A review of the use of radiotherapy in the UK for the treatment of benign clinical conditions and benign tumours

Faculty of Clinical Oncology
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Foreword

While the majority of patients treated by external beam radiation therapy (EBRT) are being treated for cancer, this form of radiotherapy can also be used to treat patients with a variety of benign (non-neoplastic) inflammatory and proliferative conditions. It can also be used to treat a wide range of benign tumours.

The Royal College of Radiologists (RCR) has therefore undertaken an evidence review of the use of radiotherapy for treating benign conditions and tumours to provide clinicians with a ‘handbook’ to consult when a patient is referred with such conditions. It is also hoped that this review will help to raise awareness of the wider potential uses of radiotherapy – beyond treating patients with cancer – among referring professions. This in turn could help to promote the development of a more evidence-based and equitable strategy for the use of radiotherapy across the UK.

With an increasingly aging population in the UK, it is possible that radiotherapy could provide a useful treatment modality with low toxicity for patients with benign conditions in an age group where the risk of radiation-induced cancer (RIC) is not clinically relevant. The review therefore recommends that radiotherapy departments should reassess their protocols for the treatment of benign diseases, including, where appropriate, the use of modern techniques.

I would like to express my grateful thanks to members of the working party (Appendix 1) – Dr Paul Hatfield, Professor Stephanie McKeown, Dr Robin Prestwich and Dr Richard Shaffer – for their extensive input and excellent contributions to this review.

I would also like to thank members of the RCR’s Clinical Oncology Professional Support and Standards Board for their kind assistance in reviewing the draft of this document and for their many helpful comments, and Gillian Dollamore, Bethan France and Holly Benson at the RCR for all their advice and support.

Professor Roger Taylor
Vice-President, Clinical Oncology
The Royal College of Radiologists
1. Introduction

The majority of patients receiving external beam radiation therapy (EBRT) are being treated for cancer. However, historically radiotherapy (RT) has been given to many patients for a variety of benign (that is, non-neoplastic) conditions, including inflammatory and proliferative conditions. Furthermore RT is also employed for the treatment of a wide range of benign neoplasms.

There are two basic hypothetical mechanisms which can be exploited for the treatment of benign conditions with RT. First, the anti-proliferative effect of RT, which can be used, for example, to reduce the risk of heterotopic ossification following hip replacement or recurrence of pigmented villonodular synovitis following a synovectomy. Second, the anti-inflammatory effect of RT can be used to treat a number of soft-tissue inflammatory conditions such as thyroid eye disease. 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 has declined. It is likely that this is largely due to the increased availability of alternative medical therapies, advances in surgery and also concerns as to the potential, if very small, risk of radiation-induced cancer (RIC). In Germany, RT is quite widely used for a range of benign conditions, however, a recent survey of UK RT departments conducted by The Royal College of Radiologists (RCR), discussed below, has established that, in general, the numbers treated are much smaller and they vary considerably from one department to another.

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. For some conditions there are larger follow-up studies on the risks of RIC. However, many of these studies are for conditions that are no longer being treated with RT; for example, tinea capitis, peptic ulcers and ankylosing spondylitis. Therefore, much of the literature is ‘historic’. 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 pterygium, randomised trials have been conducted and there is ongoing clinical research in the field of RT for macular degeneration.

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. However, 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.

Background/remit of the report

In recent years, the Faculty of Clinical Oncology of the RCR has become aware that there are varying numbers of patients in some UK RT departments being treated for benign conditions, and that a review of the evidence would be timely. This would contribute to the development of a more informed and equitable strategy for the use of RT, where it has proven efficacy, across all parts of the UK. In addition, this evidence review document can serve as a ‘handbook’ for clinicians to consult when referred a patient with a benign condition. It has been agreed that the review should include the use of RT for most benign conditions; a few have been excluded for a variety of reasons and are identified below. It has also been agreed to include some benign tumours, generally those that are rare or rarely treated with RT and for which the literature is not well known. However, a number of benign tumours were considered to be beyond the scope of this review (see below).

The document includes discussion of general principles of RT for benign conditions, including the likely morbidity. It presents an approximation of the likely risks of RIC, although risk estimates are fraught with difficulty (see Methods used for predicting risk of radiation-induced cancer [page 18]). Clearly the risk of a RIC caused by RT is an issue which needs to be discussed with patients. Indeed, it is also a factor that may influence the judgement of referring clinicians since most of these patients are referred from other clinical specialties, for example, ophthalmologists, dermatologists and orthopaedic surgeons.
Since the factors governing the risk of RIC are complex, hard to estimate and often very patient-specific (for example, age, site of irradiation, dose), guidance is given as to the most important factors that the clinical oncologist should use to advise their patients. Unfortunately, in only a few instances is there any substantive quantitative evidence of the risk of RIC since the numbers required to estimate the risk are very large and the numbers who currently receive RT for many of these conditions are relatively small; additionally they will require a very long follow-up. With this proviso, some attempt has been made to identify the risk from available evidence and international risk estimates to inform discussion with patients. This is important, as it should also be set in the context of the risks of alternative therapies. The types of evidence and the grading of recommendations used within this document are those defined by the Scottish Intercollegiate Guidelines Network (SIGN) as specified in Appendix 2.

Conditions not considered for review

1. Unsealed source RT, for example, radio-iodine for thyrotoxicosis, metaiodobenzylguanidine (MIBG) for phaeochromocytoma.

2. Aggressive fibromatosis (desmoid tumour) – patients with aggressive fibromatosis are generally managed by a sarcoma multidisciplinary team (MDT) and, as such, teams will already have considered the literature on the role of RT for this condition.

3. Craniopharyngioma – these are managed by the paediatric neuro-oncology MDT. There is extensive literature and a European protocol available.

4. Pituitary adenoma – these patients are managed by the neuro-oncology MDT, with Improving Outcomes guidance (IOG) recommendations for a specific pituitary MDT. There is extensive literature on the use of RT for pituitary adenoma and this condition was considered beyond the scope of this review.

5. Phaeochromocytoma – increasingly these are managed by neuro-endocrine MDTs. Furthermore there is a contribution from unsealed source therapy, which is beyond the scope of this review. Therefore it has been decided that phaeochromocytoma should not be included.

6. Intra-arterial brachytherapy – this has currently fallen out of use with the development of stents and other advances in treatment.

Review of activity in UK radiotherapy departments

A questionnaire survey of all UK RT departments was undertaken by the RCR requesting numbers of patients with a range of benign tumours and benign conditions treated per annum. Information on treating consultants was also requested. Questionnaires were sent to heads of service of all 61 UK departments and responses were received from 25 (41%). A summary of responses is provided in Table 1 (opposite). This demonstrated a core of activity in many centres, particularly for some benign tumours, but also for heterotopic ossification, keloid, thyroid eye disease and Dupuytren’s contracture. The large activity for trigeminal neuralgia in one centre and a large number of cases of vestibular schwannoma are related to treatment with stereotactic radiosurgery (SRS).

One important feature of this survey is the wide variation in activity for these conditions across the UK. For example, one centre treated 64 patients with keloid per annum, whereas others treated none. Many departments treat a very small number per year, yet a limited number of departments treat a significant number in some disease categories.

Regarding the centres that did not reply, it is difficult to understand whether this was because they treated no patients with benign conditions or tumour, although this seems unlikely. The responses from 25 centres confirm the inter-departmental variation and provide an idea of the range of conditions treated.

German patterns of care study on radiotherapy for benign diseases

On reviewing the literature, it is evident that, although the use of RT for benign conditions has declined in the UK, there has been greater use in Germany, which has continued to the present day. A working group in Germany reviewed the use of RT for benign disease and have provided several ‘patterns of care study’ reports. Mailed questionnaire surveys were undertaken in 1994, 1995 and 1996 requesting departmental information on RT equipment, treatment indications and patient numbers for various benign diseases. There were responses from 134 of 152 German institutions (88%). A mean of 20,082 patients were treated annually: 456 (2%) for inflammatory diseases (221 hidradenitis, 78 local infection, 23 parotitis, 134 not specified); 12,600 (63%) for degenerative diseases...
<table>
<thead>
<tr>
<th>Disease category</th>
<th>Number of centres treating</th>
<th>Total number treated per annum</th>
<th>Median number treated per annum</th>
<th>Range</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Eye</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pterygium</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Choroidal haemangioma</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Age-related macular degeneration</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Reactive lymphoid hyperplasia/orbital pseudotumour</td>
<td>4</td>
<td>9</td>
<td>2</td>
<td>1–5</td>
</tr>
<tr>
<td>Thyroid eye disease</td>
<td>19</td>
<td>81</td>
<td>3</td>
<td>1–12</td>
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<tr>
<td><strong>Orthopaedic</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Heterotopic ossification</td>
<td>14</td>
<td>32</td>
<td>2</td>
<td>1–8</td>
</tr>
<tr>
<td>Tendonitis and bursitis</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Rotator cuff syndrome</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Tennis elbow</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Painful heel syndrome</td>
<td>1</td>
<td>1</td>
<td>–</td>
<td>1</td>
</tr>
<tr>
<td>Aneurysmal bone cyst</td>
<td>1</td>
<td>1</td>
<td>–</td>
<td>1</td>
</tr>
<tr>
<td>Vertebral haemangiomas</td>
<td>1</td>
<td>1</td>
<td>–</td>
<td>1</td>
</tr>
<tr>
<td>Capsulitis</td>
<td>1</td>
<td>1</td>
<td>–</td>
<td>1</td>
</tr>
<tr>
<td><strong>Skin</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Keloid</td>
<td>15</td>
<td>117</td>
<td>2</td>
<td>1–64</td>
</tr>
<tr>
<td>Dupuytren’s</td>
<td>4</td>
<td>16</td>
<td>2</td>
<td>1–12</td>
</tr>
<tr>
<td>Pigmented nodular synovitis</td>
<td>4</td>
<td>4</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Peyronie’s disease</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Dermatitis</td>
<td>1</td>
<td>1</td>
<td>–</td>
<td>1</td>
</tr>
<tr>
<td><strong>Brain</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Trigeminal neuralgia (SRS)</td>
<td>1</td>
<td>30</td>
<td>30</td>
<td>30</td>
</tr>
<tr>
<td>Acoustic schwannoma</td>
<td>8</td>
<td>93</td>
<td>10</td>
<td>1–34</td>
</tr>
<tr>
<td><strong>Head and neck</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sialorrhoea</td>
<td>2</td>
<td>10</td>
<td>–</td>
<td>1–10</td>
</tr>
<tr>
<td>Glomus tumour</td>
<td>11</td>
<td>16</td>
<td>1</td>
<td>1–4</td>
</tr>
<tr>
<td>Juvenile nasopharyngeal angiofibroma</td>
<td>4</td>
<td>4</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td><strong>Miscellaneous</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Intra-arterial brachytherapy</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Hidradenitis</td>
<td>1</td>
<td>3</td>
<td>3</td>
<td>3</td>
</tr>
</tbody>
</table>
(2,711 peritendinitis humeroscapularis, 1,555 epicondylitis humeri, 1,382 plantar/dorsal heel spur, 2,434 degenerative osteoarthritis, 4,518 not specified); 927 (5%) for hyperproliferative diseases (146 Dupuytren’s contracture, 382 keloids, 155 Peyronie’s disease, 244 not specified); 1,210 (6%) for functional disorders (853 Graves’ orbitopathy, 357 not specified); and 4,889 (24%) for other disorders (for example, 3,680 heterotopic ossification prophylaxis). Prescribed RT doses were generally in the low dose range of <10 Gy but varied widely and inconsistently within geographic regions and institutions. The conclusion was that RT was a well-accepted and relatively frequently employed treatment modality for several benign diseases in Germany. However, there were significant departmental and geographic variations in its use.

The German Working Group on Radiotherapy of Benign Diseases produced consensus guidelines on the use of RT for these conditions. The group defined general indications for RT, including a diagnostic list.

1. Acute/chronic inflammatory disorders – for example, axillary sweat gland abscess, furuncular, carbuncular, panaritium and other infections not responding to antibiotics.

2. Acute/chronic painful degenerative disease – for example, insertion tendinitis and chronic or acute painful osteoarthritic diseases of various joints (such as hip or knee).

3. Hypertrophic (hyperproliferative) disorders of soft tissue – for example, prophylactic RT in early stages of morbus dupuytren and Ledderhose, and morbus peyronie, postoperative prophylaxis of recurrence for keloids and pterygium.

4. Functional diseases – for example, Grave’s orbitopathy, arteriovenous malformations, age-related macular degeneration or persisting lymphatic fistula.

5. Other indications – for example, prophylaxis of heterotopic ossification, prophylaxis of neointimal hyperplasia following coronary artery stent, obstruction of haemangiomas and other vascular disorders.

6. Dermatological diseases – for example, pruritis due to itching dermatoses and eczemas, inaccessible psoriatic foci.

The Working Group also defined consensus guidelines for informed consent, treatment documentation and follow-up, which included late toxicity assessment and scoring. This group has discussed their experience of using RT for the treatment of benign conditions in a fairly recent textbook.

A European Society for Radiotherapy and Oncology (ESTRO) workshop report in 2007 considered the use of RT for benign disease and a summarised consensus on this subject was provided at that time. However, for many of these conditions, most UK clinical oncologists would either find the use of RT unacceptable or not consider it. The results of the German Working Group study and the Clinical Oncology Faculty’s recent UK survey suggest that the use of RT for benign disease deserves a reappraisal, especially in light of the development of other modalities (and their associated risks) and the improved treatment targeting of modern RT equipment. This is particularly pertinent, since many of the individuals likely to benefit from current indications for RT for benign disease are in the older age group, for whom the risk of RIC is very small.

The use of modern radiotherapy techniques

An overarching principle that particularly applies when treating benign disease with RT is to minimise the volume of normal tissue being irradiated because of the long-term risk of RIC. Current RT techniques can help to achieve this. For instance, modern imaging can allow more accurate target definition and other developments in immobilisation and image guidance can allow reduced margins during treatment. Other techniques, such as intensity-modulated radiation therapy (IMRT), can achieve better conformity to complex target volumes (although this may simultaneously increase the volume of tissue receiving lower doses). In some sites, particularly the base of skull, the dose distributions achievable with proton RT may have advantages in the future when this is more widely available.
References


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. 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 section and Section 3, 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 (opposite) that there are a large number of variables pertinent to each indication.

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

<table>
<thead>
<tr>
<th>Description</th>
<th>Dose (Gray [Gy])</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Very low</td>
<td>&lt;2</td>
<td>Used clinically as part of a multiple fraction dosing regimen, very rarely used as a single dose; often used in tissue culture experiments</td>
</tr>
<tr>
<td>Low</td>
<td>2–10</td>
<td>Used for a few indications. In cell/animal experiments this is the most frequently used dose range</td>
</tr>
<tr>
<td>Intermediate</td>
<td>10–40</td>
<td>Used for most non-malignant indications in a variable number of fractions sizes. For many indications 20–30 Gy total dose is used</td>
</tr>
<tr>
<td>High</td>
<td>&gt;50</td>
<td>Used for a few benign tumours and in very small fields in stereotactic radiosurgery (SRS)</td>
</tr>
</tbody>
</table>
Table 3. Factors influencing the risk of normal tissue damage and incidence of radiation-induced cancers during radiotherapy for benign disease

<table>
<thead>
<tr>
<th>Factor</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Radiation-related</td>
<td></td>
</tr>
<tr>
<td>Dose and dose rate</td>
<td>*Most indications use standard external beam radiation therapy (EBRT).</td>
</tr>
<tr>
<td>Radiation quality</td>
<td>*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).</td>
</tr>
<tr>
<td>Radiation field size (RFS)</td>
<td>Key factor. Risk of significant late normal tissue reactions increases with RFS, especially if a radiosensitive tissue is in the field. Risk of radiation-induced cancer (RIC) also increases with RFS.</td>
</tr>
<tr>
<td>Patient-related</td>
<td></td>
</tr>
<tr>
<td>Age</td>
<td>Key factor, particularly affects risk of RIC. Risk decreases with age of radiation exposure. If &gt;60 years often of limited consequence. For children and young adults this is much more important.</td>
</tr>
</tbody>
</table>
| 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 Y rays), using treatment modalities that are standard 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, page 10). 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 Section 3. The risk of radiation-induced malignancy following low to intermediate dose RT [page 18]).

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, page 11). It is known that tissue responses within the radiation field occur both acutely, within hours of exposure, and at some considerable time later. The 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. 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.

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. 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. 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 [page 15]).

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 (page 18).
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. However, 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 second, 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). 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

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. On exposure to IR, endothelial cells swell and/or die by apoptosis. 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.

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. 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. In clinical studies, it has been shown that vascular sequelae are present in the heart and brain of patients exposed to high-dose RT. 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.

**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 fibroblasts, which is thought to trigger their terminal differentiation to postmitotic fibrocytes.

TGF-β1 also blocks of matrix proteins, decreased production/inhibition of matrix-degrading enzymes and also modulation of 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.

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.

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

**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. 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.

RT at high doses is used to control malignant disease; however, this can also induce a well-recognised inflammatory response. 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.

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 x 1 Gy is the most widely studied regimen).

The anti-inflammatory effects have been linked to a reduction in NO, tumour necrosis factor-α and/or interleukin-1β (reviewed by Arenas et al 2012). 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.[18–21] 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.
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. However, 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 (page 18).

**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.3 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.

References


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 Section 2, Normal tissue responses at radiation doses used for benign disease (page 10), there are many variables 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.\(^1\)\(^2\) 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 (page 11).
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. 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. 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). 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.

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. 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. 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.

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). 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. 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.

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.\(^\text{17}\) 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.\(^\text{18,19}\) For example, breast cancer risk after RT is greater in patients treated for Hodgkin lymphoma than Wilms’ tumour.\(^\text{20}\) 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.\(^\text{21}\)

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.\(^\text{16}\) 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.

**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. (In Sections 4–8 the risk of RIC for individual indications are further considered.)

**Skin cancer**

The incidence of non-melanoma skin cancer (NMSC) is known to be increased in individuals exposed to occupational and therapeutic IR.\(^\text{22-24}\) However, other reports suggest there is no increase in the risk of skin cancer mortality following RT for ankylosing spondylitis.\(^\text{25}\) 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.\(^\text{26}\)

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.\(^\text{23}\) 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.\(^\text{27}\)

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).\(^\text{28}\) 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 centimetres² (cm²) 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 cm² per Gy.

This means that for a 100 cm² 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.33 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.33 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 cm², 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 LTs (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. Two further publications have found similar results. Worldwide, six case reports have suggested that SRS might be associated with a risk of malignant transformation within benign tumours. 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. 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. 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%. 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. 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 five 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.

**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. 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. An increased risk has also been reported in women who were irradiated as young girls to the chest area, in particular for haemangioma. Further analysis of this cohort suggested that the mechanism underlying the risk may relate to genomic instability at an early stage of tumour development. Comparison of three recent studies confirms the linear dose response for breast cancer as found for other solid tumours.

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. 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.
**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 1Gy 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.6 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.
References


52. Rowe J. Personal communication. 2014.


Review of the role of radiotherapy for individual benign conditions and tumours
4. Head and neck paraganglioma

Background

Paragangliomas (PG) are rare vascular tumours arising from paraganglia. They can arise from the carotid bodies (carotid body tumour), vagus nerve (glomus vagale), jugular bulb (glomus jugulare) and tympanic branch of the ascending pharyngeal artery (glomus tympanicum). Median age at diagnosis is around 50 years, although PG can present at any age. Most PG are sporadic, with 7–9% having a familial aetiology. Presenting symptoms are typically due to cranial nerve dysfunction and/or a slowly enlarging neck mass. Between 2–5% of PG secrete catecholamines. Less than 5% of PG are malignant. Malignancy cannot be predicted histologically and is defined by the presence of regional or distant metastases.

Cross-sectional imaging with computed tomography (CT) and/or magnetic resonance imaging (MRI) is the key investigation. CT is the study of choice to investigate bone involvement, while MRI defines soft tissue detail, intracranial, neural and dural involvement. Biopsy is not usually performed due to the bleeding risk. PG are vascular and demonstrate early neural or blood vessel involvement, and a propensity for skull base invasion and intracranial involvement.

Management

The aims of treatment for PG have to be set in the context of their natural history. Most head and neck PG demonstrate an indolent growth pattern. One study examining growth rate with a median follow-up of 4.2 years, reported that 60% of the PGs showed a >20% increase in volume. In these cases, the median growth rate was 1.0 millimetres (mm)/year with a median tumour-doubling time of 4.2 years. Death from PG is rare and therefore the aim of treatment of PGs is to minimise/reduce morbidity rather than to improve survival.

Options for treatment include observation, surgery or external beam radiation therapy (EBRT). Traditionally, surgery has been the preferred method of primary treatment, with EBRT reserved for unresectable disease or less fit patients. The excellent results reported in external beam and radiosurgery series has challenged this approach.

Watch and wait

One series 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 is an option for selected patients with PG.

Surgery

The vascularity and skull base location of many PG make surgical management very challenging; resection of lesions with intracranial and extracranial components requires combined surgical approaches. Preoperative embolisation has been used to reduce intraoperative blood loss and facilitate complete resection. Tumour control rates are high following a complete resection. For example, Lope Ahmad et al recently reported a series of 121 jugular PGs with average follow-up of 88 months. Complete tumour resection was achieved in 82%, with a long-term tumour control rate of 96% in this group. Multiple cranial nerve injuries are commonly reported postoperatively. Lieberson et al 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 disproportionally represented. Local control rate was 87% with a high rate of reported complications of ≥46%.

External beam radiotherapy

Although EBRT was historically reserved for inoperable patients, a large number of series have reported high local control rates. For example, Lieberson et al identified a total of 34 series published in or before 2009 containing 795 patients treated with EBRT; local control rate was 91%. The rate of complications was estimated to be 3%. One imaging study of 24 patients documented that the PG decreased in size following EBRT in 61% of cases. A case report and literature review suggest that catecholamine secretion does not respond to radiotherapy (RT) and that these patients are best managed surgically. A dose of 45 Gray (Gy) in 25 fractions in five weeks is commonly utilised with a high rate of local control with a low risk of complications.
Radiosurgery

Radiosurgery is an appealing treatment modality for the treatment of PGs, with highly conformal treatment and steep dose gradients. A limited number of series have reported the use of radiosurgery for PG, particularly glomus jugulare tumours. Most series reported single institution studies with limited numbers and follow-up. Guss et al performed a meta-analysis of stereotactic radiosurgery for glomus jugulare tumours; 19 studies were included from which data for 335 glomus PG were extracted.13 Gamma knife and linac or CyberKnife-based treatments were included. Local control and symptom control were achieved in 97% and 95% of patients respectively. Although variably reported, documented complications appeared infrequent. The marginal dose prescribed in these series varied between 12–20 Gy; a marginal dose of 15 Gy is one of the more commonly reported schedules.

Comparison of surgery, external beam radiation therapy and radiosurgery

There are no randomised trials comparing treatment approaches. The majority of reports are single centre retrospective series with variable follow-up. In addition, comparison between surgically and non-surgically treated patients is difficult as historically, non-surgical approaches were considered for advanced lesions, recurrent disease or poor surgical candidates. Suarez et al performed a systematic literature review published in 2012 examining the role of surgery, EBRT and radiosurgery for PGs.6 The findings are summarised below.

Surgery: In the review, 1,084 patients with jugular PG were identified. The mean duration of follow-up was 65 months. Tumour control was achieved in 78% of patients. Tumour recurrence occurred in 6.9% of patients after a presumed total resection. Analysis of pre- and postoperative cranial nerve palsies showed that surgery resulted in an average of 0.9 additional cranial nerve palsies per patient. Also reported were the outcomes following surgery for vagal PGs in 211 patients. Tumour control rates were high at 93.3%. Cranial nerve damage was common with the vagal nerve rarely preserved.

EBRT: In 20 series, 461 patients with jugular PGs treated with EBRT were identified. The mean duration of follow-up was 113 months. Disease control, defined as alive without any evidence of progression, was achieved in 89%. Severe complications were reported in 57 patients, including sensorineural hearing loss and osteoradionecrosis. Neurological outcome was reported for 351 of these patients; a total of 242 cranial nerve palsies were present before treatment and 232 following EBRT. Only ten patients treated with EBRT for vagal PGs could be identified, all of who achieved disease control.

Stereotactic radiosurgery: The review identified 254 patients with a mean follow-up of 41 months. A reduction in tumour size following radiosurgery was documented in 32% with no change in size in 61%; overall tumour control rate was 93%. The total number of cranial nerve palsies pre- and post-radiosurgery was 306 and 279 respectively.

Ivan et al published a meta-analysis of tumour control rates and treatment-related morbidity for glomus jugulare tumours with 869 patients meeting the inclusion criteria.10 Gross total resection was performed in 351 patients, subtotal resection alone in 82 patients, subtotal resection in addition to postoperative radiosurgery in 97 patients and radiosurgery alone in 339 patients. Tumour control rates were 86%, 69%, 71% and 95% respectively. The meta-analysis also examined the rates of cranial neuropathy following treatment, comparing patients who underwent a gross total resection versus radiosurgery alone. The frequency cranial nerve deficits were: IX 38% versus 9.7%, X 26% versus 9.7%, XI 40% versus 12% and XII 18% versus 8.7% for surgery and radiosurgery respectively.

Interpretation of the surgical outcomes is complicated by several factors. Surgical techniques for base of skull surgery have advanced rapidly and older series are likely to overestimate surgical morbidity. By contrast, the advent of advanced EBRT techniques means that larger more complex surgically difficult lesions are more likely to have been treated with EBRT.
Regression of paragangliomas following radiotherapy/radiosurgery

A recent systematic review and meta-analysis of regression and local control rates following RT for jugulotympanic paragangliomas found high local control rates (tumour volume equal to or less than pre-radiotherapy), with regression in 21% of cases treated with RT/radiosurgery alone.\textsuperscript{14} Regression rates appeared higher following radiosurgery.

Malignant paragangliomas

There is insufficient evidence to guide the management of malignant PGs. One group recommends surgery followed by postoperative EBRT to a dose of 60–70 Gy depending on margins of excision.\textsuperscript{15}

Potential long-term consequences of radiotherapy

The long-term risks of radiation exposure are primarily related to radiation-induced cancer (RIC) in the brain and, as far as is possible, when using RT the dose to the brain should be minimised using modern treatment planning techniques. Apart from this, the age of treatment of the patient, the field size and dose are the most important factors to be taken into account. For older patients, the risk of a RIC is very small (see Section 3. The risk of radiation-induced malignancy following low to intermediate dose RT, [page 18]). However, 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.

Recommendations

- Watch and wait can be considered for more elderly patients with minimal symptoms (Grade C).
- Surgery should be considered as primary treatment for PG with symptomatic catecholamine secretion, rapid neurological deterioration or a life-threatening mass effect (Grade C).
- Surgery, EBRT and stereotactic radiosurgery (SRS) all offer high local control rates and are primary treatment options (Grade B).
- EBRT or SRS may be preferred for more advanced lesions due to the morbidity of surgery (Grade B).
- EBRT should be CT planned with a 3D conformal technique. Intensity-modulated radiation therapy (IMRT) may be considered as an alternative. If available, computed tomography-magnetic resonance imaging (CT-MRI) co-registration may assist gross tumour volume (GTV) delineation. The GTV-clinical target volume (CTV) margin should be at least 5 mm. The CTV-planning target volume (PTV) will depend on institutional set-up errors. A dose of 45 Gy in 25 fractions over five weeks is recommended (Grade D).
- SRS using gamma knife, linac-based or CyberKnife technologies can be used. A typical marginal prescription dose is of 15 Gy as a single fraction (Grade C).

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) (Appendix 2).\textsuperscript{14}
References


Juvenile nasopharyngeal angiofibroma

Background

Juvenile nasopharyngeal angiofibroma (JNA) is a benign rare vascular tumour. They are most common in adolescent boys with a median age of 14 years old.1 JNAs are thought to arise from the superior margin of the sphenopalatine foramen at the posterolateral wall of the roof of the nasal cavity.1,2 Presenting symptoms are most commonly nasal obstruction and recurrent epistaxis. Other reported symptoms include nasal discharge, cheek swelling, proptosis, anosmia, headaches and hearing impairment.1,3 A pink or bluish nodular mass is typically seen in the roof of the nasopharynx. Magnetic resonance imaging (MRI) with gadolinium is the diagnostic imaging investigation of choice. Computed tomography (CT) can provide complimentary 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.

There is no widely accepted single classification system. Examples of systems in use include Fisch’s, Chandler’s, Sessions and Radowski’s.4–7 Although considered benign neoplasms, JNAs can demonstrate locally aggressive behaviour infiltrating adjacent structures with a tendency to spread through the foramina into the base of skull and into the cranium. Skull base erosion is seen in approximately one-in-five cases and is due to expansion and bone resorption, rather than the cellular infiltration characteristic of 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.2 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 extra-meningeal.1

Management

Surgery

Surgery is generally considered 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 to minimise the risk of haemorrhage.1 The surgical approach is determined by tumour location, potential effect on subsequent growth of the craniofacial skeleton and available expertise. Surgical excision should aim for clear margins, as inadequate margins are associated with significant failure rates.9 A craniofacial approach is recommended for disease extending into the pterygoid plates. Potential surgical approaches are reviewed elsewhere.1,3 Local control rates with surgery have been reported in the order of 80–85%.8,10 Potential postoperative morbidity includes disturbance of mid-facial growth following craniofacial resection.11 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.3

Radiotherapy

Radiotherapy (RT) may be employed as primary treatment or upon disease recurrence. 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 recurrence rates and operative morbidity.12,13 One series of 16 cases correlated a recurrence rate of 37.5% with skull base invasion.11 RT has been used as the primary treatment modality in several series, summarised in Table (overleaf).2,9,14–19 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 35–45 Gray (Gy) commonly used. Recurrences have been noted at lower doses.14
Persistent residual abnormalities on imaging are common postradiotherapy. Tumour response to RT is slow. Post-therapeutic stable, asymptomatic radiological abnormalities should not be considered to represent persistent or recurrent disease.

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. In view of the reduced dose to non-target normal tissues, there is interest in the use of proton RT for JNA, particularly for younger patients whose growth is not complete.

### Table 4. Control rates in series of radiotherapy as primary treatment modality (adapted from Chakraborty et al) 2,9,14–19

<table>
<thead>
<tr>
<th>Author</th>
<th>Number of patients</th>
<th>RT dose/Gy</th>
<th>Local control/%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cummings et al (1984)9</td>
<td>55.0</td>
<td>30.0–35.0</td>
<td>80.0</td>
</tr>
<tr>
<td>Robinson et al (1989)16</td>
<td>10.0</td>
<td>30.0–40.0</td>
<td>100.0</td>
</tr>
<tr>
<td>McGahan et al (1989)17</td>
<td>15.0</td>
<td>32.0–46.0</td>
<td>73.0</td>
</tr>
<tr>
<td>Fields et al (1990)18</td>
<td>13.0</td>
<td>36.6–52.0</td>
<td>85.0</td>
</tr>
<tr>
<td>Reddy et al (2001)19</td>
<td>15.0</td>
<td>30.0–35.0</td>
<td>85.0</td>
</tr>
<tr>
<td>Lee et al (2002)20</td>
<td>27.0</td>
<td>30.0–55.0</td>
<td>85.0</td>
</tr>
<tr>
<td>McAfee et al (2006)21</td>
<td>22.0</td>
<td>30.0–36.0</td>
<td>91.0</td>
</tr>
<tr>
<td>Chakraborty et al (2011)22</td>
<td>8.0</td>
<td>30.0–46.0</td>
<td>87.5</td>
</tr>
</tbody>
</table>

### 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. Cataract has been reported more commonly. Other potential late side-effects include hypopituitarism and xerostomia. Highly conformal RT delivery techniques, including intensity-modulated radiation therapy (IMRT), have the potential to reduce doses to organs at risk while maintaining local control. The risks of second malignancy for conventional conformal RT versus IMRT is uncertain. One recent review comparing the likely risks of IMRT to conventional RT suggests that IMRT may increase the potential risk of radiation induced cancer (RIC) by a factor of two, which in older patients may be acceptable, but in children would less acceptable in most instances. Consequently, the use of IMRT in place of conformal RT for JNA may not be justified.

### Recommendations

- **Surgery is regarded as the treatment of choice for JNAs (Grade C).** Primary RT is an effective treatment modality if the disease is deemed incompletely resectable without excess morbidity (Grade C). Surgery or RT can be considered for recurrent disease (Grade C).

- **Conventionally fractionated doses in the mid-range of 35–45 Gy are recommended (Grade C).** There is no evidence of a dose response with doses in the higher end of this range.

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) (Appendix 2).
References


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 most commonly present between the ages of 30–60 years and are more frequent in females. 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). 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. 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. 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

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 (opposite) summarises the largest retrospective reports of outcomes of surgery followed by RT. 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. The probability of future recurrence increases with each episode of recurrence. Therefore obtaining local control becomes increasingly difficult with each recurrence, and the risk of facial nerve palsy increases with each surgical intervention. In addition, the potential for malignant transformation may increase with each recurrence – some series report up to 9% incidence of CXPA in recurrent patients.

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.

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 Gray [Gy]) so there is a small risk of long-term tissue damage in the radiation field with potential for developing a radiation-induced cancer (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.
Table 5. Outcomes after surgery and adjuvant radiotherapy for pleomorphic adenoma (adapted from Mendenhall et al)\(^1,7–10\)

<table>
<thead>
<tr>
<th></th>
<th>No of patients</th>
<th>Untreated/locally recurrent</th>
<th>Radiotherapy dose</th>
<th>Follow-up</th>
<th>Local control</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dawson and Orr (1985)(^7)</td>
<td>311</td>
<td>–</td>
<td>50–60 Gray (Gy) in 20–25 fractions or brachytherapy</td>
<td>Minimum 10 years</td>
<td>92% at 20 years</td>
</tr>
<tr>
<td>Ravasz et al (1990)(^8)</td>
<td>78</td>
<td>62/16</td>
<td>50 Gy in 25 fractions + 10–25 Gy boost</td>
<td>Median 11 years</td>
<td>Previously untreated 100%, locally recurrent 94%</td>
</tr>
<tr>
<td>Barton et al (1992)(^9)</td>
<td>187</td>
<td>115/72</td>
<td>50 Gy in 15–16 fractions or brachytherapy</td>
<td>Median 14 years</td>
<td>Previously untreated 99%, locally recurrent 88%</td>
</tr>
<tr>
<td>Liu et al (1995)(^10)</td>
<td>55</td>
<td>55/29</td>
<td>45 Gy in 20 fractions</td>
<td>Median 12.5 years</td>
<td>Previously untreated 93%, locally recurrent 82%</td>
</tr>
</tbody>
</table>

**Recommendations**

- 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).

- RT technique: 3D computed tomography (CT) planned photons. For parotid pleomorphic adenomas the target volume includes the whole parotid bed (Grade D).

- Variable RT doses are reported in the literature (see Table 5), 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).\(^1\)

The types of evidence and the grading of recommendations used within this review are based on those proposed by the the Scottish Intercollegiate Guidelines Network (SIGN) (Appendix 2).\(^22\)
References


Sialorrhea

Background

Sialorrhea (chronic drooling or excessive salivation) is defined as the unintentional loss of saliva from the mouth. Approximately 1.5 litres of saliva is produced per day. The inability to control oral secretions leads to the build-up of excess saliva in the oropharynx and consequently drooling in more severe cases. Drooling can be a feature of several neurological disorders such as amyotrophic lateral sclerosis, Parkinson’s disease, pseudobulbar palsy, stroke and cerebral palsy. For example, one study estimates that 78% of patients with Parkinson’s disease suffer with sialorrhea. In these neurological disorders sialorrhea is due to swallowing dysfunction and an inability to maintain mouth closure, with normal or near normal saliva production. The pooling of saliva in the oropharynx can lead to 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.

Management

Treatment for sialorrhea should be considered when quality of life is adversely affected. Several methods are available to try to control sialorrhea by reducing saliva secretion. The management of the condition varies with the underlying cause and age of patient. Anti-cholinergic medication is often utilised as first-line treatment. However, elderly patients with neurological disorders are often intolerant of anti-cholinergic drugs due to adverse effects including constipation, confusion and urine retention. Botulinum toxin can be injected locally to reduce saliva production by reducing cholinergic parasympathetic and post-ganglionic sympathetic activity. Botulinum toxin is well tolerated, although requires frequent repeated injections. Several surgical procedures have been attempted, including salivary duct repositioning, denervation procedures and parotidectomy. These invasive procedures have mainly been employed in younger patients, and are often not appropriate in more elderly neurologically impaired patients. Radiotherapy (RT) is known to cause xerostomia in the treatment of head and neck cancers. Therefore RT can be utilised to reduce saliva secretion to alleviate sialorrhea.

Radiotherapy

RT is a recognised risk factor for the development of benign and malignant salivary neoplasms, with a reported latency of 6–32 years. The risk of primary salivary gland malignancies is very rare, so the risk of a RT-induced malignancy is likely to be proportionally low. Adult patients with severe drooling due to neurological disease generally have a limited life expectancy due to the underlying disorder. There are only a limited number of small series reporting on the use of RT for sialorrhea; they are predominantly based on more elderly patients with neurodegenerative disorders. RT should not be used in children due to the potential risks of a radiation-induced malignancy and growth arrest leading to facial asymmetry.

Borg et al reported outcomes of 31 patients treated with RT; the most common underlying neurological disorders were stroke and Parkinson’s disease. Treatment was delivered to bilateral parotid and submandibular glands with separate ipsilateral fields. RT technique was heterogeneous, with electron treatments ranging from 6 to 18 mega-electron volts (MeV) in energy and orthovoltage therapy for other patients. A wide variety of dose fractionation regimens were employed, varying from 6 Gray (Gy) in one fraction to 44 Gy in 22 fractions. Eighty-two per cent of treatments were reported to have a response, with 64% of treatments maintaining a durable satisfactory response. The varied dose/fractionation regimens did not appear to affect the likelihood of response. Durable responses were associated with the use of electron therapy of >7 MeV. Late side-effects were uncommon and related mainly to thick saliva.

Stalpers et al reported the results of RT for 19 patients with drooling due to amyotrophic lateral sclerosis. Treatment was with either 8–14 MeV electrons or orthovoltage with a dose of 12 Gy in two fractions over one week. Of the 19 patients reported in this study, 14 had a satisfactory response to treatment. Acute side-effects included pain and dryness of the mouth, both of which were short-lived.

Guy et al treated 16 patients with amyotrophic lateral sclerosis with 20 Gy in five fractions with electrons encompassing the submandibular gland and sparing the upper parotid gland. After one month, 80% of patients reported improvement, and 43% reported improvement after six months. There was an association between the use of an electron energy >8 MeV and sustained benefit.
Kasarskis et al reported the use of treatment of a unilateral parotid gland in ten patients with amyotrophic lateral sclerosis with electrons to a dose of 15 Gy in three fractions; electron energy was selected using a computed tomography (CT) scan to ensure treatment of the deep lobe and was >9 MeV. All patients experienced an improvement in sialorrhea and half of patients were able to discontinue anticholinergic medication.

Postma et al reported a series with prospective assessment of outcomes. They identified 28 patients with sialorrhea due to Parkinson’s disease who were treated with a bilateral dose of 12 Gy in two fractions with a one-week interval. Seven patients were treated with electrons and the remainder with orthovoltage therapy. The fields were typically 8 x10 centimetres (cm) and included the parotid gland and superior part of the submandibular gland. The efficacy of RT was assessed prospectively by patient interview. Acute adverse events included dry mouth and xerostomia and were reported by 89% of patients; these settled within two weeks in half of patients. Of the patients, 21% experienced increased viscosity of saliva in the longer term. Sialorrhea was reported to improve significantly one month post-treatment and this was maintained for at least one year; quality of life was found to improve in the long term. At final follow-up, 80% of patients were found to be satisfied with the outcomes. Parotid glands secrete large volumes of serous, watery saliva. The submandibular glands produce more viscous seromucous saliva, providing around 70% of basal saliva secretion. The authors postulate that irradiation of the submandibular glands in addition to the parotid glands would prevent the long-term increase in saliva viscosity.

The efficacy of single fraction treatment was reported in an analysis of 20 patients with amyotrophic lateral sclerosis by Neppelberg et al. Following a single 7.5 Gy fraction, saliva flow was reduced by 21% three months post-treatment.

Only a very small number of patients have been retreated with RT either after a lack of response or a transient benefit. The number of patients re-irradiated makes it impossible to draw useful conclusions.

A large prospective study of 50 patients with amyotrophic lateral sclerosis with hypersalivation and prior unsuccessful treatment with medical therapy was recently reported. In this study, patients were treated with a lateral opposed pair of 6 MeV 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.

Potential long-term consequences of radiotherapy

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

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

- Most series report outcomes after treating both sides; one series reported improvements in sialorrhea after one-sided treatment only. Consideration should be given to including the submandibular glands in addition to the parotid glands in the target volume to reduce the likelihood of causing an increase in saliva viscosity. To minimise the inconvenience of treatment, the use of a small number of fractions is advisable for this group of patients. Based upon the largest prospective series, recommended schedules include 20 Gy in four fractions over ten days. Shorter schedules of 10 Gy in two fractions over three days or a single 7.5 Gy fraction may be appropriate for less fit patients (Grade C).

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

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) (Appendix 2).13

### References


5. Eye

Thyroid eye disease

Background

Thyroid eye disease (TED) or Graves’ orbitopathy is a rare condition affecting 2.9–16 cases per 100,000 population per year, and has a 5:1 female to male predominance reflecting the elevated incidence of Graves’ disease in women. Most patients have thyrotoxicosis at the time of development of TED due to Graves’ disease. In 10–20% of cases, the development of TED precedes the development of thyrotoxicosis by a number of months. Between 10–15% of cases of TED occur with current or prior hypothyroidism of autoimmune origin (Hashimoto’s thyroiditis). Following diagnosis of Graves’ disease, the main risk factor for the development of TED is smoking. Smokers also suffer more severe TED than non-smokers. TED occurs at all ages, but most commonly presents in the second and third decades; it is occasionally seen in children.

TED is an autoimmune condition, possibly as a result of shared autoantigens. 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. The natural history of TED includes an initial phase lasting a few months with progressive deterioration, spontaneous improvement which can be over a period of 1–2 years, then a chronic or burnt-out phase during which no further change is likely. The final chronic phase is likely to be due to residual fibrosis or scarring.

Symptoms of TED 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, symptoms of which include blurring not improving with blinking or refraction, impaired colour perception, reduced acuity and field loss. Typical signs of TED on examination include conjunctival oedema, eyelid oedema, lid retraction, proptosis and diplopia.

The diagnosis of TED is made clinically. Thyroid autoantibodies can increase the likelihood of the diagnosis. Cross-sectional imaging with computed tomography (CT) or magnetic resonance imaging (MRI) can be used to confirm involvement of the soft tissues and extraocular muscles. In the presence of atypical features, a biopsy should be considered to exclude alternative diagnoses including lymphoma and orbital pseudotumour.

Management

The majority of TED is mild and self-limiting, but the management of moderate or severe TED remains challenging. TED can have a significant negative impact on quality of life and employment, altering appearance and in some rare instances, threatening sight. Judging efficacy of treatment for TED is difficult due to variable natural history with spontaneous improvement characteristic, paucity of randomised controlled trials and relative rarity of moderate or severe TED. In addition, assessment of the efficacy of intervention is complicated by the lack of standardised outcome measures.

Management should include management of hyper- or hypothyroidism. Radioactive iodine for thyrotoxicosis has been reported to exacerbate pre-existing eye disease, although this risk appears to be eliminated with a course of steroids following radioiodine. Standard antithyroid drug therapies do not exacerbate eye disease. Patients should be advised to stop smoking with some evidence suggesting that smoking impairs treatment outcomes.

Mild TED may simply require local measures such as lubricants for symptoms of corneal exposure and prisms for diplopia. The treatment of moderate or severe TED represents a major challenge. Steroids with their immunosuppressive and anti-inflammatory effects still represent first-line therapy for active phase moderate or severe TED. Response rates to steroids are in the order of 33–66%, but it remains unclear whether steroids improve long-term outcome or simply hasten improvement. An intravenous steroid pulse of methylprednisolone appears more effective than oral steroids, with a clinical response usually occurring within 1–2 weeks. In the active phase of the disease, surgery is generally only indicated for more severe cases, usually in the absence of a steroid response or intolerance. TED can pose a threat to sight, usually due to optic neuropathy. Steroids and surgical optic decompression are the only treatments with proven efficacy for TED-related optic neuropathy; orbital radiotherapy (RT) only has a role as an adjunct to either of these therapies. Rehabilitation surgery can play a useful role in inactive ‘burnt out’ disease, involving decompression, muscle and eyelid surgery.

Radiotherapy

RT has been widely used for the treatment of moderate to severe active phase TED. The mechanism of action of RT is uncertain, although efficacy may relate to the
radiosensitivity of infiltrating lymphocytes and an effect upon fibroblasts. Evidence with regard to the efficacy of RT is limited. There are a few small randomised studies, along with many retrospective and observational series. In general, the reported response rate to RT is around 60%.

Randomised studies comparing radiotherapy with sham irradiation

A small number of randomised studies have compared orbital RT with sham irradiation (when the procedure is performed omitting therapeutic elements). Mouritis et al reported an improvement at six months in 18 of 30 (60%) irradiated patients compared with nine of 29 (31%) sham-irradiated patients; improvement was particularly noted for ocular mobility with no difference for exophthalmos. Gorman et al delivered RT to one orbit and sham RT to the other in 42 patients with mild-to-moderate TED, with treatments reversed six months later. No benefits of radiation were seen at six months, although at 12 months exophthalmos and extra-ocular 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 have may have been in the chronic phase of TED. In a further study, Prummel et al randomised 88 patients with mild TED to RT or sham treatment. At 12 months, the outcome for the RT group was superior in terms of eye mobility/diplopia.

Randomised studies comparing radiotherapy with steroids

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

Randomised studies have suggested a benefit for combining RT with oral steroids. Marcocci et al randomised 30 patients to RT versus a combination of steroids and RT; the ophthalmopathy index outcome was significantly superior in the combined treatment arm. In both of these studies, combined treatment appeared most effective for extraocular muscle dysfunction and soft-tissue changes which were of recent onset. A randomised study of oral versus intravenous steroids each combined with RT demonstrated an increased efficacy for intravenous steroids; the additional benefit of RT cannot be determined from this study. No study has demonstrated the superiority of RT compared with intravenous steroids.

Non-randomised studies

These studies have been the subject of several reviews. Interpretation of these studies is limited by knowledge of the natural history of TED, variable case selection, the use of multiple treatment modalities and varied methods of assessing treatment efficacy and differing duration of follow-up. In general, these series suggest that RT is an effective treatment.

Radiotherapy dose

A dose of 20 Gray (Gy) in ten fractions over two weeks has been commonly employed. Higher doses have not been found to be more effective. One study randomised 65 patients to three RT dose arms: 20 Gy in ten fractions over two weeks, 10 Gy in ten fractions over two weeks and 20 Gy in 20 fractions one fraction per week over 20 weeks. Similar response rates were seen in three objective parameters (55%, 59% and 67%), with a higher rate of treatment-induced conjunctivitis in the 20 Gy in ten fractions over two weeks’ arm (36%, 18% and 0%). Based on this single study, a lower dose of 10 Gy in ten fractions over two weeks is equally effective to 20 Gy in ten fractions over two weeks.
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.\(^24\) In general, RT has a very good safety profile with long-term follow-up.\(^8,25,26\) Several series have examined the risk of radiation-induced malignancy. For example, a series of 245 patients treated with steroids or RT with a mean 11-year follow-up detected no difference in mortality and no intracranial tumours.\(^27\) In a study including 157 patients, no tumours were identified within the radiation field by CT with a median follow-up of 11 years.\(^28\) A large series of 250 patients found that cancer-specific survival was identical to the normal population.\(^29\) In one series with long-term follow-up of 184 patients, ten developed solid tumours but none were in the radiation field.\(^20\) Based on these experiences, the risk of a radiation-induced cancer (RIC) appears very low. In terms of secondary carcinogenesis, these cohorts are of limited size and follow-up. Due to the possibility of secondary carcinogenesis, the European Group on Graves’ Orbitopathy (EUGOGO) consensus statement recommends avoiding RT below the age of 35 years.\(^4\)

The development of retinopathy in association with diabetes or hypertension has been reported following RT for TED.\(^28\) Microvascular retinal abnormalities have been detected following orbital RT.\(^29\) Diabetic retinopathy and severe hypertension are considered absolute contraindications.\(^4\) Diabetes without retinopathy may represent a risk factor for subsequent retinal changes and is considered a relative contraindication.\(^4,27\)

The current role of radiotherapy

Systematic reviews and meta-analyses have concluded that although the evidence is limited, data points to the efficacy of RT.\(^9,30\) The main benefit of RT appears to be improved orbital mobility, with responses of exophthalmos being poor.\(^8\) RT is therefore a reasonable secondline treatment when the response to steroids is inadequate and the orbital disease is in the active phase. Data suggest that combining RT with steroids is more effective than RT alone.\(^18,19\)

Potential long-term consequences of radiotherapy

The risk of RIC of the brain in adults treated with RT for TED is small at the doses used. For a typical RT regimen for TED, the risk of a 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. Specifically, for TED the radiation dose is reduced by about 60%, and the ‘at risk’ brain volume is 80% less, when compared to RT for pituitary cancer.)\(^31\) In older patients this is less of a problem as, in general, evidence for brain cancer in adults exposed to radiation is relatively low (see section on The risk of a radiation-induced malignancy following low to moderate dose radiotherapy [page 18]). However, radiation exposure in young children carries with it a significant risk of RIC.\(^32\)

Cataract development is a potential medium- to long-term dose-dependent consequence of radiation exposure of the eye. The dose above which this becomes an issue has recently been revised down to 0.5 Gy, and it has even been suggested that there is no clear threshold (see section on Normal tissue responses at radiation doses used for RT of benign disease [page 10]).\(^33,34\) Defining the latency is difficult. It can be very long for exposure at low-dose occupational levels, for example, in radiology department staff.\(^35\) At high doses, latency can be as short as one year, so even in an elderly patient there is a risk of cataract development. Nevertheless, cataracts are not life-threatening, though they can affect quality of life. The treatment for cataracts is relatively straightforward, so although this risk should be recognised it should not detract from the use of RT for TED if it is clinically indicated as the best treatment approach. Exposure at a young age will increase the lifetime risk of cataracts, and exposure occurring in childhood increases the risk of cataract by ~50% for 1 Gy exposure to the lens.\(^36\) Exposure at age ten has been reported to give an odds ratio of 1.44 at one Sievert (Sv); this risk decreases significantly with increasing age (P = 0.022).\(^37\)
Recommendations

The recent consensus statement of the EUGOGO provides an excellent summary of current evidence and provides recommendations regarding the management of TED.4

- Although orbital RT may be effective in mild TED, the potential risks generally outweigh the benefits for this self-limiting condition; occasionally RT can be considered if TED is causing significant quality of life/psychosocial problems (Grade D).
- For active moderate to severe TED with symptomatic ophthalmopathy, intravenous steroids are the mainstay of treatment (Grade C). RT can be considered in patients with restricted mobility or diplopia (Grade D). RT in combination with steroids appears to be more effective than either treatment alone (Grade A).
- RT is unlikely to be beneficial in long-standing inactive TED (Grade C).

- RT is contraindicated in the presence of diabetic retinopathy or severe hypertension; diabetes without retinopathy is a relative contraindication (Grade C).
- Clinical target volume (CTV) includes extra-ocular muscles and retro-orbital tissues bilaterally. Standard treatment is with unplanned lateral opposed photons in an immobilisation mask, with the anterior field edge placed posterior to the lens and posterior field to cover orbital apex; a technique such as a half beam block is appropriate to avoid divergence through contralateral lens. A standard dose is 20 Gy in ten fractions over two weeks (Grade B).

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) (Appendix 2).38

References


Orbital pseudotumour/idiopathic orbital inflammation

Background

Orbital pseudotumour (OP) is a rare non-malignant orbital disorder characterised by inflammation of part of the orbital structure without an identifiable local or systemic cause. Historically, many causes of orbital inflammation have been grouped together under the term ‘ orbital pseudotumour’. More recently, the term ‘idiopathic orbital inflammation’ has been used to describe the condition. The aetiology of OP remains unknown. OP presents with a median age of 40–50 years, although with a wide age range; for example, in a series of 49 patients, the mean age was 44, with a range of 4–84 years old. The gender distribution is equal. The majority of cases are unilateral, with series reporting 4–26% bilateral involvement. Patients with initially unilateral orbital involvement can subsequently develop bilateral disease. Presenting symptoms include proptosis, eyelid swelling, diplopia and pain. The rate at which symptoms develop varies from acute to subacute and occasionally chronic.

OP is a diagnosis of exclusion. The differential diagnosis includes thyroid eye disease, infectious cellulitis, sarcoid, Wegener’s granulomatosis, Sjogren’s syndrome, lymphoma and other malignant processes. Investigations include blood tests with inflammatory markers and thyroid function, and also cross-sectional imaging with computed tomography (CT) and/or magnetic resonance imaging (MRI). Appearances are of focal or diffuse changes which often involve enlarged extra-ocular muscles, optic nerve thickening or infiltration of retrobulbar tissues; these changes typically enhance with iodinated CT contrast or with gadolinium on MRI.

A biopsy by fine-needle aspiration of the orbital mass or lacrimal gland is usually indicated to exclude other diagnoses, unless the procedure would involve a significant risk to vision. The histological appearances of OP are of a chronic inflammatory infiltrate, although there is no agreed histological classification. The absence of clonality is useful to exclude lymphoma. A sclerosing pattern, composed of dense fibrous tissue with little inflammatory infiltrate, is considered by some to represent the end stage of the disease process.

Management

Steroids

Corticosteroids are established as the first line of treatment for OP. In a series of 32 patients treated for OP reported by Mombaerts et al, 27 received oral steroids with a response obtained in 21 (78%). Ten of these 27 (37%) patients obtained long-term control with steroid treatment alone. Chirapapaisan et al reported 49 patients treated with steroids; 40/49 (82%) responded clinically with a median time to response of ten days for visual loss and 18 days for oculomotor dysfunction. Of these 49 patients, 30 (61%) had a durable response to steroids. Overall, approximately half of those patients who respond initially to steroids will subsequently relapse. The likelihood of a response to steroids is strongly influenced by the pattern of disease. While many OP respond rapidly to steroids, ISOI typically show a more disappointing benefit; nevertheless steroids remain frontline therapy.

Radiotherapy

The therapeutic rationale for the use of radiotherapy (RT) is the killing of radiosensitive lymphocytes and fibroblasts. Radiation has been used for patients with a suboptimal response to steroids, refractory disease, and recurrent disease following an initial response and in patients with medical contraindications to steroid therapy. Several retrospective small series have reported outcomes following RT; these are summarised in Table 6 (opposite). The variable case mix needs to be considered in interpreting these series. In some series, several patients subsequently developed systemic lymphoma; this may suggest that in a small number of cases the original orbital pathology may have been lymphoma.
In addition, the follow-up in many of these reports is limited. Overall, moderate-dose RT appears to be an effective treatment modality; RT achieves a local control rate of 50% or higher. In the series reported by Char and Miller, a favourable response to RT was predicted by non-fibrotic lesions, a short interval between diagnosis and RT, and those with erythema at diagnosis. Similarly, Matthiesen et al noted a shorter duration of initial symptoms was associated with a more favourable response rate to RT. It is important to note that in a case series of ISOI, Lee et al reported that RT was beneficial for patients who were refractory to or intolerant of steroids.

In the series reported by Mattiesen et al, three patients underwent orbital retreatment with RT; two of these patients achieved a complete response and one a partial response. No morbidity was noted from retreatment, and the authors suggest that retreatment may be a viable option for patients failing to achieve a complete response after an initial course of RT.

RT is well tolerated. Reported acute side-effects include mild periorbital erythema, mild conjunctivitis and dry eye. Late side-effects include dry eye and cataracts.

### Table 6. Series reporting outcome of orbital pseudotumour (OP) with radiotherapy

<table>
<thead>
<tr>
<th></th>
<th>Number of patients</th>
<th>RT dose</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Matthiesen et al (2011)</td>
<td>16</td>
<td>Median 20 Gray (Gy) in ten fractions (range 14–30 Gy)</td>
<td>87.5% clinical improvement</td>
</tr>
<tr>
<td>Lee et al (2012)</td>
<td>22 (with idiopathic sclerosing orbital inflammation [ISOI])</td>
<td>Median 20 Gy in ten fractions (range 20–40 Gy)</td>
<td>Complete response in 68% Overall 64% progression-free (median follow-up 34 months)</td>
</tr>
<tr>
<td>Orcutt et al (1983)</td>
<td>22</td>
<td>25 Gy in 12 fractions</td>
<td>75% response</td>
</tr>
<tr>
<td>Lanciano et al (1990)</td>
<td>23</td>
<td>20 Gy in ten fractions</td>
<td>66% complete response Overall 54% long-term local control (median follow-up 41 months)</td>
</tr>
<tr>
<td>Austin-Seymour et al (1985)</td>
<td>20</td>
<td>Mean 23.6 Gy (range 20 Gy in ten fractions – 36 Gy in 18 fractions)</td>
<td>75% complete response</td>
</tr>
<tr>
<td>Char and Miller (1993)</td>
<td>33</td>
<td>20 Gy in ten fractions for 28 patients and 30 Gy in 15 fractions for five patients</td>
<td>55% complete response 9% near complete response</td>
</tr>
<tr>
<td>Mittal et al (1986)</td>
<td>20</td>
<td>5.5–30 Gy (mainly 20–30 Gy)</td>
<td>90% local control</td>
</tr>
</tbody>
</table>
**Immunosuppressants**

Immunosuppressant drugs have been found to be effective in the management of OP; these include azathioprine, methotrexate and ciclosporin. There is no consensus on treatment protocols, and immunosuppressants may be considered after steroid failure as an alternative to RT, or as a later treatment option.

**Surgery**

Surgery may have a role in selected cases with localised lesions. Char and Miller reported 19/25 patients managed with surgery having a near complete response. In addition, in the series of ISOI reported by Lee et al, six patients underwent surgical debulking followed by RT with long-term progression-free outcomes. Surgical resection of an intractable fibrotic mass may be a useful therapeutic option.

**Potential long-term consequences of radiotherapy**

The risk of radiation-induced cancer (RIC) of the brain in adults treated with RT for OP is likely to be similar to those calculated for thyroid eye disease (TED). To summarise briefly, the risk is small for adults but may be more important for young children. Cataract development is a potential medium- to long-term dose-dependent consequence of radiation exposure of the eye. (The risks of RIC and cataracts are discussed in more detail in the sections on Thyroid eye disease [page 42] and The risk of a radiation-induced malignancy following low to moderate dose radiotherapy [page 18].)

**Recommendations**

- Steroids are the standard firstline therapy for treatment of OP (Grade C).
- RT is an effective treatment modality in patients who are refractory to, achieve a suboptimal response to, are intolerant of, or relapse after steroid therapy (Grade C).
- A RT dose of 20 Gray (Gy) in ten fractions over two weeks to involved orbit/orbits is appropriate (Grade C).

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


Pterygium

Background

Pterygium is an area of fibrovascular proliferating tissue arising at the border between the conjunctiva and cornea, generally extending from the medial (nasal) corner of the eye to the cornea and beyond, abutting or partially extending across the cornea. The age range at presentation is very wide, from late teens/early 20s through to old age. Symptoms include irritation, excessive tear production, a sensation similar to a foreign body in the eye and/or problems with motility of the eye. In advanced cases, involvement of the cornea can eventually interfere with vision or even lead to blindness.

General management

Treatment is indicated for symptomatic cases or if there is a threat to vision from extension of the pterygium towards the pupil. Treatment may also be indicated for aesthetic reasons. Complete surgical excision is the treatment of choice. This includes several options such as excision leaving an open wound or rotation conjunctival flap (graft) or free transplant. Following surgery alone, local control rates of 50% to 70% have been reported. For recurrent cases, adjuvant treatment is generally recommended. Traditionally superficial radiotherapy (RT) using a strontium-90 (90Sr) applicator has been employed. More recently, local instillation of mitomycin-C has been employed as an option for adjuvant therapy.

Radiotherapy

The modality most frequently employed is local superficial RT with a beta-emitting 90Sr applicator, which is put in place using local anaesthesia. This delivers RT at an individualised dose rate, typically in the range 5–20 Gray (Gy)/minute, specified to the surface of the eye/conjunctiva.

Reviews of patterns of management have demonstrated variability in the use of adjuvant therapy by ophthalmologists. However, the role of RT for reducing the risk of local recurrence compared with surgery alone is well established in the literature, with evidence from randomised studies. The outcomes following RT for pterygium are given in Table 7 (opposite).1–12 These outcomes include those from single institution case series, literature reviews and randomised studies. In one randomised study of either surgery alone with excision and conjunctival autograft (flap) or combined with a single fraction of 10 Gy with 24 hours, local control was 90.8% with surgery and postoperative RT compared with 78% for surgery alone.2 The benefit of adjuvant RT (25 Gy single) has also been confirmed in a placebo-controlled (‘sham’ RT) randomised study.2 With a median follow-up of 18 months, local control was 93.2% with RT compared with 33.3% for placebo RT.

The literature on RT for pterygium includes a wide range of dose fractionation regimens, with the majority reporting use of either a small number of, or single, fractions. In a review of the literature, it has been reported that many fractionation regimens, representing a wide range of biologically effective dose (BED) values have been employed. These have ranged from 25.2 Gy to 120 Gy with little evidence of a dose–response effect. The authors concluded that regimens with a BED value of at least 30 Gy can reduce the recurrence risk to less than 10%; this can be achieved with a single fraction dose of 13–15 Gy or 17–20 Gy in two fractions or three fractions of 6–7 Gy (Kal et al 2009).6

Although the majority of series report the use of 90Sr beta irradiation, the use of superficial RT with 20 kilovoltage (kV) X-rays has been reported. A non-randomised comparison confirms the lower local control rate for RT (6.4%) compared with mitomycin-C (17.9%).12 RT has generally been delivered in the postoperative setting and most series report delivering the first fraction within 24–48 hours.

Early side-effects have included moderate conjunctivitis, local pain, visual disturbance, photophobia and an increase in tear flow. These are generally manageable with symptomatic therapy.

Potential long-term consequences of radiotherapy

Late morbidity occurs in a small minority of patients, although it is not reported in every series. Late morbidities include scleromalacia, adhesion of eyelids, cataracts and rarely scleral ulcer. There is a medium- to long-term dose-dependent risk of cataract (see the sections on Thyroid eye disease [page 42]) and Normal tissue responses with radiation doses used for RT of benign disease [page 10] for more detail).

The risk of radiation-induced cancer (RIC) of the brain in older patients treated with RT for pterygium is likely to be extremely small. However, in young adults and children RT is better avoided.
Table 7. Series reporting outcome following radiotherapy for pterygium\textsuperscript{1–12}

<table>
<thead>
<tr>
<th>Reference</th>
<th>Dose</th>
<th>Study type</th>
<th>Comments</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Yamada et al</td>
<td>20 Gy single</td>
<td>67 eyes</td>
<td>Higher risk of recurrence for larger lesions encroaching on pupil</td>
<td>11 recurred (16%)</td>
</tr>
<tr>
<td></td>
<td>20 Gy x 2</td>
<td>28 eyes</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Viani et al</td>
<td>10 x 2 Gy</td>
<td>104 eyes</td>
<td>Randomised study. Better cosmetic results from 10 x 2 Gy</td>
<td>No recurrences</td>
</tr>
<tr>
<td></td>
<td>5 x 7 Gy</td>
<td>112 eyes</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Viani et al</td>
<td>10 Gy single</td>
<td></td>
<td>Randomised study of surgery (excision plus conjunctival flap) alone versus 10 Gy single fraction</td>
<td>Median follow-up 18 months – local control (LC) 90.8% versus 78%</td>
</tr>
<tr>
<td>Nakamatsu et al</td>
<td>30 Gy in 3 fractions weekly</td>
<td>41 eyes</td>
<td>Randomised study of RT dose</td>
<td>85% 2 year LC</td>
</tr>
<tr>
<td></td>
<td>40 Gy in 4 fractions weekly</td>
<td>32 eyes</td>
<td></td>
<td>75% 2 year LC</td>
</tr>
<tr>
<td>Ali et al</td>
<td>Literature review of over 6,000 treated cases</td>
<td></td>
<td></td>
<td>LC &gt;85%. Recommend 30 Gy in 3 fractions weekly; start within 24 hours of excision.</td>
</tr>
<tr>
<td>Vastardis et al</td>
<td>36–55 Gy Fractionation?</td>
<td>58 primary, 28 recurrent cases. Not surgically treated</td>
<td></td>
<td>All regressed at least partially, no progressions with median follow-up (FU) 47 months</td>
</tr>
<tr>
<td>Kal et al</td>
<td>Literature review</td>
<td></td>
<td></td>
<td>Recurrence risk less than 10% if biologically effective dose (BED) of 30 Gy used</td>
</tr>
<tr>
<td>Viani et al</td>
<td>35 Gy in 5–7 fractions</td>
<td>737 lesions</td>
<td></td>
<td>LC 90% at 5 years and 88% at 10 years. Late toxicities: scleral malacia: 9; adhesion of eyelids: 8; cataracts: 6; scleral ulcer: 5</td>
</tr>
<tr>
<td>Isohashi et al</td>
<td>30–35 Gy in a single fraction</td>
<td>1,320 lesions</td>
<td></td>
<td>7.7% recurrences. Temporary side-effects in 15.2%, including moderate conjunctivitis, local pain, visual disturbance, photophobia, increase in tear flow. No long-term serious side-effects documented</td>
</tr>
<tr>
<td>Jurgenliemk-Schulz et al</td>
<td>25 Gy single</td>
<td></td>
<td>Randomised study of RT versus ‘sham’ RT</td>
<td>Local control: RT versus sham, 93.2% vs 33.3% (median FU 18 months)</td>
</tr>
<tr>
<td>Pajic et al,</td>
<td>50 Gy in four fractions, all weekly</td>
<td>97 lesions treated</td>
<td>Different groups received pre-op, post-op and pre + post-op</td>
<td>Local recurrence 2%</td>
</tr>
<tr>
<td>Willner et al</td>
<td>27 Gy total – 7 Gy x 1 pre-op + 5 Gy x 4 81 lesions treated with 20 kilovoltage (kV) X-rays</td>
<td></td>
<td></td>
<td>Local recurrence 9% at five years</td>
</tr>
<tr>
<td>Simsek et al</td>
<td>10–70 Gy Or mitomycin C (MMC)</td>
<td>208 eyes</td>
<td>Two groups – either RT (141 eyes) or MMC (67 eyes)</td>
<td>Recurrence rates: RT: 6.4% (mean FU 89 months); MMC: 17.9% (mean FU 14.9 months)</td>
</tr>
</tbody>
</table>
Recommendations and radiotherapy technique

- Despite favourable outcomes in the literature, the use of $^{90}$Sr irradiation in the UK for pterygium has fallen off and its role could be considered again in discussions at local and national levels (Grade D).
- RT should be commenced within 24–48 hours of surgery (Grade B).

For the use of $^{90}$Sr beta irradiation, a wide range of dose and fractionation regimens has been employed, with single fractions of 10–25 Gy fractionated up to 25 Gy with no clear dose–response effect (Grade B).

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) (Appendix 2).

References


Age-related macular degeneration

Background

Age-related macular degeneration (AMD) is a condition with a very wide prevalence. There are two types: wet (neovascular) and dry. In the dry type, slow progressive atrophy of the retina occurs and in the ‘wet type’ neovascularisation occurs in the underlying choroid. Neovascular AMD (nAMD) causes the greatest visual morbidity of the two, with an overall prevalence of 1.2%, increasing to 2.5% in those aged 65 years or older, and 6.3% in those aged 80 or older. There are estimated to be between 250,000 and 400,000 affected individuals in the UK and 39,700 new cases each year. People with nAMD often lose the ability to read, drive and recognise faces. They have an increased risk of falls and requirement for institutionalisation and may be at risk of depression. AMD accounts for more UK blind registrations than all other eye diseases combined.1,2 As the population ages, the prevalence is projected to increase by one-third over the next eight years and therefore is likely to represent an increasing demand on society in general and specifically the NHS in the future.2

Current management

Currently the standard management in the UK for nAMD, which is recommended by the National Institute of Health and Care Excellence (NICE) and the Royal College of Ophthalmologists is with intravitreal injections of ranibizumab.3,4 This drug is a recombinant monoclonal antibody directed against vascular endothelial growth factor (VEGF).5,6 VEGF mediates the growth of the abnormal incompetent new vessels that are characteristic of nAMD.5,6 These vessels cause macular oedema, haemorrhage and scarring with resultant loss of vision. Most patients require multiple intravitreal injections each year. Clinic visits are time-consuming, and patients often require assistance to attend due to ocular and/or general health issues. Lifelong treatment is usually required. Injections cause discomfort, can cause anxiety and furthermore there is a small risk of serious complications such as retinal detachment and endophthalmitis.

Radiotherapy for age-related macular degeneration

The use of radiotherapy (RT) was a preferred treatment for AMD in the late 1990s and early 2000s but with the advent of anti-VEGF drugs the use of RT has reduced significantly. However, anti-VEGF therapy involves regular monthly intra-ocular injections and patients generally remain on this long term, with ongoing monthly hospital review and retinal imaging. Each new case therefore adds to the pool of patients already being treated, and consequently the view is that there is no longer any role for RT.

Radiation for neovascular age-related macular degeneration: biological principles

Ionising radiation (IR) creates breaks in deoxyribonucleic acid (DNA) strands which result in mitotic cell death. New blood vessels in choroidal neovascular membranes are in their growth phase and, as a consequence, contain a high population of proliferating cells compared to normal retinal vessels. By contrast, the retinal neuropile and the retinal pigment epithelium are post-mitotic quiescent cellular structures with extremely low or no cell turnover. Thus IR has the potential to selectively target the neovascular tissues, fibroblasts and inflammatory cells with minimal or no deleterious effects on the retinal neuropile and the normal vasculature.7–10 Experimental studies suggest that radiation can produce a synergistic effect with anti-VEGF therapy, and in the treatment of cancer, the two modalities are often combined to target the new vessels supplying malignant tissue suggesting there could also be a role for combined therapy for nAMD.11–13

Current status of radiotherapy for age-related macular degeneration

When RT was commonly being used as a treatment for AMD, several reports such as Chakravarthy et al reported the use of external beam radiation therapy (EBRT) in a small pilot study, the outcomes of which suggested benefit to the patient.14 The same group subsequently co-ordinated a large multicentre randomised controlled trial which indicated that RT had marginal or no benefit in patients with nAMD.
A Cochrane review in 2010 concluded that RT was ineffective for nAMD.\(^{15}\)

In the past, limitations in beam size and collimation restricted the dose of RT that could be safely delivered to the posterior pole of the eye to avoid radiation to non-target intraocular structures. Many patients were treated with relatively large parallel opposed fields. Furthermore, the dose delivery could be influenced by eye movement, creating the potential for variation in the dose delivered to the target region.

However, there is now renewed interest in the use of RT devices which can precisely target the radiation to the macula.

**Epimacular brachytherapy**

The first device designed specifically to treat nAMD involved the use of an intraocular probe containing a strontium-90 (\(^{90}\)Sr) radionuclide source. Following surgical entry into the eye via a pars plana vitrectomy, the epimacular brachytherapy (EMB) device was held over the macula to deliver a dose of 24 Gray (Gy) of beta radiation to the nAMD lesion over 3–4 minutes. Initial studies of EMB demonstrated encouraging results in previously untreated patients with substantial vision gain and a very low need for anti-VEGF therapy.\(^{16,17}\) A more recent randomised trial of EMB – the CABERNET study – failed to replicate the results.\(^{18}\) However, safety was demonstrated, with a low incidence (3%) of non-vision threatening radiation retinopathy, occurring mostly in the second year. Subsequent studies tested EMB as a secondline treatment. The MERITAGE study was an uncontrolled, international study of 53 patients with chronic, active, previously treated nAMD. Following EMB, patients were found to have more stable vision despite fewer anti-VEGF injections.\(^{19}\)

**Stereotactic radiotherapy**

A customised robotically controlled device delivering low-voltage, external beam X-rays has been designed specifically to treat nAMD. This device delivers highly collimated doses via three separate beams that overlap at the macula, minimising exposure to non-target structures. A suction-coupled contact lens with marked fiducials is coupled with laser tracking to ensure that treatment is halted if the eye moves out of position, and the area of treatment is marked on a monitor in real time, as the radiation is delivered.

Although the use of conventional EBRT cannot be supported, the evaluation of stereotactic radiotherapy (SRT) using customised technology is encouraging and the subject of ongoing clinical trials.\(^{20–28}\) In particular, initial results suggest a benefit for SRT combined with anti-VEGF therapy in terms of reduced requirement for anti-VEGF injections.

**Potential long-term consequences of radiotherapy**

This patient population is primarily aged over 65. At doses used (~24 Gy), the risk of side-effects is relatively small, including radiation-induced cancer (RIC). However, the risk of cataract is not insignificant, although this is a non-malignant consequence and treatable with lens replacement. (The risks of RIC and cataracts are discussed in more detail, in the sections on Thyroid eye disease [page 42] and The risk of a radiation-induced malignancy following low to moderate dose radiotherapy [page 18].)

**Recommendations**

- There is currently insufficient evidence to support the use of RT for treatment of AMD (Grade B).
- Following the introduction of intravitreal anti-VEGF therapy and its recommendation by NICE, the routine use of EBRT for nAMD has declined to the extent it is now rarely used (Grade D).
- There is interest in exploring the potential for improved outcomes with combinations of anti-VEGF therapy with newer customised RT technologies which target the dose to the macula. This is the subject of ongoing research studies.

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) (Appendix 2).\(^{29}\)
References


Choroidal haemangioma

Background

Choroidal haemangiomas arise from the choroid vessels. They are slow growing and can occur in the context of Sturge-Weber Syndrome. The diffuse variety may occur in childhood while the local variety generally occurs at age 30–50. Various management options are available, including photodynamic therapy and photocoagulation. Recurrence and retinal detachment can complicate management of the condition.

Radiotherapy

There are only a small number of case series reported in the literature. In a series of seven eyes treated with proton therapy 20 Cobalt Gray Equivalent (CGE) in four fractions, response and retinal reattachment were seen in all cases.1 In another series of six patients with Sturge-Weber Syndrome treated for choroidal haemangioma with 20 Gray (Gy) external beam radiation therapy (EBRT), response was seen in all cases.2

Potential long-term consequences of radiotherapy

The risk of radiation-induced cancer (RIC) of the brain in adults treated with radiotherapy (RT) for choroidal haemangioma is likely to be similar to that calculated for thyroid eye disease (TED). To summarise briefly, the risk is small for adults but may be more important for young children. Cataract development is a potential medium- to long-term dose-dependent consequence of radiation exposure of the eye, although its development can be managed with lens replacement. (The risks of RIC and cataracts are discussed in more detail in the sections on Thyroid eye disease [page 42] and The risk of a radiation-induced malignancy following low to moderate dose radiotherapy [page 18].)

Recommendations

- The management of patients with choroidal haemangioma should only be undertaken in a highly specialised unit. There is only limited literature on the role of RT. The routine use of RT cannot be recommended at the present time (Grade D).

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) (Appendix 2).3

References

6. Central nervous system

Meningiomas

Background

Meningiomas account for about 20–30% of all primary brain and central nervous system tumours. Many are asymptomatic and found in the elderly, making it challenging to determine the population prevalence accurately.

The incidence of meningioma increases progressively with age. Overall, they are more common in women, with a female to male ratio of about two or three to one. For spinal meningiomas, which comprise about 10% of all meningiomas, the female to male ratio is even higher, approximately nine to one. This female predominance is less pronounced or absent in those with atypical or anaplastic meningiomas, children and those with radiation-induced meningiomas.

Older studies estimated that more than 90% of meningiomas were World Health Organization (WHO) Grade 1, approximately 5% were Grade 2, and about 2% were Grade 3. However, recent changes to the WHO classification system have tended to increase the proportion classed as Grade 2 in more recent studies.

The main risk factors for meningiomas are:

- Ionising radiation (IR): (for example, children receiving cerebral radiotherapy (RT) for childhood malignancy). The latency is often very long with rates increasing over decades
- Genetic factors: The most common being neurofibromatosis type 2 (NF2) where there is a 40–60% lifetime risk of meningiomas developing. Patients tend to develop tumours younger. They are often multiple and more frequently of higher grade
- Hormonal factors: A number of lines of evidence suggest that hormonal factors have a role in the development of meningioma. For instance, they are more common in women than men (particularly during reproductive years) and progesterone, androgen and oestrogen receptors have all been identified in tumours.

In general, meningiomas are usually well-circumscribed, slow-growing tumours that are thought to arise from mesodermal arachnoid cells. They show considerable heterogeneity in terms of location, size and behaviour. Some show barely perceptible growth, while more anaplastic forms can be locally invasive and grow rapidly.

Management of Grade 1 meningiomas

Watch and wait

In some circumstances, it can be appropriate to adopt a ‘watch and wait’ approach after the diagnosis of a meningioma. Observations of tumour growth rates in untreated patients have suggested that calcification and old age tend to predict slower growth. There is, however, considerable heterogeneity in growth rates, making radiological surveillance important if treatment is a potential option. In patients with other co-morbidities that threaten to limit their lives, active treatment or surveillance may be unnecessary.

Surgery

Surgery remains the best option for symptomatic, intracranial meningiomas if complete resection can be achieved with low morbidity. This particularly applies to tumours on the convexity of the skull, the floor of the anterior fossa and the lateral sphenoid wing.

Simpson described meningioma (WHO Grade I) recurrence rates with reference to the degree of resection – reported to be 9% after complete resection including the dural base, 19% after excision and coagulation of the dural base, 29% after excision without coagulation of the dural base, and 40% after subtotal resection.

Where tumours arise in the base of skull, it is frequently impossible to completely resect the tumour, necessitating the use of RT as an alternative or adjuvant treatment to increase control rates.

External beam radiation therapy

When used as a primary treatment, external beam radiation therapy (EBRT) appears to produce acceptable levels of tumour control (see Table 8 [page 62]). Various case series have been published which are heterogeneous in terms of dose and technique. Modern planning techniques appear to achieve better rates of local control than were seen in older series. More commonly, EBRT has been used after subtotal resection to achieve higher rates of local control. This has been shown consistently in a large number of studies (even if randomised studies have not been performed) – see Table 8. Recommended doses are usually in the range of 50–55 Gray (Gy) (1.8–2 Gy/fraction). There is no clear evidence for a dose–response curve. A paper by
Goldsmith et al is often quoted which retrospectively evaluated local control rates.\textsuperscript{18} By univariate analysis this suggested better control with doses \textgreater 52 Gy vs lower doses (ten-year local control 93\% vs 65\%), although this difference disappeared on multivariate analysis.\textsuperscript{18} In practice, a dose of 54 Gy in 30 fractions is often used with reductions to 50–52 Gy when tumours are close to the optic pathways.\textsuperscript{19}

EBRT should be computed tomography (CT) planned with a 3D conformal technique. Intensity-modulated radiation therapy (IMRT) may also be considered. If available, computed tomography–magnetic resonance imaging (CT-MRI) fusion assists gross tumour volume (GTV) delineation. In Grade 1 tumours, the GTV is effectively the clinical target volume (CTV) although the presence of ‘dural tails’ around the tumour can lead to uncertainty when outlining. A recent paper by Qi \textit{et al} carefully evaluated the pathology of resected meningiomas in the region of ‘dural tails’.\textsuperscript{40} When the tail was smoothly tapering with no nodular elements (as is usually the case in Grade 1 tumours) the amount of invasion in 16 tumours was as follows: nine – no invasion, 13 ≤0.5 centimetres (cm), 15 ≤1.0 cm, 16 ≤1.5 cm. Therefore a pragmatic view has to be taken when outlining dural tails, striking a balance between a desire for complete tumour coverage and, at the same time, a minimisation of toxicity. CTV-planning target volume (PTV) margins will depend on the immobilisation and position verification strategies in individual departments.

\textbf{Stereotactic radiosurgery}

Grade 1 meningioma is an attractive target for stereotactic radiosurgery (SRS). Tumours are often relatively small with clearly defined margins. The ability of SRS to minimise the dose to surrounding structures is also attractive in a patient group that may live for many years, and where the effects of dose to normal brain are of particular concern.

SRS is usually recommended as sole treatment for tumours \textless 3–4 cm in diameter, with clearly defined margins and sufficient distance from critical structures (particularly the optic tracts – although a gap of just a few millimetres is adequate). It can also be used adjuvantly to treat unresectable residual disease in sites such as the cavernous sinus. Localised, small-volume recurrence after previous surgery can be another suitable target.

A large number of series have been published showing high rates of progression-free survival. Table 9 (page 63) lists some of these, including a range of older studies and two much larger series published recently.\textsuperscript{41–42} The optimal dose remains unclear, although there has been a trend in recent times to use a margin dose (the dose prescribed to the isodose encompassing the lesion) of 14–15 Gy which has shown high rates of tumour control in multiple series and yet reduces the risk of toxicity. Doses \textless 12 Gy do appear to be inferior.\textsuperscript{50,62}

\textbf{External beam radiotherapy versus stereotactic radiosurgery}

There have been no randomised studies comparing the outcomes of fractionated EBRT and SRS. However, the multiple series quoted in Tables 8 and 9 would suggest similar levels of tumour control despite fractionated EBRT often being used for larger tumours.\textsuperscript{10–38, 41–61} SRS tends to carry a higher risk of oedema in some situations (associated with treatment to larger volumes: \textgreater 3 cm diameter; to higher doses: \textgreater 15–18 Gy; and to tumours in a non-basal location). Close proximity to sensory cranial nerves also carries a risk of temporary or permanent nerve damage (although rates are very low if cases are selected carefully). It does, however, achieve high rates of local control with the convenience of a single treatment and minimal toxicity in most patients. The very low dose delivered to normal brain tissue is also a positive.

Fractionated EBRT, ideally delivered with high conformality and accurate immobilisation, can also achieve excellent results and has the advantage of being suitable for larger volumes and those adjacent to sensitive sensory cranial nerves. Older series produced higher rates of toxicity, presumably due to poorer planning techniques.

\textbf{Surgery versus external beam radiation therapy/stereotactic radiosurgery}

There are no randomised comparisons of surgery against SRS or fractionated EBRT.
Table 8. The effect of external beam radiation therapy on progression-free survival
(adapted from Gondi et al (2010)10–38

<table>
<thead>
<tr>
<th>Author (year)</th>
<th>n</th>
<th>Follow-up (months)</th>
<th>Gross tumour resection (GTR)</th>
<th>Subtotal tumour resection (STR)</th>
<th>STR + EBRT or EBRT alone</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adegbite et al (1983)</td>
<td>114</td>
<td>10–276</td>
<td>90</td>
<td>45</td>
<td>82</td>
</tr>
<tr>
<td>Mirimanoff et al (1985)</td>
<td>225</td>
<td>65% &gt;60</td>
<td>93</td>
<td>63</td>
<td>–</td>
</tr>
<tr>
<td>Barbaro et al (1987)</td>
<td>135</td>
<td>78</td>
<td>96</td>
<td>60</td>
<td>80</td>
</tr>
<tr>
<td>Taylor et al (1988)</td>
<td>132</td>
<td>60% &gt;60</td>
<td>96</td>
<td>43</td>
<td>85</td>
</tr>
<tr>
<td>Glaholm et al (1990)</td>
<td>117</td>
<td>80</td>
<td>–</td>
<td>–</td>
<td>84</td>
</tr>
<tr>
<td>Peele et al (1996)</td>
<td>86</td>
<td>46</td>
<td>–</td>
<td>52</td>
<td>100</td>
</tr>
<tr>
<td>Condra et al (1997)</td>
<td>246</td>
<td>98</td>
<td>95</td>
<td>53</td>
<td>86</td>
</tr>
<tr>
<td>Vendrely et al (1999)</td>
<td>156</td>
<td>40</td>
<td>–</td>
<td>–</td>
<td>89</td>
</tr>
<tr>
<td>Maguire et al (1999)</td>
<td>28</td>
<td>41</td>
<td>–</td>
<td>–</td>
<td>92 (4-year PFS)</td>
</tr>
<tr>
<td>Wenkel et al (2000)</td>
<td>46</td>
<td>53</td>
<td>–</td>
<td>–</td>
<td>100</td>
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<td>Pourel et al (2001)</td>
<td>26</td>
<td>30</td>
<td>–</td>
<td>–</td>
<td>95</td>
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<tr>
<td>Soyuer et al (2004)</td>
<td>92</td>
<td>92</td>
<td>77</td>
<td>38</td>
<td>91</td>
</tr>
<tr>
<td>Minniti et al (2011)</td>
<td>52</td>
<td>42</td>
<td>–</td>
<td>–</td>
<td>93</td>
</tr>
<tr>
<td>Comptor et al (2012)</td>
<td>28</td>
<td>49</td>
<td>–</td>
<td>–</td>
<td>95</td>
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</table>
Table 9. Stereotactic radiosurgery – progression-free survival (adapted from Rogers et al)41–61

<table>
<thead>
<tr>
<th>Author (year)</th>
<th>n</th>
<th>Follow-up (months)</th>
<th>No histology (%)</th>
<th>Average dose (Gy)</th>
<th>≥5-year PFS (%)</th>
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</thead>
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<tr>
<td>Chang and Adler (1997)42</td>
<td>55</td>
<td>48</td>
<td>–</td>
<td>18</td>
<td>98.0</td>
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<tr>
<td>Hakim et al (1998)43</td>
<td>127</td>
<td>31</td>
<td>54</td>
<td>15</td>
<td>89.0</td>
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<tr>
<td>Chang et al (1998)44</td>
<td>24</td>
<td>46</td>
<td>–</td>
<td>17.7</td>
<td>100.0</td>
</tr>
<tr>
<td>Liscak et al (1999)45</td>
<td>53</td>
<td>19</td>
<td>64</td>
<td>12</td>
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<tr>
<td>Morita et al (1999)47</td>
<td>88</td>
<td>35</td>
<td>44</td>
<td>16</td>
<td>95.0</td>
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<tr>
<td>Roche et al (2000)48</td>
<td>80</td>
<td>31</td>
<td>63</td>
<td>14</td>
<td>93.0</td>
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<td>Stafford et al (2001)49</td>
<td>168</td>
<td>–</td>
<td>41</td>
<td>16</td>
<td>93.0</td>
</tr>
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<td>Shin et al (2001)50</td>
<td>15</td>
<td>42</td>
<td>30</td>
<td>10–12</td>
<td>75.0</td>
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<td>22</td>
<td></td>
<td></td>
<td>14–18</td>
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<tr>
<td>Nicolato et al (2002)51</td>
<td>111</td>
<td>48</td>
<td>50</td>
<td>15</td>
<td>96.0</td>
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<tr>
<td>Lee et al (2002)52</td>
<td>159</td>
<td>35</td>
<td>52</td>
<td>13</td>
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<td>Pollock et al (2003)54</td>
<td>62</td>
<td>64</td>
<td>46</td>
<td>17.7</td>
<td>95.0 (7-year PFS)</td>
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<tr>
<td>Roche et al (2003)55</td>
<td>32</td>
<td>56</td>
<td>75</td>
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<tr>
<td>Iwai et al (2003)56</td>
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<td>Flickinger et al (2003)57</td>
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<td>29</td>
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<tr>
<td>Chuang et al (2004)58</td>
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<td>75</td>
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<td>DiBiase et al (2004)59</td>
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<td>Lee et al (2007)50</td>
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<td>13.9</td>
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<td>Santacroce et al (2012)61</td>
<td>4565</td>
<td>63</td>
<td>56</td>
<td>14</td>
<td>95.0</td>
</tr>
<tr>
<td><strong>Total/range</strong></td>
<td>7,107*</td>
<td>19–75</td>
<td>30–100</td>
<td>10–18</td>
<td>75–100**</td>
</tr>
</tbody>
</table>

* Some of these will have been counted more than once
** 86–100 if doses of 12 Gy or less are excluded
Grade 2/3 (atypical and malignant meningiomas)

These are rarer than Grade I tumours and show invasive properties. As such, they fall outside the scope of these guidelines.

Potential long-term consequences of radiotherapy

Meningiomas treated by EBRT receive doses in the moderate to high range (usually ~50–60 Gy) and therefore these patients are at risk of a radiation-induced cancer (RIC) (which coincidentally, is also more likely to be a meningioma).

A recent meta-analysis of radiation-induced meningiomas suggested that they are more likely to be atypical and/or malignant than spontaneous meningiomas.63 This study analysed 66 relevant publications which had reported 143 cases of meningioma attributed to prior cranial RT (predominantly delivered to children/young adults, for indications other than meningioma). The risk of radiation-induced meningioma increased with dose, volume and, not unexpectedly, was also age-dependent, with most of the cases occurring in patients who had received RT before the age of 22.

The absolute risk of a RIC after EBRT for a meningioma is not known accurately but is likely to be slightly higher than was seen in the study by Minniti et al, examining the long-term outcomes of patients receiving postoperative EBRT for pituitary adenomas (median age 50).64 Doses in this study were predominantly in the range 40–50 Gy (lower than would be used for meningioma) and the volumes will have tended to be smaller. In that study there was a 2.4% cumulative risk of a second brain tumour at 20 years (approximately half of which were meningiomas, the remainder being more malignant tumours).

The evidence for the risks of RIC after SRS is not yet mature. In one large study of >5,000 patients (1,200 with >10 years follow-up), there was no measurable increase in brain tumours.65 A recent report on 440 patients, previously treated with gamma knife radiosurgery for vestibular schwannoma, found only one patient (0.3%) had developed a malignant tumour.66 However, both groups of authors have cautioned against assuming this technique is completely safe, especially for younger patients.

Overall, the evidence for an increased risk of RIC of the brain is small unless the exposure occurs in children and young adults. If EBRT and SRS are both an option for patients in this age group, then SRS would tend to be the preferred choice, as a way of reducing the volume of irradiated normal brain and therefore the risk of a RIC. (The above studies are discussed in more detail in The risk of a radiation-induced malignancy following low to moderate dose radiotherapy [page 18].)

It should also be noted that radiation exposure of the head carries with it a small risk of skin cancer, though there is likely to be a long latency period and any resultant tumour is likely to be benign, such as basal cell carcinoma. Other tumours that might arise are sarcomas and leukaemias; again the risks are small in adults but increased in younger patients. (For more detail see section on The risk of a radiation-induced malignancy following low to moderate dose radiotherapy [page 18].)
**Recommendations**

- Surgery remains the standard treatment for those patients with tumours in accessible areas who have acceptable operative risks. This is particularly the case in patients with ‘pressure symptoms’ (such as headache, nausea) from the size of the tumour (Grade C).

- SRS is an effective modality that is suited to smaller tumours in surgically inaccessible sites. It also lends itself to the treatment of small, clearly defined foci of residual or recurrent disease after previous surgery (Grade C).

- When SRS is used a margin dose of ~14 Gy appears effective and reduces the risk of toxicity (Grade C).

- EBRT also appears effective at controlling tumour growth and can be used for larger tumours or where the treated volume is likely to be large (for example, treating a large postoperative tumour bed) (Grade C).

- The standard dose for EBRT is 50–55 Gy (1.8–2 Gy/fraction) (Grade C).

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) (Appendix 2).67
References


**Cerebral arteriovenous malformations**

**Background**

These are congenital lesions arising from abnormal blood vessel formation. Direct arterio-venous shunts develop without appropriate intervening vascular beds. Large, prospective population-based studies have estimated the incidence of newly diagnosed cerebral arteriovenous malformations (AVMs) patients to be just over one per 100,000 person-years. The majority of patients become symptomatic in the second to fourth decades of life. The most common presentation is with an intra-cranial haemorrhage (ICH) causing neurological deficit, seizure, headache or death. Headaches and seizure can occur in the absence of a bleed. Some AVMs are identified incidentally when patients have cerebral magnetic resonance imaging (MRI) for other reasons. The annual risk of ICH for affected individuals is estimated to be in the order 2–4%, although this varies depending on the nature of the AVM. For a patient diagnosed at age 30 there is an approximate 75% lifetime risk of ICH.

Management focuses on the abnormal tangle of blood vessels at the site of the AVM known as the nidus.

**Management**

The main options for managing AVMs are:

- **Observation** – avoids the risks of treatment but the patient has an ongoing risk of bleeding

- **Surgical resection** – variable risk of procedure (depending on size, location, co-morbidities) but, if successful, can achieve immediate removal of bleeding risk. An ideal treatment if the nidus is small and surgically accessible, especially if there has been a recent bleed

- **Stereotactic radiosurgery (SRS)** – useful for smaller but surgically inaccessible lesions or when the anaesthetic/operative risk is high. Obliteration is not universal, and may take years, so there is an ongoing risk of bleeding during this pre-obliteration ‘latent period’

- **Embolisation** (rarely used as sole treatment but often used in combination with other modalities, especially for larger lesions) – can reduce risk of bleeding before surgery. Re-canalisation of embolised vessels can occur and SRS results are generally inferior when embolisation is undertaken before SRS.

The technology for all these treatment modalities has improved significantly in recent years, which means treatment decisions should be made by expert multidisciplinary teams (MDTs).

**Factors influencing choice of management**

AVMs vary in size and location. Larger lesions have a higher risk of bleeding and are more difficult to treat successfully. Some areas of the brain are more accessible surgically while others are functionally vital and very sensitive to damage (‘eloquent areas’). The Spetzler-Martin (SM) grading system is the most frequently utilised scale to predict surgical outcome.

**Spetzler-Martin Grading System for AVM**

The score from each column (Table 10, opposite) is added together to get the total grade. Most AVMs treated in SRS series are ≤Grade 3. Grade 3 lesions can be very heterogeneous.

Similar scales (combining finer discrimination of lesion sizes up to 3 centimeters (cm), patient age and AVM location) have been developed to assess the chance of a good outcome with SRS.
Radiotherapy

Radiotherapy (RT) in this context is aiming to cause ‘normal tissue’ (such as blood vessel) damage rather than ablating a tumour. Successfully obliterated lesions show granulation tissue formation, scar tissue replacement and hyaline degeneration. Perhaps unsurprisingly, conventionally fractionated RT has proved unsuccessful in achieving this. Most of the literature in this field describes single fraction SRS, although hypofractionation has occasionally been used for larger lesions with encouraging results.

The amount of time taken for successful obliteration of a nidus is highly variable and can often be several years (median 2–3 years in adults, although shorter in children).

Case selection for stereotactic radiosurgery

Case selection needs to take place in the context of a specialist vascular MDT (including surgeons, interventional radiologists and SRS clinicians). Important considerations for case selection include:

- The maximal diameter which should be <3 cm (a staged approach may be suitable for larger lesions, such as treating different parts of the lesion to a high dose on separate occasions, although results are generally quite poor). Obliteration rates are much higher (approximately 80–90%) for small lesions <5 cm3.
- Cases involving a compact nidus should be selected (as opposed to a diffuse malformation or sheet-like dural AVM) as this limits the volume of normal parenchyma being irradiated.
- Contraindications to open surgery (including anticoagulation, co-morbidities, nidus location with high operative risk)
- Deep venous drainage (factor of SM grading used in risk assessment before microsurgery).

Evidence of efficacy

No randomised comparison exists between treatment techniques. Most patients treated by SRS are those who have been turned down for neurosurgery, making direct comparison of results prone to various biases.

There is a very large volume of literature describing the results of treatments for AVM. Indeed, a large systematic literature review of AVM studies in 2011 identified 137 observational studies including 142 cohorts, totalling 13,698 patients and 46,314 patient-years of follow-up. Of the cohorts included in this review, 41 (29%) reported on microsurgery, 14 (10%) on embolisation, 69 (48%) on SRS, 7 (5%) on fractionated RT and 11 (8%) described either multimodality treatment, various treatments within one article or another treatment such as intraoperative embolisation. Only 16% of the cohorts described were prospective studies. For patients treated with SRS, only 38% achieved complete obliteration (but this had a strict definition of angiographically proven obliteration). This compares to a recently published large cohort of favourable SM I and II AVMs treated by SRS which described obliteration rates of 90% at five years when defined by less strict MRI criteria.

As expected, the systematic review demonstrated that intracranial haemorrhage rates were lower after microsurgery compared to SRS (0.18 versus 1.7 per 100 person-years). Complications leading to

Table 10. Spetzler-Martin grading system for arteriovenous malformations

<table>
<thead>
<tr>
<th>Size of AVM*</th>
<th>Eloquence of adjacent brain†</th>
<th>Pattern of venous drainage‡</th>
</tr>
</thead>
<tbody>
<tr>
<td>Small (&lt;3 centimetres [cm])</td>
<td>1 Non-eloquent</td>
<td>0 Superficial only</td>
</tr>
<tr>
<td>Medium (3–6 cm)</td>
<td>2 Eloquent</td>
<td>1 Deep component</td>
</tr>
<tr>
<td>Large (&gt;6 cm)</td>
<td>3 –</td>
<td>–</td>
</tr>
</tbody>
</table>

* Measure the largest diameter of the nidus of the lesion on angiography.
† Eloquent areas include sensorimotor, language, visual, thalamus, hypothalamus, internal capsule, brain stem, cerebellar peduncles and deep cerebellar nuclei.
‡ The lesion is considered superficial only if all drainage is via the cortical drainage system.
permanent neurological deficits or death occurred in a median 7.4% (range, 0%–40%) of patients after microsurgery versus 5.1% (range, 0%–21%) after SRS. More recent studies were associated with lower case-fatality rates.

Complications
Following SRS, there are few acute side-effects, but patients remain at risk of haemorrhage during the ‘latent period’. In the absence of controlled trials comparing observation with SRS it is hard to know exactly how this risk is altered by treatment. Some evidence suggests that the risk starts to fall as early as six months after treatment (and is less with smaller lesions, higher treatment doses and younger age) but this remains controversial.14 Once nidus obliteration has occurred, the risk of haemorrhage becomes extremely small although occasional bleeds have still been described.15–18

A significant proportion (approximately 30–50%) of patients will develop MRI changes (for example, increased contrast enhancement or T2 signal increase) at the site of treatment during the first two years after treatment. The peak incidence of this is at approximately eight months, and for most patients is asymptomatic. Persisting changes represent radionecrosis. The risk is correlated with the dose and volume of the treatment. The functional consequence depends on the location/eloquence of the treated site. Risks to adjacent organs can usually be prevented by careful planning, but late cyst formation at the treated site has been described, which can be symptomatic.15,19

Planning technique
Optimal target delineation requires the combination of bi-planar cerebral angiography and postcontrast MRI. The ‘nidus’ is outlined as the target volume (excluding feeding arteries and draining veins which unnecessarily increase the volume).

Dose
Margin dose (that is, dose prescribed to the isodose encompassing the lesion) selection takes into account two conflicting considerations.

- Increasing the dose directly correlates with the chance of obliteration (chance of obliteration is approximately 70%, 80% and 90% at doses of 16, 18 and 20 Gray (Gy) respectively.20,21 Above this the response plateaus with little further benefit above 25 Gy).
- Radiation-induced complications increase with dose and target volume, especially in certain eloquent areas of the brain (for example, brainstem or basal ganglia). The University of Pittsburgh group has published charts predicting the risk of toxicity depending on the volume of brain receiving up to 12 Gy in different locations within the brain.22

In practice, this means that larger lesions are treated to a lower dose for safety reasons and will consequently have a lower chance of successful obliteration. If initial treatment fails, some patients are retreated. This is usually using a lower dose.

Follow-up
Patients should be followed up with MRI (including magnetic resonance [MR] angiography) at six-monthly intervals. If the nidus appears to have been obliterated, the gold standard is to confirm this with an arterial angiogram. Retreatment is considered after 3–4 years if the nidus persists.

Potential long-term consequences of radiotherapy
The recommended radiation dose may cause localised radionecrosis in the long term, although the effects of this, if it occurs, are hard to predict and will critically depend on the volume and site of exposure. The benefits of SRS need to be balanced with the other risks. Clearly increasing dose and target volume and decreased age are all risk factors that will influence the likelihood of development of a radiation-induced cancer (RIC). Since the peak incidence is mid-20s, this needs to be considered carefully, although balanced against the risk of a potentially fatal bleed. The risk of RIC is further discussed in the section The risk of a radiation-induced malignancy following low to moderate dose radiotherapy (page 18).
Treatment decisions for patients with AVM should be made by expert MDTs who are familiar with all the available treatment options (surgery, interventional radiology and SRS) (Grade D).

SRS is generally recommended for patients with small lesions who have contraindications to surgery (such as anaesthetic risks or surgically inaccessible targets) (Grade D).

The dose of SRS correlates with the chance of obliteration but has to be adjusted according to target size. Margin doses of greater than 16 Gy are generally required to achieve reasonable obliteration rates (Grade C).

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) (Appendix 2).

References


Trigeminal neuralgia

Background

Trigeminal neuralgia (TN) is a condition characterised by intermittent, short (usually up to a couple of minutes) episodes of severe pain affecting the face (in the distribution of one or more branches of the trigeminal nerve). It is usually precipitated by stimulation of nerve endings (‘trigger areas’) in the trigeminal receptive area. It is rare, but more common in women than men (incidence in the US 5.7 per 100,000 women per year and 2.5 per 100,000 men per year). The incidence increases with age (with >90% cases occurring over the age of 40 and a peak incidence at ages 50–60) and the symptoms often worsen over time. It is usually unilateral (bilateral in 5%).

The diagnosis is based on the history and is best made by clinicians experienced in treating facial pain syndromes since various atypical forms exist.

The pathophysiology of the condition is unclear and controversial. Some cases are associated with vascular compression of the nerve root as it exits the pons (although this is not always seen and can also be found in unaffected individuals). Some cases can be secondary to central pathology (for example, multiple sclerosis or brain stem infarction). Cases occurring under age 40 are more commonly associated with multiple sclerosis.

Management

- Medical treatment: Various drugs have been shown to reduce the severity and frequency of attacks (such as carbamazepine, phenytoin, oxcarbazepine, lamotrigine, topiramate and baclofen). Conventional analgesics are rarely effective and act too slowly to deal with attacks when they occur. Medical treatment is usually used frontline but can be badly tolerated due to side-effects such as sedation and cognitive dysfunction.

- Surgery: There are two broad categories of surgical intervention.

  - Microvascular decompression (MVD): This requires a posterior fossa craniotomy with decompression of the nerve root if it is impinged on by aberrant vessel(s). This is generally considered the most effective and durable treatment but risks include stroke, infection, haemorrhage, cerebrospinal fluid (CSF) leak, facial numbness, weakness and hearing loss.

  - Ablative percutaneous procedures: These include radiofrequency ablation, glycerol injection and balloon compression. They target the ganglion, accessed via the foramen ovale. They can sometimes be performed under local anaesthesia, are frequently effective but carry a significant risk of trigeminal dysfunction afterwards. Failure rates also appear higher than after MVD.

Stereotactic radiosurgery (SRS): This was first used in the 1950s by Lars Leksell using early versions of the gamma knife. Much of the published literature has used the gamma knife (which is ideally suited to treating very small targets with a high level of accuracy). More recently, linac-based technologies have also been used but require exacting levels of set-up accuracy and quality assurance.

Role of stereotactic radiosurgery

There is no evidence for fractionated radiotherapy (RT) in this indication. Primate models suggest that SRS produces axonal degeneration and oedema at the site of treatment. As with percutaneous surgical procedures, there is an association between response and postprocedure numbness, suggesting that SRS works by blocking axonal transmission of ‘pain signals’. Symptom relief is often delayed by several weeks following treatment but usually predates any side-effects by many months.
Factors influencing choice of management

Medical management is usually used first, but often shows reduced efficacy over time, with patients experiencing increasingly unacceptable side-effects as doses are increased. MVD is effective but the risks may be unacceptable to many patients, especially those with co-morbidities. Patients are then considered for percutaneous surgical procedures or SRS. Both can produce good early outcomes (slightly quicker with surgical procedures) but relatively high rates of failure in following years. SRS generally produces fewer side-effects. There are no randomised trials comparing different treatment options to help guide practice.

Case selection for stereotactic radiosurgery

- Confirmed diagnosis of trigeminal neuralgia (as opposed to atypical facial pain, maxillofacial or dental conditions and so on).
- Failure of at least two drugs for a suitable period (for example, six months) to control symptoms. Unacceptable side-effects of medication.
- Surgery (MVD or ablative techniques) has failed or is inappropriate, medically contraindicated or unacceptable to the patient.

Evidence of efficacy

TN is subjective and response assessment is therefore challenging. The Barrow Neurological Institute (BNI) pain intensity score is often used.\(^5\)

BNI score:
- I No need for medication. No more pain
- II Occasional pain (well tolerated). No medication
- III Occasional pain that still requires medication to be well tolerated
- IV Pain that is not adequately controlled by medication
- V Severe pain without relief.

Most patients are BNI IV or V when treated, so many series class BNI I–III as a good outcome and most will also quote rates of BNI I. Since recurrence is common over time, various methods of documenting this have been used. Most accurate is an actuarial analysis with long follow-up. For all forms of treatment, results are better at first treatment rather than relapse. ‘Atypical’ syndromes also do less well, presumably because the pathology is less likely to be exclusively in the trigeminal nerve. This includes TN associated with multiple sclerosis where SRS can still be successful but shows lower response rates and durations.

Table 11 (opposite) lists the outcomes of various series using initial SRS with the gamma knife.\(^5\)\(^–\)\(^20\)

Table 12 (page 78) details equivalent series with linac-based technologies (including CyberKnife).\(^21\)\(^–\)\(^27\)

In general, these show high rates of response (especially given the high rates of previous treatment) but there are significant rates of failure over time (seen particularly in series with longer follow-up). Side-effects are rare and, for most patients, do not affect quality of life significantly. The series using linac-based technologies are generally smaller and have shorter follow-up.

Most centres performing SRS for TN retreat patients if they fail after an initially successful treatment. There are several published series describing further responses in this setting. Many centres use similar doses, targeted to a point on the nerve adjacent to the previous treatment.\(^28\)\(^–\)\(^31\)

Complications

SRS for TN is almost always a very well-tolerated, day-case procedure. Post-treatment numbness is often described (see Table 11, opposite).\(^5\)\(^–\)\(^20\) In the majority, this is not bothersome to the patients. Deafferentation pain or corneal numbness are both extremely rare with only occasional case reports. No cases of mastication motor deficits have been described. Retreatment produces higher rates of facial numbness as might be expected.
Table 11. Outcomes of various published series treating trigeminal neuralgia with gamma knife radiosurgery

<table>
<thead>
<tr>
<th>Series</th>
<th>n</th>
<th>Median (range) follow-up (months)</th>
<th>BNI I (%)</th>
<th>BNI I–III (%)</th>
<th>Median time to pain relief (weeks)</th>
<th>Maximum point dose to an organ (Dmax) (Gray [Gy])</th>
<th>Pain control or recurrence over time (*=actuarial results)</th>
<th>Complication rate (%) – trigeminal paraesthesia/numbness</th>
<th>Prior surgical treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kondziolka et al (1996)6</td>
<td>50</td>
<td>18 (11–36)</td>
<td>58</td>
<td>94</td>
<td>4.0</td>
<td>70 (60–90)</td>
<td>6% recurrence</td>
<td>6.0</td>
<td>64.0</td>
</tr>
<tr>
<td>Maesawa et al (2001)7</td>
<td>220</td>
<td>22 (6–78)</td>
<td>40</td>
<td>69</td>
<td>8.0</td>
<td>80 (60–90)</td>
<td>Good/excellent pain control: one year, 64%; five years, 38% (*)</td>
<td>10.0</td>
<td>61.0</td>
</tr>
<tr>
<td>Rogers et al (2000)8</td>
<td>54</td>
<td>12 (3–28)</td>
<td>35</td>
<td>89</td>
<td>2.0 (maximal in 9)</td>
<td>70 (70–80)</td>
<td>36% recurrence by 2.5 years (*)</td>
<td>9.0</td>
<td>46.0</td>
</tr>
<tr>
<td>Petit et al (2003)9</td>
<td>96</td>
<td>30 (8–66)</td>
<td>42</td>
<td>75</td>
<td>3</td>
<td>75 (70–80)</td>
<td>Recurrence rate: one year 23%; two years 33%; three years 39% (*)</td>
<td>7.0</td>
<td>31.0</td>
</tr>
<tr>
<td>Pollock et al (2002)10</td>
<td>117</td>
<td>26 (1–48)</td>
<td>59</td>
<td>75</td>
<td>3.0</td>
<td>80 (70–90)</td>
<td>Good/excellent pain control: one year 65%; three years 55% (*)</td>
<td>37.0</td>
<td>58.0</td>
</tr>
<tr>
<td>Sheehan et al (2005)11</td>
<td>151</td>
<td>19 (2–96)</td>
<td>47</td>
<td>90</td>
<td>3.5</td>
<td>80 (50–90)</td>
<td>27% recurrence</td>
<td>19.0</td>
<td>54.0</td>
</tr>
<tr>
<td>Brisman (2004)12</td>
<td>293</td>
<td>11 (5–55)</td>
<td>22</td>
<td>76</td>
<td>–</td>
<td>76.8 (75.0–76.8)</td>
<td>24% recurrence</td>
<td>Significant dysaesthesia 5%</td>
<td></td>
</tr>
<tr>
<td>Tawk et al (2005)13</td>
<td>38</td>
<td>24 (6–27)</td>
<td>44</td>
<td>70</td>
<td>–</td>
<td>80 (70–90)</td>
<td>Good/excellent pain control: 3/12 44%, two years 21%</td>
<td>37.0</td>
<td>29.0</td>
</tr>
<tr>
<td>Urgosik et al (2005)14</td>
<td>107</td>
<td>60 (12–96)</td>
<td>80</td>
<td>96</td>
<td>12.0 (to complete relief)</td>
<td>80 (70–80)</td>
<td>25%</td>
<td>20.0</td>
<td>60.0</td>
</tr>
<tr>
<td>Régis et al (2006)15</td>
<td>100</td>
<td>Minimum 12 months</td>
<td>Improved pain in 94%</td>
<td>1.5 (to initial relief)</td>
<td>85 (70–90)</td>
<td>34% recurrence (median interval 6 months)</td>
<td>10.0</td>
<td>49.0</td>
<td></td>
</tr>
<tr>
<td>Dhople et al (2009)16</td>
<td>95</td>
<td>67 (13–115)</td>
<td>64</td>
<td>81</td>
<td>2.0</td>
<td>75 (70–80)</td>
<td>Freedom from pain one year, 60%; two years, 34%; three years, 22% (*)</td>
<td>6.0</td>
<td>33.0</td>
</tr>
<tr>
<td>Han et al (2009)17</td>
<td>60</td>
<td>Mean 58 (16–107)</td>
<td>52</td>
<td>77</td>
<td>–</td>
<td>80 (75–80)</td>
<td>Actuarial recurrence-free survival: one year 85%, five years 46% (*)</td>
<td>15.0</td>
<td>22.0</td>
</tr>
<tr>
<td>Kondziolka et al (2010)18</td>
<td>503</td>
<td>24 (3–156)</td>
<td>40</td>
<td>85</td>
<td>4.0</td>
<td>80 (60–90)</td>
<td>Maintenance of BNI I-III: one year, 91%; five year 78% (*)</td>
<td>10.5</td>
<td>43.0</td>
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<tr>
<td>Riesenburger et al (2010)19</td>
<td>53</td>
<td>Mean 48 (36–66)</td>
<td>32</td>
<td>59</td>
<td>7.0</td>
<td>80 (75–90)</td>
<td>27%</td>
<td>36% (all mild)</td>
<td>41.5</td>
</tr>
<tr>
<td>Verheul et al (2010)20</td>
<td>450</td>
<td>28 (3–85)</td>
<td>56</td>
<td>75 (56%) multiple sclerosis [MS]</td>
<td>3.0</td>
<td>80</td>
<td>17% recurrence at five years (*) (idiopathic TN), 36% (MS group)</td>
<td>6% (24% after repeat treatment)</td>
<td></td>
</tr>
</tbody>
</table>
Table 12. Outcomes of various published series treating trigeminal neuralgia with linac-based radiosurgery21–27

<table>
<thead>
<tr>
<th>Series</th>
<th>n</th>
<th>Median (range) follow-up (months)</th>
<th>BNI I (%)</th>
<th>BNI I–III (%)</th>
<th>Median time to pain relief (weeks)</th>
<th>Maximum point dose to an organ (Dmax) (Gray [Gy])</th>
<th>Pain control or recurrence over time (*=actuarial results)</th>
<th>Complication rate (%) – trigeminal paraesthesia/numbness</th>
<th>Prior surgical treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Smith et al (2003)21 LA</td>
<td>60</td>
<td>Mean 23 (2–70)</td>
<td>–</td>
<td>70</td>
<td>11</td>
<td>Mean 83.3 (70–90)</td>
<td>26% recurrence</td>
<td>25</td>
<td>–</td>
</tr>
<tr>
<td>Chen et al (2004)22 LA</td>
<td>32</td>
<td>8</td>
<td>40</td>
<td>78</td>
<td>6</td>
<td>85–90 (when initial prescription)</td>
<td>–</td>
<td>6</td>
<td>31</td>
</tr>
<tr>
<td>Richards et al (2005)23 LA</td>
<td>28</td>
<td>12 (1–40)</td>
<td>57</td>
<td>75</td>
<td>4</td>
<td>80</td>
<td>46% recurrence</td>
<td>14</td>
<td>54</td>
</tr>
<tr>
<td>Villavicencio et al (2008)24 CK</td>
<td>95</td>
<td>22 (12–46)</td>
<td>–</td>
<td>67</td>
<td>2</td>
<td>75 (50–86.4)</td>
<td>45% at three years (*)</td>
<td>47</td>
<td>37</td>
</tr>
<tr>
<td>Smith et al (2011)25 LA (update of 2003 paper)</td>
<td>179</td>
<td>–</td>
<td>–</td>
<td>79</td>
<td>8</td>
<td>70–90</td>
<td>21% recurrence at three years (*)</td>
<td>50</td>
<td>–</td>
</tr>
<tr>
<td>Chen et al (2010)26 LA</td>
<td>44</td>
<td>15</td>
<td>43</td>
<td>91</td>
<td>2</td>
<td>90</td>
<td>30% recurrence at 12 months (*)</td>
<td>11</td>
<td>0</td>
</tr>
<tr>
<td>Lim et al (2005)27 CK</td>
<td>41</td>
<td>Mean 11 (6–22)</td>
<td>–</td>
<td>93</td>
<td>1</td>
<td>78 (71–86)</td>
<td>16% recurrence</td>
<td>51</td>
<td>32</td>
</tr>
</tbody>
</table>

Abbreviations: LA – standard linear accelerator; CK – CyberKnife

Planning technique

The trigeminal nerve is targeted between its emergence from the pons and the gasserian ganglion in Meckel’s cave. Magnetic resonance imaging (MRI) (T1 +/- contrast and T2 constructive interference in steady state [CISS] sequences) is used to visualise the nerve. Some groups have advocated targeting a point 2–4 mm from the pons, while others favour a more anterior position (immediately posterior to the gasserian ganglion – approximately 7 mm from the pons). With gamma knife, a single 4 mm ‘shot’ is positioned with Dmax (100%) located at the centre of the nerve at this point. The shot is positioned to ensure that the 15 Gray (Gy) isodose does not extend onto the brainstem but is as close as possible otherwise. Increasing the length of nerve irradiated (either with extra shots or because of ‘shaping’ to the shot to avoid the brainstem) seems no more effective and may increase trigeminal dysfunction.32

Dose

There is variation in practice but an absolute minimum for efficacy is felt to be 70 Gy to Dmax, with most groups advocating 80–90 Gy.10

Follow-up

Whatever treatment is used for TN, there is a high rate of treatment failure over time. Many patients require multiple interventions over prolonged periods. Care is best provided in specialist clinics where there is expertise in all the treatment modalities available.

Radiobiological considerations

TN is treated with a very high maximum dose (range ~70–90 Gy). Therefore, there is a risk of inducing a second malignancy in the skin or brain; however, the irradiated volume is very small which minimises this risk significantly. (Discussed in more detail in The risk of a radiation-induced malignancy following low to moderate dose radiotherapy [Page 18]).
Recommendations

- SRS can be a useful treatment modality in patients with TN. It is safe and well tolerated with high levels of initial response (Grade C).
- As with other treatments, there is a slow failure rate over time, but retreatment can be used effectively, albeit with a higher chance of facial numbness (Grade C).
- A maximum dose of at least 70 Gy appears necessary to be effective. Commonly a maximum dose of 80–90 Gy is used (Grade C).

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) (Appendix 2).33

References


Vestibular schwannoma (acoustic neuroma)

Background

Vestibular schwannoma (VS) is a relatively common, benign brain tumour. It accounts for about 6% of all intra-cranial tumours. A reliable register is available in Denmark where the incidence approaches 20 per million per year. Owing to its benign nature, the prevalence is closer to 200 per million. The mean age at diagnosis is approximately 45–47 years and there is a slight female preponderance. Cases almost never present below the age of 20 and the vast majority are picked up in patients over the age of 40.

Approximately 2–4% of patients with VS have neurofibromatosis type 2 (NF2), characterised by bilateral tumours (as well as meningiomas and schwannomas at other sites).

The tumour usually originates from the Schwann cells of the vestibular portion of the vestibulo-cochlear nerve. Magnetic resonance imaging (MRI) appearances are typical and usually allow an accurate diagnosis without the need for a tissue diagnosis.

Potential complications

The tumours affect the function of the VIIIth cranial nerve, typically causing asymmetric hearing loss, tinnitus, vertigo or imbalance. Larger tumours can begin to impinge on the brainstem at the cerebellopontine angle causing other cranial nerve deficits (especially V and VII), long tract signs and potentially hydrocephalus.

Natural history

The majority grow slowly or not at all (the average growth is 1–2 mm/year). Intracanalicular tumours (that is those completely within the auditory canal) are often seen to grow less than those at the cerebellopontine angle. Faster growth rate is associated with more rapid hearing loss. However, even non-growing tumours can sometimes cause progressive symptoms. There are no parameters known that predict which tumours will grow and to what extent.

Potential indications for treatment (and controversy)

No treatment modality has been shown to improve lost function. The indolent behaviour of many tumours and their relatively minor symptoms has encouraged the management of many small- and medium-sized tumours to be with an initial policy of ’watchful waiting’ (using sequential MRI and audiometric follow-up).

Possible indications for treatment include:

- Growth of a tumour which threatens to cause brainstem compression (here tumour removal or growth arrest by radiotherapy [RT] may be beneficial). The aim of treatment in this context is local control of growth. Given that treated tumours may begin to grow many years later, long follow-up is required to determine the success of treatment in this context.
- Relief of brainstem compression (usually requires surgery).
- ‘Preservation of function’. This is more controversial and opinions vary. Since surgery frequently causes loss of function, the debate mainly relates to RT approaches being used on non-compressive lesions. The lack of methodologically robust studies with sufficiently long follow-up comparing untreated control groups with treated groups makes this area open to opinion, bias and uncertainty.

Management of vestibular schwannoma

The literature on this subject is very large but most studies are case series of particular types of treatment. Given the heterogeneity of tumour sizes, behaviours and symptoms (at the time of treatment), as well as the variety of methods used to measure outcome, it is very hard to draw firm conclusions. A review of more recent literature has attempted to summarise the data for the efficacy and side-effects of the different modalities (including relevant meta-analyses) but acknowledges these limitations. Selection bias is a particular problem given that the patient populations are very different in the different treatment groups.
Watch and wait

The recent review suggested that without intervention, 29–54% of tumours will grow and 16–26% of patients will require additional treatment, with 54–63% preserving functional hearing. However, the mean follow-up in these studies was short, at just over three years. The majority of patients will live much longer than this and are likely to have much higher rates of progression and hearing loss during longer periods of follow-up.

Surgery

Surgery for VS is complex and can be performed using different techniques that have a range of pros and cons. As with other specialist operations, results are often best from high-volume centres. A positive for surgery is that further therapy is almost never required after a definitive operation. However, even the best series show rates of significant new facial palsy in the order of 20–40%, preservation of ‘useful hearing’ in only about 20–40%, and other complications (mostly trigeminal dysfunction but also, less commonly, haemorrhage, CSF leaks, wound infections, meningitis and CSF shunting) in up to half. Patients are often in hospital for at least 1–2 weeks and take a long time to recover sufficiently to return to work. Radical surgery is therefore used mainly for those tumours that are growing quickly or are bulky, and especially those impinging on the brainstem. More recently, it has become increasingly common to consider partial resection (to reduce the risk of harm) and to use RT (often stereotactic radiosurgery [SRS]) to treat residual disease.

Stereotactic radiosurgery

Single fraction SRS is a well-established treatment modality in VS. Although various technologies that can deliver such treatment are now available, the overwhelming majority of the literature relates to gamma knife. Over time, the marginal dose (usually prescribed to ~50% isodose) has reduced. This has been shown to reduce complications. Currently, the standard is to use ~12 Gray (Gy). Large series using this dose show local control rates of >90% at ten years, with low rates of facial nerve (1–2%) or trigeminal nerve (1–2%) sequelae. Further treatment is only required in about 4% of patients during this extended follow-up. Hearing preservation declines over time and it is controversial whether this is faster or slower than in untreated cases.

It is likely that other types of modern RT equipment could achieve similar results but meticulous planning and quality assurance are required with any technology if results are to be acceptable.

Some patients receiving SRS will have some swelling of the tumour in the first two years after treatment. In many cases, this will resolve during longer follow-up. Very rarely, the swelling is sufficient to precipitate brainstem compression and hydrocephalus (incidence approximately 2–3% in most studies). SRS to larger tumours is more often associated with this problem.

Fractionated stereotactic radiotherapy

Specialised, modern RT equipment is increasingly capable of delivering highly conformal, fractionated treatments to small volumes in the brain. Several groups have published results using conventionally fractionated regimens (45–56 Gy in 1.8–2 Gy fractions) to treat VS. Generally these have shorter follow-up than the SRS literature. Radiobiologically, a potential advantage of this approach may be better hearing preservation or less risk to neighbouring structures (especially the brainstem) with larger tumours. There have been no randomised comparisons with SRS, but most series demonstrate similar levels of toxicity and local control. Some authors suggest better hearing preservation rates but the quality of studies makes it hard to draw firm conclusions. Again, the experience of the team and the quality of the RT process may be particularly important in this situation. As with SRS, fractionated stereotactic radiotherapy (fSRT) can also lead to tumour swelling and a risk of hydrocephalus. In one study, there was an actuarial rate of 11% for this within 19 months of treatment (with larger tumours indenting the brainstem being most at risk). There is much less evidence for other hypofractionated regimes and these should be considered experimental at present.
Comparison between treatments

A recent paper attempted to identify methodologically robust comparison studies between treatment modalities and identified only four useful publications (none of which were randomised). All of these attempted to compare microsurgery with SRS for similar tumours (generally <3 centimetres [cm]). In these, it was shown that after SRS, there was better facial function, hearing preservation and quality of life. Given that results for fSRT are broadly similar to SRS, it is likely that this also applies to fSRT but no suitable studies exist addressing this issue.

Treatment selection

Factors influencing treatment include:

- The patient’s symptoms – is hearing preserved? What is the function of the contralateral ear? Are symptoms progressing quickly? How important is hearing preservation?
- Age and life expectancy – younger patients, with many years of life ahead, have a higher chance of running into problems from even a slowly growing tumour
- Tumour size and rate of growth (if known) – larger tumours causing pressure effects will often require surgery. Clearly growing tumours will also cause earlier problems if left
- Other patient factors – for example, preference, occupation, anaesthetic risk factors/co-morbidities
- Availability of treatment options and clinician bias.

Potential long-term consequences of radiotherapy

RT can produce an increased risk of second tumours (either malignant transformation at the site of treatment or a different tumour type in the adjacent brain). It is recognised that this can happen many years after the original treatment. Very few such cases have been described but, based on the volume irradiated and previous pituitary data, a recent review speculated a risk of 1% at 20 years. Patients present with VS at many ages, but most frequently in the fifth decade of life. Consequently, the risk of a radiation-induced second tumour needs to be considered carefully, particularly when treating younger individuals. The risk also needs to be balanced against the significant, often permanent, deficits following surgery. SRS uses lower doses than fSRT (including that to the normal brain) which might suggest that SRS is preferable to fSRT where SRS is practical (particularly in younger patients). However, no comparison studies have been done to show the relative risks or long-term sequelae between these two treatment options. For a more detailed discussion of the risks of radiation-induced cancer (RIC) see the section on The risk of a radiation-induced malignancy following low to moderate dose radiotherapy (page 18).

Recommendations

- Patients should be treated by a multidisciplinary team (MDT) familiar with, and able to provide, the different treatment options. Taking into account the factors listed above, patients can then make choices depending on their individual circumstances, priorities and preferences (Grade D).
- Surgery remains a standard treatment for VS – particularly for larger tumours compressing the brainstem (Grade C).
- SRS is an effective treatment, producing high rates of local control. When used, a margin dose of ~12–13 Gy is currently standard (Grade C).
- Conventionally fractionated stereotactic RT at a dose of 45–56 Gy in 1.8–2 Gy fractions also appears to be effective and has generally been used for larger tumours (Grade C).

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) (Appendix 2).
References


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. 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. 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.

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.

3. Collagenase (Xiapex) is the injection of an enzyme that dissolves the collagen in the Dupuytren’s cord, which can then be mechanically broken. In those fingers that are successfully straightened, there is a 35% three-year contracture recurrence rate.

Radiotherapy

There are many retrospective studies in the literature going back many decades that have indicated the efficacy of radiotherapy (RT) for Dupuytren’s disease. 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 13 (overleaf), 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.

A retrospective study with a median follow-up of six years looked at 96 patients (142 hands). 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 Gray (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 stage progression, although 23% of those with >5 years follow-up were found to have progressed. Only minor side-effects were noted.

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. 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.
A prospective trial randomising patients between two dose levels (with no control group) looked at 129 patients (198 hands). 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, looked at the outcomes of patients followed up for at least five years (median follow-up of 102 months). 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 was demonstrated in both treatment groups compared with the control group, although there was no significant difference between the two treatment groups (Table 14, opposite).

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. 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 to 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 cm², 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 the age of exposure to RT treatment. For a patient of 25 years 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 radiation-induced cancer (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 which may affect the risk in an unknown manner is the reported higher risk of dying of cancer in individuals with Dupuytren’s disease.23 As discussed in the section on The risk of a radiation-induced malignancy following low to moderate dose radiotherapy (page 18), 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.24 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 atrophy and >1% reduced wound healing.18

### Table 14. Outcome of long-term follow-up of Seegenschmiedt study of radiotherapy for Dupuytren’s disease21

<table>
<thead>
<tr>
<th>Dose</th>
<th>Regression or stable disease (%)</th>
<th>Progression (all clinical signs, %)</th>
<th>Surgery (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control (n=122)</td>
<td>38</td>
<td>62</td>
<td>30</td>
</tr>
<tr>
<td>21 Gy (n=293)</td>
<td>76</td>
<td>24</td>
<td>12</td>
</tr>
<tr>
<td>30 Gy (n=245)</td>
<td>80</td>
<td>19.5</td>
<td>8</td>
</tr>
</tbody>
</table>

**Recommendations and radiotherapy technique**

- 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). Patients with more advanced disease should be not be treated with RT, and may be offered surgical release (Grade C).

- 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).

- The aim is to treat nodules and cords to the periostium of the hand bones, for a depth of 5–15 mm. Therefore, 120–150 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).

- 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).

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) (Appendix 2).24
References


22. [www.dupuytren-online.de/downloads/Risk%20of%20cancer%20with%20radiotherapy%20of%20Morus%20Dupuytren.htm](http://www.dupuytren-online.de/downloads/Risk%20of%20cancer%20with%20radiotherapy%20of%20Morus%20Dupuytren.htm) (last accessed 19/01/2015).


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 affect children and young adults. Plantar fibromatosis presents as lumps 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 radiotherapy (RT) treatment. A small Dutch retrospective study looked at 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 Gray [Gy]) was 17%.

A German multicentre retrospective analysis looked at 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 kilovolts [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 centimetres (cm) focus to skin distance (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 or at least a partial response (SD/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 12.1% of cases had dryness after a follow-up period of >12 months.5

Potential long-term effects of radiotherapy

The dose and field size for RT of the foot for plantar fibromatosis are similar to that 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 the section on Dupuytren’s disease [page 85]).

Dryness after a follow-up period of >12 months was reported in 11% of feet irradiated for Ledderhose disease.3
Recommendations and radiotherapy technique

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

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) (Appendix 2).  

References


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 shock-wave 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 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.
3. 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.

Radiotherapy

Radiotherapy (RT) has been used since 1924 for the treatment of plantar fasciitis. Many retrospective studies have shown heel pain response to RT; for example, a German study looked at 7,947 patients and found a 70% pain response three months after RT.

Heyd et al randomised 130 patients between low-dose (LD) RT (3.0 Gray [Gy] in six fractions over three weeks) and high-dose (HD) RT (6.0 Gy in six fractions over three weeks). 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). 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 kilovoltage (kV) photons. 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, re-irradiation 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 re-irradiated 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 radiation-induced cancer (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 on Dupuytren’s disease [page 85]). This estimate is based on a field size of 60 centimetres² (cm²) 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

- 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).
- 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).

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) (Appendix 2).[11]

References

**Peyronie’s disease**

**Background**

Peyronie’s disease (PD) is a wound-healing disorder of the tunica albuginea of the penis which affects 3–9% of adult males. Clinically, any combination of plaque formation, penile pain, angulation and erectile dysfunction may appear. This condition may progress, stabilise or, uncommonly, regress during the initial acute phase (6–18 months). Surgery is considered the gold standard and includes plication, incision, and grafting or penile-prosthesis-related procedures.

**Radiotherapy**

Although radiotherapy (RT) is little used in the UK, a European survey was undertaken and published in 2008. A questionnaire was sent to 908 European RT institutions, of which 402 questionnaires (44.5%) were returned. Of these, 73 (19%) reported irradiated patients with PD. The main reasons quoted for not treating these patients were insufficient referrals from urologists or no departmental interest in treating benign diseases. The most common dose fractionation regimen was 20 Gray (Gy) in ten fractions, usually with electrons, but sometimes with orthovoltage RT. Reduction in pain was reported in approximately 80% of cases, with minimal or no side-effects.

Niewald et al from Homburg, Germany reported on 154 patients treated with RT for PD between 1983 and 2000. Seventy-two patients received RT with a dose of 30 Gy, and 25 received 36 Gy in daily fractions of 2.0 Gy. There was an improvement of deviation in 47%, reduction of number of foci in 32%, reduction of size of foci in 49%, and reduced induration in 52%.

Approximately 50% reported pain relief following RT. Side-effects were mild (radiation dermatitis).

Pambor et al from Magdeburg, Germany reported improvement in pain in a series of 58 patients treated with RT to a dose of 24–30 Gy. Meineke et al reported on 67 patients treated with RT. In 58 of 67 patients (86.6%) progression of the disease was stopped. Pain improved totally in 21 patients (84% of the patients with pain). A complete or partial regression of induration was observed in 41 of 70 patients (58.6%). In 23 of 60 patients (38.3%) an improvement of deviation was observed.

In a series from Rotterdam, Incrocci et al reported on 179 patients receiving RT between 1982 and 1997. The radiation schedule consisted of 13.5 Gy in nine fractions using orthovoltage X-rays in 123 patients or 12 Gy in six fractions using electrons in 56 patients. At a follow-up time of three months after RT 83% reported that pain was diminished or had disappeared after RT and 23% of patients reported a decrease in penile deformity. Following RT, surgical correction of penile curvature was performed in 29% of patients. RT was very well tolerated.

Rodrigues et al from Amsterdam reported on 38 patients with PD treated with orthovoltage RT between 1975 and 1993. The initial radiation dose was 9 Gy in five fractions on alternating days but in order to try to improve response the latter 16 patients received a total dose of 18 Gy in ten fractions. The higher dose of RT did not result in better symptom relief, which overall resulted in 76% experiencing reduced pain, 60% reported an improved sex life, and 48% had a diminished curvature.

**Recommendations**

Given the limited evidence base, RT should not be recommended as a standard treatment. However, if conventional treatments have proved ineffective, there is some evidence that RT can be effective for pain relief using doses in the range of 9–30 Gy (Grade C).

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) (Appendix 2).
References


Heterotopic ossification of the hip

Background

Heterotopic ossification (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 (THA). 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 15, opposite).1 Broadly, Brooker grades 3 and 4 represent severe HO which often leads to functional disability.

Management

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 non-steroidal anti-inflammatory drugs (NSAIDs) or radiotherapy (RT), may be used to minimise the risk of recurrence or to reduce the initial occurrence rate in high-risk situations.

Non-steroidal anti-inflammatory drugs

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-analysis has shown a mean overall reduction in the risk of HO after THA with NSAIDs (apart from aspirin) from 61% to 27% when compared to a placebo, and indomethacin is the current standard treatment used for this purpose.2,3 However, in a subsequent large randomised trial of ibuprofen versus placebo, despite a significant reduction in the formation of ectopic bone, there was no improvement in pain or functional ability, and there was a significant increase in major bleeding complications.4 Additionally, the use of indomethacin after acetabular fracture showed no significant reduction in the incidence of severe HO compared with placebo in a randomised trial.5 Side-effects of NSAIDs may include gastric irritation and bleeding, and renal dysfunction. It may also increase the non-union of concomitant fractures.6 COX-2 inhibitors and diclofenac have also been shown to be effective, but there are additional cardiac safety concerns about these drugs.

Radiotherapy

A summary of the evidence for the use, does and timing of radiotherapy in the prevention of HO is shown in Table 16.7–15

Dose

RT is thought to reduce the formation of ectopic bone by acting on osteoprogenitor cells, perhaps via inhibition of bone morphogenetic protein signal transduction pathways.16 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 Gray (Gy) in ten fractions.8 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.9,10 A reduction in dose below 7 Gy, however, resulted in a reduction of efficacy.11,12

Timing

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. Therefore, preoperative was compared with postoperative RT. Seegenschmiedt et al compared a preoperative dose of 7 Gy in one fraction given within four hours of surgery with a
Table 15. Brooker classification of heterotopic ossification around the hip joint

<table>
<thead>
<tr>
<th>Stage</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Bone islands within the soft tissues</td>
</tr>
<tr>
<td>2</td>
<td>Bone spurs from the pelvis or proximal end of the femur, with at least 1 centimetre (cm) between opposing bone surfaces</td>
</tr>
<tr>
<td>3</td>
<td>Bone spurs from the pelvis and/or proximal end of femur, with &lt;1 cm between opposing bone surfaces</td>
</tr>
<tr>
<td>4</td>
<td>Apparent bone ankylosis of the hip</td>
</tr>
</tbody>
</table>

Table 16. Selected studies of radiotherapy for heterotopic ossification8–15 (adapted from Balboni et al 2006)7

<table>
<thead>
<tr>
<th>Author</th>
<th>Study type</th>
<th>n (hips)</th>
<th>Treatment</th>
<th>Conclusion</th>
</tr>
</thead>
<tbody>
<tr>
<td>Coventry (1981)8</td>
<td>Retrospective</td>
<td>48</td>
<td>20 Gy in ten fractions</td>
<td>RT is effective for prevention of HO</td>
</tr>
<tr>
<td>Sylvester (1988)9</td>
<td>Retrospective</td>
<td>27</td>
<td>Postop: 20 Gy in ten fractions versus 10 Gy in five fractions</td>
<td>10 Gy in five fractions is as effective as 20 Gy in ten fractions</td>
</tr>
<tr>
<td>Lo (1988)10</td>
<td>Retrospective</td>
<td>27</td>
<td>7 Gy in one fraction</td>
<td>7 Gy in one fraction is effective</td>
</tr>
<tr>
<td>Pellegrini (1992)11</td>
<td>Prospective randomised</td>
<td>62</td>
<td>Postop 8 Gy in one fraction versus 10 Gy in five fractions</td>
<td>Single fraction is as effective as fractionated course</td>
</tr>
<tr>
<td>Healy (1995)12</td>
<td>Retrospective</td>
<td>107</td>
<td>Postop 7 Gy in one fraction versus 5.5 Gy in one fraction</td>
<td>5.5 Gy is less effective than 7 Gy</td>
</tr>
<tr>
<td>Padgett (2003)13</td>
<td>Prospective, randomised</td>
<td>59</td>
<td>Postop 5 Gy versus 10 Gy</td>
<td>Trend to 5 Gy being less effective than 10 Gy</td>
</tr>
<tr>
<td>Seegenschmiedt (1997)14</td>
<td>Prospective randomised</td>
<td>161</td>
<td>Pre-op 7 Gy in one fraction versus postop 17.5 Gy in five fractions</td>
<td>Pre-op was inferior to postop (although different doses were being compared)</td>
</tr>
<tr>
<td>Gregoritch (1994)15</td>
<td>Prospective randomised</td>
<td>124</td>
<td>Pre-op versus postop (7–8 Gy in one fraction)</td>
<td>Single fraction given pre-op is similar to that given postop</td>
</tr>
</tbody>
</table>

In most of the studies above, the radiation was given within four hours before surgery or within 3–4 days after surgery, on the basis of experimental data showing a reduction in radio-responsiveness outside of that window.17,18

postoperative dose of 17.5 Gy in five fractions given within 72 hours of surgery, and found that the postoperative RT was more effective, although the difference in doses may have been the most relevant factor.14 Gregoritch compared 7–8 Gy either given pre- or postoperatively in patients at high risk of HO, and found no difference in efficacy (26% versus 28% incidence, with 2% versus 5% clinically significant HO respectively).15
Radiotherapy field

Anterior-posterior fields are used and the dose is prescribed to the mid-point. The RT portal should encompass the regions that are mostly 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. 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.19

Radiotherapy versus non-steroidal anti-inflammatory drugs for the prevention of heterotopic ossification

Table 17 lists randomised trials comparing the use of RT and NSAIDs for the prevention of HO.6,20–27 Overall these studies analysed results from 1,143 patients. Most patients were treated after THA, but one study looked at prophylaxis after surgery for acetabular fractures.6,26 The RT was generally given postoperatively within four days, but in the Kölbl study, the RT was delivered 16–20 hours preoperatively.24 In most studies the radiation was delivered as a single fraction, but in two studies the dose was delivered in 3–4 fractions. The NSAIDs used were indomethacin, diclofenac and aspirin.

Table 17. Randomised studies of radiotherapy versus non-steroidal anti-inflammatory drugs6,20–26 (adapted from Pakos et al)27

<table>
<thead>
<tr>
<th>Study</th>
<th>Number of procedures studied</th>
<th>RT timing (pre- or postoperatively)</th>
<th>RT dose (Gy/ fractions)</th>
<th>Mean follow-up (months)</th>
<th>Incidence of HO (%)</th>
<th>Brooker 3–4</th>
<th>Any HO</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kienapfel et al (1999)</td>
<td>104</td>
<td>Postop</td>
<td>6.0 Gy in one fraction</td>
<td>13.0</td>
<td>0.0</td>
<td>0.0</td>
<td>24.5</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>36.4</td>
</tr>
<tr>
<td>Sell et al (1998)</td>
<td>154</td>
<td>Postop</td>
<td>9.9 Gy in three fractions</td>
<td>6.0</td>
<td>0.0</td>
<td>0.0</td>
<td>2.6</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>23.4</td>
</tr>
<tr>
<td>Kölbl et al (1997)</td>
<td>301</td>
<td>Postop</td>
<td>5–7 Gy in one fraction</td>
<td>12.0</td>
<td>0.5</td>
<td>1.8</td>
<td>20.7</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>15.9</td>
</tr>
<tr>
<td>Kölbl et al (1998)</td>
<td>100</td>
<td>Postop</td>
<td>7 Gy in one fraction</td>
<td>6.0</td>
<td>2.2</td>
<td>0.0</td>
<td>47.8</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>11.1</td>
</tr>
<tr>
<td><em>Burd et al (2003)</em></td>
<td>150</td>
<td>Postop</td>
<td>8 Gy in one fraction</td>
<td>14.5</td>
<td>3.8</td>
<td>11.1</td>
<td>N/A</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>N/A</td>
</tr>
<tr>
<td><em>Moore et al (1998)</em></td>
<td>72</td>
<td>Postop</td>
<td>8 Gy in one fraction</td>
<td>12.0</td>
<td>N/A</td>
<td>N/A</td>
<td>27.3</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>46.2</td>
</tr>
<tr>
<td>Bremen-Kuhne et al (1997)</td>
<td>50</td>
<td>Postop</td>
<td>6 Gy in one fraction</td>
<td>12.0</td>
<td>0.0</td>
<td>3.2</td>
<td>47.4</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>35.5</td>
</tr>
<tr>
<td>Knelles et al (1997)</td>
<td>284</td>
<td>Postop</td>
<td>12 Gy in three fractions</td>
<td>12.0</td>
<td>0.0</td>
<td>3.3</td>
<td>5.0</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>25.4</td>
</tr>
</tbody>
</table>

*The Burd et al and Moore et al studies reported results on an overlapping patient group, although Burd et al analysed the incidence of Booker 3 & 4 HO only, whereas Moore et al reported the rate of any HO.6,25
Both methods of prophylaxis produced very low rates of HO. In a meta-analysis of these trials, RT reduced the risk of Brooker grades 3–4 HO significantly better than NSAIDs (0.9% versus 2.9%, p=0.043).20 For overall HO (that is, of all Brooker grades) there was no significant difference in outcome between the two prophylactic methods.

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 radiation-induced cancer (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 malignancy 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 megavolts [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]/centimetres² [cm²]) compared to the female phantom (1.82–2.14 mSv/cm²). 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 (>60 years) 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 clinics should optimise treatment protocols to reduce the effective dose and thus the related risk of RIC.28 Since the total recommended dose is <10 Gy, other radiation-associated side-effects are unlikely to be an issue.

Recommendations

- RT and NSAIDs are both effective in the prevention of heterotopic ossification (Grade A).
- NSAIDs could be used in younger patients (for example, <50 years) due to the risk of second malignancy. However, they have not been shown to improve clinical outcomes in comparison to RT (Grade A), and they have side-effects including gastric bleeding and renal dysfunction.
- RT could be used in older patients (for example, >50 years), or in patients with pre-existing gastritis or renal dysfunction.
- RT can be given either pre- or postoperatively, and should be delivered within four hours before surgery or within 72 hours after surgery (Grade A).
- 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).
- The discussion above covers the prevention of heterotopic ossification of the hip. RT has been used to prevent HO at other sites, but data on its success are more limited.

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) (Appendix 2).29
References


Pigmented villonodular synovitis

Background

Pigmented villonodular synovitis (PVNS) is a rare proliferative process involving synovial membranes. It 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 radiotherapy (RT) in comparison with other modalities.

There are three subtypes of PVNS. Pigmented villonodular tenosynovitis (PVTS) usually affects the finger joints and occurs most often in females between the ages of 20–40. Localised pedunculated villonodular synovitis (L-PVNS) typically involves the knee joint causing a locking or clicking sensation. Diffuse pigmented villonodular synovitis (D-PVNS) most commonly affects the knee, hip or ankle joint and may mimic other conditions such as rheumatoid arthritis.

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 L-PVNS with synovectomy but for D-PVNS local recurrence risk may be of the order of 20–50%.

Radiotherapy

Ionising radiation, either in the form of external beam radiation therapy (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 reported a series of 14 patients from Princess Margaret Hospital, Toronto treated with radiotherapy (RT) between 1972 and 1992. 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 Gray (Gy) in 15 fractions.

An updated series from the same institution was reported by Griffin et al in 2012. 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. 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 who 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 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. 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 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. 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.

An alternative RT approach is the instillation of radionuclides (yttrium-90 [90Y], radioactive phosphorus [32P]) 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**

- PVNS is a rare condition and it is difficult to draw firm conclusions as to optimum management.
- For patients with D-PVNS, 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).
- 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 would probably benefit from further discussion with orthopaedic surgeons on a local and national level to define indications for consideration of postoperative RT and also the optimum radiation modality.

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) (Appendix 2).6

**References**


Vertebral haemangioma

Background

Vertebral haemangiomas are benign vascular neoplasms. As in other sites, the varieties include the capillary and cavernous subtypes. They can occur at all ages and approximately 60–70% of skeletal haemangiomas arise in the spine. The majority are asymptomatic but approximately 10% are painful, and occasional further complications such as spinal cord compression may occur.

Management

Diagnosis is based on typical radiology demonstrating vertical striation of vertebrae on plain X-ray, supported by magnetic resonance imaging.

Surgical procedures are the mainstay of treatment. Urgent treatment with surgery will be required for cord compression, although in general haemorrhage can be a surgical complication during procedures for this condition. Arterial embolisation also has a role.

Radiotherapy

As with haemangiomas at other sites, radiotherapy (RT) has been used as a treatment since the 1920s. The mechanism is presumably analogous to the late effects of RT on normal vascular tissues.

A detailed literature review summarises outcomes following treatment of 214 cases. Complete pain relief was achieved in 58.4% of cases and partial relief in 29.9%. However, many of these reports were published before the 1970s and the majority are single case reports or very small single institution case series.

Recent series include Miszczyk and Tukiendorf from Gliwice, Poland. They reported on RT for 137 cases of painful vertebral haemangioma in 101 patients. RT doses varied from 8 to 30 Gray (Gy) and dose per fraction from 2 to 15 Gy. The mean degree of pain relief was 60.5% at one month, 65.4% at six months and 78.4% at 18 months. This recent report supports the use of RT and identified prognostic factors predictive of a positive benefit, namely female gender, older age, better performance status (based on the Karnofsky performance status), increased Hb concentration, shorter duration of symptoms and lower analgesics uptake before RT.

Heyd et al reported on a multicentre survey of RT for vertebral haemangioma undertaken in Germany. Between 1969–2008, a total of 84 patients with 96 symptomatic lesions were treated in seven centres. Most were treated because of pain. The median RT dose was 34 Gy, with a median dose per fraction of 2.0 Gy. With a median follow-up of 68 months, the overall response rate was 90.5% (complete in 61.9%).

Regarding optimum dose and fractionation, Rades et al conducted a literature review and used a linear-quadratic (LQ) model to compare dose/fractionation regimens. They concluded that the best results were achieved with a dose of 36–40 Gy in two Gy fractions. Complete pain relief was achieved in 82% of patients treated with a dose of at least 36 Gy but only in 39% treated with lower doses.

Recommendations

- Historically, RT has been used as a modality for the treatment of symptomatic vertebral haemangioma. However, as with other benign conditions, much of the literature is historic, with many individual case reports or small retrospective series.
- There is some limited recent literature supporting it use (Grade C).
- It is difficult to establish what role RT has in comparison with other methods of treatment.
- There appears to be a dose–response relationship, with better responses seen for doses in the range 36–40 Gy compared to lower doses. If the multidisciplinary team (MDT) considers RT to be essential, a dose within this range would be appropriate (Grade C).

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) (Appendix 2).
References


Aneurysmal bone cyst

Background

Aneurysmal bone cyst (ABC) is a relatively rare benign osteolytic bone lesion. ABCs account for approximately 1–1.5% of all bone tumours. ABC occurs most frequently in children and young adults with the peak incidence in the second decade of life. ABCs are not true neoplasms, but involve haemorrhagic and hyperplastic processes. They are composed of blood-filled channels separated by fibrous septae. ABC may present as a primary lesion or develop secondary to a wide variety of pre-existing bone lesions. They may arise anywhere within the skeleton, more frequently in the lower extremities, but most frequently in the metaphysis of long bones. Around 15% arise in a vertebra. Presenting symptoms include bone pain and swelling, usually without inflammatory change. Pathological fracture is uncommon. Typical radiological appearances include a cystic lesion with a ballooned contour, with septae and surrounded by a thin ‘egg shell’ layer of bone. Diagnosis is based on typical pathology comprising blood-filled spaces with septae composed of fibroblasts, multinucleated giant cells and loose collagenous ground substance.

Management

Due to the nature of ABC, initial management is generally with some form of surgical approach. For indolent lesions of less than 5 centimetres (cm) diameter, curettage may be appropriate. For larger lesions and those which are clinically aggressive, a more radical procedure such as an en bloc resection may be necessary. Other procedures such as arterial embolisation or, following incomplete surgery, various adjuvant therapies including cryosurgery and instillation of a variety of substances may also be employed.

Radiotherapy

Radiotherapy (RT) is generally not the treatment of choice but may be appropriate for the treatment of patients with ABC in anatomically difficult locations and following recurrence after surgery. The radiotherapeutic literature mainly comprises individual case reports or small single institution series. Few series report more than ten patients. A review of the literature has been published.1 For a total of 194 cases given RT either as primary treatment or adjuvant following surgery, treated from 1956–2001, 87% achieved complete relief of symptoms and 3% partial relief. For 76 patients treated with primary RT following biopsy only or following recurrence, 67 (88%) achieved local control. However, RT was used in a heterogeneous range of clinical scenarios and with a very wide range of dose/fractionation regimens. Furthermore, the duration of follow-up varied considerably.

In a series of nine patients treated at the University of Florida between 1964 and 1992, six with RT alone and three after curettage, all patients achieved symptom relief.2 There were no local recurrences although four patients were lost to follow-up. In this series, the optimum dose appeared to be 26–30 Gray (Gy).

Recommendations

- Surgery is the first choice of therapy for ABC.
- There is increasing interest in the use of interventional radiology techniques.
- For patients with tumours in anatomically difficult locations and for recurrence following surgical procedures, if RT is considered by the multidisciplinary team (MDT) as essential, there is some support from the literature for its use to achieve long-term local control (Grade C).
- A dose of 30 Gy in 15 fractions would be reasonable using planning technology to avoid irradiating unnecessary normal tissue (Grade C).

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) (Appendix 2).
References


8. Skin/soft tissues

Keloid scarring

Background

Keloid scars are common benign dermal fibro-proliferative growths, and represent abnormal healing responses to injury. They result in raised scars that may be red or hyperpigmented. They are often cosmetically disfiguring, but can also cause itching and pain. In contrast to hypertrophic scars, they extend outside the confines of the original wound and do not spontaneously regress.

They may occur in response to relatively minor trauma, such as ear piercing, and particularly occur on the upper chest, shoulders and earlobes. They are more common in dark-skinned patients, but also occur at a lower rate in patients with light skin. 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.1

There is an extensive published literature on the treatment of keloid scarring, but all studies have at least one of the following limitations:

- Poor study design, with most studies being observational and lacking an appropriate control group
- Low sample size
- Many studies examine the effects of treatment on both keloids and hypertrophic scars
- Outcome measures are often not clearly defined. Many studies cite rates of ‘recurrence’ without defining precisely what this means. Other studies cite a reduction in surface area of the scar, or patient-reported measures
- Follow-up time is often short, and should be at least 12 months to be meaningful1
- Often treatment protocols within a single study are variable, with the treatment being applied at different time-points or at different doses.

Management

- Intra-lesional 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.2 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 randomised controlled trials, 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 recurrence rate is high, for instance Lawrence reported a recurrence rate of 70%.3 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 postexcision intralesional steroid injections. Meticulous surgical technique, including minimal undermining of the wound, trauma to surrounding tissues and low wound tension, should be used to minimise the risk of recurrence.
- Silicone gel sheet application: There is little evidence of the effectiveness of this treatment.
- Intralesional 5-fluorouracil: Two small randomised trials have shown a positive effect of this treatment compared with topical silicon or intralesional steroids.4,5
- Other treatments include intralesional interferon, cryotherapy, bleomycin, ultraviolet irradiation, topical imiquimod, photodynamic therapy, electrical stimulation and laser therapy.

Radiotherapy

Most studies of radiotherapy (RT) for the treatment of keloids are retrospective studies of the combination of surgery and postoperative RT. Recurrence rates vary widely, but representative figures are 7% at two years, 16% at five years, and 27% at ten years.6–8 The radiation is generally delivered with superficial/orthovoltage X-rays or with electrons within 24–72 hours of surgery, although several studies do not support the need for early postoperative treatment.6–4
These studies represent a limited evidence base supporting the effectiveness of RT when given postoperatively. In particular, most studies are retrospective and/or have small numbers, insufficient follow-up, unclear outcomes and detail the treatment of heterogeneous groups of patients including those with heterotrophic scars. However, overall they seem to compare favourably with historical recurrence rates of 45–100% after excision alone.

There are two trials comparing RT with other treatments, although both suffer from low patient numbers.

- Emad et al performed a prospective non-randomised comparison in 26 patients with 76 keloids of (i) excision with RT within 48 hours using 12 Gray (Gy) in three fractions with 120 kilovoltage (kV) RT versus (ii) cryotherapy with post-treatment intralvesional triamcinolone injection. After one year of follow-up, 18.2% of the patients in the RT group had recurrence, compared with 28.1% in the cryotherapy group.

- Sclafani et al randomised 31 patients after excision of earlobe keloids to steroid injections or to RT. They found that at ‘a minimum of 12 months’ after RT, 12.5% recurred, compared with 33% after steroid injections.

The evidence for RT given as monotherapy is even less extensive. 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.

Potential long-term effects of radiotherapy

Since the evidence from clinical trials of RT for keloid scarring is limited, 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 page 85). This risk has been identified as approximately 0.02% for a field size of 60 centimetres² (cm²), 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 un-irradiated 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 cm² 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. They used male and female anthropomorphic phantoms to estimate the risk of malignancy resulting from RT for a number of benign diseases including heterotopic ossification 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 to 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. However, for keloid treatment, with a much more focused superficial area of treatment, the risk should significantly reduce compared to 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 radiation-induced cancer; a factor that should be relatively easy to achieve when treating keloid scarring with RT. The risks of various malignancies following radiation exposure are further discussed in the section: The risk of a radiation-induced malignancy following low to moderate dose radiotherapy (page 18).
Summary and 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 postexcision treatment of keloid scarring, along with other conservative (topical) treatments.

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

- If RT is to be used, it should be administered within 24–72 hours of surgical excision (Grade D).

- Both superficial/orthovoltage (generally 60–120 kV) or electrons can be used. Reasonable single fraction doses lie in the range of 5–10 Gy, and a typical fractionated dose would be 12 Gy in three fractions given over 3–5 days (Grade C).

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) (Appendix 2).

References


Lentigo maligna

Background

Lentigo maligna or Hutchinson melanotic freckle is a macular, irregularly hyperpigmented skin lesion. They are usually found in middle aged and elderly people of Caucasian origin, most commonly in the head and neck region. Peak incidence is in the seventh and eighth decades. Aetiologically, lentigo maligna is related to a history of long-term sun exposure, explaining a predilection for sun-exposed areas including cheeks, nose, forehead and ears. The growth pattern is generally slow and in a centrifugal horizontal direction. Lesions are often large and poorly defined at presentation. Areas of clinical regression may be evident.

There is a paucity of data on the natural history of lentigo maligna melanoma and it has been postulated that lentigo maligna may be an in situ phase of lentigo maligna melanoma. The reported rate of progression of lentigo maligna to lentigo malignant melanoma is very variable, with estimates between 5% and 50%.

Biopsy is commonly performed to confirm the diagnosis and exclude an invasive melanoma. Incisional biopsy risks sampling error, but due to the size of the lesion excision may not be practical. Histological diagnosis includes the identification of atypical melanocytes in the epidermis, usually at the epidermal-dermal junction with no dermal invasion. Atypical melanocytes can extend beyond the clinical boundary; histological abnormalities have been reported significantly beyond the clinical margin.

Management

The goal of treatment is complete eradication with a good cosmetic outcome; however, this can be challenging to achieve. Management is primarily surgical and excision with clear margins provides good results with cure rates of >90%. There is no consensus on the optimal surgical margins, with 5 mm often insufficient; margins of 10 mm may be required for larger lesions. Mohs’ micrographic surgery has also been employed in view of difficulty in estimating margins, with high rates of control; one study reported a 97% cure rate with a median follow-up of 58 months.

For lesions that occupy wide areas of skin, or in proximity to critical structures such as the eye, nose or ear, excision with reconstruction may leave unsatisfactory comenisis. In these circumstances other treatments can be considered. For some patients, clinical observation may be considered an option. Non-surgical treatments have the drawback of not allowing full histological examination. A variety of treatments including topical 5-fluorouracil, retinoic acid, cryotherapy and laser ablation have been employed. Recurrence rates following cryotherapy are in the order of 0–34%. Topical treatment with imiquimod has been shown to be effective; a review of open label studies reported a clearance rate of 91%, although with very short follow-up periods.

Radiotherapy

Radiotherapy (RT) has been shown to provide high cure rates; however, these studies are restricted by their small size-limited follow-up and lack of histological confirmation of clearance. In contrast to surgery, RT has the advantage of being able to treat large lesions with wide margins.

In a European series, high doses of ‘soft’ X-rays (Grenz rays) (10–20 kilovolts [kV]) provided excellent outcomes with cure rates of 86–95%. In a large series of 96 patients with lentigo maligna treated with RT, only five patients experienced recurrences. A recent series reported 593 patients with lentigo maligna and early lentigo maligna melanoma. Treatment with Grenz rays as either radical or adjuvant therapy following excision provided complete clearance in 88% of patients. The German Cancer Society has recommended a Grenz ray therapy (12 kV) to a dose of 100–120 Gray (Gy), 10 Gy twice weekly for 5–6 weeks, when surgery is not considered appropriate.
Conventional superficial and orthovoltage X-rays have also been reported to be effective with recurrence rates of 0–14%. Tsang et al retrospectively reported the use of conventional orthovoltage RT in the treatment of 36 patients over a 20-year period. In the reported results, 27 patients received superficial X-rays up to 100 kV, with a 0.5–1 centimetre (cm) margin to a lead cut-out. The remaining nine patients received higher energy orthovoltage therapy up to 250 kV. Doses delivered were determined by the size of the lesion, and were the same as those used for the treatment of skin cancer; the most common doses were 35 Gy in five fractions over one week, 45 Gy in ten fractions over two weeks or 50 Gy in 15 fractions over three weeks. Responses were noted to be slow, over many months. With a median follow-up of six years, 32 of 36 patients had no evidence of recurrence; actuarial control probability was 86% at five years. In two of three patients treated with surgical excision after a failure to control the disease with RT, areas of invasive melanoma were detected. The authors therefore emphasised the importance of close follow-up, with a policy of excisional biopsy areas for any recurrent pigmentation. Late toxicity included mild alterations of pigmentation, areas of depigmentation, atrophy and telangiectasia. The cosmetic outcome in 11% of the patients was very poor. Radiobiology principles would suggest that schedules with smaller doses per fraction would provide better cosmetic outcomes, although at the cost of more inconvenient protracted schedules.

### Potential long-term effects of radiotherapy

The risk of a second 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 of 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

- Biopsy is recommended for diagnosis of lentigo maligna and exclusion of melanoma (Grade C).
- 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. RT provides high eradication rates if surgery is not considered appropriate (Grade C).
- RT treatment may be with superficial X-rays or electrons. 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. Typical schedules include 45 Gy in ten fractions over two weeks and 50 Gy in 15 fractions over three weeks (Grade C). Conventional fractionated RT may provide optimal long-term cosmetic results but at the cost of a more protracted treatment schedule. Histological evidence has shown that lentigo maligna can extend beyond clinically visible abnormality. Therefore treatment doses should be delivered to at least 1 cm around the clinically detectable lesion (Grade C).

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) (Appendix 2).
References


Hidradenitis suppurativa

Background

Hidradenitis suppurativa (HS) is a chronic disease characterised by recurrent, painful, deep-seated, rounded nodules and abscesses of apocrine gland-bearing skin. Subsequent suppuration, sinus tracts and hypertrophic scarring are prominent features. Onset is usually after puberty, although it is most common during the third decade and may persist into old age. The disease tends to be chronic and may develop to subcutaneous extension leading to indurations, sinus and fistula, having a profound impact on the quality of life. The prevalence in the population is approximately 1%. Axillary and inguinal involvement is more common in females, while involvement of the peri-anal and buttock areas is more prevalent in males. The exact aetiology remains unknown. The primary event is a follicular occlusion with secondary inflammation, infection and destruction of the pilosebaceo-apocrine apparatus and extension to the adjacent subcutaneous tissue. Infection is common. Shearing forces from obesity and tight clothing contribute to its development.

Management

Management depends on the stage of the disease. Early nodular lesions may be treated by antibiotics. Long-term antibiotics and zinc salts have been used as maintenance treatments. Anti-tumour necrosis factor (anti-TNF) drugs have been used in severe cases as well as steroids, oestrogens, anti-androgens and retinoids. Surgical treatment includes incision with or without drainage for limited abscesses. While there is a place for ‘conservative’ surgical procedures (including CO₂ laser) in selected cases of mild to moderate HS, radical excision of all apocrine-bearing tissue is the definitive treatment. Limited excisions are used for locally recurring draining sinuses. Total wide excision and healing with secondary intention or flaps and grafts is the only curative procedure in case of advanced disease.

Radiotherapy

Interest in the use of radiotherapy (RT) for HS has declined, but not completely, particularly in Germany. Frohlich et al reported on 231 patients undergoing RT for HS over a two-year period. Patients were treated with orthovoltage RT (175 kilovolts [kV]), with doses of 3.0–10.0 Gray (Gy) in 0.5–1.5 Gy fractions. Complete relief of symptoms at the end of RT was achieved in 89 patients (38%) and in 92 patients (40%) there was clear improvement of symptoms. Only two patients did not achieve symptomatic benefit with RT.

Recommendations

- Interest in RT for the treatment of HS has declined, and much of the literature dates back to before the 1950s, however, there is still some use of this modality in Germany.
- It is difficult to be sure how the use of RT including risks and benefits, could compare with modern antibiotics and surgical techniques.
- For a refractory case, with no alternative treatment, low-dose RT such as 10 Gy in 1.5 Gy fractions might be worth considering as a treatment option (Grade C).

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) (Appendix 2).

References

Psoriasis

Background

Psoriasis is a common chronic skin disease with a prevalence in the population of 2–3%. Psoriasis may also affect the joints and is an autoimmune disorder mediated by T-cell interactions with keratinocytes and other skin cells. The condition can also include mild to severe nail involvement. There is a subgroup of patients who have only nail psoriasis or whose nail psoriasis is the main manifestation of the disease. Of patients with psoriasis, approximately 40% have involvement of the nails.

Management

A wide variety of therapeutic interventions can be employed to treat psoriasis depending on the clinical circumstances. These include topical and systemic therapies. Therapeutic options include, for example, topical and intralesional corticosteroids and topical calcipotriol, ciclosporine, 5-fluorouracil and tazarotene. Systemic, mostly oral treatments, such as methotrexate and ciclosporine, may be very efficacious, but until now they have only been recommended in people with additionally diffuse skin or joint involvement because of the side-effects of these drugs. Other therapeutic approaches used are oral retinoids and ultra-violet (UV) phototherapy.

Radiotherapy

Historically, radiotherapy (RT) has been used to treat patients with recalcitrant disease that is resistant to other therapies, particularly nail bed lesions. Three trials have reported the effect of RT versus placebo on nail dystrophy.1-3 Lindelof studied 5 Gray (Gy) of Grenz rays in ten fractions weekly.1 Yu and King studied superficial RT 90 kilovolts (kV) given as three fractionated doses of 150 cGy every two weeks to a total of 450 cGy, and Kwang et al used electrons, with a total of 6 Gy given in eight fractions over eight weeks.2,3 In all three trials, with a total of 46 participants, a clinician assessed the severity nail psoriasis. After ten weeks, Lindelof (internally controlled study) showed a significantly better effect on psoriatic nails with Grenz ray therapy compared to placebo (P <0.05).1 However, the response was moderate. Of 22 assessable patients, one patient showed almost complete recovery; however, 14 participants showed no improvement at all. During the follow-up period of six months, there were no clear signs of further improvement.

Outcomes from treatment with RT have been included in a Cochrane review of treatments for psoriasis of the nail bed, published in 2013.4

Recommendations

- In the current era, RT is hardly ever used for psoriasis.
- There is some evidence for a moderate benefit, particularly for recalcitrant disease involving the nail beds and RT could be considered as a treatment if there were no other options.
- Dose fractionation regimens in the literature vary, but low-dose orthovoltage RT using an appropriate energy with fractions of 1–2 Gy, weekly or twice weekly to a total dose of 6–8 Gy would be appropriate (Grade B).

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) (Appendix 2).5

References

Chronic eczema

Background

Eczema is a term for a spectrum of conditions that result in the skin becoming inflamed or irritated. The most common type of eczema is known as atopic dermatitis or atopic eczema. The term ‘atopic’ refers to a group of diseases with an often inherited tendency to develop other allergic conditions, such as asthma and hay fever. Eczema affects about 10% to 20% of infants and about 3% of adults and children. In some cases the condition becomes chronic and hyperkeratotic, or associated with lichenification, with exaggerated skin markings.

General management

Most infants who develop the condition outgrow it by their tenth birthday, while a minority of patients continue to have symptoms on and off throughout life. A wide variety of topical agents are available, including corticosteroids.

Radiotherapy

Historically, radiotherapy (RT) has been employed as one of the treatments for hyperkeratotic and chronic lichenified eczemas. There is very limited recent literature on its use. In one study, the effect of superficial RT as an adjunct to topical therapy in recalcitrant chronic symmetrical palmar eczema was assessed in 15 patients by randomly allocating active treatment to one palm while the other, which received simulated therapy, served as a control. There was a significantly better response to active treatment at one month but this difference was no longer apparent at three and six months. In a series of 28 patients treated at Aarau, Switzerland, 22 with refractory eczema and six with psoriasis of palms and/or soles were irradiated twice weekly with either 0.5 or 1.0 Gray (Gy), median total dose 5–12 Gy.

The median age was 52 years (range: 27–71) and median follow-up was 20 months (range: 4–76 months). In total, 88 areas were treated. The severity of eight symptoms were scored out of 3, giving a possible total score of 24. The symptom score was 15 (6–23) before RT, two (0–16) at the end of RT, and one (0–21) at last follow-up, respectively. Improvement was reported in 83 of 88 (94%) areas treated, for all dose fractionation regimens. Five (6%) regions in three (11%) patients did not benefit from RT.

Recommendations

- Although historically RT has been employed for recalcitrant eczema, there is very little use of this modality today.
- There is very limited recent literature supporting the use of RT for chronic eczema.
- If there are no alternative options for chronic eczema, RT could be considered as an option in highly selected cases (Grade C).
- Using orthovoltage X-rays at a suitable energy a dose of 0.5 Gy twice weekly or 1.0 Gy weekly to a total dose of 4–5 Gy would be appropriate (Grade C).

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) (Appendix 2).

References

The use of radiotherapy for the prevention of gynaecomastia caused by hormonal therapy for prostate cancer

Background

Gynaecomastia is an enlargement of the male breast, and is caused by benign proliferation of the glandular component of the breast due to a change in the oestrogen:androgen activity ratio. In men with prostate cancer, it commonly follows treatment with oestrogens in metastatic disease. It can also be caused by androgen deprivation therapy (ADT), particularly with non-steroidal anti-androgen monotherapy (for example, bicalutamide), but also with leutinising hormone-releasing hormone analogues (LHRHa) with or without anti-androgen treatment.

Treatment for gynaecomastia

Overall, the treatment can be prophylactic, or given after gynaecomastia has already occurred. The mainstay of treatment is with either tamoxifen or radiotherapy (RT), with surgery reserved for cases where it is resistant to treatment and significantly affects the patient’s quality of life.

Prophylaxis of androgen deprivation therapy-induced gynaecomastia and mastalgia

Viani et al performed a meta-analysis examining the role of RT and tamoxifen in the prevention of ADT-related gynaecomastia and mastalgia. They identified five randomised controlled trials on the subject (Table 18). The overall results show that RT and tamoxifen are both effective at preventing gynaecomastia and mastalgia (Table 19, overleaf). Tamoxifen was found to be more effective than RT, with an increasing effectiveness of tamoxifen at higher doses. The Perdona trial was the only one directly comparing prophylactic RT with tamoxifen, and showed that the patients developed gynaecomastia at a rate of 69% on placebo, 8% with tamoxifen and 34% with RT.

Tunio et al performed a meta-analysis of trials looking at both prophylaxis and ‘definitive’ treatment of bicalutamide-induced gynaecomastia. This included ‘prospective controlled trials and retrospective analyses if well-controlled’, with nine studies being included in the analysis, five of which were included in the Viani meta-analysis. The other four are shown in Table 20, overleaf.

Widmark reported a study of patients randomised to complete androgen blockade (leuprorelin + flutamide) with or without RT to the prostate. Patients, non-randomly assigned, who were treated with breast bud RT, were less likely to develop gynaecomastia than those who were not (28% versus 71%).

Table 18. Randomised controlled trials evaluating the role of RT and tamoxifen for the prevention of androgen deprivation therapy-induced gynaecomastia and mastalgia (adapted from Viani et al)
Saltzstein et al randomised 107 men receiving bicalutamide following radical therapy for prostate cancer to tamoxifen 20 milligrams (mg)/day, anastrozole 1 mg/day or a placebo for three months, and then bicalutamide alone for nine months. Tamoxifen, but not anastrozole, significantly reduced the incidence of gynaecomastia/breast pain at three months compared with placebo (gynaecomastia incidence – tamoxifen 11.8%, anastrozole 63.9%, placebo 69.4%).

Bedognetti et al compared tamoxifen given daily with weekly administration (both at 20 mg per dose), and found that weekly treatment was inferior to daily treatment.

Van Poppel et al looked at treatment rather than prophylaxis of gynaecomastia, discussed below in the section on Treatment of established gynaecomastia after androgen deprivation therapy.

Van Poppel et al treated 51 patients with bicalutamide-induced gynaecomastia and/or mastalgia with two 6 Gray (Gy) fractions of RT to the breast buds, and found that there was improvement or resolution of gynaecomastia or breast pain in 33.3% and 39.5% respectively, and worsening in 33.3% and 21%.

Saltzstein et al, in the study mentioned in Table 20, found that in patients with established bicalutamide-induced gynaecomastia, tamoxifen was effective both in those who had previously been prescribed tamoxifen (65.4%; 17 of 26) and in those who had previously had a placebo (71.8%; 23/32).

### Table 19. Overall incidence of gynaecomastia and mastalgia in men with treated with androgen deprivation therapy (ADT): prophylactic radiotherapy versus tamoxifen versus controls (adapted from Viani et al)

<table>
<thead>
<tr>
<th></th>
<th>Gynaecomastia</th>
<th>Mastalgia</th>
<th>Gynaecomastia</th>
<th>Mastalgia</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control</td>
<td>62.2%</td>
<td>69.1%</td>
<td>74.8%</td>
<td>55%</td>
</tr>
<tr>
<td>Treatment</td>
<td>32.8%</td>
<td>49.2%</td>
<td>10.7%</td>
<td>7.4%</td>
</tr>
<tr>
<td>Absolute risk reduction</td>
<td>29.5%</td>
<td>19.9%</td>
<td>64.1%</td>
<td>47.6%</td>
</tr>
<tr>
<td>Number needed to treat</td>
<td>3.4</td>
<td>5</td>
<td>1.56</td>
<td>2.1</td>
</tr>
</tbody>
</table>

### Table 20. Studies included in meta-analysis of optimal therapy for bicalutamide-induced gynaecomastia that were not included in Viani et al meta-analysis (adapted from Tunio et al)

<table>
<thead>
<tr>
<th>Author (year)</th>
<th>Patients (n)</th>
<th>Intervention</th>
<th>Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Saltzstein (2005)</td>
<td>107</td>
<td>Tamoxifen versus anastrozole versus control</td>
<td>Tamoxifen – 20 mg</td>
</tr>
<tr>
<td>Van Poppel (2005)</td>
<td>51</td>
<td>RT versus control for established gynaecomastia</td>
<td>RT – 6 Gy/2 fractions</td>
</tr>
<tr>
<td>Bedognetti (2010)</td>
<td>80</td>
<td>Tamoxifen daily versus tamoxifen weekly</td>
<td>Tamoxifen – 20 mg</td>
</tr>
</tbody>
</table>
Oestrogen

The use of RT is effective in the prevention and the palliation of gynaecomastia for patients on oestrogen treatment for prostate cancer.\(^{12,13}\) In this case, tamoxifen is not used due to its anti-oestrogenic action.

Potential long-term consequences of radiotherapy

RT for gynaecomastia and mastalgia involves the use of a single low dose (10–12 Gy) to a relatively small radiation field administered to men, most of who are aged over 70. Therefore, the only issue relates to the long-term potential for radiation-induced cancer (RIC). However, given the age of this population this is unlikely to be clinically relevant as the risk of RIC will be extremely small.

Recommendations

- In prostate cancer patients on oestrogenic treatment, RT is reasonable to use for the prevention and palliation of gynaecomastia and mastalgia (Grade C).
- For prophylaxis of ADT-induced gynaecomastia and mastalgia:
  - Both tamoxifen and RT are effective as compared with placebo (Grade A)
  - Tamoxifen is more effective than RT (Grade A), but is associated with a long duration and cost of treatment
  - Tamoxifen should be given at a dose of 20 mg/day (Grade A)
  - RT is a reasonable option, including for those with a contraindication to tamoxifen, for example, those with a past history of thromboembolic disease or of stroke (Grade A).
- For treatment of ADT-induced gynaecomastia and mastalgia, both tamoxifen (Grade A) and RT (Grade C) can be effective at treating established gynaecomastia after ADT.
- Generally, RT is given as a single fraction of 10–12 Gy. Either electrons or superficial/orthovoltage treatment can be used.

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) (Appendix 2).\(^{14}\)
References


Summary and recommendations

- The primary aim of this document is to provide a summary of the evidence for the use of radiotherapy (RT) in a wide range of benign conditions, and in this respect it is hoped that the document will provide a useful resource for clinical oncologists who receive referrals for patients with these conditions.

- RT is established as a treatment modality for a number of benign tumours and it is assumed that the management of patients with the benign tumours reviewed in this document will already have been discussed in the relevant site-specific multidisciplinary team (MDT).

- There is an evidence base for the use of RT for a wide range of benign (non-neoplastic) conditions. However much of this evidence is categorised as Grade C, based largely on case reports, although randomised studies and systematic reviews exist in some areas.

- Many of the case series do not report long-term benefits and/or side-effects.

- The document has summarised the evidence for estimates of the risk of radiation-induced cancer (RIC). In most cases, the absolute risk is very small and needs to be balanced against the risk of morbidity from other treatments.

- Much of the evidence is in the RT literature and it is frequently difficult to be certain as to how the use of RT would fit into the overall multi-modality management of these conditions.

- It is hoped that this document will lead to a reappraisal of the role of RT for benign conditions. It is recommended that there should be discussion between clinical oncologists and representatives of other professional bodies at national and local levels.

- The professional groups with who this should be discussed would include ophthalmologists, orthopaedic surgeons, neurologists, dermatologists and urologists.

- It is recommended that RT departments should establish a team to review their protocols for the treatment of benign diseases including, where appropriate, the use of modern techniques.

- In view of the aging population, it is possible that RT could provide a useful treatment modality with low toxicity for patients with benign conditions in an age group where the risk of RIC is not clinically relevant.

- In England there should be discussion within the RT and stereotactic RT Clinical Reference Groups (CRGs) and the relevant commissioning organisations in Scotland, Wales and Northern Ireland regarding potential national approaches.

Approved by the Clinical Oncology Faculty Board: 26 June 2014
Appendix 1. Working party

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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 Scottish Intercollegiate Guidelines Network.1

<table>
<thead>
<tr>
<th>Grade</th>
<th>Recommendation</th>
<th>Level</th>
<th>Type</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>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</td>
<td>1++</td>
<td>High-quality meta-analyses, systematic reviews of RCTs, or RCTs with a very low risk of bias.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>1+</td>
<td>Well-conducted meta-analyses, systematic reviews of RCTs, or RCTs with a low risk of bias.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>1</td>
<td>Meta-analyses, systematic reviews of RCTs, or RCTs with a high risk of bias.</td>
</tr>
<tr>
<td>B</td>
<td>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+</td>
<td>2++</td>
<td>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</td>
</tr>
<tr>
<td></td>
<td></td>
<td>2+</td>
<td>Well-conducted case control or cohort studies with a low risk of confounding or bias and a moderate probability that the relationship is causal.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>2</td>
<td>Case control or cohort studies with a high risk of confounding or bias and a significant probability that the relationship is not causal.</td>
</tr>
<tr>
<td>C</td>
<td>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+</td>
<td>3</td>
<td>Non-analytical studies; eg, case reports, case series.</td>
</tr>
<tr>
<td>D</td>
<td>Evidence level 3 or 4; or extrapolated evidence from studies rated as 2’</td>
<td>4</td>
<td>Expert opinion</td>
</tr>
</tbody>
</table>

Reference
