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# The Clinical Value of Non-Coplanar Photon Beams in Biologically Optimized Intensity Modulated Dose Delivery on Deep-Seated Tumours

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The aim of the present study is to compare the merits of different radiobiologically optimized treatment techniques using few-field planar and non-coplanar dose delivery on an advanced cancer of the cervix, with rectum and bladder as principal organs at risk. Classically, the rational for using non-coplanar beams is to minimize the overlap of beam entrance and exit regions and to find new beam directions avoiding organs at risk, in order to reduce damage to sensitive normal tissues. Two four-beam configurations have been extensively studied. The first consists of three evenly spaced coplanar beams and a fourth non-coplanar beam. A second tetrahedral-like configuration, with two symmetric non-coplanar beams at the same gantry angle and two coplanar beams, with optimized beam directions, was also tested. The present study shows that when radiobiologically optimized intensity modulated beams are applied to such a geometry, only a marginal increase in the treatment outcome can be achieved by non-coplanar beams compared to the optimal coplanar treatment. The main reason for this result is that the high dose in the beam-overlap regions is already optimally reduced by biologically optimized intensity modulation in the plane. The large number of degrees of freedom already incorporated in the treatment by the use of intensity modulation and radiobiological optimization, leads to the saturation of the benefit acquired by a further increase in the degrees of freedom with non-coplanar beams. In conclusion, the use of coplanar radiobiologically optimized intensity modulation simplifies the dose delivery, reducing the need for non-coplanar beam portals.

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During the last 10 years 3D treatment planning systems with accurate dose calculation algorithms have been developed, but only rarely incorporating radiobiologically optimized intensity modulated treatments (1–4). Today, it is possible to optimize simultaneously several intensity modulated beams and their angles of incidence with some treatment planning systems (5, 6). These new tools allow the investigation of new and more efficient treatment techniques, such as non-coplanar biologically optimized intensity modulated treatments. However, general optimization of the dose delivery in 3D using non-coplanar beams is a complex task, due to the large number of possible beam directions that need to be tested. The present study has therefore been limited to clinically relevant beam orientations.

Multiple non-coplanar beams are today routinely used in stereotactic techniques for localized small tumours, such as brain tumours or metastases up to about 5 cm in diameter (7, 8). Interest in non-coplanar beams for localized tumours in other parts of the body, such as liver, lung or prostate tumours, has recently increased (9–15).

The treatment outcome, which in the present study is quantified in terms of the probability of tumour control without severe injury to normal tissues, is optimized using non-coplanar intensity modulated beams and compared with optimal coplanar treatments for an advanced cervix tumour. Classically, pelvic tumours have often been treated with the four-field box technique. The rectum and the bladder will then often be severally irradiated in regions close to the tumour, to doses as high as 80% of the maximum tumour dose. If the same configuration is used, for radiobiologically optimized intensity modulated beams, the probability of achieving complication free tumour control will increase by as much as 20–30% compared to classical treatments where uniform beams are used (16–22). By moving one or two of the parallel opposed beams to non-coplanar directions, a further increase in the treatment outcome may be expected, due to the possibility of a further

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reduction of the high dose beam-overlapping volume in the surrounding normal tissues.

There are two main methods that may improve the dose-distribution when using non-coplanar beams. First, proper selection of the direction of incidence of the beams provides the possibility of avoiding severe irradiation of certain organs at risk. Secondly, by separating the entrance and the exit ports of the beams as much as possible, the beam overlap is minimized and thus hot spots in normal tissues outside the tumour are reduced. This will at the same time increase the volume of normal tissue irradiated due to the longer beam path through the patient, even though some organs at risk may be avoided more effectively. Thus, maximum separated beam portals may not necessarily be the best treatment policy. Furthermore, some non-coplanar treatments may be less desirable due to non-coplanar angles that may irradiate the body almost longitudinally. Also, there are gantry and table movements that are impossible with existing therapy machines.

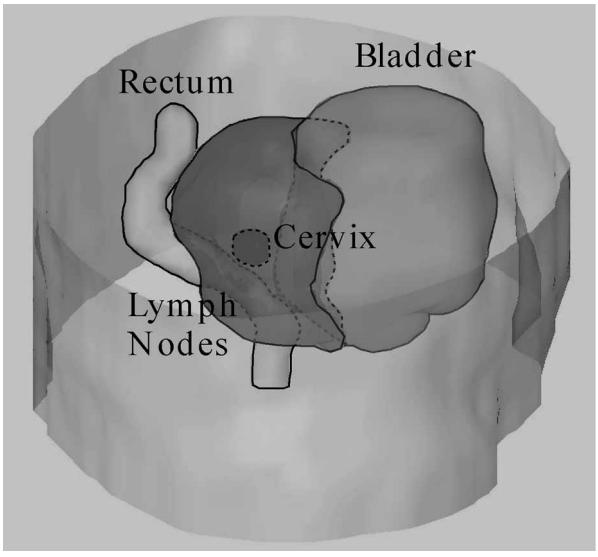


*Fig. 1.* 3D lateral view of the patient used. To simplify the visualization the femur joints are not shown.

## MATERIAL AND METHODS

### *Target geometry*

The use of biologically optimized intensity modulation may considerably improve the treatment of complex and/or concave tumours. This is largely due to the possibility of better confining the dose distribution to the target volume, while delivering a considerably lower dose to the organs at risk. Nevertheless, pelvic tumours are still difficult to treat, due to the highly sensitive normal tissues that lie in their proximity. A further improvement in the dose delivery may therefore be achieved through the use of non-coplanar beam orientations.

An advanced deep-seated cervix cancer, stage T4, with locally involved lymph nodes surrounded by several organs at risk, as shown in Fig. 1, has been treated. The three-dimensional patient anatomy information is contained in 64 axial slices consisting of 5 mm cubic voxels. The gross tumour and the locally involved lymph nodes are regarded as two separate biological target volumes associated with different biological responses. The radiobiological parameters of the different tissues involved in this study are presented in Table 1 (1), where $s$ describes the relative seriality of tissue organization, $D_{50}$ is the 50% response dose, $\gamma$ the maximum normalized gradient of the dose response relation and the relative density corresponds to the fraction of the cells belonging to the organ over the region considered. For example, the lymph node tumour tissue is assumed to contain 10% clonogenic tumour cells whereas the remaining 90% is considered to be normal tissue. This simulates a more realistic situation where tumour cells have infiltrated the normal tissue. Therefore, this tissue has to be considered during optimization, where in the calculation of the probability of injury and tumour control, the relative volume of tumour cells in each voxel is assumed.

The organs at risk are the rectum, the bladder, the femur joints and the surrounding normal tissue, largely small bowel.

In order to make the treatment plan as robust as possible, a range of variation in normal tissue and tumour radiosensitivity may be assumed (23). For example, for some patients the tumour may be more radioresistant than average, while the normal tissues may be more sensitive. This will challenge the optimization algorithm, since such a patient will be more difficult to cure. To take this possibility into account and increase patient safety, the $D_{50}$ values of the target and normal tissues were increased and reduced, respectively, by more than half standard deviation (Table 1) (23). The treatment technique will then be more tolerant to variations in patient responsiveness. However, when a patient deviates significantly from the average sensitivity a decreased treatment outcome may be seen.

### *Beam configurations*

The variation of the treatment outcome with the number of coplanar beams was studied by Söderström & Brahme (16, 20) using an exhaustive search of the whole phase space. They showed that the treatment outcome only slightly increased when more than a few beams were used. Additionally, a higher treatment outcome is reached if the angles of the beams are optimized, instead of being equally spaced (6, 17).

Thus, to make the beam direction selection highly relevant, no more than four to five beams should be used. One of the aims of clinical radiation therapy is to use a small number of beams in order to have a reasonably short treatment time while simultaneously achieving high treat-

**Table 1**

*Radiobiological data for the tumour and normal tissues involved in the case of a cervix cancer*

| Tissue | $D_{50}$/Gy | $\gamma$ | s | $\alpha/\beta$ Gy | Relative density |
|---|---|---|---|---|---|
| Small bowel | 60 | 2.0 | 1.0 | 3 | 1.0 |
| Rectum | 55 | 3.1 | 0.7 | 3 | 1.0 |
| Bladder | 60 | 3.0 | 0.2 | 3 | 1.0 |
| Femur joints | 65 | 1.2 | 0.3 | 3 | 1.0 |
| Lymph nodes (Tumour) | 70 | 3.0 | – | 10 | 0.1 |
| Cervix (Tumour) | 80 | 4.0 | – | 10 | 0.2 |

ment outcome and reliable dose delivery. An effective dose delivery may often be obtained with a tetrahedral-like beam configuration (13, 24, 25), due to maximum beam separation. For this reason, two different tetrahedral-like beam configurations with four photon beams of 50 MV from the racetrack microton MM50 were examined in this study.

The gantry angle, $\varphi$, and the non-coplanar angle, $\theta$, define the direction $\Omega(\varphi,\theta)$ of each beam (Fig. 2a). The gantry angle is defined by the axial rotational angle, whereas the non-coplanar angle is defined by the angle with a transversal plane of the patient. A non-coplanar beam angle of 0° corresponds to the axial plane of the patient that contains the isocentre. A positive non-coplanar angle corresponds to a cranio-caudal tilt and negative non-coplanar angles indicate that the entrance point of the beam is below the transversal central plane.

The problem of finding the optimal beam orientations is characterized by a high mathematical complexity, since the optimal direction of one beam depends on the position of all other beams used in the treatment. Thus, all possible beam combinations should ideally be tested. Due to the large number of calculations involved, some reasonable assumptions had to be made in the choice of the fixed variables. This will consequently restrict the domain of search; nevertheless some insight about the clinical value of non-coplanar beams can be obtained.

Therefore, two four-field configurations have been studied in detail, denoted here by: $\Omega_{3+1}$ and $\Omega_{2+2}$, as shown in Fig. 2a and 2b, respectively. The first indices represent the number of beams in the transversal plane whereas the second indicate the number of non-coplanar beams.

As an initial study, the effect of one non-coplanar beam on the treatment outcome was studied in configuration $\Omega_{3+1}$. In this configuration three beams are coplanar, evenly separated, namely at the gantry angles: 0°, 120° and 240°. The fourth beam, $\Omega_4$, moves along all the possible gantry positions, within a cone of non-coplanar angle from $-40°$ to $+40°$. The use of non-coplanar beam angles beyond this range is mainly prohibited by the extended beam path through the patient, which generally leads a higher dose to the normal tissues. The results from this configuration have revealed that a combination of beams positioned at 0°, 120° and 240° is often reasonable, but these might not be the best orientations.

The $\Omega_{2+2}$ configuration was subsequently examined in order to find the optimal orientations of two coplanar beams that are combined with two non-coplanar beams. In this configuration the beams $\Omega_1$ and $\Omega_2$ are in the plane with optimized directions. The beams $\Omega_3$ and $\Omega_4$ are coupled, having the same gantry angle and symmetric non-coplanar angles, within the range 0° to 40° (for example $\theta_3 = -30°$ and $\theta_4 = 30°$).

Finally, a configuration similar to configuration $\Omega_{3+1}$, denoted $\Omega_{3^*+1}$, was also studied. In this case, the directions of the three coplanar beams were optimized for each angle of the non-coplanar beam. This approach will find the treatment plan with the optimal directions of three coplanar beams plus one non-coplanar.

To compare these beam configurations with coplanar dose delivery, treatment plans using three, four and five coplanar beams optimized in direction and intensity were also examined. These configurations are denoted $\Omega_{3+0}$, $\Omega_{4+0}$ and $\Omega_{5+0}$, respectively.

### *Optimization algorithm*

The algorithm ORBIT (Optimization of Radiotherapy Beams using Iterative Techniques) was used for the treatment optimization. ORBIT is a versatile 3D optimization algorithm, which can optimize the beam portals, using a gradient technique, with respect to radiobiological or physical objective functions (2, 4, 19). The dose calculation formalism and the optimization algorithm have been extensively described in the literature during different stages of its development (17, 19, 26, 27). In the present study, simultaneous optimization of beam profiles and beam orientation using point monodirectional pencil beam weights has been used.

Several groups have tried different methods to solve the problem of finding optimal beam orientations (6, 9, 13, 16, 17, 20, 28–35). Angular optimization is a difficult inverse problem, since the phase space of most relevant objective functions has multiple maxima (17, 20, 34). Optimization algorithms based on simple gradient methods, such as the one used in this work, may be trapped in local maxima. Consequently, a systematic gradient exhaustive search or a simulated annealing stochastic optimization method (34, 35), considering the whole phase space, must be used to ensure that the global maximum is found. However, such

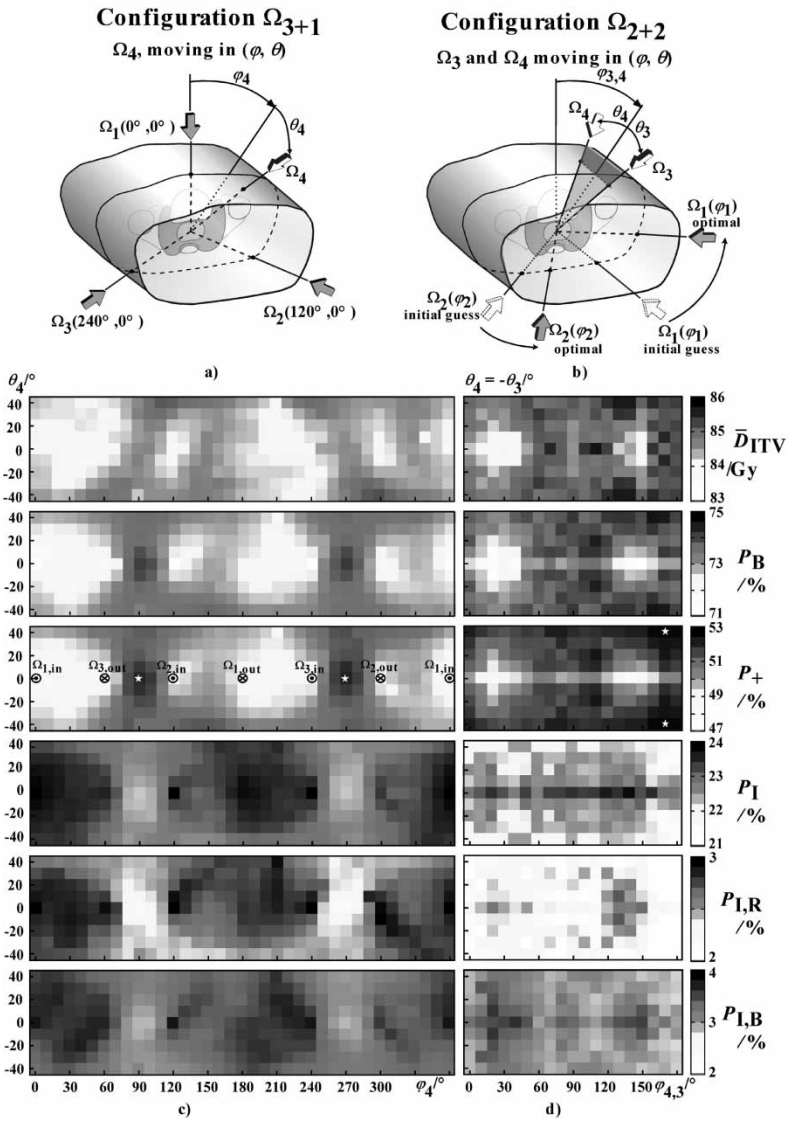


*Fig. 2.* (a) Definition of gantry and non-coplanar beam angles $\varphi$ and $\theta$, respectively. Schematical representation of the studied configurations: $\Omega_{3+1}$ and (b) $\Omega_{2+2}$. (c) Phase space of $\bar{D}_{ITV}$, $P_B$, $P_+$, $P_I$, $P_{I,R}$ and $P_{I,B}$, respectively, for the configuration $\Omega_{3+1}$ (ITV stands for internal target volume, R for rectum and B for bladder). $\Omega_{in}$ and $\Omega_{out}$ represents the beam entrance and exit, respectively. (d) Phase space of $\bar{D}_{ITV}$, $P_B$, $P_+$, $P_I$, $P_{I,R}$ and $P_{I,B}$, respectively, for the configuration $\Omega_{2+2}$. In the vertical axes, the two non-coplanar beams travel together obeying to $\theta_3 = -\theta_4$.

schemes are highly intensive computationally because of the enormous size of the search domain. Nevertheless, although the gradient method was still used to find the optimal coplanar orientations for the configuration $\Omega_{2+2}$; the optimization procedure was systematically restarted with a number of different initial beam orientations, to ensure that the global maximum was found.

### *Biological objective functions*

A biological objective function was used throughout this paper. The probability of achieving tumour control without severe complications, $P_+$, is defined as:

$$P_+ = P_B - P_I + \delta(1 - P_B)P_I \quad [1]$$

where $P_B$ is the probability of tumour control and $P_I$ is the probability for causing severe injury to the normal tissues, calculated using the relative seriality model (3, 19). The parameter $\delta$ describes the fraction of the patients with statistically independent responses in the tumour and normal tissues. For simplicity, $\delta$ in this study is considered zero. The Poisson statistical model has been used to describe the dose–response of the different tissues and tumour types. Due to the non-linear response of the tumour and normal tissues to varying doses per fraction, the probability of causing tissue injury or achieving tumour control, $P(D)$, is given by the linear quadratic model:

$$P(D) = e^{-\exp(e\gamma - \alpha D - \beta D^2)} \quad [2]$$

where $\gamma$ is the maximum normalized gradient of the dose response relation, the parameters $\alpha$ and $\beta$ account for the early and late effects in the tissue and $D$ is the total dose. The equations presented here are simplified, but the general equations can be found in Löf (4) and Löf et al. (36).

## RESULTS

### *A single non-coplanar beam, $\Omega_{3+1}$*

*Complication free cure.* Fig. 2c shows a systematic overview of the whole phase space of the probability of the complication free cure, as a function of the angle of incidence of the non-coplanar beam for the configuration $\Omega_{3+1}$. There are two kinds of symmetry in this configuration. The first is due to the symmetry of the patient geometry across the median plane. Therefore, the phase space of $P_+$ becomes approximately symmetric around the gantry angle 0°, i.e. $P_+(\varphi) = P_+(-\varphi)$. The second symmetry is due to the small difference between parallel opposed beam directions as a result of the high energy photon beam of 50 MV with an exit dose of around 50% and thus a low attenuation in soft tissues. This produces nearly the same dose distribution as when beam directions are reversed (i.e. $P_+(\varphi,\theta)$ and $P_+(\varphi+180°, -\theta)$). Compare for example the $P_+$ results in $\Omega(30°, -20°)$ and $\Omega(210°, 20°)$. For a beam with lower energy, due to a higher injury for the tissues situated in the beam entrance, compensated by the lower tissues injury in the beam exit, this symmetry is expected to be maintained for the phase space of $P_+$ and $P_I$.

The resultant range of variability for $P_+$ is slightly larger than 5%, due to a 3% variation in $P_B$ and a 2% difference in $P_I$ (Fig. 2c—$P_+$). The $P_+$ maxima are located at the gantry angles 90° and 270°, for a coplanar configuration. For these gantry angles the treatment outcome does not change significantly with increasing non-coplanar angle $\theta$. Local maxima of $P_+$ can be found, for each non-coplanar angle, at the gantry angles 30°, 90°, 150°, 210°, 270° and 330° (more clearly seen for $\theta = 0°$ in Fig. 2c—$P_+$). These local maxima are a consequence of maximally separated beams, i.e. when there is a 30° separation between the fourth beam and the fixed coplanar beams (at 0°, 120° or 240°). However, only the maxima at the gantry angles 90° and 270° are of interest. This is because only these directions combine maximum beam separation, low irradiation of organs at risk and a good beam alignment with the tumour.

*Organs at risk.* The small bowel has the largest probability of injury among normal tissues, at around 13% (not shown); the bladder follows with a probability of around 3.3% and the rectum of 2.6%, as in Fig. 2c—$P_{I,B}$ and $P_{I,R}$. These correspond to mean doses of approximately 28 Gy and 33 Gy and standard deviation around 17 Gy and 22 Gy, respectively (37). The part of normal tissue that lies inside the cervix has a probability of injury of around 5%, which is fairly constant throughout the examined phase space. The femur joints are of no major concern since injury values below 0.1% were achieved in all cases.

- *Small bowel:* The use of one non-coplanar beam increases the beam path in the small bowel, but the probability of injury is almost constant, independent of the non-coplanar angle (results not presented).
- *Bladder:* For the gantry angles of the local maxima of $P_+$, the injury for this organ is almost constant with the non-coplanar beam angles (Fig. 2c—$P_{I,B}$). An anterior beam direction with a positive non-coplanar angle, or a posterior direction with a negative non-coplanar angle, is the orientation that delivers the largest mean dose in this organ. Using instead an anterior beam with a negative non-coplanar angle (or a posterior beam with positive non-coplanar angle), the radiation field can avoid most of the bladder, decreasing its mean dose at the expense of increasing the standard deviation of the dose, leading to almost the same injury expectation (38).
- *Rectum:* This organ is extended in the cranio-caudal direction, thus there is almost no difference in the rectum dose or complication probability when the non-coplanar angle is changed. It is interesting to see that although 170° or 350° corresponds to a direction straight through the rectum, these orientations are those that deliver the lowest mean dose to this radiosensitive organ. However, the expected rectal injury is not the lowest (Fig. 2c—$P_{I,R}$).

In conclusion, the results indicate that for the present patient and beam configuration, the difference between the minimum and maximum $P_+$ is mainly due to two reasons. The first is the increase in the number of beams from three to four, which is the case when the beam $\Omega_4$ takes any orientation different from the position of the coplanar fixed beams (Fig. 2c—$P_+$). Second, the use of a suitable gantry angle increases the $P_+$ value considerably. But, for this gantry angle, no significant variation in treatment outcome is seen with a non-coplanar orientation (as for the gantry angle $\varphi_4 = 90°$ in Fig. 2c—$P_+$).

### *Two anti-symmetric non-coplanar beams, $\Omega_{2+2}$*

Due to the symmetry of the $\Omega_{3+1}$ phase space and because the calculations are very time-consuming, only half of the phase space was calculated in this case, namely for $\varphi_{3,4}$ from 0° to 180°.

*Complication free cure.* Fig. 2d shows the $P_+$ phase space for the configuration $\Omega_{2+2}$. The highest $P_+$ value found is 53.0%, for the two non-coplanar beams placed at $\Omega_3(170°, +40°)$ and $\Omega_4(170°, -40°)$, and the coplanar beams at $\Omega_1(93°, 0°)$ and $\Omega_2(240°, 0°)$.

The optimal gantry directions of the two coplanar beams, $\hat{\varphi}_1$ and $\hat{\varphi}_2$, as a function of the gantry angle of the non-coplanar beams $\varphi_3$ and $\varphi_4$, for the configuration $\Omega_{2+2}$ are shown in Fig. 3. That is, for each gantry angle $\varphi_{3,4}$ of the beams $\Omega_3$ and $\Omega_4$, the optimal directions of the coplanar beams $\Omega_1$ and $\Omega_2$ are shown on the vertical axes, for the studied symmetric non-coplanar beams $\theta_{3,4}$. To simplify the figure, only the beam entrance or exit is plotted, depending on which was more convenient. In this case, each coplanar beam is represented by an open or close symbol, whether it corresponds to the beam entrance or exit, respectively. The entrance and exit of the non-coplanar beams, $\varphi_3$ and $\varphi_4$, are represented instead by the symbols $\odot$ and $\otimes$, respectively. As an example, for $\varphi_{3,4} = 30^\circ$ the optimal gantry directions

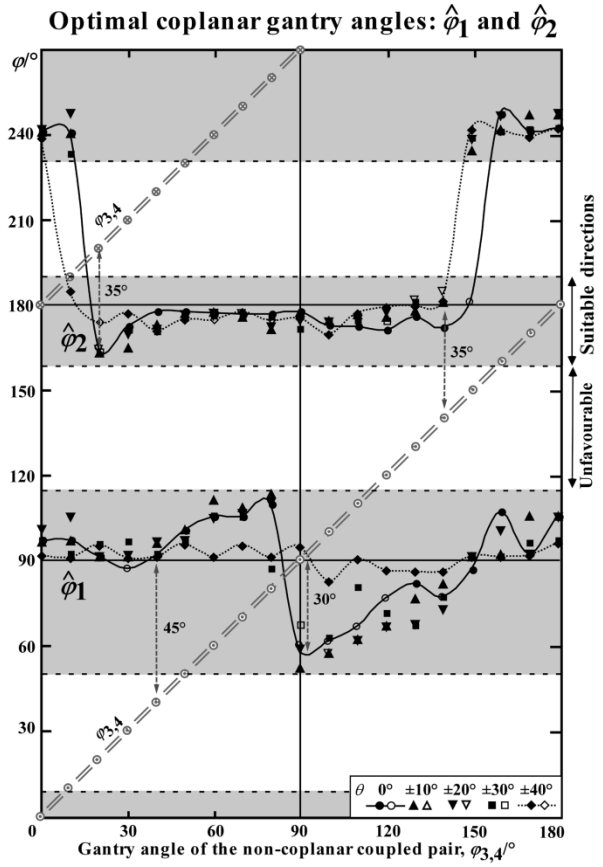


*Fig. 3.* Gantry directions for the four beams of the configuration $\Omega_{2+2}$, as a function of the gantry of the symmetric non-coplanar beams, $\varphi_{3,4}$. $\hat{\varphi}_1$ and $\hat{\varphi}_2$ are the optimal coplanar beam gantry directions of beam 1 and beam 2, respectively. To simplify the figure, only the entrance or exit of the coplanar beam is shown, represented by the solid and open dots, respectively. Five different opening angles of the non-coplanar coupled beams were investigated: 0° (●○), ±10° (▲△), ±20° (▼▽), ±30° (■□) and ±40° (◆◇). The symbols (⊙⊗), in the diagonal lines indicate the entrance and exit of the non-coplanar beams, respectively. The shadow area in the figure represents the optimal coplanar gantry orientations, while the white area indicates orientations of higher injury.

of the coplanar beams are $\hat{\varphi}_1 \sim 90^\circ$ and $\hat{\varphi}_2 \sim 175^\circ$. As seen in the figure, these last directions are almost independent of the non-coplanar angle used.

This figure illustrates a very important phenomenon in the selection of optimal beam angles: as the non-coplanar set approaches angles that are close to optimal, at around 90° and 180°, the coplanar beams are pushed away from the preferred positions. This is due to a reduction of the effective number of free variables as the beams comes closer and tend to coincide with each other. It is then more advantageous for the optimization algorithm to move the angularly optimized coplanar beams away from the preferred positions, in order to increase the flexibility in shaping the dose distribution in 3D. It is seen in Fig. 3 that this push starts when the non-coplanar beams are about 45° away from the optimal angles and that an angle lower than about 30°–35° is not allowed between two consecutive beams. Since for the non-coplanar angle $\theta = 40^\circ$, where the beam separation between the coplanar and the non-coplanar beams is larger than 30°, the optimal gantry orientation of 90° is used by the two non-coplanar and one of the coplanar beams.

Comparing the treatment outcome, as measured by $P_+$ (Fig. 2d) with the optimal beam positions shown in Fig. 3, it is seen that an equally good treatment can be performed when the preferred positions of around 90° and 180° are being used, either by the coplanar or the non-coplanar beams. This means that these optimal orientations are independent of the angle of the non-coplanar beams. Contrary to what was expected, the lower values in the $P_+$ phase space, in Fig. 2d, are associated to oblique irradiation directions, such as 20° and 140°, which make them less suitable beam orientations for a treatment with four beams (see white areas in Fig. 3).

*Organs at risk.* Because the direction of two beams in this configuration is optimized, the average complication probability in the individual organs is slightly lower than the one obtained in the configuration $\Omega_{3+1}$ (Fig. 2c and 2d—$P_{I,B}$ and $P_{I,R}$).

– *Small bowel:* The major injury in the small bowel, of approximately 9%, comes from the normal tissue that lies inside the internal target volume, which cannot be avoided without compromising tumour control. The increase in the volume irradiated, due to a longer beam path for the non-coplanar portals, only occurs for doses lower than 10 Gy, which are not clinically significant for acute or late morbidity, but may be so for secondary tumour induction. Due to both these reasons, a constant value for small bowel injury is then obtained independently of the beam configuration. The largest reduction in the injury values for this tissue occurs when going from three to four fields, when a non-coplanar angle different than 0° is used (when the non-coplanar angle is 0°, the two non-coplanar beams are superposed).

– *Bladder and rectum:* The gantry angles between 20° and 50° cause the largest bladder injury, whereas the angles between 120° and 150° are the most damaging angles for the rectum (not the angle 180°, as would be expected when using uniform beams). Although these angles are not directly in the path of the organs at risk, the relatively small separation of the beams, together with the use of sub-optimal directions, increases the risk of injury in these organs and decreases tumour control, resulting in low $P_+$ values (Fig. 2d). A non-coplanar treatment with these gantry angles increases beam separation, and thus the injury of the individual organs decreases and tumour control increases. However, when the preferred directions are used (around 90° and 180°), the choice of a non-coplanar orientation does not significantly change the injury or the tumour control, or finally the treatment outcome.

*Comparison between the best results*

Comparing these results with coplanar beam treatments, fully optimized in intensity and direction, the $P_+$ values achieved with three, four and five coplanar beams were 50.1%, 52.7% and 53.9%, respectively. Their respective optimal directions are given in Table 2. In Fig. 4 and Table 2 the best non-coplanar and coplanar dose distributions with three, four and five fields found in this study are compared. It can be observed that none of the dose distributions have hot spots in the organs at risk. The bladder and especially the rectum are very well protected from high doses. At the same time the tumour receives an almost homogeneous dose, greater than 70 Gy.

For the studied treatment plans with four fields, the treatment outcome is not significantly different in the three cases presented and may be considered from a clinical point of view to be similar, which is in agreement with other studies (15). However, the degrees of freedom were not always strictly comparable for the different configurations studied. The small degree of freedom of the fixed coplanar beams in the configuration $\Omega_{3+1}$ could explain the lower treatment outcome achieved for this configuration. To test this statement the directions of the coplanar beams were algorithmically optimized in configuration $\Omega_{3^*+1}$ and the optimal configuration found is a fully coplanar treatment, with nearly the same treatment beam geometry as the configuration $\Omega_{4+0}$ (Table 2). The small difference between the $P_+$ value obtained for the configurations $\Omega_{3^*+1}$ and $\Omega_{4+0}$ is explained by the different optimization process used.

For a five coplanar field configuration, the treatment outcome increases by 1% compared to the previous results.

## DISCUSSION

The rationale for using non-coplanar uniform beams in classical conformal radiotherapy is essentially twofold. The first motivation is to minimize the overlap regions between the entrance and exit beams in normal tissues. A reduced volume of high dose in the normal tissues surrounding the tumour is thus achieved, at the cost of increasing the low dose volume. Secondly, new beam directions may better avoid the organs at risk, decreasing the injury to normal tissues while the tumour dose is increased. Consequently the weight of the beams that avoid sensitive organs at risk can be increased and the weight of other less advantageous coplanar beams can simultaneously be decreased.

*Dose distribution*

When multiple uniform beams are used to treat a patient, relatively high dose regions always appear in the intersecting beam regions. If these regions lie within the normal tissues and especially in serially organized organs, they may cause severe injury. Therefore, when radiobiologically optimized intensity modulated beams are used, the fluence

**Table 2**

*Best results achieved for the different configurations studied. The treatment configuration $\Omega_{2+2}$ was the only non-coplanar configuration which showed a slightly higher $P_+$ value compared to the optimal coplanar treatment $\Omega_{4+0}$. The first index represents the number of coplanar beams, while the second is the number of non-coplanar beams. E is the photon beam energy in MV. $\varphi_i$ and $\theta_i$ are the gantry angle and the non-coplanar angle of beam i, with i = 1,..., 5, respectively. For the box technique the treatment outcome was calculated for: uniform (Unif.) and intensity modulated (IM) beams.*

| E MV | #Beams | Config. | $P_+$ % | $P_B$ % | $P_I$ % | $\varphi_i$ ° | $\theta_I$ ° |
|---|---|---|---|---|---|---|---|
| 50 | 3 | $\Omega_{3+0}$ | 50.1 | 73.5 | 23.4 | 106, 177, 243 | 0, 0, 0 |
| | 4 | Box (Unif.) | 19.1 | 55.0 | 35.9 | 0, 90, 180, 270 | 0, 0, 0, 0 |
| | | Box (IM) | 47.2 | 70.9 | 23.7 | 0, 90, 180, 270 | 0, 0, 0, 0 |
| | | $\Omega_{3+1}$ | 52.2 | 74.2 | 22.0 | 0, 120, 240, 270 | 0, 0, 0, 0 |
| | | $\Omega_{4+0}$ | 52.7 | 74.6 | 21.9 | 88, 115, 177, 237 | 0, 0, 0, 0 |
| | | $\Omega_{3^*+1}$ | 52.8 | 74.6 | 21.8 | 96, 120, 238, 357 | 0, 0, 0, 0 |
| | | $\Omega_{2+2}$ | 53.0 | 74.7 | 21.7 | 93, 240, 170, 170 | 0, 0, +40, −40 |
| | 5 | $\Omega_{5+0}$ | 53.9 | 74.9 | 21.0 | 5, 80, 154, 235, 291 | 0, 0, 0, 0, 0 |
| 10 | 4 | $\Omega_{4+0}$ | 52.7 | 74.3 | 21.6 | 88, 116, 237, 356 | 0, 0, 0, 0 |
| | | $\Omega_{2+2}$ | 51.2 | 73.2 | 22.0 | 5, 92, 180, 180 | 0, 0, +40, −40 |

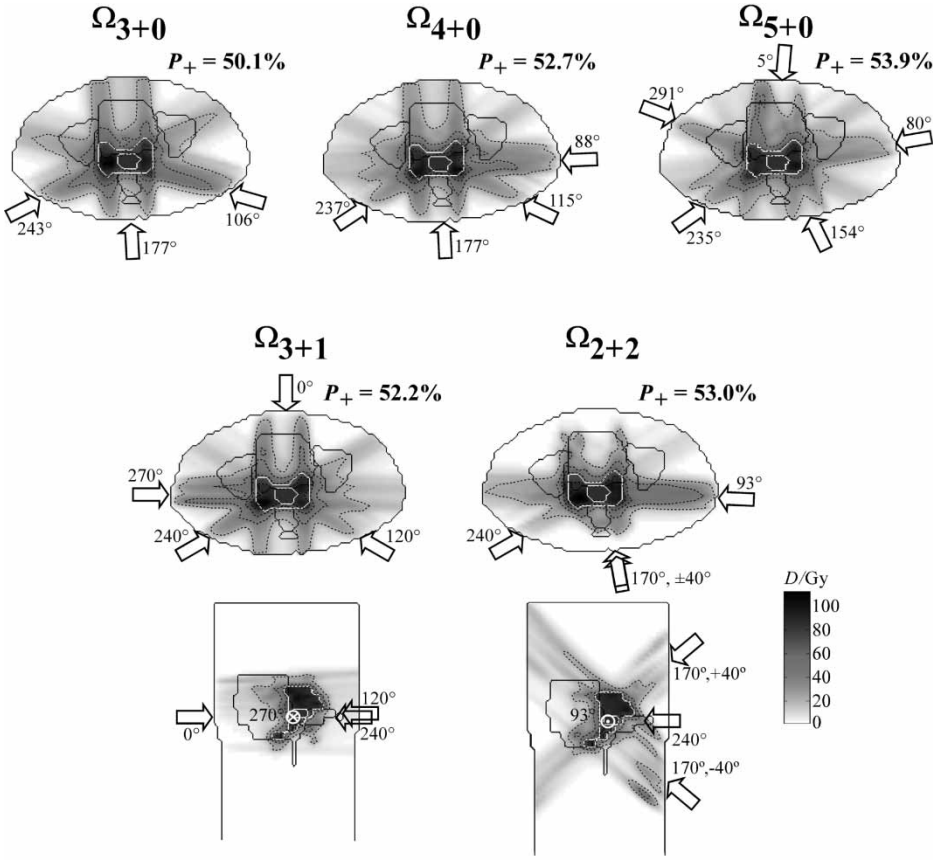


*Fig. 4.* Upper figure: optimal configuration with three, $\Omega_{3+0}$, four, $\Omega_{4+0}$ and five, $\Omega_{5+0}$ coplanar beams, respectively. The isodoses are plotted for a dose range from 20 to 100 Gy in 20 Gy intervals. Middle and lower figure: comparison between the best dose distributions obtained with the configurations $\Omega_{3+1}$ and $\Omega_{2+2}$, respectively. Both transversal and sagittal views are shown. For configuration $\Omega_{3+1}$ the optimum beam set-up is coplanar ($\theta_4 = 0^\circ$), whereas for configuration $\Omega_{2+2}$ the non-coplanar angle 40° is shown to be the most efficient treatment configuration.

distribution is shaped partly in order to avoid such hot spots and generally reduce the irradiation of organs at risk.

In Fig. 5 several isodoses levels have been selected to show the relative volume of the organ irradiated with the given dose level $D$, for small bowel, bladder, rectum and the internal target volume, respectively. For example, the first phase space panel in the figure indicates the relative volume of small bowel that receives a dose higher than 10 Gy. The third row shows the isodose corresponding to the $D_{50}$ value for each organ ($D_{50}^{\text{org.}}$). In this study, the biological objective function $P_+$ quantifies the quality of the plan. However, to explain why such effectiveness varies with different beam directions, a more basic analysis needs to be done directly from the dose distribution (schematically shown in Fig. 5). Thus, the purpose of this figure is to illustrate how the dose distribution changes when non-coplanar beams are used and to quantify the reduction of high dose regions in the organs at risk when a larger beam separation between the beams is allowed.

In fact, it can be seen that when the non-coplanar angle increases, there is no significant reduction in the percentage of volume irradiated with high doses in the organs at risk (Fig. 5—$D = 60$ Gy for bladder and $D = 55$ Gy for rectum). Similarly, there is almost no reduction for the low doses at the gantry angles around 90° and 180°. This means that the dose volume histograms are very similar and an almost constant injury and tumour control level is achieved with the non-coplanar angle (see $P_{\text{I}}$ and $P_{\text{B}}$ in the lower part of Fig. 5).

For dose values lower than 40 Gy, the probability of acute injury in the organs at risk is negligible. Thus, the increase in volume of small bowel irradiated with the non-coplanar angle for $D = 10$ Gy, due to the longer beam path in this tissue, has minimal clinical effects (Fig. 5—$D = 10$ Gy for small bowel). The main concern in using large non-coplanar irradiation angles is this longer beam path in the patient. Although it does not seem such an important factor for acute damage due to the low dose values involved, the efficient use of coplanar beams can avoid the irradiation of large volumes of normal tissues with low doses, which is an advantage with regard to secondary tumour induction and the induction of damage due to low dose hypersensitivity.

For the present treatment geometry, we can conclude that compared to radiobiological optimized intensity modulated

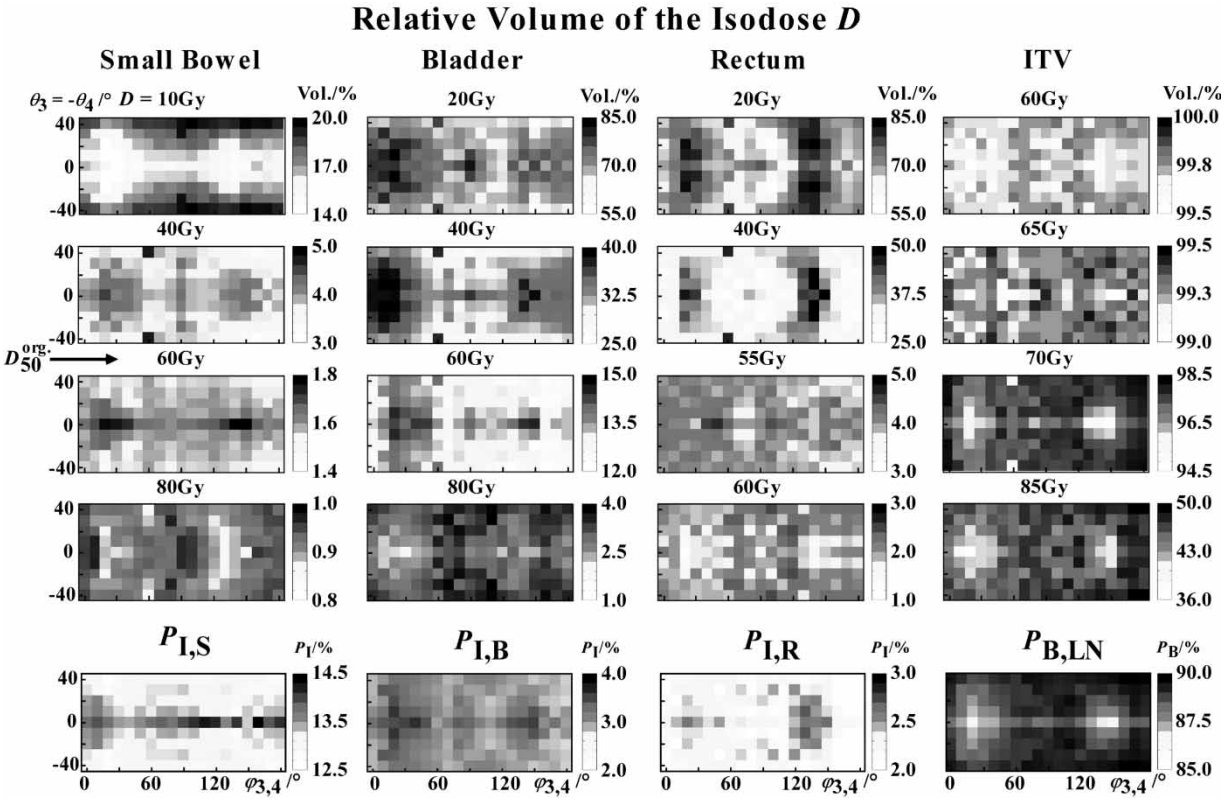


*Fig. 5.* Upper figure: relative volume of the isodose $D$ for small bowel, bladder, rectum and internal target volume, in the configuration $\Omega_{2+2}$. The figures with $D$ between 10 and 60 Gy show the dose that is delivered to the normal tissues outside the internal target volume. The figures with $D$ higher than 60 Gy show the dose delivered mainly to parts of the organs at risk that lie inside the internal target volume. Below, the phase space for the injury of the organs at risk ($P_{I,S}$ for small bowel, $P_{I,B}$ for bladder and $P_{I,R}$ for rectum) and the phase space for the probability of benefit of the tumour tissue infiltrated in the lymph nodes ($P_{B,LN}$) are illustrated.

beams placed in optimal coplanar orientations, non-coplanar fields do not reduce significantly the volume of normal tissues being irradiated. Since the radiosensitive structures, bladder and rectum, are located very close to the cervix and may partly be located inside the internal target volume (37), it is difficult to geometrically exclude any significant portion of these organs, even if very large non-coplanar angles are used (Fig. 6).

### *Number of beams*

As mentioned before, biologically optimized intensity modulation reduces the need for a very large number of beams (6, 16, 20). Due to these findings and to make beam directions highly relevant, four main beam configurations were tested in this study. Such low beam numbers reduce the problem of multiple extensive overlap regions around the tumour. Thus, the organs at risk are well protected, except in the region where they may overlap with the internal target volume. The high dose values in such regions cannot obviously be avoided, without some loss of tumour control.

The use of five coplanar beams increases the treatment outcome even further. And, coplanar techniques have practical advantages over non-coplanar techniques, since there is no need to move the patient and thus to increase the set-up errors and treatment times. On the other hand, the increased treatment complexity when using five coplanar beams may not offset the small increase in treatment outcome. Therefore, no further significant improvement in treatment outcome is expected if non-coplanar beams are used for such a high number of beams. Even so, a few calculations were performed with more than five beams and non-coplanar orientations. In none was seen an increase in the treatment outcome relative to an optimal coplanar treatment. However a more detailed study is required to fully validate this statement.

### *Beam directions*

The second argument for using non-coplanar beams is to find directions that better avoid irradiation of the organs at risk. In the configuration $\Omega_{2+2}$ the directions of the coplanar beams were optimized. From these results, it was found that the combination of beams at the gantry angles around 90° and 180° is very effective (Fig. 3). This is because, as expected, the beam fluence delivers the highest possible dose to the tumour region, where there are no organs at risk, and is set to a low value when the organs at

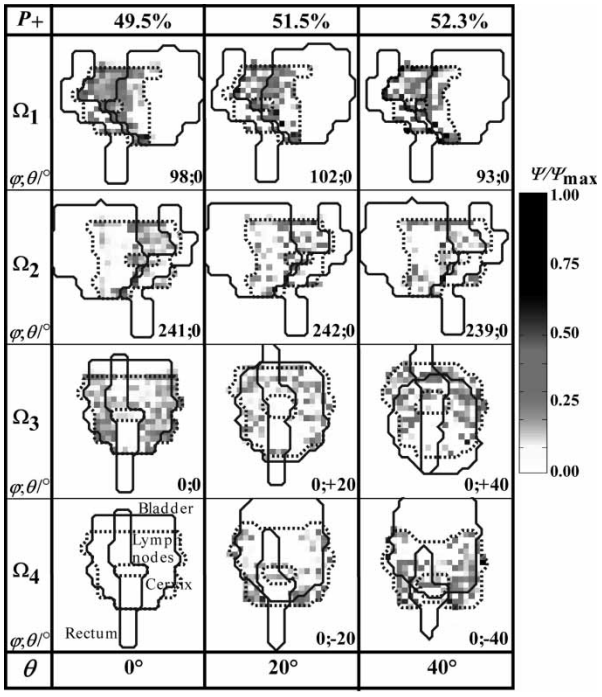


*Fig. 6.* Beam intensity for increasing non-coplanar angle, $\theta$, in the configuration $\Omega_{2+2}$ and gantry angle 0°. The dose is reduced when the beam passes through organs at risk. Thus, both longitudinal intensity modulation and lateral collimated protection is achieved.

risk are in the beam path, especially for the rectum (Fig. 6). Thus, the anterior/posterior beams (in the beams eye view) only irradiate the tumour around the rectum, leaving a cold region in the target volume in front/behind the rectum, which instead will be irradiated by the lateral beam (Figs. 4 and 6). A lateral beam orientation has the advantage of lateral protection and an anterior/posterior direction has longitudinal protection of beam intensity modulation, obtained by reducing the fluence over areas with large amounts of normal tissues, together with the build-up effect of the high-energy photon beam at 50 MV. Although there is little difference between posterior and anterior irradiation, the large dose build-up depth gives a slight preference to posterior irradiation, due to a marginally improved rectal protection. Therefore, an already efficient treatment by coplanar intensity modulated beams, even from directions such as straight through the organs at risk, makes it more difficult for non-coplanar beam directions to be competitive.

Furthermore, the oblique directions, around 60° and 110°, have also shown to be fairly favourable (Fig. 3). Therefore, it is possible that a different non-coplanar arrangement that uses the combination of these angles together with 90° and 180° might provide the best possible treatment. However, these directions are already used in the optimal four field coplanar treatment, $\Omega_{4+0}$, for which the $P_+$ value was quite similar to the maxima obtained for $\Omega_{2+2}$; see Table 2.

The global maximum for a four beam configuration distributed in the 3D space can only be found if all possible beam combinations are calculated. Because such a study is unrealistic due to time considerations, only a few directions were selected. Several different treatment configurations were optimized, but only the most interesting results were extensively analysed and presented. Thus $\Omega_{2+2}$ and $\Omega_{3^*+1}$ are among the best non-coplanar configurations obtained with four beams. In fact, the global maximum might be found for a different treatment geometry. However, the current results indicate that if the global maximum is not between the configurations presented, the extra gain will be minimal.

### *Beam separation*

One of the purposes of using non-coplanar beams is to avoid high dose regions in the organs at risk by increasing beam separation. For this patient geometry and a four beam configuration, it was found that a minimum angle between the entrance and exit of two consecutive beams is required. However, for optimally positioned intensity modulated beams, whether or not they are placed in the plane, provided they are separated by more than the minimum angle of 30°–35°, beam separation is not as important. For example, the beam separation is almost the same for the gantry direction 20° and the optimal gantry direction 90°: 35° and 30°, respectively (Fig. 3). However, the treatment outcome is larger for the latter (Fig. 2d), because although the beam separation is nearly the same, the optimal directions are used only for 90°.

### *Beam energy*

The beam in this study was a photon beam of 50 MV, which is higher than generally used. A non-coplanar beam always crosses a longer tissue path before reaching the tumour, and at the same time irradiation of the organs at risk in front of the tumour should be avoided. Both these features can be most effectively handled with a high energy photon beam due to the large build-up depth and low attenuation before reaching the tumour. Söderström et al. (39) and Söderström (40) investigated the importance of the energy in photon beams within the range of cobalt 60 to 50 MV in an advanced cervix tumour, using a three equidistant field configuration placed at 0°, 120° and 240°. These studies showed that if intensity modulated beams with energies higher than 10 MV are employed to treat deep-seated tumours, the selection of the beam energy is not very critical. Furthermore, the selection of optimal beam entry directions is not greatly affected by the photon beam energy. Therefore, the choice of a high energy beam for this study is suitable and very similar overall conclusions would be obtained with lower photon energies.

As just discussed, energy has some influence on the efficiency of the posterior irradiation direction due to the

high dose build-up. Nevertheless, the use of lower energies has advantages as well, i.e. lower exit dose and lower penumbra. Thus, some non-coplanar angles of configuration $\Omega_{2+2}$ and the optimal coplanar treatment $\Omega_{4+0}$ with four beams for a photon beam of 10 MV were calculated. The best results obtained are presented in Table 2 and confirm the conclusions obtained by Söderström et al. (39) and Söderström (40) for a coplanar treatment geometry. As suspected above, an optimal coplanar intensity modulated technique shows a slight improvement in the treatment outcome compared with non-coplanar directions. Although a more detailed study of the energy dependence in the 3D space may be of interest, it goes beyond the scope of this paper. However, the present results indicate that beam energy is of little importance not only for 2D (39, 40) but also for a 3D beam configuration.

*Patient geometry*

To verify if the same results apply to a different patient of similar geometry, some of these calculations were performed for a prostate patient. Neglecting the differences observed in organs at risk injury, due to the different patient, tumour and organs at risk dimensions, the same general conclusions were drawn. Thus, minor changes in tumour or patient geometry will still make the conclusions in this study valid.

*Patient biology*

The treatment planning system used in this work allows the specification of the relative density of tumour cells inside the target volume (Table 1). It was shown by Brahme (41) that the dose required to achieve maximum tumour control without severe injuries only slightly increases with increasing tumour cell concentration. Therefore, the assumption made for the relative density of clonogenic cells in this cervix case has no major effects in the conclusions drawn.

The patient geometry and the organ biology that were selected in this analysis comprised a clinical case that is difficult to treat. This decision was made on purpose in an effort to reach more clear conclusions. In practice, most clinical cases are easier to treat, leading to an even lower need of non-coplanar beam configurations, since the difference in treatment outcome between the coplanar and non-coplanar beam configuration is less pronounced than in this case. Some calculations were done for the standard biology found in the literature (26, 42) and the present statement applies.

*Objective function*

The biological objective function used in this work was the probability of uncomplicated tumour control, $P_+$. This might be a too idealistic objective and if a higher level of injury in the organs at risk than given by maximum $P_+$ is tolerated, non-coplanar beams will be even less advantageous, since there is no need to worry as much about beam overlap and protection of organs at risk from irradiation.

Only biological optimization can provide the optimal dose distribution, by accomplishing the right compromise between tumour control and severe normal tissue damage. Therefore, with physical optimization a lower treatment outcome will be achieved, as a consequence of the sub-optimal consideration of severe injury. However, even for this type of optimization, intensity modulated non-coplanar beams may not bring significant improvements in the treatment outcome when compared to the optimal coplanar configuration. This is because a homogeneous dose distribution in the tumour can always be obtained, due to the high number of degrees of freedom available by intensity modulation. Also, the proximity of radiosensitive normal tissues will not allow a reduction of the injury in the organs at risk without loss of tumour control, even if intensity modulated non-coplanar beams are used. Thus non-coplanar beams with physical optimization will be less useful, as also seen in the study of Pugachev et al. for prostate tumours (15).

## CONCLUSIONS

The present study illustrates the clinical advantages of biologically optimized angle of incidence and intensity modulated radiation therapy. For deep-seated target volumes surrounded by close organs at risk, non-coplanar irradiations do not always perform significantly better than optimally oriented intensity modulated coplanar treatments, when a few radiobiologically optimized photon beams are used. This is mainly due to the following:

- The reduction of the high dose volume in normal tissues, with non-coplanar techniques, is small when biologically optimized intensity modulation is used.
- Large organs at risk close to the tumour often make it difficult, also for non-coplanar beams, to significantly reduce normal tissue damage.
- With intensity modulated dose delivery, fewer beams are generally required and consequently the high dose overlap regions in the normal tissues are reduced.
- With a low number of beams, beam direction optimization is very important and it will be considerably influenced by the exact patient geometry and tumour site. The computational problem is significantly reduced by keeping the beam direction optimization in the plane. This works with a few beams, due to the efficient protection by radiobiologically optimized intensity modulated beams (even straight through the organs at risk). For a four-beam configuration, beams separation larger than $30^\circ - 35^\circ$ is generally sufficient when biologically optimized intensity modulation beam orientations are used.

The major reason why the conventional wisdom in the use of non-coplanar beams is not as effective with biological optimized intensity modulated dose delivery, is that there are many other degrees of freedom that reduce the need for non-coplanar dose delivery. Very little can be gained by using beam directions that by necessity have to cross increasing volumes of normal tissues with increasing non-coplanar angles. From a practical clinical point of view this is fortunate since non-coplanar irradiation techniques are more labour intensive, inconvenient and increase the probability for set-up errors when having to rotate both the patient and gantry.

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