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Improving Radiation Conformality in the Treatment of Non–Small Cell Lung Cancer

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Abstract

One of the many challenges of lung cancer radiotherapy is conforming the radiation dose to the target due to tumor/organ motion and the need to spare surrounding critical structures. Evolving radiotherapy technologies, such as four-dimensional (4-D) image-based motion management, daily on-board imaging and adaptive radiotherapy, have enabled us to improve the therapeutic index of radiation therapy for lung cancer by permitting the design of personalized treatments that deliver adequate doses conforming to the target while sparing the surrounding critical normal tissues. Four-dimensional computed tomography (CT) image-based motion management provides an opportunity to individualize target motion margins and reduce the risk of a geographical target miss. Daily on-board imaging and adaptive radiotherapy reduce set-up and motion/anatomy uncertainties over the course of radiotherapy. These achievements in image guidance have permitted the implementation in lung cancer patients of highly conformal treatment delivery techniques that are exquisitely sensitive to organ motion and anatomic change such as intensity-modulated radiation therapy, stereotactic body radiation therapy, and proton therapy. More clinical studies are needed to further optimize conformal radiotherapy using individualized treatment adaptations based on changes in anatomy and tumor motion during the course of radiotherapy and using functional and biological imaging to selectively escalate doses to radioresistant subregions within the tumor.

Introduction

Radiation therapy plays a central role in the management of non-small cell lung cancer (NSCLC). Using conventional 2-dimensional (2-D) radiotherapy planning to a total dose of 60–66 Gy, control of local disease has been poor (only 30 to 50%) and dose escalation has been associated with increased toxicity, particularly when concurrent chemotherapy is given.¹ Three main factors contribute to local treatment failure after radiotherapy: (1) geographic misses due to inadequacy of imaging tools for staging and radiotherapy planning; (2) geographic misses due to respiration-induced tumor motion and anatomic changes during radiation delivery; and (3) inadequate radiation dose due to concerns about toxicity. Three-dimensional conformal radiotherapy (3-D CRT)^{2–3} and, recently, stereotactic body radiation therapy (SBRT)^{4–9}, intensity-modulated radiation therapy

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(IMRT) 10, 11, and proton therapy 12–15 using dose-escalated treatment appear to improve local disease control and possibly survival with reduced toxicity in NSCLC.

The use of image-guided radiotherapy (IGRT), particularly radiotherapy planning based on positron emission tomography/computed tomography (PET/CT), four-dimensional (4-D) CT to monitor individualized tumor motion, and on-board image-guided adaptive radiotherapy during the course of treatment may allow for more accurate tumor targeting and reduced side effects (16). IGRT with radiation dose escalation or acceleration aims to confine high-dose radiation to the target, particularly high-risk areas based on functional imaging, and to avoid surrounding critical normal tissues; such a strategy could significantly improve clinical outcomes for patients with lung cancer. In this review, we address recent efforts to use physical approaches to improve the therapeutic index for the treatment of lung cancer, and particularly focus on the use of imaging to account for target motion and examine novel therapeutic techniques such as adaptive radiotherapy, IMRT, SBRT, and proton therapy.

Tumor Motion Management

A major obstacle to radiotherapy in lung cancer has been respiration-induced target motion (also known as intrafractional tumor motion), which can add considerable geometric uncertainty to treatment, particularly for highly conformal radiotherapy treatment delivery techniques such as IMRT, SBRT, and proton therapy. In IMRT, each treatment field may cover only a portion of the target and uncertainty due to motion may result in a geographical target miss. In SBRT, the target volume is usually small; therefore, missing the target can cause significant underdosing of the tumor and due to the high doses being employed, it is critical that the dose to surrounding normal tissues is minimized⁸. Proton therapy is also sensitive to motion and tissue density change, so proper management of tumor motion can prevent target underdosing and normal tissue overdosing in this approach as well 12, 17–19. The ideal solution to this problem would be to track the tumor in real time during treatment and correct beam position to match the location of the target. However, at the present time it is not possible to perform volumetric imaging during treatment with commercially available systems and therefore, true ‘real-time’ tumor tracking cannot be achieved.

A number of approaches have been developed in an attempt to address the problem of respiration induced target motion to minimize the risk of a geographic miss. One such approach is the integration of the 4D-CT into radiation treatment planning. With its multislice detectors and fast imaging reconstruction, 4D-CT performs image acquisition while the patient is breathing and thus allows for the assessment of individual organ and target motions 20. Our 4-D CT study²⁰ showed that more than 50% of NSCLC tumors moved more than 5 mm during treatment and that almost 11% moved more than 1 cm (up to 4 cm), particularly lesions near the diaphragm. For patients in whom the tumor moves less than 5 mm, simply expanding the planning target volume margin is adequate. However, for patients with substantial tumor motion, particularly more than 1 cm, an individualized tumor motion margin and motion-reducing approach should be considered.

We have previously proposed the concept of the internal gross tumor volume (IGTV), which envelops the GTV motion throughout the respiratory cycle¹⁶. Delineating the IGTV from 4-D CT images involves outlining the tumor volume on the expiratory-phase images and then registering the outline to the images from other phases to create a union of target contours enclosing all possible positions of the target. Another method of defining the IGTV is to create a maximum intensity projection (MIP) image by combining data from the multiple CT data sets with data from the respiratory cycle and modifying the IGTV by visually verifying the target volume throughout all breathing phases (typically 10) 16. Relying on the MIP image alone, without modifying the tumor volume across the breathing phases may

cause target volume underestimation, especially for lesions near the diaphragm, chest wall, and mediastinal structures ²². Even 4-D CT provides only a snapshot and a single stochastic sampling of the patient's breathing. Attention should be paid to irregular breathing and breathing pattern variations during each treatment session and over the entire treatment course and to the effects of these irregularities on the IGTV margin^{23, 24}.

If 4-D CT is not available, alternative approaches to address tumor motion should be considered; for instance, the IGTV can be delineated by combining volumes on breath-hold spiral CT at the end of expiration and at the end of inspiration ¹⁶. The breath-hold treatment delivery method is optimal for patients who can comply ²⁵. However, due to poor baseline pulmonary function many patients are not able to achieve an adequate breath hold for this technique to be feasible. Respiratory gating provides one possible alternative for²⁶ patients who cannot hold their breath for breath-hold treatment delivery but who can breathe regularly and reproducibly.

The most commonly employed form of respiratory gating involves tracking the motion of external fiducials using infrared imaging. The beam is then turned on only during a specified point in the respiratory cycle. In a clever modification of this technique, these externally placed fiducials are tracked with respect to implanted fiducials within the tumor and a correlative model is built. The beam position is then altered based upon the motion of these external fiducials in near 'real-time' during treatment (100–200 millisecond delay). The assumption here is that the correlation between tumor position and the external fiducials remain constant during the time course of radiation treatment. ²⁷ This approach is the closest to real-time tracking at the present time and is ideal for minimizing the effects of target motion not only between treatments but also during a treatment fraction ²⁸. More studies are needed to optimize tumor-tracking techniques.

Motion/Anatomy-based Adaptive Radiotherapy

Daily on-board imaging, particularly that done by cone-beam CT or CT on rails, allows for accurate patient positioning and may result in a smaller chance of target miss, smaller set-up margins, and less normal tissue exposed to high radiation doses when SBRT, IMRT, or proton therapy are used. Inter-fractional tumor motion and anatomic changes during radiotherapy are a major cause of target miss and/or over-treating normal tissues in lung cancer. As a result of these issues, an initial simulation-based treatment plan may not match the treatment delivered. In one study, researchers used weekly 4-D CT images to investigate the magnitude of the changes in tumor volume and mobility in NSCLC during 7 weeks of radiotherapy ²⁴. Tumor volume reduction ranged from 20% to 71% and tumor mobility significantly increased.

In some cases, an explicit initial determination of the IGTV may not be sufficient to cover the target, owing to variations in tumor motion and anatomy during treatment. Insufficiency of the IGTV coverage was even more severe with significant tumor underdosing in selective cases when proton treatment was used ¹⁹. Re-planning of radiotherapy using repeat 4-D CT images to adapt to changes in patient anatomy and organ motion between treatment fractions might be warranted for selective highly mobile tumors to reduce the potential for missing the target when using IMRT and proton therapy.

Improving Biological Conformality: Functional Image-guided Dose Optimization or Dose-painting

The improved capabilities of nuclear magnetic resonance imaging, spectroscopy, and PET have provided physiological and functional information about tumors and their

surroundings. Molecular imaging promises to reveal tumor biology at the genotype and phenotype levels. These developments converge to provide significant opportunities for enhancing radiotherapy success. Recent studies examining the utility of FDG-PET and hypoxic imaging as radiographic biomarkers for treatment failure have shown that high-SUV (standardized uptake value, such as $SUV > 13.8$) regions and hypoxic areas are more likely to have local recurrence after a standard dose of radiotherapy^{29, 30}. Based on biological principles, tumors are not homogeneous and in fact tumor subregions may selectively contain an enriched population of cancer stem cells that may be responsible for recurrence and distant metastasis. IMRT allows for delivery of inhomogeneous dose distributions, thereby providing the means to selectively paint the dose to subregions within the target and to further customize delivered dose distribution (Figure 1). Dose escalation to regions at high risk of tumor recurrence may further improve local control, and potentially survival, while protecting large areas of normal tissue from high-dose radiation. CT image voxel-based prescriptions of deliberately non-uniform dose distributions based on molecular imaging, i.e. dose-painting radiation therapy, can map the image data intensities to prescribed doses^{31–33}. Whereas IMRT may have significantly improved physical conformality in radiotherapy, functional imaging has launched a new era of biological conformality. Combined, these two approaches could further improve the efficacy of future radiotherapy.

Intensity-Modulated Radiation Therapy

IMRT improves dose conformality and allows integrated dose escalation/dose-painting within the target. However, IMRT for lung cancer has been delayed because of concerns that it delivers low, yet damaging, doses to larger volumes of normal lung tissue than that delivered by conventional 3-D CRT. Moreover, tumor movement due to respiration introduces another level of complexity to both the IMRT treatment planning and delivery, since each IMRT treatment field may only cover a portion of the target volume at any particular time. A great deal of concern has been expressed as to whether target motion and collimator motion during IMRT delivery have substantial interplay, thus degrading planned dose distributions³⁴. However, a recent study showed that the main effect of organ motion in IMRT is an averaging of the dose distribution over the path of tumor motion rather than resulting in systematic errors in dose delivery³⁵. Therefore, the final dose delivered to the target and normal tissue should be similar to conventional radiotherapy delivered without intensity modulation and the additional effects specific to the IMRT delivery technique appear to be relatively small.

Proposed approaches aimed at mitigating the effect of internal tumor motion in IMRT include expansion of the target margins, motion-correlated delivery (e.g., respiratory gating, external fiducial tracking), and adaptive treatment plan optimization employing a probabilistic description of motion³⁶. Currently, the Advanced Technology Consortium (ATC) of National Institutes of Health recommends that tumor motion be reduced to < 0.5 cm using compensation techniques such as breath-hold, respiratory-gated, or tumor-tracking techniques if IMRT is used (<http://www3.cancer.gov/rrp/imrt.doc>).

When designing IMRT plans for lung cancer, we recommend limiting treatment to 5–7 fields to reduce low-dose exposure to normal lung tissue and minimizing the use of very small field sizes if target motion is significant. In addition, depending on the target location and critical structures to be spared, we recommend preferential utilization of anterior/posterior beam angles if sparing of normal lung tissue is a priority and a more lateral beam arrangement if sparing the heart is a priority³⁶. When dose distribution, especially low-dose regions, is pushed away from the lung or heart, the target conformality may have to be sacrificed to a certain degree. Virtual clinical studies^{37,38} have shown that IMRT treatment

plans may be more suitable than 3-D CRT treatment plans for patients who have advanced-stage disease with large GTVs and complicated tumor/normal tissue anatomy and for patients in whom sparing the surrounding critical structures from toxicity is of particular concern. Using IMRT, the median absolute reduction in the percentage of lung volume irradiated to more than 10 Gy was 7%, and the volume irradiated to more than 20 Gy was 10%. The volumes of the heart and esophagus irradiated to about 50 Gy and the volumes of normal thoracic tissue irradiated to more than 10–40 Gy were also reduced using the IMRT plans compared with 3-D CRT. These studies noted a marginal increase in lung volume exposed to more than 5 Gy in the IMRT plans in half of the patients. Lower dose (<10 Gy) exposure to the lung could be reduced by limiting the beam arrangements, as stated above.

Clinical data indicate that IMRT reduces pneumonitis and esophagitis compared with 3-D CRT in patients with stage III NSCLC undergoing concurrent chemoradiotherapy ¹⁰. A trend towards improved survival was observed when these patients were retrospectively compared with patients in a similar group receiving 3-D CRT ^{10, 11}. A prospective comparative study is needed to validate these results. Due to the complexity and sophistication required for IMRT treatment planning when compared with that required to generate a 3D CRT plan one would assume that implementation of IMRT based treatment for lung cancer would impede dosimetric workflow. However, with the development of mature optimization algorithms and automated planning software (MDACC auto-plan, unpublished data), our institutional experience suggests that IMRT saves time compared to 3-D CRT when an experienced dosimetrist is doing the planning. IMRT appears to be more appealing for tumors located in the superior sulcus with chest wall/vertebral body involvement and may allow further dose escalation ¹⁰. We recently published our IMRT guidelines with detailed techniques for treating NSCLC ^{12, 36}.

Stereotactic Body Radiation Therapy

Two important principles of SBRT must be obeyed: (1) An ablative dose (biological effective dose, BED, >100 Gy) is required to achieve >90% local control ⁵ and (2) image-guided tumor volume delineation and on-board image-guided radiation delivery (IGRT) are required to take daily target/normal tissue motion into consideration to ensure that the target is not missed and to avoid normal tissue injury ⁹. An ablative dose of SBRT is typically delivered in <5 fractions. With such a small number of fractions, it is critical that patient positioning and target coverage be optimized for each treatment. The possibility of a geographic miss or overdosing of critical structures is increased when the target moves >1 cm or the lesion is located within 2 cm of critical structures such as the bronchial tree, esophagus, heart, brachial plexus, and spinal cord. Toxicity may be severe even fatal if critical normal tissue receives an excess dose of radiation ⁷. Conformal SBRT is therefore usually optimized to ensure that at least 95% of the prescribed dose (minimum BED of 100Gy) is delivered to the PTV which is usually defined as the IGTV plus a small margin to account for set-up uncertainty. Care must be taken to avoid excessive dose deposition to critical normal tissues in close proximity to the tumor bed (Figure 2). It has been shown that this approach can achieve 100% local control with minimal side effects (<grade 3) in centrally located lesions ⁸.

Proton Therapy

Because of the physical characteristics of protons, proton therapy delivers its therapeutic dose to a certain depth (as defined by the Bragg peak) without any exit dose. Optimizing proton beam angle/density and energy could improve conformality of radiation dose delivery to the target while avoiding critical structures. Retrospectively compared to 3-D CRT and IMRT, proton therapy, using passive scattering techniques, has been shown to

significantly reduce the dose delivered to normal lung tissue, particularly dose exposure <10 Gy, and dose to the heart, spinal cord and, in certain cases, esophagus. This is the case even when the radiation dose to the tumor was escalated from 66 Gy to 87.5 Gy in stage I and from 63 Gy to 74 Gy in stage III NSCLC³⁹. Our phase I/II clinical studies of proton therapy (74 Gy in 37 fractions with concurrent chemotherapy in stage III NSCLC and 87.5 Gy in 35 fractions in early-stage NSCLC) demonstrated efficacy and lower incidence of toxicity, including pneumonitis and esophagitis, compared with our historical results from conventional-dose (60–66 Gy) 3-D CRT and IMRT^{14–16}. Other published clinical data using proton therapy showed promising results in stage I NSCLC as well^{40, 41}.

Although passive scattering proton therapy (PSPT) appears promising in reducing toxic effects, dose-escalated radiotherapy using PSPT poses a clinical challenge when treating lung tumors in a certain subset of cases, such as tumors with contralateral hilar and/or, supraclavicular lymph node involvement, or tumors adjacent to the esophagus and spinal cord. Because the number of treatment fields in PSPT is typically limited, delivering ablative doses to targets with complex geometry or locations, such as tumors wrapped around sensitive critical structures, is very difficult. In such cases, compromised dose coverage must be considered to avoid damaging critical normal structures. Intensity-modulated proton therapy (IMPT) using scanning beams, however, might allow for simultaneous optimization of beam intensities and energies using an objective function that accounts for both target and normal-tissue constraints (Figure 3). Future studies will be needed to demonstrate the utility of IMPT.

Our virtual clinical study showed that when compared to IMRT and PSPT, IMPT improved target coverage and reduced the normal tissue dose in patients with stage IIIB NSCLC and allowed for individualized radiotherapy dose escalation from less than 63 Gy using IMRT to 74 to 87.5 Gy (relative biological effectiveness, RBE) without exceeding the maximum tolerable dose in these challenging clinical scenarios⁴². Again, IMPT has been shown to spare surrounding critical structures better than photon-based SBRT in centrally located stage I NSCLC (our unpublished data). In our opinion, IMPT will likely be the optimal conformal radiotherapy in complicated cases of lung cancer.

However, as mentioned above, proton therapy, particularly IMPT, is very sensitive to motion and anatomic changes. 4-D CT-based treatment planning is required to achieve an optimized plan that takes tumor motion into consideration. To optimize target coverage while minimizing normal tissue dose using PSPT, we design the compensator and aperture based on average values in our CT database (average CT image) but replace the IGTV with tissue densities calculated by means of the MIP¹⁸. However, tumor/anatomy may change significantly during radiotherapy, resulting in target miss and normal tissue injury, particularly in proton therapy¹⁹. Adaptive treatment planning is indicated in selective patients. For the proton scanning beam approach such as IMPT, treatment delivery with active beam-scanning introduces the problem of interplay effects when the pencil beam moves on a timescale similar to that of intra-fractional tumor motion⁴³. In situations where fractionation may not provide enough repetition to blur the interplay effects, repeated delivery or “repainting” of each field several times within a fraction has been suggested⁴³. Although proton therapy is so precise with sharp edges, the uncertainty of motion and density change remain to be further addressed particularly IMPT in lung cancer.

Summary

New technologies are evolving to improve conformality of radiation therapy to help focus the high dose on the target and spare critical normal tissues. Treatment planning based on 4-D CT images and on-board image-guided adaptive treatment delivery helps the radiation

oncologist track tumor motion and target the tumor precisely. Improved treatment accuracy and conformality in SBRT enable us to deliver doses high enough to ablate the cancer completely with minimal toxicity in early-stage NSCLC. For stage III disease, image-guided, individualized IMRT and/or proton therapy with dose escalation/acceleration can potentially reduce toxicity and increase the cure rate. Further studies to optimize treatment planning, including dose painting in high-risk areas within the target, are still needed.

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Figure 1.
PET image-guided dose-painting to 74 Gy in region with $SUV > 13.8$ using IMRT to improve biological conformality while keeping rest of target volume in 60 Gy to keep normal lung within dose volume constraint in stage IIIB NSCLC with contra-lateral mediastinal/hilar lymph node involvement.

Figure 2. Conformal ablative SBRT (50 Gy in 4 fractions) sparing surrounding critical structures in a tumor near the spinal cord (SC), bronchial tree (BT), esophagus (E), heart (H) and aorta (A). Color wash dose distributions are shown with corresponding scales.

Figure 3. Improving conformality from 3-DCRT to IMRT, PSPT and IMPT in a stage III B NSCLC with a complicated anatomy. IMPT provided optimal target coverage while sparing critical structures including spinal cord, esophagus, heart and lung.