Re Irradiation (Re RT)

Principles & Practices

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- The advancement of treatment modalities in surgery, chemotherapy and radiotherapy has improved survival rate and loco-regional control at many sites of cancer
- Many people live much longer than 5 years after their cancer diagnosis.
- Even patients are alive with residual disease for many moths to years.
- Longer survival increases risk of recurrence and 2nd malignancies
- It happens many a times in patients with good KPS.
- Biology is the king. (Tumor Biology/ Radiobiology)
- They needs to be treated with all the possible modalities all again.

Longer survival

Increases incidence of

- Recurrence

  Local/ Loco regional/ Distant

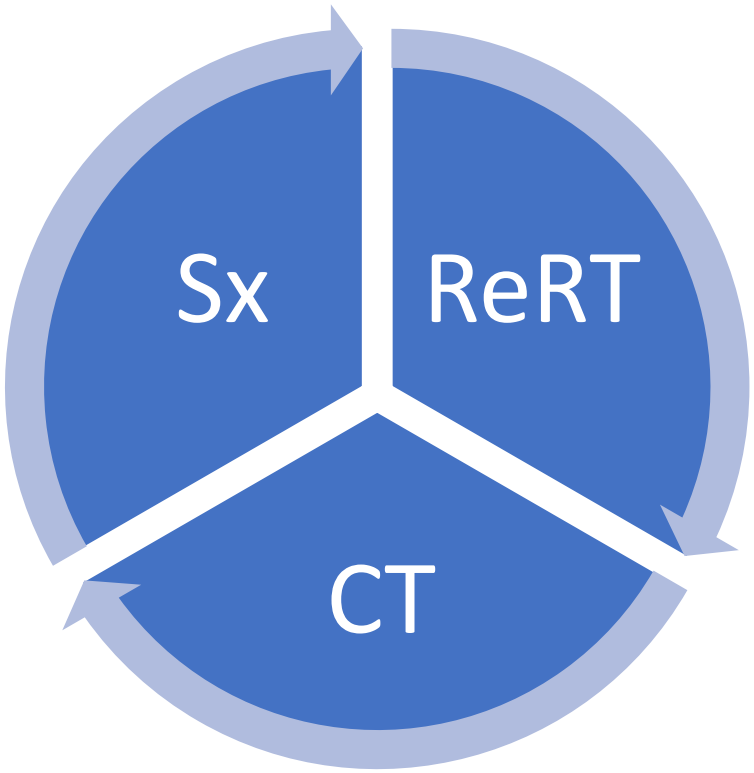
- Second primary tumor

  Outside/ Inside/ Close to previously irradiated volumes

- A recurrence means that the first cancer has come back, in the same area of the body or in a different area.
- Recurrence be local, loco regional or widespread.
- Recurrent cancer may be more aggressive than the original cancer.
- The sooner the cancer returns, the biology of the tumor tends to be more aggressive.

In-field cancer recurrence after RT and second primary tumors occurring in previously irradiated area are the real clinical challenge

Management Options



- In the absence of distant metastatic disease, **salvage surgery** provides a durable disease control.
- Where salvage surgery is not feasible or challenging, **re-irradiation (ReRT)**, alone or combined with chemotherapy or biological therapy, as an organ-preserving modality plays an important role in the treatment of such cancers

Re-irradiation (ReRT)

Defined as the use of a second course of radiation therapy with a retreatment volume that overlaps substantially with that of a previously delivered course of radiation therapy

Refers to a new course of radiotherapy either to a previously irradiated volume (irrespective of concerns of toxicity) or where the cumulative dose raises toxicity concerns

- ✓ This approach is now a viable treatment option for an increasing number of patients
  - As modern precision radiotherapy techniques have become widely available
  - As advances in systemic therapies have improved patient outcomes

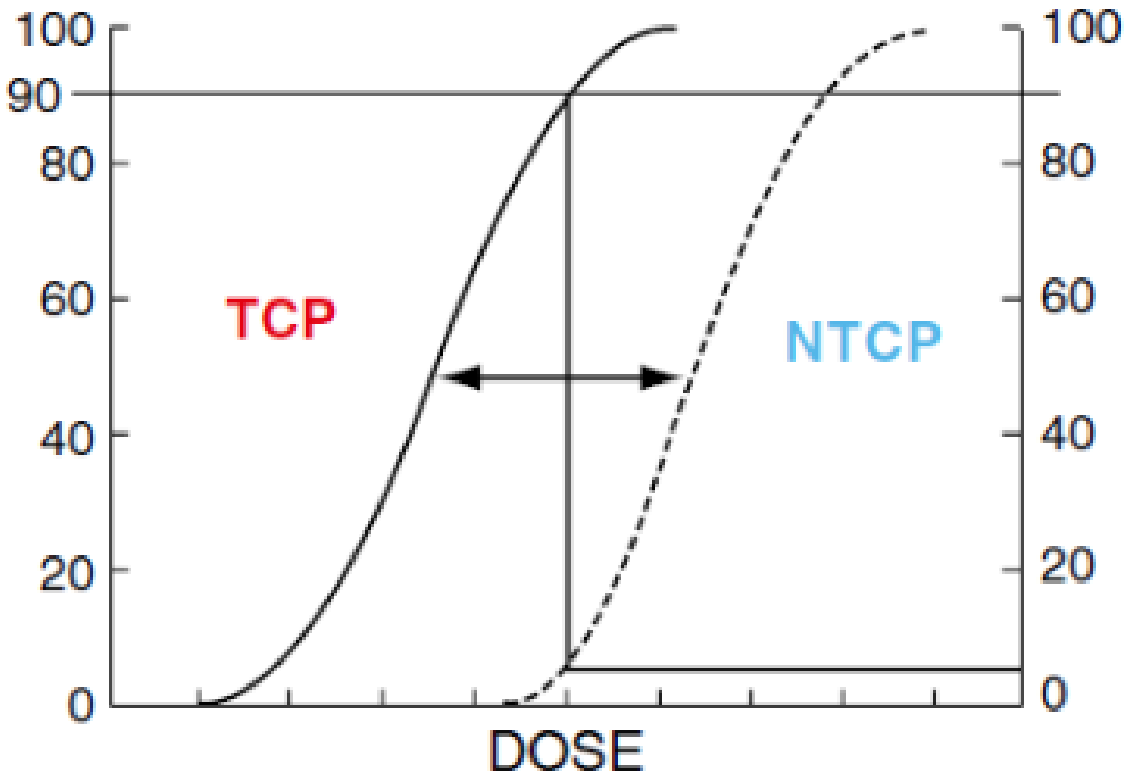
- ✓ Re-irradiation may be offered to patients with recurrent, metastatic, or new malignancies following initial radiotherapy in different anatomical regions.

The need to balance tumor control with the risk of severe toxicity from cumulative radiation doses to previously irradiated organs is the crucial challenge in re-irradiation.

Re-irradiation (ReRT)

Such treatment decisions demand not only appreciation of the relevant clinical, pathological and technical aspects but also rather ***precise knowledge on long-term recovery of occult radiation injury in various organs***

Radiobiological modelling for beginners…



Utmost goal during the treatment with radiation is to maximize the benefit for the patient (efficacy of the treatment) while sparing other vital organs from radiation that could lead to organ's toxicity.

TCP: Tumor control probability
NTCP: Normal tissue complication probability

Important to know

- Normal body organs remembers the radiation doses but with time their memories goes weak.
- Adequate knowledge of Radiobiology MUST if you are planning ReRT.

Early reacting	(skin, mucosa, lung, intestine)
Late reacting	(muscle, connective tissue, vasculature, brain, spinal cord, brainstem, lungs, heart, bladder and kidney)

Concept of Serial vs parallel organs

Calculating total cumulative dose *(RE, BED, EQD_2)*

Concept of Relative Effectiveness, BED & EQD_2

$$\text{RE: Relative Effectiveness} = \left\{1 + \frac{d}{\alpha/\beta}\right\}$$

Biologically Effective Dose

BED is not Biologically Equivalent Dose

$$BED_{EBRT} = nd\left\{1 + \frac{d}{\alpha/\beta}\right\}$$

Biologically ***Equivalent*** Doses are calculated in 2 Gy equivalents using the ***EQD_2*** equation

$$EQD_2 = \frac{BED}{1 + \frac{2}{\alpha/\beta}}$$

- The **BED** values can be calculated according to the linear-quadratic formula, which is the generally accepted standard model for dose-fractionation analysis.
- This is then expressed as 2Gy equivalent dose to allow uniform comparison of various studies.
- The aim of various pre-clinical and clinical studies, has been to estimate the total cumulative **(EQD_2)** doses also termed as Normalized Total Dose (NTD), that can be delivered to various tissues.

However, for fraction sizes beyond 5Gy, particularly high dose single fraction radiosurgery, the validity of linear quadratic model is questionable

Concept of Relative Effectiveness, BED & EQD_2

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BED example

- Treatment consists of 50 Gy in 25 fractions followed by 15 Gy in three fractions over 5 days. Assuming that the α/β ratio is 2 Gy

$$\mathrm{BED} = nd\left[1 + \frac{\mathrm{d}}{\alpha/\beta}\right]$$

- the total BED=
- $50(1 + 2/2) + 15(1 + 5/2) = 152.5\ \mathrm{Gy}_2$

BED example ***as EQD2***

- Treatment consists of 50 Gy in 25 fractions followed by 15 Gy in three fractions over 5 days. Assuming that the α/β ratio is 2 Gy

$$EQD_2 = \frac{BED}{1 + \frac{2}{\alpha/\beta}}$$

- EQD2 = 152.5/(1 + 2/2) = 76.3 Gy
- Which is an equivalent dose close to 76 Gy delivered in 38 x 2Gy fractions

Radiation Biologically Effective Dose (BED) Calculator

Calculates biologically effective dose (BED) and equivalent dose (EQD2) for cancer radiotherapy.

When to Use | Pearls/Pitfalls | Why Use

Dose per fraction: 5 Gy

Total dose
Number of fractions x dose per fraction: 25 Gy

α/β ratio
Typically 10 for early-responding tissues and tumors, 3 for late-responding tissues (normal tissue): 10

Diagnostic Result

37.50 Gy
BED

31.25 Gy
EQD_2

Copy Results | Next Steps

» Next Steps | Evidence | Creator Insights

About the Creator

Dr. John F. Fowler

Also from MDCalc...

Related Calcs

- Morphine Milligram Equivalents
- tPA Dosing for Stroke Calculator
- GI-GPA

Content Contributors

- Neil Panjwani, MD

- Spinal cord
- Brain
- Lung
- Rectum
- Bladder
- Skin & mucosal tissues
- Mesenchymal tissues

Importance of respecting tissue tolerances and their recovery before re-irradiation

- ✓ Important to remember that tissues which have once been irradiated may or may not have the same tolerance to a repeat course of radiotherapy.
- ✓ Most of the acutely reacting tissues are thought to recover from the radiation induced sequelae ***within a few months at the most*** and therefore theoretically these tissues can tolerate a repeat course of irradiation (depending on the total dose, fractionation, and technique) even 6 months down the line.

Table 1: Recommended/accepted re-irradiation normal tissue tolerances in acute reacting tissues

Organ/tissue	Accepted re-irradiation dose-fractionated (Gy)	Accepted re-irradiation dose-stereotactic (Gy)	Accepted time interval between RT courses (months)	Extent of OAR recovery
Skin/mucosa	50-60 Gy in conventional fractions	-	>6	Full
Heart	Cumulative dose to heart (BED_{3Gy}) not exceed 70 Gy_3 and point dose (0.1 cc) Dmax not <49 Gy_3[5]		>24	Partial
Lungs	30-60 Gy by EBRT[6,7]	20-30 Gy in 6-10 Gy fraction sizes 2-3 times per week for total of 3-6 fractions	>12	Central mediastinal/thoracic tumors not treated by SRT; recovery may not be complete here; peripheral tumors more amenable to SRT

BED: Biological equivalent dose, SRT: Stereotactic radiosurgery, EBRT: External beam radiation therapy, RT: Radiotherapy, OAR: Organ at risk

Importance of respecting tissue tolerances and their recovery before re-irradiation

- ✓ Late reacting tissues either do not show long term recovery or limited recovery and therefore even at the first instance are amenable to only partial volume irradiation.
- ✓ For cases in which these tissues need to be re-irradiated, doses have to be carefully calibrated to avoid crossing the tolerance limits at all.
- ✓ Tolerances of some of these normal tissues wherein data from re-irradiation studies are available.

Table 2: Recommended/accepted re-irradiation normal tissue tolerances in late reacting tissues

Organ/tissue	Accepted re-irradiation dose-fractionated (Gy)	Accepted re-irradiation dose-stereotactic (Gy)	Accepted time interval between RT courses	Extent of OAR recovery
Soft tissue/ muscle	Doses over 50 Gy conventional EBRT produce better control[16,17]		>12 months	Large scale data not available; only case serie's present
Brain/ brainstem	Cumulative BED not exceed 130-159 Gy with an α/β ratio equal 2 Gy2[18] 30-40 Gy in fractionated RT[19]	24 Gy for involved volume <20 mm, 18 Gy for volume 21-30 mm and 15 Gy for volume 31-40 mm[6]	>12 months	Partial
Spinal Cord	cumulative BED should not exceed 130 Gy2[18] 20-24 Gy in10-12 fractions[13,14]	dose threshold for thecal sac 10 Gy in single fraction and nBED of 30-35 Gy 2/2 for up to five fractions	>12 months	Partial
Heart	Cumulative dose to the heart (BED_{3Gy}) should not exceed 70 Gy_3 and the point dose (0.1 cc) Dmax not >49 Gy_3[20]		>24 months	Partial
Great vessels	cumulative BED should not exceed 90-100 Gy2[21]		>36 months interval can produce estimated 65% OAR recovery[21]	1%-2% aortic toxicities noted; carotid blowout

Table 2: Recommended/accepted re-irradiation normal tissue tolerances in late reacting tissues

Organ/tissue	Accepted re-irradiation dose-fractionated (Gy)	Accepted re-irradiation dose-stereotactic (Gy)	Accepted time interval between RT courses	Extent of OAR recovery
Head and neck soft tissues	The dose ranges from 58-60 Gy[22]	18-40 Gy in 3-5 fractions to the 65%-85% isodose line over consecutive days[6]	>6 months-1 year	Lesser volume and more mucosa means more OAR recovery
Mandible	Cumulative dose not defined, but tolerance below 100 Gy_3 without cortical breach			
Parotid	Can tolerate cumulative dose of 45 Gy[23]		>12-18 months	
Optic structures	Re-irradiation constraints limited to <8-10 Gy for 10 cm^3 volume[24]		>12 months	
Urinary bladder	Can tolerate point cumulative doses of up to 120 Gy3[25]		>6 months-1 year	
Pelvic ureter	Can tolerate point cumulative doses of up to 110 Gy3[26]		>24 months	Ureteric stenosis
Rectal mucosa and wall	Total cumulative doses 70-100 Gy with a median total dose of 85 Gy[27,28]	IORT dose of 10-20 Gy[26,28]		Peripheral neuropathy most commonly seen with IORT
Femoral heads	Blood supply to the femoral head is defining point of action. Constraint similar to blood vessels; cumulative BED should not exceed 90-100 Gy2		>2-3 years gap can help recovery	Avascular necrosis of the head is the catastrophic event
Breast soft tissues	40-50 Gy given within 4 days with PDR brachy minimum re-radiation dose in fractionated schedule is 40 Gy		Minimum 6 months	Moderate skin and subcutaneous tissue side effects seen; mainly erythemas and skin telangiectasias Expected full OAR recovery

There can be many factors which will determine such tolerance

- ✓ The interval between the two courses of radiation which will determine the extent of tissue regeneration
- ✓ The type of normal tissues at risk (serial/parallel vs acute/late)
- ✓ The volume of tissue required to undergo re-irradiation
- ✓ Observable normal tissue damage that has resulted from the previous radiation.
- ✓ Fractionation schedule used in prior course *(as higher the dose per fraction, more will be the late effects and consequent less tolerance for repeat course of radiotherapy)*
- ✓ Expected survival/ overall patient prognosis after such repeat irradiation.

The success of full dose re-irradiation depends in a variety factors like

- Cancer stage (now & then)
- Type of initial treatment (radiation dose, technique, dose per fraction, use of concurrent chemotherapy)
- Response to initial treatments
- Clinically apparent late effects from initial RT
- Residual radiation tolerance of the normal tissues
- The duration of the relapse-free interval
- The co-morbidities
- The dose fractionation of the re-irradiation course

One of the major issue remains that whether re-irradiation toxicity outweighs the potential benefits.

Prerequisites for Re-irradiation

- Confirmation of recurrence or second primary (preferably by histology)
- Precise knowledge of the late radiation response of the normal tissue within the proposed re treatment field
- Precise knowledge of the radiation dose, portals, volumes of the previous radiation
- Clarity regarding the intent of re-treatment
- Absence of distant metastases (in case of curative re irradiation)
- Salvage surgery is not feasible/too mutilating/risky
- The expected harm benefit ratio of less than 1

Basic rules of re irradiation

- Multidisciplinary evaluation for treatment of patients with recurrent cancer
- Re-irradiation should be offered for patients who have responded well to the first course of radiation
- Same center
- Minimize the overlap of the treated volumes of the two courses as far as possible
- Prophylactic irradiation to loco regional draining lymph nodal basin should be best avoided
- For patients treated with curative intent, re-irradiation to doses of 60 Gy or greater to the recurrent disease are recommended
- Try to use different portals for the second course and use different technique of radiation wherever possible e.g. EBRT –brachytherapy. /3D conformal-SBRT.
- Highly conformal radiation techniques such as IMRT are recommended over less conformal modalities
- Bigger the volume of re-irradiation – worse is the outcome
- Incorporate biological imaging for delineation of target if available
- Availability of Infrastructure and expertise

Steps for re-irradiation process

Steps	Issues
1. Defining Intent	Whether palliation or intent curative
2. Ethical and Medicolegal considerations	The patient should be explained about the potential benefit with reirradiation, options of alternative therapies, possibilities of fatal complications and serious morbities before obtaining informed consent. Proper Documentation of communication with other specialties, patient's data, radiation rationale, details and toxicity.
3. Pretreatment evaluation /assessment Biopsy	Biopsy Exclusion of contraindication for radiation Performance status Preexisting organ dysfunction Organ reserve volumes and residual normal tissue tolerances Nutritional and rehabilitation needs

Steps	Issues
4. Radiotherapy planning	Use of appropriate imaging, preferably functional Use of appropriate conformal technique /brachytherapy/SRT Target volumes definition as per ICRU recommendations Dose fractionation- consideration of the previous biological dose. Calculation of the cumulative EQD2. Normal tissue tolerance doses to include repair effects over time. TD5/2 preferred over TD5/5
5. Concurrent therapy	Chemotherapy should be incorporated for sites where it increases the chance of success like head and neck, gliomas etc and avoided in others like breast
6. Supportive care	Nutritional support Hydration Control of anemia, cytopenia, pain relief Edema and seizure prophylaxis.
7. Post treatment evaluation and follow up	Anticipation of complications and mitigation Response assessment Quality of life indices

Data regarding indications, outcomes, fractionation, concurrent treatment and cumulative doses to normal tissues is in the nascent stage.

Lack of strong evidence

There is lack of strong data over ReRT due to -

1. Lack of data from simultaneous control groups of same site
2. Variable RT/CT protocols in different trials
3. Variable treatment intent
4. As patients have been enrolled over longer time duration so there has been a change in RT techniques and side effects classification.

Re-irradiation trials suffer from lack of homogeneity and much smaller numbers to draw any statistically sound conclusions

Given the relative scarcity of high-quality evidence from prospective trials, ***Guidelines and Expert recommendations*** are crucial to ensure common standards and best practices are met when re-irradiation is considered.

Notable published guidelines and/or expert consensus documents cover

- Re-irradiation with IMRT for nasopharyngeal cancer –
- Radical thoracic re-irradiation for non-small cell lung cancer (NSCLC)
- Stereotactic body radiotherapy (SBRT) for pelvic tumour recurrences
- Brachytherapy for recurrent prostate cancer after previous RT.

International Journal of Radiation Oncology*Biology*Physics
Volume 110, Issue 3, 1 July 2021, Pages 682-695

Critical Review

International Recommendations on Reirradiation by Intensity Modulated Radiation Therapy for Locally Recurrent Nasopharyngeal Carcinoma

Wai Tong Ng FRCR *, Yoke Lim Soong FRCR †, Yong Chan Ahn MD ‡, Hussain AlHussain FRCPC §,

Advances in Radiation Oncology
Volume 6, Issue 2, March–April 2021, 100653

Scientific Article

An International Expert Survey on the Indications and Practice of Radical Thoracic Reirradiation for Non-Small Cell Lung Cancer

Robert Rulach FRCR [a b], David Ball MD [c], Kevin L.M. Chua FRCR [d],

Radiotherapy and Oncology
Volume 164, November 2021, Pages 104-114

Recommendation

An international Delphi consensus for pelvic stereotactic ablative radiotherapy re-irradiation

Finbar Slevin [a b], Katharine Aitken [c d], Filippo Alongi [e f], Stefano Arcangeli [g],

Cancer Treatment Reviews
Volume 98, July 2021, 102206

Hot Topic

Salvage stereotactic body radiotherapy (SBRT) for intraprostatic relapse after prostate cancer radiotherapy: An ESTRO ACROP Delphi consensus

Barbara A. Jereczek-Fossa [a b 1], Giulia Marvaso [a b 1], Mattia Zaffaroni [a]

Radiotherapy and Oncology
Volume 118, Issue 1, January 2016, Pages 122-130

Prostate cancer

A Delphi consensus study on salvage brachytherapy for prostate cancer relapse after radiotherapy, a Uro-GEC study

Emmie Kaljouw [a], Bradley R. Pieters [a], György Kovács [b], Peter J. Hoskin [c]

Radiotherapy and Oncology
Volume 184, July 2023, 109672

Original Article

Salvage prostate brachytherapy in radiorecurrent prostate cancer: An international Delphi consensus study

Mark T. Corkum [a], Mark K. Buyyounouski [b], Albert J. Chang [c], Hans T. Chung [d],

THE LANCET
Oncology

Volume 23, Issue 10, October 2022, Pages e469-e478

Policy Review

European Society for Radiotherapy and Oncology and European Organisation for Research and Treatment of Cancer consensus on re-irradiation: definition, reporting, and clinical decision making

Nicolaus Andratschke MD [a] †, Jonas Willmann MD [a] †, Ane L Appelt PhD [b],

Practices

- Head & Neck Cancers
- Glioma & other brain tumors
- Gynaecological cancers

Head and neck cancers

- One of the most common sites where re-irradiation is increasingly being considered.
- Because of high rates local failure and the complexity of salvage surgery.
- Approach towards the ReRT remains same but one should keep in mind the major prognostic factors that affect results of re-irradiation.
- Judicious selection is very important since there are a lot of vital organs in close proximity.
- ReRT without careful selection may increase risk of serious toxicity and impaired quality of life with an uncertain survival advantage.

Head and neck cancers

- Dose prescription should be evaluated carefully in accordance with the treatment volume, prior dose distribution and the modality of previous treatments so as to minimize the volume of overlap
- Apart from the various tumor related factors, presence of co-morbidities and preexisting organ dysfunction (like non functional organ, non healing ulcers, osteo-radio-necrosis, severe fibrosis) are probably the most important factor.
- The cumulative life time dose to organs like the spinal cord, brain stem and parotids needs to be evaluated and must be respected.
- For treatment near carotid artery, Doppler ultrasound before re-irradiation is often recommended.

Head and neck cancers

- Wherever possible, IMRT should be preferred for its obvious dosimetric advantages over conventional or 3D conformal radiation techniques.
- Advanced radiation techniques, such as tomotherapy or proton-beam therapy, may facilitate treatment near the base of skull, whereas for small volume mucosal recurrence, interstitial brachytherapy should always be tried.
- Use of concurrent chemotherapy wherever possible will definitely improve the chance of survival.
- Provision of aggressive nutritional support during the course of ReRTis essential to minimize treatment breaks.

Gliomas and other brain tumours

- Local recurrence of malignant glioma is a common problem in clinical practice.
- A standard management approach for recurrence does not exist.
- The various options available are re-surgery, re-radiotherapy, systemic therapy, and the best supportive care.
- However, the decision depends on the specific patient and tumor-related factors.
- Re-resection if possible not only improves symptoms and maintains quality of life, it can delay symptom progression, reduce corticosteroid doses, and also improve response to chemotherapy and/or radiotherapy.
- Re-irradiation is an option for a small subgroup of selected patients.

- Young patients, with good KPS, small volume residual lesion involving noneloquent areas are the ideal candidates for surgery.
- The first and foremost step before re-irradiation is establishing recurrence and differentiating from pseudo-progression.
- The most common approach involves the use of fractionated stereotactic radiotherapy with or without intensity modulation and a median total dose of 30–36 Gy.
- Effort should be made to keep the cumulative EQD2 around 100 Gy with conventional technique and slightly higher with conformal and stereotactic radiotherapy.

Gynaecological/ Pelvic cancers

- The pelvic re-irradiation must not be the first choice for such patients with recurrent pelvic tumours after a previously course of irradiation.
- These recurrences can be central or peripheral and surgery if possible is the mainstay of treatment.
- As minimal data is available on the toxicity of additional radiation therapy, this approach would be considered only when there in no other alternative for effective therapy and in the face of progressive and severe symptom.
- Pre-existing late rectal or bladder toxicity is a strong deterrent for consideration of reirradiation.
- Cumulative dose to several organs at risk like femoral heads, bone marrow, small bowel, urethra, vagina and sigmoid should also be considered.
- As per as technique is concerned preference should be given to intraoperative radiotherapy or brachy therapy. Combining surgery with postoperative radiotherapy gives best results.

Conclusions

- ✓ In the present day, the possibility of re-irradiation has increased due to the availability of image guidance, IMRT, etc., but at the same time the risk benefit ratio should be considered before deciding on the treatment.

- ✓ The knowledge of previous radiation fields, portals, dose per fraction, technique, dose distribution and exact dose to the critical organs are important determinants in prescribing dose and volume for re-irradiation.

Thank you