brain

malignancies and multiple metastatic histologies) [30,31]. In the lung, its utility was initially

limited by degradation in image quality from respiratory motion [32]. However, within the lung,

both the transfer constant derived from DCE-MRI and the apparent diffusion coefficient derived

from the intravoxel incoherent motion (IVIM) DWI model have shown the potential to

differentiate lung cancers from solitary pulmonary nodules [33], but this is not currently in

clinical use. DCE-MRI has also been compared head-to-head with PET-CT and found to have

correlations between the median absolute deviation (MAD) of peak enhancement and

standardized uptake value (SUV) for lung cancer [34]. Both DWI and DCE do suffer from

suboptimal spatial resolution, especially in the context of respiratory and cardiac motion,

although respiratory/cardiac gating and faster temporal acquisition helps mitigate this uncertainty

[27,32].

Taking functional imaging one step further, some investigators have combined PET with

MRI in an attempt to take the best of both worlds. Unlike PET/CT image acquisition which must

be done sequentially, PET/MR can be done simultaneously, improving co-localization of

imaging data; combined with improved motion correction algorithms (both for PET correction

using simultaneous MR data, and MR correction using other algorithms), PET/MR has the

potential to improve detection of small pulmonary nodules and to better delineate regions of

disease [35]. In a prospective comparison between PET/CT and PET/MR, the latter successfully

staged lung cancer without a statistically significant difference in accuracy from the former [36].

Another prospective study showed equal efficacy in determinations of resectability of lung

cancer between PET/CT and PET/MRI [37]. Motion correction algorithms are still dependent on reproducible respiratory motion, which may not be very consistent [35].

Newer developments in MRI technology, including use of hyperpolarized gases and oxygen-enhancement, allow for enhanced contrast and better characterization of function, including regional ventilation, which can reduce radiation toxicity by reducing the volume of functional lung that is being irradiated. Nonetheless, hyperpolarized gases like ^{129}Xe and ^{3}He are quite expensive, the setup is more technically demanding and oxygen-enhanced sequences are both more complex to deliver and come with increased scan times, potentially causing misregistration of images from different points in the respiratory cycle [38]. Further non-contrast enhanced techniques for assessing lung perfusion and ventilation such as arterial spin labeling (ASL) and Fourier decomposition (FD) method can be affected by respiratory motion and low signal [39]. Knowing regional differences in ventilation can aid in radiation planning to avoid dose to relatively high functioning areas in patients with reduced lung function [40].

Aside from pretreatment staging assessments, MRI may also be useful in predicting responses to treatment. In multiple other cancers, DWI has been investigated as an early predictor of tumor response to radiotherapy [41,42]. In one DWI study in lung cancers >2cm, Weller et al demonstrated satisfactory test-retest repeatability and reproducibility of ADC measurements in lung tumor during free breathing and suggest that a change in ADC > 21.9% will reflect treatment-related change [43]. A prospective study by Huang et al. examined patients prior to and after stereotactic body radiation therapy (SBRT) with DCE-MRI/PET and was able to show that changes in MR parameters, including those that are proxies for vascularity and blood flow, can provide early predictions for treatment response [44]. Others have demonstrated the utility of DCE in detecting radiation-induced lung injury [45], while both preclinical [46] and

clinical studies [47] using MRI in conjunction with hyperpolarized gases may also help identify this toxicity.

While most data examining the use of MRI in lung cancer diagnosis and treatment response has been retrospective, technical improvements in lung MRI may make this a promising technology for early lung cancer.

5. MRI in radiation treatment

In parallel with the emergence of MRI technologies and techniques for lung imaging, the superior soft tissue contrast and the ability to take advantage of real-time imaging has spurred the integration of MRI into radiation treatment (RT) delivery in the form of devices combining MRI and linear accelerators (MR-linacs). Two main MR-linac commercial systems have emerged: the Elekta MR-linac (Stockholm, Sweden) with a 1.5T magnet [48] and the ViewRay MRIdian (Oakwood Village, OH) with a 0.35T magnet [49]. The former was successfully used in prototype form in seven centers [50,51] and received FDA 510(k) approval in December 2018 with 39 units ordered to date [52]. The latter was FDA-approved in 2017 and is now in use in 18 centers in the United States and around the world [53]. Washington University in St. Louis has reported on their experience utilizing an MR-linac to optimize tumor gating with cine-MRI, particularly important for tumors with significant motion, such as lung cancer [54] (Figure 4). The same center has used an MR-linac for online adaptive radiotherapy, which allows for the radiation plan to account for day-to-day changes in anatomy and changes in target [55].

The development of the MR-linac is particularly relevant to early stage lung cancer because stereotactic body radiation therapy (SBRT) has become a mainstay of therapy for this disease. SBRT involves a high dose per fraction, which may lead to significant normal tissue

toxicities and/or higher rates of locoregional recurrence with inappropriate targeting. SBRT for the treatment of early lung cancer requires image-guidance, in the form of cone-beam CT (CBCT), or in the form of kV x-ray on Cyberknife (Accuray, Sunnyvale, California, USA). MR-linac adds an alternative image-guidance modality: MRI. Challenges for MR-guided SBRT include Lorentz forces, MRI geometric distortion, MRI to radiation isocenter uncertainty, multi-leaf collimator (MLC) position error, and uncertainties with voxel size and/or tracking. In the lung, MR-guided SBRT is faced with the additional challenges presented by lung anatomy and physiology (Figure 1).

Despite these challenges, MR-linac offers advantages to SBRT delivered with most standard linacs including the ability for online adaptive replanning and real-time image guidance. Although this capability is lacking in most standard linacs, technologies like ETHOS (Varian, Palo Alto, California, USA) also allows for similar adaptive replanning. In a simulation study of 10 patients with oligometastatic or primary unresectable disease in the central thorax or non-liver abdomen planned to receive SBRT, MRI-based adaptive planning utilizing anatomy of the day allowed for increased dose in 11 of 15 fractions; in 8 of those fractions, replanning the radiation treatment each day actually decreased dose to organs at risk (esophagus, heart, trachea, brachial plexus, total lung, and spinal cord) [56]. By using the real time visualization and online adaptive capability of MR-guided treatments to maintain planning target volume (PTV) coverage while reducing organ-at-risk (OAR) doses, the MR-linac has the potential to reduce toxicities related to the treatment of early stage lung cancer [57-59].

Initial data shows promise for use of MR-linac in early stage lung cancer. In a Phase I prospective trial of MR-guided SBRT in the treatment of oligometastatic or unresectable ultracentral thoracic tumors, 5 patients underwent SBRT to a planned dose of 50 Gy in 5

fractions and 10 out of 25 fractions were adapted. Despite not meeting the planned endpoint of feasibility, the investigators were able to improve target coverage over non-adaptive SBRT plans while correcting 100% of OAR constraint violations. No grade 3-5 toxicities occurred within the first 6 months. However, one grade 3 esophageal stricture occurred at 15 months, and one grade 4 pericardial effusion could not be ruled out as possibly related to radiation at 8 months. Lastly, local progression free survival was 100% up to 6 months and 80% at 12 months with an overall survival of 100% up to 6 months and 60% at 12 months [60].

MR-guided RT is not without challenges. Adding a magnetic field in the setting of radiation treatment creates dosimetric challenges with secondary electrons with an asymmetric penumbra and surface hot spots caused by Lorentz forces [61]. These distortions are increased in the setting of higher magnetic fields, small air cavities, and for tissue-air interfaces (critical for lung), but become less affected by field strength for large air cavities and large fields [62]. Looking specifically at dosimetric effects in the lung, the presence of a longitudinal magnetic field as opposed to a transverse field, radial spread of secondary electrons outside of the photon field were significantly minimized in low density tissues with better dose to the planning target volume (PTV) and better dose homogeneity [63]. Even within a transverse magnetic field up to 1.5T, these changes in dose distributions can be adequately managed by intensity modulated radiation therapy (IMRT) and volumetric modulated arc therapy (VMAT) planning algorithms taking into account the Lorentz forces and have been shown to reduce an initial change of 15% in the max dose (D_{max}) down to only 1.6% [64]. In another study of an inline magnetic field, dose enhancement was demonstrated at the target for smaller lesions (up to 23% for at the PTV for gross tumor volumes (GTV) of <1 cm^3), leading to potentially more conformal treatments compared to radiotherapy systems without a magnetic field [65]. In the locally advanced setting,

Bainbridge et al. demonstrated a negating of increased skin dose from the Lorentz force by reducing the PTV margin and also were able to isotoxically dose-escalate in the reduced PTV MR-linac-based plan [66]. In a study of lung SBRT patients in a 1.5T magnetic field, investigators were able to demonstrate an increased skin dose of only 1.4 Gy; with the addition of tumor tracking, they were also able to reduce the mean lung dose by 0.3 Gy without compromising dose to the target [67].

Additional studies have been conducted with Viewray's previous system with three rotating ^{60}Co sources instead of a linear accelerator (linac), finding similar dosimetry and conformality to traditional linac-based IMRT and VMAT plans. In one comparison to Pinnacle-based IMRT planning, the MRIdian plans demonstrated an average of 4% increase in heterogeneity and differences in conformity of <1-3% when compared to linac-based plans; the latter also produced better organ at risk (OAR) sparing those with mean doses <20 Gy, but similar sparing for those with mean doses >20 Gy [68].

Additional studies have found acceptable results with SBRT planning in addition to conventional planning. When examining SBRT in the lung, Park at al. demonstrated no considerable differences between OAR doses, but some inferiority of ^{60}Co plans when compared to VMAT plans with respect to conformity for PTV volumes <10cc, yet still within acceptable levels [69]. Some of the first clinical experiences with MR-guided SBRT have recently been published and indicate appropriate targeting and tracking of tumors that leads to low toxicity and appropriate local control [70]. Wojcieszynski et al. conducted a dosimetric comparison between MRIdian with three ^{60}Co heads and traditional 4D-CT/VMAT plans in 10 patients with early stage NSCLC getting SBRT. No significant differences were found in OAR constraints and target coverage between the two plans, but the MRIdian plans had a lesser conformity index,

attributed to the increased penumbrae of the cobalt sources and the larger multi-leaf collimators

(MLCs). Despite these shortcomings, all plans were deemed to be clinically acceptable [71].

In addition to the previously discussed soft tissue contrast advantages, both MR-linacs

also allow for real time tracking of tumor volumes and normal tissues for bona fide adaptive

treatment. Standard linear accelerators utilizing on-board cone beam CT (CBCT) can account for

inter-fractional target motion, but not intra-fractional motion. Additionally, unlike MRI, CBCTs

involve additional exposure to ionizing radiation to normal tissues not accounted for in the

planning process. In two different studies, additional radiation dose has been measured up to 3.5

cGy, 8.3 cGy, and 9.75 cGy for each CBCT [72,73].

Real-time tumor tracking has been validated in multiple studies. Cerviño et al.

demonstrated a mean tracking error of 0.6mm with free breathing cine-MRI, but their model

deteriorated with irregular breathing [74]. More recent studies in tracking have demonstrated

more favorable outcomes. Al-Ward et al. were able to reduce mean doses to the heart (3.0 Gy)

and lung (1.9 Gy), while lowering the lung V12.5 Gy by 300cc with 4D MRI tracking when

compared to a traditional internal target volume approach (ITV) [75]. In another study of SBRT

to lung, pancreas, and adrenal tumors with MR-guided breath-hold and visual feedback, mean

GTV geometric areas encompassed during beam-on times was 94-95%, depending on disease

site [76]. Overall, the goal is adaptive radiotherapy, in particular dose escalation and isotoxic

treatment regimens to optimize tumor control. However, onboard MR images are limited to 2D

cine and can only currently track in a single plane at a time. MR images also lack electron

density and attenuation coefficient data, unlike CTs, making dose determinations difficult,

especially in the lung [77]. To address these issues, studies are ongoing, including one by Wang

et al. which evaluated the feasibility of using synthetic CT images from MRI scans for lung

cancer radiation treatment planning, demonstrating dose differences less than 1% for both target coverage and OARs [78]. Despite these challenges, attenuation correction modeling has been improving to enable fully MR-based radiation planning [79].

MR-guided adaptive radiotherapy brings real-time tumor tracking to early stage lung cancer radiotherapy. In addition, due to its improved soft tissue contrast, MRI holds promise for the treatment of ultracentral early lung cancers with MR-guided SBRT.

6. Conclusion

As MRI is making inroads into functional assessment, response to treatment and treatment guidance for a variety of cancers, including brain [80] and prostate [81], MRI use in lung cancer has lagged behind because of inherent barriers arising from the physics of the lung itself. However, with new MR sequences and the application of functional MRI, utility for lung MRI is emerging in the early detection, staging, and surveillance of early stage lung cancer. One major limitation for lung MRI when compared with MDCT remains the detection of subcentimeter nodules. In addition, when applied to radiation treatment, MRI provides excellent soft tissue contrast for tumor and normal tissue delineation and the opportunity for true real-time adaptive therapy. Current data on MR-guided SBRT in early lung cancer are limited, but early results are promising, opening the door for dose escalation, improved normal tissue visualization and normal tissue sparing, improved motion management, and potentially improved outcomes for patients with early stage lung cancer treated with radiotherapy.

Figure Legends

Figure 1: Overview of challenges and advantages for the use of lung MRI in early lung cancer diagnosis and radiotherapy. CT= computed tomography; PET= positron-emission tomography; MRI= magnetic resonance imaging.

Figure 2: Lung tumor delineation and treatment with MR-guided radiotherapy. A TRUFI sequence obtained on the MRIdian system (Mountain View, CA) for a central non-small cell lung cancer (NSCLC). MR-guided radiotherapy allows for daily adaptive therapy to decrease dose to nearby organs at risk (Aorta-Yellow; Esophagus-Blue; Spinal Cord-Green) while maintaining dose to the tumor (GTV (Gross Tumor Volume)-Orange). This patient was treated with stereotactic body radiotherapy (SBRT) 60 Gy in 8 fractions and has no evidence of progression of disease at 6 months.

Figure 3: Comparison between CT (a) and diffusion-weighted MR (b) images of the lungs (b-value = 200 smm^{-2}). DWI detected hypointense intratumor vasculature (red arrow) and hyperintense small volume pleural effusion (green arrow), which were not discernible on CT. From the CT images it is unclear if the observed mediastinal lymph node was affected. Nevertheless, its increased signal intensity on DWI (yellow arrow) suggests its involvement. (Adapted from Kaza E. et al. Lung tumor radiotherapy treatment response assessment using Active Breathing Coordinated (ABC) Diffusion-Weighted Magnetic Resonance Imaging. Poster presentation at ISMRM 2016.)

Figure 4: MRI CINE and gating for MR-guided stereotactic body radiotherapy. A MRI CINE via the MRIdian System (Mountain View, CA) of a patient undergoing stereotactic body radiotherapy (SBRT) to a tumor in the right lower lobe. The CINE runs at 4 frames/second and the tumor (green) is tracked by the MRIdian system. Treatment is not triggered until the tumor moves into the gating structure (red). We typically set the threshold of 95% of the tumor within the gating structure to activate treatment. There may be significant motion of lower lobe tumors when comparing expiration (A) to mid-breath (B) to inspiration (C). We perform the majority of treatments with deep inspiratory breath hold secondary to patient comfort and reproducibility.

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Highlights

- Better MRI sequences and technology increase its utility in early stage lung cancer
- MRI can also provide functional data to aid in diagnosis and response evaluation
- MRI-guidance can improve radiotherapy in lung cancer despite physical challenges
- Real-time tracking and better soft tissue contrast also facilitate adaptive therapy