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Original research article

Volumetric Modulated Arc Therapy (VMAT) make a difference in retro-orbital irradiation treatment of patients with bilateral Graves' ophthalmopathy. Comparative analysis of dosimetric parameters from different radiation techniques

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ABSTRACT

Background: Graves' ophthalmopathy is the commonest extrathyroidal manifestation of Graves' disease. Treatment options include steroid therapy, corrective/decompressive surgery, radiation therapy or combination of these approaches.
Aim: Our purpose was to investigate if retro-orbital irradiation with Volumetric Modulated Arc Therapy (VMAT) yielded better target coverage and dose sparing to adjacent normal structures compared to 3-Dimensional Conformal Radiotherapy (3DCRT) and Lateral Opposing Conformed Fields (LOCF).
Methods: Fourteen consecutive patients diagnosed with bilateral Graves' ophthalmopathy were prospectively recruited into this study from August 2012 until August 2014. An individual VMAT, 3DCRT and LOF plan was created for each patient. Conformity Index (CI), Homogeneity Index (HI) and other dosimetric parameters of the targets and organs-at-risk (OAR) were analyzed in all 28 orbits compared between the different techniques.
Results: CI generated by VMAT was superior to that produced by 3DCRT($p < .001$) and LOF ($p < .001$). As expected, 3DCRT was also superior to LOF ($p = .007$). Regarding the OARs sparing dose (lens, globes, retina and lacrimal glands), VMAT showed a significant benefit when compared with 3DCRT and LOCF, with no differences between the two latter techniques.
Conclusions: VMAT should be preferred over 3DCRT and LOF for bilateral Graves' ophthalmopathy treatment.

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1. Background

Graves' ophthalmopathy (GO) is the commonest extrathyroidal manifestation of Graves' disease. The underlying pathogenesis is believed to be autoimmune-related leading to excessive infiltration of lymphocytes and excessive production of hydrophilic glycosaminoglycans and, subsequently, expansion of retro-orbital tissues and enlargement of extraocular muscles.[1] Treatment options include steroid therapy, corrective/decompressive surgery, radiation therapy (RT) or combination of these approaches.[2,3]

The rationale for using RT in GO is based on the modulating role of inflammatory response observed in irradiated tissues. Although RT is well tolerated and safe,[4,5] its use is rather limited in the management of benign disease due for fear of toxicity and the risk of radiation induced tumors. The use of complex techniques such as Volumetric Modulated Arc Therapy (VMAT) or intensity-modulated radiation therapy (IMRT) is increasing based on their superiority in target coverage and better radiation sparing of normal structures.[6–8] However, these have not been explored in GO.

2. Aim

The purpose of this study is to investigate if retro-orbital irradiation with VMAT produced better target coverage and dose sparing to adjacent normal structures as compared with 3-Dimensional Conformal Radiotherapy (3DCRT) and Lateral Opposing Conformed Fields (LOCF) for patients with bilateral Graves' ophthalmopathy.

3. Methods

Fourteen consecutive patients diagnosed with bilateral Graves' ophthalmopathy and treated with retro-orbital irradiation were prospectively recruited into this study between August 2012 and August 2014. Most of the patients were female without previous systemic, surgery or iodine therapy (Table 1).

Patients were immobilized by custom-made thermoplastic cast, and underwent computed tomography (CT) scan with slice thickness of 3 mm for image acquisition and target contouring. All 28 orbits were included in the study. Planning target volumes (PTV) were generated with a 2 mm concentric margin around the clinical target volume (CTV) (retro-orbital fatty spaces together with the main bulk, origins and insertions of the extra-ocular muscles of both eyes) was assessed as unique volume for both eyes.

The globes, lenses, optic nerves, optic chiasm, retina and lacrimal glands were outlined as organs at risk (OAR) for each individual orbit. The contouring and planning was generated by the Eclipse Treatment Planning System version 8.9 (Varian Medical Systems, Palo Alto, CA).

In accordance with Cardoso Study, showing similar efficacy for 20 vs. 10 Gy delivered in 10 fractions. All treatments, based on the study of Cardoso et al.[9] that have shown to be equally effective, were prescribed to a dose of 10 Gy in 10 fractions by LOCF, 3DCRT and reversely planned VMAT, for each individual patient in order to perform the statistical comparison of dosimetric parameters (Fig. 1). Wedges were used in LOCF, 3DCRT planning. Conformity Index (CI), Homogeneity Index (HI) together with dosimetric parameters, including the minimum, maximum, mean, and median dose, D05, D01 of the PTV and organs at risk (OAR) were all compared between the different techniques. Approval from local institutional review board was obtained.

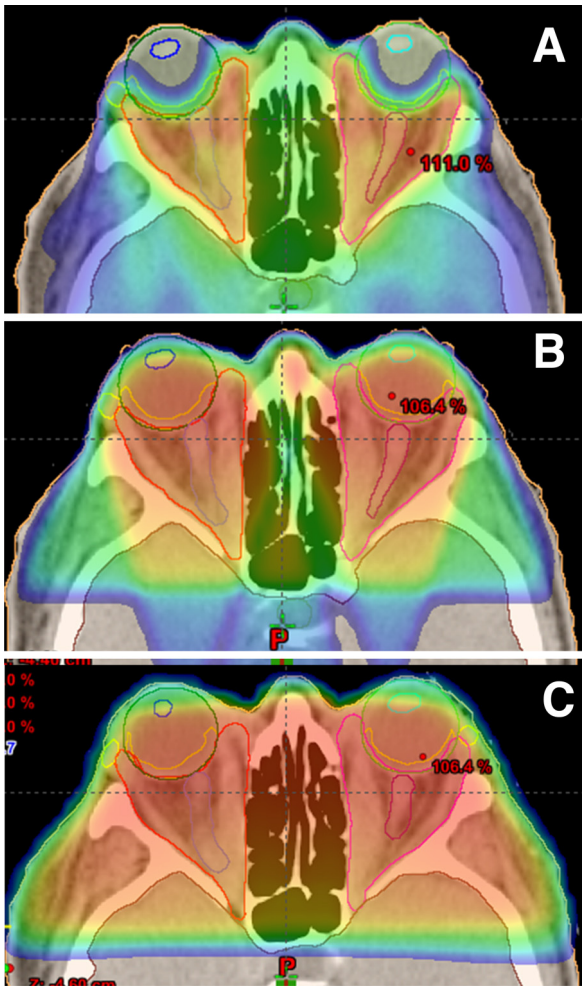

Fig. 1 – Dose distribution and target coverage by three treatment techniques. Dose distribution and target coverage by VMAT (A), 3DCRT (B) and LOF (C).

4. Statistical analysis

CI, HI and other dosimetric parameters generated by VMAT as mentioned above were compared with the other two techniques (3DCRT and LOCF) by statistical analysis. Normal distribution of values were assessed by the Kolmogorov–Smirnoff test. Those variables following normal distributions were compared using the *t*-student. A two-tailed *p*-value less than 0.05 was considered statistically significant.

Table 1 – Patient characteristics.

Patient	Age	Sex	Date of diagnosis of Graves' ophthalmopathy	Prior use of systemic steroid	Prior corrective eye operation	Prior radio-iodine therapy	Date beginning RT	Use of systemic steroid during RT	Use of anti-thyroid drugs during radiotherapy	PTV volume cc
1	73	F	1-10-2011	No	No	No	23-08-2012	Yes	Yes	37.06
2	42	F	1-04-2009	Yes	Yes	No	4-10-2012	Yes	Yes	36.6
3	74	F	1-06-2012	No	No	No	20-12-2012	No	Yes	31.6
4	65	M	1-12-2010	Yes	Yes	No	13-12-2012	Yes	Yes	31.6
5	40	F	1-04-2012	Yes	No	No	8-01-2014	No	Yes	17.8
6	59	F	1-05-2013	No	No	No	13-03-2014	Yes	Yes	39.2
7	72	F	1-06-2013	Yes	No	Yes	10-04-2014	Yes	Yes	35.3
8	46	F	1-09-2013	No	No	Yes	10-04-2014	Yes	Yes	27
9	45	F	1-06-2000	Yes	Yes	No	29-05-2014	Yes	Yes	18.4
10	47	F	9-04-2009	No	Yes	Yes	30-07-2014	Yes	Yes	40.5
11	51	F	1-01-2014	No	No	No	10-07-2014	No	Yes	20.3
12	45	F	1-01-2014	No	No	No	17-07-2014	Yes	Yes	27.9
13	37	F	1-05-14	No	No	No	30-07-2014	Yes	Yes	28.6
14	59	F	07-02-2012	Yes	No	No	30-07-2014	Yes	Yes	11.1

All statistical analyses were performed with the Statistical Packages for Social Sciences (SPSS) version 20.

5. Results

All patients completed the planned VMAT program for their Graves' ophthalmopathy treatment without interruption or acute adverse events.

5.1. *PTV coverage*

The median PTV volume of all 28 orbits was 25.27 cm^3 (range: 11.1–40.5 cm^3).

The median CI generated by VMAT was 0.79 (range: 0.55–1.93) while for 3DCRT and LOCF it was 1.4 (range: 1.42–1.90) and 1.79 (range: 0.87–2.2), respectively. Statistical comparisons confirmed that VMAT afford a significantly better CI as compared to 3DCRT ($p = 0.001$) and LOCF ($p < 0.001$). Also 3DCRT was superior to LOCF ($p = 0.007$).

The median HI generated by VMAT, 3DCRT and LOF was 1.05 (1.03–1.08), 1.08 (1.05–1.14), 1.60 (1.06–4.60) respectively, with no statistical significant differences between the three groups (Table 2).

Significant differences were also observed in other dosimetric parameters on the target tissue between the three different techniques (Table 2). Thus, when we compared the dose PTV values of VMAT vs. LOCF or 3DCRT, lower minimum ($p = 0.004$; $p = 0.040$, respectively) and higher maximum ($p < 0.001$, $p = 0.004$, respectively) were achieved, while there were no differences in the mean dose, median, D05 or D01. No significant differences were observed between 3DCRT and LOCF (Table 2).

The average monitor units (MU) consumed was greater for VMAT (268 MU), as compared to that for 3DCRT (174 MU) and LOF (120 MU) (Table 2) ($p = 0.00$; $p = 0.00$, respectively).

Comparison of PTV coverage in the right and left eye, whichever technique used were shown in Table 3. The parameters studied were superimposable to those observed when the two eyes were studied as a single PTV, with the exception of the minimum dose to the left eye PTV went out significantly in comparison to LOCF and VMAT vs. 3DCRT ($p = 0.002$; $p = 0.04$), and the mean dose comparison between LOCF and 3DCRT ($p = 0.04$).

5.2. *Organ at risk sparing*

We then compared the sparing of the OARs for the three different techniques. VMAT provided a better sparing to the globes compared with 3DCRT or LOCF for all the dosimetric parameters ($p < 0.001$) with the exception of the minimum dose that was not significantly different from LOCF. Between 3DCRT and

Table 2 – Dosimetric parameters of PTV planned by three treatment techniques.

PTV	LOCF	3DCRT	VMAT	LOCF vs. 3DCRT	LOCF vs. VMAT	3DRCT vs. VMAT
Min	8.43 (8.16–8.70)	8.15 (7.62–8.68)	7.25 (6.55–7.95)	ns	0.004	0.04
Max	10.64 (10.55–10.62)	10.65 (10.54–10.77)	10.97 (10.81–11.12)	ns	0.000	0.004
Mean	10.09 (10.03–10.15)	10.13 (110.06–10.21)	10.14 (10.04.10.24)	ns	ns	ns
Median	10.16 (10.07–10.25)	10.16 (10.08–10.24)	10.17 (10.06–10.27)	ns	ns	ns
D05	10.50 (10.42–10.58)	10.51 (10.40–10.63)	10.57 (10.43–10.70)	ns	ns	ns
D01	10.57 (10.50–10.64)	10.59 (10.47–10.71)	10.70 (10.54.10.85)	ns	ns	ns
IC	2.07 (1.68–2.45)	1.09 (1.08–1.10)	0.81 (0.59–1.04)	0.007	0.000	0.001
IH	1.10 (1.09–1.10)	1.48 (1.28–1.69)	1.10 (1.08–1.12)	ns	ns	ns
UM	11,943 (11,747–12,139)	17,379 (17,076–17,681)	26,764 (23,016–30,513)	0.000	0.000	0.000

Table 3 – Dosimetric parameters differences between right and left eye planned by three treatment techniques.

PTV Right eye	LOCF vs. 3DCRT	LOCF vs. VMAT	3DRCT vs. VMAT	PTV Left eye	LOCF vs. 3DCRT	LOCF vs. VMAT	3DRCT vs. VMAT
Min	ns	0.007	ns	Min	0.002	ns	0.04
Max	ns	0.002	0.003	Max	ns	0.001	0.003
Mean	ns	ns	ns	Mean	0.04	ns	ns
Median	ns	ns	ns	Median	ns	ns	ns
D05	ns	ns	ns	D05	ns	ns	ns
D01	ns	ns	ns	D01	ns	ns	ns

Table 4 – Dosimetric parameters of OARs planned by three treatment techniques.

	LOCF	3DCRT	VMAT	LOFT vs. 3DCRT	LOCF vs. VMAT	3DRCT vs. VMAT
R-GLOBE						
Min	2.03 (1.18–2.87)	2.82 (2.26–3.38)	1.73 (1.22–2.25)	0.003	0.003	0.000
Max	10.65 (10.57–10.72)	10.63 (10.51–1075)	10.25 (9.96–10.54)	ns	ns	0.027
Mean	8.57 (7.60–9.54)	9.22 (8.77–9.67)	6.25 (5.30–7.20)	0.030	0.030	0.000
Median	9.35 (8.16–10.53)	9.89 (9.38–10.40)	6.50 (5.23–7.77)	ns	ns	0.000
D05	10.52 (10.43–10.61)	10.58 (10.48–10.67)	9.31 (8.76–9.86)	ns	ns	0.000
D01	10.60 (10.53–10.67)	10.61 (10.50–10.72)	9.73 (9.32–10.14)	ns	ns	0.001
L-GLOBE						
Min	1.81 (1.05–2.57)	2.56 (2.17–2.96)	1.66 (1.21–2.10)	0.009	ns	0.001
Max	10.65 (10.57–10.73)	10.59 (10.46–10.72)	10.22 (9.97–10.47)	ns	0.002	0.02
Mean	8.63 (7.81– 9.46)	9.19 (8.80–9.58)	6.31 (5.53–7.09)	0.044	0.000	0.000
Median	9.47 (8.40–10.53)	9.90 (9.40–10.39)	6.43 (5.44–7.41)	ns	0.000	0.000
D05	10.56 (10.40–10.67	10.55 (10.42–10.67)	9.40 (8.98–9.82)	ns	0.000	0.000
D01	10.60 (10.50–10.71	10.58 (10.45–10.71)	9.75 (9.42–10.07	ns	0.000	0.000
R-LENS						
Min	4.03 (2.68–5.38)	5.81 (4.98–6.65)	3.47 (1.81–5.14)	0.000	0.090	0.000
Max	7.97 (6.73–9.20)	9.28 (8.80–9.77)	4.74 (1.80–5.14)	0.012	0.000	0.000
Mean	5.95 (4.47–7.43)	7.73 (7.04–8.41)	4.04 (2.31–5.77)	0.002	0.007	0.000
Median	5.94 (4.40–7.49)	7.78 (7.07–8.48)	4.03 (2.30–5.76)	0.002	0.008	0.000
D05	7.39 (6.01–8.77)	8.92 (8.37–9.47)	4.46 (2.69–6.23)	0.008	0.001	0.000
D01	7.71 (6.40–9.03)	9.12 (8.60–9.65)	4.59 (2.81–6.37)	0.010	0.001	0.000
L-LENS						
Min	3.72 (2.40–5.03)	5.80 (5.12–6.48)	3.49 (1.81–5.16)	0.001	ns	0.000
Max	7.71 (5.97–9.45)	9.03 (8.40–9.66)	4.83 (3.12–6.55)	0.032	0.001	0.000
Mean	5.71 (4.16–7.27)	7.55 (6.01–8.19)	4.13 (2.42–5.85)	0.003	0.010	0.000
Median	5.71 (4.13–7.30)	7.59 (6.94–8.24)	4.13 (2.42–5.85)	0.003	0.011	0.000
D05	7.17 (5.41–8.94)	8.67 (8.02–9.32)	4.57 (2.86–6.29)	ns	0.002	ns
D01	7.48 (5.73–9.23)	8.86 (8.20–9.53)	4.70 (2.99–6.42)	0.025	0.001	0.000
R-OPTIC NERVE						
Min	9.07(8.76–9.38)	9.46 (9.29–9.63)	9.20 (8.80–9.60)	0.005	ns	ns
Max	10.47 (10.38–10.57)	10.47 (10.33–10.61)	10.62 (10.47–10.77)	ns	ns	ns
Mean	10.02(9.95–10.09)	10.08 (9.97–10.20)	10.15 (10.05–10.26)	ns	ns	ns
Median	10.05 (9.97–10.14)	10.09 (9.98–10.21)	10.16 (10.05–10.27)	ns	.ns	ns
D05	10.39 (10.30–10.48)	10.40 (10.26–10.54)	10.47 (10.34–10.60	ns	ns	ns
D01	10.44 (10.34–10.54)	10.44 (10.30–10.58)	10.54 (10.39–10.68)	ns	ns	ns
L-OPTIC NERVE						
Min	9.22 (9.05–9.38)	9.55 (9.43–9.67)	9.32 (9.02–9.62)	0.000	ns	ns
Max	10.48 (10.37–10.60)	10.44 (10.30–10.59)	10.63 (10.39–10.86)	ns	ns	ns
Mean	10.05 (9.94–10.16)	10.09 (9.96–10.21)	10.04 (9.65–10.43)	ns	ns	ns
Median	10.10 (9.98–10.22)	10.11 (9.98–10.25)	10.21 (10.09–10.34)	ns	ns	ns
D05	10.42 (10.29–10.55)	10.38 (10.24–10.52)	10.50 (10.36–10.64)	ns	ns	ns
D01	10.46 (10.34–10.59)	10.42 (10.28–10.56)	10.57 (10.41–10.73)	ns	ns	ns
QUIASM						
Min	0.61 (−0.19 to 1.41)	3.17 (2.82–3.53)	3.90 (3.31–4.50)	0.000	0.000	0.043
Max	2.83 (1.31–4.36)	5.64 (5.11–6.18)	6.14 (5.46.6.82)	0.001	0.001	ns
Mean	1.12 (0.14–2.10)	4.48 (4.27–4.68)	4.99 (4.38–5.59)	0.000	0.000	ns
Median	1.01 (0.03–1.99)	4.64 (4.44–4.85)	4.99 (4.38–5.59)	0.000	0.000	ns
D05	2.59 (0.64–4.53)	5.11 (4.87–5.35)	5.73 (5.08–6.38)	0.015	0.004	ns
D01	2.94 (0.98–4.91)	5.38 (4.97–5.80)	5.93 (5.27–6.59)	0.018	0.008	ns

Table 4 – (*Continued*)

	LOCF	3DCRT	VMAT	LOFT vs. 3DCRT	LOCF vs. VMAT	3DRCT vs. VMAT
R-RETINA						
Min	6.97 (5.87–8.07)	7.34 (6.60–8.08)	5.24 (3.96–6.51)	ns	0.000	0.000
Max	9.89 (9.01–10.77)	10.30 (10.02–10.58)	9.47 (8.11–10.82)	ns	0.005	0.013
Mean	9.15 (8.04–10.26)	9.64 (8.96–10.32)	8.10 (6.80–9.40)	ns	0.000	0.000
Median	9.22 (8.09–10.35)	9.73 (9.04–10.43)	8.27 (6.94–9.60)	ns	0.001	0.000
D05	9.72 (8.77–10.68)	10.17 (9.80–10.55)	8.67 (7.24–10.10)	ns	0.003	0.002
D01	9.81 (8.90–10.72)	10.25 (9.94–10.56)	9.24 (7.90–10.57)	ns	0.001	0.003
L-RETINA						
Min	7.07 (5.94–8.20)	7.45 6.64–8.27)	5.45 (4.07–6.83)	ns	0.000	0.000
Max	9.88 (9.01–10.76)	10.29 (10.00–10.58)	9.39 (8.04–10.74)	ns	0.002	0.015
Mean	9.16 (8.05–10.28)	9.63 (8.95–10.32)	8.11 (6.80–9.42)	ns	0.000	0.000
Median	9.25 (8.11–10.39)	9.73 (9.03–10.42)	8.28 (6.94–9.62)	ns	0.000	0.000
D05	9.72 (8.77–10.68)	10.17 (9.78–10.55)	9.00 (7.67–10.33)	ns	0.000	0.000
D01	9.82 (8.91–10.73)	10.25 (9.92–10.57)	9.19 (7.85–10.52)	ns	0.000	0.001
R-LACRIMAL						
Min	6.17 (5.43–6.92)	5.18 (4.54–5.83)	3.71 (3.25–4.16)	0.002	0.000	0.000
Max	9.85 (9.44–10.26)	9.86 (9.61–10.12)	8.89 (8.23–9.55)	ns	0.001	0.000
Mean	8.51 (7.88–9.15)	8.18 (7.56–8.80)	6.39 (5.67–7.10)	0.040	0.000	0.000
Median	8.60 (7.90–9.30)	8.33 (7.66–9.01)	6.43 (5.60–7.26)	ns	0.000	0.000
D05	9.55 (9.08–10.01)	9.51 (9.11–9.92)	8.18 (7.46–8.91)	ns	0.000	0.000
D01	9.72 (9.28–10.16)	9.72 (9.40–10.04)	8.56 (7.86–9.27)	ns	0.001	0.000
L-LACRIMAL						
Min	5.68 (4.90–6.46)	4.49 (3.85–5.12)	4.26 (3.60–4.92	0.000	0.000	0.017
Max	9.84 (9.43–10.25)	9.62 (9.21–10.03)	8.70 (7.90–9.51)	ns	0.021	0.004
Mean	8.39 (7.86–8.91)	7.75 (6.98–8.52)	6.45 (5.65–7.25)	ns	0.000	0.000
Median	8.55 (7.99–9.11)	7.91 (7.08–8.74)	6.50 (5.62–7.39	ns	0.001	0.000
D05	9.52 (9.05–10.00)	9.26 (8.75–9.78)	8.42 (7.71–9.13)	ns	0.005	0.000
D01	9.70 (9.26–10.14)	9.49 (9.06–9.92)	8.34 (7.52–9.16)	ns	0.009	0.001

LOCF, there were only significant differences in the mean and the minimum dose.

Something similar occurred when we compared the retina. VMAT provided a better sparing in all the dosimetric parameters, with no statistical differences between the other two techniques.

Also the lens and the lacrimal gland had a better sparing with the VMAT for all the dosimetric parameters with the exception of the minimum dose that was not statistically significant against the LOCF (Table 3). It should be noted that when we compare the 3DCRT vs. LOCF the lacrimal gland showed lower minimum and mean doses with the LOCF technique; by contrast, all the dosimetric parameters in the lens were the worst with 3DCRT. These results can be explained by the fact that most anterior portions of the globes, where the lacrimal glands or lens are located, were blocked from radiation in LOCF.

There were no significant differences in the dosimetric parameters for the optic nerves between the three techniques (Table 4).

However, the situation was different when considering the sparing of the optic chiasm. The VMAT and 3DCRT techniques yielded a clear increase in the radiation dose for all the dosimetric parameters as compared to LOCF; this can be attributed to the fact that the beams directed from posterior to anterior contributed to the increased dose to the optic chiasm in contrast to the steep drop of radiation dose in that region delivered by LOF.

6. Discussion

Graves' ophthalmopathy is the most common extrathyroidal manifestation of Graves' disease. For the past 60 years, LOCF technique has been employed by radiation oncologists as a treatment of choice based on its simplicity and easiness to carry out the procedure. However, this technique is associated with obvious drawbacks, such as insufficient dose to the insertions of the extraocular muscles and the most anterior portion of the retro-orbital fat, which are commonly involved in Graves' ophthalmopathy, as well as non-homogeneous dose distribution within the target, since the anterior portion of the globes are usually blocked from the radiation portals of LOF in order to reduce the dose to the lenses.

3DCRT and IMRT were subsequently widely adopted as a current standard radiation treatment technique for head and neck and orbital tumors.[10–12] Recently, VMAT has attracted increasing attention because of its greatly improved delivery efficiency over fixed-field IMRT,[13,14] especially in those tumors which require high precision in dose administration as is the case in radiosurgery.[15–17] However, so far there has been no studies focusing on the use of VMAT for treatment of Graves' ophthalmopathy and there is only one study with IMRT used for this disease.[18]

In the present dosimetric study, we were able to demonstrate that VMAT offered a better and more conformal coverage of the PTV compared to 3DCRT and LOF and, thus,

resulted in a better CI. This would translate into a more homogeneous coverage of the PTV which would contribute to an appropriate inflammatory response in all the retro-orbital tissue.

VMAT also preserved better the adjacent normal structures when compared with 3DCRT and LOCF, due to a better dose fall off and steeper gradient. We only observed an increase of the dose in the optic chiasm when we compared VMAT and 3DCRT against the LOCF. The resultant increased dose to these structures was due to the extra dose generated by the posteriorly oriented beams in VMAT. The lack of differences in the dosimetric parameters for the optic nerves between the three techniques is due to the fact that this OAR is included in the PTV and we did not protect it, since our primary goal was to achieve an optimal coverage of the PTV and the dose administrated is too small to cause side effects.

Due to their very low critical dose for toxicity, the lenses are the only potential critical organs which might suffer from radiotherapy-induced complications, like cataract. VMAT was able to reduce doses to the lens, which reduced the risk of cataract. Whether a better target coverage achieved by VMAT may improve the clinical outcomes of patients with Graves' ophthalmopathy has to be analyzed in further trials.

7. Conclusion

Our study indicate that there is a significant benefit in terms of better target coverage and OARs sparing that support the use of VMAT for treatment of bilateral Graves's ophtalmopathy.

Conflict of interests

None declared.

Financial disclosure

None declared.

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