Abstract

**Purpose:** To evaluate automated multicriteria optimization (MCO) – designed for intensity modulated radiation therapy (IMRT), but invoked with limited segmentation – to efficiently produce high quality 3D conformal treatment (3D-CRT) plans.

**Methods:** Ten patients previously planned with 3D-CRT were replanned with a low-segment inverse multicriteria optimized technique. The MCO-3D plans used the same number of beams, beam geometry and machine parameters of the corresponding 3D plans, but were limited to an energy of 6 MV. The MCO-3D plans were optimized using a fluence-based MCO IMRT algorithm and then, after MCO navigation, segmented with a low number of segments. The 3D and MCO-3D plans were compared by evaluating mean doses to individual organs at risk (OARs), mean doses to combined OARs, homogeneity indexes (HI), monitor units (MUs), physician preference, and qualitative assessments of planning time and plan customizability.

**Results:** The MCO-3D plans significantly reduced the OAR mean doses and monitor units while maintaining good coverage and homogeneity of target volumes. MCO allows for more streamlined plan customization. All MCO-3D plans were preferred by physicians over their corresponding 3D plans.

**Conclusion:** High quality 3D plans can be produced using IMRT optimization technology, resulting in automated field-in-field type plans with good monitor unit efficiency. Adopting this technology in a clinic could streamline treatment plan production.

**Keywords:** 3D-CRT, MCO, Pareto, optimization, IMRT, segmentation
1. Introduction

3D planning, also known as forward planning, is a standard approach for delivering conformal radiotherapy to a variety of cancers. The simplicity, low cost, low maintenance and well documented outcomes of 3D planning have made it the preferred choice for many disease sites. In 3D planning, dose distribution changes are made as a direct result of the planner manually modifying various treatment parameters such as field shapes, beam weights, beam modifiers, and dose normalization.

The 2000s saw a growing interest in intensity modulated radiation therapy (IMRT), a computer optimized method of delivering radiation [1] which modulates radiation from each field through the use of a multi-leaf collimator (MLC), permitting greater conformality and better OAR sparing. However IMRT comes with its own challenges including greater susceptibility to motion [2, 3], more complex dosimetry, potentially higher monitor units and treatment time [4], increased quality assurance (QA) complexity and greater machine wear-and-tear [5]. IMRT can cost anywhere from 1.5 to four times the amount of a 3D plan [6, 7, 8], and resistance from insurance companies to reimburse for IMRT adds to the persistence of 3D conformal therapy in clinics worldwide (e.g. [9]). Some disease sites, notably prostate and head-and-neck, have moved to IMRT planning for the majority of their cases, but many common sites such as breast and lung remain in the 3D planning realm.

Due to the manual manipulation required in 3D planning it can be time-consuming to find a desirable dose distribution. Also, once a plan is created there is no way of confirming whether the plan is fully optimized. By ‘fully optimized’ we refer to a plan where any improvement of one criteria – eg. homogeneity or OAR dose – must come at the expense of worsening another planning criteria. This requirement is known as Pareto optimality. The set of Pareto optimal plans is called the Pareto surface and exploring this surface has become a valuable technique for IMRT planning [10, 11]. MCO for IMRT allows the planner to smoothly navigate through all the generated plans by mixing individual plan fluences, allowing for a quick exploration of possible plans. Comparison studies of MCO and standard planning for IMRT have shown MCO can significantly minimize the time needed to generate a plan, while producing plans preferred by the physicians [10].

Since Pareto navigation hinges on the ability to average multiple plans, IMRT (as well as intensity modulated proton therapy) is an ideal modality since fluence maps can be averaged, which leads to the averaging of dose dis-
tributions. Because common 3D conformal sites only require a small amount of intensity modulation, we hypothesized that using fluence map based MCO and a low number of segments would allow us to use the MCO-IMRT planning technique to generate high quality 3D conformal plans. In this way, we get the best of the two worlds: the relative simplicity of 3D plans with the power of numerical optimization that comes with IMRT. Empowered by an MCO Pareto surface, the planner and physician can rapidly explore dose tradeoffs. Lastly, because we are using low segments, no physical wedges, and an efficient optimizer, we reduce MUs, retain plan robustness, reduce patient treatment time and reduce the need for patient-specific QA.

2. Methods and materials

2.1. Case selection and structure definitions

Ten recently planned patients of various disease sites (breast, brain, lung, abdomen and pelvis) were selected from our institutional clinical database. These sites were chosen to show the technique across a wide range of 3D planned areas of the body.

The original physician-drawn target volumes and OARs as well as the original dosimetrist-generated target expansion volumes were used to plan and evaluate all plans. In the MCO-3D cases additional planning structures were created to help guide the optimizer. Each MCO-3D plan contained a structure expanded from the PTV radially to the edge of the CT scan but only 4cm superiorly and inferiorly, effectively creating a wide cylindrical volume. This structure was termed ‘falloff’ and was used to promote dose conformality. Some MCO-3D plans used an additional 2-3cm wall expansion around the PTV, called ‘PTVwall’, for additionally sharpening high-dose conformality.

For the breast cases, the physician-drawn targets include only the breast contour and the seroma. For planning purposes, an artificial PTV was created by taking the breast contour and contracting it from the edge of the CT scan by 2mm. This was to prevent the optimizer from aggressively trying to deliver full dose near the patient’s skin.

For all patients we also created a structure called ‘total OAR’ which was the union of all the OARs, in order to evaluate the overall mean dose to OARs.
2.2. Planning Parameters

XiO (v4.4; Elekta, Stockholm, Sweden) was used to plan and calculate all original 3D plans. We selected recent plans from the clinical database, thus the planning strategy for the 3D conformal plans was our standard clinical procedure. RayStation (v2.5; RaySearch Laboratories, Stockholm, Sweden) was used to optimize and calculate all MCO-3D plans. The MCO-3D plans matched the original 3D plans in terms of machine (Varian or Elekta), number of beams and beam geometry. The MCO-3D plans did not use any beam modifiers (i.e. wedges), and were limited to an energy of 6 MV. All MCO-3D plans followed the original 3D plan prescription dose and fractionation schemes.

Pareto surface-based MCO uses the classical optimization paradigm of objectives and constraints. Constraints are criteria which cannot be violated while objectives are functions which are minimized or maximized subject to the constraints. All OARS were assigned a ‘minimize the equivalent uniform dose (EUD)’ objective \[12, 13\]. EUD for an organ with \(n\) equi-sized voxels, each receiving \(d_i\) dose, is given by

\[
EUD = \left( \frac{1}{n} \sum_{i} d_i^a \right)^{1/a},
\]

where \(a\) is a parameter generally chosen to be greater than or equal to 1. If \(a = 1\), the EUD is the mean dose to the organ. As \(a\) is increased, the function is weighted more heavily towards larger doses. In the limit of \(a \to \infty\), the EUD approaches the maximum dose of the organ. The EUD is a convex function which makes it appealing for optimization purposes. We use \(a = 2\) which is a standard approach to controlling both the mean dose and the hotspots.

For the falloff structure we use the ‘dose-falloff’ objective. This objective penalizes doses outside the target by specifying a desired dose falloff rate (as a function of distance to the target). Voxels which violate this dose falloff are penalized quadratically based on their deviation.

In the cases where the PTVwall structure was used, this structure was given an EUD objective with an \(a\) value ranging from 20-30 to penalize high doses. The target volume (PTV in all cases) was given both objectives and constraints. The target objectives consisted of a minimum dose objective, which is a quadratic penalty on voxel underdosage, and a uniform dose objective (the standard two-sided quadratic penalty), both at the prescription
dose. The target constraints included a dose-volume constraint of at least 95% of the volume receiving the prescription dose as well as a minimum target dose of 95% of the prescription. Lastly, a constraint was given on the falloff volume as a max dose equal to 105% of the prescription dose. This served to limit the global maximum dose of the plan.

Once the objectives and constraints are entered, RayStation computes a set of Pareto optimal plans. This begins with anchor plans, which optimize each objective individually, while respecting the constraints. Once all anchor plans are generated, RayStation creates plans where two or more objectives are simultaneously optimized. These auxiliary plans help to enrich the Pareto surface for better navigation. The total number of plans computed is a user-defined parameter. In this study we used $4N$ plans for each Pareto surface, where $N$ is the number of objectives defined. After navigation, RayStation’s direct machine parameter optimization is invoked which creates a deliverable plan. In this step the system determines MLC segment shapes and weights to best create the navigated-to dose.

2.3. Determination of number of segments

Since the IMRT module of RayStation does not support higher energies or wedges, we opted to allow the MCO-3D plans a few additional segments to allow the MCO-3D plans to compete more fairly with the standard 3D conformal plans, which utilize wedges, higher energies, and field-in-fields (FIFs). RayStation allows the planner to constrain the maximum number of segments used for the segmentation of a fluence optimized plan, and it automatically determines which beams will have additional segments, with the stipulation that each beam gets at least one segment. We determined the number of segments using the following:

1. One segment per unique beam angle in the original 3D plan
2. One segment per field-in-field used in the original 3D plan.
3. We add the number of fields using higher energies (HE) than 6 MV to the number of wedges (W) used to get “HE+W”, then add additional segments to the MCO-3D plan based on the following.
   - If the HE+W = 1-2, we add 1 additional segment
   - If the HE+W = 3-5, we add 2 additional segments
   - If the HE+W = 6+, we add 3 additional segments
2.4. Pareto surface navigation and final plan selection

Each MCO-3D plan was navigated to reduce OAR doses while meeting one of the following criteria:

- the plan met or exceeded the original 3D plan’s coverage at prescription dose
- 95% of the PTV volume received prescription dose (our clinical standard).

After navigation and segmentation, normalization (scaling) was used to achieve coverage, if necessary.

2.5. Evaluation

Once all MCO-3D plans were completed they were evaluated for clinical acceptability. We evaluated each plan by comparing individual OAR mean dose, total OAR mean dose, MU and homogeneity indexes. The homogeneity index (HI) is defined as:

\[ HI = \frac{D_5 - D_{95}}{D_p} \]

where \(D_5\) is the dose to 5% of the PTV, \(D_{95}\) is the dose to 95% of the PTV, and \(D_p\) is the prescription dose. A perfectly homogeneous PTV dose would have \(D_5\), which measures hotspots, equal to \(D_{95}\), which measures the cold spots. Therefore the best achievable value for HI is 0.

All dose computations were done with the in-use clinically commissioned systems. The original 3D plans and the MCO-3D plans were exported to MimVista (Version 6.0, Cleveland, OH) for evaluation, in order to eliminate inherent differences in DVH computations by the two planning systems.

3. Results

3.1. Case descriptions

We describe each case in terms of the site, prescription, beam energies and geometries, and techniques used in the original 3D plan. For each case we state any significant difference between the original 3D plan and the MCO-3D plan regarding OAR sparing and homogeneity. We also indicate any significant difficulties encountered in the MCO-3D planning including hotspots occurring outside of the PTV, dose streaking, and maintaining an
acceptable homogeneity index within the PTV. Dose and MU comparison data for all cases are summarized in Table 1. We selected four of the cases to display the dose distribution and DVH comparisons. We selected these to show a range of results (we did not select the cases which yielded the ‘best’ results for the MCO-3D planning, we selected a representative set).

**Brain cases**

Case 1 was a posterior fossa tumor prescribed to 20 Gy. A 4 field X-shaped beam arrangement was used. The original 3D plan utilized all 10 MV beams as well as four wedges and two FIFs. The only OARs drawn were the cochleas. The MCO-3D spared both cochleas significantly more than the original 3D plan and created a much steeper dose gradient outside the PTV. This OAR sparing came at the price of a reduction in homogeneity, with an HI of .07 compared to .03 for the original plan. The PTVwall structure was helpful in controlling hotspots outside the PTV volume.

Case 2 was a left parietal tumor prescribed to 60 Gy. A 5-field beam arrangement was used: four coplanar beams and one superior vertex beam. The original 3D plan used 6 MV for all coplanar beams and 10 MV for the superior vertex beam. Three wedges were also used. The most notable sparing observed in the MCO-3D plan were in the chiasm, R. cochlea and R. optic nerve; each of their mean doses were lowered by a factor of three. There were very small increases in mean dose for the L. optic nerve and the L. cochlea. As in brain case 1, this significant OAR sparing came at the price of a small increase in the homogeneity index, from .04 to .06. The comparison between the original 3D plan and the MCO-3D plan for brain case 2 is shown in Figure 1.

**Breast cases**

Case 1 was a right sided breast to 50 Gy. This patient had a small breast and the original 3D plan employed two open tangent 6 MV fields. The HE+W number was zero, thus the MCO-3D plan utilized only two segments total (one segment for each field). The MCO-3D plan was able to drastically improve breast coverage at prescription dose (15% increase) while simultaneously reducing lung dose. Hotspots and the global maximum were kept nearly identical to the original 3D plan. The homogeneity index was improved from .31 to .18, due to the increase in coverage without an increase in hotspots.

Case 2 was a left sided breast, also to 50 Gy, which allowed us to test our technique with a case involving the whole heart, left ventricle and left
Figure 1: Axial dose distribution and DVH comparison for brain case 2. The red arrows highlight MCO-3D pushing low dose away from critical organs.

anterior descending (LAD) artery in addition to the lung. The original 3D plan utilized two open tangents and two field-in-fields. 10 MV was used on the medial side while 6 MV was used on the lateral side. The plan’s HE+W number was two, therefore we used one additional segment beyond the original number of parent fields and FIFs, for a total of five segments. Similar to case 1, the MCO-3D demonstrated superior breast coverage while simultaneously lowering whole heart, left ventricle, LAD and lung dose. Once again, hotspots remained similar to the original 3D plan and the homogeneity index improved from .43 to .21. The plan comparison is shown in Figure 2.

Thoracic cases

Case 1, the most challenging of the ten cases, was a large lung volume with a prescription dose of 42 Gy. The GTV was very extensive and branched into many nodal chains throughout the thorax. The PTV volume was 957 cubic centimeters. The original 3D plan used five coplanar fields – one anterior and four obliques. 10 MV was used for all beams as well as four wedges. The MCO-3D reduced every OAR at the expense of a small decrease in homogeneity. The plan comparison is shown in Figure 3.
Figure 2: Axial dose distribution and DVH comparison for breast case 2.

Figure 3: Axial dose distribution and DVH comparison for thoracic case 1. The circled regions indicate areas where MCO-3D clearly sculpts the dose distribution to conform to the PTV.
Case 2 was an esophagus prescribed to 55 Gy. The original plan employed a four field posterio-lateral beam arrangement. Wedges and 10 MV beams were used on all fields, leading to seven segments total for the MCO-3D plan. The MCO-3D lowered the mean dose of every OAR although not as significantly as in thoracic Case 1. There was no significant change in homogeneity however MCO-3D did encounter difficulties with high dose building up near the skin. A 2cm inner wall contour created from the external contour was necessary to help control this.

**Abdomen cases**

Case 1 was a pancreas volume prescribed to a dose of 30 Gy. A 4-field conformal beam arrangement was used. All beams were 15 MV and three wedges were used in the original plan. The MCO-3D plan lowered the mean dose of most OARs. The small bowel and R. kidney were lowered more significantly while the spinal cord dose was increased. There was a small homogeneity index increase for the MCO-3D plan, from .06 to .07.

Case 2 was a larger pancreas volume prescribed to 45 Gy. The original 3D plan used five beam angles, with 15 MV for all beams, and two wedges. The MCO-3D significantly lowered all OAR mean doses. The homogeneity index rose from .05 to .08. Initially, some dose streaking was encountered in the MCO-3D plan. This case successfully showed MCO-3D’s ability to treat larger and deeper seated abdominal volumes.

**Pelvis cases**

Case 1 was a standard four-field box prostate fossa prescribed to 64.8 Gy. The original plan used 10 MV on all beams except the AP beam which used 6 MV. The bladder and rectum were spared very well in the MCO-3D plan. Femoral head mean doses were also lower in the MCO-3D plan. Higher lateral entrances doses occurred with the MCO-3D plan. Homogeneity indexes remained the same as the original 3D plan. The comparison between the original 3D plan and the MCO-3D plan for pelvis case 1 is shown in Figure 4.

Case 2 was a three-field bladder prescribed to 39.6 Gy. The original 3D plan used two oblique laterals and one right anterior oblique beam. 10 MV was used for all three fields and two wedges were also used. The MCO-3D plan was able to reduce the mean dose to all OARs, especially the femoral heads. No significant difficulties were encountered with the MCO-3D plan, however the homogeneity index increase in this plan was the greatest, from .05 to .09.
Table 1: Dosimetric and monitor unit (MU) comparisons for all ten patient cases. For OARS, mean dose in Gy is reported, and for the target, homogeneity index HI, as defined in the text, is reported.

| Brain 1 | ORG-3D | MCO-3D | % decrease |
|---------|--------|--------|------------|
| (Posterior) | L Cochlea | 16.66 | 11.21 | 32.7 |
| | R Cochlea | 14.39 | 10.82 | 24.8 |
| | Combined ORs | 15.68 | 11.54 | 28.6 |
| | MU | 303.6 | 208.3 | 31.1 |

| Brain 2 | ORG-3D | MCO-3D | % decrease |
|---------|--------|--------|------------|
| (L. Parietal) | L Cochlea | 7.59 | 3.19 | 57.8 |
| | R Cochlea | 5.96 | 2.57 | 56.4 |
| | Combined ORs | 11.38 | 7.85 | 30.7 |
| | MU | 318.9 | 198.2 | 37.3 |

| Breast 1 | ORG-3D | MCO-3D | % decrease |
|----------|--------|--------|------------|
| (Right) | L Lung | 5.88 | 4.19 | 29.3 |
| | MU | 180.9 | 149.9 | 16.1 |

| Breast 2 | ORG-3D | MCO-3D | % decrease |
|----------|--------|--------|------------|
| (Left) | L Lung | 6.63 | 4.33 | 35.1 |
| | Heart | 0.76 | 0.36 | 52.6 |
| | LAD | 2.65 | 1.84 | 30.7 |
| | Combined ORs | 6.2 | 3.32 | 46.4 |
| | MU | 191.9 | 102.2 | 46.3 |

| Thoracic 1 | ORG-3D | MCO-3D | % decrease |
|------------|--------|--------|------------|
| (Lung) | L Lung | 23.73 | 20.4 | 13.7 |
| | R Lung | 20.84 | 17.22 | 17.1 |
| | Total Lung - GTV | 44.57 | 37.62 | 15.5 |
| | Right | 19.1 | 14.47 | 24.1 |
| | Left | 15.3 | 11.74 | 22.1 |
| | Combined ORs | 34.4 | 26.2 | 30.9 |
| | MU | 336.7 | 259.2 | 28.3 |

| Thoracic 2 | ORG-3D | MCO-3D | % decrease |
|------------|--------|--------|------------|
| (Esophagus) | L Lung | 8.59 | 7.73 | 10.3 |
| | R Lung | 7.37 | 6.2 | 17.4 |
| | Total Lung - GTV | 16.96 | 13.93 | 18.2 |
| | Right | 10.14 | 8.87 | 17.6 |
| | Left | 5.37 | 5.57 | 4.5 |
| | Combined ORs | 16.51 | 12.44 | 24.5 |
| | MU | 406.6 | 336.9 | 17.1 |
3.2. Summary of plan comparisons: doses, MUs, physician preference, and planning

In every MCO-3D plan, the majority of OAR mean doses were lowered compared to the original 3D plan. In some cases the MCO-3D plan gave one or two OARs a greater mean dose, however this slight increase was overcome by lowering others OARs even more. In the cases where some OARs are lower while others are higher it can sometimes be difficult to evaluate whether there was an overall improvement in mean OAR dose. In order to quantify the overall reduction of mean dose to organs, we evaluated the mean dose to the total OAR structure. In each case the MCO-3D had a lower total OAR mean dose, see Table 1.

After all the MCO-3D plans were generated they were coupled with their original 3D plan and sent back to the treating physician to ask which plan they preferred. In all ten cases the physicians selected the MCO-3D plans over the original 3D plans.

On average, fewer MUs were required by the MCO-3D plans. The average MU of the original 3D plans was 313 while the average MU of the MCO-3D plans was 259, a 17% decrease. This finding defeats the long held belief that inverse planning necessarily produces greater MUs than forward 3D planning: it depends on the number of segments being used. The brain cases had the
most significant total reduction in MU, with a combined total of 284 fewer MUs for MCO-3D. The least change in MU were in the breast cases.

Treatment planning times for our MCO-3D plans were similar to traditional 3D planning (although the bulk of the MCO-3D planning time was used in computing Pareto surfaces, a process which has been improved in later versions of RayStation, with more increases expected by moving to a distributed computing environment [14]). The use of higher energy beams in MCO-3D will also help the planning time by alleviating dose streaking and improving homogeneity.

4. Discussion and Conclusions

Photon treatments are typically classified as either 3D conformal plans or IMRT plans. It is more useful for understanding treatment plan optimization to think of these modalities as lying along a continuous span of treatment possibilities, from simple to complex [15]. Although somewhat counterintuitive, IMRT treatment planning is sometimes easier than 3D conformal since numerical optimization can be used to find optimal solutions, and planning software and computation power have improved dramatically since the early days of IMRT. Considering this, we speculated that if IMRT optimization was used – in particular MCO – we might be able to derive good 3D solutions from the selected IMRT plan if that plan would naturally not require too much intensity modulation. For example, IMRT optimization applied to a spherical tumor might yield relatively flat beam profiles which could then be delivered with open 3D conformal fields. In the ten cases we examined, using the IMRT optimizer to produce 3D plans led to significant OAR sparing at the cost of a small decrease in target homogeneity, and the treating physicians unanimously preferred the MCO-3D plans to the original 3D plans.

A single treatment planning system used for both 3D conformal planning and IMRT planning would be beneficial from a training and quality assurance perspective. Fewer systems means an overall operation that is easier to monitor and less prone to error [16] [17].

While this is not the place for a full discussion of the insurance and billing differences between 3D and IMRT, which is related to the historical difficulty of planning and delivering IMRT and the fact that IMRT plans are typically quality assured (QAed) by measuring the plan dose on a phantom while 3D plans are not, we suggest that clinics who adopt the MCO-3D
method presented herein discuss considering such plans as 3D. Our view on this issue is that since there is a spectrum of plan complexity between 3D conformal and IMRT, this spectrum should be realized more fully in the clinic: a plan should be as complex as necessary to achieve a desired level of dose quality. QA procedures should be standardized, and should take the form of independent software – such as a Monte Carlo system – in order to automatically verify all plans [18, 19], thus eliminating the QA distinction between 3D and IMRT plans.

In modern clinics, IMRT has become the clinical standard for sites which most strongly benefit from being able to shape the dose distribution to avoid nearby OARs. However, all sites could benefit from some intensity modulation, which is why 3D conformal therapy has evolved to include FIFs, wedges and higher energies. These advanced technologies provide dose control similar to IMRT [20]. For all of the sites studied in this paper, IMRT has been explored [9, 21, 22, 23] and is often used, but 3D remains a common modality for treatment. One likely reason for this is that IMRT may often seem overly complex, more costly and less efficient for the treatment goals in mind. Our technique on the other hand depends on the idea that a little intensity modulation goes a long way, as brought to light by the many studies which point out the vastly diminishing returns one gets from adding more complexity (larger MU and more segments) to a plan [24, 25, 26, 27]. Our planning method allows the customizeability and dosimetric benefits of MCO-IMRT with the simple and robust delivery of 3D conformal therapy.

Acknowledgment: The authors thank Tarek Halabi, Thomas Bortfeld, and Stephen Zieminski for their valuable input during the preparation of this manuscript.

References

[1] S. Webb, The physical basis of IMRT and inverse planning, British Journal of Radiology 76 (2003) 678–689.

[2] C. Coolens, P. Evans, J. Seco, S. Webb, J. Blackall, E. Rietzel, G. Chen, The susceptibility of IMRT dose distributions to intrafraction organ
motion: An investigation into smoothing filters derived from four di-

mensional computed tomography data, International Journal of Medical

Physics and Research and Practice 33 (2006) 2809.

[3] D. Gierga, G. Chen, J. Kung, M. Betke, J. Lombardi, C. Willett, Quan-
tification of respiration-induced abdominal tumor motion and its impact
on IMRT dose distributions, Int. J. Radiation Oncology Biol. Phys. 58
(2004) 1584–1595.

[4] J. Ruben, S. Davis, C. Evans, P. Jones, F. Gagliardi, M. Haynes,
A. Hunter, The effect of intensity-modulated radiotherapy on radiation-
induced second malignancies, Int. J. Radiation Oncology Biol. Phys. 70
(2008) 1530–1536.

[5] J. Sutton, D. Kabiru, M. Neu, L. Turner, P. Balter, M. Palmer, Define
baseline levels of segments per beam for intensity-modulated radiation
therapy delivery for brain, head and neck, thoracic, abdominal, and
prostate applications, Medical Dosimetry 37 (2012) 15–19.

[6] P. Nguyen, X. Gu, S. Lipsitz, T. Choueiri, W. Choi, Y. Lei, K. Hoffman,
J. Hu, Cost implications of the rapid adoption of newer technologies for
treating prostate cancer, Journal of Clinical Oncology 29 (12) (2011)
1517–1524.

[7] J. Strauss, S. Chen, A. Dickler, K. Griem, Cost effectiveness of whole
breast IMRT for reduction of moist desquamation, J Clin Oncol 25 (2007)
17004.

[8] S. Pearson, J. Ladapo, L. Prosser, Intensity modulated radiation therapy
(IMRT) for localized prostate cancer, Institute for Clinical and Economic
Review.

[9] B. Smith, I. Pan, Y. Shih, G. Smith, J. Harris, R. Punglia, L. Pierce,
R. Jagsi, J. Hayman, S. Giordano, et al., Adoption of intensity-
modulated radiation therapy for breast cancer in the united states, Jour-
nal of the National Cancer Institute 103 (10) (2011) 798–809.

[10] D. Craft, T. Hong, H. Shih, T. Bortfeld, Improved planning time and
plan quality through multicriteria optimization for intensity-modulated
radiotherapy, Int. J. Radiation Oncology Biol. Phys. 82 (1) (2012) e83–
90.
[11] A. Fredriksson, R. Bokrantz, Deliverable navigation for multicriteria intensity-modulated radiation therapy planning by combining shared and individual apertures, Tech. rep., TRITA-MAT-2013-OS4, Department of Mathematics, Royal Institute of Technology, Stockholm, Sweden (2013).

[12] A. Niemierko, A generalized concept of equivalent uniform dose, Medical Physics 26 (1999) 1100.

[13] Q. Wu, D. Djajaputra, H. Liu, L. Dong, R. Mohan, Y. Wu, Dose sculpting with generalized equivalent uniform dose, Medical Physics 32 (5) (2005) 1387–1396.

[14] R. Bokrantz, Distributed approximation of Pareto surfaces in multicriteria radiation therapy treatment planning, Physics in Medicine and Biology 58 (11) (2013) 3501.

[15] B. Meng, L. Zhu, B. Widrow, S. Boyd, L. Xing, A unified framework for 3D radiation therapy and IMRT planning: plan optimization in the beamlet domain by constraining or regularizing the fluence map variations, Physics in Medicine and Biology 55 (22) (2010) N521.

[16] T. Nolan, System changes to improve patient safety, British Medical Journal 320 (7237) (2000) 771.

[17] N. Leveson, N. Dulac, K. Marais, J. Carroll, Moving beyond normal accidents and high reliability organizations: a systems approach to safety in complex systems, Organization Studies 30 (2-3) (2009) 227–249.

[18] W. Luo, J. Li, L. Price Jr, R. and Chen, J. Yang, J. Fan, Z. Chen, S. McNeely, X. Xu, C.-M. Ma, Monte carlo based IMRT dose verification using mlc log files and R/V outputs, Medical physics 33 (2006) 2557.

[19] A. Leal, F. Sánchez-Doblado, R. Arráns, J. Roselló, E. Pavón, J. Lagares, Routine IMRT verification by means of an automated monte carlo simulation system, International Journal of Radiation Oncology* Biology* Physics 56 (1) (2003) 58–68.
[20] B. Smith, I. Pan, Y. Shih, G. Smith, J. Harris, R. Punglia, L. Pierce, R. Jagisi, J. Hayman, S. Giordano, T. Buchholz, Adoption of intensity-modulation radiation therapy for breast cancer in the United States, Journal of the National Cancer Institute 103 (2011) 798–809.

[21] L. Fenkell, I. Kaminsky, S. Breen, S. Huang, M. Van Prooijen, J. Ringash, Dosimetric comparison of IMRT vs. 3d conformal radiotherapy in the treatment of cancer of the cervical esophagus, Radiotherapy and Oncology 89 (3) (2008) 287–291.

[22] L. Muren, R. Smaaland, O. Dahl, Conformal radiotherapy of urinary bladder cancer, Radiotherapy and Oncology 73 (3) (2004) 387–398.

[23] U. Hermanto, E. K. Frija, M. J. Lii, E. L. Chang, A. Mahajan, S. Y. Woo, Intensity-modulated radiotherapy (IMRT) and conventional three-dimensional conformal radiotherapy for high-grade gliomas: does IMRT increase the integral dose to normal brain?, Int. J. Radiation Oncology Biol. Phys. 67 (4) (2007) 1135–1144.

[24] D. Craft, P. Süss, T. Bortfeld, The tradeoff between treatment plan quality and required number of monitor units in IMRT, Int. J. Radiation Oncology Biol. Phys. 67 (5) (2007) 1596–1605.

[25] X. Sun, P. Xia, A new smoothing procedure to reduce delivery segments for static MLC-based IMRT planning, Medical Physics 31 (5) (2004) 1158–1165.

[26] S. Webb, D. Convery, P. Evans, Inverse planning with constraints to generate smoothed intensity-modulated beams, Physics in Medicine and Biology 43 (1998) 2785–2794.

[27] M. Alber, F. Nüsslin, Intensity modulated photon beams subject to a minimal surface smoothing constraint, Physics in Medicine and Biology 45 (2000) N49–N52.