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Clinical Oncology
The Royal College of Radiologists

Recommendations for using radiotherapy for benign disease in the UK

March 2023

Contents

Foreword

Radiotherapy has multiple potential uses in the treatment of non-cancerous conditions but there is much variation in how it is employed in the UK. Many clinical oncologists will use radiation for one or two of these indications but there are few, if any, experts in the use of radiation for benign diseases as a whole. The Royal College of Radiologists (RCR) therefore published an evidence-based review and guideline for the use of radiotherapy for benign disease in 2015 under the leadership of Professor Roger Taylor with the intention of harmonising practice and explaining the utility of radiotherapy for these conditions.

The evidence base in this field is slow to change, so there are relatively few major updates in this second edition. There is a new chapter on total lymph node irradiation in patients who have rejection of solid organ transplants. We have removed chapters covering diseases where radiotherapy is rarely, if ever, used in the UK.

Many thanks to Roger Taylor, Tom Roques, Norma Sidek and Robin Prestwich for undertaking the review and rewriting of this document. We are also grateful to Karl Butterworth, Sara Erridge, John Frew, Sarah Jefferies, Agata Rembielak, Maria Vassilou, Richard Shaffer, Gillian Whitfield and James Wylie for helping to review and redraft relevant sections.

We would also like to thank members of the original 2014 working group whose effort has provided such a secure basis for this update: Roger Taylor, Paul Hatfield, Stephanie McKeown, Robin Prestwich and Richard Shaffer.

This guidance should prove a valuable resource for departments to review and develop their protocols for these rare indications for radiotherapy, which nonetheless can provide patients with considerable benefits.

Nicky Thorp

Introduction

There are two basic mechanisms that can be exploited for the treatment of benign conditions with radiotherapy (RT). First, the anti-proliferative effect of RT, which can be used, for example, to reduce the risk of heterotopic ossification (HO) following hip replacement or the recurrence of pigmented villonodular synovitis following a synovectomy. Second, the anti-inflammatory effect of RT can be used to treat soft-tissue inflammatory conditions such as Graves' orbitopathy (GO). RT doses employed 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 RT is often around 20 Gray (Gy) in ten fractions or its equivalent and, for most patients, acute toxicity is not a problem.

In recent decades, the use of RT for benign conditions in the UK has declined. It is likely that this is largely due to the increased availability of alternative medical therapies, advances in surgery and concerns as to the potential, if very small, risk of radiation-induced cancer (RIC). In Germany, RT is still widely used for a range of benign conditions. A 2018 patterns of care study suggests that as many as 68% of all patients receiving RT in that country do not have cancer.[1] A 2014 survey of UK RT departments conducted by the RCR, discussed in the first edition of this guidance, established that the numbers treated in the UK are much smaller and they vary considerably from one department to another. There is also a paucity of formal guidance documents about the use of RT in benign disease – the last published German guidelines are from 2015.[2–5] The International Organisation for Radiotherapy for Benign Conditions (https://iorbc.com) has recently been established.

Interpretation of the literature is problematic. Reports of the use of RT for many benign conditions comprise mainly case reports or small single-institution retrospective series. Follow-up tends to be relatively short term in comparison with the life expectancy of patients with benign conditions and it is often difficult to ascertain the long-term benefits and risks of treatment. On the other hand, for some conditions such as GO, randomised trials have been conducted recently and there is ongoing clinical research in the use of RT for other benign conditions.

For some conditions there are large follow-up studies on the risks of RIC but many of these studies are for conditions that are no longer being treated with RT; for example, tinea capitis, peptic ulcers and ankylosing spondylitis. It is very likely that one of the reasons for the decline in the use of RT for benign conditions is the fear of radiation and, in particular, concern about the risk of RIC, exemplified by the increased incidence of leukaemia following RT for ankylosing spondylitis. Bearing in mind the age range of most patients and the relatively low RT doses employed – often to peripheral areas of the body – the risks of RT may be lower than the risks of alternative pertinent therapies such as anti-inflammatory drugs and other interventions.[6]

The first edition of this document included a comprehensive section on the radiobiology of treating benign disease and chapters on all benign conditions for which RT was thought to be in use in the UK. This second edition has been streamlined to focus on the most common benign conditions for which RT is established as a treatment modality. It is hoped that the document will provide a useful resource for clinical oncologists who receive referrals for patients with these conditions. The evidence for use of radiation in benign disease continues to evolve so this document should not be viewed as a proscriptive list of the only benign conditions that can be treated with RT in the UK. The evidence base for any other indications should be carefully considered before local protocols are developed and approved.

Meningiomas are no longer included as they are managed by neuro-oncology multidisciplinary teams (MDTs) together with other central nervous system (CNS) tumours. Other chapters have been removed from this second edition in light of the fact that RT is no longer or rarely used to treat them in UK practice: orbital pseudotumour/idiopathic orbital inflammation; pterygium; age-related macular degeneration; choroidal haemangioma; cerebral arteriovenous malformations; hidradenitis suppurativa; psoriasis; chronic eczema; Peyronie's disease; vertebral haemangioma and aneurysmal bone cyst. A new section on total lymphatic irradiation (TLI) has been added.

Many of the recommendations in the remaining sections are largely unchanged from the first edition; however, the latest evidence is now included. Much of the evidence base for use of RT in benign disease is Grade C level, although randomised studies and systematic reviews exist in some areas.

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Summary of recommendations

The types of evidence and the grading of recommendations used within this review are based on those proposed by the Scottish Intercollegiate Guidelines Network (SIGN) (see appendix 2).

1 Orthopaedic/musculoskeletal

1.1 Dupuytren's disease of the hand

1.1.1 RT is effective in the early stages of Dupuytren's disease, where there is no contracture (stage N) or a contracture of up to ten degrees (N/I) (Grade B).

1.1.2 Patients with more advanced disease should not be treated with RT but may be offered surgical release (Grade C).

1.1.3 Due to the variable progression of this disease, only patients whose disease has progressed within the last 6–12 months should be treated (Grade C).

1.1.4 The aim is to treat nodules and cords to the periosteum of the hand bones, for a depth of 5–15 mm. Therefore, 120–15 kV photons, or up to 6 mega-electron volts (MeV) electrons with appropriate bolus would be reasonable. Proximal and distal margins of 1–2 cm on palpable nodules and cords, with 0.5–1 cm lateral margins should be used (Grade D).

1.1.5 RT dose: the regimen of choice is 30 Gy in ten fractions, consisting of two phases of 15 Gy in five fractions with a gap of 6–12 weeks between the two phases. An alternative fractionation is 21 Gy in seven fractions on alternate days over two weeks (Grade B).

1.2 Plantar fibromatosis (Ledderhose disease)

1.2.1 RT seems to be an effective modality of treatment for plantar fibromatosis, with good local control and symptomatic benefit (Grade B).

1.2.2 The recommended total dose would be 30 Gy in ten fractions, given in two separate phases of 15 Gy in five daily fractions, with 12 weeks between the two phases (Grade B). The RT can be delivered using orthovoltage photons or electrons as described above for Dupuytrens RT.

1.3 Plantar fasciitis

1.3.1 RT is effective and may be considered for patients who have had plantar fasciitis for more than six months and who have failed conservative management (Grade A).

1.3.2 Dose and technique: 3–6 Gy in six fractions (0.5–1 Gy per fraction) over three weeks delivered using a single lateral field, a parallel-opposed pair of lateral fields or 200–250 kV photons (Grade A).

1.4 Heterotopic ossification of the hip

1.4.1 RT and non-steroidal anti-inflammatory drugs (NSAIDs) are both effective in the prevention of HO but NSAIDs are more cost-effective (Grade A).

1.4.2 RT should be considered in people who are unable to take NSAIDs or who are at risk of more severe HO. It should be avoided in younger patients (for example <50 years).

1.4.3 RT can be given either pre- or postoperatively and should be delivered within four hours before surgery or within 96 hours after surgery (Grade A).

1.4.4 A single fraction of 7 Gy of RT seems optimal and is equivalent in efficacy to increased doses and fractions (Grades A–C), with a likely reduction in the risk of second malignancy (Grade D).

1.4.5 The discussion above covers the prevention of HO of the hip. RT has been used to prevent HO at other sites, but data on its success are more limited.

1.5 Pigmented villonodular synovitis (PVNS) / tenosynovial giant cell tumour (TSGCT)

1.5.1 TSGCT is a rare condition and it is difficult to draw firm conclusions as to optimum management.

1.5.2 For patients with diffuse TSGCT, high local control rates for surgery and postoperative RT are achieved with low toxicity. Typical RT doses are in the region of 35–40 Gy in 15–20 fractions (Grade C).

1.5.3 Although there are several recent single-institution case series supporting the use of RT for PVNS, this modality is little used in the UK, and it would probably benefit from further discussion with orthopaedic surgeons on a local and national level to define indications for postoperative RT and also the optimum radiation modality.

2 Skin

2.1 Keloid scarring

2.1.1 The evidence for RT after keloid excision seems to indicate a reasonably low recurrence rate (Grade C).

2.1.2 If RT is to be used, it should be administered ideally within 24 hours and at maximum within 72 hours of surgical excision (Grade D).

2.1.3 Superficial or orthovoltage (generally 60–120 kV) electrons or brachytherapy can be used.

2.1.4 There is no one agreed schedule that can be recommended and fractionation varies among centres, therefore the use of postoperative RT should follow local protocols and expertise.

2.1.5 Consider body-site-specific fractionation (Grade C).

2.2 Actinic keratosis (AK) and cutaneous Bowen's disease (squamous cell carcinoma [SCC] *in situ*)

2.2.1 Consider RT to treat Bowen's disease of the skin in symptomatic disease that is refractory or recurrent after other treatment modalities.

2.2.2 Doses from 25–70 Gy would appear to be effective and local recurrence rates are equally low in patients treated with high- and low-dose RT regimes. Avoid (where possible) fraction sizes over 4 Gy, which are associated with long-term poor cosmetic outcome.

2.2.3 Consider high-dose-rate brachytherapy in concave shapes, such as on scalp or dorsum of hand or foot skin.

2.3 Lentigo maligna (LM)

2.3.1 Biopsy is recommended for diagnosis of LM and exclusion of melanoma (Grade C).

2.3.2 Factors to consider in choice of treatment include the size and location of the lesion, patient age, co-morbidity and preference. Surgical excision is considered the treatment of choice (Grade C) but may not be possible without a reasonable cosmetic/functional deficit.

2.3.3 RT is an effective non-surgical treatment modality for LM (Grade C).

2.3.4 RT treatment may be with superficial X-rays, electrons or brachytherapy. Evidence to guide optimum doses is very limited, although doses similar to those used in the treatment of skin cancer are appropriate and are tailored to the site and size of the lesion and likely cosmesis. For external beam RT (EBRT), conventionally fractionated schedules may provide optimal long-term cosmetic results but at the cost of a more protracted treatment schedule; these include 54 Gy in 27 fractions (definitive), 50 Gy in 25 fractions (adjuvant). Alternative hypofractionated schedules for EBRT include 40–45 Gy in ten fractions over two weeks and 50 Gy in 15 fractions over three weeks (Grade C).

2.3.5 Histological evidence has shown that LM can extend beyond clinically visible abnormality. Therefore, treatment doses should be delivered to encompass at least a 1 cm clinical target volume (CTV) around the clinically detectable lesion and to 5 mm depth (Grade C).

3 Head and neck

3.1 Head and neck paraganglioma

3.1.1 A period of observation is usually appropriate in asymptomatic patients (Grade C).

3.1.2 Surgery, EBRT and stereotactic radio surgery (SRS) all offer high local control rates and are primary treatment options (Grade B).

3.1.3 RT is preferred for more advanced lesions due to the morbidity of surgery (Grade B).

3.1.4 An EBRT dose of 45–54 Gy in 1.8–2 Gy per fraction is recommended (Grade D).

3.1.5 For SRS a typical marginal prescription dose is 12–15 Gy as a single fraction (Grade C).

3.2 Juvenile nasopharyngeal angiofibroma (JNA)

3.2.1 Surgery is regarded as the treatment of choice for JNAs (Grade C).

3.2.2 Primary RT is an effective treatment modality if the disease is deemed incompletely resectable without excess morbidity (Grade C).

3.2.3 Surgery or RT can be considered for recurrent disease (Grade C).

3.2.4 Conventionally fractionated doses in the mid-range of 35–45 Gy are recommended, with a dose of 36 Gy in 20 fractions being appropriate, with no evidence of a dose response in the higher end of this range.

3.2.5 It is appropriate to consider proton beam therapy.

3.3 Salivary gland pleomorphic adenoma

3.3.1 High rates of local control are achieved by surgery with clear margins. Adjuvant RT improves local control in subsets of patients and is recommended for patients who are at a higher risk of recurrence, as indicated by incompletely resected tumours, positive margins or multifocal recurrences (Grade C).

3.3.2 Use 3D computed tomography (CT) planned photons and intensity-modulated radiotherapy (IMRT) or volumetric-modulated arc therapy (VMAT). For parotid pleomorphic adenomas the target volume includes the whole parotid bed (Grade D).

3.3.3 Variable RT doses are reported in the literature with no clear evidence of dose response. Although higher doses similar to those used for malignant salivary disease have been used, doses of the magnitude of 50 Gy in 25 fractions over five weeks have been commonly employed with good outcomes (Grade C).

3.4 Sialorrhea

3.4.1 RT is an effective treatment modality in palliating sialorrhea in patients with advanced neurodegenerative disorders (Grade C).

3.4.2 Recommended schedules include 20 Gy in four fractions over two weeks (two fractions per week) and 12 Gy in two fractions over one week. Retreatment may be more commonly required after the lower dose of 12 Gy in two fractions (Grade C).

3.4.3 Target volume usually includes both submandibular glands and caudal two-thirds of both parotid glands (Grade C).

3.4.4 Data on retreatment is very limited but it can be effective (Grade C).

4 Brain and eye

4.1 Graves' orbitopathy (thyroid eye disease)

4.1.1 Ensure all patients being considered for orbital RT have been assessed in a thyroid eye clinic with ophthalmologist and endocrinologist input (Grade D).

4.1.2 Consider orbital RT in moderate-to-severe active GO that has not responded to intravenous (IV) methylprednisolone (Grade D).

4.1.3 Combine RT with oral or IV steroids to improve effectiveness and reduce side-effects (Grade D).

4.1.4 Use 20 Gy in ten fractions, though lower doses may also be effective (Grade B).

4.1.5 Avoid orbital RT in people who have diabetic retinopathy or uncontrolled hypertension. Any diabetes and younger age are relative contraindications (Grade C).

4.2 Vestibular schwannoma (VS) / acoustic neuroma

4.2.1 Patients should be managed by an MDT with expertise in all treatment modalities utilised for VS (Grade D).

4.2.2 Initial management for all but the largest lesions should be active surveillance to assess the rate of enlargement.

4.2.3 Surgery should be considered for large VS compressing the brainstem (Koos IV) (Grade C).

4.2.4 SRS is standard treatment for small but enlarging VS (Koos I–III) with a marginal dose of 12–13 Gy being the current standard (Grade C).

4.2.5 Hypofractionated or conventionally fractionated RT can be considered for patents with large (Koos IV) lesions when the patient is medically unfit for surgery or wishes to avoid surgery (Grade C).

5 Total lymphatic irradiation (TLI)

5.1 Total lymphatic irradiation (TLI)

5.1.1 TLI can be considered in close liaison with the transplant centre as treatment for patients refractory to or intolerant of conventional medical immunosuppression for solid organ rejection (Grade D).

5.1.2 Recommended dose is 8 Gy in ten fractions delivered twice per week (Grade D).

5.1.3 Patients require monitoring for bone marrow suppression during treatment to avoid excessive infection/bleeding risks (Grade D).

1 Orthopaedic/ musculoskeletal

1.1 Dupuytren's disease of the hand

Background

Dupuytren's disease is a common benign proliferative disorder of the palmar fascia and is part of a group of fibromatoses that includes plantar fibromatosis (Ledderhose disease) and penile fibromatosis (Peyronie's disease). Dupuytren's disease tends to present in the sixth and seventh decade of life but can present earlier or later. The cause of these fibromatoses is unknown, but they appear to have a genetic component.[1] Additional risk factors include prior hand trauma, epilepsy and diabetes mellitus.

The early stage consists of subcutaneous palmar nodules, skin retraction and cord formation. The disease course is variable, but is more severe in males, those with a positive family history, early onset, bilateral disease and where there are ectopic lesions (such as Peyronie's disease). Eventually the cords thicken and contract and cause fixed flexion of the metacarpophalangeal or proximal interphalangeal joints of the fingers, known as Dupuytren's contracture.

Management

There is no cure for Dupuytren's disease, and it is most often treated in the advanced stages, where there is significant (for example >30 degrees) contracture, particularly where hand function is impaired.

Management is directed towards releasing the contracture and improving function. There are three main methods for release of contractures.

1. Fasciectomy is the most common approach.[2] There are several variations of this approach. In a 'limited' fasciectomy, the contracture is corrected, and some diseased tissue is removed; in a 'radical' (total) fasciectomy, the contracture is corrected with attempted removal of all fascia and disease, which can also be combined with removal of overlying diseased skin with the insertion of skin grafts (dermofasciectomy). These procedures are associated with a long recovery time and a considerable complication rate. The reported range of recurrence rates is wide at 18–73% and depends on follow-up time and definitions of recurrence.[3–6]
2. Needle aponeurotomy: a needle is used to puncture the fibrous cord in order to weaken it until it can be broken by mechanical force. This is minimally invasive but is associated with a recurrence rate of 65% at three years.[7]
3. Collagenase (Xiapex) treatment involves the injection of an enzyme that dissolves the collagen in the Dupuytren's cord, which can then be mechanically broken.[8] In those fingers that are successfully straightened, there is a 35% three-year contracture recurrence rate.[9] This product was withdrawn from Europe by the manufacturer in March 2020.

Radiotherapy

There are many retrospective studies in the literature going back many decades that have indicated the efficacy of RT for Dupuytren's disease.[10–15] However, their usefulness is generally limited by baseline differences in patients and disease characteristics, RT doses and fractionations, definitions of endpoints and short follow-up periods. The staging of Dupuytren's disease is illustrated in Table 1, where stage N is disease with no contracture,

stage N/I is disease with up to 5–10 degrees of contracture, and subsequent stages indicate disease with more severe contracture.[16,17]

A retrospective study with a median follow-up of six years reported on 96 patients (142 hands).[17] Of the patients included in this study, 70% had stage N or N/I disease. The patients were treated with 120 kilovoltage (kV) photons with a total dose of 30 Gy in ten fractions, which was split into two phases of 15 Gy in five fractions over one week, with a six-week gap between the phases. At the most recent follow-up, 11% of hands showed progression, although 23% of those with less than five years' follow-up were found to have progressed. Only minor side-effects were noted.[17]

Similarly, a retrospective study with a median follow-up of ten years looked at 99 patients (176 hands) treated with the same dose and fractionation (30 Gy in ten fractions) and demonstrated progressive disease in 16% of patients with stage N, 33% in stage N/I, 65% in stage I and 83% in stage II.[18] A third study, with a median follow-up of 13 years, looked at the outcomes of 135 patients (208 hands) treated with 30 Gy in ten fractions (as above) and demonstrated progressive disease in 31% overall, with progression by stage of: N=13%, N/I=30%, I=62%, II=86%, III/IV=100%.

Additionally, it was noted that the outcome was significantly better if the disease was treated within one year of appearance of symptoms compared with more than two years since the appearance of symptoms.[19]

Table 1. Staging classification of Dupuytren's disease[16,17]

Stage	Clinical symptoms	Extent of extension deficit
N	Nodules, cords, skin retraction etc	None
N/I*	As stage N + deformity of fingers	1–10
I	As stage N + deformity of fingers	11–45
II	As stage N + deformity of fingers	46–90
III	As stage N + deformity of fingers	91–135
IV	As stage N + deformity of fingers	>135

*In some papers, N/I is defined as 1–5° of extension deficit.

A prospective trial randomising patients between two dose levels (with no control group) looked at 129 patients (198 hands).[20] All of them had disease that had progressed within the last six months. Patients were treated with 120 kV at 40 centimetres (cm) focus to skin distance (FSD), with the aim to treat to a depth of 5–15 mm (down to the periostium of hand bones). The treated area was palpable disease with margins of 1–2 cm proximally and distally, and a lateral margin of 0.5–1 cm. Untreated areas were shielded with lead.

Patients were randomised to two phases of 15 Gy in five fractions each (as above, with an eight-week gap between the phases, total dose 30 Gy, or 21 Gy in seven fractions, given on alternate days over a period of 15 days. The treatment was generally well tolerated, with

acute Grade 1 toxicity of 38% and Grade 2 toxicity of 6%. There was a chronic toxicity rate of 5% at 12 months. At 12 months follow-up, the overall treatment failure rate was 8%, with 2% needing corrective surgery.

Progression by stage was: 0% in stage N, 3% in N/I, 15% in stage I, 40% in stage II. There was no significant difference in efficacy or toxicity between the two dose groups.

A long-term follow-up of this study, published as a textbook chapter, reported on the outcomes of patients followed up for at least five years (median follow-up of 102 months).[21] In the reported study, 406 patients (812 hands) were treated with RT (total dose 21 Gy or 30 Gy, as above, although the gap between the two phases was quoted as 10–12 weeks) and compared to a non-randomised control group of 83 patients (166 hands) who had chosen to be observed rather than treated. All had progressive disease in the last 6–12 months. Side-effects in the irradiated group were acute toxicity in 28% (2% Grade 2) and chronic toxicity in 14% (all Grade 1). Acute and chronic toxicity rates were increased in the 21 Gy group compared with the 30 Gy group. Overall, disease progression by stage was stage N=10%, N/I=41%, I=58%, II–IV=89%.

Regarding efficacy, significant reduction in disease progression and the need for surgery were demonstrated in both treatment groups compared with the control group, although there was no significant difference between the two treatment groups (Table 2).[21]

An interventional procedure guidance published by NICE in 2016[22] concluded that the evidence on RT for early Dupuytren's disease raised no major safety concerns but current evidence on its efficacy was inadequate in quantity and quality to fully endorse its use. The review concluded that RT should only be used with special arrangements for clinical governance, consent and audit or research.

The DEPART trial is a randomised multi-option study comparing observation versus RT for early disease or surgical intervention for more advanced disease with or without adjuvant RT and is presently recruiting in Australia.

Table 2. Outcome of long-term follow-up of Seegenschmiedt study of radiotherapy for Dupuytren's disease[21]

Dose	Regression or stable disease (%)	Progression (all clinical signs, %)	Surgery (%)
Control (n=122)	38	62	30
21 Gy (n=293)	76	24	12
30 Gy (n=245)	80	19.5	8

Potential long-term consequences of radiotherapy

An estimate of the statistical risk of lethal skin cancer caused by RT at age 45 for Dupuytren's disease is provided by the International Dupuytren Society in collaboration with the German Centre for Environmental and Health Research.[23] In patients exposed to RT for Dupuytren's disease (30 Gy low-energy fractionated X-rays) the risk is estimated to be about 0.02% higher than the probability of dying from cancer without RT (estimated to

be ~24 ± 0.26%). Since the excess risk is very small compared with the background risk it is impossible to evaluate this accurately in a clinical study.

It should be noted that the risk is subject to a number of assumptions. In particular, it is calculated for one hand, so the risk doubles if both hands are treated. The calculations are based on an irradiated area of 60 cm^2, which is fairly large, so the risk is reduced if the irradiated area is smaller, and it assumes that the remaining hand and body are sufficiently protected during treatment. The risk estimate is also affected by age at time of exposure to RT treatment. For a 25-year-old patient the risk is approximately double that of a 45-year-old and it is about half for an individual receiving treatment at age 60. Although rare, Dupuytren's disease can occur in children and young adults. Clearly their risk of RIC will be increased further so RT should only be used alongside careful counselling of the patient.

The above estimate applies to the risk of a fatal radiation-induced skin cancer. There may also be a risk of sarcoma; this is difficult to assess but is likely to be less than the risk for skin cancer. One factor that may affect the risk in an unknown manner is the reported higher risk of dying of cancer in individuals with Dupuytren's disease.[24] A recent study has modelled the risk of a range of cancers arising from radiation exposure for benign disease using male and female anthropomorphic phantoms.[25]

Although not exactly comparable, the calculated risk was similar to the above estimate. To the authors' knowledge, not a single case of cancer caused by radiation therapy for Dupuytren's disease has been reported in the literature.

It should be noted that there are other more immediate effects that, although less serious than cancer, have a greater probability of occurring.

For example, in a long-term follow-up of 176 radiated hands, 25% exhibited anhidrosis, 8.5% skin atropy and >1% reduced wound healing.[18]

Recommendations and radiotherapy technique

1.1.1 RT is effective in the early stages of Dupuytren's disease, where there is no contracture (stage N) or a contracture of up to ten degrees (N/I) (Grade B).

1.1.2 Patients with more advanced disease should not be treated with RT but may be offered surgical release (Grade C).

1.1.3 Due to the variable progression of this disease, only patients whose disease has progressed within the last 6–12 months should be treated (Grade C).

1.1.4 The aim is to treat nodules and cords to the periosteum of the hand bones, for a depth of 5–15 mm. Therefore, 120–150 kV photons or up to 6 MeV electrons with appropriate bolus would be reasonable. Proximal and distal margins of 1–2 cm on palpable nodules and cords, with 0.5–1 cm lateral margins should be used (Grade D).

1.1.5 RT dose: the regimen of choice is 30 Gy in ten fractions, consisting of two phases of 15 Gy in five fractions with a gap of 6–12 weeks between the two phases. An alternative fractionation is 21 Gy in seven fractions on alternate days over two weeks (Grade B).

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1.2 Plantar fibromatosis (Ledderhose disease)

Background

Ledderhose disease (plantar fibromatosis) is a rare benign hyperproliferative fibromatosis of the plantar fascia of the foot. It is histologically identical to Dupuytren's disease of the hand, and the two conditions coexist in 20–30% of cases. The underlying cause is unclear, but there is an association with genetic factors, smoking, alcoholism, diabetes mellitus and anti-epileptic use. The symptoms usually start in the third or fourth decade but may rarely affect children and young adults. Plantar fibromatosis presents as nodules attached to the central and medial part of the plantar fascia, which may cause discomfort and difficulty with walking and fitting shoes. Contractures of the toes occur rarely.

Management

Non-invasive treatments include physiotherapy, orthotics and local steroid injections. Surgical treatments range from lumpectomy or wide local excision to subtotal or radical fasciectomy with or without skin grafting. Small surgical series (30 or fewer patients in each series) have reported recurrence rates of 30–40% and a significant chance of postoperative complications such as wound healing problems, chronic pain and poor functional outcome.[1]

Radiotherapy

A limited number of studies have reported on outcomes following RT treatment.

A small Dutch retrospective study reported the outcomes of nine patients (11 feet, 26 operations) treated for Ledderhose disease.[2] The recurrence rate following surgery alone for primary disease was 90%. In recurrent disease treated with surgery alone, the recurrence rate was 67%, and with the combination of surgery and adjuvant RT (60 Gy) was 17%.

A German multicentre retrospective analysis reported the outcomes of 24 patients (33 feet).[3] Most were treated with 15 Gy in five fractions, given one fraction per week, followed by a further 15 Gy in five fractions after a six-week gap. Both orthovoltage (70–100 kV) and electron treatments were used. At a median follow-up of 22.5 months, none of the patients had progressive disease. A complete response was seen in 33%, partial response in 54.5% and 12.1% were stable. A complete resolution of pain was achieved in 58.4%. Side-effects were generally mild: Grade 1 in 25% and Grade 2 in 12.5%.

A prospective non-randomised cohort study looked at 158 consecutive patients (with 270 affected feet) presenting to a single institution with symptomatic disease that had progressed over the last 6–12 months.[4] Of these, 91 patients (136 feet) decided to undergo RT and 67 patients (134 feet) did not, serving as a control group. Most were treated with 125–150 kV photons at 40 cm FSD. The planning target volume (PTV) was defined as palpable disease with a 2 cm safety margin. The dose delivered was 15 Gy in five fractions over one week, with a further 15 Gy in five fractions repeated after 12 weeks for a total dose of 30 Gy in ten fractions. At a mean follow-up of 68 months, 92% of the irradiated group had either stable disease (SD) or at least a partial response (PR), with only 8% showing progressive disease (PD) and 5% needing salvage surgery. In the control group 62% had SD/PR and 38% had PD, with 21% needing surgery. Following RT, symptoms were improved in 79%, compared with 19% in the control group. Acute side-effects were seen in 26.5% (21.3% Grade 1, 5% Grade 2) and Grade 1 chronic changes (dryness or fibrosis) in 16.2%.

Potential long-term effects of radiotherapy

The dose and field size for RT of the foot for plantar fibromatosis are similar to those used for Dupuytren's disease. Consequently, the risk of a radiation-induced skin cancer is likely to be similar – estimated at 0.02% above background (24 ± 0.26%). The risk of developing other types of cancer will be similar to or lower than this. Age is an important modifier of risk, consequently the risk will increase if the age on treatment is below 45 and will be approximately double at age 25 years; it will decrease in individuals who are older at the time of treatment (see section 1.1 on Dupuytren's disease).

Dryness after a follow-up period of >12 months was reported in 11% of feet irradiated for Ledderhose disease.[5]

Recommendations and RT technique

1.2.1 RT seems to be an effective modality of treatment for plantar fibromatosis, with good local control and symptomatic benefit (Grade B).

1.2.2 The recommended total dose would be 30 Gy in ten fractions, given in two separate phases of 15 Gy in five daily fractions, with 12 weeks between the two phases (Grade B). The RT can be delivered using orthovoltage photons or electrons as described above for Dupuytren's RT.

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1.3 Plantar fasciitis

Background

The plantar fascia is a band of fibrous tissue that runs along the plantar surface of the foot and extends from the calcaneus bone to the metatarso-phalangeal joints. Plantar fasciitis is a very common condition, which causes heel pain in approximately 10% of the population and is a combination of inflammation and degeneration of the plantar fascia. It is most common in people between the ages of 40–60 years. However, it can occur at any age. It is twice as common in women as it is in men and is also common in athletes. It is caused by mechanical overload, which may be due to a combination of obesity, prolonged standing and walking or intense exercise, and biomechanical disturbances of the foot or lower leg. In 80% of patients complete resolution is achieved in 12 months, but some patients have more prolonged and disabling symptoms.

Management

Plantar fasciitis is a clinical diagnosis, but an ultrasound scan may be useful to rule out other causes of heel pain. In most patients, simple conservative measures are all that is required, including resting, weight loss, analgesia, icing, stretching exercises, footwear changes and orthotics.

For those cases where symptoms do not resolve with simple measures, various other treatments may be considered, including:

1. Steroid injections: these may provide short-term relief from pain but carry a risk of plantar fascia rupture.
2. Extracorporeal shockwave treatment (ESWT): this is a non-invasive treatment in which a device is used to pass acoustic shockwaves through the skin to the affected area. Local anaesthesia may be used as high-energy ESWT can be painful. Five randomised controlled trials (RCTs) compared ESWT in chronic plantar fasciitis with sham ESWT – one with conservative treatment, and one with a single corticosteroid injection. Overall, the results of studies were inconclusive, and there was evidence of a substantial placebo response.[1]
3. Ultrasonic tissue repair: this uses ultrasound imaging to guide a needle-like probe into the damaged plantar fascia tissue. Using ultrasound energy, the probe tip vibrates rapidly to break up the damaged tissue, which is suctioned out. There is scant evidence only for this method and its outcome.
4. Surgery: this should only be considered in patients who have failed adequate conservative treatment. Techniques include open or endoscopic plantar fascia division and gastrocnemius release. There is case series evidence of success, but no randomised evidence, and it may be associated with complications such as flattening of the longitudinal arch and plantar fascia rupture.[2–5]

Radiotherapy

RT has been used since 1924 for the treatment of plantar fasciitis.[6] Many retrospective studies have shown heel pain response to RT; for example, a German study reported on 7,947 patients and found a 70% pain response three months after RT.[7]

Heyd *et al* randomised 130 patients between low-dose (LD) RT (3 Gy in six fractions over three weeks) and high-dose (HD) RT (6 Gy in six fractions over three weeks).[8] Patients' feet

were treated with a single lateral field. If there was insufficient pain response, a second course of treatment was administered. Before treatment, 90.8% had severe pain and 9.8% had moderate pain. Six weeks after RT there was a response in 80% in the LD group and 84.6% in the HD group. Toxicity was minimal, with 28% experiencing a slight increase in pain during RT. Overall, at six-month follow-up, 87.7% had an improvement in pain, with no significant difference between the two groups.

Niewald *et al* performed a trial randomising patients between standard-dose (SD) RT (6 Gy in six fractions over three weeks) and LD RT (0.6 Gy in six fractions over three weeks).[9] Inclusion criteria were: clinical diagnosis of plantar fasciitis; symptoms for more than six months; heel spur seen on X-ray; Karnofsky Performance Status >70; and age >40 years. The RT was delivered using 4–6 megavolt (MV) photons using a lateral parallel-opposed pair of fields, although the protocol also allowed treatment using 200–250 kV photons.[10] The target volume was the calcaneus and plantar aponeurosis. If there was a poor response at 12 weeks, a second treatment, at the standard (6 Gy) dose, was administered. It was intended to randomise 200 patients, but only 62 patients were treated as the trial was prematurely closed due to such a large treatment effect, with a statistically significant improvement in pain and quality of life at three months in the SD group compared with the LD group.

Similar results were seen in other quality-of-life and pain scores. Of note, reirradiation was necessary in 63.6% of the LD group compared with 17.2% of the SD group, with those in the LD group who were reirradiated showing equally good results to those primarily in the SD group. Efficacy was maintained at 48 weeks, and there were no acute or chronic side-effects.

Potential long-term effects of radiotherapy

The risk of RIC after RT for plantar fasciitis will be similar to that estimated for Dupuytren's disease (0.02%) since the doses and age range are similar (see section 1.1 on Dupuytren's disease). This estimate is based on a field size of 60 cm^2 but the risk increases or decreases with the field size. The risk decreases with increasing age at treatment. As a matter of course, patients should be counselled as to the risk of RIC, which should be more strongly emphasised in younger patients.

The risk of other cancers outside the irradiated field, assuming adequate shielding for the remaining parts of the body, should be small due to the location of the radiation field at the extremity of the leg. Other possible consequences of radiation exposure at the recommended dose will be similar to those indicated for Dupuytren's disease.

Recommendations

1.3.1 RT is effective and may be considered for patients who have had plantar fasciitis for more than six months and who have failed conservative management (Grade A).

1.3.2 Dose and technique: 3–6 Gy in six fractions (0.5–1 Gy per fraction) over three weeks delivered using a single lateral field, a parallel-opposed pair of lateral fields or 200–250 kV photons (Grade A).

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1.4 Heterotopic ossification of the hip

Background

HO is the abnormal formation of mature bone within extraskeletal soft tissues. It occurs most commonly after trauma or surgical procedures, for example after total hip arthroplasty. The origin of the new bone is not entirely clear, but it is thought to result from the inappropriate differentiation of pluripotential mesenchymal cells into osteoblastic stem cells. Under the influence of inductive agents (bone morphogenic proteins), these cells form new bone. HO can occur at any age, although most hip replacements occur between the ages of 50–80 years.

In many patients HO is asymptomatic, but in some patients the new bone may cause symptoms such as swelling and tenderness, pain and limited range of motion. Risk factors include prior HO, trauma and muscle injury, and disorders such as Paget's disease and ankylosing spondylitis.

The commonly used Brooker classification of HO at the hip is based on antero–posterior plain X-ray findings (see Table 3). Broadly, Brooker grades 3 and 4 represent severe HO, which often leads to functional disability.[1]

Surgery and NSAIDs

Symptomatic HO is treated with surgery, which is delayed until at least six months after the traumatic episode to allow the bone to mature and for the inflammation to settle. Preventative measures, either NSAIDs or RT, may be used to minimise the risk of recurrence or to reduce the initial occurrence rate in high-risk situations.

Table 3. Brooker classification of heterotopic ossification around the hip joint

Age	Description
1	Bone islands within the soft tissues
2	Bone spurs from the pelvis or proximal end of the femur, with at least 1 cm between opposing bone surfaces
3	Bone spurs from the pelvis or proximal end of the femur, with <1 cm between opposing bone surfaces
4	Apparent bone ankylosis of the hip

NSAIDs are thought to prevent the formation of heterotopic bone by inhibiting the post-traumatic inflammatory response and by inhibiting the differentiation of mesenchymal cells into osteogenic cells.

Meta-analyses have shown a mean overall reduction in the risk of HO after total hip arthroplasty (THA) with NSAIDs (apart from aspirin) from 61% to 27% when compared with a placebo.[2,3] Non-selective (for example indomethacin) and selective (for example celecoxib) NSAIDs are equally effective. Side-effects of NSAIDs may include gastric irritation and bleeding, and renal dysfunction. They may also increase the non-union of concomitant fractures.[4]

Radiotherapy dose and fractionation

RT is thought to reduce the formation of ectopic bone by acting on osteoprogenitor cells, perhaps via inhibition of bone morphogenic protein signal transduction pathways. These cellular changes usually begin to happen 16 hours after surgery and peak at 32 to 48 hours postoperatively. RT was first used in 1981 in patients at high risk of HO. It was delivered using a parallel-opposed pair of photon fields to a dose of 20 Gy in ten fractions.[5] Due to worries about radiation-induced malignancy, studies were performed to investigate lower total doses of radiation for this purpose. These showed that a single fraction of RT of 7–8 Gy given within 3–4 days postoperatively was as effective as a fractionated course.[6,7]

Three recent meta-analyses from two different groups provide excellent summaries of the literature and come to broadly concordant conclusions about the evidence on dose and timing of RT. They all contain summary tables of individual RCTs.[8–10]

Overall, 20–30% of joints receiving RT progress to HO, with Brooker grades 1 or 2 much more common than grades 3 or 4. Hip joints were the most commonly irradiated – there is no evidence to suggest that rates differ with other joints. A single fraction of 7 Gy delivered postoperatively within 96 hours of surgery is the most commonly used regimen. There is some evidence of a dose response compared with lower doses than 7 Gy but there is no compelling evidence for higher doses. There is some evidence that fractionated RT is more effective than a single fraction, but it is hard to know whether this reflects the number of fractions or the total dose in the few studies where this comparison was made. The convenience of a single fraction probably outweighs any potential small benefit of multiple fractions.

The delivery of postoperative RT can present significant logistical barriers due to postoperative pain and the need to minimise early postoperative mobilisation of the joint. Preoperative RT has therefore been used, and though the optimum time interval has not been studied in depth, treatment within four hours of surgery has emerged as a standard. Studies comparing pre- and postoperative RT contain small numbers but there is no good evidence for a difference in efficacy.

RT and NSAIDs appear equally effective at reducing HO with some evidence that RT may be better at preventing more severe disease.[11] NSAIDs are considerably more cost-effective than RT.[12] RT is therefore recommended to prevent HO in people who are not able to take NSAIDs or who are at very high risk of severe HO.

Radiotherapy fields

Anterior–posterior fields are used and the dose is prescribed to the mid-point. The RT portal should encompass the regions that are most likely to form heterotopic bone, particularly the neck of the femur, the tip of the greater trochanter, between the greater trochanter and the ilium and between the lesser trochanter and the ischial ramus. Reference to preoperative plain X-rays can aid planning. Shielding (of the acetabular component or proximal to the base of the greater and lesser trochanter) has been suggested due to fears of reduction of bony ingrowth into cementless prostheses; however, shielding increases the likelihood of developing HO and does not reduce the risk of prosthetic loosening.[13] An attempt should however be made to shield the central pelvic organs to reduce the risk of RIC.

Potential long-term effects of radiotherapy

Since there are several drug treatment options for HO, it is normally wiser to restrict use of RT to individuals older than 50 since the risk of RIC will be small. However, given the low dose recommended, if there are contraindications or lack of response to NSAIDs, RT could be considered for younger patients, with appropriate counselling regarding the risk of radiation-induced malignancy and infertility.

A study using male and female anthropomorphic phantoms has estimated the risk of a RIC arising from RT for HO to range from ~2% to 4%. It was notable that the effective doses were 4–26% higher in the female phantom due to its smaller size; this increased the amount of at-risk tissue being included in the radiation field (principally lower large intestine, red marrow and gonads). As expected, the risk was also increased as the age at treatment decreased.

The effect of radiation quality and technique also modified the risk. For example, higher photon energies (15 Mv versus 6 Mv) reduced the effective dose by 1% in females or increased the effective dose by 9% in males. Individualised shielding blocks reduced the effective dose to at-risk tissues by ~26%; this dose reduction was especially found for lower large intestine and in the female phantom for the gonads. When comparing the effective dose per unit field size, the male phantom had a relatively small range (1.51–1.74 millisievert [mSv]/cm^2) compared with the female phantom (1.82–2.14 mSv/cm^2). The equivalent gonadal doses were 57–93 mSv (male) and 39–167 mSv (female); consequently, heredity effects would be important in patients who choose subsequently to have children. However, since treatments are more usually performed in older patients this is unlikely to be a major issue. The authors stressed that the range of effective doses for the different treatments at various body sites is large and they advised that clinicians should optimise treatment protocols to reduce the effective dose and thus the related risk of RIC.[14]

Since the total recommended dose is <10 Gy, other radiation-associated side-effects are unlikely to be an issue.

Recommendations

1.4.1 RT and NSAIDs are both effective in the prevention of HO but NSAIDs are more cost-effective (Grade A).

1.4.2 RT should be considered in people who are unable to take NSAIDs or who are at risk of more severe HO. It should be avoided in younger patients (for example <50 years).

1.4.3 RT can be given either pre- or postoperatively and should be delivered within four hours before surgery or within 96 hours after surgery (Grade A).

1.4.4 A single fraction of 7 Gy of RT seems optimal and is equivalent in efficacy to increased doses and fractions (Grades A–C), with a likely reduction in the risk of second malignancy (Grade D).

1.4.5 The discussion above covers the prevention of HO of the hip. RT has been used to prevent HO at other sites, but data on its success are more limited.

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1.5 Pigmented villonodular synovitis (PVNS) / tenosynovial giant cell tumour (TSGCT)

Background

PVNS and giant cell tumours of tendon sheaths are rare proliferative processes involving synovial membranes and/or extra-articular tissues. These are now considered the same disease and termed tenosynovial giant cell tumour (TSGCT), further subclassified as nodular or diffuse.

The disease has a variable course and, while usually benign, may be destructive, resulting in major symptoms and loss of function leading to amputation. Optimum treatment is not always clear, and little information exists with respect to the role of RT in comparison with other modalities.

The standard surgical approach is synovectomy, either as an open procedure or more recently via an arthroscopy procedure. High local control rates are achieved for patients with localised TSGCT with synovectomy but for diffuse disease local recurrence risk may be of the order of 20–50%.

More recently trials using tyrosine kinase inhibitors have shown worthwhile responses but questions over optimal treatment duration and control rates after stopping therapy remain.[7]

Radiotherapy

Ionising radiation, either in the form of EBRT or intra-arterial instillation of radionuclides, has been used for several decades, generally given postoperatively to reduce the risk of recurrence following synovectomy.

O'Sullivan *et al*[1] reported a series of 14 patients from Princess Margaret Hospital, Toronto, treated with RT between 1972 and 1992.[1] Six patients had primary and eight had recurrent disease. With a mean follow-up time of 69 months (range 13–250 months), only one patient had not achieved local control. Eleven patients achieved excellent or good function of the affected limb and three had fair function. All patients had greater use of the limb than at the time of treatment. No patient required amputation, and none had evidence of serious RT complications. Thus, RT could be used for the treatment of patients with severe symptoms and for those who may otherwise need to be considered for an amputation. The recommended RT dose was 35 Gy in 15 fractions.

An updated series from the same institution was reported by Griffin *et al* in 2012.[2] Fifty patients had been treated between 1992 and 2006. Twenty-eight patients (56%) were referred after at least one local recurrence. Thirty patients (60%) underwent at least two operations before RT. The mean dose of radiation delivered was 39.8 Gy. At a mean follow-up of 94 months, 47 patients (94%) had achieved local control or stabilisation of macroscopic disease.

A review of RT for PVNS was undertaken as part of a patterns of care study in Germany.[3] Responses were obtained from 189 institutions (83.2%) of which 19 (10.0%) had experience

of RT for PVNS. Of a total of 41 patients for whom information was available, 30 patients (73.2%) received postsurgical RT because of primary incomplete resection and 11 patients (26.8%) as an adjunct after complete resections of recurrences or uncertain resection status. Total RT doses ranged from 30 to 50 Gy (median 36 Gy). Local control was achieved in 95.1%, and 82.9% had no or only slight functional impairment.

In a series from Stanford, 17 patients with 18 sites of PVNS were treated with RT between 1993 and 2007.[4] Seven sites were primary presentations and 11 were recurrent, with an average of 2.5 previous surgical interventions – most commonly in the region of the knee. RT dose was 34 Gy (range 20–36 Gy). With an average follow-up of 46 months (range 8–181 months), initial local control was achieved in 75% (12/16) of the sites with previous cytoreductive surgery (mean time to recurrence was 38 months). Ultimate local control was 100% after repeat resection (mean follow-up 61 months).

Berger *et al* reported on seven diffuse PVNS patients treated with RT between 1996 and 2006.[5] The most common location was the knee joint (five patients). Patients underwent radical surgery and were treated subsequently with RT 30–50 Gy, depending on the resection status and estimated risk of relapse. With a mean follow-up time of 29 months (range 3–112 months), no evidence was found of recurrent or persisting disease in any patient.

Of the seven patients, six reported asymptomatic limb function and excellent quality of life; one patient had persistent restriction of joint movement after repeated surgery. RT had no acute adverse effects, and no late effects were seen.

Mollon *et al* conducted a systematic review and identified 35 observational studies that reported the use of surgical synovectomy to treat PVNS of the knee. A meta-analysis included 630 patients. There was low-quality evidence that the rate of recurrence of diffuse PVNS (DPVNS) was reduced by perioperative RT (odds ratio 0.31). This meta-analysis suggested that open synovectomy or synovectomy combined with perioperative RT for DPVNS is associated with a reduced rate of recurrence.[6]

An alternative RT approach is the instillation of radionuclides (yttrium-90 [^{90}Y], radioactive phosphorus [^{32}P]) into the joint space, also with high local control rates. With these techniques it is difficult to ensure uniform distribution of radionuclide and articular surface dose uniformity.

Recommendations

1.5.1 TSGCT is a rare condition, and it is difficult to draw firm conclusions as to optimum management.

1.5.2 For patients with diffuse TSGCT, high local control rates for surgery and postoperative RT are achieved with low toxicity. Typical RT doses are in the region of 35–40 Gy in 15–20 fractions (Grade C).

1.5.3 Although there are several recent single-institution case series supporting the use of RT for PVNS, this modality is little used in the UK, and it would probably benefit from further discussion with orthopaedic surgeons on a local and national level to define indications for postoperative RT and also the optimum radiation modality.

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2 Skin/soft tissues

2.1 Keloid scarring

Background

Keloid scars are classified as benign dermal fibro-proliferative growths and represent abnormal healing responses to injury. They occur in 1–16% of wound healing with the highest incidence in black skin.[1] Keloids result in raised scars that may be red or hypo- or hyperpigmented. They are often cosmetically disfiguring but can also cause itching and pain. In contrast to hypertrophic scars that are limited to the damaged skin, keloids extend outside the confines of the original wound and do not spontaneously regress. Keloids also have the tendency to invade the healthy skin and to extend beyond the initial wound limits.[2]

Keloids may occur in response to relatively minor trauma, such as ear piercing, and particularly occur on the upper chest, shoulder/scapula regions and earlobes. They are most common between the ages of 10–30 years, but also occur at a lower rate outside of this age range.

Pathophysiological abnormalities found in keloid scars include abnormal fibroblast activity, increased levels of collagen production, increased cytokine levels and a reduction in fibroblast apoptosis.[3]

There is an extensive published literature on the treatment of keloids, but many studies are observational or include small sample size or case studies only. Often studies examine the effects of treatment on both keloids and hypertrophic scars. Often treatment protocols within a single study are variable, with the treatment being applied at different time-points or at different doses. Outcome measures, including definition of 'recurrence', in published literature on keloid treatment are often not clearly described. Some studies cite a reduction in surface area of the scar or patient-reported outcomes. Follow-up time is often short, while the literature suggests at least 12–18 months follow-up to be meaningful.[3]

No single medical treatment has been shown to be effective in reducing keloid recurrence.

Steroids (creams, steroid-containing tape or intralesional steroid injection): Corticosteroids are often used as a primary and secondary treatment (such as after surgery) for keloids and have been shown to inhibit the formation of collagen by fibroblasts.[4] Triamcinolone is the steroid most often used, and the efficacy of this as a first- or second-line treatment is well established. However, there is a lack of well-designed RCTs, and no firm consensus as to dose or regimen.

Surgical excision: While other treatments can reduce the height of the scar, surgery is the only treatment that can reduce the width of the lesion. When surgery is used as the sole modality, the reported recurrence rates range from 45–100%.[5,6] Also, surgery can result in a keloid scar that is larger than the original lesion. It is therefore generally used only as part of multimodal therapy; for instance, with post excision intralesional steroid injections, cryotherapy or RT. Meticulous surgical technique, including minimal undermining of the wound, reducing trauma to surrounding tissues and low wound tension, should be used to minimise the risk of recurrence.

Other techniques: Silicone gel sheet application or compression with bandages, intralesional interferon, cryotherapy, bleomycin, ultraviolet irradiation, topical imiquimod, photodynamic therapy, electrical stimulation and laser therapy are not widely used in clinical practice. Two small, randomised trials have shown a positive effect of intralesional 5-fluorouracil compared with topical silicone or intralesional steroids.[7,8]

Radiotherapy

It is postulated that RT effectively prevents or treats keloids by suppressing angiogenesis and preventing keloidogenic inflammation, likely by inhibiting immune cell function and neovascularisation.[9,10] Evidence shows that RT inhibits histamine release from mast cells, which in turn inhibits the proliferation of fibroblasts. The time interval between surgery and RT remains controversial. Considering that the fibroblast proliferation phase occurs up to two to three days after an injury, RT should be initiated at maximum within 72 hours after keloid surgery.[11,12] Some of the best results have been obtained when RT was initiated within 24 hours after surgery.[13] Starting RT promptly after surgery requires coordinated care between surgical and RT teams.

The evidence for RT given as monotherapy in keloids is limited. RT as a sole treatment should be considered in older or frail patients, especially when symptomatic or in those with huge keloids. Ogawa noted that RT can immediately reduce pain and itchiness while reduction in size and colour of the keloids may take months.[14] Malaker *et al* performed a retrospective analysis of 86 keloids treated in 64 patients and found that 97% showed significant regression at 18 months after the treatment.[15]

RT is particularly effective when used as adjuvant treatment to surgery. A meta-analysis by Mankowski included 72 studies and showed 22% of recurrences after surgery and RT compared with 37% when RT was used alone.[13] In addition, the authors also noted that the recurrence rate varies by anatomic location with highest incidence (34%) on the chest and trunk compared with keloids located on the ear, head and neck, or extremities. Keloids localised on the ear were found to have the lowest rate of recurrence (12%). Nippon Medical School Hospital in Japan has one of the world's largest experiences in treating keloids and it reports keloid recurrence rates below 10% when RT follows surgery.[16] The team also recommends that all patients should be followed up long term at least for 18–24 months and that follow-up can stop when the scar is flat and soft.[17]

Radiotherapy technique

RT for keloids can be delivered with superficial or orthovoltage X-rays, electrons or interstitial brachytherapy. The meta-analysis by Mankowski showed that among the radiation therapy modalities used for keloid treatment, post-excisional brachytherapy had the lowest recurrence rate at 15%, compared with 23% in post-excisional RT (electron or X-ray therapy).[13]

Radiation dose

There is no research-based standardised schedule used in postoperative RT for keloids. Kal and Veen hypothesised that an α/β for keloids is in the range of 10 as for early responding tissues[18] while Flickinger found α/β to be as low as 2 and hence it is recommended to use hypofractionated RT.[19] Evidence shows that the maximal biological effective dose (BED) for keloids is 30 Gy and that any increase in BED does not improve efficacy but may increase carcinogenesis. Ogawa argues that given the different susceptibility of various body sites to recurrence, body-site-specific postoperative RT for keloids should be considered as follows:[17]

- High-recurrence sites (anterior chest wall, scapular region and suprapubic region) 18 Gy in three fractions over three days.
- Earlobes 8 Gy in one fraction.
- Other body sites, including auricle (but not earlobe) 15 Gy in two fractions over two days.

German Societies Joint Guidelines in 2020 update suggests:[24]

- 12–14 Gy with 7 MeV electrons in three to four fractions once or twice a day, treatment to start within a week from surgery.
- When using HDR brachytherapy, an overall dose should be in the range of 12–14 Gy, ideally within seven hours from surgery.

The National Center for Biotechnology Information (NCBI) has also published its own recommendations for using RT in keloids and hypertrophic scars on various anatomical treatment areas suggesting BED possibly higher than 30 Gy to further improve long-term control as some data showed that when BED exceeds 30 Gy_{10}, the recurrence rate is less than 10%.[6,21]

GEC-ESTRO guidelines on skin HDR brachytherapy suggest 5–6 Gy × 3 fractions or 5 Gy × 4 fractions (interstitial technique).[21]

There is no one agreed schedule that can be recommended, and fractionation varies among centres. The use of postoperative RT should therefore follow local protocols and expertise.

Potential long-term effects of radiotherapy

RT for keloids is generally well tolerated. In general, relatively low total radiation doses may cause common toxicity criteria (CTC) grade 1–2 toxicity to the skin and surrounding normal tissues. The most commonly seen late side-effects are telangiectasia or depigmentation in up to 19% of cases, with no CTC grade 3 or higher toxicity.[17,20] Only a handful of reports describe secondary malignancy as a result of keloid RT.[17]

Since the evidence for RT in keloids is relatively limited, with many reports containing short follow-up, it is impossible to identify the likely risks of long-term side-effects of RT in this condition. However, an estimate of the risk of radiation-induced skin cancer following exposure to the recommended dosages (~10–12 Gy) can be inferred by referring to that calculated for Dupuytren's disease (see section 1.1). This risk has been identified as approximately 0.02% for a field size of 60 cm^2, at a dose of 30 Gy in an individual of 45 years at the time of treatment.

For keloid treatments the risk will be ~0.007%. This will be against a background risk of dying of cancer in an unirradiated population of ~24 ± 0.26%. Clearly it is very small and it is unlikely that it could ever be proven due the small numbers of patients treated against this high background. This gives confidence that in older patients the risk of a radiation-induced skin cancer is minimal, although not zero.

However, there are other factors that need to be taken into account. First, the field size may be smaller than 60 cm^2, which will decrease the risk. As stressed throughout this document, the age of the patient is important. For older individuals the risk decreases further; for example, it is estimated to be half by the age of 60, that is ~0.0035%. At 25 years of age (the peak incidence age) the risk will be double (0.014%) and for younger people it will be further increased. However, overall, the risk of skin cancer is small.

These estimates do not take into account the risk of developing other cancers (such as sarcoma, leukaemia, breast cancer and so on), which depends on the tissues within the radiation field. Since the most common sites for keloid scarring are in the upper chest, shoulders and earlobes, there are potentially several structures at risk, albeit to exposure of a radiation dose that is low to moderate (<10 Gy). A study that provides some information on this risk is that of Jansen *et al*.[23] They used male and female anthropomorphic phantoms to estimate the risk of malignancy resulting from RT for a number of benign diseases including HO and arthritis. The radiation doses used for treating these indications are similar (~7 Gy) although the technique is considerably different. Using the risk estimates from this study, there is an approximate 2–4% risk of developing a tumour in a local tissue as a consequence of exposure to this dose in the hip or shoulder joint. It was notable that the effective doses were 4–26% higher in the female phantom due to its smaller size, which increased the amount of at-risk tissue in the radiation field. As expected, the risk was also increased as the age at treatment decreased.

Ogawa *et al* recommend avoidance of postoperative RT on the thyroid and mammary glands, near the gonads and in children.[17]

However, for keloid treatment, with a much more focused superficial area of treatment, the risk should significantly reduce compared with that calculated for these orthopaedic indications. It is notable that the authors stressed that the range of effective doses for the different treatments at various body sites is large and they advised that clinicians should optimise treatment protocols to reduce the effective dose and organs within the radiation field, thus reducing the related risk of RIC, a factor that should be relatively easy to achieve when treating keloid scarring with RT.[17,23]

Recommendations

While there is no robust type 1 evidence for any particular treatments for keloid scarring, the evidence base for intralesional steroid injection of keloids is reasonable. It generally forms part of the primary and post-excision treatment of keloid scarring, along with other conservative (topical) treatments.

2.1.1 The evidence for RT after keloid excision seems to indicate a reasonably low recurrence rate (Grade C).

2.1.2 If RT is to be used, it should ideally be administered less than 24 hours after surgery. It should not be used more than 72 hours after surgery (Grade D).

2.1.3 Superficial or orthovoltage (generally 60–120 kV) electrons or brachytherapy can be used.

2.1.4 There is no one agreed schedule that can be recommended and fractionation varies among centres, therefore the use of postoperative RT should follow local protocols and expertise.

2.1.5 Consider body site-specific fractionation (Grade C).

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2.2 Actinic keratosis (AK) and cutaneous Bowen's disease (SCC *in situ*)

AK (solar keratosis) is a precancerous skin condition caused by long-term exposure to ultraviolet light. Up to 5% of AK on skin may become invasive skin cancers. Large areas of skin may be affected due to skin field cancerisation.

Bowen's disease is a form of SCC *in situ* that can be transformed into invasive cutaneous SCC. Bowen's disease is more common on the lower leg where healing after RT can be impaired.

A 2012 Cochrane review of interventions for AK[1] and a 2013 Cochrane review of interventions for cutaneous SCC *in situ*[2] with subsequent 2022 update[3] did not include any studies assessing RT. AK and Bowen's disease are generally treated by dermatology or surgical services. Patients with persistent or recurrent AK or skin Bowen's disease may benefit from referral to the clinical oncology team.

RT is an effective treatment option for Bowen's disease of the skin in symptomatic cases (pain or bleeding), or when refractory or recurrent after other treatment modalities.

A literature review of the potential use of RT in Bowen's disease by Zygogianni *et al* demonstrated that doses from 25–70 Gy were effective and local recurrence rates were equally low in patients treated with high- and low-dose RT regimens.[4] RT was effective in preserving normal tissues (cosmesis and function) but fraction sizes over 4 Gy were associated with long-term poor cosmetic outcome. An Australian review suggested a dose fractionation schedule of 40–50 Gy in 10–20 fractions using superficial (110–150 kV) energy photons will achieve a local control rate of 95–100%.[5]

RT in AK has been used mainly in salvage setting. Most evidence consists of small series and case studies but indicates prolonged duration of control in heavily pretreated patients.

Techniques for RT in the treatment of AK and Bowen's disease have not been well defined. In convex shapes such as on the scalp or dorsum of hand or foot skin HDR brachytherapy has been used, while large areas of field-change may benefit from newer EBRT techniques such as VMAT.[6,7]

Recommendations

2.2.1 Consider RT to treat Bowen's disease of the skin in symptomatic disease that is refractory or recurrent after other treatment modalities, taking into account the site of disease and likelihood of healing after treatment.

2.2.2 Doses from 25–70 Gy would appear to be effective and local recurrence rates are equally low in patients treated with high- and low-dose RT regimes. Avoid (where possible) fraction sizes over 4 Gy, which are associated with long-term poor cosmetic outcome.

2.2.3 Consider HDR brachytherapy in convex shapes such as on the scalp or dorsum of hand or foot skin.

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2.3 Lentigo maligna

Lentigo maligna (LM) is a slow-growing melanoma *in situ* occurring in chronically photodamaged skin, predominantly in older people.[1] It is a macular, irregularly hyperpigmented skin lesion presenting on the sun-exposed head and neck region, typically on the cheeks, nose, forehead and ears. If untreated, LM has the potential to become invasive and progress into lentigo maligna melanoma (LMM). LMM is a distinct subtype of melanoma, classified by its association with skin subjected to an accumulative level of sun exposure.[2] Both LM and LMM lesions grow in a centrifugal horizontal direction and may spread and regress, making them appear to travel across the skin.[3]

Estimations on the risk of development of LMM from LM vary from a 5–20% lifetime risk of general progression[3] to a 50% risk reported following excision of LM with incomplete margins.[4] The risk of LM progressing into LMM increases if the lesion displays colour variations, a growing surface area, increasing border irregularity and/or raised areas.[3] Biopsy is the gold standard of LM/LMM diagnosis, but the preferred excisional biopsy may not be practical due to the larger size of these lesions and where they are located near critical structures such as the eyelid.[3] Incisional biopsy risks sampling error due to the area within the lesion selected for testing.

Management

Management is challenging due to high rates of recurrence, with optimal results following complete surgical excision compared with non-surgical techniques.[3] Margin-guided techniques such as Mohs micrographic surgery, staged excision or the spaghetti technique produce the best results with recurrence rates of <5%.[5] However, surgery may be contraindicated depending on the size and location of the lesion, the resulting cosmetic and functional outcomes and the co-morbidities of the patient.[3]

Imiquimod is only suggested where neither surgery nor RT are an option.[6] A systematic review of 41 studies on the role of imiquimod in the treatment of LM and LMM reported complete clinical clearance rates of 78%, with optimal results after >60 applications.[6] An ongoing Australian multicentre randomised control phase 3 trial comparing RT versus imiquimod (RADICAL, NCT02394132) should provide better understanding of its treatment role.[7]

Radiotherapy

RT has been shown to provide high cure rates in small studies with limited follow-up and no histological confirmation of clearance.[8] In contrast with surgery, RT has the advantage of being able to treat large lesions with wide margins. In addition to being used as definitive treatment, RT can be used adjuvantly following incomplete surgery with margin involvement.[1] Treatment can be delivered as external beam or brachytherapy.[1] The use of Grenz ray, superficial, orthovoltage and electron therapy have been reported using very heterogenous dose fractionation schedules.[9]

A recent systematic review of RT for LM and LMM included 14 studies and a total of 1,243 lesions (1,075 LM and 168 LMM).[10] Local recurrence rates ranged from 0 to 31% and were comparable with surgical series. Superficial RT was prescribed in 5–23 fractions with a total dose of 35–57 Gy. Grenz ray therapy was prescribed in 42–160 Gy in 3–13 fractions with single doses up to 20 Gy. Cosmetic results were reported as 'good' to 'excellent' for the majority of patients.[10]

Treatment planning

Further research is needed to provide a clear optimal dose fractionation schedule for RT.[10] Radiobiology principles would suggest that schedules with smaller doses per fraction would provide better cosmetic outcomes, although this may be impractical with this cohort of older patients, often with co-morbidities. The practice of an experienced centre in Sydney, Australia, has been to give a total dose of 54 Gy and 50 Gy in the definitive and adjuvant setting respectively, and to use 2 Gy per fraction to minimise late side-effects but using a higher fraction size of up to 4 Gy per fraction if required by patient factors.[11] A review of published studies has suggested a lower rate of out-of-field recurrences following treatment with larger margins from visible lesions to the treatment field edge, and CTV based upon a 1 cm expansion on gross tumour volume (GTV) has been recommended.[11] Depth of treatment is important as LM can migrate via skin appendages in continuity with the epidermis.[11] A study in patients with LM has shown that hair follicles extend to a median depth of 1.5 mm but with a range of up to 4.5 mm. Therefore, it has been recommended that RT treatment should extend to a depth of 5 mm.[11] Due to limited depth of penetration some experts have recommended that 'soft' X-rays (Grenz rays) should not be used.[1]

Follow-up and late toxicity

Resolution of pigmentation is dependent upon the eventual phagocytosis of melanin and has been reported to take two to 24 months with a median of six months.[11] A follow-up at six months is thus recommended.[1] Recurrences have been reported up to nine years after treatment,[7] therefore the authors emphasise the importance of close continuous follow-up, with a policy of an excisional biopsy in areas of recurrent pigmentation. Late toxicity includes alterations of pigmentation, telangiectasia, alopecia and skin atrophy.[10] No fibrosis or ulcerations have been reported thus far.[10]

Potential long-term effects of RT

The risk of a secondary malignant skin cancer is low (estimated at about 0.017% for an individual receiving 50 Gy to the skin at age 60 – modified from the estimation made for irradiation of the skin in Dupuytren's disease). For older patients this is therefore unlikely to be a major concern. More important is the potential for the affected area, and the margin around it, to develop a subsequent malignant melanoma resulting from inadequate control of the original disease; consequently, careful long-term monitoring of the skin is important.

Recommendations

2.3.1 Biopsy is recommended for diagnosis of LM and exclusion of melanoma (Grade C).

2.3.2 Factors to consider in choice of treatment include the size and location of the lesion, patient age, co-morbidity and preference. Surgical excision is considered the treatment of choice (Grade C) but may not be possible without a cosmetic/functional deficit.

2.3.3 RT is an effective non-surgical treatment modality of LM (Grade C).

2.3.4 RT treatment may be with superficial X-rays, electrons or brachytherapy. Evidence to guide optimum doses is very limited, although doses similar to those used in the treatment of skin cancer are appropriate and are tailored to the site and size of the lesion and likely cosmesis. For EBRT, conventionally fractionated schedules may provide optimal long-term cosmetic results but at the cost of a more protracted treatment schedule; these include 54 Gy in 27 fractions (definitive), 50 Gy in 25

fractions (adjuvant). Alternative hypofractionated schedules for EBRT include 40–45 Gy in ten fractions over two weeks and 50 Gy in 15 fractions over three weeks (Grade C).

2.3.5 Histological evidence has shown that LM can extend beyond clinically visible abnormality. Therefore, treatment doses should be delivered to encompass at least a 1 cm CTV around the clinically detectable lesion and to 5 mm depth (Grade C).

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3 Head and neck

3.1 Head and neck paraganglioma

Background

Paragangliomas (PG) are rare vascular tumours arising from neuroendocrine cells in the paraganglia. A British Skull Base Society Clinical Consensus Document from 2020 provides a very useful guide to the management of head and neck PGs.[1] Broadly, head and neck PGs include those arising in the region of the temporal bone and the neck. In the WHO classification[2] head and neck PGs are classified as: carotid body PG, jugulotympanic PG, vagal PG, laryngeal PG and miscellaneous.

Carotid body tumours typically present with a mobile slow-growing neck mass and can be associated with cranial nerve palsies (X, XII). Jugular PGs originate at the jugular bulb at the skull base and may be associated with bone destruction, often presenting with cranial nerve palsies (IX–XII). Tympanic PGs usually originate within the middle ear and present

with associated ear symptoms. Vagal PGs can present as an intraoral parapharyngeal mass and can cause defects in cranial nerves X–XII. Median age at diagnosis is around 50 years with a female predominance, although PGs can present at any age. Some are associated with cancer-predisposing syndromes. A mutation in the succinate dehydrogenase (SDH) gene complex is associated with inherited familial paragangliomic syndrome and thought prevalent in over 30% of cases.[3,4] 2–5% of PGs secrete catecholamines.[5] PGs are usually benign hypervascular lesions. Malignancy cannot be predicted histologically,[6] and is defined by the presence of regional or distant metastases; a malignant phenotype is present in 6–19% of cases with a male predominance.[4] Multiple or bilateral PGs occur in approximately 10% of sporadic and 25% of hereditary cases.[7,8]

Cross-sectional imaging with contrast-enhanced magnetic resonance imaging (MRI) is required to define soft-tissue detail, intracranial, neural and dural involvement. A skull base CT is helpful to define the extent of bone involvement for jugulotympanic PGs. Whole-body staging is also required to detect rare cases with synchronous tumours and metastatic disease. Endocrine assessment and plasma metanephrines are needed to assess for secretory PGs. Biopsy is not usually performed due to the bleeding risk. PGs are vascular, and demonstrate early neural or blood vessel involvement, and a propensity for skull base invasion and intracranial involvement. Genetic testing is appropriate for all patients in view of the proportion with familial disease in addition to stratifying the risk of aggressive behaviour and of synchronous/metachronous tumours.

Management

The aims of treatment for PG have to be set in the context of their natural history. Most head and neck PGs demonstrate an indolent growth pattern. One study examining growth rate found a volume increase of >20% was observed in 60% of the PGs with a median follow-up in the study of 4.2 years. In these cases the median growth rate was 1.0 mm/year with a median tumour doubling time of 4.2 years.[9] Death from PG is rare[10] and therefore the aim of treatment of PGs is to minimise or reduce morbidity rather than to improve survival. Options for treatment include active surveillance, surgery or RT. If immediate treatment is not required, observation is often adopted to determine tumour behaviour.[1,9,11,12] If treatment is required, the choice depends on tumour site, extent of the lesion, presence of synchronous tumours, mutation status, co-morbidity and potential for treatment-related morbidity. Local control rates are high following treatment, although surgical morbidity can be significant and late morbidity from RT needs to be considered.[4,7] The aims of treatment are different with surgery aiming to achieve a complete resection while RT aims at preventing disease progression.

Active surveillance

One study series[10] documents the outcomes of expectant management with a long follow-up. During this 32-year study none of 108 patients with 175 PGs developed metastases or died from PG; a subset of these patients had been managed expectantly. Therefore, clinical observation with surveillance imaging is an option for selected asymptomatic patients with PG, particularly with limited life expectancy.[13]

Surgery

Some tumour sites are more readily amenable to surgery, for example small jugular PGs.[14] However, the vascularity and skull base location of many PGs make surgical management very challenging. Resection of lesions with intracranial and extracranial components

requires combined surgical approaches. Preoperative embolisation has been utilised to reduce intraoperative blood loss and facilitate complete resection.[15] Multiple cranial nerve injuries are commonly reported postoperatively.[5,7,16,17] Lieberson *et al* [5] performed a literature review identifying 23 series between 1973 and 2009, reporting a total of 1,155 patients managed with open surgery. Cervical tumours were disproportionately represented. Local control rate was 87% with a high rate of reported complications of ≥46%.

External beam radiotherapy (EBRT)

Although RT was historically reserved for patients with inoperable tumours, many series have reported high local control rates. For example, Leiberson *et al* [5] identified a total of 34 series published in or before 2009 containing 795 patients treated with EBRT. The local control rate was 91% and the rate of complications was estimated to be 3%. A series of 131 patients with 156 benign PGs treated with RT reported a ten-year local control rate and cause-specific survival of 96% and 97% respectively without severe complications.[13] Dupin *et al* [18] reported an actuarial local control rate of 98.7% at ten years. A case report and literature review suggests that catecholamine secretion does not respond to RT and that these patients are best managed surgically.[19] Doses in the order of 45–54 Gy in 1.8–2 Gy per fraction have been commonly utilised with a high rate of local control with a low risk of complications.[13,18,20–22] It is important to avoid margins that are too tight that could lead to marginal misses, particularly at moderate doses with low risks of complications.[13,18]

Stereotactic radiosurgery

SRS is an appealing treatment modality for the treatment of PGs, with highly conformal treatment, steep dose gradients with patient convenience of a short treatment. Skull base PGs <3 cm are suitable for SRS.[14] Guss *et al* [23] performed a meta-analysis of SRS for 335 jugular PGs and found that local control and symptom control were achieved in 97% and 95% of patients respectively. Although variably reported, documented complications appeared infrequent. Recent series have not shown a higher rate of cranial nerve palsies with SRS[4] although the risk of hearing loss is a disadvantage. A marginal dose of at least 12–14 Gy has been recommended.[1] A recent systematic review and meta-analysis found that a median marginal dose of 15 Gy achieved local control in >90%.[24] Favourable outcomes using linear accelerator SRS have been achieved with fractionated schedules such as 18–21 Gy in three fractions,[25] which are potentially useful for larger tumours.

Surgery versus RT/SRS

There are no randomised trials comparing treatment approaches. Four large meta-analyses/systematic reviews have compared local control after surgery, RT (including radiosurgery) or combined modality treatment[7,12,17,26] and have reported high rates of local control for each treatment modality. The systematic review by Suarez *et al* [7] focused on jugular and vagal PGs, finding a higher likelihood of local control with RT and lower probability of major complication. Analysis of preoperative and postoperative cranial nerve palsies for jugular PGs showed that surgery resulted in an average of 0.9 additional cranial nerve palsies per patient. Cranial nerve damage was common following surgery for vagal PGs with the vagal nerve rarely preserved. Severe complications reported in patients treated with RT included osteoradionecrosis and sensorineural hearing loss. In the meta-analysis by Ivan *et al* [17] there was a higher rate of cranial nerve deficit for patients with jugular PGs who underwent a gross total resection versus radiosurgery alone. In a systematic review of treatment for jugulotympanic PGs stratified by the Fisch classification of disease extent, the

risk of cranial nerve damage with surgery was very low for limited disease extent (classes A and B) and high for more extensive disease (classes C and D) for which RT offered similar or better local control with lower complication rates.[12]

Regression of PGs following radiotherapy/radiosurgery

A systematic review and meta-analysis of regression and local control rates following RT for jugulotympanic PGs[27] found high local control rates (tumour volume equal to or less than pre-RT) with regression in a limited proportion of patients; regression rates appeared higher following radiosurgery.

Malignant PGs

There is insufficient evidence to definitely guide the management of malignant PGs. An approach of surgery followed by postoperative RT has been recommended, using a dose typically used for other malignant tumours (for example 60–70 Gy) depending on margins of excision.[8,14]

Potential long-term consequences of radiotherapy

The long-term risks of radiation exposure are primarily related to RIC to the brain so the dose to the brain should be minimised using highly conformal modern RT techniques with appropriate immobilisation to minimise daily set-up variation. Apart from this, the age of the patient, field size and dose are the most important factors to be taken into account. For older patients the risk of an RIC is very small (see appendix 3, section 3), but in younger patients the use of EBRT should be limited and it should only be used if significant morbidity is predicted as a consequence of surgery. In some cases there may also be sensorineural hearing loss.

Radiotherapy technique

Techniques to minimise doses to adjacent normal structures are paramount. Patients should be immobilised in a thermoplastic shell or stereotactic frame and daily cone-beam CT should be used to assess set-up errors. CTV–PTV margins of <5 mm should therefore be achievable.

A contrast-enhanced planning CT is essential to show the PG. Fusion with MRI, ideally obtained in the treatment position, can be helpful. The PG is defined as the GTV. No GTV–CTV margin is needed.

Recommendations

3.1.1 A period of observation is usually appropriate in asymptomatic patients (Grade C).

3.1.2 Surgery, EBRT and SRS all offer high local control rates and are primary treatment options (Grade B).

3.1.3 RT is preferred for more advanced lesions due to the morbidity of surgery (Grade B).

3.1.4 An EBRT dose of 45–54 Gy in 18–2 Gy per fraction is recommended (Grade D).

3.1.5 For SRS a typical marginal prescription dose is of 12–15 Gy as a single fraction (Grade C).

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3.2 Juvenile nasopharyngeal angiofibromas

Introduction

Juvenile nasopharyngeal angiofibromas (JNA) are benign rare vascular tumours. They are most common in adolescent boys/young men between the ages of 9–19 years old.[1,2] JNAs are thought to arise from the superior margin of the sphenopalatine foramen at the postero-lateral wall of the roof of the nasal cavity.[1,3] Presenting symptoms are most commonly unilateral nasal obstruction and recurrent unprovoked profuse unilateral epistaxis. Other reported symptoms include nasal discharge, cheek swelling, proptosis, anosmia, headaches and hearing impairment.[1,4] A pink or bluish nodular mass is typically seen in the roof of the nasopharynx. MRI with gadolinium is the diagnostic imaging investigation of choice. CT can provide complementary anatomical information. Typical appearances include flow voids with gadolinium enhancement of the mass. Biopsy is not usually required and carries a high risk of bleeding.[2,5]

There is no widely accepted single classification system[2] with that suggested by Radkowski more commonly used.[6]

Although considered benign neoplasms, JNAs can demonstrate locally aggressive behaviour infiltrating adjacent structures, with a tendency to spread through the foramina in the base of skull into the cranium, leading to significant morbidity.[2] Normal tissues are displaced and impacted by pressure rather than invasion.[2] Skull base erosion is seen in approximately one in five cases and is due to expansion and bone resorption, in contrast to the cellular infiltration seen in malignant processes.[1] Four distinct routes of invasion of the skull base have been described, allowing access to the anterior and middle cranial fossa, cavernous sinus and orbital fissure.[3] As shown in surgical series, although critical structures including optic pathways, pituitary gland and temporal lobes may be in close relationship to the JNA, a plane generally exists between the mass and the intracranial contents with the tumour remaining extrameningeal.[1]

Management

Surgery

Surgery is regarded as the treatment of choice for JNA. Preoperative carotid angiography is performed to demarcate the blood supply.[1] Surgery carries a risk of significant blood loss, and preoperative embolisation within 24–48 hours of surgery is utilised in order to minimise the risk of haemorrage.[2,7] The surgical approach is determined by tumour location, potential effect upon subsequent growth of the craniofacial skeleton and expertise. Surgical excision should aim for clear margins, as inadequate margins are associated with significant failure rates.[8] A craniofacial approach is recommended for disease extending into the pterygoid plates. Potential surgical approaches are reviewed elsewhere.[1,2,4] Local control rates with surgery have been reported in the order of 80–85%.[7,9] Potential postoperative morbidity includes disturbance of mid-facial growth following craniofacial resection.[10] Endoscopic surgery has been used as an adjunct in a combined surgical approach, and in some centres as the primary method of excision for more limited disease confined to the nasal cavity and/or nasopharynx or with minimal extension through the sphenopalatine foramen.[7]

Radiotherapy

RT may be employed as primary treatment in cases of likely significant morbidity from resection, for advanced disease after incomplete resection and for recurrent disease.[2,11] Surgery alone is generally adequate for extracranial disease, and RT is rarely required. However, the management of JNAs with intracranial extension is complex. Excision of lesions with extensive spread is associated with higher recurrent rates and operative morbidity.[12] For example, in a series of 95 cases with large JNAs[13] eight out of ten patients had residual disease following surgery for stage IV disease, with subsequent recurrence without RT in three of eight. One series of 16 cases correlated a recurrence rate of 37.5% with skull base invasion.[10]

RT has been used as the primary treatment modality in several series, summarised in Table 4. The patients included in these series would have been generally considered unsuitable for surgical treatment. Despite the likely advanced nature of many of these lesions, RT is an effective treatment modality generally achieving a local control rate of >80%. A wide range of doses have been used in different series. No clear dose–response relationship has been demonstrated, with doses in the range of 35 Gy to 45 Gy commonly reported. A dose of 36 Gy in 20 daily fractions has been recommended.[2] Recurrences have been noted at lower doses;[14,15] Amdur *et al* [15] reported inferior local control rates following 30–32 Gy compared with 35–36 Gy doses. Proton therapy is an option to minimise the risk of late treatment-related side-effects due to the high conformality of treatment,[2] and is currently commissioned by NHS England for treatment of JNA.

Persistent residual abnormalities on imaging are common post-RT.[3,8,16] Response to RT is often slow and disease may remain stable after successful RT.[2,3,8,14]

These data suggest that primary RT is an effective and relatively safe treatment option for patients in whom the disease is deemed inoperable without causing excessive morbidity. The potential morbidity of surgical and RT approaches needs to be carefully considered in reaching treatment decisions for more advanced disease. Most authors adopt a policy of observation in the event of residual abnormality/disease remaining *in situ* following surgery. Such patients are followed up radiologically, with the option of RT or further surgery in the event of progression.[4]

Table 4. Control rates in series of RT as primary treatment modality (adapted from Chakraborty *et al* [16])

Author	Number of patients	Radiotherapy dose (Gy)	Local control
Cummings *et al* [8] 1984	55	30–35	80%
Robinson *et al* [17] 1989	10	30–40	100% (4 yr)
McGahan *et al* [18] 1989	15	32–46	73%
Fields *et al* [19] 1990	13	36.6–52	85% (11 yr)
Reddy *et al* [20] 2001	15	30–35	85% (5 yr)
Lee *et al* [3] 2002	27	30–55	85%
McAfee *et al* [14] 2006	22	30–36	91% (12 yr)
Chakraborty *et al* [16] 2011	8	30–46	87.5% (2 yr)
Amdur *et al* [15] 2011	24	30–36	Median F/U 18 yr 77% after 30–32 Gy 91% after 35–36 Gy
Mallick *et al* [21] 2015	31	30–45	91.7% (3 yr) 70.7% (5 and 10 yr)

Potential long-term consequences of radiotherapy

The major concern with the use of RT for these young patients is late toxicity. Only a few cases of second malignancies have been described.[8,20] Cataract has been reported more commonly.[3,8,17,20] Other potential late side-effects include hypopituitarism[3] and xerostomia.[19] Highly conformal RT delivery techniques including intensity-modulated RT (IMRT) have the potential to reduce doses to organs at risk while maintaining local control.[16] The risks of second malignancy for conventional conformal RT versus IMRT is uncertain. One review comparing the likely risks of IMRT with conventional RT suggests that IMRT may increase the potential risk of RIC by a factor of two, which in older patients may be acceptable, but in children would less acceptable in most instances.[22] Consequently the use of IMRT in place of conformal RT for JNA may not be justified and it is appropriate to consider proton therapy to minimise this risk.

Recommendations

3.2.1 Surgery is regarded as the treatment of choice for JNAs (Grade C).

3.2.2 Primary RT is an effective treatment modality if the disease is deemed incompletely resectable without excess morbidity (Grade C).

3.2.3 Surgery or RT can be considered for recurrent disease (Grade C).

3.2.4 Conventionally fractionated doses in the mid-range of 35–45 Gy are recommended, with a dose of 36 Gy in 20 fractions being appropriate, with no evidence of a dose response with doses in the higher end of this range.

3.2.5 It is appropriate to consider proton beam therapy.

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3.3 Salivary gland pleomorphic adenoma

Background

Pleomorphic adenomas are benign tumours of salivary glands, arising most commonly in the superficial lobe of the parotid gland. Other salivary glands are involved less frequently. Pleomorphic adenomas are most commonly present between the ages of 30–60 years and are more frequent in females.[1] Clinical presentation is typically with a painless slow-growing mass, which, if left untreated, can lead to significant morbidity. A sudden change in size suggests malignant transformation. Approximately 3–4% of pleomorphic adenomas can become carcinoma ex pleomorphic adenoma (CXPA).[2,3] Due to the limited number of cases and variable reported rates in published series, it is difficult to identify prognostic factors for transformation; the duration of a lesion may increase its likelihood of transformation.[3] Diagnosis is made on the basis of clinical history, imaging and a fine-needle aspirate negative for malignancy.

Management

There are no prospective trials assessing the management of pleomorphic adenomas. Multiple retrospective series report very high local control of >95% following surgical excision with clear margins.[1,4–6] Therefore, surgery is the treatment of choice. The majority arise in the parotid, for which surgery entails a superficial or total parotidectomy with facial nerve dissection and preservation. However, if the tumour abuts the main trunk or branches of the facial nerve, surgery may be a more limited enucleation or capsular dissection. The capsule is not always well defined, and tumour can extend beyond the obvious tumour mass.

Radiotherapy

RT is used to increase the chance of local control in the small subset of patients at a high risk of recurrence. Table 5 summarises the largest retrospective reports of outcomes of surgery followed by RT.[7–10] High rates of local control are obtained for previously untreated pleomorphic adenoma, and slightly lower rates when RT is employed for recurrent disease. Although gross disease may sometimes be controlled with RT, local control is higher following a gross total resection.[11] The probability of future recurrence increases with each episode of recurrence.[12] Therefore, obtaining local control becomes increasingly difficult with each recurrence, and the risk of facial nerve palsy increases with each surgical intervention.[13] In addition, the potential for malignant transformation may increase with each recurrence – some series report up to 9% incidence of CXPA in patients with recurrence.[14–16]

In view of excellent outcomes following surgery alone, RT is only indicated for patients at a higher risk of recurrence. Indications include incompletely resected tumours, positive margins or multifocal recurrences. Resection of recurrence is less likely to be curative than complete excision at first presentation. The role of RT following intraoperative tumour spill

or for close margins is controversial. High local control rates of >90% following tumour spill or close margins without adjuvant RT has led some authorities not to recommend adjuvant RT in the presence of these risk factors.[1,7,17,18]

Potential long-term consequences of radiotherapy

Since surgery is the treatment of choice and RT is only indicated in a limited number of individuals the number receiving RT will be small. The recommended dose is significant (50 Gy) so there is a small risk of long-term tissue damage in the radiation field with potential for developing RIC; this is less in older patients. It has been shown that both benign and malignant tumours can develop after radiation exposure, although the risk is very low with a latency of 6–32 years. This data has been obtained from studies of atomic bomb survivors and children who have received radiation to the salivary gland for a previous malignancy.[19–21]

Table 5. Outcomes after surgery and adjuvant radiotherapy for pleomorphic adenoma (adapted from Mendenhall *et al*)[1,7–10]

	Radiotherapy dose	Follow-up	Local control
Dawson and Orr (1985)[7]	50–60 Gy in 20–25 fractions or brachytherapy	Minimum 10 years	92% at 20 years
Ravasz *et al* (1990)[8]	50 Gy in 25 fractions + 10–25 Gy boost	Median 11 years	Previously untreated 100%, locally recurrent 94%
Barton *et al* (1992)[9]	50 Gy in 15–16 fractions or brachytherapy	Median 14 years	Previously untreated 99%, locally recurrent 88%
Liu *et al* (1995)[10]	45 Gy in 20 fractions	Median 12.5 years	Previously untreated 93%, locally recurrent 82%

Recommendations

3.3.1 High rates of local control are achieved by surgery with clear margins. Adjuvant RT improves local control in subsets of patients and is recommended for patients who are at a higher risk of recurrence, as indicated by incompletely resected tumours, positive margins or multifocal recurrences (Grade C).

3.3.2 Use 3D CT planned photons and IMRT or VMAT. For parotid pleomorphic adenomas the target volume includes the whole parotid bed (Grade D).

3.3.3 Variable RT doses are reported in the literature with no clear evidence of dose response. Although higher doses similar to those used for malignant salivary disease have been used, doses in the region of 50 Gy in 25 fractions over five weeks have been commonly employed with good outcomes (Grade C).

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3.4 Sialorrhea

Introduction

Sialorrhea can be defined as excessive saliva in the mouth, resulting either from hypersecretion or facio-bulbar weakness. In neurological conditions, saliva excess is due to weakness and/or poor coordination of bulbar/facial musculature with near normal saliva production. Patients can experience impaired swallow function, limited lip seal and saliva control, and consequently drooling.[1] Drooling can be a feature of several neurological disorders such as amyotrophic lateral sclerosis, Parkinson's disease, pseudobulbar palsy, stroke and cerebral palsy. It has been estimated that 80% of patients with Parkinson's disease and 30% with amyotrophic lateral sclerosis suffer with sialorrhea.[1,2] Sialorrhea may increase risks of choking and aspiration. In addition, sialorrhea can have a major impact upon quality of life leading to social dysfunction, increased difficulty speaking, isolation and depression.[3]

Management

Treatment for sialorrhea should be considered when quality of life is adversely affected. Various treatments have been tried, varying from conservative measures such as posture changes and repetitive swallowing to interventions including medication, RT and surgery.[4] The optimal management of the condition varies with the underlying cause and age of patient. Anticholinergic medication is often utilised as a first-line pharmacological treatment and is effective in approximately 70% of patients with mild-to-moderate drooling.[5,6] However, many patients experience significant side-effects and have to discontinue treatment. Botulinum toxin can be injected locally to reduce saliva production by reducing cholinergic parasympathetic and post-ganglionic sympathetic activity.[3] Botulinum toxin is well tolerated, although requires frequent repeated injections. There is a growing evidence base to support RT to reduce saliva production and ameliorate the symptoms of sialorrhea.[4] Several surgical procedures have been attempted, including salivary duct repositioning, denervation procedures and parotidectomy.[1,7] These invasive procedures are mainly considered in younger patients resistant to medication and botulinum injections, and would rarely be considered in older patients or in patients with progressive neurological disorders and limited life expectancy.[1]

Radiotherapy

Retrospective and prospective studies[4,7–14] have demonstrated that RT is an effective treatment modality for sialorrhea. RT should not be used in children due to the potential risks of a radiation-induced malignancy and growth arrest leading to facial asymmetry. A prospective randomised pilot study comparing RT with botulinum toxin injections (n=10 patients with amyotrophic lateral sclerosis in each arm) showed similar efficacy with regard to drooling status and after three months a superior reduction in saliva flow following RT.[11] In this and another study five patients with severe swallow problems benefited less from saliva reduction.

The largest reported study by Assouline *et al* [10] was a prospective analysis of 50 patients with amyotrophic lateral sclerosis with hypersalivation and prior unsuccessful treatment with medical therapy. In this study patients were treated with a lateral opposed pair of 6 MV photons including both submandibular glands and two-thirds of both parotid glands (upper parotid and sublingual glands were avoided to prevent severe xerostomia); delivered doses were 10 Gy in two fractions over three days (n=30) or 20 Gy in four fractions over ten days

(n=20). Treatment was well tolerated. At six months post-RT, 71% of patients had a complete symptom response and 26% a partial response according to the Sialorrhea Scoring Scale. More patients treated with the higher-dose protocol had no or only mild salivation. Nine patients received a second course of RT with evidence of further clinical responses; eight of these nine patients had originally been treated with 10 Gy in two fractions. The authors concluded that the 20 Gy in four fractions regimen is an effective treatment, with the shorter fractionation of 10 Gy in two fractions an option for patients with poorer medical condition.

In a recent systematic review,[4] 216 patients were identified from ten studies (including Assouline *et al* [10]). Median duration of symptoms prior to RT was 22 months, suggesting most patients had been suffering for significant periods. These series all reported subjective outcomes, and at a median of nine months follow-up 81% of patients reported symptomatic improvement following RT. Median time to symptomatic improvement was two months (range 1–7). The duration of symptomatic benefit appeared very variable, ranging from three months to over five years.

Treatment was with a median total dose of 12 Gy (range 3–48 Gy) with a median dose per fraction of 5 Gy, and a median of two fractions per week for fractionated schedules.[4] There was no clear evidence of a dose response and the authors recommended treatment with either 12 Gy in two fractions or 20 Gy in four fractions, both with two fractions per week.

With regard to technique and target volume, there was no significant difference in symptom benefit following electron or photon therapy. The most commonly used beam arrangement was parallel-opposed photon fields, including the caudal two-thirds of bilateral parotid glands and bilateral submandibular glands. Parotid glands secrete large volumes of serous, watery saliva. The submandibular glands produce more viscous seromucous saliva, providing around 70% of basal saliva secretion.[9] It is postulated that irradiation of the submandibular glands in addition to the parotid glands would prevent the long-term increase in saliva viscosity.[9]

Only a very small number of patients have been retreated with RT either after a lack of response or a transient benefit.[7–9] The number of patients reirradiated makes it difficult to draw useful conclusions.

The most frequent toxicity reported following RT is dry mouth, with other toxicities such as mucositis, taste change and skin reaction uncommon.[4] Reported long-term toxicity is almost exclusively xerostomia/thick saliva.[4]

Potential long-term consequences of radiotherapy

For the most part patients with sialorrhea are older people and with significant reasons for being considered for RT to control excessive drooling. The risk of RIC is very small since the dose is relatively low and their life expectancy limited. However, in the rare cases where children might be considered for this approach, RT is not advised due to the potential risks of RIC and growth arrest leading to facial asymmetry.

Recommendations

3.4.1 RT is an effective treatment modality in palliating sialorrhea in patients with advanced neurodegenerative disorders (Grade C).

3.4.2 Recommended schedules include 20 Gy in four fractions over two weeks (two fractions per week) and 12 Gy in two fractions over one week. Retreatment may be more commonly required after the lower dose of 12 Gy in two fractions (Grade C).

3.4.3 Target volume usually includes both submandibular glands and caudal two-thirds of both parotid glands (Grade C).

3.4.4 Data on retreatment is very limited but it can be effective (Grade C).

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4 Brain and eye

4.1 Graves' orbitopathy (thyroid eye disease)

The 2021 European Group on Graves' orbitopathy (EUGOGO) guidelines provide an excellent summary of the treatment of GO including the role of RT and other treatments.[1]

Background

GO is a rare autoimmune condition affecting 3.3–16 women and 0.9–2.9 men per 100,000 people annually.[2] 85% of patients have thyrotoxicosis within 18 months of diagnosis but orbitopathy can precede thyroid dysfunction. The extraocular muscles and retro-ocular connective tissues are infiltrated by lymphocytes leading to oedema. Similar changes can occur in the eyelids and anterior orbital tissues. In most people, both eyes are affected.

GO starts with an active inflammatory phase before a plateau phase, where the inflammation begins to improve and the disease stabilises, and an inactive phase, where

the inflammation burns out but some symptoms persist. These phases are thought to last 18–24 months in untreated patients.

Symptoms of active GO include an altered appearance, gritty eye sensation, watery eyes, diplopia, especially at the extreme of gaze, and blurred vision. In the presence of visual disturbance it is important to exclude optic nerve compression when blurring will not improve with blinking or refraction. Nerve compression may also cause impaired colour perception, reduced acuity and field loss.[3] Typical signs on examination include conjunctival oedema, eyelid oedema, lid retraction, proptosis and diplopia.

The diagnosis is usually made clinically. Evidence of thyroid autoantibodies can increase the likelihood of the diagnosis. Cross-sectional imaging with MRI or CT can be used to confirm involvement of the soft tissues and extraocular muscles. A biopsy should be considered in the presence of atypical features to exclude alternative diagnoses including lymphoma, vasculitides, IgG4 disease and idiopathic orbital inflammation.

All patients should be referred to a specialist thyroid eye clinic for assessment and for combined ophthalmic and endocrinology input. Treatment will depend on the activity, severity and duration of disease. GO should be classified as active or inactive depending on the seven-point Clinical Activity Score. GO is considered active if three or more of the following are present: spontaneous retrobulbar pain, pain on attempting upward or downward gaze, redness of eyelids, redness of conjunctiva, swelling of lacrimal caruncule or plica, swelling of eyelids, swelling of conjunctiva.[1] Severity should be assessed according to the EUGOGO classification (Table 6). In only 5–6% of patients is the disease moderate to severe.

Management

Control of thyroid dysfunction, stopping smoking and selenium supplementation are recommended in all patients. Topical treatments like artificial tears and lubricants can be helpful.[1]

In moderate-to-severe active GO, treatment is given to shorten the active phase of the disease and therefore improve symptoms. First-line therapy is intravenous (IV) methylprednisolone with or without mycophenolate and is effective in 50–80% of patients.[4] This can be repeated at a lower dose if there has been a partial response. If there is no response then various second-line options exist – repeating IV steroids, oral steroids with cyclosporin or azathioprine, orbital RT with steroids or immune-modulating drugs such as rituximab, teprotumumab or tocilizumab.

There are no RCTs comparing RT with other approaches as second-line treatments following IV methyl prednisolone. RT is thought to be particularly effective at improving eye muscle motility and diplopia. The mechanism of action of RT has remained uncertain and is thought to potentially relate to the radiosensitivity of infiltrating lymphocytes and an effect upon fibroblasts.[5]

The 2021 EUGOGO guidelines only recommend RT as second-line treatment for moderate-to-severe active disease after IV methylprednisolone has not been effective.

Table 6. EUGOGO classification of severity of GO (from EUOGO 21)

Classification	Features
Mild GO	Patients whose features of GO have only a minor impact on daily life that have insufficient impact to justify immunomodulation or surgical treatment. They usually have one or more of the following: ▪ Minor lid retraction (<2 mm) ▪ Mild soft-tissue involvement ▪ Exophthalmos ▪ <3mm above normal for race and gender ▪ No or intermittent diplopia and corneal exposure responsive to lubricants
Moderate-to-severe GO	Patients without sight-threatening GO whose eye disease has sufficient impact on daily life to justify the risks of immunosuppression (if active) or surgical intervention (if inactive) They usually have two or more of the following: ▪ Lid retraction ≥2 mm ▪ Moderate or severe soft-tissue involvement ▪ Exophthalmos ≥3 mm above normal for race and gender ▪ Inconstant or constant diplopia
Sight-threatening (very severe) GO	Patients with dysthyroid optic neuropathy and/or corneal breakdown

This table has been taken from: Bartalena L, Kahaly GJ, Baldeschi L *et al.* The 2021 European Group on Graves' orbitopathy (EUGOGO) clinical practice guidelines for the medical management of Graves' orbitopathy. *Eur J Endocrinol* 2021; **185**: G43–G67.

Evidence for radiotherapy

There are a limited number of randomised but small studies, along with many retrospective and observational series. The reported response rate to RT is around 60% but assessment is difficult due to the long natural history of GO, variable case selection, the use of multiple treatment modalities, varied methods of assessing treatment efficacy and differing duration of follow-up.

One double-blind study randomised 56 patients to either a three-month course of steroids and sham RT or placebo and RT.[6] Around half of each group showed an improvement, mainly in soft-tissue and eye mobility. The motility effects seemed more pronounced in the irradiated group.

Small, randomised studies have suggested a benefit for combining RT with oral steroids. Marcocci *et al* [7] randomised 30 patients to RT versus a combination of steroids and RT; the ophthalmopathy index outcome was significantly superior in the combined treatment arm. Bartalena *et al* [8] randomised 24 patients to steroids versus a combination of steroids and RT; outcomes were superior in the combined treatment arm. In both studies, combined

treatment appeared most effective for extraocular muscle dysfunction and soft-tissue changes that were of recent onset.

Several randomised studies have compared orbital RT with sham radiation. Mouritis *et al* [9] reported an improvement at six months in 18 of 30 (60%) irradiated patients compared with 9 of 29 (31%) sham irradiated patients; improvement was particularly noted for ocular mobility with no difference for exophthalmos. Gorman *et al* [10] delivered RT to one orbit and sham RT to the other in 42 patients with mild-to-moderate GO, with treatments reversed six months later. No benefits of radiation were seen at six months, although at 12 months exophthalmos and extraocular muscle volume were slightly improved following RT. Interpretation of this study is limited by the long duration of eye problems of some of the patients, suggesting they may have been in the chronic phase of GO. In a further study, Prummel *et al* [11] randomised 88 patients with mild GO to RT or sham treatment. At 12 months, the outcome for the RT group was superior in terms of eye mobility/diplopia.

A multicentre 2×2 factorial double-blind RCT, CIRTED, compared RT versus sham RT and azathioprine versus placebo in 126 patients with moderate-to-severe GO alongside a 24-week course of oral prednisolone.[12] The RT dose was 20 Gy in 10–12 fractions over two to three weeks. Outcome data was available for 54 versus 49 patients receiving sham RT versus RT and for 53 versus 50 patients receiving placebo versus azathioprine. The outcome measure was a composite clinical outcome score and ophthalmopathy index at 48 weeks. The adjusted odds ratio for orbital RT was 0.89 (p=0.80) and 2.56 (p=0.054) for azathioprine; differences remained non-significant for a per protocol analysis of patients who completed RT.

Radiotherapy technique and dose

Patients are immobilised in a thermoplastic shell and CT images acquired. The CTV is the bilateral orbital fat and extraocular muscles. There is no real dosimetric advantage to using anything more complex than paired unmodulated lateral beams, each approximately 5×5cm and angled five degrees posteriorly, or half-beam blocked, to reduce exit dose through the contralateral lens.

A dose of 20 Gy in ten fractions over two weeks has been commonly employed.[6,9,12–14] A retrospective single-centre review from Germany suggests that 4.8 Gy in six fractions produced similar responses to 20 Gy in ten fractions but with more patients from the low-dose cohort having subsequent surgery.[15]

Toxicity of orbital radiotherapy

Orbital RT is usually well tolerated. Transient exacerbation of eye symptoms appears to be minimised by the concurrent use of steroids.[16]

RT should be avoided in hypertensive or diabetic retinopathy. Microvascular retinal abnormalities have been detected following orbital RT.[17] Diabetes without retinopathy may represent a risk factor for subsequent retinal changes[18] and is considered a relative contraindication. Lens doses <2 Gy should be achieved, but as these may still increase the risk of a cataract, people should be consented for this possibility.

The risk of RIC is very low.[18–21] For a typical RT regimen for GO, the risk of RIC is estimated to be about 0.2%. This estimate is based on the observed risk of a radiation-induced brain tumour following RT for pituitary cancer. The risk is assumed to be reduced by two important factors – radiation dose is reduced by about 60%, and the 'at risk' brain volume is

80% lower, when compared with RT for pituitary cancer.[22] In older patients this is less of a problem as, in general, evidence for brain cancer in adults exposed to radiation is relatively low. However, radiation exposure in young children carries with it a significant risk of RIC.[23]

Recommendations

4.1.1 Ensure all patients being considered for orbital RT have been assessed in a thyroid eye clinic with ophthalmologist and endocrinologist input (Grade D).

4.1.2 Consider orbital RT in moderate-to-severe active GO that has not responded to IV methylprednisolone (Grade D).

4.1.3 Combine RT with oral or IV steroids to improve effectiveness and reduce side-effects (Grade D).

4.1.4 Use 20 Gy in ten fractions, though lower doses may also be effective (Grade B).

4.1.5 Avoid orbital RT in people who have diabetic retinopathy or uncontrolled hypertension. Any diabetes and younger age are relative contraindications (Grade C).

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4.2 Vestibular schwannoma (VS, acoustic neuroma)

Background

VS are benign tumours arising from the Schwann cells of the vestibular portion of the eighth cranial nerve. The exact incidence is difficult to ascertain as this diagnosis is not routinely collected by cancer registries. However, in Denmark the management is centralised and they have seen the incidence increase from three per million in 1976 to 33 per million in 2015.[1] This increase is driven principally by increased use of MRI scans so more VS are identified incidentally, and by improved guidelines for management of asymmetrical hearing loss. Over this period the Danish also observed an increase in median age at time of diagnosis from 54 to 60 years and size decreased from 26 mm to 13.4 mm.

Patients classically present with asymmetrical hearing loss (>90%) and tinnitus with or without balance issues. Other symptoms include altered sensation or pain in a trigeminal distribution and for large lesions, facial nerve weakness or symptoms of brainstem compression or hydrocephalus (obstructive or communicating). Increasingly VS are diagnosed incidentally on scans for other indications. In the Danish series there were no intrameatal VS (Koos I) in the early cohort but by 2015 they accounted for half of all cases.

The majority of VS are 'sporadic' unilateral lesions and the pathophysiology of these remains unclear. However, 4–6% of patients with VS have neurofibromatosis type 2 (NF2) and classically present with bilateral VS at a much younger age (often as part of a surveillance programme). NF2 should always be considered in patients presenting with a VS under the age of 30 years.[2]

Natural history

The enlargement of VS is not linear but can change over time, with some having little change in size and others enlarging and then stabilising. Data on the proportion of enlarging lesions is variable, often reflecting the length of follow-up and the technique used. The Danish group use linear measurements and report with a median follow-up of 7.3 years that 22% of intrameatal (Koos I–II) and 38% of extrameatal (Koos III–IV) tumours enlarged.[3] Whereas, an American group using volumetric assessments report enlargement in 70% of lesions at three years and 80% by five years.[4] In this series larger initial volume and increase in volume of >50% in the first year were the strongest predictors of future enlargement.

Classification

The Koos staging system is most commonly used.

Table 7. Koos grading scale

Koos grade	
I	Intracanalicular only
II	Protruding into cerebellopontine angle but not touching brainstem
III	Touching but no displacement of the brainstem
IV	Displacement of brainstem

Management of sporadic vestibular schwannoma

Patients should be managed by an MDT with expertise in all therapeutic options.

VS in the context of NF2 and schwannomatosis should be managed in conjunction with specialists in these genetic conditions as other options such as bevacizumab may be considered.

There are no randomised trials in the management of sporadic VS so the recommendations are all based on published case series with the inherent biases of case capture, referral pathways, completeness of follow-up, healthcare funding models and healthcare provider specialisation.

Active surveillance

For all but the largest Koos IV lesions with brainstem compression, active surveillance is the recommended initial management. As set out above, the rate of enlargement of VS is very variable, with many changing little for a number of years. A second MRI scan is performed 3–12 months after initial scan and the interval thereafter is dependent on whether any change is identified and/or the size of the lesion.

Surgery

Surgery for VS is complex with a mortality of around 0.5% and acute complications such as cerebrospinal fluid (CSF) leak, haemorrhage, infection, facial nerve palsy and trigeminal

nerve dysfunction. Depending on the size of the tumour, up to 40% of patients have at least mild long-term facial nerve palsy.

As a consequence, surgery is now principally recommended in large (Koos IV) tumours or those presenting at a young age where lifetime risk of late effects, including secondary malignancy, is greater.

Surgery should not aim to remove the tumour fully at all costs. If tumour is firmly adherent to the facial nerve, subtotal resection may be considered to reduce the risk of long-term facial nerve weakness. The residuum is monitored and if it enlarges, it is usually suitable for SRS.

Stereotactic radiosurgery

SRS is now the most commonly used treatment for VS. It has been used for more than 50 years and over time the doses recommended have been dropped, which has reduced the risk of complications while maintaining local control.

A number of SRS platforms are utilised. No trials have compared the modalities though a recent meta-analysis showed similar five-year local control of 94% with linear accelerator (LINAC) SRS and 93% with Gamma Knife.[5]

The majority of VS can be treated in a single fraction. Due to the different platforms and the long follow-up required to confirm local control there is a range of doses in the literature but the consensus is that doses between 11–14 Gy have the optimal local control to side-effect profile,[2] with the majority of UK centres utilising 12–13 Gy. The prescription isodose depends on the platform (usually 50% with Gamma Knife and 70–90% with LINAC).

Based on these doses the risk of long-term facial nerve weakness is 1–3%, trigeminal nerve dysfunction 1–4% and brainstem dysfunction or hydrocephalus (obstructive or communicating) 1%. (See RCR consent for SRS for vestibular schwannoma.[6])

Almost all patients who present with some hearing prior to treatment will notice a decline in their hearing over time.

Patients should be followed up with typically annual scans for five years; thereafter frequency and duration of follow-up depends on age and fitness.

Around 30% of VS transiently enlarge following SRS so it is recommended that lesions are followed up for at least three years before it is considered that treatment has not worked.

Hypofractionated and fractionated radiotherapy

The risks of a complication following SRS are principally related to the volume of the lesion and the degree of compression of local structures such as the brainstem and trigeminal nerve. In early days of VS SRS, much higher single fractions were common (up to 25 Gy) so centres that utilised relocatable immobilisation devices developed hypofractionated and conventionally fractionated schedules.

As there are no randomised comparisons, and the planning and isodose prescriptions used vary widely, it is difficult to establish the superiority of one regime over another.[7,8] These schedules are most often utilised for patients with larger (Koos IV) VS who are medically unsuitable for surgery or wish to avoid surgery.

For fractionated treatment, total doses ranging from 45 to 54 Gy given in 25–30 daily fractions of 1.8–2.0 Gy are currently recommended.[9] Within this range, the fractionation of 50 Gy in 30 fractions over six weeks is very well tolerated and has a long history in the UK.[10,11]

For hypofractionated treatment, although there is limited outcome data, 25 Gy in five fractions is commonly used and appears to be associated with good rates of local control.

These schedules can be planned using stereotactic planning systems, or for very large lesions with fully fractionated schedules using VMAT.

Recommendations

4.2.1 Patients should be managed by an MDT with expertise in all treatment modalities utilised for VS (Grade D).

4.2.2 Initial management for all but the largest lesions should be active surveillance to assess rate of enlargement.

4.2.3 Surgery should be considered for large VS compressing brainstem (Koos IV) (Grade C).

4.2.4 SRS is standard treatment for small but enlarging VS (Koos I–III), with a marginal dose of 12–13 Gy being the current standard (Grade C).

4.2.5 Hypofractionated or conventionally fractionated RT can be considered for patents with large (Koos IV) lesions when the patient is medically unfit for surgery or wishes to avoid surgery (Grade C).

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5 Total lymphatic irradiation (TLI)

5.1 Total lymphatic irradiation (TLI)

Introduction

Immunosuppressive drugs are the mainstay of preventing graft rejection following allogeneic transplants. However, for some patients organ rejection can occur despite immunosuppressive medication. TLI is immunosuppressive with a reduction in the T-cell population and altering lymph node immunobiology.[1–3] TLI has been used as an alternative immunosuppressive treatment to slow or prevent chronic rejection for lung, heart and renal transplants, although uptake of the technique has varied widely between centres.[1–6] TLI is generally reserved for patients with solid organ rejection episodes who are refractory or not tolerating conventional anti-rejection medical therapy.[3,4] TLI is not used as a prophylactic treatment.[1]

Figure 1. Example of matched anterior–posterior fields (mantle, para-aortic including spleen, inverted Y to include femoral lymph nodes) used to deliver total lymphoid irradiation

Radiotherapy technique

There is variation in technique but the common approach involves three matched parallel-opposed fields (mantle, para-aortic including spleen, inverted Y including pelvic/inguinal lymph nodes and extending to include femoral lymph nodes).[1,3] Figure 1 shows a typical example of matched fields. The usual dose is 8 Gy in ten fractions (0.8 Gy per fraction) with two fractions per week, over five weeks.[1,3] Anti-proliferative drugs such as azathioprine, methotrexate and mycophenylate are usually stopped during treatment. Patients require monitoring of full blood counts during treatment, and in cases of significant suppression of bone marrow function, fractions are delayed.[3] A significant proportion of patients do not complete treatment, with 10 out of 37 patients in one series not completing more than eight of ten fractions predominantly due to bone-marrow toxicity.[3]

Efficacy of total lymphoid irradiation in transplant rejection

There is only a limited available literature to evaluate the effectiveness of TLI, with a recent review identifying only eight relevant publications with varied indications, outcome measures, follow-up duration and limited study sizes.[1] In the context of heart transplants there is evidence of reduced rejection episodes and lower maintenance immunosuppression.[5,7–9] TLI has been used successfully in a series of four paediatric heart transplant patients with prevention of further rejection episodes and enabling retransplantation in two of these patients.[10] Progressive bronchiolitis obliterans following lung transplantation is a major cause of late graft failure.[3] One series reported on the use of TLI in 37 lung transplant recipients with rapidly progressive bronchiolitis obliterans and demonstrated a significant decrease in the rate of decline of forced expiratory volume in one second (FEV1) following TLI. An alternative to TLI is switching immunosuppressive medication; one small randomised study of TLI versus switching to tacrolimus in 13 heart recipients with recurrent acute rejection episodes showed an equal impact of both approaches.[11] A systematic review of therapy options for lung allograft bronchiolitis obliterans identified TLI as a treatment with low-quality evidence for improvement in lung function.[12] Overall it appears that TLI has the potential to decrease solid organ rejection episodes in the short and intermediate terms. Long-term toxicity, including RT-induced malignancies, is a potential concern, although the prognosis of lung transplant patients with bronchiolitis obliterans is often unfortunately limited. Evaluation of late toxicity risks is additionally challenging, with small patient cohorts with multiple other co-morbidities or ongoing treatments including immunosuppressive drug therapy, which will predispose to cancer development.

Recommendations

5.1.1 TLI can be considered in close liaison with the transplant centre as treatment for patients refractory to or intolerant of conventional medical immunosuppression for solid organ rejection (Grade D).

5.1.2 Recommended dose is 8 Gy in ten fractions delivered twice per week (Grade D).

5.1.3 Patients require monitoring for bone-marrow suppression during treatment to avoid excessive infection and bleeding risks (Grade D).

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Appendix 1
Acknowledgements

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We are also grateful for those who helped review and redraft relevant sections:

- Karl Butterworth
- Sara Erridge
- John Frew
- Sarah Jefferies
- Agata Rembielak
- Maria Vassilou
- Richard Shaffer
- Gillian Whitfield
- James Wylie

We also acknowledge the work of the original 2014 working group who produced the first edition of this document on which this second edition is based:

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Appendix 2
Levels of evidence

The coding for evidence-based recommendations

The types of evidence and the grading of recommendations used within this review are based on those proposed by the SIGN.[1]

Recommendation		Evidence	
Grade	**Source**	**Level**	**Type**
A	At least one meta-analysis, systematic review of randomised controlled trials (RCTs), or RCT rated as 1++ and directly applicable to the target population; or a body of evidence consisting principally of studies rated as 1+, directly applicable to the target population and demonstrating overall consistency of results.	1++	High-quality meta-analyses, systematic reviews of RCTs or RCTs with a very low risk of bias.
		1+	Well-conducted meta-analyses, systematic reviews of RCTs or RCTs with a low risk of bias.
		1	Meta-analyses, systematic reviews of RCTs or RCTs with a high risk of bias.
B	A body of evidence including studies rated as 2++, directly applicable to the target population and demonstrating overall consistency of results; or extrapolated from studies rated as 1++ or 1+.	2++	High-quality systematic reviews. High-quality case control or cohort studies with a very low risk of confounding or bias and a high probability that the relationship is causal.
		2+	Well-conducted case control or cohort studies with a low risk of confounding or bias and a moderate probability that the relationship is causal.
		2	Case control or cohort studies with a high risk of confounding or bias and a significant probability that the relationship is not causal.

Recommendation		Evidence	
Grade	**Source**	**Level**	**Type**
C	A body of evidence including studies rated as 2+, directly applicable to the target population and demonstrating overall consistency of results; or extrapolated evidence rated as 2++.	3	Non-analytical studies (eg case reports, case series).
D	Evidence level 3 or 4; or extrapolated evidence from studies rated as 2+.	4	Expert opinion.

Reference

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Appendix 3 Radiobiology sections from first edition 2018

These chapters were included in the first 2018 edition of this document. The chapters have not been updated since the first edition and are included in this second edition as an appendix for reference only.

2. Normal tissue responses with radiation doses used for radiotherapy of benign disease

Background

Radiotherapy (RT) is primarily used for the treatment of malignant tumours where the risk of radiation damage is normally deemed acceptable since it is balanced against the potential benefit of controlling the malignant disease. The doses used are relatively high (see Table 2) and are constrained by known/expected toxicity to the normal tissues within the radiation volumes. In about 40% of patients, RT for malignant tumours is curative and in much of the remainder there is at least a prolongation of life; this provides a rational justification for the small but acknowledged risks of the high doses used for treating tumours.[1]

However, there are also a considerable number of benign/low malignancy tumours and non-neoplastic diseases for which RT is a potential treatment option. For each indication, the risk versus benefit is subject to many variables and these are considered individually in subsequent sections. In this and the following section, the aim is to identify the underlying mechanisms and to evaluate the risk versus benefit of using RT in these situations; not an easy task since it is clear from Table 3 that there are a large number of variables pertinent to each indication.

Table 2. Radiation dose ranges pertinent to experimental and clinical radiotherapy

Description	Dose (Gray [Gy])	Comment
Very low	<2	Used clinically as part of a multiple fraction dosing regimen, very rarely used as a single dose; often used in tissue culture experiments.
Low	2–10	Used for a few indications. In cell/animal experiments this is the most frequently used dose range.
Intermediate	10–40	Used for most non-malignant indications in a variable number of fraction sizes. For many indications 20–30 Gy total dose is used.
High	>50	Used for a few benign tumours and in very small fields in stereotactic radiosurgery (SRS).

Table 3. Factors influencing the risk of normal tissue damage and incidence of radiation-induced cancers during radiotherapy for benign disease

Factor	Comment
Radiation-related	
Dose and dose rate	*Most indications use standard external beam radiation therapy (EBRT).
Radiation quality	*Most indications use low linear energy transfer (LET) radiation; protons are used for a small number of indications in specialist centres (currently none in UK).
Radiation field size (RFS)	Key factor. Risk of significant late normal tissue reactions increases with RFS, especially if a radiosensitive tissue is in the field. The risk of radiation-induced cancer (RIC) also increases with RFS.
Patient-related	
Age	Age is a key factor, particularly affects risk of RIC. Risk decreases with age of radiation exposure. If >60 years often of limited consequence. For children and young adults this is much more important.
Early and late normal tissue reactions	*Occur in normal tissues in the radiation field. Tissue response is related to cell proliferation. 'Consequential early' effects are seen in high-turnover tissues during and immediately after RT; these can continue for some time. 'Late' effects are seen many months to years after initial exposure in slow turnover tissues.
Exposure of critical structures in the radiation field	Normal tissue effects are dependent on the radiosensitivity of the tissue(s) included in the radiation field; at doses <45 Gy this is unlikely to be an acute effect. Long term, there is potential for an increase in RIC and other non-malignant changes (rarely). Cataracts are an issue if the eye is irradiated.
Co-morbidities	Need to be dealt with on an individual patient basis. Effects are also dependent on organs at risk.
Intrinsic radiosensitivity of normal tissues	*Currently not possible to predetermine except in very rare radiosensitivity syndromes. In 'normal' individuals this is rarely evident at the moderate doses used for most benign diseases.
Alternative treatment to radiation	These are very variable and need to be considered on a case-by-case basis. If cytotoxic drugs are used they can also cause malignancy in the long term.

* Although these factors are itemised, they are less likely to cause problems in the low to moderate dose range (<40 Gy) which is used for most non-cancerous indications.

Influence of radiation-related factors

When patients with benign disease are treated with RT there are a number of radiation-related factors that require consideration. Most benign diseases are treated with external beam radiation therapy (EBRT) which involves the use of low linear energy transfer (LET) ionising radiation (IR) (normally either X- or ɣ-rays) with treatment modalities used in the clinical setting. When discussing radiation effects on tissues, it is important to define dose and, for the purposes of this discussion, doses have been grouped into four bands (Table 2). For most indications the radiation is delivered in a fraction size of 2 Gray (Gy), although for some situations this may vary. In the treatment of most benign diseases, the total dose used is in the low to intermediate range; although doses used for treating benign tumours are much closer to the standard cancer therapeutic range and for some indications, for example trigeminal neuralgia, the dose is very high (70–90 Gy) albeit over a very small volume. The influence of radiation quality and dose rate are therefore the same as normally factored in for routine RT for malignant conditions, and thus when planning RT for non-malignant conditions the same principles should be applied. However, since the total exposure to radiation is significantly less than that delivered to most patients treated for malignant tumours, the chance of overt effects related to dose and radiation quality is low.

Radiation field size (RFS) is also an important factor since the smaller the field the fewer the number of cells exposed, reducing the chance of an initiation or promotion event within cells that might ultimately lead to a tumour. Consequently, RFS should be kept to a minimum by careful treatment planning. More recently, stereotactic radio surgery (SRS) has been introduced which should have a relatively small risk, despite the high dose used, since it involves a very small RFS (discussed further in appendix 3 section 3 p72) The risk of radiation-induced malignancy following low to intermediate dose RT. Clearly the inclusion of normal tissues within the radiation field should, as far possible, be avoided; this is especially important for those known to be relatively radiosensitive such as the central nervous system (CNS), eye, breast, heart, lung, bladder and kidney. Since the total dose is likely to be intermediate to low, inclusion of these tissues should not be a limiting factor; however, consideration of these issues should also be moderated by patient-related factors.

Influence of patient-related factors

RT for benign indications involves a number of patient-related factors that show considerable variability; this makes it difficult to give a definitive evaluation of the risks versus benefits of RT for these indications (Table 3). It is known that tissue responses within the radiation field occur both acutely, within hours of exposure, and at some considerable time later. Early responses are typically found in cells and tissues that have a high turnover rate; another contributor to this effect may be the radiosensitivity of the vasculature.[4,5] Late-reacting tissues have a low cell turnover so that damaging effects are only manifested many months to years after the original exposure to IR. These reactions are also dependent on parenchymal stem cell loss which results in necrosis/fibrosis and ultimately organ dysfunction/failure if the doses are at a sufficiently 'high' level.[3]

In the treatment of malignant tumours, the dose used is limited primarily by the predicted late effects in key tissues within the radiation field; early effects may also be dose limiting if they are severe.[3] For benign disease there is a greatly reduced chance of severe reactions. As mentioned, late effects will be rare as normally the dose used will be well below the recognised thresholds, though late effects in the spine should be considered if the dose used is ≥50 Gy and the spine is in the radiation field.[5] Other tissues that may also be at

some risk of residual damage are the heart, breast, lung, bladder, kidney and lens of the eye. The eye is particularly radiosensitive and eye diseases treated with RT leave the patient susceptible to cataract formation (discussed in 'Effects of ionising radiation on the eye').

At the intermediate doses used for RT of benign disease, the most important late effect is the potential for a radiation-induced cancer (RIC) – a factor that is very age and tissue dependent. This risk has been recognised in studies of Japanese atomic bomb survivors who were exposed to whole-body irradiation and recent analysis confirms that the risk of RIC increases approximately linearly with dose. For individuals receiving targeted RT, the risk will also be proportional to the RFS and it will be significantly reduced as the age at initial IR exposure is increased. The risk of developing a RIC is more fully discussed in Section 3: The risk of radiation-induced malignancy following low to intermediate dose RT.

Patients are known to exhibit a range of sensitivities to radiation. However, RT regimens are designed to avoid excessive reactions in most normal individuals. Indeed, at the doses used for benign disease, intrinsic radiosensitivity is unlikely to influence response. There are a few severe radiosensitivity syndromes, such as ataxia telangiectasia, and patients with these syndromes are likely to show a more severe reaction to RT. These are very rare so this is unlikely to be an issue, although clinicians should be aware of their potential to cause increased normal tissue reactions.

To summarise, radiation dose, quality, field size and tissue(s) exposed are all factors that will be known to a clinician when considering treatment regimens for benign disease and all of these factors should be considered when selecting an RT protocol for these patients. The lower the dose, the less the risk, especially if no critical structures are in the radiation field. Age is a key modifying factor. Co-morbidities should also be taken into account as appropriate. The intrinsic radiosensitivity of individuals is rarely known and unlikely to be an issue, unless the patient has one of the very rare severe radiosensitivity syndromes.

The effect of radiation on normal tissues

Over the last 50 years, our understanding of the effects of IR on normal tissues has improved, though there is still much that is not fully understood. Tissues are complex structures comprising a range of interacting cells which respond differently on exposure to IR, and these responses are controlled by a large number of molecular changes. Laboratory studies have helped to inform understanding of the molecular changes that are induced by IR, and they have shown that cells respond in a variety of ways to a radiation insult.

Laboratory experiments are carried out on cells and animals, normally at a range of radiation doses between 1–10 Gy. Laboratory studies have some advantages since the radiation doses are accurately defined, the conditions more closely controlled and replicates can be carried out in the same cells or animal species; however, with the exception of a few instances, they are a poor reflection of the dose fractionation schedules used in the clinic.

A large body of evidence on normal tissue responses to IR has been gained from epidemiological studies of individuals exposed to very low doses, where radioprotection levels are important, such as in medical procedures or when occupational/accidental exposures are being evaluated. These doses are usually much less than 1 Gy, often to a poorly defined field or to the whole body. In accidental exposure situations these can be much higher, although the dose is often poorly defined. There is also a considerable body of evidence on normal tissue responses to high-dose regimens where patients are undergoing RT for malignant disease (normally 55–75 Gy to a well-defined local site).[3]

Evidence pertaining to 'intermediate' dose radiation exposure is somewhat more limited although there are studies, primarily epidemiological, which are discussed below.

Effects of ionising radiation on tissue components

Vascular tissue

Radiation-induced changes are found in tissue vasculature as early as 24 hours after exposure to IR. Capillaries are particularly radiosensitive and their response is one of the most important features of acute tissue.[6,7]

On exposure to IR, endothelial cells swell and/or die by apoptosis.[8,9] Investigation of the cell death pathways induced by IR has shown that, in many cases, cell membrane damage is mediated through activation of acid sphingomyelinase (ASM). This increases levels of ceramide – a molecule which can also be increased by IR-induced deoxyribonucleic acid (DNA) double strand breaks. This is important because ceramide can act both as a second messenger in signalling pathways and as a precursor for a range of structural or effector molecules.[8,9]

Apoptosis in endothelial cells is very dose dependent. At doses of 5–10 Gy, in vitro studies show an increase in apoptosis that can be associated with an increase in ASM and ceramide. However, exposure to 3 Gy showed endothelial cell survival linked to a different mechanism.[10] Although there is considerable evidence that the pro- and anti-apoptotic effects of ceramide are, at least in part, responsible for radiation-induced apoptosis in endothelial cells, caution must be used in extrapolating the effects found *in vitro* and the mechanisms that might be responsible *in vivo*, especially where fraction sizes are below 3 Gy.

Larger vessels are also damaged by IR, although to a lesser extent than capillaries and they have also been shown to increase in diameter to compensate for the capillary loss.[6] In clinical studies, it has been shown that vascular sequelae are present in the heart and brain of patients exposed to high-dose RT.[4] Re-evaluation of other evidence has suggested that IR effects on vascular tissue, especially following high-dose RT, have much more prolonged consequences on health than previously thought.[5]

Parenchymal tissue

Many later IR-induced changes in tissues result from changes to stromal cells, often mediated through activation of transforming growth factor β (TGF β), primarily TGF β1. IR induces TGF-β1 production by fibroblasts, which is thought to trigger their terminal differentiation to postmitotic fibrocytes that produce increased amounts of collagen.11 TGF-β1 also blocks the cell cycle which affects epithelial, endothelial and hematopoietic cells.[6] Following IR exposure TGF-β1 has a central role in tissue remodelling, control of the extracellular matrix homeostasis and ultimately the development of fibrosis. This is caused by stimulation of matrix proteins, decreased production/inhibition of matrix-degrading enzymes and also modulation of integrin expression.[12]

Like fibrosis in irradiated skin or lung tissue, delayed radiation enteritis is a relatively frequent side-effect of abdominal and pelvic RT which can even result in intestinal obstruction. After radiation exposure, intestinal mesenchymal cells – mainly smooth muscle cells and sub-epithelial myofibroblasts – are released from quiescence to engage in the healing process.[13]

Occasionally, this can be excessive resulting in the accumulation of extracellular matrix components and chronic fibrosis.[14] Clearly there are many and varied responses to radiation in normal tissues; three recent reviews provide informed discussion on the mechanisms underlying these changes.[6,15,16]

Anti-inflammatory effects

The inflammatory response following exposure to radiation is a tightly regulated process involving interaction of leukocytes with the capillary endothelium. Initially, the leucocytes roll along the capillary wall which activates the cells through local activation of inflammatory mediators; eventually they bind and migrate through the endothelial cell junctions into the interstitial space.[17] This infiltration results in accumulation of a range of immune-competent cells which cause multiple effects. The activation of macrophages is critical since it leads to production of pathological levels of nitric oxide (NO) and pro-inflammatory cytokines, causing erythema, oedema and pain. Endothelial cells also have an important role in inflammation as they express a variety of cytokines that have both pro-inflammatory and anti-inflammatory effects.[17]

RT at high doses is used to control malignant disease; however, this can also induce a well-recognised inflammatory response.[18] Conversely, at intermediate doses it can be used to reduce inflammation. For example, RT can be used in a range of conditions, particularly musculoskeletal, that have an inflammatory component. The specific indications are discussed in subsequent sections. The underlying mechanism for this anti-inflammatory effect is not completely understood; much of the evidence for the observed changes comes from low dose (0.5–5 Gy) *in vitro* studies.[17] In general, they show reduced expression of adhesion molecules such as P-, L-, E-selectins, intercellular adhesion molecule (ICAM) and vascular cell adhesion molecules (VCAM). However, caution must be exercised in extrapolating *in vitro* doses to *in vivo* scenarios since the multi-cell interactions that occur in tissues have a considerable effect on tissue sensitivity to IR.

In vivo studies of the anti-inflammatory effects of IR have been carried out in a range of rodent and rabbit models. Most show reduction in inflammation on exposure to fractions in the range 0.5–2 Gy (5 × 1 Gy is the most widely studied regimen). The anti-inflammatory effect has been linked to a reduction in NO, tumour necrosis factor-ɣ and/or interleukin-1β (reviewed by Arenas *et al* 2012).[17] In animal models of arthritis, treatment with IR (0.5–1.5 Gy fractions) caused an improvement in symptoms associated with a reduction in tissue disruption and bone loss, observable up to 30 days.[19–21] When acute systemic inflammation was induced in mice using lipopolysaccharide (LPS), RT administered one hour before the LPS had an anti-inflammatory effect which lasted for between 48–72 hours. The anti-inflammatory effect included a reduction in leucocyte adhesion which was not linked to any change in ICAM-1. However, it was attributed, at least in part, to an increase in TGF-β1.22. There are advantages to using low-dose RT in the treatment of inflammatory disease as it reduces the long-term use of anti-inflammatory agents with their attendant risks. This must be balanced against the potential for carcinogenesis at the site of treatment, a factor which is less of an issue in elderly patients, discussed further in Section 3: The risk of a radiation-induced malignancy following low to intermediate dose RT.

The effects of ionising radiation on the eye

It has been known for many years that exposure of the eye to IR carries with it a risk of later development of cataracts. Previously it was thought that the minimum dose causing

cataract formation was about 1.3 to 2 Gy (cited by Ainsbury *et al* 2009).[23] The data used to make these estimates were principally from the Japanese survivors of the atomic bomb, highly exposed workers and RT patients. However, difficulties in identifying dose estimates were acknowledged. Following their review of the available data and a number of key recent publications, Ainsbury and colleagues have suggested that the previous thresholds need to be reconsidered.[23] Although they had some difficulty in comparing studies due to their different design and outcomes, it was clear to them that the previous threshold was too high and they have recommended that it should be reduced to 0.5 Gy. Indeed, they found evidence that the risk estimate for radiation cataractogenesis might be more accurately described by a linear, no-threshold model.[23] This lower estimate has been supported in a recent analysis of cataract treatment in atomic bomb survivors; of the 6,066 examined, 1,028 required surgery for cataracts in a 20-year period.[24] This risk estimate has also been confirmed in a recent report of the International Commission of Radiation Protection (ICRP).[5]

Any exposure of the eye during RT puts the patient at risk of an increased chance of cataract formation. It should be noted that there is a very variable latency period ranging from just over one year at high-dose exposures to many years at very low-dose exposure.[23–26] When exposure occurs in childhood, an increased risk of ~50% for 1 Gy exposure to the lens has been reported.[27] When exposed at age ten, children had an odds ratio of 1.44 at 1 Sievert (Sv), which decreased to a statistically significant extent with increasing age of IR exposure ($p=0.022$).[28]

For patients treated with RT for benign disease, the doses will be well above the recommended 'thresholds', thus indicating a real risk in long-term cataract formation. There is also the potential for other pathological changes in all tissues associated with the eye. These changes have been reviewed for patients treated with high-dose RT for uveal melanoma and they might also be expected to occur with the lower doses associated with RT for benign disease, although with less frequency and severity.[29] Fortunately, cataract is a non-life-threatening side-effect of IR exposure, which can usually be treated easily and successfully.

Consequently, it is important to be aware of the risk of cataract formation when patients are receiving RT that includes exposure of the eye; however, the risk of this treatable complication should be balanced against the treatment benefits for the original indication.

Apart from cataract, at the doses employed for the treatment of benign disease, clinically relevant late toxicities from RT to the eye or its surrounding structures are rare. Although high-dose RT can result in long-term xerophthalmia, this is uncommon below a threshold dose of 30 Gy in 2 Gy fractions. The threshold doses for other significant toxicities, including corneal, uveal, retinal and optic nerve damage, are much higher than doses employed for benign diseases. However, temporary loss of eyelid hair can occur at these dose levels, and this can interfere with the blink reflex. The toxicities from irradiation of the eye and surrounding structures have been reviewed by Jeganathan *et al*.[30]

Conclusions

The current radiobiological evidence suggests that RT at the low to intermediate doses used for benign conditions will cause some cell and molecular changes, although for the most part these will be asymptomatic. The overall risk of non-malignant sequelae is real but small and is very dependent on a range of factors; the most important of these are age on exposure and dose. Recent evidence suggests that vascular disease can result from

radiation exposure. In individuals treated with high doses for malignant tumours there is a small but significant increase in the incidence of vascular sequelae. In addition, the risk of cardiovascular disease has now been found to be slightly raised in atomic bomb survivors who were exposed to much lower (whole-body) doses.[5] Extrapolating from these two large groups, it can be inferred that individuals exposed to intermediate RT doses may also have a small risk of circulatory sequelae, depending on the anatomical site treated, although for most patients it is unlikely they would be symptomatic. There is, however, a real risk of cataract formation, especially if the dose to the eye is intermediate and the patient is a child or young adult.

In general, current use of RT for benign conditions involves older patients and is often administered to less critical parts of the body, such as the limbs. For these indications, the side-effects of RT may be less than other available treatments (see sections on specific indications later in this document). However, care must be taken if RT is proposed where key radiosensitive structures are within the radiation field, particularly if the patients are young (approximately <40) and especially if they are children. The most important long-term risk following RT for benign disease is the potential for development of an RIC.

This is discussed more fully in the next section.

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3. The risk of a radiation-induced malignancy following low to intermediate dose radiotherapy

Background

Clinically, one of the most important side-effects of radiation exposure at low to intermediate doses is the risk of inducing cancer. As discussed in appendix 3 section 2 (on page 64): '*Normal tissue responses with radiation doses used for radiotherapy of benign disease' there* are many variable affecting cellular changes in normal tissues exposed to radiotherapy (RT); the risk of a radiation-induced cancer (RIC) is also subject to these influences.

Many studies have been undertaken to identify this risk for patients receiving high-dose RT for cancer. However, patients receiving intermediate doses relevant to RT for benign disease will be at a relatively lower risk, and hence investigation of this risk is more difficult. The number required to detect a small increased risk in cancer incidence, occurring many years after exposure to intermediate RT doses (10–40 Gray [Gy]) to a confined radiation field, is large; yet with a few exceptions, the numbers treated are relatively small. Consequently, there have been relatively few trials to test this. Even when numbers are increased through multi-centre trials, the ability to deliver a reasonably homogenous group of patients treated with similar radiation protocols, with similar pathologies and prolonged follow-up presents many organisational problems. Indeed, even when this is possible, by the time the data has matured, treatment options and technology will also have moved on. These studies must therefore be viewed with caution when extrapolating to the risks of current treatment protocols.

Consequently, the risk of RIC following RT for benign disease identified in this document has been assessed by a range of approaches including clinical trials, phantom studies and mathematical modelling. Where appropriate, information has also been obtained from epidemiological studies and medical series that often relate to inferior treatment techniques which are no longer in use. Though these studies are not directly relevant to current RT practice, they can still inform as to the risk of RIC for specific tissues; for example, studies of individuals treated with RT for tinea capitis (ring worm) as children and peptic ulcers in an older population.[1–3] It should be noted that the risk assessments of RICs provided in this document are estimates based on statistical probability, which is subject to a number of important variables. When communicating with patients, it should be emphasised that these risk estimates are only approximate.

Methods used for predicting risk of radiation-induced cancer

Mathematical modelling studies

The advantage of mathematical models is that they can predict future risk in response to modern treatment protocols; however, whenever possible, they should be tested against validated outcome data in irradiated cohorts.[4] The disadvantage of models is that they are theoretical and are based on a series of assumptions that may be imprecise or inaccurate. For example, previously it was proposed that as radiation dose increases above a poorly defined threshold, the risk of an RIC falls off due to the complete eradication of clonogens.[5] However, it is now known that in heavily irradiated tissue, surviving normal cells will proliferate rapidly for a few months. Therefore, it is proposed that repopulation of the tissue will derive from normal cells, and importantly any radiation-induced premalignant cells, originating at some distance from the high-dose field.[4,6] It is therefore proposed that accelerated proliferation of premalignant cells approximately cancels out the effects of cell killing, leaving a risk of RIC that increases approximately linearly with dose.

This proposed relationship was confirmed in patients receiving RT for Hodgkin lymphoma who were found to have a dose-dependent increase in risk of developing secondary lung cancers (13 years median follow-up) and breast cancers (19 years median follow-up).[7] However, although an approximately linear dose response is found in lung cancer risk following RT for peptic ulcers, some variation from linearity has been found for tumours originating in other sites with the excess relative risk reducing with increasing age of exposure.[3] An approximately linear response is also reported in studies of atomic bomb survivors though, as expected, the excess risks for different tumour sites show significant

variation with gender, attained age and age at exposure. For all solid cancers as a group, the excess absolute risks appear to increase throughout the study period, providing further evidence that radiation-associated increases in cancer risk persist throughout life, regardless of age at exposure.[8] It is therefore reasonable to presume that at intermediate doses, relevant to RT for benign diseases, the risk will be related to dose in a similar manner; the risk will be real, although small, and it will be moderated by many factors as outlined in Section 2, Table 3.

Phantom studies

Phantom studies allow investigation of long-term risks resulting from RT administered using current techniques. One such study reported on the estimated risk of RIC in patients treated with RT for heterotopic ossification, omarthritis, gonarthrosis, heel spurs and hidradenitis suppurativa.[9] The effective dose was measured and the RIC calculated using the International Commission on Radiological Protection (ICRP) 60 recommendation, which states that the average carcinogenic risk resulting from radiation exposure is 10% per Sievert (Sv) for high dose and high-dose-rate ionising radiation (IR) exposure.[10] They acknowledge that the concept of using effective dose in this type of study has limitations, although they argue that it provides a reasonable estimate of effect. The organ doses were calculated for both male and female anthropomorphic phantoms, and other risk-modifying factors such as age at exposure were taken into account. For RT of these conditions, they calculated an effective dose range of 5–400 millisieverts (mSv). For an average-aged population, the estimated number of fatal RICs due to these treatments was assessed to be between 0.5 and 40 persons per 1,000 patients treated; as expected, the risk was reduced as the age at treatment was increased. They noted that the range of effective doses for the different treatments at various body sites is large and advise there are several ways to optimise treatment protocols to reduce the effective dose and thus the related risk of RIC.

Assessment of radiation-induced cancer in cohorts exposed to low radiation doses

There have been many epidemiological studies on cohorts exposed to low or very low doses of environmental, industrial or medical irradiation. These studies have primarily investigated individuals exposed to whole-body irradiation, frequently with an ill-defined dose. However, often the numbers involved are large, making estimates somewhat more reliable. The survivors of the Japanese atomic bomb form a very large group, which has been continuously monitored within the lifespan study (LSS).[11] The most recent update of the data on haematological malignancies showed a non-linear dose response for leukaemias, other than for chronic lymphocytic leukaemia and adult T-cell leukaemia. This varied markedly with time and age at exposure, with much of the evidence for non-linearity associated with the risks of acute myeloid leukaemia.

The study confirmed previous analyses of a general decline in the excess risks of leukaemia with attained age or time since exposure; however, the radiation-associated excess leukaemia risks, especially for acute myeloid leukaemia, had persisted throughout the 55-year period of follow-up. There was a weak link for non-Hodgkin lymphoma among men although not in women, and no evidence of radiation-associated excess risks for either Hodgkin lymphoma or multiple myeloma.[12]

In contrast, an increase in most solid tumours appears after a latency time (LT) of about ten years and the numbers increase approximately linearly after that time.[8,11] Studies have also confirmed that the younger an individual was at the time of radiation exposure, the

higher the risk of developing an RIC, with a tenfold difference between children and adults, although current evidence suggests that *in utero* exposure carries a much lower risk than exposure in infancy.[8,13] Data from the LSS has shown a dramatic decrease in the incidence of RIC as a function of age of exposure, with the risk decreasing from about 15% per Sv of uniform whole-body irradiation for children <10 years to about 1% per Sv for adults exposed at >60 years.[10,14]

Assessment of radiation-induced cancer in patients treated with high-dose radiotherapy

A second large evidence base relates to patients exposed to high-dose RT for cancer (reviewed by Kumar 2012).[14] A meta-analysis of >640,000 patients, identified from cancer registries in the United States of America (USA), found there were five excess cancers per 1,000 patients which presented within 15 years of high-dose RT; this data was acquired from 15 solid tumour types.[15] A further systematic review of 28 eligible studies identified 3,434 patients who developed second cancers in 11 different organs known to receive >5 Gy. The majority of the studies showed linear dose–response curves even up to ≥60 Gy; the only exception was thyroid cancer, which showed a downturn after 20 Gy. They also confirmed that the risk varied according to the tissue of origin of the second cancer.[16]

Often several tissues with different risks of developing RIC are exposed to radiation during RT. For example, a study of 104,760 women treated with RT for cervical cancer showed they had an increased risk for all second cancers and particularly at heavily irradiated sites (colon, rectum/anus, urinary bladder, ovary and genital sites) compared to women in the general population. This persisted beyond 40 years of follow-up and was modified by age at treatment.[17] High-dose RT for a cancer in childhood carries the greatest risk of a subsequent RIC. However, since some childhood cancers have an underlying germline mutation, this may also contribute to the observed increase in susceptibility to second malignancies.[18,19] For example, breast cancer risk after RT is greater in patients treated for Hodgkin lymphoma than Wilms' tumour.[20] In addition, paediatric patients are smaller and this may provide for a further increase in risk compared to adults, since the organs surrounding the treatment site receive larger doses of scatter radiation.[21]

Since the evidence now confirms an approximately linear risk of RIC, the data obtained from cancer patients treated with high doses can be used to give some guidance as to the lesser risks of RIC following intermediate dose RT for benign disease. However, the risk of RIC varies for different tissues and there is a considerable reduction of relative risk with fractioned local RT as compared with those reported for the LSS cohort, presumably due to the much reduced RFS in RT patients.[16] Treatment protocols may also be different so any comparisons to high- and low-dose studies must be interpreted with caution.

Studies on patients exposed to ionising radiation for non-malignant conditions

There are a limited number of directly relevant studies that report the risks of RIC following irradiation for non-malignant conditions. To some extent they use similar doses and treatment protocols to current practice and therefore provide the most relevant estimates of risk. However, there is still considerable uncertainty as to their relevance to current treatment. There are many limitations inherent in these comparisons; for example, the numbers in some cohorts are small, estimation of the dose received is variable, the dose itself is variable between individuals, age on irradiation and age at follow-up vary. In addition, when extrapolating into the future, it should be noted that treatment protocols and

equipment have changed considerably in the last 50 years so that the risks of RIC must also be considered in these new situations.

4. Tissue-specific cancer risks following exposure to intermediate-dose radiotherapy

The previous section has discussed the variety of sources used to inform the assessment of RIC risks. The discussion below reviews the available information as to the risks of RIC in specific tissues.

Skin cancer

The incidence of non-melanoma skin cancer (NMSC) is known to be increased in individuals exposed to occupational and therapeutic IR.[22–24] However, other reports suggest there is no increase in the risk of skin cancer mortality following RT for ankylosing spondylitis.[25] Some of these conflicting results may, in part, be attributed to the use of skin cancer mortality as a study endpoint since NMSCs are rarely fatal. However, a cohort study of women treated for cervical cancer did not find any increased risk of NMSC after RT.[26]

The risk of RIC of the skin has a minimum LT of about ten years and then rises steadily. One of the largest follow-up studies (25 years) is of 10,000 children receiving RT for tinea capitis (mean dose 7 Gy), compared with 16,000 matched controls; this found 42 basal cell carcinomas (BCC), in contrast to the ten expected.[23] In a study of RIC in 14,140 patients following RT using Grenz rays to treat skin conditions, the excess in NMSC was 39 compared to 27 expected; the number of malignant melanomas was unaffected. Overall the authors considered the excess risk of malignant skin cancers to be very small. It should be noted they did not measure the incidence of BCC.[27] In a retrospective survey of 257 patients who had received RT for a variety of benign diseases (66% tuberculous adenopathy), a 20–50-year follow-up found 24 cases of skin cancer, which were mainly BCC in the irradiated field (a cumulative incidence of 7.8%). However, 88% had chronic radiation dermatitis suggesting they received a relatively high dose (mean estimated dose 16 Gy).[28] Since for most benign conditions treated with IR no evidence of this type of chronic skin damage is found, the data may be an overestimate of the likely incidence for modern treatment protocols.

Currently most of the positive data relating to an increased incidence of skin cancer relates to individuals irradiated as children. Other studies of adults receiving IR for benign conditions, such as tuberculosis patients exposed to multiple fluoroscopies, have not shown any significant increase in skin cancer risk. One factor which can increase the RIC risk is the extent of sun exposure to the skin, suggesting a synergistic interaction between the carcinogenic effects of IR and ultra-violet (UV) exposure.[29,30]

In a group of 5,232 individuals diagnosed with at least one BCC or squamous cell carcinoma (SCC) between 1980 and 1986, 1,690 were identified as having previous exposure to RT for a range of non-skin cancer conditions. The data showed that exposure to RT was associated with an increased risk of subsequent BCC but not SCC. The risk of BCC also showed an increase with younger age at exposure and time since initial treatment, although the trends were only marginally significant.[31] The evidence suggested that BCC resulting from IR exposure was more aggressive and therefore it was advised that it should be treated with wider excision margins. A further study has also reported that BCC developing after RT is likely to be more aggressive and recommended that these patients should be carefully monitored.[32]

Many benign indications for RT are located in the extremities and therefore the main organ at risk is the skin. Risk estimates for an approximate 100 centimetres^2 (cm^2) skin area treated to a mean dose of 3 Gy have indicated a lifetime risk of local BCC of 0.006%.[33] Using the available epidemiologic data, a cautious estimate of the lifetime risk of BCC also has been reported.[29] When the relative risk (RR) in the radiation field from 1 Gy was set at ~0.6. in a sun-exposed field the absolute lifetime risk was estimated to be ~10–5 for 1 cm^2 per Gy. This means that for a 100 cm^2 field of sun-exposed skin treated with 1 Gy, the lifetime risk of in-field BCC is ≤ 0.1%. In skin fields not exposed to sunlight, the risk would be smaller by about one order of magnitude.[29] This should be compared to the spontaneous lifetime risk which is >20%.[33]

Soft-tissue sarcoma and bone sarcoma

The overall frequency of sarcoma after RT for various diseases has been estimated to be <0.05%. No dose–response relationship has been demonstrated, but in-field soft-tissue sarcomas are very rare following exposures to doses of <10 Gy.[34] In a study of 375 patients treated for soft-tissue sarcoma, 11 were diagnosed with sarcoma 4–31 years after the primary RT (doses 12–60 Gy), most commonly with malignant fibrous histiosarcoma. However, there was only one death in this group and it has been advised that with careful monitoring of the site of IR exposure any RIC identified should be potentially curable.[35] Similarly, osteosarcoma was reported in 47 patients treated with relatively high-dose RT for benign or malignant disease 4–27 years after the primary exposure. There was a predominance of patients who had been treated in early childhood, several for retinoblastoma, and some were younger women treated for early-onset breast cancer (BCa).[34] The identification of a genetic link between sarcoma and retinoblastoma was confirmed in a study of 384 patients treated for retinoblastoma, which showed an actuarial risk for subsequent development of a sarcoma in the radiation field of 6.6% over the following 18 years.[36] A nested case-control study of secondary sarcomas (105 cases, 422 matched controls) was carried out in a cohort of 14,372 childhood cancer survivors. The secondary sarcomas occurred at a median of 11.8 years (range, 5.3–31.3) from original diagnosis; children with an initial diagnosis of Hodgkin lymphoma or primary sarcoma were more likely to develop a subsequent sarcoma. Anthracycline chemotherapy was also associated with increased risk.[37] Estimation of the lifetime risk of osteosarcoma after low-dose IR can be made based on the LSS data. Five excess cases have been documented after a mean total-body dose of 0.23 Gy which would be consistent with a lifetime risk of <0.1% for 1 Gy total-body dose.[38] This value, corrected for a typical small RT field of 100 cm^2, would indicate that the risk of radiation-induced sarcoma after RT for most benign diseases is very small, at <1 in 100,000.[33]

Leukaemias

In a key study published in 1965, the cause of death was analysed in 14,554 patients treated with RT for ankylosing spondylitis from 1935 to 1954. The total number of deaths in the cohort was 1,582 of which 52 were caused by leukaemia, compared to the five expected. It was noted that the doses used were sufficiently moderate that they did not cause any acute or chronic overt side-effects. The excess cases occurred from the first years up to about 15 years after exposure to IR.[39] Another study of 10,000 women, treated between 1925 and 1965, with intrauterine radium or external X-rays for uterine bleeding, compared the patients to a similar non-irradiated group. There were 40 leukaemia deaths, which was 70% greater

than expected.[40] This was confirmed in a later study which also reported an increase in several other solid cancer types in the pelvic area.[41]

Other patients treated with RT for benign conditions, such as for tinea capitis and peptic ulcers, were also found to have an increased risk of leukaemia.[3,42] Unlike other RICs, the risk of leukaemia may manifest itself only a few years after IR exposure and the risk remains increased for at least 25 years. The maximum risk depends on the age of IR exposure; children show an approximate twofold increase in sensitivity and a shorter LT than adults. Additionally, different leukaemia subtypes show significant differences in LT, with chronic myelocytic leukaemia having the shortest (mean ~5 years). The LSS data allows estimation of the lifetime risk of leukaemia for an adult irradiated with 1 Gy to be ~1%. For partial-body irradiation, the relative amount of irradiated red bone marrow will be considerably less and for patients exposed to a mean bone marrow dose of 1 Gy for ankylosing spondylitis, the leukaemia risk is approximately 0.2%.[33]

Brain tumours

Risk estimates for RICs arising in the brain following cranial irradiation come from studies at a range of exposure levels. Following low-dose exposure, the risk of RIC of the brain increases approximately linearly with dose; it is also age dependent, with children having the highest risk.[8,43] Survivors of the atomic bomb in Nagasaki have a dose-dependent risk of developing meningioma, assessed on distance from the hypocentre, with a long LT.[44] In a study of >10,000 children, who received low-dose RT for tinea capitis (mean brain dose 1.5 Gy), there was a sevenfold increase in the incidence of brain tumours, although most were benign (19 meningiomas, relative risk [RR] 9.5; 25 neurilemmomas RR 19), however, seven were malignant gliomas (RR 2.6).[45]

For individuals exposed to intermediate or high doses of radiation, meningiomas are also the most commonly reported tumour type although the risk is small. A multivariate analysis of 66 studies (1981–2006) identified only 143 patients (74 female and 69 male) with meningiomas attributable to prior RT to the head for a range of conditions. The overall incidence was not reported, possibly because the information was not available. Within this group, atypical (World Health Organization [WHO] Grade 2) or malignant (WHO Grade 3) meningiomas were twice as common, and they presented at a younger age, compared to spontaneous meningiomas. Importantly >80% of the patients were ≤21 years at initial RT treatment. The median LT to secondary meningioma was 19 years (males 18 versus females 24.7); no clear reason for this difference was identified. Several other factors were also found to influence LT, notably initial diagnosis, type of RT field and RT dose. Leukaemia patients had a shorter LT than those treated for benign conditions (14.9 versus 32.1 years) possibly because the former were also treated with cytotoxic chemotherapy. Those treated with higher doses for initial tumours of the brain or head and neck had intermediate LT (20.2 and 18.5 years). Patients who received lower RT doses had longer LTs, for example those who received RT for tinea capitis. Patients receiving craniospinal or cranial RT had shorter LTs compared with those exposed to partial brain RT, confirming, as expected, that the likelihood of a RIC is greater the larger the exposed volume.[46]

The risk of a RIC of the brain 20 years after surgery and external beam radiation therapy (EBRT) for pituitary cancer has been calculated as 2.4%.[47]

The development of a second brain tumour was also reported in a large study of 14,361 children who had survived >5 years following radiotherapy (RT) to the brain. Subsequently 116 of the treated children developed a second brain tumour; although the incidence was

very low it was significantly greater than in the control group. The most common second neoplasms were glioma (40) and meningiomas (66) which showed a median time to occurrence of 9 and 17 years respectively. The excess relative risk/Gray (Gy) was highest among children exposed at less than five years of age. After adjustment for radiation dose, neither original cancer diagnosis nor chemotherapy was associated with risk.[48] Two recent studies have provided additional data which are consistent with this study.[49,50]

One large retrospective study has reported on the risks of ionising radiation (IR) exposure of the brain following SRS. The incidence of radiation-induced astrocytoma was slightly lower than in a control group.[51] A more recent analysis of this cohort has been carried out, which included 7,998 patients, 2,296 with more than ten years of follow-up, 993 with more than 15 years' follow-up, and 56,788 patient-years of data. This analysis confirmed that there is no increased incidence of RIC compared with age, sex and time-matched controls. A further analysis was planned for the end of 2014.[52] Two further publications have found similar results.[53,54] Worldwide, six case reports have suggested that SRS might be associated with a risk of malignant transformation within benign tumours.[55] However, in these situations it has been suggested that the tumours might already have been more aggressive, and that this should be identified, if possible, using diagnostic tests.[56] Another follow-up study of 440 patients previously treated with gamma knife surgery for vestibular schwannoma found only one patient (0.3%) had developed a malignant tumour and ten patients (2.3%) developed delayed cyst formation.

Although the mean follow-up was 12.5 years, the authors cautioned against assuming this technique is completely safe, especially for younger patients.[54] Since solid tumours can arise many years after radiation exposure, none of the current studies have sufficient follow-up to provide definitive proof of the safety of the technique; however, for older patients the studies indicate that RIC is unlikely to be a concern.

Patients treated with intermediate doses for eye disease (typically around 20 Gy) will receive a radiation dose about 60% less, to a brain volume that is ~80% less, than is applicable to the treatment of pituitary tumours with RT. Based on these approximations it has been calculated that the risk of RIC of the brain following RT (~20 Gy) for eye indications is ~0.2%.[33]

Overall, the evidence for an increased risk of RIC of the brain is small when the radiation dose is low, unless exposure occurs at a young age. Nevertheless, following exposure to higher therapeutic doses (such as those for thyroid eye disease, pituitary tumours or meningiomas), there is a small but measurable dose-dependent risk which should be considered when counselling patients. This is particularly important for patients who have been irradiated as children or young adults.

Thyroid cancer

The thyroid of young children is the most radiosensitive organ with regard to radiation carcinogenesis; a risk that falls rapidly with increasing age. Several epidemiologic studies have identified an increased risk of thyroid cancer in children exposed to IR, where the thyroid has received a variable radiation dose; these include a large cohort (>10,000) irradiated for tinea capitis followed up for >40 years and others treated for cervical adenopathy or tonsillitis.[2,57] Most RICs of the thyroid are papillary cancers with a latency time (LT) ranging from a few to >30 years. Age is the most important factor affecting risk of RIC in the thyroid, with the RR in children irradiated under 5 to be ~20 decreasing to four in those irradiated in adolescence. For adults >40 years, there is no evidence of an increase in risk.

For children <10 years there is an estimated lifetime risk of RIC of the thyroid of 1% per Gy although in very young children this may be higher.[2,33]

Breast cancer

Most studies show that for women, exposure to breast irradiation at >40 years has only a very small risk of radiation-induced breast cancer. However, younger women (15–25) have a moderate risk and this may be higher in young girls. In one study of 601 women given RT (0.6 to 11.5 Gy; median ~3.5 Gy) for acute postpartum mastitis, 56 women had developed breast cancer after a mean follow-up of 30 years, whereas only 32 were expected.[58] Another study reported on breast cancer risk in women treated with RT for acute or chronic mastitis or fibroadenomatosis with doses ranging from <1 cGy to 50 Gy, mean 5.8 Gy (the lowest values relate to the contralateral breast in patients who only received treatment to the axilla). The incidence rate ratio in this cohort of 1,216 women decreased after ~25 years but was still above normal even 40 years after exposure. Even if there was a low dose of exposure (<2 Gy) there was a small, although not significant, increase in risk.[59] An increased risk has also been reported in women who were irradiated as young girls to the chest area, in particular for haemangioma.[60] Further analysis of this cohort suggested that the mechanism underlying the risk may relate to genomic instability at an early stage of tumour development.[61] Comparison of three recent studies confirms the linear dose response for breast cancer as found for other solid tumours.[16] The risk factor for breast cancer needs to be assessed for women exposed in specific circumstances where the breast is directly affected; the effective-dose concept which applies to a general population is unhelpful in this situation.[10] Several estimates of the risk versus benefit of mammography screening are available, however, these are very dependent on the mathematical models used. With this caveat, a cautious estimate of the lifetime risk of breast cancer for a breast exposed to 1 Gy has been made of ~5% if irradiated before 35 years of age, <3% for ages 35–45, and much less, or possibly zero, if irradiation occurs at an older age.[33]

Lung cancer

In individuals who have previously received RT in the region of the lungs, the incidence of lung cancer has also been found to show a small but measurable increase. When this was assessed in 14,106 deceased patients who had been previously treated with RT for ankylosing spondylitis (mean mediastinal dose 5 Gy), lung cancer was the most frequently reported type of RIC (40%), with a significant excess risk of 224 cases versus 184 expected.[62] In a cohort of 3,719, treated between 1937 and 1965, with RT for peptic ulcers to control gastric secretion, there was a marked inhomogeneity in the dose distribution (mean lung doses: left 1.8 Gy, right 0.6 Gy). After a mean follow-up of 25 years, there were 125 lung cancer cases observed compared to 84 expected, providing a RR of 1.24 at 1 Gy mean lung dose. However, this may have been affected by the significantly increased rate of smoking in the irradiated group.[63] This confounding factor underlines the difficulty of quantifying the risk of lung cancer, since it will be markedly affected by the amount and duration of smoking – a behaviour that is notoriously difficult to quantify. Smoking has also been found to increase significantly the excess risk of lung cancer in the LSS cohort.[64]

A more recent reanalysis of patients receiving RT for peptic ulcers confirms there is a statistically significant ($p<0.05$) excess risk for all cancers and for lung cancer, a borderline risk for stomach cancer ($p=0.07$) and leukaemia ($p=0.06$). There is also an excess risk of pancreatic cancer ($p=0.007$) when adjusted for dose–response curvature. The RR decreases with increasing age at exposure for all cancers.[3] In addition, studies on radon

exposures in mines or at home, and from smoking, show the risks of lung cancer are supra-additive. There is no information on the radiosensitivity of different parts of the lung so risks have to be determined by the mean lung dose. It has been estimated that after a mean lung dose of 1 Gy the absolute risk of RIC in the lung within 25 years is ~1%.[33]

Conclusions

The risk of RIC for benign diseases treated with RT varies considerably and is dependent primarily on the site of treatment, age, field size and dose.

For all peripheral/extremity indications (for example, Dupuytren's contracture, tennis elbow, heel spur) radiation risks are very small (discussed further in the later sections). The irradiated skin may have an increased risk of BCC that may also be multi-focal and possibly more clinically aggressive.

Consequently the site of IR exposure should be monitored long term and where BCC occurs it should be treated with wider margins. When significant amounts of red bone marrow are irradiated there is a small but real risk of subsequent leukaemia; therefore, in so far as it is possible, the mean bone marrow dose should be kept to a minimum. The risk of other solid tumours will also depend on the tissue within, or close to, the radiation field, with the risk increasing in individuals exposed at a younger age, especially if they were children or young adolescents at the time of treatment.

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The Royal College of Radiologists. *Recommendations for using radiotherapy for benign disease in the UK*. London: The Royal College of Radiologists, 2023.