Clinical study of the radiotherapy with EDGE accelerator in the treatment of the moderate and severe thyroid associated ophthalmopathy

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Abstract. – OBJECTIVE: To explore the short-term efficacy, acute complications and response factors after the radiotherapy with EDGE accelerator in patients with moderate and severe thyroid-associated ophthalmopathy (TAO).

PATIENTS AND METHODS: A total of 68 patients with moderate and severe TAO who received the radiotherapy with EDGE accelerator between August 1st, 2017 and May 1st, 2011 were enrolled in the present study. The clinical data were collected, and the efficacy and acute complications were followed up, and the response factors were analyzed.

RESULTS: Sixty-eight patients (136 eyes) were followed up for 6 months after radiotherapy. The total score after radiotherapy was significantly lower compared to that before the therapy (p<0.05), and the effective rate was 75.74%. After the radiotherapy, the patient's exophthalmia, soft tissue involvement, eye external muscle involvement, corneal involvement, decreased vision and diplopia, tearing and eyelid pain have improved. Acute complications included increased local inflammation, hair loss, pigmentation and xerophthalmias. In addition, multivariate logistic regression analysis demonstrated that thyroid hormone level was the independent factor for the response to the radiotherapy.

CONCLUSIONS: For patients with moderate and severe TAO, radiotherapy with EDGE accelerator is a safe and effective treatment option. Maintaining normal thyroid hormone level can improve the effective rate of radiotherapy.

Key Words

Thyroid-associated ophthalmopathy, Radiotherapy, EDGE IMRT.

Abbreviations

TAO: Thyroid Associated Ophthalmopathy; IMRT: Intensity-Modulated Radiation Therapy; SBRT: Stereotactic Body Radiation Therapy; CTV: Clinical Target Volume; PTV: Planning Target Volume; EOMs: Extraocular muscles; MRI: Magnetic Resonance Imaging; VMAT: Volumetric Modulated Arc Therapy; SABR: Stereotactic Ablative Body Radiosurgery; GO: Graves' Orbitopathy; 3D-CRT: 3-Dimension Conformal Radiation Therapy.

Introduction

Thyroid-associated ophthalmopathy (TAO) is an eye disease closely related to autoimmune thyroid disease[1]. The main clinical symptoms include soft tissue swelling, proptosis, diplopia, tearing, corneal ulcer, etc. Serious optic neuropathy can lead to visual impairment and even blindness. The current pathogenesis is still unclear, and there is no effective treatment, especially for patients with moderate and severe TAO[2]. Radiotherapy, which has been used clinically for decades, is an important treatment approach. With the continuous development and advancement of accelerator and radiotherapy technologies, radiotherapy technology for TAO is constantly being updated[3]. Intensity-modulated radiation therapy (IMRT) has been used in clinical practice with good therapeutic effect and few complications[4]. Currently, the most advanced new linear accelerator EDGE is being widely used in Stereotactic Body Radiation Therapy (SBRT) technology for lung cancer, prostate cancer and vertebral tumors with very good results[5]. This accelerator is characterized by a treatment tolerance of less than 1.5 mm. However, this approach has been rarely reported for IMRT technology in the treatment of TAO. Since 2008, at our hospital, EDGE was used to treat more than 100 patients with TAO. In the present study, we screened 68 patients and analyzed the short-term efficacy, acute complication and response of EDGE in patients with TAO.

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Patients and Methods

Patients

The patients were all diagnosed as moderate and severe TAO at the Department of Ophthalmology, West China Hospital of Sichuan University (Sichuan, China) between August 1st, 2017 and May 1st, 2011. They all received radiotherapy with EDGE accelerator, and were able to provide relevant clinical data. This study was approved by the Ethics Committee of West China Hospital of Sichuan University, and the patients and their families signed informed consents. Exclusion criteria were the following: loss to follow-up, single-eye irradiation, received other radiotherapy for TAO or decompressive surgery before enrollment. A total of 68 patients (136 eyes) were enrolled in the study, including 32 male and 36 female patients. The median age was 50 years.

Treatment Methods

All patients were placed in a supine position with hands by the side of the body. Their head, neck and shoulder were fixed with thermoplastic mold on the CT simulator bed (Siemens Healthineers, New York, USA). After the hot mold cooled down, the bilateral balls were placed (the treatment grating is within 1.5cm after the external hemorrhoids) at the midline of the body. The intersection was marked as the origin of the treatment center. The patients underwent a CT scan where slice sickness was 3 mm, and the scanning range was from cranial to subclavian. The scanned image was transmitted to the Eclipse planning system.

The clinician contoured the clinical target volume (CTV), including the Extraocular muscles (EOMs) and the retro-orbital fatty spaces. A 2 mm concentric margin around the CTV area was generated as planning target volume (PTV). Lenses, globes and optic nerves were outlined as organs-at-risk (OAR). All the patients received a total dose of 21.2 Gy in 10 fractions within two weeks[6]. The physicist who used Varian's EDGE accelerator model on the Eclipse planning system (60 pairs of multi-leaf collimators, with 32 pairs of blades with a width of 2.5 mm and a balance of 5 mm, with a maximum of 40 cm x 22 cm) designed the reversely planned 7- filed IMRT. The field angles were 240, 280, 320, 0, 40, 80, 120°, and all the plan used 6MV X-rays (Figure 1).

Evaluation Methods

Due to the limitations of the NOSPECS system[7], we used a more comprehensive TAO symptom evaluation system to estimate overall efficacy, which besides the eye disease index, included three important clinical symptoms: diplopia, orbital pain and tearing, that affect the quality of the patient's life. Each symptom, except for the tearing, was assigned with a score of 0, 1, 2, or 3 representing no symptoms, mild symptoms, moderate symptoms, and severe symptoms, respectively. Tearing was allocated with a score of 0 (no tearing) or 1 (tearing). The total score was 22 points. We compared the scores before and after the radiotherapy. Overall efficacy was based on the score difference between pre-radiotherapy score and after- radiotherapy score, which

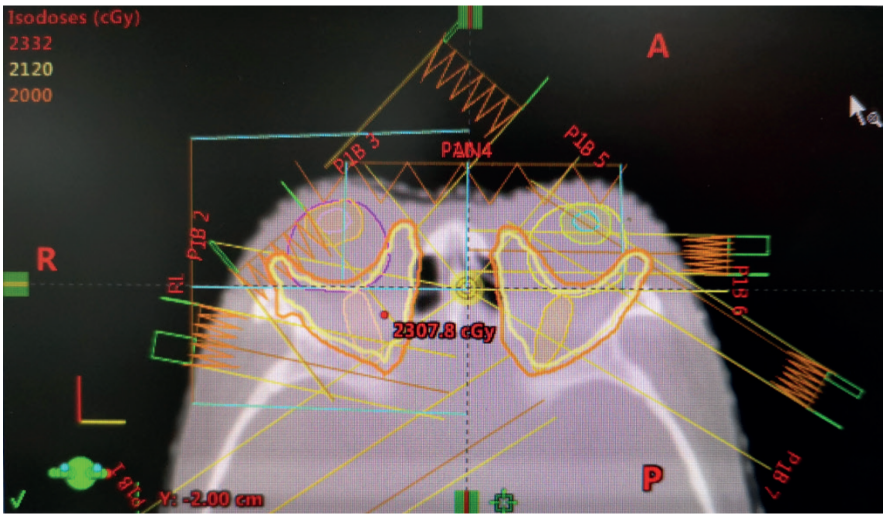

Figure 1. Planned dose and field distribution of radiotherapy.

was calculated as [(pre-radiotherapy score - after- radiotherapy score)/pre-radiotherapy score], and categorized as follows: > 66% – significant response, 33% to 66% – moderate response, 10% to 33% – mild response, and <10% – no response[8].

Furthermore, we compared the scores of each symptom and evaluated the changes in the absolute values of exophthalmos on the Magnetic Resonance Imaging (MRI, Siemens Healthineers, New York, USA), before and after treatment[9]. Acute complications were evaluated, including increased local inflammation, hair loss, hyperpigmentation and xerophthalmia, as well as the incidence, severity, and mitigation of the symptoms. Univariate analyses were performed to evaluate the influence of age, gender, smoking, duration of TAO, thyroid hormone level for the response to the radiotherapy, while multivariate regression analysis was used to determine the efficacy of each independent factor.

Statistical Analysis

The statistical analysis was performed using SPSS Statistics version 21 (SPSS Inc., Chicago, IL, USA). Wilcoxon rank sum test was used to compare the overall scores and the scores of each symptom before and after radiotherapy. Paired *t*-test was used to compare the absolute values of exophthalmos before and after radiotherapy. We calculated the effective rate of radiotherapy in each symptom, the incidence of adverse reactions, and we used a chi-square test to determine the response factors. Multivariate logistic regression analysis was performed to determine the independent factors response. All the statistical analyses were considered significant at two-tailed $p<0.05$.

Results

Overall Efficacy

We measured the sores based on the patient's proptosis, soft tissue involvement, EOMs involvement, corneal involvement, sight loss, diplopia, tearing and orbital pain. Before the radiotherapy, the average score was 8.46 (3-14), and after the treatment it was 5.43 (1-12), which indicated that the latter was significantly lower than the former one ($p<0.05$). The effective rate was 75.74%; the significant effective rate was 10.29%; the moderate effective rate was 48.53%; the mildly effective rate was 16.91%, and no response was 24.26% (Figure 2). The scores of proptosis, soft tissue involvement, EOMs involvement, corneal involvement, sight loss, diplopia, tearing and orbital pain were significantly lower after radiotherapy ($p<0.05$; Table I).

The Effective Rate of Each Symptom

The symptoms of proptosis, soft tissue involvement, EOMs involvement, corneal involvement, sight loss, diplopia, tearing and orbital pain were all improved. The effective rates are shown in Figure 3.

Exophthalmos

The absolute exophthalmos values were measured as the vertical distance from the outer edge of the eyelid to the apex of the cornea in the MRI-T2 before and after radiotherapy. The difference was not statistically significant.

Complications Evaluation

The prevalence of local inflammation was 14.52%, which was manifested as hyperemia and swelling of eyelid or conjunctival, and increased se-

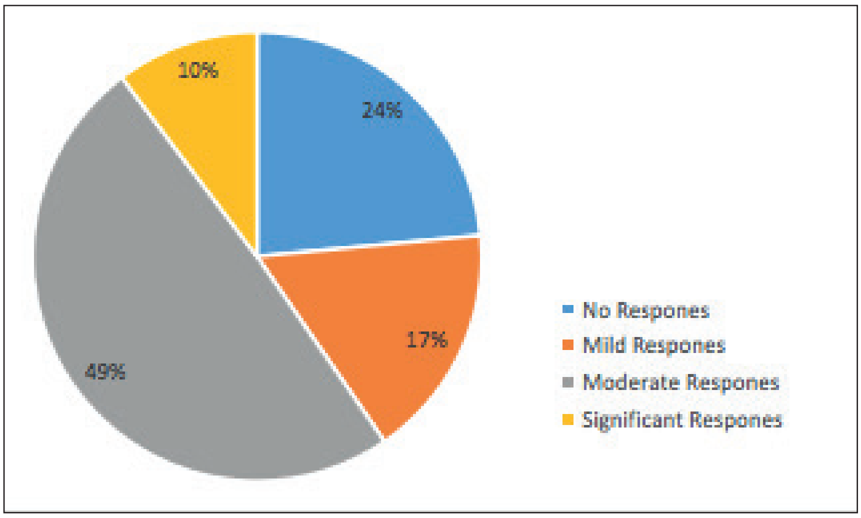

Figure 2. Overall treatment response to radiotherapy.

Table I. Overall symptom scores before and after radiotherapy.

SCORE	Before	After	z	*p*-value
Overall efficacy	8.46±2.544	5.39±2.376	-8.847	0.000
Proptosis	1.83±0.694	1.67±0.721	-2.701	0.007
Soft tissue involvement	1.53±0.750	0.82±0.658	-8.544	0.000
EOMs involvement	1.18±0.643	0.71±0.572	-6.731	0.000
Corneal involvement	0.24±0.426	0.04±0.206	-5.099	0.000
Sight loss	0.49±0.596	0.32±0.482	-4.068	0.000
Orbital pain	0.43±0.605	0.15±0.363	-5.481	0.000
Tearing	0.82±0.383	0.4±0.491	-7.616	0.000
Diplopia	1.94±0.987	1.32±0.885	-6.549	0.000

cretions. It occurred from 1 day to 1 week after the first radiotherapy, and was relieved 3 to 5 days after using eye drops. The prevalence of skin pigmentation was 4.84%. It occurred from 1 week to 4 months after radiotherapy; no special treatment was needed, and the symptoms were significantly reduced 6 months after the radiotherapy. The prevalence of hair loss was 27.42%, and it occurred 20 days to 4 months after radiotherapy. A small amount of hair around sideburns, eyebrows, and eyelashes fell off, but returned to normal six months after radiotherapy. The prevalence of xerophthalmia was 3.22%, and it occurred 4 to 6 months after radiotherapy. Symptoms were relieved by artificial tears. No cataract, radiation retinitis or secondary tumors were observed.

Analysis of the Response Factors

Univariate analysis was performed to evaluate the influence of age, gender, smoking, duration of TAO, and thyroid hormone level for the response to the radiotherapy, where the thyroid hormone level was found to be associated with the efficacy of radiotherapy (Table II).

Furthermore, multivariate logistic regression analyses were performed to determine that the thyroid hormone level was the independent factor for response to radiotherapy (Table III).

Discussion

In the present study, we used EDGE accelerator to perform the radiotherapy in 68 patients with moderate and severe TAO. The overall score, the effective rate of each symptom and the incidence of acute complications were evaluated. We found that the radiotherapy performed by EDGE accelerator was a safe and effective treatment option for moderate to severe TAO. In the analysis of the response factors, the thyroid hormone level was identified as the independent factor for response to radiotherapy.

Radiotherapy is an important treatment for TAO, since radiation can kill lymphocytes in the orbital tissue and reduce the production of cytokines. In the acute phase of TAO, a large amount

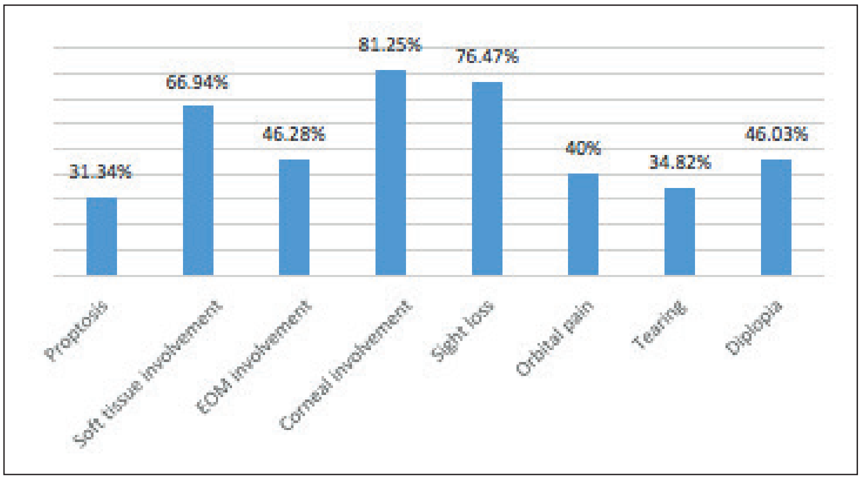

Figure 3. Effective rate for each symptom.

Table II. Univariate analysis of factors for the response to radiotherapy

Characteristics	χ^2	p-value
Sex	0.045	0.832
Age	0.981	0.322
Duration of TAO	2.447	0.118
Smoking	2.393	0.122
Thyroid hormone level	10.990	0.001

Table III. Multivariate analysis of response factors for the response to radiotherapy.

	Odds ratio	95% CI	*p*-value
Sex	0.475	0.163-1.386	0.173
Age	0.968	0.925-1.013	0.166
Duration of TAO	0.987	0.909-1.072	0.754
Smoking	0.377	0.122-1.163	0.173
Thyroid hormone level	0.375	0.117-0.647	0.003

of lymphocytic infiltration is found in orbital tissue, while little is found in the chronic phase that is mainly characterized by the fibrous connective tissue hyperplasia. In addition, radiation can inhibit the secretion of sodium hyaluronate, mucopolysaccharide and other substances from fibroblasts in the acute orbital tissue, which can reduce the edema and fibrosis. Therefore, radiotherapy is effective in the acute phase, but has limited efficiency in the chronic phase[10]. In our work, the effective rate was 75.74%, which was consistent with the previous literature reporting the effective rate of radiotherapy of about 60-90%. The proportion of patients in the acute and chronic phases in each study were different, so the calculated effective rates were also quite different. The patients enrolled in our study visited the ophthalmology clinic at our hospital several times. Only five of them did not receive glucocorticoid therapy before radiotherapy. All of them were refractory patients with moderate and severe TAO. There were more patients in the chronic phase. The symptoms associated with the acute phase, such as soft tissue involvement, corneal involvement, and orbital pain were highly improved, while the improvement of proptosis associated with chronic lesions was very modest.

If the lens is exposed to more than 7-8 Gy in a few weeks, cataracts can occur, and can even lead to blindness, which is the biggest limitation of radiotherapy for TAO[11]. With the development and advancement of accelerators and radiotherapy technology, intensity-modulated radiotherapy has shown to have improved efficiency in dosimetry, as well as the reduced complications rates[12,13]. IMRT also shows high efficiency and safety in the treatment of TAO[4].

EDGE is the most advanced linear accelerator at present. Its isocenter comprehensive mechanical precision is controlled within 0.5 mm, and the multi-leaf collimator blade width is 2.5 mm, which allows for the better utilization of the technical advantages of IMRT and better conformal of the therapeutic target area, as well as minimal damage to surrounding healthy tissue. In the present work, we obtained a 75% effective rate, and all the complications were mild, and well relieved. However, due to the follow-up period of only 6 months, long-term adverse reactions such as radioactive cataract, radioactive retinopathy and secondary tumors need to be followed up.

We analyzed the age, gender, smoking, duration of TAO and thyroid hormone levels, finding that hormonal level is the independent response factor. The treatment of TAO includes systemic therapy and local treatment. Maintaining normal thyroid hormone level through systemic therapy is very important, and it also affects the local treatment of TAO. Because the exact relationship between hyperthyroidism and TAO is still unclear, if hyperthyroidism treatment is related to the occurrence and development of TAO remains unclear[14]. In this work, we analyzed the correlation between thyroid hormone level and efficacy of radiotherapy in patients, and found that the thyroid hormone level was an independent response factor. Patients with normal thyroid hormone levels had a better response. Smoking was identified as a major risk factor for TAO very early[15]. The number of smoked cigarettes per day significantly affects the occurrence of diplopia and proptosis[16]. Recent studies[17,18] have found that hypoxia caused by smoking can lead to an excessive proliferation of orbital fibroblasts, lipogenesis and production of glycosaminoglycans and pro-inflammatory cytokines, which can cause the occurrence and the development of TAO. At the same time, smoking can reduce the therapeutic effect of chemotherapy and radiotherapy[19]. In this work, the smoking rate in male patients was 62.5%, and in female patients, it was 12.5%, which was significantly higher than that of the general population. Nevertheless, the influence of smoking on the efficacy of radiotherapy was not found in this study. This might be because after being diagnosed and learning about the importance of smoking cessation from their doctors, 90% of the patients quit smoking during and after radiotherapy. The effects of smoking may have diminished in these patients, but specific differences need to be further explored in future studies.

The current work showed that EDGE had a good effect in the treatment of TAO patients, and can be further compared with other radiotherapy techniques, such as 3DCRT (3-Dimension Conformal Radiation Therapy), VMAT (volumetric modulated arc therapy) and so on. Included patients can be used to further carry out the classification of acute phase and chronic phase, and clarify the difference of response to radiotherapy between them. At the same time, the effect of smoking cessation on the treatment effect can be further studied. At present, there are numerous studies[20] on the combination of glucocorticoids and radiotherapy, showing a comparable or better effect of one or the other. However, since it has been observed that further complications may occur[21,22], this is an aspect worth exploring.

Conclusions

Over recent years, considerable progress has been made in the study of the molecular mechanisms of TAO. Several innovative therapies[23] have been identified based on the autoimmune response of the orbital tissue, including rituximab and other drugs that target orbital fibroblast receptors or inflammatory cytokine. On the other hand, studies on the radiation techniques, treatment doses and segmentation methods of TAO radiotherapy are still lacking, which may be the reason for the lack of significant improvement in the efficiency of radiotherapy. Currently, the pathogenesis of TAO is still unclear. However, with the rapid development of molecular biology, radiotherapy technology and the emergence of relevant clinical evidence, it is believed that future studies may lead to research breakthroughs in the treatment of TAO.

Conflict of Interests

The authors declare that they have no conflict of interest.

References

1) Lazarus JH. Epidemiology of Graves' orbitopathy (GO) and relationship with thyroid disease. Best Pract Res Clin Endocrinol Metab 2012; 26: 273-279.
2) Bhatti MT, Dutton JJ. Thyroid eye disease: therapy in the active phase. J Neuroophthalmol 2014; 34: 186-197.
3) Lee VH, Ng SC, Choi CW, Luk MY, Leung TW, Au GK, Kwong DL. Comparative analysis of dosimetric parameters of three different radiation techniques for patients with Graves' ophthalmopathy treated with retro-orbital irradiation. Radiat Oncol 2012; 7: 199.
4) Li YJ, Luo Y, Xie XQ, He WM, Yi C, Li P, Wang F. The efficacy of intensity modulated radiation therapy in treating thyroid-associated ophthalmopathy and predictive factors for treatment response. Sci Rep 2017; 7: 17533.
5) Folkert MR, Timmerman RD. Stereotactic ablative body radiosurgery (SABR) or Stereotactic body radiation therapy (SBRT). Adv Drug Deliv Rev 2017; 109: 3-14.
6) Zhang FQ, Zhou JC. Radiation therapy for ocular diseases with Graves' disease. Chin J Radiat Oncol 1996; 1996: 36-38.
7) Frueh BR. Why the NOSPECS classification of Graves' eye disease should be abandoned, with suggestions for the characterization of this disease. Thyroid 1992; 2: 85-88.
8) Donaldson SS, Bagshaw MA, Kriss JP. Supervoltage orbital radiotherapy for Graves' ophthalmopathy. J Clin Endocrinol Metab 1973; 37: 276-285.
9) He ZB, Shang N. Clinical application of t2-mapping in the diagnosis of Graves' ophthalmopathy. Chin J Endocrinol Metabol 2015; 31: 327-332.
10) Liu C, Luo Q, Lu H. Study on orbital histopathology of thyroid-related eye diseases. Journal of Sichuan University 2005; 36: 436-437.
11) Hu ZJ, He JF, Li KJ, Chen J, Xie XR. Decreased microRNA-146a in CD4+T cells promote ocular inflammation in thyroid-associated ophthalmopathy by targeting NUMB. Eur Rev Med Pharmacol Sci 2017; 21: 1803-1809.
12) Veldeman L, Madani I, Hulstaer F. Evidence behind use of intensity-modulated radiotherapy: a systematic review of comparative clinical studies. Lancet Oncol 2008; 9: 367-375.
13) Xu D, Li G, Li H, Jia F. Comparison of IMRT versus 3D-CRT in the treatment of esophagus cancer: a systematic review and meta-analysis. Medicine 2017; 96: e7685.
14) Li HX, Xiang N, Hu WK, Jiao XL. Relation between therapy options for Graves' disease and the course of Graves' ophthalmopathy: a systematic review and meta-analysis. J Endocrinol Invest 2016; 39: 1225-1233.
15) Thornton J, Kelly SP, Harrison RA. Cigarette smoking and thyroid eye disease: a systematic review. Eye 2006; 21: 1135-1145.
16) Prummel MF, Wiersinga WM. Smoking and risk of Graves' disease. JAMA 1993; 269: 479.
17) Görtz G-E, Horstmann M, Aniol B. Hypoxia-dependent HIF-1 activation impacts on tissue remodeling in graves ophthalmopathy-implications for smoking. J Clin Endocr Metab 2016; 101: 4834-4842.
18) Kau HC, Wu SB, Tsai CC, Liu CJ, Wei YH. Cigarette smoke extract-induced oxidative stress and fibrosis-related genes expression in orbital fibroblasts from patients with Graves' ophthalmopathy. Oxid Med Cellular Longev 2016; 2016: 4676289.

19) Hegediüs L, Brix TH, Vestergaard P. Relationship between cigarette smoking and Graves' ophthalmopathy. J Endocrinol Invest 2004; 27: 265-271.
20) Marcocci C, Bartalena L, Bogazzi F, Bruno-Bossio G, Lepri A, Pinchera A. Orbital radiotherapy combined with high dose systemiglucocorticoids for Graves' ophthalmopathy is more effective than radiotherapy alone: results of a prospective randomized study. J Endocrinol Invest 1991; 14: 853-860.
21) Prummel MF, Mourits MP, Blank L, Berghout A, Koornneef L, Wiersinga WM. Randomized double-blind trial of prednisone versus radiotherapy in Graves' ophthalmopathy. Lancet 1993; 342: 949-954.
22) Prabhu RS, Liebman L, Wojno T, Hayek B, Hall WA, Crocker I. Clinical outcomes of radiotherapy as initial local therapy for Graves' ophthalmopathy and predictors of the need for post-radiotherapy decompressive surgery. Radiat Oncol 2012; 7: 95.
23) Wiersinga WM. Advances in treatment of active, moderate-to-severe Graves' ophthalmopathy. Lancet Diabetes Endocrinol 2017; 5: 134-142.