www.rcr.ac.uk

Clinical Oncology
The Royal College of Radiologists

Radiotherapy dose fractionation
Second edition

December 2016

Contents

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.

Since the appearance of that document, there have been dramatic changes in the delivery of radiotherapy as clinical practice has sought to keep pace with the many technological advances in the field. Thus we now have routine adoption of intensity-modulated radiotherapy (IMRT) for radical treatment coupled with rigorous image guidance using fiducial markers or cone-beam computed tomography (CT). Stereotactic radiotherapy and helical tomotherapy are now widely available.

Another important and crucial change has been the infrastructure provided by the National Institute for Health Research Cancer Network which, combined with the enthusiasm of the radiotherapy community across the UK, has resulted in the delivery of mature data from important, large, high-quality UK radiotherapy studies. Clinical trials have provided not only the evidence but also a vehicle for the supported introduction of new techniques and technologies.

There is increased understanding of the biology of the common cancers we treat. Robust, pragmatic fractionation trials in those tumours considered to have a low alpha/beta ratio challenge the conventional schedules using 1.8–2 Gray (Gy) per fraction. Hypofractionated schedules are now becoming the standard of care in prostate and breast cancer treatment. With reduced fractionation it becomes even more important to ensure accurate daily targeting of treatment using image-guided radiotherapy (IGRT). Combined modality schedules incorporating chemotherapy with radiotherapy are now universal in the delivery of radical treatment for head and neck, anal and bladder cancers.

At the other end of the spectrum, palliative radiotherapy is now well established as an area where single doses or short hypofractionated schedules should predominate, based on important clinical trials emerging from UK practice. A new paradigm has also emerged in the field of metastatic cancer, that of oligometastases, challenging the notion that all metastatic disease reflects systemic incurable malignancy. The role of radiotherapy in this setting remains under investigation and the UK is prominent in undertaking the relevant clinical trials to inform future practice.

This edition of *Radiotherapy dose fractionation* seeks to reflect the changes in practice which have evolved in the last decade. It has 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 have contributed to the final version and we are grateful to all those who responded to the consultation. I would like to express particular thanks to Professor Peter Hoskin for so ably leading the development of this new document 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 Dr David Bloomfield (Medical Director for Professional Practice, Clinical Oncology) for his oversight and to Gillian Dollamore, RCR Clinical Oncology Executive Officer, for all her advice and support.

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

Professor Roger Taylor, *Vice-President, Clinical Oncology,* The Royal College of Radiologists

Executive summary

The first edition of *Radiotherapy dose fractionation* presented guidelines derived from a rigorous appraisal of the literature as published by June 2006. In the last decade there have been major advances in the delivery of radiotherapy. Modern, state-of-the-art radiation delivery, incorporating intensity-modulated radiotherapy (IMRT) and image-guided radiotherapy (IGRT), and the advent of stereotactic body radiotherapy (SBRT) have resulted in the need for a revised document to take into account these changes alongside the more recent high-level evidence for fractionation schedules in various sites.

The Royal College of Radiologists (RCR) has therefore commissioned this publication to update the previous document and reflect changes in research and practice in the last decade.

This document aims, where possible, to recommend evidence-based treatment regimens for a given clinical situation and, where no such firm evidence exists, to present acceptable treatment options, ranked according to the level of evidence available.

In many clinical situations the available published evidence is insufficient to favour one particular treatment regimen over another. In these instances a range of acceptable fractionation schedules are available and we must await the results of future clinical trials to resolve these issues.

Where equipoise exists, and trial data are not available, clinicians should exercise considerable caution when considering changes in their treatment practice, balancing the need to optimise scarce resources with the potential hazards when changing a complex intervention such as radiotherapy.

Introduction

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

In the last decade 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.[1,2,3] 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 radiotherapt (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.

New sections have been included in this document to reflect the breadth of modern radiotherapy, in particular addressing skin, penile and renal malignancies. The role of combined-modality treatment and potential for stereotactic radiotherapy is also highlighted.

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

Evidence was graded according to guidelines defined by the Oxford Centre for Evidence-Based Medicine as shown below.[4]

Preparation of this document

Each site-specific section of this new edition of *Radiotherapy dose fractionation* has been subject to extensive peer review. The process followed 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.

Comparison with the Malthus model[5]

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 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.[5,6] 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.

References

1. Borras JM, Lievens Y, Dunscombe P *et al*. The optimal utilization proportion of external beam radiotherapy in European countries: An ESTRO-HERO analysis. *Radiother Oncol* 2015; **116**(1): 38–44.
2. Borras JM, Barton M, Grau C *et al*. The impact of cancer incidence and stage on optimal utilization of radiotherapy: Methodology of a population based analysis by the ESTRO-HERO project. *Radiother Oncol* 2015; **116**(1): 45–50.
3. Borras JM, Lievens Y, Barton M. How many new cancer patients in Europe will require radiotherapy by 2025? An ESTRO-HERO analysis. *Radiother Oncol* 2016; **119**(1): 5–11.
4. www.cebm.net/oxford-centre-evidence-based-medicine-levels-evidence-march-2009 (last accessed 22/9/16)
5. Jena R, Round C, Mee T *et al*. The Malthus programme – a new tool for estimating radiotherapy demand at a local level. *Clin Oncol (R Coll Radiol)* 2012; **24**(1): 1–3.
6. Haviland JS, Owen JR, Dewar JA *et al*. START Trialists' Group. The UK Standardisation of Breast Radiotherapy (START) trials of radiotherapy hypofractionation for treatment of early breast cancer: 10-year follow-up results of two randomised controlled trials. *Lancet Oncol* 2013; **14**(11): 1086–1094.

Oxford Centre for Evidence-based Medicine[1]

Grades of recommendation

A Consistent level 1 studies

B Consistent level 2 or 3 studies or extrapolations from level 1 studies

C Level 4 studies or extrapolations from level 2 or 3 studies

D 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

1a SR (with homogeneity*) of RCTs

1b Individual RCT (with narrow confidence interval)

1c All or none§

2a SR (with homogeneity*) of cohort studies

2b Individual cohort study (including low quality RCT; for example, <80% follow-up)

2c 'Outcomes' research; ecological studies

3a SR (with homogeneity*) of case-control studies

3b Individual case-control study

4 Case-series (and poor-quality cohort and case-control studies§§)

5 Expert opinion without explicit critical appraisal, or based on physiology, bench research or 'first principles'

SR: systematic review

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.

References

1. www.cebm.net/oxford-centre-evidence-based-medicine-levels-evidence-march-2009 (last accessed 22/9/16)

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.[1,2] 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.[3] Chemoradiotherapy improves outcome in anal cancer compared to radiotherapy alone (Level 1b).[4]

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.[5] 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).[4]

The EXTRA trial was a phase II study substituting capecitabine for 5-FU chemotherapy that reported minimal toxicity and acceptable compliance.[6] 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).[4]

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).[4,7,8]

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.[9,10]

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.[4]

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.[5,8] 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).[4,11]

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.[4]

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.[12]

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.[4]

References

1. The UKCCCR Anal Cancer Trial Working Party. Epidermoid anal cancer: results from the UKCCCR randomised trial of radiotherapy alone versus radiotherapy, 5-fluorouracil and mitomycin. *Lancet* 1996; **348**(9034): 1049–1054.
2. Bartelink H, Roelofsen F, Eschwege F *et al*. Concomitant radiotherapy and chemotherapy is superior to radiotherapy alone in the treatment of locally advanced anal cancer: results of a phase III randomized trial of the European Organisation for Research and Treatment of Cancer Radiotherapy and Gastrointestinal Cooperative Groups. *J Clin Oncol* 1997; **15**(5): 2040–2049.
3. Flam M, John M, Pajak TF *et al*. Role of mitomycin in combination with fluorouracil and radiation, and of salvage chemoradiation in the definitive nonsurgical treatment of epidermoid carcinoma of the anal canal: results of a phase III randomised intergroup study. *J Clin Oncol* 1996; **14**(9): 2527–2539.
4. www.cebm.net/oxford-centre-evidence-based-medicine-levels-evidence-march-2009 (last accessed 22/9/16)
5. James RD, Glynne-Jones R, Meadows HM *et al*. Mitomycin or cisplatin chemoradiation with or without maintenance chemotherapy for treatment of squamous cell carcinoma of the anus (ACT II): a randomised phase 3 open-label, 2x2 factorial trial. *Lancet Oncolo* 2013; **14**(6): 516–524.
6. Glynne-Jones R, Meadows H, Wan S *et al*. EXTRA – a multicenter phase II study of chemoradiation using a 5 day per week oral regimen of capecitabine and intravenous mitomycin C in anal cancer. *Int J Radiat Oncol Biol Phys* 2008; **72**(1): 119–126.
7. Kachnic LA, Winter K, Myerson RJ *et al*. RTOG 0529: a phase 2 evaluation of dose-painted intensity modulated radiation therapy in combination with 5-fluorouracil and mitomycin-C for the reduction of acute morbidity in carcinoma of the anal canal. *Int J Radiat Oncol Biol Phys* 2013; **86**(1): 27–33.
8. Gunderson LL, Winter KA, Ajani JA *et al*. Long-term update of US GI intergroup RTOG 98-11 phase III trial for anal carcinoma: survival, relapse, and colostomy failure with concurrent chemoradiation involving fluorouracil/mitomycin versus fluorouracil/cisplatin. *J Clin Oncol* 2012; **30**(35): 4344–4351.
9. Muirhead R, Adams RA, Gilbert DC *et al.* Anal cancer: developing an intensity-modulated radiotherapy solution for ACT2 fractionation. *Clin Oncol* 2014; **26**(11): 720–721.
10. www.analimrtguidance.co.uk (last accessed 22/9/16)
11. Pettit L, Meade S, Sanghera P *et al*. Can radiobiological parameters derived from squamous cell carcinoma of the head and neck be used to predict local control in anal cancer treated with chemoradiation? *Br J Radiol* 2013; **86**(1021): 20120372.
12. www.ukctg.nihr.ac.uk/trials/trial-details/trial-details?trialId=36181 (last accessed 13/10/16)

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).[1–5]

Hyperfractionation

Two published trials compare hyperfractionation with doses of 1–1.2 Gy per fraction to conventionally fractionated treatment.[6,7] Pooled analysis suggests a significant benefit from hyperfractionation with a 17% (95% confidence interval, 6–27%) improvement in the rate of local control.[8] 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).[5]

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.[9] The shorter regimen was associated with a higher rate of intestinal toxicity (Level 1b).[5]

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).[10,11] 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).[5]

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.[12] 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.[13] There was no difference in locoregional recurrence, late toxicity or overall survival between the two groups (Level 1b).[5]

Radical radiotherapy with radiosensitisation

Two UK-based randomised control trials have demonstrated that radical radiotherapy with a radiosensitiser improves outcomes compared to radiotherapy alone.[10,11] 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).[5,10] 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).[5,11] 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).[5,14]

Treatment technique

The size of the planning target volume (PTV) is critical to any discussion of dose and fractionation.[15,16] 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).[5] 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)[10,11]

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.[5]

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.[17] 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).[5] 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-).[5] 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).[5]

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.[5]

References

1. Shelley MD, Barber J, Mason MD. Surgery versus radiotherapy for muscle invasive bladder cancer. *Cochrane Database Syst Rev* 2001; **2001**(3): CD002079.
2. Booth CM, Siemens DR, Li G *et al*. Curative therapy for bladder cancer in routine clinical practice: a population-based outcomes study. *Clin Oncol (R Coll Radiol)* 2014; **26**(8): 506–514.
3. Gray PJ, Fedewa SA, Shipley WU *et al.* Use of potentially curative therapies for muscle-invasive bladder cancer in the United States: results from the National Cancer Data Base. *Eur Urol* 2013; **63**(5): 823–829.
4. Kotwal S, Choudhury A, Johnston C, Paul AB, Whelan P, Kiltie AE. Similar treatment outcomes for radical cystectomy and radical radiotherapy in invasive bladder cancer treated at a United Kingdom specialist treatment center. *Int J Radiat Oncol Biol Phys* 2008; **70**(2): 456–463.
5. www.cebm.net/oxford-centre-evidence-based-medicine-levels-evidence-march-2009 (last accessed 22/9/16)
6. Edsmyr F, Andersson L, Esposti PL, Littlebrand B, Nilsson B. Irradiation therapy with multiple small fractions per day in urinary bladder cancer. *Radiother Oncol* 1985; **4**(3): 197–203.
7. Näslund I, Nilsson B, Littbrand B. Hyperfractionated radiotherapy of bladder cancer. A ten-year follow-up of a randomized clinical trial. *Acta Oncol* 1994; **33**(4): 397–402.
8. Goldobenko GV, Matveev BP, Shipilov VI, Kilmakov BD, Tkachev S. Radiation treatment of bladder cancer using different fractionation regimens. *Med Radiol (Mosk)* 1991; **36**(5): 14–16.
9. Horwich A, Dearnaley D, Huddart R *et al*. A randomised trial of accelerated radiotherapy for localised invasive bladder cancer. *Radiother Oncol* 2005; **75**(1): 34–43.
10. James ND, Hussain SA, Hall E *et al*. Radiotherapy with or without chemotherapy in muscle-invasive bladder cancer. *N Engl J Med* 2012; **366**(16): 1477–1488.
11. Hoskin PJ, Rojas AM, Bentzen SM, Saunders MI. Radiotherapy with concurrent carbogen and nicotinamide in bladder carcinoma *J Clin Oncol* 2010; **28**(33): 4912–4918.
12. Cowan RA, McBain CA, Ryder WD *et al*. Radiotherapy for muscle-invasive carcinoma of the bladder: results of a randomized trial comparing conventional whole bladder with dose-escalated partial bladder radiotherapy. *Int J Radiat Oncol Biol Phys* 2004; **59**(1): 197–207.
13. Huddart RA, Hall E, Hussain SA *et al*. Randomized noninferiority trial of reduced high-dose volume versus standard volume radiation therapy for muscle-invasive bladder cancer: results of the BC2001 trial (CRUK/01/004). *Int J Radiat Oncol Biol Phys* 2013; **87**(2): 261–269.
14. Choudhury A, Swindell R, Logue JP *et al*. Phase II study of conformal hypofractionated radiotherapy with concurrent gemcitabine in muscle-invasive bladder cancer. *J Clin Oncol* 2011; **29**(6): 733–738.
15. Muren LP, Ekerold R, Kvinnsland Y, Dahl O. On the use of margins for geometrical uncertainties around the rectum in radiotherapy planning. *Radiother Oncol* 2004; **70**(1): 11–19.
16. Muren LP, Smaaland R, Dahl O. Conformal radiotherapy of urinary bladder cancer. *Radiother Oncol* 2004; **73**(3): 387–398.
17. Duchesne GM, Bolger JJ, Griffiths GO *et al*. A randomized trial of hypofractionated schedules of palliative radiotherapy in the management of bladder carcinoma: results of medical research council trial BA09. *Int J Radiat Oncol Biol Phys* 2000; **47**(2): 379–388.

3.
Breast cancer

Background

Breast cancer is the most common cancer in women in the UK and most patients are being diagnosed at an early stage due the success of 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).[1–3] It also reduces ipsilateral breast tumour recurrence following breast conservation in patients with a diagnosis of ductal carcinoma *in situ* (DCIS).[4,5]

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).[3,6,7]

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.[8] 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.[9] Mature data from the START and a Canadian study support the equivalence of hypofractionationed regimens to the previous standard of 2 Gy daily fractionation (Level 1b).[3,10]

There are no trials addressing 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; in fact results of the START B trial suggest that 40 Gy in 15 fractions leads to fewer late effects.[9]

Recommendation

For adjuvant radiotherapy of breast or chest wall:

40 Gy in 15 daily fractions 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.[3]

Further hypofractionation for breast radiotherapy is currently under investigation. In the FAST study, 915 women aged ≥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.[11]

The FAST Forward trial is investigating 40 Gy in 15 fractions vesus 27 or 28 Gy in five fractions over one week. The main trial closed in 2014, earliest results for local control will be available in 2019. The FAST Forward nodal study opened in 2015 with normal tissue endpoints.[12]

Partial breast irradiation

It is recognised that whole-breast radiation (WBI) can cause unacceptable toxicity in patients with large breasts. Partial breast radiation may improve this outcome, though accelerated partial breast irradiation can lead to a higher local recurrence rate, albeit still low, compared to WBI (Level 1a).[3,13] Currently the role of partial breast radiation in low-risk breast cancer is unclear; the UK Intensity Modulated and Partial Organ Radiotherapy following Breast Conservation Surgery for Early Breast Cancer (IMPORT LOW) Trial investigating two schedules of partial breast radiation versus whole-breast 40 Gy in 15 fractions has closed to accrual and was presented at the European Breast Cancer Conference in March 2016.[14] 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 partial breast radiotherapy for breast appearance and breast hardness (median follow-up 72 months). Peer-reviewed publication is awaited.

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.[15] 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).[3,16]

Breast boost

Delivery of a boost to the tumour bed following whole-breast radiotherapy reduces the risk of ipsilateral breast cancer recurrence (Level 1b).[3,17] 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 cancer.

Incomplete resection margin, where further surgery is not possible, should be an indication for breast boost regardless of age. A boost dose of 16 Gy in eight fractions or 10 Gy in five fractions is most commonly prescribed.[17] The lower dose has not been tested against the higher one in a randomised control trial (RCT), however, indirect evidence from an EORTC trial (Level 1b) shows it is equivalent to a higher boost dose of 26 Gy in patients with an 'incomplete' resection margin with lower rates of fibrosis (3.3%) at ten years.[3,18]

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 equivalently fractionated to whole breast, as given in 40 Gy in 15 fractions breast dose, rather than 2 Gy fractionation. 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.[19]

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.[20]

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).[3,21]

Breast radiotherapy may increase the risk of heart disease.[22,23] For most women irradiated in the UK, the absolute risk of developing radiation-induced heart disease is less than 1%, 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).[3,24]

Recommendations

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

16 Gy in 8 daily fractions (Grade A)[3]
10 Gy in 5 daily fractions (Grade B)[3]

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.[3]

It is entirely reasonable to hypofractionate the boost schedule, for example, a five-fraction regimen of 2.67 Gy is equivalent to 14 Gy in 2.0 Gy equivalents assuming an alpha/beta value of 3.0 Gy.[25]

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 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.[26] 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.[3,26]

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.[27] 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).[3,27] 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.[28]

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.[29] 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).[3,29]

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.[30] 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).[3,30]

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-), though this analysis was not conducted with patient level data and 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).[3,31,32] 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.[29–32]

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-).[3,33]

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.[3]

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).[3]

References

1. Early Breast Cancer Trialists' Collaborative Group (EBCTCG), Darby S, McGale P *et al*. Effect of radiotherapy after breast-conserving surgery on 10-year recurrence and 15-year breast cancer death: meta-analysis of individual patient data for 10,801 women in 17 randomised trials. *Lancet* 2011; **378**(9804): 1707–1716.
2. BCTCG (Early Breast Cancer Trialists' Collaborative Group), McGale P, Taylor C *et al*. Effect of radiotherapy after mastectomy and axillary surgery on 10-year recurrence and 20-year breast cancer mortality: meta-analysis of individual patient data for 8135 women in 22 randomised trials. *Lancet* 2014; **383**(9935): 2127–2135.
3. www.cebm.net/oxford-centre-evidence-based-medicine-levels-evidence-march-2009 (last accessed 22/9/16)
4. Early Breast Cancer Trialists' Collaborative Group (EBCTCG), Correa C, McGale P *et al*. Overview of the randomized trials of radiotherapy in ductal carcinoma-in-situ of the breast. *J Natl Cancer Inst Monogr* 2010; **2010**(41): 162–177.
5. Nilsson C, Valachis A. The role of boost and hypofractionation as adjuvant radiotherapy in patients with DCIS: A meta-analysis observational studies. *Radiother Oncol* 2015; **114**(1): 50–55.
6. Kunkler IH, Williams LJ, Jack WJ, Cameron DA, Dixon JM, PRIME II investigators. Breast-conserving surgery with or without irradiation in women aged 65 years or older with early breast cancer (PRIME II): a randomised controlled trial. *Lancet Oncol* 2015; **16**(3): 266–273.
7. McCormick B, Winter K, Hudis C *et al*. RTOG 9804: a prospective randomized trial for good-risk ductal carcinoma in situ comparing radiotherapy with observation. *J Clin Oncol* 2015; **33**(7): 709–715.
8. Fisher B, Anderson S, Bryant J *et al*. Twenty-year follow-up of a randomized trial comparing total mastectomy, lumpectomy, and lumpectomy plus irradiation for the treatment of invasive breast cancer. *N Engl J Med* 2002; **347**(16): 1233–1241.
9. Haviland JS, Owen JR, Dewar JA *et al*. The UK standardisation of breast radiotherapy (START) trials of radiotherapy hypofractionation for treatment of early breast cancer: 10-year follow-up results of two randomised controlled trials. *Lancet Oncol* 2013; **14**(11): 1086–1094.
10. Whelan TJ, Pignol JP, Levine MN *et al*. Long-term results of hypofractionated radiation therapy for breast cancer. *N Engl J Med* 2010; **362**(6): 513–520.
11. FAST Trialists Group, Agrawal RK, Alhasson A *et al*. First results of the randomised UK FAST Trial of radiotherapy hypofractionation for treatment of early breast cancer. *Radiother Oncol* 2011; **100**(1): 93–100.
12. Yarnold J, Bentzen S, Coles C, Haviland J. Hypofractionated radiotherapy for women with early breast cancer: myths and realities. *Int J Radiation Oncology Biol Phys* 2011; **79**(1): 1–9.
13. Marta GN, Macedo CR, Carvalho Hde A, Hannah San, da Silva JL, Riera R. Accelerated partial irradiation for breast cancer: systematic review and meta-analysis of 8653 women in eight randomized trials. *Radiother Oncol* 2015; **114**(1): 42–29.
14. Coles C, Agrawal R, Ah-See ML *et al*. Abstract no. 4 LBA. *Partial breast radiotherapy for women with early breast cancer. First results of local recurrence data for IMPORT LOW (CRUK/06/003)*. Official 10th European Breast Cancer Conference (EBCC-10) March 2016.

15. Veronesi U, Orecchia R, Maisonneuve P *et al*. Intraoperative radiotherapy versus external radiotherapy for early breast cancer (ELIOT): a randomised controlled equivalence trial. *Lancet Oncol* 2013; **14**(13): 1269–1277.

16. Vaidya JS, Wenz F, Bulsara M *et al*. Risk-adapted targeted intraoperative radiotherapy versus whole-breast radiotherapy for breast cancer: 5-year results for local control and overall survival from the TARGIT-A randomised trial. *Lancet* 2014; **383**(9917): 603–613.

17. Bartelink H, Maingon P, Poortmans P *et al*. Whole-breast irradiation with or without a boost for patients treated with breast-conserving surgery for early breast cancer: 20-year follow-up of a randomised phase 3 trial. *Lancet Oncol* 2015; **16**(1): 47–56.

18. Poortmans PM, Collete L, Horiot JC *et al*. Impact of the boost dose of 10 Gy versus 26 Gy in patients with early stage breast cancer after a microscopically incomplete lumpectomy: 10-year results of the randomised EORTC boost trial. *Radiotherapy Oncology* 2009; **90**(1): 80–85.

19. Donovan EM, Ciurlionis L, Fairfoul J *et al*. Planning with intensity-modulated radiotherapy and tomotherapy to modulate dose across breast to reflect recurrence risk (IMPORT High trial). *Int J Radiat Oncol Biol Phys* 2011; **79**(4): 1064–1072.

20. www.ukctg.nihr.ac.uk/trials/trial-details/trial-details?trialId=1504 (last accessed 15/11/16)

21. Mukesh MB, Barnett GC, Wilkinson JS *et al*. Randomized controlled trial of intensity-modulated radiotherapy for early breast cancer: 5-year results confirm superior overall cosmesis. *J Clin Oncol* 2013; **31**(36): 4488–4495.

22. Taylor C, Kirby A. Cardiac side-effects from breast cancer radiotherapy. *Clin Oncol (R Coll Radiol)* 2015; **27**(11): 621–629.

23. Chan EK, Woods R, Virani S *et al*. Long-term mortality from cardiac causes after adjuvant hypofractionated vs. conventional radiotherapy for localized left-sided breast cancer. *Radiother Oncol* 2015; **114**(1): 73–78.

24. Bartlett FR, Colgan RM, Donovan EM *et al*. The UK HeartSpare Study (Stage IB): randomised comparison of a voluntary breath-hold technique and prone radiotherapy after breast conserving surgery. *Radiother Oncol* 2015; **114**(1): 66–72.

25. Donovan E, Coles C, Westbury C, Yarnold J. Breast In: Hoskin PJ (ed). *External beam therapy*, 2nd edn. Oxford: Oxford University Press, 2012: 49–100.

26. Donker M, van Tienhoven G, Straver ME *et al*. Radiotherapy or surgery of the axilla after a positive sentinel node in breast cancer (EORTC 10981-22023 AMAROS): a randomised, multicentre, open-label, phase 3 non-inferiority trial. *Lancet Oncol* 2014; **15**(12): 1303–1310.

27. Giulliano AE, McCall L, Beitsch P *et al*. Locoregional recurrence after sentinel lymph node dissection with or without axillary dissection in patients with sentinel lymph node metastases: the American College of Surgeons Oncology Group Z0011 randomized trial. *Ann Surg* 2010; **252**(3): 426–432.

28. www.posnoc.co.uk (last accessed 23/9/16)

29. Whelan TJ, Olivotto IA, Parulekar WR *et al*. Regional nodal irradiation in early-stage breast cancer: results of the MA20 prospective randomised controlled trial. *N Eng J Med* 2015; **373**(4): 307–316.

30. Poortmans P, Collette S, Kirkove C *et al*. Internal mammary and medial supraclavicular irradiation in breast cancer. *N Eng J Med* 2015; **373**(4): 317–327.

31. Budach W, Kammers K, Boelke E, Matuschek C. Adjuvant radiotherapy of regional lymph nodes in breast cancer – a meta-analysis of randomized trials. *Radiat Oncol* 2013; **8**: 267.

References

32. Thorsen LB, Offersen BV, Danø H *et al*. DBCG-IMN: a population-based cohort study on the effect of internal mammary node irradiation in early node-positive breast cancer. *J Clin Oncol* 2016; **34**(4): 314–320.

33. Badiyan SN, Shah C, Arthur D *et al*. Hypofractionated regional nodal irradiation for breast cancer: examining the data and potential for future studies. *Radiother Oncol* 2014; **110**(1): 39–44.

4.

Central nervous system (CNS) tumours

Background

Two 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.[1–9] 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.

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.[10–12] 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.[13,14] The addition of temozolomide to radiotherapy for newly diagnosed glioblastoma has been shown to improve overall and progression-free survival.[15] The study only included patients under the age of 70, and therefore careful consideration should be taken before offering chemo-radiation therapy to patients over 70.

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.[16,17] In trials for anaplastic oligodendroglioma and oligoastrocytoma, the radiotherapy dose was 59.4 Gy in 33 fractions, providing Level 2a evidence for this regimen in WHO grade III glioma with oligodendroglial component.[18–20] The ongoing European Organisation for Research and Treatment of Cancer (EORTC) 26053-22054 trial in non-1p19q co-deleted WHO grade III glioma also uses 59.4 Gy in 33 fractions (EORTC 26053-22054). Previous dose determination studies in high-grade gliomas used a dose of 60 Gy in 30 fractions for grade III gliomas.[11,19]

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.[18]

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 ≥60 of Karnofsky Performance Status (KPS) ≥50 showed similar survival for 40 Gy in 15 fractions over three weeks compared to 60 Gy in 30 fractions.[20] In another randomised trial in patients aged ≥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.[21] Shorter fractionations are therefore an option in elderly patients unsuitable for chemo-radiotherapy. Results are awaited from another randomised trial in patients aged 65 years and older of good performance status, which compared 40 Gy in 15 fractions over three weeks with the same radiotherapy plus concurrent and adjuvant temozolomide.[22]

For patients with high-grade glioma and poor performance status, when treatment is indiciated, hypofractionated treatments are used.[23,24] 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.[18]

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.[25,26] 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 PCV chemotherapy after radiotherapy for high-risk low-grade glioma (age 18–39 and incompletely resected, or age ≥40 with any extent of resection).[27,28] This provides Level 2b evidence for this regimen.[18]

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.[18]

Finally, it should be noted that, given the histological heterogeneity of gliomas, molecular pathology techniques are being used for tumour phenotyping and stratification of patients to appropriate adjuvant therapy. Allocation of treatment schedule in the future is unlikely to be made solely on the basis of histological grade as indicated above.

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.[29–32] There is some evidence to suggest that local control is enhanced at doses greater than 52 Gy.[29–32]

Radiotherapy should always be considered in malignant meningioma to a dose of 60 Gy in 30 fractions. Attempts at dose escalation using radiosurgery boost and accelerated hyperfractionation failed to achieve improved local control.[31] 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.[33]

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.[34,35]

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.[18]

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.[36] 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.[37] Small inoperable pituitary tumours away from optic apparatus may be suitable for single fraction stereotactic treatment which offers a similar local control rate.[38]

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.[18]

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.[39–41]

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.[18]

References

1. Kramer S. The hazards of therapeutic irradiation of the central nervous system. *Clin Neurosurg* 1968,**15**: 301–318.
2. Marks JE, Baglan RJ, Prassa SC, Blank WF. Cerebral radionecrosis: incidence and risk in relation to dose, time, fractionation and volume. *Int J Radiat Oncol Biol Phys* 1981; **7**(2): 243–252.
3. Sheline GE, Wara WM, Smith V. Therapeutic irradiation and brain injury. *Int J Radiat Oncol Biol Phys* 1980; **6**(9): 1215–1228.
4. Leibel SA, Sheline GE. Tolerance of the brain and spinal cord to conventional radiation. In: Gutin PH, Leibel SA, Sheline GE (eds). *Radiation Injury to the Nervous system*. New York: Raven Press, 1991: 239–256.
5. Corn BW, Yousem DM, Scott CB *et al*. White matter changes are correlated significantly with radiation dose. Observations from a randomized dose-escalation trial for malignant glioma (Radiation Therapy Oncology Group 83-02). *Cancer* 1994; **74**(10): 2828–2835.
6. Emami B, Lyman J, Brown A *et al*. Tolerance of normal tissue to therapeutic irradiation. *Int J Radiat Oncol Biol Phys* 1991; **21**(1): 109–122.
7. Berg G, Blomquist E, Cavallin-Ståhl E. A systematic overview of radiation therapy effects in brain tumours. *Acta Oncologica* 2003; **42**(5–6): 582–588.
8. Marks LB, Ten Haken RK, Martel MK. Guest editor's introduction to QUANTEC: a users guide. *Int J Radiat Oncol Biol Phys* 2010; **76**(3 Suppl): S1–S2.
9. Marks LB, Yorke ED, Jackson A *et al*. Use of normal tissue complication probability models in the clinic. *Int J Radiat Oncol Biol Phys* 2010; **76**(3 Suppl): S10–9.
10. Walker MD, Strike TA, Sheline GE. An analysis of dose-effect relationship in the radiotherapy of malignant gliomas. *Int J Radiat Oncol Biol Phys* 1979; **5**(10): 1725–1731.
11. Bleehan NM, Stenning SP. A Medical Research Council trial of two radiotherapy doses in the treatment of grades 3 and 4 astrocytoma. *Br J Cancer* 1991; **64**(4): 769–774.
12. Salazar OM, Rubin P, McDonald JV, Feldstein ML. High dose radiation therapy in the treatment of glioblastoma multiforme: a preliminary report. *Int J Radiat Oncol Biol Phys* 1976; **1**(7–8): 717–727.
13. Werner-Wasik M, Scott CB, Nelson DF *et al*. Final report of a phase I/II trial of hyperfractionated and accelerated hyperfractionated radiation therapy with carmustine for adults with supratentorial malignant gliomas: Radiation Therapy Oncology Group Study 83-02. *Cancer* 1996; **77**(8): 1535–1543.
14. González DG, Menten J, Bosch DA *et al*. Accelerated radiotherapy in glioblastoma multiforme: a dose searching prospective study. *Radiother Oncol* 1994; **32**(2): 98–105.
15. Stupp R, Hegi ME, Mason WP *et al*. Effects of radiotherapy with concomitant and adjuvant temozolomide versus radiotherapy alone on survival in glioblastoma in a randomised phase III study: 5-year analysis of the EORTC-NCIC trial. *Lancet Oncol* 2009; **10**(5): 459–466.
16. Cairncross G, Wang M, Shaw E *et al*. Phase III trial of chemoradiotherapy for anaplastic oligodendroglioma: long-term results of RTOG 9402. *J Clin Oncol* 2013; **31**(3): 337–343.
17. van den Bent MJ, Brandes AA, Taphoorn MJ *et al*. Adjuvant procarbazine, lomustine, and vincristine chemotherapy in newly diagnosed anaplastic oligodendroglioma: long-term follow-up of EORTC brain tumor group study 26951. *J Clin Oncol* 2013; **31**(3): 344–350.
18. www.cebm.net/oxford-centre-evidence-based-medicine-levels-evidence-march-2009 (last accessed 26/9/16)

19. Nelson DF, Diener-West M, Horton J, Chang CH, Schoenfeld D, Nelson JS. Combined modality approach to treatment of malignant gliomas--re-evaluation of RTOG 7401/ECOG 1374 with long-term follow-up: a joint study of the Radiation Therapy Oncology Group and the Eastern Cooperative Oncology Group. *NCI Monogr* 1988; **1988**(6): 279–284.

20. Roa W, Brasher PM, Bauman G *et al*. Abbreviated course of radiation therapy in older patients with glioblastoma multiforme: a prospective randomized clinical trial. *J Clin Oncol* 2004; **22**(9): 1583–1588.

21. Malmström A, Grønberg BH, Marosi C *et al*. Temozolomide versus standard 6-week radiotherapy versus hypofractionated radiotherapy in patients older than 60 years with glioblastoma: the Nordic randomised, phase 3 trial. *Lancet Oncol* 2012; **13**(9): 916–926.

22. https://clinicaltrials.gov/ct2/show/NCT00482677 (last accessed 26/9/16)

23. McAleese JJ, Stenning SP, Ashley S *et al*. Hypofractionated radiotherapy for poor prognosis malignant glioma: matched pair survival analysis with MRC controls. *Radiother Oncol* 2003; **67**(2): 177–182.

24. Thomas R, James N, Guerrero D, Ashley S, Gregor A, Brada M. Hypofractionated radiotherapy as palliative treatment in poor prognosis patients with high grade glioma. *Radiother Oncol* 1994; **33**(2): 113–116.

25. Karim AB, Maat B, Hatlevoll R *et al*. A randomized trial on dose-response in radiation therapy of low-grade cerebral glioma: European Organisation for Research and Treatment of Cancer (EORTC) Study 22845. *Int J Radiat Oncol Biol Phys* 1996; **36**(3): 549–556.

26. Karim AB, Afra D, Cornu P *et al*. Randomized trial on the efficacy of radiotherapy for cerebral low-grade glioma in the adult: European Organisation for Research and Treatment of Cancer Study 22845 with the Medical Research Council study BR04: an interim analysis. *Int J Radiat Oncol Biol Phys* 2002; **52**(2): 316–324.

27. van den Bent MJ, Afra D, de Witte O *et al*. Long-term efficacy of early versus delayed radiotherapy for low-grade astrocytoma and oligodendroglioma in adults: the EORTC 22845 randomised trial. *Lancet* 2005; **366**(9490): 985–990.

28. Shaw E, Arusell R, Scheithauer B *et al*. Prospective randomised trial of low- versus high-dose radiation therapy in adults with supratentorial low-grade glioma: initial report of a North Central Cancer Treatment Group/Radiation Therapy Oncology Group/astern Cooperative Oncology Group Study. *J Clin Oncol* 2002; **20**(9): 2267–2276.

29. Adeberg S, Hartmann C, Welzel T *et al*. Long-term outcome after radiotherapy in patients with atypical and malignant meningiomas – clinical results in 85 patients treated in a single institution leading to optimized guidelines for early radiation therapy. *Int J Radiat Oncol Biol Phys* 2012; **83**(3): 859–864.

30. Aghi MK, Carter BS, Cosgrove GR *et al*. Long-term recurrence rates of atypical meningiomas after gross total resection with or without postoperative adjuvant radiation. *Neurosurgery* 2009; **64**(1): 56–60; discussion 60.

31. Goldsmith BJ, Wara WM, Wilson CB, Larson DA. Postoperative irradiation for subtotally resected meningiomas. A retrospective analysis of 140 patients treated from 1967 to 1990. *J Neurosurg* 1994; **80**(2): 195–201.

32. Milosevic MF, Frost PJ, Laperriere NJ, Wong CS, Simpson WJ. Radiotherapy for atypical or malignant intracranial meningioma. *Int J Radiat Oncol Biol Phys* 1996; **34**(4): 817–822.

33. https://clinicaltrials.gov/ct2/show/NCT00626730 (last accessed 13/10/16)

34. Brower JV, Amdur RJ, Kirwan J, Mendenhall WM, Friedman W. Radiation therapy for optic nerve sheath meningioma. *Pract Radiat Oncol* 2013; **3**(3): 223–288.

References

35. Roser F, Nakamura M, Martini-Thomas R, Samii M, Tatagiba M. The role of surgery in meningiomas involving the optic nerve sheath. *Clin Neurol Neurosurg* 2006; **108**(5): 470–406.

36. Erridge SC, Conkey DS, Stockton D *et al*. Radiotherapy for pituitary adenomas: long-term efficacy and toxicity. *Radiother Oncol* 2009; **93**(3): 597–601.

37. Grigsby PW, Simpson JR, Emami BN, Fineberg BB, Schwartz HG. Prognostic factors and results of surgery and postoperative irradiation in the management of pituitary adenomas. *Int J Radiat Oncol Biol Phys* 1989; **16**(6): 1411–1417.

38. Sheehan JP, Starke RM, Mathieu D *et al*. Gamma Knife radiosurgery for the management of nonfunctioning pituitary adenomas: a multicenter study. *J Neurosurg* 2013; **119**(2): 446–456.

39. Varlotto JM, Flickinger JC, Kondsiolk D *et al*. External beam irradiation of craniopharyngiomas: long-term analysis of tumor control and morbidity. *Int J Radiat Oncol Biol Phys* 2002; **54**(2): 492–499.

40. Masson-Cote L, Masucci GL, Atenafu EG *et al*. Long-term outcomes for adult craniopharyngioma following radiation therapy. *Acta Oncol* 2013; **52**(1): 153–158.

41. Harrabi SB, Adeberg S, Welzel T *et al*. Long term results after fractionated stereotactic radiotherapy (FSRT) in patients with craniopharyngioma: maximal tumor control with minimal side effects. *Radiat Oncol* 2014; **9**: 203.

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).[1,2]

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

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).[2–11]

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).[1–3,12,13] Both early and late toxicity are increased when chemotherapy is added (Level 1b).[2,12,14]

Overall treatment time, including intracavitary brachytherapy (ICBT), should not exceed 56 days for squamous carcinoma (Level 1b).[2,15–19] 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).[2,20]

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).[2] Alternatively, a simultaneous integrated intensity-modulated radiotherapy (IMRT) planned external beam radiotherapy (EBRT) boost can be considered (Level 2b).[2] 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).[2,21,22]

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]).[23,24] Dose constraints to OARs have been published based on organ volume rather than point doses (Level 2b).[2,25] 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).[26,27]

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.[28]

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

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^2) (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^2 (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.[2]

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.[32–37] 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.[35] The long-term pelvic side-effects in the brachytherapy group were less than with external beam. The PORTEC 3 trial, which is expected to report in 2017, has investigated the benefit of concurrent chemoradiotherapy and adjuvant chemotherapy compared to adjuvant radiotherapy alone, which is the current standard of care.[36]

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)

Vaginal 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 milimetres (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.[2]

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).[37,38]

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.[2]

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).[39,40]

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.[41]

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).[2] 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.[42]

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.[2]

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.[43]

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^2 (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.[2]

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).[44] The addition of concurrent chemotherapy appears to deliver a survival advantage (Level 4).[45]

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.[2]

References

1. Landoni F, Maneo A, Colombo A *et al*. Randomised study of radical surgery versus radiotherapy for stage Ib–IIa cervical cancer. *Lancet* 1997; **350**(9077): 535–540.
2. www.cebm.net/oxford-centre-evidence-based-medicine-levels-evidence-march-2009 (last accessed 26/9/16)
3. Sedlis A, Bundy BN, Rotman MZ, *et al*. A randomized trial of pelvic radiation therapy versus no further therapy in selected patients with stage IB carcinoma of the cervix after radical hysterectomy and pelvic lymphadenectomy: A Gynecologic Oncology Group Study. *Gynaecol Oncol* 1999; **73**(2): 177–183.
4. Chemoradiotherapy for Cervical Cancer Meta-analysis Collaboration (CCCMAC). Reducing uncertainties about the effects of chemoradiotherapy for cervical cancer: individual patient data meta-analysis. *Cochrane Database Syst Rev* 2010; **(1)**: CD009285.
5. Whitney CW, Sause W, Bundy BN *et al*. Randomized comparison of fluorouracil plus cisplatin versus hydroxyurea as an adjunct to radiation therapy in stage IIB–IVA carcinoma of the cervix with negative para-aortic lymph nodes: a Gynecologic Oncology Group and Southwest Oncology Group study. *J Clin Oncol* 1999; **17**(5): 1339–1348.
6. Rose PG, Bundy BN, Watkins EB *et al*. Concurrent cisplatin-based radiotherapy and chemotherapy for locally advanced cervical cancer. N Engl J Med 1999; **340**(15): 1144–1153. [erratum in *N Engl J Med* 1999; **341**(9): 708]
7. Morris M, Eifel PJ, Lu J *et al*. Pelvic radiation with concurrent chemotherapy compared with pelvic and para-aortic radiation for high-risk cervical cancer. *N Engl J Med* 1999; **340**(15): 1137–1143.
8. Keys HM, Bundy BN, Stehman FB *et al*. Cisplatin, radiation, and adjuvant hysterectomy compared with radiation and adjuvant hysterectomy for bulky stage IB cervical carcinoma. *N Engl J Med* 1999; **340**(15):1154–1161. [erratum in *N Engl J Med* 1999; **341**(9): 708].
9. Thomas GM. Improved treatment for cervical cancer – concurrent chemotherapy and radiotherapy. *N Engl J Med* 1999; **340**(15): 1198–1200.
10. Rose PG, Bundy BN. Chemoradiation for locally advanced cervical cancer: does it help? *J Clin Oncol* 2002; **20**(4): 891–893.
11. Eifel PJ, Winter K, Morris M *et al*. Pelvic irradiation with concurrent chemotherapy versus pelvic and para-aortic irradiation for high-risk cervical cancer: an update of radiation therapy oncology group trial (RTOG) 90-01. *J Clin Oncol* 2004; **22**(5): 872–880.
12. Peters WA 3rd, Liu PY, Barrett RJ 2nd *et al*. Concurrent chemotherapy and pelvic radiation therapy compared with pelvic radiation therapy alone as adjuvant therapy after radical surgery in high-risk early-stage cancer of the cervix. *J Clin Oncol* 2000; **18**(8): 1606–1613.
13. Monk BJ, Wang J, Im S *et al*. Rethinking the use of radiation and chemotherapy after radical hysterectomy: a clinical-pathologic analysis of a Gynecologic Oncology Group/Southwest Oncology Group/Radiation Therapy Oncology Group trial. *Gynecol Oncol* 2005; **96**(3): 721–728.
14. Vale CL, Tierney JF, Davidson SE, Drinkwater KJ, Symonds P. Substantial improvement in UK cervical cancer survival with chemoradiotherapy: Results of a Royal College of Radiologists' audit. *Clin Oncol (R Coll Radiol)* 2010; **22**(7): 590–601.
15. The Royal College of Radiologists. *The timely delivery of radical radiotherapy: standards and guidelines for the management of unscheduled treatment interruptions,* Third edition. London: The Royal College of Radiologists, 2008

16. Chatani M, Makayoshi Y, Masaki N, Inoue T. High-dose rate intracavitary irradiation for carcinoma of the uterine cervix. The adverse effect of treatment prolongation. *Strahlenther Onkol* 1997; **73**(7): 379–384.

17. Perez CA, Grigsby PW, Castro-Vita H, Lockett MA. Carcinoma of the uterine cervix part I. Impact of prolongation of overall treatment time and timing of brachytherapy on outcome of radiation therapy. *Int J Radiat Oncol Biol Phys* 1999; **32**(5): 1275–1288.

18. Fyles A, Keane TJ, Barton M, Simm J. The effect of treatment duration in the local control of cervix cancer. *Radiother Oncol* 1992; **25**(4): 273–279.

19. Delaloye JF, Coucke PA, Pampallona S, De Grandi P. Effect of total treatment time on event-free survival in carcinoma of the cervix. *Gynecol Oncol* 1996; **60**(1): 42–48.

20. Winter WE 3rd, Maxwell GL, Tian C *et al*. Association of hemoglobin level with survival in cervical carcinoma patients treated with concurrent cisplatin and radiotherapy: A Gynecologic Oncology Group study. *Gynecologic Oncol* 2004; **94**(2): 495–501.

21. Mohamed S, Kallehauge J, Fokdal L, Lindegaard JC, Tanderup K. Parametrial boosting in locally advanced cervical cancer: combined intracavitary/interstitial brachytherapy versus intracavitary brachytherapy plus external beam radiotherapy. *Brachytherapy* 2015; **14**(1): 23–28.

22. Huang E-Y, Lin H, Hsu HC *et al*. High external parametrial dose can increase the probability of radiation proctitis in patients with uterine cervix cancer. *Gynecol Oncol* 2000; **79**(3): 406–410.

23. Mazeron R, Castelnau-Marchand P, Dumas I *et al*. Impact of treatment time and dose escalation on local control in locally advanced cervical cancer treated by chemoradiation and image-guided pulsed-dose rate adaptive brachytherapy. *Radiother Oncol* 2015; **114**(2): 257–263.

24. Rijkmans EC, Nout RA, Rutten IH *et al*. Improved survival of patients with cervical cancer treated with image-guided brachytherapy compared with conventional brachytherapy. *Gynecol Oncol* 2014; **135**(2): 231–238.

25. Potter R, Georg P, Dimopoulos JC *et al*. Clinical outcome of protocol based image (MRI) guided adaptive brachytherapy combined with 3D conformal radiotherapy with or without chemotherapy in patients with locally advanced cervical cancer. *Radiother Oncol* 2001; **100**(1): 116–123.

26. https://clinicaltrials.gov/ct2/show/NCT01414608 (last accessed 26/9/16)

27. https://clinicaltrials.gov/ct2/show/NCT01566240?term=interlace&rank=2 (last accessed 13/10/16)

28. Yap ML, Cuartero J, Yan J *et al*. The role of elective para-aortic lymph node irradiation in patients with locally advanced cervical cancer. *Clin Oncol (R Coll Radiol)* 2014; **26**(12): 797–803.

29. Taylor A, Rockall AG, Powell ME. An atlas of the pelvic lymph node regions to aid radiotherapy target volume definitions. *Clin Oncol (R Coll Radiol)* 2007; **19**(7): 542–550.

30. Small W Jr, Mell LK, Anderson P *et al*. Consensus guidelines for delineation of the clinical target volume for intensity-modulated pelvic radiotherapy in the postoperative treatment of endometrial and cervical cancer. *Int J Radiat Oncol Biol Phys* 2008; **71**(2): 428–434.

31. Hasselle MD, Rose BS, Kochanski JD *et al*. Clinical outcomes of intensity-modulated pelvic radiation therapy for carcinoma of the cervix. *Int J Radiat Oncol Biol Phys* 2011; **80**(5): 1436–1445.

32. ASTEC study group, Kitchener H, Swart AM, Qian Q *et al*. Efficacy of systematic pelvic lymphadenectomy in endometrial cancer (MRC ASTEC trial): a randomised study. *Lancet* 2009; **373**(9658): 125–136.

References

33. Creutzberg CL, Nout RA, Lybeert ML *et al*. Fifteen-year radiotherapy outcomes of the randomised PORTEC-1 trial for endometrial carcinoma. *Int J Rad Oncol Biol Phys* 2011; **81**(4): e631–e638.

34. Keys HM, Roberts JA, Brunetto VL *et al*. A phase III trial of surgery with or without adjunctive external pelvic radiation therapy in intermediate risk endometrial adenocarcinoma: A Gynecologic Oncology Group study. *Gynecol Oncol* 2004; **92**(3): 744–751.

35. Nout RA, Smit VT, Putter H *et al*. Vaginal brachytherapy versus pelvic external beam radiotherapy for patients with endometrial cancer of high-intermediate risk (PORTEC-2): an open-label, non-inferiority, randomised trial. *Lancet* 2010; **375**(9717): 816–823

36. https://clinicaltrials.gov/ct2/show/NCT00411138?term=PORTEC+3&rank=1 (last accessed 26/9/16)

37. Churn M, Jones B. Primary radiotherapy for carcinoma of the endometrium using external beam radiotherapy and single line source brachytherapy. *Clin Oncol* 1999; **11**(4): 255–262.

38. Gill BS, Kim H, Houser C *et al*. Image-based three-dimensional conformal brachytherapy for medically inoperable endometrial carcinoma. *Brachytherapy* 2014; **13**(6): 542–547.

39. Vargo JA, Kim H, Houser CJ *et al*. Definitive salvage for vaginal recurrence of endometrial cancer: the impact of modern intensity-modulated-radiotherapy with image-based HDR brachytherapy and the interplay of the PORTEC 1 risk stratification. *Radiother Oncol* 2014; **113**(1): 126–131.

40. Jereczek-Fossa B, Badzio A, Jassem J. Recurrent endometrial cancer after surgery alone: results of salvage radiotherapy. *Int J of Radiat Oncol Biol Phys* 2000; **48**(2); 405–413.

41. Van der Velden J, Fons G, Lawrie TA. Primary groin irradiation versus primary groin surgery for early vuval cancer. *Cochrane Database Syst Rev* 2011; **5**: CD002224.

42. https://clinicaltrials.gov/ct2/show/NCT01500512?term=GROINSS&rank=1 (last accessed 26/9/16)

43. Moore DH, Ali S, Koh WJ *et al*. A phase II trial of radiation therapy and weekly cisplatin chemotherapy for the treatment of locally-advanced squamous cell carcinoma of the vulva: a gynaecological oncology group study. *Gynecol Oncol* 2012; **124**(3): 529–533.

44. Beriwal S, Bhatnagar A, Heron DE *et al*. High-dose-rate interstitial brachytherapy for gynecological malignancies. *Brachytherapy* 2006; **5**(4): 218–222.

45. Rajagopalan MS, Xu KM, Lin JF, Sukumvanich P, Krivak TC, Beriwal S. Adoption and impact of concurrent chemoradiation therapy for vaginal cancer: A National Cancer Data Base (NCDB) Study. *Gynecol Oncol* 2014; **135**(3): 495–502.

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.[1]

T1/2N0 glottic carcinoma

Hypofractionated regimens are recommended.[2] A randomised trial demonstrated the superiority of modest hypofractionation with 2.25 Gy per fraction and, in large retrospective series, fraction sizes of ≥2.25 Gy compared favourably with other reported series.[2–4] 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.[5–8] Hyperfractionated schedules have not shown a significant improvement compared with conventional fractionation.[9]

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.[10]

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).[11] 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).[10] 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.[12] 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.[11] There was no benefit of altered fractionation for patients age >70 years old (Level 1b).[10,11]

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).[10,13]

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.[14–17] 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).[10,15–17]

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).[11,18]

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.[10]

Radiotherapy alone for early stage (I/II) oropharynx/hypopharnx/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.[19] 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).[12] In a meta-analysis, there was no clear benefit for altered fractionation for the subgroup with stage I/II disease (Level 1a).[10,11]

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.[10]

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.[20] The international standard schedule is 70 Gy in 35 fractions.[20] 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.[21] 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.[22] 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).[10,23] 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.[24] 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).[10,21,25]

In patients with oropharyngeal cancer, the tumour human papilloma virus (HPV) status has been identified as a strong and independent prognostic factor for survival.[26] 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).[10]

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.[10]

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).[10,20] 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 alterated fractionation in patients ≥70 years old (Level 1a).[10,11,12,27]

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.[10]

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).[10,28] 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.[29,30] A pooled analysis identified subgroups with close/positive margins and/or extracapsular spread as benefiting from concurrent cisplatin (Level 2a).[10,31] 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.[32,33] 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).[10,33]

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.[10]

Nasopharynx carcinoma

Radiotherapy alone is used for early stage nasopharyngeal carcinoma.[34] 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).[10,35] 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).[10,36] Doses biologically equivalent to 50–60 Gy in 2 Gy per fraction are commonly used to treat at-risk sites.[34]

Recommendations

Nasopharynx 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.[10]

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.

There is no consensus for palliative radiotherapy for locally advanced head and neck cancer.

Recommendations

40 Gy in 10 fractions over 4 weeks 'split course' (Level C)[37]
21 Gy in 3 fractions over 3 weeks (Level C)[38]
14 Gy in 4 fractions which may be repeated 2 further times every 4 weeks (Level C)39

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.[10]

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, sequalae 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 ≥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.[40,41] Hyperfractionation with bi-daily irradiation at approximately 1.2 Gy per fraction can be considered (Grade C).[10,41] The use of concomitant radiosensitising agents should only be used with extreme caution.

References

1. Ho KF, Fowler JF, Sykes AJ, Yap BK, Lee LW, Slevin NJ. IMRT dose fractionation for head and neck cancer: variation in current approaches will make standardisation difficult. *Acta Oncol* 2009; **48**(3): 431–439.
2. Le QT, Fu KK, Kroll S *et al*. Influence of fraction size, total dose, and overall time on local control of T1-T2 glottic carcinoma. *Int J Radiat Oncol Biol Phys* 1997; **39**(1): 115–126.
3. Yamazaki H, Nishiyama K, Tanaka E, Koizumi M, Chatani M. Radiotherapy for early glottic carcinoma (T1N0M0): results of prospective randomized study of radiation fraction size and overall treatment time. *Int J Radiat Oncol Biol Phys* 2006; **64**(1): 77–82.
4. Chera BS, Amdur RJ, Morris CG, Kirwan JM, Mendenhall WM. T1N0 to T2N0 squamous cell carcinoma of the glottic larynx treated with definitive radiotherapy. *Int J Radiat Oncol Biol Phys* 2010; **78**(2): 461–466.
5. Gowda RV, Henk JM, Mais KL, Sykes AJ, Swindell R, Slevin NJ. Three weeks radiotherapy for T1 glottic cancer: the Christie and Royal Marsden Hospital Experience. *Radiother Oncol* 2003; **68**(2): 105–111.
6. Cheah NL, Lupton S, Marshall A, *et al*. Outcome of T1N0M0 squamous cell carcinoma of the larynx treated with short-course radiotherapy to a total dose of 50 Gy in 16 fractions: the Birmingham experience. *Clin Oncol (R Coll Radiol)* 2009; **21**(6): 494–501.
7. Ermis E, Teo M, Dyker KE, Fosker C, Sen M, Prestwich RJ. Definitive hypofractionated radiotherapy for early glottic carcinoma: experience of 55 Gy in 20 fractions. *Radiat Oncol* 2015; **10**: 203.
8. Short S, Krawitz H, Macann A *et al*. TN/TN glottic carcinoma: a comparison of two fractionation schedules. *Australas Radiol* 2006; **50**(2): 152–157.
9. Trotti A 3rd, Zhang Q, Bentzen SM *et al*. Randomized trial of hyperfractionation versus conventional fractionation in T2 squamous cell carcinoma of the vocal cord (RTOG 9512). *Int J Radiat Oncol Biol Phys* 2014; **89**(5): 958–963.
10. www.cebm.net/oxford-centre-evidence-based-medicine-levels-evidence-march-2009 (last accessed 26/9/16)
11. Bourhis J, Overgaard J, Audry H *et al*. Hyperfractionated or accelerated radiotherapy in head and neck cancer: a meta-analysis. *Lancet* 2006; **368**(9538): 843–854.
12. Overgaard J, Hansen HS, Specht L *et al*. Five compared with six fractions per week of conventional radiotherapy of squamous-cell carcinoma of head and neck: DAHANCA 6 and 7 randomised controlled trial. *Lancet* 2003; **362**(9388): 933–940.
13. Pettit L, Hartley A, Bowden SJ *et al*. Variation in volume definition between UK head and neck oncologists treating oropharyngeal carcinoma. *Clin Oncol (R Coll Radiol)* 2011; **23**(9): 654–655.
14. Sher DJ, Balboni TA, Haddad RI *et al*. Efficacy and toxicity of chemoradiotherapy using intensity-modulated radiotherapy for unknown primary of head and neck. *Int J Radiat Oncol Biol Phys* 2011; **80**(5): 1405–1411.
15. Chen AM, Farwell DG, Lau DH, Li BQ, Luu Q, Donald PJ. Radiation therapy in the management of head-and-neck cancer of unknown primary origin: how does the addition of concurrent chemotherapy affect the therapeutic ratio? *Int J Radiat Oncol Biol Phys* 2011; **81**(2): 346–352.
16. Frank SJ, Rosenthal DI, Petsuksiri J *et al*. Intensity-modulated radiotherapy for cervical node squamous cell carcinoma metastases from unknown head-and-neck primary site: M. D. Anderson Cancer Center outcomes and patterns of failure. *Int J Radiat Oncol Biol Phys* 2010; **78**(4): 1005–1010.

References

17. Shoushtari A, Saylor D, Kerr KL *et al*. Outcomes of patients with head-and-neck cancer of unknown primary origin treated with intensity-modulated radiotherapy. *Int J Radiat Oncol Biol Phys* 2011; **81**(3): e83–e91.

18. Bedi M, Firat S, Semenenko VA *et al*. Elective lymph node irradiation with intensity-modulated radiotherapy: is conventional dose fractionation necessary? *Int J Radiat Oncol Biol Phys* 2012; **83**(1): e87–e92.

19. Eisbruch A, Harris J, Garden AS *et al*. Multi-institutional trial of accelerated hypofractionated intensity-modulated radiation therapy for early-stage oropharyngeal cancer (RTOG 00-22). *Int J Radiat Oncol Biol Phys* 2010; **76**(5): 1333–1338.

20. Pignon JP, le Maitre A, Maillard E, Bourhis J, MACH-NC Collaborative Group. Meta-analysis of chemotherapy in head and neck cancer (MACH-NC): an update on 93 randomised trials and 17,346 patients. *Radiother Oncol* 2009; **92**(1): 4–14.

21. Nutting CM, Morden JP, Harrington KJ *et al*. Parotid-sparing intensity modulated versus conventional radiotherapy in head and neck cancer (PARSPORT): a phase 3 multicentre randomised controlled trial. *Lancet Oncol* 2011;**12**(2): 127–136.

22. Nguyen-Tan PF, Zhang Q, Ang KK *et al*. Randomized phase III trial to test accelerated versus standard fractionation in combination with concurrent cisplatin for head and neck carcinomas in the Radiation Therapy Oncology Group 0129 trial: long-term report of efficacy and toxicity. *J Clin Oncol* 2014; **32**(34): 3858–3866.

23. Bourhis J, Sire C, Graff P *et al*. Concomitant chemoradiotherapy versus acceleration of radiotherapy with or without concomitant chemotherapy in locally advanced head and neck carcinoma (GORTEC 99-02): an open-label phase 3 randomised trial. *Lancet Oncol* 2012; **13**(2): 145–153.

24. Meade S, Sanghera P, McConkey C *et al*. Revising the radiobiological model of synchronous chemotherapy in head-and-neck cancer: a new analysis examining reduced weighting of accelerated repopulation. *Int J Radiat Oncol Biol Phys* 2013; **86**(1): 157–163.

25. Benghiat H, Sanghera P, Cashmore J *et al*. Four week hypofractionated accelerated intensity modulated radiotherapy and synchronous carboplatin or cetuximab in biologically staged oropharyngeal carcinoma. *Cancer and Clinical Oncology* 2014; **3**(2): 2.

26. Ang KK, Harris J, Wheeler R *et al*. Human papillomavirus and survival of patients with oropharyngeal cancer. *N Engl J Med* 2010; **363**(1): 24–35.

27. Beitler JJ, Zhang Q, Fu KK *et al*. Final results of local-regional control and late toxicity of RTOG 9003: a randomized trial of altered fractionation radiation for locally advanced head and neck cancer. *Int J Radiat Oncol Biol Phys* 2014; **89**(1): 13–20.

28. Peters LJ, Goepfert H, Ang KK *et al*. Evaluation of the dose for postoperative radiation therapy of head and neck cancer: first report of a prospective randomized trial. *Int J Radiat Oncol Biol Phys* 1993; **26**(1): 3–11.

29. Cooper JS, Pajak TF, Forastiere AA *et al*. Postoperative concurrent radiotherapy and chemotherapy for high-risk squamous-cell carcinoma of the head and neck. *N Engl J Med* 2004; **350**(19): 1937–1944.

30. Bernier J, Domenge C, Ozsahin M *et al*. Postoperative irradiation with or without concomitant chemotherapy for locally advanced head and neck cancer. *N Engl J Med* 2004; **350**(19): 1945–1952.

31. Bernier J, Cooper JS, Pajak TF *et al*. Defining risk levels in locally advanced head and neck cancers: a comparative analysis of concurrent postoperative radiation plus chemotherapy trials of the EORTC (#22931) and RTOG (# 9501). *Head Neck* 2005; **27**(10): 843–850.

32. Langendijk JA, Ferlito A, Takes RP *et al*. Postoperative strategies after primary surgery for squamous cell carcinoma of the head and neck. *Oral Oncol* 2010; **46**(8): 577–585.

33. Expert Panel on Radiation Oncology-Head and Neck, Salama JK, Saba N *et al*. ACR appropriateness criteria® adjuvant therapy for resected squamous cell carcinoma of the head and neck. *Oral Oncol* 2011; **47**(7): 554–559.

34. Lee AW, Lin JC, Ng WT. Current management of nasopharyngeal cancer. *Semin Radiat Oncol* 2012; **22**(3): 233–244.

35. Lee N, Harris J, Garden AS *et al*. Intensity-modulated radiation therapy with or without chemotherapy for nasopharyngeal carcinoma: radiation therapy oncology group phase II trial 0225. *J Clin Oncol* 2009; **27**(22): 3684–3690.

36. Boon CS, Hartley A, Sanghera P. Initial efficacy of hypofractionated accelerated chemo-tomotherapy(r) for nasopharyngeal carcinoma. *Clin Oncol (R Coll Radiol)* 2015; **27**(8): 484–485.

37. Kancherla KN, Oksuz DC, Prestwich RJ *et al*. The role of split-course hypofractionated palliative radiotherapy in head and neck cancer. *Clin Oncol (R Coll Radiol)* 2011; **23**(2): 141–148.

38. Nguyen NT, Doerwald-Munoz L, Zhang H *et al*. 0-7-21 hypofractionated palliative radiotherapy: an effective treatment for advanced head and neck cancers. *Br J Radiol* 2015; **88**(1049): 20140646.

39. Corry J, Peters LJ, Costa ID *et al*. The 'QUAD SHOT' – a phase II study of palliative radiotherapy for incurable head and neck cancer. *Radiother Oncol* 2005; **77**(2): 137–142.

40. Strojan P, Corry J, Eisbruch A *et al*. Recurrent and second primary squamous cell carcinoma of the head and neck: when and how to reirradiate. *Head Neck* 2015; **37**(1): 134–150.

41. McDonald MW, Lawson J, Garg MK *et al*. ACR appropriateness criteria retreatment of recurrent head and neck cancer after prior definitive radiation expert panel on radiation oncology-head and neck cancer. *Int J Radiat Oncol Biol Phys* 2011; **80**(5): 1292–1298.

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.[1,2] Several publications have looked at access to radiotherapy treatments (Level 2a).[3–5] 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).[5–7] However, as with many tumour types, there is insufficient evidence to determine the efficacy of IMRT (Level 4).[5,7,8]

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).[5,9] 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%.[10,11]

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).[5,12]

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).[5,13–15] 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).[5,16]

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).[5,17]

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

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).[5,18]

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

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).[5,15,19–22]

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)
55Gy 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.[5]

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).[5,23]

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.[5]

Small cell lung cancer (SCLC)

Background

The evidence base now favours integration of chemotherapy and radiotherapy at all disease stages (Level 1a).[5]

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).[5,24] 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.[25,26] 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).[5]

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).[5,24] 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).[5] 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).[5]

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.[5]

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).[5,27] Further data analysis has confirmed the OS and DFS benefits are limited to those with persistent intrathoracic disease (Level 1b).[5,28]

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.[5]

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).[5,29,30]

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).[5,30]

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.[5]

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).[5] 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.[31]

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.[5]

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).[5,32–34] 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.[35]

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).[5,36]

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.[5]

References

1. www.hqip.org.uk/ncapop-library/#cancer (last accessed 28/9/16)
2. National Cancer Intelligence Network Survival by stage (NCIN) 2014: www.ncin.org.uk/publications/survival_by_stage (last accessed 28/9/16)
3. Koning CC, Aarts MJ, Struikmans H *et al*. Mapping use of radiotherapy for patients with non-small cell lung cancer in the Netherlands between 1997 and 2008. *Clin Oncol (R Coll Radiol)* 2012; **24**(2): e46–e53.
4. Delaney GP and Barton MB. Evidence-based estimates of the demand for radiotherapy. *Clin Oncol (R Coll Radiol)* 2015; **27**(2): 70–76.
5. www.cebm.net/oxford-centre-evidence-based-medicine-levels-evidence-march-2009 (last accessed 26/9/16)
6. Harris JP, Murphy JD, Hanlon AL, Le QT, Loo BW Jr, Diehn M. A population-based comparative effectiveness study of radiation therapy techniques in stage III non-small cell lung cancer. *Int J Radiat Oncol Biol Phys* 2014; **88**(4): 872–884.
7. Chan C, Lang S, Rowbottom C *et al*. Intensity-modulated radiotherapy for lung cancer: current status and future developments. *J Thorac Oncol* 2014; **9**(11): 1598–1608.
8. Bezjak A, Rumble RB, Rodrigues G, Hope A, Warde P, Members of the IMRT Indications Expert Panl. Intensity-modulated radiotherapy in the treatment of lung cancer. *Clin Oncol (R Coll Radiol)* 2012; **24**(7): 508–520.
9. Chang JY, Senan S, Paul MA *et al*. Stereotactic ablative radiotherapy versus lobectomy for operable stage I non-small-cell lung cancer: a pooled analysis of two randomised trials. *Lancet Oncol* 2016; **16**(6): 630–637.
10. Zheng X, Schipper M, Kidwell K *et al*. Survival outcome after stereotactic body radiation therapy and surgery for stage I non-small cell lung cancer: a meta-analysis. *Int J Radiat Oncol Biol Phys* 2011; **90**(3): 603–611.
11. Shirvani SM, Jiang J, Chang JY *et al*. Comparative effectiveness of 5 treatment strategies for early-stage non-small cell lung cancer in the elderly. *Int J Radiat Oncol Biol Phys* 2012; **84**(5): 1060–1070.
12. SABR UK Consortium. *Stereotactic ablative radiotherapy (SABR): A resource. Version 5.0*. Manchester: SABR UK Consortium, 2015.
13. Aupérin A, Le Péchoux C, Pignon JP *et al*. Concomitant radio-chemotherapy based on platin compounds in patients with locally advanced non-small cell lung cancer (NSCLC): a meta-analysis of individual data from 1764 patients. *Ann Oncol* 2006; **17**(3): 473–483.
14. O'Rourke N, Roqué i Figuls M, Farré Bernadó N, Macbeth F. Concurrent chemoradiotherapy in non-small cell lung cancer. *Cochrane Database Syst Rev* 2010; **16**(6): CD002140.
15. Maguire J, Khan I, McMenemin R *et al*. SOCCAR: A randomised phase II trial comparing sequential versus concurrent chemotherapy and radical hypofractionated radiotherapy in patients with inoperable stage III non-small cell lung cancer and good performance status. *Eur J Cancer* 2014; **50**(17): 2939–2949.
16. Jalal SI, Riggs HD, Melnyk A *et al*. Updated survival and outcomes for older adults with inoperable stage III non-small-cell lung cancer treated with cisplatin, etoposide, and concurrent chest radiation with or without consolidation docetaxel: analysis of a phase III trial from the Hoosier Oncology Group (HOG) and US Oncology. *Ann Oncol* 2012; **805**(23): 1730–1738.

17. Rusch VW, Giroux DJ, Kraus MJ *et al*. Induction chemoradiation and surgical resection for superior sulcus non-small-cell lung carcinomas: long-term results of Southwest Oncology Group Trial 9416 (Intergroup trial 0160). *J Clin Oncol* 2007; **25**(3): 313–318.

18. Bradley JD, Paulus R, Komaki R *et al*. Standard-dose versus high-dose conformal radiotherapy with concurrent and consolidation carboplatin plus paclitaxel with or without cetuximab for patients with stage IIIA or IIIB non-small cell lung cancer (RTOG 0617): a randomised, two-by-two factorial phase 3 study. *Lancet Oncol* 2015; **16** (2): 187–199.

19. Saunders M, Dische S, Barrett A, Harvey A, Gibson D, Palmar M. Continuous hyperfractionated accelerated radiotherapy (CHART) versus conventional radiotherapy in non-small cell lung cancer: a randomised multicentre trial. CHART Steering Committee. *Lancet* 1997; **350**(9072): 161–165.

20. Mauguen A, Le Péchoux C, Saunders MI *et al*. Hyperfractionated or accelerated radiotherapy in lung cancer: an individual patient data meta-analysis. *J Clin Oncol* 2102; **30**(22): 2788–2297.

21. Hatton M, Nankivell M, Lyn E *et al*. Induction chemotherapy and continuous hyperfractionated accelerated radiotherapy (CHART) for patients with locally advanced inoperable non-small-cell lung cancer: the MRC INCH randomized trial. *Int J Radiat Oncol Biol Phys* 2011; **81**(3): 712–718.

22. Price A, Yellowlees A, Keerie C *et al*. Radical radiotherapy with or without gemcitabine in patients with early stage medically inoperable non-small cell lung cancer. *Lung Cancer* 2012; **77**(3): 532–536.

23. Lester JF, Macbeth F, Toy E, Coles B. Palliative radiotherapy regimens for non-small-cell lung cancer. *Cochrane Database Syst Rev* 2006; **18**(4): CD002143.

24. Murray N, Coy P, Pater JL *et al*. Importance of timing for thoracic irradiation in the combined modality treatment of limited-stage small-cell lung cancer. The National Cancer Institute of Canada Clinical Trials Group. *J Clin Oncol* 1993; **11**(2): 336–344.

25. Faivre-Finn C, Snee M, Ashcroft L *et al*. CONVERT: An international randomised trial of concurrent chemo-radiotherapy (cCTRT) comparing twice-daily (BD) and once-daily (OD) radiotherapy schedules in patients with limited stage small cell lung cancer (LS-SCLC) and good performance status (PS). *J Clin Oncol* 2016; **34**: (suppl; abstr 8504).

26. Turrisi AT 3rd, Kim K, Blum R *et al*. Twice-daily compared with once-daily thoracic radiotherapy in limited small cell lung cancer treated concurrently with cisplatin and etoposide. *N Engl J Med* 1999; **340**(4): 265–271.

27. Slotman BJ, van Tinteren H, Praag JO *et al*. Use of thoracic radiotherapy for extensive stage small-cell lung cancer: a phase 3 randomised controlled trial. *Lancet* 2015; **385**(9962): 36–42.

28. Slotman BJ, van Tinteren H, Praag JO *et al*. Which patients with extensive-stage small cell lung cancer (ES-SCLC) are most likely to benefit from routine thoracic radiotherapy (TRT) following chemotherapy? *Lancet* (in press).

29. Aupérin A, Arriagada R, Pignon JP *et al*. Prophylactic cranial irradiation for patients with small-cell lung cancer in complete remission. Prophylactic Cranial Irradiation Overview Collaborative Group. *N Engl J Med* 1999; **341**(7): 476–484.

30. Le Péchoux C, Dunant A, Senan S *et al*. Prophylactic Cranial Irradiation (PCI) Collaborative Group. Standard-dose versus higher-dose prophylactic cranial irradiation (PCI) in patients with limited-stage small-cell lung cancer in complete remission after chemotherapy and thoracic radiotherapy (PCI 99-01, EORTC 22003-08004, RTOG 0212, and IFCT 99-01): a randomised clinical trial. *Lancet Oncol* 2009; **10**(5): 467–474.

References

31. Slotman B, Faivre-Finn C, Kramer G *et al*. Prophylactic cranial irradiation in extensive small-cell lung cancer. *N Engl J Med* 2007; **357**(7): 664–672.

32. Boutin C, Rey F, Viallat JR. Prevention of malignant seeding after invasive diagnostic procedures in patients with malignant pleural mesothelioma. A randomised trial of local radiotherapy. *Chest* 1995; **108**(3): 754–758.

33. Bydder S, Phillips M, Joseph DJ *et al*. A randomised trial of single dose radiotherapy to prevent procedure tract metastases by malignant pleural mesothelioma. *Br J Cancer* 2004; **91**(1): 9–10.

34. O'Rourke N, Garcia JC, Paul J, Lawless C, mcMenemin R, Hill J. A randomised controlled trial of intervention site radiotherapy in malignant pleural mesothelioma. *Radiother Oncol* 2007; **84**(1): 18–22.

35. Clive AO, Wilson P, Taylor H *et al*. Protocol for the surgical and large bore procedures in malignant pleural mesothelioma and radiotherapy trial (SMART Trial): an RCT evaluating whether prophylactic radiotherapy reduces the incidence of procedure tract metastases. *BMJ Open* 2015; **5**(1): e006673.

36. MacLeod N, Chalmers A, O'Rourke N *et al*. Is radiotherapy useful for treating pain in mesothelioma?: A phase II trial. *J Thorac Oncol* 2015; **10**(6): 944–950.

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.[1,2]

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).[3–5] 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).[5,6]

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 thee 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.[5]

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).[5,7,8] 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).[5,9]

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.[5]

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).[5,10]

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.[5]

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.[11] A dose of 30 Gy in 15 fractions over three weeks is recommended (Grade D).[5]

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.[12] 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).[13,5] 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).[14,15] 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).[5,15]

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).[5,16]

Radiotherapy is also considered for mediastinal B-cell lymphoma and extranodal sites after full-course chemotherapy.[17]

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).[5,18]

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.[5]

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).[5,19]

Natural killer (NK)/T-cell lymphoma

This is a rare entity in Western countries but is common in East Asia and Latin America.[20] 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).[5,21]

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).[5,22]

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).[5,23]

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).[5,24]

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.[5]

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).[5,24,25] 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).[5]

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.[5]

References

1. Hoskin PJ, Díez P, Williams M *et al*. Recommendations for the use of radiotherapy in nodal lymphoma. *Clin Oncol (R Coll Radiol)* 2013; **25**(1): 49–58.
2. Specht L, Yahalom J, Illidge T *et al*. Modern radiation therapy for Hodgkin lymphoma: field and dose guidelines from the International Lymphoma Radiation Oncology Group (ILROG). *Int J Radiat Oncol Biol Phys* 2014; **89**(4): 854–862.
3. Engert A, Plutschow A, Eich HT *et al*. Reduced treatment intensity in patients with early-stage Hodgkin's lymphoma. *N Engl J Med* 2010; **363**(7): 640–652.
4. Eich HT, Diehl V, Görgen H *et al*. Intensified chemotherapy and dose-reduced involved-field radiotherapy in patients with early unfavourable Hodgkin's lymphoma: Final analysis of the German Hodgkin Study Group HD11 trial. *J Clin Oncol* 2010; **28**(27): 4199–4206.
5. www.cebm.net/oxford-centre-evidence-based-medicine-levels-evidence-march-2009 (last accessed 26/9/16)
6. Radford J, Illidge T, Counsell N *et al*. Results of a trial of PET-directed therapy for early-stage Hodgkin's lymphoma. *N Eng J Med* 2015; **372**(17): 1598–1607.
7. Loeffler M, Brosteanu O, Hasenclever D *et al*. Meta-analysis of chemotherapy versus combined modality treatment trials in Hodgkin's disease. International database on Hodgkin's Disease Overview Study Group. *J Clin Oncol* 1998; **16**(3): 818–829.
8. Johnson PW, Sydes MR, Hancock BW *et al*. Consolidation radiotherapy in patients with advanced Hodgkin's lymphoma: survival data from the UKLG LY09 randomized controlled trial (ISRCTN97144519). *J Clin Oncol* 2010; **28**(20): 3352–3359.
9. Aleman BM, Raemaekers JM, Tirelli U *et al*. Involved-field radiotherapy for advanced Hodgkin's lymphoma. *N Engl J Med* 2003; **348**(24): 2396–2406.
10. Josting A, Nogová L, Franklin J *et al*. Salvage radiotherapy in patients with relapsed and refractory Hodgkin's lymphoma: A retrospective analysis from the German Hodgkin's Lymphoma Study Group. *J Clin Oncol* 2005, **23**(7): 1522–1529
11. McKay P, Fielding P, Gallop-Evans E *et al*. Guidelines for the investigation and management of nodular lymphocyte predominant Hodgkin lymphoma. *Br J Haematol* 2015; **172**(1): 32–43.
12. Miller TP, Dahlberg S, Cassady JR *et al*. Chemotherapy alone compared with chemotherapy plus radiotherapy for localized intermediate- and high-grade non-Hodgkin's lymphoma. *N Engl J Med* 1998; **339**(1): 21–26.
13. Miller TP, LeBlanc M, Spier CM *et al*. CHOP alone compared to CHOP plus radiotherapy for early stage aggressive non-Hodgkin's lymphomas: update of the South-West Oncology Group (SWOG) randomised trial. *Blood* 2001; **98**: 742a–743a (abstract).
14. Horning SJ, Weller E, Kim K *et al*. Chemotherapy with or without radiotherapy in limited-stage diffuse aggressive non-Hodgkin's lymphoma: Eastern Cooperative Oncology Group study 1484. *J Clin Oncol* 2004; **22**(15): 3032–3038.
15. Reyes F, Lepage E, Ganem G *et al*. ACVBP versus CHOP plus radiotherapy for localized aggressive lymphoma. *N Engl J Med* 2005; **352**(12): 1197–1205.
16. Held G, Murawski N, Ziepert M *et al*. Role of radiotherapy to bulky disease in elderly patients with aggressive B-cell lymphoma. *J Clin Oncol* 2014; **32**(11): 1112–1118.
17. Phan J, Mazloom A, Medeiros LJ *et al*. Benefit of consolidative radiation therapy in patients with diffuse large B-cell lymphoma treated with R-CHOP chemotherapy. *J Clin Oncol* 2010; **28**(27): 4170–4176.

18. Lowry L, Smith P, Qian W *et al*. Reduced dose radiotherapy for local control in non-Hodgkin lymphoma: a randomised phase III trial. *Radiother Oncol* 2011; **100**(1): 86–92.

19. Dabaja B, Tsang RW, Qi S *et al*. Favorable outcome in stage I-II mantle cell lymphoma: a report of 160 patients from the International Lymphoma Radiation Oncology Group (ILROG). *Innt J Rad Oncol Biol Phys* 2014; **90**(1): S151–S152.

20. Li YX, Tao B, Jin J *et al*. Radiotherapy as primary treatment for stafe IE and IIE nasal natural killer/T-cell lymphoma. *J Clin Oncol* 2006, **24**(1): 181–189.

21. Wu X, Li P, Zhao J *et al*. A clinical study of 115 patients with extranodal natural killer/T-cell lymphoma, nasal type. *Clin Oncol (R Coll Radiol)* 2008; **20**(8): 619–625.

22. Korfel A, Thiel E, Martus P *et al*. Randomized phase III study of whole-brain radiotherapy for primary CNS lymphoma. *Neurology* 2015; **84**(12): 1242–1248.

23. Morris SL. Skin lymphoma. *Clin Oncol (R Coll Radiol)* 2012; **24**(5): 371–385.

24. Hoskin PJ, Kirkwood AA, Popova B *et al*. 4 Gy versus 24 Gy radiotherapy for patients with indolent lymphoma (FORT): a randomised phase 3 non-inferiority trial. *Lancet Oncol* 2014; **15**(4): 457–463.

25. Haas RLM, Poortmans D, de Jong BM *et al*. High response rates and lasting remissions after low-dose involved field radiotherapy in indolent lymphomas. *J Clin Oncol* 2003; **21**(13): 2474–2480.

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 a price, namely the long-term effects of treatment. Long-term effects of radiotherapy include soft tissue hypoplasia, impaired bone growth, 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*.[1]

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 70% 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.[2]

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.[3]

Boys who suffer a testicular relapse are treated with testicular radiotherapy, generally with electrons, encompassing a clinical target volume (CTV) which includes both testes, scrotum and the inguinal canal super-laterally as far as the deep inguinal ring.[4]

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.[3]

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 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.[5–7]

For children with ALL, many centres advise a cranial boost in addition to the TBI with the aim of reducing the risk of CNS relapse.[8]

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)

Cranial boost where indicated after TBI:

5.4 Gy in 3 fractions 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.[3]

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.[9–11]

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.[3]

Neuroblastoma

The role of external beam radiotherapy for patients with 'bad risk' disease (for example, aged greater than one year with stage 4 disease at presentation) is to maximise the probability of local tumour control following surgical resection of the primary tumour.[12–14]

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.[3]

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 doxorubicin, 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.[15] Patients with lung metastases who do not achieve a complete response to chemotherapy should receive whole lung radiotherapy.[16]

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

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

Boost to macroscopic disease or involved nodes:

10.8 Gy in 6 fractions of 1.8 Gy over 1.5 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.[3]

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.[17–19] 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.

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.[3]

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.[20,21]

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.[3]

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.[22]

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.[3]

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.[3]

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.[23]

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.[3]

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).[24]

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.[3]

Medulloblastoma/primitive neuroectodermal tumour (PNET)

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.[25–27]

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.[3]

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.[28,29]

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.[3]

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.[30]

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.[3]

Further reading

Halperin EC, Constine LS, Tarbell NJ, Kun LE (eds). *Pediatric Radiation Oncology*. Philadelphia: Lippincott Williams & Wilkins, 2011.

Thorp N. Basic principles of paediatric radiotherapy. *Clin Oncol (R coll Radiol)* 2013; **25**(1): 3–10.

Thorp N, Taylor RE. Management of central nervous system tumours in children. *Clin Oncol (R Coll Radiol)* 2014; **26**(7): 438–445.

References

1. The Royal College of Radiologists. *Good practice guide for paediatric radiotherapy*. London: The Royal College of Radiologists, 2012.
2. Pui CH, Howard SC. Current management and challenges of malignant disease in the CNS in paediatric leukaemia. *Lancet Oncol* 2008; **9**(3): 257–268.
3. www.cebm.net/oxford-centre-evidence-based-medicine-levels-evidence-march-2009 (last accessed 30/9/16)
4. Bowman WP, Aur RJ, Hustu H, Rivera G. Isolated testicular relapse in acute lymphocytic leukaemia of childhood: categories and influence on survival. *J Clin Oncol* 1984; **2**(8): 924–929.
5. International Commission on Radiation Units and Measurements. *ICRU report 50: Prescribing, recording, and reporting photon beam therapy*. Washington, DC: International Commission on Radiation Units and Measurements, 1993.
6. Cosset JM, Girinsky T, Malaise E, Chaillet MP, Dutriex J. Clinical basis for TBI fractionation. *Radiother Oncol* 1990; **18**(Suppl 1): 60–67.
7. Gerrard G, Vail A, Taylor RE *et al*. Toxicity and dosimetry of fractionated total body irradiation prior to allogeneic bone marrow transplantation using a straightforward radiotherapy technique. *Clin Oncol (R Coll Radiol)* 1998; **10**(6): 379–383.
8. Alexander BM, Weschler D, Braun TM *et al*. Utility of cranial boost in addition to total body irradiation in the treatment of high risk acute lymphoblastic leukaemia. *Int J Radiat Oncol Biol Phys* 2005; **63**(4): 1191–1196.
9. Ruhl U, Albreacht M, Dieckmann K *et al*. Response-adapted radiotherapy in the treatment of Pediatric Hodgkin's Disease: an interim report at 5 years of the German GPOH-HD 95 trial. *Int J Radiat Oncol Biol Phys* 2001; **51**(5): 1209–1218.
10. Frew JA, Lewis J, Lucraft HH. The management of children with lymphomas. *Clin Oncol (R Coll Radiol)* 2013; **25**(1): 11–18.
11. Mauz-Körholz C, Metzger ML, Kelly KM *et al*. Pediatric Hodgkin lymphoma. *J Clin Oncol* 2015; **33**(27): 2975–2985.
12. Wolden SL, Gollamudi SV, Kushner BH *et al*. Local control with multimodality therapy for stage 4 neuroblastoma. *Int J Radiat Oncol Biol Phys* 2000; **46**(4): 969–974.
13. Gatcombe HG, Marcus RB, Katzenstein HM, Tighouart M, Esiashvili N. Excellent local control from radiation therapy for high-risk neuroblastoma. *Int J Radiat Oncol Biol Phys* 2009; **74**(5): 1549–1554.
14. Robbins JR, Krasin MJ, Atmaram S *et al*. Radiation therapy as part of local control of metastatic neuroblastoma: the St. Jude Children's Research Hospital experience. *J Pediatr Surg* 2010; **45**(4): 678–686.
15. Kalapurakal JA, Dome JS, Perlman EJ *et al*. Management of Wilms' tumour: current practice and future goals. *Lancet Oncol* 2004; **5**(1): 37–46.

References

16. Nicolin G, Taylor RE, Baughan C *et al*. Outcome after pulmonary radiotherapy in Wilms' tumour patients with pulmonary metastases at diagnosis: A UK Children's Cancer Study Group, Wilms' Tumour Working Group Study. *Int J Radiat Oncol Biol Phys* 2008; **70**(1): 175–180.

17. Terezakis SA, Wharam MD. Radiotherapy for rhabdomyosarcoma: indications and outcome. *Clin Oncol (R Coll Radiol)* 2013; **25**(1): 27–35.

18. Raney RB, Walterhouse DO, Meza JL *et al*. Results of the Intergroup Rhabdomyosarcoma Study Group D9602 protocol, using vincristine and dactinomycin with or without cyclophosphamide and radiation therapy, for newly diagnosed patients with low-risk embryonal rhabdomyosarcoma: a report from the Soft Tissue Sarcoma Committee of the Children's Oncology Group. *J Clin Oncol* 2011; **29**(10): 1312–1318.

19. Michalski JM, Meza J, Breneman JC *et al*. Influence of radiation therapy parameters on outcome in children treated with radiation therapy for localized parameningeal rhabdomyosarcoma in Intergroup Rhabdomyosarcoma Study Group trials II through IV. *Int J Radiat Oncol Biol Phys* 2004; **59**(4): 1027–1038.

20. Bölling T, Hardes J, Dirksen U. Management of bone tumours in paediatric oncology. *Clin Oncol (R Coll Radiol)* 2013; **25**(1): 19–26.

21. Lopez JL, Cabrera P, Ordonez *et al*. Role of radiation therapy in the multidisciplinary management of Ewing's sarcoma of bone in pediatric patients: an effective treatment for local control. *Rep Pract Oncol Radiother* 2011; **16**(3): 103–109.

22. Merchant TE, Kun LE, Wu S *et al*. Phase II trial of conformal radiation therapy for pediatric low-grade glioma. *J Clin Oncol* 2009; **27**(22): 3598–3604.

23. Stupp R, Mason WP, van den Bent MJ *et al*. Radiotherapy plus concomitant and adjuvant temozolomide for glioblastoma. *N Engl J Med* 2005; **352**(10): 987–996.

24. Merchant TE, Li C, Xiong X *et al*. Conformal radiotherapy after surgery for paediatric ependymoma: a prospective study. *Lancet Oncol* 2009 **10**(3): 258–266.

25. Packer RJ, Gajjar A, Vezina G *et al*. Phase III study of craniospinal radiation therapy followed by adjuvant chemotherapy for newly diagnosed average-risk medulloblastoma. *J Clin Oncol* 2006; **24**(25): 4202–4208.

26. Lannering B, Rutkowski S, Doz F *et al*. Hyperfractionated versus conventional radiotherapy followed by chemotherapy in standard-risk medulloblastoma: results from the randomized multicenter HIT-SIOP PNET 4 trial. *J Clin Oncol* 2012; **30**(26): 3187–3193.

27. Gajjar, A, Chintagumpala M, Ashley D *et al*. Risk-adapted craniospinal radiotherapy followed by high-dose chemotherapy and stem-cell rescue in children with newly diagnosed medulloblastoma (St Jude Medulloblastoma-96): long-term results from a prospective, multicentre trial. *Lancet Oncol* 2006; **7**(10): 813-820.

28. Calaminus G, Kortmann R, Worch J *et al*. SIOP CNS GCT 96: final report of outcome of a prospective, multinational nonrandomized trial for children and adults with intracranial germinoma, comparing craniospinal irradiation alone with chemotherapy followed by focal primary site irradiation for patients with localized disease. *Neuro Oncol* 2013; **15**(6): 788–796.

29. Murray MJ, Bartels U, Nishikawa R *et al*. Consensus on the management of intracranial germ-cell tumours. *Lancet Oncol* 2015; **16**(9): e470–e477.

30. Hargrave D, Bartels U, Bouffet E. Diffuse brainstem glioma in children: critical review of clinical trials. *Lancet Oncol* 2006; **7**(3): 241–248.

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.[1,2] Approximately 20–30% of patients with positive inguinal nodes have positive pelvic nodes.[1] Lymph node status is a major prognostic factor for penile cancer.[1] Surgery is the mainstay of locoregional treatment.[3] 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.[4] Radiotherapy remains an effective penile-sparing alterative and may be delivered with external beam radiotherapy (EBRT) with tissue equivalent bolus (Level 3) or brachytherapy (Level 3).[5] Brachytherapy provides good control rates with acceptable morbidity and can be considered for T1/2 and selected T3 lesions according to the 2013 Americal Brachytherapy Society-Groupe Eurpoeén de Curiethérapie-European Society of Theraputic Radiation Oncology (ABS-GEC-ESTRO) guidelines.[6,7] 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.[8–12]

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

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)[11]
55 Gy in 20 fractions over 4 weeks (Grade D)
60 in 30 fractions over 6 weeks (Grade C)[10]
66 in 33 fractions over 6.5 weeks (Grade C)[10]

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.[5]

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.[13,14] The use of either neoadjuvant or definitive radiotherapy or radiotherapy with concomitant chemotherapy are alternative approaches.[4] 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).[5] 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.[15] Combining radiotherapy with concurrent chemotherapy can be considered, although there is no direct evidence to support the combination in penile cancer (Level 4).[5]

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.[5]

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 ≥2 inguinal lymph nodes are positive or in the presence of extracapsular spread (ECS).[4] 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%.[5,16–18]

Two recent series have reported on the use of adjuvant radiotherapy for ≥2 lymph nodes or extracapsular spread.[15,19] 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 ± involved pelvic lymph node regions; analysis identified high-risk patients as having ≥3 unilateral inguinal lymph nodes, extracapsular spread or pelvic lymph node involvement.[19] 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.[15] In both of these series, outcomes were superior to a series which reported on ECS without adjuvant radiotherapy.[2] 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.[20]

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.[21]

The use of IMRT can be considered (Grade D).[5]

Recommendations

Based on the forthcoming InPACT chemoradiotherapy trial are:[21]

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.[5]

References

1. Horenblas S. Lymphadenectomy for squamous cell carcinoma of the penis. Part 2: the role and technique of lymph node dissection. *BJU Int* 2001; **88**(5): 473–483.
2. Pandey D, Mahajan V, Kannan RR. Prognostic factors in node-positive carcinoma of the penis. *J Surg Oncol* 2006; **93**(2): 133–138.
3. Pizzocaro G, Algaba F, Horenblas S *et al*. EAU penile cancer guidelines 2009. *Eur Urol* 2010; **57**(6): 1002–1012.
4. Van Poppel H, Watkin NA, Osanto S *et al*. Penile cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. *Ann Oncol* 2013; **24**(Suppl 6): vi115–vi124.
5. www.cebm.net/oxford-centre-evidence-based-medicine-levels-evidence-march-2009 (last accessed 30/9/16)
6. Crook J, Ma C, Grimard L. Radiation therapy in the management of the primary penile tumor: an update. *World J Urol* 2009; **27**(2): 189–196.
7. Crook JM, Haie-Meder C, Demanes DJ *et al*. American Brachytherapy Society-Groupe Européen de Curiétherapie-European Society of Therapeutic Radiation Oncology (ABS-GEC-ESTRO) consensus statement for penile brachytherapy. *Brachytherapy* 2013;**12**(3): 191–198.
8. Zouhair A, Coucke PA, Jeanneret W *et al*. Radiation therapy alone or combined surgery and radiation therapy in squamous-cell carcinoma of the penis? *Eur J Cancer* 2001; **37**(2): 198–203.
9. Gotsadze D, Matveev B, Zak B, Mamaladze V. Is conservative organ-sparing treatment of penile carcinoma justified? *Eur Urol* 2000; **38**(3): 306–312.
10. Sarin R, Norman AR, Steel GG, Horwich A. Treatment results and prognostic factors in 101 men treated for squamous carcinoma of the penis. *Int J Radiat Oncol Biol Phys* 1997; **38**(4): 713–722.
11. Azrif M, Logue JP, Swindell R, Cowan RA, Wylie JP, Livsey JE. External-beam radiotherapy in T1-2 N0 penile carcinoma. *Clin Oncol (R Coll Radiol)* 2006; **18**(4): 320–325.
12. Soria JC, Fizazi K, Piron D *et al*. Squamous cell carcinoma of the penis: multivariate analysis of prognostic factors and natural history in monocentric study with a conservative policy. *Ann Oncol* 1997; **8**(11): 1089–1098.
13. Pagliaro LC, Williams DL, Daliani D *et al*. Neoadjuvant paclitaxel, ifosfamide, and cisplatin chemotherapy for metastatic penile cancer: a phase II study. *J Clin Oncol* 2010; **28**(24): 3851–3857.
14. Nicholson S, Hall E, Harland SJ *et al*. Phase II trial of docetaxel, cisplatin and 5FU chemotherapy in locally advanced and metastatic penis cancer (CRUK/09/001). *Br J Cancer* 2013; **109**(10): 2554–2559.
15. Franks KN, Kancherla K, Sethugavalar B, Whelan P, Eardley I, Kiltie AE. Radiotherapy for node positive penile cancer: experience of the Leeds teaching hospitals. *J Urol* 2011; **186**(2): 524–529.
16. Culkin DJ, Beer TM. Advanced penile carcinoma. *J Urol* 2003; **170**(2 Pt 1): 359–365.
17. Ozsahin M, Jichlinski P, Weber DC *et al*. Treatment of penile carcinoma: to cut or not to cut? *Int J Radiat Oncol Biol Phys* 2006; **66**(3): 674–679.
18. Horenblas S, van Tinteren H, Delemarre JF *et al*. Squamous cell carcinoma of the penis. III. Treatment of regional lymph nodes. *J Urol* 1993; **149**(3): 492–497.

19. Graafland NM, Moonen LM, van Boven HH, van Werkhoven E, Kerst JM, Horenblas S. Inguinal recurrence following therapeutic lymphadenectomy for node positive penile carcinoma: outcome and implications for management. *J Urol* 2011; **185**(3): 888–893.

20. Chen MF, Chen WC, Wu CT, Chuang Ck, Ng KF, Chang JT. Contemporary management of penile cancer including surgery and adjuvant radiotherapy: an experience in Taiwan. *World J Urol* 2004; **22**(1): 60–66.

21. https://clinicaltrials.gov/ct2/show/NCT02305654 (last accessed 3/10/16)

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.[1] 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.[2] 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.[3]

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.[4–8]

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 α/β ratio.[9,10] 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.[4–8,11] 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).[1] 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.[12] 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).[13] 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.[14,15]

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).[1,16]

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 and the North American RTOG 0415 study.[4,17–21] 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.[4] 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.[17,22,23]

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 and the RTOG 0415 study showed non-inferiority between 73.8 Gy in 41 fractions and 70 Gy in 28 fractions.[24]

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.[25]

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.[18,26]

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.[1,27–29] 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.[30]

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.[31,32] 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.[33,34]

Recommendations

Radical radiotherapy to the prostate should be delivered using IMRT or arc (VMAT or Rapidarc) techniques with IGRT verifation. 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)

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.[1]

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.[1]

References

1. www.cebm.net/oxford-centre-evidence-based-medicine-levels-evidence-march-2009 (last accessed 30/9/16)
2. Schmidt-Hansen M, Hoskin P, Kirkbride P, Hasler E, Bromham N. Hormone and radiotherapy versus hormone or radiotherapy alone for non-metastatic prostate cancer: a systematic review with meta-analyses. *Clin Oncol (R Coll Radiol)* 2014; **26**(10): e21–e46.
3. National Institutue for Health and Care Excellence. Prostate cancer: diagnosis and management. Clinical Guideline. Cardiff: National Institutue for Health and Care Excellence, 2014.
4. Dearnaley DP, Sydes MR, Graham JD *et al*. Escalated-dose versus standard-dose conformal radiotherapy in prostate cancer: first results from the MRC RT01 randomised controlled trial. *Lancet Oncol* 2007; **8**(6): 475–487.
5. Creak A, Hall E, Eeles R *et al*. Randomised pilot study of dose escalation using conformal radiotherapy in prostate cancer: long-term follow-up. *Br J Cancer* 2013; **109**(3): 651–657.
6. Peeters ST, Heemsbergen WD, Koper PC *et al*. Dose-response in radiotherapy for localized prostate cancer: results of the Dutch multicenter randomized phase III trial comparing 68 Gy of radiotherapy with 78 Gy. *J Clin Oncol* 2006; **24**(13): 1990–1996.
7. Pollack A, Zagars GK, Starkschall *et al*. Prostate cancer radiation dose response: results of the M. D. Anderson phase III randomized trial. *Int J Radiat Oncol Biol Phys* 2002; **53**(5): 1097–1105.
8. Michalski JM, Moughan J, Purdy J *et al*. A randomized trial of 79.2 Gy versus 70.2 Gy radiation therapy (RT) for localized prostate cancer. *J Clin Oncolo* 2015; **33**(suppl 7; abstr 4).
9. Dasu A, Toma-Dasu I. Prostate alpha/beta revisited – an analysis of clinical results from 14 168 patients. *Acta Oncol* 2012; **51**(8): 963–974.
10. Proust-Lima C, Taylor JM, Sécher *et al*. Confirmation of a low alpha/beta ratio for prostate cancer treated by external beam radiation therapy alone using a post-treatment repeated-measures model for PSA dynamics. *Int J Radiat Oncol Biol Phys* 2011; **79**(1): 195–201.
11. Viani GA, Stefano EJ, Afonso SL. Higher-than-conventional radiation doses in localized prostate cancer treatment: a meta-analysis of randomized, controlled trials. *Int J Radiat Oncol Biol Phys* 2009; **74**(5): 1405–1418.
12. Cahlon O, Zelefsky MJ, Shippy A *et al*. Ultra-high dose (86.4 Gy) IMRT for localized prostate cancer: toxicity and biochemical outcomes. *Int J Radiat Oncol Biol Phys* 2008; **71**(2): 330–337.
13. Zelefsky MJ, Pei X, Chou JF *et al*. Dose escalation for prostate cancer radiotherapy: predictors of long-term biochemical tumor control and distant metastases-free survival outcomes. *Eur Urol* 2011; **60**(6): 1133–1139.
14. Lukka H, Hayter C, Julian JA *et al*. A randomized trial comparing two fractionation schedules for patients with localized prostate cancer. *J Clin Oncol* 2005; **23**(25): 6132–6138.
15. Yeoh EE, Fraser RJ, McGowan RE *et al*. Evidence for efficacy without increased toxicity of hypofractionated radiotherapy for prostate carcinoma: early results of a Phase III randomized trial. *Int J Radiat Oncol Biol Phys* 2003; **55**(4): 943–955.
16. Livsey JE, Cowan RA, Wylie JP *et al*. Hypofractionated conformal radiotherapy in carcinoma of the prostate: five-year outcome analysis. *Int J Radiat Oncol Biol Phys* 2003; **57**(5): 1254–1259.
17. Aluwini S, Pos G, Schimmel E *et al*. Hypofractionated versus conventionally fractionated radiotherapy for patients with prostate cancer (HYPRO): acute toxicity results from a randomised non-inferiority phase 3 trial. *Lancet Oncol* 2015; **16**(3): 274–283.
18. www.controlled-trials.com/ISRCTN45905321 (last accessed 3/10/16)

19. Radiation Therapy Oncology Group. RTOG 0415. *A phase III randomized study of hypofractionated 3D-CRT/IMRT versus conventionally fractionated 3D-CRT/IMRT in patients with favorable-risk prostate cancer*. Philadelphia: Radiation Therapy Oncology Group, 2007.

20. Arcangeli S, Strigari L, Gomellini S *et al*. Updated results and patterns of failure in a randomized hypofractionation trial for high-risk prostate cancer. *Int J Radiat Oncol Biol Phys* 2012; **84**(5): 1172–1178.

21. Pollack A, Walker G, Horwitz EM *et al*. Randomized trial of hypofractionated external-beam radiotherapy for prostate cancer. *J Clin Oncol* 2013; **31**(31): 3860–3868.

22. Dearnaley D, Syndikus I, Mossop H *et al*. Five year outcomes of a phase III randomised trial of conventional or hypofractionated high dose intensity modulated radiotherapy for prostate cancer (CRUK /06/16); report from the CHIPP Trial Investigators Group. Vienna: European Cancer Congress, 2015.

23. Incrocci L, Wortel RC, Aluwini S et al. Hypofractionated versus conventionally fractionated radiotherapy for prostate cancer: Five-year oncologic outcomes of the Dutch randomized phase 3 HYPRO trial LBA2. Texas: American Society for Radiation Oncolgoy ASTRO, 2015.

24. Lee R, Dignam JJ, Amin M. NRG Oncology/RTOG 0415: a randomized phase 3 noninferiority study comparing 2 fractionation schedules in patients with low-risk prostate cancer. *Int J Radiat Oncol Biol Phys* 2016; **96**(2 Supplement): S2–S3.

25. Hoskin PJ, Rojas AM, Bownes PJ, Lowe GJ, Ostler PJ, Bryant L. Randomised trial of external beam radiotherapy alone or combined with high-dose-rate brachytherapy boost for localised prostate cancer. *Radiother Oncol* 2012; **103**(2): 217–222.

26. www.isrctn.com/ISRCTN45905321 (last accessed 3/10/16)

27. Wiegel T, Bottke D, Steiner U *et al*. Phase III postoperative adjuvant radiotherapy after radical prostatectomy compared with radical prostatectomy alone in pT3 prostate cancer with postoperative undetectable prostate-specific antigen: ARO 96-02/AUO AP 09/95. *J Clin Oncol* 2009; **27**(18): 2924–2930.

28. Thompson IM, Tangen CM, Paradelo J *et al*. Adjuvant radiotherapy for pathological T3N0M0 prostate cancer significantly reduces risk of metastases and improves survival: long-term follow-up of a randomized clinical trial. *J Urol* 2009; **181**(3): 956–962.

29. Bolla M, van Poppel H, Tombal B *et al*. Postoperative radiotherapy after radical prostatectomy for high-risk prostate cancer: long-term results of a randomised controlled trial (EORTC trial 22911). *Lancet* 2012; **380**(9858): 2018–2027.

30. Parker C, Sydes MR, Catton C *et al*. Radiotherapy and androgen deprivation in combination after local surgery (RADICALS): a new Medical Research Council/National Cancer Institute of Canada phase III trial of adjuvant treatment after radical prostatectomy. *BJU Int* 2007; **99**(6): 1376–1379.

31. Pommier P, Chabaud S, Lagrance JL *et al*. Is there a role for pelvic irradiation in localized prostate adenocarcinoma? Preliminary results of GETUG-01. *J Clin Oncol* 2007; **25**(34): 5366–5373.

32. Lawton CA, DeSilvio M, Roach M 3rd *et al*. An update of the phase III trial comparing whole pelvic to prostate only radiotherapy and neoadjuvant to adjuvant total androgen suppression: updated analysis of RTOG 94-13, with emphasis on unexpected hormone/radiation interactions. *Int J Radiat Oncol Biol Phys* 2007; **69**(3): 646–655.

33. Zelefsky MJ, Kollmeier M, Cox B *et al*. Improved clinical outcomes with high-dose image guided radiotherapy compared with non-IGRT for the treatment of clinically localized prostate cancer. *Int J Radiat Oncol Biol Phys* 2012; **84**(1): 125–129.

34. Singh J, Greer PB, White MA *et al*. Treatment-related morbidity in prostate cancer: a comparison of 3-dimensional conformal radiation therapy with and without image guidance using implanted fiducial markers. *Int J Radiat Oncol Biol Phys* 2013; **85**(4): 1018–1023.

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).[1–3]

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).[4,5] The overall survival was same in both groups (Level 1b).[3] 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).[3,6]

SCRT, however, increases long-term toxicity, with poorer functional outcomes especially in terms of continence (Level 1b).[3,7] 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).[3,8]

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.[3]

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.[8] 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.[1,3,9,10] 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.[3,11,12] 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.[13] 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.[12] The efficacy and toxicity of this remains unknown (Level 2b).[3]

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).[3,14,15]

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.[3]

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.[3,16] 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).[3,17] 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.[17] 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.[18–22] 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 (≤3 centimetres [cm]) 110 Gy in 4 fractions over 6 weeks (30 Gy every 2 weeks x 3 and final boost 20 Gy) (Grade D)

cT1/cN1 or cT2 cNo/cN1 (≤3cm) 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.[3]

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.[3]

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).[3]

References

1. Colorectal Cancer Collaborative Group. Adjuvant radiotherapy for rectal cancer: a systematic overview of 8,507 patients from randomised trials. *Lancet* 2001; **358**(9290): 1291–1304.
2. Frykholm GJ, Glimelius B, Påhlman L. Preoperative or postoperative irradiation in adenocarcinoma of the rectum: final results of a randomised trial and an evaluation of late secondary effects. *Dis Colon Rectum* 1993; **36**(6): 564–572.
3. www.cebm.net/oxford-centre-evidence-based-medicine-levels-evidence-march-2009 (last accessed 30/9/16)
4. Kapiteijn E, Marijnen CA, Nagtegaal ID *et al*. Preoperative radiotherapy combined with total mesorectal excision for resectable rectal cancer. *N Engl J Med* 2001; **345**(9): 638–646.
5. Peeters KC, Marijnen CA, Nagtegaal ID *et al*. The TME trial after a median follow-up of 6 years: increased local control but no survival benefit in irradiated patients with resectable rectal carcinoma. *Ann Surg* 2007; **246**(5): 693–701.
6. Sebag-Montefiore D, Stephens RJ, Steele R. Preoperative radiotherapy versus selective postoperative chemoradiotherapy in patients with rectal cancer (MRC CR07 and NCIC-CTG C016): a multicentre, randomised trial. *Lancet* 2009; **373**(9666): 811–820.
7. Peeters KC, van de Velde CJ, Leer JW *et al*. Late side effects of short-course preoperative radiotherapy combined with total mesorectal excision for rectal cancer: increased bowel dysfunction in irradiated patients – a Dutch colorectal cancer group study. *J Clin Oncol* 2005; **23**(25): 6199–6206.
8. National Institutue for Health and Care Excellence. *Colorectal cancer: diagnosis and management. Clinical guideline 131*. London: National Institute for Health and Care Excellence, 2011.
9. Braendengen M, Tveit KM, Berglund A *et al*. Randomised phase II study comparing preoperative radiotherapy with chemoradiotherapy in nonresectable rectal cancer. *J Clin Oncol* 2008; **26**(22): 3687–3694.
10. Ceelen WP, Van Nieuwenhove Y, Fierens K. Preoperative chemoradiation versus radiation alone for stage II and III resectable rectal cancer. *Cochrane Database Syst Rev* 2009; 1: CD006041.
11. De Bruin AF, Nuyttens JJ, Ferenschild FT, Planting AS, Verhoef C, de Wilt JH. Preoperative chemoradiation with capecitabine in locally advanced rectal cancer. *Neth J Med* 2008; **66**(2): 71–76.
12. De Paoli A, Chiara S, Luppi G *et al*. Capecitabine in combination with preoperative radiation therapy in locally advanced, resectable, rectal cancer: a multicentric phase II study. *Ann Oncol* 2006; **17**(2): 246–251.
13. http://www.isrctn.com/ISRCTN09351447
14. Radu C, Berflund A, Påhlman L, Glimelius B. Short-course preoperative radiotherapy with delayed surgery in rectal cancer – a retrospective study. *Radiother Oncol* 2008; **87**(3): 343–349.
15. Hatfield P, Hingorani M, Radhakrishna G *et al*. Short-course radiotherapy, with elective delay prior to surgery, in patients with unresectable rectal cancer who have poor performance status or significant co-morbidity. *Radiother Oncol* 2008; **92**(2): 210–214.
16. Ortholan C, Romestaing P, Chapet O, Ferard JP. Correlation in rectal cancer between clinical tumor response after neoadjuvant radiotherapy and sphincter or organ preservation: 10-year results of the Lyon R 96-02 randomized trial. *Int J Rad Oncol Biol Phys* 2012; **83**(2): e65–e71.
17. Appelt AL, Vogelius IR, Pløen J *et al*. Long-term results of a randomized trial in locally advanced rectal cancer: no benefit from adding a brachytherapy boost. *Int J Rad Oncol Biol Phys* 2014; **90**(1): 110–118.

18. Sischy B, Hinson EJ, Wilkinson DR. Definitive radiation therapy for selected cancers of the rectum. *Br J Surg* 1988; **75**(9): 901–903.

19. Gerard JP, Romestaing P, Chapet O. Radiotherapy alone in the curative treatment of rectal carcinoma. *Lancet Oncol* 2003; **4**(3): 158–166.

20. Sun Myint A, Grieve RJ, McDonald AC *et al*. Combined modality treatment of early rectal cancer: the UK experience. *Clin Oncol (R Coll Radiol)* 2007; **19**(9): 674–681.

21. Dhadda A, Cast J, Hunter I. Organ preservation using contact radiotherapy for early rectal cancer: outcomes of patients treated at a single centre in the United Kingdom. *Ann Oncol* 2014; **25**(suppl 2): ii12.

22. National Institutue for Health and Care Excellence. *Low energy contact X-ray brachytherapy (the Papillon technique) for early stage rectal cancer*. London: National Institute for Health and Care Excellence, 2015.

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.[1–6]

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).[1] This is not recommended outside clinical trials at present.[7]

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.[1]

References

1. www.cebm.net/oxford-centre-evidence-based-medicine-levels-evidence-march-2009 (last accessed 30/9/16)
2. Ulutin HC, Aksu G, Fayda M, Kuzhan O, Tahmaz L, Beyzadeoglu M. The value of postoperative radiotherapy in renal cell carcinoma: a single-institution experience. *Tumori* 2006; **92**(3): 202–206.
3. Stein M, Kuten A, Halpern J, Coachman NM, Cohen Y, Robinson E. The value of postoperative irradiation in renal cell cancer. *Radiother Oncol* 1992; **24**(1): 41–44.
4. Scherer E, Wirtz C. The role of postoperative radiotherapy in the treatment of hypernephroid carcinoma. *Strahlenther Onkol* 1988; **164**(7): 371–385.
5. Kao GD, Malkowicz SB, Whittington R, D'Amico AV, Wein AJ. Locally advanced renal carcinoma: low complication rate and efficacy of postnephrectomy radiation therapy planned with CT. *Radiology* 1994; **193**(3): 725–730.
6. Makarewicz R, Zarzycka M, Kulińska G, Windorbska W. The value of postoperative radiotherapy in advanced renal cell cancer. *Neoplasma* 1998; **45**(6): 380–383.
7. Kirkbride T, Cooper T. Stereotactic body radiotherapy. Guidelines for commissioners, providers and clinicians: a national report. *Clin Oncol (R Coll Radiol)* 2011; **23**(3): 163–164

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.[1] 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.[2] Intensity-modulated radiotherapy (IMRT) or proton therapy may be appropriate when optimal dose fractionationis 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.[3,4] 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.[4] 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.[5,6] 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.[7,8]

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 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.[9]

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 ≥63 Gy.[9,10]

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.[9]

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.[11–13] Preoperative radiotherapy is deliverable with minimal toxicity.[11,12] 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).[9,13]

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.[9]

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.[14] 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).[9,15,16] 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.[9]

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).[9,17–20]

Recommendations

Doses are based upon the current Euro Ewing 2012 radiotherapy protocol.[21]

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.[9]

Lung metastases

Curative intent multimodality treatment for patients with lung metastases includes whole-lung radiotherapy (in patients who have not received busulphan).[22] 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.[23,24] 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.[22] 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.[21]

<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.[9]

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).[9,25]

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.[9]

References

1. DeLaney TF, Park L, Goldberg SI *et al*. Radiotherapy for local control of osteosarcoma. *Int J Radiat Oncol Biol Phys* 2005; **61**(2): 492–498.
2. Dickie CI, Haas R, O'Sullivan B. Adjuvant radiation for soft tissue sarcomas. *Am Soc Clin Oncol Educ Book* 2015; e634–e642.
3. Yang JC, Chang AE, Baker AR *et al*. Randomized prospective study of the benefit of adjuvant radiation therapy in the treatment of soft tissue sarcomas of the extremity. *J Clin Oncol* 1998; **16**(1): 197–203.
4. O'Sullivan B, Davis AM, Turcotte R *et al*. Preoperative versus postoperative radiotherapy in soft-tissue sarcoma of the limbs: a randomised trial. *Lancet* 2002; **359**(9325): 2235–2241.
5. Zagars GK, Ballo MT. Significance of dose in postoperative radiotherapy for soft tissue sarcoma. *Int J Radiat Oncol Biol Phys* 2003; **56**(2): 473–481.
6. Delaney TF, Kepka L, Goldberg SI *et al*. Radiation therapy for control of soft-tissue sarcomas resected with positive margins. *Int J Radiat Oncol Biol Phys* 2007; **67**(5): 1460–1469.
7. Al Yami A, Griffin AM, Ferguson PC *et al*. Positive surgical margins in soft tissue sarcoma treated with preoperative radiation: is a postoperative boost necessary? *Int J Radiat Oncol Biol Phys* 2010; **77**(4): 1191–1197.
8. Pan E, Goldberg SI, Chen YL *et al*. Role of post-operative radiation boost for soft tissue sarcomas with positive margins following pre-operative radiation and surgery. *J Surg Oncol* 2014; **110**(7): 817–822.
9. www.cebm.net/oxford-centre-evidence-based-medicine-levels-evidence-march-2009 (last accessed 30/9/16)
10. Kepka L, DeLaney TF, Suit HD, Goldberg SI. Results of radiation therapy for unresected soft-tissue sarcomas. *Int J Radiat Oncol Biol Phys* 2005; **63**(3): 852–859.
11. Jones JJ, Catton CN, O'Sullivan B *et al*. Initial results of a trial of preoperative external-beam radiation therapy and postoperative brachytherapy for retroperitoneal sarcoma. *Ann Surg Oncol* 2002; **9**(4): 346–354.
12. Pisters PW, Ballo MT, Fenstermacher MJ *et al*. Phase I trial of preoperative concurrent doxorubicin and radiation therapy, surgical resection, and intraoperative electron-beam radiation therapy for patients with localized retroperitoneal sarcoma. *J Clin Oncol* 2003; **21**(16): 3092–3097.
13. Baldini EH, Wang D, Haas RL *et al*. Treatment guidelines for preoperative radiation therapy for retroperitoneal sarcoma: preliminary consensus of an international expert panel. *Int J Radiat Oncol Biol Phys* 2015; **92**(3): 602–612.
14. Kasper B, Baumgarten C, Bonvalot S *et al*. Management of sporadic desmoid-type fibromatosis: a European consensus approach based on patients' and professionals' expertise – a sarcoma patients EuroNet and European Organisation for Research and Treatment of Cancer/Soft Tissue and Bone Sarcoma Group initiative. *Eur J Cancer* 2015; **51**(2): 127–136.
15. Keus RB, Nout RA, Blay JY *et al*. Results of a phase II pilot study of moderate dose radiotherapy for inoperable desmoid-type fibromatosis – an EORTC STBSG and ROG study (EORTC 62991-22998). *Ann Oncol* 2013; **24**(10): 2672–2676.
16. Kriz J, Eich HT, Haverkamp U *et al*. Radiotherapy is effective for desmoid tumors (aggressive fibromatosis) – long-term results of a German multicenter study. *Oncol Res Treat* 2014; **37**(5): 255–260.
17. Indelicato DJ, Keole SR, Shahlaee AH *et al*. Definitive radiotherapy for ewing tumors of extremities and pelvis: long-term disease control, limb function, and treatment toxicity. *Int J Radiat Oncol Biol Phys* 2008; **72**(3): 871–877.

18. La TH, Meyers PA, Wexler LH *et al*. Radiation therapy for Ewing's sarcoma: results from Memorial Sloan-Kettering in the modern era. *Int J Radiat Oncol Biol Phys* 2006; **64**(2): 544–550.

19. Casey DL, Meyers PA, Alektiar KM *et al*. Ewing sarcoma in adults treated with modern radiotherapy techniques. *Radiother Oncol* 2014; **113**(2): 248–253.

20. DuBois SG, Krailo MD, Gebhardt MC *et al*. Comparative evaluation of local control strategies in localized Ewing sarcoma of bone: a report from the Children's Oncology Group. *Cancer* 2015; **121**(3): 467–475.

21. http://www.isrctn.com/ISRCTN92192408 (last accessed 10/10/16)

22. Casey DL, Alektiar KM, Gerber NK, Wolden SL. Whole lung irradiation for adults with pulmonary metastases from Ewing sarcoma. *Int J Radiat Oncol Biol Phys* 2014; **89**(5): 1069–1075.

23. Ladenstein R, Pötschger U, Le Deley MC *et al*. Primary disseminated multifocal Ewing sarcoma: results of the Euro-EWING 99 trial. *J Clin Oncol* 2010; **28**(20): 3284–3291.

24. http://www.controlled-trials.com/ISRCTN61438620 (last accessed 10/10/16)

25. Soyfer V, Corn BW, Kollender Y *et al*. Radiation therapy for palliation of sarcoma metastases: a unique and uniform hypofractionation experience. *Sarcoma* 2010; **2010**: 927–972.

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 quantifield using factors related to the primary tumour.[1] A tumour >4 centimetres (cm) in size is the most important of these; rete testis involvement may also be a predictor.[2] 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.[3] In the UK this approach has now become the standard (Level 1b).[4]

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).[4,5]

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.[6] 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).[4,7,8] An alternative approach uses a single dose of carboplatin with radiation fields reduced to the involved para-aortic region only (Level 1b).[4,9]

Radiotherapy carries an excess risk of death as a result of radiation-induced cardiac disease or second cancer.[5] 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).[4,10]

Recommendations

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

Stage I seminioma 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.[4]

References

1. Warde P, Specht L, Horwich A *et al*. Prognostic factors for relapse in stage I seminoma managed by surveillance: a pooled analysis. *J Clin Oncol* 2002; **20**(22): 448–452.
2. Chung P, Daugaard G, Tyldesley S *et al*. Evaluation of a prognostic model for risk of relapse in stage I seminoma surveillance. *Cancer Med* 2015; **4**(1): 155–160.
3. Oliver RT, Mead GM, Rustin GJ *et al*. Randomized trial of carboplatin versus radiotherapy for stage I seminoma: mature results on relapse and contralateral testis cancer rates in MRC TE19/EORTC 30982 study (ISRCTN27163214). *J Clin Oncol* 2011; **29**(8): 957–962.
4. www.cebm.net/oxford-centre-evidence-based-medicine-levels-evidence-march-2009 (last accessed 30/9/16)
5. Jones WG, Fossa SD, Mead GM *et al*. Randomised trial of 30 versus 20 Gy in the adjuvant treatment of stage I testicular seminoma: a report on Medical Research Council Trial TE18, European Organisation for the Research and Treatment of Cancer Trial 30942 (ISRCTN 18525328). *J Clin Oncol* 2005; **23**(6): 1200–1208.
6. Giannatempo P, Greco T, Mariani L *et al*. Radiotherapy or chemotherapy for clinical stage IIA and IIB seminoma: a systematic review and meta-analysis of patient outcomes. *Ann Oncol* 2015; **26**(4): 657–656.
7. Oldenburg J, Fosså SD, Nuver J *et al*. Testicular seminoma and non-seminoma: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. *Ann Oncol* 2013; **24**(Suppl 6): vi125–vi132.
8. Tandstad T, Smaaland R, Solberg A *et al*. Management of seminomatous testicular cancer: a binational prospective population-based study from the Swedish Norwegian testicular cancer study group. *J Clin Oncol* 2011; **29**(6): 719–725.
9. Horwich A, Dearnaley DP, Sohaib A, Pennert K, Huddart RA. Neoadjuvant carboplatin before radiotherapy in stage IIA and IIB seminoma. *Ann Oncol* 2013; **24**(8): 2104–2107.
10. Zagars GK, Ballo MT, Lee AK, Strom SS. Mortality after cure of testicular seminoma. *J Clin Oncol* 2004; **22**(4): 640–647.

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.[1] 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.[2] Elective irradiation of first echelon lymph nodes can be considered for higher risk SCC.[3]

There are no randomised studies examining dose-fractionation; in addition, most series report use of multiple dose-fractionation schedules in historical series.[4] 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.[4, 5] Similar doses are used for BCC and SCC, although some suggest higher doses for SCCs.[6] 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.[7] 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%).[8] 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.[3] 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).[9,10]

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.[10]

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.[11] Several series have reported multiple factors predictive of regional relapse after surgery, including lymph node >3 cm, multiple involved nodes, extracapsular spread.[11,12] In the head and neck region, the use of adjuvant radiotherapy has been shown to reduce regional recurrence rates and improve disease free survival.[13] 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).[10,13] 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.[14] Radical radiotherapy can be considered if surgery is inappropriate or declined.

Recommendations

For adjuvant radiotherapy to nodal regions:

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.[10]

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.[14,15]

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).[10,16] 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).[10,17]

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.[10]

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 tendancy for edge recurrences (Level 4).[10,18–20] 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).[10,21] 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.[22] 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).[10,18,23] In most series, adjuvant doses of >50 Gy are used.[18,19,21] 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).[10,22]

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.[10]

References

1. Lovett RD, Perez CA, Shapiro SJ, Garcia DM. External irradiation of epithelial skin cancer. *Int J Radiat Oncol Biol Phys* 1990; **19**(2): 235–242.
2. Han A, Ratner D. What is the role of adjuvant radiotherapy in the treatment of cutaneous squamous cell carcinoma with perineural invasion? *Cancer* 2007; **109**(6): 1053–1059.
3. Kwan W, Wilson D, Moravan V. Radiotherapy for locally advanced basal cell and squamous cell carcinomas of the skin. *Int J Radiat Oncol Biol Phys* 2004; **60**(2): 406–411.
4. Cho M, Gordon L, Rembielak A, Woo TC. Utility of radiotherapy for treatment of basal cell carcinoma: a review. *Br J Dermatol* 2014; **171**(5): 968–973.
5. McPartlin AJ, Slevin NJ, Sykes AJ, Rembielak A. Radiotherapy treatment of non-melanoma skin cancer: a survey of current UK practice and commentary. *Br J Radiol* 2014; 87(1043): 20140501.
6. Locke J, Karimpour S, Young G, Lockett MA, Perez CA. Radiotherapy for epithelial skin cancer. *Int J Radiat Oncol Biol Phys* 2001; **51**(3): 748–755.
7. van Hezewijk M, Creutzberg CL, Putter H, *et al*. Efficacy of a hypofractionated schedule in electron beam radiotherapy for epithelial skin cancer: Analysis of 434 cases. *Radiother Oncol* 2010; **95**(2): 245–249.
8. Silverman MK, Kopf AW, Gladstein AH, Bart RS, Grin CM, Levenstein MJ. Recurrence rates of treated basal cell carcinomas. Part 4: X-ray therapy. *J Dermatol Surg Oncol* 1992; **18**(7): 549–554.
9. Chan S, Dhadda AS, Swindell R. Single fraction radiotherapy for small superficial carcinoma of the skin. *Clin Oncol (R Coll Radiol)* 2007; **19**(4): 256–259.
10. www.cebm.net/oxford-centre-evidence-based-medicine-levels-evidence-march-2009 (last accessed 30/9/16)
11. Veness MJ, Porceddu S, Palme CE, Morgan GJ. Cutaneous head and neck squamous cell carcinoma metastatic to parotid and cervical lymph nodes. *Head Neck* 2007; **29**(7): 621–631.
12. Porceddu SV, Veness MJ, Guminski A. Nonmelanoma cutaneous head and neck cancer and merkel cell carcinoma: current concepts, advances, and controversies. *J Clin Oncol* 2015; **33**(29): 3338–3345.
13. Veness MJ, Morgan GJ, Palme CE, Gebski V. Surgery and adjuvant radiotherapy in patients with cutaneous head and neck squamous cell carcinoma metastatic to lymph nodes: combined treatment should be considered best practice. *Laryngoscope* 2005; **115**(5): 870–875.
14. Strom T, Caudell JJ, Han D *et al*. Radiotherapy influences local control in patients with desmoplastic melanoma. *Cancer* 2014; **120**(9): 1369–1378.
15. Guadagnolo BA, Prieto V, Weber R, Ross MI, Zagars GK. The role of adjuvant radiotherapy in the local management of desmoplastic melanoma. *Cancer* 2014; **120**(9): 1361–1368.
16. Burmeister BH, Henderson MA, Ainslie J *et al*. Adjuvant radiotherapy versus observation alone for patients at risk of lymph-node field relapse after therapeutic lymphadenectomy for melanoma: a randomised trial. *Lancet Oncol* 2012; **13**(6): 589–597.
17. Ballo MT, Bonnen MD, Garden AS *et al*. Adjuvant irradiation for cervical lymph node metastases from melanoma. *Cancer* 2003; **97**(7): 1789–1796.
18. Lok B, Khan S, Mutter R *et al*. Selective radiotherapy for the treatment of head and neck Merkel cell carcinoma. *Cancer* 2012; **118**(16): 3937–3944.
19. Fields RC, Busam KJ, Chou JF *et al*. Recurrence after complete resection and selective use of adjuvant therapy for stage I through III Merkel cell carcinoma. *Cancer* 2012; **118**(13): 3311–3320.

20. Lewis KG, Weinstock MA, Weaver AL, Otley CC. Adjuvant local irradiation for Merkel cell carcinoma. *Arch Dermatol* 2006; **142**(6): 693–700.

21. Fang LC, Lemos B, Douglas J, Iyer J, Nghiem P. Radiation monotherapy as regional treatment for lymph node-positive Merkel cell carcinoma. *Cancer* 2010; **116**(7): 1783–1790.

22. Veness M, Foote M, Gebski V, Poulsen M. The role of radiotherapy alone in patients with merkel cell carcinoma: reporting the Australian experience of 43 patients. *Int J Radiat Oncol Biol Phys* 2010; **78**(3): 703–709.

23. Mortier L, Mirabel X, Fournier C, Piette F, Lartigau E. Radiotherapy alone for primary Merkel cell carcinoma. *Arch Dermatol* 2003; **139**(12): 1587–1590.

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.[1] 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%.[1] 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.[2] 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.[3] A systematic review of neoadjuvant concomitant chemoradiation confirmed a radiotherapy dose–response relationship with a pathological complete response.[4] An increasing body of evidence is suggestive of the safety and feasibility of doses ≥60 Gy.[3] 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%.[5]

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.[6]

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%.[7] 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.[6]

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.[8] 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.[9] A dose of 45 Gy in 25 fractions has been selected for a randomised multicentre UK trial.[10]

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.[6]

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.[11] Based on a meta-analysis, radiotherapy with concomitant chemotherapy is preferred to radiotherapy alone with conventionally fractionated doses of 40–50 Gy.[12]

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.[13]

Recommendations

Palliative brachytherapy:

12 Gy in 1 fraction (Grade B)[14]
12–16 Gy in 2 fractions (Grade B)[15,16]

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.[6]

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.[17]

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.[6]

Gastric cancer

Adjuvant radiotherapy with concomitant chemotherapy

Perioperative chemotherapy represents a standard of care in the management of locally advanced gastric cancer.[18] 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.[19] 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).[6,20]

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.[6]

Palliative treatment

Palliative radiotherapy is an effective treatment for bleeding due to gastric carcinoma, with no clear benefit for more protracted fractionation schedules.[21]

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.[6]

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.[22]

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.[23–25] 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).[6,23,24]

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.[6]

References

1. Herskovic A, Martz K, al-Sarraf M *et al*. Combined chemotherapy and radiotherapy compared with radiotherapy alone in patients with cancer of the esophagus. *N Engl J Med* 1992; **326**(24): 1593–1598.
2. Minsky BD, Pajak TF, Ginsberg RJ *et al*. INT 0123 (Radiation Therapy Oncology Group 94-05) phase III trial of combined-modality therapy for esophageal cancer: high-dose versus standard-dose radiation therapy. *J Clin Oncol* 2002; **20**(5): 1167–1174.
3. Rackley T, Leong T, Foo M, Crosby T. Definitive chemoradiotherapy for oesophageal cancer – a promising start on an exciting journey. *Clin Oncol (R Coll Radiol)* 2014; **26**(9): 533–540.
4. Geh JI, Bond SJ, Bentzen SM, Glynne-Jones R. Systematic overview of preoperative (neoadjuvant) chemoradiotherapy trials in oesophageal cancer: evidence of a radiation and chemotherapy dose response. *Radiother Oncol* 2006; **78**(3): 236–244.
5. Crosby T, Hurt CN, Falk S *et al*. Chemoradiotherapy with or without cetuximab in patients with oesophageal cancer (SCOPE1): a multicentre, phase 2/3 randomised trial. *Lancet Oncol* 2013; **14**(7): 627–637.
6. www.cebm.net/oxford-centre-evidence-based-medicine-levels-evidence-march-2009 (last accessed 30/9/16)
7. Sykes AJ, Burt PA, Slevin NJ, Stout R, Marrs JE. Radical radiotherapy for carcinoma of the oesophagus: an effective alternative to surgery. *Radiother Oncol* 1998; **48**(1): 15–21.
8. Gwynne S, Wijnhoven BP, Hulshof M, Bateman A. Role of chemoradiotherapy in oesophageal cancer -- adjuvant and neoadjuvant therapy. *Clin Oncol (R Coll Radiol)* 2014; **26**(9): 522–532.
9. Zheng B, Zheng W, Zhu Y, Lin XY, Xu BH, Chen C. Role of adjuvant chemoradiotherapy in treatment of resectable esophageal carcinoma: a meta-analysis. *Chin Med J (Engl)* 2013; **126**(6): 1178–1182.
10. Sjoquist KM, Burmeister BH, Smithers BM *et al*. Survival after neoadjuvant chemotherapy or chemoradiotherapy for resectable oesophageal carcinoma: an updated meta-analysis. *Lancet Oncol* 2011; **12**(7): 681–692.
11. van Hagen P, Hulshof MC, van Lanschot JJ *et al*. Preoperative chemoradiotherapy for esophageal or junctional cancer. *N Engl J Med* 2012; **366**(22): 2074–2084.
12. Mukherjee S, Hurt CN, Gwynne S *et al*. NEOSCOPE: a randomised Phase II study of induction chemotherapy followed by either oxaliplatin/capecitabine or paclitaxel/carboplatin based chemoradiation as pre-operative regimen for resectable oesophageal adenocarcinoma. *BMC Cancer* 2015; **15**: 48.
13. Dai Y, Li C, Xie Y *et al*. Interventions for dysphagia in oesophageal cancer. *Cochrane Database Syst Rev* 2014;**10**: CD005048.
14. Homs MY, Steyerberg EW, Eijkenboom WM *et al*. Single-dose brachytherapy versus metal stent placement for the palliation of dysphagia from oesophageal cancer: multicentre randomised trial. *Lancet* 2004; **364**(9444): 1497–1504.
15. Sur RK, Levin CV, Donde B, Sharma V, Miszczyk L, Nag S. Prospective randomized trial of HDR brachytherapy as a sole modality in palliation of advanced esophageal carcinoma – an International Atomic Energy Agency study. *Int J Radiat Oncol Biol Phys* 2002; **53**(1): 127–133.
16. Sharma V, Mahantshetty U, Dinshaw KA, Deshpande R, Sharma S. Palliation of advanced/recurrent esophageal carcinoma with high-dose-rate brachytherapy. *Int J Radiat Oncol Biol Phys* 2002; **52**(2): 310–315.

17. Penniment M. Full report of the TROG 03.01, NCIC CTG ES2 multinational phase III study in advanced esophageal cancer comparing palliation of dysphagia and quality of life in patients treated with radiotherapy or chemoradiotherapy. *J Clin Oncol* 2015; **33**: **3**: abstract 6.

18. Cunningham D, Allum WH, Stenning SP *et al*. Perioperative chemotherapy versus surgery alone for resectable gastroesophageal cancer. *N Engl J Med* 2006; **355**(1): 11–20.

19. Macdonald JS, Smalley SR, Benedetti J *et al*. Chemoradiotherapy after surgery compared with surgery alone for adenocarcinoma of the stomach or gastroesophageal junction. *N Engl J Med* 2001; **345**(10): 725–730.

20. Foo M, Crosby T, Rackley T, Leong T. Role of (chemo)-radiotherapy in resectable gastric cancer. *Clin Oncol (R Coll Radiol)* 2014; **26**(9): 541–550.

21. Chaw CL, Niblock PG, Chaw CS, Adamson DJ. The role of palliative radiotherapy for haemostasis in unresectable gastric cancer: a single-institution experience. *Ecancermedicalscience* 2014; **8**: 384.

22. Stocken DD, Büchler MW, Dervenis C *et al*. Meta-analysis of randomised adjuvant therapy trials for pancreatic cancer. *Br J Cancer* 2005; **92**(8): 1372–1381.

23. Huguet F, André T, Hammel P *et al*. Impact of chemoradiotherapy after disease control with chemotherapy in locally advanced pancreatic adenocarcinoma in GERCOR phase II and III studies. *J Clin Oncol* 2007; **25**(3): 326–331.

24. Hammel P, Huguet F, van Laethem J *et al*. Randomized multicentre phase III study in patients with locally advanced adenocarcinoma of the pancreas:gemcitabine with or without chemoradiotherapy and with or without Erlotinib-LAP 07 study. *J Clin Oncol* 2011; **29**: abstract e14619.

25. Mukherjee S, Hurt CN, Bridgewater J *et al*. Gemcitabine-based or capecitabine-based chemoradiotherapy for locally advanced pancreatic cancer (SCALOP): a multicentre, randomised, phase 2 trial. *Lancet Oncol* 2013; **14**(4): 317–326.

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).[1–4]

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.[5]

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.[4]

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.[6] Limited evidence suggests that response rates are similar to those after primary treatment.[7] 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).[4,8] 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.[4]

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.[9] 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).[4,10]

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.[4]

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.[11] 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).[4]

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.[4]

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.[4]

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.[4]

References

1. McQuay H, Carroll D, Moore RA. Radiotherapy for painful bone metastases: a systematic review. *Clin Oncol* 1997; **9**(3): 150–154.
2. Wu JS, Wong R, Johnston M *et al*. Meta-analysis of dose-fractionation radiotherapy trials for the palliation of painful bone metastases. *Int J Radiat Oncol Biol Phys* 2003; **55**(3): 594–605.
3. Sze WM, Shelley MD, Held I, Wilt TJ, Mason MD. Palliation of metastatic bone pain: single fraction versus multifraction radiotherapy – a systematic review of randomised trials. *Clin Oncol (R Coll Radiol)* 2003; **15**(6): 345–352.
4. www.cebm.net/oxford-centre-evidence-based-medicine-levels-evidence-march-2009 (last accessed 30/9/16)
5. Roos DE, Turner SL, O'Brien PC *et al*. Randomized trial of 8 Gy in 1 versus 20 Gy in 5 fractions of radiotherapy for neuropathic pain due to bone metastases. *Radiother Oncol* 2005; **75**(1): 54–63.
6. van der Linden YM, Lok YJ, Steenland E *et al*. Single fraction radiotherapy is efficacious: a further analysis of the Dutch Study controlling for the influence of retreatment. *Int J Radiat Oncol Biol Phys* 2004; **59**(2): 528–537.
7. Mithal NP, Needham PR, Hoskin PJ. Retreatment with radiotherapy for painful bone metastases. *Int J of Rad Oncol Biol Phys* 1994; **29**(5): 1011–1014.
8. Chow E, van der Linden YM, Roos D *et al*. Single versus multiple fractions of repeat radiations for painful bone metastases: a randomised, controlled, non-inferiority trial. *Lancet Oncol* 2014; **15**(2): 164–171.
9. Dearnaley DP, Bayley RJ, A'Hern RP, Gadd J, zivanovic MM, Lewington VJ. Palliation of bone metastases in prostate cancer. Hemibody irradiation or strontium-89. *Clin Oncol (R Coll Radiol)* 1992; **4**(2): 101–107.
10. Salazar OM, Sandhu T, da Motta NW *et al*. Fractionated half-body irradiation (HBI) for the rapid palliation of widespread, symptomatic, metastatic bone disease: a randomised Phase III trial of the International Atomic Energy Agency (IAEA). *Int J Radiat Oncol Biol Phys* 2001; **50**(3): 765–775.
11. van der Linden YM, Kroon HM, Dijkstra SP *et al*. Simple radiographic parameter predicts fracturing in metastatic femoral bone lesions: results from a randomised trial. *Radiother Oncol* 2003; **69**(1): 21–31.

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 recursive partitioning analysis (RPA) based system of the Radiation Therapy Oncology Group (RTOG) is simple and robust.[1]

Patients can be divided into three groups according to:

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

Patients have the worst outlook in group 3 with a KPS <70.[2] This system has been validated on a separate data set. It has been pointed out that group three includes a substantial majority of patients therefore it may be difficult to identify those unlikely to gain palliative benefit from radiotherapy.[3] It has been suggested that further subdivision of group 3 may assist in advising on treatment.[4]

The more recently developed Diagnosis-specific Graded Prognostic Assessment (DS-GPA) is primary cancer specific.[5] The data used to develop survival estimates according to DS-GPA score still do not fully reflect the latest systemic therapies and may be subject to selection biases, however, some independent validation has been reported.[5–9]

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.[10]

Solitary or oligo-metastases

The evidence from one systematic review and three randomised trials suggests benefit from adding surgery to WBRT for patients of good performance status with a solitary metastasis (Level 1a).[10–13] 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.[14] In patients with up to three brain metastases and KPS ≥70, adding SRS to WBRT improves functional independence and reduces steroid requirements at six months (Level 1b).[14,15]

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^3 [cm^3] , total volume ≤15 cm^3) has suggested that overall survival is equivalent for patients with 5–10 as compared to 2–4 metastases and therefore the number of metastases treated using SRS without WBRT may not correlate with outcome.[15,16] 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.[7,15,17–19]

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^3 with good performance status (Karnofsky Performance Status ≥70) and controlled extra-cranial disease:[2]

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.[15]

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 1–4 brain metastases.[20–23] A meta-analysis of these trials has also been published.[24] Adding WBRT to local therapy by surgery or SRS appears to improve intracranial control and reduce neurological deaths without influencing overall survival (Level 1a).[15] 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.[25] 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.[26] Avoidance of the hippocampus has been suggested as a method to limit the neurocognitive effects of WBRT. The forthcoming HIPPO study is a randomised clinical trial of conventional versus hippocampal sparing WBRT in patients with oligometastatic disease, which uses 30 Gy in ten fractions in both arms of the study.

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.[15]

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.[27–30] 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.[25] An RTOG study reported in 1980 compared three regimens: 40 Gy in 15 fractions; 30 Gy in ten fractions; and 20 Gy in five fractions.[31] 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).[15]

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.[31,32] 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).[15]

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.[33]

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.[15]

References

1. Gaspar L, Scott C, Rotman M *et al*. Recursive partitioning analysis (RPA) prognostic factors in three Radiation Therapy Oncology Groups (RTOG) brain metastases trials. *Int J Radiat Oncol Biol Phys* 1997; **37**(4): 745–751.
2. Gaspar L, Scott C, Murray K, Curran W. Validation of the RTOG recursive partitioning analysis (RPA) classification for brain metastases. *Int J Radiat Oncol Biol Phys* 2000; **47**(4): 1001–1006.
3. Lock M, Chow E, Pond GR *et al*. Prognostic factors in brain metastases: can we determine patients who do not benefit from whole-brain radiotherapy? *Clin Oncol* 2004; **16**(5): 332–338.
4. Lutterbach J, Bartelt S, Stancu E, Guttenberger R. Patients with brain metastases: hope for recursive partitioning analysis (RPA) class 3. *Radiother Oncol* 2002; **63**(3): 339–345.
5. Sperduto PW, Kased N, Roberge D *et al*. Summary report on the graded prognostic assessment: an accurate and facile diagnosis-specific tool to estimate survival for patients with brain metastases. *J Clin Oncol* 2012; **30**(4): 419–425.
6. Chamberlain MC, Silbergeld DL. Is graded prognostic assessment an improvement compared with radiation therapy oncology group's recursive partitioning analysis classification for brain metastases? *J Clin Oncol* 2012; **30**(26): 3315–3316; author reply 3316–3317.
7. Likhacheva A, Pinnix CC, Parikh NR *et al*. Predictors of survival in contemporary practice after initial radiosurgery for brain metastases. *Int J Radiat Oncol Biol Phys* 2013; **85**(3): 656–661.
8. Nieder C, Andratschke NH, Geinitz H, Grosu AL. Diagnosis-specific graded prognostic assessment score is valid in patients with brain metastases treated in routine clinical practice in two European countries. *Med Sci Monit* 2012; **18**(7): CR450–CR455.
9. Villà S, Weber DC, Moretones C *et al*. Validation of the new Graded Prognostic Assessment scale for brain metastases: a multicenter prospective study. *Radiat Oncol* 2011; **6**: 23.
10. Tsao MN, Lloyd NS, Wong RK. Clinical practice guideline on the optimal radiotherapeutic management of brain metastases. *BMC Cancer* 2005; **5**: 34.
11. Mintz AH, Kestle J, Rathbone MP *et al*. A randomized trial to assess the efficacy of surgery in addition to radiotherapy in patients with a single cerebral metastasis. *Cancer* 1996; **78**(7): 1470–1476.
12. Noordijk EM, Vecht CJ, Haaxma-Reiche H *et al*. The choice of treatment of single brain metastasis should be based on extracranial tumor activity and age. *Int J Radiat Oncol Biol Phys* 1994; **29**(4): 711–717.
13. Patchell RA, Tibbs PA, Walsh JW *et al*. A randomized trial of surgery in the treatment of single metastases to the brain. *N Engl J Med* 1990; **322**(8): 494–500.
14. Andrews DW, Scott CB, Sperduto PW *et al*. Whole brain radiation therapy with or without stereotactic radiosurgery boost for patients with one to three brain metastases: phase III results of the RTOG 9508 randomised trial. *Lancet* 2004; **363**(9422):1665–1672.
15. www.cebm.net/oxford-centre-evidence-based-medicine-levels-evidence-march-2009 (last accessed 30/9/16)
16. Yamamoto M, Serizawa T, Shuto T *et al*. Stereotactic radiosurgery for patients with multiple brain metastases (JLGK0901): a multi-institutional prospective observational study. *Lancet Oncol* 2014; **15**(4): 387–395.
17. Baschnagel AM, Meyer KD, Chen PY *et al*. Tumor volume as a predictor of survival and local control in patients with brain metastases treated with Gamma Knife surgery. *J Neurosurg* 2013; **119**(5): 1139–1144.

References

18. Bhatnagar AK, Flickinger JC, Kondziolka D, Lunsford LD. Stereotactic radiosurgery for four or more intracranial metastases. *Int J Radiat Oncol Biol Phys* 2006; **64**(3): 898–903.

19. Chen JC, Petrovich Z, O'Day S *et al*. Stereotactic radiosurgery in the treatment of metastatic disease to the brain. *Neurosurgery* 2000; **47**(2): 268–279; discussion 279–281.

20. Aoyama H, Shirato H, Tago M *et al*. Stereotactic radiosurgery plus whole-brain radiation therapy vs stereotactic radiosurgery alone for treatment of brain metastases: a randomized controlled trial. *JAMA* 2006; **295**(21): 2483–2491.

21. Aoyama H, Tago M, Kato N *et al*. Neurocognitive function of patients with brain metastasis who received either whole brain radiotherapy plus stereotactic radiosurgery or radiosurgery alone. *Int J Radiat Oncol Biol Phys* 2007; **68**(5): 1388–1395.

22. Chang EL, Wefel JS, Hess KR *et al*. Neurocognition in patients with brain metastases treated with radiosurgery or radiosurgery plus whole-brain irradiation: a randomised controlled trial. *Lancet Oncol* 2009; **10**(11): 1037–1044.

23. Kocher M, Soffietti R, Abacioglu U *et al*. Adjuvant whole-brain radiotherapy versus observation after radiosurgery or surgical resection of one to three cerebral metastases: results of the EORTC 22952-26001 study. *J Clin Oncol* 2011; **29**(2): 134–141.

24. Tsao MN, Lloyd N, Wong RK *et al*. Whole brain radiotherapy for the treatment of newly diagnosed multiple brain metastases. *Cochrane Database Syst Rev* 2012; **4**: CD003869.

25. Tsao MN, Rades D, Wirth A *et al*. Radiotherapeutic and surgical management for newly diagnosed brain metastasis(es): an American Society for Radiation Oncology evidence-based guideline. *Pract Radiat Oncol* 2012; **2**(3): 210–225.

26. Chatani M, Matayoshi Y, Masaki N, Inoue T. Radiation therapy for brain metastases from lung carcinoma. Prospective randomized trial according to the level of lactate dehydrogenase. *Strahlenther Onkol* 1994; **170**(3): 155–161.

27. Chatani M, Teshima T, Hata K *et al*. Whole brain irradiation for metastases from lung carcinoma. A clinical investigation. *Acta Radiol Oncol* 1985; **24**(4): 311–314.

28. Harwood AR, Simson WJ. Radiation therapy of cerebral metastases: a randomized prospective clinical trial. *Int J Radiat Oncol Biol Phys* 1977; **2**(11–12): 1091–1094.

29. Kurtz JM, Gelber R, Brady LW, Carella RJ, Cooper JS. The palliation of brain metastases in a favourable patient population: a randomized clinical trial by the Radiation Therapy Oncology Group. *Int J Radiat Oncol Biol Phys* 1981; **7**(7): 891–895.

30. Murray KJ, Scott C, Greenberg HM *et al*. A randomized phase III study of accelerated hyper-fractionation versus standard in patients with unresected brain metastases: a report of the Radiation Therapy Oncology Group (RTOG) 9104. *Int J Radiat Oncol Biol Phys* 1997; **39**(3): 571–574.

31. Borgelt B, Gelber R, Kramer S *et al*. The palliation of brain metastases: final results of the first two studies by the Radiation Therapy Oncology Group. *Int J Radiat Oncol Biol Phys* 1980; **6**(1): 1–9.

32. Borgelt B, Gelber R, Larson M, Hendrickson F, Griffin T, Roth R. Ultra-rapid high dose irradiation schedules for the palliation of brain metastases: final results of the first two studies by the Radiation Therapy Oncology Group. *Int J Radiat Oncol Biol Phys* 1981; **7**(12): 1633–1638.

33. Mulvenna PM, Nankivell MG, Barton R *et al*. Whole brain radiotherapy for brain metastases from non-small lung cancer: Quality of life (QoL) and overall survival (OS) results from the UK Medical Research Council QUARTZ randomised clinical trial (ISRCTN 3826061). *J Clin Oncol* 2015; **33**(15): (suppl; abstr 8005).

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.[1] 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.[2] 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 Comissioning through Evaluation (CtE) Service Specification (Level 5).[3,4] For all sites, it is recommended that the critical organ dose constraints agreed by the UK Stereotactive Ablative Radiotherapy (SABR) consortium should be followed.[5]

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.[1] 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.[6,7]

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

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.[4]

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).[5]

In the specific case of remaining spinal cord tolerance, the method described by Sahgal is recommended.[7] 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.[9]

Oligometastases: lung

Lung oligometastases present a similar clinical problem to early-stage primary lung cancer, for which stereotactic treatment is a standard of care.[10] Specifically for patients with oligometastases, an EQD2 >100 Gy is associated with approximately 90% local control at 1–2 years.[10,11] 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.[12–15] These current recommendations are consistent with the CtE Service Specification.[3]

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.[4]

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.[16] 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).[4,17,18]

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.[4]

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 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).[4,19,20]

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.[4]

References

1. Tree AC, Khoo VS, Eeles RA *et al*. Stereotactic body radiotherapy for oligometastases. *Lancet Oncol* 2013; **14**(1): e28–e37.
2. Weichselbaum RR, Hellman S. Oligometastases revisited. *Nat Rev Clin Oncol* 2011; **8**(6): 378–382.
3. www.england.nhs.uk/commissioning/spec-services/npc-crg/comm-eval (last accessed 13/10/16)
4. www.cebm.net/oxford-centre-evidence-based-medicine-levels-evidence-march-2009 (last accessed 30/9/16)
5. www.sabr.org.uk/consortium (last accessed 13/10/16)
6. Bhattacharya IS, Hoskin PJ. Stereotactic body radiotherapy for spinal and bone metastases. *Clin Oncol (R Coll Radiol)* 2015; **27**(5): 298–306.
7. Sahgal A, Atenafu EG, Chao S *et al*. Vertebral compression fracture after spine stereotactic body radiotherapy: a multi-institutional analysis with a focus on radiation dose and the spinal instability neoplastic score. *J Clin Oncol* 2013; **31**(27): 3426–3431.
8. Cox BW, Spratt DE, Lovelock M *et al*. International Spine Radiosurgery Consortium consensus guidelines for target volume definition in spinal stereotactic radiosurgery. *Int J Radiat Oncol Biol Phys* 2012; **83**(5): e597–e605.
9. Mantel F, Flentje M, Guckenberger M. Stereotactic body radiation therapy in the re-irradiation situation – a review. *Radiat Oncol* 2013; **8**: 7.
10. Solda F, Lodge M, Ashley S, Whitington A, Goldstraw P, Brada M. Stereotactic radiotherapy (SABR) for the treatment of primary non-small cell lung cancer; systematic review and comparison with a surgical cohort. *Radiother Oncol* 2013; **109**(1): 1–7.
11. Siva S, MacManus M, Ball D. Stereotactic radiotherapy for pulmonary oligometastases: a systematic review. *J Thorac Oncol* 2010; **5**(7): 1091–1099.
12. Timmerman R, McGarry R, Yiannoutsos C *et al*. Excessive toxicity when treating central tumors in a phase II study of stereotactic body radiation therapy for medically inoperable early-stage lung cancer. *J Clin Oncol* 2006; **24**(30): 4833–4839.
13. Mangona VS, Aneese AM, Marina O *et al*. Toxicity after central versus peripheral lung stereotactic body radiation therapy: a propensity score matched-pair analysis. *Int J Radiat Oncol Biol Phys*.2014; **91**(1): 124–132.
14. Nuyttens JJ, van der Voort van Zyp NC, Praag J *et al*. Outcome of four-dimensional stereotactic radiotherapy for centrally located lung tumors. *Radiother Oncol* 2012; **102**(3): 383–387.
15. Chang JY, Balter PA, Dong L *et al*. Stereotactic body radiation therapy in centrally and superiorly located stage I or isolated recurrent non-small-cell lung cancer. *Int J Radiat Oncol Biol Phys* 2008; **72**(4): 967–971.
16. Chang DT, Swaminath A, Kozak M *et al*. Stereotactic body radiotherapy for colorectal liver metastases: a pooled analysis. *Cancer* 2011; **117**(17): 4060–4069.
17. Aitken KL, Hawkins MA. Stereotactic body radiotherapy for liver metastases. *Clin Oncol (R Coll Radiol)* 2015; **27**(5): 307–315.
18. Høyer M, Swaminath A, Bydder S *et al*. Radiotherapy for liver metastases: a review of evidence. *Int J Radiat Oncol Biol Phys* 2012; **82**(3): 1047–1057.

19. Chawla S, Chen Y, Katz AW *et al*. Stereotactic body radiotherapy for treatment of adrenal metastases. *Int J Radiat Oncol Biol Phys* 2009; **75**(1): 71–75.

20. Casamassima F, Livi L, Masciullo S *et al*. Stereotactic radiotherapy for adrenal gland metastases: university of Florence experience. *Int J Radiat Oncol Biol Phys* 2012; **82**(2): 919–923.

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.[1] Multiple levels of compression are seen in up to one-third of patients.[2–4]

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 miligrams (mg) daily. There is evidence from one randomised trial that higher initial doses of 96 mg are superior to no steroids (Level 2b).[5,6] 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, ≥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).[7,8]

Ideally, the prognosis of patients should be objectively assessed using validated scores such as the Tokuhashi Score (Level 2b).[6,8,9]

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.[6,10]

For good prognosis or ambulatory patients who are not suitable for surgery, urgent radiotherapy should be given before further neurological deterioration.[3,4,8]

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.[3,4,8]

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).[6,8,11–13]

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.[14–16]

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].[16]

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.[6]

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_2 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).[6,17]

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 Gy2 (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.[6]

References

1. Levack P, Graham J, Collie D *et al*. Don't wait for a sensory level – listen to the symptoms: a prospective audit of the delays in diagnosis of malignant cord compression. *Clin Oncol (R Coll Radiol)* 2002; **14**(6): 472–480.
2. Hoskin PJ, Grover A, Bhana R. Metastatic spinal cord compression: radiotherapy results and dose fractionation. *Radiother Oncol (R Coll Radiol)* 2003; **68**(2): 175–180.
3. Metastatic Spinal Cord Compression: Diagnosis and management of adults at risk of and with metastatic spinal cord compression. NICE Clinical Guideline 75, November 2008
4. National Institute for Health and Care Excellence. *Metastatic spinal cord compression in adults: risk assessment, diagnosis and management.* London: National Institute for Health and Care Excellence, 2008.
5. Sorensen PS, Helweg-Larsen SH, Mouridsen H, Hansen HH. Effect of high dose dexamethasone in carcinomatous metastatic spinal cord compression treated with radiotherapy: a randomised trial. *Eur J Cancer* 1994; **30A**(1): 22–27.
6. www.cebm.net/oxford-centre-evidence-based-medicine-levels-evidence-march-2009 (last accessed 30/9/16)
7. Rades D, Fehlauer F, Schulte R *et al*. Prognostic Factors for local control and survival after radiotherapy of metastatic spinal cord compression. *J Clin Oncol* 2006; **24**(21): 3388–3393.
8. Prewett S, Venkitaraman R. Metastatic spinal cord compression: review of the evidence for a radiotherapy dose fractionation schedule. *Clin Onc (R Coll Radiol)* 2010; **22**(3): 222–230.
9. Tokuhashi Y, Matsuzaki H, Ods H, Oshima M, Ryu J. A revised scoring system for preoperative evaluation of metastatic spine tumor prognosis. *Spine* 2005; **30**(19): 2186–2191.
10. Patchell RA, Tibbs PA, Regine WF *et al*. Direct decompressive surgical resection in the treatment of spinal cord compression caused by metastatic cancer: a randomised trial. *Lancet* 2005; **366**(9486): 643–648.
11. Rades D, Stalpers LJ, Veninga T *et al*. Evaluation of five radiation schedules and prognostic factors for metastatic spinal cord compression. *J Clin Oncol* 2005; **23**(15): 3366–3375.
12. Maranzano E, Trippa F, Casale M *et al*. 8 Gy single-dose radiotherapy is effective in metastatic spinal cord compression: results of a phase III randomized multicentre Italian trial. *Radiotherapy Oncol* 2009; **93**(2): 174–179.
13. Maranzano E, Bellavita R, Rossi R *et al*. Short-course versus split-course radiotherapy in metastatic spinal cord compression: results of a phase III, randomized, multicenter trial. *J Clin Oncol* 2005; **23**(15): 3358–3365.
14. Rades D, Rudat V, Veninga T, Stalphers LJ, Hoskin PJ, Schild SE. Prognostic factors for functional outcome and survival after reirradiation for in-field recurrences of metastatic spinal cord compression. *Cancer* 2008; **113**(5): 1090–1096.
15. Rades D, Šegedin B, Conde-Moreno AJ *et al*. Radiotherapy With 4 Gy × 5 versus 3 Gy × 10 for metastatic epidural spinal cord compression: final results of the SCORE-2 Trial (ARO 2009/01). *J Clin Oncol* 2016; **34**(6): 597–602.
16. www.ucl.ac.uk/cancertrials/trials/scorad (last accessed 13/10/16)
17. Rades D, Stalpers L, Veninga T, Hoskin PJ. Spinal re-irradiation after short-course RT for metastatic spinal cord compression. *Int J Radiat Oncol Biol Phys* 2005; **63**(3): 872–875.

Acknowledgements

Working group

This review of Radiotherapy dose fractionation was undertaken by a working group comprising the following members:

- **Professor Peter Hoskin (Chair)**
  Mount Vernon Cancer Centre, Northwood, Middlesex
- **Dr David Bloomfield~**
  Brighton and Sussex University Hospitals
- **Dr Jeanette Dickson~~**
  Mount Vernon Cancer Centre, Northwood, Middlesex
- **Dr Raj Jena**
  Addenbrooke's Hospital, Cambridge
- **Dr Vivek Misra**
  The Christie Hospital, Manchester
- **Dr Robin Prestwich**
  St James' University Hospital, Leeds

~ Medical Director, Professional Practice, Clinical Oncology, from September 2015
~~ Medical Director, Professional Practice, Clinical Oncology, until September 2015

Contributors

The working group would like to thank the following for their contributions to this document in the form of comments on both the original draft and later revisions circulated for consultation. Those who contributed on behalf of a stakeholder group are marked with an asterisk (*).

Dr R Adams*
Dr A Bahl
Dr S Ball
Dr N Bayman
Dr H Benghiat
Dr A Birtle*
Dr C Boon
Dr M Brunt
Dr S A R Challapalli
Prof A Chalmers*
Dr N Charnley
Dr A Choudhury
Dr C Coles
Dr R Cooper
Dr C Corner
Prof R Cowan*
Dr A Crellin
Dr T Crosby
Dr C Crowley
Dr S Davidson
Dr N Davies
Prof D Dearnaley
Dr J Dewar
Dr K Dyker
Dr A Elliott
Dr S Erridge
Dr M Evans
Prof C Faivre-Finn
Dr S Falk*
Dr C Featherstone
Dr K Fife
Dr A Freebairn
Dr B Foran*
Dr E Gallop-Evans
Dr M Gaze
Dr K Geropantas
Dr D Gilbert
Dr D Gilson
Dr J Glaholm
Dr S Gwynne*
Dr G Hanna
Dr A Haridass

Acknowledgements

Dr L Harris
Dr M Harris
Dr A Hartley
Dr M Hatton*
Dr M Hawkins*
Dr A Henry
Prof R Huddart*
Prof T Illidge
Dr A Kiltie
Dr P Kirkbride
Dr M Kosmin
Dr J Lester*
Dr J Lewis
Dr F Little
Dr H Lord
Dr S Lupton
Dr N MacLeod
Dr A Makris*
Prof M Mason
Dr C McBain
Dr J McGrane
Dr A Miah*
Dr G Mikhaeel
Dr A Mitra
Dr L Moss
Dr R Muirhead
Mr R Naik*
Dr P Niblock
Dr J Nicoll
Prof C Nutting*
Dr N O'Rourke
Dr P Ostler
Dr C Parker*
Dr L Pickering
Dr H Phillips
Dr M Powell*
Prof A Price
Dr G Radhakrishna
Dr G Read
Prof N Reed*
Dr M Robinson
Dr P Robson
Dr S Rodda
Dr T Roques
Dr P Sanghera
Dr B Seddon
Dr D Sheehan
Prof S Short
Dr P L Shum
Dr N Sidek
Prof N Slevin
Prof M Spittle OBE
Dr J Staffurth
Prof A Sun Myint
Dr I Syndikus
Dr L T Tan
Dr C Taylor*
Prof R Taylor
Dr A Thomson
Dr D Thomson
Dr A Tree*
Ms J Troup*
Dr N van As
Dr R Venkitaraman
Dr A Weaver
Ms S Welham*
Dr G Whitfield*
Dr M Williams

Stakeholder groups consulted in the development of Radiotherapy dose fractionation, second edition

The following organisations contributed to the development of this document by submitting comments during the consultation process.

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

The following clinical oncology members of the National Cancer Research Institute (NCRI) Clinical Studies Groups (CSG):

- 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

Approved by the Board of the Faculty of Clinical Oncology: 24 June 2016.

The Royal College of Radiologists
63 Lincoln's Inn Fields
London WC2A 3JW

+44 (0)20 7405 1282
enquiries@rcr.ac.uk
www.rcr.ac.uk
@RCRadiologists

ISBN: 978-1-905034-74-1. BFCO(16)3.

Price
Members: £20
Non-members: £25