

## RADIATION DOSE–VOLUME EFFECTS IN THE BRAIN

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We have reviewed the published data regarding radiotherapy (RT)-induced brain injury. Radiation necrosis appears a median of 1–2 years after RT; however, cognitive decline develops over many years. The incidence and severity is dose and volume dependent and can also be increased by chemotherapy, age, diabetes, and spatial factors. For fractionated RT with a fraction size of <2.5 Gy, an incidence of radiation necrosis of 5% and 10% is predicted to occur at a biologically effective dose of 120 Gy (range, 100–140) and 150 Gy (range, 140–170), respectively. For twice-daily fractionation, a steep increase in toxicity appears to occur when the biologically effective dose is >80 Gy. For large fraction sizes ( $\geq 2.5$  Gy), the incidence and severity of toxicity is unpredictable. For single fraction radiosurgery, a clear correlation has been demonstrated between the target size and the risk of adverse events. Substantial variation among different centers' reported outcomes have prevented us from making toxicity–risk predictions. Cognitive dysfunction in children is largely seen for whole brain doses of  $\geq 18$  Gy. No substantial evidence has shown that RT induces irreversible cognitive decline in adults within 4 years of RT. © 2010 Elsevier Inc.

Radiotherapy, stereotactic radiosurgery, brain, tolerance, side effects.

### 1. CLINICAL SIGNIFICANCE

Radiotherapy (RT) plays an important role in the curative and palliative treatment of patients with primary and metastatic brain tumors. Primary brain tumors account for 22% of tumors in those <18 years of age. Brain metastases occur in  $\approx 30\%$  of patients diagnosed with solid tumors, afflicting  $\approx 170,000$  Americans annually. The acute and late effects of RT on the brain are common and represent a significant source of morbidity. Such morbidity is particularly troubling in patients with baseline tumor-related dysfunction. In addition, the radiation fields used to treat the upper aerodigestive track (*e.g.*, pharynx and nasal cavities) often include a portion of the brain.

### 2. ENDPOINTS

The acute side effects of RT to the brain include nausea, vomiting, and headache; vertigo and seizures are less fre-

quent. These symptoms are transient and generally respond to medication.

The present report summarizes the dose–volume predictors for the principal late side effects of RT to the brain: radiation necrosis and cognitive deterioration. A biopsy is rarely performed to confirm suspected radiation necrosis. The working definition used by most of the studies listed in Tables 1 and 2 was “new symptoms with suggestive radiologic findings.”

However, most investigators have reported their late toxicity rates as crude numbers according to the number of patients treated rather than the number at risk (*i.e.*, the survivors). This method understates the risk, because some subjects will have died before the toxicity has had a chance to develop. The actuarial rates have rarely been discussed. Surgery, chemotherapy, steroids, antiepileptic agents, and opioids impair neurologic and cognitive function, further confounding the interpretation of suspected RT toxicity.

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Table 1. Dose–volume predictors of radiation necrosis after stereotactic radiosurgery

Reference	Diagnosis	Technique	Patients ( <i>n</i> )	Dmin* (Gy)	RN incidence (%)	Subgroup (cm <sup>3</sup> )	RN incidence (%)	Primary toxicity predictor	Other risk factors
1	AVM	GK	823	?	5			Average dose in 20 cm <sup>3</sup>	
2	Mixed	LINAC	133	15.0 (7.0–25.0)	12.8	V <sub>10</sub> : <10 vs. >10	0 vs. 23.7	V <sub>10</sub>	Location
3	AVM	GK	307	20.9 (12–30)	10.7			V <sub>12</sub>	Location
4	AVM	LINAC	73	16 (10–22)	14	Tx volume: <1 1–3.9 4–13.9 >14	0 15 14 27	Treatment volume	Dose, previous brain insult
5	Mixed	GK	243	20 (10–30)	7			V <sub>10</sub>	Repeated radiosurgery, Glioma
6	Mixed	GK	749	18 (16–19) <sup>†</sup>	?	Prescription volume: 0.05–0.66 0.67–3 3.1–8.6 8.7–95.1	0 3 7 9	Prescription volume	
7	AVM	Proton beam	1250	10.5 (4–65)	4.1			Dose and volume combined	Older age, location
8	AVM	?	269	?	4.7			V <sub>12</sub>	
9	Brain metastases	GK	137	16 (12–25)	11.4	Tx volume: <2 >2	3.7 16	Volume	
10	Tumor	GK	129	17.3 (11–25)	30	V <sub>12</sub> : 0–5 5–10 10–15 >15	23 20 54 57	V <sub>12</sub>	Location, previous WBRT, male

*Abbreviations:* Dmin = minimal dose; RN = radiation necrosis; AVM = arteriovenous malformation; GK = gamma knife; LINAC = linear accelerator teletherapy machine; V<sub>10</sub> = percentage of volume receiving ≥10 Gy; V<sub>12</sub> = percentage of volume receiving ≥ 12 Gy; Tx = treatment; WBRT = whole brain radiotherapy.

\* Data presented as mean, with range in parentheses, unless otherwise noted.

<sup>†</sup> Range refers to 25th to 75th quartile.

### 3. CHALLENGES DEFINING VOLUMES

There is little disagreement regarding image segmentation of the entire brain, and little intra- or interfraction movement occurs. However, segmenting the brain subregions is challenging (*e.g.*, the superior boundary of the brain stem). Currently the utility of subregion definition is unclear.

### 4. REVIEW OF DOSE–VOLUME DATA

#### *Radiation necrosis*

For radiosurgery, the incidence of necrosis depends on the dose, volume, and region irradiated (1–10) (Table 1 and Fig. 1). The Radiation Therapy Oncology Group conducted a dose-escalation study that sought to define the maximal dose for targets of different sizes; all subjects had previously undergone whole brain irradiation. The maximal tolerated dose for targets 31–40 mm in diameter was 15 Gy, and for targets 21–30 mm in diameter, it was 18 Gy. For targets <20 mm, the maximal tolerated dose was >24 Gy (11). The volume of brain receiving ≥12 Gy has been shown to corre-

late with both the incidence of radiation necrosis and asymptomatic radiologic changes (Table 1).

The large variation in absolute complication rates among studies (Fig. 1) is difficult to comprehend, but it might relate to differences in the definitions of the volume and toxicity, the avoidance of critical structures, and the type and length of clinical follow-up.

For fractionated RT, the relationship between the radiation dose and radiation necrosis for partial brain irradiation is presented in Table 2 (12–19) and Fig. 2, segregated by the fractionation scheme. Different fractionation schemes were compared using the biologically effective dose (BED) (20), with an  $\alpha/\beta$  ratio of 3. For standard fractionation, a dose–response relationship exists, such that an incidence of side effects of 5% and 10% occur at a BED of 120 Gy (range, 100–140) and 150 Gy (range, 140–170), respectively (corresponding to 72 Gy [range, 60–84] and 90 Gy [range, 84–102] in 2-Gy fractions). For twice-daily fractionation, a steep increase in toxicity appears to occur when the BED is >80 Gy. For daily large fraction sizes (>2.5 Gy), the incidence

Table 2. Dose–volume predictors of radiation necrosis after fractionated radiotherapy

Reference	Patients (n)	Disease	Volume	Fraction size*	Prescribed dose (Gy)	Fractions/week*	BED (Gy)	RN incidence (%)	Comment
12	141	NPC	TL	2	66	5	110	0	5-y Actuarial rate
12	126	NPC	TL	2.5	60	4	110	0	" "
12	89	NPC	TL	2.5	60	5	110	1.4	" "
12	53	NPC	TL	3.5	59.5	3	129	8.1	" "
12	218	NPC	TL	2	62.5	5	108	1.5	" "
12	109	NPC	TL	2	62.5	5	108	1.4	" "
12	212	NPC	TL	2.5	61	4	119	0.6	" "
12	48	NPC	TL	1.6	71.2	10	115	14	" "
13	56	NPC	TL	3.8	45.6	2	103	4.8	10-y Actuarial rate
13	621	NPC	TL	4.2	50.4	2	121	18.6	" "
13	320	NPC	TL	2.5	60	2	110	4.6	" "
12	105	NPC	TL	2	67	5	112	1	Data represent dose range and fractionation parameters; mean values given; time of evaluation not clearly stated
12	378	NPC	TL	2	67	5	107	1.1	" "
12	86	NPC	TL	2.1	54	5	92	1.2	" "
12	143	NPC	TL	1.9	62	5	101	1.4	" "
12	152	NPC	TL	3	60	5	120	3.3	" "
12	18	NPC	TL	2.4	60	5	108	5.6	" "
12	82	NPC	TL	2.5	60	5	110	19.5	Time of evaluation not clearly stated
12	23	NPC	TL	1.6	67.2	10	103	34.8	" "
12	77	NPC	TL	1.6	71.2	10	131	40.3	" "
14	60	HGG	PB	1.6	51.2	10	79	1.6	Received nitrosourea; endpoint, possible RN on 18-mo imaging
14	66	HGG	PB	1.2	68.4	10	96	6.1	" "
14	51	HGG	PB	1.2	79.2	10	111	17.7	" "
15	291	HGG	PB	2	?	5	103	4	Assume $\alpha/\beta$ of 2, BED included initial and salvage RT; some patients received chemotherapy; range of fraction sizes used; time of evaluation not clearly stated
15	11	HGG	PB	2	?	5	138	9	" "
15	23	HGG	PB	2	?	5	173	17	" "
15	23	HGG	PB	2	?	5	208	22	" "
16	101	LGG	PB	1.8	50.4	5	81	2.5	
16	102	LGG	PB	1.8	64.8	5	104	11	
17	213	BM	WB	3	30	5	60	0	Median survival only 6 mo; later events might have been missed; time of evaluation not clearly stated
17	216	BM	WB+B	1.6	54.4	10	83	0.4	" "
18	63	BM	WB+B	1.6	48	10	74	0.0	" "
18	121	BM	WB+B	1.6	54.4	10	83.4	1.7	" "
18	105	BM	WB+B	1.6	64	10	98.4	1.9	" "
18	56	BM	WB+B	1.6	70.4	10	108	1.8	" "
19	11	NPC	TL	1.6	64	10	98	27	Refers to dose received by temporal lobe; time of evaluation not clearly stated
19	70	NPC	TL	1.2	70.8	10	99	0	" "

Abbreviations: NPC = nasopharyngeal cancer; TL = temporal lobe; BM = brain metastases; LGG = low-grade glioma; HGG = high grade glioma; WB = whole brain; WB+B = whole brain 32 Gy plus boost; PB = partial brain; RN = radiation necrosis.

\* For most fractions.

and severity of toxicity is unpredictable. The reader is cautioned against overinterpreting the data presented in Fig. 2, which was created from a heterogeneous data pool (*i.e.*, dif-

ferent target volumes, endpoints, sample sizes, and brain regions). No evidence has shown that children are especially at risk of radiation necrosis (21, 22).

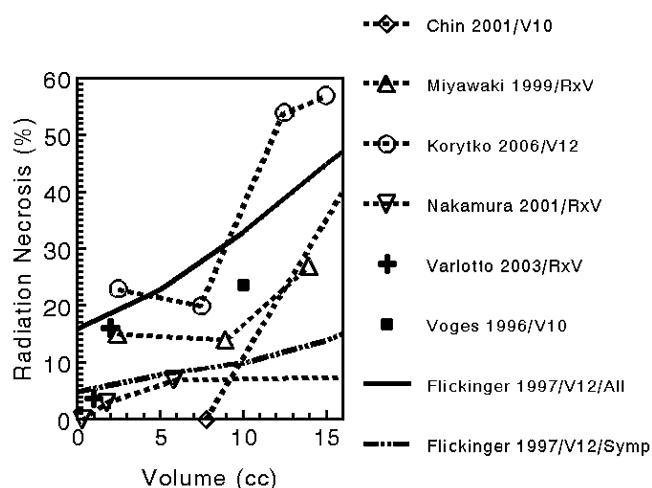


Fig. 1. Relationship between volume receiving high-dose irradiation and incidence of radiation necrosis in single-fraction stereotactic radiosurgery. Studies differed in their completeness of follow-up, definition of volume, and definition of radiation necrosis. Graph based on data presented in Table 1. Volume plotted as a point, representing mid-point of volume range.  $V_{10}$  = volume receiving 10 Gy;  $V_{12}$  = volume receiving 12 Gy; RxV = treatment volume. Flickinger data is shown for patients with either radiologic or symptomatic evidence of necrosis (marked as "All"), or only those with symptomatic necrosis (Symp). The other authors' data refers to symptomatic necrosis.

#### Neurocognitive function in children

The neurocognitive effects of cranial RT in children have been studied in several settings. With central nervous system prophylaxis for acute lymphoblastic leukemia, the addition of 24 Gy radiation to the whole brain (to a chemotherapy regimen) has been associated with a median 13-point intelligence quotient reduction at 5 years after RT and poorer academic achievement and self-image, and greater psychological distress (23) at 15 years after RT. The reported toxicities have been lower (or not detected) when 14–18 Gy was used (24–26).

In medulloblastoma, the post-RT intelligence quotients were 10–15 points better after a whole brain dose of 23.4 Gy vs. 36 Gy (27, 28). Others (29), but not all (30, 31), have also noted a dose response in the 18–36-Gy range. Differences between the studies can be explained by the inability of small studies to overcome the complex interactions among dose, volume, patient age, and follow-up length. Merchant *et al.* (32) has suggested that different regions of the brain, particularly the supratentorial area, are important in the development of RT-associated cognitive decline.

#### Neurocognitive functioning in adults

The evidence for RT-induced neurocognitive injury in adults is weak. Irreversible cognitive side effects were first highlighted in survivors who had undergone whole brain RT in 3–6 Gy/fraction (33). Subsequently, cognitive dysfunction was found to be frequently present even before RT (34). Multiple studies have demonstrated improved cognitive function after RT, because of its antitumor effects (35–

39). The results from randomized studies of “elective” whole brain RT (*e.g.*, for lung small cell carcinoma) have been difficult to interpret because those not receiving RT have tended to develop more brain metastases. In one adult study, learning impairment did not develop until 5 years after RT (40); however, few studies have followed up patients for this long.

Several studies have compared the cognitive function of patients who underwent RT with that of those who did not. Four studies with a follow-up of  $\leq 2$  years found no difference (34, 41–43). However, the two studies with  $\geq 5$  years of follow-up noted negative cognitive effects of RT; most of these patients had undergone partial brain RT (44, 45). The total doses were 56 and 60 Gy; only those receiving fraction sizes  $> 2$  Gy showed cognitive decline. Two randomized studies of high- vs. low-dose partial brain irradiation failed to discern a difference in neurocognitive outcome (46, 47); however, an insensitive instrument was used.

Two small studies suggested that whole brain RT is more detrimental than focal RT (48, 49). These findings were not confirmed by a randomized trial comparing radiosurgery and radiosurgery combined with whole brain RT, however this study used an insensitive instrument and had a short follow-up period (50).

Thus, very limited evidence is available to show that brain RT in 2-Gy fractions causes irreversible cognitive decline in adults.

## 5. FACTORS AFFECTING RISK

The radiation dose, fraction size, and volume are the major variables that influence the development of radiation necrosis. Although location does not influence the susceptibility to radiation necrosis, necrosis is far more likely to be symptomatic in certain areas (*e.g.*, corpus callosum and brain stem) (51). Other suggested risk factors for radiation necrosis include chemotherapy use, lower conformality index, shorter overall treatment time, older age, and diabetes mellitus (12, 15, 30).

Young age is the most important risk factor for neurocognitive decline in children undergoing cranial RT (29, 31, 52). Other risk factors include female gender, NF-1 mutation, extent of surgical resection, hydrocephalus, concomitant chemotherapy (especially methotrexate), location, and volume of brain irradiated (31, 53–57). An excellent review can be found in the report by Duffner (58).

The risk factors for neurocognitive decline in adults might include the volume irradiated (48, 49), large fraction size (44), and longer interval after treatment (40).

## 6. MATHEMATICAL/BIOLOGIC MODELS

The linear-quadratic model has been used to model radiation necrosis in the brain after fractionated RT (12, 13, 20). The  $\alpha/\beta$  ratio for the normal brain has been estimated to be 2.9 (13).

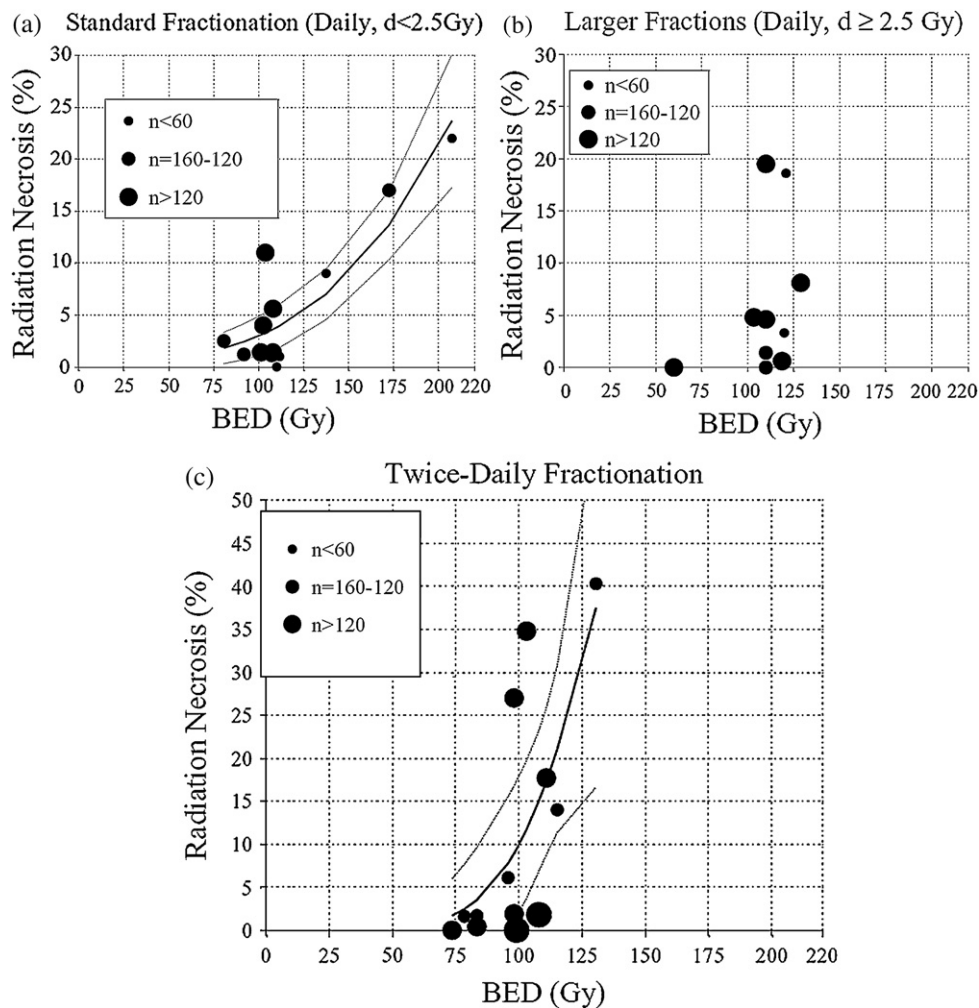


Fig. 2. Relationship between biologically effective dose (BED) and radiation necrosis after fractionated radiotherapy. Fit was done using nonlinear least-squares algorithm using Matlab software (The MathWorks, Natick, MA). Nonlinear function chosen was probit model (similar functional form to Lyman model). Dotted lines represent 95% confidence levels; each dot represents data from specific study (Table 2), n = patient numbers as shown. (a) Fraction size < 2.5 Gy; (b) fraction size  $\geq 2.5$  Gy (data too scattered to allow plotting of “best-fit” line); and (c) twice-daily radiotherapy.

For radiosurgery, a variety of models have been suggested. All are highly simplified and ignore many relevant variables, and none has been adequately validated.

## 7. SPECIAL SITUATIONS

Re-irradiation is frequently performed in the brain. A meta-analysis of brain re-irradiation (interval between courses, 3–55 months) found no cases of necrosis when the total radiation dose was < 100 Gy (normalized to 2 Gy/fraction;  $\alpha/\beta$  ratio, 2) (59).

Unlike other settings, in primary central nervous system lymphoma, RT (to  $\approx 40$  Gy) has been associated with cognitive decline, especially in those > 60 years old (60, 61). The heightened sensitivity of this population to irradiation might be explained by the tumor’s highly diffuse, angiocentric growth pattern and that most patients receive high-dose methotrexate, a potent neurotoxin. As a result, upfront full-dose RT is now often avoided in elderly patients with this dis-

ease. A lower radiation dose of 23.4 Gy might be safe even in older patients (62).

## 8. RECOMMENDED DOSE–VOLUME LIMITS

The constraints presented in the following paragraphs are the best estimates determined from the available data; however, high-level evidence is lacking. The constraints should be used with appropriate caution and interpreted within the clinical context.

### *Fractionated RT to partial brain*

For standard fractionation, a 5% and 10% risk of symptomatic radiation necrosis is predicted to occur at a BED of 120 Gy (range, 100–140) and 150 Gy (range, 140–170), respectively (corresponding to 72 Gy [range, 60–84] and 90 Gy [range, 84–102] in 2-Gy fractions). The brain is especially sensitive to fraction sizes > 2 Gy and, surprisingly, twice-daily RT.



Cognitive changes occur in children after  $\geq 18$  Gy to the entire brain. The effect of irradiation on the cognitive performance of adults is less well defined.

Emami's original estimate for fractionated partial brain RT (5% risk at 5 years for one-third brain, 60 Gy) appears to be overly conservative. We have concluded that the 5% risk at 5 years of the partial brain for normally fractionated RT is 72 Gy (range, 60–84). We emphasize that for most cancers, there is no clinical indication for giving fractionated RT  $> 60$  Gy and that, in some scenarios, an incidence of 1–5% radiation necrosis at 5 years would be unacceptably high.

### Radiosurgery

The risk of complications increases with the size of the target volume. Toxicity increases rapidly once the volume of the brain exposed to  $> 12$  Gy is  $> 5$ – $10$  cm<sup>3</sup>. Eloquent areas of the brain (brain stem, corpus callosum) require more stringent limits. The substantial variation between the reported treatment parameters and outcomes from different centers has prevented us from making precise toxicity risk predictions.

## 9. FUTURE TOXICITY STUDIES

Modern imaging modalities (*e.g.*, magnetic resonance imaging perfusion and spectroscopy, positron emission tomography) can detect damage before routine computed tomography or magnetic resonance imaging and symptom development (63–65). Hahn *et al.* (66) detected metabolic changes in normal brain that had undergone  $> 40$  Gy and correlated these with neurocognitive effects. Future studies should aim to link early imaging changes with clinically relevant endpoints, facilitating rapid and quantitative estimates of treatment-induced toxicity.

The effect of chemotherapy and newer targeted biologic agents on the incidence and severity of radiation necrosis and cognitive outcomes should be systematically addressed.

Higher functions require input from spatially disparate brain regions, producing a complex interaction between the radiation dose distribution and neurologic outcomes. A recent study demonstrated the utility of diffusion-tensor tractography in assessing the tolerance thresholds for different neurologic tracts (67).

The designation and avoidance of “key” areas of the brain is needed. For instance, the role of the hippocampus in memory formation has recently been emphasized, encouraging clinicians to limit the radiation dose to it (62). The efficacy of such approaches has not yet been proved. Also, a quick and sensitive test for neurocognitive function that can be included in clinical studies is needed.

The best method to obtain quality long-term follow-up data would be the creation of an international registry to gather and relate demographic factors, diagnoses, co-morbidities, baseline imaging findings, other treatment modalities, and the three-dimensional isodose distribution (with or without biospecimens) to outcomes. A National Cancer Institute-sponsored institution such as the Radiation Therapy Oncology Group would be well suited for both data collection and analysis.

## 10. TOXICITY SCORING

The Common Terminology Criteria for Adverse Events, version 4.0, is recommended as a tool for scoring neurocognitive dysfunction. Long-term follow-up (*e.g.*,  $\geq 5$  years) might be necessary to detect neurologic/cognitive decline. Prospective RT studies should incorporate formal neurocognitive assessments. Future studies reporting RT brain toxicity should provide a clear definition of toxicity, detailed normal brain dose–volume information, the use of repeat RT and systemic treatments, and should report toxicity as an actuarial (as opposed to a crude) rate. We recommend adoption of the “volume receiving 12 Gy” as the standard method of reporting the dose to the normal brain in radiosurgery procedures. The location should also be reported.

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