Review Article

Re-irradiation in Central Nervous System Tumors

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Abstract

Radiotherapy (RT) in relapsed brain tumors has been used sparingly because of the risk of toxicity, particularly white matter necrosis. However, evidence from preclinical animal models and increasing data from clinical series show that brain and spinal cord have marked repair potential, and re irradiation should be considered a valid option in selected patients. The choice of technique and dose fractionation for re irradiation depends on tumor characteristics (volume and location), previous RT dose and volume, and patient characteristics (age and performance status). For small volume tumors in noneloquent areas, single fraction SRS and brachytherapy may be good options. For small and intermediate volume tumors in eloquent areas, FSRT or hypofractionated RT may be used. For large volume recurrences, requiring partial brain irradiation, conventional fractionation is safer and offers palliation with minimal risk of radiation induced toxicitie.

Keywords: Brain tumor, re-irradiation, central nervous system

Introduction

Radiotherapy (RT) in relapsed brain tumors has been used sparingly because of the risk of toxicity, particularly white matter necrosis. However, evidence from preclinical animal models and increasing data from clinical series show that brain and spinal cord have marked repair potential, and re-irradiation should be considered a valid option in selected patients.

Radiobiology of Central Nervous System Toxicity

The mechanism of central nervous system (CNS) damage involves different functional and structural components. The neurons, glial cells (oligodendrocytes and astrocytes), and vascular tissue are the key players in radiation-induced damage. The phases of CNS toxicity are classified as early (days-weeks), early delayed (1–6 months), and late (>6 months). Early and early delayed phases occur due to transient demyelination due to apoptosis of oligodendrocytes. However, this damage is repaired by the stem cell compartment consisting of oligodendrocyte Type 2 astrocyte cell (O2A).[1] Late damage is a complex interplay of demyelination due to O2A cell damage and vascular changes due to endothelial damage. A critical depopulation of cells and permeability changes in the vasculature lead to hemorrhage and infarcts,which precipitates white matter necrosis.[2]

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Studies regarding recovery of CNS structures come from preclinical evidence of radiation-induced myelopathy after re-irradiation at different intervals in animal models. Brain and spinal cord are known to have a low α/β. Although sensitive to large fraction sizes, the CNS has remarkable recovery potential and can withstand up to 50% of tolerance dose after 1 year and 65%–70% of tolerance dose after 3-year interval from the first course of radiation.[3] This study comes close to clinical scenarios of head-and-neck RT where the cord has initially received a dose of around 45 Gy at conventional fractionation, and there is a requirement of a second course after ≥1 year. A risk model proposed by Nieder *et al*. suggested that an interval of <6 months and a cumulative biologically effective dose of any one course of >102 Gy were significant contributors to myelopathy risk.[4]

Re-irradiation Tolerance

Re-irradiation tolerance of brain has been extrapolated to a large extent from the preclinical studies of spinal cord. In a meta-analysis

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of 21 re-irradiation studies of gliomas, Mayer and Sminia attempted to compile information regarding cumulative dose, interval, fractionation, and effect of concurrent therapies on brain tolerance. An NTDcumulative (normalized total dose = sum of 2 Gy equivalent doses of both courses) of >100 Gy for conventionally fractionated three-dimensional conformal RT was associated with radiation-induced white matter necrosis. Smaller volumes and more conformal techniques such as fractionated stereotactic RT (FSRT) and linear accelerator-based single-fraction stereotactic radiosurgery (SRS) allow safe delivery of higher NTDcumulative doses (90–133.9 Gy for FSRT and 111.6–137.2 Gy for SRS). However, they found no correlation between time interval of the RT courses and incidence of complications. There was an unusually high rate of necrosis of 6% when hyperfractionated RT was used with a conservative cumulative dose of 87.5 Gy, indicating that complete recovery probably does not occur within 6 h.[5]

Radiation tolerance of other critical structures, however, has not been documented in as much details and recommendations cannot be made based on these few small studies. Radiation-induced optic neuropathy was reported to occur in one every ten patients who received a cumulative NTD of 86 Gy.[6]

Studies on brainstem tolerance have been reported in patients of relapsed carcinoma nasopharynx, who received re-irradiation. Brainstem was found to tolerate a cumulative D_{max} of 79 Gy, D0.1cc of 71 Gy, D0.5cc of 65 Gy, and D1.0cc of 60 Gy [Table 1].[7]

Concurrent Treatment

Higher incidence of necrosis was also reported with the use of hyperbaric oxygen in a study by Koshi *et al*., where patients received hyperbaric oxygen immediately followed by gamma knife radiosurgery. A relatively low median cumulative dose of 86 Gy was associated with an incidence of brain necrosis of 28%. This was suggested to be due to the radiosensitivity of the well-perfused surrounding normal tissue.[8] Concurrent weekly paclitaxel with fractionated SRS delivered once a week also showed high rates of necrosis of 10%.[9] Temozolomide used concurrently has not demonstrated additional late toxicity.[10] Bevacizumab in recurrent high-grade glioma used concurrently with RT (median dose 36 Gy) was found to be superior in terms of progression-free survival and overall survival in a retrospective series. Bevacizumab was also associated with lower incidence of radiation-related adverse events.[11]

Role of Brachytherapy

Brachytherapy in various forms has been explored as an option for recurrent gliomas. Low-dose rate interstitial brachytherapy with I-125 permanent seeds (15 cGy/h, lifetime dose of 100–400 Gy), temporary implants (30–60 cGy/h, 4–6 days, and 50–65 Gy) gliaSite and high dose rate Ir-192 (15–60 Gy, 7–12 days) have been used in recurrent glioblastomas (GBMs) with varying success. Patients with good Karnofsky performance status and volume <30 cc were found to benefit more from these techniques. Median survival of 10.5–12 months has been reported. However, high rates of complications including radionecrosis, meningitis, and cerebrospinal fluid leak have been reported.[12]

Target Volume Delineation

Consensus guidelines have been compiled by the American Society for Therapeutic Radiology and Oncology, with regard to volume delineation and dose prescription for re-irradiation of GBMs. Tumors <2 cm can be treated with single-fraction 24 Gy, 2–3 cm tumors with single-fraction 18 Gy, and larger tumors may be treated with FSRT at 5–6 Gy per fraction/day in 5 days. Target volume is defined as contrast-enhancing tumor on magnetic resonance imaging (MRI) + 5 mm. When conventional fractionation of 1.8–2 Gy/day is used, larger volumes may be treated safely.[13]

Imaging Challenges

Post-RT relapses can be challenging to accurately delineate on an MRI. Areas of necrosis, gliosis, and nonspecific blood–brain barrier disturbances represent challenges in identifying the tumor accurately. Biological imaging with C11 methionine positron emission tomography aids in these diagnostic dilemmas and can be used for target delineation.[14]

Quality of Life after Re-irradiation

Very few studies of brain tumor re-irradiation have reported quality of life (QOL) data. A case series reported data in patients of Grade II glioma, who received concurrent temozolomide with re-irradiation. The trial applied The Functional Assessment of Cancer Therapy/National Cancer comprehensive network brain symptom index (FBrSI)-15 questionnaires to assess the QOL and showed significant improvement in scores 8 weeks after completion of treatment.[15] Other studies report indirect measures of QOL in the form of neurological function and steroid dependence. A review of over 300 patients of GBM who received re-irradiation showed that 24%–45% had improvement in neurological status, 20%–60% had reduction in steroid requirement, and most patients recorded stabilization of performance status until progression.[16,17]

Table 1: Practical considerations

Location	Median target volume of recurrence	Fractionation	NTD
Eloquent/noneloquent	Partial brain/large volume	Conventional	81.6-101.9 Gy
Eloquent/noneloquent	Intermediate volume (25 cc)	Hypofractionation/FSRT –30 Gy/5#, 35 Gy/10#	90-133.9 Gy
Noneloquent	Small volume (10-21 cc)	SRS/brachytherapy - 18 Gy/1#, HDR-40 Gy, LDR-60 Gy	111.6-137.2 Gy

NTD: Normalized total dose, SRS: Stereotactic radiosurgery, HDR: High-dose rate, LDR: Low-dose rate, FSRT: Fractionated stereotactic radiotherapy

Newer Radiotherapeutic Modalities

High linear energy transfer radiation-like proton therapy, boron neutron capture therapy, and intraoperative RT have been tried with varying results in the setting of recurrent GBMs.[18]

Conclusion

The choice of technique and dose fractionation for re-irradiation depends on tumor characteristics (volume and location), previous RT dose and volume, and patient characteristics (age and performance status). For small-volume tumors in noneloquent areas, single-fraction SRS and brachytherapy may be good options. For small- and intermediate-volume tumors in eloquent areas, FSRT or hypofractionated RT may be used. For large-volume recurrences, requiring partial brain irradiation, conventional fractionation is safer and offers palliation with minimal risk of radiation-induced toxicities.[19]

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Conflicts of interest

There are no conflicts of interest.

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