Radiotherapy (with or without additional chemotherapy) remains the standard treatment for patients with advanced lung cancer. Stereotactic body radiotherapy (SBRT) is a common treatment technique, used successfully for patients with medically inoperable small volume lung cancer [1,2]. Results of multimodal treatment of patients with treatment volumes that are large relative to normal lung tissue are still not satisfactory. Both local and distant controls pose a major problem [3]. It is already evident that high-dose radiotherapy increases local control and cure rates. Intensity modulated radiotherapy (IMRT) allows to select optimal beam directions and their combination, which allows dose escalation without excessive toxicities, including those to the spinal cord, the esophagus, and lungs. A specific problem for IMRT of lung tumors is respiratory motion. Lung tumors and OAR can change their position in the crano-caudal and anterior–posterior direction by up to 2 cm as a function of the breathing cycle [4]. As this motion can result in alterations in target and normal tissue volume definitions, target margins and the entire dose distribution (due to “interplay” effects when an inhomogeneous fluence is projected sequentially onto a moving object), interventions to reduce the impact of intratreatment organ motion are necessary [5]. A treatment plan that modulates fluence predominantly in the transversal direction i.e. the direction of the breathing motion (anisotropic modulation) might reduce this problem, while it might still improve dose conformity over 3D-conformal radiotherapy and thus might enable dose escalation. The favorable features of the aperture based technique include faster optimizations, fewer degrees of freedom, and the avoidance of the degrading segmentation phase inherent in beamlet-based inverse planning. Moreover, if the apertures are related in a useful way to the anatomy of the patient, the possibility of simplifying the treatment verification presents itself [6]. In this study, we compared conventional 3D conformal radiotherapy treatment plans with anisotropic IMRT for patients with large volume lung cancer not suitable for SBRT and hypothesized, that the anisotropic technique is robust toward...
target movement and that with the implementation of this technique we can escalate the dose to the target, and at the same time reduce the dose to the OAR.

Methods and materials

CT-datasets of 20 patients with Stage I–IV non small cell lung cancer (NSCLC) formed the basis of this study. Specific patient characteristics are presented in Table 1.

The basis for 3D and IMRT plans were thin slice computer tomography (CT) scans acquired on a dedicated 8 slice CT simulator (Somatom Plus 4 Volume Zoom, Siemens®; 120 kV, 200 mAs/section, 10-mm thickness, 10-mm increment. 3D and IMRT plans were generated on PrecisePLAN® 2.03 for a Synergy® linac equipped with a multileaf collimator (leaf width 10 mm at isocenter) and a maximum dose rate of 600 MU/min (Elekta Oncology Systems, Crawley, UK).

The gross tumor volume (GTV) was defined as the gross mass demonstrated by planning CT images. The clinical target volume (CTV) was determined as the volume encompassing GTV, the regional lymph nodes, and an addition of a 10-mm margin. For comparative planning purposes, a planning target volume (PTV) was not used. Mean CTV and GTV sizes were 515 cm³ and 342 cm³, respectively (Table 1). GTV and CTV were contoured as non-overlapping volumes (CTV did not include GTV). Both lungs (right and left lung separately, including the healthy lung volume included in the CTV), heart and spinal cord were contoured as OAR. Two IMRT plans and one 3D plan were created for each of the 20 patients. Prescription dose was 60 Gy to the CTV and 70 Gy to the GTV. For the 3D plan, 3–6 beams, an energy of 18 MV photons and wedge filters were used. The margin between the CTV and the MLC was 0.5 mm. The 3D plans were planned to a total dose to 60 Gy (CTV plus GTV), followed by an external beam boost to a total dose of 70 Gy to the GTV (sequential 3D-Boost). IMRT plans were calculated with 6 MV an 18 MV photon energy in preliminary experiments. As expected based on previous publications, no significant differences in the results were observed, therefore only the 6 MV plans were used for the comparison [7]. For IMRT, two techniques were studied per beam energy: (a) 13 coplanar beams and (b) a 17 beam technique with 13 coplanar and 4 noncoplanar primary beam directions. Beam angles were arranged in a practical manner according to tumor and OAR position for the purpose of achieving maximal target coverage and optimal dose distributions (minor deviations from an isotropical setup). Instead of resorting to the rather complex full inverse-planning, where one has no control on segment shaping, our technique using PrecisePLAN is an extension of the conformal treatment planning technique where within each field beam eye view (BEV) a number of sub-field apertures are added.

Initially a set of segments including the entire target volume was generated manually, followed by segments that included the target volume only partially and excluded the OAR’s. The smaller apertures are designed to irradiate the tumor, while mutually sparing OARs that intrude into the target region in the BEV. A 3D dose display overlaid on the BEV simplifies and guides the manual segmentation process (Figure 1). This method leads to a relatively small number of comparatively large sized apertures and allows the planner to intentionally shape the segments for less longitudinal fluence modulation. In the next step, constraint-driven inverse optimization of segment weights based on a Cimmino algorithm was performed. Each field is individually weighted, allowing all of the fields to contribute to the total dose distribution according to the beam geometry.

Six 13-field IMRT plans were selected to assess robustness of anisotropically modulated IMRT toward motion. To simulate random breathing motion during treatment, new plans were created with the isocenters of all segments being moved randomly between 1 and 10 mm in craniocaudal direction. Dose calculation was performed using the Collapsed Cone (CC) algorithm implemented in Oncentra Masterplan® (Nucletron BV, Veenendaal, Netherlands).

Plan comparison was based on absolute dose statistics for GTV, CTV, lung tissue, heart, and spinal cord. Quantitative parameters of dose–volume relationships such as D95 (the relevant minimum dose), Dmean, Dmax for GTV and CTV and Dmean, Dmax, D95 and D90 (dose exceeded by 30%/60% of the volume) for lung tissue, spinal cord, and heart were selected for comparison. For CTV, V10 and for GTV the highest dose applied to more than 1 cc of the target volume (to assess the magnitude of clinically relevant dose peaks) and for lung tissue the V20 for the whole lung was recorded. Dose profiles and DVHs were compared between 3D- and IMRT plans. Group differences were assessed using the exact Wilcoxon signed rank test. All testing was two-tailed, with p < 0.05 considered statistically significant. Statistical procedures were performed using the IBM SPSS Statistics program (version 18, SPSS Inc., Chicago, IL).

**Results**

As a consequence of identical prescription doses and an emphasis on target coverage, mean target doses were similar for 3D and IMRT (Table 2). Wilcoxon signed rank tests showed that the differences between 3D and 13- and 17-field IMRT, were significant for CTV Dmin (43 Gy vs. 49.1 Gy vs. 48.6 Gy; p < 0.001) and CTV D95 (53.2 Gy vs. 55.0 Gy vs. 55.4 Gy; p = 0.001). GTV- and CTV DVH-metrics were therefore anchored at very similar values. Plan characteristics are therefore mainly based on OAR DVH-metrics.

There was no significant difference in Dmean for the ipsilateral lung between 3D and the 13- and 17-field IMRT plans (23.1 Gy vs. 23.0 Gy vs. 23.5 Gy; p > 0.05). There were significantly better results for D90 (3D vs. 13- vs. 17-field IMRT: 39.6 Gy vs. 37 Gy vs. 35.3 Gy; p < 0.03) in favor of the IMRT plans.

The V20 mean values for both treatment techniques were above 20% (3D vs. 13- vs. 17-field IMRT: 38.8 Gy vs. 36.3 Gy vs. 33.5 Gy), but the values of the 3D plans were higher than the values of the

<table>
<thead>
<tr>
<th>Table 1</th>
<th>Patient characteristics.</th>
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<tr>
<td></td>
<td>n (%)</td>
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<tr>
<td>Age (years)</td>
<td>68</td>
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<tr>
<td>Median</td>
<td>49–83</td>
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<tr>
<td>Gender</td>
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<tr>
<td>Male</td>
<td>4 (20)</td>
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<tr>
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<td>7 (35)</td>
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<tr>
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<tr>
<td>Squamous cell cancer</td>
<td>4 (20)</td>
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<tr>
<td>Stage IIA</td>
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<tr>
<td>Stage IIB</td>
<td>8 (40)</td>
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<tr>
<td>Stage IV</td>
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<tr>
<td>GTV (cm³)</td>
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<td>Median</td>
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<tr>
<td>Range</td>
<td>515</td>
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<tr>
<td>CTV (cm³)</td>
<td>82–1114</td>
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Abbreviations: NSCLC, non-small cell lung cancer; CTV, clinical target volume; GTV, gross tumor volume.

Data is presented as number of patients (n), with percentages in parentheses.
IMRT plans. The high baseline level of V20 is due to the large target volumes, which in most cases encompass more than 50% of the ipsilateral lung volume.

For contralateral lung, $D_{\text{mean}}$ was on average 2 Gy lower in IMRT plans than in 3D plans, although the 17-field plans showed significantly ($p = 0.005$) better results than the 13-field plans (3D vs. 13- vs. 17-field IMRT: 15.8 Gy vs. 14.8 Gy vs. 12.5 Gy). There were also slightly better results for $D_{\text{max}}$ (3D vs. 13- vs. 17-field IMRT: 23.1 Gy vs. 20 Gy vs. 18.6 Gy; $p = \text{n.s.}$) in favor of the IMRT plans, where there was a significant difference between both techniques in favor of the 17-field IMRT ($p = 0.021$).

The spinal cord dose limit of 50 Gy was always respected in the IMRT plans, among 3D plans, however, this was only possible in 17 of 20 patients (85%).

Heart $D_{\text{max}}$ (3D vs. 13- vs. 17-field IMRT: 38.2 Gy vs. 36.8 Gy vs. 37.8 Gy) is slightly reduced with IMRT ($p = \text{n.s.}$), at the expense of a minor increase in mean values and the values for the dose that is applied to >30% and >60% ($D_{30\%}$ and $D_{60\%}$) of the heart volume in the IMRT plans.

Table 3 summarizes the DVH parameters for the OAR. Figure 2 provides a representative example of the dose distributions between a 17-field IMRT plan and a 3D-plan.

The total treatment time of a plan is influenced by the number of irradiated segments, monitor units (MU) and number of primary beam directions. For a representative patient data set we measured for the IMRT plan with 13 fields a treatment time of 13.7 min, for the 17-field plan of 18 min on currently available hardware. For a 3D plan the treatment time was 4 min. The number of segments that was used for all IMRT plans was only slightly different (3D vs. 13- vs. 17-field IMRT: 5 vs. 50 vs. 61). Monitor units were only moderately higher for IMRT in comparison to 3D (3D vs. 13- vs. 17-field IMRT: 333.7 vs. 452.4 vs. 4771.1).

The influence of simulated respiratory motion on the anisotropically modulated IMRT-plan is demonstrated in Figure 3. Figure 3a shows the dose distribution in the original plan while Figure 3b shows the effect of simulated respiratory motion on the dose distribution on the same axial CT-slice. Dose distribution characteristics did not undergo major alteration. Analysis of the DVH data (CC dose calculation) showed a decrease in the mean dose by 0.7 Gy with an increase of the maximum dose of 2.8 Gy to the PTV and decrease of the mean and maximum dose of 0.2 Gy and 0.6 Gy CTV (for both target volumes without significant difference: $p > 0.05$). While mean dose to the ipsilateral lung remained unchanged, mean dose to the contralateral lung decreased by 0.5 Gy ($p > 0.05$). There was no change in the mean heart dose and the maximum spinal cord dose (in mean increase of 0.5 Gy: $p > 0.05$).

**Discussion**

Many dose-escalating trials have been introduced over the past decades in an attempt to improve treatment outcome for patients with advanced NSCLC. Already in the early 70’s, Fletcher’s group reported that dose escalation to between 80 Gy and 100 Gy is necessary to increase local control for lung cancer patients [8], which was recently confirmed in the context of hyperfractionated radiotherapy for stage I and II NSCLC [15]. The following RTOG 83-11
study did not result in improved survival with increasing radiation doses in the range of 60–79.2 Gy, which was explained with the use of 3D conventional treatment planning techniques with field margins of more than 2 cm, thus pushing the limits of lung tolerance. It appeared that the increased risk of pneumonitis was not related to the level of total dose, but rather to field size [10]. In RTOG 9311, maximum tolerable dose was 70–74 Gy [11], albeit for relatively small targets (median volumes between 32 cm³ and 79.5 cm³).

Radiotherapy dose for patients with NSCLC is limited by the sensitivity of the normal lung to radiation, especially if large volumes of the lung are exposed [12,13]. The literature on dose–volume parameters and pneumonitis is comprehensive. In the recently published review of QUANTEC, the group recommended to limit the V20 to less than 30–35% and the mean dose to less than 20–23 Gy, if one wants to limit the risk of radiation pneumonitis to less than 20%, whereby the acceptable risk level can vary for different cases [14]. In the presented work the V20 of the whole lung always exceeded 30%, but 17-field IMRT plans had the lowest values (31.8–33.5%), followed by the 13-field plans (33.6–36.3%) and the highest values were recorded for 3D plans (35.2–38.8%). Given the characteristics of the dose distribution (homogeneous dose spread, smaller lung volume treated to high doses), the parameters achieved with IMRT plans might still be clinically acceptable [15]. Zhang et al. showed in a recent publication very similar results to our study for the dose parameters to the organs at risk for patients with Stage IIIB lung carcinoma, who were treated with IMRT where all IMRT plans were renormalized with at least 95% PTV coverage to 63 Gy [16]. Murshed et al. also showed significantly better results with the use of IMRT regarding parameters predicting lung toxicity (V10 and V20), especially for medium sized and large lung tumors, at the expense of increasing V5 of the lung, the consequences of which are not yet clear [17,18].

Another problem that still exists for thoracic irradiation is the choice of the optimal beam energy, because of the fact, that the lungs are a low-density medium where electronic disequilibrium is likely to occur [19]. Based on previous publications studying the effects of number of incident beams and beam energy [7], improved results could be expected for a beam geometry with many primary incident beams. Using only lower energies reduces neutron generation and peripheral target underdosage because of re-build up as described by us and others [20,21].

In the presented work, we used two different beam configurations for the IMRT- 13 coplanar fields and 17 fields with 13 coplanar and 4 non-coplanar beams. The 17-fields technique was analogous to the work by Derycke et al. The group showed, that the use of non-coplanar beam technique offers possibilities for dose escalation in the treatment of stage III NSCLC [22]. Chapet et al. demonstrated, that optimized many-field IMRT plans may offer better coverage and dose escalation in the PTV. The use of multiple fields seems not to be associated with inferior dose parameters of the normal tissue, especially of the lung [23], which was confirmed in our study. The results for the DVH parameters for the lung tissue showed significantly lower values in the plans with 17 beam configuration. An increasing number of beams, however, typically results in an increase of volumes exposed to low doses, the effect of which is not yet clear [11,19].

The aperture based technique presented in this work ensures a limited increase in plan complexity compared to standard, forward planned 3D conformal radiotherapy, and enables dose escalation in the radiotherapy of non-small-cell lung cancer [24]. The aperture based treatment planning algorithm has the following advantages, compared to other IMRT techniques: dose calculation for a given algorithm is typically more accurate, efficiency in the use of MU is high, modulation can easily be restricted to the lateral plane, and organ motion is less problematic when using large apertures.
Anisotropic aperture based IMRT versus 3D-conformal radiotherapy

with appropriate margins. Together with the use of non-coplanar fields it should keep low-dose lung exposure at bay and possibly also reduce the exposure of the heart to a minimum [25]. A clear disadvantage of the prescribed technique is the manual input required in defining the initial set of segments.

Though commonly regarded as an approach inferior to fully inverse treatment planning, St-Hilaire et al. showed in a study that dose escalation with appropriate OAR sparing using aperture-based IMRT is feasible and superior to a typical 3D technique. In contrast to our study, they escalated the dose only for the GTV and not for the whole CTV, therefore no in-depth comparison of their and our data can be performed [24].

A matter of concern with IMRT plans used on lung tumors is their potential susceptibility breathing-induced target movements, which might lead to dosimetric uncertainty and discrepancies between planned and delivered doses. This problem is a major concern for all tumor sites in the thorax [26]. In 50% of lung tumors, a movement of 0.5–1 cm is observed, in 10% of more than 1 cm [27]. While a broad spectrum of movement patterns is observed, by far the predominant direction of movements is longitudinally in the cranio-caudal direction [4]. A key advantage of anisotropic aperture based modulation is its potential robustness toward lung motion. While even for conventional isotropic IMRT segmentation organ motion does not seem to have a dramatic effect on the delivered dose when the dose is applied with 30 or more fractions [28], whatever effect remains might be reduced by an anisotropic approach.

Another problem, could be the changing breathing pattern during the irradiation of the aperture based IMRT. The group of Wilbert et al. investigated the influence of continuous table motion on patient breathing patterns for compensation of moving targets by a robotic treatment couch during treatment of 3–5 min. They showed that even the table motion was well tolerated by all test persons. Different reactions in the breathing patterns could be observed, but changes were small and arose slowly in most cases. For 11 of 15 test persons the change in the mean cycle period was within ±1 s, which is in the range of variability of the normal breathing patterns [29]. As shown in the manuscript, the group of Bortfeld et al. showed also, that for a typical treatment with 30 fractions, the standard deviation is generally within 1% of the expected value for MLC delivery if one assumes typical motion amplitude of 5 mm (1 cm peak to peak) [29]. Our own data of the patients, treated with active breathing control (ABC) technique (publication in preparation) and the data showed above, suggests that breathing patterns are relatively stable over the duration of a typical IMRT fraction.

To prove the robustness of our approach, we simulated breathing motion by moving randomly the isocenter of all the different segments by up to 1 cm in the longitudinal axis. The choice of the simulation method for a certain delivery paradigm is difficult. Delivery paradigms and delivery speed are currently changing fast. There has been and is tremendous acceleration of the delivery process based on faster MLCs and flattening filter free delivery. The relationship of breathing motion and delivery patterns is therefore constantly changing. We therefore chose the simplest approach possible that should provide an estimate of motion effects that is certainly not optimal for a specific paradigm but should provide a good estimate over a wide range of interplay between breathing and delivery patterns, given also that breathing patterns seem to be robust per treatment fraction but may vary between fractions [29,30].

In addition, because of the fact, that the beam penumbra in the lung tends to be wider than in normal tissue and the pencil-beam calculation algorithm is not accurate in this situation, we used for this approach the collapse-cone calculation algorithm, which is known to be more accurate in lung [19]. The results showed, that the dose distribution was not changed significantly by this extreme simulation, which confirms the fact that anisotropically modulated aperture based IMRT is a highly robust method. This principle of anisotropic modulation can also be applied to fully inverse planning when certain restrictions are applied to segmentation.

While other methods such as immobilisation with a "stereotactic body frame" [31], have proven to be very robust in a hypofractionated setting, this approach is hardly feasible for a normofractionated treatment. Gated treatment or controlled breath-hold together with image guided radiotherapy (IGRT) also reduces motion relative to the treatment beam, preventing interplay effects and allowing dose escalation [30,32–35]. Both approaches, however, significantly prolong daily treatment time. This problem could be solved with the implementation of rotational therapy [36]. Volumetric modulated arc therapy (VMAT) holds the potential to dramatically further reduce treatment times to ~5 min now [37,38] and with minimal technological refinements (faster leaf speed, higher dose rate) to ~2 min even for heavily modulated treatment plans. Rao et al. compared the use of VMAT with HT and reported a 40% reduction of the treatment time with the use of VMAT, while maintaining comparable plan quality to that of the HT [39]. Also, with the implementation of SBRT and IMRT, where inhomogeneous dose distributions are applied (SBRT), or only small segments with negligible inhomogeneity across the segment are applied to create an integral homogeneous dose distribution (IMRT), there is an increasing interest in operating linear accelerators in a flattening filter free mode. Flattening Filter Free RT-delivery and fast MLCs are currently in the process of reliably shortening the duration of even the most complex IMRT-treatments such as the paradigms described in this manuscript to <<5 min [40–42].

Studies using proton therapy or a combination of proton therapy with photon based therapy showed increased tumor control and survival, due to the use of higher radiation doses and at the same time less toxicity to the normal tissue, compared to IMRT [16,43]. Kim et al. also showed that the secondary dose from proton beam therapy for lung cancer is less than or compatible to the secondary dose from conventional IMRT [44]. However, it is still limited to specialized centers while anisotropically modulated IMRT is already clinically widely available and applicable in a robust fashion in clinical practice.

Conclusion

IMRT reduces lung exposure in patients with large targets compared to 3D-conformal radiotherapy. Anisotropic modulation renders IMRT plans robust toward breathing induced organ motion, effectively preventing interplay effects while not significantly prolonging treatment time.

Conflicts of interest

None.

References


