Clinical Oncology
Principles of reirradiation

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The Royal College of Radiologists

Contents

01 Development process

These principles have been produced to guide and support clinicians in contentious areas of practice that lack strong evidence. They aim to reduce variation in UK radiotherapy practice.

An expert group in reirradiation treatment was formed to develop key principles for consideration when delivering reirradiation. Following appraisal of available literature and current practice, statements were drafted and refined. The group includes experts from across the UK representing various tumour sites.

02 Introduction

Reirradiation is a highly individualised treatment that is being increasingly used for selected patients. For the purposes of this document, it is defined as:

> Delivery of a second course of radiotherapy to a similar anatomical region as the initial course of radiotherapy, where there is overlap of previously delivered radiation dose with the proposed new radiation dose that could result in excess dose to an organ at risk (OAR) and/or significant toxicity.

Reirradiation also encompasses a situation where there is no overlap of the previously delivered and reirradiation doses but the cumulative dose to the whole organ could result in significant toxicity.

Data from retrospective studies across several different tumour sites have shown that some patients have long-term disease control after reirradiation, though this comes with the potential of the patient experiencing increased toxicity.[1,2] There are few prospective studies to guide patient selection, safe dose constraints or optimal treatment technique. In light of these uncertainties there are some considerations prior to reirradiation that are common across all anatomical sites. These include:

- Appropriate selection of patients
- The need for appropriate investigations prior to reirradiation
- An approach to account for the previous dose delivered
- Consideration of the original radiotherapy dose distribution, the reirradiation dose and dose constraints
- Choice of radiotherapy technique.

There are some aspects of reirradiation that will differ in reliability and importance depending on the tumour site. For example, image co-registration and dose accumulation are likely to be more straightforward in brain reirradiation where there have not been significant anatomical changes, compared with lung, where post-radiotherapy fibrosis can distort the thoracic OARs significantly, and the pelvis, where OARs and targets may have deformed or be displaced.

The aim of this document is to provide general principles on clinical considerations for clinical oncologists contemplating reirradiation. It provides links to tumour-site-specific guidance where available.

03 Patient indications for reirradiation

Consideration must be given to the likely benefit that reirradiation may achieve against the risk of toxicity that reirradiation may cause. It is often assumed that the longer the time between radiotherapy courses, the greater the extent of normal tissue recovery that has occurred, although data to support this assumption are extremely lacking. Time-recovery relationships are not well understood and may not be linear, will likely plateau and may not be the same or even apply to all OARs. Patients who have significant toxicity from their initial radiotherapy treatment may have had limited normal tissue recovery, which may be further exacerbated by additional radiotherapy. Alternative treatment options such as surgery, local ablative treatments or systemic treatment should always be considered alongside the option of reirradiation.

General principles for patient selection:

- All cases should be discussed in tumour-specific multidisciplinary teams (MDTs).
- All cases should also be discussed in a separate multidisciplinary radiotherapy forum.
- Ideally, there should be a minimum of six months from completion of primary treatment to consideration of reirradiation.
- Reirradiation is likely to be inappropriate for patients with long-standing severe late toxicity from their initial radiotherapy, or if they experienced non-haematological grade 4 toxicity during their initial treatment in an organ likely to receive a clinically significant dose of reirradiation.
- Other radical treatment options, such as surgery, microwave ablation or systemic therapy, should be considered through an MDT discussion, especially if such treatments have a predicted lower rate of toxicity or higher control rate than reirradiation.
- Eastern Cooperative Oncology Group (ECOG) performance status (PS) should be 2 or better.
- If previous brachytherapy was delivered, specialist advice on dose accumulation, dose calculation and biological effect should be sought.
- Outside a clinical trial, stereotactic ablative radiotherapy (SABR) reirradiation should not be used if the tumour is infiltrating the lumen of a visceral organ, for example the gastrointestinal tract, respiratory tract or bladder wall.

04 Assessments required prior to reirradiation

The role of pre-reirradiation assessments when radical treatment is proposed is to ensure patients truly have locally or regionally recurrent disease and have no distant metastases. Accordingly, these guidelines are similar to the tumour-site-specific guidelines for staging *de novo* disease. Additionally, review of the previous radiotherapy plan is essential to assess previous treatment technique, patient position and gross anatomical change as well as how much dose was delivered and where it was delivered. The planned reirradiation treatment should be classified according to the system developed by Andratschke *et al*,[3] to aid identification of normal tissue risks and tumour control probability.

- Prior to reirradiation, the patient should be restaged using the standard investigations that are approved for the tumour-specific primary treatment, including positron emission tomography-computed tomography (PET-CT) to exclude occult metastatic disease.
- Review of initial radiotherapy plans is essential unless there are exceptional circumstances. If not available then the previous plan should be reconstructed based on available information.
- Baseline tumour markers should be performed where appropriate.
- A biopsy to confirm recurrence should be considered.
- Consideration should be given to tumour-site-specific tests such as pulmonary function tests (PFT), dimercaptosuccinic acid (DMSA) and baseline cortisol.

05 Radiotherapy treatment

There are several sources of uncertainty in radiotherapy planning for reirradiation. The following statements have been divided into the different stages of radiotherapy planning.

Image registration of previous radiotherapy plan

- Image registration can be prone to uncertainties and should be interpreted with caution and with clinical judgement:
  - Anatomical change in the region of interest can be treatment related (eg post-surgery after neoadjuvant radiotherapy for rectal cancer) and this may result in previously unirradiated tissue entering the reirradiation field.
- Rigid and deformable registration strategies are available but have significant limitations and uncertainties and therefore should be interpreted with caution.
- Uncertainties in registration can be minimised by reproducing the primary radiotherapy set-up, trying to match patient position, using the same immobilisation devices and patient preparation (eg bladder, bowel, stomach), where appropriate. In some circumstances, however, an alternative set-up may be preferred (eg opposite bladder filling to move previously irradiated bowel).
- Where possible, previous reference marks or tattoos should be used to reduce the chance of set-up errors on treatment.

Dose accumulation

- Previous delivered dose should be converted into biological effective dose (BED) or equivalent dose in 2 Gray (Gy) fractions (EQD2).
- Manual dose calculations, including the choice of alpha–beta ratios, should be independently checked by a second individual with appropriate reirradiation experience. If unavailable within your centre, advice should be sought externally.
- Cumulative doses in EQD2 or BED should be recorded, including with reference to the alpha–beta used for calculation. Choice of alpha–beta should be guided by the literature. If recovery is incorporated, this should also be clearly documented.
- To account for variation in position of a region of high dose as a result of either movement or deformation, it may be advisable to expand this region of concern in order to adopt a ‘worst-case scenario’ approach when reviewing a plan sum.
- Normal tissue recovery is difficult to predict and not well understood. Applying a discount in the previous dose delivered is at the discretion of the clinician.[4]
- The planned dose to be delivered to the OARs at reirradiation (also in BED or EQD2) should be added to the already delivered dose (converted to BED or EDQ2, with or without a discount for recovery) to give an estimate of normal tissue cumulative dose.

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Radiotherapy treatment

- In the majority of cases, appropriate cumulative doses to OARs should be prioritised over planning target volume (PTV) coverage or dose, and this may require PTV under-coverage. There may be situations where the risk of tumour progression could cause serious sequalae. In these cases, the PTV may be prioritised over the OAR constraint after careful consideration.
- Consensus-based dose constraints for some normal tissues are available in the tumour-specific guidelines.[5,6,7,8,9]
- Summated plans in physical dose alone are inadequate for assessment of cumulative dose and put the patient at risk of unrecognised normal tissue overdose (especially important for SABR reirradiation).

Reirradiation dose prescription

- Reirradiation dose is site specific and determined by technique, intent and OAR constraints.

Technique

- Highly conformal techniques are recommended and may include SABR (where commissioned), brachytherapy, or conventionally or hyperfractionated intensity-modulated radiation therapy (IMRT).
- The addition of concurrent treatment may be appropriate depending on the systemic agent in question and the patient's fitness. This could add to toxicity and potentially adds uncertainties to cumulative dose calculations.

Contouring

- Target and OARs should be contoured with the aid of supporting imaging to inform the most accurate delineation and provide information on potential target and OAR motion; for example, fusion of magnetic resonance imaging (MRI) and PET with planning CT, modelling of deformation with variable bladder filling.
- Consideration should be given to going back and delineating OARs on the original radiation plan if this will assist with cumulative OAR dose calculations.
- Awareness of inaccuracies in the assessment of cumulative doses is required, especially when there have been large deformations between treatment courses.

Review

- Reirradiation contouring and plans should be subject to a prospective peer review process.[10]
- PTV coverage should be compromised where appropriate or dose reduced to limit dose to OARs.
- Further counselling with the patient should take place after the planning process to discuss and consent to any likely toxicity that becomes apparent during the planning process.

05
Radiotherapy treatment

Treatment verification

The accuracy of reirradiation is essential given that often the retreatment dose is close to the OAR constraints and the OAR may be in close proximity to the PTV.

- Cone-beam CT at every fraction and online matching on a daily basis are recommended for SABR treatments and may be appropriate for other schedules as well, depending on PTV margins and proximity to OARs.
- Clear instructions must be relayed to the treating team regarding concerns for potential OARs approaching tolerance.

On-treatment review

- Patients should be reviewed on treatment with similar frequency to *de novo* treatment.
- Acute toxicity should be monitored and recorded according to the current Common Terminology Criteria for Adverse Events (CTCAE).[11]

Follow-up

- Follow-up of patients should be at the discretion of the treating clinician but at least as frequent as following *de novo* treatment. More frequent follow-up may be considered based on extent of dose overlap and observed acute toxicity.
- Standard follow-up and imaging schedules should be followed as a minimum. Biomarkers can be used in addition to or instead of imaging where relevant.
- At clinical review, acute and late toxicity should be monitored and recorded according to the current CTCAE.[11]

Multiple isocentres

- Use the same planning scan where in the same organ or geographical site.
- Consider using the same number of fractions for ease of dose-volume histogram (DVH) calculation.
- Prior to treatment, consideration should be given to scheduling and matching.

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