



# Radiotherapy dose fractionation **Third edition**

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## Foreword

The *Radiotherapy dose fractionation guidance*, published in 2006, was heralded as 'the most important contribution that the Faculty has made to the practice of radiotherapy in the UK'. It was certainly highly successful and remains the most widely accessed guidance document from the Faculty of Clinical Oncology of all time. This is a tribute to the original working party, their commitment to providing an evidence- rather than tradition-based document and widespread involvement of Fellows with extensive open consultation prior to publication.

The second edition published in December 2016 reflected the changes in practice which had evolved in the previous decade. It remained faithful to the vision of the original document, focusing on clear evidence-based recommendations wherever possible. In total, 110 Fellows and a number of stakeholder groups contributed to the final version and we are grateful to all those who responded to the consultation.

The Professional Support and Standards Board (PSSB) review all RCR publications on a regular basis to ensure they remain up to date. This third edition has therefore been produced to take account of further published evidence. Many thanks to PSSB members and other colleagues for their work in ensuring this edition is up to date. There are particular updates to the chapters on central nervous system tumours, paediatric cancer and brain metastases with smaller changes in many of the other sections.

I would like to express particular thanks to Professor Peter Hoskin for so ably leading the development the second edition and this updated version and to members of his Working Group – Dr Jeanette Dickson, Dr Raj Jena, Dr Robin Prestwich and Dr Vivek Misra – for their extensive input and excellent contributions. Thanks are due also to the former RCR Officers who co-ordinated the second edition, Professor Roger Taylor and Dr David Bloomfield, and to Gillian Dollamore and Sarah Griffin at the RCR for all their tireless coordination, advice and support.

The document is available on the RCR website to enable easy and wide access. We hope it will meet with similar approval to its predecessors and will continue to provide a definitive guide to dose fractionation in the UK.

**Dr Tom Roques**, Medical Director for Professional Practice, Clinical Oncology, The Royal College of Radiologists

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## Introduction

The original guidance on *Radiotherapy dose fractionation* was introduced against a background of considerable variation in clinical practice across the UK.

Since that 2006 first edition there has been greater standardisation of treatment reflecting many influences, including more widespread appreciation of evidence-based practice, nationwide involvement in clinical trials addressing fractionation questions within the National Cancer Research Network and National Institute for Health Research and organisation of cancer care within networks charged with adherence to local and national guidelines.

Despite these advances, radiotherapy in the UK remains under-resourced both in terms of equipment and manpower, as evidenced by our standing in the recently published Health Economics in Radiation Oncology (HERO) analyses of European radiotherapy practice.<sup>1,2,3</sup> There is a continual challenge to upgrade linear accelerators to ensure modern therapy using intensity-modulated radiotherapy (IMRT), image-guided radiotherapy (IGRT) and stereotactic body radiotherapy (SBRT) can be delivered as routine to all appropriate patients in a system where resources for capital expenditure are severely limited.

It has been important to recognise that, despite changes to redefine fractionation during the past decade, many clinical scenarios, particularly for palliative treatments, will still require conventional therapy techniques and this is also reflected in these guidelines to ensure a comprehensive cover of clinical radiotherapy.

The second edition highlighted the role of combined-modality treatment and potential for stereotactic radiotherapy.

Brachytherapy may form part of the patient's treatment but was not considered further as part of this project.

The third edition includes particular updates on central nervous system tumours, brain metastases and paediatric cancers as well as smaller updates on other sections.

This document has graded evidence according to guidelines defined by the Oxford Centre for Evidence-Based Medicine as shown below.<sup>4</sup>

### Preparation of this document

The third edition has been reviewed by members of the RCR's Clinical Oncology Professional Support and Standards Board and the working party of the second edition to ensure that the guideline continues to reflect current practice at a time of rapid change in radiotherapy technologies.

Most of the guidance remains unchanged from the second edition which was subject to extensive peer review. The process for the review of this second edition, on which the content of this third edition is based, is summarised below:

#### First stage consultation

Reviewers, based on those who contributed to the 2006 document, two members of the RCR's Clinical Oncology Professional Support and Standards Board (PSSB) and additional site-specific experts, were invited to review the sections of the 2006 document relevant to their site specialty and to advise on current fractionation schedules and the new evidence base for these.

#### Second stage consultation

Each chapter was revised by the working group, taking account of comments received from reviewers. These revised chapters were sent to all those who had commented at the first stage of consultation and were also posted on the Clinical Oncology Online Fora on the RCR website.

All Clinical Oncology Fellows and members were notified by email of the review of the original document and invited to contribute their views on the revised chapters. A notice about the review was included in two editions of the RCR monthly news ebulletin.

### Third stage consultation

Following further editing in light of comments received, revised chapters were sent to stakeholder groups:

- British Association of Head and Neck Oncologists
- British Thoracic Society
- British Uro-oncology Group
- Children's Cancer and Leukaemia Group
- National Cancer Research Institute (NCRI) Clinical and Translational Radiotherapy Research Working Group (CTRad)
- Radiotherapy Clinical Reference Group

They were also sent to clinical oncology members of the following NCRI clinical studies groups:

- Bladder and renal cancer
- Breast cancer
- Brain tumour
- Colorectal cancer
- Gynaecological cancers
- Head and neck cancer
- Lung cancer
- Lymphoma
- Prostate cancer
- Sarcoma
- Skin cancer
- Testis cancer
- Upper gastrointestinal

Comments received from the above were again reviewed by the working group, leading to a final draft of the second edition which was published in 2016.

### Update of guidance – third edition

For this third edition, chapters were initially reviewed by the RCR's Clinical Oncology Professional Support and Standards Board, in consultation with other site-specialty experts as necessary. The review was not intended as a full peer review, but rather as a sense check of the document to ensure it continued to contain accurate and up-to-date information.

Suggested changes to the document were considered by Professor Peter Hoskin, lead author of the second edition, and the rest of the working party, and a final draft of this third edition was agreed.

### Comparison with the Malthus model<sup>5</sup>

The Malthus model is an evidence-based radiotherapy demand simulation tool, originally commissioned by the National Health Service in England (NHS England) in 2011. The model incorporates clinical decision trees which encode best practice for 22 different adult tumour types. The radiotherapy indications were established by a review of published

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literature and surveys of key opinion leaders. The most recent refresh of the clinical decision trees was undertaken in March 2014.

The Malthus team has undertaken a sense check of fractionation regimens referenced in this document. While a wider range of alternative fractionation regimens for specific indications are cited in this document, there is a high level of concordance in the cited fractionation regimens from both sources.

The salient differences are as follows:

- **Hypofractionation**

At release, the Malthus model defaulted to 2 Gray (Gy) per fraction regimens for curative indications with the exception of adjuvant breast radiotherapy, where robust evidence for hypofractionation from the the UK Standardisation of Breast Radiotherapy (START) trial and other studies was present.<sup>5,6</sup> The Malthus team acknowledged that stronger evidence now exists for hypofractionation in curative treatment of head and neck, and prostate cancer, as discussed in the relevant sections of this document.

- **Palliative treatment of head and neck cancer**

The use of 40 Gy in ten fractions as a split course, 21 Gy in three fractions over three weeks and 14 Gy in four fractions were not included in the Malthus decision tree. There is, however, a lack of high-quality evidence in this area and the regimens listed in the report are likely to reflect current practice from key opinion leaders in the UK.

Finally, it is important to emphasise that this is not a comprehensive text on radiotherapy. Limited background has been included to give each section context and where appropriate some detail of the evidence base from which the recommendations are derived has been given. We have deliberately avoided giving specific recommendations on treatment fields, volume or technique, which are considered to be outside the scope of this document.

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## Oxford Centre for Evidence-based Medicine<sup>1</sup>

### Grades of recommendation

<b>A</b>	Consistent level 1 studies	<b>C</b>	Level 4 studies or extrapolations from level 2 or 3 studies
<b>B</b>	Consistent level 2 or 3 studies or extrapolations from level 1 studies	<b>D</b>	Level 5 evidence or troublingly inconsistent or inconclusive studies of any level

*'Extrapolations' are where data is used in a situation that has potentially clinically important differences than the original study situation.*

### Levels of evidence

<b>1a</b>	SR (with homogeneity*) of RCTs	<b>3a</b>	SR (with homogeneity*) of case-control studies
<b>1b</b>	Individual RCT (with narrow confidence interval)	<b>3b</b>	Individual case-control study
<b>1c</b>	All or none <sup>§</sup>	<b>4</b>	Case-series (and poor-quality cohort and case-control studies <sup>§§</sup> )
<b>2a</b>	SR (with homogeneity*) of cohort studies	<b>5</b>	Expert opinion without explicit critical appraisal, or based on physiology, bench research or 'first principles'
<b>2b</b>	Individual cohort study (including low quality RCT; for example, <80% follow-up)		SR: systematic review
<b>2c</b>	'Outcomes' research; ecological studies		RCT: randomised controlled trial

\* In this context, homogeneity means a systematic review that is free of worrisome variations (heterogeneity) in the directions and degrees of results between individual studies. Not all systematic reviews with statistically significant heterogeneity need be worrisome, and not all worrisome heterogeneity need be statistically significant. As noted above, studies displaying worrisome heterogeneity should be tagged with a '-' at the end of their designated level.

§ Met when all patients died before the treatment became available, but some now survive on it; or when some patients died before the Rx became available, but none now die on it.

§§ In this context, poor-quality cohort study means one that failed to clearly define comparison groups and/or failed to measure exposures and outcomes in the same (preferably blinded), objective way in both exposed and non-exposed individuals and/or failed to identify or appropriately control known confounders and/or failed to carry out a sufficiently long and complete follow-up of patients. In this context, poor quality case-control study means one that failed to clearly define comparison groups and/or failed to measure exposures and outcomes in the same (preferably blinded), objective way in both cases and controls and/or failed to identify or appropriately control known confounders.

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# 1.

## Anal cancer

### Background

There are approximately 1,000–1,200 registrations of squamous carcinoma of the anus per year in the UK. Despite its rarity, a succession of phase III trials have been conducted which have established the standard treatment of this disease; radical treatment with chemoradiotherapy allowing sphincter preservation.

### Radical treatment

Both the United Kingdom Co-ordinating Committee on Cancer Research (UKCCCR) anal cancer trial (45 Gray [Gy] in 20 or 25 fractions with a boost) and an European Organisation for Research and Treatment of Cancer (EORTC) trial demonstrated improved outcome for concomitant chemoradiotherapy using mitomycin C and 5-fluorouracil (5-FU) when compared with radiotherapy alone.<sup>1,2</sup> A statistically significant reduction in locoregional failure was demonstrated in both trials. A further phase III trial performed by the Radiotherapy Oncology Group (RTOG) demonstrated improved colostomy-free survival when mitomycin C was added to 5-FU chemoradiation.<sup>3</sup> Chemoradiotherapy improves outcome in anal cancer compared to radiotherapy alone (Level 1b).<sup>4</sup>

The UKCCCR ACT2 trial compared concomitant mitomycin C and 5-FU with cisplatin and 5-FU when combined with a two-phase radiotherapy technique delivering a total dose of 50.4 Gy in 28 fractions.<sup>5</sup> A second randomisation tested the role of two subsequent cycles of cisplatin 5-FU chemotherapy against no further treatment. There was no significant difference between concurrent chemotherapy regimens, and no progression-free survival benefit to the addition of adjuvant chemotherapy (Level 1b).<sup>4</sup>

The EXTRA trial was a phase II study substituting capecitabine for 5-FU chemotherapy that reported minimal toxicity and acceptable compliance.<sup>6</sup> Substitution of 5-FU with capecitabine has been thoroughly investigated in other tumour sites and the two drugs have been proven to be equally effective (Level 2b).<sup>4</sup>

### Treatment technique

The phase 2 RTOG 0529 trial treated patients with inverse planned intensity-modulated radiotherapy (IMRT) and reported reduced toxicity to that seen in the RTOG 9811 trial where standard conformal radiotherapy techniques were used (Level 2b).<sup>4,7,8</sup>

It is recommended that a standard atlas for delineating volumes is used for IMRT or arc radiotherapy. Expert opinion was sought from a number of UK clinicians to create a consensus guideline which is based on ACT II volumes but adapted for inverse planning.<sup>9,10</sup>

### Recommendations

#### **For standard planned two-phase radical chemoradiation for anal cancers:**

50.4 Gy in 28 daily fractions (Grade A)

**Phase 1:** 30.6 Gy in 17 fractions over 3.5 weeks

**Phase 2:** 19.8 Gy in 11 fractions over 2.2 weeks

The types of evidence and the grading of recommendations used within this review are based on those proposed by the Oxford Centre for Evidence-based medicine.<sup>4</sup>

### Node positive patients

Analyses of both the UKCCR ACT II and RTOG 9811 trial have highlighted that locally advanced and node-positive tumours have a significantly reduced disease-free survival and overall survival.<sup>5,8</sup> As a result, current guidance and recent trials have used a higher dose for these patients when using IMRT or arc radiotherapy.

However, due to the excellent outcomes in ACT II in node-negative cancers, the recommended prophylactic nodal dose remains the same and has been calculated to deliver the same biologically effective dose over 28 fractions with IMRT or arc radiotherapy which was previously delivered over 17 fractions during standard 2-phase radiotherapy (Level 5).<sup>4,11</sup>

#### Recommendations

##### **For radical inverse planned IMRT or arc radiotherapy (chemoradiotherapy) of anal cancers**

###### **Dose to primary (early stage):**

50.4 Gy in 28 fractions over 5.5 weeks (Grade D)

###### **Dose to primary and involved nodes (advanced stage):**

53.2 Gy in 28 fractions over 5.5 weeks (Grade D)

###### **Dose to uninvolved nodes (prophylactic):**

40 Gy in 28 fractions over 5.5 weeks (Grade D)

The types of evidence and the grading of recommendations used within this review are based on those proposed by the Oxford Centre for Evidence-based medicine.<sup>4</sup>

The Personalising Anal Cancer Radiotherapy Dose (PLATO) trial looking at dose escalation in locally advanced anal cancers and dose de-escalation in early small-node negative tumours is currently in set up in the UK and will inform dose fractionation for anal cancers in the future.<sup>12</sup>

### Palliative treatment

There are no good-quality trials evaluating different dose fractionation schedules for palliative treatment. An appropriate regime should be chosen after considering the patient's likely prognosis, disease burden, symptoms and performance status.

#### Recommendations

##### **For palliative treatment of anal cancer (Grade D):**

30 Gy in 10 fractions over 2 weeks

20 Gy in 5 fractions over 2 weeks

The types of evidence and the grading of recommendations used within this review are based on those proposed by the Oxford Centre for Evidence-based medicine.<sup>4</sup>

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## 2. Bladder cancer

### Radical treatment

#### Conventional fractionation (dose per fraction 1.8–2.0 Gray [Gy])

The radiotherapeutic regimens used in studies comparing radiotherapy and surgery for bladder cancer have been delivered using either a conventional regimen of 60–64 Gy in 30–32 fractions over 6–6.5 weeks or hypofractionated radiotherapy of 52.5–55 Gy in 20 fractions (Level 2b).<sup>1–5</sup>

#### Hyperfractionation

Two published trials compare hyperfractionation with doses of 1–1.2 Gy per fraction to conventionally fractionated treatment.<sup>6,7</sup> Pooled analysis suggests a significant benefit from hyperfractionation with a 17% (95% confidence interval, 6–27%) improvement in the rate of local control.<sup>8</sup> However, the regimens in both arms of these studies used split courses with overall treatment times of eight weeks. This approach would no longer be considered acceptable in a control arm (Level 1b).<sup>5</sup>

#### Accelerated fractionation

There was no evidence of clinical benefit from 60.8 Gy in 32 fractions given using two fractions per day of 1.9 Gy over a treatment time of 26 days when compared to a standard regime of 64 Gy in 32 fractions over 45 days.<sup>9</sup> The shorter regimen was associated with a higher rate of intestinal toxicity (Level 1b).<sup>5</sup>

#### Hypofractionation

The two UK-based randomised controlled trials published in the last five years allowed the use of both conventional (60 Gy in 30 fractions) and hypofractionated radiotherapy (55 Gy in 20 fractions).<sup>10,11</sup> Although neither study was powered to detect a difference in outcome based on dose and fractionation, there was no difference seen between conventional and hypofractionated radiotherapy (Level 2b).<sup>5</sup>

#### Partial bladder irradiation

Partial bladder radiotherapy has been studied in two UK-based trials. A trial from Manchester compared whole bladder radiotherapy 52.5 Gy in 20 fractions with partial bladder irradiation of 57.5 Gy in 20 fractions and 55 Gy in 16 fractions.<sup>12</sup> There was no significant difference in local control at five years between the three groups, and late toxicity was similar in all three arms. The BC2001 sub-study compared whole bladder high-dose irradiation with reduced high-dose volume radiation therapy.<sup>13</sup> There was no difference in locoregional recurrence, late toxicity or overall survival between the two groups (Level 1b).<sup>5</sup>

#### Radical radiotherapy with radiosensitisation

Two UK-based randomised control trials have demonstrated that radical radiotherapy with a radiosensitiser improves outcomes compared to radiotherapy alone.<sup>10,11</sup> BC2001 compared radical radiotherapy alone with radical radiotherapy given concurrently with mitomycin C and 5-fluorouracil (5-FU), with the chemoradiotherapy arm showing significantly better two-year locoregional recurrence rates of 67% versus 54% (Level 1b).<sup>5,10</sup> The Bladder Carbogen Nicotinamide (BCON) investigators compared radical radiotherapy alone to radical radiotherapy given concurrently with carbogen and nicotinamide with a significant improvement in three-year overall survival of 13% in the experimental arm (Level 1b).<sup>5,11</sup> Some centres within the UK use a weekly gemcitabine chemoradiation protocol based on a multicentre phase II study which has shown acceptable toxicity and comparable outcomes

to those in the literature with a three-year overall survival of 75% and 88% achieving a complete endoscopic response at first check cystoscopy (Level 2b).<sup>5,14</sup>

### Treatment technique

The size of the planning target volume (PTV) is critical to any discussion of dose and fractionation.<sup>15,16</sup> Some centres use a two-phase (large pelvic volume/small bladder volume) approach, although there is no robust evidence for this approach improving survival outcomes for patients (Level 5).<sup>5</sup> There is no published evidence using fraction sizes other than 1.8–2 Gy for this approach. All of the dose-fractionation regimens discussed below are based on the assumption that the PTV is <1,000 millilitres (ml) and that three-dimensional (3-D) image-based planning techniques are used. There is also increasing use of adaptive radiotherapy techniques for bladder treatment using a 'plan of the day' based on imaging prior to delivery of each fraction. The fractionation evidence has not been tested in this setting, but there is no reason to believe that the recommendations below do not apply to the adaptive setting also.

### Recommendations

#### For radical radiotherapy to the bladder:

52.5–55 Gy in 20 fractions over 4 weeks

60–64 Gy in 30–32 fractions over 6–6.5 weeks (Grade B)

There is robust evidence that radiotherapy with a radiosensitiser using carbogen and nicotinamide or chemotherapy improves outcomes for patients with organ-confined muscle-invasive bladder cancer (Grade A)<sup>10,11</sup>

The types of evidence and the grading of recommendations used within this review are based on those proposed by the Oxford Centre for Evidence-based medicine.<sup>5</sup>

### Palliative radiotherapy

The Medical Research Council (MRC) randomised trial BA09 clearly established that 21 Gy in three fractions on alternate weekdays in one week (4–6 elapsed days) is as effective as 35 Gy in ten fractions in two weeks in palliating symptoms in patients with bladder cancer.<sup>17</sup> There was no statistically significant difference in the rate of symptom relief (64% versus 71%;  $p=0.192$ ; 95% confidence interval for the 7% rate difference, –2% to +13%), nor was there any significant difference in the duration of symptomatic relief (Level 1b).<sup>5</sup> Other palliative regimes which are in use in the UK are 20 Gy in five fractions and 30–36 Gy in 5–6 fractions over 5–6 weeks (Level 2-).<sup>5</sup> These regimes are also used for frail patients not fit for radical radiotherapy treatment.

In the hypofractionated bladder radiotherapy with or without image-guided adaptive planning (HYBRID) trial, a dose of 30–36 Gy in 5–6 fractions given weekly has been used.

For very frail patients, a 6–8 Gy single fraction of pelvic radiotherapy often provides symptomatic relief (Level 4).<sup>5</sup>

## Recommendations

### **For the palliation of local symptoms from bladder cancer:**

21 Gy in 3 fractions on alternate days in 1 week is the regimen of choice (Grade A)

30–36 Gy in 5–6 fractions weekly has also been used in this setting (Grade D)

A single fraction of 6–8 Gy may provide useful palliation in patients who are unfit for the recommended regimen (Grade D)

The types of evidence and the grading of recommendations used within this review are based on those proposed by the Oxford Centre for Evidence-based medicine.<sup>5</sup>

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## 3. Breast cancer

### Background

Breast cancer is the most common cancer in women in the UK and most patients are diagnosed at an early stage due to the NHS Breast Screening Programme. Radiotherapy has long been established as an important treatment modality in the adjuvant and palliative setting in breast cancer. Technological advances and results of pivotal trials have led to significant changes in practice in the UK in the last few years.

### Adjuvant radiotherapy to the breast or chest wall

Radiotherapy increases both local control and overall survival in the conservation management of primary breast cancer in selected patients after mastectomy (Level 1a).<sup>1-3</sup> It also reduces ipsilateral breast tumour recurrence following breast conservation in patients with a diagnosis of ductal carcinoma *in situ* (DCIS).<sup>4,5</sup>

Although radiotherapy reduces the risk of recurrence for both DCIS and invasive disease for all patient groups, given the small benefits of adjuvant radiotherapy following breast-conserving surgery in low-risk patient groups, it is reasonable to consider omission of radiotherapy in patients with oestrogen receptor positive, node negative tumours which are less than 3 centimetres (cm) in maximum diameter and who are aged over 70 years, with low-risk biological features such as low-grade, no lymphovascular invasion and HER-2 negativity (Level 1b).<sup>3,6,7</sup>

The previous standard breast fractionation was a regimen of 50 Gray (Gy) in 25 fractions over five weeks as reported in the National Surgical Adjuvant Breast and Bowel Project (NSABP) breast cancer trials.<sup>8</sup> Currently the most widely used UK regimen is the hypofractionated regimen of 40 Gy in 15 fractions over three weeks as used in the UK START Study B.<sup>9</sup> Mature data from the START B trial and a Canadian study demonstrate the equivalence of hypofractionated regimens to the previous standard of 2 Gy daily fractionation (Level 1b).<sup>3,10</sup>

There are no trials comparing 40 Gy in 15 fractions versus 50 Gy in 25 fractions following breast reconstruction, but there is no radiobiological reason to recommend 50 Gy in 25 fractions in this situation. The results of the START B trial demonstrate that 40 Gy in 15 fractions leads to fewer late effects.<sup>9</sup>

#### Recommendation

##### **For adjuvant radiotherapy of breast or chest wall:**

40 Gy in 15 daily fractions of 2.67 Gy over 3 weeks (Grade A)

The types of evidence and the grading of recommendations used within this review are based on those proposed by the Oxford Centre for Evidence-based medicine.<sup>3</sup>

Further hypofractionation for breast radiotherapy is currently under investigation. In the FAST study, 915 women aged  $\geq 50$  years with node negative early breast cancer were randomly assigned after microscopic complete tumour resection to 50 Gy in 25 fractions versus 28.5 or 30 Gy in five, once-weekly fractions of 5.7 or 6.0 Gy respectively, to the whole breast. The primary endpoint was two-year change in photographic breast appearance. At three years median follow-up, 28.5 Gy in five fractions was comparable to 50 Gy in 25 fractions, and significantly milder than 30 Gy in five fractions, in terms of adverse effects in



the breast. There were two local recurrences which were both in the 50 Gy in 25 fractions arm. Mature local recurrence and late effects data are awaited.<sup>11</sup>

The FAST Forward trial is investigating 40 Gy in 15 fractions versus 26 or 27 Gy in five fractions over one week. The main trial closed in 2014. Five-year local control data will be available in 2019. The FAST Forward nodal study opened in 2015 with normal tissue endpoints.<sup>12</sup> In 2018, this was modified to a two-arm study comparing 40 Gy in 15 fractions over three weeks against 26 Gy in five fractions over one week.

### Partial breast irradiation

It is recognised that whole-breast radiation (WBI) can cause significant toxicity in patients with large breasts. Partial breast radiation may improve this outcome, though accelerated partial breast irradiation (APBI) could reduce acute and late side-effects. A meta-analysis has shown that APBI is associated with a higher local recurrence rate, albeit still low, compared to WBI (Level 1a).<sup>13</sup> However, this meta-analysis included studies covering a broad range of APBI techniques and selection criteria. The UK Intensity Modulated and Partial Organ Radiotherapy Following Breast Conservation Surgery for Early Breast Cancer (IMPORT LOW) Trial compared two schedules of partial breast radiation versus whole-breast 40 Gy in 15 fractions and was presented at the European Breast Cancer Conference in March 2016.<sup>14</sup> For each of the test groups, non-inferiority, assessed against the prespecified 2.5% threshold, was demonstrated. Local relapse (LR) rates were very low across all groups, as were moderate/marked normal tissue events, with a statistically significant improvement for breast appearance and breast hardness (median follow-up 72 months) for partial breast radiotherapy.

Two trials of intraoperative radiation therapy (IORT) have reported: the External Radiotherapy for Early Breast Cancer (ELIOT) trial reported an ipsilateral breast tumour recurrence rate of 4.4% at five years with IORT and 0.4% with WBI.<sup>15</sup> This gave a hazard ratio for ipsilateral relapse with IORT of 9.3 (95% confidence interval [CI] 3.3–26.3) compared to WBI. The TARGIT A trial has insufficient median follow up to draw firm conclusions (Level 2b).<sup>3,16</sup>

Multicatheter interstitial brachytherapy is an alternative approach to APBI. One large non-inferiority trial has shown equivalence at five years with a predefined 3% difference comparing APBI with interstitial brachytherapy and whole-breast radiotherapy to 50 Gy in 25 fractions.<sup>17</sup>

### Breast boost

Delivery of a boost to the tumour bed following whole-breast radiotherapy reduces the risk of ipsilateral breast cancer recurrence (Level 1b).<sup>3,18</sup> However, there is no impact on overall survival and it doubles the risk of moderate or severe fibrosis.

The proportional benefit is similar across all age groups but the absolute benefit falls with increasing age and hence the biggest absolute benefit is in women under 50 years of age. There is also a greater absolute benefit of boost in high-grade (G3) cancer.

Incomplete resection margins, where further surgery is not possible, are an indication for breast boost regardless of age. A boost dose of 16 Gy in eight fractions or equivalent is most commonly prescribed.<sup>18</sup>

A multidisciplinary consensus meeting held at The Royal College of Radiologists (RCR) in March 2016 concluded that it would be reasonable for the boost dose to be hypofractionated, as given in 40 Gy in 15 fractions breast dose, rather than 2 Gy fractionation. A dose of 16 Gy in eight fractions is equivalent to a hypofractionated dose of 13.35 Gy in five fractions of 2.67 Gy or 12 Gy in four fractions of 3 Gy assuming an alpha/beta value for breast carcinoma of 3 Gy.

Appreciation of the volume of the boost and the need for accurate delivery was emphasised. It is recognised that there is no direct clinical trial evidence for this approach.

The UK dose-escalated, intensity-modulated radiotherapy (IMRT) for women treated by breast conservation surgery and appropriate systemic therapy for early breast cancer (IMPORT-HIGH) trial closed in 2015. Patients were randomised to sequential versus simultaneous integrated boost (IMRT and image-guided radiotherapy [IGRT]) including dose escalation.<sup>19</sup>

The breast boost volume should be defined by localising the tumour bed. Surgical clips should be routinely placed during a wide local excision to aid localisation of the tumour bed.

There is currently insufficient evidence to recommend IORT for tumour bed boost; the TARGIT B trial is currently recruiting (Clinical Trials Group, University College London, UK Clinical Research Network ID 14208) and randomising to convention external beam boost versus IORT boost in high-risk disease.<sup>20</sup>

### Radiotherapy technique

Two-dimensional (2-D) computed tomography-based planning is no longer recommended for adjuvant radiotherapy to the breast or chest wall.

Simple, forward-planned, field-in-field IMRT reduces the late toxicity and improves cosmetic outcome following adjuvant whole-breast radiotherapy (Level 1b).<sup>3,21</sup>

Breast radiotherapy may increase the risk of heart disease.<sup>22,23</sup> For most women irradiated in the UK, the absolute risk of developing radiation-induced heart disease is less than 1% at 20 years, but risk varies according to a woman's pre-existing risk of heart disease and her heart radiation dose. Techniques to limit heart dose without reducing target dose should be considered for women with left-sided breast cancer. These include multileaf collimation (MLC) cardiac shielding and voluntary breath holding (Level 2b).<sup>3,24</sup>

### Recommendations

#### **For boost after whole-breast radiotherapy in women with a higher risk of local recurrence:**

16 Gy in 8 daily fractions of 2 Gy (Grade A) or an equivalent hypofractionated schedule:<sup>3</sup>

13.35 Gy in five fractions of 2.67 Gy or 12 Gy in four fractions of 3 Gy (Grade C)

The types of evidence and the grading of recommendations used within this review are based on those proposed by the Oxford Centre for Evidence-based medicine.<sup>3</sup>

## Regional nodal irradiation

### Axilla and supraclavicular fossa

Axillary sentinel lymph node biopsy (SLNB) is now the British Association of Surgical Oncologists (BASO) recommended standard procedure for axillary staging in early breast cancer with clinically negative lymph nodes. For most patients with clinically positive nodes a level III axillary lymph node dissection (ALND) remains the standard procedure.

Nodal irradiation is not recommended following a negative SLNB.

Following a positive SLNB, the AMAROS trial demonstrated an axillary recurrence rate of 0.43% for ALND versus 1.19% for axillary radiotherapy after a median follow-up of 6.1 years.<sup>25</sup> The trial was underpowered for the planned non-inferiority test due to the low number of events. Axillary radiotherapy produced lower long-term toxicity compared to ALND (Level 2b), though the effects of RT on cardiovascular health and second malignancies in this study are not known.<sup>3,25</sup>

The American College of Surgeons Oncology Group (ACOS-OG) Z0011 trial demonstrated a low axillary recurrence rate of 0.9% versus 0.5% for SLNB + standard breast RT compared to SLNB followed by ALND + standard breast RT in a RCT comparing ANLD versus no axillary treatment in women with T1/T2 N0 breast cancer undergoing breast-conserving treatment.<sup>27</sup> Most patients were over 50 years of age and had grade 1 or 2, T1, oestrogen receptor positive, ductal cancer with no LVI (Level 2b).<sup>3,26</sup> However, there are significant methodological concerns about the Z0011 trial, including the statistical power of the study. There was a potential for bias in this study as the radiation oncologists were aware of the treatment allocation and it is unclear whether this influenced their decision about how much of the axilla to treat with tangential radiotherapy. Generalisability of the results is limited as some centres recruited fewer than five patients, axillary recurrence was not a prespecified endpoint, mastectomy patients were excluded and preoperative axillary ultrasound was not performed in contrast to standard UK practice.

The UK pragmatic, randomised, multicentre, non-inferiority trial (POSNOC) trial is currently recruiting patients with 1–2 positive sentinel lymph nodes and randomising them to standard adjuvant therapy *and* axillary treatment (ALND or axillary radiotherapy) versus standard adjuvant therapy alone. The primary endpoint is axillary recurrence at five years. When available, the results will provide a more definitive answer to the question of managing a positive SLNB axilla.<sup>27</sup>

Radiotherapy to the ipsilateral supraclavicular fossa (SCF) is recommended for N2 or N3 disease following ALND. Axillary radiotherapy following ALND produces significant toxicity and should only be recommended in women with very high risk of recurrence (high proportion of involved nodes, extensive extra-nodal disease or biologically aggressive cancer). There is no evidence that radiotherapy to the axilla following ALND improves overall survival from breast cancer.

The North American MA20 trial randomised node positive or high-risk node-negative patients to WBI versus WBI plus regional nodal irradiation (RNI) including the ipsilateral axilla, SCF and internal mammary chain, dose 50 Gy in 25 fractions.<sup>28</sup> It demonstrated improved disease-free survival (DFS) in the RNI group (82% versus 77%, hazard ratio [HR] 0.76,  $p=0.01$ ) after a median follow-up of 9.5 years. The primary end point of improved overall survival was not met. There was a small absolute increase in the risk of acute pneumonitis and late lymphoedema in the RNI group (Level 1b).<sup>3,28</sup>

The EORTC 22922/10925 trial randomised patients with medial or centrally located breast cancers irrespective of nodal status or node-positive lateral tumours to WBI/chest wall irradiation versus WBI/chest wall irradiation plus RNI defined as ipsilateral medial SCF and internal mammary nodes, dose 50 Gy in 25 fractions.<sup>29</sup> After a median follow-up of ten years, it demonstrated an improvement in DFS in the RNI group (72.1% versus 69.1%, HR 0.89,  $p=0.04$ ). The primary end point of improved overall survival was not met (Level 1b).<sup>3,29</sup>

Both the MA20 and EORTC 22922/10925 trials demonstrated improved distant-disease-free survival, but this did not translate to improved overall survival and the long-term effects of RNI on cardiovascular morbidity and mortality and second cancer rates in these trials is not known. However a meta-analysis of these studies published before the full results became available suggests an improvement in overall survival (Level 1a-), although this analysis was not conducted with patient level data. A Danish population based non-randomised cohort study has shown improved survival with internal mammary nodal (IMN) irradiation especially in women with larger (>50 millimetres [mm]) tumours or with more than four involved nodes (Level 2b).<sup>3,30,31</sup> Hence RNI to include the internal mammary chain along with ipsilateral axilla and SCF may be considered for patients fitting the MA20 and EORTC 22922/10925 criteria to reduce breast cancer recurrence, but careful patient selection is advised and the lack of data on cardiac effects of IMN irradiation and second cancers should be taken into account.<sup>28-31</sup>

Data for hypofractionated nodal irradiation is limited to small subsets of patients from RCTs (14% in START A, 7% in START B) but shows no increase in toxicity compared to standard fractionation nodal irradiation (Level 1b-).<sup>3,32</sup>

### Recommendation

#### Where indicated, for regional nodal irradiation:

40 Gy in 15 daily fractions (Grade B)

The types of evidence and the grading of recommendations used within this review are based on those proposed by the Oxford Centre for Evidence-based medicine.<sup>3</sup>

### Palliative treatment

There are no good-quality head-to-head trials evaluating the optimum schedules for palliative radiotherapy to the breast, chest wall or regional nodes. The most common doses range from 20 Gy to 40 Gy over 5–15 fractions. Weekly treatments over 5–6 weeks to a total of 30–36 Gy are also commonly used (Grade D).<sup>3</sup>

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## 4.

### Central nervous system (CNS) tumours

#### Background

Three important considerations underpin the choice of treatment fractionation in neuro-oncology. First, the results of treatment vary widely and, second, the brain and spinal cord are susceptible to late radiation damage which is strongly dependent on radiation dose per fraction. The Quantitative Analysis of Normal Tissue Effects in the Clinic (QUANTEC) papers published in 2010 provide details of normal tissue tolerances for brain, brainstem, optic nerves and chiasm, hearing and spinal cord.<sup>1–9</sup> Patients with a life expectancy of more than 12–18 months are rarely treated with doses per fraction greater than 2 Gray (Gy). With increased use of inverse planned intensity-modulated radiotherapy (IMRT), consideration must be given to appropriate dose constraints to serial structures, balancing tumour control against risk of toxicity. Finally, our understanding of tumours, in particular the gliomas, has changed substantially recently, and there is clearly a key role for isocitrate dehydrogenase (IDH) mutations and chromosomal (1p/19q) codeletions. This is likely to further evolve over time.

#### High-grade glioma

##### Radical treatment

Retrospective analyses and one randomised trial have demonstrated a dose–response relationship for high-grade glioma up to, but not beyond, 60 Gy in 30 fractions.<sup>10–12</sup> This has led to the adoption of the dose regimen of 60–65 Gy delivered in 1.8–2.0 Gy fractions as standard in the therapy of better prognosis patients with high-grade malignant glioma. Further attempts to improve response through hyperfractionation or accelerated fractionation have not demonstrated a significant survival benefit.<sup>13,14</sup> The addition of temozolomide to radiotherapy for newly diagnosed glioblastoma has been shown to improve overall and progression-free survival.<sup>15</sup> The first trial only included patients under the age of 70. However, a subsequent study included older patients and found similar benefits from the addition of temozolomide.<sup>16</sup>

For World Health Organization (WHO) grade III gliomas with 1p and 19q chromosomal co-deletion, the addition of procarbazine, lomustine and vincristine (PCV) chemotherapy, either before or after radiotherapy, has recently been shown to improve overall survival.<sup>17,18</sup> The addition of temozolomide after radiotherapy has been shown to improve survival in patients with grade III non-1p 19q co-deleted tumours and final results of this trial are still awaited. Recent trials for grade III glioma (anaplastic oligodendroglioma and oligoastrocytoma, and non-1p19q co-deleted WHO grade III glioma) have all used a radiotherapy dose of 59.4 Gy in 33 fractions, providing Level 2a evidence for this regimen in WHO grade III glioma.<sup>19–22</sup> Previous dose determination studies in high-grade gliomas used a dose of 60 Gy in 30 fractions for grade III gliomas.<sup>11,20</sup>



### Recommendations

#### **For patients of good performance status:**

##### **WHO Grade IV glioma (GBM)**

60 Gy in 30 daily fractions over 6 weeks (Grade A)

##### **WHO Grade III glioma**

59.4 Gy in 33 fractions over 6.5 weeks (Grade A)

60 Gy in 30 fractions over 6 weeks (Grade B)

The types of evidence and the grading of recommendations used within this review are based on those proposed by the Oxford Centre for Evidence-based medicine.<sup>19</sup>

### Palliative treatment

Increasing age is a significant negative prognostic factor for patients with glioblastoma. Several trials in older patients have evaluated shorter courses of radiotherapy. One randomised trial which recruited patients aged  $\geq 60$  of Karnofsky Performance Status (KPS)  $\geq 50$  showed similar survival for 40 Gy in 15 fractions over three weeks compared to 60 Gy in 30 fractions.<sup>21</sup> In another randomised trial in patients aged  $\geq 60$  principally of WHO performance status 0–2, 34 Gy in ten fractions appeared to have similar survival rates in patients over 60 and better survival in patients over 70 than 60 Gy in 30 fractions of radiotherapy alone.<sup>23</sup> Shorter fractionations are therefore an option in elderly patients unsuitable for chemo-radiotherapy. The recent results using 40 Gy in 15 fractions in older patients combined with concurrent and adjuvant temozolomide suggest that this may be the best option in fit, older patients.<sup>16</sup>

For patients with high-grade glioma and poor performance status, when treatment is indicated, hypofractionated treatments are used.<sup>24,25</sup> The most commonly adopted regimen in the UK is 30 Gy in six fractions over two weeks.

### Recommendations

#### **Elderly patients with glioblastoma unsuitable for chemo-radiotherapy:**

40 Gy in 15 fractions over 3 weeks (Grade A)

34 Gy in 10 fractions over 2 weeks (Grade B)

30 Gy in 6 fractions over 2 weeks (Grade C)

#### **For patients of poor performance status being treated for high-grade glioma:**

30 Gy in 6 fractions over 2 weeks (Grade C)

The types of evidence and the grading of recommendations used within this review are based on those proposed by the Oxford Centre for Evidence-based medicine.<sup>19</sup>

### Low-grade glioma

For low-grade glioma, two prospective randomised dose comparison trials have demonstrated no difference in outcome between 45 Gy in 25 fractions and 59.4 Gy in 33

fractions and between 50.4 Gy in 28 fractions and 64.8 Gy in 36 fractions.<sup>26,27</sup> As a result, a standard dose of 50.4 Gy in 28 fractions of 1.8 Gy is accepted practice in the UK and internationally. A dose of 54 Gy in 30 fractions over six weeks was used in a randomised study of the timing of radiotherapy and also in the Radiation Therapy Oncology Group (RTOG) 9802 randomised trial which showed an overall survival benefit for the addition of adjuvant procarbazine, lomustine and vincristine (PCV) chemotherapy after radiotherapy for high-risk low-grade glioma (age 18–39 and incompletely resected, or age  $\geq 40$  with any extent of resection).<sup>28,29</sup> This provides Level 2b evidence for this regimen.<sup>19</sup>

### Recommendations

50.4 Gy in 28 daily fractions over 5.5 weeks (Grade A)

54 Gy in 30 daily fractions over 6 weeks (Grade B)

The types of evidence and the grading of recommendations used within this review are based on those proposed by the Oxford Centre for Evidence-based medicine.<sup>19</sup>

Finally, data from molecular pathology are likely to further refine these guidelines.

## Meningioma

For benign meningioma (WHO grade I), radiotherapy may be used as radical treatment or postoperatively after incomplete resection or recurrence. Radiological surveillance is often an appropriate option for benign meningioma, depending on tumour growth, location and the risk to the patient from further tumour growth. Randomised clinical trial evidence is lacking, but generally excellent rates of local control are reported with radiotherapy doses of 50–54 Gy in 25–30 fractions. Small-volume benign tumours away from critical structures (for example, optic apparatus) may also be treated with stereotactic radiosurgery (SRS). Multiple series confirm long-term local control rates in excess of 80% using both fractionation and SRS. Lower doses have been used in more recent series with similar local control rates.

Radiotherapy should be considered for recurrent or incompletely resected meningioma of atypical histology. As for other benign intracranial tumours, fractionation has been governed by tolerance of local structures and adjacent brain tissue. There is an absence of prospective randomised clinical trial evidence for the use of adjuvant radiation therapy. However, multiple institutional series have demonstrated an improvement in local control and overall survival with adjuvant radiotherapy doses of 50.4–59.4 Gy in 28–33 fractions.<sup>30–33</sup> There is some evidence to suggest that local control is enhanced at doses greater than 52 Gy.<sup>30–33</sup>

Patients with grade 2 meningiomas are at higher risk of relapse, and standard practice has historically been to give radiotherapy. The role of adjuvant radiotherapy, balanced against the neuro-cognitive side-effects, in patients with completely resected meningioma are being explored in the ROAM study (EORTC 1308). In patients who have incompletely resected tumours, radiotherapy has been offered at a dose of 60 Gy in 30 fractions. Attempts at dose escalation using radiosurgery boost and accelerated hyperfractionation have failed to achieve improved local control.<sup>32</sup> The EORTC 26021-22021 phase II trial (NCT00626730) of postoperative radiotherapy for atypical and malignant meningiomas which treated Simpson stage 1–3 to 60 Gy and Simpson stages 4–5 to 70 Gy closed in 2013 and is in follow-up.<sup>34</sup>

Special consideration should be given to meningioma of the optic nerve sheath. There is now evidence from multiple institutional series that radiotherapy should be considered as a primary treatment option to achieve tumour control and consequentially prevent visual deterioration and symptomatic proptosis.<sup>35,36</sup>

### Recommendations

#### Tumour grade 1:

50.4–54 Gy in 28–30 fractions over 5.5–6 weeks (Grade C)

50–55 Gy in 30–33 fractions over 6–6.5 weeks (Grade C)

#### Grade 2:

54–60 Gy in 30 fractions over 6 weeks (Grade D)

#### Grade 3:

60 Gy in 30 fractions over 6 weeks (Grade D)

The types of evidence and the grading of recommendations used within this review are based on those proposed by the Oxford Centre for Evidence-based medicine.<sup>19</sup>

## Pituitary tumours

Fractionation has been governed by tolerance of the local structures and prospective data is lacking. There are consistent reports of high local control when using 45 Gy in 25 fractions for non-functioning pituitary adenomas.<sup>37</sup> This is commonly accepted as the standard dose for tumours without adverse features including suprasellar extension. There is data to suggest that the dose response may increase up to about 50 Gy, however, higher doses are generally reserved for tumours with adverse features.<sup>38</sup> Small inoperable pituitary tumours away from optic apparatus may be suitable for single fraction stereotactic treatment which offers a similar local control rate.<sup>39</sup>

Although radiological control rates are high, biochemical remission rates for functional tumours vary considerably using conventional doses of 45–54 Gy (1.8–2 Gy per fraction). No clear dose response has been defined using fractionated treatment, however, higher marginal doses are used when using single fraction stereotactic treatment.

### Recommendation

45 Gy in 25 fractions over 5 weeks (Grade D)

The types of evidence and the grading of recommendations used within this review are based on those proposed by the Oxford Centre for Evidence-based medicine.<sup>19</sup>

## Craniopharyngioma

Radiation therapy is typically used as an adjunct to surgery after maximal tumour resection. Doses between 50–60 Gy in 30 fractions have been used. Historical studies of postoperative radiotherapy showed a dose of 55 Gy to be a threshold dose in terms of local disease control, though concern over the risk of radiation induced optic neuropathy has resulted in median doses of 50–52.2 Gy in more recently published series.<sup>40–42</sup>

### Recommendations

50–55 Gy in 30–33 fractions over 6–6.5 weeks (Grade D)

52.2–54 Gy in 27–28 fractions over 5.5 weeks (Grade D)

The types of evidence and the grading of recommendations used within this review are based on those proposed by the Oxford Centre for Evidence-based medicine.<sup>19</sup>

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## 5. Gynaecological cancers

### Cervix cancer

#### Background

Patients presenting with small volume International Federation of Gynaecologists and Obstetricians (FIGO) stage IB1 and IIA disease can be treated either by radical hysterectomy and lymphadenectomy or radical radiotherapy as primary procedures. The two approaches have equivalent survival rates (Level 1b).<sup>1,2</sup>

The combination of surgery and radiotherapy increases morbidity and should be avoided if possible.<sup>1,3</sup> Postoperative chemoradiotherapy is indicated for patients with poor prognostic features discovered at surgery (positive nodes, positive margins or extensive lymphovascular space involvement) (Level 1b).<sup>2-4</sup>

Local control and survival are increased by the addition of concomitant chemotherapy in all stages, although the benefit may be smaller when only one node is positive or when the tumour size is <2 centimetres (cm) (Level 1b).<sup>2-11</sup>

Randomised studies of radiotherapy have used fractionation regimens of 40–50.4 Gray (Gy) in daily 1.8–2 Gy fractions over 4–5.5 weeks (Level 1b).<sup>1-3,12,13</sup> Both early and late toxicity are increased when chemotherapy is added (Level 1b).<sup>2,12,14</sup>

Overall treatment time, including intracavitary brachytherapy (ICBT), should not exceed 56 days for squamous carcinoma (Level 1b).<sup>2,15-19</sup> Haemoglobin levels during treatment are prognostic, with the best outcomes in those whose haemoglobin remains greater than 12 grams per decilitre (g/dl) throughout treatment (Level 2b).<sup>2,20</sup>

Small-volume parametrial disease can be often be encompassed within the brachytherapy dose-envelope using a combination of interstitial and intracavitary brachytherapy (ISBT and ICBT) (Level 2b).<sup>2</sup> Alternatively, a simultaneous integrated intensity-modulated radiotherapy (IMRT) planned external beam radiotherapy (EBRT) boost can be considered (Level 2b).<sup>2</sup> Boosting parametrial disease conventionally with three-dimensional conformal radiotherapy (3D-CRT) or parallel opposed fields with midline blocking does not usually allow organs at risk (OAR) constraints to be met and is not recommended (Level 1b).<sup>2,21,22</sup>

Evidence from cohort series supports the use of image-guided brachytherapy (IGBT) to reduce late toxicities and facilitate delivery of >80–85 Gy (combined external beam and brachytherapy equivalent dose in 2 Gy per fraction [EQD2]).<sup>23,24</sup> Dose constraints to OARs have been published based on organ volume rather than point doses (Level 2b).<sup>2,25</sup> These doses can only be achieved within normal tissue constraints when doses of <50 Gy are delivered by external beam radiotherapy.

Currently, there is no evidence of improvements in survival to support the routine use of neoadjuvant or adjuvant chemotherapy in addition to primary chemoradiotherapy. This question is being addressed by two international trials: Cisplatin and Radiation Therapy with or without Carboplatin and Paclitaxel in Patients with Locally Advanced Cervical Cancer (OUTBACK) and Induction Chemotherapy Plus Chemoradiation as First Line Treatment for Locally Advanced Cervical Cancer (INTERLACE).<sup>26,27</sup>

#### Treatment technique

The planning target volume (PTV) for treating pelvic malignancy normally encompasses the lymphatic drainage of the true pelvis and may be extended further, depending on the extent and type of malignancy, to include the para-aortic nodes, the inguinal nodes or the vagina.<sup>28</sup>



Nodal atlases have been developed to assist in the outlining of the female pelvis.<sup>29,30</sup> Significantly less toxicity is seen if EBRT is delivered using IMRT or volumetric-modulated arc therapy (VMAT) rather than 3D-CRT (Level 2b).<sup>2,31</sup>

## Recommendations

### Post-operative external beam:

40 Gy in 20 fractions over 4 weeks (Grade A)  
 45 Gy in 25 fractions over 5 weeks (Grade A)  
 50 Gy in 25 fractions over 5 weeks (Grade A)  
 50.4 Gy in 28 fractions over 5.5 weeks (Grade A)

Delivered with weekly concurrent cisplatin 40 milligrams per metre squared (mg/m<sup>2</sup>) (Grade A)

### Definitive primary treatment

#### External beam radiotherapy:

40 Gy in 20 fractions over 4 weeks (Grade A)  
 45 Gy in 25 fractions over 5 weeks (Grade A)  
 50 Gy in 25 fractions over 5 weeks (Grade A)  
 50.4 Gy in 28 fractions over 5.5 weeks (Grade A)

Delivered with weekly concurrent cisplatin 40 mg/m<sup>2</sup> (Grade A)

#### Involved pelvic and para-aortic lymph nodes should receive:

57–60 Gy in 28 fractions over 5.5 week using a simultaneous integrated boost (Grade C)

#### Parametrial disease that cannot be encompassed by ICBT and ISBT may receive:

57–60 Gy in 25–28 fractions over 5–5.5 weeks  
 65 Gy in 28 fractions over 5.5 weeks using a simultaneous integrated boost (Grade C)

#### **EBRT should be followed by image-guided brachytherapy so that a total dose of 80–85 Gy EQD2 is delivered to the high-risk clinical target volume (CTV) (Level 2b).**

#### **This is achieved with:**

45 Gy in 25 fractions over 5 weeks external beam followed by high-dose rate (HDR) 28 Gy in 4 fractions (Grade B)

#### **Other fractionation schedules in use for brachytherapy after the external beam schedules given above are:**

**HDR:** 6–7.5 Gy per fraction for 3–5 fractions (Grade C)

**Pulsed dose rate (PDR):** 17 Gy per fraction at 1 Gy per hour for 2 fractions, 7–10 days apart (Grade C)

#### **Overall treatment time, including brachytherapy should be no more than 56 days for squamous cancers (Level 1b)**

The types of evidence and the grading of recommendations used within this review are based on those proposed by the Oxford Centre for Evidence-based medicine.<sup>2</sup>

## Endometrial cancer

### Adjuvant therapy in operable disease

The majority of patients present with organ-confined disease and surgery is the primary treatment.

Trials of pelvic radiotherapy consistently show a reduction in local recurrences but no overall survival benefit.<sup>32–37</sup> The Vaginal Brachytherapy Versus Pelvic External Beam Radiotherapy for Patients with Endometrial Cancer of High–Intermediate Risk (PORTEC 2) trial showed equivalent outcome for patients with some intermediate risk features who received either adjuvant vaginal brachytherapy (VBT) or external beam radiotherapy.<sup>35</sup> The long-term pelvic side-effects in the brachytherapy group were less than with external beam. The PORTEC 3 trial has investigated the benefit of concurrent chemoradiotherapy and adjuvant chemotherapy compared to adjuvant radiotherapy alone, which has been the current standard of care. This shows an advantage for the combined approach in stage III patients after hysterectomy.<sup>36,37</sup>

#### Recommendations

##### High-risk patients

###### Postoperative adjuvant external beam radiotherapy:

46 Gy in 23 fractions over 4.5 weeks (Grade A)

48.6 Gy in 27 fractions over 5.5 weeks (Grade A)

Other schedules in use include 45 Gy in 25 fractions (Grade D) and 50.4 Gy in 28 fractions (Grade D)

Stage III patients should receive chemoradiation with cisplatin followed by adjuvant carboplatin and paclitaxel (Grade A)

###### **Vault brachytherapy may follow the above schedules in patients with cervical involvement although there is no strong evidence base for this practice:**

**HDR:** 8 Gy at 5 millimetres (mm) in 2 fractions (Level 1b)

**PDR:** 19 Gy at 5 mm at 1 Gy per hour given in 1 fraction (Level 1b)

##### Intermediate risk patients

###### Vaginal vault brachytherapy:

###### **HDR:**

21 Gy at 5mm in 3 fractions over 3 weeks (Grade A)

12–30 Gy at 5 mm in 3–8 fractions (Grade C)

**PDR:** 28 Gy at 5 mm in 1 Gy pulse per hour given in 2 fractions delivered in 7–10 days (Level 1b)

The types of evidence and the grading of recommendations used within this review are based on those proposed by the Oxford Centre for Evidence-based medicine.<sup>2</sup>

## Definitive radiotherapy for inoperable disease

Endometrial carcinoma may be inoperable because of medical co-morbidity or advanced disease stage. Accurate staging can be achieved using magnetic resonance imaging (MRI). Radiotherapy can control stage I and II disease and may have a role in more advanced cases (Level 2a).<sup>38,39</sup>

### Recommendations

#### Brachytherapy alone

##### HDR:

36 Gy in 5 fractions (Grade C) prescribed to the uterine serosa  
37.5 Gy in 6 fractions (Grade C) prescribed to the uterine serosa

#### Combination therapy

##### External beam:

45 Gy in 25 fractions over 5 weeks (Grade C)  
50 Gy in 25 fractions over 5 weeks (Grade C)

##### Brachytherapy:

##### HDR:

28 Gy in 4 fractions (Grade C) prescribed to the uterine serosa  
25 Gy in 5 fractions (Grade C) prescribed to the uterine serosa

The types of evidence and the grading of recommendations used within this review are based on those proposed by the Oxford Centre for Evidence-based medicine.<sup>2</sup>

## Endometrial carcinoma: salvage

Recurrent uterine corpus carcinoma in a previously unirradiated pelvis can be treated, and sometimes salvaged, with radiotherapy (external beam alone, external beam combined with brachytherapy or brachytherapy alone). Data of any sort are sparse, with no randomised trials. Doses of greater than 60 Gy EQD2 including brachytherapy should be delivered, provided rectal and bladder constraints are respected (Level 2c).<sup>40,41</sup>

## Vulva

### Adjuvant therapy in operable disease

For those with operable vulval cancer, surgical resection of the primary with inguinal lymphadenectomy remains the treatment of choice.<sup>42</sup>

Adjuvant radiotherapy may be considered for those with incomplete resection, two or more positive lymph nodes or any extracapsular spread. Concurrent chemotherapy with cisplatin is used, but without a strong evidence base to support it (Grade C).<sup>2</sup> The Gronigen International Study on Sentinel Nodes in Vulvar Cancer (GROINSS – II) study is comparing surgery with either definitive radical radiotherapy or radical chemoradiotherapy where sentinel lymph node metastases <2 mm are detected.<sup>43</sup>

### Recommendation

#### **Postoperative radiotherapy to vulva, pelvic and inguinal nodes:**

45 Gy in 25 fractions over 5 weeks (Grade C)

50 Gy in 25 fractions over 5 weeks (Grade C)

The types of evidence and the grading of recommendations used within this review are based on those proposed by the Oxford Centre for Evidence-based medicine.<sup>2</sup>

### **Inoperable vulval carcinoma**

Data in this area are sparse with no randomised studies. Potential therapeutic options include definitive chemo-radiotherapy, treating the primary and nodes. Consideration should then be given to surgical removal of residual disease or a second phase of radiotherapy with electrons or brachytherapy.<sup>44</sup>

### Recommendation

#### **Inoperable vulval cancer:**

45 Gy in 25 fractions over 5 weeks (Grade C)

50 Gy in 25 fractions over 5 weeks (Grade C)

50.4 Gy in 28 fractions over 5.5 weeks (Grade C)

External beam radiotherapy may be given with weekly cisplatin 40 mg/m<sup>2</sup> (Grade C)

#### **The primary and involved nodes should be boosted using electrons, simultaneous integrated boost (SIB) with IMRT or brachytherapy to deliver a total dose of 60–65 Gy EQD2 (Grade C)**

The types of evidence and the grading of recommendations used within this review are based on those proposed by the Oxford Centre for Evidence-based medicine.<sup>2</sup>

### **Vaginal carcinoma**

The rarity of vaginal carcinoma has led to therapy recommendations being derived from single institution series accrued over many years and extrapolation from cervical carcinoma data with no randomised trials. Therapy with EBRT in combination with either ISBT or ICBT is accepted practice with doses of between 70–80 Gy EQD2 appearing to confer survival advantage (Level 4).<sup>45</sup> The addition of concurrent chemotherapy appears to deliver a survival advantage (Level 4).<sup>46</sup>

### Recommendation

#### **Definitive therapy of vaginal carcinoma:**

45–50 Gy in 25 fractions over 5 weeks (Grade C)

Followed by ISBT or ICBT HDR 18.75–20 Gy in 5 fractions (Grade C)

The types of evidence and the grading of recommendations used within this review are based on those proposed by the Oxford Centre for Evidence-based medicine.<sup>2</sup>

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## 6. Head and neck cancer

### Background

Intensity-modulated radiotherapy (IMRT) is the accepted standard radiotherapy for patients undergoing primary and adjuvant radiotherapy for head and neck squamous cell carcinomas; exceptions are T1/T2N0 glottic cancer and the use of low-dose palliative radiotherapy. The international standard for definitive treatment remains 70 Gray (Gy) in daily fractions of 2 Gy over seven weeks, although altered fractionation regimens have been widely used. In the UK, many centres have adopted 65–66 Gy in 30 fractions over six weeks as a standard regimen. Most centres employ a simultaneous integrated boost technique with IMRT to treat all target volumes and elective lymph node regions to varying dose levels in each fraction (rather than the use of multiple phases or a matched neck field). This has led to altered fractionation regimens for either high-dose or elective treatment volumes.<sup>1</sup>

### T1/2N0 glottic carcinoma

Hypofractionated regimens are recommended.<sup>2</sup> A randomised trial demonstrated the superiority of modest hypofractionation with 2.25 Gy per fraction and, in large retrospective series, fraction sizes of  $\geq 2.25$  Gy compared favourably with other reported series.<sup>2–4</sup> Several UK series have reported high rates of local control with shorter more hypofractionated schedules including 50–52.5 Gy in 16 fractions over three weeks for T1 disease and 55 Gy in 20 fractions for T1 and T2 disease.<sup>5–8</sup> Hyperfractionated schedules have not shown a significant improvement compared with conventional fractionation.<sup>9</sup>

#### Recommendations

63 Gy in 28 fractions over 5.5 weeks (Grade B)

50 Gy in 16 fractions over 3 weeks (T1 disease only) (Grade C)

55 Gy in 20 fractions over 4 weeks (Grade C)

The types of evidence and the grading of recommendations used within this review are based on those proposed by the Oxford Centre for Evidence-based medicine.<sup>10</sup>

### Role of modified fractionation in head and neck squamous cell carcinoma (HNSCC) (non-nasopharyngeal)

A meta-analysis of 15 trials of altered fractionation without chemotherapy in non-nasopharyngeal head and neck squamous cell carcinoma (predominantly oropharynx and larynx cancers) showed a modest benefit in overall survival (3.4% at five years) and local control (6.4% at five years).<sup>11</sup> The overall survival benefit was mainly seen with hyperfractionation (8.2% at five years) although these schedules are difficult to implement and are not widely used (Level 1a).<sup>10</sup> The Danish Head and Neck Cancer Group (DAHANCA) regimen of six fractions per week showed an improvement of 10% in five-year locoregional control in patients treated without chemotherapy with transiently increased acute toxicity.<sup>12</sup> In the meta-analysis the overall survival benefit of acceleration without a total dose reduction was 2% at five years, and 1.7% at five years with a total dose reduction.<sup>11</sup> There was no benefit of altered fractionation for patients age >70 years old (Level 1b).<sup>10,11</sup>



## Elective lymph node and mucosal doses with IMRT

A biological equivalent dose (EQD2) of 50 Gy in 25 fractions is a standard dose to electively treat lymph node regions. Although there is no direct evidence of the need for higher doses for microscopic disease, some centres favour the use of an additional 'intermediate' risk higher elective dose, such as a biological equivalent to 60 Gy in 30 fractions, to regions deemed to be at higher risk of harbouring disease, particularly radiologically equivocal areas for nodal disease (Level 4).<sup>10,13</sup>

In the management of head and neck carcinomas of unknown primary, commonly used mucosal doses are the biological equivalent of 50–60 Gy in 25–30 fractions.<sup>14–17</sup> Several series have suggested that doses at the lower end of this dose range are associated with very low rates of subsequent emergence of a mucosal primary (Level 4).<sup>10,15–17</sup>

To incorporate elective lymph node and mucosal doses into a single phase IMRT plan, two approaches to dose fractionation can be adopted: i) accept moderate hypofractionation to sites of known disease while retaining a conventional fraction size (1.8–2 Gy) for elective lymph node treatment or ii) retain a conventional fraction size to known disease and deliver a reduced fraction size to the elective lymph node regions (for example, 1.5–1.6 Gy). An increasing number of series suggest that elective lymph node irradiation may be safely delivered with a reduced fraction size (Level 4).<sup>11,18</sup>

### Recommendations

#### **For elective nodal treatment using IMRT with a matched lower neck technique:**

50 Gy in 25 fractions over 5 weeks to the matched neck (Grade C)

#### **Elective treatment within the IMRT plan, the following dose levels are appropriate:**

54 Gy in 30 fractions over 6 weeks (Grade C)

56–57 Gy in 35 fractions over 7 weeks (Grade C)

60 Gy in 30 fractions over 6 weeks or 63 Gy in 35 fractions over 7 weeks may be additionally used for 'intermediate' risk regions (Grade D)

The types of evidence and the grading of recommendations used within this review are based on those proposed by the Oxford Centre for Evidence-based medicine.<sup>10</sup>

## Radiotherapy alone for early stage (I/II) oropharynx/hypopharynx/larynx cancer (excluding T1/2 glottic carcinoma)

Single modality treatment with surgery or radiotherapy is the standard of care. The relative merits of conventional versus altered fractionation remain unclear. IMRT with modest acceleration has shown high rates of local control with low rates of late toxicity.<sup>19</sup> Patients with early stage disease accounted for >50% of patients in the DAHANCA 6 and 7 trial which demonstrated a substantial benefit of shortening overall treatment time without reduction in total dose (66–68 Gy in 33–34 fractions delivered at five versus six fractions per week).<sup>12</sup> In a meta-analysis, there was no clear benefit for altered fractionation for the subgroup with stage I/II disease (Level 1a).<sup>10,11</sup>

### Recommendations

#### **Stage I/II oropharynx, hypopharynx or non-glottic larynx cancer:**

70 Gy in 35 fractions over 7 weeks (Grade C)

65–66 Gy in 30 fractions over 6 weeks (Grade C)

66 Gy in 33 fractions or 70 Gy in 35 fractions, 6 fractions per week over 6 weeks (Grade B)

The types of evidence and the grading of recommendations used within this review are based on those proposed by the Oxford Centre for Evidence-based medicine.<sup>10</sup>

### **Radiotherapy with concomitant chemotherapy for stage III/IVa/b HNSCC (excluding nasopharyngeal carcinoma)**

Radiotherapy with concurrent cisplatin is the current standard of care for the definitive management of stage III/IV patients <70 years of age with adequate performance status.<sup>20</sup> The international standard schedule is 70 Gy in 35 fractions.<sup>20</sup> Although not directly compared, a modestly hypofractionated schedule of 65–66 Gy in 30 fractions has been adopted as standard practice in a number of UK trials and centres.<sup>21</sup> There has been considerable interest in combining perceived benefits of altered fractionation with concurrent chemotherapy. However, the Radiation Therapy Oncology Group (RTOG) 0129 trial compared 72 Gy in 42 fractions delivered over six weeks with two cycles of concurrent chemotherapy with a standard arm of 70 Gy in 35 fractions over seven weeks with three cycles of concurrent chemotherapy with no difference seen between the arms.<sup>22</sup> The three arm Groupe d'Oncologie Radiothérapie Tête et Cou (GORTEC) 99-02 phase III trial compared 70 Gy in 35 fractions over seven weeks with three cycles of concurrent chemotherapy with 70 Gy over six weeks with two cycles of concurrent chemotherapy and a very accelerated radiotherapy alone arm of 64.8 Gy in 3.5 weeks; there was no benefit of modest acceleration with concurrent chemotherapy while the accelerated radiotherapy alone arm was inferior (Level 1b).<sup>10,23</sup> These data support a hypothesis that concurrent cisplatin may suppress tumour repopulation during radiotherapy, leading to a lower than expected tumour biologically equivalent dose with modestly accelerated schedules.<sup>24</sup> Reported outcomes for hypofractionated IMRT schedules with concomitant chemotherapy (65 Gy in 30 fractions over six weeks or 55 Gy in 20 fractions over four weeks) do not as yet support this hypothesis (Level 2b).<sup>10,21,25</sup>

In patients with oropharyngeal cancer, the tumour human papilloma virus (HPV) status has been identified as a strong and independent prognostic factor for survival.<sup>26</sup> In the anticipation of robust evidence from ongoing de-escalation studies, radiotherapy dose and fractionation for HPV positive oropharyngeal carcinomas should be no different to that for HPV negative oropharyngeal tumours (Grade D).<sup>10</sup>

### Recommendations

#### **Radiotherapy with concomitant chemotherapy:**

70 Gy in 35 fractions over 7 weeks (Grade A)

65–66 Gy in 30 fractions over 6 weeks (Grade C)

The types of evidence and the grading of recommendations used within this review are based on those proposed by the Oxford Centre for Evidence-based Medicine.<sup>10</sup>

## Radiotherapy alone for stage III/IVa/b HNSCC (excluding nasopharyngeal carcinoma)

The meta-analysis does not show a benefit of concomitant chemotherapy in patients >70 years old (Level 1a).<sup>10,20</sup> Concomitant chemotherapy or cetuximab may not be appropriate for some patients <70 years old due to co-morbidity, fitness or patient choice. Altered fractionation is an option for fit patients <70 years old treated with radiotherapy alone with superior local control and no increase in late toxicity; meta-analysis of altered fractionation studies did not show a benefit for altered fractionation in patients ≥70 years old (Level 1a).<sup>10,11,12,27</sup>

### Recommendations

#### Radiotherapy without concomitant radiotherapy:

66 Gy in 33 fractions or 70 Gy in 35 fractions, 6 fractions per week, over 6 weeks (Grade A)

70 Gy in 35 fractions over 7 weeks (Grade B)

65–66 Gy in 30 fractions over 6 weeks (Grade C)

The types of evidence and the grading of recommendations used within this review are based on those proposed by the Oxford Centre for Evidence-based Medicine.<sup>10</sup>

## Postoperative radiotherapy

There are few studies of radiation dose with postoperative radiotherapy with or without chemotherapy. Historical studies suggest that for adjuvant radiotherapy alone, patients with extracapsular extension benefitted from doses of 63 Gy and for other patients there was no benefit >57.6 Gy (Level 2b).<sup>10,28</sup> Adjuvant doses of 60–66 Gy in 30–33 fractions were used in the RTOG and European Organisation for Research and Treatment of Cancer (EORTC) trials investigating the role of concurrent chemotherapy.<sup>29,30</sup> A pooled analysis identified subgroups with close/positive margins and/or extracapsular spread as benefiting from concurrent cisplatin (Level 2a).<sup>10,31</sup> Based on limited evidence of a dose-effect in the adjuvant setting, a dose of 66 Gy in 33 fractions is considered standard in the presence of high-risk pathological findings, and 60 Gy in 30 fractions is widely used in the absence of high-risk features.<sup>32,33</sup> Doses equivalent to 50–54 Gy in 2 Gy per fraction are commonly used for lower risk areas at risk of microscopic disease (Level 4).<sup>10,33</sup>

### Recommendation

#### Postoperative radiotherapy:

60 Gy in 30 fractions over 6 weeks (Grade B)

A dose of up to 66 Gy in 33 fractions over 6.5 weeks may be delivered to high-risk subvolumes (areas surrounding extracapsular spread and/or positive/close margins) (Grade B)

The types of evidence and the grading of recommendations used within this review are based on those proposed by the Oxford Centre for Evidence-based Medicine.<sup>10</sup>

## Nasopharyngeal carcinoma

Radiotherapy alone is used for early stage nasopharyngeal carcinoma.<sup>34</sup> For locally advanced disease, conventionally fractionated radiotherapy combined with chemotherapy is currently recommended. RTOG phase 2 trials have used a high, intermediate and elective three dose level approach of 70 Gy, 59.4 Gy and 54 Gy in 33 fractions (Level 2b).<sup>10,35</sup> A case series of altered fractionation using 65 Gy in 30 fractions with an elective dose level of 54 Gy in 30 fractions has reported disease outcomes and toxicity (Level 4).<sup>10,36</sup> Doses biologically equivalent to 50–60 Gy in 2 Gy per fraction are commonly used to treat at-risk sites.<sup>34</sup>

### Recommendations

#### Nasopharyngeal cancer:

70 Gy in 35 fractions over 7 weeks (Grade A)

70 Gy in 33 fractions over 6.5 weeks (Grade B)

65 Gy in 30 fractions over 6 weeks (Grade C)

The types of evidence and the grading of recommendations used within this review are based on those proposed by the Oxford Centre for Evidence-based Medicine.<sup>10</sup>

## Palliative radiotherapy schedules

Palliative radiotherapy is used in a very heterogenous group of patients, and may range from the use of a single fraction to stop bleeding/fungation to the use of high doses to achieve longer-term disease control while accepting that a cure is not possible. Decisions with regard to palliative radiotherapy dose fractionation take into account symptoms, disease extent and co-morbidity. When higher doses are delivered, three-dimensional (3D) conformal radiotherapy or IMRT are often required due to proximity to critical structures.

### Recommendations

Examples of appropriate dose fractionations include:

40 Gy in 10 fractions over 4 weeks 'split course' (Level C)<sup>38</sup>

21 Gy in 3 fractions over 3 weeks (Level C)<sup>39</sup>

20 Gy in 5 fractions over 1 week (Level C)<sup>40</sup>

14 Gy in 4 fractions which may be repeated 2 further times every 4 weeks (Level C)<sup>41</sup>

The types of evidence and the grading of recommendations used within this review are based on those proposed by the Oxford Centre for Evidence-based Medicine.<sup>10</sup>

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## Re-irradiation

Re-irradiation with curative intent can be an option for selected patients with limited local recurrence or new primary disease who are unsuitable for surgical treatment/decline surgery. Re-irradiation may also be considered following salvage surgery with adverse histological features (for example, positive margins, extracapsular spread). Patient selection, choice of dose fractionation and dose constraints are individualised dependent on the extent of recurrence, time from previous radiotherapy, sequelae of prior treatment, proximity to organs at risk, performance status, co-morbidity and nutritional status. Radiotherapy target volumes are limited to high-risk areas only and do not include elective regions. Ideally the aim should be to deliver a dose equivalent of  $\geq 60$  Gy in 2 Gy per fraction, although the dose may need to be reduced on an individual basis if organ at risk tolerances are exceeded.<sup>40,41</sup> Hyperfractionation with bi-daily irradiation at approximately 1.2 Gy per fraction can be considered (Grade C).<sup>10,41</sup> The use of concomitant radiosensitising agents should only be used with extreme caution.

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## 7. Lung cancer

### Background

Overall survival has increased in lung cancer in the past ten years, with the vast majority of the gains occurring in disease stages I–III. There has been very little, if any improvement seen in outcomes for stage IV patients.<sup>1,2</sup> Several publications have looked at access to radiotherapy treatments (Level 2a).<sup>3–5</sup> Although many of these do not distinguish between radical and palliative treatment, it appears that the proportion of lung cancer patients in the UK accessing radiotherapy remains lower than expected.

Lung cancer staging has improved with routine use of positron emission tomography-computed tomography (PET-CT) and endobronchial ultrasound (EBUS). Routine use of intravenous (IV) contrast in planning has improved mediastinal target delineation. Significant technological advances have taken place in the delivery of radiotherapy. For radical radiotherapy, four-dimensional computed tomography (4DCT) planning is replacing three-dimensional conformal radiotherapy (3DCRT) as the standard of care. Bulky tumours in certain anatomical locations, such as the paravertebral gutter, have improved dosimetry with intensity-modulated radiotherapy (IMRT) and can more often meet normal tissue constraints (NTC) than those planned conformally (Level 2c).<sup>5–7</sup> However, as with many tumour types, there is insufficient evidence to determine the efficacy of IMRT (Level 4).<sup>5,7,8</sup>

### Non-small cell lung cancer (NSCLC): curative therapy

#### Background

For patients with stage I and II lung cancer, anatomically based surgical resection remains the treatment of choice. There is an emerging body of literature to support ablative therapies in node-negative patients, of which stereotactic ablative radiotherapy (SABR) has the most mature evidence base. There are, as yet, no completed randomised studies. The two international randomised studies, which closed due to poor accrual, have been published in pooled form (Level 2b).<sup>5,9</sup> There are a number of multi-institutional prospective as well as retrospective series. Most concentrate on medically inoperable patients who are, by definition, less well than their surgical counterparts. Published outcomes both in terms of overall survival (OS) and disease-free survival (DFS) approach surgical series. Two-year survival has been reported as 70% and five-year survival 43%.<sup>10,11</sup>

For medically inoperable patients with node negative tumours less than 5 centimetres (cm) and in a favourable anatomical position, stereotactic ablative radiotherapy (SABR) is the treatment of choice. The best outcomes occur when the tumour receives >100 Gray (Gy) equivalent dose in 2 Gy per fraction EQD2 biologically equivalent dose (BED). Treatment should be delivered with an interfraction interval of greater than 40 hours but less than four days (Level 2a).<sup>5,12</sup>

Stage III NSCLC is an extremely heterogeneous group in terms of tumour size and extent of nodal involvement. Concurrent chemoradiotherapy has been demonstrated in meta-analyses to give superior outcomes when compared with sequential chemoradiotherapy or radiotherapy alone, but the optimum dose fractionation schedule has yet to be defined (Level 1a).<sup>5,13–15</sup> Concurrent schedules have an increased incidence of grade three oesophageal toxicities (Level 1b) and elderly patients with good performance status and few co-morbidities derive as much benefit from concurrent therapy as their younger counterparts (Level 1b).<sup>5,16</sup>

Although trimodality therapy remains an option, there is no evidence of benefit over definitive chemoradiotherapy. The only tumour group where there is some evidence to support the use of trimodality therapy is Pancoast tumours (Level 1b).<sup>5,17</sup>

There is no evidence of benefit for chemotherapy delivered either neoadjuvantly or adjuvantly to those receiving concurrent regimes (Level 1b).<sup>5</sup>

Dose escalation has been investigated in many studies. The recently published Radiation Therapy Oncology Group (RTOG) 0617 trial did not demonstrate a survival benefit in the escalated arm. This trial has received significant interest and review of individual data. The quality assurance of the radiotherapy delivered may have been the cause of the lack of a positive outcome so it is likely that this issue will be revisited (Level 1b).<sup>5,18</sup>

For those unable to tolerate concurrent chemoradiotherapy, a sequential approach demonstrates survival benefit over radiotherapy alone.<sup>15</sup> The optimum therapy schedule has yet to be defined (Level 1a).<sup>5</sup>

Patients unfit for systemic therapy should be treated with radiotherapy alone. Accelerated fractionation schedules seem to improve outcomes (Level 1b) and can be safely combined with concurrent and neoadjuvant approaches (Level 1b).<sup>5,15,19–22</sup>

### Recommendations

#### Medically inoperable T1–3 (≤5 cm) N0:

SABR using:

- 54 Gy in 3 fractions over 5–8 days (Grade B)
- 55 Gy in 5 fractions over 10–14 days (Grade B)
- 60 Gy in 5 fractions over 10–14 days (Grade B)
- 60 Gy in 8 fractions over 10–20 days (Grade B)

#### Medically inoperable stage I and II:

- 54 Gy in 36 fractions treating thrice daily over 12 consecutive days continuous, hyperfractionated, accelerated radiotherapy (CHART) (Grade A)
- 55 Gy in 20 fractions (Grade C)

#### STAGE III:

##### Concurrent:

- 55 Gy in 20 fractions over 4 weeks with cisplatin and vinorelbine (Grade A)
- 60 Gy in 30 fractions over 6 weeks with cisplatin and etoposide (Grade A)
- 66 Gy in 33 fractions over 6.5 weeks with cisplatin and etoposide (Grade A)

##### Sequential:

- 55 Gy in 20 fractions over 4 weeks (Grade A)
- 60 Gy in 30 fractions over 6 weeks (Grade B)
- 66 Gy in 33 fractions over 6.5 weeks (Grade B)
- 54 Gy in 36 fractions treating thrice daily over 12 consecutive days (CHART) (Grade B)

##### Radiotherapy alone:

- 54 Gy in 36 fractions treating thrice daily over 12 consecutive days (CHART) (Grade A)
- 66 Gy in 33 fractions over 6.5 weeks (Grade A)
- 55 Gy in 20 fractions over 4 weeks (Grade B)

#### Pancoast tumours (T3–4 N0–1):

- 45 Gy in 25 fractions over 5 weeks with cisplatin and etoposide followed by surgery (Level 2b)

The types of evidence and the grading of recommendations used within this review are based on those proposed by the Oxford Centre for Evidence-based Medicine.<sup>5</sup>

## Non-small cell lung cancer (NSCLC): palliative radiotherapy

### Background

The early trials were undertaken predominantly in patients unexposed to chemotherapy. Current practice would see a significant proportion of patients receiving sequential chemoradiotherapy, with good performance status (PS) stage III patients managed with radical concurrent chemoradiotherapy.

Overall the trials demonstrate that short-course radiotherapy can palliate intrathoracic symptoms as well as long-course, but for those with good PS, higher doses confer a moderate survival advantage at the expense of extra toxicity (Level 1a).<sup>5,23</sup>

### Recommendations

#### For those with good PS:

39 Gy in 13 fractions over 2.5 weeks with cord dose limited to 36 Gy (Grade A)

36 Gy in 12 fractions over 2.5 weeks (Grade A)

30 Gy in 10 fractions over 2 weeks (Grade A)

20 Gy in 5 fractions over 1 week (Grade A)

#### For those with poor PS:

17 Gy in 2 fractions over 8 days (Grade A)

10 Gy in 1 fractions (Grade A)

The types of evidence and the grading of recommendations used within this review are based on those proposed by the Oxford Centre for Evidence-based Medicine.<sup>5</sup>

## Small cell lung cancer (SCLC)

### Background

The evidence base now favours integration of chemotherapy and radiotherapy at all disease stages (Level 1a).<sup>5</sup>

### Concurrent chemoradiotherapy (stages I–III)

For patients with T1–4 and N0–3 SCLC, there is evidence for concurrent chemoradiotherapy with radiotherapy starting no later than day one cycle three of chemotherapy (Level 1a).<sup>5,24</sup> The UK-led phase III Concurrent Once-Daily Versus Twice Daily Radiotherapy (CONVERT) trial has compared the internationally accepted standard of 45 Gy in 30 fractions treating twice daily over three weeks with 66 Gy in 33 daily fractions over six weeks, finding no difference between the two schedules.<sup>25,26</sup> In addition, a US intergroup study is currently recruiting, which compares three fractionation schedules (45 Gy in 30 fractions treating twice daily; 70 Gy in 35 daily fractions and 61.2 Gy over five weeks treating once daily until day 21 and twice daily thereafter) (Level 1b).<sup>5</sup>

One trial of early versus late concurrent thoracic radiotherapy used 40 Gy in 15 daily fractions using a simple parallel opposed pair with cord shielding (Level 1b).<sup>5,24</sup> This can shield the tumour and, in the modern era, cord constraints would be met using 3DCRT.

## Sequential chemoradiotherapy (stages I–III)

For those patients who, due to tumour size or co-morbidities, cannot be treated with concurrent chemoradiotherapy, sequential chemoradiotherapy is the best alternative (Level 1a).<sup>5</sup> There is no definitive evidence to indicate the optimal schedule in this patient group, although many use 40 Gy in 15 daily fractions (Level 2b).<sup>5</sup>

### Recommendations

#### **Concurrent chemoradiotherapy with cisplatin and etoposide should be delivered with either:**

45 Gy in 30 fractions treating twice daily over 3 weeks (Grade A)

66 Gy in 33 fractions over 6.5 weeks (Grade A)

40 Gy in 15 fractions over 3 weeks (Grade B)

#### **Sequential chemoradiotherapy:**

40 Gy in 15 daily fractions over 3 weeks (Grade B)

50 Gy in 25 fractions over 5 weeks (Grade B)

The types of evidence and the grading of recommendations used within this review are based on those proposed by the Oxford Centre for Evidence-based Medicine.<sup>5</sup>

## SCLC: palliative thoracic radiotherapy

### Background

A recent European Organisation for Research and Treatment of Cancer (EORTC) trial randomised 498 patients with metastatic SCLC, who had not progressed during primary chemotherapy to prophylactic cranial irradiation (PCI), with or without thoracic radiotherapy with 30 Gy in ten daily fractions in addition. The trial did not meet its primary endpoint of improved OS at one year, but OS at two years was in favour of mediastinal consolidation (Level 1b).<sup>5,27</sup> Further data analysis has confirmed the OS and DFS benefits are limited to those with persistent intrathoracic disease (Level 1b).<sup>5,28</sup>

### Recommendation

Those patients with metastatic SCLC who respond to primary chemotherapy but have persistent intrathoracic disease or thoracic symptoms should be considered for thoracic consolidation radiotherapy with 30 Gy in 10 fractions over 2 weeks (Grade A).

The types of evidence and the grading of recommendations used within this review are based on those proposed by the Oxford Centre for Evidence-based Medicine.<sup>5</sup>

### Prophylactic cranial irradiation (PCI) (stages I–III)

Meta-analysis of patients with stages I–III SCLC in complete or near complete thoracic remission following primary chemoradiotherapy have an increased OS and decreased incidence of intracerebral relapse when PCI is delivered (Level 1a).<sup>5,29,30</sup>

25 Gy in ten fractions over 14 days carries the same disease relapse rate but lower mortality when compared with 36 Gy in 18 fractions over 24 days (Level 1a).<sup>5,30</sup>

#### Recommendations

**Selected patients with locally advanced metastatic SCLC who respond to primary chemotherapy should be offered PCI. Acceptable schedules are:**

- 20 Gy in 5 fractions over 1 week (Grade A)
- 30 Gy in 10 fractions over 2 weeks (Grade A)
- 25 Gy in 10 fractions over 2 weeks (Grade A)
- 30 Gy in 12 fractions over 2.5 weeks (Grade A)

The types of evidence and the grading of recommendations used within this review are based on those proposed by the Oxford Centre for Evidence-based Medicine.<sup>5</sup>

### Prophylactic cranial irradiation (PCI) (stage IV)

Patients with stage IV SCLC who had any response to primary chemotherapy were randomised to either PCI with one of five schedules (20–30 Gy in 5–12 daily fractions) or no PCI. The treatment arms had an increased OS and reduced symptomatic incidence of brain metastases (Level 1b).<sup>5</sup> 85% of patients were treated with either 30 Gy in ten fractions or 20 Gy in five fractions. Two thirds received 20 Gy in five fractions. The trial excluded patients above 75 years of age.<sup>31</sup>

#### Recommendations

**Selected patients with metastatic SCLC who respond to primary chemotherapy should be offered PCI. Acceptable schedules are:**

- 20 Gy in 5 fractions over 1 week (Grade A)
- 30 Gy in 10 fractions over 2 weeks (Grade A)
- 25 Gy in 10 fractions over 2 weeks (Grade A)
- 30 Gy in 12 fractions over 2.5 weeks (Grade A)

The types of evidence and the grading of recommendations used within this review are based on those proposed by the Oxford Centre for Evidence-based Medicine.<sup>5</sup>

## Mesothelioma

### Background

The use of prophylactic irradiation of tracts of pleural interventions has been thought to reduce the incidence of chest wall recurrence. Three small randomised studies have been reported, one demonstrating benefit, two not (Level 1b).<sup>5,32-34</sup> Currently in the UK, two studies are addressing this issue. The Prophylactic Irradiation of Tracts (PIT) trial (closed to recruitment in December 2015) randomises those with a visible scar following minor pleural interventions between 21 Gy in three daily fractions using electrons or no treatment. The Simultaneous Modulated Accelerated Radiation Therapy (SMART) trial randomised those with larger pleural interventions between immediate radiotherapy with 21 Gy in three daily fractions or treatment deferred until tract metastases occurred. The SMART trial has been verbally presented (January 2016), with no benefit of immediate radiotherapy demonstrated.<sup>35</sup>

For those patients with a diagnosis of mesothelioma and chest wall pain, controversy exists about the utility of radiotherapy, especially where the pain is poorly localised. A recently published non-randomised study demonstrates a 35% response rate when chest wall radiotherapy is delivered to patients with localised pain (Level 2c).<sup>5,36</sup>

### Recommendation

Routine prophylactic irradiation of tracts is not recommended (Level 1b)

#### **Selected patients with chest wall pain may benefit from radiotherapy with either:**

20 Gy in 5 fractions over 1 week (Grade C)

36 Gy in 6 fractions treating twice per week (Grade D)

The types of evidence and the grading of recommendations used within this review are based on those proposed by the Oxford Centre for Evidence-based Medicine.<sup>5</sup>

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## 8. Lymphoma

### Hodgkin lymphoma

#### Background

Over the last 30 years, combination chemotherapy has become integral to the standard of care for both early and late stage Hodgkin lymphoma. Previous techniques employing the traditional mantle and inverted Y fields are no longer practiced. Involved field radiotherapy (IFRT), which has been the standard until recently, is being replaced by involved node radiotherapy (INRT) or involved-site radiotherapy (ISRT), further reducing the treated volume for consolidation or residual disease after chemotherapy.<sup>1,2</sup> There should be every effort to reduce cardiac and lung doses when treating the mediastinum with good evidence to support the use of intensity-modulated radiotherapy (IMRT) and deep inspiration breath hold (DIBH) in this setting.<sup>3</sup>

#### Early Hodgkin lymphoma

Studies by the German Hodgkin Disease Study Group have shown no difference in outcome between two cycles of Adriamycin bleomycin vinblastine dacarbazine (ABVD) and 20 Gray (Gy) in ten fraction IFRT in the favourable subgroup or four cycles of ABVD and 30 Gy IFRT in the unfavourable subgroup (Level 1b).<sup>4-6</sup> Radiotherapy after chemotherapy in PET-negative patients reduces the later risk of relapse, but the absolute reduction in progression-free survival (PFS) was only 4% at three years in the RAPID trial (Level 1b).<sup>8,7</sup>

#### Recommendations

##### For patients with early Hodgkin lymphoma:

**Favourable group:** 2 cycles of ABVD chemotherapy followed by 20 Gy in 10 fractions over 2 weeks (Grade A)

**Unfavourable group:** 4 cycles of ABVD followed by 30 Gy in 15 fractions over 3 weeks (Grade A)

For selected patients who are PET negative after three cycles of ABVD, the relative risks of relapse from omitting radiotherapy and the late toxicity from giving radiotherapy should be considered and discussed with the patient (Grade A)

The types of evidence and the grading of recommendations used within this review are based on those proposed by the Oxford Centre for Evidence-based Medicine.<sup>6</sup>

#### Advanced Hodgkin lymphoma

The role of radiotherapy in advanced Hodgkin disease after full-dose combination chemotherapy is controversial. One overview showed that combined-modality therapy conferred no survival benefit but did increase the risk of long-term fatal complications (cardiac and second cancer), while another, using UK National Cancer Research Institute (NCRI) study data, has shown an improved survival in patients with Hodgkin lymphoma who received radiotherapy compared to those who did not (Level 1a).<sup>6,8,9</sup> A European Organisation for Research and Treatment of Cancer (EORTC) study demonstrated that radiotherapy did not improve the outcome for patients who had a complete remission after mustine, vincristine, procarbazine, prednisolone-adriamycin bleomycin vinblastine (MOPP-ABV) chemotherapy, but that irradiation may benefit patients with a partial response after

chemotherapy (Level 1b).<sup>5,9</sup>

#### Recommendation

In advanced Hodgkin lymphoma, radiotherapy for residual disease is indicated after partial response to chemotherapy.

30–34 Gy in 15–20 fractions over 3 to 4 weeks (Grade B)

The types of evidence and the grading of recommendations used within this review are based on those proposed by the Oxford Centre for Evidence-based Medicine.<sup>6</sup>

#### Relapsed Hodgkin lymphoma

High-dose chemotherapy and stem cell transplantation remain the international standard of care for many younger patients with relapsed Hodgkin lymphoma.

In some patients with a single site of relapse, particularly occurring late, after previous treatment, re-induction as for early disease combined with IFRT may be appropriate, using a dose of 30–34 Gy in 15–20 fractions over 3–4 weeks.

If the site has not previously been irradiated, radiotherapy alone has been used for selected patients (Grade D).<sup>6,11</sup>

#### Recommendations

For palliative treatments no definitive recommendations can be made and dose will depend on the clinical situation. The following may be used:

30 Gy in 10 fractions over 2 weeks (Grade D)

20 Gy in 5 fractions over 1 week (Grade D)

Single doses of 7–8 Gy (Grade D)

The types of evidence and the grading of recommendations used within this review are based on those proposed by the Oxford Centre for Evidence-based Medicine.<sup>6</sup>

#### Nodular lymphocyte Hodgkin lymphoma

IFRT alone, without chemotherapy, results in high PFS and overall survival (OS) rates and is considered an adequate treatment for early stage disease.<sup>12</sup> A dose of 30 Gy in 15 fractions over three weeks is recommended (Grade D).<sup>6</sup>

#### Aggressive non-Hodgkin lymphoma (NHL)

In aggressive lymphomas, radiotherapy alone is not recommended except in palliative situations or where the patient is too frail for chemotherapy.

#### Consolidation IFRT in aggressive non-Hodgkin lymphoma

Following the landmark study comparing eight cycles of cyclophosphamide, doxorubicin, vincristine and prednisone (CHOP) chemotherapy to three cycles of CHOP followed by IFRT with 40–45 Gy in 1.8–2 Gy fractions, combined modality therapy was established as the standard of care.<sup>13</sup> Longer term follow-up has shown convergence of the survival

curves, as a result of an excess of relapses and deaths from lymphoma in the group given CHOP plus radiotherapy (Level 1b).<sup>14,6</sup> In a further study, patients who received eight cycles of CHOP chemotherapy and achieved complete remission, 30 Gy in daily 2 Gy fractions improved local control (Level 1b).<sup>15,16</sup> A further trial in patients aged <61 years with no adverse prognostic factors has shown improved event-free and overall survival rates with doxorubicin, cyclophosphamide, vindesine, bleomycin and prednisone (ACVBP) chemotherapy over those achieved by CHOP plus IFRT (Level 1b).<sup>6,16</sup>

There are therefore two treatment approaches to the patient with early aggressive NHL: short-course immunochemotherapy rituximab, cyclophosphamide, doxorubicin, vincristine and prednisone (R-CHOP) followed by IFRT or full-course R-CHOP with six to eight cycles alone. The relative merits should be discussed with the patient. There is no evidence to suggest that early PET response can be used to individualise treatment the schedule at present.

Recent evidence from the rituximab with CHOP over age 60 years (RICOVER) trial suggests that there may be a role for radiotherapy in advanced stage diffuse large B-cell lymphoma (DLBCL) given to bulky sites of disease at presentation after chemotherapy (Level 2b).<sup>6,17</sup>

Radiotherapy is also considered for mediastinal B-cell lymphoma and extranodal sites after full-course chemotherapy.<sup>18</sup>

A randomised trial of radiotherapy dose comparing 30 Gy to 40–45 Gy (all in daily two Gy fractions) has demonstrated that in aggressive NHL 30 Gy is equivalent to a higher dose for local PFS and OS. All patients with aggressive NHL receiving radiotherapy should therefore be given 30 Gy in 15 fractions over three weeks (Level 1b).<sup>6,19</sup>

### Recommendation

#### **For patients with aggressive non-Hodgkin lymphoma:**

30 Gy in 15 fractions over 3 weeks is recommended as part of planned combined modality therapy (Grade B).

The types of evidence and the grading of recommendations used within this review are based on those proposed by the Oxford Centre for Evidence-based Medicine.<sup>6</sup>

## Mantle cell lymphoma

This disease has a poor prognosis. The vast majority of patients require systemic treatment, although the standard of care is not yet established. In combined modality treatment, there is no evidence that mantle cell lymphomas respond differently to radiation compared to other aggressive lymphomas. A recent retrospective multi-institutional study of stage 1–2 patients reported favourable outcomes with combined modality or radiotherapy alone with two-thirds and half of the patients being free of disease at five and ten years respectively. Median dose was 35 Gy (range 12–45 Gy) (Grade C).<sup>6,20</sup>

## Natural killer (NK)/T-cell lymphoma

This is a rare entity in Western countries but is common in East Asia and Latin America.<sup>20</sup> Chemoradiation using cisplatin-based schedules and L-asparaginase are now standard, followed by consolidation chemotherapy. This type of lymphoma requires a higher dose than other T-cell lymphomas and a dose of at least 50 Gy in 25 fractions over five weeks should be given (Grade C).<sup>6,22</sup>

## Central nervous system lymphoma (CNS) lymphoma

The role of radiotherapy in CNS lymphoma is controversial in view of the significant late effects on cognitive function. It may be indicated after chemotherapy, particularly where there is an incomplete response and also in relapsed disease. Standard lymphoma doses are considered inadequate in the CNS and recommended doses would be 40–45 Gy in 20–25 fractions over four to five weeks (Grade C).<sup>6,23</sup>

## Mycosis fungoides

This will typically be a widespread skin infiltration with radiotherapy used for palliation of thicker plaques. Doses of 8 Gy in two fractions or 12 Gy in three fractions are recommended (Grade C).<sup>6,24</sup>

## Indolent lymphoma

Indolent lymphoma includes follicular lymphoma, small lymphocytic lymphoma and marginal zone lymphoma. Stage I indolent lymphoma has, for many years, been treated with radical IFRT. In advanced stage indolent lymphoma, IFRT may be indicated for control of local symptomatic disease.

A randomised trial comparing 24 Gy to 40 Gy (all in 2 Gy fractions) included patients with early stage indolent lymphoma. There was no difference in local PFS or OS between these two dose arms. A subsequent study randomised patients with follicular and marginal zone lymphoma to receive either 24 Gy in 12 fractions or 4 Gy in two fractions. At 12 weeks, the complete response rate was 68% after 24 Gy and 49% after 4 Gy. Local PFS was also strongly in favour of the 24 Gy arm with a hazard ratio for local progression of 3.42 (95% confidence interval [CI]: 2.10–5.57). Toxicity was low in both arms (Level 1b).<sup>6,25</sup>

### Recommendation

#### **For the radical treatment of stage I, indolent lymphoma, or durable palliation in more advanced stages:**

24 Gy in 12 fractions over 2.5 weeks (Grade B)

The types of evidence and the grading of recommendations used within this review are based on those proposed by the Oxford Centre for Evidence-based Medicine.<sup>6</sup>

## Palliative treatment of non-Hodgkin lymphoma

In patients with follicular lymphoma, high response rates have been achieved after low-dose IFRT (4 Gy in 1 or 2 fractions), however, the randomised trial comparing 4 Gy to 24 Gy showed that, while effective in many patients, 4 Gy was inferior for local control (Level 1b).<sup>6,25,26</sup> Where short-term palliation is the aim of treatment, 4 Gy in 2 fractions may be considered.

For aggressive lymphoma, a single dose of 8 Gy or short-course palliation such as 20 Gy in five fractions or 30 Gy in ten fractions are effective and appropriate for the palliative treatment of many patients with a limited prognosis (Grade D).<sup>6</sup>

### Recommendations

**In the palliative management of lymphoma, there is evidence to support the following regimens:**

#### **Indolent lymphoma:**

24 Gy in daily 2 Gy fractions over 2.5 weeks (Grade A)

#### **For short-term palliation in follicular or marginal zone lymphoma:**

4 Gy in 2 fractions (Grade A)

#### **Intermediate/high-grade lymphoma:**

Single dose 8–10 Gy (Grade D)

20 Gy in 5 fractions over 1 week (Grade D)

30 Gy in 10 fractions over 2 weeks (Grade D)

The types of evidence and the grading of recommendations used within this review are based on those proposed by the Oxford Centre for Evidence-based Medicine.<sup>6</sup>

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## 9. Paediatric cancer

### Background

Radiotherapy (RT) is an important modality of therapy in the local control of paediatric malignancies and the majority of paediatric tumours are radiosensitive. However, for many children, long-term survival comes at the price of long-term effects of treatment. Long-term effects of radiotherapy include soft tissue hypoplasia, impaired bone growth, endocrine dysfunction, impaired fertility, neuropsychological effects of irradiation of the central nervous system (CNS) and radiation-induced malignancy.

Currently, 40–50% of children with cancer receive radiotherapy as part of their initial treatment. It is extremely important that radiotherapy for children should be undertaken only in specialised centres associated with the Children's Cancer and Leukaemia Group (CCLG) paediatric oncology centres. The paediatric radiotherapy team should include a specialist paediatric therapy radiographer, specialist nurse and play specialist. The components of the paediatric multidisciplinary team are described in The Royal College of Radiologists' *Good practice guidance for paediatric radiology*.<sup>1</sup>

Wherever possible parents of children requiring radiotherapy should be offered the opportunity for their child to have treatment within an appropriate National Cancer Research Institute (NCRI) portfolio or international trial.

*Radiotherapy for children should only be carried out in designated departments associated with CCLG centres. The current document summarises typical dose-fractionation policies as applied in CCLG centres in the UK.*

### Leukaemia

The leukaemias account for the largest group of paediatric malignancies, with approximately 80% having acute lymphoblastic leukaemia (ALL). The remainder have acute non-lymphoblastic leukaemia (ANLL), usually acute myeloid leukaemia (AML) or, rarely, chronic myeloid leukaemia (CML). Currently more than 85% with ALL and 65% with AML are long-term survivors. During the 1960s and 1970s, the routine use of prophylactic whole-brain radiotherapy (WBRT) and intrathecal methotrexate reduced the risk of CNS relapse to less than 10%. In current protocols, the use of WBRT is no longer standard but may be employed for patients who present with CNS involvement.<sup>2</sup>

#### Recommendation

##### **Whole brain radiotherapy childhood leukaemia:**

24 Gray (Gy) in 15 fractions of 1.6 Gy daily over 3 weeks (Level B)

The types of evidence and the grading of recommendations used within this review are based on those proposed by the Oxford Centre for Evidence-based Medicine.<sup>3</sup>

Boys who suffer a testicular relapse may be treated with testicular radiotherapy, generally with electrons, encompassing a clinical target volume (CTV) which includes both testes, scrotum and the inguinal canal supero-laterally as far as the deep inguinal ring.<sup>4</sup>

### Recommendation

#### **Testicular irradiation in childhood leukaemia:**

24 Gy in 12 fractions of 2.0 Gy daily over 2.5 weeks (Level B)

The types of evidence and the grading of recommendations used within this review are based on those proposed by the Oxford Centre for Evidence-based Medicine.<sup>3</sup>

### Total body irradiation (TBI)

As in the treatment of adults with haematological malignancies, TBI is an important technique usually used together with high-dose cyclophosphamide (cyclo-TBI) as the conditioning regimen prior to bone marrow transplantation (BMT). Individual techniques for TBI have evolved in different departments, often depending on availability of treatment machines. TBI planning may use CT and dosimetry is usually based on *in vivo* measurements. For such a large and complex target volume, it is not feasible to adhere to the International Commission on Radiation Units and Measurements (ICRU) 50 guidelines of a range of -5% to +7%; a range of -10% to +10% is more realistic.<sup>5-7</sup>

### Recommendations

#### **TBI in childhood leukaemia:**

14.4 Gy in 8 fractions of 1.8 Gy twice daily with a minimum interfraction interval of 6 hours over 4 days (Level C)

12 Gy in 6 fractions of 2 Gy twice daily with a minimum interfraction interval of 6 hours over 4 days (Level C)

#### **Cranial boost where indicated after TBI:**

5.4 Gy in 3 fractions of 1.8 Gy over 3 days (Level D)

#### **TBI for bone marrow transplant (BMT) in benign haematological disorders, for example, Fanconi's anaemia and thalassaemia:**

2–3 Gy single dose (Level D)

The types of evidence and the grading of recommendations used within this review are based on those proposed by the Oxford Centre for Evidence-based Medicine.<sup>3</sup>

### Hodgkin lymphoma

The survival rate for children with Hodgkin lymphoma is approximately 90%. In current protocols, the aims are to maintain this good overall survival rate and reduce long-term effects.<sup>9-11</sup> Typically patients are selected for radiotherapy if their disease does not respond well on 18F-fluorodeoxyglucose (18F-FDG) positron emission tomography-computed tomography (PET-CT) reassessment after initial chemotherapy. All sites initially involved are usually treated.

### Recommendations

#### **Hodgkin lymphoma: sites of initial involvement:**

19.8 Gy in 11 fractions over 2.2 weeks. Where there is significant residual disease (Level B)

#### **Hodgkin lymphoma: residual disease following chemotherapy or bulky sites:**

Boost of 10 Gy in 5 fractions over 1 week (Level B)

The types of evidence and the grading of recommendations used within this review are based on those proposed by the Oxford Centre for Evidence-based Medicine.<sup>3</sup>

## Neuroblastoma

Patients with neuroblastoma are risk-stratified at presentation by age, stage and molecular pathology. External-beam radiotherapy to the primary tumour bed is indicated for all patients with 'high risk' disease (for example, aged greater than one year with stage M4 disease at presentation, patients with localised disease and MYCN amplification at presentation, and selected patients with intermediate-risk disease). The intent is to maximise the probability of local tumour control following chemotherapy and surgical resection of the primary tumour.<sup>12-14</sup>

### Recommendation

#### **Neuroblastoma: postoperative radiotherapy to the tumour bed:**

21 Gy in 14 fractions over 3 weeks (Level B)

The types of evidence and the grading of recommendations used within this review are based on those proposed by the Oxford Centre for Evidence-based Medicine.<sup>3</sup>

## Wilms' tumour (nephroblastoma)

In Europe, the series of International Society of Paediatric Oncology (SIOP) studies have been based on preoperative chemotherapy to 'downstage' the primary, reducing the surgical morbidity, particularly the number who have tumour rupture at surgery and the number who require flank radiotherapy. Initial treatment is with preoperative chemotherapy with actinomycin-D and vincristine, with delayed nephrectomy after six weeks of preoperative chemotherapy. Postoperative adjuvant therapy is based on subsequent pathological staging and allocation of risk status (good risk versus intermediate risk versus poor risk histology).

Postoperative chemotherapy is given using the drugs vincristine, actinomycin D and sometimes other drugs; the number of drugs and duration are dependent upon the staging.

Postoperative flank radiotherapy is employed for stage III patients, that is, those with incompletely resected primary tumours, pre- or perioperative tumour rupture or histologically involved lymph nodes. Patients with gross pre- or perioperative tumour

rupture or disseminated intra-abdominal disease should receive whole abdominal radiotherapy.<sup>15</sup> Patients with lung metastases who do not achieve a complete response to chemotherapy should receive whole lung radiotherapy.<sup>16</sup>

### Recommendations

#### **Wilms' tumour: postoperative radiotherapy to flank:**

**Intermediate risk:** 14.4 Gy in 8 fractions of 1.8 Gy daily over 1.5 weeks (Level B)

**High risk:** 25.2 Gy in 14 fractions of 1.8 Gy over 2 weeks (Level B)

#### **Wilms' tumour: whole abdominal radiotherapy**

Depending upon histopathological risk group:

15 Gy in 10 fractions over 2 weeks (Level B) or

21 Gy in 14 fractions of 1.5 Gy over 2 weeks (Level B)

#### **Wilms' tumour: whole lung radiotherapy**

15 Gy in 10 fractions of 1.5 Gy over 2 weeks (Level B)

The types of evidence and the grading of recommendations used within this review are based on those proposed by the Oxford Centre for Evidence-based Medicine.<sup>3</sup>

## Rhabdomyosarcoma

The basis of treatment has generally involved the use of intensive chemotherapy with the aim of improving survival, and reducing the use of local therapy with surgery and/or radiotherapy, thus minimising long-term effects. Treatment is stratified according to risk groups based on parameters such as histological subtype (embryonal versus alveolar histology), stage of disease and primary tumour site. Patients in the 'low-risk' category, that is, those with localised tumours which are microscopically completely resected, are treated with chemotherapy using actinomycin-D and vincristine for nine weeks.<sup>17-19</sup> Standard risk tumours are those which are locally more extensive but at selected favourable sites, for example, the vagina, uterus or paratestis, and are treated with ifosfamide, vincristine and actinomycin-D. Poor responders switch to a six-drug combination. High-risk tumours include other incompletely resected tumours, including all those arising in parameningeal sites (nasopharynx, middle ear) and those with involved lymph nodes. These are treated with further chemotherapy.

Brachytherapy, typically in conjunction with conservative surgery, may be considered for very carefully selected patients such as those with localised embryonal bladder/prostate and female genital tract rhabdomyosarcoma. Such patients should be referred to a specialist centre with experience in this type of treatment.

### Recommendations

#### **Embryonal rhabdomyosarcoma:**

##### **Post-chemotherapy, no surgery:**

41.4 Gy in 23 fractions of 1.8 Gy following complete response to chemotherapy and 50.4 Gy in 28 fractions of 1.8 Gy for incomplete response (Level B)

Consider boost of 5.4 Gy in 3 fractions of 1.8 Gy for large tumours and/or poor response to chemotherapy

##### **Postoperative:**

36 Gy in 20 fractions of 1.8 Gy (Level B)

#### **Alveolar rhabdomyosarcoma:**

##### **Post-chemotherapy, no surgery:**

50.4 Gy in 28 fractions of 1.8 Gy (Level B)

Consider boost of 5.4 Gy in 3 fractions of 1.8 Gy for large tumours and/or poor response to chemotherapy

##### **Postoperative:**

41.4 Gy in 23 fractions of 1.8 Gy (Level B)

The types of evidence and the grading of recommendations used within this review are based on those proposed by the Oxford Centre for Evidence-based Medicine.<sup>3</sup>

### **Ewings sarcoma/peripheral primitive neuroectodermal tumour (PPNET)**

Initial treatment is with chemotherapy in conjunction with the appropriate use of local therapy. The decision as to whether surgery, radiotherapy or both should be employed for local control of the primary tumour demands careful multidisciplinary discussion. In previous series, patients' survival has been better following local treatment with surgery compared with radiotherapy alone. However, these series are confounded by selection bias with patients with smaller tumours selected for surgery.<sup>20,21</sup>

**Recommendations****Ewings and PPNET:****Phase 1 and postoperative volume:**

45 Gy in fractions of 1.8 Gy over 5 weeks (Level B)

**Phase 2 for macroscopic disease:**

9.6 Gy in fractions of 1.8–2.0 Gy (Level B)

**Ewings and PPNET:****Whole lung radiotherapy:**

15 Gy in 10 fractions over 2 weeks (Level B)

The types of evidence and the grading of recommendations used within this review are based on those proposed by the Oxford Centre for Evidence-based Medicine.<sup>3</sup>

**Central nervous system tumours****Low-grade astrocytoma**

These comprise the most common group of paediatric CNS tumours. Modern management is based on the recognition that low-grade gliomas may undergo long periods of 'quiescence' even when not completely resected. The current five-year survival rate is 85%, but late relapse is not uncommon.

Treatment is initially with surgical resection, as complete as is considered safe.

In the recently closed SIOP Low-Grade Glioma (LGG2) study, those over the age of seven were treated with radiotherapy. Those aged seven or under received chemotherapy with the aim of delaying radiotherapy.<sup>22</sup>

**Recommendation****Low-grade astrocytoma:**

54 Gy in 30 fractions of 1.8 Gy daily over 6 weeks (Level B)

The types of evidence and the grading of recommendations used within this review are based on those proposed by the Oxford Centre for Evidence-based Medicine.<sup>3</sup>

For patients who present with spinal cord primary low-grade glioma, the management policy will be similar.

**Recommendation****Low-grade spinal astrocytoma:**

50.4 Gy in 28 fractions of 1.8 Gy over 5.5 weeks (Level B)

The types of evidence and the grading of recommendations used within this review are based on those proposed by the Oxford Centre for Evidence-based Medicine.<sup>3</sup>

### High-grade astrocytoma

Unlike adults, high-grade astrocytomas are uncommon in childhood. However, in common with adults, the outlook is generally poor. Survival is currently approximately 20% at five years. Current management is based on surgical resection and postoperative chemoradiotherapy with temozolomide.<sup>23</sup>

#### Recommendation

##### High-grade astrocytoma:

**Under 14 years:** 54 Gy in 30 fractions over 6 weeks (Level B)

**Over 14 years:** 60 Gy in 30 fractions over 6 weeks (Level B)

The types of evidence and the grading of recommendations used within this review are based on those proposed by the Oxford Centre for Evidence-based Medicine.<sup>3</sup>

### Ependymoma

The overall five-year survival rate is approximately 50–60%. In the majority of studies, prognostic factors include tumour grade and extent of resection. The predominant site of relapse is within the local tumour bed. The majority of collaborative groups now recommend an increased radiotherapy dose (59.4 Gy with conformal techniques) taking care to limit the dose to the brainstem and other adjacent critical structures.<sup>24</sup>

#### Recommendation

##### Ependymoma:

59.4 Gy in 33 fractions in 6.5 weeks (Level B)

The types of evidence and the grading of recommendations used within this review are based on those proposed by the Oxford Centre for Evidence-based Medicine.<sup>3</sup>

### Medulloblastoma

Medulloblastoma is a primitive neuronal tumour which arises in the cerebellum. It is notable for its propensity for metastatic spread via the craniospinal fluid (CSF) and its radiosensitivity. PNET arises elsewhere in the CNS, usually the supratentorial cerebral cortex, where they are referred to as supratentorial PNET (StPNET). PNET arising in the pineal area are referred to as pineoblastoma.

Standard therapy for medulloblastoma/PNET is initial maximal surgical resection followed by craniospinal radiotherapy and a 'boost' to the primary site.

Current studies are based on the allocation of risk status. Standard-risk disease refers to non-metastatic medulloblastoma with complete or near-complete surgical resection. High-risk disease includes patients with medulloblastoma with metastases or postsurgical residue and StPNET.

It is standard practice to employ adjuvant chemotherapy (vincristine, CCNU, cisplatin) following radiotherapy for patients with standard-risk disease and more intensive chemotherapy for high-risk disease.<sup>25–27</sup>

### Recommendations

#### Medulloblastoma/PNET:

##### Standard-risk craniospinal:

23.4 Gy in 13 fractions over 2.5 weeks (Level B) followed by boost to tumour bed or whole posterior fossa

30.6 Gy in 17 fractions in 3.5 weeks (Level B)

##### High-risk medulloblastoma and StPNET craniospinal

36.0 Gy in 20 fractions over 4 weeks (Level B)

39.6 Gy in 22 fractions over 4.4 weeks (St Jude's regimen for M2–3) (Level B)

Followed by boost to primary site to a total of 54.0–55.8 Gy in 1.8 Gy fractions (Level B)

Boost to sites of metastases to a total of 50.4 Gy (spinal) and 54–55.8 Gy (intracranial) in 1.8 Gy fractions (Level B)

The types of evidence and the grading of recommendations used within this review are based on those proposed by the Oxford Centre for Evidence-based Medicine.<sup>3</sup>

## Intracranial germ cell tumours

Intracranial germ cell tumours account for approximately 30% of paediatric germ cell tumours. For germinoma, although in the past craniospinal radiotherapy has been standard, future trials will explore the role of chemotherapy and whole ventricular radiotherapy. Patients with non-germinoma receive platinum based chemotherapy and radiotherapy, either focal for non-metastatic disease or craniospinal for metastatic disease.<sup>28,29</sup>

### Recommendations

#### Germinoma – craniospinal radiotherapy, no chemotherapy:

24 Gy in 15 fractions over 3 weeks followed by boost to primary site (Level B)

16 Gy in 10 daily fractions over 2 weeks (Level B)

#### Germinoma – post-chemotherapy: whole ventricular radiotherapy:

24 Gy in 15 fractions over 3 weeks followed by boost to residual disease (Level B)

16 Gy in 10 daily fractions over 2 weeks (Level B)

#### Non-germinomatous tumours – primary tumour:

54 Gy in 30 fractions over 6 weeks (Level B)

#### Meningeal metastases – craniospinal axis:

30 Gy in 20 fractions over 4 weeks (Level B)

The types of evidence and the grading of recommendations used within this review are based on those proposed by the Oxford Centre for Evidence-based Medicine.<sup>3</sup>



## Brain stem glioma

This includes tumours arising in the midbrain, pons and medulla. Historically they were regarded as a single entity. However, it is now clear that they can be subdivided into focal (5–10%), dorsal exophytic (10–20%), cervico-medullary (5–10%) and diffuse intrinsic tumours (75–85%).

The majority of children with brain stem gliomas have diffuse intrinsic pontine glioma (DIPG), which are usually high-grade astrocytomas. Their prognosis is very poor with a median survival of approximately nine months and very few long-term survivors.<sup>30</sup>

### Recommendation

#### Brain stem glioma:

54 Gy in 30 fractions over 6 weeks (Level B)

The types of evidence and the grading of recommendations used within this review are based on those proposed by the Oxford Centre for Evidence-based Medicine.<sup>3</sup>

## Further reading

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## 10. Penile cancer

### Background

Squamous cell carcinoma of the penis is rare; treatment needs to consider both the primary lesion and the potential for lymphatic dissemination. Bilateral lymph node involvement is common due to the rich penile lymphatic drainage. Lymph node spread generally occurs in a predictable manner, involving superficial inguinal, then deep inguinal and then pelvic lymph nodes.<sup>1,2</sup> Approximately 20–30% of patients with positive inguinal nodes have positive pelvic nodes.<sup>1</sup> Lymph node status is a major prognostic factor for penile cancer.<sup>1</sup> Surgery is the mainstay of locoregional treatment.<sup>3</sup> There is a lack of high level evidence to guide management.

### Radical radiotherapy for primary lesion

Primary disease is rarely managed non-surgically in the current era, with the development of penile-preserving and reconstruction surgical techniques and the need for surgical lymph node management.<sup>4</sup> Radiotherapy remains an effective penile-sparing alternative and may be delivered with external beam radiotherapy (EBRT) with tissue equivalent bolus (Level 3) or brachytherapy (Level 3).<sup>5</sup> Brachytherapy provides good control rates with acceptable morbidity and can be considered for T1/2 and selected T3 lesions according to the 2013 American Brachytherapy Society-Groupe Européen de Curiethérapie-European Society of Therapeutic Radiation Oncology (ABS-GEC-ESTRO) guidelines.<sup>6,7</sup> Only a limited number of series have reported outcomes with EBRT; a higher risk of local failure has been associated with a total dose <60 Gray (Gy) (dose per fraction <2 Gy, treatment time >45 days), T3 or greater disease and higher tumour grade.<sup>8–12</sup>

Lymph nodes are managed with either a sentinel lymph node biopsy or dissection.<sup>4</sup> Elective irradiation of clinically and radiologically N0 inguinal lymph nodes is of unproven efficacy and is not performed.<sup>4</sup>

If a primary penile cancer is treated non-surgically, either interstitial brachytherapy or EBRT are appropriate.

#### Recommendations

50 Gy in 16 fractions over 3 weeks (Grade C)<sup>11</sup>

55 Gy in 20 fractions over 4 weeks (Grade D)

60 in 30 fractions over 6 weeks (Grade C)<sup>10</sup>

66 in 33 fractions over 6.5 weeks (Grade C)<sup>10</sup>

The types of evidence and the grading of recommendations used within this review are based on those proposed by the Oxford Centre for Evidence-based Medicine.<sup>5</sup>

### Unresectable primary and lymph node disease or locoregionally recurrent tumour

For patients with resectable primary and lymph node disease, up front surgery is the standard approach. For unresectable disease, there is interest in the use of multimodality treatment, although there is no standard approach. Neoadjuvant chemotherapy is an option with a view to downstaging the disease to facilitate surgery.<sup>13,14</sup> The use of either neoadjuvant or definitive radiotherapy or radiotherapy with concomitant chemotherapy are alternative approaches.<sup>4</sup> The radiotherapy target volume is individualised, but may include

the whole pelvis with a boost to sites of gross disease; intensity-modulated radiotherapy (IMRT) may have a role in improving the tolerability of treatment (Grade D).<sup>5</sup> One reported schedule is 45 Gy in 20 fractions to the whole pelvis and inguinal regions followed by a 12 Gy in five fraction boost to gross disease.<sup>15</sup> Combining radiotherapy with concurrent chemotherapy can be considered, although there is no direct evidence to support the combination in penile cancer (Level 4).<sup>5</sup>

### Recommendations

#### Dose to pelvis/inguinal regions:

45–50 Gy in 25 fractions over 5 weeks (Grade D)

50.4 Gy in 28 fractions over 5.5 weeks (Grade D)

45 Gy in 20 fractions over 4 weeks (Grade D)

Boost dose to gross disease: up to a total of 55–66 Gy depending on tumour volume/site (Grade D)

The types of evidence and the grading of recommendations used within this review are based on those proposed by the Oxford Centre for Evidence-based Medicine.<sup>5</sup>

### Adjuvant radiotherapy

The current European Society for Medical Oncology (ESMO) guidelines recommendation for patients with mobile inguinal lymph nodes is an inguinal dissection with a subsequent pelvic lymph node dissection if  $\geq 2$  inguinal lymph nodes are positive or in the presence of extracapsular spread (ECS).<sup>4</sup> The subsequent role of adjuvant radiotherapy is controversial based on limited data (Level 2, Grade D), with the rationale provided by the observation of a significant rate of lymph node recurrence in patients treated with lymphadenectomy with positive lymph node rates varying between 25% and 77%.<sup>5,16–18</sup>

Two recent series have reported on the use of adjuvant radiotherapy for  $\geq 2$  lymph nodes or extracapsular spread.<sup>15,19</sup> In the series of 161 patients from The Netherlands Cancer Institute, 67 patients received adjuvant radiotherapy to a dose of 50 Gy in 25 fractions, delivered to the involved inguinal lymph nodes  $\pm$  involved pelvic lymph node regions; analysis identified high-risk patients as having  $\geq 3$  unilateral inguinal lymph nodes, extracapsular spread or pelvic lymph node involvement.<sup>19</sup> In a series from Leeds, the target volume include the whole pelvis and inguinal regions to a dose of 45 Gy in 20 fractions followed by a boost to gross disease of 12 Gy in five fractions.<sup>15</sup> In both of these series, outcomes were superior to a series which reported on ECS without adjuvant radiotherapy.<sup>2</sup> One small series reported the adjuvant treatment of nine patients to a conventionally fractionated dose of 54 Gy after dissection of pathological lymph nodes, with only one regional recurrence compared with three of five patients who did not receive adjuvant radiotherapy.<sup>20</sup>

The role of concurrent chemotherapy remains an important unanswered question, extrapolated from other disease sites, with the caution that toxicity will be increased in a cohort of patients who are usually elderly. A forthcoming trial of chemoradiation, (International Advanced Penile Cancer Trial, InPACT) will provide more data.<sup>21</sup>

The use of IMRT can be considered (Grade D).<sup>5</sup>

### Recommendations

#### **Based on the forthcoming InPACT chemoradiotherapy trial are:<sup>21</sup>**

54 Gy in 25 fractions over 5 weeks to inguinal regions

Boost sites of residual disease to 57 Gy (Grade D)

#### **Pelvic dose:**

45 Gy in 25 fractions over 5 weeks with the option of a boost up to 54 Gy in 25 fractions to sites of residual disease or external iliac lymph nodes in high-risk patients (Grade D)

#### **Other schedules in use include:**

45 Gy in 25 fractions over 5 weeks or  
50.4 Gy in 28 fractions over 5.5 weeks

to pelvis/inguinal regions, with the option of a boost in 1.8–2 Gy per fraction to high-risk areas up to total of 55–66 Gy depending upon the size of boost volume/risk factors (Grade D).

45 Gy in 20 fractions over 4 weeks to pelvis/inguinal regions with 10–12 Gy in 5 fraction boost (Grade D)

The types of evidence and the grading of recommendations used within this review are based on those proposed by the Oxford Centre for Evidence-based Medicine.<sup>5</sup>

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## 11. Prostate cancer

### Background

Early prostate cancer is being diagnosed more frequently because of prostate-specific antigen (PSA) screening. This change in natural history poses new management opportunities and external-beam radiotherapy (EBRT) is only one of several options, which include active surveillance and monitoring, radical surgery and brachytherapy.

### Hormonal therapy and radiation dose

There is Grade A evidence in favour of neoadjuvant or adjuvant androgen deprivation therapy (ADT) for patients with intermediate or high-risk (PSA >10 or Gleason score >7 or T2C–T3) prostate cancer treated with radical radiotherapy, although with the likelihood of significant toxicity reducing quality of life.<sup>1</sup> A systematic review of 14 randomised phase III clinical trials showed benefit which increases as the risk factors of stage, PSA and Gleason score increase.<sup>2</sup> The National Institute for Health and Care Excellence (NICE) guidelines recommend six months of ADT for intermediate-risk patients, which may be extended for up to three years in high-risk localised prostate cancer.<sup>3</sup>

There are now five randomised dose escalation studies which have demonstrated superior biochemical relapse-free survival (bRFS) with doses from 74–80 Gray (Gy) compared to lower doses. As yet, however, this has not translated into an overall survival advantage.<sup>4–8</sup>

### Fractionation

A full discussion of the radiobiology of prostate cancer is outside of the remit of this guideline. There is consistent evidence from large retrospective series to support the hypothesis that prostate cancer has a low  $\alpha\beta$  ratio.<sup>9,10</sup> Hypofractionation, using fraction sizes >2 Gy per day, may therefore be radiobiologically advantageous.

### Conventional fractionation (doses-per-fraction in the range 1.8–2 Gy)

The results of conventional fractionation have been comprehensively reviewed and reported. Dose escalation has been shown to improve bRFS in randomised controlled trials (RCT) (64 Gy versus 74 Gy, 68 Gy versus 78 Gy, 70 Gy versus 78 Gy, 70.2 Gy versus 79.2 Gy) as well as meta-analysis.<sup>4–8,11</sup> Unfortunately, this has not translated into improved overall survival as yet.

There is evidence (Grade B) that doses beyond 80 Gy can now be delivered safely with image-guided intensity-modulated radiotherapy (IMRT).<sup>1</sup> There are no reported randomised trials of higher levels of dose escalation, but results from the Memorial Sloan Kettering Cancer Center have shown that the late grade II gastrointestinal toxicity rates of patients treated to 86.4 Gy in fraction sizes of 1.8 Gy was 3%, with <1% developing late grade III gastrointestinal toxicity.<sup>12</sup> Analysis of outcomes from this series showed that the ten-year failure free survival (bNED) was significantly improved by dose escalation: 84% (>75.6 Gy) versus 70% for low-risk disease ( $p=0.04$ ), 76% (>81 Gy) versus 57% for intermediate-risk disease ( $p=0.0001$ ) and 55% (>81 Gy) versus 41% for high-risk patients ( $p=0.0001$ ).<sup>13</sup> In a multivariate analysis including the use of six-months ADT, a dose >81 Gy ( $p=0.027$ ) and ADT ( $p=0.052$ ) were found to be predictive factors for distant metastasis-free survival, but not overall survival.

## Hypofractionation (doses of 2.5 Gy per fraction and above)

Two historical randomised trials which compared hypofractionation (52.5–55 Gy in 20 fractions) with control arms of 60–66 Gy in 33 fractions in 6.5 weeks, doses that, by current standards, are low. The results show a trend towards a lower four-year bNED rate with hypofractionation.<sup>14,15</sup>

The Christie Hospital has reported their experience using 50 Gy in 16 fractions with a conformal technique. The overall bNED rates at five years were 82% for low grade; 56% for intermediate and 39% for high risk. These outcomes are comparable to those achieved using more protracted regimens (Level 2b) with toxicity greater than or equal to Radiation Therapy Oncology Group (RTOG) grade 2 in 5% for bladder and 9% for gastrointestinal (GI).<sup>1,16</sup>

Nearly 8,000 patients have been randomised into completed and ongoing trials of hypofractionation; including the Conventional or Hypofractionated High Dose Intensity Modulated Radiotherapy for Prostate Cancer (CHHiP) trial, the Hypofractionated versus Conventionally Fractionated Radiotherapy for Patients with Localised Prostate Cancer (HYPRO) trial, the Scandinavian-led Phase III Study of HYPOfractionated Radiotherapy of Intermediate Risk Localised Prostate Cancer (HYPO) study, the Canadian PROFIT study and the North American RTOG 0415 study.<sup>4,17–21</sup> Toxicity of moderate hypofractionation at two-year follow-up (based on physician reported outcomes) was as low as with conventional fractionation in the CHHiP study, which compared 74 Gy in 37 fractions to 60 Gy in 20 fractions and 57 Gy in 19 fractions.<sup>4</sup> There is a suggestion that equivalent disease-free survival (DFS) can be obtained at the expense of increased genitourinary (GU) or GI toxicity although overall toxicity remains acceptable.<sup>17,22,23</sup>

Results, in terms of disease control, from three of the hypofractionation trials have now been presented in abstract form. The CHHiP trial showed non-inferiority between 60 Gy in 20 fractions and 74 Gy in 37 fractions; the HYPRO study showed non-inferiority between 78 Gy in 39 fractions and 64.6 Gy in 19 fractions; PROFIT showed non-inferiority between 78 Gy in 39 fractions and 60 Gy in 20 fractions and the RTOG 0415 study showed non-inferiority between 73.8 Gy in 41 fractions and 70 Gy in 28 fractions.<sup>24,25</sup>

High-dose-rate (HDR) brachytherapy is an alternative means of delivering hypofractionated radiation as a boost to achieve dose escalation after 45–46 Gy in 1.8–2 Gy daily fractions or 37.5 Gy in 15 fractions.<sup>26–28</sup> The ASCENDE-RT trial shows that low dose rate (LDR) brachytherapy as a boost after 46 Gy in 23 fractions is superior to external-beam 76 Gy in 38 fractions.<sup>28</sup>

Profound hypofractionation (defined as 6 Gy per fraction or more) has been shown to be feasible and safe in cohort studies, with high levels of disease control in low-risk patients. The Prostate Advances in Comparative Evidence (PACE) trial is randomising between standard of care (surgery or image-guided intensity-modulated radiotherapy [IG-IMRT]), and stereotactic radiotherapy (36.25 Gy in five fractions); HYPO compares 78 Gy in 39 fractions versus 42.7 Gy in seven fractions and has recruited 1,000 patients in Scandinavia with a target recruitment of 1,920 patients.<sup>18,269</sup>

## Postoperative radiotherapy

There is evidence (Grade A) from three randomised trials, that adjuvant postoperative radiotherapy using 60–64 Gy and 2 Gy per fraction improves recurrence rates in postoperative patients considered to be at high risk of recurrence.<sup>1,30–29</sup> The optimal timing of postoperative radiotherapy in this group, whether immediate or at first evidence of PSA recurrence, is not known; this and the benefit of adjuvant ADT in the postoperative setting are the two primary questions being addressed in the ongoing Medical Research Council (MRC) Radiotherapy and Androgen Deprivation in Combination After Local Surgery (RADICALS) trial, using either 66 Gy in 33 fractions or 52.5 Gy in 20 fractions.<sup>33</sup>

## Radiotherapy technique

Dose escalation increases the side-effects of treatment. This can be mitigated by using IMRT or arc techniques (volumetric modulated arc therapy [VMAT] or Rapidarc®) to minimise dose to the organs at risk. The role of lymph node irradiation remains uncertain.<sup>34,35</sup> It is possible to identify patients who have a significant risk of lymph node involvement, but the results of randomised trials to address the value of elective nodal irradiation are equivocal. It may be considered for high-risk patients, recognising that the larger volume is associated with higher toxicity.

IMRT or arc techniques (VMAT or Rapidarc) with appropriate IGRT are the standard of care when delivering high-dose radiation to the prostate. Fiducial markers or cone beam images should be used for verification to minimise interfraction variation.<sup>36,37</sup>

### Recommendations

**Radical radiotherapy to the prostate should be delivered using IMRT or arc (VMAT or Rapidarc) techniques with IGRT verification. Acceptable regimens include:**

74–78 Gy to the prostate in 37–39 fractions over 7.5 weeks (Grade A)  
60 Gy in 20 fractions over 4 weeks (Grade A)

Or using a brachytherapy boost:

37.5 Gy in 15 fractions over 3 weeks followed by 15 Gy HDR brachytherapy boost (Grade B)

46 Gy in 23 fractions over 4.5 weeks followed by 115 Gy LDR brachytherapy boost (Grade B)

### **Nodal irradiation:**

55–60 Gy in 37 fractions over 7.5 weeks or equivalent (Grade D)

### **Postoperatively:**

66 Gy in 33 fractions over 6.5 weeks or  
52.5 Gy in 20 fractions over 4 weeks (Grade C)

The types of evidence and the grading of recommendations used within this review are based on those proposed by the Oxford Centre for Evidence-based Medicine.<sup>1</sup>

## Palliative radiotherapy

Palliative radiotherapy may be indicated in the event of troublesome haemorrhage, outflow obstruction or pressure symptoms. There is no evidence to guide fractionation.

### Recommendations

#### **For palliation standard schedules are used as follows:**

21 Gy in 3 fractions, alternate days over 1 week (Grade D)

20 Gy in 5 fractions over 1 week (Grade D)

30 Gy in 10 fractions over 2 weeks (Grade D)

8–10 Gy single dose (Grade D)

The types of evidence and the grading of recommendations used within this review are based on those proposed by the Oxford Centre for Evidence-based Medicine.<sup>1</sup>

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## 12. Rectal cancer

### Background

Rectal cancer is less common than colon cancer but presents difficult treatment decisions because, while it is frequently curable, treatment may involve radical surgery including the need for a colostomy, which can have a profound effect on a survivor's quality of life.

Equally, recurrent rectal cancers produce distressing symptoms and are difficult to treat and frequently require re-irradiation for symptom control, exenterative surgery or both.

The aim of radiotherapy in rectal cancers is to allow radical treatment to take place for more advanced cancers or to reduce the risk of relapse for early stage cancers (neoadjuvant therapy). In recurrent or incurable disease, radiotherapy can reduce the disease burden and help control symptoms.

### Neoadjuvant therapy

#### Operable tumours

Preoperative radiotherapy is preferred to postoperative treatment as the preoperative technique is more effective and less toxic (Level 1a).<sup>1-3</sup>

For operable rectal cancers, as defined by preoperative pelvic magnetic resonance (MR) scan and staging chest, and abdomen and pelvis computed tomography (CT) scans, preoperative short-course rectal radiotherapy (SCRT) has been evaluated in several prospective randomised controlled trials (RCTs). The Dutch total mesorectal excision (TME) versus SCRT (25 Gray [Gy] in five fractions) + TME trial demonstrated a reduction in local recurrence rate, though with a longer median follow-up of 6.1 years the benefit appears to decrease (10.9% versus 5.6%; 49% relative reduction in risk).<sup>4,5</sup> The overall survival was same in both groups (Level 1b).<sup>3</sup> The MRC-07 trial demonstrated the advantage of SCRT (25 Gy in five fractions) for operable rectal cancer over selective postoperative (chemo-) radiation, in terms of reducing the relative risk of local recurrence after a median follow-up of four years by 61% (HR 0.39, CI 0.27–0.58). This translates to an absolute reduction in risk of local relapse of 6.2% at three years. There is also an absolute improvement in disease free survival of 6% at three years with no effect on overall survival (Level 1b).<sup>3,6</sup>

SCRT, however, increases long-term toxicity, with poorer functional outcomes especially in terms of continence (Level 1b).<sup>3,7</sup> The benefit seems to be mainly for cancers in the mid-rectum and 'intermediate-risk' cancers as defined in the National Institute of Health and Care Excellence (NICE) guidance (Level 1b).<sup>3,8</sup>

#### Recommendation

##### **Short course preoperative radiotherapy:**

25 Gy in 5 daily fractions (Grade A)

Followed by definitive surgery within a week

The types of evidence and the grading of recommendations used within this review are based on those proposed by the Oxford Centre for Evidence-based Medicine.<sup>3</sup>



### Inoperable tumours

For inoperable cancers, cancers which involve or threaten the circumferential margin or for cancers deemed to be at high risk of relapse (NICE guidance), down-staging treatment is recommended.<sup>8</sup> If not otherwise contraindicated, concurrent chemotherapy is recommended to improve response rates.

Doses of >30 Gy improve the response rate and long-course chemo-radiotherapy (LCCRT) has been shown to improve response rate and the likelihood of a R0 resection compared to long-course radiotherapy alone (Level 1a), though the sphincter preservation rate and long-term outcomes appear to be similar.<sup>1,3,9,10</sup> A dose of 45–50.4 Gy in 1.8 Gy per fraction with concurrent chemotherapy is commonly used in the UK, though there is little good quality RCT research underpinning this.

Fluorouracil (5-FU)-based chemotherapy has been used in all major trials since the 1980s and more recently, capecitabine has been shown to have similar efficacy in several phase 2 studies (Level 2b); it has replaced infusional 5-FU as the drug of choice for LCCRT to the rectum.<sup>3,11,12</sup> The UK ARISTOTLE trial (EUDRACT No. 2008-005782-59) is currently investigating the effect of the addition of intravenous (IV) irinotecan to capecitabine on local control rates in advanced rectal cancers.<sup>13</sup> Some authors have reported a 'boost' of 5.4 Gy in three fractions to the gross tumour volume plus margin following 45 Gy in 25 fractions to a larger volume.<sup>12</sup> The efficacy and toxicity of this remains unknown (Level 2b).<sup>3</sup>

Retrospective series from Sweden and the UK, looking at patients with locally advanced unresectable rectal cancer who are unfit for standard LCCRT, treated with 25 Gy in five fractions, have reported significant tumour regression, with 60–80% of patients going on to have delayed surgery (Level 2c).<sup>3,14,15</sup>

#### Recommendations

##### For downstaging LCCRT:

45 Gy in 25 daily fractions with concurrent chemotherapy (Grade A)  
Optional boost of 5.4 Gy in 3 (Grade C) fractions to smaller volume  
50.4 Gy in 28 daily fractions with concurrent chemotherapy (Grade A)

##### For patients not fit for chemotherapy:

45 Gy in 25 daily fractions (Grade A) with or without boost  
50.4 Gy in 28 daily fractions (Grade A)

##### For elderly patients or those with significant co-morbidities:

25 Gy in 5 daily fractions (Grade B)

The types of evidence and the grading of recommendations used within this review are based on those proposed by the Oxford Centre for Evidence-based Medicine.<sup>3</sup>

## Brachytherapy

Low-energy contact brachytherapy (Papillion technique) and high-dose rate (HDR) brachytherapy have both been used, generally in combination with external beam radiotherapy (EBRT), for the treatment of rectal cancers. The aim of treatment has been either palliative or as part of neoadjuvant treatment to improve response. In patients unfit for surgery, these techniques can be used to improve local control.

Apart from one RCT (Level 1b), most of the evidence for the Papillion technique comes from case series and retrospective analyses.<sup>3,16</sup> Similarly, there is only one published RCT evaluating a neoadjuvant 10 Gy in two fractions HDR brachytherapy boost (endoluminal) along with 50.4 Gy in 28 fractions of EBRT (Level 1b).<sup>3,17</sup> This trial showed no improvement in pathological complete response (pCR) or long-term survival despite a better R0 resection rate for T3 tumours treated with HDR brachytherapy boost along with standard chemoradiotherapy.<sup>17</sup> There is increasing experience in the UK and worldwide of the use of the Papillon technique, usually in combination with EBRT, for the radical treatment of patients not suitable for surgery or those who refuse a stoma.<sup>18–22</sup> It is also used for the palliative treatment of patients with a recurrence or metastases not suitable for surgery.

Contact radiotherapy is also offered to patients with a resected pT1 malignant polyp in combination with EBRT, though there is no randomised trial evidence comparing this approach with radical surgery. It may be most appropriate for elderly, frail patients who cannot undergo radical resection.

Dose recommendations are derived from published trials and current consensus among UK centres offering brachytherapy.

### Recommendations

#### Postoperative:

pT1 or pT2 with R1 resection if patient refuses further surgery  
60 Gy in 2 weekly fractions followed by EBRT (Grade B)

#### Radical treatment (unfit patients or those who refuse surgery):

cT1/cNo ( $\leq 3$  centimetres [cm]) 110 Gy in 4 fractions over 6 weeks (30 Gy every 2 weeks  $\times 3$  and final boost 20 Gy) (Grade D)

cT1/cN1 or cT2 cNo/cN1 ( $\leq 3$ cm) low-energy contact brachytherapy should be followed by EBRT (SCRT or external beam chemoradiotherapy (EBCRT)) (Grade D)

#### High-risk patients not fit for surgery cT1, cT2, cT3a, (>3 cm)

45 Gy in 25 fractions or 50.4 Gy in 28 fractions over 5–5.5 weeks with concurrent chemotherapy (Grade D)

or 25 Gy in 5 daily fractions in 1 week in patients not fit for chemotherapy (Grade D)

#### followed by:

contact radiotherapy boost 90 Gy in 3 fractions over 4 weeks to responders (regression to  $< 3$  cm) and consider final boost 20 Gy (total 110 Gy in 4 fractions over 6 weeks) (Grade D)

HDR brachytherapy 12 Gy in 2 fractions (Grade D)

Consider salvage surgery if no response after (EBCRT)

The types of evidence and the grading of recommendations used within this review are based on those proposed by the Oxford Centre for Evidence-based Medicine.<sup>3</sup>

### Palliative treatment

There are no good-quality trials evaluating different dose fractionation schedules for palliative treatment. An appropriate regime should be chosen after considering the patient's likely prognosis, disease burden, symptoms and performance status.

#### Recommendations

30 Gy in 10 daily fractions (Level D)

20–25 Gy in 5 daily fractions (Level D)

HDR brachytherapy 10 Gy at 1 cm single dose (Level D)

The types of evidence and the grading of recommendations used within this review are based on those proposed by the Oxford Centre for Evidence-based Medicine.<sup>3</sup>

### Re-irradiation

Following previous SCRT or LCCRT, some patients will experience a local or regional relapse. Such patients should be discussed in specialist multidisciplinary team meetings (MDTMs) with the relevant expertise in treating recurrent rectal cancer.

Where possible, recurrences after neoadjuvant radiotherapy should be treated with surgery or systemic therapy, avoiding further radiation. However, if surgery is not feasible with clear margins or holds excess risks, re-irradiation should be considered for limited volumes, including the use of stereotactic body radiotherapy (SABR) techniques. This may yield good symptomatic relief as a palliative treatment and long-term control is possible.

When curative resection is to be considered but re-irradiation is required to achieve this, currently, hyperfractionated chemoradiotherapy should be preferred to limit late toxic (Grade D).<sup>3</sup>

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## 13. Renal cancer

There are limited indications for radiotherapy in renal cancer, apart from the treatment of bone and brain metastases, which are covered in the relevant sections of this document (sections 18 and 19).

It has no role in neoadjuvant or primary treatment.

### Adjuvant radiotherapy

Adjuvant radiotherapy is not currently recommended.

There is evidence (Grade C) of improvement in local control when radiotherapy is given adjuvantly postoperatively in high-risk patients with T3 localised tumours using doses of 41.4–63 Gray (Gy) in 1.8–2 Gy fractions.<sup>1–6</sup>

Stereotactic body radiotherapy (SBRT) has been used for highly selected patients with localised primary tumours (>T1a) who are not able to have surgery. Doses of 40–45 Gy in five fractions have been used (Grade C).<sup>1</sup> This is not recommended outside clinical trials at present.<sup>7</sup>

### Palliative radiotherapy

Palliative radiotherapy may be considered for persistent haematuria or pain from large soft tissue masses. Single doses of 8–10 Gy in poor performance status patients (Grade D) for haematuria and 30 Gy in ten fractions for soft tissue masses and pain (Grade D) may be used.<sup>1</sup>

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## 14. Sarcoma

### Background

Radiotherapy is widely used as an adjunct to surgery in the management of soft tissue sarcomas as the risk of failure in the surgical bed can be high. For bone sarcomas, radiotherapy is only occasionally employed in the management of osteosarcomas; indications include incompletely resected or unresectable primary disease.<sup>1</sup> By contrast, radiotherapy remains an integral part of multimodality treatment for Ewings' sarcoma. Clinical experience suggests that sarcomas vary widely in radiosensitivity. Radiotherapy is delivered with conventional fractionation, with no established role for hypo- or hyperfractionation in treatment with curative intent.<sup>2</sup> Intensity-modulated radiotherapy (IMRT) or proton therapy may be appropriate when optimal dose fractionation is not achievable with conventional techniques.

### Resectable extremity soft tissue sarcomas

Surgery is the primary treatment modality in the majority of soft tissue sarcomas. Adjuvant radiotherapy is used to reduce the probability of local recurrence and facilitate surgical sparing of function.<sup>3,4</sup> There are no randomised trials in soft tissue sarcomas dealing purely with dose-fractionation. External beam radiotherapy (EBRT) can be delivered pre- or postoperatively. The Canadian Sarcoma Group SR-2 trial randomised patients to preoperative radiotherapy with 50 Gray (Gy) in 25 fractions compared with postoperative radiotherapy with 66 Gy in 33 fractions.<sup>4</sup> The results suggest that local control is similar with pre- or postoperative radiotherapy, but that preoperative treatment is associated with an increased rate of acute wound complications (predominantly in the lower limb) and that postoperative treatment leads to increased limb fibrosis, joint stiffness, oedema and bone fractures.

Local control is superior with total postoperative doses >64 Gy in the presence of high-risk features for local failure or positive margins.<sup>5,6</sup> If preoperative radiotherapy is delivered, there is no evidence to support a role for a subsequent postoperative boost in the event of positive resection margins.<sup>7,8</sup>

#### Recommendations

##### **Preoperative radiotherapy:**

50 Gy in 25 fractions over 5 weeks (Grade C)

##### **Postoperative radiotherapy:**

50 Gy in 25 fractions over 5 weeks plus a 10 Gy in 5 fraction boost over 1 week for average risk (Grade C)

For post-operative treatment, a boost of up to 16 Gy in 8 fractions over 1.5 weeks is recommended for disease considered at higher risk of local recurrence due to positive margins (Grade C)

This boost may be limited to 10 Gy in 5 fractions at certain anatomical sites (for example, across joints, Achilles tendon, brachial plexus)

The types of evidence and the grading of recommendations used within this review are based on those proposed by the Oxford Centre for Evidence-based Medicine.<sup>9</sup>



## Unresectable extremity soft tissue sarcomas

Where there are no metastases at presentation, patients may be considered for radical radiotherapy with the aim of achieving local control. There is Level 2+ evidence to support a total dose to tumour of  $\geq 63$  Gy.<sup>9,10</sup>

### Recommendation

66 Gy in 33 fractions over 6.5 weeks (Grade C)

The types of evidence and the grading of recommendations used within this review are based on those proposed by the Oxford Centre for Evidence-based Medicine.<sup>9</sup>

## Retroperitoneal soft tissue sarcomas

Surgery is the mainstay of treatment for retroperitoneal sarcomas, however, locoregional recurrence remains the predominant pattern of disease recurrence. The role of radiotherapy remains unproven, with limited supporting data.<sup>11–13</sup> Preoperative radiotherapy is deliverable with minimal toxicity.<sup>11,12</sup> An international expert consensus panel recently concluded that preoperative radiotherapy is preferable to postoperative and provided guidelines on which patients this may be appropriate for, while acknowledging the limited evidence base (Level 4).<sup>9,13</sup>

### Recommendations

#### Preoperative radiotherapy:

50 Gy in 25 fractions over 5 weeks or  
50.4 Gy in 28 fractions over 5.5 weeks (Grade C)

The types of evidence and the grading of recommendations used within this review are based on those proposed by the Oxford Centre for Evidence-based Medicine.<sup>9</sup>

## Desmoid tumours

These rare tumours are locally aggressive but do not metastasise. Consensus now supports a multidisciplinary specialist approach to management, with a period of observation most frequently recommended as initial management.<sup>14</sup> For patients with inoperable disease for whom radiotherapy is judged to be indicated, there is evidence to support the use of 56 Gy in 28 fractions in an attempt to delay progression (Level 4).<sup>9,15,16</sup> Radiotherapy may also be used, at similar doses, to prevent or delay recurrence in patients who have residual disease after surgical excision, if clinically indicated. However, it should be noted that positive margins do not necessarily result in disease progression, so this is not an absolute indication for radiotherapy.

### Recommendation

#### **Definitive or postoperative radiotherapy:**

56 Gy in 28 fractions over 5.5 weeks (Grade C)

The types of evidence and the grading of recommendations used within this review are based on those proposed by the Oxford Centre for Evidence-based Medicine.<sup>9</sup>

### Ewing's-type tumours and primitive neuroectodermal tumour (PNET)

When surgical resection is feasible or appropriate, this is usually carried out after preliminary chemotherapeutic cytoreduction. Where a radical surgical margin is not achieved, then there is evidence to suggest that postoperative radiotherapy at a dose of 54–60 Gy in 28–30 fractions for gross disease, and at least 45 Gy in 25 fractions for microscopic disease, might be beneficial. Surgical resection may not be feasible or appropriate for certain anatomical sites (for example, spine, pelvis), in which case radiotherapy can be used as a radical treatment, although evidence suggests that it is not quite as effective as surgery in achieving local tumour control; evidence indicates that doses of 55–56 Gy in 1.8 Gy fractions can be effective (Level 2b).<sup>9,17–20</sup>

### Recommendations

Doses are based upon the current Euro Ewing 2012 radiotherapy protocol.<sup>21</sup>

#### **For preoperative treatment:**

50.4 Gy in 28 fractions as a single phase. Dose may be reduced to 45 Gy in 25 fractions if necessary due to proximity to organs at risk (Grade C)

#### **Unresectable disease or incomplete macroscopic clearance:**

54 Gy in 30 fractions. A phase 2 boost of 5.4 Gy in 3 fractions may be used respecting organ at risk constraints (Grade C)

#### **For paraspinal tumours:**

50.4 Gy in 30 fractions either as a single phase or an initial phase of 45 Gy in 25 fractions followed by a boost of 5.4 Gy in 3 fractions

#### **For patients at risk of microscopic disease following surgery:**

54 Gy in 30 fractions, delivered with an initial phase of 45 Gy in 25 fractions followed by a 9 Gy in 5 fraction boost (Grade C)

The types of evidence and the grading of recommendations used within this review are based on those proposed by the Oxford Centre for Evidence-based Medicine.<sup>9</sup>

## Lung metastases

Curative intent multimodality treatment for patients with lung metastases includes whole-lung radiotherapy (in patients who have not received busulphan).<sup>22</sup> Recommended doses for whole-lung radiotherapy in the EURO EWING 99 study were 15 Gy (for patients <14 years of age) or 18 Gy (patients >14 years) delivered with 1.5 Gy daily fractions or alternatively using bi-daily fractionation with 1.25 Gy per fraction.<sup>23,24</sup> An appropriate bi-daily fractionation schedule would be 17.5 Gy in 14 fractions of 1.25 Gy per fraction over two weeks with a minimum of a six-hour inter-fraction interval. Other centres have reported that a dose of 15 Gy in ten fractions over three weeks is well tolerated in an adult population.<sup>22</sup> Whole-lung radiotherapy should be computed tomography (CT) planned with an inhomogeneity correction.

### Recommendations

#### Whole-lung radiotherapy:

Doses are based on the current Euro Ewing 2012 radiotherapy protocol.<sup>21</sup>

#### <14 years of age:

15 Gy in 10 fractions over 2 weeks (Grade C)

#### ≥14 years of age:

18 Gy in 12 fractions over 2.5 weeks (Grade C)

The types of evidence and the grading of recommendations used within this review are based on those proposed by the Oxford Centre for Evidence-based Medicine.<sup>9</sup>

## Palliation

Radiotherapy is used to palliate locally uncontrolled and distant disease. With little evidence available, the selection of dose-fractionation schedules is individualised. Higher total doses maybe appropriate for selected patients with local disease to obtain more durable local control. In patients with metastatic soft tissue sarcoma, a recent series reported a high rate of durable pain control with a dose of 39 Gy in 13 fractions (Level 4).<sup>9,25</sup>

### Recommendations

8 Gy in a single fraction (Grade D)

20 Gy in 5 fractions over 1 week (Grade D)

30 Gy in 5 fractions over 5 weeks (Grade D)

30 Gy in 10 fractions over 2 weeks (Grade D)

36 Gy in 12 fractions over 2.5 weeks (Grade D)

39 Gy in 13 fractions over 2.5 weeks (Grade D)

40 Gy in 15 fractions over 3 weeks (Grade D)

The types of evidence and the grading of recommendations used within this review are based on those proposed by the Oxford Centre for Evidence-based Medicine.<sup>9</sup>

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## 15. Seminoma

### Background

Stage I seminoma has between a 15–20% risk of relapse; surveillance without treatment is one option. Relapses principally occur in the para-aortic nodes and the risk can be quantified using factors related to the primary tumour.<sup>1</sup> A tumour >4 centimetres (cm) in size is the most important of these; rete testis involvement may also be a predictor.<sup>2</sup> Adjuvant treatment rather than surveillance may be offered in such cases.

A single dose of carboplatin has been shown to achieve results equal to radiotherapy in terms of overall tumour control and early survival in the TE19 randomised trial.<sup>3</sup> In the UK this approach has now become the standard (Level 1b).<sup>4</sup>

If radiotherapy is considered in this setting then a dose of 20 Gray (Gy) in ten daily fractions treating the para-aortic node chain only has been shown to be as effective as 30 Gy or larger fields (Level 1b).<sup>4,5</sup>

Radiotherapy may also be considered for selected patients with stage IIA and IIB seminoma where there are metastatic para-aortic nodes up to 5 cm.<sup>6</sup> A dose of 30 Gy in 15 daily fractions to the para-aortic nodal chain and ipsilateral iliac nodes is recommended. A boost of 5 Gy to enlarged lymph nodes may be considered (Level 2b).<sup>4,7,8</sup> An alternative approach uses a single dose of carboplatin with radiation fields reduced to the involved para-aortic region only (Level 1b).<sup>4,9</sup>

Radiotherapy carries an excess risk of death as a result of radiation-induced cardiac disease or second cancer.<sup>5</sup> Thirty-year follow-up shows that the relative risk of second malignancy is 1.4; this translates into an increase in the risk of cancer from 15% for the normal population to 25% for the seminoma cohort at 30 years (Level 2b).<sup>4,10</sup>

### Recommendations

Single agent carboplatin will be the usual adjuvant treatment for high-risk stage I disease seminoma (Grade B)

#### **Stage I seminoma for which adjuvant para-aortic radiotherapy is indicated:**

20 Gy in 10 fractions over 2 weeks (Grade A)

#### **Stage IIA or IIB seminoma: para-aortic and ipsilateral iliac radiotherapy (dog leg) or para-aortic radiotherapy alone after carboplatin:**

30 Gy in 15 fractions over 3 weeks (Grade B)

The types of evidence and the grading of recommendations used within this review are based on those proposed by the Oxford Centre for Evidence-based Medicine.<sup>4</sup>

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## 16.

### Skin cancer

## Squamous cell carcinoma and basal cell carcinoma

### Background

Surgery and radiotherapy are both highly effective curative treatment modalities for squamous cell carcinoma (SCC) and basal cell carcinoma (BCC). The choice of treatment modality is determined by factors including age, tumour size and functional/cosmetic outcomes. Surgery is generally preferred for younger patients. Primary radiotherapy is often preferred for regions around the lower eyelids, nose and ear, where better functional/cosmetic results can be achieved. Radiotherapy to the lower leg is often avoided in elderly patients due to the risk of radionecrosis. There appears to be a slightly higher local recurrence rate following radiotherapy for SCCs compared with BCCs.<sup>1</sup> Postoperative radiotherapy for SCC can be considered for high-risk features, for example, positive or close margins, perineural invasion, tumour depth >4 millimetres (mm) and poor differentiation.<sup>2</sup> Elective irradiation of first echelon lymph nodes can be considered for higher risk SCC.<sup>3</sup>

There are no randomised studies examining dose-fractionation; in addition, most series report use of multiple dose-fractionation schedules in historical series.<sup>4</sup> As a consequence, there is wide variation in both total dose and dose per fraction in commonly used schedules, with a variety of pragmatic hypofractionated schedules being widely used.<sup>4,5</sup> Similar doses are used for BCC and SCC, although some suggest higher doses for SCCs.<sup>6</sup> More protracted treatment regimens may provide superior cosmetic results.

A large retrospective study of patients with SCC and BCC showed that schedules of 54 Gray (Gy) in 18 fractions or 44 Gy in ten fractions had similar efficacy with good cosmetic outcomes.<sup>7</sup> A schedule of 34 Gy in five fractions was shown to provide high rates of local control for BCC (five-year recurrence rate of 7%).<sup>8</sup> In a retrospective series employing multiple schedules for BCC and SCC, including 35 Gy in five fractions, no difference in control rates was found between different fractionation schedules.<sup>3</sup> In a large retrospective series of 1,005 predominantly small BCCs/SCCs, single fraction doses of 18, 20 and 22.5 Gy provided a five-year local control rate of 90%; the skin necrosis-free rate at five years was only 84% and necrosis occurred more frequently with the 22.5 Gy dose (Level 4).<sup>9,10</sup>

The relative biological effectiveness of electrons and photons is around 10% less than that for superficial X-rays; treatment with electrons or photons therefore, theoretically, requires a corresponding increase in dose, although this is often not considered in practice.

### Recommendations

**The choice of dose fractionation takes into account patient factors, tumour and field size. The following schedules are examples of those appropriate for the treatment of skin SCCs and BCCs either definitively or adjuvantly:**

Single fraction 18–20 Gy (usually in elderly patients with field size <3 cm) (Grade C)  
 32.5–35 Gy in 5 fractions over 1 week (usually small lesions <4 cm) (Grade C)  
 45 Gy in 10 fractions over 2–3 weeks (Grade C)  
 50 Gy in 15–20 fractions over 3–4 weeks (Grade C)  
 55 Gy in 20 fractions over 4 weeks (Grade C)

### **If large area and in area of poor radiation tolerance:**

60 Gy in 30 fractions over 6 weeks (Grade C)

The types of evidence and the grading of recommendations used within this review are based on those proposed by the Oxford Centre for Evidence-based Medicine.<sup>10</sup>



## Squamous cell carcinoma and regional lymph node disease

### Background

Surgical management of regional lymph node disease is regarded as the treatment of choice. Relapse rates after therapeutic surgery alone to regional lymph node disease are high.<sup>11</sup> Several series have reported multiple factors predictive of regional relapse after surgery, including lymph node >3 cm, multiple involved nodes, extracapsular spread.<sup>11,12</sup> In the head and neck region, the use of adjuvant radiotherapy has been shown to reduce regional recurrence rates and improve disease free survival.<sup>13</sup> In a large retrospective series, the median dose employed was 60 Gy in 30 fractions with a dose of 50 Gy in 25 fractions to elective at risk regions (Level 4).<sup>10,13</sup> Optimal adjuvant dose fractionation will depend upon the anatomical site. In the head and neck region, doses of up to 66 Gy in 33 fractions can be considered in the presence of extracapsular spread.<sup>14</sup> Radical radiotherapy can be considered if surgery is inappropriate or declined.

### Recommendations

#### **For adjuvant radiotherapy to nodal regions considered at high risk of relapse after therapeutic lymphadenectomy:**

50–60 Gy in 25–30 fractions over 5–6 weeks (Grade C)

#### **Where there are high pathological risk features in the head and neck region:**

66 Gy in 33 fractions over 6.5 weeks (Grade C)

The types of evidence and the grading of recommendations used within this review are based on those proposed by the Oxford Centre for Evidence-based Medicine.<sup>10</sup>

## Melanoma

### Background

The primary treatment for cutaneous melanoma is complete local excision. Adjuvant radiotherapy to the primary site is not usually indicated, other than in rare cases of desmoplastic melanoma, which is a rare subtype associated with perineural spread and increased risk of local failure. Adjuvant radiotherapy to the primary site can be considered for desmoplastic melanoma resected with close margins, perineural invasion or lesions thicker than 4 mm.<sup>14,15</sup>

For patients at high risk of regional recurrence after a therapeutic lymphadenectomy, adjuvant hypofractionated radiotherapy with a dose of 48 Gy in 20 fractions over four weeks has been shown in a Trans Tasmann Radiation Oncology Group (TROG) phase III trial to reduce the risk of regional recurrence, although has no effect on overall survival (Level 1b).<sup>10,16</sup> Hypofractionated schedules have commonly been used for melanoma although no direct comparison with conventional 2 Gy per day fractionation has been performed. The MD Anderson Cancer Centre has reported an alternative hypofractionated schedule of 30 Gy in five fractions (two fractions per week) with high rates of regional control (Level 4).<sup>10,17</sup>

## Recommendations

### Adjuvant radiotherapy to nodal regions:

48 Gy in 20 fractions over 4 weeks (Grade A)

50–60 Gy in 25–30 fractions over 5–6 weeks (Grade C)

The types of evidence and the grading of recommendations used within this review are based on those proposed by the Oxford Centre for Evidence-based Medicine.<sup>10</sup>

## Merkel cell carcinoma

### Background

Merkel cell cancer is a rare, aggressive, neuroendocrine skin malignancy with a propensity for locoregional and distant recurrence. The primary therapy for Merkel cell carcinoma is surgery. Merkel cell cancer is considered radiosensitive and multiple retrospective series provide evidence that adjuvant postoperative radiotherapy to the primary tumour bed and draining lymphatics provides high rates of locoregional control for higher risk tumours; wide margins are required due to a tendency for edge recurrences (Level 4).<sup>10,18–20</sup> A prospective cohort study in patients with lymph node positive disease has demonstrated that radiotherapy alone to the regional lymph nodes provides equally high rates of regional control, comparable to surgical outcomes, with no overall survival difference (Level 2b).<sup>10,21</sup> Elective lymph node treatment is not always feasible depending upon the anatomical site of the primary tumour and patient fitness. There are no randomised trials to assess the optimal dose fractionation. Radical radiotherapy can be considered in medically inoperable patients or when the functional/cosmetic deficits due to surgery are considered excessively morbid. Limited data suggest that definitive radiotherapy can be effective. In a series of 43 patients an in-field control rate of 75% was achieved; doses of 50–55 Gy in 20–25 fractions were recommended.<sup>22</sup> In a small series, a dose of 60 Gy was effective in the definitive treatment of the primary lesion, while others have employed doses of up to 70 Gy (Level 4).<sup>10,18,23</sup> In most series, adjuvant doses of >50 Gy are used.<sup>18,19,21</sup> For some patients, such as frail elderly patients, a conventionally fractionated schedule may be considered excessively burdensome and shorter hypofractionated schedules may be considered. Consistent with the radiosensitivity of the disease, lower doses of 20 Gy in five fractions or 30 Gy in ten fractions have been reported to potentially eradicate low volume disease in poor performance status patients (Level 4).<sup>10,22</sup>

## Recommendations

### Primary and/or draining lymph node regions:

#### For definitive treatment:

60–66 Gy in 30–33 fractions in 6–6.5 weeks (Grade C)

50–55 Gy in 20–25 fractions in 4–5 weeks (Grade C)

40–45 Gy in 15 fractions over 3 weeks (Grade D)

#### For adjuvant treatment:

50–60 Gy in 25–30 fractions over 5–6 weeks (Grade C)

40–45 Gy in 15 fractions over 3 weeks (Grade D)

The types of evidence and the grading of recommendations used within this review are based on those proposed by the Oxford Centre for Evidence-based Medicine.<sup>10</sup>

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## 17.

### Upper gastrointestinal cancer

#### Oesophagus

##### Radical treatment

For patients with localised disease, the standard curative approach to treatment is either surgery + perioperative chemotherapy, surgery ± neoadjuvant chemoradiotherapy or definitive radiotherapy ± concomitant chemotherapy.

##### Radiation with concomitant chemotherapy

Radiation with concomitant chemotherapy is superior to radiotherapy alone.<sup>1</sup> The landmark Radiation Therapy Oncology Group (RTOG) 85-01 trial showed a survival advantage for concomitant chemoradiation (50 Gray [Gy] in 25 fractions) with two concurrent and two adjuvant cycles of cisplatin and fluorouracil (5-FU), compared with radiotherapy alone (64 Gy in 32 fractions), with five-year survival rates of 27% versus 0%.<sup>1</sup> The subsequent INT0123 trial failed to show a benefit of dose escalation to 64.8 Gy compared with 50.4 Gy with the same cisplatin/5-FU chemotherapy in both arms.<sup>2</sup> Treatment-related deaths were increased in the dose-escalated arm, although the majority of these occurred prior to the delivery of >50 Gy and cannot be attributed to dose escalation.<sup>3</sup> A systematic review of neoadjuvant concomitant chemoradiation confirmed a radiotherapy dose–response relationship with a pathological complete response.<sup>4</sup> An increasing body of evidence is suggestive of the safety and feasibility of doses ≥60 Gy.<sup>3</sup> Outcomes have improved in modern trials using more conformal radiotherapy techniques with improved patient selection and radiotherapy quality assurance; in a recent UK study, radiotherapy combined with cisplatin and capecitabine showed two-year survival rates of 56%.<sup>5</sup>

##### Recommendations

##### **Radiation with concomitant chemotherapy:**

50 Gy in 25 fractions over 5 weeks (Grade A)

50.4 Gy in 28 fractions over 5.5 weeks (Grade A)

For upper third oesophageal carcinoma, moderate dose escalation with intensity-modulated radiotherapy (IMRT) can be considered wherever possible, within the context of a clinical trial (Grade C)

The types of evidence and the grading of recommendations used within this review are based on those proposed by the Oxford Centre for Evidence-based Medicine.<sup>6</sup>

##### Definitive radiotherapy alone

In a series of 101 patients in whom the majority of tumours were <5 centrimeters (cm) in length, radiotherapy alone to a dose of 45–52.5 Gy in 15–16 fractions achieved a five-year survival of 21%.<sup>7</sup> Radiotherapy is an option for patients in whom the use of concurrent chemotherapy is contraindicated.

### Recommendations

#### Radiotherapy alone:

50 Gy in 15–16 fractions over 3 weeks (Grade C)

50–55 Gy in 20 fractions over 4 weeks (Grade D)

60 Gy in 30 fractions over 6 weeks (Grade D)

The types of evidence and the grading of recommendations used within this review are based on those proposed by the Oxford Centre for Evidence-based Medicine.<sup>6</sup>

### Preoperative radiation with concomitant chemotherapy

Recent meta-analyses have demonstrated a significant improvement in overall survival using multimodality treatment over surgery alone; an advantage for neoadjuvant concomitant chemoradiotherapy over chemotherapy has not been established.<sup>8</sup> A recent trial of neoadjuvant radiotherapy with concomitant carboplatin and paclitaxel and 41.4 Gy in 23 fractions versus surgery alone demonstrated an increase in median survival from 24–49 months and no increase in perioperative mortality.<sup>9</sup> A dose of 45 Gy in 25 fractions has been selected for a randomised multicentre UK trial.<sup>10</sup>

### Recommendations

#### Neoadjuvant radiation with concomitant chemotherapy:

41.4 Gy in 23 fractions over 4.5 weeks (Grade A)

45 Gy in 25 fractions over 5 weeks (Grade B)

The types of evidence and the grading of recommendations used within this review are based on those proposed by the Oxford Centre for Evidence-based Medicine.<sup>6</sup>

### Postoperative radiotherapy

Adjuvant (chemo)radiotherapy can be considered for patients with positive margins and prognosis likely to be influenced by local relapse, although evidence for the benefit of adjuvant (chemo)radiotherapy is uncertain.<sup>11</sup> Based on a meta-analysis, radiotherapy with concomitant chemotherapy is preferred to radiotherapy alone with conventionally fractionated doses of 40–50 Gy.<sup>12</sup>

### Palliative treatment

There is increasing evidence that intraluminal brachytherapy provides effective relief of dysphagia, with improved quality of life. An updated Cochrane review on interventions for dysphagia in oesophageal cancer has concluded that, when compared to self-expanding metal stents, brachytherapy has fewer requirements for re-intervention, improved survival and better quality of life.<sup>13</sup>

### Recommendations

#### **Palliative brachytherapy:**

12 Gy in 1 fraction (Grade B)<sup>14</sup>

12–16 Gy in 2 fractions (Grade B)<sup>15,16</sup>

The types of evidence and the grading of recommendations used within this review are based on those proposed by the Oxford Centre for Evidence-based Medicine.<sup>6</sup>

Palliative radiotherapy alone should be considered for symptom improvement in oesophageal cancer. Concurrent chemoradiotherapy has not been shown to be advantageous in a phase III trial in which radiotherapy doses were 35 Gy in 15 fractions or 30 Gy in ten fractions.<sup>17</sup>

### Recommendations

#### **Palliative external beam radiotherapy:**

30 Gy in 10 fractions over 2 weeks (Grade C)

35 Gy in 15 fractions over 3 weeks (Grade C)

20 Gy in 5 fractions over 1 week (Grade D)

40 Gy in 15 fractions over 3 weeks (Grade D)

The types of evidence and the grading of recommendations used within this review are based on those proposed by the Oxford Centre for Evidence-based Medicine.<sup>6</sup>

## Gastric cancer

### **Adjuvant radiotherapy with concomitant chemotherapy**

Perioperative chemotherapy represents a standard of care in the management of locally advanced gastric cancer.<sup>18</sup> Adjuvant radiotherapy with concomitant chemotherapy represents an alternative approach. The INT0116 trial provided evidence of a survival benefit for postoperative concomitant chemoradiotherapy, however, this trial had poor surgical quality control with 54% of patients undergoing a D0 resection.<sup>19</sup> In patients with a high risk of relapse who did not undergo preoperative chemotherapy, especially in the absence of a D2 resection, adjuvant radiotherapy with concomitant 5-FU or capecitabine can be considered (Level 2b).<sup>6,20</sup>

### Recommendation

#### **Adjuvant radiotherapy with concomitant chemotherapy:**

45 Gy in 25 fractions over 5 weeks (Grade B)

The types of evidence and the grading of recommendations used within this review are based on those proposed by the Oxford Centre for Evidence-based Medicine.<sup>6</sup>



### Palliative treatment

Palliative radiotherapy is an effective treatment for bleeding due to gastric carcinoma, with no clear benefit for more protracted fractionation schedules.<sup>21</sup>

#### Recommendations

6–8 Gy in 1 fraction (Grade D)

20 Gy in 5 fractions over 1 week (Grade D)

The types of evidence and the grading of recommendations used within this review are based on those proposed by the Oxford Centre for Evidence-based Medicine.<sup>6</sup>

## Pancreas cancer

### Radical treatment

#### *Chemoradiotherapy*

Based on a very limited evidence base, adjuvant radiotherapy with concomitant chemotherapy is occasionally used in some centres for patients who are resection margin positive; a dose of 45 Gy in 25 fractions is appropriate for adjuvant treatment.<sup>22</sup>

Standard treatment options for patients with locally advanced inoperable pancreas cancer include chemotherapy alone or induction chemotherapy followed by radiotherapy and concomitant chemotherapy in responding or stable disease after induction chemotherapy.<sup>23–25</sup> One randomised study showed a small survival benefit in favour of consolidation radiotherapy with concomitant chemotherapy, although this was not confirmed in a subsequent study (Level 1b).<sup>6,23,24</sup>

#### Recommendations

#### **Radiotherapy with concomitant chemotherapy following induction chemotherapy:**

50.4 Gy in 28 fractions over 5.5 weeks (Grade B)

54 Gy in 30 fractions over 6 weeks (Grade B)

45 Gy in 25 fractions over 5 weeks (Grade D)

The types of evidence and the grading of recommendations used within this review are based on those proposed by the Oxford Centre for Evidence-based Medicine.<sup>6</sup>

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## 18.

### Bone metastases

#### Localised bone pain in established metastatic disease

##### Background

Uncomplicated local bone pain responds well with response rates of 70–80% after localised external beam treatment. Since response may take 4–6 weeks to achieve, it is recommended that consideration be given to the patient's prognosis before treatment. A number of large randomised controlled trials have been undertaken to explore the optimal dose. Three reviews have been completed using the Cochrane methodology. On the basis of this information, the recommended fractionation is a single dose of 8 Gray (Gy) (Level 1a).<sup>1–4</sup>

Bone metastases may give rise to pain with neuropathic features rather than simple bone pain. One randomised controlled trial specifically addressed this question, comparing single-dose 8 Gy to multifraction treatment, for most patients 20 Gy in five fractions. No major advantage for the multifraction arm was identified, and the recommendation therefore is that these patients should also receive a single dose of 8 Gy.<sup>5</sup>

##### Recommendation

##### **For the initial therapy of pain from bone metastases:**

8 Gy single dose (Grade A)

The types of evidence and the grading of recommendations used within this review are based on those proposed by the Oxford Centre for Evidence-based Medicine.<sup>4</sup>

#### Bone metastases in oligometastatic disease

In the context of oligometastatic disease, stereotactic body radiotherapy (SBRT) can achieve local control rates of 80% and treatment has been shown to be well tolerated, with low rates of spinal cord myelopathy (see section 20).

##### Retreatment

Retreatment should be considered in patients still having clinically significant pain after 4–6 weeks despite optimal analgesic. After a single dose, around 25% of patients may need re-treatment at some point.<sup>6</sup> Limited evidence suggests that response rates are similar to those after primary treatment.<sup>7</sup> There are no data to guide optimal dose fractionation for retreatment; a randomised trial compared 8 Gy single dose with 20 Gy in five fractions (eight fractions over the spinal cord) and showed no significant difference (Level 1b).<sup>4,8</sup> Both may be considered acceptable treatments for re-irradiation.

##### Recommendations

##### **For the re-irradiation of bone metastases:**

8 Gy single dose (Grade B)

20 Gy in 5 daily fractions (or 8 fractions over the spinal cord) over 1 week (Grade B)

The types of evidence and the grading of recommendations used within this review are based on those proposed by the Oxford Centre for Evidence-based Medicine.<sup>4</sup>

## Scattered bone pain

For metastatic bone pain at several sites despite adequate analgesia, wide-field or hemibody external beam radiotherapy (EBRT) may be effective. Appropriate pre-medication, such as dexamethasone and a 5HT3 antagonist is advised to reduce radiation-induced nausea and vomiting. There are no randomised data to compare such treatment to isotope therapy, but case-control comparisons suggest that all are equally effective. However, EBRT is associated with more toxicity in terms of gastrointestinal and bone marrow side-effects.<sup>9</sup> A large international study tested two, four and five fraction regimens, but there is no evidence to suggest that any of these are superior to giving the treatment in a single-dose (Level 4).<sup>4,10</sup>

### Recommendation

#### **For patients with scattered bone pain:**

Upper hemibody 6 Gy single dose (Grade C)

Lower hemibody 8 Gy single dose (Grade C)

The types of evidence and the grading of recommendations used within this review are based on those proposed by the Oxford Centre for Evidence-based Medicine.<sup>4</sup>

## Pathological fracture

### Prophylaxis

Bone metastases with high risk of pathological fracture can be identified from their radiological appearances. Suggested parameters include: those with > 50% cortical destruction, >3 centimetre (cm) maximum diameter, axial cortical involvement >3 cm and multifocal lytic disease.<sup>11</sup> Surgical fixation should be considered.

If radiotherapy is to be used, there is no consensus on the best fractionation in this setting. Higher risk lesions were in general excluded from fractionation trials. Common practice would be for these patients to receive a fractionated regimen such as 20 Gy in five fractions or 8 Gy single dose (Level 5).<sup>4</sup>

### Recommendation

#### **To prevent pathological fracture:**

8 Gy single dose (Level 4) or

20 Gy in 5 fractions over 1 week (Level 4)

The types of evidence and the grading of recommendations used within this review are based on those proposed by the Oxford Centre for Evidence-based Medicine.<sup>4</sup>

### Established fracture

Bones such as ribs, vertebrae and pelvic and shoulder girdle bones are not amenable to surgical fixation and can be treated with local radiotherapy. There is no consensus on optimal fractionation.

#### Recommendation

##### **For inoperable pathological fractures:**

8 Gy single dose (Grade D) or  
20 Gy in 5 fractions over 1 week (Grade D)

The types of evidence and the grading of recommendations used within this review are based on those proposed by the Oxford Centre for Evidence-based Medicine.<sup>4</sup>

### Postoperative radiotherapy

After internal fixation of a fracture or prophylactic pinning of a high-risk lesion, postoperative radiotherapy is often recommended. There is limited literature to support its efficacy and no consensus on dose. Treatment should be considered for all patients with persisting bone pain after surgery. In cases where treatment is given with the aim of enabling bone healing and long-term rehabilitation, consideration should be given to performance status and predicted survival.

#### Recommendations

##### **Postoperative radiotherapy after fixation of bone metastases:**

8 Gy single dose (Grade D) or  
20 Gy in 5 fractions over 1 week (Grade D)

The types of evidence and the grading of recommendations used within this review are based on those proposed by the Oxford Centre for Evidence-based Medicine.<sup>4</sup>

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## 19. Brain metastases

### Background

This is a heterogeneous population of patients with diverse underlying histologies, differences in disease burden outside the central nervous system (CNS) and differing systemic therapy options. As such, it is helpful to classify patients according to a simplified system. The original recursive partitioning analysis (RPA) based system of the Radiation Therapy Oncology Group (RTOG) is simple and robust, but has now been replaced by the Graded Prognostic Assessment (GPA) and the disease-specific GPA (dsGPA).<sup>1-9</sup> These prognostic scores continue to evolve, and still do not fully reflect the latest systemic therapies.<sup>5,10</sup>

Patients can be divided into three groups according to disease specific factors, but in general these three of importance:

- Karnofsky Performance Status (KPS) (at least 70)
- Control of the primary tumour
- Brain as the only site of disease.

Patients who fail to meet all three criteria tend to have a very poor prognosis, and may not benefit from treatment.

The regimens most commonly used for the whole-brain radiotherapy (WBRT) treatment of cerebral metastases are 30 Gy in ten fractions over two weeks or 20 Gy in five fractions over one week. For patients with limited disease, other approaches, including gamma knife or stereotactic radiosurgery (SRS) and intraoperative radiotherapy are feasible. The following discussion draws heavily on a systematic review performed as part of the Cancer Care Ontario programme in evidence-based care.<sup>11</sup>

### Solitary or oligo-metastases

The evidence from one systematic review and three randomised trials suggests benefit from adding surgery to whole brain radiotherapy (WBRT) for patients of good performance status with a solitary metastasis (Level 1a).<sup>11-14</sup> Stereotactic radiosurgery (SRS) added to WBRT offers a survival benefit for selected patients with a solitary metastasis, as well as for patients of RPA Class I with up to three metastases.<sup>15</sup> In patients with up to three brain metastases and KPS  $\geq 70$ , adding SRS to WBRT improves functional independence and reduces steroid requirements at six months (Level 1b).<sup>15,16</sup>

Patients with more than three brain metastases were not included in these trials. Moreover, it is recognised that the number of brain metastases detected on magnetic resonance imaging (MRI) is technique dependent. For small-volume disease, a prospective observational study (Level 2+) in patients with up to ten metastases (largest  $< 10$  centimetres<sup>3</sup> [cm<sup>3</sup>], total volume  $\leq 15$  cm<sup>3</sup>) has suggested that overall survival is equivalent for patients with five to ten as compared to two to four metastases and therefore the number of metastases treated using SRS without WBRT may not correlate with outcome.<sup>16,17</sup> Several retrospective studies (Level 3) have shown that the total volume of brain metastases correlates better with outcomes, including local control, distant intracranial relapse and overall survival after SRS than number of brain metastases.<sup>7,16,18-20</sup>



### Recommendations

#### Solitary metastases:

##### Surgery or SRS:

Lesion diameter

<20 millimetres (mm) – 24 Gy single dose (Grade B)

21–30 mm – 18 Gy single dose (Grade B)

31–40 mm – 15 Gy single dose (Grade B)

#### Multiple metastases up to total volume of 20 cm<sup>3</sup> with good performance status (Karnofsky Performance Status ≥70) and controlled extra-cranial disease:<sup>2</sup>

##### SRS:

Lesion diameter

<20 mm – 24 Gy single dose (Grade C)

21–30 mm – 18 Gy single dose (Grade C)

31–40 mm – 15 Gy single dose (Grade C)

The types of evidence and the grading of recommendations used within this review are based on those proposed by the Oxford Centre for Evidence-based Medicine.<sup>16</sup>

## Whole-brain radiotherapy with SRS

While WBRT was part of the initial treatment of patients in the above-mentioned trials of surgery or SRS, three randomised trials have now investigated the addition of WBRT to surgery or SRS for patients with one to four brain metastases.<sup>21–24</sup> A meta-analysis of these trials has also been published.<sup>25</sup> Adding WBRT to local therapy by surgery or SRS appears to improve intracranial control and reduce neurological deaths without influencing overall survival (Level 1a).<sup>16</sup> However, the addition of WBRT to SRS has been shown in one small randomised trial to result in a significantly greater risk of neurocognitive deficits at three months, and for this reason many groups now choose to defer WBRT.<sup>26</sup> Post-treatment MRI surveillance was used in all three trials and is recommended by some expert groups, but high-level evidence about the value of MRI surveillance is lacking.<sup>27</sup> Avoidance of the hippocampus has been suggested as a method to limit the neurocognitive effects of WBRT, but as yet there is little data to support this.

### Recommendation

#### WBRT with SRS:

30 Gy in 10 fractions over 2 weeks (Grade A)

The types of evidence and the grading of recommendations used within this review are based on those proposed by the Oxford Centre for Evidence-based Medicine.<sup>16</sup>

## Adjuvant postoperative SRS and hypofractionation

While WBRT reduces the risk of intra-cranial relapse postoperatively, the lack of impact on overall survival has led to the exploration of SRS to the stereotactic cavity.<sup>16</sup> In line

with previous data, radiotherapy after surgery reduces the risk of intra-cranial relapse, and radiotherapy restricted to the tumour bed appears to be non-inferior to whole brain radiotherapy.<sup>28,29</sup> However, technical problems and optimal dose and fractionation schedules are as yet unclear. For patients with larger metastases >2 cm diameter, there has been interest in hypofractionated SRS, delivered as 3–5 fractions. As yet, there is no data to support an optimal dose-fractionation schedule.

## Whole-brain radiotherapy for multiple metastases

### Background

Several randomised trials have compared different radiotherapy regimens for patients with multiple cerebral metastases. Most have used 30 Gy in ten fractions as the control arm and have compared this regimen to either higher or lower doses.<sup>30–33</sup> Only one small study of 70 patients has compared the six-month survival rate after 30 Gy in ten fractions to that after 20 Gy in five fractions. There was no significant difference.<sup>26</sup> A Radiation Therapy Oncology Group (RTOG) study reported in 1980 compared three regimens: 40 Gy in 15 fractions; 30 Gy in ten fractions; and 20 Gy in five fractions.<sup>34</sup> The median survival in all three groups was between 3.2 months and 3.5 months ( $P>0.05$ ). There is, therefore, no clear evidence that 20 Gy in five fractions is inferior to, or better than, 30 Gy in ten fractions (Level 1b).<sup>16</sup>

Other regimens assessed in RTOG randomised trials included: 10 Gy single-dose and 30–40 Gy in 10–20 fractions; 40 Gy in 20 fractions; 40 Gy in 15 fractions; 30 Gy in 15 fractions and 30 Gy in ten fractions.<sup>34,35</sup> There was no statistically significant difference in median survival. The trial results suggest that regimens using only one or two fractions are inferior to 30 Gy in ten fractions, but that there is no improvement in survival when dose is increased beyond 30 Gy in ten fractions (Level 1b).<sup>16</sup>

Patients in RPA Class III have such a poor prognosis that it may be difficult to justify any radiation treatment at all. Careful consideration should be given to patients with non-small cell lung cancer. The Medical Research Council (MRC) QUARTZ study shows no significant benefit in terms of survival or quality adjusted life years for WBRT over optimal supportive care.<sup>36</sup>

### Recommendation

#### Multiple cerebral metastases:

30 Gy in 10 fractions over 2 weeks (Grade A)

20 Gy in 5 fractions over 1 week (Grade A)

The types of evidence and the grading of recommendations used within this review are based on those proposed by the Oxford Centre for Evidence-based Medicine.<sup>16</sup>

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## 20. Oligometastases

### Background

The oligometastatic state can be defined as 1–3 isolated metastatic sites, typically occurring more than six months after successful treatment of primary disease.<sup>1</sup> In colorectal cancer (in addition to sarcoma and other sites), surgical treatment of oligometastatic disease (most frequently liver metastases) is associated with prolonged overall survival.<sup>2</sup> Multiple single-arm studies have shown that stereotactic radiotherapy is effective and well tolerated in the oligometastatic setting, across multiple histologies and anatomical sites. Thus, it may be deployed as an alternative to surgery or where surgery is not possible.

There is no randomised data, and no established consensus for dose fractionation in radiotherapy for oligometastatic disease. Recommendations have been derived from systematic reviews of non-randomised studies (prospective and retrospective [Level 3a]), along with expert consensus from the Commissioning through Evaluation (CtE) Service Specification (Level 5).<sup>3,4</sup> For all sites, it is recommended that the critical organ dose constraints agreed by the UK Stereotactic Ablative Radiotherapy (SABR) consortium should be followed.<sup>5</sup>

It is not possible to discuss dose fractionation without discussing treatment technique. The majority of evidence comes from stereotactic body radiotherapy (SBRT or stereotactic ablative radiotherapy [SABR]). Developments in radiotherapy technology have allowed the safe delivery with high-precision of an ablative dose in five or fewer fractions. Patients have been treated using dedicated stereotactic systems (such as Cyberknife) and using conventional gantry-based systems with stereotactic capability. The optimal system for delivery is unknown, but image guidance, either with implanted fiducials and/or soft tissue tomography, is essential. Dose fractionation recommendations are, however, independent of the stereotactic platform used.

### Oligometastases: bone (including spine) and lymph nodes

In this setting, treatment can expect to achieve a local control around of 80% and progression-free survival (PFS) of approximately 20% at 2–3 years.<sup>1</sup> Doses delivering a biologically equivalent dose (BED) at 2 Gray (Gy) per fraction (EQD2) >100 Gy, and those tumours ≤3 centimetres (cm) have best outcomes. Treatment is, in general, well tolerated with myelopathy rates for spinal treatments being less than 1% in most series.<sup>6,7</sup>

Contouring for spinal treatment should be based on the expert consensus guidelines by Cox et al (Level 5).<sup>4,8</sup>

#### Recommendations

##### Initial treatment:

18–24 Gy single dose (Grade C)

30–45 Gy in 3 fractions over 1 week (10–15 Gy per fraction given on alternate days) (Grade C)

##### Retreatment

Pelvis: 30 Gy in 5 fractions over 2 weeks, given on alternate days (Grade C)

Spine: 20–30 Gy in 2–5 fractions over 1–2 weeks, given on alternate days (Grade C)

The types of evidence and the grading of recommendations used within this review are based on those proposed by the Oxford Centre for Evidence-based Medicine.<sup>4</sup>

In this setting, it is vital to take into account the dose previously received by critical organs. As far as possible, cumulative doses to critical organs should be calculated and, allowing for recovery, tolerances described in the UK SABR consensus document should not be exceeded, if necessary modifying prescription doses to the planning target volume (PTV).<sup>5</sup>

In the specific case of remaining spinal cord tolerance, the method described by Sahgal is recommended.<sup>7</sup> Following this, the maximum cumulative dose to the thecal sac (similar to cord planning organ at risk volume [PRV]), at a minimum of six months after initial irradiation, should not exceed a BED of 140 Gy ( $\alpha\beta=2$  Gy). For other organs, there is no consensus on recovery of tolerance following radiation and clinical judgment, along with the available literature, should be used.<sup>9</sup>

### Oligometastases: lung

Lung oligometastases present a similar clinical problem to early-stage primary lung cancer, for which stereotactic treatment is a standard of care.<sup>10</sup> Specifically for patients with oligometastases, an EQD2 >100 Gy is associated with approximately 90% local control at 1–2 years.<sup>10,11</sup> Although Timmerman *et al* found a significant increase in toxicity when treating central lung tumours, other series have found no increase in toxicity when treating with more than three fractions.<sup>12–15</sup> These current recommendations are consistent with the CtE Service Specification.<sup>3</sup>

#### Recommendations

48–54 Gy in 3 fractions over 1 week given on alternate days (Grade C)

#### **Peripheral lung oligometastases in contact with chest wall or where three fraction constraints cannot be met:**

55–60 Gy in 5 fractions over 2 weeks given on alternate days (Grade C)

#### **Lung oligometastases in the central lung/mediastinum:**

60 Gy in 8 fractions over 1 week given on alternate days (Level 4)

The types of evidence and the grading of recommendations used within this review are based on those proposed by the Oxford Centre for Evidence-based Medicine.<sup>4</sup>

### Oligometastases: liver

The use of surgery and radiofrequency ablation to treat liver oligometastases is well established. For colorectal liver tumours under 6 centimetres (cm) in diameter, local control above 90% at one year can be achieved with stereotactic doses of at least 48 Gy in three fractions.<sup>16</sup> This analysis included patients who were heavily pre-treated with systemic therapy. Further reviews have indicated this dose is effective in other tumour types, with grade 3–4 toxicity of 1–10% (Level 3a).<sup>4,17,18</sup>

#### Recommendations

45–50 Gy in 3 fractions over 1 week, given on alternate days (Grade C)

#### **For larger PTV volumes or where dose constraints cannot be met with a three-fraction approach:**

50–60 Gy in 5 fractions over 2 weeks (Grade C)

The types of evidence and the grading of recommendations used within this review are based on those proposed by the Oxford Centre for Evidence-based Medicine.<sup>4</sup>

### Oligometastases: adrenal

Due to a rich sinusoidal blood supply, adrenal metastases are frequently observed in patients with melanoma, breast, lung, kidney and gastrointestinal tumours. Based on observations of enhanced survival in patients undergoing adrenalectomy for oligometastatic disease, stereotactic radiotherapy has also been used. Local control rates vary from 55% to 90% with doses ranging from 16 Gy in four fractions to 50 Gy in ten fractions (Level 4).<sup>4,19,20</sup>

#### Recommendation

30–36 Gy in 3 fractions over 1 week (Grade C)

The types of evidence and the grading of recommendations used within this review are based on those proposed by the Oxford Centre for Evidence-based Medicine.<sup>4</sup>



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## 21.

### Metastatic spinal cord compression (MSCC)

#### Background

Patients with symptoms suggestive of spinal cord compression, particularly severe back or root pain, should be investigated urgently with whole spine magnetic resonance imaging (MRI) to define sites and levels of compression accurately.<sup>1</sup> Multiple levels of compression are seen in up to one-third of patients.<sup>2-4</sup>

On clinical suspicion of MSCC or once a diagnosis has been established, all patients should be started on steroids; the UK convention is to give dexamethasone in 16 milligrams (mg) daily. There is evidence from one randomised trial that higher initial doses of 96 mg are superior to no steroids (Level 2b).<sup>5,6</sup> No dose comparison between 16 mg and higher doses has been undertaken.

Systemic anti-cancer treatment may be more appropriate than radiotherapy for some malignancies, for example, lymphomas, plasma-cell tumours, germ cell tumours or untreated small cell cancers.

Long-term outcome from MSCC depends on the degree of paralysis and overall prognosis for the cancer; with poorer outcomes associated with non-ambulatory status, poor performance status,  $\geq 3$  involved vertebrae, presence of other bone metastases, presence of visceral metastases and shorter time to developing motor deficits. Non-breast/prostate/haematological primaries also confer a worse prognosis (Level 2c).<sup>7,8</sup>

Ideally, the prognosis of patients should be objectively assessed using validated scores such as the Tokuhashi Score (Level 2b).<sup>6,8,9</sup>

Patients with a good expected prognosis, especially those who are ambulatory, should be discussed with a spinal- or neurosurgeon to consider spinal decompression and stabilisation surgery followed by radiotherapy. This intervention has been shown to improve neurological status and overall survival in patients with MSCC (Level 1b) compared to radiotherapy alone.<sup>6,10</sup>

For good prognosis or ambulatory patients who are not suitable for surgery, urgent radiotherapy should be given before further neurological deterioration.<sup>3,4,8</sup>

For poor prognosis or non-ambulatory patients, radiotherapy should be considered either to preserve neurological function (in ambulatory patients) or for pain relief only if paraplegia has been established for >24 hours.<sup>3,4,8</sup>

Current evidence on dose and fractionation for MSCC largely consists of retrospective series, prospective non-randomised studies looking at several different treatment schedules or prospective randomised control trials (RCTs) using schedules not commonly used in UK, including split course schedules (Level 2b).<sup>6,8,11-13</sup>

The current evidence suggests no benefit for doses higher than 30 Gray (Gy) in ten daily fractions. More hypofractionated regimes (8 Gy in a single exposure, 20 Gy in five daily fractions) are most commonly used in the UK and are as effective as longer schedules in terms of pain relief, neurological benefit and survival. There may be fewer in-field recurrences with longer schedules and fewer patients treated with longer courses are treated with further radiotherapy to the same area for recurrent MSCC (Level 2b), however, a recent randomised trial found that 20 Gy in five fractions was not inferior to 30 Gy in ten fractions for motor function or ambulatory status.<sup>14-16</sup>

Ambulant patients with an expected better prognosis may, therefore, benefit from longer courses of treatment to prevent recurrence and need for retreatment.

The SCORAD III prospective RCT is currently recruiting and randomising patients with an expected prognosis of >12 weeks to either a single exposure of 8 Gy or 20 Gy in five daily fractions. The results of this trial will inform decisions regarding the optimal schedule in the future [UKCRN ID 7952].<sup>16</sup>

### Recommendations

#### **Metastatic spinal cord compression: non-ambulant patients or ambulant patients with a poor prognosis:**

8 Gy single dose (Grade B)

or

20 Gy in 5 daily fractions over 1 week (Grade B)

#### **Metastatic spinal cord compression: ambulant patients with a good prognosis or post-spinal surgery:**

20 Gy in 5 daily fractions over 1 week (Grade B)

or

30 Gy in 10 daily fractions over 2 weeks (Grade B)

The types of evidence and the grading of recommendations used within this review are based on those proposed by the Oxford Centre for Evidence-based Medicine.<sup>6</sup>

There is response to retreatment after initial benefit from radiotherapy for recurrent MSCC. The absolute maximum retreatment dose has not been established, but a cumulative biologically equivalent dose (BED) (initial + reirradiation) of 120 Gy<sub>2</sub> appears to be safe and effective. Evidence indicates that the effect of previous radiation, time to develop motor deficit, presence of visceral metastases and performance status have an impact on effectiveness of repeat treatment but schedule of treatment does not (Level 2c).<sup>6,17</sup>

### Recommendation

#### **Metastatic spinal cord compression: re-irradiation:**

8 Gy single dose or 20 Gy in 5 daily fractions prescribed at depth.

Maximum cumulative BED <120 Gy<sub>2</sub> (Grade C)

The types of evidence and the grading of recommendations used within this review are based on those proposed by the Oxford Centre for Evidence-based Medicine.<sup>6</sup>

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- British Thoracic Society
- British Uro-Oncology Group
- Children's Cancer and Leukaemia Group
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- Brain tumour
- Colorectal cancer
- Gynaecological cancers
- Head and neck cancer
- Lung cancer
- Lymphoma
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