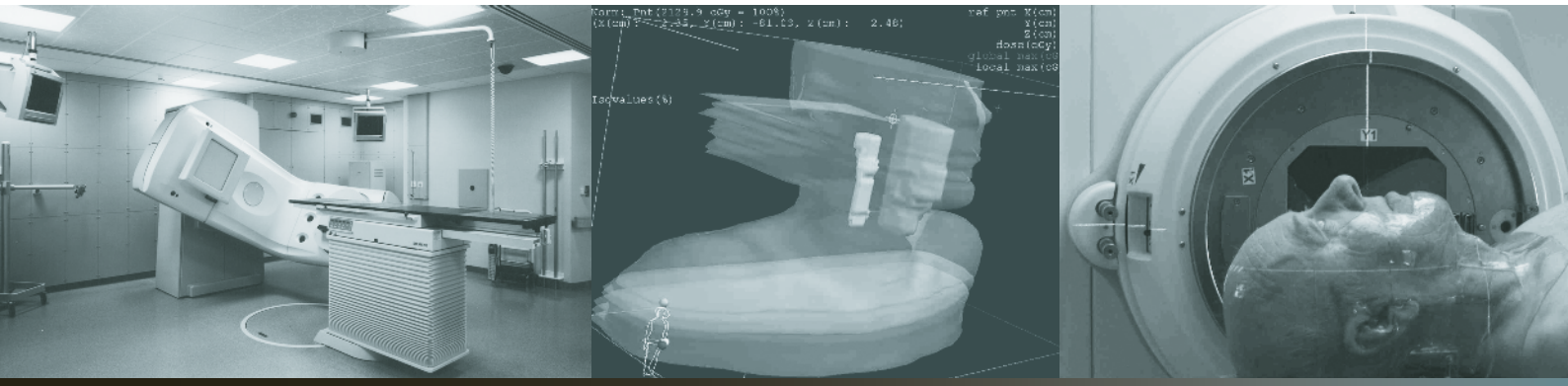
The Royal College of Radiologists

Board of Faculty of Clinical Oncology



Radiotherapy Dose-Fractionation

The Royal College of Radiologists, a registered charity, exists to advance the science and practice of Radiology and Oncology.

It produces standards documents to provide guidance to Clinical Oncologists and others involved in the delivery of cancer services with the aim of defining good practice, advancing practice and improving services for the benefit of patients.

This document is designed to support, not dictate, decision making. Clinical practice is varied. Although guidance can, to some extent, encompass a part of this variation, there can be no set of guidelines that will deal with all possible eventualities. This is where clinical judgement and guidelines complement each other. Clinical practice is changing rapidly. Readers are referred back to the source literature to inform their clinical judgment.

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Contents

1. Dean's foreword

It is with a strong feeling of privilege and pride that I write this introduction to our Dose-Fractionation document. Since the establishment of the Faculty of Clinical Oncology in 1992, we have published nearly 50 documents relating to many aspects of our professional lives, oncology service management and specific clinical problem areas.

I have no compunction in stating that this one is the most important contribution that the Faculty as an entity has made to the practice of Radiotherapy in the UK during these last 15 years. It has also involved more Fellows and been subject to more open consultation than any previous document, and yet from inception to delivery this enormous project has taken only 18 months.

So many of our Fellows have played an active part that it would dangerous for me to attempt to start identifying individuals but there is one exception to that principle. Michael Williams convinced me that the Officers' dream of pulling together the evidence base for UK fractionation policies in a professional and non-confrontational way was achievable. He has, as many of you know, personally led the process very actively throughout, has harnessed the many disparate talents of our drafters and edited the document into a style that I think we can be very proud of. I do feel that I need to record the Faculty's enormous debt to him in particular and to the members of the working party and the contributors.

I am also very excited for the Faculty because we are now going to publish the full document on the College website in a manner that allows each subspecialty chapter to be published individually, but in a standard RCR format. It is the intention of Officers that the individual site orientated chapters will become the responsibility of the Faculty's new Site Orientated eNetworks (SOeNs) and that they will be stimulated to review their element of the advice annually. They will be able to modify, rework and republish their chapter(s) when it is agreed that it is professionally possible to support change. We are, therefore, taking our most important Faculty project and, utilising the new college IT resources, thrusting it into the electronic era for the benefit, we believe, of UK Radiotherapy and its present and future patients.

Dr Robin Hunter

Vice-President and Dean
Faculty of Clinical Oncology
June 2006

2. Executive summary

2.1 One in three patients in the UK develops cancer during their lifetime, and 50% of these patients should receive radiotherapy treatment. The demand for radiotherapy is increasing at 3% per annum.

2.2 Surveys demonstrate variations in radiotherapy practice with some departments conforming to the international norm of curative treatment delivered over a 6–7 week period and others, at least in part due to historical resource constraint, delivering curative regimens of 3–4 weeks' duration.

2.3 The Royal College of Radiologists (RCR) has therefore commissioned this report, in order to identify fractionation regimens for which there is high quality evidence for both safety and efficacy.

2.4 The report also identifies areas where further research is required to provide such evidence.

2.5 The report aims, where possible, to recommend evidence-based treatment regimen(s) 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.

2.6 It has only been possible to make ten Grade A recommendations for radical treatment and six for palliative treatment.

2.7 In many clinical situations, a state of equipoise exists, where the available published evidence is insufficient to favour one particular treatment regimen over another. We await the results of clinical trials to resolve these issues.

2.8 *W*here equipoise exists, and trial data are not available, clinicians should exercise considerable caution when considering changes in their treatment practice, based on the understandable desire to minimise resource utilisation. Radiotherapy is a complex intervention, and great harm can result from well-intentioned changes in practice, based solely on theory or an inadequate evidence base.

3. Introduction

3.1 Background

3.1.1 Radiotherapy fractionation in the UK differs from that in the rest of the world. Over the last 60 years, alternative radiotherapy fractionation regimens have been developed in the UK, at least in part to conserve resources. Shorter regimens using fewer fractions than North America and Europe are often used in radical treatment. This is based on extensive and well-documented clinical research particularly in Manchester and Edinburgh.[1–5] In much of the USA and Europe fractions of 2 Gy or less are the standard of care.[6]

3.1.2 Clinical practice in the UK was surveyed in 1989.[7] Clinicians were asked about the prescriptions which they would write for patients in six different cancer scenarios. A wide variety of dose-fractionation regimens was demonstrated and in only one of the six scenarios did more than 25% of clinical oncologists say they would prescribe the same treatment regimen.

3.1.3 An audit of radiotherapy practice in the UK in September 2003 showed that practice had become more uniform and closer to practice in North America and Europe over the last 15 years.[8] However, there were significant variations in both radical and palliative treatment. For radical radiotherapy, 54% of prescriptions were for a fraction size of 1.8–2.0 Gy, but the distribution was bi-modal and 20% of patients were prescribed fraction sizes of 2.7–3.0 Gy.[8] There were important differences in resource use for the treatment of common malignancies.

3.1.4 The Board of Faculty of Clinical Oncology therefore convened a working party in 2004 with the following terms of reference:

- To develop a statement on evidence-based clinical practice from published peer-reviewed evidence.
- To produce short consensus statements about the management of the major malignancies, including palliative treatment.
- To define evidence-based radiotherapy regimens for each major malignancy.
- To identify trials in progress which may have a major effect on practice.
- To identify other significant areas for clinical trial.

3.1.5 The focus of this project was on linear accelerator use, and skin cancer was consequently excluded from consideration. In addition, rarer malignancies were excluded unless they had a particularly good evidence base, as the impact on resource use would be slight.

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

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3.2 Methodology

3.2.1 Small sub-groups of three to four clinical oncologists were convened to produce short consensus statements about the management of the major malignancies and appropriate dose-fractionation. It was already known that there are few randomised trials of fractionation regimens and that the evidence would consist largely of studies in which defining the optimum radiotherapy regimen was not the primary objective of the trial. It was considered that expert consensus would give good access to the literature and also to trials in progress.

3.2.2 The document was collated by a small working party and revisions reviewed by the initial sub-groups. The draft document was then posted on the RCR web site for wider consultation and was downloaded by 307 individuals. All comments were addressed and individually replied to.

3.2.3 We have based our recommendations on clinical trials and case series published in peer-reviewed journals. Unpublished data and departmental audits, which are not in the public domain, have not been used. These latter data provide important reassurance about the quality of services and should ideally be published in the peer-reviewed literature.

3.2.4 Evidence was graded according to guidelines defined by the Scottish Intercollegiate Guideline Network (SIGN): www.sign.ac.uk/guidelines/fulltext/50/section6.html.

The SIGN grading system is reproduced with permission on page 9.

3.2.5 We have been reluctant to use the word "recommendation" in a large number of instances, because the available evidence does not support the use of such a strong term. We have grouped and graded the available evidence according to the SIGN system from level 1++ to level 4 and collated it into summary statements, rating A and B as recommendations and C and D as acceptable practice.

3.2.6 There are few randomised trials that compare radiotherapy regimens. Where these are available and have a very low risk of bias they will provide level 1++ evidence and permit a Grade A recommendation.

3.2.7 Many trials involving radiotherapy do not address a radiotherapy question. They will therefore contribute evidence about radiotherapy as a high quality cohort study providing level 2++ evidence and permitting a Grade B recommendation.

3.2.8 In some trials, level 1 evidence for improved survival or local control is associated with detailed data concerning late effects, but in others such data are either not included or trial-specific measurement tools have been used. The cited papers should always be read in detail when interpreting this guidance document.

The SIGN Grading System

Levels of evidence	
1++	High quality meta analyses, systematic reviews of RCTs, or RCTs with a very low risk of bias
1+	Well conducted meta analyses, systematic reviews of RCTs, or RCTs with a low risk of bias
1 -	Meta analyses, systematic reviews of RCTs, or RCTs with a high risk of bias
2++	High quality systematic reviews of case-control or cohort studies. High quality case-control or cohort studies with a very low risk of confounding, bias, or chance and a high probability that the relationship is causal
2+	Well conducted case control or cohort studies with a low risk of confounding, bias, or chance and a moderate probability that the relationship is causal
2 -	Case control or cohort studies with a high risk of confounding, bias, or chance and a significant risk that the relationship is not causal
3	Non-analytic studies, e.g. case reports, case series
4	Expert opinion

Grades of recommendation	
A	At least one meta analysis, systematic review, or RCT rated as 1++, and directly applicable to the target population; or a systematic review of RCTs or a body of evidence consisting principally of studies rated as 1+, directly applicable to the target population, and demonstrating overall consistency of results
B	A body of evidence including studies rated as 2++, directly applicable to the target population, and demonstrating overall consistency of results; or extrapolated evidence from studies rated as 1++ or 1+
C	A body of evidence including studies rated as 2+, directly applicable to the target population and demonstrating overall consistency of results; or extrapolated evidence from studies rated as 2++
D	Evidence level 3 or 4; or extrapolated evidence from studies rated as 2

RCT, Randomised clinical trial.

Reference

1 SIGN 50: ***A Guideline Developers' Handbook*** (Feb 2001) Sect 6.3
"Forming Guideline Recommendations": www.sign.ac.uk/guidelines/fulltext/50/section6.html

3.3 Fractionation in radiotherapy: A brief history

3.3.1 Radiation therapy evolved as an empirical art, not an exact science. Clinical innovation and experience have consistently been followed by attempts to explain the underlying biology. Fractionation was introduced, not because of an appreciation of the nuances of radiobiology, but because the technological limitations of the early therapy machines meant that any treatments had to be given using interrupted regimens. Freund's famous treatment of the girl with the hairy naevus was delivered in 10 daily fractions: from the 24th November to the 3rd of December 1896.[1] Once more reliable equipment became available, single fraction treatments were tried but, after over 20 years of clinical use, it became evident that the so-called "therapia magna sterilans" was clinically ineffective. Contrary to myth, fractionation did not evolve along linguistic lines with German speakers all using massive single doses and Francophones delivering fractionated treatments. Even within Hapsburg Vienna there were differences of opinion: Freund persisted in his use of multiple small fractions; Kienbock used the "expeditive" method, with the total dose delivered in four fractions; and, Holzknecht used his chromoradiometer to monitor treatments delivered as a single large fraction.[2]

3.3.2 Nowadays, we comfortably base our clinical practice on the rational foundations provided by the five Rs of radiobiology without, perhaps, realising that all five Rs were in place within 15 years of the discovery of x-rays: intrinsic **R**adioresistance;[3,4] (**R**e)oxygenation;[5] **R**epair;[6] **R**epopulation;[7] and **R**edistribution.[8] The French, in particular, Regaud, Coutard and their successor, Baclesse, enthusiastically adopted fractionated regimens, and by the early 1920s Coutard was able to demonstrate uncomplicated control of laryngeal cancer using low dose-rate protracted radiotherapy: daily fractions lasting 2–3 hours given to ingeniously immobilised patients on regimens lasting 4–6 weeks. Baclesse extended protraction even further: treating breast cancer with daily doses of 200R (1.8 Gy) given over 10 minutes using regimens of up to 4 months.

3.3.3 Questions of economics and consumption of resources arose early. Despite Jungling's demonstration of an unacceptable (23%) rate of necrosis when treating cancer of the larynx with large fractions,[9] German radiotherapists were, because of cost, unable to adopt Coutard's protracted, low dose-rate, approach. Instead, Holzknecht, Pape, Bork, Schwarz and others used fractionated radiotherapy at high dose-rates per fraction, including multiple fractions per day. As early as 1937, Schwarz had suggested a regimen using 70R (0.63 Gy) thrice daily with 4-hour intervals between fractions.[10]

3.3.4 By the mid 1930s, daily fractions for 4–6 weeks to total doses up to 6,500R were being widely used. In Manchester, in the late 1930s, there was a shortfall in machine capacity and, on the basis of clinical judgment, Ralston Paterson decreased the number of fractions to 16, and the dose to 5,000R, with an overall treatment time of just over 3 weeks.[11] It is a testimony to his clinical acumen that this regimen has provided efficient and effective treatment for more than 60 years.[12]

3.3.5 Gilbert Fletcher who, despite his name, was actually a Belgian, trained in Paris and moved to the USA. He took his Parisian beliefs about the virtues of protracted radiotherapy with him and, primarily as a result of his influence and teaching,[13] there is a belief amongst radiation oncologists in the USA that to treat using fewer than 30 fractions is inherently dangerous. Coincidentally, owing to reimbursement practices in the USA, regimens using fewer than 30 fractions are also less lucrative.

3.3.6 Frank Ellis built on the work of Reisner, Mischer, Strandquist and Cohen and introduced the concept of NSD (Nominal Standard Dose) into clinical radiotherapy.[14] This was an

attempt to enable clinicians to change from one fractionation regimen to another, whilst maintaining equivalent biological effects on both tumour and normal tissues. It was an exercise in modelling and extrapolation. With hindsight, the assumptions behind the NSD formula now seem questionable,[15] but, at the time, the equations, and their derivatives, were adopted enthusiastically. Unfortunately, the NSD model omitted consideration of the importance of dose-per-fraction in determining late effects in normal tissues. When safe regimens using 30 fractions were converted, using the NSD concept, to their "equivalent" in 10–15 fractions, the biological effects on late reacting normal tissues were systematically underestimated.

3.3.7 Currently, the linear quadratic (LQ) model dominates the field of mathematical radiobiology.[16–18] This model incorporates the effect of dose-per-fraction and can, by making additional assumptions, also incorporate the effects of repopulation during a course of fractionated radiotherapy. The α/β ratio is the dose of radiation (in Gy) at which the amount of cell killing that is directly proportional to dose is equal to the amount of cell killing proportional to dose squared. It is an indication of the curviness of the cell survival curve. The curvier the curve, the lower the α/β ratio and the greater the sparing effect of fractionation on tissue damage. Put crudely, the α component represents the intrinsic radiosensitivity of the target cells and the β component represents the extent to which damage can be repaired.

3.3.8 A model is no more than a representation; it is not the reality. The consequence is that we can have no single model that accurately describes what we need to know any more than we can have any one map that tells us everything about a territory. The map is not the territory; the model is not the biology.

3.3.9 The LQ model of radiation-induced cell killing is the model that, for now at least, is considered best at providing a rational basis for comparisons between different regimens of treatment. It has been widely developed, discussed and interpreted and, rather than reiterate these arguments here, a selection of relevant references is appended,[19–29] particularly with respect to the use of the biologically effective dose (BED) concept.

3.3.10 All of the fractionation regimens that have been used throughout 100 years of clinical radiotherapy represent some form of compromise between: (1) as many fractions as possible, which will tend to exaggerate survival differences between tumour cells and normal cells after treatment; and (2) the avoidance of undue protraction of treatment regimens, so as to minimise the opportunities for tumour cell repopulation during treatment. The most important lessons that history has taught us are these:

- There can be no single regimen of treatment delivery that will be appropriate for all tumours in all patients.
- Mathematical modelling without accurate clinical observation is an exercise that is both futile and dangerous.
- Fractionation cannot be considered in isolation. There is a complex interdependence between total dose, dose-per-fraction, overall treatment time, treated volume, beam parameters, prescribing conventions and quality control procedures. There is, of course, nothing intrinsically unsafe about doses >2 Gy per fraction; but, if attention is not paid to these other details, then disasters can occur when higher doses-per-fraction are used.
- Clinical advances precede, and are preceded by, advances in our basic understanding of radiation biology.

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3.4 Fractionation and organs at risk (OAR)

3.4.1 The tolerance of normal tissues to the late effects of radiation limits the dose that can safely be prescribed to the tumour. The tolerance dose varies between tissues and is influenced by the proportion of the organ treated, the length of follow-up and the end point assessed. For some tissues, continued function is impaired by low doses, while for others necrosis occurring at higher doses is the critical event.[1]

3.4.2 It would therefore be helpful to identify an evidence-based summary of acceptable dose-fractionation regimens for OAR. Emami, et al.[2] reviewed the literature on (often small) series of patients who had suffered major complications. The data that they were able to review consisted mainly of several small series of patients who had suffered major complications. They sought to define the dose at which 5% of patients would suffer a major complication—they did not attempt to define a "safe" dose. The limitations of the data meant that expert opinion was an important influence in drawing up their recommendations. Data were even scantier for any relationship between the volume irradiated and the dose required to cause normal tissue complications. This is an important consideration as radiotherapy planning becomes more sophisticated. A further complication is that tolerance may be reduced by chemotherapy.

3.4.3 Dose–volume relationships have been analysed in detail in the radical radiotherapy of non-small cell lung cancer.[3] The percentage of total lung volume receiving in excess of 20 Gy was statistically significant predictor for the development of ≥ grade 2 pneumonitis. If this value was < 25%, then dose escalation was considered acceptable. Higher values prompted revision of the radiotherapy plan and all fatal cases of pnuemonitis occurred in patients with a V20 value exceeding 35%. As we move into the era of IMRT (Intensity Modulated Radiation Therapy) with unconstrained beam arrangements these data may no longer be valid. The V20 value has also been found useful in limiting the incidence of radiation pneumonitis in treatment with hypo-fractionated radiotherapy[4].

3.4.4 Most clinical oncologists will err on the side of caution when considering the prescribed dose to an OAR. This caution may bring with it a decreased probability of tumour control but, from the clinician's perspective, failing to cure may be preferable to causing harm.[5] As an example, consider the spinal cord: the recommended tolerance dose in the UK is 48 Gy in 2Gy daily fractions (or equivalent),[6] whereas in 1998, more than 25% of a world wide survey of radiation oncologists accepted a tolerance dose of ≥ 50 Gy in 2Gy daily fractions.[5] Dose–response relationships for tumour control are steep and this 4–5% dose increase might lead to a 10% increase in probability of tumour control. Yet a 0.5–1% increase in the risk of treatment-related paraplegia is, for many radiation oncologists, unacceptable. We know far too little of patients' views on such choices, but in the context of adjuvant therapy for breast cancer, the RAGE group data have been very valuable.[7]

3.4.5 It is therefore not possible to make dogmatic statements about safe fractionation regimens for particular OAR. In addition, the Emami paper only considered radiotherapy given in 1.8–2.0 Gy per day, 5 days a week. The question of fractionation and dose to OAR has to be determined by clinical judgement. This might well involve frank discussions between patients and their oncologists concerning the relative balance between potential benefit and potential harm.

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3.5 Radiation therapy as a complex intervention

3.5.1 Radiation therapy is a complex medical intervention[1] with many components which both independently and interdependently contribute to risks and benefits. Factors include the biological effect of the therapy on cancers and normal tissues (dose, fraction size, number of fractions, overall time) but also the organisational behaviours and processes underpinning its delivery:

- Case selection for curative treatment.
- Delineation of the target volume and normal tissues at risk.
- Planning and prescription.
- Preparation for and support during treatment.
- Immobilisation techniques.
- Treatment delivery.
- Verification.
- Support during treatment.
- Care after treatment.

3.5.2 The risks and benefits of particular radiotherapy regimens cannot be considered in isolation. The published literature rarely includes detailed descriptions of the issues highlighted above, leaving uncertainties about the level of risk associated with a fractionation change or the process changes required.

3.5.3 The profile and co-morbidity of patients considered suitable for radical radiotherapy are changing with an increasing number of older patients with at least two other significant chronic illnesses, e.g., diabetes and heart disease.[2] Many trials in the past excluded elderly patients or those with the co-morbidities now expected in modern practice. This may be of particular concern in pelvic radiation therapy and in the central nervous system and could affect the relative safety of different fractionation regimens. There is no evidence to quantify the complex relationships between fractionation regimen, co-morbidity and the risks of serious late effect.

3.5.4 Surrogate surveys suggest that case selection for radical treatment varies both between different oncologists and different countries, particularly in more advanced disease.[3–5] There are also significant differences in case selection for combined modality therapy.[5,6] Historically, those departments using shorter fractionation regimens, e.g., Manchester,[7] had tighter restrictions on the target volume acceptable for radical therapy than those using shrinking-field, lower dose-per-fraction regimens.[8]

3.5.5 Planning and treatment delivery systems vary across the UK and change has been slow. For example in 2004, less than 50% of departments used computed tomography or magnetic resonance imaging simulation to plan breast fields[9] and, as late as 1998, nearly one-quarter of departments were not using ICRU (International Commission on Radiation Units and Measurements) prescription guidance for pelvic radiotherapy.[6] The implementation of guidance on treatment verification[10,11] has been slow and this is, in part, the result of funding problems and failure to prioritise this key step in the pathway.[11,12]

3.5.6 Decisions about the value of radiation therapy rest on a careful assessment of risk and benefit. However, in many studies evidence of improvement in survival, local control or symptoms is not linked with detailed data on side effects. If the local control is improved

without a survival advantage, then the benefit of treatment and consequently the acceptable risk are lower. This is illustrated by the changing role of post-operative radiotherapy in breast cancer over the last 20 years. Since the 1940s, radiotherapy after mastectomy for breast cancer has been known to reduce the risk of local relapse, but its use began to decline in the 1980s because of a failure to demonstrate an overall survival advantage. Between 1997 and 2001, results from the Danish breast trials demonstrated a significant survival advantage associated with the addition of radiotherapy to systemic chemotherapy. Supplementary analysis of late effects demonstrated that the radiation technique used in the trial did not increase the risk of ischaemic heart disease at 12 years,[13,14] confirming that improved radiotherapy technique and reduced late effects had converted an improvement in local control with no survival advantage to a survival advantage of similar size to that of systemic treatment.

3.5.7 At the other end of the spectrum, even when prognosis is very poor, late effects and radiotherapy technique are important; for example, Dische et al. demonstrated a significant incidence of radiation myelitis in patients with advanced bronchial cancer treated with 35 Gy in 6 fractions when the cord dose was above 33.5 Gy for patients who lived longer than 6 months.[15] Similarly, there have been reports of radiation myelitis using 8.5 Gy twice.[16,17]

3.5.8 Clusters of adverse late effects in radiation therapy attributed to changes in fractionation, e.g., radiation induced brachial plexopathy[18–20] and pelvic damage associated with the treatment of cervical cancer[21] have involved changes in addition to fractionation, in particular, in equipment, planning and treatment delivery. These details have not always been reported, sometimes because it has been only in retrospect that a particular aspect was recognised as significant.[22] This emphasises that fractionation changes must not be considered in isolation. Custom and practice in a department experienced in using a particular regimen may not be obvious to those working elsewhere. The items listed in Section 3.5.1 will all need to be considered. Rather than relying on the published literature alone, detailed process protocols and quality assurance arrangements must be studied in conjunction with fractionation changes.

3.5.9 The precise details of the target volume in the pre-operative treatment of rectal cancer influenced post-operative mortality in a series of Swedish trials.[23] The volume irradiated is critical in many settings and is likely to be particularly important in dose escalation studies, for example in prostate cancer.

3.5.10 Anecdotal evidence suggests there have been unreported problems when oncologists trained in one department have moved to another and introduced unfamiliar fractionation regimens without all staff being fully aware of restrictions related to case selection, normal tissue limits, planning, delivery and verification of apparently equivalent doses. Most problems have related to the use of higher doses-per-fraction where case selection and volume restrictions are much tighter, particularly in the presence of sub-optimal planning and treatment processes.

3.5.11 The published literature on newer treatments is limited by lack of long-term follow-up for large numbers of cases, e.g., chemoradiotherapy for cervical cancer and high-dose radiation for prostate cancer. The 1993 UK audit of cervical cancer late effects demonstrated the challenge for any individual department to detect even quite significant changes in the rate of late effects associated with treatment of a particular site.[6,24] There is currently no national registration of the late consequences of treatment to allow trends in late effects to be documented nationally.

3.5.12 Clinical trials have an important impact in increasing the uniformity of treatment. They now routinely specify precise details of the tumour target volume and its treatment, according to ICRU Reports 50 and 62. In addition, it is now usual to include detailed quality assurance procedures to ensure that similar treatment is delivered on a day-to-day basis in all participating centres.[25,26] The National Radiotherapy Clinical Trials Quality Assurance Team will have an important role in the future.

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3.6 Radiotherapy planning and dose-prescription

3.6.1 For many sites conformal radiotherapy is now standard practice as it reduces the unnecessary irradiation of normal tissues and may permit dose escalation.[1] See, for example, the sections on gynaecological malignancy (4.6.1), lung cancer (4.8.3), and prostate cancer (4.11.7).

3.6.2 When multiple fields are used, the dose should be prescribed to the intersection point, as recommended in ICRU Reports 50 and 62.[2,3] The minimum and maximum doses within the PTV (Planning Target Volume) should lie within the parameters recommended by the ICRU (–5% to +7% of the prescribed dose).

3.6.3 For single-field treatments, such as those used in the palliation of bone metastases, the prescription point is a matter of individual clinical judgment. Typically, for a direct posterior spinal field, the prescription point would be 5 cm below the surface, but this could be varied according to the build of the patient, the beam energy, etc. Recommendations and suggestions included in this document for single-field treatments are based on the assumption that the prescribing clinicians will be aware of the dose to the critical normal tissues, such as spinal cord, when choosing the appropriate depth at which to prescribe.

3.6.4 For spinal cord compression, detailed consideration of the depth of the target is required. This is facilitated by CT planning. Parallel-opposed fields may be required.

3.6.5 During a planned course of fractionated radiotherapy, it may be necessary, for operational or clinical reasons, to alter dose-fractionation. Guidance is available elsewhere for dealing with unscheduled gaps during treatment.[4–6]

3.6.6 When fractionation has to be changed for clinical reasons, such as unexpectedly severe toxicity or failure of response, then these alterations are a matter for individual clinical judgement.

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4. Guidance on radiotherapy dose-fractionation

4.1 Anal cancer

4.1.1 There are approximately 700–800 registrations of squamous carcinoma of the anus per year in the UK. Despite its rarity, three phase III trials that included 1,005 patients have established the standard treatment of this disease.

4.1.2 The UKCCCR (United Kingdom Co-ordinating Committee on Cancer Research) anal cancer trial used a dose of 45 Gy in 20 or 25 fractions with a boost (ACT1).[1] This study and an EORTC (European Organisation for Research and Treatment of Cancer) trial[2] both demonstrated improved outcome for concomitant chemoradiotherapy using mitomycin C and 5-fluorouracil (5-FU) when compared with radiotherapy alone. A statistically significant reduction in locoregional failure was demonstrated in both trials. A further phase III trial,[3] performed by the RTOG (Radiotherapy Oncology Group) demonstrated improved colostomy-free survival when mitomycin C was added to 5-FU chemoradiation. Chemoradiotherapy improves outcome in anal cancer compared to radiotherapy alone (Grade A).

4.1.3 Large volume treatments are no longer recommended because of late effects (level 4). Subsequent Phase II studies[4,5] reported the use of a shrinking-field technique delivering 50 Gy in 25 fractions over 5 weeks when combined with mitomycin C and 5-FU. Similar or improved outcome was reported compared to the previous phase III trials. This approach has been adopted as the control arm of the current NCRN ACT2 trial (level 4).

4.1.4 The current NCRN (National Cancer Research Network) ACT2 trial compares concomitant mitomycin C and 5-FU with cisplatin 5-FU when combined with a two-phase radiotherapy technique delivering a total dose of 50.4 Gy in 28 fractions. The second randomisation tests the role of two subsequent cycles of cisplatin 5-FU chemotherapy against no further treatment.[5]

4.1.5 Whether treated within or outwith the ACT2 trial, the recommended dose of radiation when given with combination chemotherapy is 50.4 Gy in 28 fractions (level 4). Higher total radiation doses may be considered for locally advanced disease, although there is no clear evidence of additional benefit (level 4).

In the management of anal cancer with combined chemoradiotherapy, a radiation dose of 50.4 Gy in 28 daily fractions of 1.8 Gy using shrinking fields is acceptable (Grade D).

4.1.6 There is inadequate research evidence to recommend a dose-fractionation regimen for patients who are considered unfit for standard chemoradiotherapy or who require treatment with palliative intent.

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4.2 Bladder cancer

4.2.1 The size of the planning target volume (PTV) is critical to any discussion of dose and fractionation.[1,2] Some centres use a two-phase (large pelvic volume/small bladder volume) approach: 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 < 1000 ml and that 3-D conformal planning techniques are used.

Conventional fractionation (dose-per-fraction 1.8–2.0 Gy)

4.2.2 The radio-therapeutic regimens used in trials comparing radiotherapy to surgery for bladder cancer have provided a "conventional" regimen of 60–64 Gy in 30–32 fractions over 6–6.5 weeks (level 2++).[3]

Hyper-fractionation (dose-per-fraction 1.5 Gy or less)

4.2.3 Two published trials compare hyper-fractionation (with doses of 1–1.2 Gy per fraction) to conventionally fractionated treatment.[4–6] Pooled analysis suggests a significant benefit from hyper-fractionation with a 17% (95% confidence interval, 6–27%) improvement in the rate of local control. 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 the control arm.

Accelerated fractionation

4.2.4 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 to a standard regime of 64 Gy in 32 fractions over 45 days.[7] The shorter regimen was associated with a higher rate of intestinal toxicity (level 1+ evidence).

Hypo-fractionation (doses-per-fraction ≥ 2.5 Gy)

4.2.5 There are six published trials investigating regimens using fractions of ≥ 2.5 Gy in the radical treatment of bladder cancer.[8–14] Five of them were published more than twenty years ago. In the RTOG 7104 trial[8] 55 Gy in 20 fractions (split 10 + 10 with a 2-week gap) was compared to 60 Gy in 30 fractions over 6 weeks. There was no difference in tumour control or in side effects. A small randomised trial from Edinburgh (before the introduction of conformal techniques) established that 55 Gy was the optimal dose, when using 20 fractions over 4 weeks.[9] Subsequently, the recommended dose was revised downwards to 52.5 Gy (level 1+).[10]

4.2.6 The most recent trial, from Manchester, used modern conformal techniques and 3-D planning.[15] It compared whole bladder radiotherapy (WBRT dose 52.5 Gy in 20 fractions) to partial bladder irradiation (PBRT) using two different regimens: a 20-fraction regimen and a 16-fraction regimen. The prescribed doses for the PBRT regimens varied according to the size of the PTV (52.5–57.5 Gy for the 20 fraction regimen; 50–55 Gy for the 16-fraction regimen). There was no statistically significant difference between the three arms in local control at 5 years. A trend suggesting inferior results with the 16-fraction regimen has caused the Christie to abandon this regimen for the treatment of bladder cancer. The rates of gastrointestinal and genitourinary toxicity were similar in all three arms (level 1++).

For radical radiotherapy to the bladder only, regimens of 50–52.5 Gy in 20 daily fractions are neither better nor worse than regimens of 60–64 Gy in 30–32 daily fractions when using modern planning and conformal techniques (Grade B).

Palliative radiotherapy for bladder cancer

4.2.7 The MRC (Medical Research Council) 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.[16] 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 1+ evidence).

For very frail patients, a 6–8-Gy single fraction of pelvic radiotherapy often provides symptomatic relief (level 4).

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).

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

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4.3 Breast cancer

Radiotherapy to the breast or chest wall

4.3.1 Radiotherapy has a key role in the conservation management of primary breast cancer, where it increases both local control and overall survival.[1–3] It performs the same role in selected patients after mastectomy.[4]

4.3.2 The formal introduction of MDT (Multidisciplinary Team) working has helped to standardise practice in the UK over the last decade. Appropriate case selection for breast conservation and systematic monitoring of microscopic excision margins have each been influential in minimising local relapse risk.[5]

4.3.3 The role of breast irradiation after tumour excision is widely accepted, but there is no consensus on which dose regimen should be used.[6] A regimen of 50 Gy in 25 fractions has been used in the National Surgical Adjuvant Breast and Bowel Project (NSABP) breast cancer trials.[7]

4.3.4 Shorter fractionation regimens delivering 40 Gy in 15 or 16 fractions have been described in cohort studies.[8] Some of these series include treatment to the axilla.[9] A regimen of 45 Gy in 20 daily fractions after simple mastectomy has been reported to give acceptable late effects and local control rates (level 2+, Grade C).[10] The axilla was routinely treated and no case of brachial plexopathy was described.[10]

4.3.5 A Canadian trial of radiotherapy to the breast alone randomised 1,234 patients to 42.5 Gy in 16 fractions over 22 days or to 50 Gy in 25 fractions over 35 days.[6] There was no difference in disease-free survival or overall survival between the study arms, both of which showed an excellent or good global cosmetic outcome at 3 years in 77% of patients (level 1++). Local recurrence occurred in 44 patients and, although similarly distributed between arms, the confidence limits are too wide to draw reliable conclusions.

4.3.6 The Royal Marsden / Gloucestershire Oncology Centre Trial of breast fractionation included a minority of patients receiving treatment to the axilla.[11] A total of 1,410 patients were randomised between 50 Gy in 25 fractions and two 13-fraction regimens testing 3.0 Gy or 3.3 Gy over 5 weeks (treating 5 times per fortnight). It was possible to determine a 13 fraction dose regimen equivalent to 50 Gy in 25 fractions in terms of long-term normal tissue effects (level 1++) . Local recurrence rates and overall survival have not yet been published but are expected in 2006.

For the treatment of breast cancer, the following regimens are recommended in terms of normal tissue effect on the breast:

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

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

42.5 Gy in 16 daily fractions over 3.5 weeks (Grade B).

Data on tumour control are inadequate to draw any firm conclusions and the results of the START trials are awaited.

4.3.7 The irradiation of women with large breasts has been associated with poor cosmetic results with both conventional and hypo-fractionated techniques.[12] It has been suggested that this adverse effect is the consequence of greater radiation dose inhomogeneity. This is a significant clinical problem which is addressed in two clinical trials of 3-D treatment planning.[13,14]

4.3.8 Ductal carcinoma *in situ* has been treated with 2 Gy fractions in all published trials.[4] There is no *a priori* reason to believe that fraction size plays a different role in this condition than in invasive disease.

Breast boost radiotherapy

4.3.9 Three randomised trials evaluating a tumour bed boost after whole breast radiotherapy have shown a small but statistically significant benefit to the delivery of a boost dose in patients with invasive tumours.[15–17]

4.3.10 The EORTC boost trial reported the greatest absolute benefit in the subgroup of women < 50 years of age given a boost of 16 Gy in 8 fractions after 50 Gy in 25 fractions to the whole breast in women with complete microscopic tumour excision.[15]

4.3.11 A range of fractionation regimens is currently in use in the UK, and this area requires both audit and research. Further randomised trials of sequential boost therapy are unlikely in patients with completely excised invasive disease.

Axillary radiotherapy

4.3.12 Historically, some of the most serious radiation related side effects have been associated with radiation of the axilla and supraclavicular fossa using a combination of sub-optimal fractionation and poor technique (see Section 3.5.8). The START trial quality assurance protocols have been important in standardising technique and fractionation.[18]

4.3.13 Late effects are influenced by surgical practice which is currently changing. Level II and III axillary clearance is effective in controlling regional disease with reported recurrence rates of 3–5% at 5 years.[19,20] BASO (British Association of Surgical Oncologists) currently recommends that patients with histologically involved axillary nodes following node sampling should have radiotherapy unless a subsequent axillary clearance is carried out.[20] Lesser degrees of surgery without axillary radiotherapy lead to correspondingly higher rates of axillary recurrence.[21] The Edinburgh study of 45 Gy in 20 daily fractions in patients receiving selective axillary radiotherapy for positive nodes after axillary sampling demonstrated similar control to that of axillary clearance, (level 2+, Grade C).[22]

4.3.14 Sentinel node biopsy is being widely adopted in the UK, but there is a significant learning curve of 30–40 cases before satisfactory results are obtained, demonstrated in both UK and American trials.[23]

4.3.15 It is not yet clear how positive sentinel nodes will be managed. The EORTC AMAROS trial compares axillary dissection against axillary radiotherapy in patients with positive sentinel nodes. The ACOS-OG Z0011 trial compares axillary dissection against observation. These studies will not report for some years.

Large cohort studies have reported on the treatment of the axilla and the following regimens are recommended:

50 Gy in 25 daily fractions over 5 weeks (Grade B)
40 Gy in 15 daily fractions over 3 weeks (Grade B).

The results of the START trial are now awaited.

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4.4 Central nervous system (CNS) malignancy

Radiotherapy fractionation in the CNS

4.4.1 Two important considerations underpin decision-making in radiation neuro-oncology. Firstly, the results of treatment vary widely and, secondly, the brain and spinal cord are susceptible to late radiation damage which is strongly dependent on radiation dose-per-fraction. Although there is an extensive (predominantly older) literature on CNS radiation damage, it is still difficult to give precise tolerance limits.[1–6] Quoted threshold doses are 35 Gy in 10 fractions, 60 Gy in 35 fractions or 76 Gy in 60 fractions. Patients with a life expectancy of more than 12–18 months are rarely treated with doses-per-fraction greater than 2 Gy. In effect, the fractionation of radical radiotherapy for CNS tumours is based almost entirely upon avoidance of late radiation damage. The tolerance of the brainstem (50 Gy in 25 fractions) and optic chiasm (55 Gy in 30 fractions) may impose a lower dose limit and necessitate changes in planning. There is considerable uniformity of practice in the UK[7] (level 4) and a systematic overview of clinical trials is recently available.[8]

High-grade glioma

4.4.2 Retrospective analyses[9] and one randomised trial[10] have demonstrated a dose–response relationship for high-grade glioma up to, but not beyond, 60 Gy in 30 fractions.[11] This has led to the adoption of the dose regimen of 60–65 Gy delivered in 1.8–2.0 Gy fractions as standard in the therapy of better prognosis patients with high-grade malignant glioma (level 1+). Further attempts to improve response through hyper-fractionation[12] or accelerated fractionation[13] have failed. The addition of temozolomide to radiotherapy for newly diagnosed glioblastoma has been shown to improve overall and progression-free survival (level 1+, Grade B).[14]

For patients of good performance status being treated for high-grade glioma, a total dose of 60 Gy in 30 daily fractions in 6 weeks is recommended (Grade A).

4.4.3 Treatment is not always appropriate for patients with high-grade glioma and poor performance status but, when it is, hypo-fractionated treatments may be beneficial.[15,16] The most commonly adopted regimen in the UK is 30 Gy in 6 fractions over 2 weeks (level 2+), often delivered by using a parallel pair.

For patients of poor performance status being treated for high-grade glioma, a total dose of 30 Gy in 6 fractions over 2 weeks is acceptable as a palliative treatment (Grade C).

Low-grade glioma

4.4.4 For low-grade glioma two prospective randomised dose comparison trials have demonstrated no difference in outcome between 45 Gy in 25 fractions and 59.4 Gy in 33 fractions[17] and between 50.4 Gy in 28 fractions and 64.8 Gy in 36 fractions.[18] As a result, a standard dose of 45–50.4 Gy in 25–28 fractions of 1.8 Gy is accepted practice in the UK and internationally (level 1++). A dose of 54 Gy in 30 fractions in 6 weeks has been used in a randomised study of the timing of radiotherapy.[19] This provides level 2++ evidence for this regimen.

For patients with low-grade gliomas, a total dose of 45–50.4 Gy in 25–28 daily fractions of 1.8 Gy is recommended (Grade A).

There is evidence to recommend the use of 54 Gy in 30 daily fractions of 1.8 Gy (Grade B).

Pituitary tumours

4.4.5 In this context, fractionation is entirely governed by the tolerance of the normal CNS, and there are no randomised studies of fractionation in this area. There is, however, remarkable uniformity of practice using 45 Gy in 25 fractions for small pituitary tumours without suprasellar extension (level 2+).[20,21] Some centres have used slightly higher doses[22] which might be indicated for tumours with adverse factors (level 4, Grade D). Treatment of the elderly may require particular care.[23]

For small benign pituitary tumours, the dose should usually be no more than 45 Gy in 25 fractions of 1.8 Gy (Grade C).

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4.5 Gastro-oesophageal cancer

4.5.1 The evidence base for dose-fractionation in the radiotherapy of gastro-oesophageal cancer is poor. The majority of regimens, particularly those prescribed with palliative intent, are empirical in nature. Multimodality therapies linking radiotherapy with both chemotherapy and surgery are evolving rapidly.

Oesophageal cancer: Definitive chemoradiotherapy

4.5.2 Randomised trial data and meta-analysis confirm local control and overall survival advantages with chemoradiotherapy compared to radiotherapy alone. This is at the expense of increased toxicity, and therefore careful patient selection is necessary. Most experience has been with cisplatin and 5-FU, the dominant study being the "Herskovic" RTOG 85-01 study where a dose of 50 Gy in 25 fractions was used (level 2++).[1]

A Cochrane review of the advantages of chemoradiotherapy over radiotherapy alone in 13 trials has confirmed a benefit to combined modality therapy, with a reduction in mortality of 9% and an improved local control rate of 5% at the expense of increased toxicity.[2]

For patients with oesophageal cancer, chemoradiotherapy as definitive management is recommended when improved outcomes can be justified against potential increased toxicity (Grade A).

For such patients 5-FU chemotherapy is recommended with a radiotherapy dose of 50.4 Gy in 28 daily fractions or 50 Gy in 25 daily fractions (Grade B).

Oesophageal cancer: Definitive radiotherapy

4.5.3 In a series of 101 patients treated at the Christie Hospital in Manchester between 1985 and 1994, 3- and 5-year survival figures of 27% and 21% respectively were recorded using a dose of 50 Gy in 15 or 16 fractions.[3] The majority of tumours (96/101) were 5 cm or less in length. Radical treatment to limited volumes should therefore not be ruled out for short tumours when chemotherapy is contraindicated. Other fractionation regimens used are 50–55 Gy in 20 fractions, or 60 Gy in 30 fractions.

For patients with short oesophageal cancers, radical radiotherapy alone may be appropriate. The following regimens are acceptable:

50 Gy in 15 or 16 daily fractions (Grade C)

50–55 Gy in 20 daily fractions (Grade D)

60 Gy in 30 daily fractions (Grade D).

Oesophageal cancer: Post-operative radiotherapy

4.5.4 A Chinese study randomised 495 well-staged patients with squamous carcinoma to receive either surgery alone (S) or surgery and post-operative radiotherapy (S+R).[4] The radiotherapy included supraclavicular fossae (SCF), mediastinum and the anastomosis to an initial dose of 40 Gy. A further 10 Gy was given to the SCF and 20 Gy to the mediastinum by a different technique, allowing a maximum dose to the transposed stomach of 50 Gy. The analysis showed a highly significant difference in 3-year survival in stage III disease between the S and S+R arms (23.3% versus 43.2%) (level 1–).

The applicability of findings from the Chinese study to UK practice, where the majority of tumours are adenocarcinomas and many patients receive pre-operative chemotherapy, is unclear. Case selection is difficult, but a suitable subset of patients might be those with a positive circumferential margin but with a low burden of positive lymph nodes. For selected high-risk patients with R1 resected oesophageal tumours, particularly squamous cancers, post-operative radiotherapy 45–60 Gy (with or without chemotherapy) in daily 2 Gy fractions has a questionable role (Grade D).

Oesophageal cancer: Pre-operative chemoradiotherapy (CRT)

4.5.5 The MRC (Medical Research Council) OEO2 Trial has established pre-operative chemotherapy with cisplatin and 5-FU as standard practice in the UK.[5] While the results of the "Walsh" study[6] have influenced practice in the USA, neoadjuvant chemoradiotherapy has not become routine in the UK. Recent meta-analyses suggest minor improvement in 3-year survival.[7,8] A Cochrane review is being undertaken. Significant concerns remain about increased post-operative morbidity and mortality, but recent data suggest this may be minimal in specialist centres.[9–11] Further evidence about the value of adding radiotherapy to chemotherapy and surgery for particular groups of patients is required. Pre-operative chemoradiotherapy for oesophageal cancer should only be performed where unit audit demonstrates acceptable post-operative complication rates, or within the context of a clinical trial (Grade B).

Oesophageal cancer: Palliative radiotherapy

4.5.6 The role of external beam radiotherapy has a poor evidence base. The use of stents has changed clinical practice in patients with critical dysphagia.[12] Short fractionation regimens are widely used with safety in patients for whom more radical treatment is inappropriate. One recent trial[13] supports the continued use of palliative radiotherapy with survival and quality-of-life benefits. Brachytherapy may also have a role in palliation. There is randomised trial evidence that single-dose intraluminal brachytherapy provides better long-term relief of dysphagia with improved quality of life than stents but with a longer time to symptomatic relief.[14] The optimal dose of brachytherapy may be with more than 1 fraction and a higher dose. There is evidence that this can improve survival.[15]

Palliative single-dose brachytherapy should be considered as an option for the relief of dysphagia (Grade B).

Palliative external beam radiotherapy for oesophageal cancer has a role and should be considered together with other approaches. The following regimens are acceptable:

30 Gy in 10 daily fractions (Grade D)

20 Gy in 5 daily fractions (Grade D).

Gastric carcinoma: Post-operative chemoradiotherapy

4.5.7 The "Macdonald" SWOG (Southwest Oncology Group) 9008 study of post-operative chemoradiotherapy provided evidence of survival benefit but had poor surgical quality control.[16] It remains controversial whether the results can be translated into clinical practice where surgical resections are carried out to high standards. The MRC MAGIC study[17] showed survival benefit with peri-operative chemotherapy alone. The next MRC gastric cancer study will be peri-operative chemotherapy, with or without biological agents.

Post-operative chemoradiotherapy for gastric cancer should only be performed where unit audit demonstrates acceptable morbidity, or within the context of a clinical trial (Grade B).

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4.6 Gynaecological malignancy

4.6.1 The planning target volume for treating pelvic malignancy normally encompasses the whole of the true pelvis and may be extended further, depending on the extent and type of malignancy to include the para-aortic nodes, the inguinal nodes or the vagina. This volume necessarily includes a large volume of small and large bowel. Although "beams-eye-view" planning allows increased accuracy in shielding the bowel in uninvolved areas of the pelvis,[1] the tolerance of the small bowel determines the dose and fractionation in treating gynaecological cancer.

Uterine corpus carcinoma

4.6.2 The majority of patients present with organ-confined disease, and surgery is the primary treatment. Adjuvant radiotherapy is only indicated for patients at high risk of recurrence.[2] Patients treated with daily fractions of 1.8–2.0 Gy to a total dose of 45–46 Gy over 4.5–5 weeks show an acceptable level of toxicity in prospective studies (level 2+).[3] The ASTEC trial used fraction sizes no greater than 2 Gy and doses of 40–46 Gy in 20–25 fractions over 4–5 weeks (level 4).[4] Selected patients may receive a brachytherapy boost to the vaginal vault using low-, medium- or high-dose rate afterloading radioactive sources.

For patients with operable uterine corpus carcinoma the following post-operative external beam regimens are acceptable:

45–46 Gy in 1.8–2 Gy daily fractions over 4.5–5 weeks (Grade C)

40–46 Gy in 20–25 daily fractions over 4–5 weeks (Grade D).

Uterine corpus carcinoma may be inoperable because of co-morbidity, obesity or advanced disease. Radiotherapy can control stage I and II disease and may have a role in more advanced cases.[5]

Early-stage cervical carcinoma

4.6.3 Patients presenting with small volume FIGO (International Federation of Gynaecologists and Obstetricians) stage Ib1 and IIa disease can be treated either by radical hysterectomy and lymphadenectomy as primary procedures, or by radical radiotherapy. The two approaches have equivalent survival rates. The combination of surgery and radiotherapy increases morbidity and should be avoided, if possible.[6,7] Post-operative radiotherapy is indicated for patients with poor prognosis features discovered at surgery (positive nodes, positive margins or extensive lymphovascular space involvement).[7] Local control and survival are increased by the addition of concomitant chemotherapy (level 1+),[8] although the benefit may be smaller when only one node is positive or when the tumour size is < 2 cm.[9] The role of chemo-radiotherapy as primary treatment for low-risk early stage disease remains to be established, as these patients were not included in any of the randomised clinical trials.

Randomised studies of radiotherapy have utilised fractionation regimens of 40–50.4 Gy in daily 1.8–2 Gy fractions over 4–5.5 weeks (level 2++).[4–6] Early toxicity is increased, if chemotherapy is added;[8] data on late toxicity are not yet available.

Cohort studies documenting technique, results and late effects have been published using radiotherapy alone in 40–45 Gy in 20 daily fractions of 2–2.25 Gy over 4 weeks followed by intracavitary brachytherapy (level 2+).[10–12]

For patients with high-risk early stage cervical carcinoma, the following external beam regimens have been used:

40–50.4 Gy in 1.8–2 Gy daily fractions over 4–5.5 weeks with concomitant chemotherapy (Grade B)

40–45 Gy in 20 daily fractions over 4 weeks (Grade C).

Locally advanced cervical carcinoma

4.6.4 Treatment comprises external beam irradiation to the primary tumour and regional lymph nodes followed by one or more brachytherapy treatments, wherever possible. Strong level 1+ evidence from five clinical trials[8,13–18] indicates that concomitant cisplatin chemotherapy improves survival particularly in stage II disease (Grade A). One trial examining this regimen showed no benefit.[19] The most common fractionation regimen used in these trials is 45 Gy in 25 fractions over 5 weeks (ranging from 40 to 50.4 Gy in 1.8–2 Gy fractions over 4–5.5 weeks) (level 2++ evidence). There is evidence that overall treatment time should be as short as possible and should not exceed 56 days for squamous carcinoma.[20–24] The haemoglobin level should be above 12 g/dl throughout the course of treatment (level 2+, Grade C).[25]

For patients with locally advanced cervical carcinoma, concomitant platinum-based chemotherapy is recommended (Grade A).

There is good evidence to recommend radiotherapy with 40–50.4 Gy in 1.8–2 Gy daily fractions over 4–5.5 weeks (Grade B).

Overall treatment time should not exceed 56 days (Grade B).

Operable vulval cancer

4.6.5 Treatment should be surgery to the primary and nodes as indicated by risk factors.[26] Those with positive nodes should receive adjuvant post-operative radiotherapy to inguinal and pelvic nodes.[27]

For selected patients with operable vulval cancer, radiotherapy with 45 Gy in 25 fractions of 1.8 Gy over 5 weeks to the inguinal and pelvic nodes is recommended (Grade B).

Inoperable vulval cancer

4.6.6 Treatment should be chemo-radiotherapy in the first instance, delivering 45 Gy in 25 fractions to the primary and nodes. Consideration should then be given to surgical removal of residual disease or a second phase of radiotherapy with electrons or brachytherapy to a total dose of 60–65 Gy in 1.8–2.0 Gy fractions.[28,29]

For patients with inoperable vulval cancer, chemoradiotherapy with 45 Gy in 25 daily fractions of 1.8 Gy over 5 weeks followed by completion surgery or further radiotherapy is recommended (Grade B).

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4.7 Head and neck cancer

4.7.1 In the management of head and neck cancer, the work of Gilbert Fletcher had a huge influence in establishing doses of 60–70 Gy given in daily fractions of 1.8–2 Gy over 6.5–7 weeks as an international convention.[1,2] Nevertheless, alternative fractionations have been widely used and were reviewed in the nine-centre (UK and North America) patterns of fractionation ACR (American College of Radiology) study of tonsil cancer.[3]

Modified fractionation radiotherapy

4.7.2 Alternatives to the 2 Gy per day, 5 times a week convention can be conveniently summarised as:

(a) Hyper-fractionation.

(b) Moderate acceleration.

(c) Marked acceleration plus hyper-fractionation (e.g., CHART).

(d) Marked acceleration with hypo-fractionation.

Randomised trials have demonstrated therapeutic gains for all four approaches.[4] Unfortunately, many trials are flawed in design.

(a) Hyper-fractionation (same treatment time, higher total dose, and more than 5 fractions per week). The EORTC oropharynx trial[5] showed an absolute improvement in 5-year local control of 19% with 80.5 Gy; the RTOG 4-arm trial[6] showed improvement in 2-year local control of 8.4% with 81.6 Gy. These approaches have not been widely adopted due to patient inconvenience, logistics and cost.

(b) Moderate acceleration (similar total dose, reduction of treatment time by 1–2 weeks, and more than 5 fractions per week). The DAHANCA regimen of 6 fractions per week, reducing treatment time by about a week, showed improvement in 5-year local control of 10%.[7] The RTOG 4-arm trial[6] showed improvement in 2-year local control of 8.5% with the concomitant boost regimen of 72 Gy in 6 weeks. Acute toxicity was enhanced with these modifications, but late effects were not significantly increased.

(c) Marked acceleration plus hyper-fractionation (reduction of treatment time by more than 2 weeks, reduced total dose, and more than 5 fractions per week). The CHART regimen (54 Gy in 12 days) showed similar local control, but fewer late effects than conventional regimens; it was advantageous in particular subgroups of patients.[8] The GORTEC study of 63 Gy in just over 3 weeks showed improved local control of 24% but with severe acute toxicity.[9] Neither of these regimens is used routinely in the UK.

(d) Marked acceleration with hypo-fractionation (less than conventional number of large-sized fractions) has only been tested in the BIR (British Institute of Radiology) two larynx trial of short versus long regimens (mainly 2 Gy given 5 times per week). It showed no significant difference in local control or overall survival, but fewer late effects for the short (high fraction size) 3–4-week regimens;[10] however, this "pragmatic" study has been criticised for variable dose definition, prescription and delivery (uncompensated gaps). A high quality cohort of patients treated for laryngeal cancer with 50–52.5 Gy in 20 daily fractions over 4 weeks has been published.[11] In addition, the control arm of the neutron studies provides a further cohort of patients treated with 20 daily fractions over 4 weeks (level 2+).[12]

Radiotherapy with chemotherapy

4.7.3

Induction chemotherapy with full-dose cisplatin and 5-FU may produce a small survival benefit.[13] In contrast, synchronous chemoradiotherapy clearly produces improved local control, which on meta-analysis translates into an improvement in overall survival of 8%.[13] However, both acute and late normal tissue toxicity is increased giving rise to concern that a true therapeutic gain has not been achieved. Nevertheless, platinum-based single agent chemotherapy is now widely used with radiotherapy. Synchronous chemotherapy should also be considered for high-risk post-operative cases given either with 4-week (50–52.5 Gy) or conventional regimens (60–66 Gy).[14]

Stage I and Stage II disease (T1/T2 No) (larynx only)

4.7.4 Patients with stage I or II laryngeal cancer can be treated effectively with both short (16–20 fraction) (level 2+)[15] and conventional (2 Gy) regimens,[2] noting that short fractionation regimens remain a minority practice internationally, with a less robust evidence base than that for conventional treatment.[2,15]

Patients with Stage I or II laryngeal cancer can be treated effectively with both short and conventional regimens:

64–70 Gy in daily 2 Gy fractions over 6.5–7 weeks (Grade B)

54–55 Gy in 20 daily fractions over 4 weeks (Grade C)

50–52.5 Gy in 16 daily fractions over 3 weeks (small volume only) (Grade C).

Stage III and Stage IV disease (fit patients, any node positive; T3/T4 No)

4.7.5 Fit patients with Stage III or IV head and neck cancer treated with definitive radiotherapy should not be treated with conventional fractionation alone (10 Gy per week). Treatment should be with either modified fractionation or synchronous chemoradiotherapy. The moderately accelerated regimens, e.g., DAHANCA (66–68 Gy in 5.5 weeks)[7] or concomitant boost (72 Gy in 6 weeks),[6] seem most attractive. The radiotherapy regimens used with platinum-based chemotherapy are usually delivered over 6–7 weeks, but there is also considerable experience in using chemo-radiotherapy over 4 weeks (Grade C).[16]

For fit patients with Stage III or IV head and neck cancer offered definitive radiotherapy, the following regimens are recommended:

Moderately accelerated radiotherapy, e.g., 66–68 Gy in 2 Gy fractions 6 times a week over 5.5 weeks (Grade A)

72 Gy in 6 weeks using concomitant boost (Grade A)

66–70 Gy in 6.5–7 weeks plus synchronous chemotherapy (Grade A).

Medical co-morbidity

4.7.6 Patients with extensive medical co-morbidity may be treated with definitive radiotherapy alone, in conventional or short regimens (Grade D).

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4.8 Lung cancer

4.8.1 In 2005, both NICE (National Institute for Health and Clinical Excellence) and SIGN (Scottish Intercollegiate Guidelines Network) published guidelines on the management of lung cancer.[1,2] These were developed using formal methodology based on systematic review of the evidence. This section therefore draws largely on the recommendations from these guidelines.

4.8.2 There are two main histological types of lung cancer for which the rationale of treatment is different. Although 40–50% of patients are initially managed by radiotherapy,[3] 90% of such treatments are palliative.[4]

4.8.3 For radical treatment, conformal 3-D radiotherapy should be considered best practice in order to limit the unnecessary irradiation of normal tissues[5–7] (Grade C).

Non-small cell lung cancer (NSCLC): curative thoracic radiotherapy

4.8.4 NSCLC is the most common type of lung cancer (75–85%) of which only 15–25% are potentially curable. At present, radical radiotherapy offers the only chance of cure for medically inoperable NSCLC (Stage I and II) and for locally advanced disease (Stage III). Although high-dose radiotherapy is the treatment of choice, the outcome remains poor with 5-year survival rates of 10% after conventional radiotherapy.[8–11] Patterns of failure indicate that local recurrence is a major cause of death.[9,11] Several reviews summarise the variety of fractionation regimens used either alone or combined with chemotherapy worldwide.[12–15]

4.8.5 In the UK, three fractionation regimens are most commonly used:

(a) Accelerated hypo-fractionated radiotherapy
52.5–55 Gy in 20 daily fractions given over 4 weeks. This accelerated hypo-fractionated regimen, with or without the addition of chemotherapy,[16] is now the most commonly used in the UK (Grade C).[17] The NCRN SOCCAR trial has been designed to assess the benefit of concurrent versus sequential chemotherapy in combination with this fractionation regimen.

(b) Conventional radiotherapy
60–66 Gy in 2 Gy fractions over 6.5 weeks. This is usually now combined with concurrent or adjuvant chemotherapy (Grade B).[18,19]

(c) Continuous hyper-fractionated accelerated radiotherapy (CHART)
This regimen delivers 54 Gy in 36 fractions delivered 3 times daily over 12 elapsed days. In a randomised multi-centre trial, CHART gave a 22% reduction in the relative risk of death compared to conventional radiotherapy.[10,11] It has been endorsed in national guidelines.[1,2] The precise radiotherapy regimen appears to be critical as 60 Gy in 30 fractions over 3 weeks was no better than 60 Gy in 30 fractions over 6 weeks.[20] The role of chemotherapy given prior to CHART is to be the subject of the INCH trial, another NCRN randomised controlled trial.

4.8.6 The role of adjuvant chemotherapy has been established by a meta-analysis, which showed a 13% reduction in the risk of death with platinum-based chemoradiotherapy compared to conventional radiotherapy alone.[21] There is now a suggestion that there is benefit from concurrent chemotherapy, and this is the subject of the SOCCAR study.

For patients with NSCLC offered radical radiotherapy, the following regimens are recommended:

CHART - 54 Gy in 36 fractions over 12 consecutive days (Grade A)

Conventional radiotherapy - 60–66 Gy in daily 2 Gy fractions over 6–6.5 weeks with neo-adjuvant or concurrent chemotherapy (Grade B).

NSCLC: palliative thoracic radiotherapy

4.8.7 Recent reviews reveal little consensus on the optimal palliative regimen. Although randomised studies show that patients with poor performance status do not benefit from high-dose multi-fractionated radiotherapy, those with good performance status may benefit.[4,22]

Between 1985 and 1992, the MRC conducted three randomised trials to determine appropriate thoracic regimens for intrathoracic symptom palliation in patients with unresectable NSCLC ineligible for curative radiotherapy.[23–25] The then standard 30 Gy in 10 fractions (F10) and 27 Gy in 6 fractions (F6) were compared to 17 Gy in 2 fractions (F2) in patients with moderate to poor performance status. Median duration of symptom palliation, survival and radiation-induced morbidity were similar for all groups. F2 was recommended, since it was as effective as multi-fraction regimens and more cost effective.[23]

In patients with NSCLC and moderate to poor performance status, 17 Gy in 2 fractions over 7 days offers effective palliation (Grade A).

Case selection for short palliative regimens is critical, because spinal cord injury has been reported in patients who survived longer than expected.[26,27] Treatment is usually given using a parallel pair: dose to the spinal cord should be calculated and dose reduction or shielding may be appropriate (level 2+, Grade C).

4.8.8 F2 was then compared with 1 fraction of 10 Gy in patients with poor performance status, but whose main symptoms arose from intrathoracic tumour. Duration of palliation was similar and substantially less dysphagia was reported for 1 fraction.[24]

In patients with NSCLC and poor performance status, a single dose of 10 Gy is recommended for effective palliation (Grade A).

4.8.9 F2 was compared with 39 Gy in 13 fractions (F13) in patients with good performance status. Although dysphagia with F13 was worse, median survival was improved giving a modest therapeutic gain (level 1+).[25] A recent Canadian study has provided further evidence for survival benefit with the fractionated higher dose treatment of 20 Gy in 5 fractions as compared to a 10 Gy single dose in patients with a good performance status (level 1+).[28] Other regimens such as 27 Gy in 6 fractions are also commonly used in the UK (level 4, Grade D).

In patients with good performance status treated palliatively for NSCLC, higher doses improve survival (Grade A).

The following regimens are recommended:

39 Gy in 13 fractions (Grade B)

20 Gy in 5 fractions (Grade B).

Small cell lung cancer (SCLC)

4.8.10 As SCLC is a systemic disease, current treatment integrates chemotherapy and radiotherapy. Two meta-analyses underpin the role of thoracic radiotherapy for loco-regional control and survival in limited disease SCLC.[29,30] Consolidation radiotherapy is recommended for such patients if they achieve a response to chemotherapy (Grade A).

There is evidence that compared to doses of 35 Gy, doses of up to 50 Gy in 2 Gy fractions are associated with improved loco-regional control (level 2+, Grade C).[31–34]

There is also evidence for benefit from early concurrent radiotherapy.[35–38] One study[39] has demonstrated significant survival benefit for hyper-fractionated, accelerated concurrent chemoradiotherapy with 45 Gy in 30 fractions over 3 weeks, although the control arm in this trial was 45 Gy in 25 fractions over 5 weeks which is more protracted than in previous trials. This factor may have contributed to the difference (Grade C).[39] The issues of optimal dose and fractionation of radiotherapy remain unresolved and further research should be supported.

4.8.11 Patients with limited SCLC and complete or good partial response after chemotherapy should be considered for prophylactic cranial irradiation as it decreases the incidence of cerebral relapse and improves overall survival.[40] Published series support fractionation of 24–30 Gy in 8–10 fractions and there is an ongoing EORTC trial randomising between 25 Gy in 10 fractions and 36 Gy in 18 fractions.

For selected patients with SCLC, prophylactic cranial radiotherapy 24–30 Gy in 8–10 daily fractions is recommended for achieving good partial or complete response (Grade A).

4.8.12 Extensive SCLC is a difficult management issue. While response rates to therapy are relatively high, durable responses are rare, and long-term survival rates are dismal.[41] Platinum-based combination chemotherapy is the mainstay of treatment.[41,42] The main goal for patients with a limited prognosis is improving their quality of life.[43]

If thoracic radiotherapy is indicated for patients with extensive SCLC, then the palliative regimens described above are acceptable (Grade D).

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4.9 Lymphoma

Hodgkin's lymphoma

4.9.1 Over the last 30 years, combination chemotherapy has become the standard of care for both early and late Hodgkin's lymphoma. The role of radiotherapy following chemotherapy, and the radiation dose required, are the subject of ongoing studies.

Early Hodgkin's lymphoma

4.9.2 Studies by the German Hodgkin's group[1] have shown no difference in outcome between 2 or 4 cycles of ABVD chemotherapy and 20 or 30 Gy IFRT (Involved Field Radiotherapy) delivered in 2 Gy fractions, but follow-up is too short to be sure that important differences will not emerge (level 1–). The role of radiotherapy after chemotherapy in PET-negative patients is the subject of a current NCRN trial.

For selected patients with early Hodgkin's disease treatment with ABVD chemotherapy followed by IFRT 30 Gy in daily 2 Gy fractions over 2–3 weeks is recommended (Grade B).

Advanced Hodgkin's lymphoma

4.9.3 The role of radiotherapy in advanced Hodgkin's disease after full-dose combination chemotherapy is controversial. An overview showed that combined-modality therapy conferred no survival benefit but did increase the risk of long-term fatal complications (cardiac and second cancer).[2] Recently, an EORTC study[3] demonstrated that radiotherapy did not improve the outcome for patients who had a complete remission after MOPP-ABV chemotherapy (level 1+) but that irradiation may benefit patients with a partial response after chemotherapy (level 2+).

In the management of advanced Hodgkin's lymphoma, radiotherapy for residual disease may be indicated after partial response to chemotherapy. If so, 30–34 Gy in 15–20 fractions of 1.8–2.0 Gy over 3–4 weeks is acceptable (Grade C).

4.9.4 IFRT remains a critical component of the brief chemotherapy regimen known as Stanford V, which consists of 12 weeks of alternating myelosuppressive / non-myelosuppressive chemotherapy:[4,5] Radiotherapy is delivered to sites of bulk disease larger than 5 cm (level 2+). The dose is between 34 and 35 Gy in 17–20 fractions of 1.8–2.0 Gy (Grade C).

Relapsed Hodgkin's lymphoma

4.9.5 In some patients with a single site of relapse, particularly occurring late, after previous treatment, re-induction as for early disease combined with IFRT may be appropriate, if the site has not previously been irradiated (Grade D). Radiotherapy alone has been used for selected patients (level 2–, Grade D).[6] High dose chemotherapy and stem cell transplantation remains the international standard of care for many younger patients with relapsed Hodgkin's lymphoma.

4.9.6 For palliative treatments no definitive recommendations can be made and dose will depend on the clinical situation. Doses ranging from 30 Gy in 10 fractions to a single 7–8 Gy fraction are all reasonable (Grade D).

Intermediate / high-grade non-Hodgkin's lymphoma (NHL)

4.9.7 In high-grade (diffuse) lymphomas, treated with radiotherapy alone, a review of the EORTC data[7] has reported a higher incidence of relapse (30%) in patients who received < 45 Gy compared to only 13% in patients who received > 45 Gy. In a BNLI (British National Lymphoma Investigation) trial of local radiotherapy alone in grade II NHL,[8] a dose–response for radiotherapy control up to 45 Gy was reported in a group of 85 patients (level 2+).

Consolidation IFRT in limited stage aggressive non-Hodgkin's lymphoma

4.9.8 Following the landmark study comparing 8 cycles of CHOP chemotherapy to 3 cycles of CHOP followed by IFRT with 40–45 Gy in 1.8–2 Gy fractions, combined modality therapy was established as the standard of care (level 1+).[9] Longer-term follow-up has shown convergence of the survival curves, as a result of an excess of relapses and death from lymphoma in the group given CHOP plus radiotherapy.[10] Chemotherapy alone may be the preferred option depending on the toxicity of planned IFRT (e.g., the necessity for bilateral parotid irradiation).

In a further study, patients who received 8 cycles of CHOP chemotherapy and achieved complete remission, 30 Gy in daily 2 Gy fractions improved local control (level 1+).[11] A recent trial in patients aged < 61 years with no adverse prognostic factors has shown improved event free and overall survival rates with ACVBP chemotherapy, over those achieved by CHOP plus IFRT.[12] The role of immuno-chemotherapy (R-CHOP)[13] remains to be established in early stage disease.

A randomised trial of radiotherapy dose comparing 30 Gy to 40–45 Gy (all in daily 2 Gy fractions) has recently been completed. The result has yet to be fully published, but an early analysis has shown no difference in local control (level 1).[14]

For selected patients with Stage I or II aggressive non-Hodgkin's lymphoma, radiotherapy with 30–45 Gy in daily 2 Gy fractions over 3–4 1/2 weeks to involved fields is recommended as part of planned combined modality therapy (Grade B).

Nasal natural killer / T-cell lymphoma

4.9.9 This is a rare entity in Western countries but is common in East Asia and Latin America.[15] A cohort of 107 patients with Stage IE and IIE disease has been reported.[15] Initial radiotherapy was superior to initial chemotherapy. The addition of chemotherapy to radiotherapy did not improve survival. The median radiotherapy dose was 50 Gy (range 40–65 Gy) at a dose-per-fraction of 2 Gy (level 2+, grade D).[15]

Low-grade lymphoma

4.9.10 Low-grade lymphoma includes follicular lymphoma, small lymphocytic lymphoma and marginal zone lymphoma. Stage I low-grade lymphoma has for many years been treated with radical IFRT. A review of a series of 175 cases in EORTC studies showed no improvement in local control with doses above 25 Gy (level 2–).[7] In a large series from Toronto,[16] no dose–response was seen in low-grade lymphoma for doses > 20 Gy (level 2–). These retrospective series are subject to bias as patients with bulkier disease might have been selected to receive higher doses. A randomised trial comparing 24 Gy to 40 Gy (all in 2 Gy fractions) has recently been completed. The result is yet to be fully published, but an early analysis has shown no difference in local control (level 1).[14]

For the radical treatment of stage I, low-grade lymphoma, 24–40 Gy in 2 Gy fractions over 2.5–4 weeks is acceptable (Grade C).

Mantle cell lymphoma

4.9.11 This disease has a poor prognosis even if Stage I. The vast majority of patients require systemic treatment, although the standard of care is not yet established. In combined modality treatment, there is little evidence on which to base recommendations, and doses of 40 Gy in 20 fractions are most frequently used (Grade D).

Palliative treatment of non-Hodgkin's lymphoma

4.9.12 For low-grade lymphoma, large series show no evidence of dose–response for local control with doses > 25 Gy[7] or 20 Gy[16] (level 2–). In patients with follicular lymphoma high response rates have been achieved after low dose IFRT (4 Gy in 1 or 2 fractions) (level 2+).[17–19] These low doses are to be explored in a randomised trial of radiotherapy and compared to 24 Gy in 12 daily fractions in the palliative management of follicular lymphoma (FORT study).

For intermediate / high-grade lymphoma a single dose of 8 Gy or short course palliation are effective and appropriate for the palliative treatment of many patients with a limited prognosis (level 4).

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

Follicular lymphoma – advanced stage –
4 Gy in 1 or 2 fractions to wide fields (Grade B)

Low-grade lymphoma –
24 Gy in daily 2 Gy fractions over 2.5 weeks as for radical treatment (Grade C)

Intermediate / high-grade lymphoma – single dose 8 Gy or short course palliation, e.g., 20 Gy in 5 fractions (Grade D).

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4.10 Paediatric cancer

4.10.1 Childhood cancer is rare. There are only about 1,500 cases per year in the UK. Management is centralised in the UK to twenty Paediatric Oncology Centres recognised by the United Kingdom Children's Cancer Study Group (UKCCSG). These are served by eighteen specialised paediatric radiotherapy centres. Treatment of children in other radiotherapy facilities is not recommended.

4.10.2 The standard of care for children with cancer is for treatment, wherever possible, within national or international clinical studies supported by the UKCCSG. There is evidence that trial entry improves patient survival compared to patients treated off protocol.[1] Overall, the uncertainty principle operates and new treatments tested are, on average, as likely to be inferior as they are superior to standard treatments.[2] The radiotherapy regimens within study protocols are based on the best evidence available, are peer-reviewed, and represent an international consensus of best practice.

For children receiving radical radiotherapy, fraction sizes of 2 Gy or less (according to UKCCSG or international protocols) are recommended (Grade B).

4.10.3 Cure rates for childhood cancer are good, with over 70% of children becoming long-term survivors. Cured patients have life expectancies measured in many decades, and quality of life factors are important.

4.10.4 Most childhood cancers are treated with combined modality therapy, involving surgery and chemotherapy as well as radiotherapy. These may have late developing adverse effects on normal tissues, affecting organ function, growth and development, cosmesis, and quality of life. Potential additive or supra-additive toxicities due to drug–radiation interactions must be borne in mind. Paediatric radiotherapy should be meticulously planned, with careful attention given to the doses received by organs at risk which may differ from adult practice, e.g., epiphyses must be avoided.

4.10.5 In palliative treatment of children with malignancy, the most important elements are liaising closely with paediatric oncologists and other specialties and providing a rapid, responsive and individualised service for each child. Childhood tumours are generally extremely radiosensitive and prognosis is very limited. Single doses of 8 Gy are often effective. However, in some circumstances high-dose palliative treatment is indicated, for example, in the management of bone and other sarcomas.

Palliative treatments for children with cancer can be given in single fractions of 6–8 Gy, ranging up to 40 Gy in 15 fractions depending upon clinical circumstances and field size (Grade D).

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4.11 Prostate cancer

Introduction

4.11.1 Early prostate cancer is being diagnosed more frequently because of PSA (Prostate Specific Antigen) screening. This change in natural history poses new management opportunities, and external-beam radiotherapy is only one of several options. These include: active surveillance and monitoring, radical surgery, and brachytherapy. Cryotherapy and high intensity focused ultrasound may have roles in the future.

Hormonal therapy and radiation dose

4.11.2 This guidance is concerned with radiotherapy dose-fractionation in the radical treatment of prostate cancer with external beam radiotherapy. The interaction of hormonal therapy and radiation dose is complex and interpretations of the available evidence are divergent.

4.11.3 The role of neoadjuvant or adjuvant androgen deprivation with LHRH (luteinizing hormone-related hormone) analogues depends on the risk group of the patient. For patients with low risk (PSA ≤ 10 and Gleason 2–6 and T1 to T2c) early prostate cancer, there is no proven role for adjuvant hormone therapy.

4.11.4 There is Grade A evidence in favour of neoadjuvant or adjuvant hormone therapy for patients with intermediate or high-risk (PSA > 10 or Gleason score > 7 or T ≥ 3) prostate cancer treated with radical radiotherapy, with seven randomised phase III clinical trials (level 1++) showing benefit.[1–7] Very few patients in these trials had low risk (PSA ≤ 10 and Gleason 2–6 and T1 to T2c) disease, and no firm recommendations on the use of hormone therapy can be made for this group. Men who have advanced localised disease (T3 and Gleason score ≥ 8) benefit from prolonged hormonal therapy (2 years of androgen suppression) compared to short course androgen therapy alone.[7] For patients in the intermediate risk group, there may be a balance between higher doses of radiotherapy and the use of neoadjuvant hormone therapy. Ongoing studies address this question.

4.11.5 In patients who do receive longer-term hormone therapy, there is no evidence that doses > 70 Gy are beneficial. In addition, prostate volume and prostate target volume are reduced by up to 46% following neoadjuvant therapy with associated sparing of the bladder and rectum.[8]

Radiotherapy technique

4.11.6 Because of the issues outlined above, the fractionation schemes which follow are considered independently of the use of hormonal therapy. Fractionation and technique must be considered together. Some centres use a two-phase (large pelvic volume / small prostate volume) approach: there is no published evidence using fraction sizes other than 1.8–2.0 Gy for this approach. It has been advocated in selected cases considered to have a risk of lymph node metastases > 15% (level 1–).[9,10] In the following discussion any consideration of fraction sizes > 2.2 Gy applies to PTVs (Planning Target Volumes) of < 1000 ml.

4.11.7 Since technique directly affects the tolerable dose, and since most UK centres now use 3-D conformal radiotherapy, the following comments deal solely with this technique (level 1+).[11–13] Conformal radiotherapy, using multileaf collimators which allow treatment using an irregular shaped beam, is the optimum mode of delivery. It has been recommended that all centres should provide this form of treatment (Grade A).[14]

Radiobiological modelling

4.11.8 The results and implications of radiobiological modelling of external beam treatment for prostate cancer are controversial.[15] Plausible arguments have been developed for both hypo-fractionation (fraction sizes of ≥ 2.5 Gy)[16,17] and for hyper-fractionation (fraction sizes of ≤1.5 Gy).[18] The advice that follows is based exclusively on clinical studies.

Hyper-fractionation (doses-per-fraction of ≤1.5 Gy)

4.11.9 There are two studies reporting results of hyper-fractionated radiotherapy for prostate cancer.[18,19] Level 3 evidence supports the following conclusions: in terms of efficacy, there is no disadvantage (other than conspicuous consumption) in using hyper-fractionation compared to conventional fractionation; there may be some decrease in late genitourinary, but not late gastrointestinal, toxicity.

Conventional fractionation (doses-per-fraction in the range 1.8 Gy–2.2 Gy)

4.11.10 The results of conventional fractionation have been comprehensively reviewed and reported.[20] Unfortunately, this systematic review completely overlooked the use of 20 fraction regimens in the radical treatment of prostate cancer. It does, however, provide a vast amount of information on the reported experience with doses of > 60 Gy given in 1.8–2.0 Gy fractions.

As technology has evolved, doses have increased from 60 to 65 Gy in 30–35 fractions using 2-D planning through 65–78 Gy using 3-D conformal techniques, and up to 80 Gy and beyond using IMRT. Four randomised trials[12, 21–23] have addressed the question: does dose-escalation improve freedom from failure or biochemical evidence of disease control (bNED)? The MD Anderson trial[12] in 305 patients with T1–3 disease showed a 6% improvement in failure-free survival at 6 years when 78 Gy in 39 fractions was compared to 70 Gy in 35 fractions. For the subgroup of patients with a PSA > 10 ng/ml, a 19% PSA control advantage was seen. The increase in failure-free survival was accompanied by an increase in late rectal complications (level 1+) which may now be avoidable with adjustments to radiotherapy technique (level 4).

The RMH (Royal Marsden Hospital) pilot trial of 126 patients[21] showed a statistically non-significant improvement of 12% in freedom from PSA failure when 74 Gy in 37 fractions was compared to 64 Gy in 32 fractions. Patients treated to a higher dose had a higher rate of late bowel complications (level 1+).

The Dutch trial, which has reported toxicity data only, also found an increased rate of serious late rectal complications in patients treated with 78 Gy when compared to patients treated with 68 Gy (10% versus 2% at 3 years) (level 1+).[22]

The recent trial comparing photon therapy alone (70 Gy) to photons + proton boost (79 Gy equivalent) showed a 19% increase in PSA control with the higher dose, but a doubling of bowel toxicity (level 1+).[23]

Hypo-fractionation (doses of 2.5 Gy per fraction and above)

4.11.11 Despite extensive use of such regimens, both in the UK and abroad, the number of reported series and trials is small. Two randomised trials[24,25] have compared hypo-fractionation to conventional fractionation in the radical radiotherapy treatment of prostate cancer. The hypo-fractionated regimens were 55 Gy in 20 fractions in 4 weeks[25] and 52.5 Gy in 20 fractions in 4 weeks.[24] Both regimens used control arms of ≤ 66 Gy in 33 fractions in 6.5 weeks, doses that, by current standards, might be considered low (see above). The results show a trend towards lower 4-year bNED rate with hypo-fractionation. The

evidence suggests that, although 20 fraction regimens can be effective and safe, doses of ≤ 55 Gy may be too low. In the UK, the CHHIP randomised controlled trial is comparing 2 Gy (total dose 74 Gy) and 3 Gy (total doses 57 Gy and 60 Gy) and has already recruited 300 patients. Broadly similar trials are planned in Canada and The Netherlands, comparing 78 Gy in 2 Gy fractions and 60 Gy and 63 Gy in 20 and 21 fractions respectively.

The Christie Hospital[26] has used 50 Gy in 16 fractions using a conformal technique. The overall bNED rates at 5 years were 65% (T1); 62% (T2); 38% (T3 and 4), comparable to those achieved using more protracted regimens (level 2+).

Experience, demand and capacity will influence departmental policies for the management of prostate cancer with external beam radiotherapy.

Given inter-departmental variations in definition of PTV, radiotherapy technique (conformal, IMRT), prescribing conventions and use of adjuvant hormone therapy, it is not appropriate to make any universal recommendation concerning dose.

Acceptable regimens include:

74–78 Gy to the prostate in 37–39 fractions over 7.5–8 weeks (Grade A)

50 Gy in 16 daily fractions over 3.5 weeks to the prostate only (Grade C)

20 fraction regimens have been extensively used—the optimal dose is uncertain, but is probably at least 55 Gy (Grade D).

4.11.12 This is a rapidly changing area of clinical practice and further clinical trials should be encouraged and supported.

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4.12 Rectal cancer

4.12.1 Radiotherapy is used in the treatment of patients with rectal cancer to reduce the risk of local recurrence (level 1++),[1] to improve the likelihood of achieving a pathologically complete resection margin as defined by circumferential margin > 1 mm, and in palliation. Its use as a definitive treatment and to improve sphincter preservation in low rectal cancer remains experimental.

Pre-operative radiotherapy is preferred to post-operative treatment as the pre-operative technique is more effective and less toxic.[1,2] All rectal cancer adjuvant radiotherapy should be planned using a three-or four-field plan, with shielding of normal tissue to reduce toxicity. Computed tomography planning facilities should be used. Two regimens of pre-operative radiotherapy have a clear evidence base: short- and long-course.

4.12.2 Short-course pre-operative radiotherapy has been shown in large randomised trials[3,4] to reduce the risk of local recurrence in operable rectal cancer, even prior to high quality total mesorectal excision surgery.[4] The fractionation regimen used is 25 Gy in 5 fractions over 1 week administered to a posterior pelvic volume as defined in the MRC CR07 protocol.[5] The development of this regimen, dose–response and details of technique have been described.[6] This treatment may impair wound healing and increase the rate of faecal incontinence; sexual functioning may also be affected. Nevertheless, overall quality of life is no different.[7] Surgery should be scheduled within 1 week of the final fraction. The CR07 trial will report in early 2006.

When short-course pre-operative radiotherapy is indicated for rectal cancer, 25 Gy in 5 daily fractions over 1 week, with surgery within 1 week is recommended (Grade A).

4.12.3 Long-course pre-operative radiotherapy giving 45 Gy in 25 fractions over 5 weeks followed by a 6–10 week gap prior to surgery is also widely used.[8] It has the advantage of being able to be combined with synchronous chemotherapy and is able to downstage patients with advanced disease allowing resection of previously unresectable tumours. A reduced volume boost dose of 5.4–9 Gy in 3-5 fractions may be used. The German CAO/ARO/AIO-94 study protocol has convincingly shown improved loco-regional control and less toxicity with preoperative 5-FU based chemoradiotherapy[9] when compared to post-operative combined modality treatment for Stage II and III resectable rectal cancer.

For selected patients with rectal cancer pre-operative radiotherapy with 45 Gy in 25 daily fractions over 5 weeks, followed by surgery after a 6–10 week gap is recommended (Grade A).

4.12.4 Post-operative radiotherapy is the North American standard of care[10,11] and is given in combination with post-operative adjuvant chemotherapy. The standard fractionation is again 45 Gy in 25 fractions in 5 weeks with an optional reduced volume boost of 5.4–9 Gy in 3-5 fractions. The technique and case selection is described in the selective post-operative treatment arm of the MRC CR07 protocol.[5]

Selected patients should be offered post-operative radiotherapy for rectal cancer with 45 Gy in 25 daily fractions over 5 weeks (Grade B).

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4.13 Sarcoma

Introduction

4.13.1 Clinical experience suggests that sarcomas vary widely in radiosensitivity. There is level 1++ evidence showing that post-operative radiotherapy lowers the risk of local recurrence.[1] The combination of conservative surgery and radiotherapy has proven successful in preserving the limbs of patients with extremity soft tissue sarcomas.

Resectable tumours

4.13.2 Surgery is the primary treatment in the majority of soft tissue sarcomas. Adjuvant radiotherapy is used to reduce the probability of local recurrence and facilitate surgical sparing of function. The results of the Canadian SR.2 trial suggest that the timing of treatment (whether pre-operative or post-operative) does not influence local control but may affect function.[2,3] Pre-operative radiotherapy of extremity sarcomas was associated with an increased risk of wound complications but less long-term functional deficit. This finding may be partially explained by the lower total doses used in the patients treated pre-operatively.[4] Where expertise in brachytherapy is available, this is a reasonable alternative to external beam therapy in high-grade sarcomas. There are no randomised trials in sarcomas purely dealing with fractionation. However, the excellent Canadian SR.2 study provides level 2+ evidence upon which to base practice.[3] There is also level 2+ evidence that local control is improved after gross total resection in those cases with features predictive of a higher than average local recurrence rate if the dose of post-operative radiotherapy is > 64 Gy.[5]

For patients with sarcoma, acceptable regimens for combined surgery and radiotherapy are as follows:

Pre-operative radiotherapy 50 Gy in 25 daily fractions of 2 Gy (Grade C)

Post-operative radiotherapy 50 Gy in 25 daily fractions of 2 Gy plus 10 Gy boost in 5 fractions over 1 week (average risk) (Grade C).

For post-operative treatment an increased boost of 16 Gy in 8 daily fractions over 1.5 weeks is recommended for those with a higher than average risk of local recurrence (Grade C).

Unresectable tumours

4.13.3 Where there are no metastases at presentation, patients may be considered for radical radiotherapy as the sole treatment. There is level 2+ evidence to support a total dose to tumour of 66 Gy in 33 fractions.[6]

For patients with unresectable sarcomas, who are in good general condition and have no evidence of metastatic disease, a total dose to tumour of 66 Gy in 33 fractions of 2 Gy over 6.5 weeks is acceptable (Grade C).

Desmoid tumours

4.13.4 These rare tumours are locally aggressive, do not metastasise and are best treated by surgery. For patients with inoperable disease, there is level 2+ evidence to support the use of 56 Gy in 28 fractions in an attempt to delay progression. Radiotherapy may also be used, at similar doses, to prevent or delay recurrence in patients who have residual disease after surgical excision.[7–9]

For the definitive or post-operative management of desmoid tumours, a radiotherapy dose of 50–56 Gy in 25–28 daily fractions over 5–5.5 weeks is acceptable (Grade C).

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

4.13.5 When surgical resection is feasible or appropriate, this is usually carried out after preliminary chemotherapeutic cytoreduction. Where a radical surgical margin is not achieved, then there is level 3 evidence to suggest that post-operative radiotherapy at a dose of 55–60 Gy in 28–30 fractions for gross disease, and of 45 Gy in 25 fractions for microscopic disease, might be beneficial.[10]

For Ewing's tumours and other PNET occurring in adults, a radiotherapy dose of 45 Gy in 25 daily fractions over 5 weeks for microscopic disease and 55–60 Gy in 28–30 daily fractions over 5.5–6 weeks for gross disease is acceptable (Grade D).

Palliation

4.13.6 Level 4 evidence suggests that palliative treatments can achieve a useful effect. Doses may vary from single 8 Gy to higher doses (e.g., 20 Gy in 5 fractions and up to 40 Gy in 15–20 fractions) for large volume local disease in selected patients.

Palliative treatments for sarcoma can be given in single fractions of 6–8 Gy ranging up to 40 Gy in 15 fractions, depending upon clinical circumstances and field size (Grade D).

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4.14 Seminoma

4.14.1 Stage I seminoma has a risk of relapse of between 15 and 20% and surveillance without treatment is one option. Relapses principally occur in the para-aortic nodes and the risk can be quantitated using factors related to the primary tumour[1] (level 2+, grade C).

4.14.2 Optimal radiotherapy has been defined in a series of trials by the Medical Research Council. All used 2 Gy fractions. The first study showed that irradiating the para-aortic region, rather than a dog-leg field, was not associated with an increased relapse rate (level 1+).[2]

4.14.3 A second study showed that the radiation dose could be reduced from 30 Gy in 15 fractions to 20 Gy in 10 fractions (level 1+).[3] 20 Gy in 8 fractions over 10 days delivered to the para-aortic region has also been shown to be effective with overall 5-year survival of 98% and recurrence-free survival at 5 years of 96% (level 2++).[4]

4.14.4 Radiotherapy carries an excess risk of death as a result of cardiac disease or second cancer.[5] 30-year follow-up shows that the relative risk of second malignancy is 1.4 and 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.[6]

4.14.5 There has therefore been interest in chemotherapy as an alternative to radiotherapy. Oliver, et al,. have now shown that a single dose of carboplatin can achieve results equal to radiotherapy in terms of overall tumour control and early survival (level 1+).[7] Distant relapse is less common but para-aortic relapse is more common. Second tumours in the contralateral testis are reduced. It is expected that long-term second malignancy at other sites will be lower if radiotherapy is not given (level 4, Grade D). The assumption is that radiation is mainly responsible for the increased second cancer incidence, but genetic factors may also have a role to play. Recent reductions in radiation field size and dose may have reduced the second cancer risk (level 4, Grade D).

For those patients in whom para-aortic radiotherapy is indicated, 20 Gy in 10 fractions of 2 Gy over 2 weeks (Grade B) or 20 Gy in 8 fractions over 10 days (Grade B) are recommended.

Early results indicate that carboplatin is as effective as para-aortic radiotherapy (Grade B).

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4.15 Bone metastases

Localised bone pain

4.15.1 Uncomplicated local bone pain responds well with response rates of 70–80% after localised external beam treatment. Since response may take 4–6 weeks to achieve, it is recommended that consideration be given to the patient's prognosis before treatment. A number of large randomised controlled trials have been undertaken to explore the optimal dose. Three reviews have been completed using the Cochrane methodology. On the basis of this information, the recommended fractionation is a single dose of 8 Gy.[1–3]

4.15.2 Bone metastases may give rise to pain with neuropathic features rather than simple bone pain. One randomised controlled trial specifically addressed this question comparing single-dose 8 Gy to multi-fraction treatment, for most patients 20 Gy in 5 fractions. No major advantage for the multi-fraction arm was identified, and the recommendation therefore is that these patients should also receive a single dose of 8 Gy.[4]

For the initial therapy of pain from bone metastases, a single fraction of 8 Gy is recommended (Grade A).

Re-treatment

4.15.3 Re-treatment should be considered in patients still having clinically significant pain despite optimal analgesic use after 4–6 weeks. After a single dose, around 25% of patients may need re-treatment at some point.[5] Limited evidence suggests that response rates are similar to those after primary treatment.[6] There are no data to guide optimal dose-fractionation for re-treatment and this issue is the subject of a current prospective trial randomising between a single dose of 8 Gy and 20 Gy given in 5 daily fractions (8 fractions if over spinal cord; see Section 4.17.10). These may both be considered acceptable treatments for re-irradiation, pending the results of this trial.

For the re-irradiation of bone metastases, 8 Gy single dose or 20 Gy in 5 daily fractions should be considered (Grade C).

For re-treatments covering the spinal cord 20 Gy in 8 fractions should be considered (Grade D).

Scattered bone pain

4.15.4 For metastatic bone pain at several sites, wide-field or hemibody external beam radiotherapy is effective. There are no randomised data to compare such treatment to isotope therapy, but case–control comparisons suggest that all are equally effective. However, external beam radiotherapy is associated with more toxicity in terms of gastrointestinal and bone marrow side effects.[7] A large international study tested 2, 4, and 5 fraction regimens, but there is no evidence to suggest that any of these are superior to giving the treatment in a single-dose.[8]

For patients with scattered bone pain, the following regimens are acceptable:

Upper hemibody 6 Gy single dose (Grade C)

Lower hemibody 8 Gy single dose (Grade C)

Isotope therapy (Grade C).

Pathological fracture

4.15.5 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 multi-focal lytic disease.[9] Surgical fixation should be considered. If radiotherapy is to be used, there is no consensus on the best fractionation in this setting. Such 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 4).

If radiotherapy is to be given in an attempt to prevent pathological fracture, patients may be treated with 20 Gy in 5 fractions (Grade D) or 8 Gy single dose (Grade D).

Established fracture

4.15.6 Bones such as ribs, vertebrae and pelvic and shoulder girdle bones are not amenable to surgical fixation and will be treated with local radiotherapy. Again, there is no consensus on optimal fractionation. However, a regimen such as 20 Gy in 5 fractions or 8 Gy single dose is recommended (level 4).

Patients with inoperable pathological fractures may be treated with 20 Gy in 5 fractions or 8 Gy single dose (Grade D).

Post-operative treatment

4.15.7 After internal fixation of a fracture or prophylactic pinning of a high-risk lesion, post-operative radiotherapy is often recommended. There is limited literature to support its efficacy and no consensus on dose. Recommendations would be, as above, for a fractionated regimen such as 20 Gy in 5 fractions or 8 Gy single dose to be given in this setting, where considered appropriate. Treatment should be considered for all patients with persisting bone pain after surgery. In cases in whom treatment is given with the aim of enabling bone healing and long-term rehabilitation, then consideration should be given to performance status and predicted survival before treatment is recommended.

Post-operative radiotherapy after fixation of bone metastases can include 20 Gy in 5 fractions or 8 Gy single dose (Grade D).

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4.16 Cerebral metastases

4.16.1 This is a heterogeneous population of patients with:

- Different histologies.
- Single or multiple metastases.
- Differences in performance status.
- Differences in the presence or absence of uncontrolled disease outwith the CNS.
- Different options for systemic therapies.

It is therefore helpful to classify patients according to a simplified system. Specifically, the RPA (recursive partitioning analysis) based system of the RTOG is simple and robust.[1]

Patients can be divided into three groups according to:

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

Patients have the worst outlook in group 3 with a KPS < 70.[1] This system has been validated on a separate data-set.[2] It has been pointed out that group 3 includes a substantial majority of patients: it may be difficult to identify those unlikely to gain palliative benefit from radiotherapy.[3] It has been suggested that further sub-division of group 3 may assist in advising on treatment.[4]

4.16.2 The regimens most commonly used for the treatment of cerebral metastases are 30 Gy in 10 fractions and 20 Gy in 5 fractions. For patients with limited disease, other approaches, including gamma knife or stereotactic radiosurgery (SRS) and intra-operative radiotherapy are feasible. There are two broad categories of patient to consider: those with single (potentially resectable) metastases and those with multiple metastases. The following discussion draws heavily on a systematic review performed as part of the Cancer Care Ontario programme in evidence-based care.[5]

Single metastases

4.16.3 The evidence from one systematic review[5] and three randomised trials [6–8] (level 1+) suggests benefit from adding surgery to whole-brain radiotherapy. Stereotactic radiosurgery appears to achieve the same result as neurosurgery and may be the treatment of choice where it is available (level 1+, Grade B).[9] It is recommended that these treatment combinations be offered to patients with cerebral metastases who are in good general condition and whose extra-cranial disease is controlled (or potentially controllable) and those who have a solitary metastasis suitable for surgery (RPA group 1) (Grade A). As discussed below, whole brain radiotherapy of 30 Gy in 10 daily fractions is recommended (Grade A).

Multiple metastases

4.16.4 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 to either higher or lower doses.[10–15]

4.16.5 Surprisingly, there is only one small study (of 70 patients) comparing the 6-month survival rate after 30 Gy in 10 fractions to that after 20 Gy in 5 fractions. There was no significant difference.[10] An RTOG study reported in 1980 compared three regimens: 40 Gy in 15 fractions; 30 Gy in 10 fractions; and 20 Gy in 5 fractions.[16] 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. Other regimens assessed in RTOG randomised trials included: 10 Gy single-dose and 30–40 Gy in 10–20 fractions; 40 Gy in 20 fractions and 40 Gy in 15 fractions and 30 Gy in 15 fractions and 30 Gy in 10 fractions.[16,17] There was no statistically significant difference in median survival. The trial results suggest that regimens using only 1 or 2 fractions are inferior to 30 Gy in 10 fractions, but that there is no improvement in survival when dose is increased beyond 30 Gy in 10 fractions (level 1+ evidence).

4.16.6 For patients with poor performance status and for whom treatment is judged to be necessary, the regimen of 12 Gy in 2 fractions is convenient and moderately effective (level 1+, Grade B).[15]

4.16.7 Patients in RPA Class III have such a poor prognosis that it may be difficult to justify any radiation treatment at all. These patients are those with a Karnofsky performance status < 70. It is reported that it is difficult to identify patients in this group who are unlikely to gain palliative benefit from whole-brain radiotherapy.[3] It has also been suggested that further sub-division may help in making these decisions.[4]

For patients with multiple cerebral metastases in whom treatment is considered worthwhile, regimens of 20 Gy in 5 fractions or 30 Gy in 10 fractions are both recommended (Grade A).
For patients with poor performance status, radiotherapy may not be indicated. If it is, however, then 12 Gy in 2 fractions is an acceptable regimen (Grade B).

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4.17 Spinal cord compression

4.17.1 Patients with symptoms suggestive of spinal cord compression, particularly severe back or root pain[1] should be investigated urgently with whole spine MRI to define sites and levels of compression accurately. Multiple levels of compression are seen in up to one-third of patients.[2]

4.17.2 All patients should have a histological or cytological diagnosis of malignancy before treatment. This may have been established earlier in the patient's course and reliance on an earlier diagnosis is a matter for clinical judgement. In those with no prior diagnosis of malignancy, needle biopsy or open biopsy should be undertaken prior to radiotherapy starting.

4.17.3 Chemotherapy may have a role in the management of sensitive malignancies such as lymphoma, plasma cell tumour, germ cell tumour and previously untreated small-cell carcinoma of the lung. This guidance refers to the management of metastatic carcinoma.

4.17.4 Once a histological diagnosis has been established, all patients should be started on steroids; UK convention is to give dexamethasone 16 mg daily. There is evidence from one randomised trial that higher initial doses of 96 mg are superior to no steroids;[3] no dose comparison between 16 mg and higher doses has been undertaken.

4.17.5 Neurosurgical referral should be considered, because combined modality therapy has a better outcome in selected cases (level 1+).[4]

4.17.6 There are three goals of treatment with radiotherapy.

- Prevention of neurological deterioration.
- Improvement of neurological function.
- Pain relief.

4.17.7 Good prognosis patients can be defined as those presenting with good performance status: either ambulant or with only a short history (< 24 hours) of immobility.[5] These patients should receive urgent treatment within 24 hours of diagnosis. Many radiotherapy regimens have been used worldwide, including various split course regimens. 20 Gy in 5 fractions is widely used. 30 Gy in 10 fractions has been recommended to reduce the risk of in-field recurrence (level 2+).[6]

For patients with spinal cord compression and < 24 hours of immobility, urgent treatment is indicated. If radiotherapy is prescribed, then 20 Gy in 5 daily fractions or 30 Gy in 10 daily fractions are acceptable regimens (Grade C).

4.17.8 Poor prognosis patients are those who are expected to live < 6 months and who have a poor chance of neurological recovery. They can be identified as those with unfavourable histology, neurological dysfunction and poor performance status.[7] In practice, this group includes those with established paraplegia for more than 24 hours. In these patients the median survival is of the order of 1–2 months. Treatment in established paraplegia will rarely improve neurological function.[1] Case selection is critical because of the risk of spinal cord injury[7] and in-field recurrence if survival is prolonged.[6] A single dose of 8 Gy is considered suitable (level 2+).[6,8] A recent trial in poor prognosis patients compared two unusual split course regimens[9] and has been criticised because there was no standard arm.[7]

For patients with spinal cord compression and established paraplegia for more than 24 hours, radiotherapy is indicated for pain relief: rare patients may show neurological recovery. A single dose of 8 Gy is acceptable (Grade C).

4.17.9 Post-operative treatment after either laminectomy or anterior fixation may be considered. One randomised controlled trial has compared surgery and post-operative radiotherapy to radiotherapy alone in selected good performance status patients with a single site of cord compression and found that the combined treatment was superior.[4] The dose in this trial was 30 Gy in 10 fractions. This has not been compared to other dose-fractionation regimens and our recommendation is for doses of 30 Gy in 10 fractions or 20 Gy in 5 fractions.

After surgery for spinal cord compression, post-operative fractionated radiotherapy delivering 30 Gy in 10 daily fractions or 20 Gy in 5 daily fractions is acceptable (Grade C).

4.17.10 Recurrence of spinal cord compression may occur. In one series of previously untreated prostate cancer patients, recurrence was seen in 45% of patients surviving at 2 years.[10] There is a suggestion that higher recurrence rates are linked to short treatments which should therefore be reserved only for poor prognosis patients (level 2+).[6] Re-treatment should be considered if recurrence occurs.[11] Surgical decompression may be appropriate in good prognosis patients. Where re-irradiation is given, then the risk of exceeding spinal cord tolerance must be balanced against the risk of neurological deterioration from tumour growth and the probability of late radiation effects within the expected lifespan of the patient. The risks of re-treatment depend on the radiotherapy dose and fractionation given at presentation.[11] Myelopathy has been reported as unlikely, if the cumulative biologically effective dose is ≤ 100 Gy_2 (level 2+). No allowance for recovery of injury was made; the re-treatment interval was 2–40 months.[11]

For patients with recurrent spinal cord compression, re-treatment within the limits of spinal cord tolerance should be considered (Grade D).

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5. Summary of recommendations

5.1 This document has reviewed the evidence base for radiotherapy dose-fractionation regimens. The aim has been to define safe and effective fractionation from peer-reviewed publications. Convenience for patients and efficient use of resources have been important secondary aims.

5.2 The tables that follow summarise the evidence base for radiotherapy fractionation. We have only been able to make ten Grade A recommendations for radical treatment and six for palliative treatment.

5.3 The gaps in the evidence base identify areas for possible clinical trials. The full results of the START trials in breast cancer are awaited in 2006, but the normal tissue results have already changed pre-conceptions about late normal tissue fractionation response.

5.4 It is of some interest that much of the evidence that underpins this document has come from cohort studies. It is suggested that in the future, there is a need to conduct well designed, observational studies in addition to randomised clinical trials if more rapid progress is to be made in defining optimal fractionation regimens. Information technology will have a useful role to play in facilitating high-quality observational studies. Investment in approaches that use electronic linkage to routinely collected data to underpin prospective cohort studies is recommended (see Section 7).

Table 1 Fractionation for radical treatment

		Indication	Fractionation	Grade of recommendation
Grade A recommendation				
4.4	Central nervous system	High grade glioma Low grade glioma	30 25–28	A A
4.7	Head and neck	Stage III and IV Accelerated radiotherapy Concomitant boost Chemoradiotherapy	 33–34 30 33–35	 A A A
4.8	Non-small cell lung cancer	Continuous hyper-fractionated accelerated radiotherapy (CHART)	36	A
4.8	Small-cell lung cancer (localised)	Prophylactic cranial radiotherapy	8–10	A
4.11	Prostate	Prostate	37–39	A
4.12	Rectal	Pre-operative (short) Pre-operative chemoradiotherapy	5 25	A A
Grade B recommendation				
4.2	Bladder	Bladder only	20 or 30–32	B
4.3	Breast	Breast post-operative treatment Axilla	15, 16, 25 15, 25	B, B, B B, B
4.4	Central nervous system	Low grade glioma	30	B
4.5	Oesophagus	Chemoradiotherapy	25–28	B
4.6	Gynaecological	Cervical cancer Operable vulval cancer Inoperable vulval cancer	20–28 25 25	B B B
4.7	Head and neck	Stage I and II (larynx only)	32–35	B
4.8	Non-small cell lung cancer	Conventional (with neo-adjuvant or concurrent chemotherapy)	30–33	B
4.9	Hodgkin's lymphoma	Chemotherapy and involved field radiotherapy	15	B
4.9	Non-Hodgkin's lymphoma	Chemotherapy and involved field radiotherapy for aggressive lymphoma	15–23	B
4.10	Paediatric	Fraction size 2 Gy or less	10–33	B
4.12	Rectal	Post-operative	25	B
4.14	Seminoma	Para-aortic	8 or 10	B
Grade C acceptable practice				
4.4	Central nervous system	Pituitary tumours	25	C
4.5	Oesophagus	Definitive radiotherapy	15–16	C
4.6	Gynaecological	Uterine corpus	20–25	D
4.6	Gynaecological	Cervical cancer	20	C
4.7	Head and Neck	Stage I and II (larynx cancer) Stage I and II (larynx cancer) Stage III and IV (chemoradiotherapy)	16 20 20	C C C
4.8	Non-small cell lung cancer	Accelerated hypo-fractionation Conventional (without neo-adjuvant or concurrent chemotherapy)	25 20 30–33	C C C
4.8	Small-cell lung cancer (localised)	High dose radiotherapy Early radiotherapy with concurrent chemotherapy	25 30	C C
4.9	Hodgkin's lymphoma	Post-chemotherapy radiotherapy	15–20	C
4.9	Non-Hodgkin's lymphoma	Involved field radiotherapy for low grade lymphoma	12–20	C
4.11	Prostate	Prostate only	16	C
4.13	Sarcoma	Pre-operative Post-operative Unresectable Desmoid	25 30 or 33 33 25–28	C C, C C C

Grade D acceptable practice				
4.1	Anal cancer	Chemoradiotherapy	28	D
4.5	Oesophagus	Post-operative radiotherapy Definitive radiotherapy	23–30 20 or 30	D D, D
4.6	Gynaecological	Uterine corpus	20–25	D
4.11	Prostate	Prostate only	20	D
4.13	Sarcoma	Ewing's	25–30	D

Table 2 Fractionation for palliative treatment

		Indication	Fractionation	Grade of recommendation
Grade A recommendation				
4.2	Bladder	Local symptoms	3	A
4.8	Non-small cell lung cancer	Moderate to poor performance status Poor performance status	2 1	A A
4.15	Bone metastases	Initial therapy	1	A
4.16	Cerebral metastases	Multiple metastases Solitary metastasis (consider surgery)	5 or 10 10	A A
Grade B recommendation				
4.5	Oesophagus	Single dose brachytherapy	1	B
4.9	Lymphoma	Widespread follicular lymphoma	1 or 2	B
4.8	Non-small cell lung cancer	Good performance status Good performance status	13 5	B B
4.16	Cerebral metastases	Multiple metastases (poor performance status) Solitary metastasis (with stereotactic radiosurgery)	2 10	B B
Grade C acceptable practice				
4.4	Central nervous system	Poor prognosis glioma	6	C
4.9	Lymphoma	Low grade	12	C
4.15	Bone metastases	Re-treatment Pathological fracture Scattered bone pain	1 or 5 1 or 5 1	C C C
4.17	Spinal cord compression	Established paraplegia Post-operative Evolving neurology	1 5 or 10 5 or 10	C C C
Grade D acceptable practice				
4.2	Bladder	Bladder – unfit patients	1	D
4.5	Oesophagus	Local symptoms	5 or 10	D
4.7	Head and Neck	Advanced	20 or 32–35	D
4.8	Non-small cell lung cancer	Good performance status	6	D
4.8	Small-cell lung cancer (extensive)	Regimens as for NSCLC	1 or 2	D
4.9	Lymphoma	Hodgkin's lymphoma Intermediate-high grade lymphoma	1–10 1 or 5	D D
4.10	Paediatric	–	1–15	D
4.13	Sarcoma	–	1–15	D
4.15	Bone metastases	Pathological fracture	1 or 5	D
4.17	Spinal cord compression	Re-treatment	1 or 5	D

6. Planning for the future

Cancer incidence

6.1 In determining the likely future radiotherapy workload, the first step is to determine current cancer incidence and then to project it forward into the future. This work has already been undertaken in Scotland by the Scottish Executive which has recently published updated figures.[1] Similar work is now in hand in England.

Radiotherapy referral rates

6.2 In predicting radiotherapy usage the next step is to identify evidenced-based indications and apply them to a population model. This has been undertaken in Ontario by Tyldesley[2] and in Australia by Delaney, *et al.*[3,4] The Australian NCCI (National Cancer Control Initiative) has published a document detailing evidence-based radiotherapy referrals for the Australian population. This states that 53% of cancer patients should receive radiotherapy as part of their initial management. A European overview has been published which indicates substantial under-provision in the UK.[5]

Projected radiotherapy fractionation

6.3 The Scottish Executive has developed this work further and has defined the likely radiotherapy fractionation that they predict will be required in 2015.[6,7] This is on the basis of the current literature and professional opinion determined by questionnaire. Their predictions are compared with the fractionation recommended in this document in *Table 3*. There is quite close correspondence in the figures, particularly bearing in mind that the current work defines contemporary practice and the Scottish figures look ahead for a decade. Work is in hand to adapt the Scottish model to the English population and radiotherapy practice.

Productivity

6.4 Once the number of radiotherapy fractions required by the population has been determined, then the number of linear accelerators required per million population will be determined by their output. This can be summarised as fractions per linear accelerator per year and this

will be a function of:

- Fractions per hour.
- Hours per day.
- Days per year.

Long-term planning

6.5 All of these factors including the expansion and development of the workforce and its training need to be taken into account in the long-term planning for radiotherapy service provision. In England, this is the function of the National Radiotherapy Advisory Group (NRAG). A report is expected in Autumn 2006.

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Table 3 UK radiotherapy fractionation recommendations

		RCR document	Grade	Scottish 2015	Comment
4.1	Anal	28	D	–	
4.2	Bladder				
	–radical	20 or 30–32	B	25–30	
	–palliative	3	A	10	
	–to metastases	1	A	5	
4.3	Breast	15	B	15–25	
		16	B		
		25	B		
		20	C		
4.4	Central nervous system				
	–low grade	25–28	A	28	
	–high grade				
	–good prognosis	30	A	30	
	–poor prognosis	6	C	6	
	–pituitary tumours	25	C	–	
4.5	Oesophagus				
	–radical	–	–	20–25	
	–chemoradiotherapy	25 or 28	B	–	
	–definitive radiotherapy	15–16 or 20 or 30	C/D/D	–	
	–post-operative	23–30	D	20–25	
	–palliative	5 or 10	D	10	
	Stomach	–	–	–	
4.6	Gynaecological				
	–uterus	20–25	C/D	25	
	–cervix	20–28	B/C	25	
	–palliative	–	–	10	
4.7	Head and neck				
	–radical RT	–	A/B	35	
	–Stage I or II larynx	32–35	B	–	
		16 or 20	C	–	
	–Stage III or IV	33–35	A	–	
4.8	Lung				
	–radical RT	-	-	36–39	
	–CHART	36	A	–	
	–conventional	30–33	B	–	
	–hypofractionated	20	C	–	
	–post-operative	–	–	25–28	
	–localised small cell	25–30	C	25–35	Plus prophylactic cranial RT
	–palliative	1, 2, 5 or 13	A/B	5	
4.9	Lymphoma				
	–Hodgkin's lymphoma	15–20	B/C	15	
	–low grade NHL	12–20	C	10–15	
	–intermediate grade NHL	15–23	B	15–20	
4.10	Paediatrics	10–33		–	1.6–2.0-Gy fraction
4.11	Prostate				
	–radical	37–39	A	32–41	
		16	B		
		20	D		
	–to metastases	1	A		
4.12	Rectal				
	–short pre-operative	5	A	5	
	–chemo-RT pre-operative	25	A	25	
	–local palliation	–	–	10	
	–metastases	1	A	1	
	–post-operative	25	B	25	
4.13	Sarcoma	25–33	C	?	

4.14	Seminoma	0–10	B	0–15	
4.15	Bone metastases	–	–	1–5	
	–initial therapy	1	A	–	
	–re-treat or complex	1–5	C/D	–	
4.16	Cerebral metastases		–	5	
	–good performance status	5–10	A	–	
	–poor performance status	2	B	–	
4.17	Spinal cord compression		–	–	
	–short history	5–10	C	–	
	–established paraplegia	1	C	–	
	–post-operative	5–10	C	–	
	Colon				
	–post-operative	–		25	
	–brain	–		5	
	–bone	–		1	
	Renal				
	–palliative to Kidney	–		10	
	–metastases	1		5	
	Melanoma	–		20	
	Pancreas	–		25	

7 Clinical audit, service development and research

Over the last 3 years, recognition of the low level of investment in both radiotherapy service development and research has led to an increased focus on radiotherapy.

Clinical audit has been a labour intensive activity because data usually have to be collected by hand separately from the process of treatment. In the UK this has now changed with the work of NATCANSAT (www.canceruk.net). Electronic data can be automatically extracted from record and verify systems and at the moment 5 years' data from 252,968 records have been analysed. Linkage to patient information systems and the use of the NHS number as a unique identifier permit further linkage to geographical systems and to Cancer Registries. It is also possible to determine from the NHS Information Authority whether or not the patient is alive or dead, and this allows the generation of survival curves by diagnosis and by consultant.

This advanced technology will permit departmental audit to be an automatic undertaking using nationally agreed standards. The data can be anonymised with individual identifiers fed back to departments and clinicians; however, there is still a lack of measures of late effects which can easily be linked to this data.

Analysis of the NCRI cancer research data base (CRD) in 2002/3 confirmed that only 6% of the NCRI overall spend was on radiotherapy or radiobiology. The NCRI Radiotherapy and Related Radiobiology Progress Review Group and its partner organisations prioritised areas for radiotherapy research including:

- The technical aspects of radiotherapy.
- The biological base for advancing radiotherapy (including the manipulation of the programming of radiotherapy in terms of fractionation and overall time).
- The quantification and analysis of the late effects of radiotherapy on normal tissue.

The need for a better research infrastructure has led to formation of the Academic Clinical Oncology and Radiobiological Research Network (ACORRN). The NCRI radiotherapy study group is developing a portfolio of clinical studies around themes including: technical radiotherapy and quality assurance, translational research, late effects of treatment, and palliative radiotherapy. The National Quality Assurance Programme for Radiotherapy Clinical Trials has been established to support departments entering patients into new clinical trials involving radiotherapy.

Useful information also is emerging from the Cancer Services Collaborative Improvement Partnership (CSIP) Radiotherapy Group looking at streamlining pathways from decision-to-treat with radiation therapy to treatment delivery, including better understanding of the patient experience of the processes involved in the planning and delivery of radiation therapy.

There is increasing recognition of the need for closer alignment between audit, research and service improvement activity and the need to increase the understanding about the role of radiotherapy amongst non-oncology professionals and the general public, if radiation therapy research and development are to be prioritised in the future.

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Working Party

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Contributors

The working party is grateful to the following for contributions to this document in the production of initial drafts or for comments during its production.

Dr D Ash
Professor A Barrett
Dr R Barton
Dr P Blake
Dr D Bloomfield
Dr R Buchanan
Dr N Burnet
Dr F Calman
Dr C Coles
Dr R Cowan
Dr F Cowie
Dr A Crellin
Dr S Davidson
Professor D Dearnaley
Dr J Dewar
Dr J Dobbs
Dr S Erridge
Dr R Gattamaneni
Dr M Gaze
Dr I Geh
Dr J Glaholm
Dr R Glynne-Jones
Dr R Grieve
Dr N Gupta
Dr M Harrison
Professor A Horwich
Professor P Hoskin
Dr G Howard
Dr R Huddart
Professor T Illidge
Dr S Jefferies
Professor B Jones
Dr P Kirkbride
Dr I Kunkler
Dr S Larsson
Dr B Lavery
Dr J Logue
Dr H Lucraft
Dr W Makin
Professor M Mason
Professor T Maughan
Dr M Moody
Dr D Morgan
Dr G Morgan
Dr S Morgan
Dr G Newman
Dr C Nutting
Dr N O'Rourke
Dr H Patterson
Professor A Price
Professor P Price
Professor R Rampling
Dr N Reed
Dr T Roberts
Dr G Robertson
Dr M Robinson
Dr T Roques
Dr G Ross
Dr S Russell
Professor M Saunders
Dr D Sebag-Montefiore
Dr B Seddon
Dr N Slevin
Dr M Sokal
Dr C Smith
Dr L T Tan
Dr T Taylor
Dr J Townley
Dr P Warde
Professor J Yarnold

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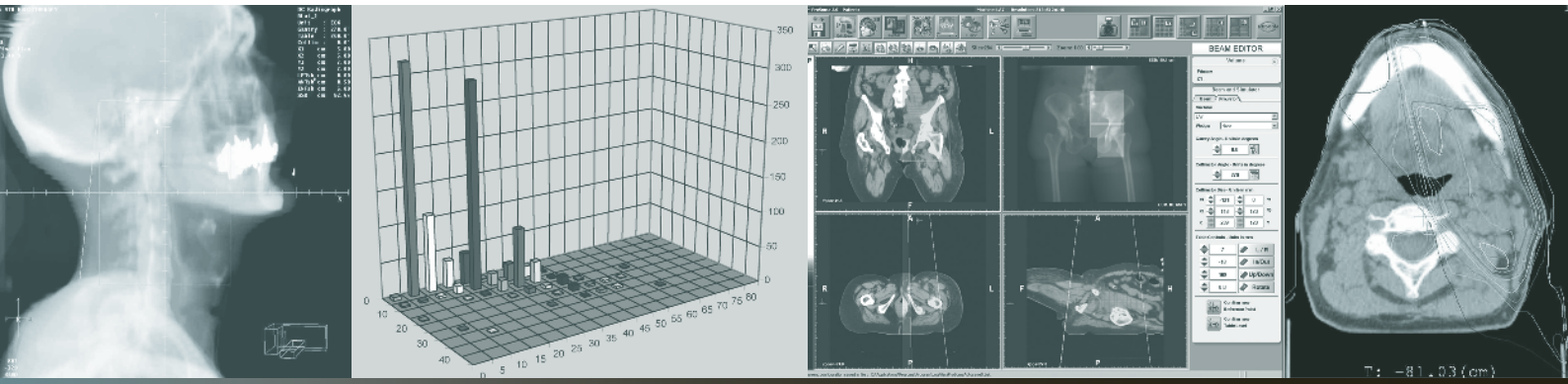
The Royal College of Radiologists 38 Portland Place London W1B 1JQ

Tel +44 (0)20 7636 4432 | Fax +44 (0)20 7323 3100 | Email enquiries@rcr.ac.uk | URL www.rcr.ac.uk |



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