Comparison of the helical tomotherapy against the multileaf collimator-based intensity-modulated radiotherapy and 3D conformal radiation modalities in lung cancer radiotherapy

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Objectives: The aim of this study was to compare three-dimensional (3D) conformal radiotherapy and the two different forms of IMRT in lung cancer radiotherapy.

Methods: Cases of four lung cancer patients were investigated by developing a 3D conformal treatment plan, a linac MLC-based step-and-shoot IMRT plan and an HT plan for each case. With the use of the complication-free tumour control probability (P_+) index and the uniform dose concept as the common prescription point of the plans, the different treatment plans were compared based on radiobiological measures.

Results: The applied plan evaluation method shows the MLC-based IMRT and the HT treatment plans are almost equivalent over the clinically useful dose prescription range; however, the 3D conformal plan inferior. At the optimal dose levels, the 3D conformal treatment plans give an average P_+ of 48.1% for a effective uniform dose to the internal target volume (ITV) of 62.4 Gy, whereas the corresponding MLC-based IMRT treatment plans are more effective by an average ΔP_+ of 27.0% for a Δ effective uniform dose of 16.3 Gy. Similarly, the HT treatment plans are more effective than the 3D-conformal plans by an average ΔP_+ of 23.8% for a Δ effective uniform dose of 11.6 Gy.

Conclusion: A radiobiological treatment plan evaluation can provide a closer association of the delivered treatment with the clinical outcome by taking into account the dose–response relations of the irradiated tumours and normal tissues. The use of P_+ –effective uniform dose diagrams can complement the traditional tools of evaluation to compare and effectively evaluate different treatment plans.

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One of the major constraints in radiation therapy is the low-tolerance doses characterising the involved organs at risk (OARs). In treatments where these OARs are near the frequently large gross tumour volume (GTV) and clinical target volume (CTV), the dose delivered is more limited [1, 2]. It has been demonstrated that intensity modulated radiotherapy (IMRT) can produce better results than conventional and simple conformal radiation therapy techniques via a significant reduction of radiation dose and toxicity delivered to the critical organs [3]. Today, several treatment planning systems (TPSs) perform physical IMRT optimisation. Helical tomotherapy (HT) is a recently developed technology for radiation therapy, characterised by dose distributions of higher dose conformality than other IMRT techniques [4, 5]. In HT technology, the radiation dose is delivered helically through 51 projections per rotation. Reports on the physical comparison of dose distributions delivered by three-dimensional (3D) conformal and IMRT techniques

have been published recently [6, 7]. However, the use of radiobiological measures in comparison studies of the effectiveness of dose distributions between HT and other 3D conformal and IMRT modalities, including linac-based IMRT using multileaf collimators (MLCs) in a step-and-shoot mode, are very limited. Consequently, the question regarding the comparison of the effectiveness of the corresponding dose distributions and the need for a change in the treatment methodology of a certain institution still remains.

The selection of the best plan can be a challenging task owing to the variations that exist in the optimisation methodology, which may lead to significant discrepancies between the integral doses and the expected response probabilities. The dose–volume histogram (DVH) and the maximum, minimum, mean and standard deviation of a dose distribution are usually the criteria used for radiotherapy treatment plan evaluation nowadays. Nevertheless, all the above evaluation factors do not account for the radiobiological characteristics of the tumours or normal tissues involved. In some situations, competing plans are characterised by significant discrepancies in radiobiological outcomes even though they have similar

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mean, maximum and minimum doses [8]. In order to deal with such cases, the use of the biologically effective uniform dose ($\bar{D}$) and complication-free tumour control (P_+) have been proposed as alternative tools for radiotherapy treatment plan evaluation [9]. The biologically effective uniform dose, $\bar{D}$, is a concept assuming that different dose distributions are equivalent when causing the same probability for tumour control or normal tissue complication [8]. The $\bar{D}$ concept indicates the fact that a closer relation exists between the response probabilities which are averaged over both dose distribution and organ radiosensitivity with the corresponding clinical outcome.

The aim of this study is to explore the use of radio-biological measures to compare the 3D conformal, MLC-based IMRT and HT radiation modalities in lung cancer radiotherapy. To achieve this goal, the evaluation of four lung cancer cases is carried out. For each patient, two treatment plans have been developed using the Philips (ADAC laboratories, Milpitas, CA) pinnacle treatment planning system (TPS) and one plan using an HT TPS. The maximum, minimum and mean doses were calculated, and the P_+ index and the dose $\bar{D}$ were derived and analysed. In order to reveal the value of biological and physical factors in assessing treatment plans, a parallel physical and biological evaluation was performed to compare the merits of the incident beam profiles and projections and to further estimate the probabilities of achieving complication-free tumour control [10–14].

Methods and materials

In this study, the clinical cases of four lung cancer patients were selected. For final approval of the different treatment configurations, the following clinical criteria were used: (1) uniform dose to the internal target volume (ITV) (standard deviation less than 5%), (2) minimum dose to the surrounding healthy tissue stroma and (3) minimum dose to the OARs (below their respective tolerance dose). A dose prescription of 60 Gy in 30 fractions, giving 200 cGy per fraction, was applied. The basic characteristics of the three treatment plans were:

- 3D conformal treatment plan: anteroposterior, right anterior oblique, right posterior oblique and postero-anterior beam projections
- MLC-based IMRT treatment plan: six coplanar beams of 6 MV energy, delivered at gantry angles of 330, 230, 180, 130, 30 and 10 degrees.
- HT treatment plan: a pitch of 0.3, a width jaw setting of 2.5 and a modulation factor of 2.0.

All calculations were performed using the convolution/superposition dose calculation algorithm, which accounts for density inhomogeneity effects [15, 16].

Treatment planning and respective treatment modalities

The treatment delivery machines used for the linac 3D conformal treatment plans, MLC-based step-and-shoot IMRT plans and HT plans were a Varian linac 21EX with a dose calculation grid resolution of $3 \times 3 \times 3 \text{ mm}^3$ (Varian

Medical Systems, Palo Alto, CA) and a Hi-Art II TomoTherapy (TomoTherapy, Inc. Madison, WI). The Varian linear accelerator model was a 21EX outfitted with a MILLENNIUM 120-leaf MLC. The HT unit had a 64-leaf binary MLC and had been commissioned for 2.5 and 5.0 cm jaw models. The HT plans were helically delivered from 51 beam angles per rotation. In order to produce the sinogram intensity modulation, it is required to achieve the prescribed objectives. The $2.5 \times 40 \text{ cm}$ slit beam was modulated by a binary multileaf collimator. A Pinnacle (ADAC Laboratories, Milpitas, CA; version 7.6c) TPS was used for the 3D conformal and MLC-based IMRT linear accelerator plans. A dedicated tomotherapy treatment planning station, version 2.1.2, was used for the HT plan. The delineations of the target and OARs were performed on the Pinnacle planning station, and this information was subsequently transferred to the tomotherapy planning station using the digital imaging and communications in medicine—radiotherapy (DICOM-RT) protocol.

A CT simulation was performed by setting the patients in the treatment position using rigid immobilisation devices. The internal target volume (ITV) was created by expanding the gross tumour volume (GTV) with an appropriate margin for organ motion. The guidelines for the dose prescription and fractionation schedule were the same for all the plans. For the 3D conformal and MLC-based IMRT plans, all the beams were coplanar and equally spaced around the patient with 6 MV energy. At the end of the HT treatment planning process, the dose matrix was exported to the Pinnacle workstation for comparative analysis and evaluation. The export of the dose matrix from the tomotherapy TPS and its transfer to the Pinnacle planning station was performed through an in-house-developed software tool, which assures the correct alignment and scale of the dose matrix with the patient's anatomy [17].

The following optimisation constraints were applied during the production of all the treatment plans. For tumours, the importance value was set to 50, and maximum and minimum dose penalties were set to 100. For organs at risk, the importance value was set to 15, whereas maximum dose and DVH point penalties were set to 1 and 20, respectively. After the completion of the optimisation, the same physician reviewed the DVHs and the isodose distributions for final approval of the treatment plans. The values of relevant statistical parameters such as maximum, minimum and mean doses as well as the irradiated volume and density of normal tissues were collected for analysis.

Radiobiological treatment plan evaluation

The dose–response relation of tumours and normal tissues is described by the Poisson model, expressed by the following equation, which is derived by the combination of equations (A18) and (A19) in the work of Ågren-Gronqvist, Källman and colleagues [18, 19]:

$$P(D) = \exp\left(-e^{c\gamma - (D/D_{50}) \times (c\gamma - \ln 2)}\right) \quad (1)$$

where $P(D)$ is the probability to control the tumour or induce a certain injury to a normal tissue that is

irradiated uniformly with a dose D . D_{50} is the dose that gives a 50% response and γ is the maximum normalised dose–response gradient. The values of the D_{50} and γ parameters depend on the organ and type of clinical end point and they are regularly derived directly from clinical data [13, 14, 20–22]. The dose distributions had to be corrected for the fractionation effects; hence, the use of the relevant α/β ratios was necessary. The organ response to a non-uniform dose distribution is derived from an expanded version of equation (1) for tumours, whereas the response of a normal tissue to a non-uniform dose distribution can be calculated by the relative seriality model that accounts for the volume effect [19, 22]. According to this model, the overall probability of injury, P_I , for a number of OARs is expressed by the equation:

$$P_I = 1 - \prod_{j=1}^{N_{\text{organs}}} \left(1 - \left[1 - \prod_{i=1}^{M_j} \left(1 - P^j(D_i)^{s_j} \right)^{\Delta v_i} \right]^{1/s_j} \right) \quad (2)$$

where N_{organs} is the total number of vital OARs. $P^j(D_i)$ is the probability of response of organ j having the reference volume and being irradiated to dose D_i as described by equation (1). $\Delta v_i = \Delta V_i/V_{\text{ref}}$ is the fractional subvolume of the organ that is irradiated compared with the reference volume for which the values of D_{50} and γ have been calculated. M_j is the total number of voxels or subvolumes in the organ j , and s_j is the relative seriality parameter characterising the internal organ structure. The value $s \approx 1$ corresponds to a serial structure whereas $s \approx 0$ corresponds to a parallel structure.

The structural organisation in tumours is assumed to be parallel since the eradication of all their clonogenic cells is required. Moreover, the eradication of every individual tumour has to be achieved in complex multitarget cancer cases. This pattern indicates that the different targets are related through a parallel organisation fashion. Hence, the overall probability of benefit, P_B , is given by the expression:

$$P_B = \prod_{j=1}^{N_{\text{tumours}}} \left(\prod_{i=1}^{M_j} P^j(D_i)^{\Delta v_i} \right) \quad (3)$$

where N_{tumours} is the total number of tumours or targets involved in the clinical case.

It should be mentioned that other models such as the Lyman-Kutcher-Burman (LKB) [23–25] and parallel [26] could also have been used, selecting the appropriate response parameter sets. Table 1 presents the dose–response parameters of the organs used. The parameter set is based on published data [11–14, 20, 21, 27–30]. In certain cases (like oesophagus) the relative seriality values appear to be larger than one. This is equivalent to a serial tissue whose FSUs are so sparsely distributed that there are voxels without an FSU inside them [19]. The uncertainties associated with these parameters are of the order of 5% for D_{50} , 30% for γ and 90% for s , defining the confidence interval of the entire dose–response curve around its best estimate [31]. Our study assumes that the patient is of an average radiosensitivity and is thus characterised by the mean estimates of the radiobiological parameters presented.

The effectiveness of the different treatment plans is evaluated through the concepts of the biologically effective uniform dose, $\bar{D}$, and the scalar quantity, P_+ , which expresses the probability of achieving tumour control without causing severe damage to normal tissues [9]. In this study, the probability of getting benefit from a treatment (tumour control) is denoted by P_B , whereas the probability for causing severe injury to normal tissues is denoted by P_I [3, 22]. Therefore, P_+ can be estimated from the following equation [18]:

$$P_+ = P_B - P_{B \cap I} \approx P_B - P_I \quad (4)$$

In this study, the $\bar{D}$ concept is additionally used together with other dosimetric quantities to evaluate the treatment plans. The biologically effective uniform dose is defined as the dose that causes the same tumour control or normal tissue complication probability as the actual dose distribution given to the patient. In the former case the biologically effective uniform dose is denoted as $\bar{D}_B$, whereas in the latter case it is $\bar{D}_I$. The notation $\bar{D}$ indicates that the quantity has been averaged over both the dosimetric (dose distribution) and the biological (dose–response relations) information of the clinical case. The general expression of $\bar{D}$ for a given tumour or normal tissue does not depend on the applied radiobiological model. For the Poisson model and for a tissue of uniform radiosensitivity, $\bar{D}$ is derived from the analytical formula:

$$P(\bar{D}) \equiv P(\bar{D}) \Rightarrow \bar{D} = \frac{e^{\gamma - \ln(-\ln(P(\bar{D})))}}{e^{\gamma - \ln(\ln 2)}} \quad (5)$$

where $\bar{D}$ denotes the 3D dose distribution. A number of plan trials can be compared based on radiobiological end points using this concept by normalising their dose distributions to a common prescription point ($\bar{D}$) and plotting the tissue response probability *vs* $\bar{D}$. The treatment plans of the study were radiobiologically evaluated using the radiation sensitivities of the tumour and the OARs involved, although conventional physical criteria like DVHs, isodose charts, etc, were also employed since the objective was the normal tissue tolerance estimation against the optimum target dose needed [32, 33].

Table 1. Summary of the model parameter values for the lung cancer case. D_{50} is the 50% response dose, γ is the maximum normalised value of the dose–response gradient and s is the relative seriality, which characterises the volume dependence of the organ

Relative seriality model	Parameter values			
	D_{50} (Gy)	γ	s	α/β
Lung cancer				
ITV	49.2	1.0	—	10.0
Spinal cord	57.0	6.7	1.0	3.0
Oesophagus	68.0	2.8	3.4	3.0
Heart	70.7	0.96	1.0	10.0
Lung	30.1	0.97	0.01	3.0

ITV, internal target volume.

Results

Figure 1 illustrates the comparison of the isodose curve distributions of the 3D conformal, MLC-based IMRT and HT treatment plans in transverse, coronal and sagittal views. In this clinical case of lung cancer, the sensitive OARs are spinal cord, oesophagus, heart and ipsilateral and contralateral lungs. Studying the isodose curve distributions, it is clear that the 3D conformal treatment plan has a quite large dose spread outside the ITV but a moderate inhomogeneity inside the ITV. The HT plan has a higher dose spread outside the ITV than the MLC-based IMRT but a lower inhomogeneity inside the ITV.

Regarding the OARs, the 3D conformal treatment plan delivered higher doses to the oesophagus and lungs than the MLC-based IMRT and HT plans at the initially prescribed dose level in most of the cases. Between the MLC-based IMRT and HT modalities, the former delivered lower effective doses to the oesophagus and contralateral and ipsilateral lungs (Table 2, $\bar{D}$ columns). In all cases, the mean dose, $\bar{D}$, to the ITV is very close to the corresponding $\bar{D}$ values owing to the small dose

variations within the ITV. In contrast, the dose distributions within the OARs are characterised by quite larger variations with the largest ones being observed in the 3D conformal plans. This has a consequence that the $\bar{D}$ values of the normal tissues are greater than the corresponding mean dose values ($\bar{D}$), especially for the spinal cord and oesophagus.

In Figure 2, the treatment plans of the different radiation modalities were compared in terms of DVHs, and in Figure 3 the corresponding dose–response curves are compared in the same way. In each diagram of Figures 2 and 3, four histograms or dose–response curves are presented, which correspond to the four patients examined. The dose–response curves of the ITV and each OAR (spinal cord, oesophagus, heart, and contralateral and ipsilateral lung) are presented. In the diagrams of Figure 3, all the response curves are normalised to the mean dose to the ITV ($\bar{D}_{ITV}$). In these diagrams, the curves show how the expected tissue response changes with dose prescription since the same dose distribution is kept at all dose levels. Intercomparisons of the different modalities can also be performed by using the concepts $\bar{D}_B$ for the normalisation. In Figure 4, the dose–response curves have

Figure 1. The reference CT slice of a lung cancer patient is shown for the three-dimensional (3D) conformal, multileaf collimator (MLC)-based intensity-modulated radiotherapy tomotherapy (IMRT) and helical tomotherapy treatment plans in transverse (left), coronal (middle) and sagittal (right) planes. The anatomical structures involved are illustrated together with the isodose lines of the applied dose distributions to be delivered to the patient.

been normalised to $\bar{D}_B$, forcing the response curves of the ITV (P_B) of the different treatment plans to coincide. This approach gives emphasis to the therapeutic window characterising each treatment plan. The four diagrams in Figure 4 correspond to the four lung cancer patients; they are presented in order of increasing efficiency of the treatments or decreasing complexity of the clinical case (from upper left to lower right). The physical and biological comparisons are summarised in Tables 2 and 3.

For the planned dose prescription, the average P_+ value for the 3D conformal treatment plan was found to be equal to 31.0% for $\bar{D}_{ITV}=61.0$ Gy and for $\bar{D}_B=60.9$ Gy. The average total control probability, P_B , was found to be 71.9% and the average total complication probability, P_L , was 40.9%. Compared with the 3D conformal plans, for the MLC-based radiation modality the average P_+ value is 31.9% higher for $\Delta\bar{D}_{ITV} = -0.4$ Gy and $\Delta\bar{D}_B = -0.4$ Gy. The average total control probability, P_B , is 0.8% lower while the average total complication probability, P_L , is lower by -32.7%. Similarly, for the HT plans, the average P_+ value was 27.2% higher for $\Delta\bar{D}_{ITV} = -0.1$ Gy and $\Delta\bar{D}_B = -0.4$ Gy. The respective average total control probability, P_B , is 1.0% lower and the average total complication probability, P_L , is lower by -28.2%. At the optimum dose level, which maximises the complication-free tumour control, for the 3D conformal plans the average P_+ value becomes 48.1% for a $\bar{D}_B$ of 62.4 Gy, having average $P_B=68.3\%$ and $P_L=20.2\%$. In comparison to these values, for the MLC-based IMRT the optimum P_+ value increases on average by 27.0% for a $\Delta\bar{D}_B$ of 16.3 Gy, having average $\Delta P_B=14.4\%$ and $\Delta P_L = -12.7\%$. Finally, for the HT plans the optimum P_+ value increases on average by 23.8% for a $\Delta\bar{D}_B$ of 11.6 Gy, having average $\Delta P_B=12.0\%$ and $\Delta P_L=-11.8\%$.

In Figures 3 and 4, a more schematical description of the radiobiological evaluation of the three treatment plans is presented. It is shown that both the HT and the MLC-based IMRT dose distributions are characterised by a high conformality to the ITV, sparing very well the OARs involved. The mean doses to the ITV at the prescribed dose level of the distributions are high and very close to the optimum level in most of the cases. This would maximise their control with a good compensation for normal tissue complications, but this characteristic does not hold for the 3D conformal treatment plan, where the complications expected for the oesophagus and the ipsilateral lung are significantly high in most of the cases. With the exception of the oesophagus and ipsilateral lung, in the HT treatment plan, the mean and maximum doses in the OARs are low, ensuring low levels of complications expected. For all four plans, the maximum doses of the oesophagus and lung appear to increase as a result of their proximity to the ITV.

Discussion

Up-to-date studies have been carried out regarding comparisons of the HT against the 3D conformal treatment techniques as well as against IMRT for lung cancer [34]. However, these studies performed only dosimetric comparisons between the different radiation modalities without examining the impact of the observed

differences on the expected treatment outcome. Our study covers this important gap in the assessment of the clinical effectiveness of the different modalities by interpreting the dosimetric characteristics of the different treatment plans into expected rates of tumour control and normal tissue complications.

In order to evaluate the clinical effectiveness of 3D conformal radiotherapy, MLC-based IMRT and helical tomotherapy, the dose distribution uniformity in the target volume and the dose level constraints are usually defined as the evaluation and classification parameters of the different radiation modalities. In the upper part of Figure 1 it is seen that the 3D conformal radiation modality delivers a high dose to a large volume since the ITV is covered with the preferred isodose curve, but the oesophagus and lung are not well protected. In the MLC-based IMRT and HT plans, the ITV is sufficiently covered with the prescribed dose. However, the oesophagus and the ipsilateral lung are spared more with the MLC-based IMRT than with HT, whereas all the other OARs are spared equally well. The results show that HT and MLC-based IMRT may produce dose distributions with fairly homogeneous doses to the ITV and small integral doses to the healthy organs.

The differences observed on the DVHs comparing the 3D conformal, MLC-based IMRT and HT treatment plans are not always reflected in the radiobiological evaluation. This is because the different tissues respond in different ways to a certain dose distribution. In this sense, two dose distributions irradiating the same tissue may have equal values of mean dose and standard deviation, but different response probabilities. Figure 4, where the $\bar{D}_B$ is used, shows a coincidence of the curves corresponding to the response of the ITV (P_B). In this way, the classification and the superiority of the plans are determined by comparing the response curves of the OARs. The $\bar{D}$ concept is based on the fact that a 3D dose distribution may be reduced to a single dose, causing the same response probability. The use of the mean dose delivered to the ITV does not provide a common base of dose scaling in order to compare different plans, and this is because for the same control rate different mean doses to the ITV are delivered by different plans. Furthermore, it is harder to compare the effect of the treatment to the residual involved organs using this scale.

As shown in Figure 4, the expected complication-free tumour control for the MLC-based IMRT treatment plans are better than that of the 3D conformal plans over the whole range of clinically prescribed doses, whereas the HT treatment plans are worse than the MLC-based IMRT plans but within the uncertainty range of radiobiological modelling. The explanation is that although the HT irradiates the ITV a little more effectively, the MLC-based IMRT dose distribution achieves better sparing to the oesophagus and ipsilateral lung, as shown in Tables 2 and 3. In comparison with the 3D conformal plan, both the MLC-based IMRT and HT plans show higher tumour control and much lower complication probabilities at the same dose prescription. It is important to mention that, in certain cases, although the HT plan delivers a lower mean dose to the oesophagus with a little larger standard deviation than the MLC-based IMRT, a significantly higher complication probability is shown owing to its greater maximum dose and to the high relative

Table 2. Summary of the physical dosimetric quantities and the expected tumour control or normal tissue complications of the three-dimensional conformal, multileaf collimator-based intensity-modulated radiotherapy (IMRT) and helical tomotherapy treatment plans for the four lung cancer patients. The indices C, P and T refer to conformal, IMRT (planned in Pinnacle) and tomotherapy

Tissue	P_C (%)	ΔP_P (%)	ΔP_T (%)	$\bar{D}_C$	$\Delta \bar{D}_P$	$\Delta \bar{D}_T$	$\bar{D}_C$	$\Delta \bar{D}_P$	$\Delta \bar{D}_T$	D_{max_C}	ΔD_{max_P}	ΔD_{max_T}	D_{min_C}	ΔD_{min_P}	ΔD_{min_T}
ITV	73.4	-3.4	-2.2	61.8	-2.0	-1.3	61.8	-2.0	-1.3	64.9	-2.7	-1.8	56.7	-9.9	-5.4
	72.6	1.6	4.9	61.3	0.9	3.1	61.4	1.0	3.0	65.4	0.8	2.2	54.4	-8.3	-5.6
	67.7	5.3	2.9	58.6	3.0	1.6	58.6	2.9	1.5	60.2	3.9	0.4	54.6	2.0	4.9
Spinal cord	73.9	-6.5	-9.4	62.1	-3.6	-5.1	62.2	-3.8	-3.4	69.5	-7.1	-4.2	58.6	-3.8	-28.9
	77.4	-77.4	-77.4	60.1	-11.6	-11.6	42.2	-30.1	-28.8	64.6	-35.1	-29.3	1.1	-0.6	0.0
	0.0	0.0	0.0	48.5	0.3	0.0	19.4	2.8	-2.8	47.4	2.1	-5.1	0.3	0.0	0.3
	0.0	0.0	0.0	48.5	0.0	0.0	0.9	2.0	5.7	6.5	12.4	21.7	0.3	0.0	-0.2
	0.0	0.0	0.0	48.5	0.0	0.0	3.4	-1.6	-2.6	20.8	-0.3	-4.6	0.1	0.2	0.2
Oesophagus	21.2	-8.8	-4.8	60.9	-1.9	-0.9	44.4	-16.8	-5.8	63.2	-1.9	-1.0	0.5	0.0	1.1
	15.4	-13.0	-6.8	59.7	-4.3	-1.7	33.9	-10.4	-13.5	63.1	-1.6	2.5	5.7	-3.6	-3.3
	0.0	0.0	0.0	48.3	0.0	0.0	1.0	4.5	3.1	7.9	7.8	7.8	0.2	0.2	0.2
Heart	0.0	0.0	0.0	48.3	0.0	0.0	4.3	-1.9	-3.0	33.8	-12.8	-17.3	0.3	0.0	0.0
	35.2	-32.4	-32.7	60.8	-23.3	-23.9	57.6	-33.7	-34.7	67.8	-6.5	-5.7	2.1	1.2	2.7
	0.0	0.0	0.0	17.9	0.8	-1.4	5.5	1.0	1.4	47.1	-8.8	-10.9	0.3	0.0	0.0
Contralateral lung	0.0	0.0	0.0	0.2	-0.1	0.2	0.1	-0.1	0.2	2.2	-1.5	-1.0	0.3	0.0	-0.2
	0.0	0.0	0.0	6.1	-5.9	-6.0	2.9	-2.8	-2.9	22.2	-21.3	-21.6	0.9	-0.5	-0.5
	8.1	-5.1	-4.3	22.9	-3.8	-3.0	19.4	-1.5	-0.7	66.7	-6.4	-4.3	0.4	0.1	0.5
	0.0	0.0	0.0	4.9	-0.8	2.0	4.5	-0.7	2.0	56.2	-27.5	-29.9	0.3	0.0	0.0
	0.0	0.0	0.0	0.5	2.3	2.8	0.4	2.2	2.7	52.8	-22.2	-38.1	0.3	0.0	-0.2
Ipsilateral lung	0.0	0.0	0.0	3.8	-3.1	-3.4	3.5	-2.9	-3.2	17.5	-2.7	-6.2	0.2	0.0	0.0
	34.1	-31.0	-28.7	31.7	-12.6	-10.5	27.7	-9.9	-7.9	67.4	-6.6	-4.9	0.4	0.1	0.7
	47.8	-39.0	-33.0	35.3	-12.1	-9.5	31.8	-11.2	-8.9	65.5	0.1	0.3	0.3	0.0	0.0
	13.7	-12.1	-11.1	25.4	-8.4	-6.8	20.7	-7.7	-6.1	61.5	2.3	-0.6	0.3	0.0	-0.2
	0.8	-0.8	-0.8	15.3	-9.1	-11.1	12.3	-7.0	-8.8	65.9	-32.3	-31.2	0.4	-0.2	-0.2

ITV, internal target volume.

Figure 2. The dose–volume histograms of the internal target volume and those of the organs at risk (spinal cord, oesophagus, heart, contralateral lung and ipsilateral lung) are shown for the four lung cancer patients and the three radiation modalities. 3D-CRT, three-dimensional chemoradiotherapy; IMRT, intensity-modulated radiotherapy; ITV, internal target volume.

seriality value of oesophagus. The same holds for the 3D conformal plan, delivering to the oesophagus a high mean dose as well as a high maximum dose. The highest mean doses to the ipsilateral lung, which is a parallel organ (characterised by a low relative seriality value), is delivered by the 3D conformal plan and this is the dominating factor for the large complication probabilities in most of the cases. In this case, although the dose variation is large, the $\bar{D}$ value does not deviate much from the corresponding mean dose, $\bar{D}$, because of the low relative seriality values characterising lung tissue. As far as tissues of parallel internal organisation are concerned, dose inhomogeneity does not affect so much their response, which is mainly determined by the mean dose.

In Figure 4, the clinically established dose prescription, corresponding to a certain uniform dose in the ITV, deviates from the optimal dose level that the radiobiological evaluation gives for the different treatment plans. In Table 3 it is observed that in most of the cases the planned dose prescription of the MLC-based IMRT plans lies below the optimum, and this is due to the acceptable compromise being achieved. Nevertheless, when the radiobiological data of the different tissues are available, a margin of improvement is indicated. With a small increase in the dose prescription, the gain in tumour control is larger than the increment in normal tissue complications until a balance is reached. Because of these points, the clinically prescribed dose level is

Figure 3. The dose–response curves of the internal target volume and those of the organs at risk (spinal cord, oesophagus, heart and contralateral lung and ipsilateral lung) are shown for the four lung cancer patients and the three radiation modalities. In the diagrams, the prescription dose levels are also presented. The curves are plotted using the mean dose to the internal target volume on the dose axis. IMRT, intensity-modulated radiotherapy; 3D-CRT, three-dimensional chemoradiotherapy.

lower than the optimum level by an average $\Delta\bar{D}$ of 18.2 Gy. Similarly, in the case of the HT plans, the planned dose prescription is lower than the optimum dose level ($\Delta\bar{D}=13.6$ Gy). The radiobiological evaluation showed that increasing the level of the dose distribution increased the complication probabilities at a much lower rate than the tumour control probability until an equilibrium point was reached. Finally, in the case of the 3D conformal treatment plan, the dose prescription is higher than the optimum dose level by an average $\Delta\bar{D}$ of 1.5 Gy. This is because a quite high risk for normal tissue

complications had to be accepted in order to ensure an adequate tumour control probability.

In the DVH diagrams (Figure 2), high doses to the more radioresistant ITV are observed. For the MLC-based IMRT and HT plans, the OARs receive quite low doses and their response curves are well separated from the targets. This broadens the therapeutic window of the treatment leading to a better clinical outcome than expected, as shown in Figure 4. It can also be seen that the width of the therapeutic window broadens with the height of the curve of $P_{+1/2}$ [35]. Therefore, the width of

Figure 4. In the four diagrams, the P_+ , P_B and P_I curves of the three radiation modalities are plotted using the $\bar{D}_B$ as the dose level unit. Each diagram corresponds to a patient and they have been ordered in terms of increasing treatment efficiency (from upper left to lower right). The confidence intervals of the dose-response curves are also presented. The vertical lines indicate the initial dose prescription. IMRT, intensity-modulated radiotherapy; MLC, multileaf collimator; 3D, three-dimensional.

the P_+ curve expresses the separation between the response curves of the tumours and the healthy tissues involved. The width of the therapeutic window also gives an indication of how robust the treatment plan is against the dose delivered and against the patient radiosensitivity uncertainties. At the same time, the optimum treatment modality is indicated, since the most conformal treatment plan generates a higher value of P_+ . Apart from just optimising physical functions, the use of this method takes into account patient-specific characteristics.

It has been shown that radiation doses to OARs can be significantly limited when using IMRT. Nevertheless, when CTV is adjacent to highly radiosensitive critical organs, the ITV expansion often does not allow for sparing greater parts of an organ. A preferential OAR sparing allows a margin expansion of the GTV and CTV as well as it expanding the possibilities for dose escalation. Dose inhomogeneity within an organ is generally associated with the delivery of different radiation doses to different regions. The effect of this inhomogeneity is to produce a concurrent radiation local boost, giving a higher total radiation dose to a limited region [36]. Even though a very accurate set-up can be provided taking a CT immediately before each treatment fraction, organ motion normally is not taken into account during a treatment session [37–39]. The amount of movement during quiet respiration might be assumed to be less than during full inspiration and expiration, but the few studies published present discrepancies between their results. During quiet respiration, the amount of movement in the craniocaudal axis may reach 20 mm. These dose delivery uncertainties are expected to affect the more conformal dose distributions since these distributions are so well fitted to the radiosensitivity map of the individual patient that small misalignment between the irradiating beams and the patient may significantly reduce the effectiveness of the treatment. In a relevant investigation for the case of prostate cancer, it was demonstrated that the treatment effectiveness of IMRT was reduced more than that of 3D-chemoradiotherapy (CRT). However, the effectiveness of IMRT remained better than that of 3D-CRT in all the examined combinations of beam to patient misalignments [3].

A key point of this study is the usefulness of $P-\bar{D}$ diagrams (Figure 3). These diagrams combine the dosimetric information of the delivered dose distribution with the radiobiological information of the organs involved. The definition of the P_+ concept does not precisely depict the clinical way of thinking. It would be more reasonable if the different terms related to the tumour control and to the normal tissue complication probabilities were accompanied by some weighting factors, which could be clinically adjusted. With the use of the $\bar{D}$ concept on the dose axis, the control and complication probabilities regarding the different targets and OARs can be individually examined. The major advantage is that the $\bar{D}$ concept forces the total control or total complication probabilities of different plans to coincide.

The results of this study depend strongly on the accuracy of the radiobiological models and the parameters describing the dose-response relation of the different tumours and normal tissues. Nevertheless, it is known that all the existing models are based on certain assumptions and they take into account only certain biological mechanisms. Furthermore, the determination of the model parameters expressing the effective radiosensitivity of the tissues is subject to the uncertainties imposed by inaccuracies in the patient set-up during radiotherapy, the lack of knowledge of the interpatient and inpatient radiosensitivity and the inconsistencies in treatment methodology [40–42]. Consequently, the determined model parameters (such as D_{50} , γ and s) and the corresponding dose-response curves have their respective confidence intervals. In the present study, most of the tissue response parameters have been taken from recently published clinical studies, where the confidence intervals have been significantly reduced (e.g. uncertainty of around 5% in the determination of D_{50}). Therefore, in many cancer sites the expected response of a tissue may be known within a range of clinically acceptable uncertainties. In Figure 4, the confidence intervals of the P_B , P_I and P_+ response curves have been calculated. This uncertainty in the absolute knowledge of the expected responses does not affect the principle conclusions of the study.

Table 3. Summary of the radiobiological evaluation and comparison of the three-dimensional (3D) conformal, multileaf collimator (MLC)-based intensity-modulated radiotherapy (IMRT) and helical tomotherapy treatment plans for the four lung cancer patients

Radiation modality	3D conformal		Difference from 3D conformal	MLC-based IMRT		Helical tomotherapy	
Dose prescription	Clinical	Optimum P_+		Clinical	Optimum P_+	Clinical	Optimum P_+
P_+ (%)	-19.6	21.5	ΔP_+ (%)	69.6	32.3	64.9	30.8
	16.6	26.5		46.4	36.7	38.6	30.5
	54.0	55.7		17.4	28.6	14.0	23.4
	73.0	88.7		-5.7	10.6	-8.6	10.4
P_B (%)	73.4	46.2	ΔP_B (%)	-3.4	16.2	-2.2	16.2
	72.6	55.7		1.6	21.0	4.9	14.6
	67.7	76.9		5.3	15.1	2.9	12.4
	73.9	94.5		-6.5	5.1	-9.4	4.6
P_I (%)	93.0	24.7	ΔP_I (%)	-73.1	-16.1	-67.1	-14.5
	55.9	29.2		-44.8	-15.7	-33.7	-15.9
	13.7	21.2		-12.1	-13.4	-11.1	-11.0
	0.8	5.8		-0.8	-5.4	-0.8	-5.8
$\bar{D}_B$ (Gy)	61.8	49.0	$\Delta \bar{D}_B$ (Gy)	-2.0	7.0	-1.3	7.0
	61.3	53.0		0.9	10.9	3.1	7.1
	58.6	64.0		3.0	15.0	1.6	11.0
	62.1	83.7		-3.6	32.2	-5.1	21.5
$\bar{D}_I$ (Gy)	42.8	25.2	$\Delta \bar{D}_I$ (Gy)	-18.8	-4.8	-17.4	-4.2
	31.5	26.2		-10.1	-4.0	-6.9	-4.1
	22.3	24.4		-7.2	-4.4	-5.8	-3.4
	13.6	19.0		-8.5	-7.0	-10.5	-11.1

By examining four lung cancer patients of increasing clinical complexity, a more accurate picture of the comparisons could be achieved. In the present analysis, it was found that the main characteristics of the three radiation modalities are repeated. However, this was expected since the different treatment plans were produced using optimisation algorithms, which calculated the final dose distributions based on some pre-defined criteria (inverse physical optimisation). Thus, although a general intermodality comparison cannot be performed, an indication of the effectiveness of the three radiation modalities can be given for certain cancer types. General conclusions regarding the optimum selection of the treatment method are outside the scope of this paper. Nevertheless, apart from the 3D conformal radiation modality, both the MLC-based IMRT and HT modalities appear to have similar possibilities in producing highly conformal dose distributions. Possibly, the very large number of degrees of freedom characterising the radiobiologically guided IMRTs makes it difficult to find a clear difference between them [43]. The potentially superior radiobiological results of the MLC-based IMRT and HT compared with the 3D conformal modality can be even better demonstrated by using more severe end points in normal tissue complications. Furthermore, the findings of this study show that P_+ and $\bar{D}$ concepts were found to be very useful in comparing IMRT plans and they can give preference for selecting a better treatment plan. The $(P - \bar{D})$ diagrams presented can be considered as the radiobiological version of the extensively used DVH diagrams.

Conclusion

The clinical effectiveness of a simple 3D conformal, an HT and an MLC-based IMRT was evaluated for four lung cancer patients. Using both physical and biological

criteria, this evaluation showed that the 3D conformal radiation modality has a poor expected clinical outcome compared with the HT and MLC-based IMRT plans. The MLC-based IMRT plan is more effective than the respective HT over the clinically prescribed dose region. Treatment plans delivering low integral doses to the healthy tissues and fairly homogeneous doses to the ITV can be produced either by HT and/or MLC-based IMRT radiation modalities.

The therapeutic indices P_+ and $\bar{D}$ can be used as figures of merit for a treatment plan, and their use may increase the probability to accomplish a good treatment result. Radiological treatment planning provides a closer relation of the treatment delivered with the clinical outcome and additional information about the combination of the dose distribution with the radiosensitivity map of the patient. For a clinically relevant quantification of a dose distribution, the use of radiobiological parameters is necessary. The application of the P_+ and $\bar{D}$ concepts on the representative 3D conformal, MLC-based IMRT and HT treatment plans of four lung cancer cases revealed differences in the expected therapeutic impact of the three radiation modalities. This study concludes that clinical cases, which may look dosimetrically similar, can be quite different in radiobiological terms. The use of $P - \bar{D}$ diagrams can complement the traditional tools of evaluation, such as DVHs, in order to compare and effectively evaluate different treatment plans.

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