



## Editorial

## Is There Still a Role for Radiation Therapy in the Management of Benign Disease?

B. Fionda<sup>\*</sup>, A. Rembielak<sup>†‡</sup>

<sup>\*</sup> U.O.C. Radioterapia Oncologica, Dipartimento di Diagnostica per Immagini, Radioterapia Oncologica Ed Ematologia, Fondazione Policlinico Universitario A. Gemelli IRCCS, Rome, Italy

<sup>†</sup> Department of Clinical Oncology, The Christie NHS Foundation Trust, Manchester, UK

<sup>‡</sup> Division of Cancer Sciences, School of Medical Sciences, Faculty of Biology, Medicine and Health, The University of Manchester, Manchester, UK

Recently the Royal College of Radiologists have updated their recommendations on the use of radiotherapy for treating benign disease. It is hoped that this publication will help to raise awareness of the wider potential use of radiation, beyond malignancy [1].

Radiotherapy for benign diseases is not a novel approach and has been a useful treatment modality for these indications since the discovery of radiation more than a century ago. Although there are more than a hundred benign conditions that can be treated with radiotherapy, this scope has steadily been reduced, leading to fewer and fewer benign conditions being considered for radiation treatment [2]. Nowadays in the UK there is rather limited use of radiotherapy for benign conditions in contrast to practice in other parts of the world, for example in Germany.

The clinical picture was further complicated by the recent COVID-19 pandemic, which led to the dramatic change in radiotherapy delivery in general, with more hypofractionated schedules being offered [3]. Some authors indicated that the biggest drop in radiotherapy delivery was seen specifically in benign disorders [4].

Apart from the COVID-19 pandemic, however, the reason for such a decline is multifactorial and needs to be considered at several levels, including clinical, educational, communication and research.

At the clinical level, many non-radiation-based treatments have emerged and successfully replaced radiotherapy. One of these examples is the discovery of new anti-inflammatory drugs offering efficient management and a more favourable toxicity profile with no radiation-related toxicity. In addition, many surgical techniques have been

introduced over the decades, some offering minimal intervention with excellent cosmetic and functional outcomes, hence replacing radiotherapy in certain clinical indications. Regarding educational level, the declining use of radiotherapy has led to reduced opportunities to pass these skills on to the new generations of radiation oncologists. Among non-radiation specialists, the perceived risk of developing radiation-related toxicity, especially late side-effects, including radiation-induced malignancies, is regarded as one of the most feared adverse events. It is often discussed without consideration that the dose of radiotherapy used in benign conditions is much lower than in malignant disease, hence the risk of toxicity is significantly reduced [5]. There is very limited literature evidence and a limited number of randomised clinical trials involving radiotherapy in benign disease. Therefore, in communication with patients such techniques often transpire as under-researched, making the consultation and patient's decision very challenging.

A recently published literature review on indications for radiotherapy in benign diseases confirmed that radiotherapy is still utilised in various benign conditions, especially in situations where previous non-radiation-based treatments have failed or resulted in excessive toxicities or when there is concern regarding further cosmetic or functional outcomes [6]. Such management should always be discussed within the framework of a multidisciplinary team. Radiotherapy is reported to be an effective modality, frequently only with a single treatment, with a rapid (within 24 h) and often long-lasting (from months to years) relief from symptoms, especially in inflammatory conditions [7].

There are at least two major classifications used among clinicians for radiotherapy in benign indications: anatomical and functional. The anatomical classification includes eyes, head and neck, skin, brain, bones and joints, heart and peripheral vascular system. In the functional classification

Author for correspondence: A. Rembielak, Department of Clinical Oncology, The Christie NHS Foundation Trust, Manchester, UK.

E-mail address: [agata.rembielak@nhs.net](mailto:agata.rembielak@nhs.net) (A. Rembielak).

there are four categories: degenerative, hyperproliferative, functional and focal. Table 1 shows the list of main benign conditions treated with radiotherapy. Noticeably, the level of evidence available is extremely heterogeneous. Only about a half of the indications are supported by randomised controlled trials, whereas in the remaining indications there is mainly evidence from prospective observational or retrospective cohort studies.

As mentioned earlier, the Royal College of Radiologists have published their 2023 recommendations on the role of radiotherapy in benign disease. Its 2015 edition listed hidradenitis suppurativa, psoriasis and chronic eczema, among others [8,9]. Keloids represent one of the most widely used indication for radiotherapy. In the literature there are now relatively large series supported by detailed radiobiological analysis. They provide useful clinical guidance as for the radiotherapy timing and treatment schedules. Keloids can also be considered for brachytherapy (interventional radiotherapy) with literature data supporting its favourable dosimetric profile [9]. Unfortunately, the data in other benign skin disease are less robust, with highly variable clinical practice among different radiotherapy centres [10].

The choice of the optimal treatment schedule needs to be based on the most recent findings of radiobiology and molecular biology. It has been shown that by targeting mitotic fibroblasts, myofibroblasts and other inflammatory cells with radiotherapy, these cells may show an altered production of free radicals to hamper proliferative activity and interfere with growth factors and cytokines [11]. Such molecular interaction plays a beneficial therapeutic role, especially in benign conditions such as painful degenerative musculoskeletal and hyperproliferative disorders (e.g. Dupuytren's contracture and Ledderhose's disease [12]). It

is also postulated that radiotherapy mitigates inflammation and facilitates healing by polarising macrophages to an anti-inflammatory or M2 phenotype [8].

Recent developments in modern radiotherapy techniques allows dose to be delivered exclusively within the area of interest, sparing the surrounding tissues and ultimately leading to a further reduction in long-term toxicity. Similarly, brachytherapy offers delivery of high doses of radiotherapy only around the radioactive sources, with a rapid fall-off of dose to the surrounding tissues and organs at risk. The available data suggest that the risks of inducing secondary malignancy following radiotherapy for benign disease is very low and such treatment should be considered in selected patients, particularly the elderly [5].

It is hoped that with increased interest in radiotherapy for benign conditions there will be an international call for well-designed and conducted randomised clinical trials in the field. In some circumstances where such studies are difficult to conduct, for example in rare indications, systematic reviews and possible meta-analysis could help with higher quality evidence. Pterygium is one of these rare conditions where multiple drug-based treatment options (bevacizumab, 5-fluorouracil, mitomycin C) are used in the postoperative setting to reduce local recurrence. Yet, there is still a role for adjuvant radiotherapy, as shown in the meta-analysis by Zeng *et al.* [13].

International networking and close communication play a pivotal role in the further development of radiotherapy in benign conditions. Recently, the International Organisation for Radiotherapy for Benign Conditions (IORBC) has been launched with an aim to promote the awareness of radiotherapy for benign conditions and to deliver education and training to radiation and other healthcare specialists, with the ultimate goal of improved patient outcomes [14]. It is

**Table 1**

List of potential indications of benign conditions that may be treated by radiation therapy with focus on level of evidence according to Oxford Centre of Evidence-based Medicine classification (modified from [6])

		Functional category					
		Degenerative	Hyperproliferative	Functional	Focal lesion		
Anatomical site	Eye		Pterygium	1a	Graves' disease Orbital pseudotumour	1a 4	
	Head and neck				Sialorrhoea	4	
	Skin		Keloid	1a	Lymphatic fistula	4	
	Brain				Arteriovenous malformation	1b	
					Meningioma	1a	
					Acoustic neuroma	2a	
					Pituitary adenoma	4	
					Trigeminal neuralgia	4	
	Bones and joints	Arthritis Tendinitis	1b 1b	Dupuytren's disease Ledderhose's disease	1b 4	Heterotopic ossification	1a
	Heart and peripheral vascular system				Coronary stent restenosis Vascular stent restenosis	1a 1a	
				Refractory cardiac arrhythmias	4		

hoped that guidelines and recommendations will increase acceptance of radiotherapy use in the treatment of benign diseases, but clinical studies and trials are required to gain wider clinician and patient acceptance.

## Conflicts of interest

The authors declare no conflicts of interest.

## Author Contributions

BF and AR are guarantors of integrity of the entire study. BF and AR were responsible for study concepts and design. BF was responsible for literature research. BF and AR were responsible for experimental studies and data analysis. BF was responsible for manuscript preparation. AR was responsible for manuscript editing.

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