Optimizing radiosurgery with photons for ocular melanoma

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1. Introduction

Linac-based radiosurgery with photons has been investigated and applied for more than twenty years [1,2]. Classical radiosurgery of ocular melanoma (OM) uses multiple conformal arcs with multi-leaf collimators prescribing to the 80% isodose line [1]. Photons have been shown to achieve adequate target coverage for treating ocular melanoma compared to protons [3,4], and acceptable to excellent clinical results have been reported for Linac-based radiosurgery [5-7]. The challenge with photons relies in achieving steep dose gradients avoiding unnecessary dose to neighbouring structures. Eye positioning for photon therapy is more complex as compared to proton therapy due to variable beam angles used. Approaches with open eye gaze fixation or forced fixation with suction-based devices may rule out specific beam field geometries and thus limit the degree of freedom to optimize the dose distribution. The most patient-convenient approach is to have the patient positioned with eyes closed without any need of medication or specific interventions, and a X-ray based positioning verification system based on tissue markers surrounding the tumor and target structure and treating patients with their eyes closed has been proposed previously [8].

Volumetric modulated arc therapy (VMAT) has been increasingly promoted in radiosurgery during the last years mostly because it can treat multiple lesions with one isocenter [9,10]. However, the combination of non-coplanar arcs with IMRT improves dose coverage and homogeneity, because it allows steep dose fall-offs by adding static IMRT [11]. Here we investigate, whether automated planning with multiple, non-coplanar modulated arcs, known as VMAT or IMAT (intensity modulated arc therapy) could result in treatment plans comparable to the quality of plans with DCA-IMRT.

2. Materials and methods

2.1. Patients

For this retrospective treatment planning comparison, patients who were selected to generate the AP model for the prediction of dose volume constraints.
treated between 2014 and 2016 for curative radiotherapy of ocular, non-metastatic melanoma were enrolled. Patients were treated with a dose fractionation of $5 \times 10 \text{ Gy}$ on five consecutive days. All patients included into this study have given their approval to use their data for scientific research, and all were treated with the Hybrid-Arc™ technique. Prior to radiotherapy planning, three ophthalmological tantalum markers (Altomed Ltd., Boldon, UK) were attached on the sclera surrounding the tumor. A fourth marker was sutured to the opposite half of the bulb. Magnetic resonance imaging (MRI) and a planning computer tomography (CT) were obtained and fused images served for target volume definition. The gross tumor volume (GTV) was outlined on the MRI obtained after placement of the peritumoral fiducial markers and verified on the CT images. The margins to obtain the planning target volume (PTV) were two mm in general and occasionally three mm in the direction of the vitreous body or in direction of retinal detachment.

The treated plans for DCA-IMRT were manually optimized for a photon linear accelerator (Novalis-TrueBeam™, BrainLab and Varian Medical Systems) with a dynamic high-definition multi-leaf collimator. The dose was normalized to the mean value of the PTV. Clinically accepted and delivered treatment plans served as reference in this study. All treatment plans were verified with the physician before treatment. During treatment image-guidance by means of the ExacTrac™ 6.0.6 and Robotics® 2.0 (BrainLab, Feldkirchen, Germany) was used, positioning was verified prior to each beam or arc fraction. Tantalum markers were used for the positioning verification. The daily energy dose fractions of flattening filter free (FFF) 5.6 MeV photons were delivered by the frameless BrainLab® radiosurgery system.

Fig. 1. Isodoses of DCA-IMRT (a,b,c) and VMAT (d,e,f) of a representative case. Axial (a and d), coronal (b and e), and sagittal planes (c and f). Scale as in Fig. 1a applies to all images, showing dose ranging from 20 to 52 Gy.
2.2. Planning of multiple conformal arcs with IMRT and beam geometry

All patients treated for ocular non-metastatic melanoma were planned to be treated with DCA-IMRT by the module HybridArc™ (HA) of the treatment planning system iPlan® RT Dose 4.5.3 and 4.5.4 (BrainLab AG, Feldkirchen, Germany). On average, a combination of six dynamic conformal arcs, ranging from five to six, with six intensity-modulated static fields, ranging from five to eight, were used. A single isocenter for each plan was used. The beam arrangement was set in such a way that no beam went through the ipsilateral cornea or the contralateral eye. The geometry of the non-coplanar dynamic conformal arcs was manually optimized. The arc lengths ranged from 30° to 110° and the couch kick angle increments ranged from 15° to 60°. The dose contribution of the arcs to the target was approximately 70% of the prescribed dose. Subsequently, IMRT fields delivered the remaining 30% of the prescribed dose. The couch angles used for the IMRT fields were the same as those used for the dynamic conformal arcs. Thus the additional IMRT fields could be delivered “on the way” without waste of time. The IMRT fields were optimized with a maximum beamlet size of 2.0 mm in dynamic leaf sequencing. The dose calculation algorithm used was BrainLAB PencilBeam X, using a kernel resolution of 0.63 mm. One effective parameter to find a good compromise on coverage of planning target volume and sparing of organs at risk (OARs) is the percentage of IMRT dose; this value ranged from 27 to 36%.

2.3. Planning with VMAT

The plan optimization with VMAT was automated using RapidPlan™ (RP) (Varian Inc., Palo Alto, USA) with the photon optimizer version 13.6.23 and Acuros version 13.6.23 as algorithm for dose calculation. RP is a fully integrated module in the treatment planning system Eclipse, similar to the “manual” inverse optimizer module and has been previously explained [12]. Briefly, RP automates the optimization process by generating a line of objectives constraints based on the geometry of the PTV and OARs. The objectives are set just below the inferior boundary of the predicted result. Therefore the plans generated with RP are independent from the planner knowledge and the results are, in general, at least as good or better than the plans manually.

Fig. 2. Average dose volume histograms of 13 plans calculated with DCA-IMRT (dotted line) or VMAT (solid line). (a) PTV, (b) Eye without PTV, (c) ipsilateral cornea, (d) ipsilateral lens, (e) ipsilateral lacrimal gland, and (f) ipsilateral optic nerve.
optimized [12,13].

The model generated for the present study was built in a similar way as for the other validated and clinically implemented models used for disease of the brain, lung and prostate. The model created in RP was generated from 28 irradiated patients treated with DCA-IMRT, distinct from the thirteen cases used for the planning comparison, who were not included in the model in order to avoid a bias of the results. Plans optimized with RP were not included in the model. The optimization constraints used for each OARs consisted on a line of DVH objectives as well as a maximum allowed dose. These constraints were automatically generated by the system based on the predicted achievable dose distribution from the RP model. The constraints and objectives for the PTV, were predefined in the RP model. The lower and upper constraints were set between 150 and 200. The contralateral eye was given a priority of 50. The ipsilateral eye and cornea was given a maximal dose with a priority of 70 to 90. The dose to the ipsilateral lacrimal gland for D20 Gy was set at a priority of 50–70. The priority for the Dmax for the ipsilateral lens and optic nerve was set at 90–120.

All patients were planned with VMAT for Linac TrueBeam™ (Varian Inc., Palo Alto, USA), having the same specification as the one used for the optimization and treatment with HA. Six arcs with three to five couch kicks were used. The angle separation between the different couch positions was at least fifteen degrees. The beam geometry was manually set case by case in order minimize the entrance dose through an OAR. Density compensation for tantalum tissue marker density was not applied.

2.4. Plan comparison

The treatment calculation grid size for DCA-IMRT and VMAT was 1 mm for voxels within the PTV, and never exceeded 1.5 mm at opposite site of the tumor in the eye. The linac used in both institutions had similar specification (TrueBeam and Novalis STx have both a HDMLC) and the same beam energy was used (6MV). Dose volume histograms (DVHs) were calculated for the PTV and OARs of each plan. As OARs, we scored cornea, lens, lacrimal gland, optic nerve, and the entire eye, and the entire eye without the PTV. For comparison purposes, DVHs were normalized to the mean dose of the PTV (50 Gy over five fractions). Target dose distribution was evaluated according to the target coverage defined as the volume enclosed by the 95% and 107% isodose line, V95% or V107%, respectively, and dose to the critical structures, such as lenses, cornea, lacrimal glands and optic nerve were analyzed. Dose homogeneity was defined by the homogeneity index (HI) defined as HI = (D95% – D5%) / Dmean, where D5% and D95% are the dose to 5% or 95%, respectively of the target and Dmean is the mean dose to the target [14]. The conformity index (CI) was defined as CI = 1 + [V95% (NT) – V95% (PTV)] / V(PTV), where V95%, (NT) is the normal tissue volume covered by the 95% prescribed dose, V95% (PTV) is the target volume covered by 95% of the prescribed dose and V(PTV) is the target volume [15]. Statistical analysis was performed using a Wilcoxon test. A p-value of < 0.05 was accepted as significant.

The dose to the OARs was evaluated accordingly to the mean dose for all OARs, the maximal dose defined as the dose to a volume of 0.03 cm³, D0.03cm3. For the ipsilateral lacrimal gland, an addition parameter was used, the volume receiving 20 Gy, V20Gy.

An evaluation of the robustness in respect to a motion of the eye was performed. The robustness of the plan was evaluated based on the target volume covered by the 95% prescribed dose, V95%. A simulation of an eye motion resulting in a translation of the target by 2 mm in each direction: left-right, cranial-caudal and ventral-dorsal was performed. The isocenter remained at the same location, only the target was shifted in a single direction at one moment. This simulation was performed for five right-sided cases.

3. Results

3.1. Clinical aspects

Since December 2014 until August 2016, 28 consecutive patients with a mean age of 68 years with ocular melanoma were treated with fractionated radiosurgery on 5 consecutive working days with 5 × 10 Gy and served as model to establish automated planning with VMAT. After a median follow-up of seventeen months, no local relapse was observed. Enucleation was necessary in one patient due to erosive keratitis 31 months after the end of radiotherapy. Metastatic progression to the liver was seen in two patients. In one case, 20 months after radiotherapy metastatic liver disease was observed. Another patient suffered metastasis to the liver fifteen months after DCA-IMRT and was treated with hemihepatectomy. He died from postoperative infection at the age of 87 years.

3.2. PTV coverage

Beam geometries for DCA-IMRT were 5–6 dynamic conformal arcs and 5 to 8 IMRT fields. VMAT plans used 6 arcs for each case. The quality of the PTV coverage was defined by the comparison of 13 cases recalculated with VMAT and plans optimized with RP. The isodose map in axial coronal, and sagittal planes shows steeper dose fall off with DCA-IMRT compared with VMAT (Fig. 1). The average dose volume histogram is shown in Fig. 2a, showing that the target volume coverage achieved with DCA-IMRT and VMAT was similar under ICRU-criteria. Minor qualitative differences were detected. Dose exceeding 107% in 7 patients (54%) replanned with VMAT was observed. The homogeneity index (HI) for the PTV was 0.06 ranging from 0.01 to 0.13 for DCA-IMRT and 0.1 ranging from 0.05 to 0.12 for VMAT, respectively (p < 0.01). The conformity index for DCA-IMRT was 1.24 (1.05–1.77) and 1.31 (1.11–1.50) for VMAT (p = 0.25). The robustness of plans with DCA-IMRT and VMAT was analyzed for the first five right-sided cases. It was based on the effect of a target motion in one direction on the V95%. VMAT gave significant better results than DCA-IMRT when a target motion would occur in the lateral with a median V95% of 88.4% (83.5%–90.4%) vs. 81.4% (78.4%–84.9%), in caudal, 90.3% (85.7%–94.0%) vs. 85.0% (78.5%–86.3%) or dorsal direction, 89.2% (86.4%–91.5%) vs. 85.1% (79.5%–86.0%) direction (p < 0.01) by 2 mm. The median average V95% after target displacement was 83.3% (81.3%–86.2%) ± 3.4% for DCA-IMRT and 87.4% (83.5%–90.6%) for VMAT (p < 0.01) (Fig. 3).

3.3. Organs at risk

DCA-IMRT and VMAT were compared regarding dose delivered to

![Fig. 3. Analysis of robustness for DCA-IMRT and VMAT. Shift in 6 directions was analyzed. Significant differences were noticed in lateral, caudal, and dorsal direction (p < 0.05).](image-url)
neighbouring structures. Treatment was feasible within clinical accep-
table limits for DCA-IMRT and VMAT, although better dose sparing was
achieved with DCA-IMRT (Table 1). With DCA-IMRT, dose to the con-
tralateral eye was avoided, leaving dose only from scattered photons.
The dose to the contralateral eye was 0.1 Gy (0.1 Gy–0.3 Gy) for DCA-
IMRT and 1.4 Gy (0.2 Gy–1.6 Gy) for VMAT (p < 0.01). The dose de-
ivered to the ipsilateral eye was greater for VMAT than for DCA-IMRT.
On average, the dose given to the affected eye excluding the target
volume was 22.4 Gy (12.3 Gy–33.7 Gy) for DCA-IMRT and 1.4 Gy
(0.2 Gy–1.6 Gy) for VMAT (p < 0.01). The dose de-
ferred to the ipsilateral eye was greater for VMAT than for DCA-IMRT.

On the other hand, a smaller volume of the eye excluding the target
volume was 22.4 Gy (12.3 Gy–33.7 Gy) for DCA-IMRT and 1.4 Gy
(0.2 Gy–1.6 Gy) for VMAT (p < 0.01). The dose de-
ferred to the ipsilateral eye was greater for VMAT than for DCA-IMRT.

4. Discussion

Multi-leaf collimator-based stereotactic radiotherapy has been a
standard for many years for treating OM [1]. We currently offer pa-
tients stereotactic radiosurgery if brachytherapy with 131I-Ruthenium eye
applicators is not feasible or might result in suboptimal tumor dose
coverage [16]. DCA-IMRT uses dynamic conformal arcs to supply steep
dose gradients between the tumor and normal tissue and need not many
monitor units; IMRT is used to homogenize the dose distribution in the
planning target volume and reduce dose to neighbouring organs. In the
case of photon beam therapy for eye tumors, both characteristics of
dose distributions are needed, because some of the ipsilateral organs at

Abbreviations: DCA-IMRT: dynamic conformal arcs combined with multiple non-coplanar static intensity-modulated radiotherapy; VMAT = volumetric modulated arc therapy; PTV = planning target volume; V107% = volume receiving a dose of 107% or more; D0.03cm3 = dose to 0.03 cm3 of the respective organ. * Significance (p < 0.05).

| Abbreviation          | DCA-IMRT | VMAT | p-value |
|-----------------------|----------|------|---------|
| Mean dose (Gy)        |          |      |         |
| Ipsilateral optic nerve |         |      |         |
| Mean dose (Gy)        | 28.1     | 31.1 | < 0.01  |
| Contra. lacrymal gland | 24.6     | 22.0 | < 0.01  |
| Ipsilateral eye       | 22.4     | 27.2 | < 0.01  |
| Contra. lacrymal gland | 24.6     | 22.0 | < 0.01  |
| Mean dose (Gy)        | 12.5     | 14.0 | < 0.01  |
| Mean dose (Gy)        | 12.5     | 14.0 | < 0.01  |
| Mean dose (Gy)        | 12.5     | 14.0 | < 0.01  |

Table 1

Dose volume histogram parameters: comparison of DCA-IMRT and VMAT.
the implementation of optimal beam geometry will likely challenge proton therapy in the future and reassessment of the optimal modality as function of clinical presentation seems justified [6,22,23].

DCA-IMRT is an optimal treatment technique for photon beam therapy of OM. As a result, we regularly achieved excellent homogeneity and conformity indices for the planning target volumes. We observed all dose preconditions comply with ICRU report 62. If two thirds of the therapeutic dose is given by means of dynamic conformal arcs, we obtain dose gradients, which are not feasible with either conformal arcs, IMRT or VMAT alone.

Conflict of interest statement

Jerome Krayenbühl, Lothar Krause, Mrkus Wösle and Dr. Ciernik have no conflict of interests.

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