MRI-Guided Adaptive Lung Cancer Radiotherapy

**Abstract**

**Background:** Many methods are currently used to fulfill the goal of radiation therapy to deliver sufficient dose to tumors while sparing surrounding tissues. Due to respiratory motion, lung tumors are non-static, making this goal more difficult. The use of surrogates and internal fiducial markers are currently used to track lung tumor motion during treatment, however they offer room for improvement.

**Objectives:** To research new technology used in the hybrid MR-linear accelerator for treating lung tumors with adaptive radiation therapy in order to determine its effectiveness in more precisely targeting the tumor and avoiding surrounding tissues.

**Methods:** A literature review was conducted to find information on adaptive radiation therapy for lung cancer using the MR-linac. Research was conducted through the use of online databases, print journals and textbooks.

**Results:** Research demonstrated that many algorithms have been tested and approved for the clinical use of the MR-linac in adaptive lung cancer radiotherapy. Capabilities of the MR-linac in the treatment of lung cancer were found to be real-time tumor tracking, online plan adaptation, interfraction changes, and adjustments for magnetic field dose effects. Disadvantages and further improvements were also discovered.

**Conclusions:** The MR-linac has been found to be a clinically acceptable treatment machine for lung cancer radiotherapy due to its unique capabilities which allow it to track the tumor motion and deliver more precise treatment. As these accelerators begin to be implemented in more radiation oncology departments, it is important for practicing radiation therapists to understand the technology in order to operate it safely and effectively.

**Introduction**

 One of the main goals in radiation therapy is to deliver ample dose to the tumor while sparing dose to the surrounding healthy tissues and organs at risk. This task is more complicated for lung tumors not only because the tumor position is not constant due to the patient’s respiration, but also because the position of surrounding healthy organs is not constant. If tumor motion within the respiratory cycle is not accounted for during treatment, the tumor is likely to be under dosed while surrounding tissue is likely to be overdosed. Current internal target volume (ITV) approaches to treat non-static lung tumors also have the potential to under dose the target and overdose surrounding tissues if the actual motion of the tumor does not fit the original ITV plan.1-4 Interfractional changes, such as differences in the tumor’s size or shape in response to radiation, can also pose challenges for precise dose delivery.3,5-6

 Current practice on a conventional computed tomography (CT) linac utilizes different means of tumor tracking that are sufficient in delivering the correct dose to the tumor and sparing normal tissue, but offer room for improvement.5,7 A plastic box taped to the patient’s stomach is often used to track the patient’s breathing and correlate to tumor position based off the four-dimensional (4D) gated CT scan taken during simulation.5,7 These surrogates are not always completely accurate in placement of the actual tumor and they do not always keep track of the current position of surrounding organs at risk.5,7 Internal fiducial markers, which are placed directly into the tumor and therefore can be tracked throughout treatment, are another method currently used to track tumor motion.5,7 However, initial placement of the fiducial markers must be accurate, this method can be costly, and it poses surgical risk to the patient.5,7 Many kilovoltage (KV) images must be taken throughout treatment to monitor motion as well, which delivers excess dose.5,7 The introduction of the new hybrid MR-linac offers promising solutions to each of these downfalls in current practice for lung cancer radiotherapy through the option of real-time adaptive radiotherapy. As the magnetic resonance (MR)-linac becomes more widely used, it is important for practicing radiation therapists to understand its capabilities in order to use it to their advantage to treat patients safely and effectively.

**Methods**

 A literature review was conducted to find information on the use of magnetic resonance imaging (MRI) in the radiation treatment of lung cancer. Research was completed using different search engines such as PubMed and MEDLINE, Journal articles, and textbooks. In each database, different combinations of search terms were used including “MR linac”, “adaptive radiation therapy”, “lung cancer”, “radiation therapy”, “magnetic resonance imaging”, “lung cancer radiotherapy”, “tumor tracking”, and “plan adaptation”. Searches were refined to “English-language articles” published “within the last five years” to be sure recent, relevant information was found. Journals including “Radiation Therapist” and “PRO Journal” were reviewed for articles discussing the MR linac as well as the Principles and Practice of Radiation Therapy Fourth Edition textbook.

**Review of Literature**

 **Improvements made by the MR-linac**

 The use of MRI offers many advantages for lung cancer adaptive radiotherapy in terms of real-time tumor tracking to monitor intrafraction motion and create plan adaptations, along with correcting for interfraction motion.1,3,5-6,8-9,11 Adaptive radiotherapy is a term that describes any technique that allows for the plan to be altered throughout treatment to deliver precise dose to the patient-specific anatomy.1 Due to the superior soft tissue contrast of the MR-linac, delineation between tumor and normal tissues is improved, as well as the ability to distinguish between tumors and other conditions such as atelectasis or pleural effusion.1-2,5-10 With greater soft tissue contrast, the tumor and surrounding tissues can also be better visualized in real-time, aiding in intrafraction plan adaptations.1-2,5-10 The use of MRI also saves the patient from additional dose exposure as there is no use of ionizing radiation in the imaging process.1,5-6,9 This is important in the process of real-time tumor tracking where images are constantly being taken throughout treatment which would add substantial dose through the use of megavoltage (MV) or KV imaging.

**Real-time tumor tracking**

The challenge of lung tumor motion with respiration is addressed through the capability of real-time tumor tracking and plan adaptation on the MR linac.5-6,8-9,11 Although many other forms of tumor tracking have been sufficient and improved dose delivery in the past, the use of multi-leaf collimator (MLC) tracking in real-time has demonstrated superiority.5,9,11 Its ability to directly visualize the motion of the tumor and deliver radiation dose to the tumor only, sets it apart from other methods.5,9,11 It is unrealistic to assume patients’ breathing patterns will be consistent to their planning CT, and respiratory gating adds substantial time onto treatment fractions and may not always be accurate to tumor position.5,9,11 The use of real-time MLC tracking eliminates these inconsistencies and uncertainties and allows for individualization during each treatment fraction.5,9,11

A study completed by Kumar et al8 demonstrated that tumor tracking with the MR-linac can be accurately completed with a completely free-breathing protocol. This is advantageous as breath-hold plans can be uncomfortable, especially for patients suffering lung cancer who have restricted lung capacity, and may then be unreliable.8 A non-invasive, free-breathing process is utilized in MLC tumor tracking where an algorithm can monitor MRI images and collaborate with software that can control each individual MLC leaf during tumor motion.5,9,11 The shape of the MLC leaves constantly change in real-time as instructed by the algorithm to match the motion of the tumor through different phases of respiration.5,9,11 This real-time tracking can also be used to visualize the position of surrounding organs at risk and make sure they are exposed as little as possible to the delivered dose.5,9 This process allows the patient to be relaxed throughout treatment and for dose-delivery to be more accurate to the tumor each day.5,8-9,11

Cervino et al7 researched different algorithms for tumor tracking with MRI. The study concluded that a template matching (TM) algorithm could accurately track lung tumor motion in real-time for both regular and irregular breathing patterns.7 This algorithm defines a template based off of a chosen region of interest encompassing only the target volume that is shown on the first image of the series.7 The algorithm then compares the template created on the first image to the following image and shifts the focus area to the greatest point of correlation between the two images.7 This pattern is repeated throughout each and every image of the series in order for the template to have maximum alignment to the tumor volume at all times.7

 Surrogate tracking of the diaphragm was included, meaning that the motion of the diaphragm with respiration was measured as a representation of the tumor motion.7 This surrogate tracking was included in this study to compare accuracy to the TM algorithm as it measures tumor motion directly.7 Cervino et al7 found comparable results with and without surrogate tracking of the diaphragm, demonstrating reliability of the TM system. It is important that the TM system is able to accurately track real-time lung tumor motion with both regular and irregular breathing because it is recognized that patient’s breathing will rarely be a regular pattern. Lung tumor motion is able to be reliably tracked in real-time with the use of the TM algorithm, and this is a crucial aspect in the accuracy of making online plan adaptations.7

**Online plan adaptations**

 While monitoring tumor motion in real-time through the use of the TM algorithm and MLC tracking, the MR-linac provides the ability to implement adaptive radiation therapy by creating online plan adaptations to the anatomy of the day.1,3,5-8 It is advantageous to track the tumor in real-time and make plan adaptations to the location of the tumor at each moment in order to deliver the most precise treatment. With current practice of image-guided radiation therapy (IGRT), it is possible that the patient moves or internal anatomy changes between acquiring the image and the time of dose delivery. A rapid workflow is necessary to obtain images while tracking motion, examine contours, create a re-plan, complete quality assurance and dosimetry calculations, and deliver treatment while the patient is in position.1,5-6 The algorithms used on the MR-linac have demonstrated the ability to complete this workflow in less than 30 seconds, making this adaptive radiation therapy realistic.6

Kontaxis et al3 explains an intensity-modulated radiation therapy (IMRT) system called the adaptive sequencer (ASEQ). This system contains an algorithm, or a set of rules or process that is followed when completing computer calculations, which allows for intrafraction plan adaptation based off the position of the anatomy each day.3 The algorithm initially starts with a desired dose distribution that is input by staff.3 This desired distribution is ultimately achieved through many different segments of delivery.3 The sequencing algorithm repeats, and during each repetition, many beams are optimized to target the desired dose of that segment.3 These beams are analyzed, and the portion with the most ideal dose-delivery is selected for that segment of treatment.3 The dose delivered in each particular segment is calculated and subtracted from the total desired distribution.3 The dose from each previous section is used to form the target and dose for the succeeding segment.3 This loop is continuously repeated throughout each fraction with the ultimate goal being to reach similarity between the delivered dose and the prescribed dose for treatment.3

 In current practice for delivering IMRT treatments, couch shifts and rotations are applied in order to help align the anatomy from the daily image to the region of interest on the planning image.2 It is important to note that due to the bore shape on the MR-linac, couch shifts cannot be applied in all directions, which the algorithm must account for when computing plan adaptations.1-2,5 Software within the algorithm allows for shifts to be made within the plan itself to match the daily anatomy, rather than physically shifting the table.2 This capability is referred to as a virtual couch shift.2 Virtual couch shifts are completed during each analyzed and adapted segment of each fraction while keeping the same isocenter.2

 This method for completing treatment plans provides superiority when compared to current ITV approaches.1-4 An ITV plan encompasses the entire area of tumor motion demonstrated on the planning scan from the first slice to the last.3 The use of ITV approaches provides potential to underestimate total motion of the tumor and therefore result in geometric miss if the tumor moves outside of the planned volume.3-4 This approach also leads to greater dose exposure of surrounding healthy tissues as the treated volume must be larger, and limits dose escalation to the tumor in an attempt to avoid overdosing those surrounding structures.1-3 Using online adaptive re-planning to the anatomy of the day, while tracking the motion of the tumor, allows for smaller planned target volumes (PTVs) and tighter margins.1-4 This leads to the ability to increase dose to the tumor without geometric miss and spare dose to surrounding healthy tissues, potentially improving clinical outcomes.1-4,9

**Accounting for interfraction changes**

While monitoring intrafractional changes and real-time tumor motion helps deliver precise and accurate dose, interfractional changes to the tumor can also be expected and must be accounted for. Imperfections in set up and inconsistency in daily IGRT alignment can create variability in tumor position.6 Tumor response to treatment may also change the size and/or shape of the tumor between fractions.6 With the MR-linac, these changes are monitored on the images taken during each fraction and accounted for in the planning algorithm as well.3,6 Daily plans are adjusted to fit the size, shape, and general position of the tumor each day prior to accounting for intrafractional changes such as motion due to respiration.3

As the algorithm continuously subtracts the delivered dose of each segment from the total for each individual fraction, it similarly monitors the delivered dose for each fraction as a whole.3 The total delivered dose for each fraction is compared to the total prescribed dose, and any missing or excess dose delivered in the previous fraction is applied to the following fraction.3 As this is completed, conformity between the total delivered dose and the total prescribed dose for treatment can be achieved.3 It is important to be sure that not only the daily delivered dose matches the daily prescribed dose, but that the total treatment dose matches the total prescribed dose as well. Surrounding organ at risk tolerances must be kept within limits throughout the treatment course as well as adequate dose delivery to the tumor.

Daily imaging with MRI further allows for lung tumor response to treatment and healthy tissue control to be monitored interfractionally.6 With positive response to treatment, tumors may shrink in size or change shape, and tumors that are not responding well may continue to grow. Due to the excellent soft-tissue contrast of MRI, the difference between tumor tissue and other tissues becomes more clear, which allows for changes to be better analyzed.1-2,5-11 Monitoring response daily can help the physician determine if any changes need to occur in terms of prescription or general treatment plan. In current practice, if a plan needs to be changed in the middle of a patient’s treatment scheme due to interfractional changes, often the patient must miss a day or two of treatment while a re-plan is completed. With the MR-linac’s ability for online plan adaptations, the physician is able to make changes to more accurately treat that individual tumor, and interfraction plan adaptations can be made immediately by the algorithm.3,6

 **Magnetic field dose effects**

As the potential to monitor real-time tumor motion and apply daily treatment plan adjustments along with interfraction corrections is attractive, one valid concern in the combination of MRI with a linear accelerator is how the magnetic field would affect dose delivery. Magnetic resonance imaging works by utilizing the hydrogen nucleus which is plentiful in the human body.6,10 Normally, the proton of each hydrogen nucleus is continuously spinning and axes between different protons are aligned aimlessly.6,10 When exposed to an MR machine, proton axes from each hydrogen atom in the body are aligned in the direction of the magnetic field produced by the machine.6,10 The patient is exposed to radiofrequency waves that cause the protons to misalign again and release signals which are detected by the MR machine.6,10 These signals are then measured and reconstructed to create images of the patient’s body.6,10

When combining MRI with a linear accelerator, the Lorentz force has an effect on the dose distribution.1,5,9,12 According to the Encyclopaedia Britannica,13 the Lorentz force is “the force exerted on a charged particle moving with velocity through an electric and magnetic field”, in this instance created by the MRI. When delivering radiation through a linear accelerator in combination with a magnetic field, dose changes can be caused by an effect which occurs as a result of the Lorentz force, coined the electron return effect.1,9,12 The primary photon beam is not affected, but the electron return effect causes secondary electrons to change direction, possibly being forced back into tissue and creating undesirable dose.1,5,9,12 This effect is particularly prominent at tissue-air interfaces, such as near the lung.12 The most significant dose changes have been found at these interfaces, which is concerning when treating a lung tumor.12 However, multiple studies2,5,9,12 have found that Monte Carlo-based algorithms are accurately able to model this effect in their dose calculations and account for these forces within their results.According to these studies,2,5,9,12 if the electron return effect is accounted for in the dose distribution and plan optimization, clinically acceptable plans are able to be delivered in the presence of a magnetic field.

Due to the way MR images are created, electron densities and attenuation coefficients are not provided as they are in CT images.2,5-6 Electron densities are used to calculate dose delivery; therefore, the absence of that information in MR is problematic.2,5-6 To gain electron density and attenuation coefficient information, pseudo-CT images can be created from the obtained MR image.2,5-6 This is completed by classifying different tissues in the MR image and giving them a pseudo-Hounsfield Unit value.2 The creation of an accurate pseudo-CT image is more challenging in the lung when compared to more homogeneous anatomy regions because both bone and lung demonstrate less MR signal than tissue.5 However, Wang et al14 demonstrated similar dosimetry between MR-based pseudo-CT images of the lung and actual CT images that is clinically acceptable for treatment.

**Disadvantages and further improvements**

 Some potential disadvantages to the use of the MR-linac and daily plan adaptation have been identified and may need to be further addressed to improve this form of treatment. The first drawback is that the MR-linac would not support patients with implanted objects such as pins, screws, clips, and pacemakers due to the strength of the magnetic field.6,10 Additionally, the transition may be costly as new nonferromagnetic immobilization devices and other tools may need to be purchased for use on this machine.6,10 Another potential drawback is that any changes to the treatment plan must be approved by the physician.5 With daily plan adaptations, physicians may be required to be present at the linear accelerator much more regularly in their already busy schedules.5 Lastly, as shrinking fields is a benefit to spare dose to surrounding tissues and allow for dose escalation at the site of the tumor, it may also reduce coverage of any nearby microscopic disease.1

**Conclusion**

When delivering radiation therapy to the lung, a highly mobile organ, uncertainty can be created in exact tumor position despite many past advancements and monitoring techniques. This literature review has demonstrated a new technique to deliver precise and accurate radiation dose to lung tumors through the use of the MR-linac. Daily adaptive radiation therapy is made possible on the MR-linac through its capability to track lung tumor motion in real-time, recognize interfraction changes, and create immediate online plan adaptations to match the anatomy of the day.1,3,5-6,9 Algorithms have been studied3,5,7 and have been demonstrated to produce clinically acceptable results in each of these areas. There are some disadvantages to this technology including: not all patients will qualify for its use, it is costly, physicians must be available more often, and its ability to shrink fields may miss microscopic disease.1,5-6,10 Further research should be completed on these areas for improvement.

This information is important for practicing radiation therapists because it can aid in their ability to deliver precise, detailed, accurate treatment to lung cancer patients. Radiation can be extremely detrimental when not delivered correctly, so technology that has the ability to adjust a plan in real-time based off of the current anatomy can support radiation therapists’ safe and accurate delivery of treatment. As the MR-linac is implemented into more radiation oncology departments, radiation therapists will need to be informed on how the technology works in order to operate it safely and effectively. Although there is always room for improvement, the development and capabilities of the MR-linac offers a promising future for effective adaptive radiation therapy for lung cancer.

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