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Review Article

Radiobiology of Re-irradiations

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Abstract

The treatment options for recurrent tumors are limited. Re irradiation is being increasingly considered as an option, in view of the advances in treatment techniques, particularly the ability to document doses, overlay plans, intensity modulation, and image guidance. preclinical and clinical studies has been to estimate the total cumulative doses (EQD2) also termed as normalized total dose (NTD) that can be delivered to various tissues. In this review article reirradiation radiobiology of different tissues and dose fractionation have been discussed.

Keywords: Myelopathy, normalized total dose, re-irradiation

Introduction

The treatment options for recurrent tumors are limited. Re-irradiation is being increasingly considered as an option, in view of the advances in treatment techniques, particularly the ability to document doses, overlay plans, intensity modulation, and image guidance. However, data regarding indications, outcomes, fractionation, concurrent treatment, and cumulative doses to normal tissues are in the nascent stage. Unlike first-line radiation regimens, which have been tried and tested in several large prospective randomized trials, re-irradiation trials suffer from lack of homogeneity and much smaller numbers to draw any statistically sound conclusions. This review attempts to collate the existing evidence about the radiobiological considerations in re-irradiation.

The various factors that need to be taken into consideration are the type of normal tissues at risk, the dose fractionation, interval from previous radiation, the current extent of disease, overall patient prognosis, and observable normal tissue damage that has resulted from the previous radiation.

Calculating Total Cumulative Dose

Tissues are broadly divided into early responding and late responding. The early responding tissues (high α/β ratio) have a rapidly proliferating stem cell compartment, which migrate into the irradiated tissue and restore normal architecture and function rapidly. The α/β ratio is considered to be 10 for such tissues and thereby the physical dose gives a fair idea of the biologically effective dose (BED) at various fractionation schedules. However, for tissues with low proliferative capacity (low α/β ratio, approximately 3), BED rather than physical dose should be considered while evaluating irradiation protocols.[1] 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 2 Gy equivalent dose (EQD2) to allow uniform comparison of various studies. The aim of various preclinical and clinical studies has been to estimate the total cumulative doses (EQD2) also termed as normalized total dose (NTD)[2] that can be delivered to various tissues. However, for large fraction sizes, particularly high-dose single-fraction radiosurgery, the validity of linear-quadratic model is questionable.[3]

Spinal Cord

Experiments in rhesus monkeys studied by Ang *et al*. looked at re-irradiation tolerance at varying time intervals after the first course and concluded that for a time interval of 1, 2, and 3 years between the treatment courses, cumulative doses of

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150%, 156%, and 167% of the first-line setting's tolerance dose appear possible.[4] Similar experiments in guinea pigs by Mason *et al*. reiterated the importance of initial dose of radiotherapy. If the maximum tolerable dose has been delivered in the initial setting, then recovery is minimal. However, if 60% of tolerance dose is delivered, then recovery is almost complete (residual injury 8%–30%).[5] These findings have also been reflected in clinical experience in humans. Neider *et al*. compiled individual patient's data from multiple reports and proposed a risk assessment model for myelopathy. The factors which contribute to the score include cumulative BED (assuming α/β of 2 for cervical and thoracic spinal cord and 4 for lumbar), time interval <6 months between the two courses, and any single course with a BED ≥102 Gy 2.

Example 1

A patient receives radiotherapy for a head and neck malignancy with conventional parallel opposed pair up to a total dose of 45 Gy at 3 Gy per fraction. He develops a recurrence after 3 years and is planned for radiotherapy up to a total dose of 45 Gy in 25 fractions. His calculated risk of radiation myelopathy is as follows (Refer to Tables 1 and 2 for Risk Score and Risk Group classification):

- Step 1: Initial BED received by cervical spinal cord ($\alpha/\beta = 2$)
  nd $(1 + d/\alpha/\beta) = 45\ (1 + 3/2) = 112.5$ Gy
- Step 2: BED of second course of radiation therapy (RT)
  nd $(1 + d/\alpha/\beta) = 45\ (1 + 1.8/2) = 85.5$ Gy
- Step 3: Calculation of cumulative BED
  Initial course BED + second course BED = 112.5 + 85.5 = 198 Gy
- Step 4: Calculation of radiation myelopathy risk score:
  Cumulative BED score = 8
  Interval <6 m = No
  One BED course ≥102 Gy = yes → multiply risk score by 4.5
  Risk score = 8 × 4.5 = 36
- Step 5: Risk group for development of radiation myelopathy
  Risk score is 36. Since risk score is >6, patient has "high risk" (90%) for development of radiation myelopathy.

The same treatment if delivered by intensity-modulated RT (IMRT) in the initial setting would, however, reduce the risk of myelopathy significantly, by reducing the dose per fraction and total dose received and thereby reducing BED.

Example 2

A patient receives radiotherapy for a head and neck malignancy with IMRT up to a total dose of 70 Gy in 35 fractions, with spinal cord receiving maximum dose of 45 Gy in 35 fractions. He develops a recurrence after 3 years and is planned for radiotherapy up to a total dose of 45 Gy in 25 fractions. His calculated risk of radiation myelopathy is as follows (Refer to Tables 1 and 2 for Risk Score and Risk Group classification):

- Step 1: Initial BED received by cervical spinal cord ($\alpha/\beta = 2$)
  nd $(1 + d/\alpha/\beta) = 45\ (1 + 1.28/2) = 73.8$ Gy
- Step 2: BED of second course of RT
  nd $(1 + d/\alpha/\beta) = 45\ (1 + 1.8/2) = 85.5$ Gy
- Step 3: Calculation of cumulative BED
  Initial course BED + second course BED = 159.3 Gy
- Step 4: Calculation of radiation myelopathy risk score:
  Cumulative BED score = 4
  Interval <6 m = No
  One BED course ≥102 Gy = No
  Risk score = 4
- Step 5: Risk group for development of radiation myelopathy
  Since risk score is 4, patient has "intermediate risk" (33%) for development of radiation myelopathy.

Modern radiation techniques such as IMRT thus make re-irradiation much safer by delivering less than maximum tolerable dose to spinal cord, thereby providing opportunity for near complete recovery.

Brain

The biology of radiation damage in the brain is similar to that of the spinal cord and is characterized by a long period of latency. The earliest evidence of damage is in the form of segmental demyelination and nodal widening which can be observed by 2 weeks. Remyelination can be observed by 2 months. After a latent period of 4–6 months, areas of white matter necrosis can be observed, as a result of critical depopulation of oligodendrocytes and vascular damage. The probability of occurrence of necrosis and the latent period is a function of dose.[7]

Re-irradiation is being considered as a valid option for recurrent gliomas in select cases. There have been several large case series reporting re-irradiation doses and incidence of radiation necrosis. The normalized total dose (NTDcumulative) which can be delivered depends on the re-irradiation volume and the technique of radiotherapy. A comprehensive account of clinical data available for re-irradiation of brain was presented by Mayer and Sminia in 2008. An NTDcumulative of >100 Gy for conventional fractionation was associated with radiation-induced white matter necrosis. Smaller volumes and more conformal techniques such as fractionated stereotactic radiotherapy and linear accelerator-based single-fraction stereotactic radiosurgery (SRS) allow safe delivery of higher NTDcumulative doses (90–133.9 Gy for fractionated stereotactic RT and 111.6–137.2 Gy for SRS). However, they found no correlation between time interval of the radiotherapy courses and incidence of complications.[8]

Lung

Re-irradiation of the lung has historically been used in a palliative setting. With a wide variety of systemic treatments available for the treatment of lung cancers, survival is increasing and thereby the scope for re-irradiation in the setting of a localized relapse or for symptom control. The lung is considered a late reacting tissue with an estimated α/β ratio of 4.[9] The primary end point of radiation damage is radiation pneumonitis and more uncommonly bronchial stricture, necrosis, and fistulas. The tolerance dose for the lung

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is fairly established in the *de novo* setting, with conventional fractionation. It is a function of dose and volume (V20, mean lung dose, etc.). In the relapsed setting, multiple factors affect the tolerance of the lung – prior RT dose, systemic treatments, prior surgery, cardiac function, tumor size, and location. Stereotactic radiotherapy allows delivery of meaningful doses without excessive spillage into normal lung.

Clinical data on the use of re-irradiation with conventional fractionation in non-small cell lung cancer show that it is feasible. In a series of 34 patients, who received a median dose of 60 Gy in the initial course and received a second course of median dose 50 Gy after a median interval of 23 months, 75% showed symptomatic improvement, but 19 patients had symptomatic pneumonitis, none of which were fatal.[10] Subsequently, a prospective trial with similar cumulative doses reported much lesser incidence of radiation pneumonitis (22% grade 1–2, no grade 3 or >pneumonitis).[11] With the use of stereotactic RT, delivery of much higher doses was found to be feasible. While a BED of >100 Gy is recommended for primary stereotactic ablative body radiotherapy, in the salvage setting, more conservative dose fractionation (40–50 Gy in 4 fractions) equivalent to a BED of 80 Gy has been recommended and found to be safe.[12,13]

Bladder

The bladder is considered a late reacting tissue due to the low proliferating potential of urothelial cells. However, acute radiation cystitis occurs within 2–4 weeks of starting radiotherapy and presents as reduced bladder capacity due to functional biochemical changes (release of prostaglandins by urothelium). The late effect on the bladder may present after a long latent period of several years and is characterized by ulceration, telangiectasia, fibrosis presenting as reduced bladder capacity, dysuria, and hematuria. The α/β for late effects is considered to be 6, in contrast to other late responding tissues with α/β of 3, which implies less dependency on fraction size. The dose-volume tolerance parameters prescribed for the bladder are difficult to interpret as volume changes with bladder filling and not all areas of the bladder have equal functional importance.[14]

Re-irradiation experiments on mouse bladder suggest that long-term recovery of bladder injury after a course of radiotherapy is poor. Thereby, a longer time interval between courses does not provide additional tolerance unlike other organs such as brain and lung. The re-irradiation dose delivered hence entirely depends on the initial dose received and cumulative doses can only be as high as bladder tolerance to a single course of RT.[15] Clinical studies with stereotactic body RT (SBRT) for pelvic relapses suggest that maximum cumulative dose (EQD2) can be as high as 120 Gy 3 to a volume of 10cc.[16]

Rectum

Late rectal toxicity is a major concern in pelvic radiotherapy. Attempts are made to reduce rectal dose while treating prostate and cervical malignancies using IMRT and brachytherapy. Clinical studies in cervical cancer have demonstrated clear correlation between rectal dose-volume parameters and toxicity. Using a cutoff of D2cc dose of <75 Gy results in <5% rate of late rectal toxicity. However, it is difficult to define such precise cumulative dose constraints for rectum in re-irradiation.[17] Studies have reported acceptable toxicity to the rectum after re-irradiation with stereotactic techniques. A study by Abusaris *et al*. utilized CyberKnife to deliver SBRT to 27 patients who had prior pelvic radiotherapy. A cumulative dose of up to 110 Gy 3 was allowed to 10cc of rectum. With this limit, none of the patients experienced Grade 3 or more toxicity.[16] Re-irradiation has also been used in selected cases of primary rectal cancers with local relapse, having previously received pre- or postoperative radiotherapy. Patients were treated with three or four coplanar fields with either hyperfractionated (1.2 Gy per fraction, 2 fractions per day) or with conventional 1.8–2 Gy per fraction up to a cumulative dose of 85.8 Gy (70.6–108 Gy). Late toxicities reported were chronic Grade 3 diarrhea (22%), small bowel obstruction (15%), fistula (4%), and skin ulceration (2%). Patients who received hyperfractionated RT and had an interval of >24 months since the first course of RT had significantly less toxicities.[18]

Skin and Mucosal Tissues

Skin after radiation therapy is characterized by a faint, dried epidermis and changes in the structure of keratinization. The superficial epithelial cells are acutely responding and are assumed to have an α/β of 10 while subcutaneous tissues that lie at a depth of >5 mm are responsible for late effects and are assumed to have an α/β of 3. Based on animal experiments of mouse tail re-irradiation, it was found that up to 90% of tolerance dose could be given after an interval of 6 weeks to 10 months from prior radiation with tolerance dose. The tolerance dose after third irradiation reduced to 65%.[19] The Radiation Therapy Oncology Group reported the skin tolerance of 5% ulceration in an irradiated area of 5 cm × 5 cm to be 70 Gy.[20] Re-irradiation studies in recurrent skin cancers using superficial X rays has shown that a cumulative BED of 110 Gy to skin surface and not more than 55 Gy at 5 mm depth was tolerable.[21] In subsequent studies of recurrent breast cancers using megavoltage photons, cumulative doses (EQD2) up to 100 Gy have been reported, with 10% of acute Grade 3 toxicity, 8.5% of Grade 3 fibrosis, and 2% of skin necrosis.[22]

Re-irradiation studies in the head and neck up to total cumulative doses of 120 Gy reported Grade 2 and 3 late toxicities in the form of cervical fibrosis (41%) and mucosal necrosis (21%).[23]

The tolerance of skin and mucosal acute effects seems to be tolerable in the dose range of 110–120 Gy EQD2, with slightly higher incidence of late Grade 2–3 toxicities.

Mesenchymal Tissues

The mesenchymal tissues including cartilage, bone, and muscle are often not given any constraints in planning. Radiotherapy to cartilage up to even 10 Gy results in growth retardation in children. High dose

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Table 1: Risk score for development of radiation myelopathy

	Factors									
	0	1	2	3	4	5	6	7	8	9
Cumulative BED (Gy2)	≤120	120.1-130	130.1-140	140.1-150	150.1-160	160.1-170	170.1-180	180.1-190	190.1-200	>200
Interval <6 months					×4.5					
One BED course ≥102					×4.5					

BED: Biologically effective dose

Table 2: Risk group for development of radiation myelopathy

Risk group	Score	Myelopathy (%)
Low risk	≤3	0
Intermediate	4-6	33
High	>6	90

to bones results in osteoradionecrosis (ORN) and fractures. The dose-volume parameters for mandible for the end point of necrosis have been quoted in various studies. Studies in oral and oropharyngeal cancers showed D2%>65 Gy,[24] V43 ≥42%, and V24 ≥94%[24] to be associated with increased risk of necrosis. The risk of necrosis of the mandible is around 5 with megavoltage radiotherapy with modern techniques. Studies on re-irradiation suggest that the incidence of ORN with a cumulative dose of 120 Gy is reported to be 8%–11%, the incidence being higher in patients treated at a time interval of <3 years, concurrent chemotherapy, and higher total dose.[25,26] Although it has been proposed that cumulative dose to the mandible should not exceed 70 Gy, it is unclear what volume can tolerate this dose.[27]

Carotid blowout is one of the life-threatening complications of re-irradiation in the head and neck. Its incidence has been reported to be between 5% and 8%.[27] Factors associated with increased risk of blowout include >180° encasement of carotid, skin ulceration, and irradiation of lymph nodes.[28]

Altered Fractionation

The role of hyperfractionation has been explored in various sites such as head and neck and non-small cell lung cancer. The concept of hyperfractionation seems particularly attractive in the re-irradiation setting. The delivery of multiple small fractions (<1.8–2 Gy) per day, with sufficient time between fractions to allow for sublethal damage repair (>6 h), offers a therapeutic gain in terms of reducing late effects of normal tissues which have a low α/β (1.5–5 Gy). In contrast, the high α/β values (6–14 Gy) observed for acutely responding normal tissues indicate that the response is relatively linear over the dose range of clinical interest. Another strategy to increase therapeutic gain is to limit the treatment volume using techniques which are highly conformal such as stereotactic radiotherapy, brachytherapy, and intraoperative radiotherapy.[29]

Low-dose ultrafractionation

In vitro studies have shown that some human tumor cell lines are sensitive to low radiation doses of ≤1 Gy, a phenomenon that has been termed low-dose hypersensitivity (HRS). This radiosensitivity seems to be more apparent in radioresistant cells such as glioma cell lines. The mechanism underlying HRS in specific cell types appears to be related to defective DNA repair systems and cell cycle regulation. HRS is more likely to affect early responding proliferative tissue and hence a novel concept for re-irradiation. A prospective randomized trial was initiated by EORTC-NCIC in newly diagnosed inoperable glioblastoma patients, with a regimen of 0.75 Gy per fraction, 3 fractions per day with a minimum of 4 h interval (5 days a week; 6 consecutive weeks), before the establishment of Stupp regimen.[30] This trial showed a marked number of long-term survivors with a 2-year survival rate of 15.48%.[31] Subsequently, a Phase II trial was conducted with this regimen in combination with temozolomide which showed median overall survival (OS) of 16 months and 2-year OS of 32.4% which was superior to the Stupp trial results.[32] A case series of 11 patients utilized low-dose ultrafractionation for re-irradiation in various sites and reported effective palliation with minimal toxicity. This concept appears promising and warrants larger prospective trials in re-irradiation setting.[33]

Response Modifiers

Strategies to enhance radiation sensitivity including various chemotherapy drugs, targeted therapy, and hyperthermia have been used concurrently in the re-irradiation setting. The mechanism is being similar to their use in the first line. Common radiosensitizers are cisplatin and cetuximab in the head and neck and 5-fluorouracil in the rectum. With the emerging role of immunotherapy and its potential interaction with radiotherapy, it remains to be seen whether this strategy adds to the armamentarium of radiation response modifiers.

Conclusion

The knowledge of early and late effects of radiotherapy, recovery of normal tissues, and the use of modern techniques has made the application of re-irradiation safer and a potentially curative option for recurrences.

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Conflicts of interest

There are no conflicts of interest.

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