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Original research article

Implementation of a dose gradient method into optimization of dose distribution in prostate cancer 3D-CRT plans

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ABSTRACT

Aim: The aim of this work is to present a method of beam weight and wedge angle optimization for patients with prostate cancer.

Background: 3D-CRT is usually realized with forward planning based on a trial and error method. Several authors have published a few methods of beam weight optimization applicable to the 3D-CRT. Still, none on these methods is in common use.

Materials and methods: Optimization is based on the assumption that the best plan is achieved if dose gradient at ICRU point is equal to zero. Our optimization algorithm requires beam quality index, depth of maximum dose, profiles of wedged fields and maximum dose to femoral heads. The method was tested for 10 patients with prostate cancer, treated with the 3-field technique. Optimized plans were compared with plans prepared by 12 experienced planners. Dose standard deviation in target volume, and minimum and maximum doses were analyzed.

Results: The quality of plans obtained with the proposed optimization algorithms was comparable to that prepared by experienced planners. Mean difference in target dose standard deviation was 0.1% in favor of the plans prepared by planners for optimization of beam weights and wedge angles. Introducing a correction factor for patient body outline for dose gradient at ICRU point improved dose distribution homogeneity. On average, a 0.1% lower standard deviation was achieved with the optimization algorithm. No significant difference in mean dose–volume histogram for the rectum was observed.

Conclusions: Optimization shortens very much time planning. The average planning time was 5 min and less than a minute for forward and computer optimization, respectively.

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1. Background

Prostate cancers are among the most frequent cancers.[1–3] Radiotherapy of prostate cancer is usually performed with conformal therapy (3D-CRT) or intensity modulated radiotherapy (IMRT).[4–7] Despite many years of using 3D-CRT plans, the best beam arrangement is still discussed.[8–13] For this aim, also mathematical optimization methods are used. Sherouse[14] presented a method of 3D-CRT radiotherapy planning based on dose gradient analysis. He analyzed the method on some theoretical cases and described mathematical formalism of 3D-CRT radiotherapy planning based on dose gradient analysis for open beams.[14] Sherouse claimed that mathematical gradient analysis "holds promise as the basis of a technique for automatic selection of wedge angles, collimator angles, and relative beam weights as a part of a clinical treatment design system."[14] Algorithm based on dose gradient analysis applied to two and three beams therapy was proposed by Dai.[15] Dose gradient analysis method is one of many optimization methods, such as simulated annealing,[11,16] genetic algorithms,[17] omni-wedge technique,[18,19] and others.[20–23] Any of these methods is in common use, so in everyday practice analysis of dose distribution and selection of beam weights and wedges is done by a planner using a trial and error process. This process, even in simple cases, might be quite time consuming. Therefore, faster methods that may support trial and error methods are searched for.

2. Aim

In this work, we developed optimization method based on dose gradient analysis. Proposed method was tested for prostate cancer patients irradiated with the three-field technique (one AP field and two wedged lateral fields). In our work, we show how one can achieve uniform dose distribution in target volume by optimization of beam weights and wedge angles.

3. Materials and methods

3.1. *Treatment techniques*

Prostate cancer patients irradiated in our hospital receive 65 Gy in 25 fractions (2.6 Gy per fraction). Patients are treated with the IMRT or 3D-CRT technique. In case of 3D-CRT, the three-field technique is used (photon 15 MV beams), open AP field and two lateral wedged fields without collimator rotation.[24] The shape of fields is obtained with a multileaf collimator.

In this work, we tested our optimization algorithm for 10 patients. We had chosen patients who had different body shape and dimensions. Mean age of those patients was 70 years (range 62–75). PTV was defined as CTV (prostate gland and seminal vesicles) with 1 cm margin. Mean PTV volume was 199.3 cc. Rectum and bladder were contoured based on the internal protocol. Mean rectum volume was 57.5 cc, mean bladder volume was 157.3 cc.

Before CT scan (slice thickness of 3 mm) patients were obligated to empty their rectum. In order to keep the patients' bladder full they were asked to empty their bladder and then to drink half a liter of water 1 h before a CT scan. Patients were positioned supine with a knee-wedge for better reproducibility.[24]

3.2. *Optimization of beam weights and wedge angles*

We assumed that the most homogeneous dose distribution in the PTV is obtained if dose gradient is zero at ICRU point (which was set in the center of mass of PTV and where isocenter was set to). Mathematically, that can be achieved by solving the following set of equations:

$$\begin{cases} \sum_{i=1}^{3} w_i \cdot D_i(\mathrm{ICRU}) = D_p(\mathrm{ICRU}) \\ \sum_{i=1}^{3} w_i \cdot \nabla D_i(\mathrm{ICRU}) = 0 \end{cases} \quad (1)$$

where w_i are beam weights (for ith beam). In our model beam normalization is calculated with the formula: $(\mathrm{PDD}(d)/\mathrm{PDD}(\mathrm{ICRU})) \cdot (D_p/n)$, where $n = 3$ and d is the depth of the ICRU Reference Point for the nth beam. This means that weights are proportional to the dose delivered from each single beam to ICRU point. The first equation of formula (1) guarantees that the dose at ICRU point would be equal to prescribed dose D_p. Second equation sets the dose gradient at ICRU point to zero. This set of equations has exactly one solution. We calculated PDD(d) with the formula described by Gerbi[25]:

$$\mathrm{PDD}_{\mathrm{SSD}}(d) = 10^{[p_1 + p_2 d + (p_3 + p_4 d)\log(A/P)]} \quad (2)$$

In Eq. (2), p_i are factors which depend on the beam quality index ($\mathrm{TPR}_{20/10}$), d stands for depth, A and P are field area and periphery, respectively. PDD was recalculated from one SSD to another with the formula:

$$\mathrm{PDD}_2(d, A_s, \mathrm{SSD}_2) = \mathrm{PDD}_1(d, A_s, \mathrm{SSD}_1)\frac{\mathrm{TAR}(d, A_{d_2})}{\mathrm{TAR}(d, A_{d_1})} \cdot \left(\frac{\mathrm{SSD}_2 + d_{\max}}{\mathrm{SSD}_2 + d}\right)^2 \cdot \left(\frac{\mathrm{SSD}_1 + d_{\max}}{\mathrm{SSD}_1 + d}\right)^{-2} \quad (3)$$

The factor $\mathrm{TAR}(d, A_{d_2})/\mathrm{TAR}(d, A_{d_1})$ is very close to 1, and therefore was neglected.

Let us denote dose gradient ∇D_i as $\nabla(DD, PR)$ where DD, PR are the dose gradient components along the central axis and perpendicular to the central beam axis, respectively. Dose gradient from an open beam is connected with the depth dose (DD) curve, and dose gradient for wedged beams depends on DD (in the central axis direction) and on the profile shape (in the transversal axis direction). Finally, the dose gradient is a vector sum of these two gradients.

In order to calculate dose gradient component transversal to the beam axis, we fit line to the dose profile for wedged beams in the surrounding of the central axis in the distance of ±1 cm from the axis. Linear fitting was done with the least

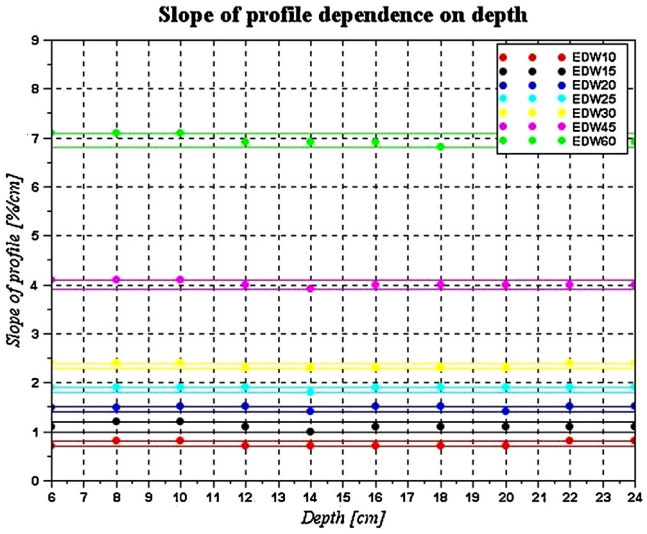

Fig. 1 – Comparison of slope value for different depths and different wedges.

square method. We checked how the slope was changing with the depth for depths from 6 cm to 24 cm (see Fig. 1). Mean standard deviation of the slope for different depths was equal to 3% of the mean slope value. This was interpreted as a low dependence between depth and slope.

To calculate beam weights, the following parameters were introduced: depth of ICRU point along the central beam axis, field size, wedge angle (represented by the slope of central part of profile), depth of maximum dose (d_{max}) and beam quality index ($TPR_{20/10}$).

The organs at risk for patients with prostate cancer are the rectum, bladder and femoral heads. Didem et al.[9] showed that there is a relationship between dose received by the rectum and femoral heads. To spare the rectum as much as possible, the technique using two lateral opposing fields should be used. Such beam arrangement leads to dose to femoral heads being too high. To decrease the dose to femoral heads, the AP field is added.[24] The smaller wedge angles are used in lateral beams, the smaller dose would be received by the rectum. In order to calculate beam weights and the smallest possible wedge angle with which femoral heads tolerance dose would be met, weights and wedge angle optimization was done. Maximum tolerance dose to the femoral heads is not well defined.[8,9,26] In our clinic, we accepted the maximum dose of 50 Gy (in fraction dose of 2 Gy). While giving input parameters to the optimizer, we used 49.5 Gy. Mathematically, the problem described above can be introduced by the following set of equations which has to be solved:

$$\begin{cases} \sum_{i=1}^{3} w_i \cdot D_i(\mathrm{ICRU}) = D_p(\mathrm{ICRU}) \\ \sum_{i=1}^{3} w_i \cdot \nabla D_i(\mathrm{ICRU}) = 0 \\ \sum_{i=1}^{3} w_i \cdot D_i(\mathrm{FH}) = D_{\max}(\mathrm{FH}) \end{cases} \quad (4)$$

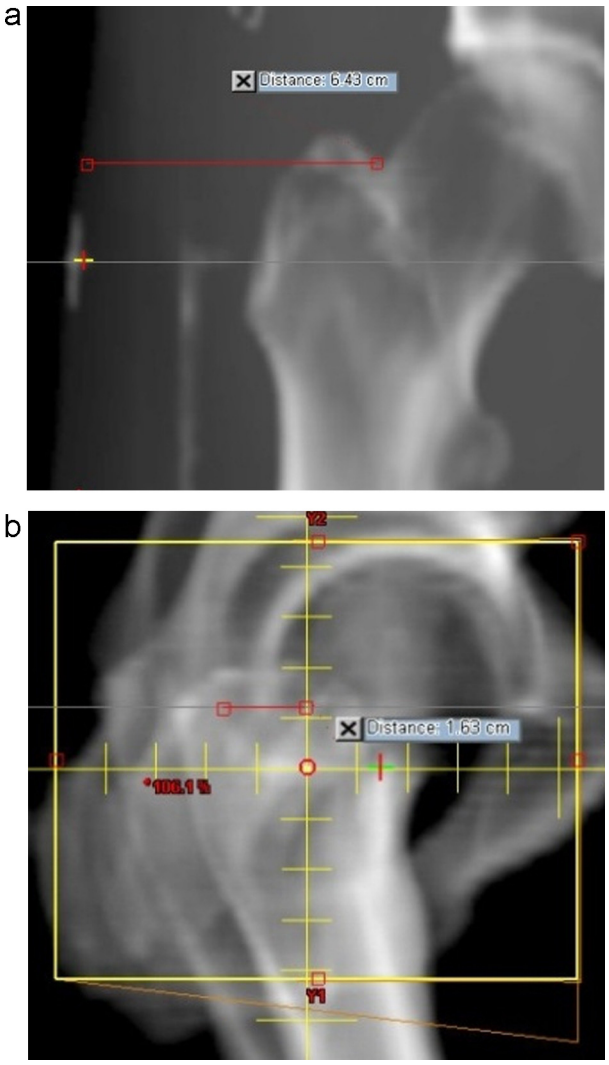

Fig. 2 – The method of defining femoral head dose calculation point on the basis of DRR images for gantry angle 0° (a) and 90°/270° (b).

The equation added to set of equations (1) formulates the condition for maximum dose in the femoral heads (D_{max}(FH)) which should not be exceeded. The dose to the femoral heads was estimated with dose at a point defined with the help of digitally reconstructed radiographs. On the Digitally Reconstructed Radiographs (DRR), the maximum distance of the femoral heads from the central beam axis and minimum distance between the femoral heads and body surface were obtained (see Fig. 2). This selection guaranteed that the dose to the femoral heads was calculated in the highest dose region of lateral wedged fields. The dose distribution in this region is quite homogenous so the error of maximum dose estimation is small. Due to the limitation of Gerbi's model, the smallest depth was 4 cm.[25]

The optimal wedge angle (between 0° and 60°) can be easily obtained with the effective wedge technique[27] by using superposition of open and wedged fields with adequate weights.

3.3. Implementation of a model for prostate case

After calculating beam weights and wedge angles, which was done by solving set of equations (4) in an analytic way with the help of a computer software, they were introduced into treatment planning system (TPS) – Eclipse version 9 with Pencil Beam algorithm (8.2.23). Pencil Beam algorithm may influence the accuracy of calculations if large amount of gases are present in the rectum. According to our protocol, if during planning CT distended rectum is observed, the new CT examination is made. We compared statistical parameters of dose distribution achieved with the beam weight optimization method and by experienced planners. We compared dose distribution homogeneity in terms of: standard deviation, minimum and maximum dose in target volume.

In order to compare (in terms of standard deviation) the quality of treatment plans obtained by planners with our model, we have simplified the geometry. For this work, planners were obliged to use open fields of defined shape (beam penumbra jaws were set to isotropic external margin of 1 cm from the target border). In this work, we used mechanic wedges, although in clinical routine we mostly use dynamic wedges. We performed comparisons for 10 patients previously treated in our center. We had chosen patients with different LR dimensions and AP distance.

The body shape may work as an additional wedge. Therefore, we analyzed the influence of body shape on homogeneity of dose distribution in the PTV. For each patient, for lateral fields, the profile of open beams dose distribution at ICRU point was calculated. Dose gradient component ∇BS related to body shape, which is transversal to the beam axis, was calculated by fitting line to the dose profile for open field in the surrounding of the central axis in the distance of ± 1 cm from the axis. Linear fitting was done with the least square method. For the optimization process, resulting perpendicular dose gradient ∇PR took into account the wedged beam profile ∇PRF and body shape as well:

$$\nabla(PR) = \nabla(BS) + \nabla(PRF) \quad (5)$$

This gradient was used for calculation of the best uniform dose distribution.

3.4. Verification of optimization methods

The optimal plans were compared with plans prepared by experienced planners. Dose distributions were compared in terms of minimum and maximum doses to PTV, standard deviation in PTV, maximum doses in the femoral heads and dose–volume parameters for the rectum (volume receiving dose higher than 20%, 50%, 80% of prescribed dose). We averaged dose volume histograms (DVH) for all patients and all planners.

3.5. Reference plans and statistics

Reference plans for ten patients were prepared by 12 experienced planners who prepare more than 200 plans each year. The aim of their work was to prepare the most homogenous dose distribution in PTV using lateral fields modified with any wedge angle, while the maximum dose to the femoral heads could not exceed 50 Gy. The aim was reached by changing beam weights. The results of dose distribution homogeneity in the PTV of manual and computer software driven optimization were compared in terms of standard deviations. We also measured and compared the time required to calculate optimal weights and put results into TPS with the time required to choose beam weights by a trial and error process.

3.6. Calculations

All calculations were carried out with a free Scilab software.[28] Next, a windows based program implemented in the free Python language[29] was prepared.

4. Results

4.1. Optimization of beam weights and wedge angles

All plans created with the optimization algorithm fulfilled the maximum 50 Gy tolerance dose in the femoral heads.

In Fig. 3a we show results of the comparison between standard deviation of dose distribution in PTV achieved with the optimization algorithm (bars) and achieved by planners (horizontal line with 95% confidence interval). The mean value of standard deviation of dose distribution in the target volume for all patients and all planners was 88.1 cGy–1.4% (range 1.1–1.6%). Mean value of standard deviation achieved with the optimization algorithm was 91.7 cGy–1.4% (range 1.0–1.9%). For seven patients, there was no difference in standard deviation. For two patients, standard deviation achieved by planners was lower by 0.4% than achieved with the optimization algorithm. For one patient, the optimization method gave 0.1% better dose distribution in the target volume.

After taking into consideration the influence of patient's body shape on dose distribution, results obtained by the optimization algorithm were at least as good as those achieved by planners. Mean standard deviation for all patients was 83.8 cGy–1.3% (range 0.9–1.6%), and for planners, as said before: 88.1 cGy–1.4% (range 1.1–1.6%). In this case, for six patients we did not see any difference between standard deviation achieved with the optimization algorithm and by planners. For two patients, standard deviation achieved with the optimization algorithm was 0.1% lower than achieved by planners. For the other two patients, the difference was smaller by 0.2% in favor of the optimization algorithm. Kolmogorov–Smirnov test for normal distribution was done for dose standard deviation values obtained by planners. It showed that data did not come from normal distribution. That is why, the bootstrap method (with 10,000 resamples) was used to check if results from optimization are different (with 95% confidence interval). For five patients, no significant difference was seen. For the other 5 patients standard deviation from optimization was significantly lower than the mean std obtained by planners. Detailed results are shown in Fig. 3b.

In Fig. 4 we show DVHs for one of the femoral heads averaged for all patients and all planners. It can be seen that some of the planners decided to minimize dose in the femoral heads (planners minimum dose). That caused higher dose in the rectum. Anyway, no significant difference was obtained between

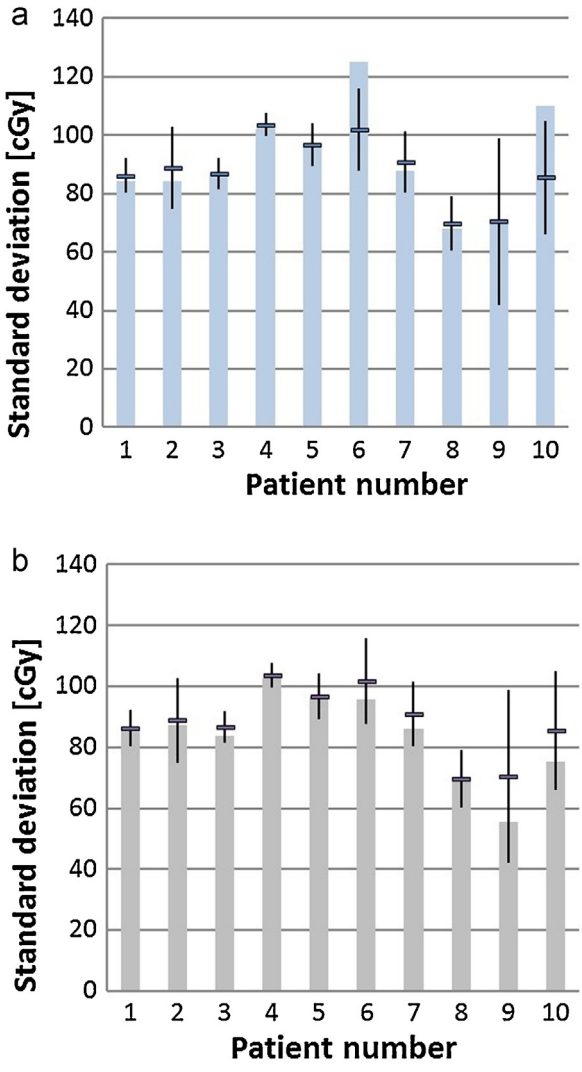

Fig. 3 – Comparison of dose standard deviation achieved with weights and wedge angles optimization algorithm (bars) and by experienced planners (mean value with two standard deviations of that mean value). (a) Standard patient body model; (b) after taking into account profiles from open beams.

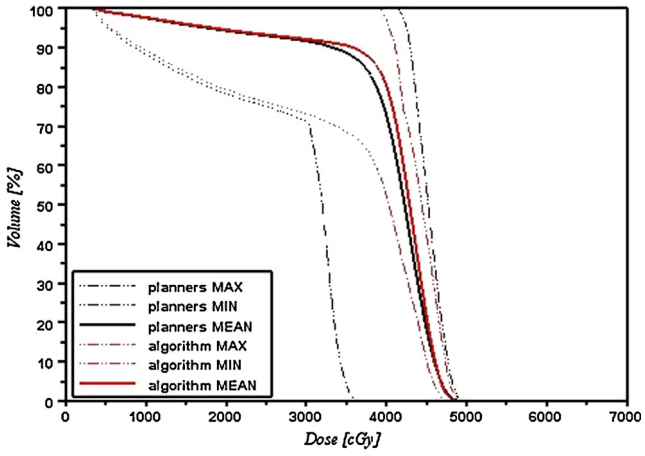

Fig. 4 – Comparison of averaged left femoral head DVH achieved with beams weights and wedge angle optimization algorithm (red) and by experienced planners (black) after taking into account profiles from open beams. In both cases minimum and maximum values of DVH are shown (dotted lines).

average results obtained with the optimization algorithm and by experienced planners.

Comparison of the rectum volume receiving dose higher than 20%, 50% and 80% of prescribed dose was done for all patients and for all planners. No significant difference between results achieved with the optimization algorithm and by experienced planners was observed.

The average time required to prepare the plan supported by the optimization method (calculate beam weights and wedge angles, and introduce them into TPS) was 0.75 min. The planners needed on average 5 min to prepare the plans.

5. Discussion

In forward 3D-CRT planning, the planner must determine several parameters of the plan. The most important of them are the number of beams and their position (for isocentric techniques, angles of beams) with respect to the target volume and sensitive structures. Modern treatment planning systems have specific tools facilitating these tasks. The position of the isocenter may be automatically defined by placing the isocenter at the center of the mass of either PTV or CTV. The shape of each beam may be defined automatically with the user's defined margin. However, to the best of our knowledge, there is no commercially available treatment planning system that supports a user in choosing the optimal wedge angles and weights in the 3D-CRT mode. In this work, using the idea proposed by Shorouse,[14] we describe the method which might be applicable for 3D-CRT treatment planning.

In our work, we analyzed the gradient in 2D space with additional equation giving a constraint for dose in the mass center of the target volume (ICRU point) and also in the femoral heads. The same wedge angle fields for both lateral fields were used. The collimator angle was always set to zero degree. The set of two equations had one unique solution, which leads to achieve the uniform dose distribution through PTV. Adding the third equation allowed to fulfill the requirements for maximum tolerance dose in the femoral heads.

Dai and Zhu[15] noticed that there is a problem in taking into account patient body shape and tissue inhomogeneity. In our work, we solved this problem in a very elegant way. We identified the influence of patients body shape on open beams profiles as an additional wedge. We showed that introducing profiles from open fields is sufficient enough.

Optimization methods based on simulated annealing tested by Oldnam[11,12] achieved standard deviation which were by 0–0.5% smaller than achieved by the planner. On average, standard deviations differed by 0.2%. In our case the difference between standard deviations obtained with the optimization method and by planners were: 0.1% and −0.1%, if body shape was taken account for. It should be stressed that Oldman et al.[11,12] in their tests with simulated annealing compared

results achieved with optimization with results achieved by one planner. Our analysis shows that results obtained by different planners are in some cases significantly different. It means that the decision how to arrange beam weights was not easy and clear. This situation was observed for patients with a body shape working as a big additional wedge. Consequently, optimization for standard patient obtained worse dose distribution than planners.

We showed, like Oldman et al.,[11,12] that using our optimization algorithm shortened planning time very much. The sevenfold reduction in planning time for weights and wedges optimization was observed. We agree with those authors that saved time can be used to more detailed CT analysis or planning higher number of patients. It should be mentioned here that for beam arrangement used in prostate case it is quite easy to find the optimal beam weighting with a trial and error method. In more complicated beam arrangements, our method might be more profitable. This will be tested in our further work.

In our opinion the optimization algorithm may be especially useful in virtual planning of palliative cases. Nowadays, the box technique is quite often used in such cases. It seems to be possible to reduce dose to the rectum with simultaneous reduction of irradiation time by introducing the three-field technique (especially while using dynamic wedges). Quantities required to run optimization can be checked on simulation machine, by selecting isocenter and checking on X-ray images the distance between the femoral heads and patient's body surface.

Oldman et al. in their work[11] on optimization methods for prostate cancer patients emphasized that the advantage of their optimization method is that it gives a possibility of achieving 3D-CRT plan with non-uniform dose distribution inside the target volume which takes effect in dose reduction in the rectum volume. This aim may be also obtained with our method by introducing small changes to Eqs. (3) and (4).

Nowadays main effort in TPS development is directed to searching optimization methods for IMRT and VMAT techniques. One cannot forget that 3D-CRT would be used in clinical practice as well, also because we do 3D-CRT plans for many palliative cases, which has not been done before. In our country, more than 40% of patients have palliative treatment. Therefore, using 3D-CRT instead of standard 2D treatment is time-restricted. Our work shows that it is possible to create very easy and effective methods of dose distribution optimization for 3D-CRT plans.

6. Conclusions

Proposed optimization algorithm allows to achieve dose distributions at least comparable with those obtained by experienced planners. Even tenfold time reduction in selecting beam weights can be achieved. Advantage of the proposed method is a small number of input parameters which are required for optimization. Our optimization algorithm can calculate beam weights without initial dose calculation on CT images.

Conflict of interest

None declared.

Financial disclosure

None declared.

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REFERENCES

1. Siegel R, Naishadham D, Jemal A. Cancer statistics: 2012. *CA Cancer J Clin* 2012;**62**:10–29.
2. Jemal A, Bray F, Center MM, Ferlay J, Ward E, Forman D. Global cancer statistics. *CA Cancer J Clin* 2011;**61**:69–90.
3. Weir HK, Thum MJ, Hankey BJ, et al. Annual report to the nation on the status of cancer, 1975–2000, featuring the uses of surveillance data for cancer prevention and control. *J Natl Cancer Inst* 2003;**95**(17):1276–99.
4. Zalefsky MJ, Fuks Z, Happersett L, et al. Clinical experience with intensity modulated radiation therapy (IMRT) in prostate cancer. *Radiother Oncol* 2000;**55**:241–9.
5. Corletto D, Iori M, Paiusco M, et al. Inverse and forward optimization of one- and two-dimensional intensity modulated radiation therapy-based treatment of concave-shaped planning target volumes: the case of prostate cancer. *Radiother Oncol* 2003;**66**:185–95.
6. De Meerleer GO, Vakaet LAML, De Gersem WRT, De Wagter C, De Naeyer B, De Neve W. Radiotherapy of prostate cancer with or without intensity modulated beams: a planning comparison. *Int J Radiat Oncol Biol Phys* 2000;**47**(3): 639–48.
7. Nutting CM, Convery DJ, Cosgrove VP, et al. Reduction of small and large bowel irradiation using an optimized intensity-modulated pelvic radiotherapy technique in patients with prostate cancer. *Int J Radiat Oncol Biol Phys* 2000;**48**(3):649–56.
8. Bedford JL, Khoo VS, Oldham M, Dearnaley DP, Webb S. A comparison of coplanar four-field techniques for conformal radiotherapy of the prostate. *Radiother Oncol* 1999;**51**: 225–35.
9. Karacetin D, Cakır A, Agaoglu F, Camlıca H, Ergen A, Dizdar Y, et al. Dose distribution in 3-dimensional conformal radiotherapy for prostate cancer: comparison of femur doses for four treatment techniques. *J Radiother Pract* 2010;**9**:41–51.
10. Fiorino C, Reni M, Cattaneo GM, Bolognesi A, Calandrino R. Comparing 3-, 4- and 6-fields techniques for conformal irradiation of prostate and seminal vesicles using dose–volume histograms. *Radiother Oncol* 1997;**44**:251–7.

11. Oldman M, Neal AJ, Webb S. The optimisation of wedge filters in radiotherapy of the prostate. *Radiother Oncol* 1995;**37**:209–20.
12. Oldman M, Neal AJ, Webb S. A comparison of conventional 'forward planning' with inverse planning for 3D radiotherapy of the prostate. *Radiother Oncol* 1995;**35**:248–62.
13. Milecki P, Piotrowski T, Dymnicka M, Malicki J, Stryczyńska G. The comparison between the three-field and four-field techniques of planning of radiotherapy in prostate cancer. *Rep Pract Oncol Radiother* 2001;**6**(1):31.
14. Scherouse GW. A mathematical basis for selection of wedge angle and orientation. *Med Phys* 1993;**20**(4):1211–8.
15. Dai J, Zhu Y. Selecting beam weight and wedge filter on the basis of dose gradient analysis. *Med Phys* 2000;**27**(8):1746–52.
16. Li JG, Boyer LA, Xing L. Clinical implementation of wedge filter optimization in three-dimensional radiotherapy treatment planning. *Radiother Oncol* 1999;**53**:257–64.
17. Ezzell GA. Genetic and geometric optimization of three-dimensional radiation therapy treatment planning. *Med Phys* 1996;**23**(3):293–305.
18. Dai J, Zhu Y. Comparison of two algorithms for determining beam weights and wedge filters. *J Appl Clin Med Phys* 2002;**3**(3):190–9.
19. Xing L, Hamilton RJ, Pelizzari C, Chen GTY. A three-dimensional algorithm for optimizing beam weights and wedge filters. *Med Phys* 1998;**25**(10):1858–65.
20. Redpath AT, Vickery BL, Wright DH. A new technique for radiotherapy planning using quadratic programming. *Phys Med Biol* 1976;**21**(5):781–91.
21. Starkschall G. A constrained least-squares optimization method for external beam radiation therapy treatment planning. *Med Phys* 1984;**11**(5):659–65.
22. McDonald SC, Rubin P. Optimization of external beam radiation therapy. *Int J Radiat Oncol Biol Phys* 1997;**2**(3/4):307–17.
23. Powlis WD, Altschuler MD, Censor Y, Buhle EL. Semi-automated radiotherapy treatment planning with a mathematical model to satisfy treatment goals. *Int J Radiat Oncol Biol Phys* 1989;**16**(1):271–6.
24. Piziorska M, Kukołowicz P, Zawadzka A, Pilichowska M, Pęczkowski P. Adaptive off-line protocol for prostate external radiotherapy with cone beam computer tomography. *Strahlenther Onkol* 2012;**188**:1003–9.
25. Gerbi BJ. A mathematical expression for %DD accurate from Co-60 to 24MV. *Med Phys* 1991;**18**(4):724–6.
26. Emami B, Lyman J, Brown A, et al. Tolerance of normal tissue to therapeutic irradiation. *Int J Radiat Oncol Biol Phys* 1991;**21**:109–22.
27. Zwicker RD, Shahabi S, Wu A, Sternick ES. Effective wedge angles for 6-MV wedges. *Med Phys* 1985;**12**(3):347–9.
28. http://www.scilab.org/
29. http://www.python.org/