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LETTER TO THE EDITOR

Hyperarc VMAT Technique in the Treatment of Thyroid Ophthalmopathy

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Dear Editor,

Thyroid ophthalmopathy (TO) is one of Graves' disease's (GD) most common extrathyroidal complications. It is present in 20-25% of patients with GD at the time of diagnosis.[1] Radiological findings of extraocular muscle involvement in asymptomatic patients are observed on magnetic resonance imaging (MRI).[2] Although the underlying mechanism is not fully elucidated, it is assumed to be an autoimmune disease caused by auto-antibodies developed against similar antigens of the thyroid and orbit.[3] Orbital fibroblasts proliferate and induce an inflammatory response by stimulating the synthesis of glycosaminoglycans. Edema, pain, total/subtotal vision loss, proptosis, diplopia, periorbital edema, and compressive optic neuropathy may occur secondary to inflammation.[4]

Although the primary treatment of TO is steroids; Rituximab, Selenium, Cyclosporine, Radiotherapy (RT), and surgery are other treatment options used in cases that do not respond to primary treatment. High-dose steroid use can cause serious acute and chronic side effects such as weight gain, hypertension, immunosuppression, and Cushing's syndrome. RT can be used with or without low-dose steroids as an alternative to high-dose glucocorticoid use.[5] The main mechanisms of RT in the treatment of TO are as follows; reducing the proliferation of fibroblasts and permanently stopping the inflammatory process. Side effects that may develop due to RT are tumor formation, cataracts, and retinopathy. However, there are also studies in the literature in which these side effects are not observed.[6]

Hyperarc (HA, Varian Medical Systems) is a novel automated isocentric Volumetric Arc Therapy (VMAT) technique.[7] With this technique, stereotactic radiosurgery treatment planning in single isocentric and non-coplanar areas can be achieved with optimal dose distribution. The previous studies on the subject have shown that this technique provides successful results in stereotactic RT of single and multiple brain metastases.[8,9] After confirmation of better dose distribution with HA, the tendency to use HA in the conventional treatment of many different diseases has increased.[10] Studies have reported that the plans obtained with the HA technique are superior to other VMAT and Intensity Modulated Radiotherapy (IMRT) techniques in terms of dose gradient and low dose distribution.[8-10] There is a long survival expectancy in similar patients and long-term side effects such as secondary malignancy are important in these patient groups. Which technique is better for low-dose areas, often neglected in current guidelines, is a topic of current debate. In this study, different techniques were compared in terms of low dose distribution.

In this case report, the HyperArc planning technique, which is a technique generally preferred in stereotactic RT, was tried to be applied in benign disease, in a large RT area, and with a low dose. In this study, it was aimed to dosimetrically compare the HA treatment planning algorithm with 3D Conformal Radiotherapy (3DCRT), VMAT, and Helical IMRT techniques in the RT of a patient diagnosed with Graves' Ophthalmopathy. In addition, the patient's short-term treatment results are presented.

A 39-year-old female patient, who was followed up for 1 year due to hyperthyroidism and was using Methimazole (10 mg/day), was admitted to the hospital with eye pain in November 2020. The patient, who was

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evaluated in detail by the ophthalmology and endocrine department, was diagnosed with TO, and steroid therapy (prednol 72 mg/day) was started for treatment. In the 2nd month follow-up after steroid treatment, it was observed that eye pain continued and limitation of eye movements developed. In addition, diabetes mellitus and Cushing's disease were observed due to high-dose steroids. The dose was reduced in steroid therapy for side-effect control. The patient was evaluated in the multidisciplinary council, and it was decided to continue the treatment with RT. In orbital MRI before RT, an appearance compatible with proptosis and an increase in the bilateral retro-orbital adipose tissue thickness were observed after the contrast agent injection with edema in T2 sequences reaching 10 mm in the thickest part of the extraocular muscles (Fig. 1). Simulation computed tomography (CT) was performed on the patient with a slice thickness of 1.25 mm. Extraocular eye muscles and retrobulbar adipose tissue are contoured as the Clinical Target Volume. The lens, optic chiasma, lacrimal gland, macula, brain, pituitary gland, and hippocampus were contoured as organs at risk. Due to the patient's young age and long life expectancy, RT plans were tried with different devices and algorithms to reduce the risk of treatment-related complications.

The 3DCRT, VMAT, and HA plans were created by using the VARIAN planning system; the helical IMRT plan was obtained using the RadixAct. In treatment plans, it is aimed that 95% of the target volume receives 95% of the prescribed dose. The degree of importance of the organ at risk was reported to the medical physicist who planned the RT (1. Lens, 2. Frontal Lobe, 3. Macula, 4. Lacrimal gland) and critical organ dose comparisons were given in Table 1 and Fig. 2. The plans were compared in detail, then the patient was treated with the HA plan as it provided the most negligible OAR doses and optimal target organ dose-volume values. The target volume dose cover-

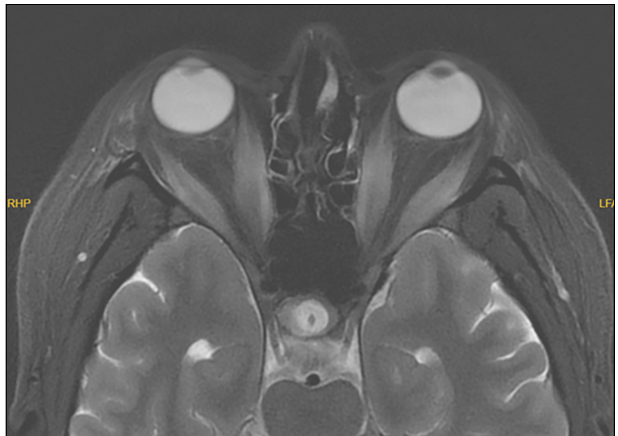

Fig. 1. Patient's pre-radiotherapy orbital MRI.
MRI: Magnetic resonance imaging; RHP: Right head-posterior; LFA: Left foot-anterior.

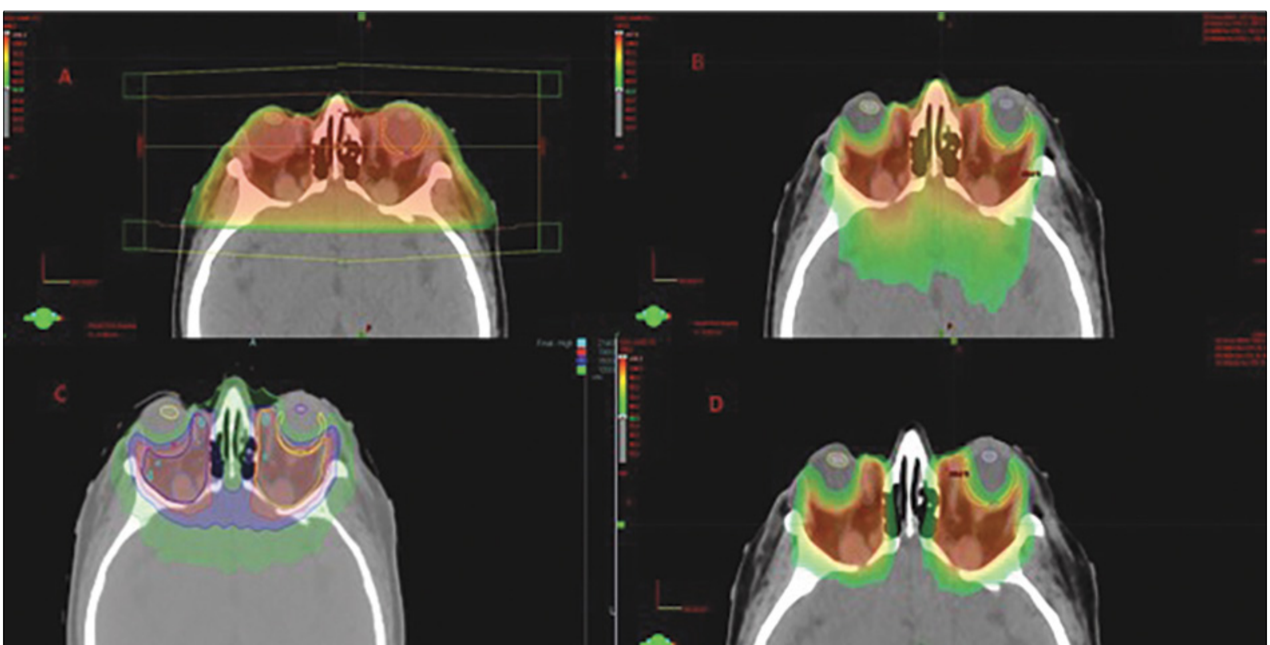

Fig. 2. Dose distribution of the patient in different planning techniques with 50% isodose line in green.
A: 3DCRT; B: VMAT; C: TOMOTHERAPY; D: HA. 3DCRT: 3D Conformal Radiotherapy; VMAT: Volumetric Arc Therapy; HA: Hyperarc.

Table 1 Dose distributions obtained in plans made with different planning techniques

Parameters	3DCRT (cGy)	VMAT (cGy)	TOMOTHERAPY (cGy)	HYPERARC (cGy)
Frontal Lobe Mean	329	280	335	398
Frontal Lobe Max	2048	2012	2074	1910
Lens L Max	2063	638	436	504
Lens L Mean	1986	416	246	334
Lens R Max	2063	636	306	478
Lens R Mean	1970	436	206	288
Lacrimal Gland L Max	2078	1968	2129	1982
Lacrimal Gland L Mean	1986	1566	1968	1456
Lacrimal Gland R Max	2076	2026	2150	2014
Lacrimal Gland R Mean	1960	1462	1848	1356
Makula R Max	2096	1826	2094	1844
Makula L Max	2106	1926	2046	1860
Retina R Max	2119	2130	2094	2136
Retina L Max	2120	2106	2111	2114
CTV R				
D98	94.7	98.4	93.6	97
D95	96.3	99.6	97.7	98.5
D2	105.0	104	107.7	104.5
CTV L				
D98	95	98	94.9	97
D95	96.5	99.6	98.3	98.5
D2	105	104.3	108.1	104.5
MU	231.7	731.1	4715,5	1043,6

3DCRT: 3D Conformal Radiotherapy; VMAT: Volumetric Arc Therapy; Max: Maximum dose; CTV: Clinical target volume; D98: Minimum dose to 98% of the target volume; D95: Minimum dose to 95% of the target volume; D2: Minimum dose to 2% of the target volume; MU: Monitor unit

age was better and the frontal lobe, macula, lens dose, and gradient index were lower in the plan performed with the HA technique compared to 3DCRT, helical IMRT, and VMAT. Although the lens dose was found to be lower in the Helical IMRT plan, because the dose coverage was low and the calculated treatment time was long, HA treatment was found to be more appropriate. During the 2-week treatment period, RT was administered with a fractional dose of 2 Gy and a total dose of 20 Gy. Pain situations were questioned at the beginning of RT, on the 6th day (mid-treatment-when a total of 10 Gy has been completed), and at the end of RT. The eye was examined to evaluate the limitation of movement. Methylprednisolone (8 mg/day) was given to the patient during the treatment. Although the patient describes a significant reduction in pain during the treatment process, there is minimal improvement in eye movement limitation. At the end of the treatment, an ocular CT scan showed a decrease in edema of the extraocular muscles (Planning CT: EOM R:7.1 cc EOM L:7.7 cc, 2nd month CT: EOM R:6.5 cc EOM L:7.1cc). In the 2nd month follow-up of the patient after RT, a decrease in eye pain and preorbital edema and a significant improvement in eye movement limitation were observed compared to pre-RT. The patient was questioned in terms of side effects, and no acute side effects were observed. Close follow-up of the patient by ophthalmology and endocrine clinics continues.

Orbital RT has been used in the treatment of TO since 1915.[11,12] In the past, irradiations were applied with the Lateral Counter-Field (LOF) technique due to its easy setup and fast application procedures. In this technique, since a block was placed in the anterior part to protect the lens, the entire target volume did not receive an effective dose, and a homogeneous dose distribution could not be achieved. In the first studies, conventional RT was used by opening two lateral areas from the anterior border of the lateral bone canthus. Cataract due to lens damage was prevented using the half beam technique (HBT).[12,13] When the HBT is used in severe proptosis cases, extraocular muscles and soft-tissue areas receive low doses, which leads to a decrease in treatment success.[14] Two lateral area

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techniques without half beam block (non-split beam technique [NSBT]) were applied as an alternative to the HBT. In NSBT, the lens and lacrimal glands were exposed to high-dose radiation.[15] With technology development, 3D-CRT, a more effective technique for better target volume coverage and preserving normal tissues, has replaced this technique. Later, IMRT emerged as an advanced RT technique that could better dose distribution in irregular and complex structures and began to take its place in orbital irradiation.[16] There are some reservations about its use in this benign disease due to RT's side effects, which are used as an alternative in cases resistant to steroid treatment. Cataracts and secondary malignancies that may occur due to RT are the main concerns. In the study of Bartalena et al.,[5] the incidence of cataracts was 10% in patients who underwent orbital RT. The prevalence of cataracts was higher, although not significantly compared with the general population. No tumors were observed in 157 patients submitted to CT scans of orbital and adjacent regions. In the study of Wakelkamp et al.,[6] when RT (29%) and glucocorticoid groups(34%) were compared, cataract development rates were found to be similar. In addition, intracranial tumors were not detected in any of the patients who received RT. In summary, although a significant increase in serious long-term adverse effects associated with RT has not been reported in the literature.

RT decision should be made with caution in patients with comorbidities that predispose to retinopathy, such as hypertension and diabetes mellitus. In our case, diabetes mellitus and hypertension developed secondary to steroid treatment. However, in the multidisciplinary council evaluation, it was decided that RT would be appropriate for the patient because it would take a long time to reach alternative treatment options. In this patient, the retina and macula were also contoured and there were no hotspots in these areas (Fig. 2). The target tissue received the effective dose and normal tissues such as the lens were below the tolerance dose.

In a recent study evaluating the results of radiotherapy using the IMRT technique in treating ophthalmopathy, Li et al.[16] reported the treatment results of 178 patients. This study reported that patients received a significant treatment response within 6 months after treatment. In cases whose symptom duration is longer than 18 months and who continue to smoke; it has been reported that RT has less treatment success. In the case series, the rate of cataracts was reported as 2.25%.

Dosimetric studies on the treatment of TO are also available in the literature. Lee et al.[17] reported the dosimetric superiority of IMRT in their dosimetric study, in which they evaluated ten patients diagnosed with TO and receiving IMRT treatment. According to their results, IMRT is significantly superior than 3DCRT and LOF and it provides better dose tolerance in the globe, lenses, and optic nerves and has a better conformity index and homogeneity index. In the study by Nguyen et al.,[18] in which seven patients were evaluated retrospectively, Tomotherapy, traditional HBT, and NSBT were compared dosimetrically. Target dose administration was better in tomotherapy; however, lens doses were higher than others. Unlike this study, the lowest lens dose was obtained with tomotherapy in our study. The reason for this is that; there is a comparison with the 3D technique in the study of Nguyen et al.;[18] in our study, different IMRT techniques were also compared. In the study by Valentine et al.,[19] HA, VMAT, and 2FPO (2-Area Parallel Opposite) techniques were compared dosimetrically in TO. They obtained better results with HA in critical organ doses, especially lens and lacrimal gland doses. In our study, it was aimed primarily to protect the lens doses. Ten Gy, the dose limitation specified in the study of Emami et al.,[20] could not be achieved only in 3DCRT among the techniques we compared.

Although the HA technique is a widely used method for stereotactic radiosurgery in brain metastases, its use has increased in other diseases as it provides better dose distributions and critical organ doses[8-10] We planned to use the HA technique to have a long life expectancy, a better treatment plan and to minimize the side effects of our patient.

Dosimetric and clinical trials using different and modern techniques for better RT plans into treatment are interesting research topics. In this case, we compared HA and other IMRT techniques with conformal RT in our clinic. In our study, frontal lobe doses were also evaluated considering the patient's age. Dose limitations were generally provided with the HA technique outside of this area. However, the clinical significance of the higher dose distribution observed in the frontal lobe is unknown.

RT is an important treatment option for the treatment of steroid-resistant TO. In the treatment of this benign disease, there is a need for dosimetric and clinical studies comparing modern RT techniques to apply the effective dose to the target area with minimum side effects.

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