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Adaptive Radiotherapy for Lung Cancer

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Lung cancer radiation therapy (RT) is associated with complex geometrical uncertainties, such as respiratory motion, differential baseline shifts between primary tumor and involved lymph nodes, and anatomical changes due to treatment response. Generous safety margins required to account for these uncertainties limit the potential of dose escalation to improve treatment outcome. Four dimensional inverse planning incorporating pretreatment patient-specific respiratory motion information into the treatment plan already improves treatment plan quality. More importantly, repetitive imaging during treatment quantifies patient-specific intrafraction, interfraction, and progressive geometrical variations. These patient-specific parameters subsequently can drive adaptive plan modification correcting for systematic errors while incorporating random errors. Adaptive RT therefore has the potential to considerably improve the accuracy of RT, reducing the exposure of organs at risk, facilitating safe dose escalation, and improving local control as well as overall survival.
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Lung cancer is the most common cause of cancer mortality.[1] Worldwide some 1.4 million new cases of this disease are diagnosed each year, accounting for 12% of all cancer cases.[2] Surgery is the treatment of choice, but about 80% of the lung cancer patients are (medically or technically) inoperable due to locoregional tumor extension, extrathoracic spread or poor physical condition at the time of diagnosis.[1] External beam radiotherapy (RT) is the primary treatment modality for inoperable lung cancer patients often combined with chemotherapy.

The current prognosis for non–small-cell lung cancer (NSCLC) treated with RT is poor, with a 5-year survival of 5%-40% depending on the tumor stage.[3] Several dose-escalation trials reported an improved local control with increasing dose[4-7] leading to increased failure-free intervals and survival.[6-8] In a large meta-analysis, the influence of improved local control rates on overall survival in NSCLC patients with stage III disease was confirmed.[9] Dose escalation, however, also leads to an increased exposure of organs-at-risk (OAR), such as lung, heart, esophagus, and spinal cord. Radiation pneumonitis is an important dose-limiting toxicity which correlates well with the V_{20}[10] and the mean lung dose (MLD).[11] Dose-effect relationship could be established between the V_5-V_{30}/MLD and radiation pneumonitis.[12-14] Similarly, the V_{35}, V_{40}, and V_{60} significantly correlate with esophagitis.[15-17] Dose escalation therefore leads to an increased and possibly unacceptable normal tissue complication probability.

Several authors have shown that the use of intensity-modulated RT can reduce the radiation exposure to critical normal tissues.[18-20] However, substantial geometrical uncertainties are associated with RT of lung cancer patients influencing the accuracy of imaging, treatment planning, and treatment delivery. Generally, generous safety margins are applied around the target such that tumor underdosage due to these geometrical uncertainties are avoided with an acceptable probability.[21] Reduction of geometrical uncertainties and associated safety margins is therefore warranted to reduce the exposure to OAR and allow safe dose escalation.

Several strategies have been proposed to reduce geometrical uncertainties. Classical electronic portal imaging proved to be effective in reducing setup errors.[22] Visualization of soft-tissue contrast differences, however, is poor with portal imaging, limiting its ability to correct variations of the target and OAR relative to the bony anatomy. Moreover, the projective nature of planar imaging systems intrinsically limits the ability to discriminate different anatomical structures.

More advanced image-guided systems like kilovoltage (kV) cone beam computed tomography (CBCT),[23] megavoltage-CBCT (MV-CBCT),[24] and Tomotherapy[25] have the ability to visualize the tumor and OAR in three dimensions (3D) just before treatment. These systems therefore enable online corrections, aligning the time-averaged mean target

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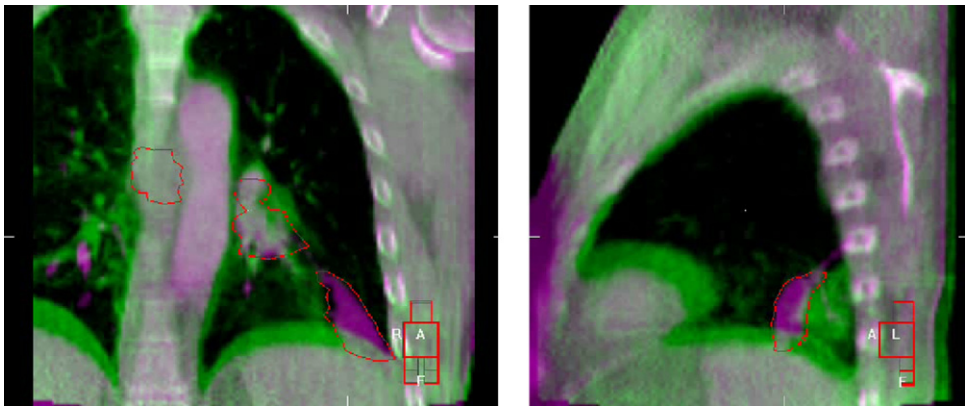

Figure 1 Example of differential motion between primary tumor and involved lymph nodes depicting coronal (left) and sagittal (right) views of a planning CT (purple) and CBCT (green) in a complementary color overlay. Scans were registered on the bony anatomy (vertebrae) yielding a reasonable to good alignment of the nodal regions (left 2 red contours in coronal view) and a clear misalignment of the primary tumor (right contour in coronal view and also visible in sagittal view).

position with the planned position through a couch shift, thereby further increasing the precision of RT. Such a correction strategy is highly suitable for stereotactic body radiotherapy (SBRT), where T1-2N0M0 lung tumors (often in the periphery of the lung far away from critical structures) are treated with a high dose in just a few fractions. In case of nodal involvement, however, differential motion between primary tumor and lymph nodes invalidates the use of couch shifts to reduce these errors, as exemplified in Figure 1. Additionally, in case of planned dose distributions close to the tolerance limits of OAR, correcting for target misalignment in the presence of differential motion might overexpose these OAR. Moreover, geometrical uncertainties induced by progressive changes like dissolving or occurring atelectasis and tumor regression cannot be reduced by couch shifts.

Adaptive radiotherapy (ART), in which an active feedback loop is utilized to build an individualized patient model to modify the treatment plan, has the potential to account for these geometrical uncertainties. In this article we will first describe the relevant geometrical uncertainties present in RT of lung tumors and margins required to account for these. Subsequently, various adaptive correction strategies will be described that can be used to reduce these uncertainties allowing for dose escalation, improve tumor control probability, and overall survival.

Geometrical Uncertainties

There are many sources of geometrical uncertainties present during the RT process. The expected range of uncertainties (or errors) is often expressed in terms of their standard deviation (SD). Errors that are identical for every fraction are called systematic errors while errors that vary day by day are called random errors: random errors blur the cumulative dose distribution, whereas systematic errors shift the cumulative dose distribution.[21,26,27]

Delineation/Target Definition Uncertainties

Target and OAR are generally defined on a planning CT scan. Especially for lung cancer, large uncertainties are associated with target delineation based on CT information alone. Both intra- and interobserver variability have considerable impact on the consistency of delineated structures,[28,29] especially at the tumor-atelectasis and lymph node regions.[30] Inclusion of fluorodeoxyglucose-positron emission tomography (FDG-PET) reduces the overall 3D observer variation substantially from 1.0 cm (1 SD) for CT alone to 0.4 cm (1 SD) for FDG-PET-CT.[30] Note that the beams will be shaped by the delineated structures, not to the actual tumor. Delineation uncertainty is thus a purely systematic error that will influence all treatment fractions in an identical way. Image-guided radiation therapy or ART do not have the ability to solve this problem.

Microscopic Disease

Microscopic tumor extensions cannot be visualized with current imaging modalities. Extent of microscopic disease beyond the visible tumor is therefore estimated based on microscopic tumor spread probability models, quantified using surgical resection specimens.[31] Grills et al[32] concluded that the margin to cover microscopic extensions in 90% of stage I adenocarcinoma would be 9 mm. It is important to realize that patients who are candidates for a thoracotomy and patients receiving thoracic irradiation for lung cancer are quite different. Also, the analysis of the tissue specimens is hampered by tissue deformations and undersampling.[33] As a result, the accuracy of microscopic tumor spread probability models is limited, leaving considerable uncertainties for the individual patient. On the other hand, the required dose levels for the microscopic cells beyond the visible tumor is unknown but might be substantially lower than necessary for the gross tumour volume (GTV).[34,35]

Setup Error

Interfractional setup error, defined as a position difference between plan and treatment of the bony anatomy, has been studied extensively in the literature.[22,36] In particular, mobility of the skin with respect to the bony anatomy limits the reproducibility of the patient setup. In the thoracic region, setup errors are generally quite large: 2-4 mm (1 SD).[37,38] Intrafractionally, motion of the bony anatomy seems to be limited during the 5- to 15-minute beam delivery of normal fractionated RT: <1 mm SD.[38] In SBRT, the delivery times are substantially longer, and the intrafractional stability somewhat decreases.[39,40]

Organ Motion

Respiratory motion greater than 2 cm has been observed for tumors located close to the diaphragm and occasionally in other positions, but are generally smaller than 1 cm.[36,41-43] Respiratory motion induces uncertainties and artifacts in conventional 3D-CT[44] and PET imaging[45] and affects the dose distribution during treatment delivery.[46] Moreover, considerable interfraction baseline variation has been observed, i.e., variability in the location of the respiratory trajectory relative to the bony anatomy.[47-50] These baseline variations are similar in magnitude to bony setup errors, although the (physiological) processes causing baseline variations are not well understood. The shape of the trajectory seems more or less constant at the minute to minute time scale.[50-52]

Summary

A variety of geometrical uncertainties affect the accuracy of RT of lung cancer. Table 1 summarizes the estimates of the systematic and random components of these uncertainties. All uncertainties are expressed by their SD.

Treatment Preparation

Respiratory Correlated Imaging

To reduce the uncertainties and artifacts induced by respiratory motion during CT/CBCT scanning, several groups have developed respiratory correlated acquisition techniques.[53-56] By retrospectively sorting data using a respiratory signal, a four-dimensional (4D) CT dataset is obtained containing 3D-CT images at multiple phases of the respiratory cycle. Respiratory correlated imaging reduces motion artifacts such that the mean position, trajectory, and shape of moving anatomy can be determined with higher accuracy.[57] Recently, motion compensated (MC)-CBCT reconstruction algorithms have been developed, improving image quality while at the same time reducing image acquisition times and/or improving dose efficiency.[58-61] A 4D-CT or MC-CT, however, still contains artifacts due to residual motion and breathing irregularities and is still only a snapshot of the patient's respiratory behavior.

Wolthaus et al[62] developed a novel method to exploit the 4D-CT data for treatment planning by extracting a single frame of a 4D-CT, in which the moving tumor is closest to its time averaged mean position, the midventilation-scan. The midventilation-scan ensures that no respiratory motion–induced systematic errors are propagated into the treatment planning process.

Table 1 Summary of the Different Components of the Uncorrected Geometrical Uncertainties Present During RT of Lung Cancer Patients as Obtained From Different Studies Expressed by Their Standard Deviations

Source	Systematic	Random
Target definition[30]	2-7 mm	—
Microscopic spread[31]	2-3 mm	—
Respiratory motion[42]	0-7 mm	0-7 mm
Interfraction setup error[38]	4 mm	4 mm
Interfraction baseline shifts[50]	4 mm	3 mm
Mean target intrafraction motion[40]	1-2 mm	1-2 mm

Population-Based Margins

Geometrical uncertainties can be incorporated into the treatment planning process by taking margins around the clinical target volume (CTV), thereby defining the planning target volume (PTV), as recommended by the International Commission on Radiation Units and Measurements (ICRU)-Report 50[63] and 62.[64] Several population-based margin recipes (MR) have been published.[65-67] van Herk et al[21] derived a recipe to deliver at least 95% of the prescribed dose to 90% of patients:

$$M = 2.5\sum + b\sqrt{(\sigma^2 + \sigma_p^2)} - b\sigma_p, \qquad (1)$$

with M as the CTV-to-PTV margin, $\sum$ the total SD of the systematic errors, σ the total SD of the random errors, σ_p describes the width of the penumbra modeled by a cumulative Gaussian, and b the value of the inverse cumulative standard-normal distribution at the prescribed PTV minimum dose level. The underlying assumption is that the resulting PTV is large compared with the width of penumbra. The various components of systematic and random uncertainties are summed in quadrature to calculate the total SD. Eq. 1 reflects the fact that the effect of random errors on the planned dose distribution depends on the penumbra width as illustrated in Figure 2. In lung, where the increased range of secondary electrons results in a broadening of the beam penumbra,[68] the additional margin required for the random errors is quite small. Systematic errors have thus a dominant effect on the cumulative dose, especially in lung. Note that these observations apply to RT using MV-photons. In case of proton or heavy-ion therapy, the effect of random errors might be substantially larger.

Individualized Margins

Traditionally, margins are based on population statistics. With patient-specific characterization of tumor motion, however, it becomes possible to generate patient-specific treatment volumes. Separate margins have been proposed for positioning uncertainty (setup margins) and for organ motion (internal margins).[69] Several authors have therefore proposed the use of an internal target volume (ITV) that encompasses

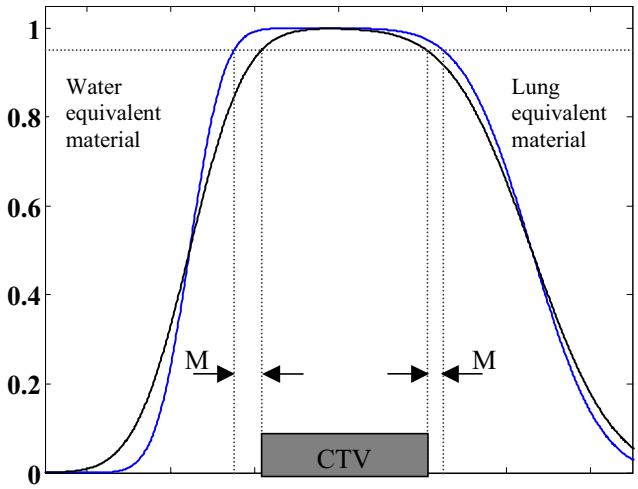

Figure 2 Diagram to illustrate the effect of random errors on dose distributions for water equivalent material (left) and lung tissue (right). The planned dose profile (blue) is convolved with the random error distribution producing the blurred dose profile (black). A margin M is used such that the blurred dose profile covers the CTV prescription dose (horizontal dashed line). The required margin on the right is substantially smaller due to the wider penumbra. Note that the required margin would reduce for lower prescription doses.

all motion and shape changes over the respiratory cycle based on a composite of delineations of an inspiration and expiration breath-hold scans,[70,71] a composite of delineations on several phases of a 4D-CT[72] or delineation on a 4D-CT maximum intensity projection.[72,73] In case of gated delivery techniques (see below), the ITV only encompasses part of the respiratory cycle within the gating window.[74] Subsequently, the ITV is expanded to a PTV to account for other geometrical uncertainties. However, because setup errors and internal organ motion are generally uncorrelated, a linear addition of these uncertainties is, in general, not correct.[21,67] Moreover, respiratory motion blurs the dose distribution similar to random errors[75,76] provided that the time-averaged tumor position is accurately known. This blurring can be described by a convolution with the probability distribution function (PDF) that describes the nature of the motion. Note that the combined effect of respiratory motion, other random errors, and penumbra of the dose distribution often can be approximated by a Gaussian distribution even if the respiratory motion PDF is non-Gaussian. The overall random SD can thus be approximated by

$$\sigma \approx \sqrt{(\sigma_r^2 + \sigma_o^2)} \qquad (2)$$

with σ_r as the SD of the tumor respiratory motion PDF and σ_0 the SD of the other random errors. Note that σ_r can often be approximated by A/3 with A the peak-to-peak amplitude. Once the patient's respiratory amplitude is estimated from fluoroscopy or 4D-CT, a patient-specific margin can be calculated using Eq. 1 and 2. In Figure 3, it is illustrated that the ITV concept to account for breathing motion generates larger margins than the MR described above. The latter indicates that the effect of respiratory motion during treatment delivery is small even for considerable tumor motion. Similar findings were observed using phantom experiments.[46] Similarly, Harsolia et al[77] reported that margins based on random components of tumor motion were considerably smaller than the ITV.

Other patient-specific variabilities, such as setup error, baseline shifts, and amplitude changes are still unknown at the pretreatment phase. Initial treatment plans should therefore be based on population statistics of these parameters. Repetitive imaging is required to quantify patient-specific inter- and intrafraction variabilities. Once these are estimated, margins can be further individualized[49] as described later in the text.

Treatment Planning

Intensity modulated RT treatment plans can deliver RT doses 25%-30% higher than 3D-conformal radiotherapy in node-positive patients and in patients with lymph nodes and target volumes close to the esophagus.[18,78] Margins can be used to incorporate geometrical uncertainties into the treatment planning process. Alternatively, geometrical uncertainties can be explicitly taken into account in the planning dose calculation and optimization.[79,80] Compared with conventional treatment planning, these methods commonly include the temporal variation observed in a 4D image in the planning dose evaluation, and therefore are called 4D inverse planning. Frequently, these efforts are based on a convolution method tailored to the patient-specific respiratory tumor motion PDF assessed by pretreatment 4D-CT or fluoroscopy.[81-84] By blurring the dose distribution with respiration, a dose distribution is obtained that is a close approximation to the dose distribution resulting from incorporating the full 4D anatomy variation over the respiratory cycle.[83,85,86] Alter-

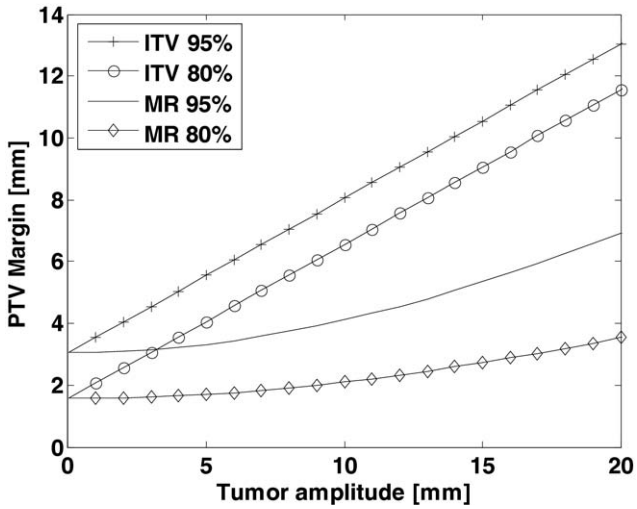

Figure 3 PTV margin as a function of the peak-to-peak tumor amplitude of respiratory motion for different margin expansion concepts, ITV and margin recipe (MR; Eq 1 and 2), and different prescription dose levels based on the random uncertainties ($\Sigma = 0$) in Table 1. The ITV concept clearly generates larger margins than the margin recipe. Margins for (residual) systematic uncertainties need to be added according to Eq 1.

natively, Keall et al[87] described a method to simultaneously optimize the dose distribution on each phase of the 4D-CT and accumulate the contributions of each phase to a reference phase for evaluation to design a treatment plan where the radiation beam tracks the respiration-induced target motion.

In case of 4D treatment plan optimization tailored to respiratory motion alone, additional PTV margins are required to compensate for the residual geometrical uncertainties. Separating respiratory motion from other random uncertainties, however, effectively leads to a linear addition of these 2 components instead of an addition in quadrature (Eq. 2), and thus to too generous dose distributions. Hugo et al,[49] by contrast did include the combined PDF of both respiratory motion and setup errors into the optimization. Moreover, systematic errors, which have a large impact on the difference between the planned and delivered dose distribution, can also be incorporated into the inverse plan optimization.[88,89]

During the pretreatment planning optimization process, only patient-specific information regarding respiratory motion is available, while this patient-specific information is often just a snapshot of the patient's respiratory behavior. To further improve the accuracy and plan quality, additional information on the patient-specific systematic and random variations in mean position and amplitude is required that can be fed back into an adaptive treatment plan optimization process.[49]

Breathing Adapted RT

Repetitive measurement of respiration-induced motion during the first few treatment fractions allows for a more accurate characterization of the patients' respiratory tumor motion PDF, quantify changes with the pretreatment PDF, and adapt the treatment plan to these changes. For most patients, however, the respiratory tumor motion PDF is quite constant.[50] Hugo et al[51] evaluated an adaptive protocol, correcting for interfraction change in the respiratory pattern and found little effect on margin size due to most patients having only small daily changes in the respiratory pattern. Moreover, the impact of respiration-induced motion on the accumulated CTV dose is relatively small in lung cancer provided that the time-averaged mean position is correctly positioned.[62,80,90,91] Methods to further increase the precision of RT by removing the dose-blurring effect of the motion require active motion compensation techniques like gated RT,[92,93] breath-hold,[94] and tumor tracking.[87,95,96] These techniques adapt the treatment equipment to maintain a constant target position in the beam's eye view when the beam is on.

Corrections for intrafraction motion require an extremely robust motion detection of the tumor, otherwise uncertainties cannot be reduced.[97] Fluoroscopy has been proposed to track the tumor,[98] possibly in combination with implanted markers.[93] As fluoroscopic tracking delivers skin dose up to 2 cGy/min,[99] often external surrogates for tumor motion are used (eg, motion of the external surface). Such surrogates have to be calibrated with the actual tumor motion to keep it reliable in the presence of changes in respiratory pattern.[100] Hybrid approaches supplement fluoroscopy data with external surrogates and generate a correlation model between them. The external surrogate is then adapting the treatment equipment, and low-frequency fluoroscopy is used to validate and possible update the correlation model. Such a hybrid approach has been used to track lung tumors using the CyberKnife[101] and is being investigated for multi leave collimator (MLC)-based tracking.[102]

Finally, accurate prediction models are required to account for inevitable system delays that are generally based on mathematical models or adaptive filters. An interesting alternative to tumor tracking is tumor trailing, where only the time averaged mean position is followed to account for possible time trends.[103] Trailing strategies have the potential to improve conformity of the delivered dose to the target in the presence of irregular motion, while the mechanical limitations of implementing tumor trailing are less rigorous than those of real-time tracking.

Adaptive Management of Interfraction Variability

Considerable systematic tumor baseline shifts have been observed in lung cancer patients.[50] In case of node-negative patients, image-guided corrections aligning the time averaged mean target position can reduce these errors. In case of involved lymph nodes, however, differential baseline shifts between primary tumor and nodes invalidates the use of couch shifts to reduce these errors, thus currently requiring large PTV margins. Significant PTV margin reductions can be achieved by adaptive plan modification following repetitive imaging.[104] That is, by utilizing population-based margins during the initial stages of treatment, during which time, daily images are acquired to construct patient-specific statistical estimates of the systematic and random uncertainties in the target positions, an adapted plan can be designed that incorporates the patient-specific estimates.

Hugo et al[51] compared several image-guided and adaptive strategies for the management of interfraction variability, such as margins based on patient population statistics adapted to the pretreatment respiratory amplitude, off-line adaptive plan modification based on patient-specific systematic error, and online correction. They concluded that the greatest margin reduction was achieved by the off-line adaptive strategy confirming that the management of systematic baseline variations is important. A daily online correction strategy that also manages the random component only moderately improved the accuracy. Similar results were reported by Harsolia et al[77] achieving 39% and 44% decreased PTV volumes with 4D-off-line ART and 4D-online ART techniquesrespectively, resulting in reduced mean lung doses of 26% and 31%.

The above-mentioned papers studied node-negative patient groups that still could be corrected online by a couch shift. An adaptive strategy suitable for node-positive patients requires deformable registration to account for differential motion[105,106] as depicted in Figure 4. For Fraction 1 to N, delivering a treatment plan based on population statistics

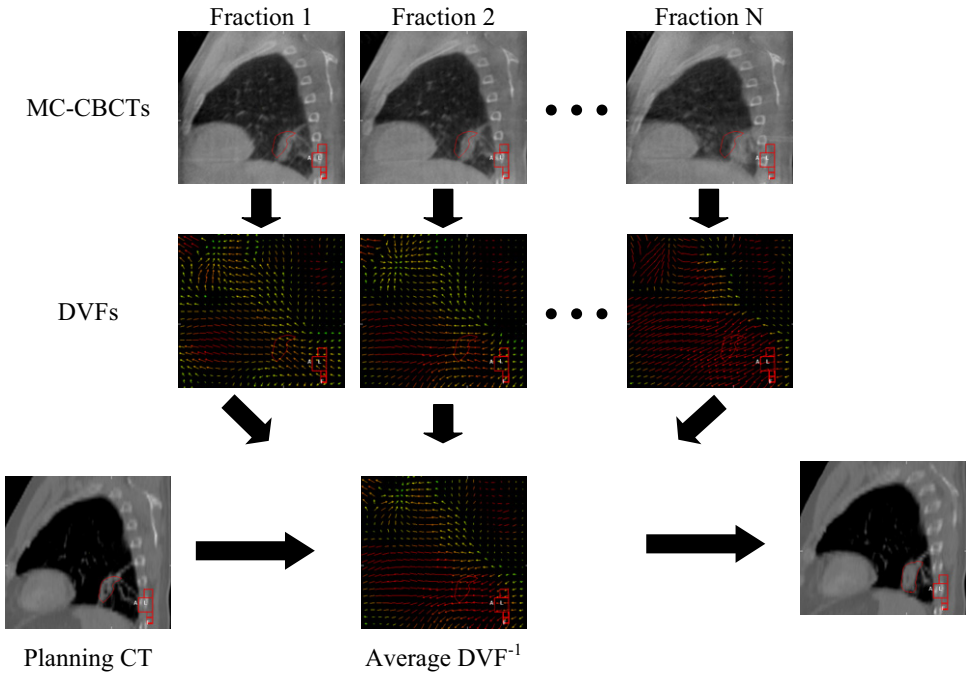

Figure 4 Schematic representation of an adaptive strategy suitable for management of systematic baseline shifts node-positive patients. For fraction 1 to N delivering a treatment plan based on population statistics adapted to the pretreatment respiratory amplitude, MC-CBCTs are acquired. Each MC-CBCT is deformable registered to the planning CT providing N deformation vector fields (DVF). Applying the inverse of the average DVF to the planning CT generates a CT scan that represents the average patient anatomy over the first N fractions.

adapted to the pretreatment respiratory amplitude, MC-CBCTs are acquired. Each MC-CBCT is deformable registered to the planning CT providing N deformation vector fields (DVF). Applying the inverse of the average DVF over these N fractions to the planning CT generates a CT scan that represents the average patient anatomy over the first N fractions, eliminating systematic errors originating from setup errors or baseline shifts. Note that this average anatomy never existed in reality. Subsequently, an adapted treatment plan can be designed on this new CT scan, with smaller margins accounting for residual random uncertainties.

To evaluate PTV margin reduction by this adaptive replanning strategy, we evaluated repeat CBCT scans for 20 node-positive lung cancer patients. Required margins were retrospectively calculated taking into account delineation uncertainty ($\Sigma = 2$ mm), residual bony anatomy setup error after online setup correction ($\Sigma = \sigma = 1$ mm), residual baseline variation after adaptive replanning, and respiratory motion (10 mm peak-to-peak amplitude). Uncorrected baseline variations were 4.2 mm (systematic) and 2.1 mm (random) in the craniocaudal -direction requiring a 14-mm margin. Adaptive replanning considerably reduced the required margin dropping to 8 mm after 5 of the 24 fractions as depicted in Figure 5.

Further refinements are possible by analyzing the variability over the combined DVFs used for the deformable registration and motion-compensated CBCT reconstruction. These DVFs describe the local positional PDFs and can be incorporated into the treatment plan optimization process as described above to obtain dose distributions that are robust against these patient-specific variabilities. It is important to note, however, that patient-specific variability derived from just a few measurements (scans) has a large uncertainty.[107] Better predictions are obtained with Kalman or Bayesian style approaches,[108,109] where the variability of individual patient data are combined in a weighted method with population data.

Finally, discrepancies between the planned and the delivered dose before replanning can be estimated and accommo-

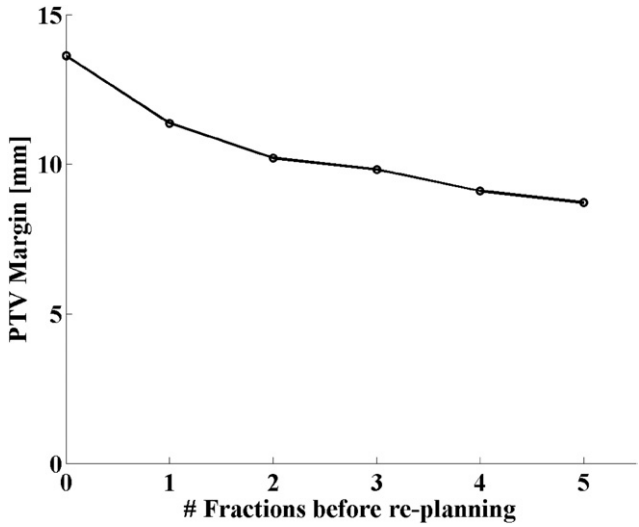

Figure 5 Reduction in the required PTV margin following adaptive replanning based on the first 1-5 initial fractions used to obtain an estimate of the systematic baseline shift.

dated. That is, by recalculating the dose on the repeat imaging sets, applying the DVFs to reformat the dose distributions to the planning CT geometry and accumulate the daily fraction doses, a more likely estimate of the delivered dose can be obtained. This estimate can then be used as a background dose for the adaptive plan reoptimization.[110]

Adaptive Management of Treatment Response

Treatment response can cause changes in tumor size, anatomical changes in the surrounding OAR, and changes in the tumors biological activity. Adaptive management of each type of change has the potential to improve treatment efficacy as described further.

Tumor Regression

Tumor shrinkage has been studied using various imaging modalities, such as electronic portal imaging, repetitive CT scanning, or PET-CT scanning. The regression rates per day reported in these studies vary considerably between 0.6% and 2.4%/d (Table 2). Tumor regression potentially allows for plan adaptation to enable dose escalation or reduce exposure to OAR. Effective adaptation, however, requires sufficient regression early during treatment.

In a relatively large group of 114 consecutive lung cancer patients, van Zwienen et al[111] observed noticeable regression in only 40% of the patients. In 8% of the patients, a volume reduction of >25% was seen in the third week and additionally of 17% in the fourth week. Woodford et al[112] described a potential for dose escalation for patients with at least 30% GTV decrease at any point measured with MV-CT in the first 20 fractions of treatment. Feng et al[113] performed a planning study and reported a meaningful dose escalation of 30-102 Gy or a reduction in normal tissue complication probability of 0.4%-3% based on a mid-RT PET adapted plan. The use of subsequent FDG PET/CT during treatment at a dose of 50 Gy was studied by Gillham et al.[114] Despite tumor shrinkage an adaptive strategy would result only in a modest improvement in dose escalation in their analysis, because a large part of the normal tissue tolerance was already applied.

Reduced metabolic activity on FDG-PET does not necessarily correlate with cell death or complete responses in tumors. Moreover, shrinkage of the GTV does not necessarily imply shrinkage of the CTV. We observed 2 types of tumor regression as illustrated in Figure 6. (1) The surrounding lung tissue can move consistently with the regressing tumor. This behavior is consistent with a tumor that pushed away the surrounding tissue when growing. In such a case, field adaptation seems safe as tissue previously not part of the target volume moved into the high dose region. (2) The surrounding tissue remains in its original location, while the tumor erodes, ie, the CTV seems to be constant while the GTV shrinks. This behavior is consistent with a tumor that infiltrates into the surrounding tissue when growing. In such a case, delivering the planned dose to the original CTV seems appropriate, possibly boosting the regressing GTV. Therefore, careful analysis of regression patterns is required before adaptive plan modifications can be safely applied.

Anatomical Changes

Lung tissue and other intrathoracic tissues can progressively deform/change shape over the 5-7 weeks of treatment. Especially in lung cancer patients with frequently large obstructive tumors invading central airways atelectasis, pleural effusion, and/or inflammatory or infectious conditions might occur.[115] Furthermore, lung reventilation due to reopening of air-ways following lung atelectasis can change both the breathing pattern and regional lung and tumor configuration and tumor and lymph node location as well (Fig. 7).

Van Zwienen et al[111] analyzed repetitive CBCT scans of 114 consecutive lung cancer patients (cT1N0 to cT4N3) treated with conventional RT with a dose of 45-88 Gy with an overall treatment time of 5-6 weeks. Tumor regression was observed in 46 patients (40%), while only 1 patient (1%)

Table 2 Tumor and Lymph Node Regression Rate in Volume Percentage Per Day Reported During the Thoracic Irradiation of Lung Cancer Patients in Different Studies Using Electronic Portal Imaging, Repetitive CT- or FDG-PET/CT Scanning

	No. Patients	Modality	Regression Rate (%/d)	Observations
Erridge 2003 Edinburgh–NKI/AvL	25	EPID	−0.9	Microscopic extensions mentioned
Kupelian 2005 M.D. Anderson	10	In room MV-CT	−1.2	Increased dose to PTV and lungs
Siker 2006 Wisconsin	25	MVCT	−2.4	Mixed group, radical, palliative and stereotactic RT
Bosmans 2008 Maastro	23	FDG-PET/CT	−0.39	Lymph node regression only
McDermott 2006 NKI/AvL	1	EPID	−1.5	Increased dose to PTV and lungs
Underberg 2006 VUMC	40	4D-CT and conventional CT	−1.4	Volume. increase 1st and 2nd wk
Britton 2007 M.D. Anderson	8	In room KV-CT	−1.3	Volume increase 1st and 2nd wk
Woodford 2007 Ontario	17	In room MV-CT	−0.79	
Fox 2009 Johns Hopkins	22	MVCT	−1.2	Regression greater (−1.4%) in first 3 wk
Feng 2009 Michigan	14	Mid-RT FDG-PET/CT	−1.4	Planning study
Van Zwienen 2008 NKI/AvL	114	In room kV-CBCT	−0.6	Frequent anatomical changes occurred

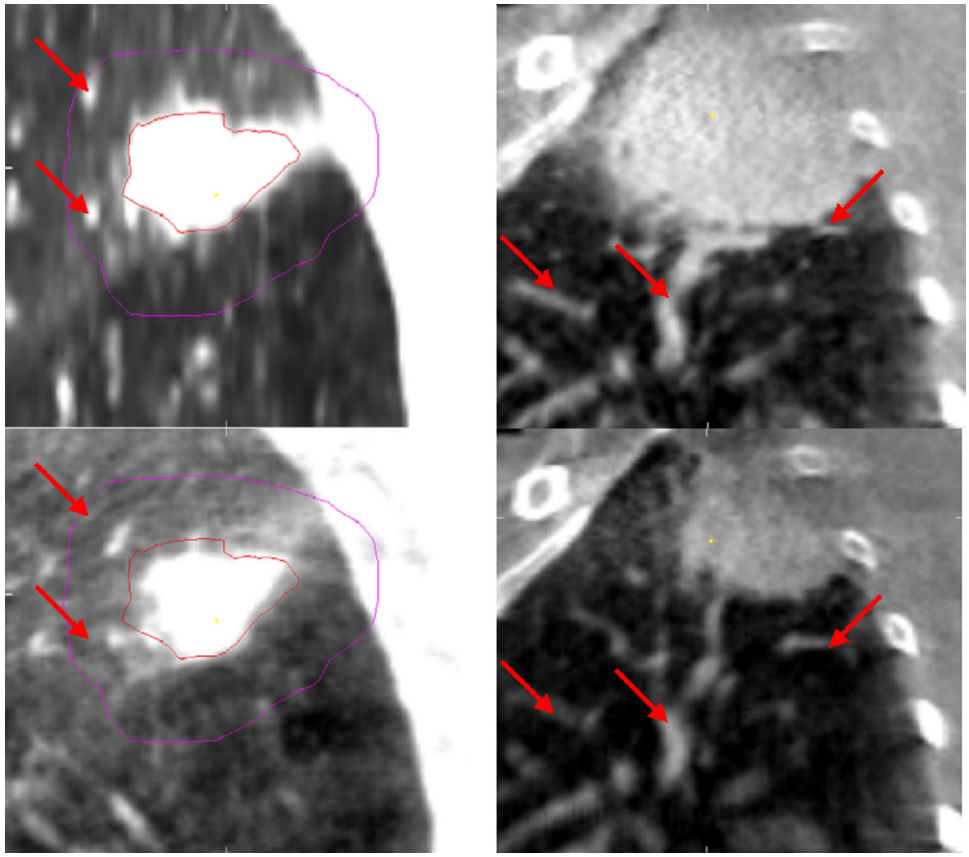

Figure 6 Illustration of 2 different types of tumor regression. Left, the surrounding tissue moves consistently with the regressing tumor. Right, the position of the surround tissue remains constant while the tumor erodes.

showed tumor progression during treatment. Changes in atelectasis were reported for 33 patients (29%); 26 dissolving (23%) and 7 increasing (6%) pleural effusion occurred in 15 patients (13%).

Progressive anatomical changes are difficult to predict. It is therefore recommended to frequently image over the course of treatment in case of pretreatment atelectasis, centrally located and/or large volume tumors. Ideally, the adapted treatment plan would take into account the discrepancy between the planned and actually delivered dose before plan adaptation provided sufficient imaging data are available to quantify the rate of changes, similarly as described above. In practice,

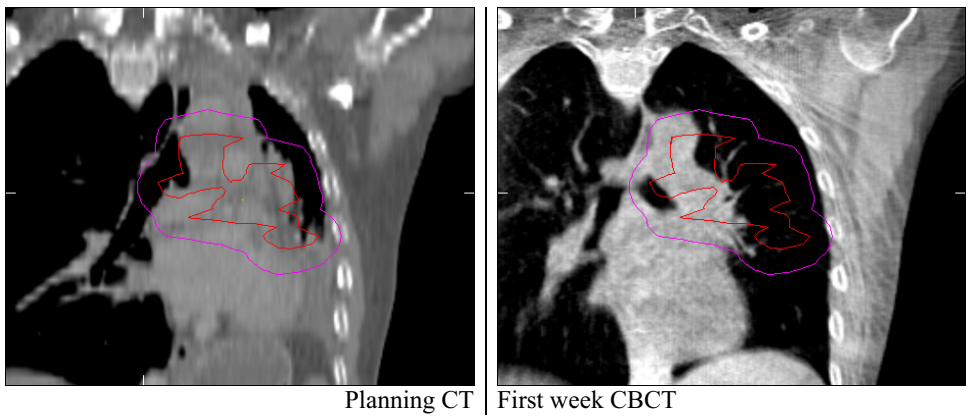

Figure 7 Example of progressive anatomical changes requiring plan adaptation depicting the planning CT (left) and first week CBCT (right) aligned on the bony anatomy. Pretreatment GTV (red) and PTV (purple) delineations are overlaid on both scans. Due to shrinkage of the tumor the atelectasis (seen on the planning CT scan) dissolved and a shift of mediastinal structures to the normal position occurred (seen on the CBCT scan). As a consequence, the dose distribution changed, the dense tissue of the collapsed lung dissolved, the tumor, and subcarinal lymph node moved outside the PTV and excessive irradiation of normal lung tissue occurred.

accurate registration in the presence of large anatomical changes is challenging at best. More research is required to improve the registration accuracy of deformable registration algorithms.

Biological Response

Next to anatomical changes, biological response to treatment might have the potential for adaptive plan modification. Imaging with FDG-PET is increasingly used to monitor tumor response in NSCLC patients undergoing (chemo−)RT. Quantitative assessment of therapy-induced changes in tumor FDG uptake may allow prediction of tumor response and/or radiation-induced lung toxicity. Early identification of nonresponding patients or patients at high risk for radiation-induced lung toxicity has the potential to reduce significantly side effects and costs of ineffective or toxic treatment at a time when adaptation of the irradiation or treatment strategy is still open.

To completely exclude influences of inflammation it was recommended to use FDG-PET for assessment of tumor response 2-6 months after the end of the irradiation.[116,117] However, FDG-PET results 3-4 weeks after chemo-RT already accurately predicts histopathological responders with an accuracy of 89%.[118] Moreover, Aerts et al[119] reported that these post-treatment residual metabolic-active areas within the tumor largely corresponded with the high FDG uptake area of the pre-RT scan. These findings enable selective boosting of high FDG uptake areas within the tumor and are subject of ongoing clinical trials. For adaptive RT, however, response assessment over the course of therapy is required that modify patient-specific treatment response predictions.

An increased FDG uptake in the lung early during the irradiation in NSCLC patients was correlated with increased lung toxicity.[120] This early finding of increased lung toxicity probability might be useful in selecting NSCLC patients at risk during treatment and adapt the treatment plan accordingly. Confirming studies, however, are warranted. Regarding tumor response, FDG-PET scanning performed during radiation enabled the prediction of residual metabolic active tumor regions.[121]

van Baardwijk et al[122] reported on time trends in the maximum uptake in the primary tumor on FDG-PET (SUV_{max}) during thoracic RT in a group of 23 patients. A trend in FDG increase in the first week and a significant decrease in the second week and 70 days after RT was observed. Metabolic responders showed a significant increase in SUV_{max} during the first week and had a higher SUV_{max} at any time point. It is assumed that this difference in SUV_{max} in time reflects a complex mechanism of intrinsic and extrinsic factors in which hypoxia may play a role. A large heterogeneity between the individual patients was reported in this small study as well as in other studies.[113,123] Further research is ongoing to study if these early predictors of response may safely allow RT adaptations. Note that with initial treatment plans close to the tolerance limits of OAR, potential for further dose escalation to non-responders will be limited. Adaptive plan modifications to response are thus likely to primarily reduce toxicity by dose de-escalation for responders and/or palliative schedules to nonresponders.

Conclusions and Discussion

ART considerable improves the accuracy of RT of lung cancer. The improved accuracy allows for dose escalation without compromising on the dose to the OAR. Individualized margins tailored to the patient-specific respiratory motion have been clinically implemented on a large scale. The ITV approach is the most popular method despite the fact that it tends to generate too large target volumes. This is probably due to the simplicity of the method and the intuition behind (if you always hit it, you never miss it). In practice, however, the ITV concept is often used with fairly small ITV-to-PTV expansions. Especially in the AP direction, where breathing motion is generally small, whereas baseline variations can be considerable, this might lead to too small margins if these are not corrected for.

Breathing adapted RT by correlated delivery techniques has drawn considerable attention. This is partly due to the popularity of the ITV concept suggesting that large margin reduction can be achieved. Compared with 4D inverse planning techniques possible margin reductions are modest while extremely robust motion detection of the tumor is required, otherwise uncertainties cannot be reduced or are even increased.

Adaptive management of interfractional patient variation has not yet been clinically implemented on a large-scale for lung cancer radiation therapy. Most efforts to reduce PTV margins focused on online image guided correction protocols especially for SBRT. An off-line adaptive process for conventional fractionated RT of NSCLC has been implemented in the William Beaumont Hospital since early 2002.[124] Patient daily treatment is verified using in-room kV fluoroscopy, to calculate the mean target position and the SD of the respiratory motion that is compared with predesigned tolerances to determine if patient position correction and planning modification of beam aperture would be needed.

Adaptive management of anatomical and biological response has large potential. More data, however, are required before large-scale clinical implementation. Robust quantification of modes of tumor regression and validated threshold to identify responders and nonresponders are lacking.

Large-scale implementation of ART requires a significant effort of the vendors of treatment planning and treatment delivery systems, since adequate tools are only available in large research institutes. Fast, robust, and validated (deformable) registration techniques are required to quantify patient-specific systematic and random errors. Moreover, adaptive workflows need to be available to reduce workload. Currently, an adaptive plan is often designed in a treatment planning system and has to go through a chain of quality assurance and scheduling steps before use. While this is a burden for the workload, the adaptive treatment plan captures the same treatment intent as the original plan, with generally only modest modifications and similar scheduling. The rela-

tion between the original and the ART plan should be exploited to reduce the workload of adaptive strategies.

Finally, uncertainties in target definition and microscopic spread cannot be managed by image-guided and adaptive protocols and fall therefore outside the scope of this study. With improvements in treatment delivery accuracy, however, these uncertainties are quickly becoming the weakest link in RT of lung cancer.

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References

1. Non-small Cell Lung Cancer Collaborative Group: Chemotherapy for non-small cell lung cancer. Cochrane Database Syst Rev CD002139, 2000
2. Ferlay J, Bray F, Pisani P, et al: GLOBOCAN 2002: Cancer incidence, mortality and prevalence worldwide, in IARC CancerBase. Lyon, France, IARC Press, 2004
3. Parkin DM, Bray F, Ferlay J, et al: Global cancer statistics, 2002. CA Cancer J Clin 55:74-108, 2005
4. Martel MK, Ten Haken RK, Hazuka MB, et al: Estimation of tumor control probability model parameters from 3-D dose distributions of non-small cell lung cancer patients. Lung Cancer 24:31-37, 1999
5. Mehta M, Scrimger R, Mackie R, et al: A new approach to dose escalation in non-small-cell lung cancer. Int J Radiat Oncol Biol Phys 49:23-33, 2001
6. 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
7. Belderbos JS, Heemsbergen WD, De Jaeger K, et al: Final results of a phase I/II dose escalation trial in non-small-cell lung cancer using three-dimensional conformal radiotherapy. Int J Radiat Oncol Biol Phys 66:126-134, 2006
8. Schaake-Koning C, van den Bogaert W, Dalesio O, et al: Effects of concomitant cisplatin and radiotherapy on inoperable non-small-cell lung cancer. N Engl J Med 326:524-530, 1992
9. Auperin A, Rolland E, Curran W, et al: Concomitant radio-chemotherapy (RT-CT) versus sequential RT-CT in locally advanced non-small cell lung cancer (NSCLC): A meta-analysis using individual patient data (IPD) from randomised clinical trials (RCTs): A1-05. J Thorac Oncol 2:S310, 2007
10. Graham MV, Purdy JA, Emami B, et al: Clinical dose-volume histogram analysis for pneumonitis after 3D treatment for non-small cell lung cancer (NSCLC). Int J Radiat Oncol Biol Phys 45:323-329, 1999
11. Martel MK, Ten Haken RK, Hazuka MB, et al: Dose-volume histogram and 3-D treatment planning evaluation of patients with pneumonitis. Int J Radiat Oncol Biol Phys 28:575-581, 1994
12. Kwa SL, Lebesque JV, Theuws JC, et al: Radiation pneumonitis as a function of mean lung dose: An analysis of pooled data of 540 patients. Int J Radiat Oncol Biol Phys 42:1-9, 1998
13. Yorke ED, Jackson A, Rosenzweig KE, et al: Correlation of dosimetric factors and radiation pneumonitis for non-small-cell lung cancer patients in a recently completed dose escalation study. Int J Radiat Oncol Biol Phys 63:672-682, 2005
14. Bradley J, Graham MV, Winter K, et al: Toxicity and outcome results of RTOG 9311: A phase I–II dose-escalation study using three-dimensional conformal radiotherapy in patients with inoperable non-small-cell lung carcinoma. Int J Radiat Oncol Biol Phys 61:318-328, 2005
15. Belderbos J, Heemsbergen W, Hoogeman M, et al: Acute esophageal toxicity in non-small cell lung cancer patients after high dose conformal radiotherapy. Radiother Oncol 75:157-164, 2005
16. Chapet O, Fraass BA, Ten Haken RK: Multiple fields may offer better esophagus sparing without increased probability of lung toxicity in optimized IMRT of lung tumors. Int J Radiat Oncol Biol Phys 65:255-265, 2006
17. Bradley J, Deasy JO, Bentzen S, et al: Dosimetric correlates for acute esophagitis in patients treated with radiotherapy for lung carcinoma. Int J Radiat Oncol Biol Phys 58:1106-1113, 2004
18. Grills IS, Yan D, Martinez AA, et al: Potential for reduced toxicity and dose escalation in the treatment of inoperable non-small-cell lung cancer: A comparison of intensity-modulated radiation therapy (IMRT), 3D conformal radiation, and elective nodal irradiation. Int J Radiat Oncol Biol Phys 57:875-890, 2003
19. Chapet O, Kong FM, Lee JS, et al: Normal tissue complication probability modeling for acute esophagitis in patients treated with conformal radiation therapy for non-small cell lung cancer. Radiother Oncol 77:176-181, 2005
20. Schwarz M, Alber M, Lebesque JV, et al: Dose heterogeneity in the target volume and intensity-modulated radiotherapy to escalate the dose in the treatment of non-small-cell lung cancer. Int J Radiat Oncol Biol Phys 62:561-570, 2005
21. van Herk M, Remeijer P, Rasch C, et al: The probability of correct target dosage: Dose-population histograms for deriving treatment margins in radiotherapy. Int J Radiat Oncol Biol Phys 47:1121-1135, 2000
22. Erridge SC, Seppenwoolde Y, Muller SH, et al: Portal imaging to assess set-up errors, tumor motion and tumor shrinkage during conformal radiotherapy of non-small cell lung cancer. Radiother Oncol 66:75-85, 2003
23. Jaffray DA, Siewerdsen JH, Wong JW, et al: Flat-panel cone-beam computed tomography for image-guided radiation therapy. Int J Radiat Oncol Biol Phys 53:1337-1349, 2002
24. Pouliot J, Bani-Hashemi A, Chen J, et al: Low-dose megavoltage cone-beam CT for radiation therapy. Int J Radiat Oncol Biol Phys 61:552-560, 2005
25. Mackie TR, Balog J, Ruchala K, et al: Tomotherapy. Semin Radiat Oncol 9:108-117, 1999
26. Bijhold J, Lebesque JV, Hart AA, et al: Maximizing setup accuracy using portal images as applied to a conformal boost technique for prostatic cancer. Radiother Oncol 24:261-271, 1992
27. Leong J: Implementation of random positioning error in computerised radiation treatment planning systems as a result of fractionation. Phys Med Biol 32:327-334, 1987
28. Valley JF, Mirimanoff RO: Comparison of treatment techniques for lung cancer. Radiother Oncol 28:168-173, 1993
29. Ketting CH, Austin-Seymour M, Kalet I, et al: Automated planning target volume generation: An evaluation pitting a computer-based tool against human experts. Int J Radiat Oncol Biol Phys 37:697-704, 1997
30. Steenbakkers RJ, Duppen JC, Fitton I, et al: Reduction of observer variation using matched CT-PET for lung cancer delineation: A three-dimensional analysis. Int J Radiat Oncol Biol Phys 64:435-448, 2006
31. Giraud P, Antoine M, Larrouy A, et al: Evaluation of microscopic tumor extension in non-small-cell lung cancer for three-dimensional conformal radiotherapy planning. Int J Radiat Oncol Biol Phys 48: 1015-1024, 2000
32. Grills IS, Fitch DL, Goldstein NS, et al: Clinicopathologic analysis of microscopic extension in lung adenocarcinoma: Defining clinical target volume for radiotherapy. Int J Radiat Oncol Biol Phys 69:334-341, 2007
33. Stroom J, Blaauwgeers H, van Baardwijk A, et al: Feasibility of pathology-correlated lung imaging for accurate target definition of lung tumors. Int J Radiat Oncol Biol Phys 69:267-275, 2007
34. Marks LB: A standard dose of radiation for "microscopic disease" is not appropriate. Cancer 66:2498-2502, 1990
35. Withers HR, Peters LJ, Taylor JM: Dose-response relationship for ra-

diation therapy of subclinical disease. Int J Radiat Oncol Biol Phys 31:353-359, 1995
36. Ekberg L, Holmberg O, Wittgren L, et al: What margins should be added to the clinical target volume in radiotherapy treatment planning for lung cancer? Radiother Oncol 48:71-77, 1998
37. de Boer HC, van Sornsen de Koste JR, et al: Analysis and reduction of 3D systematic and random setup errors during the simulation and treatment of lung cancer patients with CT-based external beam radiotherapy dose planning. Int J Radiat Oncol Biol Phys 49:857-868, 2001
38. Borst GR, Sonke JJ, Betgen A, et al: Kilo-voltage cone-beam computed tomography setup measurements for lung cancer patients; first clinical results and comparison with electronic portal-imaging device. Int J Radiat Oncol Biol Phys 68:555-561, 2007
39. Purdie TG, Bissonnette JP, Franks K, et al: Cone-beam computed tomography for on-line image guidance of lung stereotactic radiotherapy: Localization, verification, and intrafraction tumor position. Int J Radiat Oncol Biol Phys 68:243-252, 2007
40. Sonke JJ, Rossi M, Wolthaus J, et al: Frameless stereotactic body radiotherapy for lung cancer using four-dimensional cone beam CT guidance. Int J Radiat Oncol Biol Phys 74:567-574, 2009
41. Ross CS, Hussey DH, Pennington EC, et al: Analysis of movement of intrathoracic neoplasms using ultrafast computerized tomography. Int J Radiat Oncol Biol Phys 18:671-677, 1990
42. Seppenwoolde Y, Shirato H, Kitamura K, et al: Precise and real-time measurement of 3D tumor motion in lung due to breathing and heartbeat, measured during radiotherapy. Int J Radiat Oncol Biol Phys 53:822-834, 2002
43. Pantarotto JR, Piet AH, Vincent A, et al: Motion Analysis of 100 mediastinal lymph nodes: Potential pitfalls in treatment planning and adaptive strategies. Int J Radiat Oncol Biol Phys 74:1092-1099, 2009
44. Balter JM, Ten Haken RK, Lawrence TS, et al: Uncertainties in CT-based radiation therapy treatment planning associated with patient breathing. Int J Radiat Oncol Biol Phys 36:167-174, 1996
45. Nehmeh SA, Erdi YE: Respiratory motion in positron emission tomography/computed tomography: A review. Semin Nucl Med 38:167-176, 2008
46. Engelsman M, Damen EM, De Jaeger K, et al: The effect of breathing and set-up errors on the cumulative dose to a lung tumor. Radiother Oncol 60:95-105, 2001
47. Wulf J, Hadinger U, Oppitz U, et al: Stereotactic radiotherapy of extracranial targets: CT-simulation and accuracy of treatment in the stereotactic body frame. Radiother Oncol 57:225-236, 2000
48. Chang J, Mageras GS, Yorke E, et al: Observation of interfractional variations in lung tumor position using respiratory gated and ungated megavoltage cone-beam computed tomography. Int J Radiat Oncol Biol Phys 67:1548-1558, 2007
49. Hugo GD, Yan D, Liang J: Population and patient-specific target margins for 4D adaptive radiotherapy to account for intra- and inter-fraction variation in lung tumour position. Phys Med Biol 52:257-274, 2007
50. Sonke JJ, Lebesque J, van Herk M: Variability of four-dimensional computed tomography patient models. Int J Radiat Oncol Biol Phys 70:590-598, 2008
51. Hugo G, Vargas C, Liang J, et al: Changes in the respiratory pattern during radiotherapy for cancer in the lung. Radiother Oncol 78:326-331, 2006
52. Purdie TG, Moseley DJ, Bissonnette JP, et al: Respiration correlated cone-beam computed tomography and 4DCT for evaluating target motion in stereotactic lung radiation therapy. Acta Oncol 45:915-922, 2006
53. Ford EC, Mageras GS, Yorke E, et al: Respiration-correlated spiral CT: A method of measuring respiratory-induced anatomic motion for radiation treatment planning. Med Phys 30:88-97, 2003
54. Vedam SS, Keall PJ, Kini VR, et al: Acquiring a four-dimensional computed tomography dataset using an external respiratory signal. Phys Med Biol 48:45-62, 2003
55. Low DA, Nystrom M, Kalinin E, et al: A method for the reconstruction of four-dimensional synchronized CT scans acquired during free breathing. Med Phys 30:1254-1263, 2003
56. Sonke JJ, Zijp L, Remeijer P, et al: Respiratory correlated cone beam CT. Med Phys 32:1176-1186, 2005
57. Keall PJ, Mageras GS, Balter JM, et al: The management of respiratory motion in radiation oncology report of AAPM Task Group 76. Med Phys 33:3874-3900, 2006
58. Li T, Koong A, Xing L: Enhanced 4D cone-beam CT with inter-phase motion model. Med Phys 34:3688-3695, 2007
59. Zeng R, Fessler JA, Balter JM: Estimating 3-D respiratory motion from orbiting views by tomographic image registration. IEEE Trans Med Imaging 26:153-163, 2007
60. Wolthaus JW, Sonke JJ, van Herk M, et al: Reconstruction of a time-averaged midposition CT scan for radiotherapy planning of lung cancer patients using deformable registration. Med Phys 35:3998-4011, 2008
61. Rit S, Wolthaus JW, van Herk M, et al: On-the-fly motion-compensated cone-beam CT using an a priori model of the respiratory motion. Med Phys 36:2283-2296, 2009
62. Wolthaus JW, Schneider C, Sonke JJ, et al: Mid-ventilation CT scan construction from four-dimensional respiration-correlated CT scans for radiotherapy planning of lung cancer patients. Int J Radiat Oncol Biol Phys 65:1560-1571, 2006
63. International Commission on Radiation Units and Measurements: ICRU Report 50. Prescribing, recording and reporting photo beam therapy. Bethesda, MD, International Commission on Radiation Units and Measurements, 1993
64. International Commission on Radiation Units and Measurements: ICRU Report 62. Prescribing, recording and reporting photo beam therapy (supplement to ICRU Report 50). Bethesda, MD, International Commission on Radiation Units and Measurements, 1999
65. Antolak JA, Rosen CCH II, Childress CH, et al: Prostate target volume variations during a course of radiotherapy. Int J Radiat Oncol Biol Phys 42:661-672, 1998
66. Stroom JC, Koper PC, Korevaar GA, et al: Internal organ motion in prostate cancer patients treated in prone and supine treatment position. Radiother Oncol 51:237-248, 1999
67. Craig T, Battista J, Moiseenko V, et al: Considerations for the implementation of target volume protocols in radiation therapy. Int J Radiat Oncol Biol Phys 49:241-250, 2001
68. Miller RC, Bonner JA, Kline RW: Impact of beam energy and field margin on penumbra at lung tumor-lung parenchyma interfaces. Int J Radiat Oncol Biol Phys 41:707-713, 1998
69. Aaltonen P, Brahme A, Lax I, et al: Specification of dose delivery in radiation therapy. Recommendation by the Nordic Association of Clinical Physics (NACP). Acta Oncol 36:1-32, 1997 (suppl 10)
70. Allen AM, Siracuse KM, Hayman JA, et al: Evaluation of the influence of breathing on the movement and modeling of lung tumors. Int J Radiat Oncol Biol Phys 58:1251-1257, 2004
71. Shih HA, Jiang SB, Aljarrah KM, et al: Internal target volume determined with expansion margins beyond composite gross tumor volume in three-dimensional conformal radiotherapy for lung cancer. Int J Radiat Oncol Biol Phys 60:613-622, 2004
72. Underberg RW, Lagerwaard FJ, Slotman BJ, et al: Use of maximum intensity projections (MIP) for target volume generation in 4DCT scans for lung cancer. Int J Radiat Oncol Biol Phys 63:253-260, 2005
73. Rietzel E, Liu AK, Chen GT, et al: Maximum-intensity volumes for fast contouring of lung tumors including respiratory motion in 4DCT planning. Int J Radiat Oncol Biol Phys 71:1245-1252, 2008
74. Underberg RW, Lagerwaard FJ, Slotman BJ, et al: Benefit of respiration-gated stereotactic radiotherapy for stage I lung cancer: An analysis of 4DCT datasets. Int J Radiat Oncol Biol Phys 62:554-560, 2005
75. Lujan AE, Larsen EW, Balter JM, et al: A method for incorporating organ motion due to breathing into 3D dose calculations. Med Phys 26:715-720, 1999
76. McKenzie AL: How should breathing motion be combined with other errors when drawing margins around clinical target volumes? Br J Radiol 73:973-977, 2000
77. Harsolia A, Hugo GD, Kestin LL, et al: Dosimetric advantages of four-dimensional adaptive image-guided radiotherapy for lung tumors us-

ing online cone-beam computed tomography. Int J Radiat Oncol Biol Phys 70:582-589, 2008
78. Liu HH, Wang X, Dong L, et al: Feasibility of sparing lung and other thoracic structures with intensity-modulated radiotherapy for non-small-cell lung cancer. Int J Radiat Oncol Biol Phys 58:1268-1279, 2004
79. Li JG, Xing L: Inverse planning incorporating organ motion. Med Phys 27:1573-1578, 2000
80. Engelsman M, Remeijer P, van Herk M, et al: The theoretical benefit of beam fringe compensation and field size reduction for iso-normal tissue complication probability dose escalation in radiotherapy of lung cancer. Med Phys 30:1086-1095, 2003
81. Zhang T, Jeraj R, Keller H, et al: Treatment plan optimization incorporating respiratory motion. Med Phys 31:1576-1586, 2004
82. Chetty IJ, Rosu M, McShan DL, et al: Accounting for center-of-mass target motion using convolution methods in Monte Carlo-based dose calculations of the lung. Med Phys 31:925-932, 2004
83. Trofimov A, Rietzel E, Lu HM, et al: Temporo-spatial IMRT optimization: Concepts, implementation and initial results. Phys Med Biol 50:2779-2798, 2005
84. Li X, Zhang P, Mah D, et al: Novel lung IMRT planning algorithms with nonuniform dose delivery strategy to account for respiratory motion. Med Phys 33:3390-3398, 2006
85. Mexner V, Wolthaus JW, van Herk M, et al: Effects of respiration-induced density variations on dose distributions in radiotherapy of lung cancer. Int J Radiat Oncol Biol Phys 74:1266-1275, 2009
86. Zhang P, Hugo GD, Yan D: Planning study comparison of real-time target tracking and four-dimensional inverse planning for managing patient respiratory motion. Int J Radiat Oncol Biol Phys 72:1221-1227, 2008
87. Keall PJ, Joshi S, Vedam SS, et al: Four-dimensional radiotherapy planning for DMLC-based respiratory motion tracking. Med Phys 32:942-951, 2005
88. Löf J, Lind BK, Brahme A: An adaptive control algorithm for optimization of intensity modulated radiotherapy considering uncertainties in beam profiles, patient set-up and internal organ motion. Phys Med Biol 43:1605-1628, 1998
89. Witte MG, van der Geer J, Schneider C: IMRT optimization including random and systematic geometric errors based on the expectation of TCP and NTCP. Med Phys 34:3544-3555, 2007
90. Ten Haken RK, Balter JM, Marsh LH, et al: Potential benefits of eliminating planning target volume expansions for patient breathing in the treatment of liver tumors. Int J Radiat Oncol Biol Phys 38:613-617, 1997
91. Guckenberger M, Krieger T, Richter A, et al: Potential of image-guidance, gating and real-time tracking to improve accuracy in pulmonary stereotactic body radiotherapy. Radiother Oncol 91: 288-295, 2009
92. Kubo HD, Hill BC: Respiration gated radiotherapy treatment: A technical study. Phys Med Biol 41:83-91, 1996
93. Shirato H, Shimizu S, Shimizu T, et al: Real-time tumour-tracking radiotherapy. Lancet 353:1331-1332, 1999
94. Wong JW, Sharpe MB, Jaffray DA, et al: The use of active breathing control (ABC) to reduce margin for breathing motion. Int J Radiat Oncol Biol Phys 44:911-919, 1999
95. Adler JR Jr, Chang SD, Murphy MJ, et al: The Cyberknife: A frameless robotic system for radiosurgery. Stereotact Funct Neurosurg 69:124-128, 1997
96. Casamassima F, Cavedon C, Francescon P, et al: Use of motion tracking in stereotactic body radiotherapy: Evaluation of uncertainty in off-target dose distribution and optimization strategies. Acta Oncol 45:943-947, 2006
97. Korreman SS, Juhler-Nottrup T, Boyer AL: Respiratory gated beam delivery cannot facilitate margin reduction, unless combined with respiratory correlated image guidance. Radiother Oncol 86:61-68, 2008
98. Lin T, Cervino LI, Tang X, et al: Fluoroscopic tumor tracking for image-guided lung cancer radiotherapy. Phys Med Biol 54:981-992, 2009
99. Shirato H, Shimizu S, Kunieda T: Physical aspects of a real-time tumor-tracking system for gated radiotherapy. Int J Radiat Oncol Biol Phys 48:1187-1195, 2000
100. Juhler Nottrup T, Korreman SS, Pedersen AN, et al: Intra- and inter-fraction breathing variations during curative radiotherapy for lung cancer. Radiother Oncol 84:40-48, 2007
101. Chen QS, Weinhous MS, Deibel FC: Fluoroscopic study of tumor motion due to breathing: Facilitating precise radiation therapy for lung cancer patients. Med Phys 28:1850-1856, 2001
102. Keall PJ, Kini VR, Vedam SS: Motion adaptive x-ray therapy: A feasibility study. Phys Med Biol 46:1-10, 2001
103. Trofimov A, Vrancic C, Chan TC, et al: Tumor trailing strategy for intensity-modulated radiation therapy of moving targets. Med Phys 35:1718-1733, 2008
104. Yan D, Wong J, Vicini F, et al: Adaptive modification of treatment planning to minimize the deleterious effects of treatment setup errors. Int J Radiat Oncol Biol Phys 38:197-206, 1997
105. Brock KK, McShan DL, Ten Haken RK, et al: Inclusion of organ deformation in dose calculations. Med Phys 30:290-295, 2003
106. Kessler ML: Image registration and data fusion in radiation therapy. Br J Radiol 79:S99-S108, 2006
107. Unkelbach J, Oelfke U: Incorporating organ movements in inverse planning: Assessing dose uncertainties by Bayesian inference. Phys Med Biol 50:121-139, 2005
108. Lam KL, Ten Haken RK, Litzenberg D, et al: An application of Bayesian statistical methods to adaptive radiotherapy. Phys Med Biol 50: 3849-3858, 2005
109. Yan D, Wong JW, Gustafson G, et al: A new model for "accept or reject" strategies in off-line and on-line megavoltage treatment evaluation. Int J Radiat Oncol Biol Phys 31:943-952, 1995
110. Yan D, Jaffray DA, Wong JW: A model to accumulate fractionated dose in a deforming organ. Int J Radiat Oncol Biol Phys 44:665-675, 1999
111. 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
112. Woodford C, Yartsev S, Dar ARV: 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
113. 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
114. Gillham C, Zips D, Ponisch F, et al: Additional PET/CT in week 5-6 of radiotherapy for patients with stage III non-small cell lung cancer as a means of dose escalation planning? Radiother Oncol 88:335-341, 2008
115. Cohade C, Wahl RL: Applications of positron emission tomography/computed tomography image fusion in clinical positron emission tomography—clinical use, interpretation methods, diagnostic improvements. Semin Nucl Med 33:228-237, 2003
116. van Loon J, Grutters J, Wanders R, et al: Follow-up with 18FDG-PET-CT after radical radiotherapy with or without chemotherapy allows the detection of potentially curable progressive disease in non-small cell lung cancer patients: A prospective study. Eur J Cancer 45:588-595, 2009
117. Kased N, Erasmus JJ, Komaki R, et al: Prognostic value of posttreatment [18F] fluorodeoxyglucose uptake of primary non-small cell lung carcinoma treated with radiation therapy with or without chemotherapy: A brief review. J Thorac Oncol 3:534-538, 2008
118. Yamamoto Y, Nishiyama Y, Monden T, et al: Correlation of FDG-PET findings with histopathology in the assessment of response to induction chemoradiotherapy in non-small cell lung cancer. Eur J Nucl Med Mol Imaging 33:140-147, 2006
119. Aerts HJ, Bosmans G, van Baardwijk AA, et al: Stability of 18F-deoxyglucose uptake locations within tumor during radiotherapy for NSCLC: A prospective study. Int J Radiat Oncol Biol Phys 71:1402-1407, 2008

120. De Ruysscher D, Houben A, Aerts HJ, et al: Increased (18)F-deoxyglucose uptake in the lung during the first weeks of radiotherapy is correlated with subsequent radiation-induced lung toxicity (RILT): A prospective pilot study. Radiother Oncol 91:415-420, 2009
121. Kong FM, Frey KA, Quint LE, et al: A pilot study of [18F]fluorodeoxyglucose positron emission tomography scans during and after radiation-based therapy in patients with nonsmall-cell lung cancer. J Clin Oncol 25:3116-3123, 2007
122. van Baardwijk A, Bosmans G, Dekker A, et al: Time trends in the maximal uptake of FDG on PET scan during thoracic radiotherapy. A prospective study in locally advanced non-small cell lung cancer (NSCLC) patients. Radiother Oncol 82:145-152, 2007
123. Erdi YE, Macapinlac H, Rosenzweig KE, et al: Use of PET to monitor the response of lung cancer to radiation treatment. Eur J Nucl Med 27:861-866, 2000
124. Yan D, Lockman D, Martinez A, et al: Computed tomography guided management of interfractional patient variation. Semin Radiat Oncol 15:168-179, 2005