



Treatment of benign tumours and related pathologies with radiotherapy: experience of the General Hospital of Mexico

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ABSTRACT

Background: Benign diseases include tumours or localized growths with low potential for progression. The use of radiotherapy (RT) at a low dose (LD) or intermediate dose for benign pathologies has been widely proposed and studied. Currently, the use of RT is limited mainly to hyperproliferative and inflammatory diseases as a first or second line of treatment.

Materials and methods: This was a retrospective, observational and descriptive study conducted in the Radiotherapy Unit of the Oncology Service of the General Hospital of Mexico “Dr. Eduardo Liceaga” from January 2, 2016, to December 31, 2020. Patients diagnosed with benign pathology and treated with RT were included. The response to treatment was recorded based on the imaging study report and/or clinical review that determined control of the disease, and toxicity was recorded based on the RTOG evaluation for acute effects and CTCAE V. 4.0 for chronic effects.

Results: The records of 222 patients were analysed. The mean follow-up duration was 31.53 months (range 6–61), and the median was 24 months. Of all of the analysed pathologies that were treated with RT, keloid scars predominated in 112 patients (50.5%), and paragangliomas predominated in 72 patients (32.4%); the other patients were treated for rare pathologies. The prescribed dose was dependent on the diagnosis, with the mean dose being 31.63 Gy (1500–6000 cGy) and the median being 2000 cGy. Most of the cases of acute and chronic toxicity were grades 1 and 2, and a disease response was achieved in 94.1% of the patients.

Conclusion: Our series shows that for cases of benign pathology, RT offers acceptable toxicity, improves quality of life and yields a good response, achieving disease control. These results suggest the inclusion of inflammatory pathology among the indications for treatment.

Key words: IMRT; low doses; external beam radiation therapy

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Introduction

Benign diseases include tumours or localized growths with low potential for progression that do not metastasize to distant sites [1]. They comprise well-differentiated cells; when treated late, they can produce a voluminous tumour and be locally aggressive or can cause secondary secretory symp-

toms that alter the patient’s quality of life. The use of low-dose radiotherapy (LDRT) or intermediate-dose RT for benign pathologies has been widely proposed and studied, and in some countries, such as Germany, it is used frequently. The empirical use of X-rays for benign diseases began after 1895 [1]. In 1898, 4 cases of juvenile arthritis became the first documented benign pathologies treated with RT

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[2]. In the past, LDRT or intermediate-dose RT was used to treat peptic ulcers, tinea capitis and uterine bleeding; at present, RT is limited mainly to the first- or second-line treatment of hyperproliferative and inflammatory diseases.

In 2012, a registry of departments in the United Kingdom was created to evaluate patients by year and estimate the use of RT for benign pathologies. Twenty-five of 61 departments (41%) responded, reporting treatment of pathologies including heterotopic ossification, keloid scarring, Graves' disease and Dupuytren's disease, and trigeminal neuralgia and vestibular schwannoma were treated with radiosurgery [3]. The German RT Group for benign diseases, together with the German Society of Radiotherapy and Oncology (DEGRO), reviewed the experience from 1930 to 1990 and developed the first national guidelines for the use of RT for acute and chronic inflammatory diseases, degenerative joint disease and acute and chronic pain, with an update between 2010 and 2013 [4, 5]. RT constitutes 8–10% of treatments used for benign pathology [6, 7].

The main objective of this article is to analyse the disease response in patients diagnosed with a benign pathology treated with RT at the General Hospital of Mexico; more specifically, the study sought to evaluate the acute and chronic toxicity of the treatment using different radiation techniques.

Materials and methods

This was a retrospective, observational and descriptive study conducted at the Radiotherapy Unit of the Oncology Service of the General Hospital of Mexico "Dr. Eduardo Liceaga" from January 2, 2016, to December 31, 2020. The digital records and treatment files of patients with benign disease treated at the RT unit were reviewed. The inclusion criteria were as follows: patients of any sex; age > 18 years; diagnosis of benign pathology by imaging study, histopathology and/or clinical evaluation; complete clinical and digital record in the Eclipse V.13.5 planning system; and follow-up > 6 months. The exclusion criteria were age < 18 years, incomplete clinical and digital records, inconclusive radiation treatment results, or follow-up < 6 months. The clinical records and those of the digital system of the Eclipse planning program version 13.5 were

analysed to collect the study variables and generate a database with the SPSS statistical program version 25, considering the previously described inclusion and exclusion criteria. At the initial consultation, the patients were evaluated, and the type of radiation treatment and the prescription dose were determined. Patient simulation took place using a General Electric CT simulator from 2016 until October 2018 and a Phillips 16-slice CT simulator from December 2018 to 2020. External RT treatment was performed using a Varian linear accelerator, and high-dose brachytherapy was performed using Nucletron equipment prior to October 2016 and GamaMed Plus equipment with an Iridium 192 source from December 2016 to 2020. Treatment results were assessed using an imaging study and/or clinical review to determine control of the disease, and toxicity was recorded based on the RTOG evaluation for acute effects and the CTCAE version 4.0 for chronic effects. Follow-up results were captured using the clinical record from the first consultation to the last control appointment. Statistical analyses were performed using measures of central tendency and dispersion for quantitative variables and descriptive and contingency tables for qualitative variables. The correlation of the response to treatment and the toxicity of RT were analysed with the chi-square test of SPSS statistics version 25.

Results

A total of 239 files were reviewed, and 17 were excluded because they did not meet the inclusion criteria. The records of 222 patients were analysed. The mean follow-up duration for this study was 31.53 months (range 6-61), with a median of 24 months. The mean age was 39.41 years (18 to 80), 75.2% of the patients (167) were women, and 24.8% (55) were men.

Among the analysed pathologies, RT treatment for keloid scars predominated in 112 patients (50.5%), and treatment for paragangliomas predominated in 72 (32.4%). The other diagnoses and locations are shown in Table 1. The indication for RT was radical in 96 patients (43.2%), adjuvant in 123 patients (55.4%) and salvage in three patients (1.4%) (Tab. 2). The RT modality was photon treatment in 108 patients (48.6%), electron radiation in 48 pa-

Table 1. Site of presentation and number of cases

Diagnosis	Location (cases)	Total (%)
Keloid scar	Ear:	112 (50.5)
	Lobule (61)	
	Hélix (41)	
	Concha (3)	
	Anti-hélix (2)	
	Neck (1)	
	Thorax (3)	
Abdomen (1)		
Paraganglioma	Carotid (67)	72 (32.4)
	Jugulotympanic (5)	
Fibromatosis	Arm (2)	8 (3.6)
	Abdomen (2)	
	Nasal (2)	
	Subscapular (1)	
	SCV (1)	
Pituitary adenoma	Pituitary gland (6)	6 (2.7)
Retinal hemangioma	Retina (5)	5 (2.3)
Graves ophtalmopathy	Eye (4)	4 (1.8)
Pigmented villonodular synovitis	Knee (1)	3 (1.4)
	Subscapular (2)	
Hemangiopericytoma	Frontal lobe (1)	2 (0.9)
	Meninges (1)	
Histiocytosis II (Rosai Dorfman)	Brainstem (1)	2 (0.9)
	Nasal (1)	
Haemophilic pseudotumor	Arm (1)	2 (0.9)
	Pelvis (1)	
Castleman disease	Meninges (1)	1 (0.5)
Inverted papilloma	Nasal (1)	1 (0.5)
Dermatofibroma	Arm (1)	1 (0.5)
Histiocytosis I (Langerhans cells)	Hypothalamus (1)	1 (0.5)
POEMS syndrome	Pelvis (1)	1 (0.5)
Lymphangioma	Neck (1)	1 (0.5)

SCV — supraclavicular; POEMS — polyneuropathy (P), organomegaly (O), endocrinopathy (E), monoclonal protein (M), skin changes (S)

tients (21.6%) and brachytherapy with a high dose rate (HDR) in 66 patients (29.7%); HDR brachytherapy was used exclusively for treating keloid scars. The other 46 patients with keloid scars were treated with electron radiation, as were one patient with pigmented villonodular synovitis and one with dermatofibroma; the remaining 108 patients received photon treatment. Regarding the technique used for external photon RT, 27 patients (12.2%) received conformal radiation therapy, 56 patients (25.2%) received intensity modulated radiation therapy (IMRT), and 25

patients (11.3%) received modulated volumetric arc therapy (VMAT). The prescribed doses by pathology are shown in Table 3; the mean was 31.63 Gy (1500–6000 cGy; median: 2000 cGy; standard deviation: 1743 cGy).

The acute toxicity rates are shown in Table 4; toxicity was grade 1 in 30.6% of patients, grade 2 in 12.6%, and grade 3 in 2.2%. Radiodermatitis was present in 17% of the keloid scarring cases and 22% of the paragangliomas as well as in six patients with fibromatosis, two with pigmented villonodular synovitis, one with haemophilic pseudotumour and one with dermatofibroma. Xerostomia, dysgeusia and mucositis occurred more frequently in patients with paraganglioma (23%, 18% and 8.3%, respectively); dysphagia occurred in only 3% of patients. One patient with histiocytosis II and inverted papilloma also presented with xerostomia. Three patients with retinal haemangioma and one with Graves' ophthalmopathy had conjunctivitis, and epiphora were present in three patients with Graves' disease. Headaches occurred in three patients with pituitary adenoma and two with haemangiopericytoma. One patient with fibromatosis presented with diarrhoea.

The chronic toxicity rates are shown in Table 5. Toxicity was grade 1 in 46%, grade 2 in 3% and grade 3 in 0.4% of patients. Those with keloid scarring presented with hypopigmentation, fibrosis, atrophy, telangiectasia, and hyperpigmentation at rates of 17%, 14%, 10%, 5% and 1.7%, respectively. Two patients with fibromatosis, one patient with pigmented villonodular synovitis and one patient with dermatofibroma presented with fibrosis. Among the paraganglioma patients, 30% presented with xerostomia, 27.7% with dysgeusia, and 1% with dysphagia. Three patients with retinal haemangiomas and two with Graves' ophthalmopathy had keratitis; two patients with Graves' disease had epiphora, and one with haemangiopericytoma had headaches.

Acute and chronic toxicity were significantly correlated with the RT dose and modality, at $p < 0.001$ (lower toxicity was associated with electron RT), but they were not significantly correlated with the external photon RT technique ($p = 0.16$ and $p = 0.4$, respectively).

Disease response at the end of the treatment was achieved in 99.5% (221 patients), while one patient with keloid scarring did not respond. At the end

Table 2. Diagnosis and indication for radiotherapy (RT)

Diagnosis	Indication			Total
	Radical	Adjuvant	Salvage	
Paraganglioma	72	0	0	72
Pituitary adenoma	5	1	0	6
Pigmented villonodular synovitis	1	2	0	3
Castleman disease	1	0	0	1
Inverted papilloma	0	1	0	1
Histiocytosis I	1	0	0	1
Lymphangioma	1	0	0	1
Hemangiopericitoma	0	2	0	2
Keloid scar	3	109	0	112
Histiocytosis II	2	0	0	2
POEMS syndrome	1	0	0	1
Dermatofibroma	1	0	0	1
Retinal hemangioma	5	0	0	5
Haemophilic Pseudotumor	2	0	0	2
Graves Ophtalmopathy	1	0	3	4
Fibromatosis	0	8	0	8
Total	96	123	3	222

POEMS — polyneuropathy (P), organomegaly (O), endocrinopathy (E), monoclonal protein (M), skin changes (S)

Table 3. Dose per pathology

Diagnosis	Dose [Gy]
Keloid scar	15–21
Paraganglioma	50–54
Fibromatosis	45–60
Pituitary adenoma	45–54
Retinal hemangioma	20–34
Graves ophtalmopathy	20
Pigmented villonodular synovitis	36
Hemangiopericytoma	50.4–54
Histiocytosis II (Rosai Dorfman)	20
Haemophilic pseudotumor	20–24
POEMS syndrome	20
Dermatofibroma	60
Histiocytosis I (Langerhans cells)	20
Inverted papilloma	50.4
Castleman disease	20
Lymphangioma	36

POEMS — polyneuropathy (P), organomegaly (O), endocrinopathy (E), monoclonal protein (M), skin changes (S)

of follow-up, 12 patients (all with keloid scars) showed recurrence, while control was achieved in

Table 4. Acute toxicity

	Number of patients	Percentage
None	121	54.5
Radiodermatitis	45	20.3
Xerostomy	22	9.9
Dysgeusia	13	5.9
Mucositis	6	2.7
Cephalea	5	2.3
Conjunctivitis	4	1.8
Epiphora	3	1.4
Dysphagia	2	0.9
Diarrhea	1	0.5
Total	222	100

94.1% of those who responded. When the Pearson chi-square test was performed to determine the correlation between the response and RT dose, no significance was found ($p < 0.2$), but the correlation between the disease response and RT modality was significant ($p < 0.002$). Of the 12 cases of recurrence, eight received electron RT, and four received brachytherapy.

Table 5. Chronic toxicity

	Number of patients	Percentage
None	110	49.5
Xerostomy	23	10.4
Dysgeusia	21	9.5
Fibrosis	20	9.0
Hypopigmentation	19	8.6
Atrophy	12	5.4
Telangiectasia	6	2.7
Keratitis	5	2.3
Epiphora	2	0.9
Hyperpigmentation	2	0.9
Cephalea	1	0.5
Dysphagia	1	0.5
Total	222	100

Discussion

The level of acceptance of RT for benign disorders is low in many countries [8]. Given the lack of supporting evidence, it is very important to understand the types of pathologies treated with RT and improve patients' therapeutic options [9]. There are two hypothetical mechanisms: anti-inflammatory and antiproliferative. Regarding the anti-inflammatory effect [2–6 Gy], a dose (< 0.5 Gy/fraction) can interact differently during the inflammatory process, causing a reduction in endothelium-leukocyte interactions, vasodilation and the production of adhesion molecules. Antiproliferative treatment (8–10 Gy) results in a delay in the mitotic cell cycle that prevents tissue cell growth. Immunomodulation treatment (> 10 Gy) regulates the antigenic stimulus of lymphocytes, suppressing the local autoimmune process [2, 10, 11].

RT as a treatment for benign diseases is proven to be safe, effective and tolerable, and our clinical experience confirms the results published in the literature [2]. The study population was predominantly female, which was attributable to the increased prevalence of keloid scarring in women (due to perforation and the use of earrings) and to the inclusion of paragangliomas, which the literature reports are more common in women than in men [12–16]. Keloids are entities that occur in 5 to 15% of wounds, and their frequency is 15 times higher in people with highly pigmented skin than in those

with less pigmented skin. The proliferation of fibroblasts is responsible for keloid scars, and LDRT is effective at inhibiting proliferation and inducing apoptosis of target cells via the expression of cytokines in macrophages, leukocytes and endothelial cells, thereby modulating the inflammatory cascade [12–14]. Surgical resection followed by RT is the standard treatment for keloid scarring; surgery alone has an unacceptable recurrence rate (45 to 100%) [13]. In our series, there were 12 recurrences (10.7%); four of these were in patients with a history of up to four surgeries, which impaired their response, and the others were lesions located in stress sites. Thus, adjuvant RT prevents the formation of abnormal scars and offers a good cosmetic result, with a success rate of 60–90%.

Paragangliomas are lesions with a prevalence of 1 to 10 cases per million inhabitants. Since 1950, patients have been treated with RT as an alternative to surgery, with local control rates of 95% [15, 16]. Paragangliomas were the second most frequently treated pathology in our series. RT stopped the progression of symptomatic disease, and all of the paraganglioma patients received photon treatment (IMRT/VMAT); however, the limitations of the study related to the follow-up period must be taken into account since recurrences occurred up to 18 years later. The most frequent location is the carotid, and paragangliomas in this location have a lower recurrence rate than jugulotympanic tumours [15, 16]; in our series, both showed 100% response and control at 45 months.

Dr. N. Ploughman previously presented his experience with radiosurgery for benign intracranial diseases, and the focus was on acoustic neuromas, pituitary adenomas and arteriovenous malformations, with good results (obliteration of 80% of 1-cm lesions and 65% of 3-cm lesions) [17]. Graves' ophthalmopathy involves alterations in the soft tissue of the orbit [18, 19], an active pituitary adenoma can cause hormonal alterations [20], and desmoid tumours have a high recurrence rate after surgical resection; RT is a management option for these pathologies [21]. Additionally, RT can prevent the ossification of arthroplasties, reduce pain in trigeminal neuralgia, and preserve the organ and its function by avoiding aggressive surgeries (in cases of aggressive fibromatosis) [22].

Pituitary adenomas constitute 10% of all intracranial neoplasms in adults. This review included

six patients with pituitary adenomas. Several authors, including Gittoes et al. 1998, have shown that the addition of RT to surgery improves 10-year progression-free survival, from 68% among patients who receive surgery alone to 93% among those receiving surgery plus RT. Moreover, the control rates of radical RT have been shown to approach 95% at 5 and 10 years [17]. In our series, five patients were treated in this context.

Of the cases of retinal haemangioma, one was associated with Von Hippel Lindau disease, and another was associated with type 1 neurofibromatosis. External RT absorbs the exudates associated with retinal detachment at fractional doses of 20–25 Gy. Visual acuity improves in 55% to 80% of cases [19], and the cases reported here showed clinical improvement at one and three months of treatment with AB ultrasound, with a reduction in exudates.

The prevalence of histiocytosis is one per million people, and localization to the central nervous system, excluding the pituitary gland, occurs in 2 to 4% of cases [9]. In this study, this location was uncommon, and adequate control was achieved in the radical treatment context, with acceptable toxicity.

Graves' ophthalmopathy was treated with doses of 20 Gy in 10 fractions; three of four patients received salvage RT, two were refractory to steroids, and one had already undergone decompressive surgery of the medial walls and floor of the orbit. The clinical effectiveness of RT in the management of degenerative pain disorders with a single dose of 0.3 to 0.7 Gy and a total dose of 3 to 10 Gy for pain relief is evident [4], as was observed in the patient with POEMS syndrome.

There are pathologies that require higher doses in the range of 50 to 60 Gy in fractions of 1.8 to 2 Gy due to the characteristics of the pathology (e.g., paragangliomas, haemangiopericytomas, dermatofibromas and fibromatosis). Broerse et al. and Jung found a low risk of tumour induction based on mathematical models; they found that after the fourth decade of life, the lifetime attributable risk is lower than that of the general population [11].

RT for benign pathology has a low toxicity rate, and treatment techniques such as VMAT and IMRT [23] are highly conforming in terms of treatment volume and doses in healthy tissue [24–26]. There is a direct relationship between the radiation dose and the volume of normal tissues associated with

toxicity [11]. Most of our patients had grade 1 and 2 toxicity, and the associations with the RT dose and modality were significant ($p < 0.001$) (lower toxicity was observed with electron RT).

The response to treatment was 94.1%, and the association between disease control at the end of the follow-up and the RT modality was significant ($p < 0.002$). Of the 12 keloid patients who showed recurrence, eight were treated with electrons and 4 with brachytherapy. This reinforces the reports of other publications that brachytherapy is one of the best techniques for the treatment of keloids.

Conclusion

In general, the use of RT for benign pathology has a good response, achieving disease control, improving quality of life and offering acceptable toxicity, as reported in our series. These results prompt the proposal to include inflammatory pathology among our treatment indications.

Conflict of interest

There is no conflict of interest.

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