Normal Tissue Effects: Retreatment

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Learning Objectives

- Understand the response of normal tissues to re-irradiation
- Use concepts of radiobiology to identify low risk vs. high-risk scenarios for re-irradiation
- Be able to suggest strategies to mitigate risks if re-irradiation is to occur
- Apply learned concepts to clinical retreatment decision making → tomorrow's workshop

Outline

- Cases to illustrate low vs. high-risk re-irradiation scenarios and introduce important concepts
  - Dose dependence
  - Time interval dependence
  - OAR dependence

- Model of OAR response to radiotherapy

- Evidence on re-irradiation
  - Radiobiology research
  - Clinical research

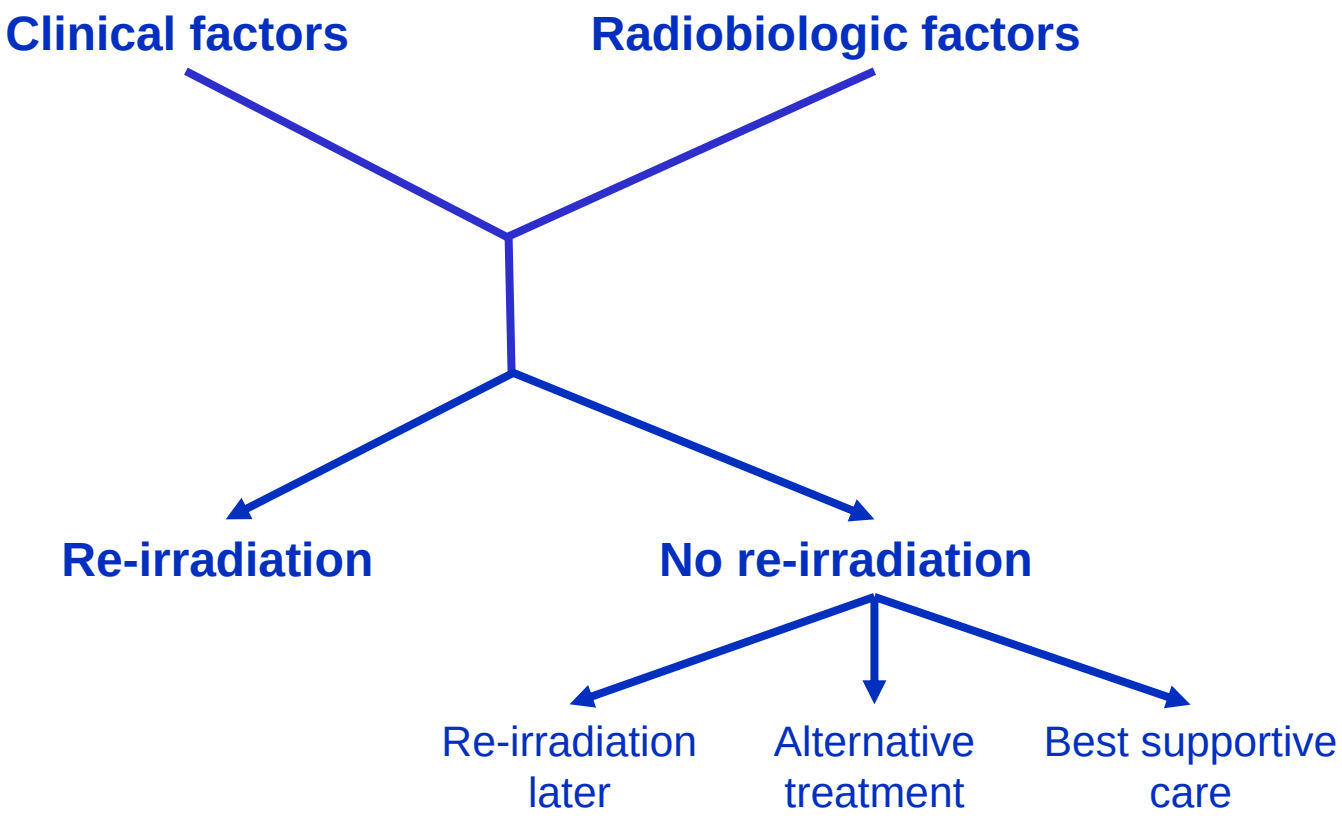
Why Re-irradiate?

- Despite usually giving a maximal effective and safe dose with the initial radiotherapy course, recurrences can still happen
- Local recurrence or marginal recurrence can sometimes be managed safely with surgery or systemic therapy, but often these are not feasible
- Radiation oncologists are often called on to consider re-irradiation in these situations, as these recurrences often become symptomatic and potentially life-threatening
- Have to weigh the risks of re-irradiation against the risks of doing nothing

Why is Re-irradiation Problematic?

- OARs close to the previous prescription dose volume might have received a dose already close to maximum tolerance
- Exceeding tolerance not only leads to worse acute toxicity, but also to more likely and severe late toxicity, which can also be significantly symptomatic or life-threatening
- As patients live longer with better treatments, requests for re-irradiation are likely to become more frequent
- **Navigating the competing risks of disease progression and radiation toxicity is very challenging – we need an approach**

Systematic Approach to Re-irradiation



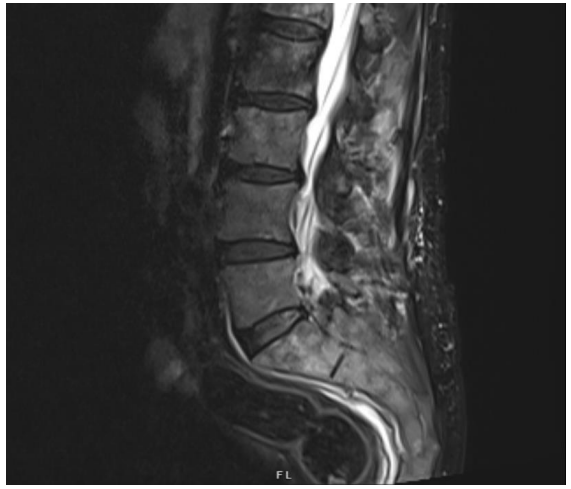
Clinical Factors for Consideration

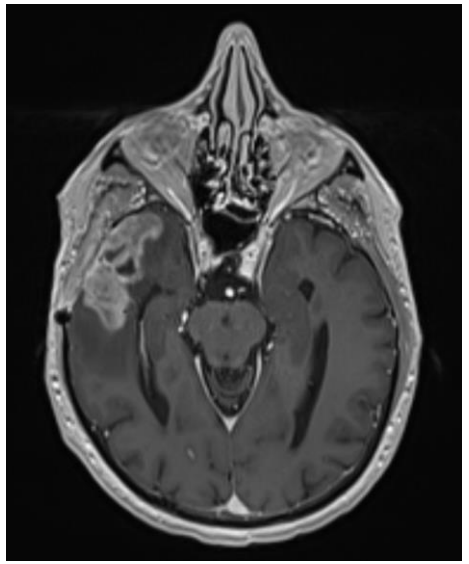
- Alternative treatment options
  - surgery
  - systemic therapy
  - interventional radiology procedures
  - endoscopic interventions
- Curative or palliative intent
  - affects choice of dose/fractionation
- Acute and late effects from previous RT
  - a surrogate measure of baseline patient radiosensitivity
- Other clinical issues
  - patient performance status and prognosis – limited prognosis might argue against aggressive re-irradiation, but may also mean that late effects are less likely to be experienced
  - patient preference

Radiobiologic Factors for Consideration

- OARs involved for re-irradiation
- Previous RT effective dose to at-risk OARs
- Re-irradiation effective dose to at-risk OARs
- Volume of re-irradiation
- Time interval from previous RT

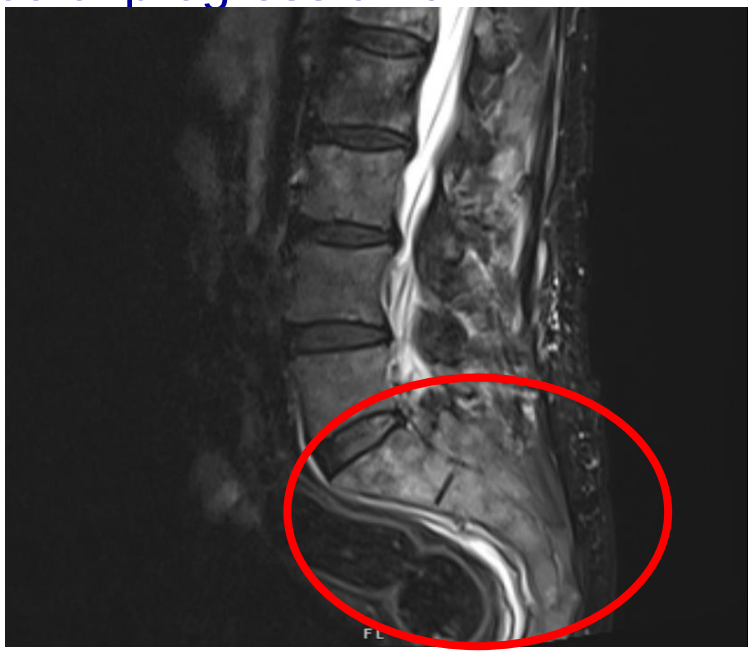
Cases





Scenario 1

- 70 y/o patient presented with diffuse bony metastases from a metastatic prostate cancer
- Received 20/5 APPA to lumbosacral spine and pelvis in June 2020 with good pain relief
- Developed castrate resistance, now with recurrent pain in sacral area with evidence of progression on MRI



- Very common scenario in palliative radiotherapy

Clinical Considerations

- Alternatives:
  - Pain medication only: will need more and more
  - Systemic therapy: likely too slow to take effect
  - Surgery: not feasible
- Indication:
  - Palliative intent – low doses sufficient
- Previous side effects:
  - Patient had mild nausea with previous RT, well controlled with ondansetron. No late side effects
- Other clinical issues:
  - Patient being considered for chemo soon, wants shorter treatment and a quick start

Radiobiologic Considerations

- OARs most at-risk: cauda and small bowel
- Previous RT dose:
  - 20/5: 30 Gy EQD2 (α/β=2Gy) or 28 Gy EQD2 (α/β=3Gy)
- Re-irradiation RT dose:
  - Multiple options still possible for effective palliation:
    - 8/1 (21.7 Gy α/β=1.5, 20 Gy α/β=2, 17.6 Gy α/β=3)
      - Total EQD2 50 Gy (α/β=2) or 45.6 Gy (α/β=3)
    - 15/5 (19.3 Gy α/β=1.5, 18.8 Gy α/β=2, 18 Gy α/β=3)
      - Total EQD2 48.8 Gy (α/β=2) or 46 Gy (α/β=3)
- Volume of proposed re-irradiation:
  - Entire sacrum, likely can use smaller field than previous APPA with 4-field or IMRT approach
- Time interval from previous RT:
  - More than 3 years since previous palliative-dose RT. Some degree of OAR recovery would have occurred. Cumulative EQD2s are likely over-estimates

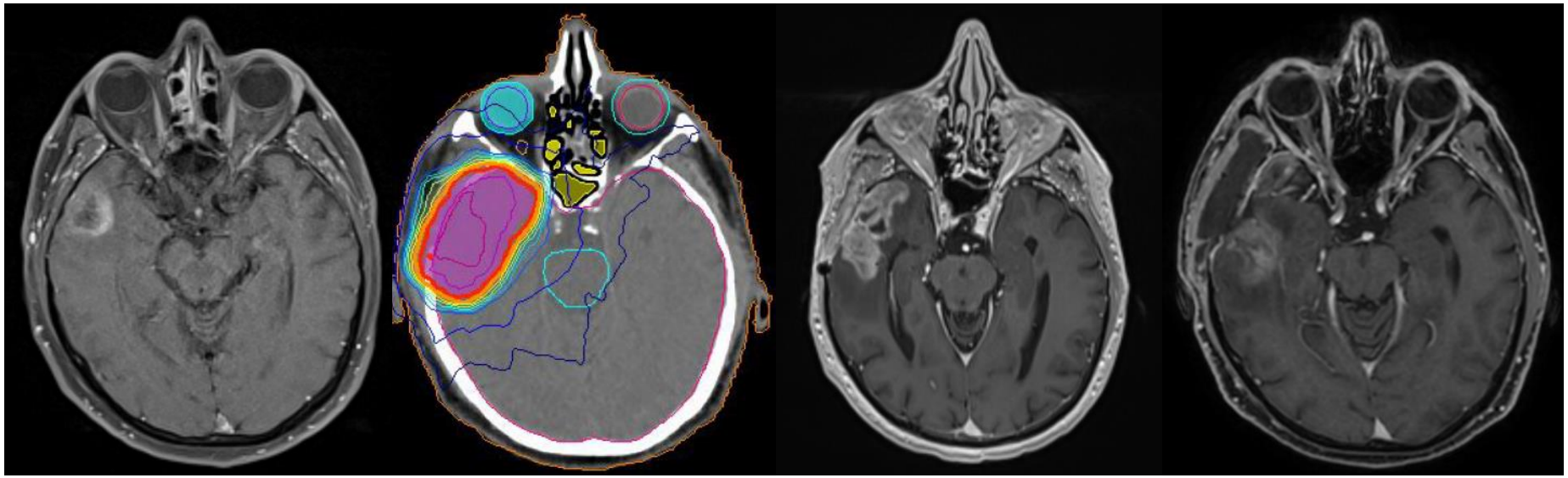
Re-Irradiation Decision

Clinical Factors		**Radiobiologic Factors** OARs: cauda and small bowel	
Alternatives	Pain medications (suboptimal)	**Previous RT dose**	20/5 (moderate)
Indication	Palliative	**Re-irradiation dose**	8/1 vs. 15/5
Previous side effects	Minimal acute or late	**Previous RT volume**	Large
Other considerations	Shorter treatment and quick start	**Re-irradiation RT volume**	Smaller
		Time interval	Long

- **Example of a low-risk re-irradiation scenario**
  - Cumulative EQD2 below max for both OARs (cauda, bowel) even without considering long-term recovery
- What should we do?
  - 8/1
  - 4-field or IMRT

Scenario 2

- 66 y/o patient treated with chemoradiotherapy for a glioblastoma, 60 Gy in 30 fractions completed May 2023.
- Progressive disease noted Mar 2024. The patient had repeat surgery with gross residual disease.



- Glioblastoma is incurable and local recurrence is common. Requests for re-irradiation is also common.

Re-Irradiation Decision

Clinical Factors		**Radiobiologic Factors** OARs: brain, optic pathway, cochlea	
Alternatives	Chemotherapy alone (likely not effective)	**Previous RT dose**	60/30 (already brain max), optic nerve received up to 54Gy
Indication	Palliative – GBM is incurable	**Re-irradiation dose**	30-35/10
Previous side effects	Within normal limits. No radiation late effects noted	**Previous RT volume**	Tumour + large normal brain margin
Other considerations	Patient is ECOG1-2, persistent headaches and seizures after surgery	**Re-irradiation RT volume**	Residual tumour only
		Time interval	Short, limited recovery

- Higher risk re-irradiation scenario, but benefits still likely outweigh risks
- Limited prognosis of recurrent GBM may actually decrease the impact of late effects (e.g. radionecrosis) as late effects may not have sufficient time to manifest. This can leave patients with more of the beneficial effects of re-irradiation in the time they have left

Mitigation Strategies

- Reduce re-irradiation dose
  - Choose an effective regimen with the lowest cumulative EQD2 for the OARs of concern
  - Avoid full-dose re-irradiation if possible
- Reduce re-irradiation volume
  - In all re-irradiation scenarios, attempt to limit volume of re-irradiation to the minimum – this helps limit OAR dose
  - Limit the CTV margin, and use 0 CTV margin if appropriate
  - Try to limit PTV with better immobilization
  - Use conformal techniques if logistically feasible
  - Reduce coverage criteria, if necessary (e.g. 95% PTV by 90% Rx dose instead of 95%)
- Delay re-irradiation if possible
  - Explore alternative options first
  - In the palliative setting, wait until symptoms are imminent or present

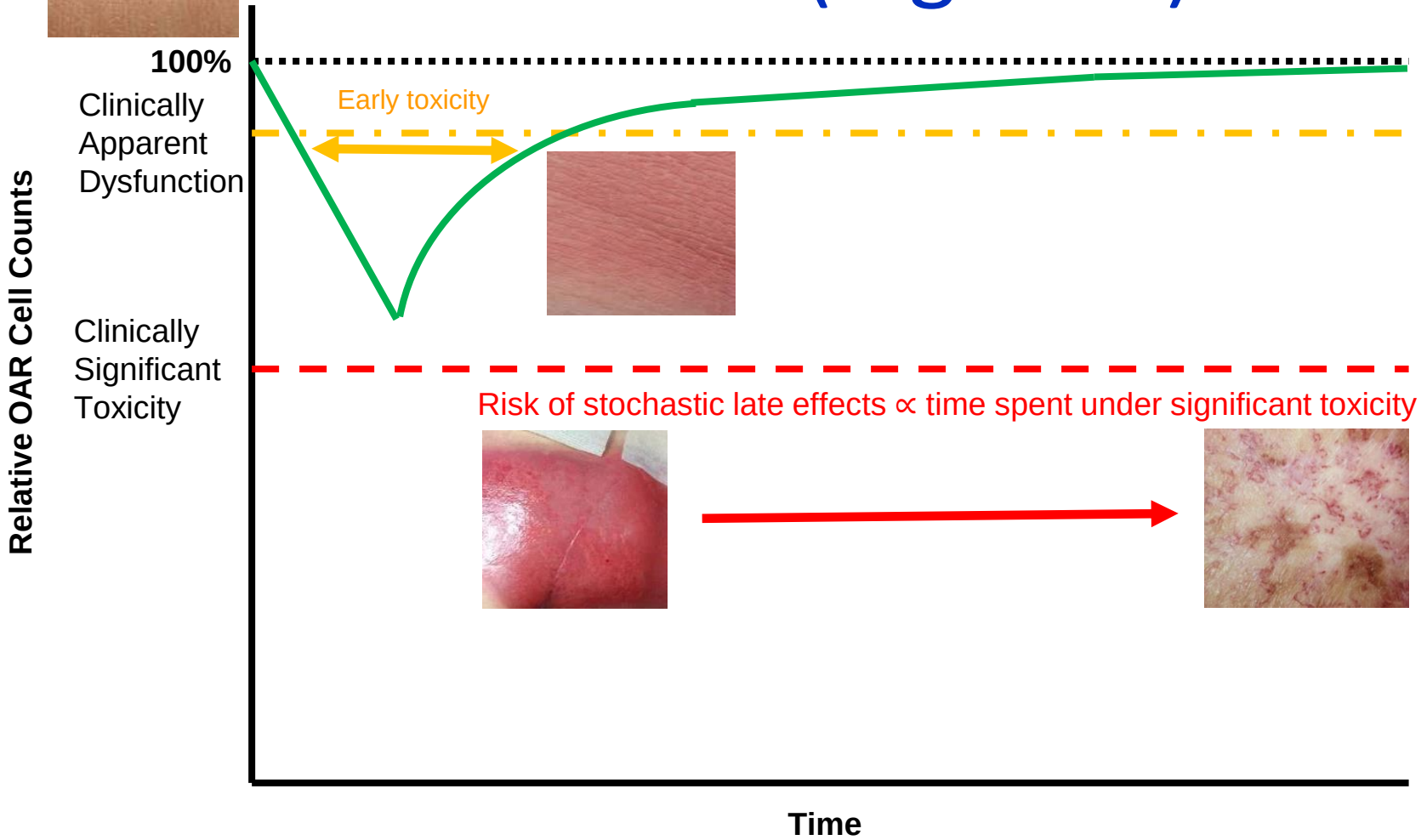
Radiobiological Model for OAR Damage

- Clinical OAR toxicity is a consequence of cell loss from radiation
  - More radiation -> more cell loss -> more clinically apparent toxicity

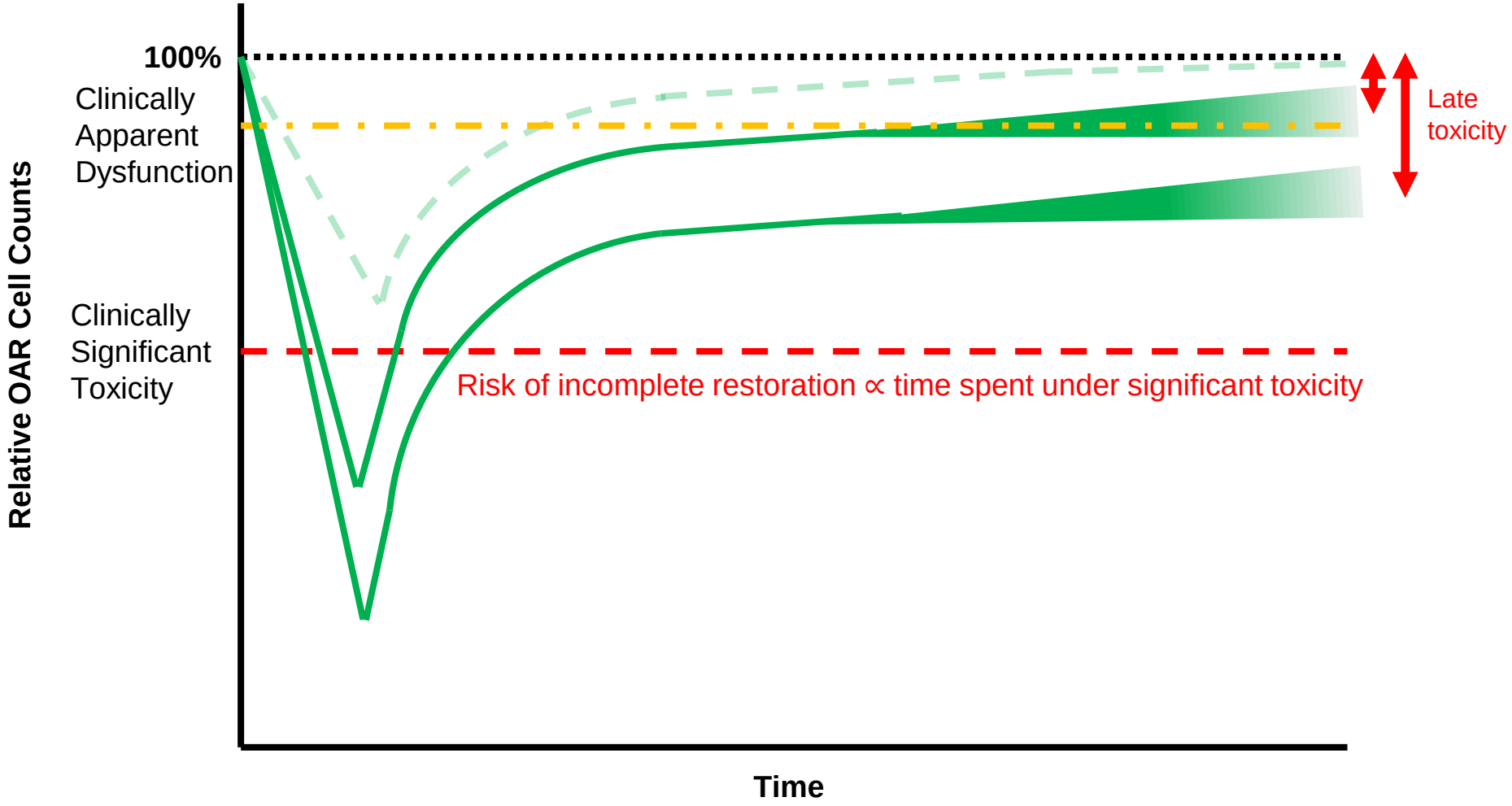
- OARs have an inherent capacity to restore radiation damage over time, and that such capacity is different for different types of OAR and different types of toxicity
  - Incomplete restoration = chronic OAR toxicity

- We hypothesize that the impact of re-irradiation on clinical OAR toxicity depends on the degree of restoration from the previous course of radiation, which is influenced by:
  - Previous and re-irradiation dose
  - Timing of re-irradiation

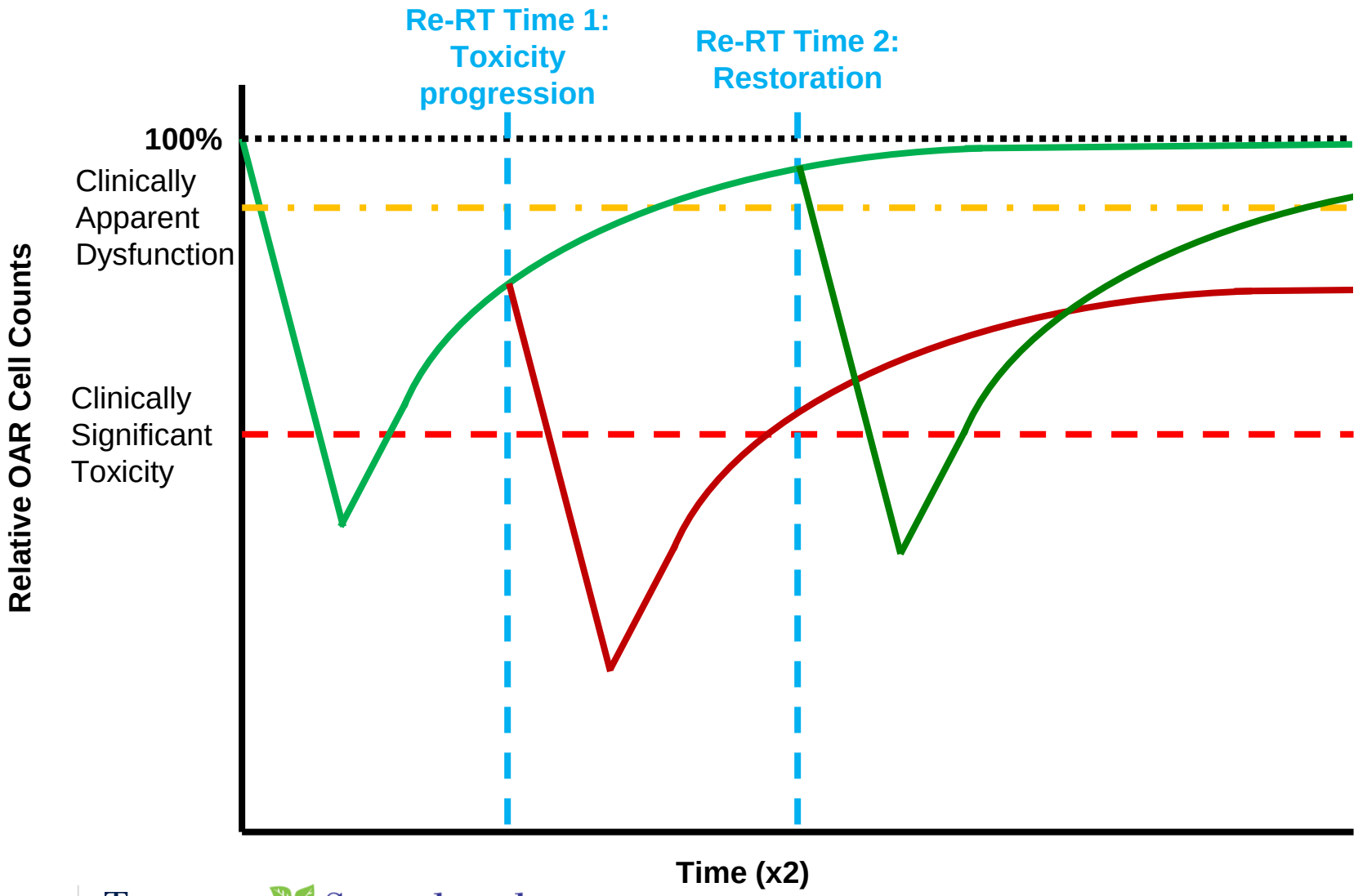
Model of OAR Response
Ideal OAR (e.g. skin)



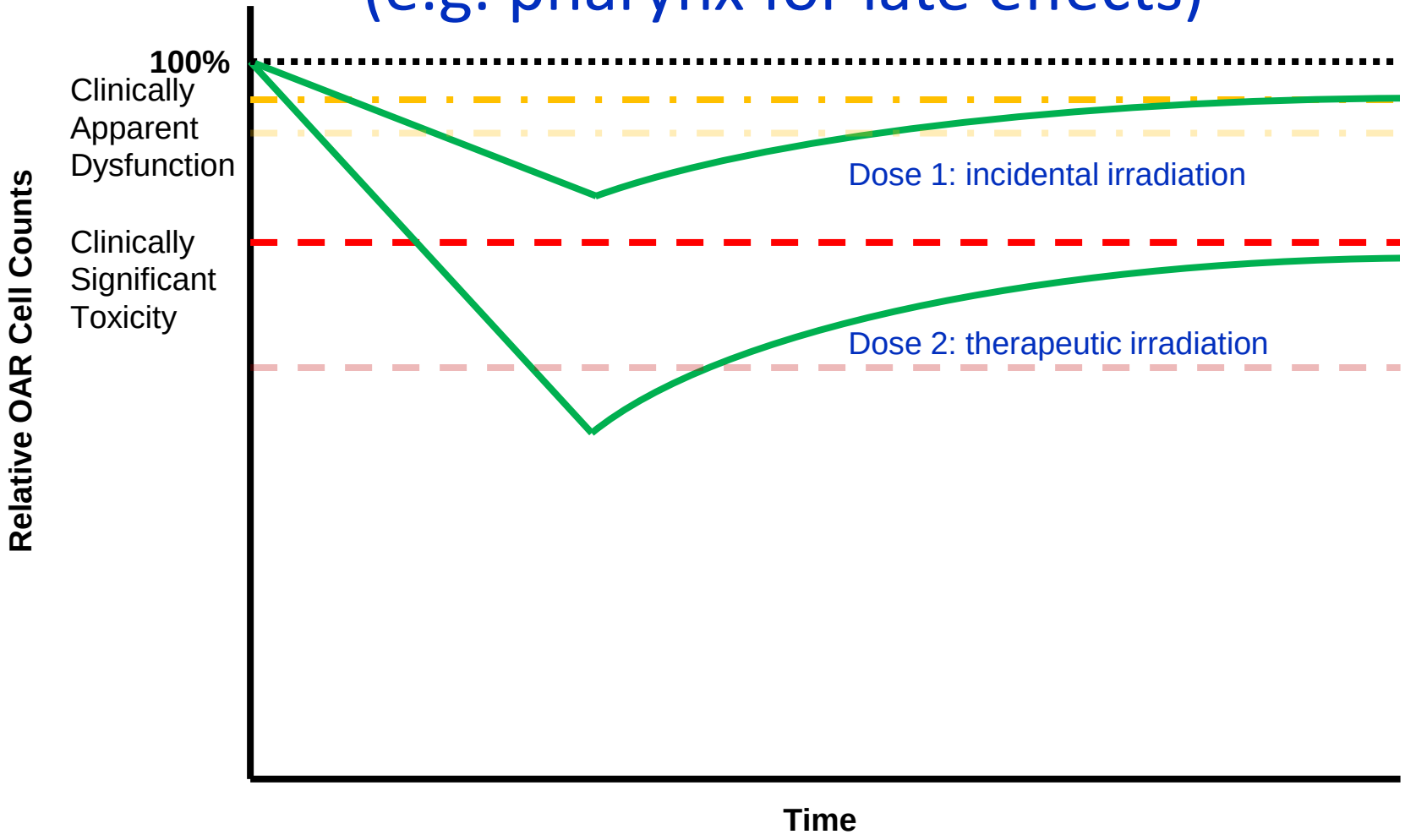
Effect of Dose



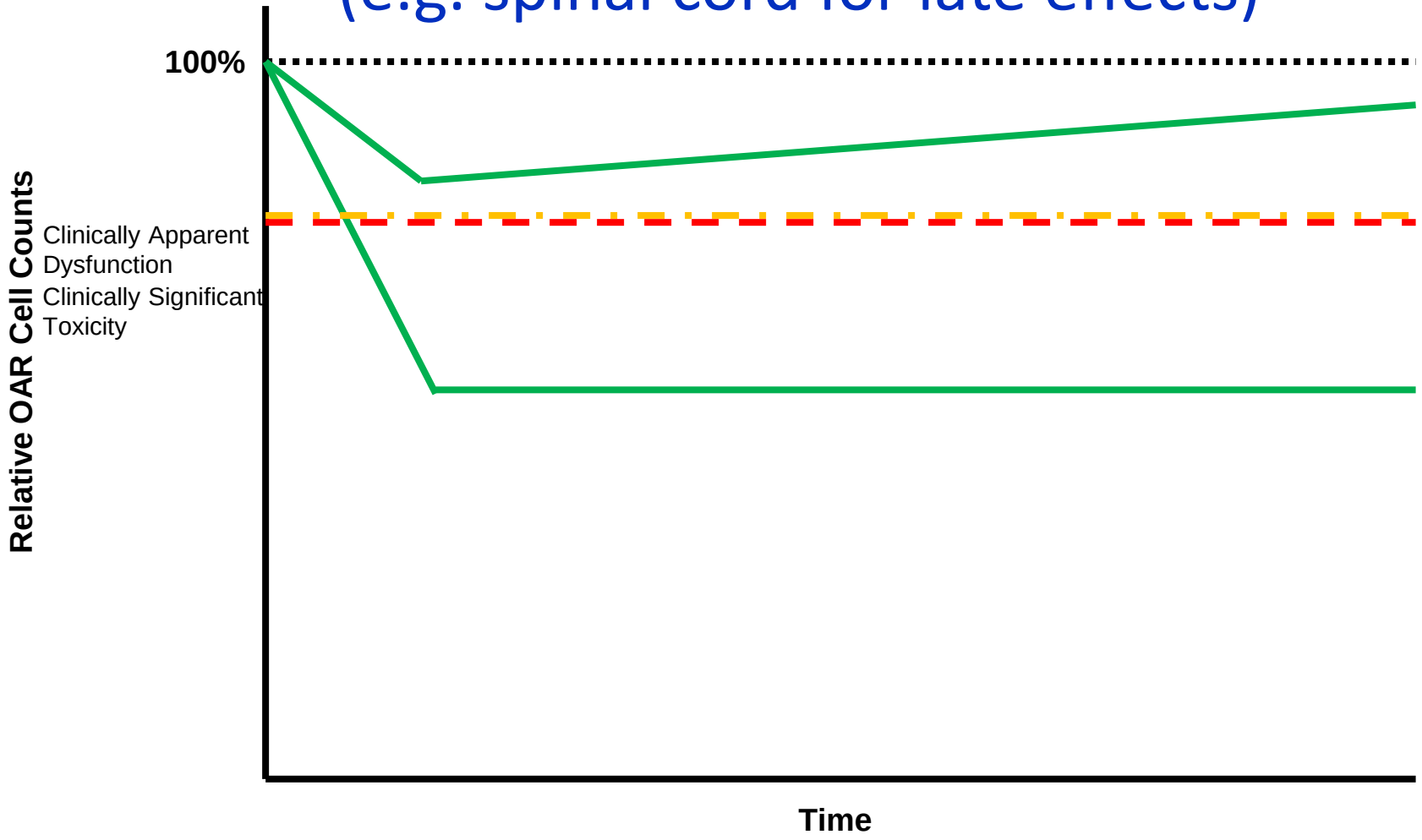
Effect of Time



Effect of OAR
Moderate Restoration Capacity
(e.g. pharynx for late effects)



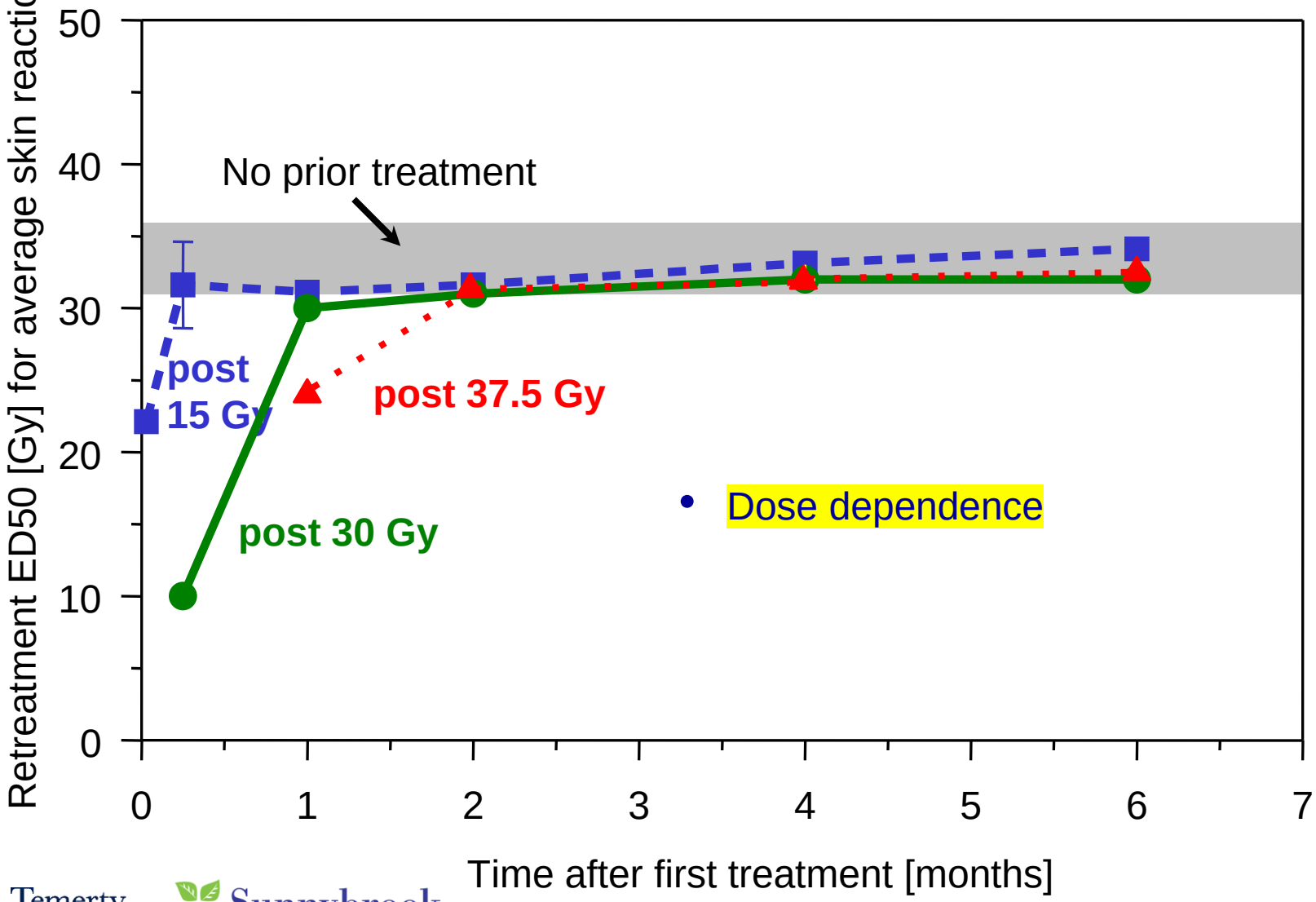
Effect of OAR
Poor Restoration Capacity
(e.g. spinal cord for late effects)



Model of OAR Response

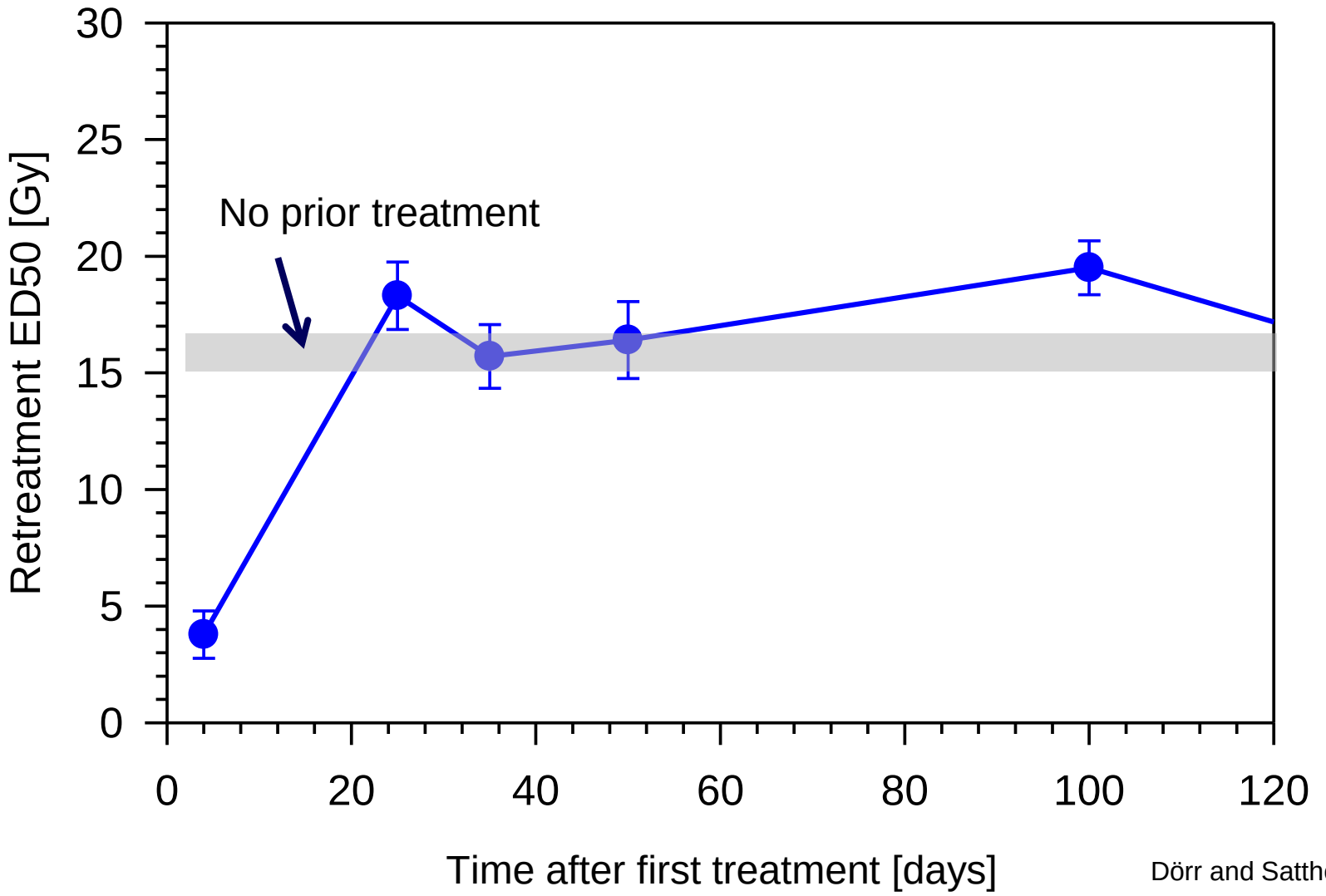
- How well does this mental model fit with experimental observations?
- Radiobiological research has been invaluable in demonstrating the dose, time and OAR-dependence of re-irradiation's early and late effects
- We'll start with early effects

Early skin reactions
mouse foot epidermis



modified from: Terry et al., IJRB 1989

Early mucosal reactions
radiation effects – urinary bladder



Dörr and Satthoff

Early Effects

- If sufficient time is allowed before retreatment, early effects may be completely restored. i.e. early effects with re-irradiation is the same as first-time radiation
  - Oral mucosa: 3-4 weeks
  - Epidermis: 8-12 weeks

Effect of dose

- ↑dose: ↑severity and ↑time to recovery

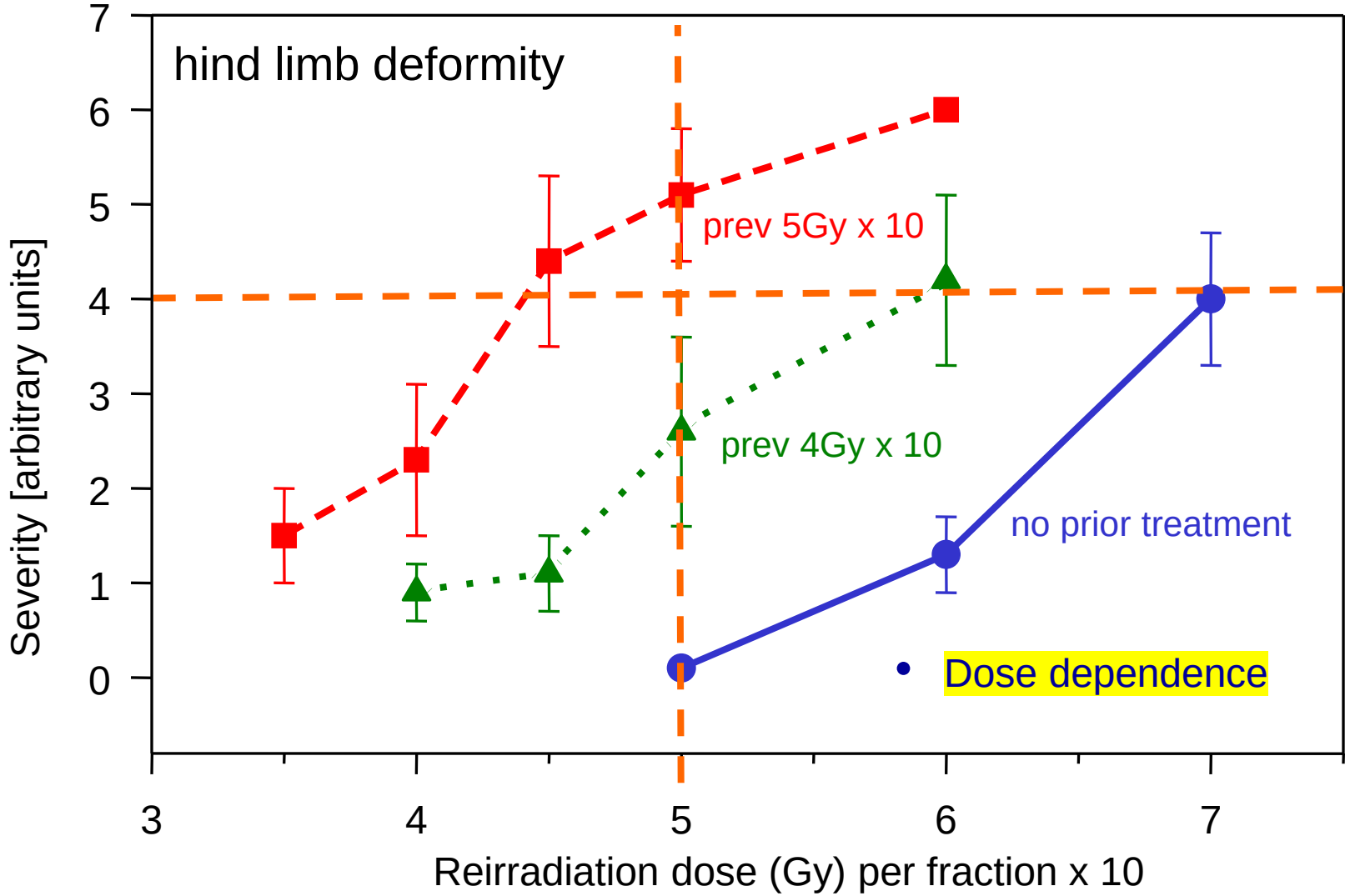
Model of OAR Response

- NB:
  - The response of OAR to radiation depends on both the specific outcome and the timing of that outcome (acute vs. late)
  - e.g. the pharynx can behave as an ‘ideal’ OAR with good capacity for restoration after radiation with regards to acute mucositis, but behave as an OAR with only moderate capacity for restoration with regards to late dryness.

Late Effects

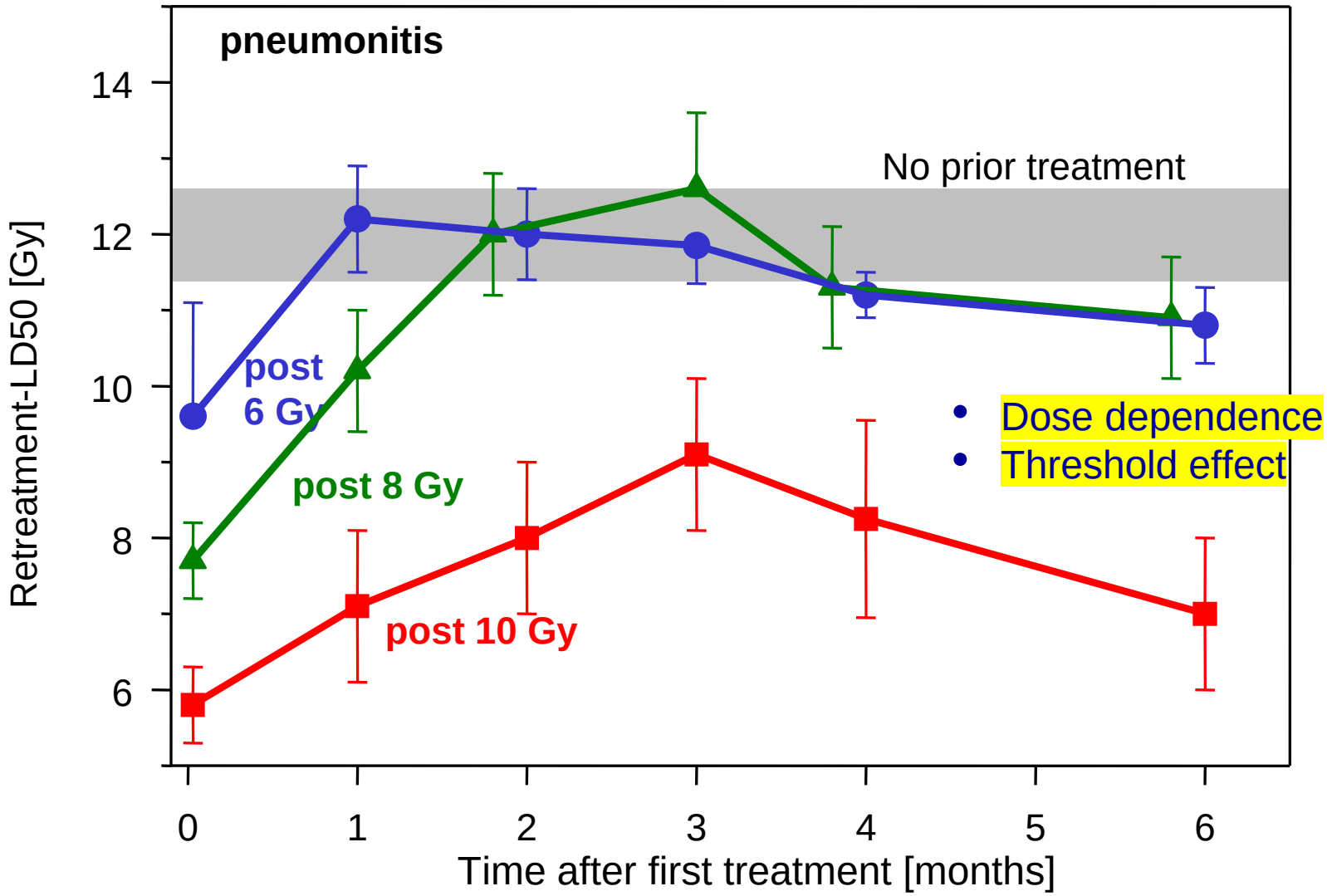
- Late effect risks are dependent on similar factors as early effects
- Restorative capacity for late effects likely more limited, and there may be a threshold effect (dose at which full restoration no longer possible)
- Latent time to expression of stochastic late effects is decreased after retreatment

Late effects – soft tissues



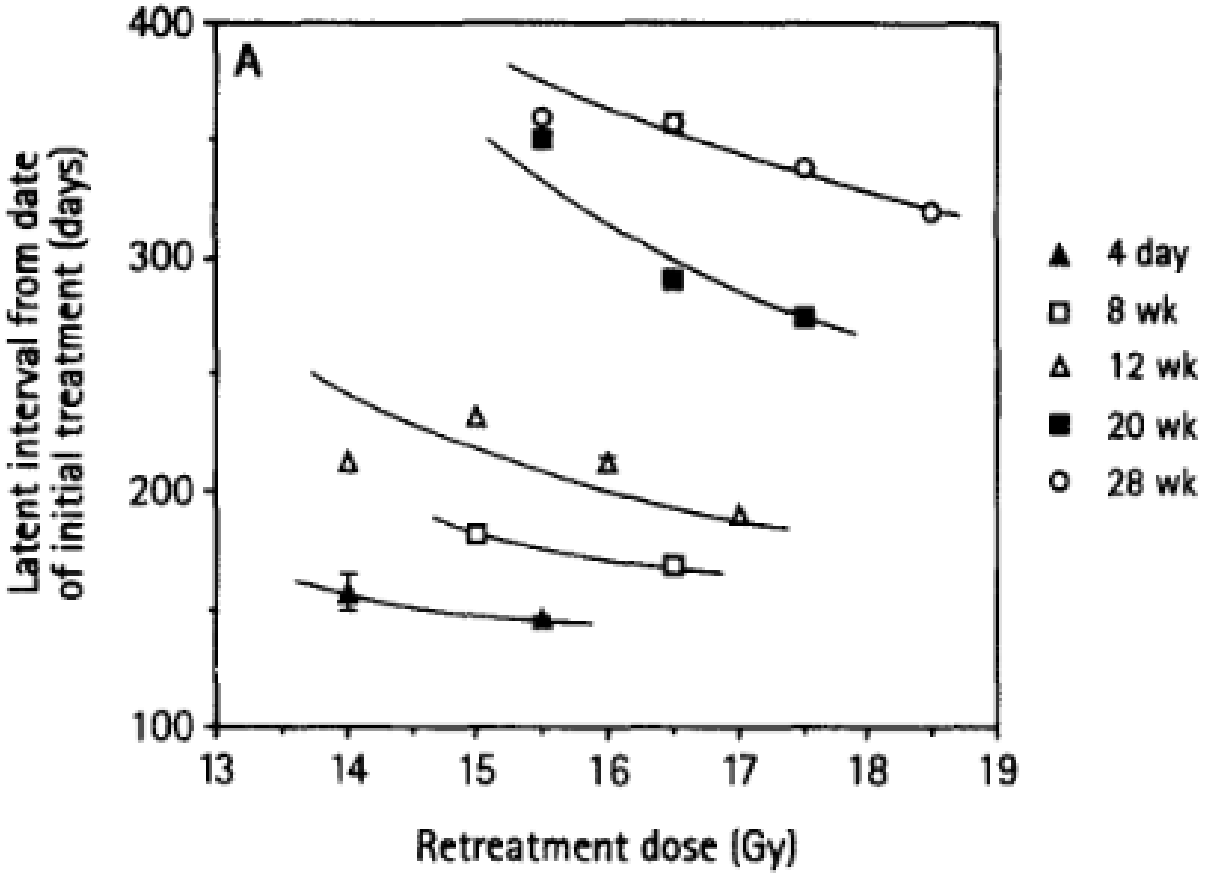
Modified from: Brown and Probert, Radiol. 1975

Late effects - lung



Modified from: Terry et al., IJROBP 1988

Late effects – rat spinal cord

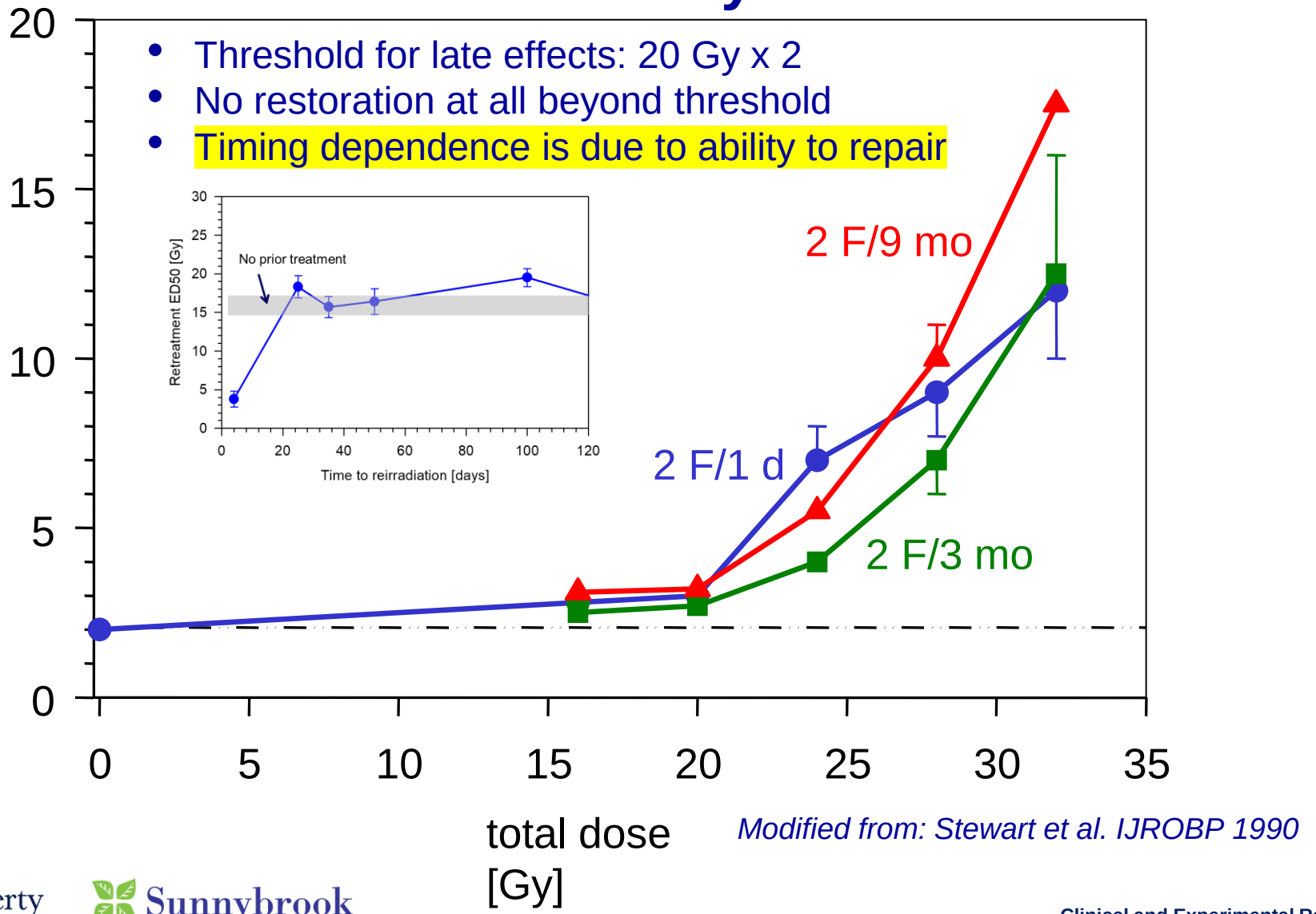


- Timing dependence

- Latency to late effect (forelimb paralysis) longer with longer interval between treatments
- Latency to late effect longer with lower re-irradiation dose
- Effect of re-irradiation dose more noticeable when the interval was longer

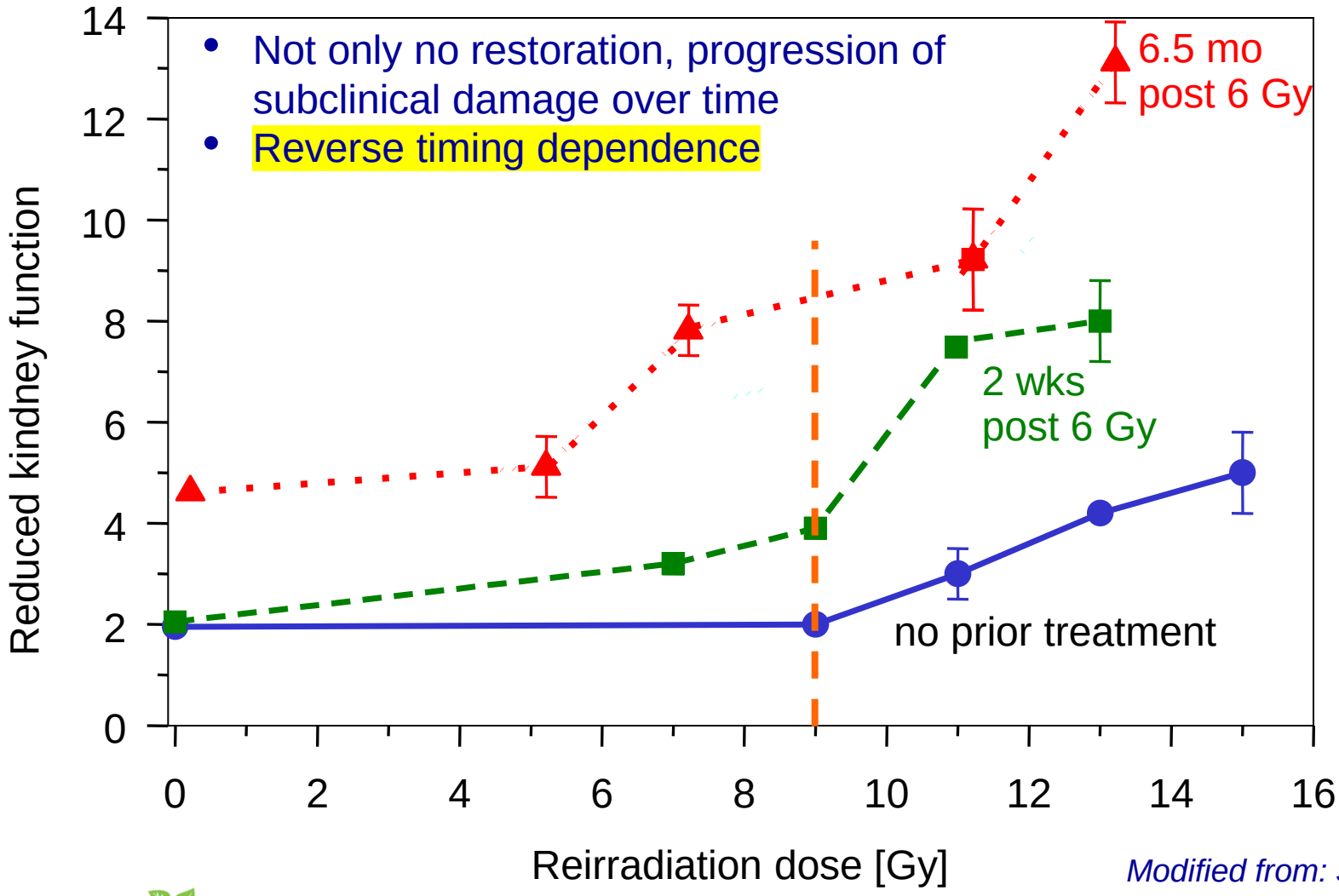
Wong et al. IJROBP 1997

Late effects – urinary bladder



Modified from: Stewart et al. IJROBP 1990

Late effects – kidney



Modified from: Stewart et al. IJRB 1989

Late effects

Effect of dose

- ↑dose: ↑risk and ↓time to late effects
- >threshold dose: incomplete restoration, progression of subclinical damage

Effect of timing

- ↓time between courses: ↑risk and ↓time to late effects for toxicity where repair is possible
- If repair is not possible: no timing dependence
- If damage actually progresses over time: reverse timing dependence
  - Best to give maximum possible dose upfront and avoid reirradiation if at all possible

Late effects

- Even for the same OAR, restorative potential differs for early effects and late effects, with **late effects being less likely to have complete restoration**, and more likely have a lasting effect on the patient

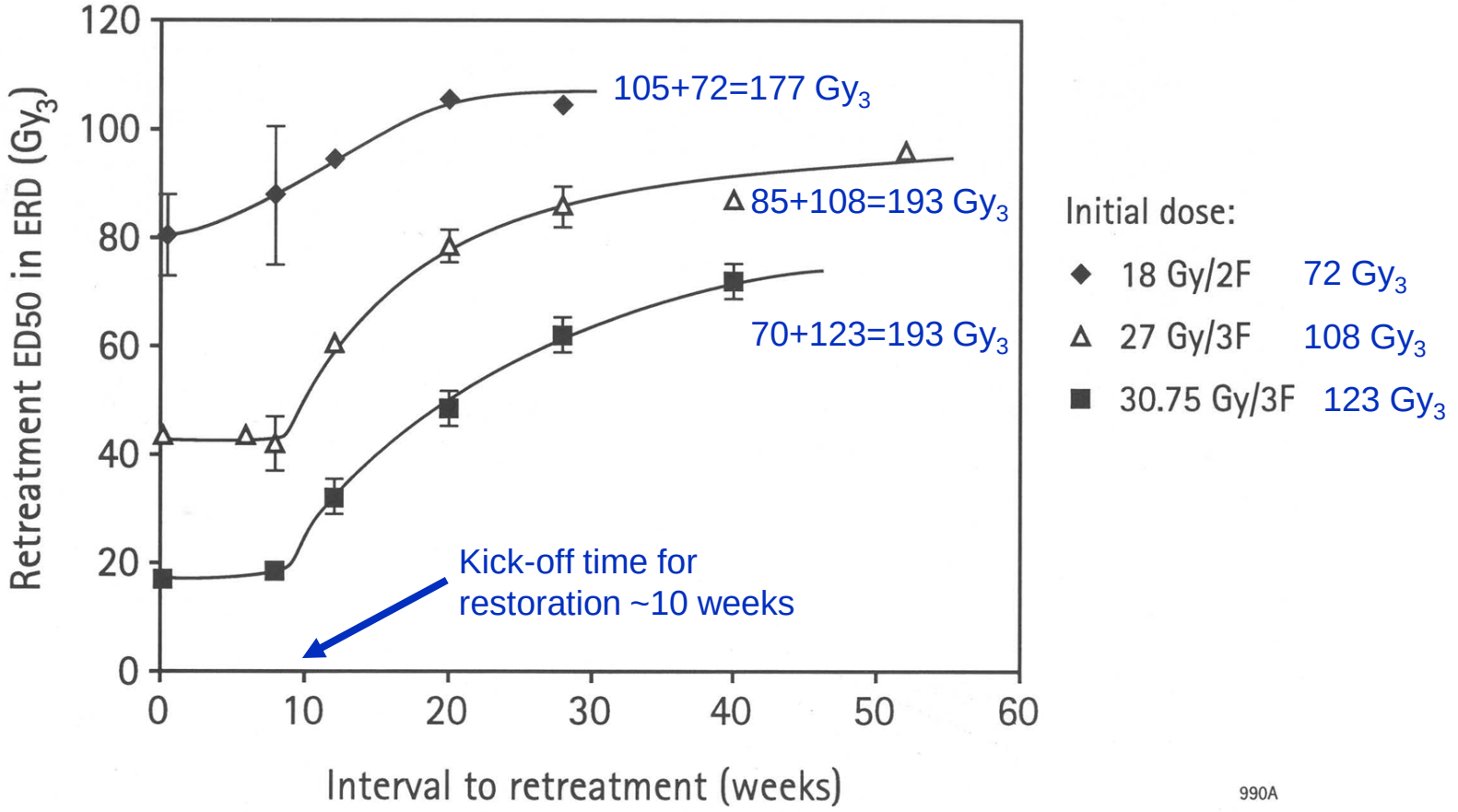
- Main focus for risk of re-irradiation is therefore **late effects**

Late effects: Focus on Spinal Cord

- The Spinal Cord is one of the most frequently irradiated and re-irradiated organs
- Central location makes it difficult to avoid even when not treating in its immediate vicinity
- Palliative radiotherapy for spine bony pain, cord compression and now spine SBRT further increases repeat direct exposure of the spinal cord to irradiation
- Much research has been done to define the radiation and re-irradiation tolerance of the spinal cord, as the much-feared late **radiation myelopathy** can given patients permanent weakness, numbness and/or paresthesias

Spinal cord: Rat Animal Model

Outcome: Forelimb paralysis



Hao & Wong, 1997

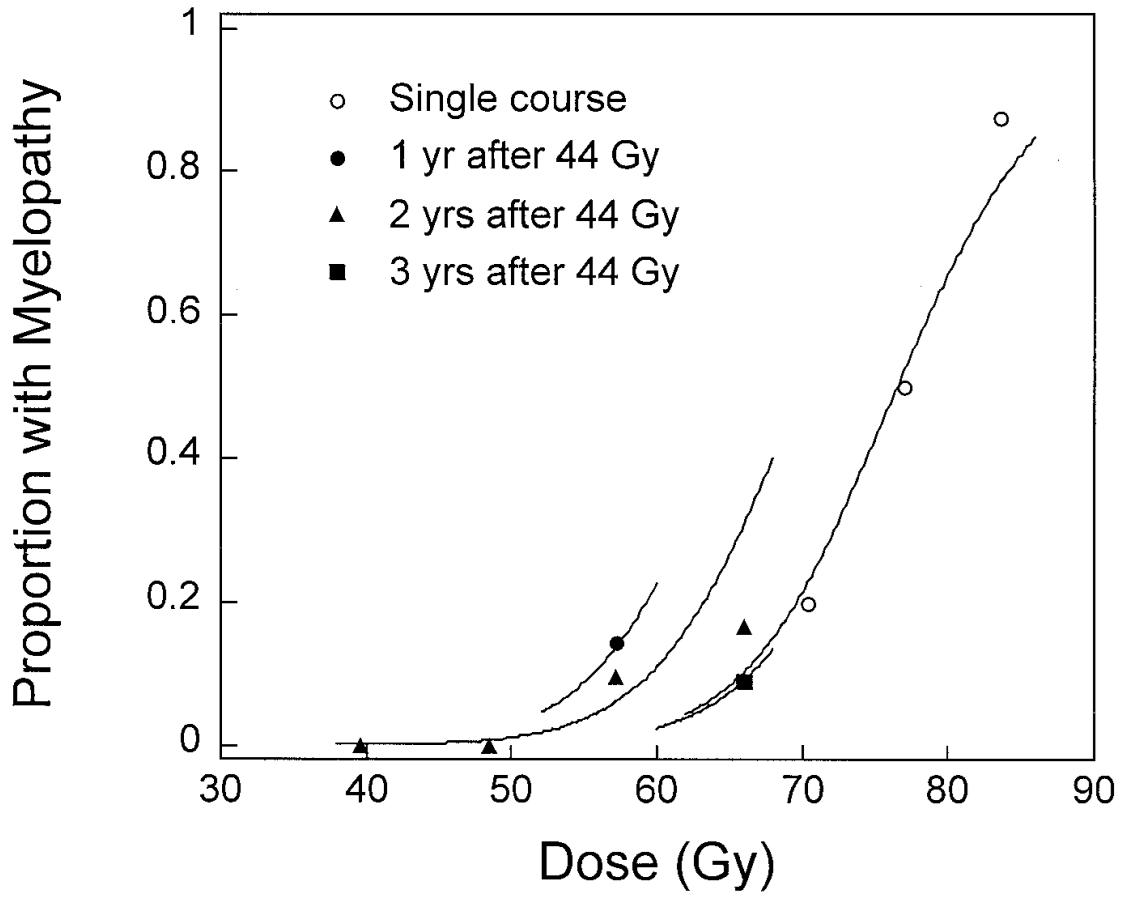
Spinal cord: Rat Animal Model

Estimated α/β value
De novo treatment: 2.4 Gy
Retreatment: 3 Gy

Spinal cord remains sensitive to fractionation in the retreatment scenario, though maybe slightly less than in the de novo setting

Wong et al, Radiother Oncol,1993

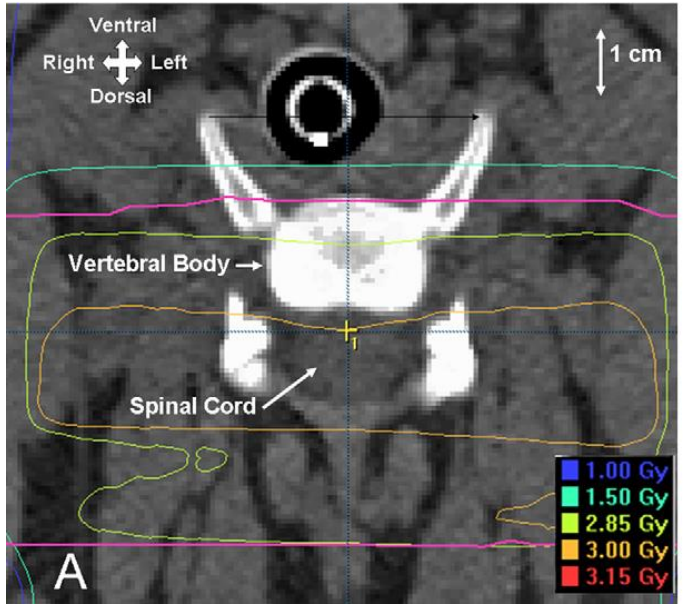
Spinal Cord: Monkey Animal Model

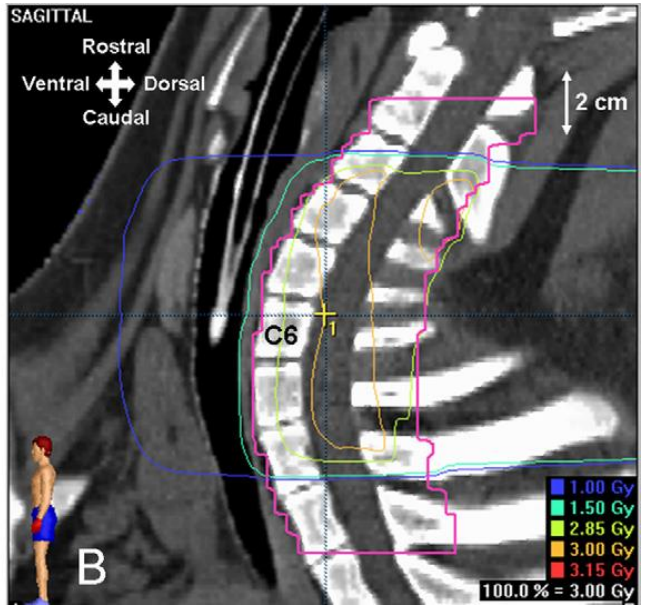


- The 1-year and 2-year after 44 Gy trendlines were shifted to the left – effect of previous RT
- The 3-year after 44 Gy data point was coincident with the no previous RT trendline – complete recovery?
- Spinal cord recovery is very time-consuming

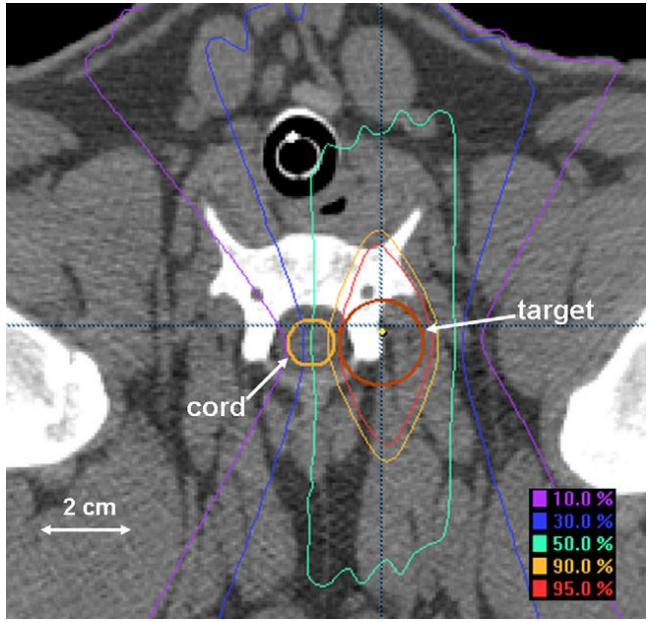
Ang et al, Red J, 2001

Spinal Cord: Swine Animal Model





Initial RT 30 Gy/10



Initial RT dose: 30 Gy/10
Retreatment after 1 yr
SBRT: 14-24 Gy/1
Dmax to cord: 14.9-25.4 Gy

Medin et al, 2012

Spinal Cord: Swine Animal Model

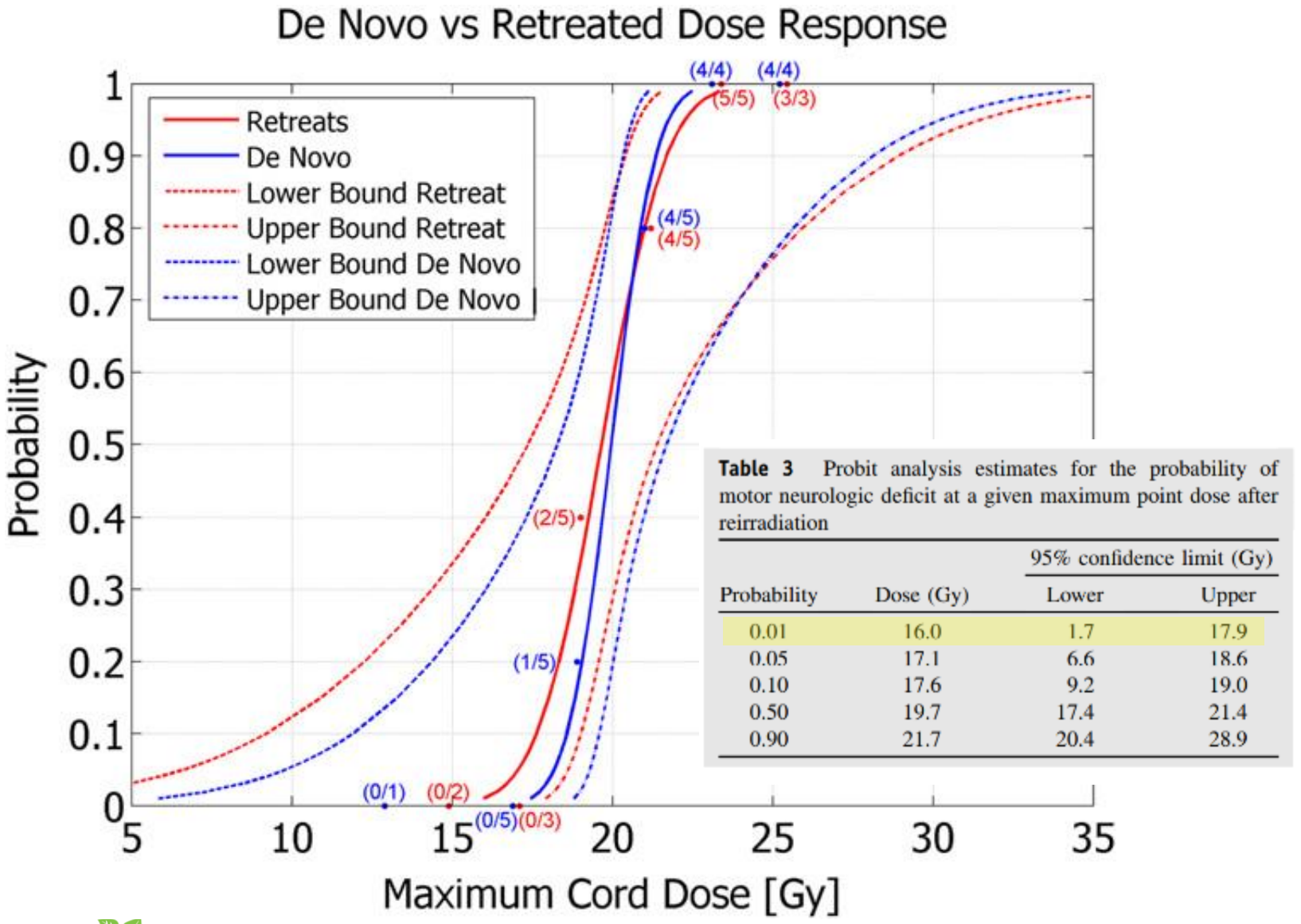


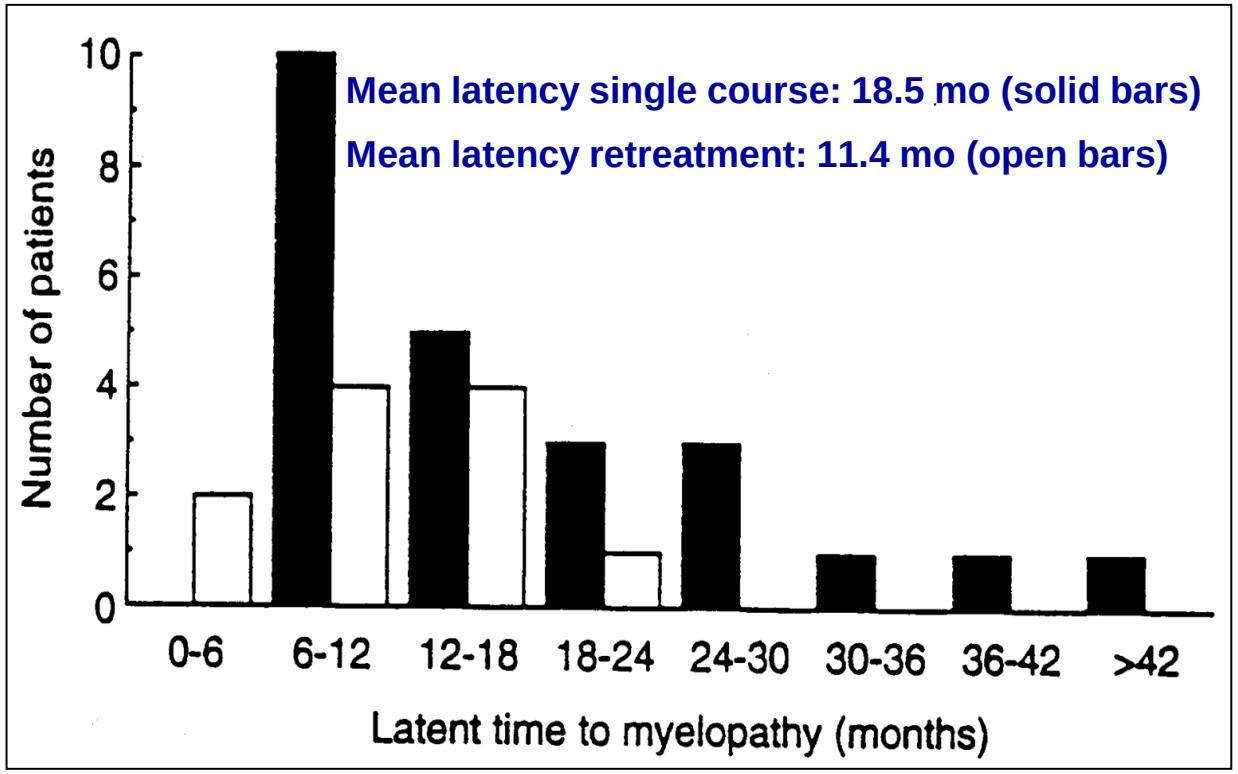
Table 3 Probit analysis estimates for the probability of motor neurologic deficit at a given maximum point dose after reirradiation

		95% confidence limit (Gy)	
Probability	Dose (Gy)	Lower	Upper
0.01	16.0	1.7	17.9
0.05	17.1	6.6	18.6
0.10	17.6	9.2	19.0
0.50	19.7	17.4	21.4
0.90	21.7	20.4	28.9

Medin et al, 2012

Spinal Cord: Human Data

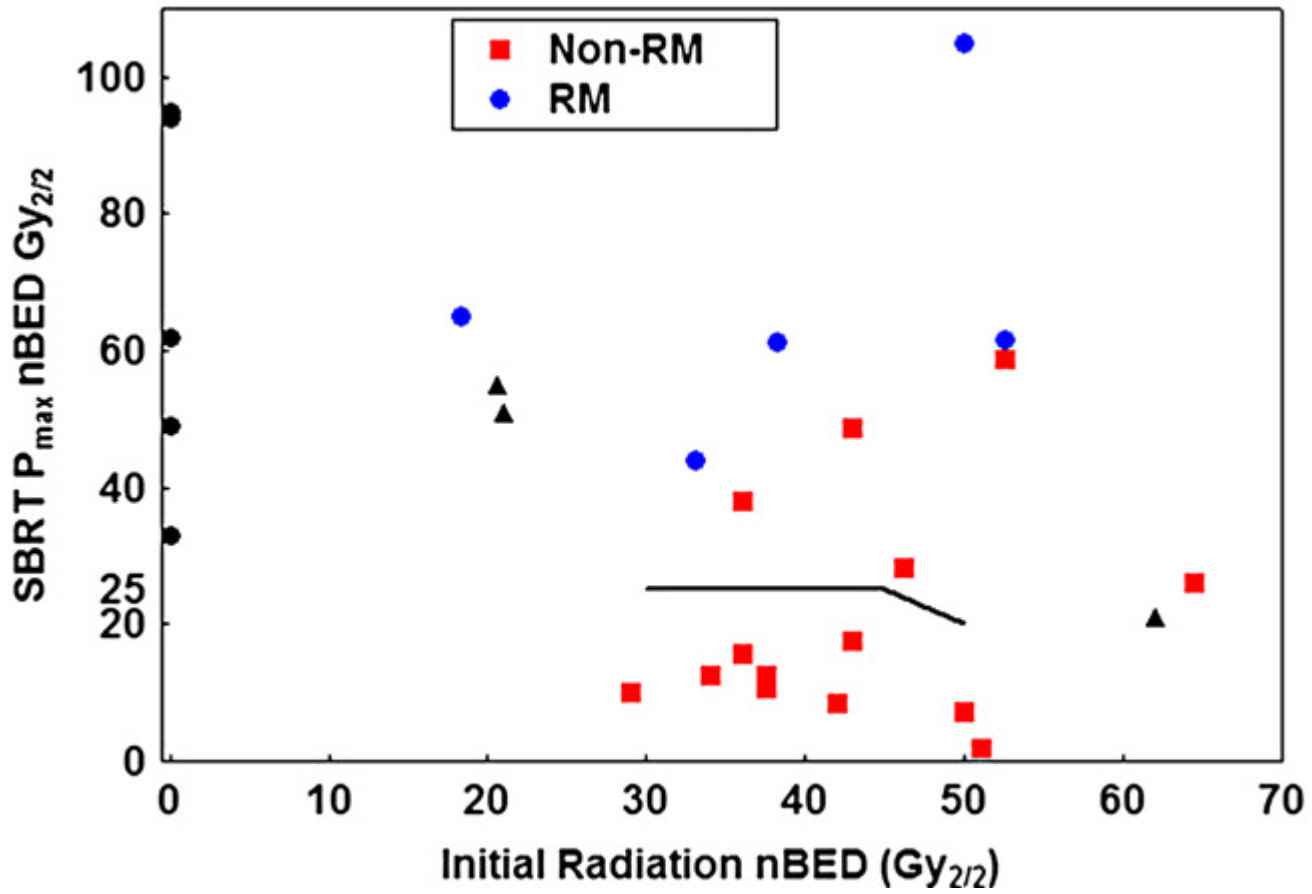
- Mainly retrospective
- Latent time to myelopathy after re-irradiation were significantly shorter (avg. 11 months) than after a single course of treatment (avg. 19 mo) *(Wong, 1994)*



Human Data

- Myelopathy is rarely observed by design, but this also limits our ability to study the phenomenon

- Review of literature (n = 40) *(Nieder, 2005)*, risk factors for radiation myelopathy:
  - dose of ≥102 Gy_2 for one of the radiation courses
  - interval of less than 2 months between radiation courses



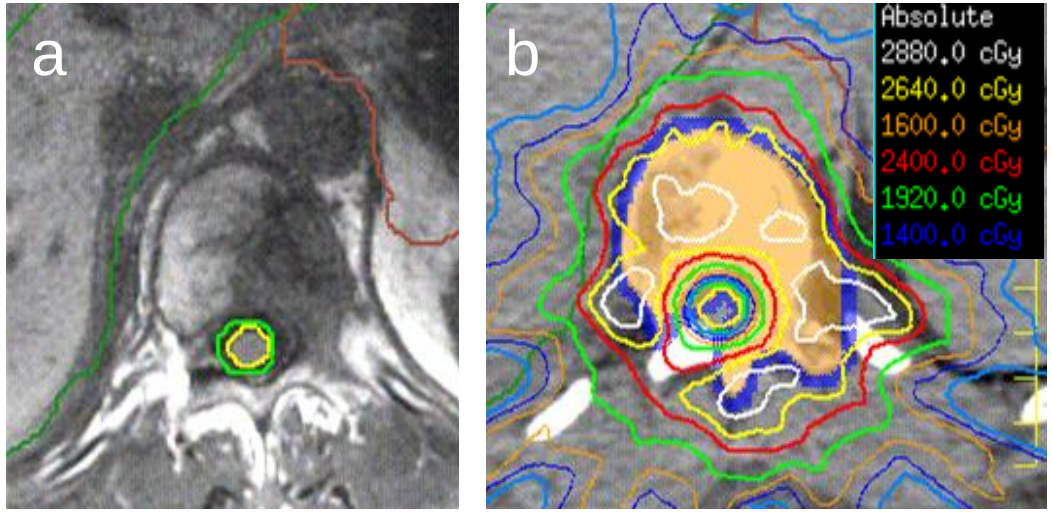
▲ RM cases, non-SBRT, *Wong 1994*

● RM cases, SBRT, no prior RT, *Sahgal 2011*

- Re-irradiation thecal sac D_{max} EQD2 <25Gy
- Total thecal sac D_{max} EQD2 <70Gy
- Interval to re-irradiation >5 mo

Sahgal A, IJROBP, 2012

Reported SBRT point maximum dose limits to the thecal sac



Prior Radiation	1 fx SBRT D_{max} limit	2 fx SBRT D_{max} limit	3 fx SBRT D_{max} limit	4 fx SBRT D_{max} limit	5 fx SBRT D_{max} limit
20 Gy in 5 fx to 45 Gy in 25 fx	9 Gy	12.2 Gy	14.5 Gy	16.2 Gy	18 Gy
50 Gy in 25 fx	N/A	11 Gy	12.5 Gy	14 Gy	15.5 Gy
>50 Gy in 25 fx	N/A	N/A	N/A	N/A	N/A

Sahgal A, IJROBP, 2012

Clinical Implications

- There is restoration of occult injury in the human spinal cord
  - Speed and full extent not well defined

- It may be reasonable to accept a higher tolerance for retreatment as dictated by clinical situation; patient input is important

Other Evidence for Non-Palliative, High-Dose Re-irradiation

- A non-exhaustive list
- Breast
  - Likely can tolerate up to cumulative EQD2s of >100 Gy (Merino, Tran and Czarnota, Oncotarget 2015), given sufficient time for restoration (>1 year)
  - Multiple prospective trials underway for adjuvant breast external beam re-irradiation (26/5 or 40/15) after repeat lumpectomy for recurrent breast cancer
  - Minimize re-irradiation volume with typically partial breast radiation

- Nasopharynx
  - Limited options other than re-irradiation for patients with locally recurrent head and neck cancer
  - High-risk situation due to numerous sensitive OARs, infiltrative growth pattern, previous high-dose exposure (70 Gy with chemo) and usually short time interval
  - Consensus guidelines (Lee et al. IJROBP 2021) recommends up to 81 Gy EQD2 cumulative for brainstem/optics, 67.5 Gy for spinal cord, 105 Gy to brain, with induction chemo to down-stage if possible, and limiting CTV to max 5 mm and PTV to max 3 mm

Other Evidence for Non-Palliative, High-Dose Re-irradiation

- Brain
  - Local recurrence after initial chemoradiation for GBM is common, with limited treatment options. Brain has reasonable recovery potential.
  - Hypofractionated re-irradiation has been tested in RCTs (RTOG1205) to be better than systemic therapy alone, with acceptable toxicity (5% grade 3 AE)
  - Minimize re-irradiation volume by eliminating CTV (typically 1-2 cm)

- Lung
  - With increasing use of lung SBRT and acceptance of the oligometastatic/oligoprogression paradigm, repeat lung SBRT is increasingly common
  - Lung appears generally to have good restorative potential, and repeat lung SBRT even in close proximity to previous high-dose lung RT/SBRT appear well tolerated, with acceptable rates of pneumonitis
  - Main risk is to major bronchi and vessels when the lesion is close to the central chest

Re-irradiation: Summary

- Higher initial and re-irradiation dose predict higher toxicity
- Larger re-irradiation volume predict higher toxicity
- Shorter interval to re-irradiation predict higher toxicity (generally)
- Different OARs, and different early/late effects for the same OAR, can have different sensitivities to re-irradiation
- When clinically appropriate, reduce re-irradiation dose, reduce re-irradiation volume and delay re-irradiation until necessary
- Systemic therapy's impact is unclear. However, any radiosensitizing systemic therapy should likely be held during re-irradiation, unless supported by prospective evidence to the contrary

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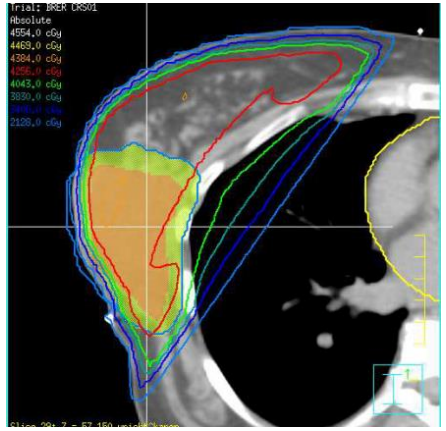
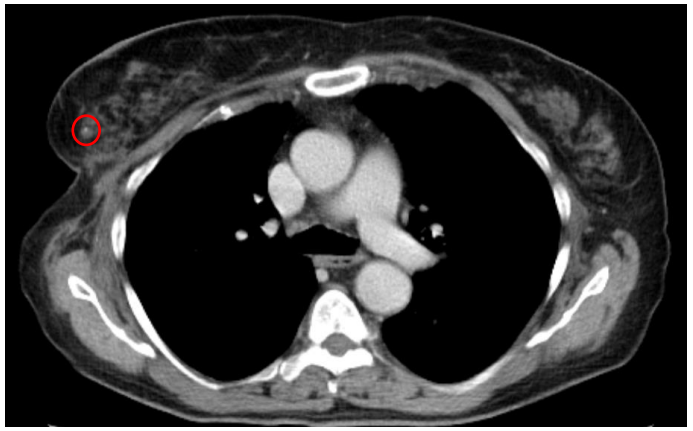
April 27, 2023

Scenario 3

- 56 y/o patient treated with lumpectomy and adjuvant whole breast radiotherapy 42.6 Gy in 16 fractions with a 12.5 Gy in 5 fraction boost for a left-sided pT1c N0 IDC in 2015. She had persistent mild fibrosis in the breast.
- In 2023 she had a biopsy-proven ipsilateral breast recurrence. The surgeon performed another lumpectomy that showed pT2 (3 cm) N0 ER+/Her2- disease and referred her back for radiation.





- Increasing common scenario in breast cancer treatment

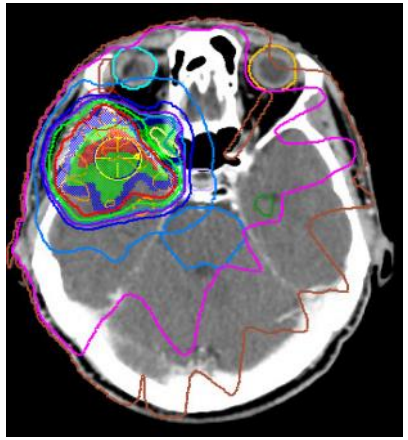
Re-Irradiation Decision

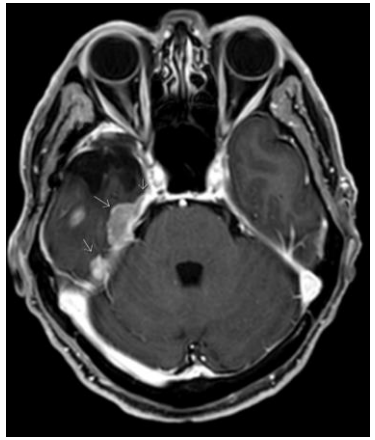
Clinical Factors		**Radiobiologic Factors** OARs: breast	
Alternatives	Completion mastectomy, Endocrine therapy alone (Suboptimal)	**Previous RT dose**	42.4/16 + 12.5/5 Moderately high dose
Indication	Curative – higher doses needed	**Re-irradiation dose**	40/15 (45/25 and 26/5 likely also feasible)
Previous side effects	Within normal limits, mild late residual fibrosis	**Previous RT volume**	Whole breast
Other considerations	Patient is otherwise very healthy and high-functioning	**Re-irradiation RT volume**	Partial breast
		Time interval	Very long, good recovery potential

- As data accumulated, breast re-irradiation to standard adjuvant radiotherapy doses was quite well tolerated, indicating a high potential for recovery
- Partial breast irradiation to 45 Gy/25 (and even 40/15 or 26/5, which is being investigated) is typically done with low acute or late toxicity. Brachytherapy is an option in certain centres as well.

Scenario 4

- 60 y/o patient with meningiomatosis, initial presented with a grade 2 meningioma treated with surgery and adjuvant 70 Gy/35 in Feb 2022.
- Developed multiple further meningiomas in various locations. In 2024 he developed new large meningioma plaques in close proximity to the region previously treated to 70 Gy/35
- Patient is otherwise well and wishes for a curative treatment





- Rare clinical condition and rare re-irradiation scenario

Re-Irradiation Decision

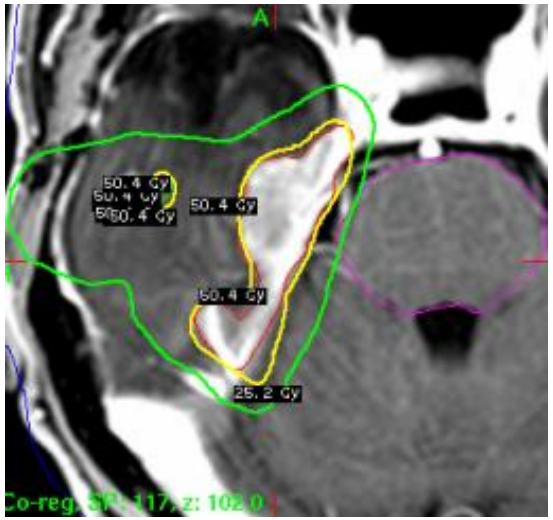
Clinical Factors		**Radiobiologic Factors** OARs: brain, optic pathway, brainstem	
Alternatives	None – area too large to feasibly resect, no drug option	**Previous RT dose**	70/35, optic nerve received 61 Gy, brainstem received 48 Gy
Indication	Curative	**Re-irradiation dose**	??? At least 60 Gy needed to have a chance at long-term control
Previous side effects	Within normal limits. No obvious late effects	**Previous RT volume**	Moderate
Other considerations	Not controlling the disease will likely lead to seizures, pain and eventually death	**Re-irradiation RT volume**	Moderate, immediately adjacent to previous volume
		Time interval	2 years, mild to moderate recovery

Scenario 4

- Some creativity required – let's consider the mitigation strategies
- Reduce re-irradiation dose
  - At least 60 Gy required for control, but this is with relatively homogeneous dose distributions with standard IMRT techniques
  - SRS with central heterogeneity may achieve control with lower margin dose where OARs are closest
  - Fractionated SRS will further protect OARs
- Reduce re-irradiation volume
  - SRS with semi-rigid immobilization can significantly reduce PTV size and dose to OARs
  - Sacrifice PTV coverage to spare OARs

Scenario 4

- Fully fractionated Gamma Knife SRS (50.4 Gy/28) was done
- Coverage: 90% of PTV, 99% of GTV by 50.4 Gy
- Optics Dmax 11.8 Gy/28
- Brainstem Dmax 31.9 Gy/28



We’d love your feedback!

Lecture Evaluation

Program Evaluation