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Original contributions

Physical and radiobiological rationale for advantages and limitations for Intensity-Modulated Radiotherapy (IMRT)*

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A 3D – conformal optimization techniques (3D-CRT) became an important tool for the improvement of therapeutic gain. Intensity-Modulated Radiation Therapy (IMRT) is one step further and it offers intriguing challenge to conformal spatial distribution of the prescribed dose to the tumour target and to spare critical normal tissues. Six different prospective treatment plans for locally advanced lung cancer were used to analyse advantages and limitations for the IMRT. The respective DVHs are converted into Biologically Normalized DVHs (BNDVH) and limitations of large and small penalty factors are discussed. BNDVHs shows substantial differences in the distribution of "biological" doses as compared with physical DVHs. Even a small geographical miss due to set-up error has significant impact on the predicted uncomplicated TCP.
The results of radiobiological simulations suggest that IMRT may increase the steepness of TCP leading to higher therapeutic benefit. Furthermore, altered hyperfractionated irradiation allows to increase "biological" dose within the target without increase the risk of late complications. Because of the potential risk of geographical miss in IMRT, physical DVHs should be converted into BNDVHs and more than one biological penalty factor should be considered, especially in the case of large volumes of critical organs.

Fizyczne i radiobiologiczne podstawy korzyści i ograniczeń w radioterapii z modulacją intensywności dawki (IMRT)

Techniki trójwymiarowego planowania radioterapii dostosowawczej (3D – CRT) stworzyły możliwości zwiększenia biologicznego zysku terapeutycznego. Radioterapia z modulacją intensywności dawki (IMRT) jest kolejnym krokiem postępu w radioterapii i oferuje możliwość dostosowania zaplanowanej dawki promieniowania do obszaru guza nowotworowego, z jednoczasową ochroną zdrowych tkanek. Analizie poddano 6 różnych planów leczenia promieniami chorych na miejscowo zaawansowanego raka płuca i oceniano korzyści oraz ograniczenia wynikające z zastosowania IMRT. Fizyczne histogramy Dawki-Objętości (DOH) przeliczono na Biologicznie Znormalizowane DOH (BZDOH) i oceniono wpływ małych i dużych czynników ograniczających dla tkanek zdrowych. Stwierdzono wyraźne różnice w rozkładzie dawek biologicznych w BZDOH w porównaniu do „fizycznych" DOH. Nawet niewielki „błąd geograficzny", wynikający z niedostatecznej precyzji w pozycji i unieruchomieniu chorego, ma znamienny wpływ na przewidywaną szansę miejscowego wyleczenia (TCP), bez powikłań popromiennych.
Wyniki symulacji radiobiologicznej wskazują, że IMRT może wpłynąć na zwiększenie kąta nachylenia krzywej TCP i w ten sposób zwiększyć zysk terapeutyczny. Ponadto, zmienny sposób hiperfrakcjonowanego napromieniania umożliwia zwiększenie „dawki biologicznej" w obszarze guza, bez wzrostu ryzyka późnych powikłań. IMRT wiąże się z ryzykiem „błędu geograficznego", dlatego fizyczne DOH powinny być uzupełnione o BZDOH i w przypadku dużej objętości narządu krytycznego należy uwzględnić więcej niż jeden czynnik ograniczony.

Kay words: IMRT, Biologically Normalized Dose-Volume Histograms, geographical miss, volume effect
Słowa kluczowe: IMRT, Biologiczne Znormalizowane Histogramy Dawki-Objętości, błąd geograficzny, czynnik objętości

Introduction

Radiation therapy is entering into a new era, in which radiation and molecular biology are the objects of increasing interest, and they are quickly coming into the use for clinical practice. Recent advances in computer-controlled treatment machines have allowed the 3D-conformal optimization techniques (3D-CRT) to become as important as new biological tools for the improvement of therapeutic

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gain. Intensity-Modulated Radiation Therapy (IMRT) is one step further in computer-aided optimization. In this approach intensity distributions within each of a set of beams are determined by the mathematical inversion of a desired dose distribution. The IMRT offers intriguing challenge to conformal spatial distribution of the prescribed dose to the tumour target and to spare critical normal tissues.

However, even with IMRT, it is impossible to achieve the ideal dose distribution, that is, 100% dose in the tumour and 0% in the surrounding critical tissues. The IMRT planning can be considered optimal if it leads to a dose distribution that is as close to the desired dose distribution as physically possible. One important concern is that the objectives of optimization are only surrogates of the desired clinical outcome, and physical optimum does not necessarily mean radiobiological optimum. Thus, it seems important to consider both physical and radiobiological criteria in the IMRT treatment planning to achieve physically and biologically optimal beam profiles which may results in complication – free tumour control [1, 2, 3].

Among many tumour sites and stages, non-small cell lung cancer patients (NSCLC) with locally advanced and unresectable tumour mass are likely to be important candidates to the IMRT. About 30-40 % of patients with NSCLC have no metastases, but locally advanced tumour at the time of diagnosis, and they are potentially curable by radiotherapy combined or not with chemotherapy. However the results of conventional treatment with 60-65 Gy are generally poor mainly due to the frequent inability of local tumour eradication which likely leads to the later development of distant metastases. The 3D-CRT or IMRT offer the potential to escalate the dose to the target with concomitant relative sparing of normal tissues

The present paper analyzes biological and physical aspects of the IMRT planning compared with 3-D conformal and conventional techniques using different fractionation schemes.

Methods and materials

The IMRT technique using the Helios programme has been used for the last 7 months at the Centre of Oncology in Gliwice. To search for optimal physical and biological dose delivery, six categories of data were included in the analysis.

Treatment techniques

Six different prospective treatment plans are used: (1) IMRT as a sole treatment; (2) IMRT with simulation of a small (1-2 mm) geographical miss of tumour mass reflecting set-up error; (3) IMRT as a boost of 20 Gy to 3D-CRT of 50 Gy; (4) 3D--CRT with MLC; (5) conventional stationary 50 Gy + 3D-CRT boost of 20 Gy, and (6) conventional AP-PA two fields stationary technique. For all six examples dose fractionation of 70 Gy in 35 fractions in 49 days was assumed as physical standard.

DVH and BNDVH

Six physical dose-volume histograms (DVH) were used to find the optimal solution. The merit of IMRT is seen in its ability to reduce dose to the most radiosensitive structures and to deliver it homogeneously into the target (tumour) which needs a high dose to be controlled. The strategy should be therefore to find the best plan within physical limits. Before doing this, one has to define clinically meaningfull objectives and constraints. At first glance it may look simple, but it is, in fact, one of the most critical and important elements of the radiotherapy planning. The optimization objectives and constraints proposed and implemented up to now can be classified into physical and radiobiological criteria. Combination of both types have to be considered.

Physical criteria mean the criteria that can be expressed in terms of well-defined and measurable physical quantities, such as dose and volume.

Based on Bartfeld [4] suggestions, a simple constraint as the limitation of maximal dose in critical organ to the accepted tolerance level is usually used. Since lungs are critical normal structures with a large volume effect the use of a strict constraint is sometimes too restrictive to be fulfilled especially when the critical organ is in the immediate neighbourhood of the target volume or surrounding it. Therefore, the constraint is often relaxed by introducing a weighting factor, called as a *penalty factors*. A *small penalty factor* allows for some overdose beyond the limit as its consequence is only a relative mild reaction. For lung no more than 30 Gy to 10% of the whole organ was assumed. A *large penalty factor* however would not allow any overdose because it may lead to complications which have to be prevented by all means: thus it was assumed that 33% of lung volume should not receive more than 15 Gy. In contrast the *large penalty factor* for spinal cord is very restrictive and defines 0% of volume for dose higher than 45 Gy. *Penalty factors* are visualized as a barrier with a corner at the point ($D_{max}V_{max}$) in the DVHs, and can be defined as proportional to the square of the excess dose beyond the tolerance.

To assess radiobiological criteria, according to Niemierko [5, 6], DVHs are converted into Biologically Normalized histograms (BNDVH) using the of modified linear-quadratic formula to normalize dose fractionation to that if given in 2 Gy fractions:

$$NTD_{2.0} = TD_i\ (\alpha/\beta + d_i) / (\alpha/\beta + 2.0)$$

where NTD is normalized equivalent dose, TD_i is physical total dose given in fractions of d_i. α/β ratios of 15.0 Gy for tumour, 3.0 Gy for lung and 2.0 Gy for spinal cord have been used. The BNDVH curves for tumour and critical organs were recalculated for change in dose per fraction from 2.0 Gy to 1.5 Gy and 1.2 Gy and for hyperfractionated escalated schedule to increase local tumour control probability (TCP). Correction for change in overall treatment time is not accounted for the analysis.

TCP and dose fractionation optimization

For beneficial outcome with complete and long term tumour control, no tumour clonogens must survive. Thus, the relationship between tumour cure probability (TCP) and dose is described by a sigmoid curve. According Poisson statistics TCP correlates with the average number of surviving clonogenes per tumour by the following formula [4, 5]:

$$TCP = e^{-x}$$

Because the x is the product of surviving fraction (SF) and initial cell number (M), (x = SF x M), and SF is a function of total dose and $_{eff}D_o$ ($_{eff}D_o$ is the average fractionated dose necessary to reduce survival to 0.37 (e^{-1}), – $SF = e^{-TD/_{eff}D_o}$, therefore the increase of TD by three $_{eff}D_o$ is sufficient to increase the TCP from 10% to 90%.

This simple relationship implies that any increase in the TCP (i.e. from TCP_i to TCP_z) would need n x $_{eff}D_o$ increase in total dose, where $n = Ln\ (Ln\ TCP_i / Ln\ TCP_z)$. Thus any change in TDi ((D) would produce change in TCP_i into TCP_z by

$$Ln\ TCP_z = Ln\ TCP_i / e^{-(\Delta D/_{eff}D_o)}$$

For the present calculation an $_{eff}D_o$ of 5 Gy was used as suggested by Howard Thames.

The same method can be used to search the impact of heterogeneity in dose distribution on change in Normal Tissue Complication Risk (NTCR). The way how to incorporate this concept into BNDVHs is described by Brahme in details elsewhere [3].

Using Choi data sets [7] for local control for lung cancer and data sets of Rubin et al. [8], Keane [9] Philips and Margolis [10] for late severe complication of in the lung and spinal cord the respective dose response curves were estimated. From the analyzed BNDVHs total doses for various fractionation scheme are subtracted to estimate changes in the TCP and NTCR depending on the BNDVH dose distribution and fractionation.

Radiation Therapy Operation Characteristic (RTOC)

To analyze advantages and traps of the IMRT related to various techniques and the risk of geographical miss due to set-up error it is important to estimate the probability of uncomplicated tumour control, that is therapeutic gain. The space in which operational decisions are made is represented by so called RTOC space – "two times two squares" restricted by dose-related continuum of the TCP and of the NTCR (P_i). This concept was proposed for radiotherapy in 1985 by Andrews [11] and used by Agren et al. [1] to optimize radiation treatment for head and neck tumours.

Diagonal lines (solid) in Fig. 8A called iso-utility or iso-benefit curves conform with the equation:

$$TCP \times (1 - P_i) = k$$

which means the probability of benefit times the probability of no complication (that is,$1 - P_i$) is a constant value "***k***". From this, for a given "***k***" value, as the TCP increases the probability of no complication decreases. In clinical situation there are many pairs of TCP and P_i but there is the only one pair that is optimum for a given therapeutic situation (the highest TCP and the lowest P_i).

The RTOC space is splited by iso-benefit curves and each one curve corresponds to a specific "k" value. Using clinical data (pairs or TCP and Pi) for a given fractionation schedule or treatment technique probabilities of both benefit and complication are monotonic increasing with dose and presented as an asceding curve bending upward and outward to the right. At some point this curve becomes the tangent to the highest attainable iso-benefit curve which provides the highest "k" value for the optimal treatment conditions. This sort of analysis seems extremely important when the IMRT advantages are weighted against physical and biological traps.

Results and discussion

Figures 1, 2 and 3 show examples of physical dose distribution for option (1), (2), (3). Table I includes physical doses within the target and critical organs. At first glance, it may look there is no significant difference in dose delivered to the target when conventional, conformal or IMRT technique are used. However there is substantial sparing effect of critical organs in favour of the IMRT, but at this level it is difficult to decide which option is objectively optimal.

The next step is the analysis of DVHs. Three DHVs for the respective treatment techniques have been chosen for the presentations and converted into BNDVHs, i.e. for the IMRT alone, IMRT as 20 Gy boost to conformal (MLC) technique and IMRT with set-up error (geographical miss). The IMRT alone (Fig. 4) dose distribution in critical organs do not exceed penalty limitations (Tab. II) and shows optimal solution for both the target and the critical organs. IMRT as a boost (Fig. 6) could be considered as feasible one, however 26% of lung volume receiving the dose above the threshold level makes this option unacceptable. In contrast, BNDVH for IMRT with set-up error (Fig. 5) shows dose distribution in lung below large penalty barrier but for spinal cord even 1% above penalty barrier can not be accepted.

For the target, it looks much worse because 40% of tumour volume would receive the dose lower than D_{mod} (Tab. II). Figure 6 shows that for the IMRT given as a boost, doses higher than 70 Gy cover more than 90% of target volume compared to 70% of target volume in the case of IMRT alone.

Since, as yet, there is limited experience as to what is achievable with intensity modulated beams, even small target underdosage may produce radiobiological "*double-*

Tab I. Physical dose in the target and critical organs depending on the technique of radiation treatment of the lung cancer

Technique	Target			Lung		Spinal cord	
	VOL. (cm^3)	Dmod. (Gy)	Dmin. (Gy)	Vol. (cm^3)	Dmax. (Gy)	Vol. (cm^3)	Dmin. (Gy)
(1) IMRT	120	70.7 ± 4.3	53.1	3350	55.2 ± 14.1	56.9	34.1 ± 14.8
(2) IMRT (mov.)	118	70.3 ± 5.4	43.6	3400	63.4 ± 14.3	"	33.6 ± 15.0
(3) (AP – PA) + IMRT (boost)	119	72.0 ± 4.2	63.7	3600	65.2 ± 10.2 (R) 76.6 ± 12.6	"	58.7 ± 9.5
(4) CONFORMAL (MLC)	119	70.0 ± 7.3	37.3	3651	59.5 ± 7.3 (R) 71.3 ± 20.2	"	25.7 ± 11.3
(5) (AP – PA) + CONFORMAL (MLC)	120	70.7 ± 5.3	33.8	3220	65.2 ± 11.6 (R) 72.4 ± 26.7	"	28.3 ± 16.3
(6) CONVENTIONAL (AP – PA)	120	74.5 ± 2.4	57.3	3137	73.7 ± 17.5 (R) 77.5 ± 43.9	"	72.4 ± 46.1

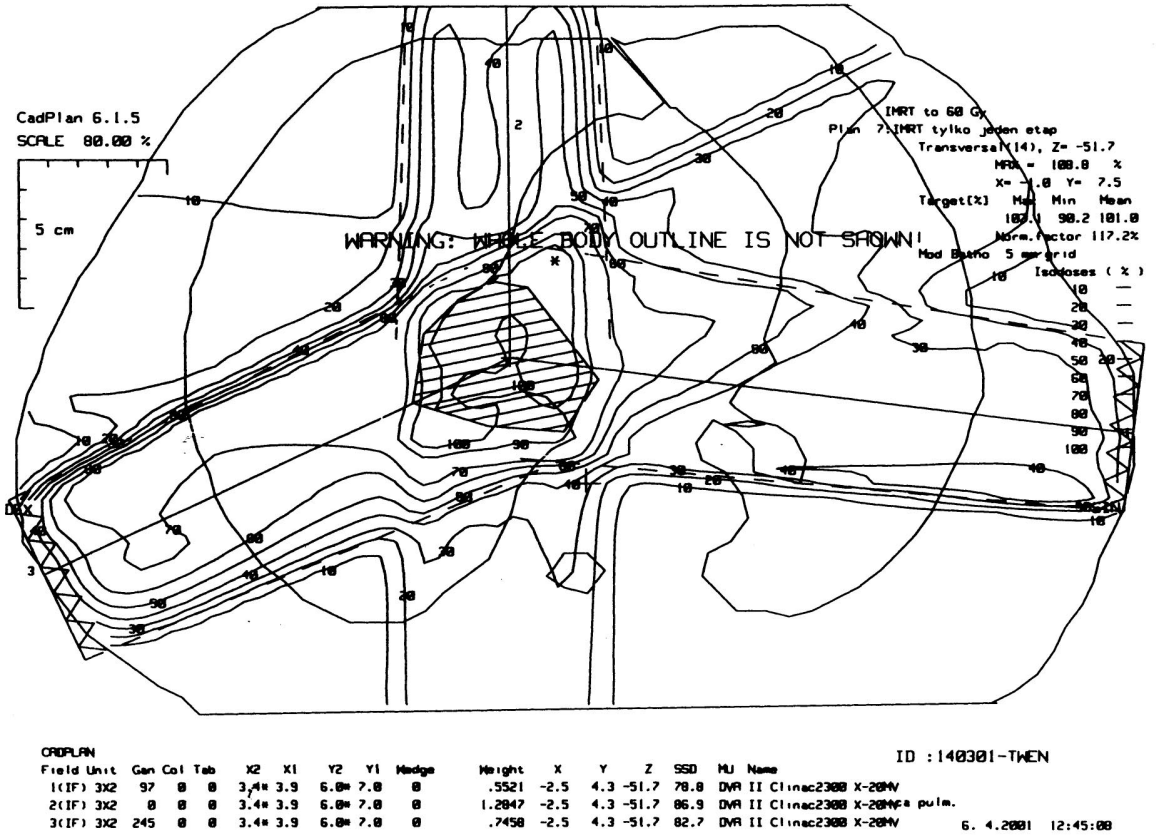

Fig 1. Dose distribution for lung cancer using IMRT-alone

-trouble" that is not clinically acceptable. Therefore, the optimum dose distribution for IMRT defined by so called "closeness" should be considered in the sense that it will lead to a dose distribution which is as close to the desired distribution as physically and radiobiologically possible. A physical DVH might be considered as optimum where-

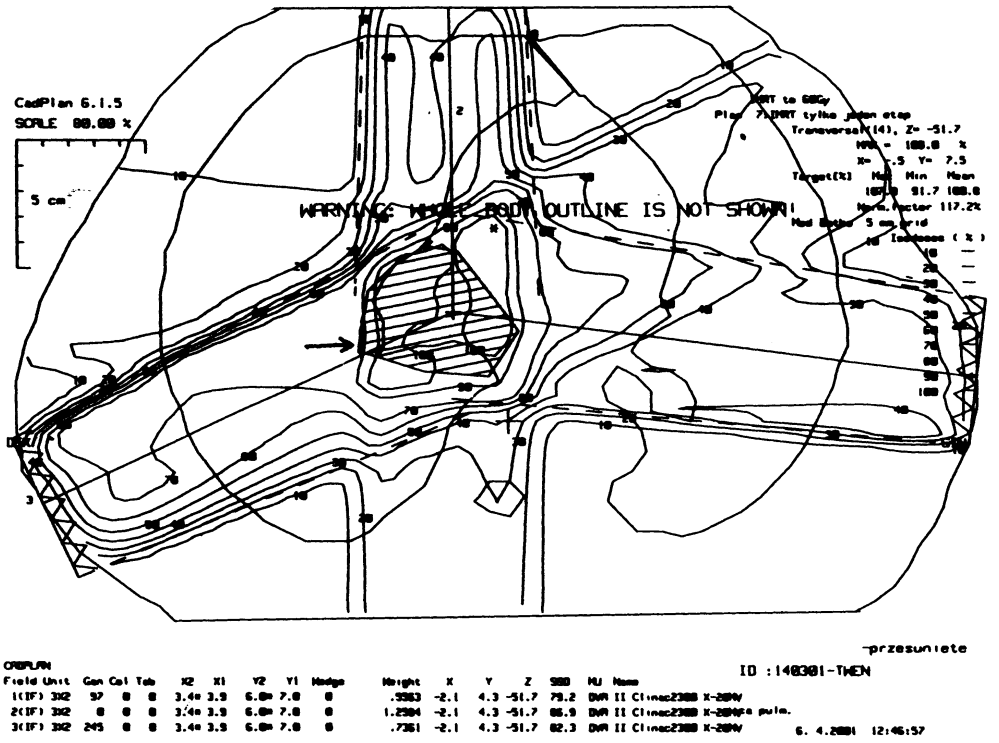

Fig. 2. Dose distribution for lung cancer using IMRT with geographical miss within the target volume

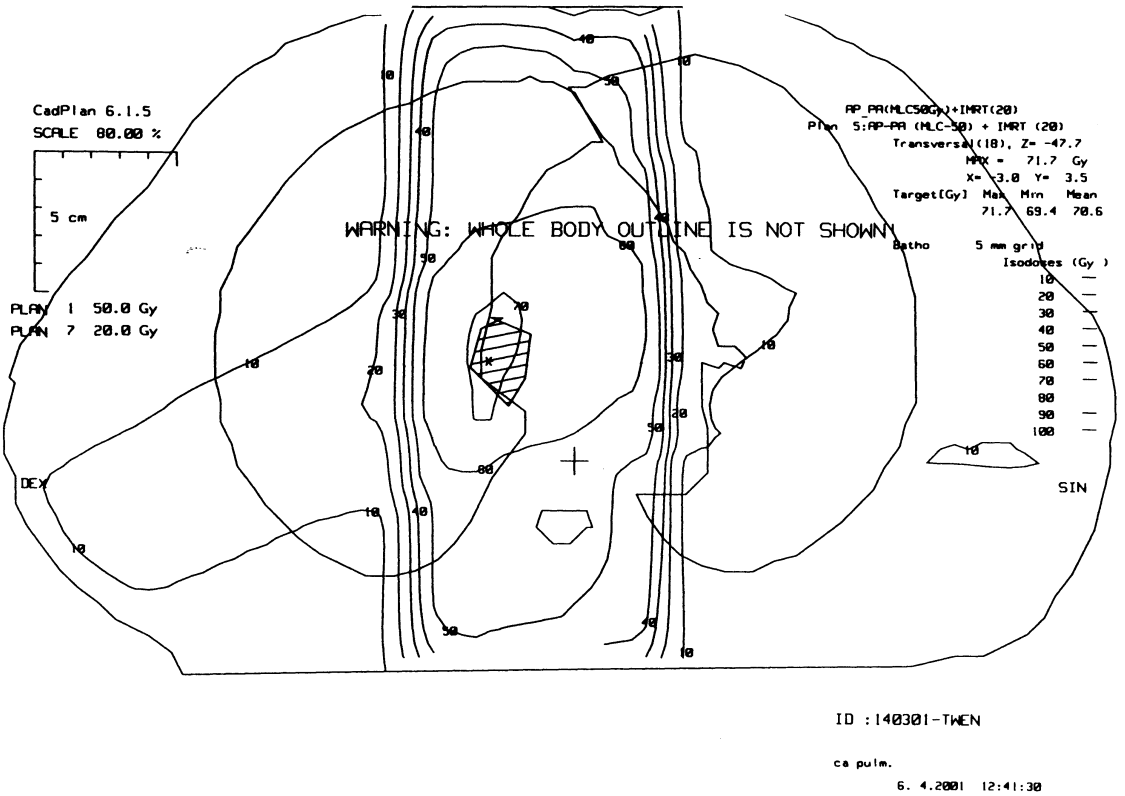

Fig. 3. Dose distribution for lung cancer using IMRT for 20 Gy boost

as radiobiologically it is not necessarily true and the reverse may also happen when the dose distribution within critical organs exceeds the prescribed limit whereas the normalized DVH (BNDVH) satisfies the prescribed constraints (Fig. 4-6, dashed lines).

For the present examples the main goal was to deliver 70 Gy in 35 fractions to the planning target volume (PTV) while keeping the dose of 46 Gy to spinal cord and of no more than 30 Gy to more than 10% of the lung volume. Generally the critical organs are assigned a priority relative to the target volume. Besides penalty limits the scheme of dose fractionation plays also an important role. Because late responding normal tissues are significantly more sensitive to change in dose per fraction, any decrease in fraction size below 2 Gy may have important impact on dose distribution curves within these tissues. For IMRT alone (Fig. 4) and IMRT with set-up error (Fig. 5), for dose per fraction smaller than 2 Gy the BNDVH curves for spinal cord and lung (dashed lines) are shifted to the left, below penalty limits. It has to be pointed out that this effect is only due to the change in dose fractionation but not the results of changes in the number,

Tab. II. Physical (TD) and biologically iso-effective (NTD) dose distribution in tumour and critical organ volumes depending of radiotherapy techniques (* Normalized Total Dose given in 1.2 Gy fractions, iso-effective to 70 Gy)

Technique	Tumour				Lung		Spinal cord	
	$TD_{phys.}$	NTD for d=1.5Gy (α/β= 15 Gy)		ISO-$NTD_{1.5(1.2)}$* for 70 Gy	TD (α/β= 3.0 Gy)	$NTD_{1.5(1.2)}$*	TD (α/β= 2.0 Gy)	$NTD_{1.5(1.2)}$*
				% VOLUME				
	< 70 Gy				> 30 Gy		> 46 Gy	
(1) IMRT	30%	⇒	45%	11%	17%	8%	2%	0%
(2) IMRT (mov.)	40%	⇒	65%	17%	18%	0%	1%	0%
(3) (AP – PA) MLC + IMRT (boost)	7.5%*	⇒	75%	0.5%*	(R) 27%	(R) 26%*!	45%	25% (0%*)
(4) CONFORMAL (MLC)	80%	⇒	95%	60%!	3%	2%	0%	0%
(5) (AP – PA) + CONFORMAL (MLC)	50%	⇒	85%	20%	11%	10%	0%	0%
(6) CONVENTIONAL (AP – PA)	3%	⇒	20%	0%!	8%	7%	52%!	48%*!

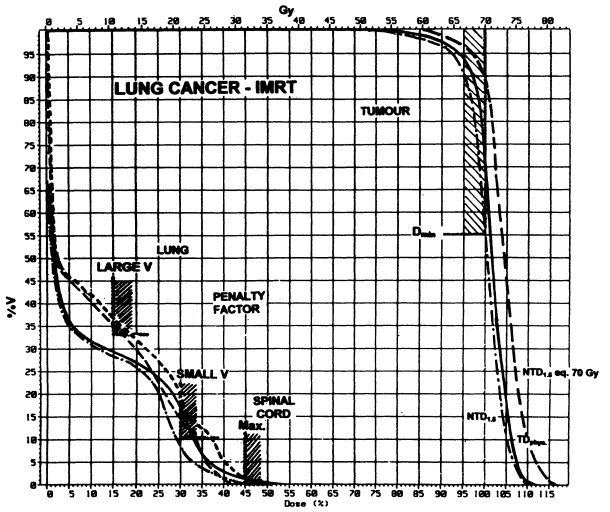

Fig. 4. Biologically Normalized BNDVH for lung cancer (IMRT-alone).
Solid lines represent tumour and lung, dotted line is for spinal cord – all represent 2.0 Gy conventional fractionation. Dashed lines (shifted to the left) illustrate respective biologically equivalent doses if given in 1.5 Gy fractions. Dashed lines for tumour (shifted to the right) represent hyperfractionation b.i.d. given in 1.5 Gy fractions ($NTD_{1.5}$ eq, 70 Gy).

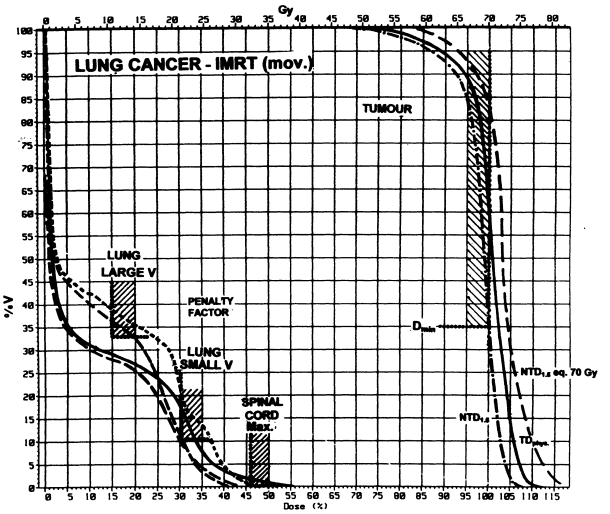

Fig. 5. Biologically Normalized BNDVH for lung cancer (IMRT with geographical miss within the target). Legend as in Fig. 4.

angle and weight of the beams. In contrast, the IMRT boost option (Fig. 6) shows that although the NTCR for spinal cord may drop down to less than 1% by decreasing the fraction size from 2.0 Gy to 1.2 Gy, the modified fractionation does not change the already high NTCR for right lung (large penalty limit) which is even around 90% for about 15% of lung volume. It makes the IMRT-boost option unacceptable. For the next two options (4) and (5) the NTCR for spinal cord has been maintained at 0% level independent of dose fractionation (Tab. II). The conventional option (6) is totally unacceptable.

For anatomic structures such as lung where the volume effect is large and the tolerance in relatively low, the IMRT tries to balance the desire to reduce the dose outside the target volume against the desire to maintain uniform dose in the target volume, resulting in inhomogeneous dose distribution, even at the cost of allowing a small amount of lung volume to receive higher dose. However, the reduction of the dose around the target periphery may result in an inhomogeneous dose pattern in the target. It might be serious biological trap *(double-trouble*) if only the purely physical dose-based objectives are considered. Therefore, optimization of the dose intensity distribution may fail to yield better results unless such biological indices as the TCP, TCR and volume effect are accounted for. Table II illustrates a substantial TCP decrease reflecting the dose gradient within the target volume. The physical "cold spots" in the target enlarge by 15-20% when the effect of dose fractionation is taken into account, and for the IMRT-boost option by even 67.5%. It will result in dramatic decrease of the TCP. One has to bear in mind that a standard 70 Gy in 2 Gy fractions is not biologically the same as 70 Gy in 1.5 Gy or 1.2 Gy fractions. Furthermore, a dose gradient within the target reflects indirectly a gradient in fraction size if the number of fractions is constant. Thus, the target dose curves are shifted to the left in BNDVHs (Fig. 4-6) and the target volume outside of the desired dose constraint enlarges.

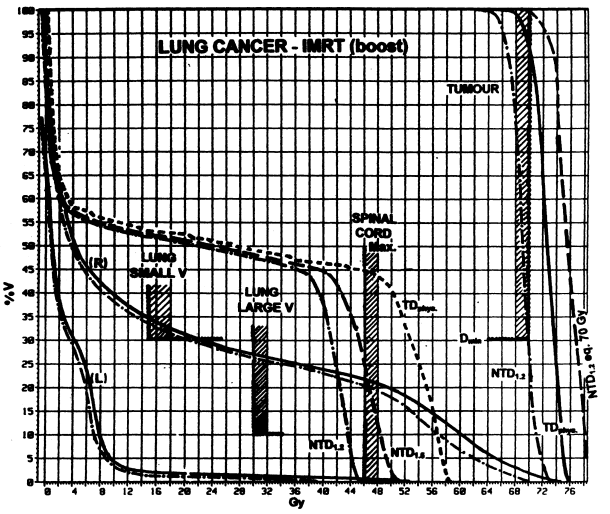

Fig. 6. Biologically Normalized BNDVH for lung cancer (IMRT for 20 Gy boost). Legend as in Fig. 4.

Despite the rearrangement of the angles and weights of the beam improvement of dose distribution can be achieved by changing dose fractionation. It seems the decrease of fraction size and the use of twice-a-day fractionation (b.i.d.) could be a useful method to reduce heterogeneity of dose distribution in the target volume (cold spots), and consequently to increase the TCP. Using smaller doses per fraction it is important to correct total dose as biologically equivalent to the designed dose (iso--NTD1.5 eq. 70 Gy in Fig. 4-6). It shifts the respective target-dose to higher doses, and results in a pronounced increase of the target volume uniformly covered by the designated dose (i.e. from 70% to 89% for the IMRT-

-alone option – Tab. II). Moreover, the use of smaller doses per fraction (i.e. hyperfractionation) is in favour of late responding normal tissue because tolerance dose for small and large lung volume increases by 11%, i.e. from 30 Gy to 33.3 Gy and from 15 Gy to 16.6 Gy respectively, and from 46 Gy to 52.5 Gy for spinal cord, resulting in displacement of the respective penalty limits to higher doses on the BNDVHs. It suggests that changes in dose fractionation might be advantageous for both TCP and NTCR and be useful for comparing rival plans and for optimization, because for the IMRT it may decrease the dose to the target volume in order to ensure a low enough dose to the lung and to the spinal cord.

Geometric uncertainty set-up error, volume effect

In 1978, Hendrickson [12] considered the precision of radiation delivery system and specified the four P's of human error: precision of daily dose delivery, prescription of tumour dose, physical dosimetry, and planning of an individual's treatment. All criteria for the GTV, CTV, PTV and Organ at Risk margins, set-up error, patient movements and managing geometric uncertainties in the IMRT are presented in details by Jaffray et al. [13] and Ekberg et al. [14], and it is not the aim of this paper to discuss these problems. It becomes clear that biological optimization of the IMRT needs to take into account all uncertainties concerning target volume, critical organ, safely margins in relation to the anatomical structures. Any geometric (dosimetric also) error leads to geographical miss which must be considered as the major trap for the IMRT planning. Missing the a tumour mass by even 1-2 mm is detrimental for treatment outcome and maybe the cause of dramatic decrease in the TCP, independently on how sophisticated the used technique of irradiation.

Using PVI and dosimetry in vivo we have found that the set-up error standard deviation is on average 2.49 mm ±1.23 mm in all directions for 15% of irradiated patients, and the dosimetric error of ±6% for 11% of patients. Although all these errors have been corrected it implies that the QA procedures as it is proposed by Bartfeld [4] and Ekberg et al. [14] must be fulfilled in all steps of inverse planning to avoid the risk of getting trapped in local minima within the target volume.

The effect of geographical miss is simulated on Figure 2 and Figure 5. Although dose distributions in spinal cord and lung are acceptable, a substantial dose gradient below the desired dose for more than 40% of the target volume makes this option not feasible.

The volume-effect is an important constraint for the IMRT technique. This objective can be specified only in terms of the desired dose or dose ranges in the critical organ, and it becomes crucial for large volumes, such as lung. Incorporating volume effects in a limited manner by dividing normal tissue into multiple regions will not solve the general problem since there is an infinitive number combinations of dose and volume that lead to the same clinical end-point [2, 6]. This is better to incorporate volume-effect in a form consistent with the way critical organ responds to radiation, namely in the form of NTCRs.

To compute the NTCR one can employ a version of Lyman's model [15], in which volume effect can be expressed in the form of a power law, that is:

$$TD_{5/50}(V_i) = TD_{5/50}^{(1)} / V_i^{n}$$

where $TD_{5/50}$ is the tolerance dose for 5% or 50% NTCR for a uniformly irradiated organ and $TD_{5/50}(V_i)$ is the respective tolerance dose when only a fraction V_i of the whole volume is irradiated. The parameter "***n***" reflects the magnitude of the volume effect. For small organs, such as the spinal cord or the rectum, "***n***" is small. For large volume such as the lung, "***n***" is large. Mohan et al. [2] estimated an "***n***" value of 0.12 for the rectum, 0.87 for the lung and 0.05 for the spinal cord. It shows that for spinal cord volume-effect is of less importance, and it does not matter whether short or long sections of the spinal cord are involved, the TD does not change a lot, whereas for the lung volume-effect it plays a major role. For the present analysis a simple way of volume-effect estimation has been used. According to Rubin et al. [8] large penalty limit of 15 Gy for more than 66% of the lung volume and a large penalty a factor of 30 Gy for more than 10% volume have been chosen. According to Lyman's equation the latter one could even be larger, up to 42.4 Gy or up to 47 Gy for 1.5 Gy dose per fraction*).

Therefore, considering penalty limits for the lung the BNDVHs (Tab. II) all technique options are acceptable except the IMRT-boost option [3]. This option was used as an example to illustrate that BNDVH for two lungs should be considered separately because biological dose distribution for one lung could be within the limits whereas it does not in the second one (Fig. 6). Furthermore, it seems practically useful to incorporate to the BNDVH two penalty limits, for small and medium volume if a total volume of the critical organ is large.

Low dose trap

There is radiobiological evidence that within the region of very small doses per fraction (below 1.0 Gy) the L-Q model may underestimate iso-effectiveness of small doses because the initial small part of cell survival curve is pro-

*) assuming that 33% of the lung volume can receive TD_5 = 15 Gy thus 10% of the volume will receive:

$$\begin{aligned} V\ corr &= V_x^{n} / V_i^{n} \\ &= 0.10^{0.87} / 0.33^{0.87} \\ &= 7.413 / 2.62 \\ &= 2.82 \end{aligned}$$

$$\begin{aligned} \text{Thus } TD_{5(10\%\ V)} &= TD_{5(33\%\ V)} \times 2.82 \\ &= 42.4\ \text{Gy} \end{aligned}$$

If 1.5 Gy fractions will be used instead of 2.0 Gy, the $TD_{5(10\%)}$ can even increase to

$$\begin{aligned} TD_{5(10\%)1.5\ Gy} &= 42.4\ \text{Gy}\ (\alpha/\beta + 2.0) / (\alpha/\beta + 1.5) \\ &= 42.2 \times 1.11 \\ &= 47\ \text{Gy} \end{aligned}$$

assuming that α/β ratio = 3 Gy

bably very steep and much steeper than that for the range of higher doses. Thus 20 Gy in 35-40 fractions could be as *risky* as 70-80 Gy in the same number of fractions. Because the IMRT offers a high and rapid gradient of dose within the irradiated volume, peripheral regions close the skin surface could be at a similar risk of late normal tissue effects as the part of critical organs receiving high dose given in 2 Gy fractions. This suggestion comes from experimental studies as yet, and it is not documented in the clinic. However, this problem should not be ignored.

RTOC optimization

Based on the results of step-analyses which have been performed till now, optimization of dose distribution and dose fractionation seems to purely arbitrary and subjective. The RTOC model is the objective way to estimate the optimal therapeutic dose level and its distribution producing the highest TCP and the lowest NTCR possible [1, 11]. For the present study the RTOC is used as an example to demonstrate the way in which it can be incorporated into the IMRT planning, as its final step.

To estimate standard (conventional) dose response curve for the tumour (TCP) and for the normal lung (NTCR) clinical data concerning lung cancer control and late fibrosis in the lung have been extracted from the literature [7, 8, 9, 10], and the respective dose-response curves are shown in Figure 7A. Dashed line shifted to the left represents the NTCR for late lung fibrosis if large volumes of critical organ are involved. It is much steeper than the respective NTCR curve for small volumes of the lung (solid line). The dotted line represents late complication-free tumour control probability (therapeutic gain) it shows a very narrow "therapeutic window" suggesting that using conventional stationary technique and dose fractionation to the lung cancer patient one may not expect significant improvement in the TCP without increase in the risk of late complications.

The therapeutic advantage of the IMRT is clearly illustrated in Figure 7B. The dose to the tumour is significantly higher due to dose escalation and hyperfractionation and the respective TCP curve becomes steeper than that for conventional stationary treatment (Figure 7B). At the same time, the dose to the lung is reduced (dose gradient in BNDVH and sparing effect of lower dose per

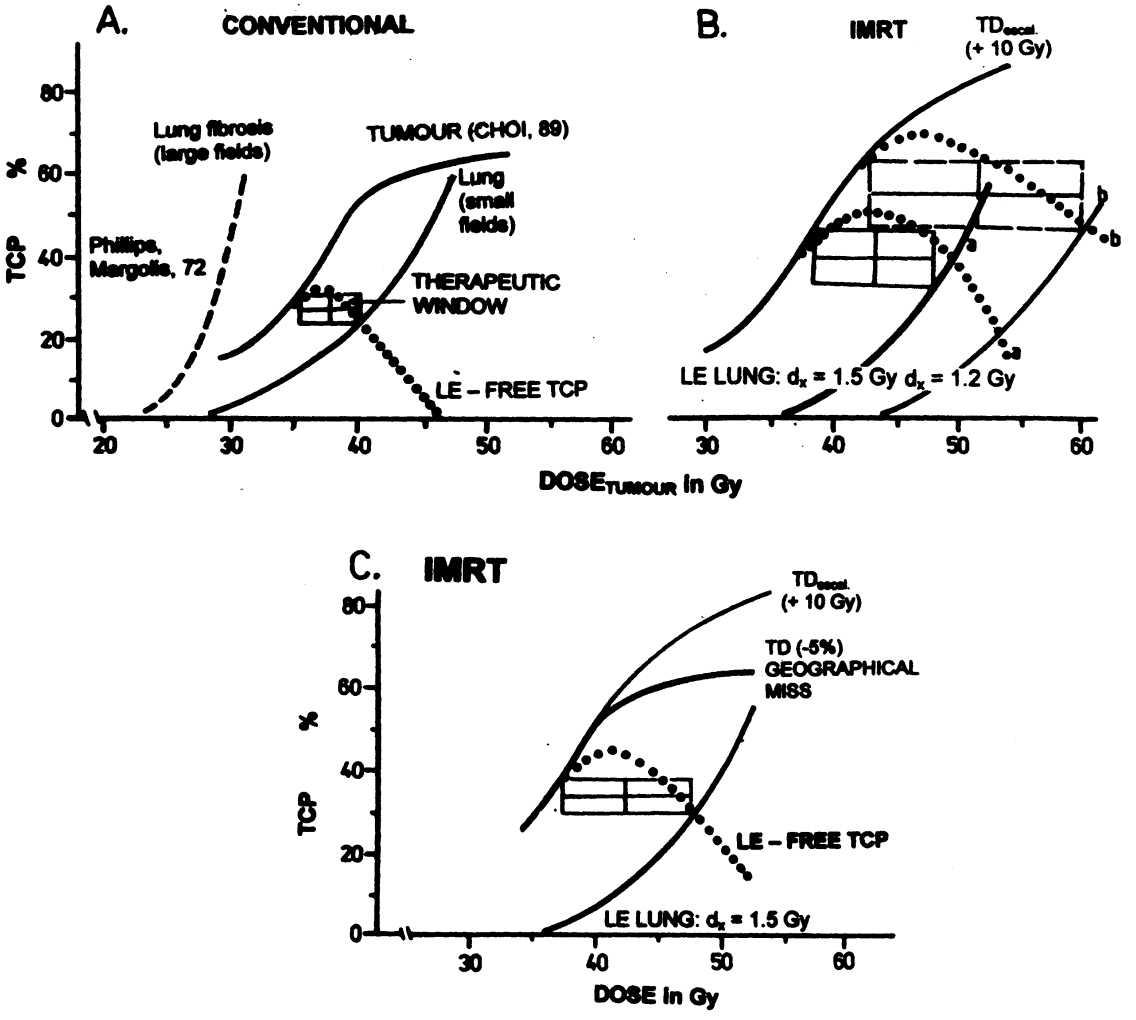

Fig. 7. Tumour Cure Probability (TCP) and late complications (LE) dose-response curve for lung: (a) conventional treatment planning and fractionation; (b) IMRT with dose escalation of 70 Gy; curves (a) and (b) represent LR for treatment with 1.5 Gy and 1.2 Gy fractions respectively; (c) IMRT with the decrease in effective TD by 5% due to geographical miss. In all figures dotted line represents late complication-free TCP which is considered as a therapeutic gain.

fraction) and the NTCR curves are shifted to the right into the region of higher tolerance doses. As the result, the "therapeutic window" is opened up substantially and the peak of the bell-shaped curve (dotted lines in Fig. 7B) for complication-free TCP increases from 55% to 73% (Fig.7B-a), and even to 82% (Fig. 7B-b) if the dose per fraction of 1.2 Gy is used (Tab. III). This significant increase of therapeutic gain can be achieved because physical optimization of the IMRT is strengthened by radiobiological effect of escalated dose fractionation.

Figure 7C illustrates therapeutic trap as the effect of geographical miss. It is not the aim of this paper to discuss all situations and factors leading to such trap but even 5% decrease in the desired effective dose within a small part of the tumour volume can neutralize the advantages of IMRT by flattening the TCP curve, and the bell-shaped curve automatically drops down to 53% (Tab. II).

Dose-response curves in Fig. 7 are the source of TCP and NTCR paired values for continuously increasing dose units. They have been used to construct the RTOC curves in Figure 8 and to estimate iso-utility "***k***" values for the analyzed IMRT options. This method offers the objective choice of the optimal technique and dose fractionation options. The "***k***" values established from the RTOC curves (Tab. III) describe optimal therapeutic gain (TG). The TG is the difference between TCP and NTCR rates for given "***k***" values. The IMRT alone gives 20% increase in the TG (complication-free TCP) compared with conventional stationary treatment. Further increase in the TG can be expected for the IMRT combined with altered dose fractionation for which the highest "***k***" value of 0.721 reflects 70% increase in the TG, and it is optimal IMRT option.

Tab. III. Maximal iso-benefit *"k"* values taken from Figure 3 and the respective TCP and LER (Late Effect Risk) values corresponding with optimal fractionation schedules

Technique	k- value	TCP	LER	Fractionation *
Conventional	0.397	55%	25%	46 Gy/23fx./32 d.
IMRT	0.567	73%	22%	48 Gy/32 fx./16-21 d.
IMRT escal.	0.721	82%	12%	55.2 Gy/46 fx./23-29 d.
Disadvantage (geographical miss) IMRT	0.435	53%	18%	not applicable

[therapeutic gain (late-effect-free TCP) is equal TCP – LER;
* calculations are based on theoretical examples only, and should not be used as a guidelines for routine practice)]

Conclusions

It seems clear that the IMRT is a "happy hour" option for critical normal tissues, but in the same time it might be "double-trouble" for the tumour it the treatment is not accurately planned. Of great significance is the manner in which the objectives of optimization are specified. Usually, they are specified only in terms of the desired physical dose or dose ranges in the target volume and normal tissues. Pure, physical DVH may increase the potential risk of geographical miss which always results in dramatic decrease of tumour control probability. The present paper demonstrates that to strengthen IMRT optimization it is imperative that criteria of optimization should be specified in a clinically relevant manner, and they should include dose-volume effects, normalization of iso-effective doses depending on change in the dose per fraction, TCP and NTCR indices. Finally BNDVHs should be converted into the RTOC iso-utility curves which can accurately

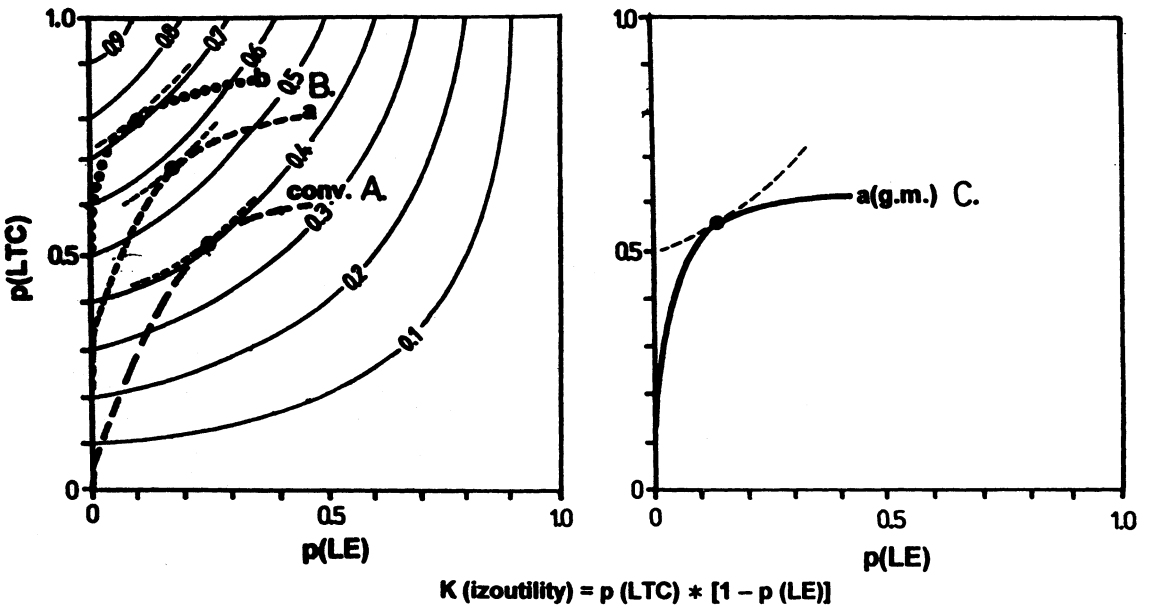

Fig. 8. RTOC modelling of iso-benefit (utility) curves to optimize treatment technique and dose fractionation. RTOC curves tangent to the iso-benefit curve gives the highest "k" value for optimal treatment (see Tab. II)

and objectively indicate optimal IMRT solution. Under these circumstances, the use of biological indices and constraints for small volumes of tumour and critical organs seems less important. However, for large volumes of anatomic structures such as the lung biological optimization of IMRT planning is of major importance. It seems that the use of more than one biological penalty factor (i.e. TD_5 for small and medium or large volume) for critical organ can improve accuracy of the optimization. Furthermore, IMRT combined with altered dose fractionation (i.e. accelerated hyperfractionation) may effectively convert the classical problem of a *"double-trouble"* into a *"double advantage"* because not only the relative dose to the critical organ is reduced, but the dose per fraction is also reduced, and the dose within the target can be escalated. However, it has to be acknowledged that for the majority of tumour types and critical organs the proposed biological indices are still simplistic and poorly documented and good data are sparse. Thus, there is the urgent need to collect clinical data on tumour and normal tissue radiation response in order to improve optimization of IMRT planning.

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