Does the IMRT technique allow improvement of treatment plans (e.g. lung sparing) for lung cancer patients with small lung volume: a planning study

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SUMMARY

AIM: We evaluated whether intensity-modulated radiation therapy (IMRT) may offer any advantages in comparison with three-dimensional conformal radiotherapy (3D-CRT) for patients with small lung volume (SLV).

METHODS: Treatment planning was performed for 10 NSCLC patients with the smallest lung volume (mean: 2241 cc) among 200 patients from our database. For each patient 3D-CRT and IMRT plans were prepared. The goal was to deliver 66 Gy/33 fractions, with dose constraints: mean lung dose (MLD)<20Gy, V20<35%; spinal cord – D_{max}<45 Gy. When the plan could not meet these criteria, total dose was reduced. The 3D-CRT and IMRT plans were compared. We investigated: prescribed dose, coverage and conformity indices, MLD, V5-V65 in the lung.

RESULTS: In 4 out of 10 plans, 3D-CRT did not allow 66 Gy to be delivered, because of predicted pulmonary toxicity. These 4 cases included 3 for which we did not reach 66 Gy with IMRT; still, for these 3 plans the total dose was increased by an average of 9 Gy with IMRT in comparison with 3D-CRT. Coverage indices were similar for both techniques. Conformity indices were better for IMRT plans. MLD was lower in five IMRT and two 3D-CRT plans if equal doses were delivered. The decrease in MLD was seen for cases with large PTV and high PTV/lung volume ratio. Lung V5 was lower for all 3D-CRT plans, 47% vs. 57% for IMRT; V15 and above were larger for 3D-CRT

CONCLUSION: In the planning study, IMRT seems to be a promising technique for cases with SLV, especially when associated with large PTV.

KEY WORDS: IMRT, lung cancer, radiotherapy, lung volume, planning study

BACKGROUND

The lung is a volumetric organ at risk; its radiation damage depends on the volume irradiated, so the maximum pulmonary volume should be spared from radiation. The risk for pneumonitis depends on the lung volume exceeding a threshold dose of 20 Gy [1]. In many cases of radiotherapy for lung cancer pulmonary toxicity becomes a factor limiting therapy. Tumour, even a large one, may happen to a patient with small or large lung volume. In the case of small lung volume the ratio of tumour to healthy lung becomes unfavourable, which may preclude a possibility of delivering doses lower than 20 Gy to a sufficient percentage of lung volume. Most dosimetrists and radiation oncologists know that small lung volume is a real challenge for planning. Intensity-modulated radiation therapy (IMRT) is an emerging cancer treatment technology, which has shown a capacity for better normal tissue sparing in a number of sites [2]. In planning studies, IMRT has also demonstrated a potential for reduced toxicity and dose escalation for lung cancer radiotherapy [3–5]. This incited us to investigate the potential role of IMRT in treatment

of those challenging cases, i.e. lung cancer in patients with small lung volume.

AIM

We investigated whether IMRT could give any advantage in comparison with standard three-dimensional conformal radiotherapy (3D-CRT) in patients with lung cancer and small lung volume in terms of sparing normal tissues and/or delivering higher doses.

MATERIAL AND METHODS

Ten non-small-cell lung cancer (NSCLC) patients with the smallest lung volume were chosen from 200 previously irradiated lung cancer patients from the database of our department. Mean lung volume in those 10 patients was 2240 cubic centimetres (range: 1886 – 2634 cc). CT scans done for previous planning treatment of those patients were used. Slice thickness on the CT scan was 5 mm. Patients were planned with free breathing in supine position on a lung board with both arms above the head. On each patient planning CT axial scans the gross tumour volume (GTV) was delineated and included the primary tumour and any hilar or mediastinal lymph nodes with a short-axis diameter of at least 1 cm on the CT scan. Then the clinical target volume (CTV) was created encompassing the GTV with a 5 mm margin within the lung without elective nodal irradiation. Finally, the planning target volume (PTV) included CTV with a 1 cm margin. Mean PTV volume was 297 cc, ranging from 27 cc to 611 cc.

For each patient one 3D-CRT and one IMRT plan were prepared by two physicists using the commercial treatment planning system Eclipse, version 6.5 with Helios optimization module for IMRT optimization employing the Pencil Beam algorithm with Modified Batho for inhomogeneity correction.

We decided to design 3 coplanar beams in 3D-CRT plans, which is our departmental policy. In IMRT plans there were 5 coplanar beams used. In 3D-CRT as well as in IMRT plans only 6 MV photon beams were used. Fig. 1 shows the typical beam arrangement and dose distribution for both analyzed techniques. We intended to deliver 66 Gy in 33 fractions keeping dose constraints typical for our department, as follows: mean lung dose (MLD) ≤ 20 Gy, lung V20 which is the volume of lung receiving a dose of 20 Gy or higher ≤ 35%, heart V40 ≤ 50%, maximum spinal cord dose ≤ 45 Gy, and length of oesophagus receiving at least 60 Gy no longer than 10 cm. Keeping dose constraints for the lung was a main planning objective. When achieving intended pulmonary dose restrictions was not possible, total dose had to be reduced.

After that, the plans were compared in pairs, for each patient. We took into account: total dose, coverage and conformity indices,

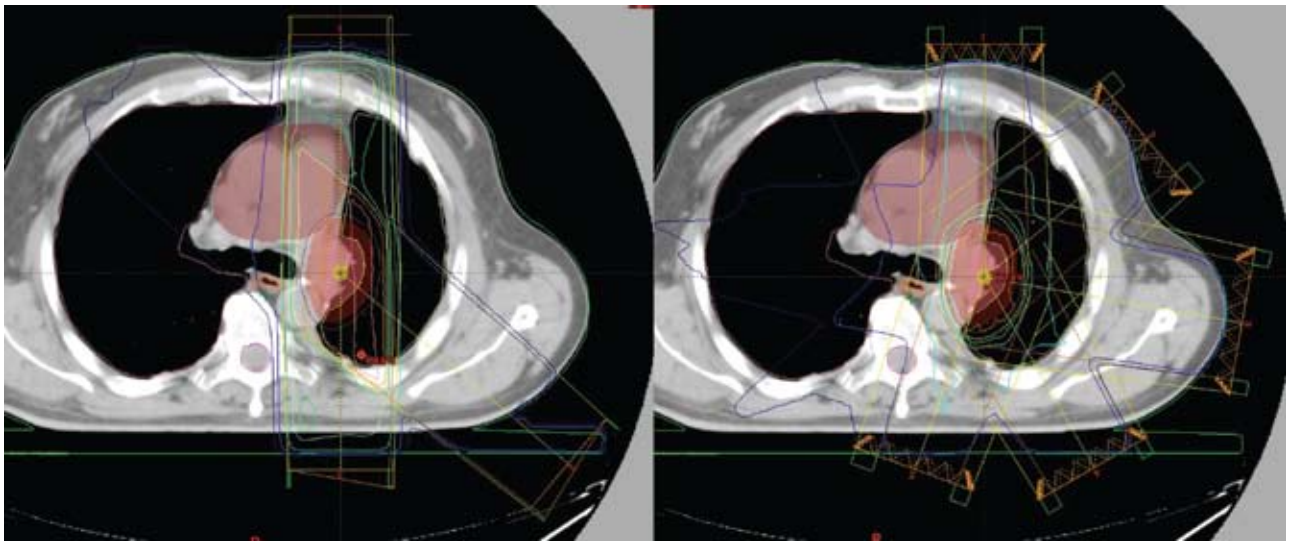

Fig. 1. Beam arrangement and dose distribution in 3D-CRT (on the left) and in IMRT (on the right) technique

mean lung doses (MLD), lung V5-V65 at 5 Gy intervals, and any relationship between PTV volume, lung volume and MLD.

We analysed whether it was possible to deliver the full total dose while keeping dose constraints in both studied techniques.

Then the coverage and conformity indices were calculated. Coverage index (CovI) was defined as the volume of PTV receiving equal to or more than the indicated dose (Dind) divided by the PTV volume. $CovI=V_{Dind}(PTV)/V(PTV)$. Conformity index (CI) was defined as the sum of value 1 plus the ratio of the normal tissue volume receiving equal to or more than the indicated dose to the PTV volume receiving equal to or more than the indicated dose. $CI=1+[V_{Dind}(norm)/V_{Dind}\ (PTV)]$. The indicated doses for CovI and CI calculations were selected as 95% of the total dose [6].

At the end, we made an attempt to find any relationship between volumes of lung, PTV and MLD. The correlation between size of PTV expressed by percentage of lung volume and MLD for both techniques was explored.

RESULTS

Total dose

In 6 patients a total dose of 66 Gy was successfully achieved for both types of plans. Among the remaining four cases with failure to achieve 66 Gy it was still possible to deliver a higher dose using IMRT for three patients, on average 9 Gy higher. The mean PTV in patients receiving the full total dose was 206 cc, while in the whole group it was 297 cc. Fig. 2 shows total doses achieved in consecutive patients. Considering all 10 cases the mean IMRT total dose was 3 Gy higher than the mean 3D-CRT total dose. In two plans (one 3D-CRT and one IMRT) a constraint of 20 Gy for MLD was slightly exceeded (respectively by 1 Gy and 0.2 Gy), as we did not want to further complicate the beam arrangements, and all other dose constraints, including V20 for lung, were respected.

Coverage and conformity indices

The best possible result for coverage index (CovI) was a value of 1.0. For both techniques in all cases, CovI was almost equal to 1.0. Mean result for IMRT plans was 0.995, while mean result for 3D-CRT plans was 0.992.

Conformity index (CI) reaching a value of 1.0 is also the best possible. It improved significantly with the use of IMRT, which means better normal tissue sparing from high doses. Mean CI for IMRT plans was 1.48, while mean CI for 3D-CRT plans was 2.27. CI was better for IMRT in all patients.

Lung doses

In five patients (No. 1, 2, 3, 6 and 7) with equal total doses mean lung dose (MLD) was lower using IMRT. Even though the average total dose in IMRT technique was higher the mean lung dose was still lower with IMRT. Fig. 3

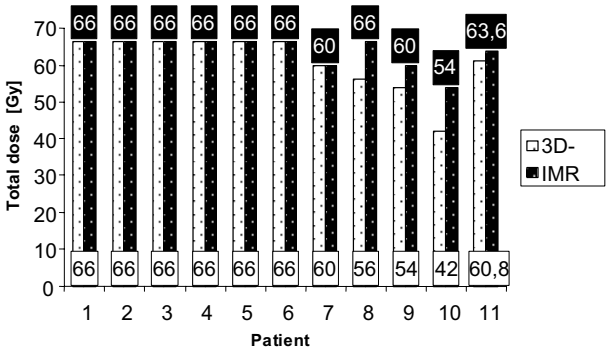

Fig. 2. Total doses in consecutive patients, 11 is the mean value for all patients. 3D-CRT – total dose achieved in 3D-CRT; IMRT – total dose achieved in IMRT

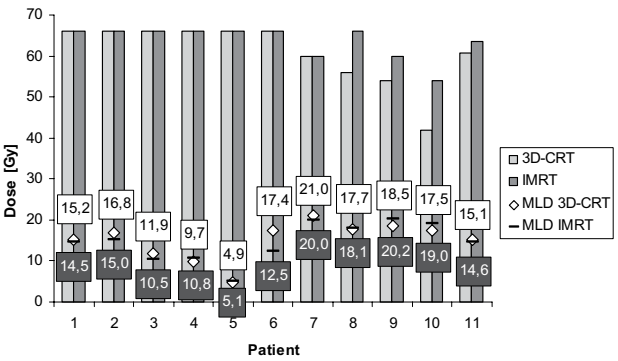

Fig. 3. Mean lung doses and total doses in consecutive patients, 11 is the mean value for all patients. 3D-CRT – total dose achieved in 3D-CRT plan; IMRT – total dose achieved in IMRT plan; MLD 3D-CRT – mean lung dose in 3D-CRT plan (value in the white box); MLD IMRT – mean lung dose in IMRT plan (value in the black box)

shows the relationship of MLD and total dose delivered for both studied techniques.

Comparing lung V5 to V65 volumes at 5 Gy intervals we found that lung V5 (volume of lung receiving at least 5 Gy) was significantly higher for IMRT regardless of total dose. In Table 1 we present V5-V65 values for both techniques, separately for all patients and for patients receiving a full dose.

PTV / lung volume ratio and MLD relationship

We found the relationship between size of PTV as a percentage of lung volume and ratio of mean lung dose in 3D-CRT plan to mean lung dose in IMRT. PTV/lung volume ratio was 0.10 for 6 patients receiving 66 Gy and 0.13 for the whole group. Mean lung doses were expressed as the percentage of the total dose to make this comparison suitable for different dose level patients. In other words PTV/lung volume ratio was compared with 3D-CRT MLD/IMRT MLD ratio and the correlation was found. We displayed this on a graph (Fig. 4). We can draw the conclusion that for large PTV IMRT can be beneficial. The bigger is PTV and the smaller is lung volume, the larger is the size of PTV as a percentage of lung volume and also the greater is the advantage of IMRT concerning MLD.

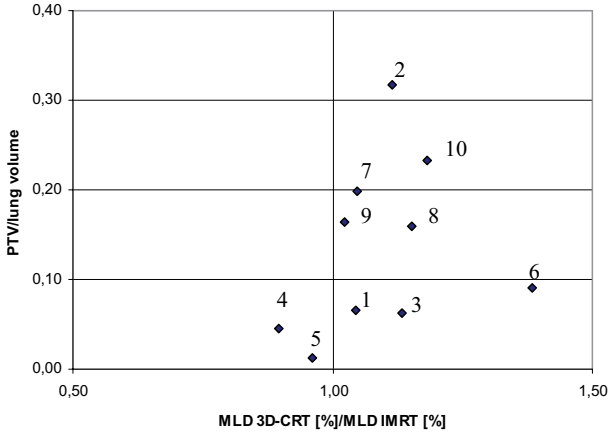

Fig. 4. Correlation of PTV/lung volume ratio to 3D-CRT MLD/IMRT MLD ratio in consecutive patients. Mean lung doses expressed by percentage of total doses

DISCUSSION

Our study shares the limitations of other planning studies. One of these limitations is the usually very limited number of patients included. In our study, the small number of patients is not surprising, because patients with small lung volume of about 2.0 litres are treated with curative intent very rarely, as they are challenging for planning, especially when PTV is large. Observer's (planner's) bias may hap-

Table 1. Mean values of lung volume receiving particular doses. From V5 (volume of lung receiving at least 5 Gy) to V65 at 5 Gy intervals: IMRT 66 Gy – for 6 IMRT plans delivering full dose; 3D-CRT 66 Gy – for 6 3D-CRT plans delivering full dose; IMRT all – for all IMRT plans; 3D-CRT all – for all 3D-CRT plans

	IMRT 66 Gy	3D-CRT 66 Gy	IMRT all	3D-CRT all
V5	46.5 %	35.1 %	56.5 %	47.4 %
V10	24.5 %	25.0 %	34.1 %	35.1 %
V15	19.9 %	21.6 %	27.4 %	28.3 %
V20	17.4 %	19.5 %	23.4 %	24.9 %
V25	15.5 %	17.9 %	20.8 %	22.6 %
V30	13.5 %	16.9 %	18.3 %	20.3 %
V35	11.2 %	15.5 %	15.5 %	18.0 %
V40	9.5 %	14.4 %	13.2 %	16.1 %
V45	8.1 %	13.1 %	11.4 %	13.5 %
V50	6.9 %	10.8 %	9.5 %	12.5 %
V55	5.6 %	9.1 %	7.1 %	8.8 %
V60	4.5 %	7.7 %	4.6 %	8.0 %
V65	1.5 %	4.3 %	1.7 %	4.3 %

pen in such studies. There is a risk of systematically producing better plans for the studied experimental technique if a new technique is preferred by a planner. This is also experience dependent. To reduce this bias the plans were prepared by two physicists most experienced in thoracic malignancies as well as having some experience in IMRT planning. Each plan was collectively discussed and particular problems were solved after detailed discussion involving two physicians involved in the study. The weakest point of the planning studies is that we are not certain that the advantage shown in those studies represents a real clinical benefit, and all these studies are only the beginning of more extensive research. We do not know either whether the plans realized in such studies are possible to be implemented in routine practice. There are ATC (Advanced Technologies Consortium) guidelines for the use of IMRT [7] to make sure that the predicted prescribed dose is delivered. In the lung at least two crucial issues arise: one is the issue of heterogeneity and the other is respiratory motion. To minimize the effect of tissue heterogeneity advanced dose calculating algorithms should be used; inhomogeneity correction is essential. In this study the commercial algorithm of Eclipse v 6.5 was used, which is Pencil Beam with the inhomogeneity correction Modified Batho. We are aware that this one is not the best existing algorithm, but the same algorithm calculated doses for both 3D-CRT and IMRT plans. Therefore the same dose uncertainty related to dose calculation may happen to both IMRT and 3D-CRT plans. Moreover, using only 6 MV photon beams minimizes the dose uncertainty in the lung given by temporary planning systems. However, the better conformity index for IMRT technique indicating steeper dose follow-off may cause bigger clinical consequences of any uncertainties. This problem is additionally magnified by respiratory motion. According to ATC guidelines the breathing control technique should be used for IMRT in thoracic malignancies. Respiratory gating seems the most suitable in lung cancer patients. In our study, we used free breathing CT scans for planning 3D-CRT as well as IMRT. This means that the problem of target and critical structures motion, and the dose uncertainty related to this, was not solved.

Studies on patients with SLV and the use of IMRT virtually do not exist. Studied groups involve patients with advanced or recurrent disease [5], inoperable [3] or with large target volume [8]. The Murshed study [5] is a planning IMRT study of patients with stage III-IV and recurrent NSCLC previously irradiated with 3D-CRT. Grills et al. [3] compared four techniques, including similarly to our study 3D-CRT and IMRT, in a spectrum of inoperable NSCLC patients. Yartsev et al. [8] analysed 3D-CRT and IMRT treatment plans for huge PTVs in stage III NSCLC patients. In this work, targets included elective nodal area and reached as much as 2 litres.

In NSCLC radiotherapy the size matters but it is not only the size of the target but also the size, i.e. volume, of lungs. Both parameters impact on dose-volume histograms. Mean lung dose and V20 are proved to correlate with clinical risk of radiation pneumonitis [13]. MLD of less than 18 or 20 Gy is associated with an acceptable rate of grade 2-3 pneumonitis and may be used as a reference limit for safe clinical practice in patients with lung cancer [14]. There is great variation regarding the risk of toxicity and the absolute cut-off values of V20, probably because V20 is a point measure and brings no information about spatial dose distribution. We took V20<35% after Graham et al. [1]. In recent studies concerning highly conformal techniques other dosimetric descriptors mentioned below such as V5 are underlined.

All these dosimetric parameters help to find a balance between expected toxicity and delivering a high enough dose. In our study, the IMRT technique allowed higher total doses to be delivered, which was similar to the results of Grills et al. [3]. Mean lung dose and V20 were dosimetric constraints for lungs in both cases but threshold doses were more restrictive than in our study, e.g. lung V20≤25%, MLD≤15%. While doses to organs at risk did not exceed selected levels, total dose could be higher. The authors concluded that, keeping the same dose constraints for both techniques, IMRT may allow dose escalation especially in node positive cases.

The ratio of PTV to lung volume which we concluded is important was also noticed by Baisden et al. [9], who analyzing only Tomo-

Therapy IMRT plans tested the hypothesis that maximum acceptable total dose to be delivered depends on PTV and lung volume. IMRT was found to be possibly beneficial in a group of patients with a high PTV / lung volume ratio. The unquestionable advantage of IMRT is better conformity so that there is better sparing of normal tissues from high doses. But is it really a benefit in the lung? With IMRT a large lung volume is irradiated at low doses, and we are still learning about the consequences of this phenomenon. Liu et al. [4] reported a comparison of 3D-CRT and IMRT concerning healthy lung tissue doses. V20 was reduced with IMRT. To reduce V10 or V5 the number of beams in IMRT had to be decreased. How important irradiating a large volume at low doses might be can be seen in Allen's et al. [10] study, where six out of thirteen patients developed fatal pneumonitis even though pulmonary dose restrictions were kept. Mean lung dose was limited to 15 Gy and V20 to 20% but unfortunately V5 encompassed almost the whole lung – mean 90% in patients who did not develop pneumonitis and mean 98.6% in those who did. According to Wang et al. [11] V5≥45% seems to correlate well with treatment related pneumonitis. In our study mean IMRT lung V5 was as high as 57%, which is too much according to those mentioned criteria. Six patients receiving the full intended total dose with both techniques had lower mean V5 in their IMRT plans compared to all IMRT plans, and those six patients had lower mean V5 in 3D-CRT plans compared to all 3D-CRT plans (Figure 5). The V5 parameter will always be higher for treatment plans with a higher number of beams, so it is not surprising that V5 in IMRT was higher than V5 in 3D-CRT. But what is interesting when the planning was less challenging and expected total dose could be delivered, the volume of lung irradiated with small doses was smaller compared with more complicated cases in which we could not deliver 66 Gy.

In our study, the use of IMRT allowed higher total doses to be delivered. How meaningful is this end-point was not validated in prospective phase III trials. The selection bias in radiotherapy dose escalation protocols should be considered. Weiss et al. [12] reported a dose-escalation planning study

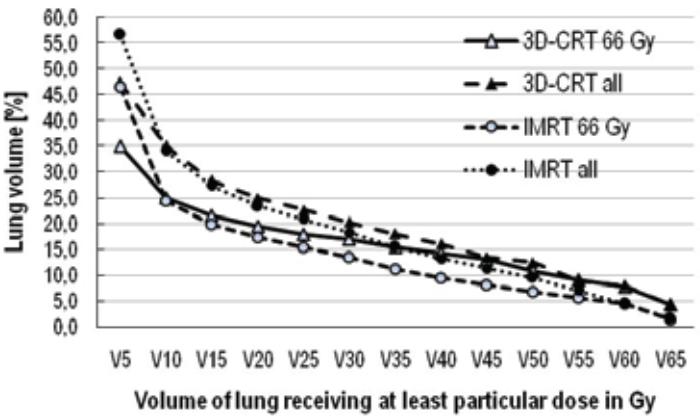

Fig. 5. Mean values of lung volume receiving particular doses. From V5 (volume of lung receiving at least 5 Gy) to V65 at 5 Gy intervals: IMRT 66 Gy – for 6 IMRT plans delivering full dose; 3D-CRT 66 Gy – for 6 3D-CRT plans delivering full dose; IMRT all – for all IMRT plans; 3D-CRT all – for all 3D-CRT plans

performed on NSCLC patients. In this virtual trial some patients were not eligible for higher dose levels, even though they had met the eligibility criteria at lower dose levels. As a result, the authors suggest that estimated outcome between patients who had been eligible for higher doses and those who had met the selection criteria only for lower doses was significantly different. The authors also stated that interpretation and comparison of dose-escalation studies is a challenging task since some of the patients enrolled primarily in the study are not even eligible for the lowest doses. Consequently there is selection bias at the very beginning and huge differences occur between patients eligible and ineligible for the study. In our study no patient enrolled was then excluded. Similarly, in our study the differences in PTV volumes and PTV/lung volume ratios were observed comparing the full dose patient group with the reduced total dose group in favour of the former. This may indicate better predicted outcome for patients with smaller PTV, even without an attempt at dose escalation compared with the remainder. Despite all the limitations of our study we were able to demonstrate the potential benefit of IMRT in cases where small lung volume coexists with large PTV. We found PTV/lung volume ratio to be an important factor deciding the feasibility of dose escalation. We suggest that for

NSCLC with SLV and large PTV/lung volume ratio IMRT with gating is worthy of further clinical studies. Further studies are certainly needed to assess the feasibility and benefit of such a sophisticated radiotherapy method.

CONCLUSIONS

In our planning study we demonstrated that patients with small lung volume may benefit from IMRT, especially when the dose should be delivered to a large target volume. What is also of significance, IMRT might facilitate dose escalation in this group of patients.

Radiotherapists should be cautious when implementing IMRT in small lung volume patients because little is known about the clinical consequences of delivering low doses to a large lung volume and we still have doubt about the certainty of doses delivered to moving and complex targets with this highly conformal technique.

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