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Review Article

Progress of Radiotherapy in Thyroid Associated Ophthalmopathy

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Abstract

Thyroid-Associated Ophthalmopathy (TAO) is an autoimmune disease, and the pathogenesis is not completely clear. The diagnosis and treatment of TAO are still controversial, especially the efficacy and safety of radiotherapy. The pathogenesis and treatment of TAO were summarized, and the application and progress of radiotherapy were emphatically reviewed in this review.

Keywords: Radiotherapy; Thyroid Associated Ophthalmopathy

Thyroid associated ophthalmopathy (TAO), also known as Graves Ophthalmopathy (GO), is an organ-specific autoimmune disease and the most common extrathyroidal manifestation of Graves' Disease (GD) , The highest incidence of orbital diseases in adults [1].TAO mainly manifests as inflammatory infiltration of the orbital tissue, which causes a variety of histopathological changes, leading to an increase in the volume of extraocular muscles and orbital adipose tissue, and patients with eye discomfort, protruding eyes, decreased vision, and even blindness, which seriously affects the quality of life of patients. Although some progress has been made in pathogenesis, there are still many problems to be solved in diagnosis and treatment, especially the classification of patients based on disease severity and activity scores has become increasingly important. Multiple studies have demonstrated the effectiveness and safety of radiation therapy (RTia) in moderate-to- severe TAO treatment, especially Intensity Modulated Radiation Therapy (IMRT) can provide a more uniform dose distribution, the largest The degree of exposure to normal tissue is reduced, thereby minimizing the risk of side effects. This article briefly analyzes the pathogenesis, treatment plan, and especially the application of radiotherapy technology for TAO.

TAO's pathogenesis

Tao is associated with a variety of histopathological changes that induce the inflammatory process, leading to extraocular muscles and The volume of orbital adipose tissue increases. The pathogenesis is that the body's autoimmune balance is broken under the influence of antigen stimulation, environment, genetics and other factors, T and B lymphocytes are activated, and various cytokines and adhesion molecules are secreted and expressed, such as Interleukin (IL) -1β, IL -2, IL-4, IL-5, IL-6, IL-10, Interferon (IFN) -γ and Tumor Necrosis Factor (TNF)

-α, and simultaneously release Glycosaminoglycans (GAGs), causing orbital inflammation and Extraocular muscle edema; and stimulate fibroblast proliferation and differentiation into mature fat, causing adipose tissue hyperplasia, patients with eye discomfort, protruding eyes, decreased vision, or even blindness. In addition, Thyroid Stimulating Hormone Receptor (TSHR) can be activated by binding to T lymphocytes (mainly CD4+), stimulate TSHR autoantibodies, infiltrate the orbit and release cytokines [2-5], and have a positive correlation with activity [6]. Insulin-Like Growth Factor (IGF-1) receptors can induce the expression of IL-16 and

RANTES in orbital fibroblasts, leading to the activation of T cells and stimulating their differentiation into adipocytes [2,3]. Smoking [4] and radioactive iodine therapy [5] are high-risk factors for the onset of tao. Smoking can affect humoral immunity and cellular immunity by inhibiting t-cell activation. Radioactive iodine treatment can increase tshr and trigger inflammatory reactions. In terms of genetics, Human leukocyte antigen (hla) class II genes and tnf-α gene polymorphisms are also related to the occurrence and severity of thyroid eye disease [6].

Rating

Classification of TAO patients based on severity and activity can help determine treatment options and aid treatment decisions [7].

Severity Classification

The classification of TAO severity is based on the expert consensus proposed by the European Graves Eye Disease Expert Group (EUGOGO) in 2016, and it is recommended to be divided into three categories [7] based on subjective symptoms and objective signs: Mild: It has a slight impact on daily life and does not require immunosuppressive agents or surgery.Patients had ≥1 of the following manifestations: slight eyelid contracture (<2 mm), mild soft tissue involvement, exophthalmos <3 mm, no or transient diplopia, corneal exposure but effective use of lubricant. Moderate to severe: It has effects on daily life, no vision loss, and requires immunosuppressive agents (active phase) or surgical intervention (quiescent phase). Patients had ≥ 1 of the following manifestations: eyelid retraction ≥ 2 mm, moderate or severe soft tissue involvement, exophthalmos ≥ 3 mm, continuous or intermittent diplopia, and mild corneal exposure.

Threat to vision: Optic neuropathy and / or corneal rupture with thyroid dysfunction. Intervene immediately.

Activity Score

The activity score is based on the CAS (Clinical Activity Score) score, and ≥ 3 points are considered to be active [8] (Table 1).

Clinical Manifestations and Signs	On-Site	Comparison	Score
Spontaneous eyeball or post-ball	Yes		1
Pain during eye movements, more	Yes		1
Red eyelids	Yes		1
Conjunctival congestion	Yes		1
Eyelid swelling	Yes		1
Bulbar conjunctival edema	Yes		1
Swelling of tears	Yes		1
Increased eyeball protrusion ≥ 2 mm		Yes	1
Eye movements in any direction within		Yes	1
Sight loss on Snellen chart by one line		Yes	1

Table 1: Items of clinical activity score.

If no evaluation has been performed before, only the first 7 items will be evaluated, and ≥3 / 7 will be considered as active.

Treatment

Choice of treatment plan

Choose a treatment plan [7] based on Tao's severity and activity score. Mild: Symptoms can improve on their own, and regular follow-up can be used. It is recommended to use a lubricant to relieve symptoms, no need Perform hormone therapy and radiation therapy. Moderate to severe: immunosuppressive, anti-inflammatory, and / or radiotherapy is recommended during the active phase, and hands are considered during the stationary phase Surgical treatment. Vision has been threatened, immunosuppressive or anti-inflammatory treatment is preferred; surgery is ineffective if the effect is poor or ineffective.

Surgical treatment

Including orbital decompression surgery and corrective surgery. The main purpose of orbital decompression is to reduce infraorbital pressure and make the eyeball recede. It is often used in patients with exposed keratitis, corneal ulcers, subluxation of the eyeball caused by severe protrusion of the eyeball, and patients with visual field defect and decreased vision caused by optic nerve compression. You can also choose surgery after treatment failure. Corrective surgery includes extraocular muscle surgery and eyelid surgery. It is suitable for patients with continuous diplopia.

The stable phase of treatment

Drug treatment

Glucocorticoids (GCs) are currently recognized as first-line treatment options for moderate-to-severe active TAO. It is effective, but it is easy to relapse after discontinuation, and complications such as Cushing's syndrome, weight gain, hypertension, diabetes, and liver function are affected. Damage, osteoporosis and other high incidence. Studies have shown that high-dose intravenous shock therapy is better than oral hormone therapy and has fewer side effects [9], but it has a high probability of serious side effects such as fatal acute liver failure, cardio-cerebral vascular events, and autoimmune encephalitis. Increase [10]. At the same time, the effect of glucocorticoid combined with radiotherapy is better than that of glucocorticoid alone [11]. Other drugs such as immune suppressants (etanercept, immunoglobulin, triptolide, so-

matostatins), rituximab have been shown to be beneficial [12,13], but large sample, multicenter clinical studies are still needed Research to verify.

Radiation Therapy

The mechanism of radiotherapy for TAO is that the radiation emitted by radiotherapy has a non-specific anti-inflammatory effect on lymphocytes infiltrated in the post-ball tissue and the high sensitivity of lymphocytes to radiation [14], while patients with Tao mainly show extraocular muscles, bulbs Post-adipocyte infiltration of lymphocytes, so radiation therapy can effectively reduce extraocular muscles, post-ball adipose tissue hyperplasia, and thus reduce eyeball protrusion and edema. Therefore, this can be considered as a substitute for systemic resistance

Anti-inflammatory therapy [15]. Although radiotherapy can induce the production of pro-inflammatory cytokines and lead to the inflammatory response of the irradiated tissue, Low-Dose Radiotherapy (LD-RT) can regulate the inflammatory response and produce anti-inflammatory effects. Inflammation is a strictly regulated and regulated process. LD-RT exerts anti-inflammatory effects involving a series of white blood cell-endothelial cell interactions called rolling, adhesion and migration into interstitial space. In the first step, white blood cells are activated by the action of a local inflammatory mediator. This activation allows attachment to Endothelial cells migrate to the interstitial space. The next step is to accumulate various immune-active cells such as lymphocytes, granulocytes and monocytes/ macrophages. And some cytokines, such as Interleukin (IL) -1, Tumors Necrosis Factor-α (TNF-α), il-6, il-8, and il-12 have pro-inflammatory effects, while other cytokines occur due to together with transforming growth factor (TGF) -α, il-10, and il-4 It has an anti-inflammatory effect [16,17]. Hypotheses explaining the anti-inflammatory mechanism of LD-RT include reduced leukocyte-endothelial cell adhesion, induction of apoptosis in cells containing inflammatory infiltration, and decreased expression of adhesion molecules (p-, l-, e-selectin, icam, vcam), Reduction of iNOS results in reduction of nitric oxide NO and reactive oxygen species ROS, and increased nuclear factor activation kapp (and increased expression of anti-inflammatory cytokines (il- 10, TGF-1) [18]. LD-RT can induce pro-inflammatory cytokines such as TNF-α, interleukin-1α at 24 and 48 hours NF-eB)

(IL-1α) and iNOS levels decreased, and increased HO-1 and induced heat shock protein 70 (HSP70) levels. Therefore, it is necessary to treat LD-RT once every 48-72 hours in clinic. In vitro studies have shown that the potent anti-inflammatory effects of LD-RT are produced by inhibiting leukocyte-endothelial cell interactions at doses <0.7Gy. This effect was observed during the first 48 hours after irradiation and showed a negative correlation with TNF-α concentration and NF-κB activation. In vivo animal studies have shown that LD-RT improves clinical symptoms and improves inflammation and pain. The efficacy of LD-RT has been proven for the treatment of inflammatory diseases such as osteoarthritis, epicondylitis of the humerus, and scapulohumeral-scapularis.

Exposure dose and fractionation

At present, the clinical practice of 2Gy each time for 2 consecutive weeks, the total dose of 20Gy, but the optimal dose is still controversial. Regarding the single dose, Arenas, et al. [18] believe that the optimal dose range of LD-RT is 0.5-1.5Gy. Kahaly, et al. [19] demonstrated that there was no significant difference in the therapeutic efficacy of the above regimens by comparing the three doses and fractionated regimens (20Gy / 20 weeks; 10Gy / 2 weeks; 20Gy / 2 weeks), but 1Gy per week for 20 consecutive days Weeks, the small-dose long-course method with a total dose of 20 Gy showed better tolerance. Cardoso, et al. [20] achieved satisfactory results with a regimen of 1Gy per week for 10 consecutive weeks with a total dose of 10Gy.

efficacy

For patients with moderate to severe active TAO, compared with hormonal therapy, radiotherapy has better efficacy and safety [18], especially for those who are ineffective in hormonal therapy, partially effective or relapsed after withdrawal, and within the first year of symptoms and signs Radiation therapy is more effective [21], which may be related to the patient's fibrosis. In addition, multiple studies have found that radiation therapy combined with hormonal therapy is more effective than any single treatment [22,23], mainly because GCS has a fast onset of action, which can compensate for the shortcomings of slow onset of radiotherapy, and GCs can reduce the effects of radiotherapy. Excessive inflammation is exacerbated, and radiotherapy can reduce the risk of recurrence of eye disease caused by GCs reduction or drug withdrawal.

Side effects

Tao is a benign disease. The potential risks caused by radiation therapy and possible long-term side effects and the occurrence of secondary tumors are the main reasons that have caused controversy and limited the application of this technology. The most common side effect is chronic dry eye, which can be instilled. Artificial tears were relieved. Cataract incidence was small (1%), radioactive Retinopathy is extremely rare, mainly related to the exposure dose, a total of 20Gy is safe, but the incidence of diabetic retinopathy and hypertensive fundus lesions will increase [24]. The secondary tumor caused by radiotherapy is the most serious and unacceptable complication in TAO treatment, but there is no real case report at present, and long-term follow-up observation is still needed. Therefore, patients under 35 years of age (potential long-term carcinogenic risk), patients with severe hypertension, diabetes, and retinopathy are considered contraindications to radiotherapy. Wakelkamp, et al. [25] conducted a long-term follow-up of the treatment response and normal tissue complications after post-ball irradiation. The average follow- up time was 11 ± 3 years, and no late adverse reactions were found.

Radiotherapy Technology

At present, TAO radiotherapy usually uses two fields of opposite irradiation (LOF). The front of the field is located behind the orbit, the posterior is located at the lower edge of the orbital wall, the outer boundary is the outer edge of the orbital wall, and the medial boundary is the ethmoid sinus wall. The shooting field range includes the front and back boundaries of the target area and shields normal tissues at the same time. The shooting field angle is usually 5 degrees to reduce the load on the crystal. Because the plan is easy to set up and set up, it is widely used in clinical practice. However, in order to reduce the exposure dose of the lens when making the plan, the front part of the eyeball is usually not included in the range of the shooting field, resulting in a significant lack of dose in the forefront of extraocular muscles and posterior orbital fat and uneven distribution of dose in the target area. With the continuous development of radiotherapy technology, 3 dimensional conformal radiation therapy (3D-CRT), Intensity Modulated Radiation Therapy (IMRT), and volume modulated radiation therapy (Volumetric modulated arc therapy, VMAT) and other new radiotherapy technologies have attracted much attention due to their superior target area coverage, dose uniformity, and better protection of normal structures. 3d-crt can ensure that all organs in the field are irradiated with the same dose, while imrt and vmrt can modify the boundary of the target area and minimize the exposure dose of the surrounding normal tissue. Because the shape of the target area is usually irregular, the rays are straight Irradiation, therefore, during the irradiation process, any normal tissue close to the target area can receive radiation. The vmrt technology can emit scattered rays to the target area with higher accuracy and accuracy, resulting in fewer side effects while achieving the same efficacy. The short treatment time of vmrt can increase the tolerance of the treatment and reduce the possibility of fractional errors. Based on the above theory, He Dan, et al. [26] found that compared with LOF, 3D-CRT has better target conformation and high dose distribution, and reduces the exposure dose of surrounding normal tissues. Victor, et al. [27] compared the three technologies mentioned above and found that IMRT has better target area coverage and dose uniformity than LOF and 3D-CRT, but also increased planning time, treatment time and hop count (MU), It is not as good as LOF and 3D- CRT in terms of endangering organ protection. It may be because the lead field of the target area of the LOF technology can effectively reduce the multi-leaf grating.

Scattering caused by (mlc), and can take advantage of the prominent features of patients' eyeballs, leading to the danger of organs such as crystals and eyeballs that can be kept away from the target area when using lof technology to reduce the exposure dose. In addition, it is also confirmed in the ntcp model The imrt can increase the risk of radiation complications such as cataract, but the risk is very small and can be ignored clinically. With the application of vmat, it has higher accuracy and precision than 3d-crt and lof, which can achieve the same in at the same time, it has fewer side effects, and the treatment time of vmat is shorter, which improves the tolerance of the treatment and reduces the possibility of fractional errors. It has a better application prospect, but its cost is high and it has not been routinely used in clinical practice [28-30].

Radionuclide therapy

32 p brachytherapy is more effective than retro-orbital radiotherapy, and patients with dry eyes and tears can be significantly improved on the day of the former treatment [31]. Regarding side effects, although 32 p is 3 to 5 days after brachytherapy Some patients may experience recurrence of ocular symptoms, but they can resolve on their own after 2 days, and no serious adverse reactions and secondary tumors have been reported so far. In short,32 p brachytherapy has fewer side effects and simple operation than hormone therapy. It is a promising treatment method, but from the perspective of safety, the optimal dosage and long-term side effects of 32 p brachytherapy remain to be determined.

Conclusion

In summary, regarding the pathogenesis of TAO, current research shows that humoral immunity, cellular immunity and related cytokines, autoantibodies, smoking, genetic factors, etc. all play a certain role, but deeper research is still needed to further Reveal the mechanism of its occurrence and development in order to find more specific treatments.

Radiotherapy has obvious advantages over hormonal treatment in the treatment of TAO, especially for patients with moderate to severe active phase, which can achieve better efficacy and lower toxicity, and there have been no reports of radiation-induced tumors, but long-term follow-up observation is still needed Therefore, conducting reasonable and appropriate clinical research is necessary to determine the safest and most effective dose, grading and radiotherapy technology in Tao radiotherapy. In addition, it is necessary to create more detailed and objective evaluation criteria for side effects in order to conduct a uniform comparison. the study.

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