Chapter 24 – Retreatment after Radiotherapy

12/5/2024

Factors to consider

1. The **dose and volume** treated during the initial radiotherapy and the extent to which the retreatment fields overlap with the initial fields
2. Whether **chemotherapy** was added to the initial radiotherapy
3. The **time interval** that has elapsed since the initial therapy
4. The **tissues and organs** involved because they differ markedly in their ability to recover
5. **Highly conformal techniques**, such as stereotactic radiosurgery, stereotactic body radiotherapy (SBRT), or brachytherapy, are most appropriate
6. Whether there are **alternative options** to radiation that could be considered

Pre-Clinical Data – Early Responding Tissue

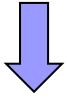
Early Skin Reaction – Rodent

- Radiation-induced skin damage can recover well, with restoration of almost full radiation tolerance
- Recovery occurs quickly after low doses, but more slowly as the initial dose is increased

Pre-Clinical Data – Early Responding Tissue

Early Responding Tissue

- Self-renewing tissues characterized by a rapidly proliferating stem cell compartment
- If some stem cells survive within the irradiated volume, or if undamaged stem cells can migrate into the irradiated volume from outside, the tissue architecture may be partially or completely restored



Rapidly proliferating tissues generally recover well from the initial radiotherapy and will tolerate re-irradiation to almost full doses, provided sufficient time is allowed

Pre-Clinical Data – Late Responding Tissue

Late Skin Fibrosis – Rodent

- Using hind limb deformation as an endpoint, representing late subcutaneous fibrosis, much poorer retreatment tolerance was observed

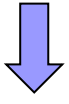
Myelopathy – Rodent & Rhesus Moneys

- Retreatment with reduced doses is possible after an interval of 3 to 6 months
- 44 Gy/22 fx $\rightarrow$ 57.2 Gy-66 Gy: only 4 of 45 moneys developed myeloparesis (1-3 yr interval b/w courses)

Pre-Clinical Data – Late Responding Tissue

Late Responding Tissue

- Late responding tissues do not have a rapidly proliferating stem cell compartment
- Some tissues do have mitotic activity (review Casarett's classification)

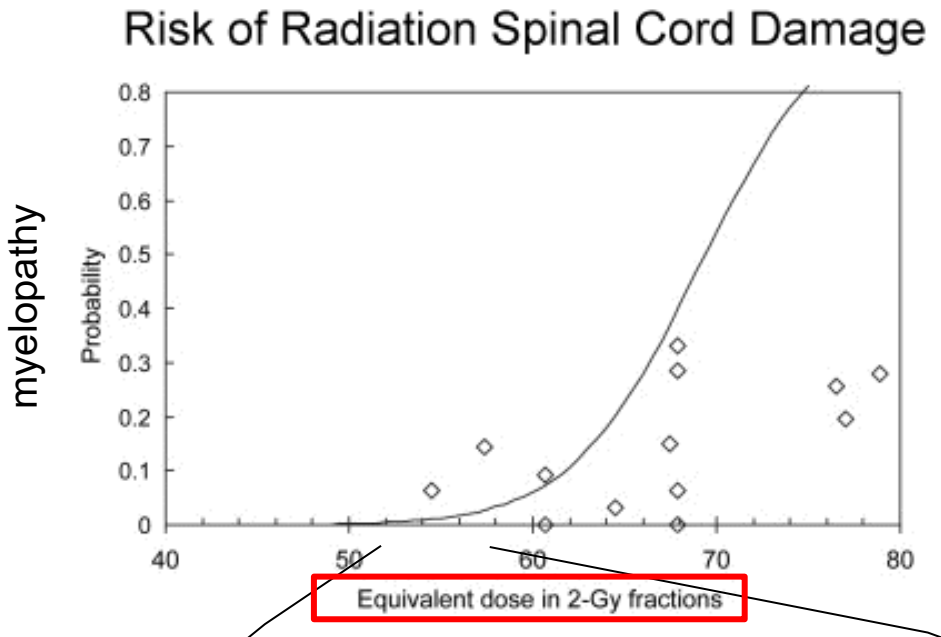


- Most late-responding tissues are much less able to tolerate retreatment because they do not have the ability to recover from the initial damage
- Some slowly proliferating tissues are capable of partial proliferative and functional recovery, although this takes months and some residual damage remains

Clinical Studies

- Unconventional fractionation patterns are often used for retreatment schedules
- It is therefore necessary to express data in terms of **BED**, calculated on the basis of the linear quadratic model, using an α/β of 10 for early-responding tissues and 3 for late-responding tissues
- Alternatively, dose is expressed as equivalent dose of 2 Gy per fraction, i.e., **EQD2**

Spinal Cord – Single Course



Risk < 1% for doses 50-55 Gy

Risk ~ 5% for doses 55-60 Gy

Spinal Cord

22 pts received re-irradiation to the spinal cord; 6 developed myelopathy

Table 2. Clinical Data on Reirradiation Tolerance of the Spinal Cord

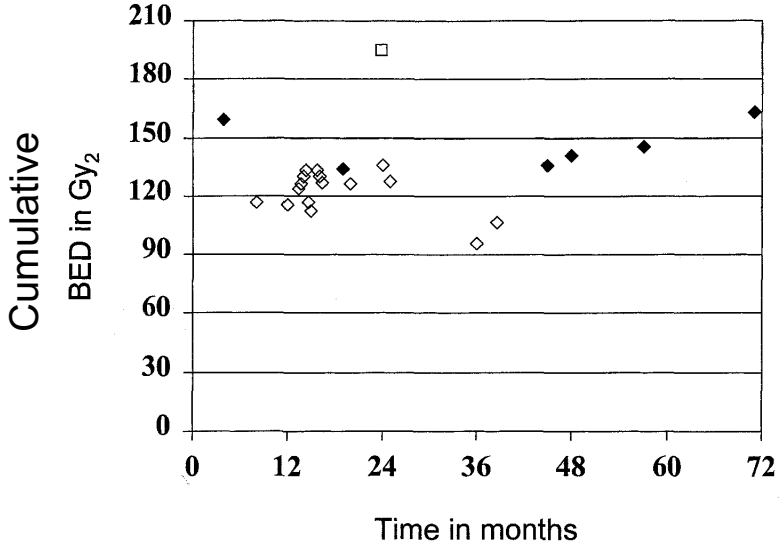
Study	*First Course Dose (BED)*	*Reirradiation Dose (BED)*	*Cumulative BED*	*Interval*
Jackson[11]	45 Gy (90 Gy_2)	24 Gy (43 Gy_2)	133 Gy_2	6 to 48 mo*
	45 Gy (90 Gy_2)	20 Gy (40 Gy_2)	130 Gy_2	6 to 48 mo*
	45 Gy (90 Gy_2)	17 Gy (27 Gy_2)	117 Gy_2	6 to 48 mo*
	45 Gy (90 Gy_2)	20 Gy (40 Gy_2)	130 Gy_2	6 to 48 mo*
	45 Gy (90 Gy_2)	21 Gy (36 Gy_2)	126 Gy_2	6 to 48 mo*
	45 Gy (90 Gy_2)	19 Gy (37 Gy_2)	127 Gy_2	6 to 48 mo*
	45 Gy (90 Gy_2)	20 Gy (34 Gy_2)	124 Gy_2	6 to 48 mo*
	45 Gy (90 Gy_2)	21 Gy (43 Gy_2)	133 Gy_2	6 to 48 mo*
	45 Gy (90 Gy_2)	15 Gy (23 Gy_2)	113 Gy_2	6 to 48 mo*
Bauman[28]	36.8 Gy (66 Gy_2)	30 Gy (60 Gy_2)	126 Gy_2	20 mo
	30 Gy (50 Gy_2)†	40 Gy (67 Gy_2)†	117 Gy_2	8 mo
Magrini[29]	30 Gy (55.5 Gy_2)	40 Gy (80 Gy_2)	135.5 Gy_2	2 yr
	30 Gy (55.5 Gy_2)	30 Gy (60 Gy_2)	115.5 Gy_2	1 yr
	30 Gy (55.5 Gy_2)	20 Gy (40 Gy_2)	95.5 Gy_2	3 yr
	30 Gy (55.5 Gy_2)	27 Gy (51.3 Gy_2)	106.8 Gy_2	3 yr
	30 Gy (55.5 Gy_2)	36 Gy (72 Gy_2)	127.5 Gy_2	2 yr
Wong[30]	42 Gy (102 Gy_2)	14 Gy (32 Gy_2)	134 Gy_2	19 mo
	20 Gy (33 Gy_2)	43 Gy (108 Gy_2)	141 Gy_2	48 mo
	16 Gy (42 Gy_2)	22 Gy (103 Gy_2)	145 Gy_2	57 mo
	48 Gy (102 Gy_2)	18 Gy (34 Gy_2)	136 Gy_2	45 mo
	31 Gy (56 Gy_2)	30 Gy (107 Gy_2)	163 Gy_2	71 mo
	21 Gy (56 Gy_2)	36 Gy (103 Gy_2)	159 Gy_2	4 mo

NOTE. Patients reported in 4 studies. None of the patients in the first 3 series, but all 6 patients of the last series developed radiation myelopathy; all data are included in Fig 1.
*Exact interval unknown (range 6 to 48 months, median 15 months).
†Two fractions per day.

- Re-irradiation is quite safe when the initial dose did not exceed 90 Gy_2
- However, the spinal cord tolerance is lower when the 1st or 2nd course exceeds 100 Gy_2

Nieder & Ang 2000

Spinal Cord



- In patients with long-term follow-up, a cumulative BED of **130-135** Gy_2 appears to be a threshold for detection of electrophysiological abnormality
- There is no or little additional recovery after more than 24 months

Spinal Cord

Time interval b/w the courses RT must be considered; majority > 6 mo

Table 3. Summary of published reports involving reirradiation of the spinal cord

Institution	Cases of myelopathy/ total patients	Median F/U (months)	BED, initial course, (Gy_3) Median (Range)	BED, reirradiation (Gy_3) Median (range)	Interval between courses (months) Median (range)	Total BED (Gy_3) Median (range)	2- Gy dose equivalent, α/β = 3 Gy Median (range)	2- Gy dose equivalent, α/β = 1 Gy Median (range)
MSK (36)	0/37	8	60 (10–101)	16 5–50	19 (2–125)	79 (21–117)	47 (13–70)	51 (8–100)
VU (37)	0/34		—	—	—	<100	<60	<60
Munich (38, 39)	0/15	30	70 (34–83)	50 (38–83)	30 (6–96)	115 (91–166)	69 (54–100)	70 (48–107)
Mayo (40)	4/54	4*	60	37	10 (1–51)	97	58	62
Cases with myelopathy	4		All 60	73† (29–115)	9 (5–21)	133 (109–175)	80 (65–105)	83 (69–89)
Henry Ford (41)	0/1	60	75	72	144	147	88	86
UCI (42)	0/1	8	75	42	37	117	70	67
Ontario (43)	0/2	>3–9	(40–56)	(18–35)	(8–20)	(58–91)	(35–57)	(28–51)
VU (44)	0/8		56 (29–78)	42 (36–83)	30 (4–152)	106 (65–159)	64 (39–96)	69 (48–93)
Brescia (45)	0/5	168	47 (32–47)	55 (33–67)	24 (12–36)	94 (80–113)	57 (48–68)	56 (47–67)
Hamburg (46)	0/62	12	29 (29–47)	29 (29–47)	6 (2–40)	69 (59–77)	41 (35–46)	53 (48–57)
Melbourne (47)	0/6	15	All 73	36 (32–39)	15	106 (103–109)	63 (62–65)	66 (64–68)
Princess Margaret (48)	11/–	11	72 (28–96)	42 (14–86)	11 (2–71)	115 (100–138)	69 (60–83)	80 (65–94)
Cases with myelopathy								
Stereotactic body radiotherapy								
Korea (49)	1/3	24	(60–81)	(64–154)	(18–120)	(145–235)	(87–141)	(98–179)
Case with myelopathy	1		81	154	18	235	141	179
No myelopathy	2		60, 81	64, 90	54, 120	145, 150	87, 90	98,114

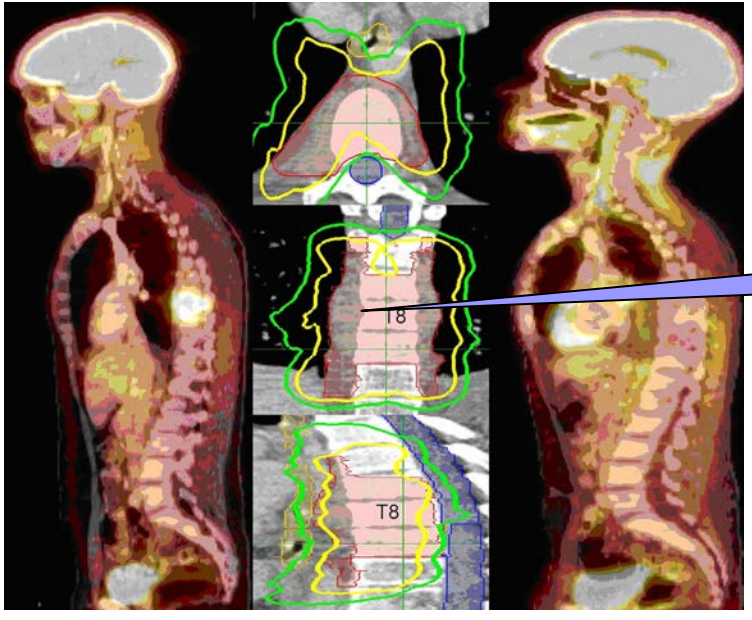
* Overall survival.
† One patient received two courses of reirradiation, 1 received three courses.

Note very few cases of myelopathy with cumulative doses ≤ 60 Gy at 2 Gy equivalent

Int. J. Radiation Oncology Biol. Phys., Vol. 76, No. 3, Supplement, pp. S42–S49, 2010

Spinal Cord – SBRT

39 pts with 60 spine metastases; all treated with SBRT; 37 metastases were re-irradiation



PTV 30 Gy isodose 20 Gy isodose

Highly conformal SBRT makes it possible to retreat spinal cord without unacceptable toxicity

1st course – 30 Gy in 10 fx to T9-L1
Re-treatment – 30 Gy in 5 fx to T8

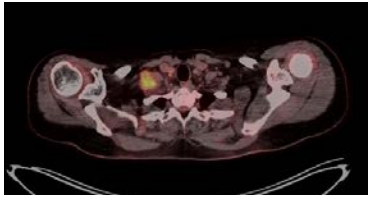
Outcome

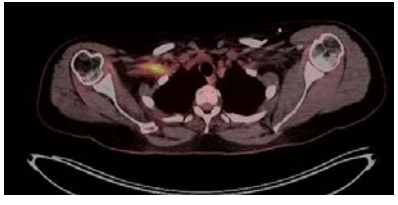
- In 6 of 8 failures, the minimum distance from the tumor to the thecal sac was ≤ 1 mm
- Among 39 metastases which had 6 mo follow up, no radiation-induced myelopathy or radiculopathy occurred

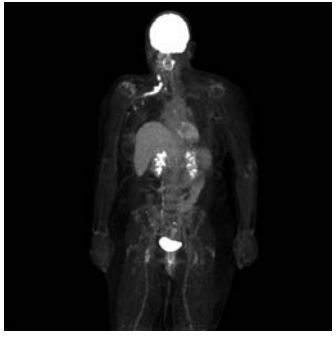
Sahgal 2009; IJROBP 74:723-731

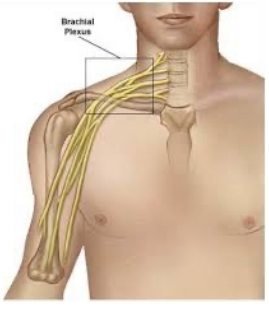
Case Study – Patient WJ

- 52 yo F
- 2016 – triple negative R breast cancer; treated with neoadjuvant chemo followed by breast surgery and adjuvant radiation therapy
  - 50.4 Gy in 28 fractions to the right breast, axilla, supraclav followed by a boost of 10 Gy in 5 fractions to the lumpectomy cavity (completed 06/2017)
- 05/2022 – developed brain metastasis; treated with GK SRS
- 07/2022 – FDG uptake in the right supraclav fossa infiltrating into the muscle; right shoulder numbness/pain/weakness; biopsy was consistent with recurrence







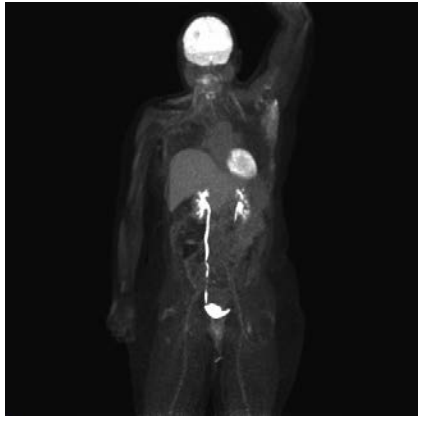


Would you retreat her supraclav? What is the organ at risk?

Case Study

- She had significant pain and no use of the right arm
- 12/2022-1/2023 – 1.2 Gy BID x 30 fx over 3 weeks to a total dose of 36 Gy
- PET/CT showed complete resolution of the FDG uptake in the right supraclav
- Pain improved though still no range of motion
- She developed additional brain metastases and received GK SRS, last in 12/2023

PET 08/2024



Re-Irradiation

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Locally recurrent head and neck malignancies after definitive radiation or chemoradiation represent challenging clinical scenarios requiring careful consideration of individualized risks and benefits before deciding upon the next best course of th...

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Treatment of recurrent gliomas is especially challenging, as many of these patients have previously been treated with extensive surgery, radiation, or systemic therapy. Due to this, the optimum therapy for patients with recurrent glioma is controv...

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Pages 253-261. Simone, Charles B., MD, FACRO, Plastaras, John P., MD, PhD, Jabbour, Salma K., MD, Lee, Anna, MD, MPH, Lee, Nancy Y., MD, FASTRO, Choi, J. Isabelle, MD, Frank, Steven J., MD, Chang, Joe Y., MD, PhD, FASTRO, and Bradley, Jeffrey, MD, FASTRO, FACR.

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