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Clinical Oncology
The Royal College of Radiologists

Radiotherapy dose fractionation
Second edition

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Foreword

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

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

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

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

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

This edition of *Radiotherapy dose fractionation* seeks to reflect the changes in practice which have evolved in the last decade. It has remained faithful to the vision of the original document, focusing on clear evidence-based recommendations wherever possible. In total, 110 Fellows and a number of stakeholder groups have contributed to the final version and we are grateful to all those who responded to the consultation. I would like to express particular thanks to Professor Peter Hoskin for so ably leading the development of this new document and to members of his Working Group – Dr Jeanette Dickson, Dr Raj Jena, Dr Robin Prestwich and Dr Vivek Misra – for their extensive input and excellent contributions. Thanks are due also to Dr David Bloomfield (Medical Director for Professional Practice, Clinical Oncology) for his oversight and to Gillian Dollamore, RCR Clinical Oncology Executive Officer, for all her advice and support.

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

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

Executive summary

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

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

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

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

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

Introduction

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

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

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

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

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

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

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

Preparation of this document

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

First stage consultation

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

Second stage consultation

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

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

Third stage consultation

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

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

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

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

Comments received from the above were again reviewed by the working group, leading to a final draft.

Comparison with the Mathus model[5]

The Malthus model is an evidence-based radiotherapy demand simulation tool, originally commissioned by the National Health Service in England (NHS England) in 2011. The model incorporates clinical decision trees which encode best practice for 22 different adult tumour types. The radiotherapy indications were established by a review of published literature and surveys of key opinion leaders. The most recent refresh of the clinical decision trees was undertaken in March 2014.

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

The salient differences are as follows:

- **Hypofractionation**
  At release, the Malthus model defaulted to 2 Gray (Gy) per fraction regimens for curative indications with the exception of adjuvant breast radiotherapy, where robust evidence for hypofractionation from the the UK Standardisation of Breast Radiotherapy (START) trial and other studies was present.[5,6] The Malthus team acknowledged that stronger evidence now exists for hypofractionation in curative treatment of head and neck, and prostate cancer, as discussed in the relevant sections of this document.
- **Palliative treatment of head and neck cancer**
  The use of 40 Gy in ten fractions as a split course, 21 Gy in three fractions over three weeks and 14 Gy in four fractions were not included in the Malthus decision tree. There is, however, a lack of high-quality evidence in this area and the regimens listed in the report are likely to reflect current practice from key opinion leaders in the UK.

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

References

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

Oxford Centre for Evidence-based Medicine[1]

Grades of recommendation

A Consistent level 1 studies

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

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

D Level 5 evidence or troublingly inconsistent or inconclusive studies of any level

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

Levels of evidence

1a SR (with homogeneity*) of RCTs

1b Individual RCT (with narrow confidence interval)

1c All or none§

2a SR (with homogeneity*) of cohort studies

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

2c 'Outcomes' research; ecological studies

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

3b Individual case-control study

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

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

SR: systematic review

RCT: randomised controlled trial

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

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

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

References

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