Irradiation of malignant exophthalmos in the course of Graves Basedow disease

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SUMMARY

AIM: To present results of irradiation of ophthalmopathy in the course of Graves-Basedow disease performed in the Radiotherapy Laboratory in University Children's Hospital in Cracow by staff of the Oncology Clinic, Collegium Medicum Jagiellonian University (CM UJ).

MATERIAL AND METHOD: During the period of 2000–2003 therapeutic irradiation of the retrobulbar area was performed in 121 patients with malignant exophthalmos using a total dose of 20 Gy/ 10 fractions of 6 MV photonic beam in the Radiotherapy Laboratory in University Children's Hospital in Cracow. Execution of the treatment plan was controlled by in vivo dose measurements using semiconducting detectors, MOSFET type. Radiotherapy was preceded by intravenous corticosteroid therapy (Solu Medrol) with a dose of 2g/ week for 4 weeks.

RESULTS: During the irradiation treatment 9 patients (7.4%) developed an acute post-radiation reaction of transient character. Ophthalmological control examination revealed an improvement in 97 patients (80.2%) in the form of reduction or total regression of ophthalmopathy symptoms; in 21 other patients (17.3%) stabilization was noted and progression in 3 (2.5%).

CONCLUSIONS: Radiotherapy is a well-tolerated method of ophthalmopathy treatment in the course of Graves-Basedow disease. Efficacy of radiotherapy as an exclusive method of malignant exophthalmos treatment seems to be lower in comparison to irradiation combined with corticosteroid therapy.

KEY WORDS: malignant exophthalmos, radiotherapy, combined treatment

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INTRODUCTION

Radiotherapy has been for many years one of the methods used in treatment of ophthalmopathy occurring in the course of Graves-Basedow disease [1, 2]. The aim of this therapeutic procedure is first of all to inhibit disease progression and reduce or eliminate the functional impairment of the organ of sight and to improve the patient's appearance. It is significant that ophthalmopathy irradiation is accompanied by few side effects [3, 4, 5, 6, 7, 8, 9, 10].

The disease is a result of an autoimmunological process. Activated suppressor T lymphocytes infiltrate the muscles moving the eyeball which leads to their thickening. Some cytokines stimulate orbital fibroblasts to synthesise glycosaminoglycans that absorb water in the retrobulbar area [11, 12, 13, 14, 15, 16, 17, 18]. As a result of this the patient starts to develop ophthalmic symptoms involving periorbital soft tissues, eyelids, oculomotor muscles and even optic nerves [19, 20, 21].

AIM

Diagnosis of ophthalmopathy is mainly based on clinical data. The aim of ophthalmological examination is to assess the state of eyelids, conjunctivas, exophthalmos, oculomotor muscle dysfunction, cornea and visual acuity [22, 23, 24]. In the case of euthyreosis an imaging examination of orbital regions (computed tomography – CT, magnetic resonance – MR) is performed to find the cause of ophthalmic symptoms [25, 26, 27, 28, 29, 30, 31, 32, 33].

MATERIAL AND METHOD

Patients with infiltrative ophthalmopathy in the course of Graves-Basedow disease are qualified in our centre for irradiation treatment according to the following criteria:

1) euthyreosis assessed on the basis of TSH, T3, T4, FT4 levels,

2) qualification for therapy by a consulting ophthalmologist, i.e. ophthalmic symptoms according to the Werner modified scale correspond at least to 3c class [34, 35],

3) CT of the orbits shows characteristic features of Graves-Basedow disease (thickening of straight muscles in both orbits which may be accompanied by increased fat tissue, damaged optic nerve and enlargement of the lacrimal gland),

4) patient's consent to proposed treatment.

Patients were initially treated with glucocorticosteroids (Solu Medrol) administered intravenously – 2g per week for 4 weeks in the Endocrinology Clinic CM UJ. Ambulatory irradiation of retrobulbar areas was performed in the Radiotherapy Laboratory in University Children's Hospital in Cracow by staff of the Oncology Clinic, CM UJ. Overall during the period from January 2000 to December 2003 121 patients were irradiated (91 women – 75.2% and 30 men – 24.8%). Mean age was 55.1 (age range: 32 – 85).

Before the treatment initiation an individual plexiglass mask was created for all the patients which allowed the limits of irradiation fields to be reconstructed. CT examination of the orbits was performed in all the patients for therapy planning purposes. Due to the need to precisely define the distance between irradiation field margins and lenses, the distance between tomography layers was 3 mm. Irradiation technique was based on exposing the retrobulbar area to the effect of two opposite, isocentric beams which would create one, common (flat) line from the lens direction (Fig. 1) [36, 37]. The area of extraorbital structures was protected by shields made of Wood's alloy. Dimensions of the irradiation field were within limits of 4 cm x 5 cm. To irradiate the retrobulbar areas a photon beam (energy of 6 MV) emitted by a Mevatron Primus accelerator was used. Planned dosage of radiation was 20 Gy applied in 10 fractions. The schedule of ophthalmopathy was arranged in the treatment planning system. Each patient had a planning tumour volume (PTV) area projected (left PTV and right PTV containing retrobulbar area together with peribulbar muscles and critical organs, i.e. lenses and eyeballs). Evaluation of dose distribution in the treated area and critical organs was possible as a result of the use of dose volume histograms (DVH) from the treatment planning system (Fig. 2). Execution of the treatment plan was controlled by in vivo measurements of doses using semiconducting, MOSFET type detectors. Dosage was controlled once during

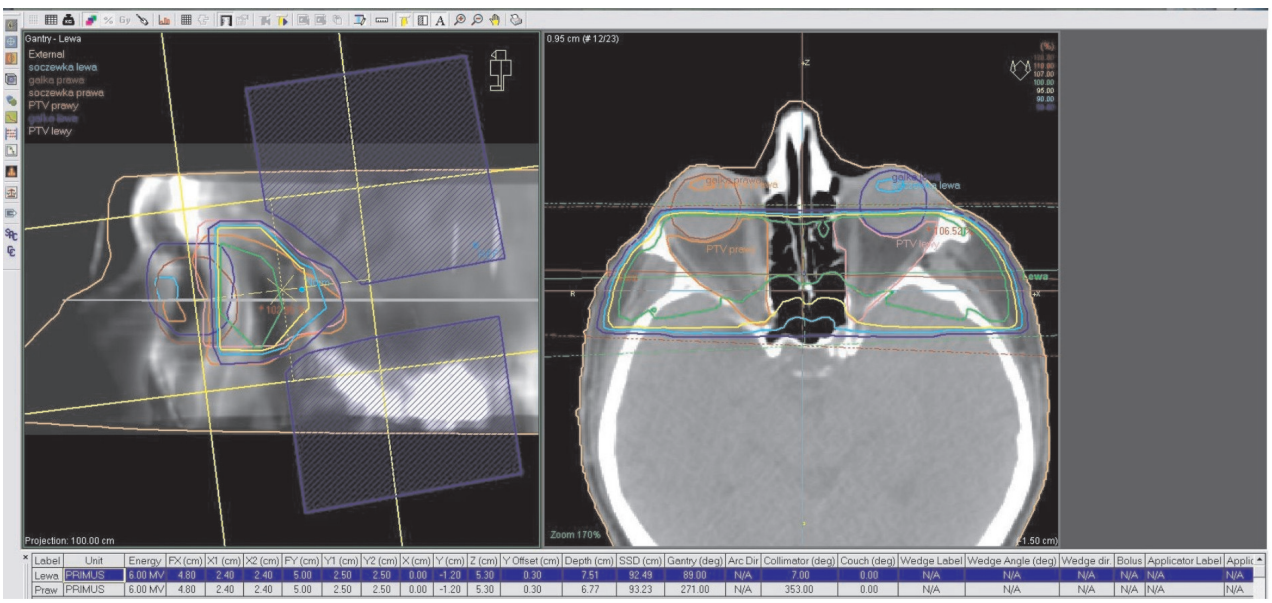

Fig. 1. System of beams and dose distribution durring irradiation of the retrobullar area in Graves Basedow disease

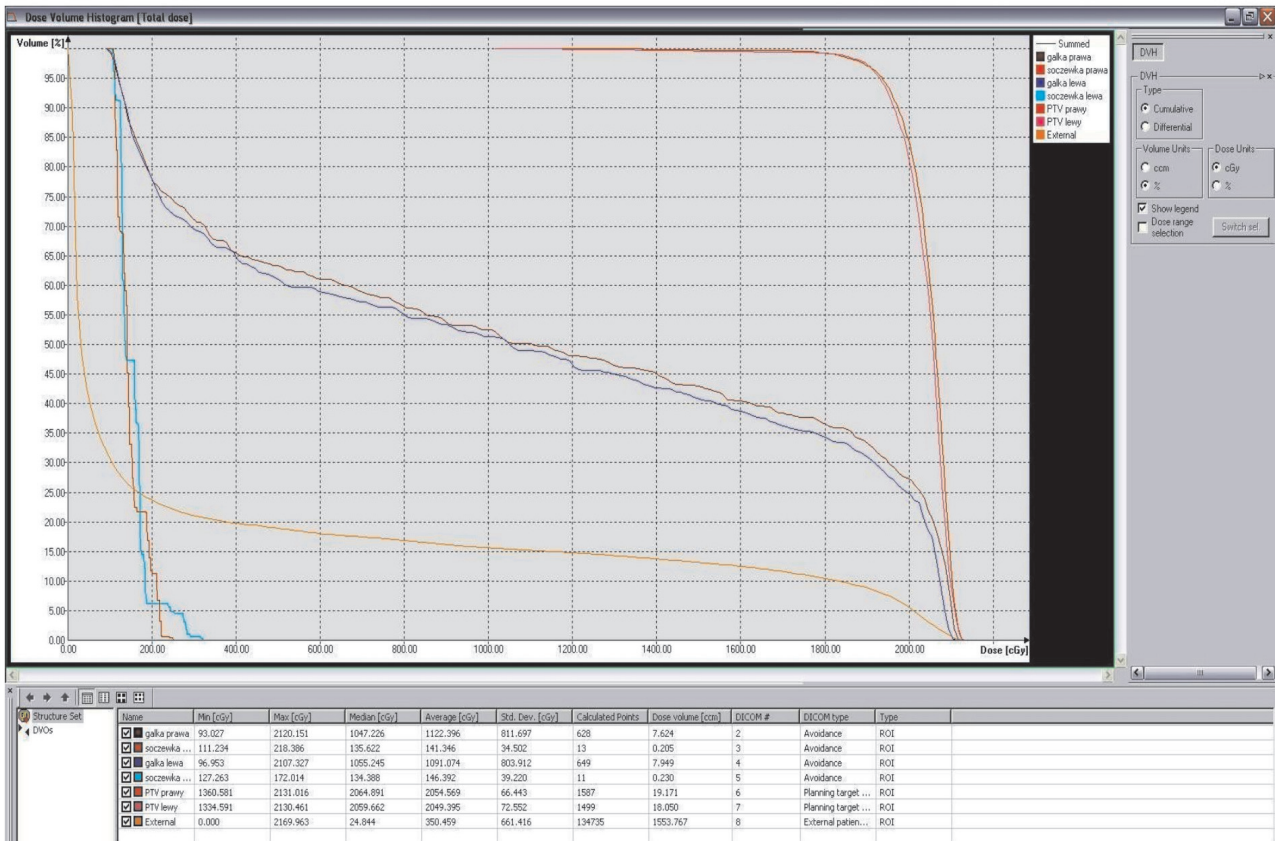

Fig. 2. Histogram obtained from the treatment planning system during irradiation of the retrobullar area in Graves Basedow disease

the treatment. Detectors were placed under the patient's mask on the left and right eyelid and on the mask in the middle of irradiated fields. The detected dose was compared to the planned dose read from the treatment planning system. Control of treatment quality was also performed by comparing portal images (created in every patient beginning irradiation treatment) to images from the treatment planning system.

RESULTS

From among 121 patients treated 11 (9.1%) did not receive a planned treatment dosage. One patient (0.8%) irradiated up to the dose of 14 Gy/ 7 fractions did not report for further therapy. In 5 patients (4.1%) a dose of 16 Gy/ 8 fractions was used and in another 5 (4.1%) a dose of 18 Gy/ 9 fractions (from the total, 6 were due to prolonged device malfunction and 4 quitted treatment).

9 patients (7.4%) developed during the irradiation treatment an acute post-radiation reaction. 3 patients (2.5%) experienced intensified lacrimation and swelling of the eyelids (one of the patients suffered from double vision as well), 2 (1.6%) had a slight skin erythema in areas subjected to high doses, 1 (0.8%) had intensified lacrimation and deterioration of visual acuity, in 1 (0.8%) patient erythema was accompanied by a burning sensation of the eyeballs, in 1 (0.8%) slight lacrimation occurred and in another 1 (0.8%) intensified double vision and deterioration of visual acuity were present. Symptoms mentioned above were of transient character.

During the radiotherapy 10 patients (8.3%) reported improvement of local state (4 – increased movement range of eyeballs, 3 – decreased exophthalmos, 2 – regression of diplopia and lacrimation and 1 – reduction of eyeball pain).

In a control ophthalmological examination performed at 3, 6 and 12 months after irradiation, stabilization was noted in 21 patients (17.3%) and progression in 3 (2.5%). A further 97 patients (80.2%) presented improvement in the form of reduction or total regression of ophthalmopathy symptoms.

As a result of DVH (dose volume histograms) use from the treatment planning system it was possible to check the dose distribution in the treated area and critical organs. It is presented in Table 1.

Table 1 analysis shows that the mean dose in the PTV area was: left PTV – 19.99 Gy and right PTV – 19.94 Gy. Taking into consideration a dose which was planned for all the patients, it was possible to conclude that the left lens received a mean dose of 1.38 Gy and the right lens a mean dose of 1.34 Gy. The dose which is allowed for a lens is within the range of 6 – 8 Gy.

Analysis of dosimetric, in vivo measurements shows that the mean dose calculated for 10 fractions of irradiation and measured by detectors placed on the eyelids was 0.7 Gy. The difference between the dose planned for lenses and the one achieved in measurements in vivo results from the fact that detectors are placed on the surface of the patient's eyelids.

DISCUSSION

The course of Graves-Basedow disease and coexistent ophthalmopathy is very variable. Even after several years of stabilization a recurrence of the disease is often observed [1, 38, 39]. The majority of patients experiences a spontaneous, idiopathic improvement [1, 38, 40].

Corticosteroids and irradiation of retrobulbar areas are still important elements of treatment, blocking local inflammatory reaction and stabilizing the disease process [41]. These methods lead to a reduction of existing symptoms in only 40-70% [42]. Therefore surgical treatment is often required [33, 41, 43, 45].

The aim of radiotherapy in the course of Graves-Basedow disease is to eliminate radiosensitive lymphocytic infiltrations of eyeball muscles and fibroblasts while preserving normal functions and anatomical structures localized inside the orbital cavity [21, 46]. Efficacy of radiotherapy as an exclusive method of ophthalmopathy treatment in the course of Graves-Basedow disease is about 55-60% [47, 48, 49]. According to various data total improvement is between 44% and 93% [2].

At least two clinical control trials prove that combining high-dose corticotherapy with irradiation treatment is most effective in treatment of malignant exophthalmos [1, 50, 51, 52]. Corticosteroids can reduce the side effects of radiotherapy while radiotherapy reduces the frequency of relapses after steroid therapy [1, 18, 53].

Current indications for ophthalmopathy treatment with irradiation in the course of Graves-Basedow disease are: steroid-resistant exophthalmos, contraindications to steroid use, uncontrolled or progressing side effects during use of small steroid doses, progression of ophthalmic symptoms after surgical orbit decompression, and nagging symptoms from soft, peribulbar tissues [2, 38, 39, 40, 41]. Radiotherapy should be used in patients older than 35, in a state of euthyreosis and with short

Table 1. Dosage in areas (PTV, lenses, eyeballs) during the whole therapy in a group of 121 patients subjected to radiotherapy (10 fractions per 2 Gy)

areas	dose[cGy]	
	maximal	mean
Left PTV	2096	1999
Right PTV	2099	1994
Left lens	138	110
Right lens	134	113
Left eyeball	2010	998.2
Right eyeball	2023	988.5

duration of symptoms (<6 months; according to other authors <18 months) [2, 4, 24, 34, 42, 43, 44]. In the case of ophthalmopathy in one eye (10% of cases in general) both retrobulbar areas should be irradiated [2]. It is not recommended to use radiotherapy for cosmetic reasons, in patients previously irradiated, in case of isolated exophthalmos or isolated dysfunction of oculomotor muscles with no signs of inflammation, spontaneous remission and in the case of diabetic retinopathy and other forms of diseases involving microvessels [2, 41]. In such situations surgery constitutes an elective treatment. Diabetes mellitus is a controversial contraindication to radiotherapy of the retrobulbar areas as it may increase the risk of retinopathy induced by radiotherapy [45, 46]. Other authors believe that diabetes mellitus is an indication for irradiation because a patient with diabetes mellitus is not a good candidate for steroid therapy or surgical methods [2].

The efficacy of radiotherapy depends on factors such as: duration of symptoms (>6–12 months), male gender, coexistent hyperthyroidism, and smoking. Their presence reduces the effects of therapy [24, 49, 65, 66, 67, 68]. Response to treatment occurs within the first 6 months after the end of therapy but an improvement may appear later [69, 70]. The most susceptible to radiotherapy are soft, periorbital tissues and oculomotor muscles. The percentage of responses is 50% to 80% [3, 7, 47, 71, 72, 73, 74, 75, 76, 77].

Improvement of cornea damage and vision impairment reaches 71–75% [5, 71]. Radiotherapy does not significantly reduce exophthalmos or movement impairment of eyeballs [44, 49, 76, 77, 79, 80, 81, 82, 83, 84].

Radiotherapy of the retrobulbar areas is generally believed to be a safe and well-tolerated treatment [3, 4, 5, 6, 7, 8, 9, 10, 44, 48, 56, 69, 85]. In the discussed material an acute post-radiation reaction was present in 11/121 (9.1%) and was of transient character. Complications of irradiating the retrobulbar areas present in the literature, including erythema of the eyelids, swelling of periorbital tissues and conjunctivas, headaches, loss of hair, and blurred vision, were also transient and mild [45, 59]. Late complications of irradiating retrobulbar areas are: retinopathy, neoplasms induced by irradiation and cataract [86, 87, 88, 89, 90, 91, 92]. 3 cases (2.5%) of cataract were reported after irradiation in the presented material and they were related to the physiological aging process rather than to radiotherapy. Cataract was diagnosed before beginning irradiation of malignant exophthalmos in patients older than 60. No diabetic retinopathy was noted in the group of patients with diabetes mellitus after combined therapy (9.9%). Secondary malignant neoplasms of a previously irradiated area were not detected either.

Treatment of malignant exophthalmos is not fully satisfactory so far, so new methods of therapy are being researched. Great expectations are connected with the use of cytokine antagonists, especially pentoxifylline, somatostatin analogues and colchicine. Trials related to these drugs are so far experimental [1, 11, 18, 44, 45, 93].

Currently the majority of centres point to a combination of glucocorticosteroids with irradiation as the best form of treatment [94, 95].

CONCLUSIONS

1. Radiotherapy is a well tolerated method of ophthalmopathy treatment in the course of Graves-Basedow disease.

2. The efficacy of radiotherapy as an exclusive method of malignant exophthalmos treatment seems to be lower than that of irradiation combined with corticosteroid treatment.

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