Review Article

Image guidance in proton therapy for lung cancer

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Abstract: Proton therapy is a promising but challenging treatment modality for the management of lung cancer. The technical challenges are due to respiratory motion, low dose tolerance of adjacent normal tissue and tissue density heterogeneity. Different imaging modalities are applied at various steps of lung proton therapy to provide information on target definition, target motion, proton range, patient setup and treatment outcome assessment. Imaging data is used to guide treatment design, treatment delivery, and treatment adaptation to ensure the treatment goal is achieved. This review article will summarize and compare various imaging techniques that can be used in every step of lung proton therapy to address these challenges.

Keywords: Proton therapy; lung cancer; imaging guidance

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Introduction

Lung cancer is the leading cause of cancer mortality in the world (1). Lung cancer radiation therapy is often efficacious for patients with disease limited to the thorax, but carries the risk of significant morbidities, particularly radiation induced pneumonitis (2,3). About 50% of patients with locally advanced lung cancer (1) receive radiotherapy.

The major technical challenges in lung radiation therapy are threefold: target motion due to respiration, the presence of low dose tolerance normal lung tissue surrounding the target, and large tissue heterogeneities (4). With each incremental technological advancement, the impact of these challenges has gradually diminished over the years. One major advancement is the development of four dimensional computed tomography (4DCT) which enabled the visualization and capture of the motion envelope of the gross tumor volume (GTV) (5). The information would then be used to manage the effect of motion in beam delivery, e.g., use of diaphragm compression boards, delineation of the internal target volume (ITV) for treatment, or design of a gated beam delivery system to irradiate only when the target is within a certain beam aperture window. Various other imaging technologies along with 4DCT have been developed and applied in the field of radiation therapy.

The second major challenge of dose conformity and normal tissue sparing was addressed by the advancement of beam delivery technologies such as intensity modulated radiation therapy (IMRT) (6,7), Tomotherapy (8), volumetric modulated arc therapy (VMAT) (9), and proton therapy (10). These improvement enable better 3D dose distribution that conforms to the target while maximizing the sparing of surrounding normal tissue. The superior dose distribution delivered by treatment modalities utilizing those new technologies are also confirmed by clinical observations (4,11).

The last major challenge of accurate dose computation was addressed by the introduction of advanced dose calculation algorithms with better heterogeneity correction methods (12-14). For proton therapy, the dose calculation accuracy is limited by two factors: the CT Hounsfield unit (HU) to proton stopping-power-ratio (SPR) conversion

accuracy (15) and the lack of lateral heterogeneity correction in the analytical dose models (16). Those uncertainties are usually addressed by the addition of distal and proximal margins during planning. Advanced imaging technology such as dual energy CT (DECT) and proton CT (pCT) may be useful to improve the accuracy of treatment delivery.

With the advancement in imaging technology, imaging has become an indispensable part of radiation therapy. Various imaging techniques are used in every step of radiation therapy from patient simulation, target definition, patient setup, motion monitoring, treatment adaptation, and treatment outcome prediction. It provides assurance as to the quality of treatment we deliver to the patient. In the following sections we will review the different types of imaging modalities that are currently used or are in development for use in various stages of lung cancer proton therapy.

Review

Imaging in lung cancer detection and staging

Due to its high imaging resolution, fast acquisition time, and availability, CT is the main imaging technique for detecting lung nodules (17-20). With the introduction of low dose CT (LDCT) (21,22), lung cancer screening using LDCT can significantly reduce mortality from lung cancer in the appropriate high-risk population (18,23-25).

The role of magnetic resonance imaging (MRI) in detecting and staging of lung cancer remains limited. Lung MRI is subject to motion artifacts due to the longer acquisition time (26,27). In addition, the low proton density in the lung parenchyma produces low signal for imaging. Traditionally, MRI is limited to assessing mediastinum and chest wall invasion due to a lower degree of motion extent in the region of interest and the superior soft tissue contrast compared to CT. However, with fast imaging sequences and high field magnets, MRI is able to provide similar detectability compared to CT (28-30).

Positron emission tomography (PET) or PET/CT is a functional imaging modality. Fluorine 18 fluorodeoxyglucose (FDG) PET provides semi-quantitative information on cell metabolic activity which can highlight the primary target and the involved lymph nodes. It has been routinely used along with CT for lung cancer staging (31).

Imaging in simulation and treatment planning

Simulation is the process of designing treatment setup and acquiring patient anatomic information for treatment planning. The CT simulator is the primary choice due to its fast acquisition time, high spatial resolution, and quantitative body composition representation (32). Free breathing CT imaging is a snapshot of the patient body in which any target motion would be blurred during the acquisition. For lung cancer, it is important to quantify target motion during the simulation. 4DCT provides a series of 3D images representing different phases of the breathing cycle and is routinely used in lung proton therapy (5,33-41). The time-resolved images are generated by oversampling the region of interest at multiple time points followed by retrospective data resorting using the acquired breathing motion signal (5,33). The breathing motion signal is usually acquired by looking at patient body surface surrogates, e.g., the infrared reflection cube placed on the patient abdomen, or laser displacement sensor (37,38). Usually 20 images will be oversampled to generate up to ten 3D volumes representing the phases of the breathing cycle. In addition, the maximum intensity projection (MIP) and average (CT-AVE) images, in which each pixel value is either the maximum or the average HU of that pixel across all phases respectively, would be generated as well. Based on these time-resolved images, several techniques have been adopted by different proton centers for treatment planning and beam delivery.

The choice of motion management strategy dictates the planning approach. With respiratory gating, a specific tumor location within the respiratory motion range will trigger the beam. Therefore, only the image set from a specific breathing phase is selected for treatment planning. It has been suggested that the exhalation phase image should be used for planning since the target has the longest dwell time at exhalation (37-39). The GTV, clinical target volume (CTV), and planning target volume (PTV) are defined following the International Committee on Radiation Units and Measurements (ICRU) recommendations. The setup uncertainty and respiration stability of the gating system are incorporated in the PTV margin. In lung stereotactic body radiation therapy (SBRT), a selected motion phase could also be used for planning. The mid-ventilation phase images defined as the 30% of the breathing cycle was proposed for contouring and dose calculation for the treatment of proton lung SBRT patients (41). The argument is based on the study showing that mid-ventilation images represented the time averaged position of the tumor location and enables a reduction of the irradiated volume as well as the least proton range degradation (42). However, gated delivery

has a lower duty cycle to deliver proton beam therapy compared to non-gated delivery and may make respiratory gating infeasible for a significant percentage of lung cancer patients (43).

Without respiratory gating, the full range of tumor motion extent should be considered during planning. A popular approach is to define the internal gross tumor volume (IGTV) as the envelope of the GTV on all breathing phases. The CTV is then generated by adding a margin that considers the microscopic extension of the disease as the target of the proton beam (34-36). There are several images that can be used for proton range determination: the CT-AVE, MIP, and individual phase images of the 4DCT. Proton ranges determined by MIP is the largest when compared to the other image sets. This conservative approach has been adopted by Loma Linda (34). At the University of Florida, the CT-AVE was used for treatment planning (36). A study from MD Anderson compared the use of free breathing CT, CT-AVE, MIP, and CT-AVE with density overwritten IGTV of 100 HU (AVE-RIGTV) for planning. Judging by the overall target coverage and normal tissue sparing, the use of AVE-RIGTV was determined to be the best choice for planning (44). A 4D treatment planning approach similar to the MIP based planning has been developed at the Massachusetts General Hospital (40). A group of plans was first generated for individual breathing phase CT images. The final 4D plan is the composite of those plans with the maximum proton range, modulation, and beam aperture to ensure the target coverage. These studies were performed using scattered proton beam delivery. In pencil beam scanning (PBS) beam delivery, there is potential dose distribution degradation (interplay effect) arising from the relative motion between the tumor and the beam delivery parameters that must be considered. In a 4D Monte Carlo (MC) study of PBS lung treatments (45), it was found that the interplay effect is highly patient specific, dependent on the motion amplitude, beam spot size, tumor location and beam delivery parameters. Large degradations of dose distribution were observed in a single fraction but improved significantly using conventional fractionation. In a study of the interplay effect for stage III lung cancer treatment with intensity modulated proton therapy (IMPT), dynamic dose distributions were estimated by assuming realistic breathing patterns in a dynamic dose delivery (46) and calculating a 4D composite dose derived from forward calculating the dose in each phase of the 4DCT. The authors concluded that delivered dose may be reliably estimated using 4D composite dose despite of the interplay effect. There are several disadvantages to using 4DCT for capturing motion. In addition to potential irregular breathing resulting in 4D image artifacts, the captured motion is only a snapshot of several breathing cycles and may therefore under- or over-estimate motion during treatment. One solution is to map motion information extracted from a 4D MRI onto a static 3D CT to create a virtual 4D-CT (MRI) (47) that is potentially free from 4DCT artifacts and is therefore more robust for 4D dose calculations.

CT imaging is used to determine the proton range and dose distribution. The HU represents the linear attenuation coefficient of the imaged object for kV X-rays. It is strongly related to the electron density of the object which is used for megavoltage photon dose computation. For proton therapy, the proton stopping power ratio (SPR) used for range determination and dose computation is determined by the electron density and the mean excitation energy of the material. Using traditional single energy CT (SECT), the calibration process is a single dimensional map of electron density projection to a 2-dimension map of electron density and mean excitation energy. Comprehensive analysis by Yang *et al.* (15) showed that the commonly used stoichiometric calibration method (48) has a combined uncertainty of 3–3.4% in proton SPR determination. The dominant contributor of SPR uncertainties was the fact that the calibration process cannot differentiate soft tissues with composition variations that have different SPR but the same HU in SECT.

In order to acquire more accurate material information for proton SPR determination, the use of DECT has been proposed (49) to remove the HU degeneracy of soft tissues in SECT. Various methods have been proposed to correlate the DECT HUs to the proton SPR (50-54). A recent theoretical study by Han *et al.* (50) utilized a basis vector model (BVM) to calculate proton SPR from 90 and 140 kVp DECT images. The BVM assumes that X-ray attenuation derived from CT are linear combinations of the corresponding quantities from several basis materials. Their calculated root-mean-square error of proton SPR was 0.2% for 175 MeV protons. The experimental study conducted by Hansen *et al.* (55) showed that the proton SPR determination by DECT has 0.5% (maximum of 1%) uncertainty when performed in calibration conditions. For phantoms outside of the calibration range, the estimated uncertainty was less than 2%. The optimum energy pair to acquire DECT for proton SPR calculation was also investigated by Yang *et al.* (56). Based on their report, the kV-MV DECT pair

of 100 kVp and 1 MV improved the accuracy of SPR estimation substantially over the kV-kV or MV-MV DECT methods due to less susceptibility to CT number uncertainties and artifacts such as imaging noise and beam hardening effects. DECT is already commercially available through several vendors. However, it has not been routinely used in proton clinics at the time of writing. DECT has been implemented commercially using various technologies including, dual source, and fast kV switching or sequential scans. One potential problem with the use of DECT for lung proton therapy is respiratory motion when the image pair is not acquired simultaneously. Photon counting CT (PCCT) is a potential solution that acquires simultaneous multi-energy CT using a single source and photon counting detector (57). PCCT is an emerging technology that uses photon counting detectors that measure individual photon energies rather than integrated charges from all photons on a conventional CT.

Another approach to improve the proton SPR determination is using pCT (58-61). pCT uses high energy protons as the imaging beam. It measures the residual range of protons exiting the imaged object. Since the only factor governing the residual range is the proton SPR of the imaged object, the reconstructed image is a direct map of the proton SPR. A simulation study performed by Hansen *et al.* (55) reported that pCT has a maximum proton SPR uncertainty of 0.5% which is superior to any other clinically available methods. Despite its advantage for proton therapy simulation over X-ray CT, pCT requires a much higher proton energy for imaging than treatment since the proton beam is used in transmission mode. pCT has inferior imaging resolution compared to CT due to proton scatter. Currently, there are no commercially available pCT systems other than several prototypes for small phantom studies.

MR-only simulation has been shown to be a feasible solution in radiation therapy. MR images are robust, have high fidelity and contrast that are suitable for treatment planning (62). The newly introduced Philips Ingenia MR-RT system (Philips Medical Systems, Best, The Netherlands) uses a fast imaging sequence to reduce the acquisition time to about 12 min (63). The MR image is then converted to a synthetic CT image using the Magnetic Resonance for Calculating Attenuation (MRCAT) algorithm developed by Philips (Philips, Vantaa, Finland). MRCAT generates pseudo-HUs by categorizing patient body into air, fat, soft tissue, spongy bone, and compact bone based on MR signals (64,65). A predetermined HU value will be assigned to each material for dose computation. A recent study investigated the feasibility of using the synthetic CT image for prostate cancer proton therapy (66). The range difference calculated based on MRCAT and CT images has a median value of 0.1 and 3 mm for the 96th percentile. For lung proton therapy, MR-only simulation faces challenges because of the low signal from lung and higher range determination accuracy requirement. More investigations are needed to determine its feasibility for clinical applications.

Image guidance during treatment delivery

Image guidance tools for proton therapy systems

In-room imaging tools are an indispensable part of the image guided radiation therapy workflow. All proton delivery systems have at least some type of orthogonal X-ray radiograph system for patient setup (67,68). Some systems have onboard imagers mounted on the gantry or nozzle and can be used for cone beam CT (CBCT) acquisition. One of the X-ray tube may be mounted on the nozzle to acquire the beams-eye-view (BEV) (68,69). Since the virtual proton and X-ray sources are not coincident, the BEV acquired by the X-ray tube is only an approximation of the proton BEV. Patient alignment for lung proton therapy is primarily accomplished using orthogonal X-ray imaging matched to bony anatomy.

Compared to orthogonal radiographs, CT provides a 3D volumetric image with superior soft tissue contrast. CT based image guidance has long been introduced to proton therapy (70). Early solutions implemented at the Paul Scherrer Institute featured a CT situated next to the treatment room. Patients would be setup on a moveable couch and imaged in the CT room. The patient would then be transported on the couch and docked in the treatment room. X-ray radiographs would then be acquired to verify patient location prior to treatment. With the development of portable CT scanners and 6 degree robotic couch (71), in-room CT is now clinically available. Due to the size of the CT scanner, these systems have separate CT imaging and treatment isocenter positions.

Kilovoltage CBCT has been an indispensable tool (72) for lung photon therapy. For proton therapy, CBCT has been implemented by utilizing a gantry or nozzle mounted X-ray imaging system for image acquisition (73). X-ray projection images are acquired through gantry rotation in a similar way CBCT is acquired on linacs. Since some proton systems have either a fixed beam or a compact but limited angle gantry. An alternative implementation that does not

require a gantry is the use of customized robotic C-arm CBCT system that can be deployed to image off treatment isocenter (74) or at treatment isocenter (75).

MRI has also been proposed as an image guidance tool for proton therapy (76,77). It has superior soft tissue contrast and no moving parts for 3D imaging. Those properties allow MRI for real-time motion monitoring (78,79) and on-line adaptive proton therapy workflow. The main difference from photon therapy, however is that the magnetic field would have less impact on the proton dose distribution, although the magnetic field causes the proton beam to be laterally displaced. Raaymakers *et al.* (76) demonstrated no effect of the magnetic field on the dose distribution can be detected at tissue-air interfaces, which is due to the low-energy of the secondary electrons released by the heavy protons but there is a lateral displacement of 1 mm for a 0.5 T field. Due to technical challenges such as magnetic perturbation on beam monitoring systems, shielding design of the magnetic and radio-frequency fields between the accelerator and MRI, this technology remains at the conceptual development and testing phase (80).

Image guidance for patient setup and intra-fractional motion management

Lung cancer radiation therapy is challenging because of respiratory motion. In clinical practice, the motion management strategy dictates the simulation, treatment planning, and imaging modalities used during treatment. Motion management can be categorized into two approaches: non-gated delivery, or gated delivery with tumor or respiratory phase tracking. Non-gated delivery is the least technically challenging and the most popular method for the passive scattering (PS) proton therapy system. Combining 4D-CT derived IGTV and proper margins; the beam aperture design encompasses all potential tumor positions. Motion reduction devices such as breath hold or abdominal compression may be used. Image guidance in this setup only requires aligning the patient to bony anatomy with orthogonal X-rays. If in-room CT or CBCT is available, matching can be performed to soft tissue while verifying the reproducibility of the patient setup with the breath hold or compression device. Fiducial markers may be considered when CT or CBCT images are not available during the setup to improve accuracy. However, the presence of traditional solid fiducial markers or electronic transponders could significantly perturb the proton dose distribution (81,82) by casting a dose shadow due to its high density. Novel gel based fiducial markers with high radiograph visibility, but similar proton stopping power to soft tissue creates less dose perturbation, has been introduced for proton therapy (83) and may be potentially useful for image guidance or tracking motion in lung proton therapy (84).

In gated delivery, the proton beam turns on only when the target has moved to a predetermined window. Compared to non-gated delivery, a smaller motion margin may be used, thereby sparing more normal tissue. However, the target location throughout the treatment needs to be monitored and communicated to the beam triggering system. Multiple modalities have been developed for use as gating signal. Those modalities can be classified into internal tumor monitoring with implanted markers or external surrogate monitoring. The implanted markers, e.g., fiducial markers (85), radio frequency (RF) transponders (86,87), and electromagnetic coils (88), which represent the true tumor location are required to be monitored by externally placed detectors. Currently no proton therapy system has integrated X-ray imagers or RF antennas for real time tumor motion monitoring due to concerns of significant dose perturbation introduced by the markers and limited space in the treatment room. On the other hand, external surrogate monitoring is easier to realize. Laser distance sensors (88,89) and surface imaging (90-92) are two examples of this category. Laser distance sensors use triangulation to calculate the subject's movement by measuring the reflected laser beam change in space. It has sub-millimeter accuracy and has been used routinely in Japanese centers to monitor respiratory motion (37,38). Surface imaging uses cameras to capture pseudo-random light pattern projected on the patient surface. The patient surface change would be calculated from the pattern change of the projected lights. Compared to other imaging modalities, it uses non-ionization radiation, and is able to monitor a large surface constantly from a distance. Currently there are several commercially available products including VisionRT (AlignRT, London, UK), Catalyst (C-RAD, Uppsala, Sweden), and humediQ (humediQ, Munich, Germany). Those systems usually require several cameras/projectors to be mounted in the treatment room ceiling to work. Sub-millimeter accuracy can be achieved in well controlled experiment setups (92,93). However, in clinical setup, the accuracy would also be affected by patient skin tone, ambient light level, temperature of the camera, and selection of the monitoring region of interest. Technological assessment between optical and electromagnetic tracking technologies showed that optical

tracking has better potential than electromagnetic tracking for use in PBS proton therapy (88). Nevertheless, caution should be taken when using beam gating because latency time between the generation of the triggering signal and beam turn on/off have to be considered along with potential poor correlation between internal tumor motion and external monitoring surrogates.

In vivo imaging for proton range verification

There are several sources of uncertainty in lung proton therapy: the conversion of the CT HU to proton stopping power, setup uncertainties, motion, and patient anatomical change during treatment. As the proton beams can pass through very inhomogeneous tissues including lung, soft tissue and bone, the delivery uncertainties can create large effect in the proton dose distribution (35). Online monitoring tools of the proton range is therefore desirable for treatment plan dose verification.

Nuclear interactions of protons with tissue nuclei can lead to the production of β+ emitters (primarily ^{15}O and ^{11}C with 122 and 1,218 s half-lives) along the proton beam path. Imaging these β+ emitters using PET techniques has been proposed as a way to perform range monitoring in proton radiotherapy (94,95). Since energy deposition by protons is through electromagnetic interactions while the generation of β+ emitters is through nuclear interactions, the PET image is spatially correlated but not directly proportional to the deposited dose distribution (96). Hence, the accuracy of proton range verification is defined as the difference in range as measured in the acquired PET image to that calculated in a MC simulation of the β+ emitters (MC map) generated within the patient. Another challenge is to transfer patient from the treatment position to the PET acquisition position, where time delay occurs and more short-lived isotopes decay away, while the longer-lived isotopes encounter biological washout especially if the PET scanner was situated in a different room. Dedicated in-room PET was used to monitor proton range in brain patients (97). In-line PET was proposed to image the decay signal during or right after treatment (96-98) and performed on various disease sites. Such technology has yet to be verified and applied to lung proton treatment where motion is a challenge. Laube *et al.* (99) developed a 4D PT-PET algorithm that considers intra-fractional target motion and motion compensated dose delivery with scanned ion beams. The technology of PET for proton beam range verification is evolving but is not routinely integrated into a prospective quality assurance system.

During proton irradiation, high energy gamma rays are also emitted by the decay of excited nuclei resulting from interactions between the proton beam and patient tissue. Imaging of these prompt gammas (PG) emitted during the short timescale of the nuclear byproducts is a potential proton range verification tool during beam delivery (100,101). Compared to PET imaging PG imaging does not suffer from the complication of biological washout has a shorter imaging time and is ideally suited for imaging discrete pencil beam spots. In addition to localizing the spatial location of the PG source, the spectroscopic properties of the PG emission lends itself to the determination of carbon and oxygen concentration (102). The clinical application of PG imaging for range verification has been demonstrated in double scattering (103) and PBS modes (104) for brain treatment using a PG camera with a slit collimator design. The feasibility of PG imaging for lung treatment range verification has not been demonstrated yet because several technical hurdles limit the applicability of this modality. These limitations include respiratory motion, which complicates the analysis of the PG emission profile and the low density of lung tissue that decreases PG emission signal from within lung tissue.

Imaging for adaptive planning

Proton dose distribution is particularly sensitive to anatomic changes and motion effects. The typical dose fractionation for locally advanced NSCLC is about 7 weeks (11). During the course of treatment, tumor regression or shrinkage, lung density change due to atelectasis, pleural effusion, and motion pattern change can occur. It is necessary to monitor the tumor response throughout the course of treatment and modify the original plan as needed. MD Anderson Cancer Center was an early adopter of adaptive lung proton therapy (35,105,106). Usually an evaluation 4DCT is acquired during week 3 or 4 of treatment or as clinically indicated and assessed by the physician. The original plan will be forward calculated on the newly acquired 4DCT to evaluate the target coverage and normal tissue dose. If the target received <95% of the prescription dose or the normal tissue exceeded the dose constraints, a re-plan will be performed based on the new 4DCT. Koay *et al.* (106) reported about 20% patients required a re-plan, particularly for patients with large thoracic tumor which recessed significantly during the course of treatment.

Other than 4DCT, CBCT has also been investigated for use in adaptive planning purposes. With more commercial

proton systems equipped with onboard imager that has volumetric imaging capability, CBCT acquired during treatment would be a handy tool to monitor the target change or use for re-planning. The image quality of CBCTs is inferior to multi-detector CT images due to photon scatter and the HUs are generally not accurate for proton dose calculations. Veiga *et al.* (107) used deformable image registration to register the CBCT and the planning CT images to generate a virtual CT for dose estimation. This technique mapped the HUs from the planning CT onto the CBCT. They found the current method is limited by the uncertainty associated with deformable registration as well as the image quality of CBCT. Their adaptive procedure was adequate when gross errors occurred but could not recover subtle anatomic or density changes in tumors with complex topology. For identification of anatomic change and estimation of dose to target and other organs at risk such as the spinal cord and heart, CBCT will play an important role as a trigger for adaptive lung proton therapy as it can be acquired prior to each treatment and complements the use of evaluation 4DCT when re-planning is required.

Conclusions

After more than a century of growth, the radiation therapy field has developed advanced therapeutic machines that generate well-selected types of ionization radiation for cancer therapy. Treatment can be realized through various types of advanced beam deliver mechanisms. The challenge of radiation therapy has shifted from how to deliver treatment to how to assure that the right treatment is delivered to the right place with the right response. Imaging can provide assurance to the simple human logic of "to see is to believe". With more and more imaging modalities developed or under development for integration to the radiation therapy workflow, firm control of individual steps of cancer treatment can be gained. Lung proton therapy is the utilization of the most advanced therapy modality for this traditionally challenging disease. Looking forward, there will be more use of imaging in the treatment workflow to answer questions from target definition, target localization, treatment delivery, to treatment response.

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Footnote

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