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ORIGINAL ARTICLE

Radiotherapy for benign diseases: a retrospective analysis

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Summary

Purpose: *Radiotherapy of benign diseases has become a frequently discussed subject while there are neither generally accepted guidelines about the indications of radiotherapy, doses and fractionation schedules nor adequate data about the risks and the effectiveness of irradiation. We have retrospectively analyzed the patients who were irradiated for benign diseases in our department.*

Patients and methods: *During the period 1978-1997, a total of 262 patients were irradiated for benign diseases. Megavoltage equipment was used for irradiation of 253 patients, while the remaining 9 patients were irradiated by orthovoltage equipments. The diseases were grouped in 5 categories, and the distribution of the patients referred and irradiated per year was analyzed. Radiotherapy doses, fractionation, response rates and follow-up were evaluated.*

Results: *The number of irradiated patients has been increasing since the 1990's. The most common indication for irradiation was Graves' ophthalmopathy and the incidence of this group has increased after 1992. On the other hand, the number of patients irradiated for soft tissue, bone and skin diseases, except aggressive fibromatosis, has declined in the past 15 years. Response rates were more than 60% for most of the diseases. The patients' follow-up ranged between 1 and 156 months (median 4 months), but it was rather short for most of them.*

Conclusion: *We observed common problems about the irradiation of benign diseases such as variations on the accepted indications, the treatment schedules and follow-up.*

Key words: benign diseases, indications, radiotherapy, treatment concepts

Introduction

The use of radiotherapy for treating benign diseases has become a frequent topic of discussion among the international radiation oncology community in recent years. Radiation has been used for several decades, however its popularity and its use have been significantly reduced, especially in Western Europe and North America, after reports about the risk of induction of second cancers [1-3]. On the contrary, radiotherapy is accepted as a common treatment modality in Central and Eastern European countries [4].

There are few randomized studies about the administration of radiotherapy in benign diseases [5-8]. Most of the reports are retrospective series. It seems that there are few recommendations on radiotherapy indications, total dose, fractionation and follow-up strategies. Recently, Micke and Seegenschmiedt published the guidelines for radiotherapy of benign diseases on behalf of the German Group on Radiotherapy of Benign Diseases, which may be a good example for other centers or countries [9].

We performed a retrospective demographic analysis of the patients who were referred and irradiated in our department for benign diseases in order to

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review the applications of radiotherapy in benign diseases, set out basic trends and compare our results with the trends prevailing in Europe, the USA and the rest of the World.

Patients and methods

Between 1978-1997, a total of 32,147 patients were referred to our department and 338 (1%) of them were found to have benign diseases. Two hundred sixty-two (77.5%) of them were treated by radiotherapy, and 206 of these 262 cases had been treated by other modalities prior to irradiation. Most of the patients had been treated by medications such as antiinflammatory drugs, corticosteroids etc., however they had not responded to these treatments. It was not possible to outline clear indications, since there were no written recommendations of the department other than general literature information. The number of patients who were referred or irradiated per year also revealed that there has been an increasing trend over the years (Figure 1). The female/male ratio was 1.7 and the patients' median age was 48 years (range 3.5 months – 88 years).

The benign diseases were grouped in 5 main categories as follows: vascular diseases; autoimmune diseases; infectious diseases; bone, soft tissue and skin diseases; and Graves' ophthalmopathy (Table 1).

Table 1. Categorization of benign diseases and number of referred / irradiated patients

Vascular diseases (97/62)
Arteriovenous malformations
Vertebral hemangiomas
Non-vertebral hemangiomas
Autoimmune diseases(13/11)
Rheumatoid arthritis
Ankylosing spondylitis
Behçet's disease
Infectious diseases(3/1)
Osteomyelitis
Tinea capitis
Hydatid cyst
Graves' opthalmopathy(145/133)
Bone, soft tissue, and skin diseases(80/55)
Tendinitis
Keloids
Heterotopic ossification
Aggressive fibromatosis
Spondyloarthritis
Synovitis
Acne vulgaris
Keratoderma
Orbital pseudotumor
Paronychia
Pylomatrixoma
Verruca vulgaris
Benign seborhoid gland adenoma
Psoriasis

Results

The patients with Graves' ophthalmopathy comprised the largest group among the 5 categories, with vascular diseases ranking second, and bone and soft tissue diseases third (Figure 2).

The increase in the number of irradiated patients over the years, with 5-year intervals, was related with the increase in the number of patients irradiated for Graves' ophthalmopathy, the incidence of which significantly increased, especially in the 1990's (72%, Figure 3). However, irradiation of bone and soft tis-

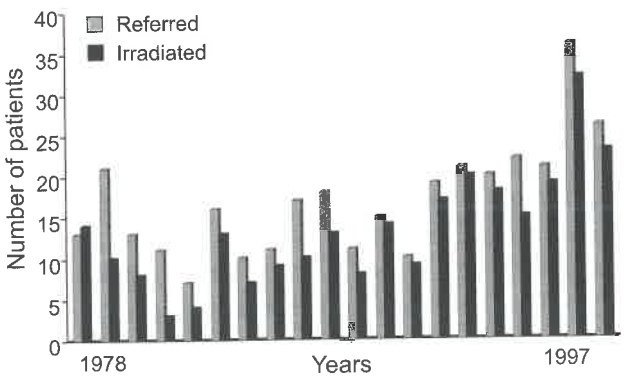


Figure 1. Distribution of the cases per year.

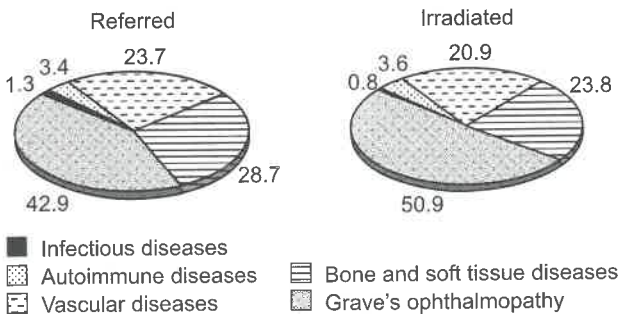


Figure 2. Percent distribution of the cases according to the main groups.

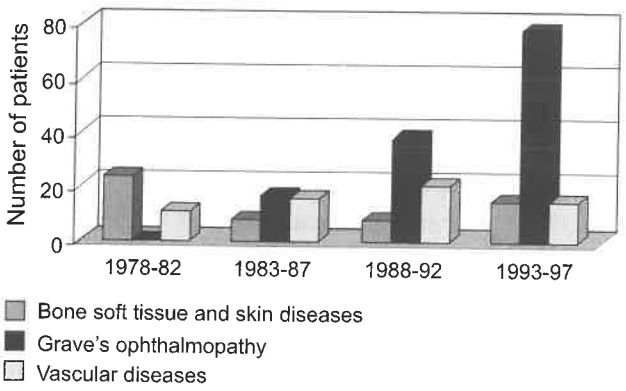


Figure 3. Distribution of the irradiated cases by 5-year intervals.

sue diseases, except aggressive fibromatosis, diminished after 1978-1982 (Figure 2).

Most of the patients were irradiated by megavoltage treatment equipment, while only 9 patients were treated by orthovoltage equipment. The doses were mostly under 30 Gy, except aggressive fibromatosis. The dose ranges were different, but not too wide. Usually, fractionated radiotherapy was used. The treatment schedule, median radiotherapy doses, fractionation and treatment time are shown in Table 2. One or two opposed fields were used during radiation for most of the patients. Total lymphoid irradiation was performed for rheumatoid arthritis and Behçet's disease.

Follow-up was rather short in most of the categories, ranging between 1 and 156 months (median 4 months) and only in 78 (29.7%) cases it was more than 12 months.

Discussion

In recent years, treatment of benign diseases with radiotherapy has been diminished, especially among the European and North American radiation oncology practices, who have adopted a more skeptical view towards the role of irradiation, after reports about the risks of radiation-induced tumors and chronic ulceration after retrobulbar irradiation for Graves' ophthalmopathy [1,2,6]. However, only one of these reports addressed the issue indicating proper risk factors related to the postirradiation tumor induction [2]. Broerse et al. found little increase in the risk of a radiation-induced tumor, however the contribution of the increase in this risk to the overall lifetime risk was unclear. Furthermore, after the 4th decade of life this risk decreased to normal risk levels [10].

There is no sufficient information about the mechanisms by which radiotherapy can therapeutically

Table 2. Radiotherapy schedule, fractionation and dose

Disease	*Type of radiotherapy*	*Dose/fraction (Gy)*	*Total dose (Gy)*	*Median dose (Gy)*	*Treatment duration (weeks)*
Graves' ophthalmopathy	Photons	1.5-2	15-20	20	2
Vascular diseases					
vertebral hemangioma	Photons	2-3	20-30	25	2-3
nonvertebral hemangioma	Photons, Electrons, Orthovoltage	0.9-3	2-30	20.6	1-4
arteriovenous malformations	Photons	2	2-30	26	1-7
Bone, soft tissue, skin diseases					
Tendinitis	Photons	1.5-2	6-24	9	1-3
Keloids	Electrons, Orthovoltage	2-2.5	2-25	20	3
Heterotopic ossification	Photons	7.5-8	7.5-8	7.5	1 day
Aggressive fibromatosis	Photons	2	40-60	60	6-7
Other	Photons,Orthovoltage		6-30	9	1-3
Autoimmune diseases					
Rheumatoid arthritis	Photons	1.5	22.5-24	22.5	4-7
Behçet's disease	Photons	1.5	21.5-24	21.5	4-11
Infectious diseases					
Hydratid cyst	Photons	3	36	36	3

Photons=Co60,9-18 MV; Electron=6-9 MeV; Orthovoltage=50-240 kV

influence benign diseases. Few reports are published related to this subject in the past 10 years [11-13]. Antiproliferative effect, increase in capillary perfusion, release of cytokins, destruction of inflammatory tissues are several possible mechanisms of radiotherapy in benign diseases, however none of them can accurately explain the real mechanism or mechanisms, therefore more prospective multicentric studies are needed over this issue.

Our study shows that the proportion of patients receiving radiation therapy for benign diseases is as low as in most of the other countries. However, there is no published data on the usage of radiotherapy for benign diseases in Turkey. Our department is one of the oldest and most important reference centers in our country, therefore we believe that this series may serve as a guide for radiotherapy in benign diseases in Turkey for the recent years. Leer et al. state that keloid prevention, Graves' ophthalmopathy, prevention of heterotopic bone formation, aggressive fibromatosis and pterygium are the most accepted indications for radiotherapy among the medical community worldwide [4]. In our analysis, the largest disease group, both referred and treated by radiotherapy, was Graves' ophthalmopathy. The incidence of this group has been increasing since 1992, a probable explanation of which could be collaboration between ophthalmologists and radiotherapists.

In our series the incidence of Graves' ophthalmopathy has increased, unlike in Germany, while the incidence of irradiated benign bone and soft tissue diseases has decreased [14]. Radiotherapy is widely accepted as treatment modality for the prevention of heterotopic bone formation. Although it is commonly used in Europe and North America, the usage of radiotherapy in heterotopic bone formation is very low in Turkey [4]. Our orthopedic surgeons believe that this is partially attributable to the rare incidence of heterotopic bone formation in Turkish people.

Irradiation of other degenerative diseases such as arthrosis, arthritis or synovitis seems to be a controversial issue in different countries. In central Europe, especially in Germany, it is the most common disease group, while in other parts of Europe and North America it is used occasionally [4,14]. The incidence of this group diminished after 1983 in North America. This may be due to the reports about risks of radiation-induced malignancies, improvements in other therapeutic approaches, and the lack of information between other disciplines.

We irradiated 5 patients with Behçet's disease as an unusual indication which has not been included in the questionnaire of the Leer's survey. Those patients were unresponsive to previous therapies such as corticosteroids and/or immunosuppressive agents. Total lymphoid irradiation was given in order to suppress the immune system, and 4 out of 5 patients achieved disease regression or stabilization during a 13-month follow-up [15].

The number of our patients who were irradiated for aggressive fibromatosis is very low compared with other countries, including North America [4]. However, the incidence of aggressive fibromatosis shows a slow tendency for increase after 1995.

In our analysis we have grouped the benign diseases in 5 categories. However, it should be noted that there is no generally benign disease categorization accepted worldwide. Micke and Seegenscmidth in their guidelines grouped the benign diseases in 6 categories: acute/chronic inflammatory diseases, acute/chronic painful degenerative diseases, hyperproliferative diseases of soft tissue, functional diseases, dermatologic diseases, and other diseases [9]. Furthermore, there is no general agreement on the maximum treatment dose and fractionation, and, accordingly, dose ranges vary widely. Although, in our series, the maximum and minimum doses did not vary too much, other centers have reported much broader range of maximum doses [14]. In general, fractionated radiotherapy is preferred, except in the case of heterotopic ossification [8,14]. In our department, we used frequently megavoltage radiation, unlike in Germany.

In our series, the follow-up of patients with benign diseases, other than desmoid tumors and Graves' ophthalmopathy, was not as good. Patients' follow-up is a common and important problem worldwide. Due to such short follow-up, response to radiotherapy and radiation-induced cancer risk can not be assessed adequately.

There are new benign conditions where radiation is used, such as endovascular brachytherapy for peripheral vascular diseases and for radiotherapy macular degeneration, and also prevailing issues such as indications for other diseases [16-18]. Maximum doses and fractionation should be clearly addressed, especially by means of randomized studies, in order to utilize the therapeutic advantage of radiotherapy, however performing radiotherapeutic randomized studies for benign diseases is not easy since radiotherapy is a seldom used modality. Comparative studies with other treatment modalities are also needed. There are randomized studies for two diseases only: Graves' ophthalmopathy and heterotopic ossification [6-8].

As a conclusion, every effort should be done to draw clear guidelines and generally accepted stan-

dards prior to the introduction of radiotherapy for benign diseases through prospective randomized studies and basic research. *In vitro* and *in vivo* studies should also be carried out to assess the effect of low-dose radiation.

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