ELSEVIER

Seminars in
RADIATION
ONCOLOGY

Anatomical Adaptation—Early Clinical Evidence of Benefit and Future Needs in Lung Cancer

James Kavanaugh, MS, Geoffrey Hugo, PhD, Cliff G. Robinson, MD, and Michael C. Roach, MD

Definitive treatment of locally advanced non–small-cell lung cancer with radiation is challenging. During the course of treatment, anatomical changes such as tumor regression, tumor displacement/deformation, pleural effusion, and/or atelectasis can result in a deviation of the administered radiation dose from the intended prescribed treatment and thereby worsen local control and toxicity. Adaptive radiotherapy can help correct for these changes and can be generally categorized into 3 philosophical paradigms: (1) maintenance of prescribed dose to the initially defined target volume; (2) dose reduction to healthy organs while maintaining initial prescribed dose to a regressing tumor volume; or (3) dose escalation to a regressing tumor volume with isotoxicity to healthy organs. Numerous single institution studies have investigated these methods, and results from large prospective clinical trials will hopefully provide consensus on the method, utility, and efficacy of implementing adaptive radiation therapy (ART) in a clinical setting. Additional development into standardization and automation of the ART workflow, specifically in identifying when ART is warranted and in reducing the manual clinical effort needed to produce an adaptive plan, will be paramount to making ART feasible for the broader radiation therapy community.
Semin Radiat Oncol 29:274–283

Introduction

According to the American Cancer Society, lung cancer is the leading cause of cancer related deaths in the United States, with 234,030 new cases expected to be diagnosed and 154,050 estimated deaths in 2018.[1] Between 80% and 85% of all occurrences are diagnosed as non–small-cell lung cancer (NSCLC) histopathology and 10%-15% as small-cell lung cancer, with approximately 30% of NSCLC patients assigned to locally advanced stage III following the TNM classification guidelines at initial diagnosis.[2,3] The standard of care for unresectable locally advanced stage III NSCLC is platinum-based concurrent chemoradiotherapy as a primary treatment option, with a prescribed radiation dose of 60-70 Gy, delivered over 30-35 treatment fractions.[4-6] Recent studies show that the addition of durvalumab as subsequent immunotherapy improves median progression-free survival (17.2 months vs 5.6 months) and 24 month overall survival (66.3% vs 55.6%) compared to concurrent chemoradiotherapy.[7,8] However, the 5-year overall survival remains quite poor, ranging from 15% to 35% for American Joint Committee on Cancer seventh edition stage IIIA and 5% - 10% for American Joint Committee on Cancer seventh edition stage IIIB.[9]

A contributing factor in the low reported overall survival is the relatively high local failure rates associated with the standard definitive chemoradiation treatment. Two phase III clinical trials (Radiation Therapy Oncology Group [RTOG] 9410, RTOG 0617) report similar local failure rates of 30%-31% at 2 years posttreatment in the standard-dose arms of each trial.[4,10] Initial evidence by multiple groups suggested that dose escalation of the treated tumor volume could improve both local control and overall survival.[11-13] RTOG 0617 investigated the impact of dose escalation by randomly comparing standard-dose (60 Gy in 30 fractions) to high dose (74 Gy in 37 fractions). It reported that pure dose escalation to a treatment volume defined on the initial imaging datasets resulted in significantly worse median overall

Department of Radiation Oncology, Washington University School of Medicine, Saint Louis, MO
No conflicts of interest to report.
Funding: None.
Address reprint requests to: Michael C Roach, MD, Department of Radiation Oncology, Washington University School of Medicine, 660 S. Euclid Ave Campus Box 8824, Saint Louis, MO 63110.
E-mail: roachm@wustl.edu

https://doi.org/10.1016/j.semradonc.2019.02.009
1053-4296/

survival (20.3 months vs 28.7 months, $P = 0.004$) compared to the standard-dose arm. Normal tissue toxicities provide further challenges in disease management. RTOG 0617 reported 20% grade 3 pulmonary toxicity in both arms, and grade 3 esophagitis in 7% vs 21% of patients in the low and high dose arms, respectively. RTOG 0617 also reported that heart dose had a significant impact on survival. Given this, more work is needed to reduce rates of local failure and normal tissue toxicities.

One area of improvement in the treatment of lung cancer with radiation focuses on adaptively modifying the radiation delivery to account for midtreatment anatomical changes to the tumor and lungs. During the course of treatment, anatomical changes such as tumor regression, tumor displacement, pleural effusion, and/or atelectasis may result in a deviation of the administered radiation dose from the intended prescribed treatment.[14-19] The opening of airways by the resolution of atelectasis or tumor regression can impact the breathing pattern and relative position of primary and nodal targets. The prevalence of midtreatment anatomical changes to the lungs in large cohorts of patients have been reported by several groups, as shown in Table 1.[19-22] Additionally, the magnitude of tumor regression during treatment, shown in Table 2, has been broadly reported.[14,22-28] This large range of reported changes in several patient populations makes it difficult to generate a posteriori guidelines for when a patient should be adaptively planned and requires that patients' anatomy be monitored during treatment to assess the scope of observed anatomical changes. For situations in which the patient's anatomy changes during treatment, it may be possible to employ adaptive radiation therapy (ART) to modify the treatment plan to maintain and/or escalate dosimetric coverage of the target while minimizing excessive dose to surrounding healthy tissue.[18,19,29,30] However, there is limited consensus on when ART is warranted, how it should be delivered, and the magnitude of the overall clinical benefit. This work presents the current status and ongoing research of adaptive radiotherapy in the treatment of advanced stage III lung cancer.

Adaptive radiotherapy in the treatment of lung cancer can be generally categorized into 3 philosophical paradigms: (1) maintenance of prescribed dose to the initially defined target volume; (2) dose reduction to healthy organs while maintaining initial prescribed dose to a regressing tumor volume; or (3) dose escalation to a regressing tumor volume with isotoxicity to healthy organs. The application of each paradigm has a stated end point of either improving local control or reducing normal tissue complications based on different observed anatomical changes. The mechanism for identifying the need for ART and subsequent implementation of ART depends on the clinician's specified end point and can depend on a host of patient and tumor specific factors. A broad range of data, objectives of lung ART, and clinical programs for implementation of lung ART have been investigated. The following sections will discuss the large and impactful studies in each philosophical paradigm.

Lung ART for Dose Maintenance

Adaptive modification to maintain the prescribed dose to the initial tumor volume is often motivated by the changes in atelectasis, pleural effusion, geometric baseline shifts, and/or tumor deformation relative to the initial simulation, as represented in Figure 1. The impact of tumor position caused by the reported lung density changes has been shown to range from 0.5 cm to 2.4 cm, with a corresponding dosimetric consequence of under-dosing the target volume and increasing dose to surrounding healthy organs.[31,32] In this approach, the relative target volume is maintained to ensure coverage of subclinical disease while accounting for deformation changes or positional changes between the primary and nodal targets, with ART triggered based upon predefined targets or surrogate alignment visible on daily 3D cone-beam computed tomography (CBCT) imaging.

One of the first reported clinical outcomes of this ART strategy were by Tvilum and colleagues who investigated midtreatment plan modifications based upon soft tissue tumor match with reduced treatment margins.[30] The adaptive strategy utilized daily online evaluation by radiation therapists aligning the patient to the soft tissue, instead of bony-anatomy, and looking at the position of the tumor, lymph nodes, and thoracic vertebral bodies within standard tolerances. Gross changes in lung density due to atelectasis, effusions, or pneumonia were also evaluated. After daily setup with 3D CBCT, the radiation therapist evaluated the following alignment tolerances relative to CT simulation baseline: the position of the tumor (2 mm), the position of lymph nodes via designated surrogate structures (5 mm), the position of the thoracic vertebrae (5 mm or 10 mm depending on the dose plan), changes in lung density, body contour changes (15 mm), or changes in the mediastinum and heart (10 mm). If any changes above tolerance were observed for 3 consecutive fractions, a medical physicist would evaluate whether the patient would benefit from rescanning and replanning. Implementation of these strict online adaptive evaluation rules and soft-tissue alignment allowed for clinical target volume (CTV) to planning target volume (PTV) margin reduction. The nonadaptive margins were 10 mm radially for both the primary tumor and nodal targets, with 13 mm in the craniocaudal direction. Smaller CTV to PTV

Table 1 Lung Density Changes Observed Across Multiple Large Patient Studies During Radiation Therapy Treatments

Study	No. Patients	Tumor Anatomical Shift	Atelectasis	Pleural Effusion
Kwint (2014)	177	27%	19%	6%
Elsayad (2016)	71	10%	20%	25%
Moller (2014)	163	–	15%	8%
Van Zwienen (2008)	114	–	29%	13%

Table 2 Tumor Regression Rates for Patients Diagnosed With Stage III NSCLC Treated With Definitive Radiation

Study	No. Patients	Imaging Modality	Volume	Midtreatment Tumor Reduction		Near End of treatment Tumor Reduction	
				Median Fraction (Range)	Median Regression (Range)	Median Fraction (Range)	Median Regression (Range)
Kataria (2014)	15	Helical kVCT	GTVp	22nd-23rd	−34% (−13.8% to −73.0%)	–	–
Spoelstra (2009)	21	Helical kVCT	ITVp	15th (14th-17th)	Not reported (+47% to −25%)	–	–
Berkovic (2015)	41	kV CBCT	GTVp	–	–	30th	−42.1% (−4.0% to −69.3%)*
Fox (2009)	22	Helical kVCT	GTVp	15th (4th-20th)	−24.7% (+0.3% to −61.7%)	25th (21st-33rd)	−44.3% (−0.2% to −81.6%)
Wald (2017)	52	kV CBCT	GTVp	11th	−30% (+24.0% to −84.3%)	30th (24th-35th)	−62% (−3.4% to 91.2%)
Elsayad (2016)	37	kV CBCT	GTVp	–	–	30th	−35% (+22% to −78%)
Ramella (2017)	50	Helical kVCT	CTV	–	–	"When replanned"	−42% (−15% to −67%)*
Seibert (2007)	17	MVCT	GTVp	–	–	32nd (25th-37th)	−58.5% (+18% to −79%)

Studies Include a Combination of Sequential and Concurrent Chemotherapy.
* mean. CBCT, cone beam CT. GTVp, primary gross tumor volume. ITVp, primary internal target volume. CTV, clinical target volume.

margins were used for adaptive patients, with 9 mm radial margins and 10 mm craniocaudal margins for the nodal targets and 4 mm radial margins with 5 mm in the craniocaudal direction for primary tumor volumes. The strict on-treatment monitoring and reduced target margins for adaptive patients had the added benefit of increased dosimetric sparing for adjacent and overlapping organs-at-risk. Thus, all adaptive lung patients had some dosimetric sparing from the initiation of treatment, compared to nonadaptive treatments, and the adaptive benefit was not limited to those who exhibited substantial target reduction and a corresponding midtreatment plan adaptation.

The efficacy of this adaptive strategy was evaluated clinically in a prospective study involving 109 patients, comparing a cohort of 54 consecutive lung cancer patients treated with ART to a cohort of 55 treated with the standard clinical margins and alignment. Both cohorts were treated with intensity modulated radiation therapy (IMRT) with identical normal tissue constraints and with 4-dimensional CT scans and free breathing fludeoxyglucose F-18 (FDG) positron emission tomography (PET) scans acquired at the time of planning. Both groups had identical 5 mm gross tumor volume (GTV) to CTV expansions. In the nonadaptive group, patients were set up each day based on alignment to thoracic vertebrae. Twelve of the 54 patients in the adaptive group were replanned. In the nonadaptive group, 5 patients were replanned due to large changes found incidentally. Contouring on the replanning 4D CT scan was based upon both rigid and deformed transfers from the original simulation scan. Notably during replanning, the volume of the targets was intentionally kept unchanged, even if a noticeable shrinkage had occurred.

The results demonstrated that despite using smaller margins, an adaptive approach with alignment to the primary tumor based on soft tissue match improved local regional control. The incidence of local regional failure at 1 year was 53% for the nonadaptive group and 35% for the adaptive group ($P = 0.05$). There was 1 marginal failure in the adaptive group and 4 in the nonadaptive group. These were located outside the nodal GTV but within 2 cm of the 95% isodose line. Median progression free survival for the adaptive group was 10 months (95% confidence interval 8-12 months), and 8 months (95% confidence interval 6-9 months) for the nonadaptive group. With regards to toxicity, there was no significant difference in the incidences of severe dysphagia or severe pneumonitis between the 2 groups.

Møller and colleagues applied the same ART rules as an extension of the cohort described earlier by Tvilum et al.[18] Their review of 233 consecutive patients showed that 27% were adapted,[18] with 63 patients replanned once, 10 replanned twice, and 3 replanned 3 times. The daily manual evaluation by the therapists correctly identified 98% of the patients requiring resimulation. Fifty-nine (75%) of the patients selected for replanning were felt to truly benefit from it by correcting a decrease in target coverage or an overdosage of the spinal cord. Reportedly, the treatment plan was not adapted to shrinking tumors and absolute CTV size was unchanged.

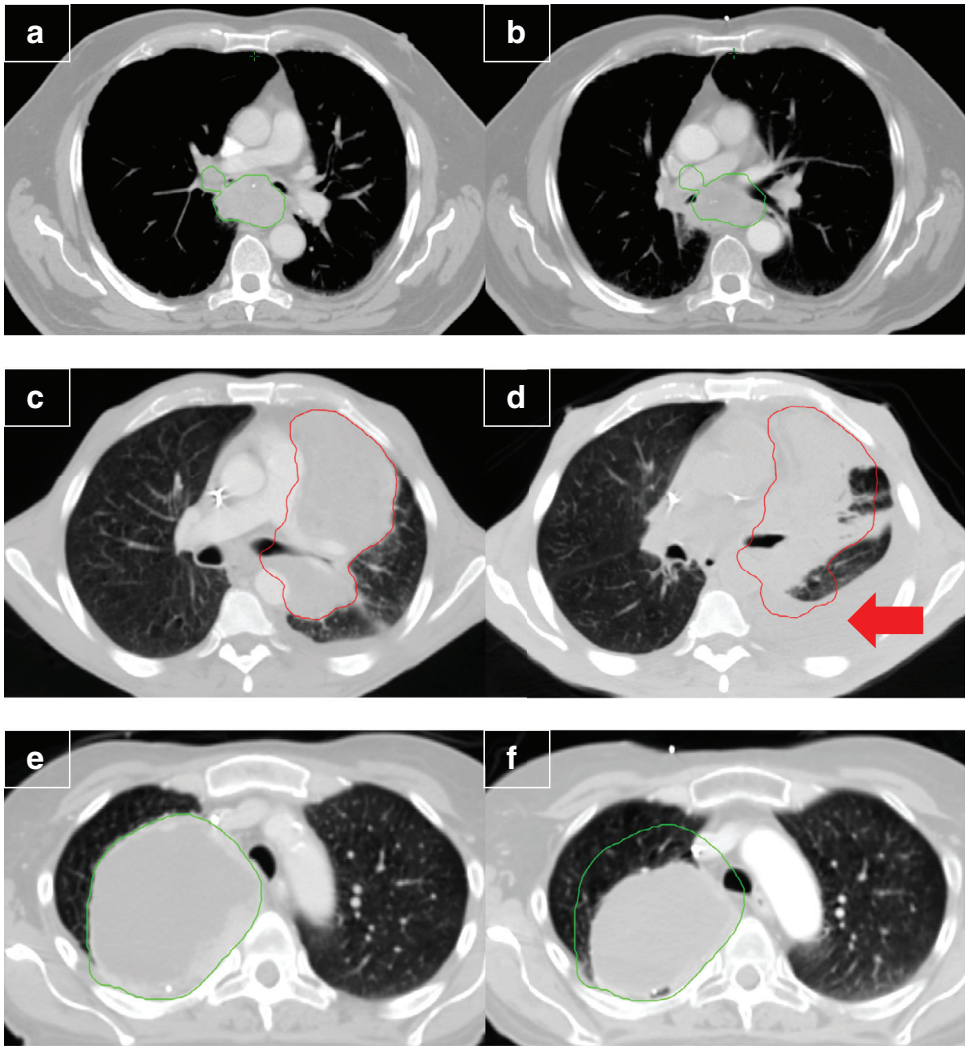

Figure 1 Common anatomical changes, including geometric displacement (a, b), pleural effusion (c,d), and tumor regression (e, f), in 3 patients with NSCLC undergoing definitive chemoradiation therapy that would require consideration for adaptive radiotherapy. The gross tumor volume contour defined on the initial planning CT is delineated in each image, with the midtreatment patient anatomy illustrated by images b, d, and f. The effusion is shown by the arrow in (d).

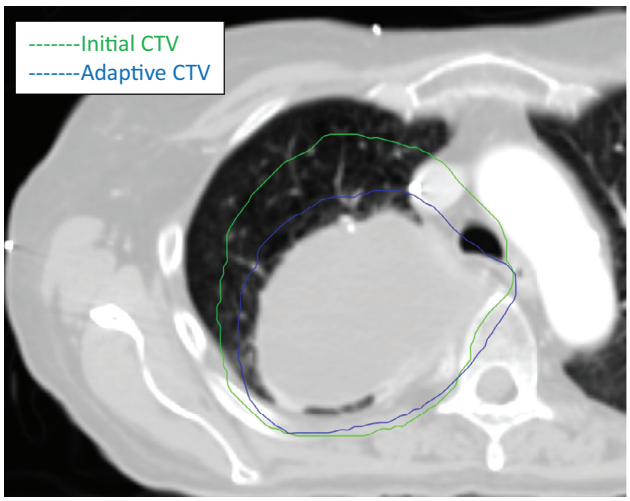

Figure 2 A midtreatment CT scan illustrating substantial tumor regression. The volume between the initial CTV and adaptive CTV represents regions that may still contain subclinical disease.

Lung ART for Normal Tissue Sparing

A second ART approach to treating lung cancer utilizes the geometric benefits of tumor regression to maintain the prescribed dose to a reduced treatment volume in order to increase dosimetric sparing to healthy adjacent organs. An initial study by Woodford et al quantified tumor regression of 17 NSCLC patients treated to 60 Gy in 30 fractions, with daily delineation of the GTV on an MV CT.[15] An average GTV volume reduction of 38% was observed, with a range of 12%-87%. The rate of tumor regression was categorized into 3 groups based on when regression occurred during treatment: (1) limited initial tumor regression followed by a rapid decrease in volume and subsequent plateau; (2) linear tumor regression throughout treatment; and (3) variable tumor regression. Patients who exhibited significant tumor reduction of more than 30% within the first 20 fractions of treatment have the greatest potential for dose reduction to

healthy organs such as the heart and lungs. However, as both the risk of OAR toxicities and tumor regression are patient specific, concrete rules on if a given patient would benefit from ART were not feasible for this approach.

LARTIA was a similar prospective study reported by Ramella and colleagues that used weekly noncontrast CT simulations for 217 patients to evaluate the need for ART based on tumor regression.[23] For each weekly simulation, physicians judged whether target reduction was (1) present and clinically significant, (2) present and clinically insignificant, or (3) absent. Replanning with an IV contrast CT scan was performed in 50 of the 217 patients, with the goal of maintaining prescription coverage of the reduced CTV volume (mean initial 154.9 cm^3 and replanned 90.7 cm^3) and reducing dose to healthy lung tissue. The primary end point of the study was a reduction in grade 3 or higher pulmonary toxicity in comparison to the historical rate of 13%-17% reported in RTOG 9410. This study reported rates of acute and late grade 3 or higher pulmonary toxicity of 2% and 4% respectively, a significant reduction. Local failures were infield, marginal, and out of field in 20%, 6%, and 4% of cases respectively. This total local failure rate of 30% was felt comparable to a rate of 33% in the standard fractionation arm of RTOG 9410 and 31% in the standard dose arm of RTOG 0617. On the study, neither age, sex, total dose, concurrent chemotherapy, nor use of induction chemotherapy were associated with a change in the local recurrence rate. The initial mean CTV was larger in patients with a local relapse than those without (168 cm^3 vs 146 cm^3), though this was not statistically significant.

Lung ART for Dose Escalation

In contrast to adaptation solely to avoid underdosing the target or reducing dose to healthy organs, there is interest in using adaptive therapy to escalate doses to targets for patients exhibiting tumor regression. This approach increases the dose to the reduced target volume while maintaining biologically equivalent isotoxic doses to healthy adjacent organs, with the goal of increased local control with similar organ toxicities.[16,33] Dose escalation for lung ART is typically achieved utilizing midtreatment 4D CT imaging with the adaptive plan delivering either a simultaneous integrated boost to the reduced target volume or adding a boost at the end of treatment.[16,34]

The frequency of adaptive imaging within studies can either be determined subjectively based on observed tumor regression, or systematically at specified intervals across the duration of treatment. In an in silico study, Weiss et al proposed adaptation based upon 4D CT scans taken during the second and fourth weeks of treatment.[16] The initial prescribed dose of 2 Gy/fx was delivered for the first 15 fractions of treatment, with adaptive replanning on the week 2 scan to account for volume and shape changes of the target, applied for the 16th-25th fractions. A second adaptive plan incorporating dose escalation up to 4 Gy/fx to the decreased primary tumor was created on the week 4 CT scan to be delivered as a hypofractionated simultaneous integrated boost without extending treatment fractions. Dose escalation was performed until either (1) the normalized mean lung dose exceeded the 66-Gy plan by more than 1 Gy or (2) any of the limiting normal tissue biologically equivalent doses at 2 Gy fractions (EQD2) was reached. For both adaptive plans, the delineated initial CTV was deformably warped to ensure the boost CTV provided acceptable dosimetric coverage of microscopic disease while using IMRT for high dose conformality and plan optimization. Using the isotoxic approach, a feasibility study demonstrated the ability to safely increase the EQD2 by up to 13.4 Gy and a corresponding expected tumor control probability by 22%.

Increasingly, there is interest in using a PET image during the course of chemoradiation therapy both to predict clinical outcomes[35] and to adapt treatment. One of the earliest was a pilot study by Kong and colleagues that accrued 15 patients in 2004 and 2005.[36] FDG PET CT scans were acquired 2 weeks before radiation, at the delivery of 45 Gy, and 3-4 months after completion of radiation. The dose of 45 Gy was selected given that this dose might have allowed adequate control of microscopic disease, while also allowing a reasonable amount of time remaining to deliver the adaptive plan. Of the 15 patients, 11 had a partial metabolic response, 2 a complete metabolic response, and 2 stable disease at 45 Gy. All of the FDG avid primary tumors had a reduction in the maximum SUV, while the non-FDG avid primary tumors changed minimally. Mean decreases in CT and PET tumor volumes were 26% and 44%, respectively.

A later dosimetric study of a theoretical target boost based on these mid-RT PETs showed the potential for a meaningful dose escalation of 30-102 Gy (mean 58 Gy) or a reduction in normal tissue complication probability of 0.4%-3% in 5 of 6 patients with smaller yet residual tumor volumes.[37] First, standard plans were constructed encompassing the composite pretreatment CT and PET volumes to either a maximum normal tissue complication probability (NTCP) of 15% for pneumonitis or a maximum PTV dose of 90 Gy, whichever was limiting. Three additional adaptive treatment plans were generated with each boosting only the midpoint PET PTV. The first adaptive plan delivered 46 Gy to the initial PTV, then boosted the remaining PTV volume to which ever was limiting, a maximum lung NTCP of 15% or 90 Gy to the PTV. The second adaptive plan delivered 60 Gy to the initial PTV, then boosted the residual PET disease to a maximum lung NTCP that matched that of the original plan. The 3rd adaptive plan delivered 60 Gy to initial PTV, then boosted the residual PET avid disease to a maximum lung NTCP of 15%. A similar prospective study of patients undergoing PET-CT scans after receiving approximately 40 Gy showed that adapted plans delivering 26 Gy to the residual metabolic tumor volume resulted in lower doses for all the organs at risk when compared to the initial plan.[38]

This initial pilot study led to a phase 2 clinical study conducted at 2 academic medical centers with 42 patients, where adaptive plans were created based on a PET-CT scan

taken late in treatment after the equivalent of 40-50 Gy of conventionally fractionated radiation (EQD2) was delivered. All patients received individualized radiation doses to an uninvolved lung NTCP of up to 17.2% for grade 2 or greater pneumonitis. The radiation was delivered in 30 daily fractions of 2.1-5.0 Gy, with 2.1-2.85 Gy fractions used for an initial dose of approximately 50 Gy EQD2. For the adaptive phase, dose escalation up to 2.85-5.0 Gy per fraction was used up to a maximum dose of 86 Gy, limited by the uninvolved lung NTCP, corresponding to an EQD2 of 92 Gy to the tumor. The primary endpoint was local tumor control, and the investigators found an encouraging infield tumor control rate, with only 18% failing infield at 2 years.[39] Toxicity rates were also encouraging with grade 3 esophagitis in 12% of patients and grade 3 pneumonitis in 7%.

A similar prospective study was reported by Kelsey and colleagues where 29 patients underwent a 2nd planning PET-CT scan after receiving approximately 50 Gy of conventional radiation.[40] They showed a complete response in 2 patients, partial response in 24 patients, and new distant metastases in 3 patients. Those with a complete response finished treatment as planned at 60 Gy, and those with distant metastases had treatment ended early. Selective dose escalation to the interim residual GTV to 70-74 Gy was done in 17 patients at the discretion of the principal investigator. Dose escalation was not pursued due to normal tissue constraints in 3 patients, poorly defined residual disease in 2 patients, acute toxicity in 1 patient, and refusal of current therapy in 1 patient. The interim GTV was defined as residual disease based solely on subjective visual analysis of the PET-CT. Other objective metrics such as a maximum SUV of 2.5, 40% of maximum SUV, and 150% of the SUV mean in the aorta were examined but were not found to reliably define volumes accurately. For those receiving a boost, the median GTV at treatment initiation was 78 mL (range, 19-419 mL) and after 50 Gy, the median GTV was 29 mL (range, 1-157 mL). Adaptive planning to the residual GTV allowed for significant dose reductions to the lungs, heart, and esophagus when compared with a simulated nonadaptive plan to the same total dose. Two-year local failure was estimated at 28%. There was no grade 3 esophagitis or pneumonitis reported.

Such studies led to the launch of RTOG 1106 (NCT01507428), a multi-institutional randomized controlled trial investigating whether adaptation and dose escalation based on a PET-CT scan taken after 4 weeks of treatment improves freedom from local and regional progression at 2 years. In this trial, patients were randomized to a control arm with uniform radiation dose to 60 Gy in 30 conventional fractions of 2 Gy vs an experimental arm. In the experimental arm, the residual tumor after an initial dose of 39.6 Gy (18 fractions of 2.2 Gy) was escalated after 46.2 Gy (21 fractions of 2.2 Gy) to between 66 and 80.4 Gy using fractions of 2.2-3.8 Gy while still limiting the mean dose of the lung on the composite plan to 20 Gy. Accrual has completed with results expected soon. Similar phase II and III randomized multicenter trials have been launched and are recruiting in China (NCT02790190), France (NCT02473133), Denmark (NCT02354274), the Netherlands[41] (NCT01024829), and Canada (NCT02788461).[42]

Lung ART for Proton Therapy

Adaptation may be even more critical with proton therapy to maintain target coverage and avoid overdosing critical structures, mainly due to the elevated sensitivity of proton range to changes in tissue density.[43,44] In addition to tumor regression, interfraction motion of organs such as changes in pleural fluid and the opening or blocking of major airways all create density changes that can result in large range uncertainties and corresponding large changes in the dose distribution. This is even more critical with pencil-beam scanning intensity modulated proton therapy with the interplay of target motion and the timing of the delivery of pencil beam spots.[45] These factors led to the development of recommendations from the Particle Therapy Co-Operative Group Thoracic and Lymphoma Subcommittee for weekly repeat 4D-CT verification simulations,[46] as up to 60% of intensity modulated proton therapy patients have been reported to require adaptive planning due to changes in anatomy.[47-49]

Importantly, adaptation does not appear to compromise rates of disease control with proton therapy. A secondary analysis of 212 patients enrolled on a prospective randomized comparative trial of IMRT and passive scatter proton therapy showed that large tumors and the use of proton therapy independently predicted the need for adaptive planning.[50] Although the 5-year overall survival was poorer for patients with large tumor vs small tumors or for large tumors without adaptive planning, the rate of overall survival for patients with large tumors who received adaptive planning was similar to the overall survival for patients with small tumors. Of the 212 patients, 27 had local failure and 23 had marginal failure, where marginal failure was defined as between the ITV and a 10 mm expansion on the PTV. The only independent predictor of a marginal failure was T3 or T4 status, not treatment modality.

Clinical Challenges for ART Lung Cancer

When to Adapt?

Currently, the trigger for acquiring a resimulation is reactive and subjective, based on anatomical changes observed in the on-treatment 3D imaging. When substantial anatomical changes are observed, adapting at least once midtreatment provides the patient with a significant dosimetric advantage.[15,51] Unfortunately, despite extensive investigation, there are limited correlations between tumor characteristics at time of initial simulation and if/when significant anatomical changes may occur during treatment. Thus, at a minimum, weekly 3D imaging is recommended during radiation

therapy for patients with locally advanced lung cancer to assess the position and scope of anatomical changes.[22]

The type of patient specific changes indicating a need for adaptation depends on which adaptive philosophy will be utilized. Woodford et al looked at 17 patients and found advantages for patients exhibiting at least 30% tumor regression by volume within the first 20 fractions of treatment when reducing the GTV to spare dose to the lung and heart.[15] Within these 17 patients, the pattern of tumor regression varied extensively, supporting the need for frequent on-treatment imaging. Similar results were reported by Berkovic et al, who examined the relationship between tumor regression and dosimetric consequences in 41 patients and developed look-up tables relating dosimetric sparing for lungs given specific observed GTV volume reductions.[14] In general, the maximum dosimetric benefit occurred when adapting around fraction 15, however this was largely patient dependent and most significant for patients with large initial GTVs. Similar patient specific rules to trigger ART based on density changes to the lungs and geometric migration of the tumor volume were developed by Tvilum et al, as described previously.[19,30] In all studies, the application of patient-specific guidelines to assess the need for ART required moderate-to-extensive manual effort to accurately evaluate and quantify anatomical changes.

How to Adapt?

There are several considerations that explain the lack of consensus regarding which adaptive paradigm provides the most clinical benefit, or least risk, for individual patients. One key point of debate is the need and scope of dosimetric coverage of possible subclinical disease within the initial CTV but outside the midtreatment defined adaptive volume, as illustrated in Figure 2. For these cases, there is uncertainty regarding whether the subclinical disease remains stationary or migrates anatomically with the regression of the GVT. Additionally, should subclinical disease remain stationary, there is debate regarding whether a minimum therapeutic dose is appropriate to the initial treatment volume. As described above, an approach to localize the originally-defined CTV was developed and evaluated in an in silico feasibility study by Weiss et al, with a goal of treating this remaining subclinical disease to a fixed prescription dose.[16,52] Alternatively, Guckenberger et al demonstrated that an isotoxic dose escalation may sterilize this subclinical disease without this additional targeting approach, under several assumptions about clonogen density in this region.[53] In actual clinical data, local control results from the LARTIA study suggest the subclinical disease in this "rind" around the primary tumor may be well-controlled with an isotoxic OAR sparing approach, however more extensive prospective studies are needed.[23]

A second consideration is the efficacy, utility, and safety of dose escalation in the adaptive treatment of lung cancer. The multi-institutional prospective clinical trial RTOG 0617 showed that dose escalation from 60 Gy to 74 Gy using nonadaptive therapy leads to worse patient survival.[10] However, ART may provide a role in reducing toxicity and safely escalating dose. It may also enable safe hypofractionation in the locally advanced setting. However, early indications leveraging the dosimetric advantages of dose escalation on midtreatment tumor regression, while providing evidence of increased local control with equivalent organ toxicities, are predominantly provided by single institutions on limited patient datasets. The upcoming anticipated results of RTOG 1106 and similar studies worldwide will soon provide guidance in the methodology and scope of dose escalation based upon mid-treatment imaging.

Future Improvements

The effort required to implement and utilize a manual decision support workflow to identify when ART may be beneficial for lung cancer patients may be too extensive for routine clinical practice with existing tools and staff resources. Additionally, most manual decision support tools rely on the ability of clinical staff to accurately and efficiently review on-treatment imaging against specific decision support criteria, a process that is inherently subjective.[54] In order to implement an efficient, comprehensive daily ART decision support evaluation, all anatomical changes impacting the dosimetric fidelity of the IMRT plan need to be quantified and incorporated into an automated prediction model. Brink et al provided one of the first investigations into the feasibility of an automated tool to provide a measure of the GTV volume observed on the daily CBCT images and correlated early/midtreatment GTV regression to the final end of treatment GTV volume.[55] More recently, van den Bosch et al developed an automated method to evaluate density changes within the treatment volume, mediastinum, and lung-region based on user-specified thresholds to changes in water-equivalent path lengths within the specified volumes as calculated on daily CBCT imaging.[56] The automated methodology correctly identified 89% of consensus cases that required ART, as defined by 2 expert observers (1 physician and 1 physicist), while producing a false positive rate of 34%. These experts used institutional guidelines to determine whether ART was needed: change of the tumor size of at least 1 cm in 1 direction, shift of the visible tumor outside the PTV, difficulties in localization of the tumor (eg, due to surrounding atelectasis or pleural effusion), a shift of the mediastinal structures (limit approximately 1 cm) or changes in atelectasis or pleural effusions. Extending this proof-of-concept study utilizing modern machine learning and radiomics methodologies offers the potential to improve the sensitivity and specificity while reducing false positive rates.

Daily dose accumulation offers the potential to directly track and respond to the dosimetric changes occurring during treatment. Most dose accumulation algorithms rely on accurate deformation maps generated by deformable image registration techniques, which can exhibit increasing inaccuracies when large anatomical variations occur between the two image datasets.[57,58] The commonly

observed anatomical changes in lung cancer may cause a significant loss of accuracy when using conventional image intensity-based deformable image registration algorithms.[59] Improvements in deformable image registration within lung tissue, including biomechanical models, vessel-enhanced, and mass-preserving cost functions, offer the potential to improve dose accumulation in the presence of large anatomical changes such as tumor regression, pleural effusions, and atelectasis.[58,60]

Recently, linear accelerators coupled to magnetic resonance imagers (MRIs) have become commercially available. Given that advanced stage lung tumors often invade central structures and have regional spread to mediastinal lymph nodes, using MRI for daily pretreatment alignment may allow for a reduction in the setup component of CTV-PTV margin when compared to CBCT.[61] These same machines have also allowed for online adaptation.[62] The combination of real time tracking and online adaptation has also been proposed to allow for safer dose escalation in more advanced lung cancers with better OAR sparing, particularly within the central thorax near the proximal bronchial tree, esophagus, and heart.[63] A retrospective in silico study of patients receiving hypofractionated radiation therapy alone for more advanced central lung malignancies showed that after one week of treatment at fraction 6, there was significant on-treatment MRI-defined GTV reduction, with a median reduction of 27%.[64] Application of the initial plan at fraction 6 resulted in violations of OAR constraints in approximately half of patients. Adaptive planning was able to reverse all of these OAR violations and in 40% of fractions corrected for OAR constraint violations, PTV coverage was able to be increased concomitantly. Prospective clinical trials of this combination of MR for both alignment and adaptation are being planned at several institutions with MR image guided radiation therapy.

Conclusions

The role of adaptive radiotherapy in the treatment of locally advanced stage III lung cancer offers the potential to improve therapeutic outcomes, whether through dose escalation or organ-at-risk sparing. Numerous smaller studies have investigated several methods in applying ART to the lung cancer patient population and results from large prospective clinical trials will hopefully provide consensus on the method, utility, and efficacy of implementing ART in a clinical setting. Additional development into standardization and automation of the ART workflow, specifically in identifying when ART is warranted and in reducing the manual clinical effort needed to produce an adaptive plan, will be paramount making it feasible for the broader radiation therapy community.

References

1. American Cancer Society. Cancer Facts & Figures Available at: https://www.cancer.org/cancer/lung-cancer.html; 2018
2. Goldstraw P, Crowley J, Chansky K, et al: The IASLC Lung Cancer Staging Project: Proposals for the revision of the TNM stage groupings in the forthcoming (seventh) edition of the TNM classification of malignant tumours. J Thorac Oncol 2:706-714, 2007
3. Aupérin A, Le Péchoux C, Rolland E, et al: Meta-analysis of concomitant versus sequential radiochemotherapy in locally advanced non−small-cell lung cancer. J Clin Oncol 28:2181-2190, 2010
4. Curran Jr1 WJ, Paulus R, Langer CJ, et al: Sequential vs concurrent chemoradiation for stage iii non-small cell lung cancer: Randomized phase III trial RTOG 9410. J Natl Cancer Inst 103:1452-1460, 2011
5. Vansteenkiste J, De Ruysscher D, Eberhardt WE, et al: Early and locally advanced Non-Small-Cell Lung Cancer (NSCLC): ESMO clinical practice guidelines for diagnosis, treatment and follow-up. Ann Oncol 24
6. Yoon SM, Shaikh T, Hallman M: Therapeutic management options for stage III non-small cell lung cancer. World J Clin Oncol 8:1, 2017
7. Antonia SJ, Villegas A, Daniel D, et al: Durvalumab after chemoradiotherapy in Stage III Non−small-cell lung cancer. N Engl J Med 2017. https://doi.org/10.1056/NEJMoa1709937. NEJMoa1709937
8. Antonia SJ, Villegas A, Daniel D, et al: Overall survival with durvalumab after chemoradiotherapy in Stage III NSCLC. N Engl J Med 2018. https://doi.org/10.1056/NEJMoa1809697. NEJMoa1809697
9. Edge SB, Compton CC: The American Joint Committee on Cancer : The 7th edition of the AJCC cancer staging manual and the future of TNM. Ann Surg Oncol 2010: 1471-1474. https://doi.org/10.1245/s10434-010-0985-4
10. Bradley JD, Paulus R, Komaki R, et al: Standard-dose versus high-dose conformal radiotherapy with concurrent and consolidation carboplatin plus paclitaxel with or without cetuximab for patients with stage IIIA or IIIB non-small-cell lung cancer (RTOG 0617): A randomised, two-by-two factorial p. Lancet Oncol 16:187-199, 2015
11. Bradley JD, Moughan J, Graham MV, et al: A Phase I/II Radiation Dose Escalation Study With concurrent chemotherapy for patients with inoperable Stages I to III Non-Small-Cell Lung Cancer: Phase I Results of RTOG 0117. Int J Radiat Oncol Biol Phys 77:367-372, 2010
12. Machtay M, Bae K, Movsas B, et al: Higher biologically effective dose of radiotherapy is associated with improved outcomes for locally advanced non-small cell lung carcinoma treated with chemoradiation: An analysis of the radiation therapy oncology group. Int J Radiat Oncol Biol Phys 82:425-434, 2012
13. Kong FM, Ten Haken RK, Schipper MJ, et al: High-dose radiation improved local tumor control and overall survival in patients with inoperable/unresectable non-small-cell lung cancer: Long-term results of a radiation dose escalation study. Int J Radiat Oncol Biol Phys 63:324-333, 2005
14. Berkovic P, Paelinck L, Lievens Y, et al: Adaptive radiotherapy for locally advanced non-small cell lung cancer, can we predict when and for whom? Acta Oncol 54:1438-1444, 2015
15. Woodford C, Yartsev S, Dar AR, et al: Adaptive radiotherapy planning on decreasing gross tumor volumes as seen on megavoltage computed tomography images. Int J Radiat Oncol Biol Phys 69:1316-1322, 2007
16. Weiss E, Fatyga M, Wu Y, et al: Dose escalation for locally advanced lung cancer using adaptive radiation therapy with simultaneous integrated volume-adapted boost. Int J Radiat Oncol Biol Phys 86:414-419, 2013
17. Sibolt P, Ottosson W, Sjostrom D, et al: Adaptation requirements due to anatomical changes in free-breathing and deep-inspiration breath-hold for standard and dose-escalated radiotherapy of lung cancer patients. Acta Oncol 54:1453-1460, 2015
18. Møller DS, Holt MI, Alber M, et al: Adaptive radiotherapy for advanced lung cancer ensures target coverage and decreases lung dose. Radiother Oncol 121:32-38, 2016
19. Kwint M, Conijn S, Schaake E, et al: Intra thoracic anatomical changes in lung cancer patients during the course of radiotherapy. Radiother Oncol 113:392-397, 2014
20. Moller DS, Khalil AA, Knap MM, Hoffman L: Adaptive radiotherapy of lung cancer patients with pleural effusion or atelectasis. Radiother Oncol 110:517-522, 2014
21. Van Zwienen M, van Beek S, Belderbos J, et al: Anatomical changes during radiotherapy of lung cancer patients. Int J Radiat Oncol Biol Phys 72:s111, 2008

22. Elsayad K, Kriz J, Reinartz G, et al: Cone-beam CT-guided radiotherapy in the management of lung cancer. Strahlentherapie Onkol 192:83-91, 2016
23. Ramella S, Fiore M, Silipigni S, et al: Local control and toxicity of adaptive radiotherapy using weekly CT imaging: Results from the LARTIA Trial in Stage III NSCLC. J Thorac Oncol 12:1122-1130, 2017
24. Spoelstra FOB, Pantarotto JR, van Sörnsen de Koste JR, et al: Role of adaptive radiotherapy during concomitant chemoradiotherapy for lung cancer: Analysis of data from a prospective clinical trial. Int J Radiat Oncol Biol Phys 75:1092-1097, 2009
25. Fox J, Ford E, Redmond K, et al: Quantification of tumor volume changes during radiotherapy for non-small-cell lung cancer. Int J Radiat Oncol Biol Phys 74:341-348, 2009
26. Kataria T, Gupta D, Bisht SS, et al: Adaptive radiotherapy in lung cancer: Dosimetric benefits and clinical outcome. Br J Radiol 87:20130643, 2014
27. Wald P, Mo X, Barney C, et al: Prognostic value of primary tumor volume changes on kV-CBCT during definitive chemoradiotherapy for stage III non−small cell lung cancer. J Thorac Oncol 12:1779-1787, 2017
28. Seibert RM, Ramsey CR, Hines JW, et al: A model for predicting lung cancer response to therapy. Int J Radiat Oncol Biol Phys 67:601-609, 2007
29. Kong F, Ten Haken R, Schipper M, et al: A phase II trial of mid-treatment FDG-PET adaptive, individualized radiation therapy plus concurrent chemotherapy in patients with non-small cell lung cancer (NSCLC). J Clin Onocology 31:7522, 2013
30. Tvilum M, Khalil AA, Møller DS, et al: Clinical outcome of image-guided adaptive radiotherapy in the treatment of lung cancer patients. Acta Oncol 54:1430-1437, 2015
31. Tennyson N, Weiss E, Sleeman W, et al: Effect of variations in atelectasis on tumor displacement during radiation therapy for locally advanced lung cancer. Adv Radiat Oncol 2:19-26, 2017
32. Roman NO, Shepherd W, Mukhopadhyay N, et al: Interfractional positional variability of fiducial markers and primary tumors in locally advanced non-small-cell lung cancer during audiovisual biofeedback radiotherapy. Int J Radiat Oncol Biol Phys 83:1566-1572, 2012
33. Christodoulou M, Bayman N, McCloskey P, et al: New radiotherapy approaches in locally advanced non-small cell lung cancer. Eur J Cancer 50:525-534, 2014
34. Guckenberger M, Wilbert J, Richter A, et al: Potential of adaptive radiotherapy to escalate the radiation dose in combined radiochemotherapy for locally advanced non-small cell lung cancer. Int J Radiat Oncol Biol Phys 79:901-908, 2011
35. Cremonesi M, Gilardi L, Ferrari ME, et al: Role of interim 18F-FDG-PET/CT for the early prediction of clinical outcomes of Non-Small Cell Lung Cancer (NSCLC) during radiotherapy or chemo-radiotherapy. A systematic review. Eur J Nucl Med Mol Imaging 44:1915-1927, 2017
36. Kong F-MS, Frey KA, Quint LE, et al: A pilot study of [^{18} F]fluorodeoxyglucose positron emission tomography scans during and after radiation-based therapy in patients with non−small-cell lung cancer. J Clin Oncol 25:3116-3123, 2007
37. Feng M, Kong FM, Gross M, et al: Using fluorodeoxyglucose positron emission tomography to assess tumor volume during radiotherapy for non-small-cell lung cancer and its potential impact on adaptive dose escalation and normal tissue sparing. Int J Radiat Oncol Biol Phys 73:1228-1234, 2009
38. Xiao L, Liu N, Zhang G, et al: Late-course adaptive adjustment based on metabolic tumor volume changes during radiotherapy may reduce radiation toxicity in patients with non-small cell lung cancer. PLoS One 12:1-11, 2017
39. Kong F-M, Ten Haken RK, Schipper M, et al: Effect of Midtreatment PET/CT-adapted radiation therapy with concurrent chemotherapy in patients with locally advanced non−small-cell lung cancer. JAMA Oncol 3:1358-1365, 2017
40. Kelsey CR, Christensen JD, Chino JP, et al: Adaptive planning using positron emission tomography for locally advanced lung cancer: A feasibility study. Pract Radiat Oncol 6:96-104, 2016
41. Van Elmpt W, De Ruysscher D, van der Salm A, et al: The PET-boost randomised phase II dose-escalation trial in non-small cell lung cancer. Radiother Oncol 104:67-71, 2012
42. Raman S, Bissonnette JP, Warner A, et al: Rationale and Protocol for a Canadian Multicenter Phase II Randomized Trial assessing selective metabolically adaptive radiation dose escalation in locally advanced non−small-cell lung cancer (NCT02788461). Clin Lung Cancer 19:e699-e703, 2018
43. Koay EJ, Lege D, Mohan R, et al: Adaptive/nonadaptive proton radiation planning and outcomes in a phase II trial for locally advanced non-small cell lung cancer. Int J Radiat Oncol Biol Phys 84:1093-1100, 2012
44. Veiga C, Janssens G, Teng CL, et al: First clinical investigation of cone beam computed tomography and deformable registration for adaptive proton therapy for lung cancer. Int J Radiat Oncol Biol Phys 95:549-559, 2016
45. Kardar L, Li Y, Li X, et al: Evaluation and mitigation of the interplay effects of intensity modulated proton therapy for lung cancer in a clinical setting. Pract Radiat Oncol 4:E259-E268, 2014
46. Chang JY, Zhang X, Knopf A, et al: Consensus guidelines for implementing pencil-beam scanning Proton Therapy for Thoracic Malignancies on Behalf of the PTCOG thoracic and lymphoma subcommittee. Int J Radiat Oncol Biol Phys 99:41-50, 2017
47. Szeto YZ, Witte MG, van Kranen SR, et al: Effects of anatomical changes on pencil beam scanning proton plans in locally advanced NSCLC patients. Radiother Oncol 120:286-292, 2016
48. Chang JY, Li H, Zhu XR, et al: Clinical implementation of intensity modulated proton therapy for thoracic malignancies. Int J Radiat Oncol Biol Phys 90:809-818, 2014
49. Hoffmann L, Alber M, Jensen MF, et al: Adaptation is mandatory for intensity modulated proton therapy of advanced lung cancer to ensure target coverage. Radiother Oncol 122:400-405, 2017
50. Yang P, Xu T, Gomez DR, et al: Patterns of local-regional failure after intensity-modulated radiation therapy or passive scattering proton therapy with concurrent chemotherapy for non-small cell lung cancer. Int J Radiat Oncol 0, 2018.
51. Dial C, Weiss E, Siebers JV, et al: Benefits of adaptive radiation therapy in lung cancer as a function of replanning frequency. Med Phys 43:1787-1794, 2016
52. Hugo GD, Weiss E, Badawi A, et al: Localization accuracy of the clinical target volume during image-guided radiotherapy of lung cancer. Int J Radiat Oncol Biol Phys 81:560-567, 2011
53. Guckenberger M, Richter A, Wilbert J, et al: Adaptive radiotherapy for locally advanced non-small-cell lung cancer does not underdose the microscopic disease and has the potential to increase tumor control. Int J Radiat Oncol Biol Phys 81:275-282, 2011
54. Boejen A: A learning programme qualifying radiation therapists to manage daily online adaptive radiotherapy. Acta Oncol 2015: 1-14. https://doi.org/10.3109/0284186X.2015.1062914
55. Brink C, Bernchou U, Bertelsen A, et al: Locoregional control of non-small cell lung cancer in relation to automated early assessment of tumor regression on cone beam computed tomography. Int J Radiat Oncol Biol Phys 89:916-923, 2014
56. van den Bosch M, Öllers M, Reymen B, et al: Automatic selection of lung cancer patients for adaptive radiotherapy using cone-beam CT imaging. Phys Imaging Radiat Oncol 1:21-27, 2017
57. Zhong H, Chetty IJ: Caution must be exercised when performing deformable dose accumulation for tumors undergoing mass changes during fractionated radiation therapy. Int J Radiat Oncol Biol Phys 97:182-183, 2017
58. Guy CL, Weiss E, Christensen GE, et al: CALIPER: A deformable image registration algorithm for large geometric changes during radiotherapy for locally-advanced non-small cell lung cancer. Med Phys 2018. https://doi.org/10.1002/mp.12891
59. Zhong H, Kim J, Gordon JJ, et al: In: Jaffray DDA, ed. World Congress on Medical Physics and Biomedical Engineering, June 7-12, 2015, Toronto, Canada. Springer International Publishing; 2015:579-582. https://doi.org/10.1007/978-3-319-19387-8_142
60. Cazoulat G, Owen D, Matuszak MM, et al: Biomechanical deformable image registration of longitudinal lung CT images using vessel information. Phys Med Biol 61:4826-4839, 2016

61. Bainbridge H, Salem A, Tijssen RHN, et al: Magnetic resonance imaging in precision radiation therapy for lung cancer. Transl Lung Cancer Res 6:689-707, 2017
62. Acharya S, Fischer-Valuck BW, Kashani R, et al: Online magnetic resonance image guided adaptive radiation therapy: First clinical applications. Int J Radiat Oncol Biol Phys 94:394-403, 2016
63. Henke L, Kashani R, Yang D, et al: Simulated online adaptive magnetic resonance–guided stereotactic body radiation therapy for the treatment of oligometastatic disease of the abdomen and central thorax: Characterization of potential advantages. Int J Radiat Oncol Biol Phys 96:1078-1086, 2016
64. Henke LE, Kashani R, Hilliard J, et al: In silico trial of MR-guided mid-treatment adaptive planning for hypofractionated stereotactic radiation therapy in centrally located thoracic tumors. Int J Radiat Oncol Biol Phys 102:987-995, 2018