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Editorial

Radiotherapy for Benign Disease: Current Evidence, Benefits and Risks

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Most patients treated by external beam radiotherapy are being treated for cancer. However, historically, many patients have been treated with radiotherapy for a variety of benign (i.e. non-neoplastic) conditions. Furthermore, radiotherapy is also used for the treatment of a wide range of benign tumours [1].

In recent years, the Faculty of Clinical Oncology of the Royal College of Radiologists has become aware that, within the UK, the use of radiotherapy for benign conditions has declined, with varying and often small patient numbers being treated. This editorial aims to highlight this issue and to summarise a recent report by a Royal College of Radiologists working group [2]. The report is designed to inform the development of a more evidence-based and equitable strategy for the use of radiotherapy, where it has proven efficacy, across all parts of the UK. Furthermore, the document will serve as a 'handbook' for clinicians to consult when referred a patient with a benign condition. It was agreed that the review should include the use of radiotherapy for most benign conditions historically treated by external beam radiotherapy and selected conditions treated by stereotactic (brain) radiotherapy. The review also includes selected benign tumours, generally those that are rarely treated by radiotherapy and where the literature is not well known (see Table 1).

In order to provide an estimate of the current use of radiotherapy for benign disease, a questionnaire survey of radiotherapy departments throughout the UK was undertaken in 2012. This requested the numbers of patients treated per annum for a range of benign tumours and non-malignant conditions. Responses were received from 25/61 departments (41%). This showed a core of activity in many centres, particularly for some benign tumours. When radiotherapy was used for non-malignant conditions, those most commonly treated were heterotopic ossification, keloid scarring, thyroid eye disease and Dupuytren's contracture. The large activity for treatment of trigeminal neuralgia (in one centre) and vestibular schwannoma were related to treatment with stereotactic radiosurgery. One important feature was the wide variation in practice across the UK. For example, one centre annually treated about 64 patients with keloid scarring, whereas most others treated none. As the degree of variation was not clear before the survey, potential reasons that might explain the inter-departmental variation were not asked for. Details of numbers treated for individual conditions are provided in the main document. There are conditions that are considered to be more appropriate for treatment than others, for example most departments (19/25; 76%) reported treating patients with thyroid eye disease, but no department reported treating patients with pterygium, although this was often treated up to the 1980s.

The review includes discussion of the radiobiological principles of radiotherapy for benign conditions, including the potential influence of a wide range of radiotherapy-related and patient-specific factors. The exposure of normal tissues to ionising radiation in the intermediate dose range (about 20–40 Gy) is discussed, including the vascular, stromal and anti-inflammatory sequelae. Broadly, there are two basic mechanisms that can be exploited. First, the anti-proliferative effect of radiotherapy [3–5], which, for example, can be exploited to reduce the risk of heterotopic ossification after hip replacement. Second, the anti-inflammatory effect [6] can be used for the treatment of a number of soft tissue inflammatory conditions, such as thyroid eye disease.

The radiotherapy doses used for the treatment of benign conditions are often well below the range used to treat cancer. For example, a so-called 'anti-inflammatory dose' of

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Table 1
Individual diseases reviewed

Disease group	Diseases reviewed with the number of centres out of 25 respondents reporting treatment
Head and neck	Paragangliomas (11) Juvenile nasopharyngeal angiofibroma (4) Pleomorphic adenoma (N) Sialorrhea (2)
Eye	Thyroid eye disease (19) Orbital pseudotumour (4) Pterygium (0) Age-related macular degeneration (0) Choroidal haemangioma (0)
Central nervous system	Grade 1 meningioma (N) Cerebral arterio-venous malformations (N) Trigeminal neuralgia (1) Vestibular schwannoma (8)
Orthopaedic/ musculoskeletal	Dupuytren's disease of the hand (4) Plantar fibromatosis of the foot (Ledderhose disease) (N) Plantar fasciitis (1) Peyronie's disease (0) Heterotopic ossification of the hip (14) Pigmented villonodular synovitis (PVNS) (4) Vertebral haemangioma (1) Aneurbysmal bone cyst (1)
Skin/soft tissues	Keloid scarring (15) Lentigo maligna (N) Hidradenitis suppurativa (1) Psoriasis (N) Chronic eczema (1) Prevention and treatment of gynaecomastia due to endocrine therapy for prostate cancer (N)

N – not included in the original questionnaire survey, but reviewed in the main document.

radiotherapy is often around 20 Gy in 10 fractions or its equivalent. The highest doses used are for the treatment of benign tumours (40–50 Gy in 2 Gy fractions) and, consequently, for most patients acute toxicity is rarely a problem. The most important age-dependent side-effect for these radiation doses is the potential increased risk of radiation-induced cancer (RIC). This is considered for a range of tissues and is further detailed in the discussion of the individual indications.

Interpretation of the literature on radiotherapy for benign conditions is problematic. Much of the evidence is based on case reports and single institution case series, although randomised studies and systematic reviews do exist. Many of the more substantial studies using radiation in the dose range applicable to treating benign disease relate to regimens no longer in use and delivered with obsolete equipment, e.g. ankylosing spondylitis [7–9]. Consequently, extrapolation to current treatment indications with modern techniques is problematic. Although these groups have been followed-up for many years, many other studies tend to have relatively short-term follow-up. This may be a problem for younger individuals and especially children in terms of balancing the long-term benefits and risks. For some conditions evidence is more complete; for example, there have been randomised trials into the benefits of radiotherapy for treating pterygium [10,11] and there is ongoing clinical research in the field of radiotherapy for macular degeneration.

The decline in the use of radiotherapy for benign conditions is probably multifactorial, but important factors would be increased availability of alternative medical therapies, advances in surgery and also concerns as to the potential risk, if very small, of RIC. This is exemplified by the increased incidence of leukaemia after radiotherapy for ankylosing spondylitis [7–9]. However, bearing in mind the age range of most patients and the relatively low radiotherapy doses used, often to peripheral areas of the body, the risks of radiotherapy may be lower than the risks of alternative therapies such as anti-inflammatory drugs or other interventions. Clearly, the risk of RIC is an issue that needs to be discussed with patients. Indeed, it is also a factor that may influence the judgement of referring clinicians, for example ophthalmologists, dermatologists and orthopaedic surgeons. As the factors governing the risk of RIC are complex, hard to estimate and often very patient specific (e.g. age, site of irradiation, dose, etc.), guidance is provided as to the most important factors that should be used to advise patients and referers [12–14]. Unfortunately, only in a few instances is there any substantive quantitative evidence of RIC risk, as the numbers required to estimate risk are very large and the numbers who currently receive radiotherapy for many of these conditions is relatively small; additionally they would require very long follow-up to detect RIC. With these provisos, an attempt has been made to identify the risk to inform discussion with patients considered for radiotherapy for a wide range of benign conditions (Table 1).

The limited use of radiotherapy for benign conditions in the UK is in contrast to practice in Germany. This has been informed by the reports of the German Working Group on Radiotherapy of Benign Diseases, which has extensively reviewed the use of radiotherapy for benign disease in a series of Patterns of Care Study reports. The conclusions were that radiotherapy was a well-accepted modality that was relatively often used for a wide range of benign diseases; however, significant departmental and geographical variations in its use were evident. At that time (2000–2002) they provided consensus guidelines on the use of radiotherapy [15,16], informed consent, treatment documentation and follow-up, including late toxicity scoring. A European Society for Radiotherapy and Oncology workshop in 2004 also reviewed the use of radiotherapy for benign disease and a consensus summary was published [17].

As with treating cancer, an overarching principle that also applies when treating benign disease is to minimise the volume of irradiated normal tissue. Current radiotherapy techniques can help to achieve this. For instance, modern imaging can allow more accurate target definition and other developments in immobilisation and image guidance can

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allow reduced margins. Techniques such as intensity-modulated radiotherapy, can achieve better conformality to complex target volumes, although this may increase the volume of tissue receiving lower doses. In some sites, particularly the skull base, dose distributions achievable with proton therapy may have advantages. It is important to note that there are currently only limited data regarding the application of modern radiotherapy techniques to the treatment of benign conditions, including the implications for RIC risks from treatments such as intensity-modulated radiotherapy.

Much of the evidence reviewed is derived from radiotherapeutic literature, and it is frequently difficult to be certain as to how the use of radiotherapy would fit into the overall multimodality management of these conditions. It is hoped that this new review will lead to a reappraisal of the role of radiotherapy for benign conditions. It is recommended that there should be discussion at national and local levels between clinical oncologists and representatives of other professional bodies that often provide the primary consultants for these disparate conditions, e.g. ophthalmologists, orthopaedic surgeons, neurologists, dermatologists and urologists.

It is recommended that radiotherapy departments should review their protocols for the treatment of benign diseases, including, where appropriate, the use of modern techniques. In view of the ageing population it is possible that radiotherapy could provide a useful treatment modality, with low toxicity, for patients with a range of benign conditions in an age group where the risk of RIC is not clinically relevant. Even in younger patients the benefits versus risk may be acceptable. It is hoped that the disease-specific information contained in the document will assist clinicians in the consent process, in particular advising patients on the balance between risks and benefits.

In England there should be discussion within the Radiotherapy and Stereotactic Radiotherapy Clinical Reference Groups and the relevant commissioning organisations in Scotland, Wales and Northern Ireland regarding potential national approaches.

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