Clinical Oncology

Radiotherapy dose fractionation

Fourth edition

JANUARY 2024

The Royal College of Radiologists

Contents

Introduction

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

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

The legal record of the radiotherapy treatment to be delivered is the radiotherapy treatment prescription. Since the radiotherapy prescription is frequently used by clinical providers as evidence that the justification of treatment – and sometimes the verification of exposures – has been completed, all radiotherapy prescriptions should be as complete as possible. These should include: unique patient identification; diagnosis; anatomical region to be treated including laterality; identity of the prescribing practitioner; treatment intent; date the prescription was completed (written); modality; definition of volumes; specification of absorbed dose and/or dose-volume requirements for the planning target volume (PTV); fractionation scheme; normal tissue constraints; overall treatment time; physical technique, energy and, where relevant, absorbed dose-distribution(s) planned and details of any other associated treatment requirements, for example chemotherapy, cardiac implantable electronic devices (CIED), prostheses. The record of the prescription may be represented as a single document or a collection of data items across the oncology management system and treatment planning system.

It has been important to recognise that, despite adoption of intensity-modulated radiotherapy (IMRT), image-guided radiotherapy (IGRT), volumetric modulated arc radiotherapy (VMAT) and stereotactic body radiotherapy (SBRT) with changes to redefine fractionation during the past decade, many clinical scenarios, particularly for palliative treatments, will still require conventional therapy techniques, and this is reflected in these guidelines to ensure a comprehensive cover of clinical radiotherapy.

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

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

Oxford Centre for Evidence-Based Medicine

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 are used in a situation that has potentially clinically important differences from 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

* By homogeneity we mean 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 Rx became available, but some now survive on it; or when some patients died before the Rx became available, but none now die on it.

§§ By poor-quality cohort study we mean 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. By poor-quality case-control study we mean 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.

Reference

www.cebm.ox.ac.uk/resources/levels-of-evidence/oxford-centre-for-evidence-based-medicine-levels-of-evidence-march-2009 (last accessed 28/11/2023).

Preparation of this document

For this fourth edition, chapters were reviewed by site-specialty experts in consultation with various stakeholder groups and the wider RCR membership. This edition was edited by Professor Peter Hoskin and oversight was provided by Dr Nicky Thorp and the RCR's Clinical Oncology Professional Support and Standards Board.

Finally, it is important to emphasise that this is an evidence-based guide to fractionation, 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.

Acknowledgements

This review of *Radiotherapy dose fractionation* was led by Professor Peter Hoskin (Mount Vernon Cancer Centre) with oversight provided by Dr Nicky Thorp (Medical Director, Professional Practice, Clinical Oncology) and the RCR's Clinical Oncology Professional Support and Standards Board.

Lead authors

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Stakeholders

In addition, the RCR would like to thank the following stakeholder groups who were consulted in the development of this edition.

- Action Kidney Cancer
- British Association of Head & Neck Oncologists
- British Gynaecological Cancer Society
- British Uro-Oncology Group
- Children's Cancer and Leukaemia Group
- National Cancer Research Institute (NCRI) Clinical Studies Groups (CSG)*
- SABR UK Consortium
- UK Breast Cancer Group

The RCR would also like to acknowledge those who contributed to earlier versions of the radiotherapy dose fractionation document – for full details please see first, second and third editions, which are available upon request from guidance@rcr.ac.uk).

**prior to their closure in July 2023*

01 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 a 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 with 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]

Analyses of both the UKCCR ACT II and RTOG 9811 trials 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 (to the primary tumour and involved nodes) for these patients when using IMRT or arc radiotherapy.

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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 – T1/2 NO):

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

Dose to primary and involved nodes (advanced stage – T3/4 or N+):

• 53.2 Gy in 28 fractions over 5.5 weeks (Grade A)

Dose to uninvolved nodes (prophylactic):

• 40 Gy in 28 fractions over 5.5 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.[4]

The UK Personalising Anal Cancer Radiotherapy Dose (PLATO) trial investigated dose escalation in locally advanced anal cancers, and dose de-escalation in early small-node-negative tumours is currently in follow-up 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.

Recommendation

For palliative treatment of anal cancer:

• 30 Gy in 10 fractions over 2 weeks (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.[4]

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02 Bladder cancer

Radical treatment

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

The regimens used in studies comparing radiotherapy and surgery for bladder cancer have been 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 with 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 8 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 2 fractions per day of 1.9 Gy over a treatment time of 26 days when compared with 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

Two UK-based randomised controlled trials allowed the use of both conventional (60–64 Gy in 30–32 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. A subsequent individual patient data meta-analysis of these trials demonstrated non-inferiority of hypofractionated radiotherapy in terms of invasive locoregional disease-free survival and toxicity. Superiority for locoregional disease-free survival was confirmed for 55 Gy in 20 fractions (Level 1a).[5,12]

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.[13] There was no significant difference in local control at 5 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.[14] There was no difference in locoregional recurrence, late toxicity or overall survival between the two groups (Level 1b).[5]

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Radical radiotherapy with radiosensitisation

Two UK-based randomised control trials have demonstrated that radical radiotherapy with a radiosensitiser improves outcomes compared with 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 2-year locoregional recurrence rates of 67% versus 54% (Level 1b).[5,10] The Bladder Carbogen Nicotinamide (BCON) investigators compared radical radiotherapy alone with radical radiotherapy given concurrently with carbogen and nicotinamide, with a significant improvement in 3-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 with those in the literature, with a 3-year overall survival of 75% and 88% achieving a complete endoscopic response at first check cystoscopy (Level 2b).[5,15]

Adjuvant radiotherapy

There is currently insufficient evidence to recommend adjuvant radiotherapy following radical cystectomy. A randomised phase II study reported superior outcomes in patients with high-risk disease (T3b+, Grade 3 or positive lymph nodes) who received adjuvant radiotherapy sandwiched between cycles of adjuvant chemotherapy, compared with adjuvant chemotherapy alone.[16] However a systematic review of 28 studies investigating adjuvant radiotherapy for bladder cancer and upper tract urothelial cancer found no clear benefit of adjuvant radiotherapy and noted the quality of the data was limited.[17]

Treatment technique

The size of the planning target volume (PTV) is critical to any discussion of dose and fractionation.[18,19] 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. A phase II trial looking at the use of intensity-modulated radiotherapy (IMRT) to the bladder and pelvic nodes demonstrated low levels of pelvic nodal recurrence rates and toxicity.[20] IMRT or volumetric modulated arc therapy (VMAT) techniques can therefore also be used to deliver bladder radiotherapy (Level 2b).[5]

There is increasing use of adaptive radiotherapy techniques for bladder treatment using a ‘plan of the day’ based on imaging prior to delivery of each fraction, allowing smaller anisotropic margins to be applied. The practical implementation of this technique was shown in the phase II HYBRID trial, looking at plan of the day in weekly ultra-fractionated radiotherapy, which demonstrated improved acute Grade 3 non-genitourinary toxicity rates compared with standard planning.[21] The RAIDER trial, currently recruiting, has developed plan of the day PTV margins and implementation guidance.[22] Whether the adaptive approach leads to improved outcomes is yet to be established. The fractionation evidence has not been tested in this setting, but there is no reason to believe that the recommendations do not apply to the adaptive setting also.

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Recommendations

For radical radiotherapy to the bladder:

- 55 Gy in 20 fractions over 4 weeks is the regimen of choice (Grade A)
- 64 Gy in 32 fractions over 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 3 fractions on alternate weekdays in 1 week (4–6 elapsed days) is as effective as 35 Gy in 10 fractions in 2 weeks in palliating symptoms in patients with bladder cancer.[23] 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 that are in use in the UK are 20 Gy in 5 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 with a 1-year invasive, local recurrence-free rate of 86% in patients with localised muscle-invasive bladder cancer unsuitable for radical treatment (Level 2b).[5,21]

Recommendations

For patients unsuitable for radical treatment of bladder cancer:

- 21 Gy in 3 fractions on alternate days in 1 week (Grade A)
- 36 Gy in 6 fractions weekly with or without adaptive planning (Grade B)

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)
- 36 Gy in 6 fractions weekly with or without adaptive planning (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]

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03 Breast cancer

Background

Breast cancer is the most common cancer worldwide, and most patients in the UK are diagnosed at an early stage. Radiotherapy has long been established as an important treatment modality in the adjuvant and palliative setting in breast cancer. The delivery of breast radiotherapy must be adapted based on the individual patients' risk of recurrence, and the risk–benefit ratio of treatment must be discussed with patients, enabling a shared care decision. Technological advances and results of pivotal trials have led to significant changes in practice in the UK in the past few years.

Adjuvant radiotherapy to the breast or chest wall

Radiotherapy can increase both local control and overall survival in the conservative management of invasive primary breast cancer and in selected patients after mastectomy (Level 1a).[1–4] It can also reduce ipsilateral breast tumour recurrence following breast conservation in patients with a diagnosis of ductal carcinoma *in situ* (DCIS).[5,6]

Evolution of hypofractionation from 50 Gray (Gy) in 25 fractions over 5 weeks to 26 Gy in 5 fractions over 1 week

Historically the 2 Gy per fraction regimen of 50 Gy in 25 fractions over 5 weeks was the standard of care as reported in the National Surgical Adjuvant Breast and Bowel Project (NSABP) breast cancer trials.[7] There was a practice change following publication of the START trials, and the most widely used UK regimen was the hypofractionated regimen of 40 Gy in 15 fractions over 3 weeks as used in the UK START-B trial.[8–9] Mature data from the START-A, B and P trials and the Canadian OCOG study demonstrate the equivalence of hypofractionated regimens for efficacy with evidence of some reduced normal tissue effects compared with the previous standard of 2 Gy daily fractionation (Level 1b).[3,8–13]

Following the publication of the UK FAST-Forward trial in 2020,[14] there has been a rapid change in practice to delivering 26 Gy in 5 fractions over 1 week as the standard of care. The FAST-Forward trial was carried out in patients with early invasive breast carcinoma (pT1–3, pN0–1, M0) after breast-conserving surgery (BCS) or mastectomy.[14] Patients were randomised on a 1:1:1 ratio to 40 Gy in 15 fractions over 3 weeks (UK standard of care), 26 Gy in 5 fractions over 1 week or 27 Gy in 5 fractions over 1 week.

4,096 patients were recruited from November 2011 to June 2014 with a median follow-up of 71.5 months. The primary endpoint of 5-year ipsilateral breast tumour relapse was estimated as 2.1% (95% confidence interval [CI] 1.4–3.1), 1.7% (1.2–2.6) and 1.4% (0.9–2.2) after 40 Gy, 27 Gy and 26 Gy respectively.

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At 5 years, moderate or marked clinician-assessed normal tissue effects were observed in 98/986 (9.9%), 155/1,005 (15.4%) and 122/1,020 (11.9%) of the 40 Gy, 27 Gy and 26 Gy groups respectively, all less than observed in the START trials. The odds ratio versus 40 Gy across all clinician assessments in the 5-year period were 1.55 (CI 1.32–1.83, p<0.0001) and 1.12 (0.94–1.34, p=0.20) for 27 Gy and 26 Gy respectively. Assessments by patients and via photographs showed the risk of normal tissue effects was higher for 27 Gy, but not for 26 Gy, compared with the control group. Statistically the only significant difference between 26 Gy and 40 Gy was for moderate/marked breast induration outside the tumour bed, but this is highly unlikely to be clinically significant with small absolute numbers (2.1% for 26 Gy; 20 cases).

Following the publication of FAST-Forward[14] NICE guidance is to offer 26 Gy in 5 fractions over 1 week to the whole breast as the standard of care (Level 1b).[3,4]

Ductal carcinoma *in situ*

The FAST-Forward trial was not offered to patients with DCIS only;[14] however, this patient group can still be offered 26 Gy in 5 fractions over 1 week for whole-breast radiotherapy. This follows the similar pragmatic implementation of 40 Gy in 15 fractions over 3 weeks for DCIS following the UK START-B trial,[8–9] given breast radiotherapy for DCIS does not appear to have a survival advantage.[15] It would be challenging to carry out a trial of 26 Gy in 5 fractions over 1 week as the low anticipated local recurrence rate would require a very large number of participants and it is questionable whether there would be equipoise for randomisation in the UK. Furthermore, the BIG-TROG DCIS trial[16] demonstrated there was no difference in efficacy or side-effects with moderate hypofractionation versus 50 Gy in 25 fractions over 5 weeks. NICE guidance is to offer 26 Gy in 5 fractions over 1 week to the whole breast in patients with DCIS.[4]

Chest wall ± reconstruction

The RCR consensus (2020)[17] states that 26 Gy in 5 fractions over 1 week should be offered for chest wall radiotherapy. Within FAST-Forward, participants who had mastectomies at baseline included 91 patients (6.7%) in the 40 Gy group, 89 patients (6.5%) in the 27 Gy group and 84 patients (6.1%) in 26 Gy group, with a solitary reported recurrence in a 40 Gy-treated patient.[14] Regarding reconstruction, the RCR consensus (2020)[17] is that 26 Gy in 5 fractions over 1 week should be considered for chest wall radiotherapy with reconstruction. Of note, the trial had immediate reconstruction rates of <1% across all groups; however, there is no biological reason why patients with immediate reconstruction should have a higher risk of normal tissue toxicity or capsular contracture with 26 Gy in 5 fractions (versus 40 Gy in 15 fractions). The consensus statement for chest wall irradiation with reconstruction is to consider the 5-fraction schedule and, if used, centres may wish to audit their practice. This is also reflected in the NICE guidance for early and locally advanced breast cancer: diagnosis and management (updated June 2023).[4]

Co-morbidity and frailty

For patients with co-morbidity and/or frailty, making daily radiotherapy difficult, the RCR consensus (2020)[17] is to consider 28.5 Gy in 5 fractions over 5 weeks as well as 26 Gy in 5 fractions over 1 week following on from the FAST results.[18] 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 5, once-weekly fractions of 5.7 Gy or 6.0 Gy respectively to the whole breast. The primary endpoint was a 2-year change in photographic breast appearance. The 10-year FAST trial results found no statistically significant difference in normal tissue event rates in the 28.5 Gy group versus the 50 Gy group,[18] although normal tissue event rates were higher in the 30 Gy group.

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Recommendation

For adjuvant radiotherapy of non-nodal breast or chest wall without immediate reconstruction:

• 26 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.[3]

Partial breast irradiation (PBI)

PBI may be an option for patients with a low risk of local relapse. Risk of local relapse is highest in the region of the tumour bed,[19] therefore radiotherapy can be delivered to this region only, sparing the whole breast and potentially reducing side-effects.[20] A meta-analysis showed that PBI is associated with a higher local recurrence rate, albeit still low, compared with WBI (Level 1a).[3,21] However, this meta-analysis included studies covering a broad range of PBI techniques and selection criteria. Some of the trials have included older surgical and radiation techniques. Techniques used to deliver PBI include external beam radiotherapy (EBRT), brachytherapy and intraoperative radiotherapy (IORT).

PBI can be considered for patients ≥50 years, with low-risk tumour features as follows: Grades 1–2, ≤3 cm, oestrogen receptor positive (ER+), progesterone receptor positive (PR+) or human epidermal growth factor receptor negative (HER2-ve) node-negative tumours, as per the RCR consensus (2016).[22] The consensus is to deliver PBI using EBRT, as per the IMPORT LOW trial,[23] or multicatheter brachytherapy using fractionation, as per the GEC-ESTRO trial.[24] NICE guidance recommends using EBRT when delivering PBI.[4]

There are a number of international PBI trials using EBRT that have reported, but this discussion is focused on the UK-led IMPORT LOW trial, as this is the PBI technique most commonly used in the UK.[23] Within IMPORT LOW, 2,018 women were randomised to receive 40 Gy to the whole breast (control), 36 Gy to the whole breast and 40 Gy to the partial breast (reduced-dose group), or 40 Gy to the partial breast only (partial breast group) in 15 daily treatment fractions using simple field-in-field technique. Local relapse rates were 1.1% (95% CI 0.5–2.3), 0.2% (0.02–1.2) and 0.5% (0.2–1.4) in the WBI, reduced-dose and PBI groups respectively at 72 months (median follow-up). The dose/fractionation in all groups were identical meaning the irradiated volume was the only variable within the trial and significantly less toxicity was found in the two test groups versus the control group.

PBI can be delivered in 1 week using the techniques in IMPORT LOW.[23] Both the FAST-Forward [14] and IMPORT LOW [23] trials were designed in parallel with the same dose/fractionation used in the control groups and with a pre-plan to consider the data together for 5 fractions of PBI. FAST-Forward showed non-inferiority with 40 Gy in 15 fractions for efficacy and similar toxicity. In addition, IMPORT LOW showed non-inferiority with 40 Gy in 15 fractions for efficacy *and* reduced toxicity. These results have enabled the FAST-Forward fractionation to be seamlessly adopted for PBI, and NICE guidance is to offer 26 Gy in 5 fractions over 1 week for partial breast radiotherapy.[4]

Regarding multicatheter interstitial brachytherapy, GEC-ESTRO randomly assigned women to PBI with interstitial brachytherapy, either high dose rate or pulsed dose rate versus WBI 50 Gy with a 10 Gy tumour bed boost.[24] At 10 years (median follow-up), the local recurrence rates were 1.58% (95% CI 0.37–2.8) in the WBI group and 3.51% (1.99–5.03) in the PBI group.[25]

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Difference in 10-year rates between the groups was 1.93% (95% CI −0.018–3.87; p=0.074). There was a significantly lower incidence of treatment-related Grade 3 late side-effects in patients in the PBI group compared with those in the WBI group. Fibrosis was the commonest Grade 3 adverse event in both treatment groups although overall numbers were very low.

With respect to IORT, the ELIOT[26] and TARGIT trials[27–28] used this technique with ELIOT delivering electrons (IOeRT) and TARGIT using photons. ELIOT randomised women to 50 Gy in 25 fractions over 5 weeks plus boost versus IOeRT 21 Gy to tumour bed.[26] The 5-year local relapse was 4.5% (95% CI 2.7–6.1) and 0.4% (95% CI 0.0–1.0) for the IOeRT and WBI groups respectively (hazard ratio [HR] 9.3; 95% CI 3.3–26.3). Local relapse rates in the IOeRT group were significantly greater than in patients receiving WBI but no difference in overall survival was seen. Of note, several patients in the trial had high-risk features and ELIOT (and other trials) began recruitment prior to the establishment of GEC-ESTRO/ASTRO guidelines.[29–30] Toxicity was not systematically recorded but a difference in skin toxicity favouring IOeRT was reported, although IOeRT patients were found to have increased fat necrosis.[26]

Participants within the TARGIT trial were randomised to IORT using 50 kV photons or WBI. The two strata within the trial consisted of pre-pathology where IORT was delivered at time of BCS, and post-pathology where IORT was delivered after BCS where the wound was reopened.[27–28] Patients receiving IORT in the pre-pathology strata required additional WBI (20% of patients) due to unfavourable histology results after final surgery.[27] There was no systematic collection of toxicity data. TARGIT-IORT is not recommended for routine commissioning for adjuvant treatment of early invasive breast cancer during breast-conserving surgical removal of the tumour. NICE guidance recommends that if TARGIT-IORT is delivered it should only be done on machines that are already available and in conjunction with NHS England specified clinical governance, data collection and submission arrangements. Patients should be offered the NICE patient information and decision aid if being offered TARGIT-IORT.[31]

Recommendation

For partial breast radiotherapy using external beam radiotherapy:

- 26 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.[3]

Safe omission of radiotherapy following BCS

Given the substantial reduction in local recurrences over the previous 3 decades in mostly high-income countries,[32] the risks of breast radiotherapy may outweigh the benefits for some patients at very low risk of local recurrence. These risks include normal tissue toxicities,[9] cardiac morbidity[33] and second malignancies.[34] In omission of radiotherapy RCTs conducted so far, an increase in local recurrence without radiotherapy has been demonstrated but without any increase in breast cancer death.[35–37] In addition, it has not been possible to identify which patients are at very low risk of recurrence, but an unplanned subgroup analysis from PRIME II suggested that such a group may be identified.[37] The 10-year update of PRIME II has now been reported.[38] At a median follow-up of 9.1 years, the cumulative incidence of local breast cancer recurrence was 9.5% (95% CI 6.8–12.3) in the no-radiotherapy group and 0.9% (0.1–1.7) in the radiotherapy group (HR 10.4; 95% CI 4.1–26.1; p<0.001). There was no statistical difference in overall or breast cancer-specific survival between groups.

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The biomarker-directed PRIMETIME study (using IHC4+C incorporating Ki-67) investigating whether radiotherapy can be safely avoided in women with very low-risk breast cancer has now completed recruitment and we await the results.[39] The British Association of Surgical Oncology (BASO) II trial found avoidance of both radiotherapy and endocrine therapy to be detrimental; therefore; compliance with endocrine therapy should be encouraged, especially if radiotherapy is omitted.[36]

The RCR consensus (2016) is that avoidance of radiotherapy should be considered in patients ≥70 years out of a research study and ≥60 years in study with T1N0 oestrogen receptor positive (ER+), progesterone receptor positive (PR+), human epidermal growth factor receptor negative (HER2-ve) or Grades 1–2 tumours **and** who are willing to take adjuvant endocrine therapy for a minimum of 5 years **and** have regular mammograms for 10 years.[22] NICE guidance is similarly to consider omitting radiotherapy in women who have a very low absolute risk of local recurrence (defined as women aged 65 and over with tumours T1N0, ER-positive, HER2-negative and Grades 1–2) willing to take adjuvant endocrine therapy for a minimum of 5 years.[4] The predicted absolute risks and benefits of radiotherapy should be discussed with individual patients in order to reach a shared decision.

Breast boost

Delivery of a boost to the tumour bed following whole-breast radiotherapy reduces the risk of ipsilateral breast cancer recurrence (Level 1b).[3,40] However, there is no impact on overall survival, and it approximately doubles the risk of moderate or severe fibrosis.

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

Positive resection margins, where further surgery is not possible, are an indication for breast boost regardless of age.

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.[22]

Breast boost may be delivered as a sequential normofractionated or hypofractionated boost, or a 15-fraction simultaneous integrated boost (SIB); for example, 48 Gy to the boost volume and 40 Gy to the rest of the breast all over 3 weeks (as per IMPORT HIGH discussed below).[41]

Regarding dose and fractionation for the sequential boost, 13.35 Gy in 5 fractions of 2.67 Gy or 12 Gy in 4 fractions of 3 Gy assuming an α/β value for breast carcinoma of 3 Gy is similar to a dose of 16 Gy in 8 fractions.[22]

The UK IMPORT HIGH trial of simultaneous integrated boost (SIB) was carried out in women with early high-risk invasive breast carcinoma (pT1–3pN0–pN3aM0) after BCS.[41] Patients were randomised on a 1:1:1 basis between 40 Gy/15 fractions to whole breast (WB) + 16 Gy/8 fractions sequential photon boost to tumour bed (40+16 Gy; control), 36 Gy/15 fractions to WB, 40 Gy to partial breast + 48 Gy (48 Gy) or 53 Gy (53 Gy) in 15 fractions SIB to tumour bed. The primary endpoint was ipsilateral breast tumour relapse (IBTR) and 2,617 women consented to the trial. Smaller, more targeted boost volumes were used for all treatment groups with a median boost clinical target volume (CTV) of 13 cc. After a median follow-up of 74.0 months, the 5-year IBTR incidence was 1.9% (95% CI 1.2–3.1) for 40+16 Gy, 2.0% (1.2–3.2) for 48 Gy, 3.2% (2.2–4.7) for 53 Gy with 76 IBTR events (40+16 Gy: n=20, 48 Gy: n=21, 53 Gy: n=35). The estimated absolute differences versus 40+16 Gy were 0.1% (−0.8–1.7) for 48 Gy, 1.4% (0.03–3.8) for 53 Gy and the upper confidence limit for 48 Gy versus 40+16 Gy indicated non-inferiority for 48 Gy.

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For clinician-reported assessments, 5-year prevalence of moderate/marked breast induration was 6% (36/600) for 40+16 Gy, 5.2% (34/653) for 48 Gy and 8.9% (56/627) for 53 Gy. Comparisons were similar between groups for 5-year cross-sectional, time to event and longitudinal analyses, with similar levels of moderate/marked adverse events for 48 Gy versus 40+16 Gy and increased risk of adverse events for 53 Gy versus 48 Gy. Patient-reported moderate/marked breast hardness/firmness at 5 years was significantly lower for 48 Gy versus 40+16 Gy (RR 0.54, 95% CI 0.38–0.78, p=0.001) and higher after 53 Gy versus 48 Gy (RR 1.61, 95% CI 1.1.0–2.35, p=0.008).

The trial found that the local relapse event incidence is low in this higher-risk breast cancer group treated with small boost volumes and image-guided radiotherapy, whether the boost is delivered sequentially or simultaneously. Rates of 5-year moderate/marked adverse events were low.[41] SIB is a safe treatment with reduced patient visits, and further escalation of boost dose does not appear advantageous.

Radiotherapy technique

Two-dimensional (2-D) computed tomography-based planning is no longer recommended for adjuvant radiotherapy to the breast or chest wall. The ESTRO guidelines for volume-based breast radiotherapy planning are recommended for contouring breast, chest wall, nodal groups and organs at risk.[42]

Simple, forward-planned, field-in-field intensity-modulated radiation therapy (IMRT) reduces late toxicity and improves cosmetic outcome compared with a non-IMRT technique, following adjuvant whole-breast radiotherapy (Level 1b).[3,43]

Breast radiotherapy may slightly increase the lifetime risk of heart disease for some people.[33,44–45] For most women irradiated in the UK, the absolute risk of developing radiation-induced heart disease is less than 1% risk to age 80 years, but the risk varies according to pre-existing risk of heart disease and mean heart radiation dose. Techniques to limit heart dose without reducing target dose coverage should be considered for patients with left-sided breast cancer and those requiring internal mammary nodal irradiation. These include multileaf collimation (MLC) cardiac shielding and voluntary deep inspiration breath hold (DIBH) techniques (Level 2b).[3,45] Wide tangents technique or intensity-modulated arc techniques (IMAT), both using DIBH, are recommended.

Recommendations

For patients requiring a boost:

- 15 fractions SIB, 48 Gy to boost volume and 40 Gy to rest of breast (Grade A)
- 26 Gy in 5 fractions whole-breast radiotherapy plus either a sequential normo-fractionated boost or a hypofractionated boost (delivered in no more than 5 fractions); for example, 13.35 Gy in 5 fractions of 2.67 Gy or 12 Gy in 4 fractions of 3 Gy (Grade C)

The types of evidence and the grading of recommendations used within this review are based on those proposed by the Oxford Centre for Evidence-Based Medicine.[3]

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Regional nodal irradiation

Axilla and supraclavicular fossa

Axillary sentinel lymph node biopsy (SLNB) is the recommended standard procedure for axillary staging in early breast cancer with clinically negative lymph nodes.[46] Most patients with clinically positive nodes will require axillary treatment.

Nodal irradiation is not recommended following a negative SLNB.[4]

Following a positive SLNB, the AMAROS trial demonstrated an axillary recurrence rate of 0.93% for ALND versus 1.82% for axillary radiotherapy after a median follow-up of 10 years.[47] 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 with ALND (Level 2b).[3]

The American College of Surgeons Oncology Group (ACOS-OG) Z0011 trial demonstrated low axillary recurrence rates with no significant differences for SLNB plus standard breast radiotherapy compared with SLNB followed by ALND plus standard breast radiotherapy in an RCT comparing ALND versus no axillary treatment in women with T1/T2 clinically N0 but with 1–2 positive sentinel lymph nodes involved undergoing breast-conserving treatment at 10 years.[48] Most patients were over 50 years of age and had Grade 1 or 2, T1, oestrogen receptor positive, ductal cancer with no lymphovascular invasion (LVI) (Level 2b).[3,48] However, there are significant methodological concerns about the Z0011 trial.[49]

The UK randomised, multicentre, non-inferiority POSNOC trial has completed recruitment in patients with 1–2 positive sentinel lymph nodes, randomised to standard adjuvant therapy and axillary treatment (ALND or axillary radiotherapy) versus standard adjuvant therapy alone.[50] The primary endpoint is axillary recurrence at 5 years. When available, it is anticipated that the results may provide a definitive answer to the question of managing a positive SLNB axilla.

Radiotherapy to the ipsilateral supraclavicular fossa (SCF), now referred to as nodal levels 3 and 4, is recommended for N2 or N3 disease following ALND. Axillary radiotherapy following ALND produces significant toxicity if it specifically targets the operated nodal levels and should only be considered in patients with very high risk of recurrence (high proportion of involved nodes, extensive extranodal disease or biologically aggressive cancer) and high suspicion of residual cancer within the surgically operated nodal region. There is no evidence that radiotherapy to the operated axilla following ALND improves overall survival from breast cancer, but it increases the risk of lymphoedema.

The UK FAST-Forward nodal substudy is testing whether a 1-week schedule of adjuvant radiotherapy to Levels 1–3 axilla ± Level 4 (SCF) is non-inferior to a standard 3-week schedule in terms of patient-reported arm swelling and function in patients with early breast cancer.[51] The 1-week schedules were as per the main FAST-Forward trial, but the 27 Gy treatment schedule was closed early due to an increase in normal tissue effects from the main trial, which were statistically but not necessarily clinically significant. The definitive assessment of normal tissue non-inferiority will be at 5 years; however, preliminary descriptive 3-year data have shown that moderate/marked changes are low overall as assessed by patients and clinicians.[52] It should also be noted that this study did not include internal mammary chain (IMC) irradiation as this had not been widely adopted in the UK at the time of recruitment.

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 IMC, dose 50 Gy in 25 fractions.[53] It demonstrated improved disease-free survival (DFS) in the RNI group (82% versus 77%, HR 0.76, p=0.01) after a median follow-up of 9.5 years.

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The primary endpoint 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).[3,53]

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.[54] After a median follow-up of 10 years, it demonstrated an improvement in DFS in the RNI group (72.1% versus 69.1%, HR 0.89, p=0.04). The primary endpoint of improved overall survival was not met (Level 1b).[3,54]

Both the MA20[53] and EORTC 22922/10925[54] trials demonstrated improved distant DFS, 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 are not known. 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 4 involved nodes (Level 2b).[3,55]

The EBCTCG carried out a regional nodal individual patient data meta-analysis consisting of 14,324 women participating in 16 trials.[56] Trials initiated between 1961 and 1978 were categorised as 'older' trials where participants were treated with historical radiation techniques using direct anterior radiation beams. Of note, radiation within this group did not usually involve radiotherapy to the chest wall in node-positive disease and was only given to the regional nodes in the interventional groups. In contrast, trials started between 1989 and 2008 were categorised as 'newer' trials and patients treated with more advanced radiotherapy techniques. It was found that in the 2,157 patients who participated in the 8 'older' trials, radiotherapy did not reduce breast cancer mortality (RR 1.04, 95% CI 0.91–1·20; p=0.55) but significantly increased non-breast cancer mortality. However, in the 12,167 patients who participated in the 8 'newer' trials, regional node radiotherapy significantly reduced recurrence (RR 0.88, 95% CI 0.81–0.95; p=0.0008). The main effect was on distant recurrence as few regional node recurrences were reported. In addition, radiotherapy significantly reduced breast cancer mortality (RR 0.87, 95% CI 0.80–0.94; p=0.0010) but there was no significant increase in non-breast cancer mortality. It is likely that the differences in findings between the 'older' and 'newer' trials are related to advancements in radiotherapy techniques over the decades, in addition to the inclusion of breast and chest wall radiotherapy, as well as regional nodal radiotherapy in the newer trials. Although rate ratio (proportional benefit) of regional radiotherapy is similar across all subgroups, the absolute benefit varies according to the individual patient's risk of recurrence. For example, for those patients with node-negative disease, 1–3 lymph nodes positive or 4 or more lymph nodes positive, the reduction in 15-year breast cancer mortality was 1–2%, 2–3% and 4–5% respectively.

Regarding data for hypofractionated nodal irradiation, the DBCG Skagen-1 trial is a phase 3 randomised trial of 40 Gy in 15 fractions over 3 weeks versus 50 Gy in 25 fractions over 5 weeks in 2,946 node-positive patients.[57] Tumour bed boosts were delivered as SIB using similar techniques to IMPORT HIGH. RNI included the IMC. The primary endpoint was the risk of ipsilateral arm lymphoedema ≥10% at 3 years after radiotherapy compared with the contralateral arm. The results presented in abstract form demonstrated low event rates and no differences between the patients receiving 40 Gy and 50 Gy. There was also no difference in locoregional recurrence, distant recurrence or overall mortality.[57] The Skagen-1 trial was the first RCT to report 40 Gy/15 fractions versus 50 Gy/25 fractions for RNI including IMC irradiation, and no increase in toxicity with 40 Gy in 15 fractions was observed.

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In addition, the HypoG-01 trial reported results in abstract form.[58] The HypoG-01 trial is a phase 3 randomised trial of 40 Gy in 15 fractions over 3 weeks versus 50 Gy in 25 fractions over 5 weeks in 1,265 patients. All patients received nodal and chest wall or breast radiotherapy. The primary endpoint was time to occurrence of arm lymphoedema after radiotherapy defined as ≥10% increase in arm circumference compared with the contralateral arm. At 3 years, ipsilateral arm lymphoedema rates were similar in both groups and it was found that 40 Gy/15 fractions is non-inferior to 50 Gy/25 fractions in terms of lymphoedema risk. Both HypoG-01 and DBCG Skagen-1 provide evidence supporting the use of 40 Gy in 15 fractions over 3 weeks with regard to lymphoedema risk.

Recommendation

For regional nodal irradiation:

- 40 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.[3]

Palliative treatment

There is limited trial evidence 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]

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04 Central nervous system (CNS) tumours

Treatment of brain and spinal cord tumours presents specific challenges as radiation toxicity can have deleterious effects on a patient's function and cognition. The choice of dose, fractionation and technique needs to take into account the risk of neurological sequelae as well as tumour control.[1] The acute and late toxicities relate to the maximum or mean doses to structures such as optic chiasm, optic nerves, brainstem, cochlea, eyes, and the volume and location of brain parenchyma irradiated. Studies have shown that one of the principal factors determining late cognitive impairment is fraction size,[2] so for patients with longer life expectancy (over 12–18 months), fraction sizes of 1.8–2.0 Gy are usually recommended. In order to minimise dose to adjacent organs at risk, patients are standardly treated using advanced radiotherapy techniques.

Intracranial glioma

In 2021, WHO published a new classification of brain tumours that incorporates molecular and genetic features.[3] One of the main changes is to separate glial series tumours into IDH wildtype and IDH mutated. While many tumours can be classified as wildtype on immunohistochemistry, for younger patients or if there are any unusual features, sequencing is required as some mutations are otherwise missed.

IDH wildtype glioma

The majority of these are Grade 4 lesions and termed glioblastoma, IDH wildtype (GBM IDH WT).

If a tumour has the morphology of a Grade 2 or 3 glioma but is IDH wildtype on sequencing then additional analysis is required. If there is evidence of one or more of telomerase reverse transcriptase (TERT) promotor mutation, epidermal growth factor receptor (EGFR) gene amplification or gain of entire chromosome 7 and low entire chromosome 10 (7+/10–) then the tumour is managed as a GBM IDH WT. If these features are not present, particularly in a younger person, then this may be a rare lower-grade glioma subtype and needs to be managed accordingly.

GBM IDH WT is further subclassified into those with O6-methylguanine-DNA methyl-transferase (MGMT) promotor methylation and those without. MGMT methylation is both predictive of likelihood of response to temozolomide chemotherapy, but also prognostic, independent of use of temozolomide. However, it is important to note which testing technique has been utilised (pyrosequencing or PCR are recommended), and that the underlying biological mechanisms are complex, so recommendation based on MGMT methylation alone on the use or not of temozolomide is not clear cut.[4]

Factors that also need to be considered when assessing the optimum dose and fractionation for patients with GBM IDH WT include performance status, age, cognitive impairments, volume of residual disease (and surrogate of steroid dose), location of tumour, and co-morbidities.[5]

Several trials have been conducted examining dose escalation and none have identified an improvement in overall survival with doses more than 60 Gy using 2 Gy per fraction.

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Several studies have compared this schedule with hypofractionated schedules; a Canadian trial looked at 40 Gy in 15 fractions in older patients or less fit younger patients and showed equivalence.[6] A Swedish study looked at a shorter schedule of 34 Gy in 10 fractions compared with 60 Gy in 30 fractions, and those patients over the age of 70 years had a detrimental survival with the prolonged course.[7] Consequently, shorter-course schedules are recommended for those over the age of 70 years. Some trials have used 65 years of age as the cut-off for 'elderly', whereas others have used 70 years of age. Consequently, the optimal management of people between 65 and 70 years of age needs to be assessed on a case-by-case basis.

Concurrent and adjuvant temozolomide has been shown to improve overall survival in patients with methylated GBM IDH WT when added to 60 Gy in 30 fractions,[8] and for older patients with 40 Gy in 15 fractions.[9] The addition of temozolomide may be considered in patients with unmethylated tumours, but the survival gain is more marginal.

For less fit patients, short-course treatments such as the Swedish 34 Gy in 10 fractions[7] or the UK schedule of 30 Gy in 6 fractions on alternative days over 2 weeks[10,11] may be considered, but in this group the survival gain may be minimal.

Recommendations

Glioblastoma, IDH wildtype:

Good performance status (KPS 80–100) and aged <70 with minimal residual tumour:

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

Moderate performance status (KPS 60–70), or aged over 70:

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

Poor performance (KPS 50–60) may be considered for shorter-course treatments such as:

• 34 Gy in 10 fractions (Grade B) or 30 Gy in 6 fractions 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.[12]

IDH mutated glioma

The IDH mutated tumours are further subdivided into those with 1p19q codeletion (previously called oligodendroglioma) or without 1p19q codeletion (astrocytoma).

Non-codeleted IDH mutated glioma

These tumours are Grade 2, 3 or 4 depending on morphology.

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Grade 2

Grade 2 non-codeleted IDH mutated gliomas (diffuse astrocytoma) have a good survival. Previous studies (conducted prior to recognition of IDH) comparing immediate with deferred radiotherapy showed that, for many patients, initial active surveillance is a reasonable option.[13] However, certain features (age >40 years, tumour >4 cm, crossing midline and neurological deficit) are associated with a poorer prognosis, so those patients may be considered for earlier treatment.[14]

The European Organisation for Research and Treatment of Cancer (EORTC) looked at initial radiotherapy (using 50.4 Gy in 28 fractions) compared with chemotherapy (temozolomide) and showed superior progression-free survival for patients with non-codeleted tumours managed with radiotherapy.[15]

There have been two studies examining dose escalation in patients with Grade 2 glioma (EORTC 45 Gy in 25 fractions[16] versus 60 Gy 30 in fractions, and Radiation Therapy Oncology Group (RTOG) 50.4 Gy in 28 fractions versus 64.8 Gy in 36 fractions).[17] Both studies failed to demonstrate an improvement in survival, and the toxicity was increased in the dose escalation arms. Consequently, the lower doses are recommended, though recent trials have used 50.4 Gy in 28 fractions.[15,18]

If there are some concerning features on the pathology (eg higher proliferation) or imaging (increased perfusion) dose escalation (eg to 54 Gy in 30 fractions[19] or using an integrated boost) may be considered.

Analysis of the long-term results of a trial of patients with Grade 2 glioma either >40 years or with >2 cc residual disease comparing radiotherapy alone (54 Gy in 30 fractions) with or without adjuvant PCV (procarbazine, CCNU and vincristine) demonstrated marked increase in overall survival with the addition of adjuvant PCV (for IDH mutated tumours with or without 1p19q).[19] Consequently, there is a trend for patients who meet these criteria to consider radiotherapy and adjuvant chemotherapy earlier.

Whether or not PCV is the optimal chemotherapy for non-codeleted tumours remains debated as there has not been a trial of adjuvant temozolomide in this group.

Grade 3

The management of Grade 3 IDH mutated non-codeleted gliomas (anaplastic astrocytoma) has been assessed in the CATNON trial. This study gave 59.4 Gy in 33 fractions and then assessed use of concurrent and/or adjuvant temozolomide. Though the final analysis is awaited, initial analysis of the data demonstrates significant improvement in overall survival with the use of adjuvant temozolomide, but to date there is no survival gain from the use of concurrent temozolomide.[20]

For some patients, particularly if there are logistical issues or the radiotherapy volume is small, 60 Gy in 30 fractions may be considered.[21]

Grade 4

Grade 4 IDH mutated gliomas were previously classified as glioblastoma but were given a new classification in WHO 21 in recognition that they have a better prognosis (median survival around 36 months compared with 14 months for GBM IDH wildtype).[22,23]

The optimal management of this new subgroup has not been tested in clinical trials, but as they were included in prior glioblastoma trials they are managed according to these protocols.

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Most Grade 4 IDH mutated gliomas have MGMT methylation and, as they occur mainly in younger age groups, the majority are treated with 60 Gy in 30 fractions with concurrent and adjuvant temozolomide.[8] If the patient is older, has poor performance status or very large tumour volume then the schedules used for IDH wildtype tumours may be considered.

Recommendations

IDH mutated non-codeleted:

Grade 2:

- 50.4 Gy in 28 fractions (or 45 Gy in 25 fractions or 54 Gy in 30 fractions) with adjuvant PCV (Grade A) or adjuvant temozolomide (Grade D)

Grade 3:

- 59.4 Gy in 33 daily fractions over 6.5 weeks with adjuvant temozolomide (Grade A)

Grade 4:

- 60 Gy in 30 daily fractions over 6 weeks with or without concurrent and adjuvant temozolomide (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.[12]

Codeleted IDH mutated glioma

Though these are graded into Grade 2 (oligodendroglioma) and Grade 3 (anaplastic oligodendroglioma), this distinction appears to have minimal impact on overall survival, with a median survival of 13 to 15 years), so it is important to consider late effects when managing these patients.[24]

Grade 2

These patients were included in the RTOG 9802 Grade 2 trial mentioned above, which used 54 Gy in 30 fractions with and without adjuvant PCV.[19] This group of IDH mutated and codeleted gliomas had the greatest gain from the addition of PCV.[25]

However, many of these tumours are slow growing and occur in younger patients, so for many with minimal residual postoperative tumour, active surveillance is often the initial management approach, with radiotherapy and PCV utilised when there is evidence of radiological or symptomatic (eg increasing seizure frequency) progression.[5]

Grade 3

Two trials examined radiotherapy giving 59.4 Gy in 33 fractions with or without adjuvant/neoadjuvant PCV,[26,27] and both demonstrated an improvement in overall survival with the addition of chemotherapy.

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For most patients with Grade 3 codeleted gliomas, immediate postoperative radiotherapy and chemotherapy is recommended, though for some with minimal residual disease and only foci of anaplasia, active surveillance may be an appropriate management strategy.

As with non-codeleted Grade 3 gliomas, if there are logistical issues or the radiotherapy volume is small then 60 Gy in 30 fractions may be considered.

Recommendations

IDH mutated codeleted:

Grade 2:

- 50.4 Gy in 28 fractions (or 45 Gy in 25 fractions or 54 Gy in 30 fractions) with adjuvant PCV (Grade A)

Grade 3:

- 59.4 Gy in 33 daily fractions over 6.5 weeks with adjuvant PCV (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.[12]

Protons

Protons are not routinely recommended for patients with Grade 3 or 4 gliomas, or for people over the age of 25 with a Grade 2 glioma. However, they may be considered in those under the age of 25 with an IDH-mutant, 1p19q codeleted Grade 2 glioma to try to minimise the volume of normal tissue receiving medium or low doses.[28]

Studies comparing the impact on quality of life and cognition between photons and protons in good-prognosis patients are due to start recruitment soon.

Reirradiation

There is increased interest in the use of reirradiation, particularly in patients who have relapsed after a reasonable interval of local control (usually >12 months). Schedules utilised vary depending on tumour biology, interval from initial presentation and tumour volume.[29]

There is one randomised phase II trial in glioblastoma (RTOG 1205[30]), which randomised patients to bevacizumab with or without reirradiation giving 35 Gy in 10 fractions. Although there was no improvement in overall survival, the proportion of patients with progression-free survival at 6 months was significantly higher in the reirradiation arm. In the UK a schedule of 35 Gy in 10 fractions is being increasingly used, particularly for glioblastoma. A UK trial is under way comparing reirradiation with palliative chemotherapy (BRIOCHE), which will hopefully provide more evidence on the impact of reirradiation on survival.

For patients with a lower-grade glioma without possible transformation, schedules using 1.8 Gy per fraction should be considered (eg 45–50.4 Gy in 25 to 28 fractions).

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Spinal cord glioma

Gliomas of the spinal cord are rare lesions with a wide range of clinical behaviour.[31,32] Though pathological confirmation is recommended in most cases, due to the risks of increasing neurological deficits, some are treated empirically with radiotherapy. The dose of radiotherapy must balance maximising odds of tumour control with risk of spinal cord injury.

Recommendation

- 54 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.[12]

Meningioma

Meningiomas are graded 1, 2 (atypical) and 3 (anaplastic). Grading historically has been based on morphological features, but it has been long recognised that there are lesions where the behaviour was not accurately reflected by this approach alone. Consequently, the new WHO 2021 grading incorporates some molecular markers. For example, lesions with TERT promotor mutation and/or CDKN2A/B homozygous deletion are now classified as Grade 3 due to their much higher rate of local recurrence.

Many meningiomas are picked up as incidental findings on magnetic resonance imaging (MRI) for another symptom and often require surveillance alone. For lesions that are causing symptoms and/or are enlarging, surgery remains the mainstay of treatment, but for some locations, particularly around the base of the skull, surgery can have a high risk of complications. Therefore, following multidisciplinary discussion,[33] radiotherapy is sometimes recommended without pathological confirmation.

Grade 1 or no pathological conformation

Radiotherapy may be used as radical treatment if inoperable or postoperatively after incomplete resection or on recurrence.[34,35] There are three types of radiotherapy utilised for meningiomas: conventionally fractionated (1.8–2.0 Gy per day) using VMAT or fractionated stereotactic radiotherapy (fSRT), single-fraction stereotactic radiosurgery (SRS) or hypofractionated SRS (fraction size >5 Gy). The choice of modality depends on lesion location and volume.

Lesions in close proximity to critical structures, particularly the optic nerves and chiasm, are more commonly treated with conventionally fractionated radiotherapy due to the dose limitations when giving single fractions (eg chiasm tolerance is <10 Gy in 1 fraction or <25 Gy in 5 fractions).[36,37] Respective case series suggest that single-fraction SRS is less effective in larger tumours than 7.5–10 cc.[38–40] The risk of toxicity (particularly oedema) increases with volume of lesion so conventional fractionation is usually used for lesions >3 cm.[41]

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Conventionally fractionated radiotherapy

Randomised clinical trial evidence is lacking, but generally excellent rates of local control (80–100%) are reported with radiotherapy doses of 50–54 Gy in 25–30 fractions.[33] A combined photon/proton trial showed no benefit from escalating the dose to 63 Gy relative biological effectiveness (RBE).[42]

Radiosurgery

Small-volume (<7.5–10 cc) meningiomas away from critical structures (eg >5 mm from optic apparatus such as optic nerves, chiasm and tracts) may also be treated with single-fraction SRS. Doses utilised range from 12 to 16 Gy. One large retrospective series suggests that local control appears to be inferior for doses less than 13.5 Gy[43] and another showed no gain from doses over 15 Gy,[38] so it appears 14–15 Gy is the optimal dose range.

Hypofractionated SRS can also be used for smaller meningiomas (<3 cm max diameter) that are close (<5 mm) to critical structures such as the brainstem. There are a wide range of schedules and prescription isodoses used in the retrospective series. However, the most commonly used schedule is 25 Gy in 5 daily fractions.[44–46]

Grade 2 (atypical)

Patients with Grade 2 meningiomas are at higher risk of relapse, even after complete (Simpson I–III) resection, but the use of adjuvant radiotherapy must be balanced against potential long-term side-effects such as neuro-cognitive toxicity.[47]

Practice has varied internationally; the ROAM trial (EORTC 1308) has been conducted in which patients with completely resected Grade 2 meningiomas were randomised between 60 Gy in 30 fractions and surveillance alone.[48] Recruitment is complete, but the results have not yet been reported.

RTOG 0539 was a non-randomised phase II study delivering 54 Gy in 30 fractions for patients with Grade 2 meningioma with gross total resection (Simpson I–III),[49] and 54 Gy with integrated boost to 60 Gy if there was a subtotal resection (Simpson IV–V).[50] The 3-year progression-free survival was 93.8% and 57.1%, respectively.

The EORTC conducted a non-randomised phase II trial (22042) delivering 60 Gy in 30 fractions in those with Simpson I–III, with a 10 Gy boost if Simpson IV–V. The vast majority (82%) had gross total resection, and 3-year progression-free survival was 88.7%, which exceeded the predicted 70%.[51]

The use of radiosurgery for Grade 2 meningioma remains controversial due to the margins required (most standard radiotherapy trials use 1 cm margin from gross tumour volume [GTV] to clinical target volume [CTV]) to reduce local recurrence. The dose margins and fraction have not yet been established.[47]

Grade 3 (anaplastic)

Anaplastic meningiomas are rare (<3% of meningiomas, though this will increase with new molecular classification) so data on optimal management are limited. They were included in the RTOG 0539 high-risk arm and EORTC 22042, but the numbers in each study are small: 17 and 9, respectively.[50,51]

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Retrospective studies show that, though reduced after adjuvant radiotherapy, the risk of recurrence both locally and in other areas of the meninges remains high, and though dose escalation has been considered, whether this approach is beneficial is yet to be established.[47]

Recommendations

Grade 1:

- VMAT 50–54 Gy in 25–30 fractions over 5–6 weeks (Grade C)
- SRS 13–15 Gy in a single fraction (Grade C)
- SRS 25 Gy in 5 fractions (Grade D)

Grade 2:

- VMAT 54–60 Gy in 30 fractions over 6 weeks (Grade B)

Grade 3:

- VMAT 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.[12]

Pituitary adenoma

Pituitary lesions account for 15% of intracranial tumours and the majority are benign adenomas, but around a third invade local structures.[52]

They are categorised into functioning (hormone-secreting – ACTH, growth hormone, prolactin, TSH or gonadotrophins) or non-functioning lesions.

They may require treatment due to their hormone secretion or due to pressure on surrounding structures such as the optic chiasm.

The primary treatment is usually surgery (or dopamine agonists for prolactinomas) with radiotherapy reserved for:

- Recurrent or progressive non-secreting tumours following surgical excision, residual disease close to optic apparatus with the concern of threat to vision
- Lesions with adverse pathological features such as Ki 67 >3%[52]
- Secretory tumours with persistent hormone elevation despite maximal hormone blockade
- Patients not medically fit for surgery.

Prevention of further enlargement following radiotherapy is achieved in over 90%[53,54] at 10 years with the majority of patients treated using 45 Gy in 25 fractions.[55,56] However, if there are adverse features, such as large size or marked local invasion then dose escalation to 50.4–54 Gy using 1.8 Gy per fraction may be considered.[52,56] Advanced planning and set-up techniques should be utilised to minimise doses to adjacent organs at risk, particularly the chiasm.

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The rate of biochemical cure for functioning lesions is, however, much lower, with most conventionally fractionated series quoting 35–50%. To try to increase biochemical cure, there has been interest in utilising SRS for lesions >3 mm from optic apparatus and <3 cm in size. However, there are no randomised studies, just single-centre series with minimal data on lesion size and varying length of follow-up.[57]

The NHS England commissioning guidelines also state that hypofractionated SRT (2–5 fractions) can be considered in patients with non-functional adenomas where the optic apparatus is involved (eg 25 Gy in 5 fractions). This was restricted to non-functional lesions due to lack of evidence in functional lesions.[58]

The use of proton treatment for pituitary tumours is still under investigation. Currently in the UK, patients <25 years with pituitary adenomas are eligible based on theoretical reduction in late effects in surrounding structures.

Recommendation

• 45–54 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.[12]

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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. For those who have not achieved a complete pathological response following neoadjuvant chemoradiotherapy and surgery, adjuvant nivolumab has been shown to improve progression-free survival.[1]

Due to the differing chemosensitivity and radiosensitivity of squamous cell cancer (SCC) and adenocarcinoma (ACA), treatment paradigms for oesophageal SCC and ACA have taken divergent paths.[2]

Definitive radiation with concomitant chemotherapy

Radiation with concomitant chemotherapy is superior to radiotherapy alone.[3] Cisplatin and fluorouracil (5-FU) became the standard of care in definitive chemoradiotherapy following the publication of the landmark Radiation Therapy Oncology Group (RTOG) 85-01 trial. This trial showed a survival advantage for concomitant chemoradiation (50 Gray [Gy] in 25 fractions) with two concurrent and two adjuvant cycles of cisplatin and 5-FU) compared with radiotherapy alone (64 Gy in 32 fractions), with 5-year survival rates of 27% versus 0%.[3]

Outcomes have improved in modern trials using more conformal radiotherapy techniques with improved patient selection and radiotherapy quality assurance; in the UK SCOPE1 study, radiotherapy combined with cisplatin and capecitabine reported 2-year survival rates of 56% with a median overall survival of 34.5 months in long-term follow-up.[4]

Cisplatin is associated with significant toxicity. Weekly carboplatin and paclitaxel combined with radiotherapy is increasingly being used in the definitive setting due to its favourable toxicity profile. Several phase II studies have shown that carboplatin and paclitaxel given concurrently with definitive radiotherapy in oesophageal cancer is both tolerable and active.[5,6] Retrospective UK data also suggest that overall survival is comparable with those undergoing cisplatin and 5-FU chemotherapy.[7]

A systematic review of neoadjuvant concomitant chemoradiation confirmed a radiotherapy dose response relationship with pathological complete response.[8] Although an increasing body of evidence is suggestive of the safety and feasibility of doses ≥60 Gy,[9,10] currently there are no randomised control trials to support the use of radiotherapy doses >50.4 Gy in the definitive treatment of oesophageal cancer. The 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.[11] 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.[9] Subsequent studies of dose escalation have focused on attempting to reduce toxicity by taking advantage of the progress in radiotherapy techniques and escalating dose to smaller volumes but have again failed to show an improvement in local control or survival.[12,13]

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Chemoradiotherapy is recommended for tumours of the upper third oesophagus where extensive surgery would also involve a laryngectomy. Unlike SCC of the head and neck region, there is limited evidence for dose escalation beyond 50 Gy for upper third oesophageal SCC. A single-institution retrospective study of 23 patients with SCC of the upper third oesophagus treated with 60–66 Gy in 30 fractions using IMRT demonstrated dose escalation was well tolerated with good local control rates.[14] In addition a single-institution phase II prospective study in India of post-cricoid and upper oesophageal SCC treated with IMRT to a dose of either 66 Gy in 30 fractions or 63 Gy in 35 fractions showed 2-year locoregional control rates and cause-specific survival of 59.6% and 44.8% respectively.[15] However, prospective evidence to support this approach is lacking and future research is required.

Recommendations

Definitive 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) 60–66 Gy in 30 fractions over 6 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.[16]

Definitive radiotherapy alone

Single-modality radiotherapy is an option for patients not suitable for concurrent chemotherapy. Hypofractionation has been shown to be safe and tolerable with outcomes superior to those seen with conventionally fractionated radiotherapy. In a series of 101 patients in whom the majority of tumours were <5 cm in length, radiotherapy alone to a dose of 45–52.5 Gy in 15–16 fractions achieved a 5-year survival of 21%.[17] More recently a retrospective UK single-centre analysis of 61 consecutive patients managed with hypofractionated radiotherapy with radical intent (50 Gy in 16 fractions or 50–52.5 Gy in 20 fractions) revealed 3-year survival of 56.9% and median overall survival of 29 months.[18]

Recommendations

Radiotherapy alone:

- 45–52.5 Gy in 15–16 fractions over 3 weeks (Grade C)
- 50–55 Gy in 20 fractions over 4 weeks (Grade C)
- 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.[16]

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Preoperative (neoadjuvant) radiation with concomitant chemotherapy

Despite adequate preoperative staging, 25–30% of patients treated with primary surgery have microscopically positive resection margins (R1) and the 5-year survival rate rarely exceeds 40%. Multimodal therapy including perioperative chemotherapy and neoadjuvant chemoradiotherapy aim to improve outcomes by downstaging the tumour and eradicating micrometastatic disease.

The landmark trial of neoadjuvant chemoradiotherapy is the Dutch CROSS trial. Radiotherapy with concomitant carboplatin and paclitaxel and 41.4 Gy in 23 fractions versus surgery alone demonstrated an increase in median survival from 24 to 49 months and no increase in perioperative mortality.[19] Complete pathologic response rates of 23% in patients with ACA and 49% in patients with SCC were observed in the chemoradiation arm. NEOSCOPE, a multicentre study of preoperative chemoradiotherapy, showed that neoadjuvant carboplatin and paclitaxel with radiotherapy to a dose of 45 Gy could be safely delivered to patients with locally advanced resectable oesophageal adenocarcinoma with acceptable toxicity and low incidence of postoperative mortality.[20] Walsh *et al* investigated a dose of 40 Gy in 15 fractions following 2 cycles of neoadjuvant chemotherapy, demonstrating improved median survival of 17 months versus 12 months with surgery alone.[21] However, due to limited evidence supporting this dose fractionation, this approach should currently be considered only as part of a clinical trial.

Following the results of the Checkmate 577 trial, adjuvant nivolumab for 12 months is recommended for patients with completely resected oesophageal or gastro-oesophageal junction cancer who have residual disease after previous neoadjuvant chemoradiotherapy.[1]

Based on the results of two large randomised controlled studies, perioperative chemotherapy represents another standard of care for resectable adenocarcinoma.[22,23] The use of epirubicin, cisplatin and fluorouracil (ECF) chemotherapy has now largely been superseded by fluorouracil, leucovorin, oxaliplatin, docetaxel (FLOT) due to the expectation of higher efficacy.

Recommendations

Neoadjuvant radiation with concomitant chemotherapy:

Squamous cell carcinoma:

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

Adenocarcinoma:

- 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.[16]

Postoperative radiotherapy

There is limited and heterogeneous evidence exploring postoperative radiotherapy, which has hindered attempts at meta-analyses. It may have a role in patients who have positive margins and prognosis estimated to be mainly influenced by local relapse.[24,25] Based on available data,

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if radiotherapy is given, concomitant chemoradiotherapy is preferred to radiotherapy alone with conventionally fractionated doses of 40–50 Gy.[26]

Recommendations

Postoperative radiation with concomitant chemotherapy:

- At the current time no clear recommendations around the indications for radiotherapy can be made because of lack of available evidence
- Consider in patients who have positive margins and prognosis estimated to be mainly influenced by local relapse (Grade D)
- If radiotherapy is given, concomitant chemotherapy is preferred to radiotherapy alone with conventionally fractionated doses of 40–50 Gy (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.[16]

Palliative treatment

Advanced disease can cause local symptoms such as dysphagia, bleeding and pain, but there is a lack of robust controlled trial evidence for the role of palliative radiotherapy in oesophageal cancer and the optimal schedule for symptom control is unknown.

Brachytherapy

There is evidence that intraluminal brachytherapy with palliative intent is a valid alternative to stenting in patients with dysphagia and longer life expectancy.[27–29] An updated Cochrane review on interventions for dysphagia in oesophageal cancer has concluded that, when compared with self-expanding metal stents, brachytherapy provided an improvement in long-term relief from dysphagia and possibly a better quality of life.[30]

Recommendations

Palliative brachytherapy:

- 12 Gy in 1 fraction (Grade B)
- 12–16 Gy in 2 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.[16]

External beam radiotherapy

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 10 fractions.[31]

The UK ROCS study has shown that palliative radiotherapy in addition to oesophageal stenting does not improve outcomes over stent insertion alone and should not be routinely offered.[32]

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Extrapolating evidence from gastric cancer, short-course radiotherapy is an effective treatment that can palliate bleeding from oesophageal and junctional tumours.[33–35]

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 C)
- 40 Gy in 15 fractions over 3 weeks (Grade D)
- 8 Gy in 1 fraction (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.[16]

Gastric cancer

Perioperative therapy

Surgery (to achieve R0 resection with appropriate lymphadenectomy) remains the only radical treatment for gastric cancer, with combined modality treatment indicated for all but very early, stage IA disease. Potentially operable >stage IB disease should be managed with perioperative chemotherapy[22,23] (Grade A).

The role of neoadjuvant chemoradiotherapy is being investigated by the TOPGEAR[36] and CRITICS II[37] studies, but there is currently no phase III evidence to support this approach.

Adjuvant radiotherapy with concomitant chemotherapy

In 2001, the US Intergroup 0116 trial[38] reported a survival benefit with postoperative chemoradiotherapy compared with surgery alone. However, as only 10% of the trial population had undergone the recommended D2 lymphadenectomy, and patients did not undergo any perioperative chemotherapy, the true benefit of postoperative chemoradiotherapy in the context of optimal surgical technique and perioperative treatment remain unclear.

Subsequent trials (ARTIST I,[39] CRITICS,[40] ARTIST II[41]) have failed to further define the optimal role of adjuvant radiotherapy. As such, adjuvant chemoradiotherapy is reserved only for selected high-risk patients who have not undergone preoperative chemotherapy or have not achieved an R0 resection, following multidisciplinary team discussion (Grade B).

Recommendation

Adjuvant radiotherapy with concomitant chemotherapy:

- 45 Gy in 25 fractions over 5 weeks with concomitant 5-FU or capecitabine (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.[16]

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Palliative radiotherapy

Palliative radiotherapy can be an effective treatment for haemostasis of bleeding gastric tumours.[33] Though there is no clear evidence to suggest any dose/fractionation is superior in terms of symptom palliation, single-fraction treatments may be preferred due to reduced toxicity, shorter treatment time and potential for future retreatment if required.[34,35]

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.[16]

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Cervix cancer

Background

Patients presenting with small-volume International Federation of Gynecology and Obstetrics (FIGO) Stages 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; 120 g/l) throughout treatment (Level 2b).[2,20]

Parametrial disease can be encompassed within the brachytherapy dose envelope using a combination of interstitial brachytherapy (ISBT) and ICBT (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 >85 Gy (combined external beam and brachytherapy equivalent dose in 2 Gy per fraction [EQD2]).[23,24] Dose constraints to OAR 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 (EBRT).

There is no evidence to support the routine use of adjuvant chemotherapy following primary chemoradiotherapy. The OUTBACK trial (cisplatin and radiation therapy with or without carboplatin and paclitaxel in patients with locally advanced cervical cancer)[26] failed to demonstrate an improvement in either overall survival or progression-free survival in keeping with earlier studies. In contrast, however, the INTERLACE study recently presented in abstract form suggests there may be an advantage for selected patients, which may change this view once the full results are published.[27]

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Treatment technique

The clinical target volume (CTV) for treating pelvic malignancy normally encompasses the lymphatic drainage of the cervix pelvis including the internal, external and common iliac nodes and presacral nodes. This 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 intensity-modulated radiation therapy (IMRT) or volumetric-modulated arc therapy (VMAT) rather than 3D-CRT (Level 2b).[2,31]

Recommendations

Definitive primary treatment

External beam radiotherapy:

- 45 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:

- 55–60 Gy in 25–28 fractions over 5.5 weeks using a simultaneous integrated boost (Grade C)

Brachytherapy[32]

The high total doses required of 85–90 Gy to the high-risk CTV (HR-CTV) D90 are achieved by adding to the external beam schedules above:

- High-dose rate (HDR) brachytherapy 28 Gy in 4 fractions (Grade B)
- For small-volume tumours (<30 ml) a 3-fraction schedule may be considered (7.7 Gy × 3)

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

Postoperative external beam:

- 45 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)

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]

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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.[33–36] 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 EBRT.[35] The long-term pelvic side-effects in the brachytherapy group were less than with external beam.

The PORTEC 3 trial has investigated the benefit of concurrent chemoradiotherapy and adjuvant chemotherapy compared with adjuvant radiotherapy alone, which has been the current standard of care. This shows an advantage for the combined approach in Stage III and serous histology after hysterectomy.[36]

A more sophisticated approach using molecular classification of the tumour has been proposed and is under evaluation in clinical trials but as yet the evidence is not sufficiently robust to be considered a standard of care.

Recommendations

High-risk patients

Postoperative adjuvant EBRT:

- 46 Gy in 23 fractions over 4.5 weeks (Grade A)
- 45 Gy in 25 fractions over 5 weeks (Grade A)
- 48.6 Gy in 27 fractions over 5.5 weeks (Grade A)
- Stage III patients should receive chemoradiation with cisplatin followed by adjuvant carboplatin and paclitaxel (Grade A)

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

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

Intermediate-risk patients

Vaginal vault brachytherapy:

- HDR: 21 Gy at 5 mm in 3 fractions over 2–3 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.[2]

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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 Stages 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 positive resection margins, two or more positive lymph nodes or any extracapsular spread. Concurrent chemotherapy with

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cisplatin is used, but without a strong evidence base to support it (Grade C). The Gronigen International Study on Sentinel Nodes in Vulvar Cancer (GROINSS-II) compared surgery with either definitive radical radiotherapy or radical chemoradiotherapy where sentinel lymph node metastases <2 mm were detected.[42] Inguinofemoral radiotherapy to a dose of 50 Gy is a safe alternative to inguinofemoral lymphadenectomy for micrometastases <2 mm but inguinofemoral lymphadenectomy is recommended for macrometastases (Grade C).

Recommendations

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 chemoradiotherapy, treating the primary and regional nodes. Consideration should then be given to surgical removal of residual disease or a second phase of radiotherapy with electrons or brachytherapy.[43]

Recommendations

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)
- EBRT may be given with weekly cisplatin 40 mg/m^2 (Grade C)
- The primary and involved nodes should be boosted using a simultaneous integrated boost (SIB) with VMAT or brachytherapy to deliver a total dose of 60–68 Gy EQD2[44] (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 70–80 Gy EQD2 appearing to confer survival advantage (Level 4).[45] The addition of concurrent chemotherapy appears to deliver a survival advantage (Level 4).[46,47]

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Recommendations

Definitive therapy of vaginal carcinoma:

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

Followed by HDR brachytherapy: note the lower vagina is less tolerant of very high doses. A total EQD2 dose of 70–80 Gy should be the aim:

• Upper vagina: 24–28 Gy in 4 fractions (Grade C)
• Lower vagina: 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]

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Background

Intensity-modulated radiotherapy (IMRT) is the accepted standard radiotherapy for patients undergoing primary and adjuvant radiotherapy for head and neck squamous cell carcinomas (HNSCC); exceptions are T1/T2N0 glottic cancer. The international standard for definitive treatment remains 70 Gy in 35 daily fractions of 2 Gy over 7 weeks, although altered fractionation regimens have been widely used. In the UK, many centres have adopted 65–66 Gy in 30 fractions over 6 weeks as a standard regimen. A simultaneous integrated boost technique with IMRT is routinely used to treat all target volumes and elective lymph node regions to varying dose levels in each fraction.

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

An updated meta-analysis[1] compared conventional with altered fractionation across 34 trials including 11,969 patients in both radical and adjuvant settings. Altered fractionation was associated with a 3.1% survival benefit at 5 years, with the benefit being restricted to hyperfractionation (8.1% survival benefit at 5 years) (Level 1a). Moderately accelerated radiotherapy was only associated with a reduction in local failures, while hyperfractionated radiotherapy was associated with improved local and regional control. There was a reduced impact with increasing age. Altered fractionation schedules had higher rates of acute toxicity with no difference in late toxicity. Hyperfractionation is difficult to implement and not widely used. Based upon the absence of benefit for regional control, it was suggested that pure acceleration is only considered for patients with low nodal burden.[1] Most of the data pre-dates the human papilloma virus (HPV) era and the applicability of altered fractionation to HPV-related oropharyngeal disease is uncertain. A second comparison was performed between altered fractionation and the use of conventionally fractionated concurrent chemoradiotherapy in five trials with 986 patients; overall survival was inferior with altered fractionation (−5.8% survival difference at 5 years) (Level 1b). Several randomised trials have failed to show any benefit of combining moderate acceleration with concurrent chemotherapy.[2–5]

T1/2N0 glottic carcinoma

There is a dose response relationship in the treatment of early glottic cancer.[6] A meta-analysis of 1,762 patients with early-stage glottic carcinoma reported that altered fractionation was associated with a lower rate of local failure in a pooled analysis of randomised trials (hazard ratio 0.62) and retrospective studies (hazard ratio 0.40).[7] Both hypofractionation (HR 0.55; 95% CI 0.33–0.91) and hyperfractionation (HR 0.65; 95% CI 0.43–0.97) were superior to conventional fractionation (Level 1a). The benefit of altered fractionation is likely to at least in part be related to reduced overall treatment time, consistent with prior analyses.[8] The benefit was pronounced for T1 glottic disease and included anterior commissure involvement.[7] Several UK series have reported high rates of local control with short hypofractionated

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schedules including 50–52.5 Gy in 16 fractions over 3 weeks for T1 disease and 55 Gy in 20 fractions for T1 and T2 disease.[9–11] Patients with T2 glottic cancers are underrepresented and the impact of altered fractionation for this group remains an open question.[7] Treatment approaches in line with those for advanced disease may be appropriate for higher-risk T2 glottic disease (eg bulky, transglottic).

Recommendations

For irradiation of primary site only (when elective lymph node irradiation is not required):

- 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.[12]

Radiotherapy alone for oropharynx/hypopharynx/larynx cancer (excluding T1/2 glottic carcinoma)

Single-modality treatment with surgery or radiotherapy is the standard of care for early-stage disease. For locoregionally advanced disease, the use of concurrent chemotherapy may not be appropriate for some patients due to co-morbidity or limited performance status.

Conventional fractionation remains standard. A retrospective multicentre comparison of patients treated with radiotherapy alone with schedules of 70 Gy in 35 fractions or 65–66 Gy in 30 fractions showed no difference in disease outcomes or late toxicity.[13] In the meta-analysis of altered fractionation, there was no interaction between tumour stage and the impact of altered fractionation; based upon the local control benefit modest acceleration can be considered when treating patients with low nodal burden with radiotherapy alone.[1]

Recommendations

- 70 Gy in 35 fractions over 7 weeks (Grade A)
- 65–66 Gy in 30 fractions over 6 weeks (Grade C)
- 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.[12]

Radiotherapy with concomitant chemotherapy for oropharynx/hypopharynx/larynx cancer

Radiotherapy with concurrent chemotherapy is the current standard of care for the definitive management of patients with more advanced disease. The international standard schedule

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is 70 Gy in 35 fractions. The ongoing Torpedo trial[14] in oropharynx cancer patients has adopted a similar dose fractionation of 70 Gy in 33 fractions over 6.5 weeks. 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.[4,15] HPV status in oropharyngeal carcinoma is a strong independent prognostic factor for survival.[16] However, in the anticipation of robust phase III 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).

Recommendations

- 70 Gy in 35 fractions over 7 weeks (Grade B)
- 70 Gy in 33 fractions over 6.5 weeks (for oropharyngeal carcinomas) (Grade C)
- 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.[12]

Elective lymph node irradiation

The dose to elective lymph node regions is based upon historical consensus and is generally delivered as a radiobiological equivalent dose of approximately 50 Gy (EQD2). This is usually achieved as part of a single radiotherapy plan with a reduced fraction size (eg 1.5–1.6 Gy) to elective lymph node volumes compared with conventional fractionation to high-dose target volumes. Data suggest that elective lymph node irradiation may be safely delivered with a reduced fraction size.[17] Although an elective lymph node EQD2 of 50 Gy remains standard there is ongoing interest in dose de-escalation. A randomised trial of 200 patients compared an elective nodal EQD2 dose of 50 Gy versus 40 Gy and reported long-term results showing no difference in elective nodal failure between these doses.[18] In a retrospective cohort of 233 HNSCC patients (90% HPV negative) who received an elective nodal dose of 40 Gy, the 2-year actuarial rate of elective volume recurrence was low (3.9%).[19]

Recommendations

- Standard dose for elective lymph node target volumes is to deliver an EQD2 50 Gy (using α/β=10).

Within a single-phase 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)

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Head and neck squamous cell carcinoma of unknown primary

Dose fractionation to the neck for gross disease, in the adjuvant setting and to elective nodal volumes will parallel that for HNSCC of known primary sites. Rates of primary emergence are low, with a meta-analysis of retrospective series showing lower rates of primary site emergence for patients treated with neck and mucosal radiotherapy versus neck only (12% versus 16%).[20] These data are largely from an era before positron emission tomography (PET) so relevance to modern practice with the increasing use of base of tongue mucosectomies is uncertain. Putative mucosal sites of origin may be treated, with selection of mucosal sites dependent upon the clinical scenario/HPV status.[21] An EQD2 dose of 50 Gy (using α/β=10) is recommended if mucosal irradiation is being utilised, with multiple series reporting very low rates of subsequent emergence of a mucosal primary.[22,23] Treating involved neck only is also a valid strategy, with evidence supporting this approach when patients are thoroughly investigated with modern diagnostic techniques.[24]

Recommendations

Dose and fractionation to neck target volumes are the same as those used for HNSCC of known primary sites. When mucosal irradiation is to be delivered to potential mucosal primary sites, the number of fractions is dependent upon neck management. Appropriate doses to the mucosal target are:

- 54 Gy in 30 fractions over 6 weeks (Grade C)
- 56 Gy in 33 fractions over 6 weeks (Grade C)
- 56–57 Gy in 35 fractions over 7 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.[12]

Postoperative radiotherapy: primary site and neck

Adjuvant doses to both the primary site and dissected neck have been developed on a background of very limited randomised data to guide a dose response relationship.[25] Historical studies showed no clear dose response for radiation doses ≥57.6 Gy (1.7 Gy/fraction), although patients with extranodal extension (ENE) had higher recurrence rates at 57.6 Gy than ≥63 Gy (1.8 Gy/fraction).[26] Postoperative doses of 60–66 Gy in 30–33 fractions were used in the Radiation Therapy Oncology Group (RTOG) and European Organisation for Research and Treatment of Cancer (EORTC) trials investigating the role of concurrent chemotherapy.[27,28] Modern adjuvant studies give a dose of 60 Gy in 30 fractions with an optional boost of 6 Gy in the presence of ENE.[29,30] A recent database analysis of adjuvant radiotherapy for HNSCC in 15,836 patients did not demonstrate a survival benefit from dose escalation beyond EQD2 60 Gy even in the presence of high-risk factors.[28] A meta-analysis of accelerated versus conventionally fractionated radiotherapy in high-risk adjuvant patients did not show a benefit of altered fractionation[31] (Level 1a). De-escalation of dose in the context of HPV-related oropharyngeal disease is currently being investigated.[32]

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There is uncertainty regarding the optimal dose to surgically dissected and pathologically negative neck nodal levels. A dose of 60 Gy in 30 fractions has been commonly used.[33] In ongoing adjuvant studies of HPV-related oropharyngeal disease[32] an EQD2 dose of 50 Gy (using α/β=10) is used.

Recommendations

- 60 Gy in 30 fractions over 6 weeks to surgically treated areas (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)
- 54–60 Gy in 30 fractions to surgically dissected and pathologically node-negative neck nodal levels (Grade C)
- 54–56 Gy in 30–33 fractions over 6 to 6.5 weeks to undissected elective lymph node regions (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.[12]

Sinonasal carcinoma

Sinonasal malignancy is rare and heterogenous with multiple pathological types and patterns of invasion. For most pathological types, the standard of care is surgery followed by consideration of adjuvant (chemo)radiotherapy for resectable disease. Radiotherapy doses used are broadly similar for squamous and non-squamous histological subtypes. In a retrospective analysis, adjuvant doses of ≥60 Gy were associated with improved survival outcomes on univariate analysis.[34] Centres have reported favourable outcomes with a dose of 60 Gy in 30 fractions with a 6 Gy boost if positive surgical margins were present.[35] A UK survey of clinical practice and workshop[36] found consensus for a dose of 60 Gy in 30 fractions following an R0 resection, while for an R1 resection there was a lack of consensus between 60 Gy in 30 fractions and 66 Gy in 33 fractions.

Esthesioneuroblastoma (olfactory neuroblastoma) is a rare malignancy, often treated with a combined modality approach. A wide range of radiotherapy doses have been reported in the literature and it is not possible to define a clear dose response. It has been recommended that similar doses to those used for other sinonasal tumours are appropriate.[37]

Recommendations

- 60 Gy in 30 fractions over 6 weeks (Grade C)
- Increased dose of 66 Gy in 33 fractions over 6.5 weeks can be considered following an R1 resection (Grade C)
- 70 Gy in 35 fractions over 7 weeks for unresectable disease or R2 resection (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.[12]

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Nasopharyngeal carcinoma (NPC)

There is a clear radiotherapy dose response relationship; underdose of the tumour target (≥65 Gy when treating 2 Gy per fraction) is associated with inferior local control and survival.[38] A commonly agreed standard total dose is in the order of 70 Gy in 33–35 fractions or equivalent (2–2.12 Gy per fraction), with 54–60 Gy for at-risk areas.[39,40] Use of a dose of 65 Gy in 30 fractions has also been reported within the UK.[41] Lower radiotherapy doses are routinely used for the treatment of children and adolescents with NPC.[42]

Recommendations

- 70 Gy in 35 fractions over 7 weeks (Grade A)
- 70 Gy in 33 fractions over 6.5 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.[12]

Salivary gland malignancies

Surgery is the primary treatment modality and adjuvant radiotherapy is routinely recommended for T3/4 disease, adenoid cystic carcinoma or other adverse pathological features. Dose response data are lacking and postoperative radiotherapy is given at a dose of at least EQD2 of 60 Gy (using α/β=10) to the high-dose target volume.[43,44] A dose of EQD2 66 Gy can be considered in the event of positive margins. Perineural infiltration is a risk factor for recurrence; adenoid cystic carcinomas are particularly prone to nerve invasion. Nerves at risk may be treated electively to the skull base;[44] a dose in the order of EQD2 50–60 Gy is appropriate (Grade D).

Recommendations

For adjuvant radiotherapy:

- 60 Gy in 30 fractions over 6 weeks (Grade C)
- Increased dose of 66 Gy in 33 fractions over 6.5 weeks can be considered following an R1 resection (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.[12]

Reirradiation

Reirradiation for recurrent or second primary head and neck cancers with curative intent is highly challenging and individualised in a heterogenous group of patients. Appropriate patient selection is addressed in the RCR *Head and neck consensus statements 2022*.[45]

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An analysis of volume, dose and fractionation by the Multi-Institution Reirradiation (MIRI) Collaborative[46] has suggested that elective nodal irradiation does not improve locoregional control rates. Altered fractionation, including hyperfractionation, was not advantageous compared with conventional fractionation in terms of disease control or late toxicity (Grade C). There was a dose response relationship for definitive reirradiation, with reirradiation IMRT to doses of ≥66 Gy (conventionally fractionated) appearing safe and associated with improved disease outcomes (Grade C). Following surgery with no residual gross disease, conventionally fractionated doses of 50–66 Gy appeared adequate (Grade C). There is growing evidence that stereotactic body radiotherapy (SBRT) reirradiation is relatively safe with, to date, no clear evidence of benefit compared with IMRT for disease control.[46–49] Brachytherapy either as definitive or adjuvant treatment is a further option with acceptable toxicity.[50,51]

Palliative radiotherapy

Palliative radiotherapy is used in a very heterogenous group of patients and may range from the use of a single fraction to stop bleeding or fungation to the use of high doses to achieve longer-term disease control while accepting that a cure is not possible. Hypofractionated palliative radiotherapy can be used for symptoms such as pain, swallowing, breathing and speech.[52] Response is dose related so some selected patients with good performance status and more limited disease burden may benefit from more intensive schedules.[52] There is no high-level evidence on which to recommend a specific palliative radiotherapy schedule,[52] with a survey of UK practice showing a host of different schedules in use.[53] The use of conformal radiotherapy techniques is appropriate to facilitate the delivery of higher-dose schedules.

Recommendations

Examples of some appropriate dose fractionation schedules include:

- 8–10 Gy in 1 fraction (Grade D)
- 25 Gy in 5 fractions over 1 week[54] (Grade C)
- 20 Gy in 5 fractions over 1 week[53] (Grade D)
- 30 Gy in 10 fractions over 2 weeks (Grade D)
- 24 Gy in 3 fractions over 3 weeks (fractions on day 1, 8, 22)[55] (Grade C)
- 40 Gy in 10 fractions over 4 weeks ‘split course’[56] (Grade C)
- 14 Gy in 4 fractions, which may be repeated 2 further times every 4 weeks (Grade C)[57]

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.[12]

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Head and neck cancer

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08 Hepato-pancreato-biliary cancer (HPB)

Liver

Liver malignancies are either primary or secondary liver cancers. Primary liver cancer comprises hepatocellular carcinoma (HCC) and biliary tract cancers, which include intrahepatic cholangiocarcinoma (IHC).

Primary liver cancer

The incidence of primary liver cancer in the UK is estimated at 6,200 new cases per year and is projected to rise by 38% by 2035. It is currently the eighth most common cause of cancer death in the UK (2017–2019).[1]

Optimal treatment of primary liver cancers relies on a multidisciplinary approach, taking into account disease stage, liver function, medical co-morbidities (particularly presence of liver cirrhosis) and patient fitness. It is recommended that the treatment selection and subsequent radiation therapy delivered to patients with HCC or biliary tract cancers should only proceed following formal specialist hepatobiliary multidisciplinary team review and involve the care of a hepatologist.

The American Society for Radiation Oncology (ASTRO) has recently published a guideline on the use of external beam radiotherapy (EBRT) in the treatment of primary liver malignancies, which has been endorsed by the European Society for Therapeutic Radiation Oncology (ESTRO).[3]

Liver cancers are often treated with highly conformal EBRT delivered in hypofractionated schedules or stereotactic ablative body radiotherapy (SABR).* The ASTRO guidelines cover the definition of hypofractionation (including moderate hypofractionation and ultra-hypofractionation) and SABR.[3]

* We are applying the term SABR to include the term SBRT (stereotactic body radiotherapy). The definition of SABR and ultra-hypofractionation is as per the *ASTRO external beam radiation therapy for primary liver cancers: an ASTRO clinical practice guideline*.

Hepatocellular carcinoma

The Barcelona Clinic Liver Cancer (BCLC) group staging, prognosis and treatment guidelines were updated in 2022 and are commonly cited when making clinical decisions regarding the treatment of HCC.[4] Retrospective and prospective studies have demonstrated the safety and efficacy of EBRT (SABR and proton beam therapy [PBT]) in all BCLC stages.[5]

The European Society for Medical Oncology (ESMO) and the American Association for the Study of Liver Diseases (AASLD) have published guidance recommending EBRT as a treatment option for selected patients with HCC.[6] Furthermore, the National Comprehensive Cancer Network (NCCN) 2022 guidelines recommend the use of EBRT for liver-confined HCC.[7]

EBRT can also be considered for palliation of HCC.[3]

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Radical treatment

Hypofractionation/ultra-hypofractionation

Radiotherapy for HCC should aim for a biological equivalent dose (BED) 10 as close to 100 Gy as possible, in as few fractions as possible, while still meeting the mandatory organ-at-risk (OAR) constraints defined by SABR-C.[8,9] The fractionation schedule prescribed should be adapted depending on location in relation to the proximity to the high-risk zone and tumour size.[8] Larger tumours may be treated in 10 or 15 fractions.[8]

A phase II randomised controlled trial (RCT) provides evidence for PBT delivered in a 15-fraction regimen, with a prescription dose ranging from 67.5 Gy for peripheral tumours to 58.05 Gy for central tumours located ≤2 cm from the porta hepatis.[10] The trial included tumours with HCC (53%) and IHC histology (47%) with median tumour size of 5.7 cm. It demonstrated a 95% 2-year local control with 3.6% rate of Child-Pugh score deterioration.[10]

The NRG Oncology GI-003 RCT is comparing proton versus photon treatments utilising the same stratified fractionation schedules described above of 5 and 15 fractions (NCT03186898) to determine if the treatment of HCC with protons compared with photons has an effect on overall survival.[10]

Stereotactic ablative body radiotherapy (SABR)

SABR is recommended for the treatment of HCC (histological or radiological diagnosis) in those unsuitable for surgery, transplant or transarterial chemoembolisation (TACE) or in those who have become refractory to TACE. Such patients should have a Child-Pugh score of A, have fewer than 5 discrete lesions and have no single lesion greater than 6 cm.[9,11,12]

The SABR Consortium Guidelines have utilised these inclusion and exclusion criteria with a recommended dose based on a risk-adapted approach dependent on the mean liver dose (MLD) delivered to liver-GTV structure.[13]

Preoperative and adjuvant radiotherapy

In HCC with macrovascular invasion (MVI) randomised phase III trials have demonstrated that EBRT improved survival when given pre-operatively compared with surgery alone and in conjunction with TACE compared with sorafenib alone.[14,15]

SABR has been shown to be a safe and effective option as a bridge to liver transplantation[16] (Grade C).

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Recommendations

Definitive radiation for HCC

SABR:

For selected patients with Child-Pugh A, solitary tumour only with maximum tumour diameter <5 cm and which meets OAR constraint for 3 fractions. This schedule is not recommended for treating more than one tumour region.

• 45 Gy in 3 fractions (Grade B)

For all other patients having SABR:

• 30–50 Gy in 5 fractions (Grade B)

Hypofractionation:

• 45–67.5 Gy in 15 fractions (Grade B)
• 40–60 Gy in 10 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.[2]

Biliary tract cancer (BTC)

The survival rates of IHC remain poor with observed 1-, 3- and 5-year survival of 36.3%, 12.8% and 8.1% respectively.[17] Surgery remains the only potential curative treatment option. In those suitable, surgery combined with chemoradiotherapy, radiotherapy or chemotherapy is associated with a reduced risk of mortality compared with those having non-surgical interventions alone.[17]

Radical radiotherapy

Conventional fractionation

Unresectable biliary tract cancers (excluding gallbladder cancer) may be treated with conventional fractionation of 50.4 Gy in 28 fractions with concurrent fluoropyrimidine.

Hypofractionation

In unresectable biliary tract cancers (excluding gallbladder cancer) hypofractionation with photon radiotherapy is an acceptable option for intrahepatic tumours, but such cases should only be treated at centres with experience.

The 15-fraction schedule has been used in the completed ABC 07 study with interim evidence of safety for this dose fractionation regime.

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Stereotactic ablative body radiotherapy (SABR)

Unresectable BTC can be treated with SABR to a dose of 50 Gy in 5 fractions (as per the ABC 07 study) in experienced centres.

Recommendations

Unresectable disease (BTC excluding gallbladder cancer)

Conventional fractionation:

• 50.4 Gy in 28 fractions with concurrent fluropyrimidine (Grade B)

Hypofractionation:

• 45–67.5 Gy in 15 fractions (Grade C)

SABR:

• 40–50 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]

Preoperative radiotherapy

Hypofractionation

Preoperative chemoradiation, including with PBT, prior to liver transplantation improves survival.[18–20] The use of PBT enables optimal dose delivery while sparing the dose to the diseased background liver.[10]

Preoperative PBT for neoadjuvant treatment prior to orthotopic liver transplantation (OLT) is indicated in selected patients with IHC on a background of primary sclerosing cholangitis. The criteria have been defined as histological proof of hilar cholangiocarcinoma, less than 3 cm in size and with no evidence of metastases to the retroperitoneal lymph nodes or other sites. PBT is delivered at a dose of 67.5 Gy (RBE=1.1) to the primary tumour region and 45 Gy (RBE=1.1) to the elective nodal region in 15 fractions.

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Recommendations

Preoperative radiotherapy prior to OLT

Conventional fractionation:

- 45 Gy in 25 fractions concurrent with fluoropyrimidine followed by intraluminal brachytherapy boost 10–16 Gy to tumour (Grade C)

Hypofractionation:

- PBT: 45–67.5 Gy in 15 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]

Postoperative radiotherapy

Conventional fractionation

Postoperative EBRT using conventional intensity-modulated radiation therapy (IMRT) with concurrent fluoropyrimidine is an option for resected extrahepatic cholangiocarcinoma and gallbladder cancer.[21] Target volumes should cover the draining regional lymph nodes: porta hepatis, coeliac, superior mesenteric, gastrohepatic and para-aortic with 45 Gy in 1.8 Gy/fraction and the tumour bed, depending on margin positivity, with 50–60 Gy in 1.8–2 Gy/fraction as per SWOG S0809. SWOG S0809 reported a 2-year survival of 65% (95% CI, 53% to 74%) for patients undergoing postoperative radiotherapy with concurrent chemotherapy.[21]

Recommendation

Adjuvant radiotherapy following surgical resection

Conventional fractionation:

- 45 Gy in 1.8 Gy/fraction to the nodes and 50–60 Gy in 1.8–2 Gy/fraction to the tumour bed (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.[2]

For details on treatment of liver oligometastases please refer to the 'Extracranial oligometastases' chapter.

Palliative treatment

Palliative radiotherapy may help alleviate the symptoms caused by the presence of primary and secondary liver cancers. It has been found to improve symptoms such as pain, abdominal discomfort and nausea and thereby improve quality of life.[22,23] Patients with a performance

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status of 0–2 and an estimated prognosis of 3 months or more should be considered for palliative radiotherapy.

Patients may be treated with 25 Gy in 5 fractions if the V10 Gy to the normal liver is <70% and the MLD is <15 Gy. If these constraints are not met, 8 Gy in 1 fraction can be used as an appropriate palliative dose.

Recommendations

- 25 Gy in 5 fractions (Grade C)
- 30–40 Gy in 10 fractions (Grade C)
- 8 Gy in 1 fraction (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.[2]

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Pancreas

Radical treatment

Standard treatment for patients with locally advanced inoperable pancreatic cancer* consists of chemotherapy, which may be followed by radiation or chemoradiation in responding or stable disease after induction chemotherapy.[1,2]

* Locally advanced inoperable pancreatic cancer includes patients who are medically unfit for surgery and/or surgically unresectable.

Conventionally fractionated radiotherapy with concurrent chemotherapy

The use of conventionally fractionated radiotherapy (50.4–54 Gy in 28–30 fractions) with concurrent chemotherapy following induction chemotherapy has been investigated and has not been shown to improve overall survival (OS) compared with chemotherapy alone[1,2] (Level 1b).

In the LAP07 trial, 54 Gy in 30 fractions was used with concurrent capecitabine following 4 months of gemcitabine chemotherapy with or without erlotinib. While median OS did not improve with the addition of chemoradiotherapy (CRT) (16.5 versus 15.2 months; p=0.08), chemoradiotherapy was associated with reduced rates of local progression (32% versus 46%; p=0.03) and a trend towards improved progression-free survival (PFS)[2] (hazard ratio [HR], 0.78; p=0.06) (Level 1b).

In the SCALOP-2 trial, dose escalation from 50.4 Gy in 28 fractions to 60 Gy in 30 fractions combined with capecitabine was evaluated. There was no improvement in median OS (15.6 versus 16.9 months). However, 1-year local progression (no metastasis) was reduced (26.7% to 15.2%) and 1-year local progression (with or without metastasis) was reduced (33.3% to 23.9%).[3] There was no significant added toxicity of the 60 Gy regimen compared with the 50.4 Gy regimen (Level 1b).

Hypofractionated radiotherapy with concurrent chemotherapy

Since the COVID-19 pandemic, a hypofractionated regimen of 45 Gy in 15 fractions has been used with concurrent capecitabine.[4] This dose and fractionation was based on published data (predominantly retrospective US experience) where this dose had been used within dose-escalated regimens of up to 67.5 Gy, delivered using a simultaneous integrated boost (SIB) approach. A dose of 45 Gy in 15 fractions was recommended in COVID-19 guidance[4] because the biological equivalent dose (BED) 10 of this dose was comparable to the standard 50.4 Gy in 28 fractions regimen used in the UK (Level 2b).

Dose escalation with a SIB up to 67.5 Gy in 15 fractions is not recommended outside of a clinical trial or study with robust quality-assured image guidance.[5,6]

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Recommendations

Conventionally fractionated or hypofractionated radiotherapy with concomitant chemotherapy following induction chemotherapy:

- 50.4 Gy in 28 fractions over 5.5 weeks (Grade B)
- 54–60 Gy in 30 fractions over 6 weeks (Grade B)
- 45 Gy in 15 fractions over 3 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.[7]

Stereotactic ablative body radiotherapy (SABR)

Patients with locally advanced non-metastatic pancreatic cancer (LANMPC) may be eligible for SABR if no progression after initial systemic treatment has been seen or they are part of clinical trials.[8–11]

Initial trials demonstrated the safety and efficacy of delivering doses of 33–35 Gy in 5 fractions,[12] and the safety of increasing dose to 40 Gy in 5 fractions has been demonstrated in prospective clinical trials[13] (Level 2b).

SABR was compared with conventional fractionation in the CRiSP (conventionally fractionated radiation therapy versus stereotactic body radiation therapy for locally advanced pancreatic cancer) meta-analysis.[14] The meta-analysis reported an estimate for 2-year OS of 26.9% for SABR versus 13.7% for conventionally fractionated radiotherapy (CFRT). The estimate for acute grade 3/4 toxicity was 5.6% for SABR versus 37.7% for CFRT. Petrelli *et al*[15] performed a systematic review and pooled analysis of 19 trials in SABR for locally advanced pancreatic cancer (LAPC), where the range of doses delivered was 18–50 Gy in 1–8 fractions. The median OS was 17 months (Level 2a).

Recommendation

SABR following induction chemotherapy:

- 33–40 Gy in 5 fractions delivered daily (with a minimum 16–18 hours gap) or on alternate days over 2 weeks
- Treatment gaps should be kept to ≤4 days (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.[7]

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Preoperative chemoradiotherapy

Preoperative radiotherapy was investigated during the PREOPANC study,[16] where a dose of 36 Gy in 15 fractions was used in combination with full-dose gemcitabine. There was improvement in median OS (15.7 months versus 14.3 months), but the 5-year OS rate was 20.5% with neoadjuvant chemoradiation and 6.5% with upfront surgery, and this was consistent across the prespecified subgroups, including resectable and borderline resectable pancreatic cancer. In addition, R0 resection was achieved in 72% in the neoadjuvant chemoradiotherapy group compared with 43% in the upfront surgery group (p<0.001) (Level 1b). The predefined subgroup of patients with suspected resectable pancreatic ductal adenocarcinoma (PDAC) showed no significant difference in OS, disease-free survival (DFS), locoregional failure-free interval (LFFI) and distant metastases-free survival (DMFI). The predefined subgroup of patients with suspected borderline resectable PDAC showed a significantly improved OS, DFS and LFFI for preoperative chemoradiotherapy.

The more recent PreopPanc 2 trial[17] comparing neoadjuvant Folfirinox versus gemcitabine and gemcitabine concurrent chemoradiation has demonstrated no difference in clinical outcomes. Median OS was 21.9% versus 21.3%, respectively (hazard ratio 0.87; 95% confidence interval [CI] 0.68–1.12; p=0.28). Resection rates (77% versus 75%, respectively; p=0.7). The serious adverse rates (49% versus 43%, respectively; p=0.26) were similar between treatment arms.

The CONKO-007 trial studied the role of sequential chemotherapy and chemoradiotherapy for patients with initially unresectable disease. Patients received induction chemotherapy for 3 months (gemcitabine or FOLFIRINOX), then were randomised to continuing chemotherapy or chemoradiation (50.4 Gy in 28 fractions with concurrent gemcitabine). Median PFS (HR 0.919, p=0.540) and OS (HR 0.964, p=0.766) did not differ significantly in both arms. However, PFS rate was higher in the CRT arm after 2 years. OS rates for circumferential resection margin (CRM) negative R0 surgery at 87.5% (1 year) and 67.2% (2 years) were significantly higher (p<0.01) than for CRM plus R0 surgery at 66.7% (1 year) and 41.2% (2 years), as well as for patients without or with incomplete surgery at 68.5% (1 year) and 26.4% (2 years).[18]

A retrospective multicentre study (AEGO group), which included patients with both borderline resectable pancreatic cancer and LAPC, suggested a signal for improved outcomes with the addition of consolidation of chemoradiation prior to surgery after induction FOLFIRINOX, particularly in those with borderline resectable disease. In those with borderline resectable pancreatic cancer, DFS was improved (23.9 versus 16.6 months, p=0.01) and there was a trend to improved OS (not reached versus 28.7 months, p=0.09) after preoperative CRT. The median dose given was 50 Gy (range 49–54 Gy) in 1.8–2 Gy per fraction and was given predominantly with concurrent capecitabine.[19]

The ESPAC-5F prospective study randomised patients with borderline resectable disease to either immediate surgery or neoadjuvant therapy (2 cycles of GEMCAP, 4 cycles of neoadjuvant FOLFIRINOX or chemoradiation with 50.4 Gy in 28 fractions with concurrent capecitabine). The resection rate was the same in each arm (62% for immediate surgery and 55% for neoadjuvant therapy, p=0.668) and the R0 resection rate was 15% and 23% respectively. However, the 1-year survival rate was higher in those who received neoadjuvant therapy: 40% for immediate surgery and 77% for neoadjuvant therapy (HR=0.27, 95% CI 0.13–0.55).[20]

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Recommendations

Preoperative chemoradiotherapy (should be considered as a treatment option, particularly in borderline resectable pancreatic cancer):

- 36 Gy in 15 fractions over 3 weeks (Grade A)
- 50.4 Gy in 28 fractions over 5.5 weeks (Grade B)
- 54 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.[7]

Adjuvant chemoradiotherapy

Adjuvant radiotherapy may be considered in selected cases following multidisciplinary team discussion for patients with high-risk features on postoperative histology, following a complete course of adjuvant chemotherapy. Radiotherapy is delivered with concurrent fluoropyrimidine or gemcitabine chemotherapy. Doses of 50.4 Gy in 28 fractions have been used in this situation.[21–25]

Recommendation

Adjuvant chemoradiotherapy, following adjuvant chemotherapy:

- 50.4 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.[7]

Palliative treatment

Palliative radiotherapy can be considered for relief of pain or for haemostasis.

There is little evidence available to inform dose and fractionation, so regimen should be selected on an individual patient basis.

Recommendations

Palliative radiotherapy:

- 30–36 Gy in 10–12 fractions over 2 weeks (Grade D)
- 20–25 Gy in 5 fractions over 1 week (Grade D)
- 8–10 Gy in 1 fraction (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.[7]

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09 Lung cancer

Background

Lung cancer is the leading cause of cancer mortality in the United Kingdom.[1] Major advances in molecular biology, drug development, improvement in surgical and radiotherapy techniques, immunotherapy revolution and patient education are improving outcomes, but survival remains poor in comparison with many other cancers.[1]

The National Lung Cancer Audit (NLCA) was established in 2004 aiming to improve lung cancer care and through annual publications has documented sustained improvements over the past 20 years. However, NLCA data used to look at uptake of treatment continue to suggest that the proportion of patients with lung cancer in the United Kingdom accessing radiotherapy remains lower than expected.[2]

The routine use of positron emission tomography computed tomography (PET-CT) and endobronchial ultrasound (EBUS) and increasing access to navigational bronchoscopy improves lung cancer staging. Significant technological advances are adopted into radiotherapy practice; for radical radiotherapy, four-dimensional computed tomography (4DCT) planning to account for respiratory motion has become the norm, replacing three-dimensional conformal radiotherapy (3DCRT). By combining 4DCT with the improved dosimetry from intensity-modulated radiotherapy (IMRT) and volumetric modulated arc therapy (VMAT) techniques, meeting normal tissue constraints for bulky tumours in awkward anatomical locations is increasingly feasible. However, as with many tumour types, there is limited evidence from trials that determine the efficacy of these techniques (Level 4).[3–5]

The World Health Organization declared COVID-19 a pandemic on 11 March 2020. General guidance on delivery of radiotherapy during the pandemic has been provided by the National Institute for Health and Care Excellence (NICE).[6] One recommendation is to consider alternative dose fractionation schedules or radiotherapy techniques. As a result, several reduced-fractionation, curative-intent radiotherapy regimes were introduced into lung cancer practice in the United Kingdom.[7]

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

Background

Stages I and II lung cancer are best managed with surgical resection. The Radiation Therapy Oncology Group (RTOG) 1021,[8] STARS,[9] ROSEL[10] and SABRTooth[11] studies evaluated stereotactic ablative body radiotherapy (SABR) against surgery in early-stage lung cancer; all studies closed early due to poor accrual. The STARS and ROSEL data have been published in pooled form (Level 2b); of the 58 patients examined, the 3-year recurrence-free and overall survival were >80% in both groups.[12]

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There is a strong body of literature to support SABR for stage I patients who have a high surgical risk,[13] with Level 1 evidence of superiority compared with more conventionally fractionated radiotherapy.[14] NHS England and the United Kingdom SABR Consortium support SABR for the radical treatment of node-negative tumours less than 5 cm that are in a favourable anatomical position. The best outcome is achieved when the tumour receives >100 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 4 days.[15]

Stage III NSCLC is a heterogeneous group in terms of tumour size, invasion of local structures, and lymph node involvement. Concurrent chemoradiotherapy has been demonstrated in meta-analyses to give superior outcomes when compared with sequential chemoradiotherapy or radiotherapy alone.[16,17] In those who have not progressed following concurrent chemoradiotherapy and have maintained good performance status (PS), sequential durvalumab immunotherapy should be offered, as evidenced by the landmark PACIFIC trial, which reports 5-year overall survival and progression-free survival of 42.9% and 33.1%.[18]

The optimal dose fractionation schedule for radical radiotherapy is not defined. For concurrent chemo-radiotherapy schedules 60 Gy in 30 fractions has become a standard,[19] but there is an increased incidence of Grade 3 oesophageal toxicity (Level 1b) using this approach. Older patients with good PS and few co-morbidities derive as much benefit from concurrent therapy as their younger counterparts (Level 1b).[20,21]

Dose escalation, intensification and adaptation have been evaluated in several phase I/II studies and many have shown promising results.[22–29] In contrast, the randomised RTOG 0617 trial did not demonstrate an overall survival benefit in the dose-escalated arm.[30] The recent United Kingdom ADSCaN trial[31] failed to reach the recruitment target, and with the response to the COVID-19 pandemic introducing 15 fraction schedules into UK practice,[7] the optimal dose fractionation schedule of radical radiotherapy is yet to be defined.

Although tri-modality therapy is an option recommended in NICE guidance[32] there is little evidence of benefit over definitive chemoradiotherapy, except in Pancoast tumours,[33] where studies looking at higher dose fractionations are ongoing.

For those unable to tolerate concurrent chemoradiotherapy, a sequential approach demonstrates survival benefit over radiotherapy alone.[34] Patients unfit for systemic therapy should be treated with radiotherapy alone. Accelerated fractionation schedules seem to improve outcomes[35,36] and can be safely combined with concurrent and neoadjuvant approaches.[37–39]

The 1998 postoperative radiotherapy (PORT) meta-analysis highlighted the adverse impact of PORT on overall survival, with 7% survival detriment at 2 years.[40] Subgroup analysis suggests the negative effect of PORT was greatest in N0-1 disease. The LungART trial evaluated the role of PORT in pN2 disease, a group at higher risk of locoregional recurrence. LungART reported the addition of PORT reduced mediastinal relapse (25% versus 46%), but these gains did not translate into an improvement in disease-free survival, partly because of an increase in cardiopulmonary toxicity.[41] This additional evidence indicates the role for PORT is limited; PORT can be considered in instances of R1 resection.

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Recommendations

Medically inoperable T1–T2b (≤5 cm) N0 Favourable Anatomical Position*:
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 8 fractions over 10–20 days (Grade B)

Medically inoperable stages I and II Unfavourable Anatomical Position**:

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

*Corresponds to peripheral tumours >2 cm from any mediastinal critical structure, including the bronchial tree, oesophagus, heart, brachial plexus, major vessels, spinal cord, phrenic nerve and recurrent laryngeal nerve.[42]

**Corresponds to ultra-central[43] ITV ≤1 cm from the proximal bronchial tree (PBT) or overlaps central structures (defined as major vessels, heart, oesophagus, spinal cord, phrenic and recurrent laryngeal nerve, brachial plexus, trachea).
Note: Central tumours (<2 cm from mediastinal critical structures) require individual assessment as they can be managed as occurring in Favourable Anatomical Position. More detailed guidance on the optimal SABR practice for central disease are found in the United Kingdom SABR Consortium Resource (version 7 to be published in 2023).[15]

Stage III:

Concurrent (with platinum doublet chemotherapy):

- 55 Gy in 20 fractions over 4 weeks (Grade A)
- 60 Gy in 30 fractions over 6 weeks (Grade A)
- 66 Gy in 33 fractions over 6.5 weeks (Grade A)

Sequential chemoradiotherapy or radiotherapy alone:

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

Pancoast tumours (T3–4 N0–1):

- 45 Gy in 25 fractions over 5 weeks with cisplatin and etoposide followed by surgery

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.[44]

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

Background

The trials of palliative radiotherapy were largely undertaken 30 years ago in patients unexposed to systemic anti-cancer therapy. These trials demonstrated that short-course radiotherapy palliates intrathoracic symptoms as well as long-course, but for those with good PS, higher doses confer a modest survival advantage at the expense of extra toxicity.[45] The upcoming United Kingdom TOURIST platform trial will be testing timing, dose and fractionation for palliative thoracic radiotherapy in combination with modern systemic therapies.[46]

Recommendations

NSCLC 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)

NSCLC with poor PS:

- 17 Gy in 2 fractions over 8 days (Grade A)
- 10 Gy in 1 fraction (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.[44]

Non-small cell lung cancer (NSCLC): whole-brain radiotherapy

Background

There is no evidence supporting the use of prophylactic cranial irradiation in NSCLC. The international QUARTZ trial provides Level 1 evidence for whole-brain radiotherapy (WBRT) and randomised patients between best supportive care with or without WBRT. The primary outcome measure was quality-adjusted life years, and the study showed no significant difference in overall survival, overall quality of life or dexamethasone use between the two groups.[47]

WBRT should not be routinely offered to patients with cerebral metastasis, though stereotactic radiosurgery or stereotactic radiotherapy (see chapter on 'Brain metastases') to the brain can be considered for good PS patients with disease amenable to treatment. For those with volumes unsuitable for a stereotactic approach, WBRT may be considered in those patients with driver mutations maintaining good PS.

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Recommendation

NSCLC offered whole-brain radiotherapy:

• 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.[44]

Small cell lung cancer (SCLC)

Background

The evidence base supports the integration of chemotherapy and radiotherapy at all disease stages.[48]

Stages I–III

Concurrent chemoradiotherapy should be offered with radiotherapy starting no later than day 1 of cycle 3 of chemotherapy.[49–51] The UK phase III CONVERT (concurrent once daily versus twice daily radiotherapy) trial found no significant difference between the two standard fractionation schedules,[50] evidence supported by the CALGB 30610/RTOG 0538 trial.[52]

For those patients who due to tumour size or co-morbidities cannot be treated with concurrent chemoradiotherapy, sequential chemoradiotherapy is the best alternative. There is no definitive evidence to indicate the optimal schedule in this patient group, although many use 40 Gy in 15 fractions over 3 weeks.[51]

Recommendations

Stages I–III SCLC offered concurrent chemoradiotherapy:

• 45 Gy in 30 fractions twice daily over 3 weeks (Grade A)
• 66 Gy in 33 fractions over 6.5 weeks (Grade A)

Stages I–III SCLC offered sequential chemoradiotherapy:

• 40–50 Gy in 15–20 daily fractions over 3–4 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.[44]

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SCLC: palliative thoracic radiotherapy

Background

The CREST trial evaluated the role of thoracic radiotherapy in patients with metastatic SCLC on completion of their primary chemotherapy treatment.[53] Although the primary endpoint was not met, the improvement seen in 2-year overall survival supports mediastinal consolidation with a significant improvement in progression-free survival and near 50% reduction in intrathoracic progression. Post hoc analysis describes the benefit of consolidation thoracic radiotherapy may be limited to those with persistent intrathoracic disease.[54]

Recommendation

Stage IV SCLC offered consolidation thoracic radiotherapy:

- 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.[44]

Prophylactic cranial irradiation

Meta-analysis of patients with stages I–III SCLC in complete or near complete thoracic remission following primary chemoradiotherapy have an increased overall survival and decreased incidence of intracerebral relapse when prophylactic cranial irradiation (PCI) is delivered.[55] Fractionation studies favoured the lower-dose schedule of 25 Gy in 10 fractions, which gave a similar intracranial relapse rate and better survival when compared with 36 Gy in 18 fractions over 24 days.[56]

Subsequent studies established a similar benefit for PCI in patients with stage IV SCLC with an increased overall survival and reduced symptomatic incidence of brain metastases.[57] Within this study 5 fraction schedules were permitted, though 85% of patients treated received either 30 Gy in 10 fractions or 20 Gy in 5 fractions.

The routine use of PCI is being challenged by concerns about the short-term and long-term neurocognitive effect, and data from the Japanese trial,[58] which compared PCI with magnetic resonance imaging (MRI) surveillance did not demonstrate a survival advantage with the addition of PCI. The upcoming PRIMALung trial will test the validity of the Japanese finding for the European population.[59]

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Recommendations

Stages I–III SCLC offered PCI:

- 25 Gy in 10 fractions over 2 weeks (Grade A)

Stage IV SCLC offered PCI:

- 20 Gy in 5 fractions over 1 week (Grade A)
- 25 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.[44]

Mesothelioma

Background

The use of prophylactic irradiation of tracts of pleural interventions has historically been thought to reduce the incidence of chest wall recurrence. The PIT[60] and SMART[61] trials evaluated prophylactic chest wall irradiation in the prevention of procedure-tract metastases. Both studies were negative and the routine prophylactic irradiation of procedure tracts can no longer be recommended.

For those patients with symptomatic chest wall disease, chest wall irradiation is associated with a response rate of 35%.[62,63] Dose fractionation was examined further in the SYSTEMS 2 study, which will hopefully publish results in 2024.[64]

Recommendation

Mesothelioma with chest wall pain offered thoracic radiotherapy:

- 20 Gy in 5 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.[44]

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Hodgkin lymphoma

Background

Over the past 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 practised. Involved-field radiotherapy (IFRT) has been 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] There should be every effort to reduce cardiac and lung doses when treating the mediastinum, with good evidence to support the use of intensity-modulated radiotherapy (IMRT) and deep inspiration breath hold (DIBH) in this setting.[3,4]

Early Hodgkin lymphoma

The HD-10 study by the German Hodgkin Study Group (GHSG) showed no difference in outcome in the favourable subgroup (stages I–II without risk factors) between two cycles of adriamycin, bleomycin, vinblastine and dacarbazine (ABVD) and 20 Gray (Gy) in 10 fractions IFRT or four cycles of ABVD and 30 Gy IFRT (Level 1b).[5–6] In early unfavourable disease, the GHSG HD-11 study established 4 cycles of ABVD and 30 Gy as the best arm.[7]

Subsequently, three large randomised controlled trials (RCTs)[8–10] testing the omission of radiotherapy in patients achieving complete metabolic response (CMR) on interim positron emission tomography (PET) scanning showed that the omission of radiotherapy results in increased relapse rates when ABVD chemotherapy is used.

One study in early-stage unfavourable (stages I–II with risk factors) Hodgkin lymphoma using a 2+2 approach (escalated BEACOPP $\times$ 2 + ABVD $\times$ 2) showed that the omission of radiotherapy in patients achieving CMR after all chemotherapy was not inferior in terms of 5-year progression-free survival (Level 1b).[6,11]

Combined modality treatment therefore remains to be the standard of care in ABVD-treated early-stage Hodgkin lymphoma but the decision on radiotherapy needs to be carefully considered on an individual patient basis, taking account of their age, sex, smoking history and the anatomical disease distribution, and weighing up predicted risks of late toxicity against potential benefit of improved disease control.[12,13]

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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 patients treated with escalated BEACOPP×2 + ABVD ×2, radiotherapy can be omitted if there is CMR on PET scanning after chemotherapy (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.[6]

Advanced Hodgkin lymphoma

The role of radiotherapy in advanced Hodgkin disease after full-dose combination chemotherapy is controversial and has changed with the introduction of PET imaging.

In the context of ABVD chemotherapy, two Italian RCTs[14,15] randomised patients with initial bulk disease (defined as >5 cm) who demonstrated CMR on both interim (post cycle 2) and end of treatment PET after 6 cycles to radiotherapy (30 Gy in 15 fractions) or no radiotherapy. The two studies showed no statistically significant benefit from consolidation radiotherapy to sites of initial bulk, although they were not powered adequately (Level 1b).[6] The outcomes of the chemotherapy alone arms were excellent, suggesting that any potential benefit from radiotherapy would be very small. The benefit of radiotherapy in patients with partial metabolic response and who continue on ABVD is unknown, as these patients were escalated to more intensive chemotherapy.

In the context of escalated BEACOPP chemotherapy, the GHSG HD-15 study[16] showed that patients achieving CMR do well without radiotherapy to sites of bulk, and patients who have residual fluorodeoxyglucose (FDG) uptake on PET may benefit from consolidation radiotherapy (30 Gy in 15 fractions) (Level 1b).[6]

Recommendation

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

- 30–36 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.[6]

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Relapsed Hodgkin lymphoma

High-dose chemotherapy and stem cell transplantation remain the international standard of care for many younger patients with relapsed Hodgkin lymphoma following previous combined modality treatment. Selected cases of early-stage disease, who relapse after previous chemotherapy alone treatment, may be successfully salvaged with radiotherapy.

The presence of residual PET-positive disease following salvage systemic treatment is an adverse prognostic factor for early relapse after stem cell transplant.[17] Radiotherapy to areas of persistent disease can be used to induce a better remission status. Dose will depend upon the patient's response to salvage systemic treatment and normal tissue constraints.[18]

In some patients with a single site of relapse, particularly occurring late, after previous treatment, reinduction as for early disease combined with ISRT may be appropriate, using a dose of 30–36 Gy in 15–20 fractions over 3–4 weeks (Grade D).[6,18]

Recommendations

In relapsed/refractory disease, the following may be used:

To consolidate complete response following systemic treatment:

- 30 Gy in 15 fractions over 3 weeks (Grade D)
- Persistent disease seen following systemic treatment:
- 36–40 Gy in 18–20 fractions over 3–4 weeks (Grade D)

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 dose of 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.[6]

Nodular lymphocyte-predominant Hodgkin lymphoma

ISRT alone, without chemotherapy, results in high progression-free survival (PFS) and overall survival (OS) rates and is considered an adequate treatment for early-stage disease.[19] A dose of 30 Gy in 15 fractions over 3 weeks is recommended (Grade D).[6,20]

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Aggressive non-Hodgkin lymphoma (NHL)

The most common subtype of aggressive NHL is diffuse large B-cell lymphoma (DLBCL). Radiotherapy has been used as part of combined modality treatment for localised disease or as a consolidation after chemoimmunotherapy in selected cases of advanced-stage disease, most commonly for bulky sites. Historical studies used radiotherapy doses of 40–45 Gy in DLBCL but the BNLI study, published in 2011, demonstrated that 30 Gy is equivalent to higher doses in aggressive NHL (Level 1b).[6,26]

Of note, the evidence for dose fractionation in aggressive NHL comes predominantly from data on DLBCL. However, less common subtypes, such as peripheral T-cell lymphomas, were also included in the BNLI study, albeit in much smaller numbers. The extrapolation of dose fractionation schedules from DLBCL to the other less common subtypes of aggressive NHL is therefore considered reasonable, given the limited data available for the rarer subtypes. An exception to this is NK/T-cell lymphoma (see separate section below).

Localised DLBCL

The standard of care is short-course chemotherapy (R-CHOP ×3) followed by ISRT, or alternatively 6 cycles of R-CHOP alone. The two options have similar oncological outcomes based on historical data.[21,22] However, they differ in their toxicity profile and choice may therefore depend on site of disease, age, sex and co-morbidities of patients and their preference.

More recently, selected cases with very good prognosis (age <60, IPI=0, no bulk) achieved a similar outcome with 4 cycles of R-CHOP and 2 additional cycles of rituximab without radiotherapy (Level 1b).[6,23]

Advanced DLBCL

In advanced-stage disease, the RICOVER-60 study showed a PFS and OS benefit for radiotherapy (36 Gy in 18 fractions) given to initial sites of bulk and extranodal disease after 6 cycles of R-CHOP-14 in patients with DLBCL aged >60 years (Level 1b).[6,24] In patients aged <60 years, the UNFOLDER RCT[25] (reported in abstract form only) showed a 16% benefit in 3-year event-free survival in those assigned to receive radiotherapy versus no radiotherapy (Level 2b).[7] Based on these studies, radiotherapy has been offered as consolidation for bulky sites after R-CHOP. However, it remains currently unknown if patients achieving CMR after R-CHOP still benefit from radiotherapy, and there are no randomised studies to answer this question.

Chemorefractory DLBCL

In patients with residual disease after chemotherapy, higher doses of 36–40 Gy in 2 Gy fractions should be considered (Level 2b).[27–29]

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Bridging to chimeric antigen receptors cell therapy (CAR-T)

CAR-T is an effective salvage treatment for relapsed or refractory DLBCL and primary mediastinal B-cell lymphoma. Radiotherapy has been used successfully as a bridging therapy to halt disease progression and maintain patient condition during the period of cell manufacture. Several small studies reported a range of doses and treatment duration, usually chosen depending on treatment site and to minimise delay of CAR-T infusion (Level 2b).[6,30]

Recommendations

For patients with DLBCL:

- In early-stage DLBCL, 30 Gy in 15 fractions over 3 weeks is recommended as part of combined modality treatment (Grade B)
- In patients with CMR receiving consolidation radiotherapy (eg to initial sites of bulk), a dose of 30 Gy in 15 fractions over 3 weeks is recommended (Grade B)
- In patients with incomplete response to systemic treatment, consider higher doses of 36 Gy–40 Gy in 18–20 fractions over 3–4 weeks (Grade C)
- Extrapolation of these dose recommendations to other less common subtypes of aggressive NHL is reasonable (with the exception of NK/T-cell lymphoma; see separate section below)

For bridging to CAR-T:

- 30 Gy in 10–15 fractions over 2–3 weeks or 20 Gy in 5 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.[6]

Mantle cell lymphoma (MCL)

The vast majority of patients present with advanced disease and require systemic treatment. However, MCL is radiosensitive and responds well even to low doses of radiation, making radiotherapy a useful option for local control or palliation of specific disease sites. MCL less frequently presents as localised disease; radiotherapy alone has been used and is associated with reasonable outcomes. Doses in the range of 4–30 Gy can be used.[31–34]

Natural killer (NK)/T-cell lymphoma

This is a rare entity in Western countries but is common in East Asia and Latin America. 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 45–50 Gy in 25 fractions over 5 weeks should be given (Grade C).[6,35,36]

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Central nervous system lymphoma (CNS) lymphoma

The landmark IELSG32 trial[37] established the MATRIx chemo-immunotherapy schedule (methotrexate, cytarabine, thiotepa and rituximab) as a new standard of care in primary CNS lymphoma for fit patients (Level 1b).[6] Following systemic treatment, patients were consolidated with either autologous stem cell transplantation (ASCT) or whole-brain radiotherapy (36 Gy in 20 fractions over 4 weeks with additional 9 Gy in 5 fraction boost to tumour bed in cases of partial response). There was no significant difference in 2-year PFS (80% for WBRT) but neurocognitive deficit was noted in a subset of the WBRT cohort at 2-year follow-up (Level 1b).[6,38]

Escalation beyond 36 Gy to the whole brain in patients who have achieved a complete response following high-dose methotrexate-based chemotherapy has not been shown to offer additional clinical benefit (Level 2b)[6,39] but could increase neurotoxicity.

In view of the observed neurotoxicity seen with consolidation WBRT, the standard of care for primary CNS lymphoma is consolidation ASCT after MATRIx chemotherapy. In patients not fit for ASCT or those not responding to systemic treatment, radiotherapy may be used as consolidation or palliation. Dose choice will depend on patient fitness, age and predicted risk of neurotoxicity.

Of note, in patients with a complete response to rituximab, methotrexate, procarbazine and vincristine (R-MPV), a reduced dose of 23.4 Gy in 1.8 Gy fractions to the whole brain resulted in 2-year PFS of 77% with minimal neurotoxicity (Level 2b).[6,40]

Recommendations

- For patients with primary CNS lymphoma not fit for consolidation ASCT or those not responding to chemotherapy, consider consolidation WBRT with a dose of 23.4–36 Gy in 1.8 fractions (Grade B)
- In the palliative setting, consider 20 Gy in 5 fractions (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]

Palliative treatment of aggressive non-Hodgkin lymphoma

For aggressive lymphoma, a single dose of 8 Gy or short-course palliation such as 20 Gy in 5 fractions or 30 Gy in 10 fractions are effective and appropriate for the palliative treatment of many patients with limited prognosis (Grade D.)[6]

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Recommendations

In the palliative management of aggressive non-Hodgkin lymphoma, the following are recommended:

- 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.[6]

Mycosis fungoides

This will typically be a widespread skin infiltration with radiotherapy used for palliation of thicker plaques. Doses of 8 Gy in 2 fractions or 12 Gy in 3 fractions are recommended (Grade C).[6,41]

Indolent lymphoma

Indolent lymphoma includes follicular lymphoma, marginal zone lymphoma (including extranodal marginal zone lymphoma, MALT), small lymphocytic lymphoma, lymphoplasmacytic lymphoma and other rarer types. Stage I indolent lymphoma has, for many years, been treated with radical radiotherapy. In advanced-stage indolent lymphoma, radiotherapy may be indicated for control of local symptomatic disease.

A randomised trial comparing 24 Gy with 40 Gy (all in 2 Gy fractions) included patients with early-stage indolent lymphoma.[26] There was no difference in local PFS or OS between these two dose arms (Level 1b).[6] A subsequent study[42] randomised patients with follicular and marginal zone lymphoma to receive either 24 Gy in 12 fractions or 4 Gy in 2 fractions.

At 12 weeks, the complete response rate was 68% after 24 Gy and 49% after 4 Gy. Toxicity was low in both arms (Level 1b).[6] PFS at 5 years was reported as 89.9% with 24 Gy and 70.4% with 4 Gy,[43] establishing 24 Gy as the standard dose for definitive radiotherapy (Level 1b).[6] However, 4 Gy remains a useful alternative in selected cases for palliation, providing good outcomes with low toxicity and more patient convenience.

Recommendations

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 A)
- 4 Gy in 2 fractions is an alternative option for palliation (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.[6]

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11 Paediatric cancer

Background

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

Currently, 40–50% of children with cancer receive radiotherapy as part of their initial treatment. 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 RCR *Good practice guidance for paediatric radiology*.[1]

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

Radiotherapy for children should only be carried out in designated departments associated with Children's Cancer and Leukaemia Group (CCLG) principal treatment 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 leukaemias, usually acute myeloid leukaemia (AML) or, rarely, chronic myeloid leukaemia (CML). Currently more than 85% with ALL and 65% with AML are long-term survivors.

In current protocols, WBRT may be employed for patients with relapsed or refractory CNS involvement, either alone, as detailed below, or delivered as a boost (see total body irradiation section) prior to total body irradiation.[2,3]

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Recommendation

Whole-brain radiotherapy in 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.[4]

Children with a testicular relapse may be treated with testicular radiotherapy, generally using orthovoltage or electrons, encompassing a clinical target volume (CTV) that includes both testes, the scrotum and the inguinal canal supero-laterally as far as the deep inguinal ring, either alone, as detailed below, or delivered as a boost (see total body irradiation section) prior to total body irradiation.[5]

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.[4]

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 or etoposide as the conditioning regimen prior to bone marrow transplantation (BMT).[6,7] Individual techniques for TBI have evolved in different departments due to a number of factors including available equipment and bunker size. TBI planning often utilises CT in addition to *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.[7–10]

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Recommendations

TBI in childhood leukaemia:

- 13.2–14.4 Gy in 8 fractions of 1.65–1.8 Gy twice daily, with a minimum interfraction interval of 6 hours over 4 days (Level C)
- 12 Gy in 6 fractions of 2 Gy twice daily with a minimum interfraction interval of 6 hours over 3 days (Level C)

Cranial boost where indicated (given in the days prior to TBI):

- 5.4–6 Gy in 3–4 fractions of 1.5–1.8 Gy daily over 3 days (Level C)

Testicular boost where indicated (given in the days prior to TBI):

- 5.4–6 Gy in 3–4 fractions of 1.5–1.8 Gy daily over 3 days (Level C)
- 4 Gy single fraction over 1 day (Level C)

TBI for reduced-intensity cord transplant or benign haematological disorders (eg Fanconi's anaemia and thalassaemia):

- 2–4 Gy single dose (Level 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]

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.[11–13] Patients are stratified into treatment risk groups (TL-1, TL-2 and TL-3) based on stage and risk factors such as disease bulk and erythrocyte sedimentation rate (ESR) levels, as defined in the recent international EuroNet pHL-C2 study.

Typically patients are selected for radiotherapy if their disease demonstrates an inadequate response on 18F-fluorodeoxyglucose (18F-FDG) positron emission tomography computed tomography (PET-CT) early response reassessment after initial chemotherapy (2 cycles of OEPA).[14] An involved-site approach encompassing all sites initially involved is recommended, with an additional boost recommended for TL-2 and TL-3 patients if there is residual avid disease at the end of chemotherapy on the late-response assessment FDG PET-CT scan.

The EuroNet pHL-C2 phase III trial investigated a strategy of chemotherapy intensification (DECOPDAC) and response-adapted radiotherapy strategy for TL-2 and TL-3 patients. Only FDG PET-positive sites of disease at the end of chemotherapy (late-response assessment) are irradiated to a dose of 28.8 Gy in 16 fractions of 1.8 Gy daily over 3.5 weeks. The results of this trial are expected in the next 6–12 months and if positive the experimental radiotherapy strategy will be adopted as the standard of care for patients receiving DECOPDAC chemotherapy.

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Given the current risk-stratified approach, which looks to limit the use of radiotherapy as part of initial treatment, many patients who relapse may never have received radiotherapy before or may relapse at sites previously not irradiated. For these patients, radiotherapy should be considered as part of the relapsed salvage treatment strategy, but this should be carefully tailored taking into consideration any previous radiotherapy and the potential toxicity from the required involved-site radiotherapy.[15]

Recommendations

Hodgkin lymphoma: upfront treatment of initial involved sites:

• 19.8 Gy in 11 fractions of 1.8 Gy daily over 2.5 weeks (Level B)

Hodgkin lymphoma: residual FDG-avid disease following completion of chemotherapy:

• Boost of 10 Gy in 5 fractions of 2 Gy daily over 1 week (Level B)

Refractory/relapsed Hodgkin lymphoma at radiotherapy naive sites:

• 30.6 Gy in 17 fractions of 1.8 Gy daily over 3.5 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.[4]

Neuroblastoma

Patients with neuroblastoma are risk-stratified at presentation by age, stage and molecular pathology. External beam radiotherapy to the primary tumour bed is indicated for all patients with high-risk (including metastatic) disease and selected patients with intermediate-risk disease. The intent is to maximise the probability of local tumour control following induction chemotherapy, surgical resection of the primary tumour and high-dose chemotherapy.[16–18] The role of dose escalation to 36 Gy in the context of macroscopic residual disease is currently under investigation within the SIOPEN HR-NBL2 phase III international trial.

Recommendations

Neuroblastoma: postoperative radiotherapy to the tumour bed:

• 21 Gy in 14 fractions of 1.5 Gy daily over 2.5 weeks (Level B) or
• 21.6 Gy in 12 fractions of 1.8 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.[4]

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Wilms' tumour (nephroblastoma)

In Europe, the International Society of Paediatric Oncology (SIOP) UMBRELLA study approach utilises preoperative chemotherapy to 'downstage' the primary and reduce the surgical morbidity, the risk of tumour rupture at surgery and the number who require adjuvant flank radiotherapy. After 6 weeks of initial preoperative actinomycin-D and vincristine (VA) chemotherapy, patients proceed to delayed nephrectomy. Postoperative adjuvant therapy is based on postoperative pathological staging and allocation of risk status (good risk versus intermediate risk versus poor risk histology).

Postoperative chemotherapy again uses vincristine, actinomycin-D, with the duration and the requirement for other drugs dependent upon the staging and risk grouping.

Postoperative flank radiotherapy is employed for stage III patients, including 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 and pelvic radiotherapy.[19] Patients with lung metastases who do not achieve a complete response to chemotherapy should receive whole-lung radiotherapy.[20]

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, stage II (except blastemal subtype*) and stage III (all histology):** 25.2 Gy in 14 fractions of 1.8 Gy daily over 2.5 weeks (Level B)
- **Boost to macroscopic residual disease after surgery (intermediate risk):** delivering a total dose of 25.2 Gy in 14 fractions of 1.8 Gy per fraction (or equivalent), for example an additional 10.8 Gy in 6 fractions of 1.8 Gy daily over 1.5 weeks after receiving 14.4 Gy (Level B)
- **Boost to macroscopic residual disease after surgery (high risk):** delivering a total dose of 36 Gy in 20 fractions of 1.8 Gy per fraction (or equivalent), for example an additional 10.8 Gy in 6 fractions of 1.8 Gy daily over 1.5 weeks after receiving 25.2 Gy (Level B)

Wilms' tumour: whole-abdominal and pelvic radiotherapy:

Depending upon histopathological risk group:

- **Intermediate risk:** 15 Gy in 10 fractions of 1.5 Gy daily over 2 weeks (Level B)
- **High risk:** 19.5 Gy in 13 fractions of 1.5 Gy daily over 2.5 weeks (Level B) ± boost to flank delivering a total dose of 25.2 Gy in 14 fractions of 1.8 Gy daily over 2.5 weeks (or equivalent)

**The poor prognosis of blastemal subtype is caused by metastases and not by increased local recurrence, therefore radiotherapy to primary tumour bed in stage II disease is not recommended.*

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Recommendations (contd)

Wilms' tumour: whole-lung radiotherapy:

- **Intermediate risk:** 12 Gy in 8 fractions of 1.5 Gy daily over 1.5 weeks (Level B)
- **High risk:** 15 Gy in 10 fractions of 1.5 Gy daily over 2 weeks (Level B)
- For infants (<1 year) a lower dose per fraction (1.2–1.5 Gy daily) may be considered on an individualised basis. If multiple areas require treatment, simultaneous treatment to avoid overlap of fields is preferable.

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]

Rhabdomyosarcoma (RMS)

The basis of treatment involves multimodality treatment with induction chemotherapy followed by local therapy utilising surgery and/or radiotherapy.[21–24] Treatment is stratified according to risk groups based on parameters such as PAX01 fusion gene status (positive versus negative), stage of disease, age and primary tumour site. High-risk RMS are treated with 9 cycles of induction ifosfamide, vincristine and actinomycin-D (IVA) chemotherapy, and very high risk (including metastatic disease) receive similar chemotherapy with 4 cycles also incorporating doxorubicin; both high-risk and very high-risk patients receive low-dose maintenance chemotherapy (6 months and 12 months respectively) after the completion of the induction phase. Standard-risk patients receive only 5 cycles of IVA and 4 cycles of VA if they are also having radiotherapy, and patients in the low-risk category, with localised tumours at a favourable site that are microscopically completely resected, receive only 8 cycles of actinomycin-D and vincristine chemotherapy for 22 weeks.[18–20]

It is important to ensure that the choice of local therapy offers the most optimal local control, carefully balanced with the risk of long-term effects in the decision-making process. The benefits of dose escalation for tumours at unfavourable sites and in adults (both adjuvant and primary radiotherapy) are being explored in the FaR-RMS trial currently open to recruitment.

Brachytherapy may be considered for very carefully selected patients such as those with localised embryonal bladder/prostate and female genital tract RMS.[25,26] Such patients should be referred to a specialist centre with experience in this type of treatment.

In the metastatic setting, radical irradiation of all metastatic sites may confer a survival advantage in selected patients, usually with only 1 or 2 metastatic sites.[27] The role of metastatic radiotherapy in the wider setting is currently being investigated within the FaR-RMS trial.

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Recommendations

Unresectable disease, definitive radiotherapy:

- 50.4 Gy in 28 fractions of 1.8 Gy daily over 5.5 weeks, if incomplete response, given at 2 dose levels: 41.4 Gy in 23 fractions of 1.8 Gy daily to disease at presentation, followed by 9 Gy in 5 fractions of 1.8 Gy daily boost to residual disease (Level B)
- Can consider boost, delivering a total dose of 55.8 Gy in 31 fractions (an additional 5.4 Gy in 3 fractions of 1.8 Gy daily) for large tumours with poor response to induction chemotherapy (Level B)

or

- 41.4 Gy in 23 fractions of 1.8 Gy daily over 4.5 weeks following complete response to induction chemotherapy (Level B)

Resectable disease, pre- or postoperative radiotherapy:

- 41.4 Gy in 23 fractions of 1.8 Gy daily over 4.5 weeks
- Boost to macroscopic residual disease after surgery: delivering a total dose of 50.4 Gy in 28 fractions of 1.8 Gy per fraction (or equivalent), for example an additional 9 Gy in 5 fractions of 1.8 Gy daily over 1 week after receiving 41.4 Gy (Level B)

Definitive radiotherapy for metastatic sites:

- Bone, nodal and soft-tissue metastases: 41.4 Gy in 23 fractions of 1.8 Gy daily (or equivalent)
- Whole-lung radiotherapy: 15 Gy in 10 fractions of 1.5 Gy daily
- Whole-abdominal and pelvic radiotherapy: 24 Gy in 16 fractions of 1.5 Gy daily (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.[4]

Ewing sarcoma

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.[28,29] In some situations, definitive radiotherapy may be more appropriate than surgery, particularly in cases requiring extensive resection at pelvic or spinal locations.[30,31]

The upcoming Inter-Ewing-1 trial will evaluate the role of dose escalation for definitive radiotherapy and the optimal dose for postoperative radiotherapy. Centres are encouraged to consider patients for the trial as appropriate when the trial is open to recruitment.

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Paediatric cancer

Recommendations

Preoperative radiotherapy:

- 50.4 Gy in 28 fractions of 1.8 Gy daily over 5.5 weeks (Level B)
- 45 Gy in 25 fractions of 1.8 Gy daily over 5 weeks can be considered, particularly if there are concerns about organ tolerance or wound healing

Postoperative radiotherapy:

- 54 Gy in 30 fractions of 1.8 Gy daily over 6 weeks, delivered in 2 phases: 45 Gy in 25 fractions followed by a boost of 9 Gy in 5 fractions (Level B)

Definitive radiotherapy:

- 54 Gy in 30 fractions of 1.8 Gy daily
- A boost of 5.4 Gy in 3 fractions of 1.8 Gy daily sequentially, or delivering up to 60 Gy as a simultaneous integrated boost may be considered (Level B)

Whole-lung radiotherapy:

- <14 years of age: 15 Gy in 10 fractions of 1.5 Gy daily over 2 weeks
- ≥14 years of age: 18 Gy in 12 fractions of 1.5 Gy 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.[4]

Central nervous system tumours

Low-grade glioma

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 5-year survival rate is 85%, but late relapse is not uncommon.

Treatment is initially with surgical resection, as complete as is considered safe. Systemic therapy is increasingly being used. Decision on the sequencing of systemic therapy and timing of radiotherapy should be made on an individualised basis based on burden of symptoms, age, site and extent of tumour. In general, radiotherapy is delayed or avoided where possible, especially in NF1 and young patients.[32–34]

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Recommendation

Low-grade glioma:

• 50.4–54 Gy in 28–30 fractions of 1.8 Gy daily over 5.5–6 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.[4]

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

Recommendation

Low-grade spinal glioma:

• 50.1–50.4 Gy in 28–30 fractions of 1.67–1.8 Gy daily over 5.5–6 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.[4]

High-grade glioma

Unlike in adults, high-grade gliomas are uncommon in childhood. However, in common with adults, the outlook is generally poor. Survival is currently approximately 20% at 5 years. Current management is based on surgical resection and postoperative chemoradiotherapy with temozolomide.[24]

Diffuse midline gliomas (DMG), H3 K27M-mutant, arising in the midbrain, pons, medulla and thalami, are considered high-grade glioma. Their prognosis is very poor, particularly those arising in the brainstem, with a median survival of approximately 9 months and very few long-term survivors.[35] Urgent upfront radiotherapy is the mainstay of treatment for these patients for symptom control. Hypofractionation can be used to minimise time spent on treatment for patients with brainstem tumours and those with poor performance status.[36] Reirradiation can be considered if there has been a time interval (usually at least 6 months) between the end of initial radiotherapy treatment and disease progression.[37]

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Paediatric cancer

Recommendations

High-grade glioma:

• 54–59.4 Gy in 30–33 fractions of 1.8 Gy daily over 6 weeks (Level B)

Diffuse midline glioma of the brainstem:

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

or

• 39 Gy in 13 fractions of 3 Gy daily over 2.5 weeks (Level B)

Diffuse midline glioma of the brainstem – reirradiation:

• 20 Gy in 10 fractions of 2 Gy daily given 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.[4]

Ependymoma

The overall 5-year survival rate is approximately 50–60%. Prognostic factors include tumour grade and extent of resection, with the predominant site of relapse within the local tumour bed. The majority of collaborative groups now recommend the use of a higher radiotherapy dose (59.4 Gy with highly conformal techniques) taking care to limit the dose to the brainstem and other adjacent critical structures.[38,39]

Recommendations

Intracranial ependymoma:

• 59.4 Gy in 33 fractions of 1.8 Gy daily over 6.5 weeks (Level B)
• 54 Gy in 30 fractions of 1.8 Gy daily over 6 weeks in very young children <18 months, poor neurological status or multiple surgeries

Spinal ependymoma:

• 50.4–54 Gy in 28–30 fractions of 1.8 Gy daily over 5.5–6 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.[4]

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Medulloblastoma

Medulloblastoma is an embryonal tumour of the CNS, which arises in the cerebellum. It is notable for its propensity for metastatic spread via the craniospinal fluid (CSF) and its radiosensitivity. Embryonal tumours can arise elsewhere in the CNS and are now referred to as CNS embryonal tumours, with those arising in the pineal area defined as pineoblastoma.

Standard therapy for medulloblastoma, other CNS embryonal tumours and pineoblastoma 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.[40,41] Standard-risk disease refers to non-metastatic medulloblastoma with complete or near complete surgical resection.

High-risk disease includes patients with medulloblastoma with large cell histology, metastases or postsurgical residue.

It is standard practice to employ adjuvant chemotherapy (vincristine, CCNU, cisplatin and/or cyclophosphamide, vincristine) following radiotherapy for patients with standard-risk and high-risk disease, although more intensive chemotherapy is utilised in some high-risk disease protocols, including one of the arms in the current SIOP high-risk medulloblastoma study.[42–44]

Recommendations

Medulloblastoma, CNS embryonal tumours and pineoblastoma:

Standard-risk craniospinal:

- 23.4 Gy in 13 fractions of 1.8 Gy daily over 2.5 weeks (Level B) followed by boost of 30.6 Gy in 17 fractions of 1.8 Gy daily in 3.5 weeks to tumour bed or whole posterior fossa to a total dose of 54 Gy (Level B)

High-risk craniospinal:

- 36.0 Gy in 20 fractions of 1.8 Gy daily over 4 weeks (Level B)
- 39.6 Gy in 22 fractions of 1.8 Gy daily over 4.5 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 fractions of 1.8 Gy daily (Level B)
- Boost to sites of metastases to a total of 45–50.4 Gy (spinal) and 54–55.8 Gy (intracranial) fractions of 1.8 Gy daily (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.[4]

Intracranial germ cell tumours

Intracranial germ cell tumours (GCT) account for approximately 30% of paediatric GCT. Localised disease for both germinoma and non-germinoma GCT refers to unifocal or bifocal disease involving only the pineal and/or the pituitary/suprasellar region.

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For germinoma, craniospinal radiotherapy is no longer the standard of care for all stages, with initial chemotherapy and whole-ventricular radiotherapy ± boost now offered to patients with localised disease.[45]

Patients with non-germinoma receive platinum-based chemotherapy and radiotherapy, either whole-ventricular radiotherapy with focal boost for non-metastatic disease[46] or craniospinal for metastatic disease.[47]

Recommendations

Germinoma, post-chemotherapy, localised disease – whole-ventricular radiotherapy:

- 24 Gy in 15 fractions of 1.6 Gy daily over 3 weeks
- Bifocal tumours, and those localised to suprasellar or pineal regions not achieving complete radiological response (CR) with induction chemotherapy, should receive a further boost to residual disease of 16 Gy in 10 fractions of 1.6 Gy daily over 2 weeks, delivering a total dose of 40 Gy (Level B)

Germinoma, localised with no chemotherapy or metastatic disease – craniospinal radiotherapy:

- 24 Gy in 15 fractions of 1.6 Gy daily over 3 weeks followed by boost to primary and metastatic sites of 16 Gy in 10 daily fractions of 1.6 Gy daily over 2 weeks (Level B)

Non-germinomatous GCT, localised disease – whole-ventricular radiotherapy:

- 24 Gy in 15 fractions of 1.6 Gy daily over 3 weeks followed by a boost to primary tumour to a total dose of 54 Gy, in fractions not exceeding 1.8 Gy daily (Level B)
- A simultaneous integrated boost approach can be used to treat the primary site(s) to 27 Gy in 15 fractions (1.8 Gy daily) concurrently with the whole ventricles receiving 24 Gy in 15 fractions (1.6 Gy daily). This is followed by a boost of 27 Gy in 15 fractions to the primary site(s) only, with a total dose to the primary site(s) of 54 Gy in 30 fractions of 1.8 Gy daily over 6 weeks.

Non-germinomatous GCT, meningeal metastases – craniospinal radiotherapy:

- 30 Gy in 20 fractions of 1.5 Gy daily over 4 weeks (Level B). Boost to primary and metastatic sites of 24 Gy in 15 fractions (intracranial) or 20.8 Gy in 13 fractions (spinal) of 1.6 Gy daily over 2.5–3 weeks, delivering a total dose of 54 Gy intracranially and 50.8 Gy to involved spinal sites
- If more than two-thirds of spine is involved with macroscopic disease, the total dose should be limited to 45 Gy (ie additional boost of 15 Gy in 10 fractions of 1.5 Gy daily 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]

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Craniopharyngioma

Radiotherapy is usually recommended when tumour resection is incomplete. In select cases where morbidity of radiation outweighs the benefits, such as in very young children with minimal residual disease, it may be appropriate to defer radiotherapy until there is clear tumour progression.[48] Experience with doses of 50–54 Gy, with fraction sizes not exceeding 1.8 Gy daily, have been reported internationally.[49,50] However, there remains a lack of evidence to demonstrate that a higher radiation dose improves local control rate. Given concern over the risk of optic neuropathy and brainstem toxicity, particularly for young patients with this type of benign tumour, a cautious approach to treat to a dose of 50.4 Gy in 28 fractions of 1.8 Gy daily over 5.5 weeks may be favoured.

Recommendation

• 50.1–54 Gy in 28–30 fractions of 1.67–1.8 Gy daily over 5.5–6 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.[4]

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12 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, 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 American Brachytherapy Society–Groupe Européen de Curiethérapie–European Society of Therapeutic Radiation Oncology (ABS–GEC–ESTRO) guidelines.[6,7,8,9] 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.[10–14]

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 Gy in 30 fractions over 6 weeks (Grade C)[10]
- 66 Gy in 33 fractions over 6.5 weeks (Grade C)[10]
- 70 Gy in 35 fractions over 7 weeks (Grade C)[15]

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]

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Unresectable primary and lymph node disease or locoregionally recurrent tumour

For patients with resectable primary and lymph node disease, primary 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.[16,17] 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 inguinal and pelvic lymph node regions with a boost to sites of gross disease using intensity-modulated radiotherapy (IMRT). 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 rationale for considering adjuvant radiotherapy is provided by the observation of a significant rate of lymph node recurrence in patients treated with lymphadenectomy with positive lymph nodes recurrence rates varying between 25% and 77%[5,18–20] and extrapolation from other HPV-driven squamous cell carcinoma (SCC) tumour sites. The role of adjuvant radiotherapy in penile cancer is controversial based on limited data (Level 2, Grade D) due to rarity of this disease and the lack of randomised controlled trial data.

Two previous series have reported on the use of adjuvant radiotherapy for ≥2 lymph nodes or ECS[21,22] using doses of 45–57 Gy over 20–25 fractions. In both series, outcomes were superior to those that reported on ECS without adjuvant radiotherapy.[2]

A recent UK multi-institutional case series of adjuvant radiotherapy of 146 patients with pN3 disease reported its outcomes.[23] The ipsilateral pelvis received radiotherapy if extranodal extension was present following pelvic lymph node dissection or if pelvic lymph node dissection was not performed. Radiotherapy doses used were 45–54 Gy over 20–27 fractions and typically given in combination with weekly low-dose platinum-based chemotherapy.

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Rates of 5-year recurrence-free survival, cancer-specific survival and overall survival were better than previously documented for pN3 disease without adjuvant treatment.[23]

A multi-institutional retrospective analysis was carried out to review the benefit of adjuvant radiotherapy in addition to adjuvant chemotherapy after inguinal surgery for penile cancer.[24] This study looked at 93 patients across 9 centres and reported longer cancer-specific survival with additional radiotherapy (28.5%) compared with adjuvant chemotherapy alone (16.2%, p=0.036).[24] Further prospective studies would be required to confirm these findings.

A current trial of chemoradiation (International Penile Advanced Cancer Trial, InPACT, NCT02305654) is still recruiting and aims to determine prospectively the relative benefits and sequencing of surgery, chemotherapy and chemoradiotherapy in the management of patients with inguinal lymph node positive penile cancer.[25,26]

Recommendations

Inguinal dose:

- 54 Gy in 25 fractions over 5 weeks[21]
- Boost sites of residual disease to 57 Gy (Grade D)

Pelvic dose:

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

or

- 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]

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13 Prostate cancer

Background

Prostate cancer is a common malignancy, with 52,300 cases diagnosed annually in the UK.[1] Standard management for low-risk groups is surveillance. External beam radiotherapy (EBRT) is a non-surgical curative treatment modality for patients with localised intermediate, high-risk or locally advanced prostate cancer.[2–4] Depending on staging, performance status, urinary symptoms and co-morbidities, EBRT, brachytherapy or a combination of both can be used and many patients benefit from the addition of androgen deprivation therapy (ADT) to EBRT.

Androgen deprivation therapy and additional systemic therapies

The relative risk reduction for disease progression and metastatic relapse with the addition of ADT to EBRT applies to all risk groups. For lower-risk groups (low and intermediate risk with favourable features),[3] the addition of short-duration ADT (6 months) to radiotherapy (RT) significantly improves metastasis-free survival (MFS) (HR 0.83 [95% CI 0.77–0.89], p<0.0001).[5,6] ADT started at the time of RT performs better for all disease-related endpoints with no differences in toxicity compared with neoadjuvant scheduling.[7] Extending neoadjuvant ADT does not improve outcomes compared with shorter neoadjuvant ADT and the same adjuvant treatment.[5] For patients with intermediate risk with unfavourable features or high-risk patients treated with radical RT, ADT prolongation from 6 to 18–36 months improves all disease-related endpoints including MFS (HR 0.84 [95 CI 0.78–0.91], p<0.0001).[5,8]

The Radiation Therapy Oncology Group (RTOG) 9413 trial found a significant interaction between RT field size and ADT sequencing. Neoadjuvant and concurrent ADT had a more favourable 10-year progression-free survival (PFS) with prostate and pelvic nodal RT and adjuvant ADT; the reverse was true when prostate-only RT was delivered.[9] Local dose escalation does not negate the benefits of ADT.[10,11] In a meta-analysis, the addition of docetaxel to EBRT and long-term ADT for patients with localised high-risk disease improved failure-free survival (FFS) but not other survival endpoints, with a greater risk of any grade and Grade ≥3 adverse events (OR 3.19, [95% CI 2.70–3.77]; p<0.001).[12] In patients with non-metastatic, high-risk localised disease, abiraterone + ADT was associated with significantly better OS (HR 0.69, 95% CI 0.50–0.95), MFS (HR 0.63, 95% 0.45–0.88) and FFS (HR 0.53, 95% CI 0.41–0.70). There were no significant differences between abiraterone + ADT and abiraterone + enzalutamide + ADT for any of the survival endpoints studied.[13]

In summary, for patients treated with prostate-only RT and 6 months of ADT, radiotherapy should commence shortly after starting ADT; for extended-course ADT (>12 months) and prostate and pelvic nodal RT (PNRT), any neoadjuvant, concurrent and adjuvant sequencing can be used.

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Prostate cancer

Prostate-only radiotherapy

There are now five randomised radiation dose escalation studies that have demonstrated superior biochemical relapse-free survival with whole-gland doses ranging from (conventionally fractionated) 74 to 80 Gray (Gy)[14]. However, this has not translated into an OS benefit.[10,15] Further whole-gland dose escalation is limited by concerns about excessive toxicities. Focal dose escalation to the dominant intraprostatic nodules (DIL) identified on staging mpMRI and/or prostate-specific membrane antigen positron emission tomography (PSMA PET) scan has been shown to improve biochemical control in a phase III randomised FLAME trial compared with the standard 78 Gy whole-gland RT.[16]

Hypofractionation (fraction size of 2.5 Gy and above)

So far, over 8,000 patients have been treated in randomised trials of moderate hypofractionation schedules (fraction size 3.0–3.4 Gy), and findings of these trials suggest that moderate hypofractionation results in similar oncological outcomes in terms of disease-free survival, MFS and OS. There appears to be little to no increase in both acute and late toxicities in a recent Cochrane review.[17,18] In the UK, the CHHiP fractionation schedule of 60 Gy in 20 fractions is currently the recommended schedule.[19]

Stereotactic radiotherapy

Ultra-hypofractionation (stereotactic ablative body radiotherapy [SABR] defined as fraction size of 6 Gy or more) has been shown to be feasible and safe in cohort studies, with high levels of disease control.[20] HYPO-RT-PC compared 78 Gy in 39 fractions versus 42.7 Gy in 7 fractions without hormone therapy in 1,200 patients with intermediate-to-high-risk prostate cancer. SABR has a non-inferior biochemical control compared with conventional fractionation. Early side-effects were more pronounced with SABR whereas late toxicities were similar in both treatment groups.[21,22] The PACE-B trial randomised 874 patients between conventional or stereotactic radiotherapy (36.25 Gy in 5 fractions) without ADT; SABR did not increase either gastrointestinal (GI) or genitourinary (GU) acute toxicities.[23] At 2 years, incidence of G2+ GI toxicities was low with no differences between groups; however, incidence of CTCAE G2+ GU toxicity was higher with SABR (6.4% versus 11.1%, p=0.02); the increase in RTOG G2+ GU toxicity was not statistically significant.

Brachytherapy

Prostate brachytherapy allows radiation dose escalation beyond what would be achievable by EBRT. In addition, there are fewer issues with changes in prostate position during treatment delivery.[24] Brachytherapy as monotherapy for low-risk and intermediate-risk patients with favourable features can be used as a single implant, most commonly with iodine-125 (I-125) seeds. For low-dose-rate (LDR) I-125 monotherapy the prescription dose to the CTV is 145 Gy.[25,26] An alternative option is fractionated high-dose-rate (HDR) brachytherapy with a recommended dose of 27 Gy in 2 treatments 1–2 weeks apart; single-fraction HDR schedules are associated with higher biochemical relapse rates.[27] For high-risk patients LDR or HDR brachytherapy in combination with ADT and EBRT to the prostate or prostate and pelvic nodes is an effective treatment.[10,28–30] Brachytherapy boost may be delivered before or after EBRT. Recommended fractionation schedule for LDR boost is 110 Gy and for HDR boost it is 15 Gy. Recommended EBRT schedules are 37 Gy in 15 fractions for prostate-only RT. Most published series for brachytherapy and EBRT combinations have used 46 Gy in 23 fractions for PNRT. For the pelvic nodal dose, please refer to the discussion below.

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In a meta-analysis of three RCTs, there was a significant benefit in 5-year biochemical-progression-free survival in favour of brachytherapy and EBRT combination versus EBRT alone (HR 0.49 [95% CI, 0.37–0.66], p<0.01) with no difference in 5-year OS. Late Grade 3 or worse toxicities were higher in the combination arms for both GU and GI with large confidence intervals: GU (RR 2.19 [95% CI, 0.76–6.30], p=0.15) and GI toxicities (RR 1.85 [95% CI, 1.00–3.41], p=0.05).[31] Omitting ADT for brachytherapy and EBRT combinations results in an inferior OS.[32]

Pelvic nodal radiotherapy

There is no large randomised trial evidence (GETUG-01, RTOG 9413) supporting that PNRT improves oncological outcomes.[33,34] A recent smaller trial showed improved biochemical control with PNRT.[35] However, in this study more than 80% of patients had staging PSMA PET, confirming N0 staging, pelvic nodes were treated to L4/5 level and the dose used was 68 Gy (prostate) and 50 Gy (lymph nodes) in 25 fractions. The acute toxicities were similar in both arms, but there was more late bladder toxicity in the PNRT arm.[36] Equivalent PNRT biological effective doses are 47 Gy in 20 fractions and 50–60 Gy in 37–39 fractions; the doses are computed for α/β=1.5 or 3 without time corrections. Commonly used schedules in the UK (46 Gy in 23 fractions and 44 Gy in 20 fractions) have a lower BED and may not control microscopic nodal disease. Results from the PIVOTALboost and RTOG 0924 trials are awaited to better define the role of PNRT. Patients with positive pelvic lymph nodes at the initial staging scans should be considered for PNRT as part of their management.[37] The PEARLS trial is currently recruiting, delivering 44 Gy in 20 fractions to uninvolved nodes with a boost to involved nodes of 51 Gy.[38]

Postoperative radiotherapy

From three randomised trials (RADICALS-RT, GETUG-17, RAVES) and a meta-analysis, there is no evidence that event-free survival improves with adjuvant radiotherapy compared with early salvage radiotherapy (HR 0.95, 95% CI 0.75–1.21; p=0.70), with only 1 percentage point change in 5-year event-free survival (89% versus 88%).[39–42] The use of hormone therapy in combination with salvage postoperative radiotherapy has been tested in three randomised controlled trials. RTOG 9601 showed a survival benefit with 24 months of bicalutamide.[43] GETUG-16 showed a PFS but not an OS benefit; the 12-year OS was 86% for radiation therapy plus goserelin versus 85% for radiation therapy alone.[44] In the SPORRT trial, 1,716 patients were randomised to prostate bed RT, prostate bed RT plus 6 months ADT or PNRT plus 6 months ADT. At a median follow-up of 8.2 years, the 5-year FFS rates were 70.9% (95% CI 67.0–74.9) in group 1, 81.3% (78.0–84.6) in group 2 and 87.4% (84.7–90.2) in group 3.[45] There is currently no evidence supporting dose escalation in postoperative settings that would improve outcomes. Recommended schedules are either 66 Gy (46–50 Gy for nodes) in 33 fractions or 52.5–55 Gy (44 Gy for nodes) in 20 fractions.[37]

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Recommendations

Prostate-only RT:

- 60 Gy in 20 fractions over 4 weeks (Grade A)

In addition to a brachytherapy boost:

- 37.5 Gy in 15 fractions (prostate only) over 3 weeks before or after 15 Gy HDR brachytherapy boost (Grade A)
- 46 Gy in 23 fractions (prostate and pelvic nodes) over 4.5 weeks followed by 15 Gy HDR or 115 Gy LDR brachytherapy boost (Grade A)

Stereotactic radiotherapy (SBRT):

- 36.25 Gy in 5 fractions (Grade A)

Pelvic nodal RT:

- 50 Gy in 25 fractions over 5 weeks or equivalent (Grade A)
- 46 Gy in 23 fractions over 4.5 weeks (Grade A)
- 44–47 Gy in 20 fractions over 4 weeks (Grade D)

Postoperative RT:

- 66 Gy in 33 fractions over 6.5 weeks or
- 52.5–55 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.[46]

Palliative radiotherapy

For patients with high-risk localised disease, who are not fit or unsuitable for daily treatment and unsuitable for a watch and wait policy, hypofractionated radiotherapy may be used similar to the schedule tested in the STAMPEDE trial.[47] Prostate radiotherapy should be considered for patients with metastatic hormone-sensitive prostate cancer with a low metastatic burden (defined as per the CHAARTED trial), which showed an improvement in PFS and OS.[48] In the castration-resistant group, useful and long-term disease control is possible and symptom relief for troublesome haemorrhage, pain, outflow obstruction or pressure symptoms can be achieved with palliative RT. There are only cohort studies as supporting evidence that patients with a reasonable life expectancy benefit from radiotherapy in this setting.[8,49–52]

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Recommendations

Recommended palliative RT schedules

High-risk localised disease, unsuitable for longer-course fractionation and hormone-sensitive disease with low metastatic burden:

- 55–60 Gy in 20 fractions over 4 weeks (Grade A)
- 30–36 Gy in 6 fractions over 6 weeks (Grade A)

Castration-resistant disease with local progression and/or symptoms:

- 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.[46]

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14 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 reirradiation 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).

Total neoadjuvant therapy (TNT) uses chemotherapy in addition to radiotherapy in the neoadjuvant setting.

In recurrent or incurable disease, radiotherapy can reduce the disease burden and help control symptoms.

NICE guidance published in 2020 recommends preoperative radiotherapy with or without chemotherapy for rectal cancer staged as cT1–T2, cN1–N2 or cT3–T4, any N0–2, M0, as the evidence from several randomised controlled trials shows that this approach reduces local recurrence and has better overall and disease-free survival compared with no preoperative radiotherapy.[1]

Neoadjuvant therapy

Risk-reducing radiotherapy

Preoperative radiotherapy is preferred to postoperative treatment as the preoperative technique is more effective and less toxic (Level 1a).[2–5]

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 5 fractions) plus 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).[6,7] The overall survival was the same in both groups (Level 1b).[4] The MRC-07 trial demonstrated the advantage of SCRT (25 Gy in 5 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 4 years by 61% (hazard ratio [HR] 0.39, confidence interval [CI] 0.27–0.58). This translates to an absolute reduction in risk of local relapse of 6.2% at 3 years. There is also an absolute improvement in disease-free survival of 6% at 3 years with no effect on overall survival (Level 1b).[4,8]

The Stockholm III trial evaluated SCRT (25 Gy in 5 fractions) followed by immediate surgery versus delayed surgery after 4–8 weeks or long-course radiotherapy (50 Gy in 25 fractions).

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The rate of local recurrence was similar in all arms but the rate of postoperative complications was significantly higher in the SCRT and immediate surgery compared with the delayed surgery arm.[9]

SCRT, however, increases long-term toxicity, with poorer functional outcomes, especially in terms of continence (Level 1b).[4,10,11]

Recommendation

Short-course preoperative radiotherapy:

- 25 Gy in 5 daily fractions (Grade A)
- Followed by definitive surgery either within a week or delayed surgery

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]

Down-staging radiotherapy

For inoperable cancers, cancers that involve or threaten the circumferential margin or cancers deemed to be at high risk of relapse, down-staging treatment is recommended.[12,13]

Doses of >30 Gy improve the response rate, and long-course chemoradiotherapy (LCCRT) has been shown to improve response rate and the likelihood of R0 resection compared with long-course radiotherapy alone (Level 1a), though the sphincter preservation rate and long-term outcomes appear to be similar.[2,4,12,13] A dose of 45–50.4 Gy in 1.8 Gy per fraction with concurrent chemotherapy is commonly used in the UK.

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.[4,14,15] Addition of a second agent such as irinotecan or oxaliplatin has not demonstrated improvement in outcomes and is not recommended (Level 1A).[4,16–19]

TNT has been shown in multiple trials to reduce local recurrence rates (STELLAR/Prodige 23), reduce distant free metastasis (STELLAR, RAPIDO, Prodige 23) and improve clinical and pathological complete response (RAPIDO, OPRA, Prodige 23) for high-risk rectal cancers. Two studies have found an overall survival benefit at 3 years, with one showing at 8 years that benefit was not maintained.[20–23]

Some authors have reported a ‘boost’ of 5.4 Gy in 3 fractions to the gross tumour volume plus margin following 45 Gy in 25 fractions to a larger volume.[15] The efficacy and toxicity of this remains unknown (Level 2b).[4] A simultaneous integrated boost of 50 Gy in 25 fractions is recommended. A dose of 52 Gy in 25 fractions is an alternative and is equivalent to 54 Gy in 30 fractions used in the EXPERT study, with minimal acute toxicity.[24,25] Higher doses correlate to improved response rates rather than local relapse rate and hence doses of greater than 50 Gy should only be considered for boosting disease that lies outside the resection margin or for an organ-preservation approach.[26]

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 5 fractions, have reported significant tumour regression, with 60–80% of patients going on to have delayed surgery (Level 2c).[4,27,28]

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Recommendations

For down-staging LCCRT:

- 45 Gy in 25 daily fractions with concurrent chemotherapy (Grade A); optional boost of 5.4 Gy in 3 fractions to smaller volume (Grade C) or
- 50 Gy in 25 fractions simultaneous integrated boost (SIB) (Grade C)

For patients not suitable for chemotherapy:

- 45 Gy in 25 daily fractions (Grade A) with or without boost
- 25 Gy in 5 daily fractions (Grade B)

For total neoadjuvant therapy:

- 25 Gy in 5 daily fractions (Grade A)
- 45 Gy in 25 daily fractions with concurrent chemotherapy (Grade A); optional boost of 5.4 Gy in 3 fractions to smaller volume (Grade C) or
- 50 Gy in 25 fractions SIB (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]

Brachytherapy

Low-energy contact brachytherapy[29,30] (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. In patients unfit for surgery or who choose to not have surgery, these techniques can be used to improve local control.

For tumours less than 5 cm in size (T2–T3b, N0-1, node <8 mm), LCCRT plus contact radiotherapy significantly improves the 3-year organ-preservation rate, especially with tumours <3 cm where contact boost was delivered before LCCRT (Level 1b).[31]

There is one published RCT evaluating a neoadjuvant 10 Gy in 2 fractions HDR brachytherapy boost (endoluminal) along with 50.4 Gy in 28 fractions of EBRT (Level 1b).[4,32] This trial showed no improvement in pathological complete response (pCR) or long-term survival despite a better R0 resection rate for T3 tumours.

Contact radiotherapy can be used following endoscopic resection if there are adverse pathological features (CONTEM 1).

Contact radiotherapy can be used for the palliative treatment of patients with a recurrence or metastases.

Dose recommendations are derived from published trials and current consensus among UK centres offering brachytherapy.[33–37]

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Recommendations

Postoperative:

- pT1 or pT2 with adverse pathological features: 60 Gy in 2 fractions over 2 weeks followed by EBRT (Grade B)

Radical treatment (<3 cm):

- cT1/cN0: 90–110 Gy in 3–4 fractions (30 Gy ×3 and final boost 20 Gy) over 3–6 weeks (Grade C)
- cT1/cN1 or cT2–T3b cN0/cN1 (node <8 mm): 90–110 Gy in 3–4 fractions (30 Gy ×3) and optional final boost (20 Gy) over 3–6 weeks, followed by EBRT (Grade A)

Radical treatment (>3 cm):

- cT1/cN1 or cT2–T3b cN0/cN1 (node <8 mm): EBRT followed by contact radiotherapy or HDR boost if regression to <3 cm: 90 Gy in 3 fractions (30 Gy ×3) and optional final boost (20 Gy) over 3–6 weeks (Grade A) or
- HDR brachytherapy 12 Gy in 2 fractions (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]

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 (Grade D)
- 20–25 Gy in 5 daily fractions (Grade D)
- HDR brachytherapy 10 Gy at 1 cm 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.[4]

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Reirradiation

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, reirradiation should be considered for limited volumes, including the use of stereotactic ablative 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 reirradiation is required to achieve this, currently hyperfractionated chemoradiotherapy should be preferred to limit late toxicity (Grade D).[3]

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15 Renal cancer

Background

Primary kidney cancer is the seventh commonest cancer in the UK.[1] Approximately 20% present with metastatic disease and another 20–25% develop metastases after radical treatment to the primary (usually radical nephrectomy/nephron-sparing surgery). Historically kidney cancer has been considered intrinsically radioresistant based on a small amount of experimental data. Two xenograft models have measured α/β ratios as 2.6 and 6.9 Gy.[2] A possible mechanism may be the activation of HIF1α (which is characteristic of clear cell cancers owing to von Hippel-Linda [VHL] mutations) stimulating endothelial cell survival, but preclinical models suggested ablative doses of radiotherapy can overcome this, inducing cell death by alternative means to DNA damage and mitotic catastrophe.[3]

Primary radiotherapy

Neoadjuvant or adjuvant conventional radiotherapy for primary renal cell carcinoma (RCC)

Historical series including small randomised trials of pre- or postoperative radiotherapy gave inconsistent results and used a variety of doses and outdated techniques, with higher doses giving significant toxicity.[3] There is therefore no current role for these approaches.

Stereotactic radiotherapy for primary renal cancer

Surgical resection remains the standard of care in localised disease, but surgery is not feasible in all due to both disease and patient factors including co-morbidities. Stereotactic radiotherapy is less invasive than standard of care surgery, with the potential for faster recovery times and fewer side-effects, though there are no direct comparisons in a trial setting.

In a pooled analysis of 190 patients from 12 international centres, the cumulative 5-year incidence of local failure was 5.5%. Both single and multifraction regimes were used and 29% of patients had a single kidney.[4,5]

In a meta-analysis of 372 patients, median follow-up was 28 months, median tumour size was 4.6 cm, local control 97.2% and glomerular filtration rate reduction 7.7 ml/min; Grade 3–4 toxicity was 1.5%.[6]

Stereotactic radiotherapy is now recommended in the NCCN 2022 guidelines for medically inoperable patients with stage I kidney cancer.[7] Stereotactic radiotherapy can be used for tumours that are not suitable for thermal ablative techniques (cryoablation or radiofrequency ablation), such as larger tumours and those close to the collecting system or major vessels.

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Palliative radiotherapy to symptomatic renal primary

For bleeding or pain from a renal primary, embolisation, palliative nephrectomy or systemic therapy are generally preferred to radiotherapy. However, palliative radiotherapy is occasionally used. Dose should be individualised to the patient's circumstances and potential toxicity (proximity of liver, stomach, small bowel etc).

Metastatic renal cancer

Palliative radiotherapy to metastatic disease

A dose response to palliative radiotherapy has been found in some retrospective series but not others.[8,9,10] Radiotherapy is likely to have been underused in palliation of metastatic disease because of preconceptions of radioresistance.[11] Fractionated radiotherapy (30 Gy in 10 fractions/20 Gy in 5 fractions) is recommended particularly for large masses, and 8–10 Gy in a single fraction for those of poor performance status.

Oligometastatic renal cancer

Some favourable-prognosis patients have oligometastatic disease.[12] These patients can have prolonged drug-free survival with treatment of individual metastases, either with surgery or high-dose palliative radiotherapy or stereotactic radiotherapy. Common sites of oligometastases in renal cancer include lung, brain, bone, thyroid, pancreas, soft tissue and head and neck sites including sinuses.

Stereotactic radiotherapy can be used for sites of oligometastases and may be appropriate for oligo-progressive areas in patients responding to systemic therapy. Stereotactic radiotherapy has been shown to have excellent rates of local control in several series. The potential of stereotactic radiotherapy to treat oligometastatic RCC was established through multiple retrospective series and prospective trials, with local control rates >85% at 2 years for metastatic lesions for both clear cell and non-clear cell RCC and a meta-analysis showing 90% local control.[13,14]

See the 'Oligometastases' chapter for treatment principles.

Head of pancreas/duodenum

Pancreatic metastases are common and associated with a favourable prognosis. They are frequently asymptomatic, but metastases at the head of the pancreas may invade the duodenum and cause major gastrointestinal bleeding. High-dose palliative radiotherapy with IMRT (50 Gy in 20–25 fractions), or stereotactic radiotherapy if there is not direct duodenal invasion, can lead to prolonged disease control.[15]

Combination of radiotherapy with systemic therapy

Anti-angiogenic tyrosine kinase inhibitors (TKIs): Caution should be exercised when combining anti-angiogenic TKIs with palliative radiotherapy, particularly when the field encompasses a critical tissue such as brain, spinal cord, liver or small bowel. Although there are no formal guidelines, drug interruption would be advisable when using higher palliative doses over critical structures.[16]

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Immunotherapy: Two phase II trials have used the combination of radiotherapy and immunotherapy in metastatic disease and this combination is associated with an acceptable safety profile.[17,18] In the oligometastatic disease setting stereotactic radiotherapy and short-course pembrolizumab is well tolerated, with excellent local control.[19]

Recommendations

Primary renal cancer:

- Stereotactic radiotherapy is safe and effective for medically inoperable patients with primary renal cancer; either single-fraction (26 Gy in 1 fraction) or multifraction regimens (42 Gy in 3 fractions/40 Gy in 5 fractions) are recommended (Grade B, Level 2a)

Oligometastases:

- Stereotactic radiotherapy has a role in treating oligometastatic renal cancer (Grade B, Level 2a)

Palliative radiotherapy for symptom relief:

- Fractionated radiotherapy (30 Gy in 10 fractions/20 Gy in 5 fractions) is recommended particularly for large masses; consider 8–10 Gy in a single fraction for those of poor performance status (Grade C, 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.[20]

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16 Sarcoma

Background

Bone and soft-tissue sarcomas have more than 100 different histological subtypes and should be managed under the guidance of a bone and soft-tissue sarcoma centre. Radiotherapy is commonly used as an adjunct to surgery or used as a primary or palliative treatment.[1] Radiotherapy is an integral part of the multimodality treatment of Ewing sarcoma and rhabdomyosarcoma.[2,3] Clinical experience reports sarcomas vary widely in radiosensitivity, and this can influence its application in the timing of radiotherapy. The standard of care is to deliver radiotherapy with conventional fractionation when treatment is with curative intent. However, hypofractionated schedules are considered in selected cases. Intensity-modulated radiotherapy (IMRT), volumetric-modulated arc therapy (VMAT) or proton therapy may be appropriate when optimal dose fractionation is not achievable with conventional techniques. The principles of stereotactic body radiotherapy (SBRT) for oligometastatic disease follow the guidance in SBRT guidelines.[4,5]

Extremity soft-tissue sarcomas

Surgery is the primary treatment modality in most soft-tissue sarcomas. Radiotherapy is recommended as an adjunct to limb-conservation surgical approaches. For large, deep-seated, high-grade tumours, radiotherapy is recommended as an adjunct in the preoperative or postoperative settings to improve local control rates to greater than 80%.[6] The Canadian Sarcoma Group SR-2 trial randomised patients to preoperative radiotherapy with 50 Gray (Gy) in 25 daily fractions compared with postoperative radiotherapy with 66 Gy in 33 daily fractions.[7] Preoperative radiotherapy and postoperative radiotherapy have comparable local control rates, but preoperative radiotherapy is associated with increased wound complications (predominantly in the distal lower limb) and postoperative radiotherapy leads to increased limb fibrosis, joint stiffness, lymphoedema and bone fractures.[8] Tumour location, proximity to critical normal tissues and ability to resect widely impact on the decision regarding the use and timing of surgery and radiotherapy. International consensus is to recommend radiotherapy to be delivered in the preoperative setting. This allows smaller volumes to be treated to a lower total dose, which translates to a potential decreased functional morbidity.[1,9,10]

Histopathological subtypes differ in their risk for local recurrence and responsiveness to radiotherapy. Myxoid liposarcomas are relatively sensitive to radiotherapy and may have a significant reduction in size with preoperative radiotherapy.[11] Myxofibrosarcomas have a high propensity for local recurrence as they are highly infiltrative and have higher rates of positive margins after surgery.[12] Given this increased risk of local recurrence associated with myxofibrosarcomas, radiotherapy is recommended to improve local control.

Patients with localised unresectable disease may be considered for radical radiotherapy with the aim of achieving local control. A total dose of 64 Gy at 2.0 Gy per fraction is recommended.[13,14</]

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Technique

IMRT-based treatment is preferred over conventional techniques in the majority of cases, providing dose homogeneity and reduced incidence of high-grade toxicities, such as fibrosis.

Alternative preoperative radiotherapy schedules

Modern radiotherapy and surgical techniques have improved outcomes for extremity soft-tissue sarcomas applying conventional fractionation schedules. Preoperative hypofractionated schedules have been evaluated but are yet to report comparable local control rates and toxicity profile.[15] The safety and efficacy of dose de-escalation for myxoid liposarcoma continues to be under investigation following an initial phase II study demonstrating comparable local control to historical controls.[10] Further, a randomised study is evaluating a postoperative dose of 50 Gy in 25 daily fractions for patients with negative resection margins.

Recommendations

Preoperative radiotherapy:

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

Postoperative radiotherapy:

- 50 Gy in 25 fractions over 5 weeks plus 10 Gy in 5-fraction boost over 1 week for average risk (Grade C)
- For postoperative treatment, a boost of up to 16 Gy in 8 fractions over 1.5 weeks is recommended for disease considered at higher risk of local recurrence due to positive margins (Grade C)
- This boost may be limited to 10 Gy in 5 fractions at certain anatomical sites (for example, across joints, Achilles tendon, brachial plexus)

Unresectable: primary radiotherapy

- 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.[16]

Retroperitoneal soft-tissue sarcomas

Surgery is the mainstay of treatment for retroperitoneal sarcomas (RPS), but locoregional recurrence remains the predominant pattern of disease recurrence. An international expert consensus panel concluded that preoperative radiotherapy is preferable to postoperative radiotherapy when radiotherapy is recommended as an adjunct to surgery. The EORTC STRASS trial investigated the addition of radiotherapy to the surgical management of RPS. This trial randomised patients to preoperative radiotherapy (50.4 Gy in 28 daily fractions)

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followed by surgery versus surgery alone. The primary outcome was abdominal recurrence-free survival. The trial did not show a statistically significant abdominal recurrence-free survival benefit for the addition of radiotherapy to surgical resection. Surgical morbidity was not statistically different between the two arms.[17] Exploratory analyses suggested that preoperative radiotherapy might improve the local control in grades 1–2 liposarcoma, whereas there did not appear to be a radiotherapy benefit for leiomyosarcoma and high-grade de-differentiated liposarcoma. The STRASS trial investigators also collected data, known as STREXIT, on non-enrolment cases. The STREXIT study also demonstrated improved outcome in G1–2 liposarcoma.[18] In conclusion, preoperative radiotherapy is recommended in selected cases in discussion with sarcoma surgical colleagues where concern is raised of a high risk of local recurrence following an anticipated close resection margin.

Recommendation

Preoperative radiotherapy:

• 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.[16]

Desmoid tumours

Fibromatosis or desmoid tumour is a proliferation of well-differentiated myofibroblasts and fibroblasts with low to moderate mitotic activity. The process is locally aggressive but does not metastasise. An international consensus recommends a multidisciplinary sarcoma specialist approach with, if clinically suitable, a period of surveillance recommended as initial management.[19] Radiotherapy is considered in very selective cases: unresectable tumours growing rapidly in critical anatomical sites or as adjunct following surgery, especially if further surgery would result in significant morbidity or functional deficit, failed systemic therapy or symptom relief.[20]

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.[16]

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Ewing-type tumours and primitive neuroectodermal tumour (PNET)

When surgical resection is feasible or appropriate, this is usually carried out after preliminary chemotherapeutic cytoreduction. Ewing sarcoma is a radiosensitive disease. If it is anticipated that surgery will result in a marginal resection, preoperative radiotherapy is considered at 45–50.4 Gy in 1.8 Gy per fraction. Where surgery has been considered as primary local treatment and a radical surgical clear resection margin is not achieved and/or there is >10% residual viable disease remaining 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, head and neck, spine, pelvis), in which case radiotherapy can be used as a primary 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.[21]

Recommendations

Doses are based upon the current Euro Ewing 2012 radiotherapy protocol.[22]

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 fractions 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.[16]

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Ewing-type tumours: Lung metastases

Curative intent multimodality treatment for patients with lung metastases includes whole-lung radiotherapy (in patients who have not received busulphan).[23] 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.[24,25] An appropriate bi-daily fractionation schedule would be 17.5 Gy in 14 fractions of 1.25 Gy per fraction over 2 weeks with a minimum of a 6-hour interfraction interval. Other centres have reported that a dose of 15 Gy in 10 fractions over 3 weeks is well tolerated in an adult population.[23] Whole-lung radiotherapy should be computed tomography (CT) planned with an inhomogeneity correction.

Recommendations

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

Whole-lung radiotherapy:

<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.[16]

Rhabdomyosarcoma

Paediatric-type rhabdomyosarcomas (alveolar and embryonal) are relatively radiosensitive disease. In the current FAR-RMS protocol, disease is classified according to PAX-FOXO1 status (PAX-FOXO1 positive is classified as unfavourable disease). When surgical resection is feasible or appropriate, this is usually carried out after preliminary chemotherapeutic cytoreduction. If it is anticipated surgery will result in a marginal resection, preoperative radiotherapy is considered. Where surgery has been considered as primary local treatment and a radical surgical clear resection margin is not achieved then postoperative radiotherapy is recommended. Surgical resection may not be feasible or appropriate for certain anatomical sites (for example, head and neck, spine, pelvis), in which case radiotherapy can be used as a primary radical treatment.[3]

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Recommendations

Primary disease and involved lymph nodes where applicable:

- Complete response after induction chemotherapy: 41.4 Gy in 23 daily fractions over 4.5 weeks for preoperative radiotherapy or postoperative radiotherapy
- Incomplete response after induction chemotherapy and inoperable disease: 50.4 Gy in 28 daily fractions over 5.5 weeks

Metastatic disease:

- Favourable disease (PAX-FOXO1 negative): all sites – 41.4 Gy in 23 daily fractions over 4.5 weeks

Additional considerations:

In cases of malignant ascites, or diffuse peritoneal involvement, whole-abdominal radiotherapy should be considered. The usual dose will be 24 Gy in 16 daily fractions (or equivalent), followed by a boost to the primary tumour site (where identifiable) up to a dose of 41.4 Gy (microscopic disease) or 50.4 Gy (macroscopic disease).

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.[16]

Bone sarcomas

Patients should be treated within a dedicated bone sarcoma centre to determine the suitability of radiotherapy.

Osteosarcoma

Radiotherapy is recommended in the management of osteosarcomas, for unresectable primary tumours where surgery would be unacceptably morbid or as adjuvant treatment of tumours at high risk of local recurrence and with limited options for further surgery.[25]

Chondrosarcoma

Radiotherapy can be considered for unresectable disease (primary or recurrent), after incomplete surgery and for symptom palliation. Modern radiotherapy techniques with the ability to safely deliver high doses, including heavy particle therapy, should be considered whenever felt to be technically appropriate. High-dose radiotherapy is recommended for patients with skull base chondrosarcomas, based on the excellent outcome reported (80–90% local control rates).

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Chordoma

Chordomas arise from the persistent notochordal elements in the spine (sacrum 50%, mobile spine 20%) and in the skull base (30%). Extraskeletal cases are extremely rare. Patients with chordoma should be managed within a bone sarcoma multidisciplinary team (MDT). Local control will be with surgery or radiotherapy or both. Base of skull chordoma should be discussed at an appropriate MDT with the necessary expertise.[26–28]

Recommendations

Chordoma:

- Adjuvant radiotherapy: 70.2–75.6 Gy in 39–42 fractions depending on resection margins
- Radiotherapy can also be given as a split preoperative and postoperative schedule
- Definitive radiotherapy: 75.6 Gy in 42 fractions

Chondrosarcoma and osteosarcoma:

- Adjuvant radiotherapy limb: 60–66 Gy in 30–33 fractions depending on margins
- Adjuvant radiotherapy for pelvis and spine: 68.4–75.6 Gy in 38–42 fractions depending on margins and site
- Definitive radiotherapy: 75.6 Gy in 42 fractions

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.[16]

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 may be 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 (biologically effective dose [BED] 68 Gy with $\alpha\beta$=4) (Level 4); this may be limited to 36 Gy in 12 fractions when in close proximity to critical structures.[9,29]

Recommendations

Additional palliative radiotherapy schedules to consider in sarcoma include:

- 36 Gy in 6 fractions over 6 weeks (Grade D)
- 36 Gy in 12 fractions over 2.5 weeks (Grade D)
- 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.[16]

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17 Seminoma

Background

Stage I seminoma has a 15–20% risk of relapse; surveillance without treatment is one option. Relapses principally occur in the para-aortic nodes and the risk can be quantified using factors related to the primary tumour.[1] A tumour >4 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] This approach has now become the standard of care (Level 1b).[4]

If radiotherapy is considered in this setting then a dose of 20 Gy in 10 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]

Germ cell neoplasia *in situ* is a premalignant change of testicular tissue with a high rate of progression to invasive cancer. In patients with solitary testis, radiotherapy is recommended as an alternative to surgery where patients have adequate testosterone production to avoid replacement therapy (Level 2b).[4,6,7] This approach may preserve testosterone production but would still cause infertility, though there is a risk of later Leydig cell insufficiency, with studies reporting a testosterone decline of 3.6% per year and a 30–50% risk of requiring testosterone replacement in their lifetime.[8]

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.[9] A dose of 30 Gy in 15 daily fractions to the para-aortic nodal chain and ipsilateral iliac nodes is recommended. A boost of 5–6 Gy to enlarged lymph nodes may be considered (Level 2b).[4,10,11]

Multimodal treatment strategy is an alternative approach in stages IIA and IIB seminoma, which combines a single dose of carboplatin followed by radiotherapy with a de-escalated field size. One technique is to treat the para-aortic node chain only to 30 Gy in 15 fractions (Level 1b).[4,12] The other technique treats involved node only but stratifies stage IIA to receive 30 Gy in 15 fractions and stage IIB to receive 36 Gy in 18 fractions (Level 1b).[4,13,14]

Radiotherapy carries an excess risk of death as a result of radiation-induced second cancer.[5] Follow-up at 30 years 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).[4,15] These data are mainly from patients receiving para-aortic and pelvic radiotherapy. The risk for patients receiving para-aortic radiotherapy only is predicted to be lower but long-term data are lacking.[16]

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Seminoma

Recommendations

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

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

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

Germ cell neoplasia *in situ* in patients with solitary testis:

• 18–20 Gy in 9–10 fractions over 2 weeks (Grade B)

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)

Involved-node only radiotherapy after carboplatin:

• Stage IIA seminoma – 30 Gy in 15 fractions over 3 weeks (Grade B)
• Stage IIB seminoma – 36 Gy in 18 fractions over 3.5 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.[4]

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18 Skin cancer

Squamous cell carcinoma and basal cell carcinoma

Background

Surgery and radiotherapy are both highly effective curative treatment modalities for cutaneous squamous cell carcinoma (SCC) and basal cell carcinoma (BCC). The choice of treatment modality is determined by factors including tumour size, location, performance status (PS), age 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 function and cosmetic results can be achieved. Radiotherapy to the lower leg can lead to high risk of radionecrosis and ulceration due to poor vasculature, especially in older patients. Skin radiotherapy can be delivered as external beam or brachytherapy.[1] Brachytherapy is reported to offer favourable cosmesis over external beam in selected patients with SCC and BCC.[2,3] There appears to be a slightly higher local recurrence rate following radiotherapy for SCC compared with BCC.[4–6]

Postoperative radiotherapy for SCC should be considered for high-risk features.[7,8] Elective irradiation of first-echelon lymph nodes can be considered for higher-risk SCC.[8,9]

There are no randomised studies examining dose fractionation; in addition, most historical series report use of multiple dose fractionation schedules.[10] 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.[10,11] Similar doses are used for BCC and SCC, although some suggest higher doses for SCC.[12]

Standard fractionation has long been considered a standard approach to reduce long-term toxicity.[5] A meta-analysis of patients with SCC and BCC showed that hypofractionation has favourable cosmesis and recommended the use of regimens with BED3 of ~100 Gy, such as 50 Gy in 15 fractions, 36.75 Gy in 7 fractions or 35 Gy in 5 fractions, as they result in ‘good’ long-term cosmesis in 80% of patients.[5]

In a large retrospective series of 1,005 predominantly small BCCs and SCCs, single-fraction doses of 18, 20 and 22.5 Gy provided a 5-year local control rate of 90%; the skin necrosis-free rate at 5 years was 84% and skin necrosis occurred more frequently with the 22.5 Gy dose (Level 4).[13,14]

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.[15]

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Recommendations

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 (field size <3 cm) (Grade C)
- 32.5–35 Gy in 4–5 fractions over 1 week (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/or in area of poor radiation tolerance:

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

The choice of dose fractionation considers patient factors, tumour and field size.

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.[14]

Squamous cell carcinoma and regional lymph node disease

Background

Surgical management of regional lymph node disease is regarded as the treatment of choice. Retrospective studies have demonstrated an association of higher regional disease control rates with surgery and adjuvant radiotherapy.[7,8]

Several series report multiple factors predictive of regional relapse after surgery, including lymph node ≥3 cm, multiple involved nodes and extracapsular spread.[7,8,16,17]

In the head and neck region, the use of adjuvant radiotherapy has been shown to reduce regional recurrence rates and improve disease-free survival.[18]

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).[18] 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.[8]

Radical radiotherapy can be considered if surgery is inappropriate or declined.

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Recommendations

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

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

In 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.[14]

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Melanoma

Background

Melanoma has high repair capacity; this is evidenced by per fraction cell kill seen in *in vitro* cell lines irradiated with 2 Gy fractions.[1,2] Despite the high repair capacity, radiotherapy has an established role in certain circumstances and modest hypofractionation beyond 2.5 Gy per fraction may be advantageous, although randomised data defining the most effective dose fractionation schedule is lacking.

The primary treatment for cutaneous melanoma is complete local excision followed by adjuvant systemic therapy in those at high risk of cancer recurrence. Adjuvant radiotherapy 48 Gy in 20 daily fractions over 4 weeks delivered to the lymph node basin after lymphadenectomy reduces risk of relapse in the lymph node basin when compared with surveillance (21% versus 36%, p=0.023). Adjuvant radiotherapy delivered to the lymph node basin has no impact on relapse-free or overall survival.[3] An alternative hypofractionated schedule of 30 Gy in 5 fractions over 2.5 weeks is reported retrospectively from a single centre with high rates of locoregional control (94%) and low rates of late Grade 2 toxicity (10%).[4] The data for mucosal melanoma in the postoperative setting mirror the above, with adjuvant radiotherapy impacting upon local control (HR 0.51 [95% CI 0.35–0.76], p=0.155) but not impacting on risk of distant metastasis (HR 2.26 [95% CI 1.01–5.05], p=0.006).[5]

Adjuvant radiotherapy delivered to the lymph node basin in high-risk melanoma is associated with 20% risk of high-grade toxicity and is therefore not considered as the standard of care; this is because improvements in local control do not translate to improvements in the rate of distant metastatic spread or overall survival.[3]

Definitive radiotherapy for melanoma has a role where the primary disease is unresectable. Small case series in mucosal melanomas report 50% 3-year local control with hypofractionated regimens, an example being 50 Gy in 15 daily fractions over 3 weeks.[6,7]

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Desmoplastic melanoma is a rare melanoma subtype predominantly developing in sun-exposed sites and is associated with perineural spread with an increased risk of local recurrence.[8,9] Adjuvant radiotherapy 48 Gy in 20 daily fractions over 4 weeks improves local control (HR 0.48 [95% CI 0.27–0.87], p=0.02) in instances where the pathological resection margins were less than 8 mm.[8–10] There is no benefit from adjuvant radiotherapy where resection margins are 8 mm or greater.[10]

Lentigo maligna is an *in situ* melanoma developing in regions of sun-damaged skin characterised by atypical melanocytes involving the dermo-epidermal junction. Lentigo maligna can progress to lentigo maligna melanoma in up to 50% of cases. The gold standard approach is surgical resection with a 5 mm margin with Mohs' surgery considered for selected anatomical sites. Non-surgical approaches include topical therapies and radiotherapy; both non-surgical approaches have advantages in this often older patient population where the primary lesion can be ill defined and where extensive surgical resection and reconstruction has added morbidity. Systematic review reports 5% recurrence rate of lentigo maligna at 3 years following definitive radiotherapy.[11] Reported schedules extend from 35 Gy in 5 fractions over 5 weeks to 54 Gy in 27 fractions over 5.5 weeks. The RADICAL trial (NCT02394132) evaluating 2-year local recurrence in those treated with non-surgical therapies has completed recruitment and is in follow-up.[12]

20–30% of patients with advanced melanoma develop brain metastases within the first year of diagnosis.[13] Historical data report that whole-brain radiotherapy (WBRT) improves neurological symptoms in 76%, with 31% reporting complete symptom response.[14] Despite this, the median overall survival of the cohort was short at 10 and 14 weeks.[14]

Modern systemic therapies offer high overall response rate within the brain; most of the systemic therapies can be combined or sequenced alongside stereotactic radiosurgery or stereotactic radiotherapy (see chapter on 'Brain metastases'). WBRT should now not be routinely offered to patients with brain metastases. The sequencing of stereotactic radiosurgery and stereotactic radiotherapy alongside systemic therapy is being explored in clinical trials.

Radiotherapy for palliation of symptomatic melanoma metastases outside brain is effective, yielding complete and partial pain response in 9–25% and 35–75% of instances.[15–17] Standard palliative schedules such as 20 Gy in 5 fractions over 7 days or 8 Gy in 1 fraction are feasible for those whose PS precludes longer fractionated schedules.

Large case series report total dose greater than 30 Gy to be associated with improved palliative outcomes.[17] The choice of dose and fractionation in the palliative setting should be tailored to the needs of each patient.

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Recommendations

Adjuvant radiotherapy to the lymph node basin improves local control but is not considered as the standard of care for high-risk melanoma:

- 48 Gy in 20 fractions over 4 weeks (Grade A)
- 50–60 Gy in 25–30 fractions over 5–6 weeks (Grade C)

Definitive radiotherapy to primary unresectable disease:

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

Desmoplastic melanoma:

- 48 Gy in 20 fractions over 4 weeks (Grade C)

Palliative radiotherapy:

- 30 Gy in 10 fractions over 2 weeks (Grade C)
- 20 Gy in 5 fractions over 1 week (Grade B)
- 8 Gy in 1 fraction over 1 day (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]

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Merkel cell carcinoma

Background

Merkel cell carcinoma (MCC) is an uncommon but highly aggressive cutaneous neuroendocrine tumour with the highest mortality rate compared with other skin cancers.[1] Advanced aged, immunosuppression, Merkel cell polyomavirus and ultraviolet light exposure are hypothesised to be risk factors.[2–4]

International guidance for stages I–III MCC recommends surgery with a 1–2 cm margin as the primary treatment, with radiotherapy to the tumour bed and draining lymphatics reserved for postoperative high-risk cases, close margins or inoperable disease.[5,6]

MCC is radiosensitive,[7] and this has led to an established role for radiation therapy in primary management, particularly in Australia.[8,9] Due to the rare nature of this tumour, previous studies have largely been limited to case series with relatively small heterogeneous samples, and thus optimal management and dose and fractionation for MCC remains a subject of some debate. There are no randomised controlled trials to assess optimal dose and fractionation.

A large retrospective analysis of 2,735 patients from the National Cancer Database for patients with stages I–III MCC found that adjuvant radiotherapy doses of less than 50 Gy were associated with an increased hazard of death in all stages and anatomical sites (Level 3a).[10]

Radiotherapy in the radical setting can provide clinically meaningful outcomes with locoregional control rates of 75–85% with radiotherapy doses of 60–66 Gy in conventional 2 Gy fractions (Level 3a).[5,6,11] For T1 MCC, a dose of 57 Gy in 24 fractions is appropriate (Level 5).[12]

Hypofractionation can be considered; a retrospective study of 241 patients demonstrated that 45–50 Gy in 20 fractions and 30–35 Gy in 10 fractions produced no difference in infield or distant recurrence over 2 years compared with conventionally fractioned regimens (Level 3b).[13]

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Recommendations

Primary MCC and/or draining lymph node regions:

Definitive treatment:

- 60–66 Gy in 30–33 fractions over 6–6.5 weeks (Grade C)
- 50–55 Gy in 20–25 fractions over 4–5 weeks (Grade C)
- 45–50 Gy in 20 fractions over 4 weeks (Grade D)
- 30–35 Gy in 10 fractions over 2 weeks (Grade D)

Adjuvant treatment:

- 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.[14]

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Reirradiation

Background

Reirradiation of the skin can be considered in the radical, adjuvant (following salvage surgery) or palliative settings in instances where the benefits of exposure to further radiotherapy have been discussed within the multidisciplinary team.

Beyond small case series, there are no data to define the approach to skin reirradiation; the risks and benefits of skin reirradiation should be discussed with the patient.

Palliative radiotherapy to the skin

Background

Palliative radiotherapy is an excellent option for patients where there are no viable curative options.

Radiotherapy in this setting aims to reduce local symptoms and prevent disease-related complications such as bleeding or ulceration but can also potentially achieve local control. Palliative treatment should be minimally invasive and of short duration, especially for patients with poor PS or short life expectancy and for those unable to travel for multiple hospital visits.

Several hypofractionated regimes are used in palliative radiotherapy for skin cancer but it is not possible to offer evidence-based guidelines. Commonly used schedules include single exposure of 12–20 Gy for field size <3 cm, 14.8 Gy in 4 fractions twice daily over 2 consecutive days and repeated at 4-weekly intervals for a further 2 courses (QUAD shot, also used in reirradiation), 20 Gy in 2 fractions 1 week apart, 30 Gy in 10 fractions over 14 days, 30.6 Gy in 3 fractions over 14 days, 40.2 Gy in 6 fractions over 35 days, 35 Gy in 5 fractions 3 times a week, and 8 Gy per fraction delivered on days 0, 7 and 21.[1–5]

Longer treatment schedules should be considered in patients with favourable prognosis and expected longer-term disease control.[2]

Palliative radiotherapy schedules should be distinguished from radical treatment used in older or frail patients, such as adaptive split-course radiotherapy or mono- or biweekly hypofractionation.[6,7]

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Cutaneous and subcutaneous metastasis from non-skin primaries

Background

Local radiotherapy is an underused modality for the palliative treatment of symptomatic cutaneous and subcutaneous metastases from non-skin primary cancers.[8] Radiotherapy schedules used in cutaneous and subcutaneous metastases are consistent with those used in palliative radiotherapy for a skin cancer primary. Field size and dose per fraction will need to be kept in consideration to avoid skin necrosis.

Recommendations

Palliative radiotherapy:

- Single exposure of 12–20 Gy field size <3 cm (Grade C)
- 14.8 Gy in 4 fractions twice daily over 2 consecutive days and repeated at 4-weekly intervals for a further 2 courses (QUAT shot, also used in reirradiation) (Grade C)
- 20 Gy in 2 fractions 1 week apart (Grade C)
- 20 Gy in 5 fractions over 5 days (Grade C)
- 30 Gy in 10 fractions over 14 days (Grade C)
- 30.6 Gy in 3 fractions over 14 days (Grade C)
- 40.2 Gy in 6 fractions over 35 days (Grade C)
- 35 Gy in 5 fractions 3 times a week (Grade C)
- 8 Gy per fraction delivered on days 0, 7 and 21 (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]

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19 Bone metastases

Localised bone pain in established metastatic disease

Background

Bone metastases may be classified as uncomplicated (accounting for around two-thirds of cases) or complicated, defined by features suggestive of impending or actual fracture, associated soft-tissue mass or neurological deficits.[1,2]

Uncomplicated bone metastases

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, which have been subject to systematic review and meta-analyses. On the basis of this information, the recommended fractionation is a single dose of 8 Gray (Gy) (Level 1a).[3–5]

Recommendation

For the initial treatment 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.[6]

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 myelopathy (see chapter on oligometastases).

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 retreatment at some point.[7] Limited evidence suggests that response rates are similar

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to those after primary treatment.[8] There are no data to guide optimal dose fractionation for retreatment; a randomised trial compared 8 Gy single dose with 20 Gy in 5 fractions (8 fractions over the spinal cord) and showed no significant difference (Level 1b).[6,9] Both may be considered acceptable treatments for reirradiation.

Complicated bone metastases

Neuropathic pain

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 with multifraction treatment, for most patients 20 Gy in 5 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.[10]

Recommendations

For the reirradiation 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)

For the treatment of neuropathic 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.[6]

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 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 5 fractions or 8 Gy single dose (Level 5).

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Recommendations

To prevent pathological fracture:

- 8 Gy single dose (Grade C) or
- 20 Gy in 5 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.[6]

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.

Recommendations

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.[6]

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.[6]

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20 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. Prognostic scores including the disease-specific graded prognostic assessment (dsGPA) may assist in predicting prognosis but are often not in routine clinical use.[1] The management of these patients continues to be variable and individualised and should be coordinated within multidisciplinary teams.

Prognosis from brain metastases has improved in recent years, likely driven by advances in systemic therapy, but continues to be poor for a subgroup of patients.[1] Three important criteria when deciding on management of patients with brain metastases are:

- Prognosis of at least 6 months
- Controlled or treatable extracranial disease
- Karnofsky performance status of at least 70.

Patients who fail to meet these criteria have worse outcomes following irradiation of their intracranial metastatic disease and so may not benefit from treatment. Age may not be a significant prognostic indicator, and older patients may benefit from aggressive treatment of their brain metastases.[2]

For the purposes of this guidance, stereotactic radiosurgery (SRS) is considered equivalent across the commonly used stereotactic platforms of linear accelerators, Gamma Knife and CyberKnife. Though studies exist describing dosimetric differences between these platforms, there is no definitive evidence of a difference in clinical outcomes. The use of systemic therapies with intracranial penetrance is increasing, but their role in the place of, or in conjunction with, radiation therapy is yet to be fully established[3] and is outside the scope of this document.

SRS for solitary metastases

Radiation therapy of brain metastases has evolved from whole-brain radiotherapy (WBRT), to SRS with adjuvant WBRT, to SRS alone. Studies have shown SRS alone results in similar overall survival rates and so adjuvant WBRT is typically omitted to avoid associated neurocognitive side-effects.[4] Lesions larger than 4 cm in diameter are unlikely to be suitable for SRS due to an unacceptable dose of irradiated normal brain tissue and subsequent risk of radionecrosis, although the latest ASTRO guidelines recommend a maximum diameter of no more than 6 cm.[5] The recently published HyTEC report found that metastases treated in a single fraction with a normal tissue volume (excluding gross tumour volume) receiving more than 12 Gy (V12 Gy) to 5 cm^3, 10 cm^3 or >15 cm^3 resulted in radionecrosis rates of approximately 10%, 15% and 20% respectively.[6] Therefore, lesions larger than 2–3 cm in diameter, lesions in close proximity to a critical organ at risk or lesions where the V12 Gy is greater than 10 cm^3 should be considered for fractionated or staged radiosurgery. One study found improved local control and less radiation necrosis for metastases larger than 2 cm in diameter when treated with a fractionated regimen of 27 Gy in 3 daily fractions compared with a single fraction.[7]

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30 Gy in 5 daily fractions is another commonly used hypofractionated regimen,[8,9] while 35 Gy in 5 daily fractions has also been prospectively evaluated and is sometimes used.[10] Staged radiosurgery is an adaptive approach where large lesions are reimaged, planned and treated at 2- or 3-weekly intervals and is used in place of fractionation at some centres.[11]

SRS for multiple metastases

Early trials of SRS in brain metastases included patients with up to 3 lesions.[12] Prospective, randomised data now exist to support the use of SRS alone for up to 4 metastases[13] and prospective, observational data support the use of SRS alone for up to 10 metastases.[14] The use of SRS alone for more than 10 metastases is controversial and not supported by international guidelines due to a lack of evidence.[5] Trials are currently recruiting to compare overall survival outcomes for patients including those with more than 10 metastases treated with SRS versus hippocampal-sparing WBRT, and results are awaited (trial identifiers NCT03550391, NCT01592968, NCT03075072 and NCT03775330). However NHS clinical commissioning criteria for the use of SRS in brain metastases do not specify a maximum number and instead specify a total intracranial disease volume limit of 20 cm^3, [15] while the European Association of Neuro-Oncology (EANO) recommends a stricter limit of 15 cm^3. [16]

Recommendations

Single-fraction SRS:

Lesion diameter:

- <20 mm – 21–24 Gy single dose (Grade B)
- 21–30 mm – 18 Gy single dose (Grade B)
- 31–40 mm – 15 Gy single dose (Grade B) (consider hypofractionated SRS)

Hypofractionated SRS:

- 24–27 Gy in 3 daily fractions (Grade B)
- 30 Gy in 5 daily fractions (Grade B)
- 35 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.[17]

WBRT for single or multiple metastases

Patients not suitable for SRS can be considered for WBRT, although certain patient subgroups may not benefit. The Medical Research Council (MRC) QUARTZ trial found those with non-small cell lung cancer (NSCLC) and a limited prognosis had no overall survival or quality-of-life benefit with WBRT over best supportive care.[18] Several randomised trials have compared different radiotherapy regimens for patients with multiple cerebral metastases. Most have used 30 Gy in 10 fractions as the control arm and have compared this regimen with either higher or lower doses.[19–22] Only one small study of 70 patients has compared the 6-month survival rate after 30 Gy in 10 fractions with that after 20 Gy in 5 fractions, and this found no significant difference.[23] A Radiation Therapy Oncology Group (RTOG) study reported in

1980 compared three regimens: 40 Gy in 15 fractions, 30 Gy in 10 fractions and 20 Gy in 5 fractions.[24] 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 5 fractions is inferior to, or better than, 30 Gy in 10 fractions (Level 1b). No improvement in survival has been shown when dose is increased beyond 30 Gy in 10 fractions (Level 1b).

Methods to reduce the risk of neurocognitive decline associated with WBRT include hippocampal sparing, provided no lesion is within close proximity of the hippocampus.[25] A randomised controlled study of the concurrent use of the glutamate receptor antagonist memantine did not reach the primary endpoint of reduced decline in cognitive function and so has not received approval from the National Institute for Health and Care Excellence (NICE) in the United Kingdom.[26]

Recommendations

Whole-brain radiotherapy ± hippocampal sparing:

- 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.[17]

Postoperative radiotherapy

Evidence from two randomised trials suggests an overall survival benefit from adding surgery to WBRT for patients of good performance status with a solitary metastasis (Level 1a).[27,28] Though a third trial did not show an overall survival benefit, this may have been due to the high proportion of poor-performance status patients included.[29] Surgical resection without adjuvant WBRT carries twice the risk of cavity recurrence.[30] SRS to the surgical cavity has shown similar overall survival rates and less neurocognitive decline than adjuvant WBRT and so is generally preferred.[31] Preoperative SRS looks to mitigate against the issues of difficulty contouring the surgical cavity and relatively high subsequent focal leptomeningeal rates, and trials have opened in some centres internationally to compare outcomes with adjuvant SRS. Results from these trials are awaited (trial identifiers NCT03741673, NCT04503772).

Currently, SRS to the surgical cavity following complete resection of cerebral metastases is not recommended by NHS England due to a lack of evidence of improvement in overall survival compared with observation alone. However, where there is evidence of residual or recurrent disease, SRS should be considered.

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Recommendations

Adjuvant SRS, adapted from various studies:[5,32,33]

Cavity volume (cm3)	Equivalent sphere diameter (cm)	Single-fraction SRS dose (Gy)	Level of evidence
<4.2	<2.0	20 Gy	B
≥4.2 to <8.0	≥2.0 to <2.5	18 Gy	B
≥8.0 to <14.4	≥2.5 to <3	17 Gy	B
≥14.4 to <20	≥3 to <3.5	15 Gy (or fractionated SRS)	C
≥20 to <30	≥3.5 to <4	For fractionated SRS	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.[17]

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21 Extracranial oligometastases

Background

This document is intended to provide an outline of the evidence-based dose fractionation schedules published in the latest UK SABR Consortium guidelines[1] and should be read in conjunction with these guidelines.

The metachronous oligometastatic state can be defined as 1–5 metastatic sites, typically occurring more than 6 months after successful treatment of primary disease.[2,3] At present NHS commissioning allows treatment of up to 3 metachronous oligometastases.

Oligometastases can occur at different sites including bone (including spine), lymph node, lung, liver and adrenal. 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.[4] The SABR-COMET phase II trial randomised 99 patients, across multiple locally controlled primary cancers, using stereotactic ablative body radiotherapy (SABR) to treat 1–5 oligometastases occurring more than 3 months after primary treatment.[5] This trial showed improved 5-year overall survival with the addition of SABR (42% versus 18%).

Other randomised trials have supported the benefit of metastasis-directed therapy in metachronous oligometastatic prostate cancer[6,7] and painful spinal metastases.[8–11] The UK has completed a Commissioning through Evaluation programme review, finding very low rates of severe G3+ toxicity (≤2% for any toxicity) across 1,422 patients treated for 1–3 extracranial metachronous oligometastases.[12] Meta-analysis of 21 prospective SABR studies has suggested grade 3–5 toxicity rates of 1.7% for acute and 1.2% for late effects respectively.[13] Thus, although phase III data are awaited, metastasis-directed therapy may be deployed for metachronous oligometastatic disease, as an alternative to surgery or where surgery is not possible or deemed too high risk.

Research is ongoing into the role of SABR for oligometastases in both the synchronous[14,15] and oligoprogressive settings,[16] but the NRG BR002 randomised data[17] for synchronous oligometastatic breast cancer have failed to show a benefit, so SABR is not currently recommended in the oligoprogressive or synchronous settings outside a clinical trial.

There is no established consensus on dose fractionation for oligometastatic disease. Recommendations have been derived from systematic reviews of non-randomised studies (prospective and retrospective [Level 3a]), along with expert consensus from the Commissioning through Evaluation Service Specification (Level 5).[1] For all sites, it is recommended that the critical organ dose constraints agreed by the UK SABR Consortium should be considered.[18]

The dose fractionation recommendations here provide guidance only, and when delivering SABR clinicians must balance the priorities of delivering an ablative tumour dose while respecting dose constraints to the surrounding organs at risk. Therefore, the total dose may be lowered at the discretion of the treating clinician and radiotherapy team dependent on individual patient and dosimetric factors. Even at reduced SABR doses, the equivalent dose in 2 Gy per fraction will often exceed the common total doses used for palliative radiotherapy.

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The dose fractionation regimes recommended are independent of the platform used to deliver SABR.

Oligometastases: bone (including spine) and lymph nodes

In this setting, treatment can expect to achieve local control in around 80% and progression-free survival (PFS) of approximately 20% at 2–3 years.[2] Treatment is, in general, well tolerated with myelopathy rates for spinal treatments being less than 1% in most series.[19,20]

Contouring for spinal treatment should be based on the expert consensus guidelines by Cox *et al* (Level 5).[21] Similarly, expert consensus contouring guidelines for non-spinal bone oligometastases and sacral oligometastases can be considered.[22,23]

Recommendations

Initial treatment

Spine (excluding sacrum):

- 18–24 Gy single dose (Grade B)
- 24 Gy in 2 fractions (Grade B)
- 24–27 Gy in 3 alternate day or daily fractions (Grade C)

Sacrum:

- 27–30 Gy in 3 alternate day or daily fractions (Grade C)

Bone:

- 30 Gy in 3 fractions over 1 week (10 Gy per fraction given on alternate days or daily) (Grade C)
- 30 Gy in 5 fractions over 1 week (Grade C)
- 20 Gy in 1 fraction (Grade C)

Nodes:

- 30–45 Gy in 3 fractions over 1 week (10–15 Gy per fraction given on alternate days or daily) (Grade C)
- 30 Gy in 5 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.[24]

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Reirradiation

Often patients will have received prior radiotherapy and, in this setting, it is vital to consider 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).[18]

In the specific case of remaining spinal cord tolerance, the method described by Sahgal is recommended.[19] Following this, the maximum cumulative point dose to the thecal sac (similar to cord planning organ at risk volume [PRV]), at a minimum of 6 months after initial irradiation, should not exceed a biologically effective dose (BED) of 140 Gy (α/β=2 Gy). Similarly, Nieder *et al* recommend a cumulative cord BED of less than or equal to 135.5 Gy (α/β=2 Gy) when the interval between radiotherapy courses is not shorter than 6 months.[25] For other organs at risk, there is, to date, no robust evidence to guide safe constraints.[26]

Recommendations

Reirradiation

Pelvis:

• 30 Gy in 5 fractions, given on alternate days or daily (Grade C)

Spine:

• 20–30 Gy in 2–5 fractions, 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.[24]

Oligometastases: lung

Lung oligometastases present a similar clinical problem to early-stage primary lung cancer, for which stereotactic treatment is a standard of care.[27] Specifically for patients with oligometastases, a BED >100 Gy is associated with approximately 90% local control at 1–2 years.[27,28] 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 3 fractions.[29–32] The dose fractionation schedules are based on those used for primary lung cancer SABR schedules but lower doses may be acceptable at the discretion of the treating clinician.

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Recommendations

Peripheral lung oligometastases not abutting chest wall:

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

Peripheral lung oligometastases in contact with chest wall, or consider where 3-fraction constraints are challenging:

• 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 3 weeks 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.[24]

Oligometastases: liver

The use of surgery and radiofrequency ablation to treat liver oligometastases is well established for colorectal tumours. A phase II randomised trial reported improved overall survival with radiofrequency ablation (RFA) of liver metastases (CLOCC trial EORTC-NCRI CCSG-ALM Intergroup 40004).[33] For colorectal liver tumours under 6 centimetres (cm) in diameter, local control above 90% at 1 year can be achieved with stereotactic doses of at least 48 Gy in 3 fractions.[34] This analysis included patients who were heavily pre-treated with systemic therapy. Consideration should be given to the functional liver remnant. Further reviews have indicated this dose is effective in other tumour types, with grades 3–4 toxicity, most commonly elevated liver enzymes or gastrointestinal toxicity, of 1–10% (Level 3a).[35,36]

Recommendations

• 24–30 Gy in a single fraction (Grade C)
• 40–60 Gy in 3 fractions over 1 week, on alternate days (Grade C)
• 50–60 Gy in 5 fractions on alternate days or daily (Grade C)

For oligometastases 6 cm or more in size, or where constraints cannot be met:

• 40–60 Gy in 10 daily fractions

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.[24]

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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 non-randomised observations of enhanced survival in patients undergoing adrenalectomy for oligometastatic disease, stereotactic radiotherapy has also been used. Meta-analysis of 39 studies (2009–2019) has shown pooled local control rates of 82% at 1 year and 63% at 2 years, across a wide range of dose fractionation schedules.[37]

Recommendations

- 30–36 Gy in 3 fractions on alternate days (Grade C)
- 40–45 Gy in 5 fractions on alternate days or daily (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.[24]

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22 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]

On clinical suspicion of MSCC or once a diagnosis has been established, all patients should be started on steroids; give dexamethasone in 16 milligrams (mg) daily.[2]

Systemic anti-cancer treatment may be more appropriate than radiotherapy for some malignancies, such as 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; poorer outcomes are 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. Breast, prostate and haematological primary origin confer the best prognosis; lung and bladder sites have a poor outcome (Level 2c).[3,4]

Ideally, the prognosis of patients should be objectively assessed using validated scores such as the SCORAD index, which identifies primary breast or prostate cancer and good ambulatory status at presentation as favourable prognostic factors for both survival and ambulation after treatment (Level 2b).[5]

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 selected patients with a single site of MSCC and prognosis >3 months (Level 1b) compared with radiotherapy alone.[6]

For good-prognosis or ambulatory patients who are not suitable for surgery, urgent radiotherapy should be given before further neurological deterioration.[2]

For poor-prognosis ambulatory patients, radiotherapy should be considered to preserve neurological function.

For non-ambulatory patients, if paraplegia has been established for >24 hours, radiotherapy has a role for pain relief but little improvement in function can be expected.[2]

A systematic review and meta-analysis of published studies comparing short course (8 Gy in 1 dose or 20 Gy in 5 fractions) with long course (all schedules >1 week) identified 14 studies with 2,239 patients. The analysis showed similar survival rates and functional outcome between the two groups although local control rates were higher in the group receiving longer-course schedules. Ambulant patients with an expected better prognosis may therefore benefit from longer courses of treatment to prevent recurrence and need for retreatment.[7]

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The SCORAD trial randomised 686 patients with metastatic spinal cord or cauda equina compression, life expectancy greater than 8 weeks and no previous radiotherapy to the same area to receive either 20 Gy in 5 fractions or a single dose of 8 Gy.[8] While the primary endpoint of non-inferiority (defined at –11%) difference was not met, there was no significant difference in all other endpoints including ambulatory status, pain and survival at 4, 8 and 12 weeks. SCORAD was included in a meta-analysis including three randomised trials comparing single doses of 8–10 Gy with fractionated radiotherapy.[9] There was no observed difference with respect to motor response, bladder dysfunction and OS between the two groups. It should be noted that these studies included patients with a median survival of only 3 to 4 months.

The NICE guidelines have been updated and recommend a single dose of 8 Gy for all patients with consideration of SBRT if the patient has ≤3 metastases.[10]

Recommendations

Metastatic spinal cord compression: non-ambulant patients or ambulant patients with a prognosis <6 months:

- 8 Gy single dose (Grade A)

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.[11]

There is response to retreatment after initial benefit from radiotherapy for recurrent MSCC.

Using conventional radiotherapy techniques a cumulative biologically equivalent dose (BED) of ≤135.5 Gy when the interval is >6 months and each course is ≤99 Gy BED using an α/β ratio of 2 is recommended (50 Gy in 25 fractions = BED 100 Gy2 and 20 Gy in 5 fractions = BED 60 Gy2).[12] 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 treatment schedule does not (Level 2c).[13]

Stereotactic body radiotherapy (SBRT) may be considered for reirradiation but dose tolerances for the spinal cord are based on only a small number of cases. The spinal Dmax is quoted as the relevant cumulative dose constraint; a median Dmax of 25 Gy2 BED from SBRT and cumulative Dmax of 105 Gy2 BED with a minimum interval of 5 months is recommended.[14]

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Recommendations

Metastatic spinal cord compression: reirradiation after 8 Gy single dose or 20 Gy in 5 fractions:

Conventional radiotherapy prescribed at depth:

- 8 Gy single dose or 20 Gy in 5 daily fractions; maximum cumulative BED ≤135.5 Gy 2 (Grade C)

or using SBRT, defined at Dmax:

- 9 Gy in 1 dose, 12.2 Gy in 2 fractions or 14.5 Gy in 3 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.[11]

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