Normal Tissue Effects: Retreatment

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when it matters MOST

Disclosure

- None.
- Thanks to Drs. Wolfgang Dorr and Shun Wong for permitting the use of some of their teaching slides in this course.

Learning Objectives

- Review clinical cases
- Understand the radiobiological factors that influence clinical decision regarding retreatment/re-irradiation
- Understand the radiobiology that underlies normal tissue tolerance to retreatment
- Apply fundamental radiobiological concepts to clinical retreatment decision making

Radiation Effects - 7 ~~6~~ Rs of Radiotherapy

radiosensitivity (intrinsic)
repair
redistribution
repopulation
reoxygenation
i**r**radiated volume

long term r ecovery

Indications for Retreatment

- Locoregional recurrence
- Local progression causing recurrent symptoms
- Second primary cancer

Clinical Factors for Consideration

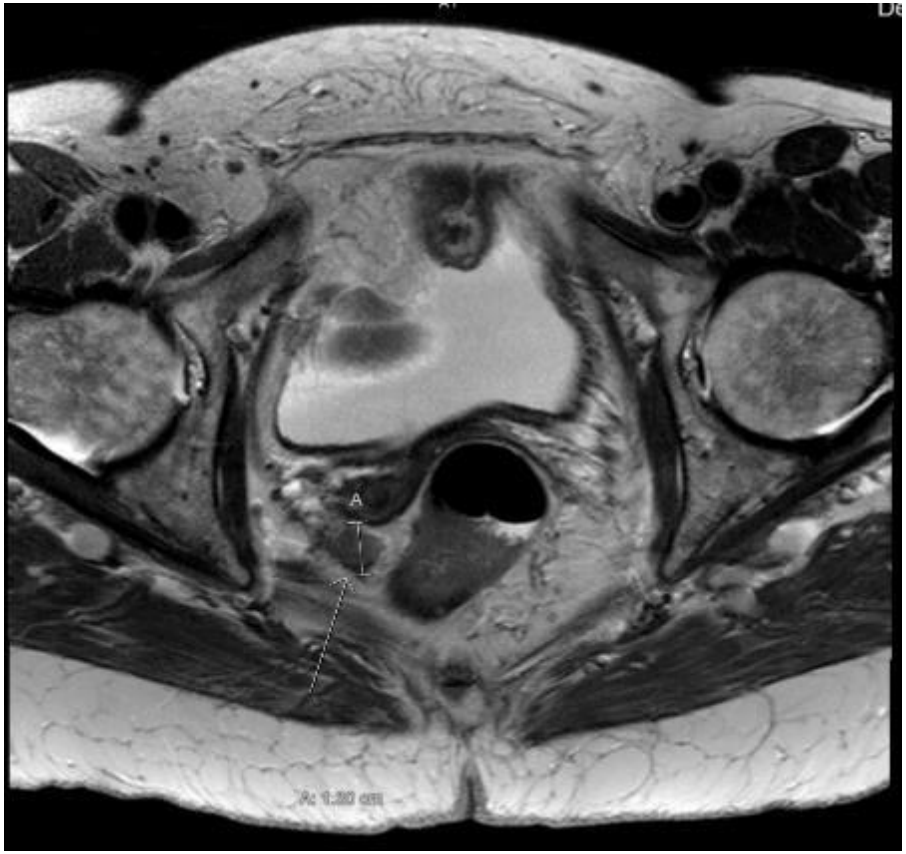
- Curative or palliative intent
- Alternative treatment options
  * surgery
  * systemic therapy
  * interventional radiology procedures
  * endoscopic interventions
- Late effects from previous RT
- Other clinical issues
  * patient performance status
  * patient preference

Radiobiological Factors for Consideration

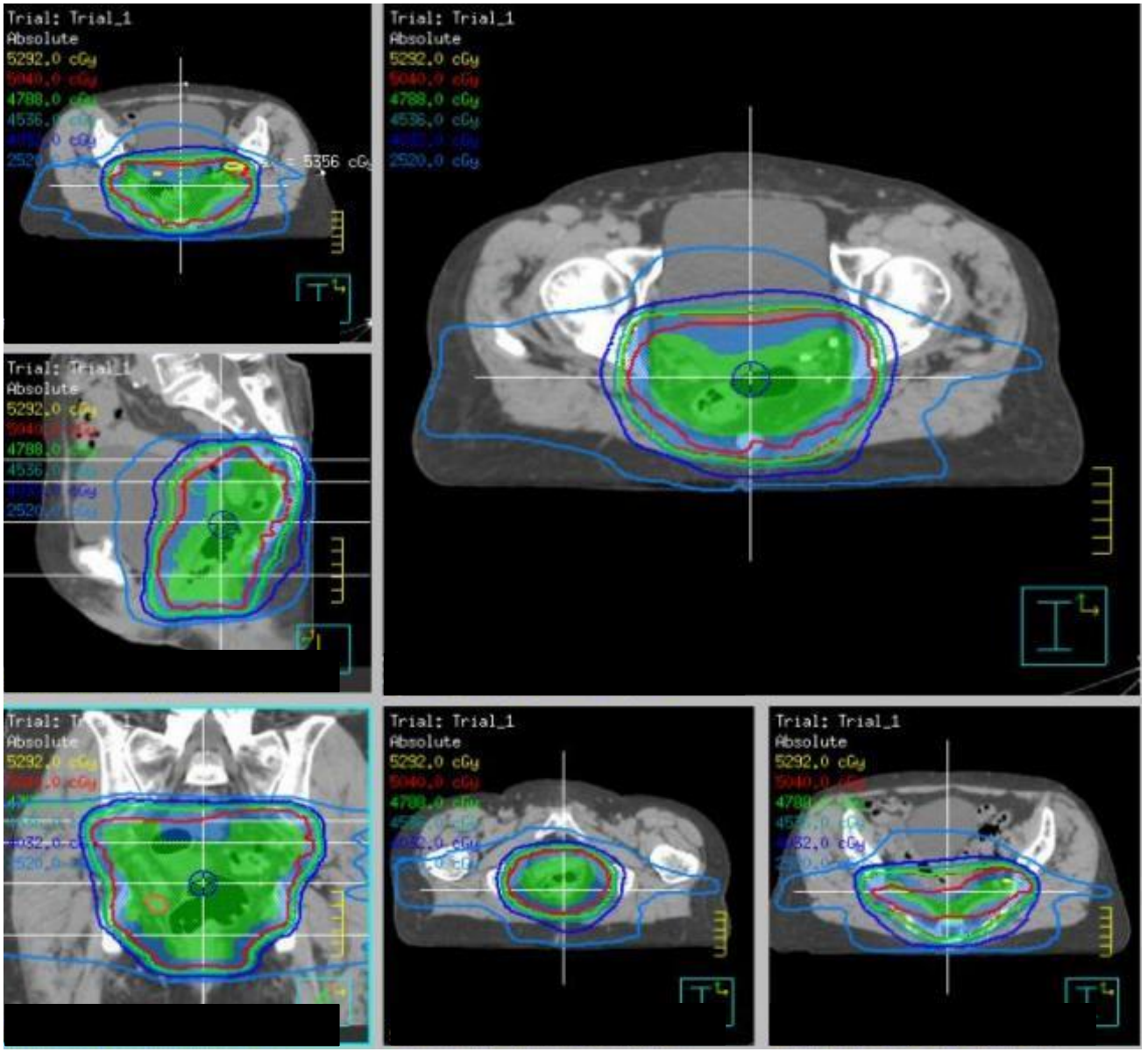
- Dose fractionation
- Volume irradiated during previous RT
- Time interval from previous RT
- Radiobiology (long term recovery) of OARs

Scenario 1 (local recurrence)

- 2013: Transanal excision for a pT2 low grade rectal adenoCa arising from a villous adenoma on surveillance
- 2018: New enlarged mesorectal lymph nodes biopsy confirmed adenocarcinoma



1st course (2018): Neoadjuvant chemoRT 50.4 Gy/28 fr + capecitabine



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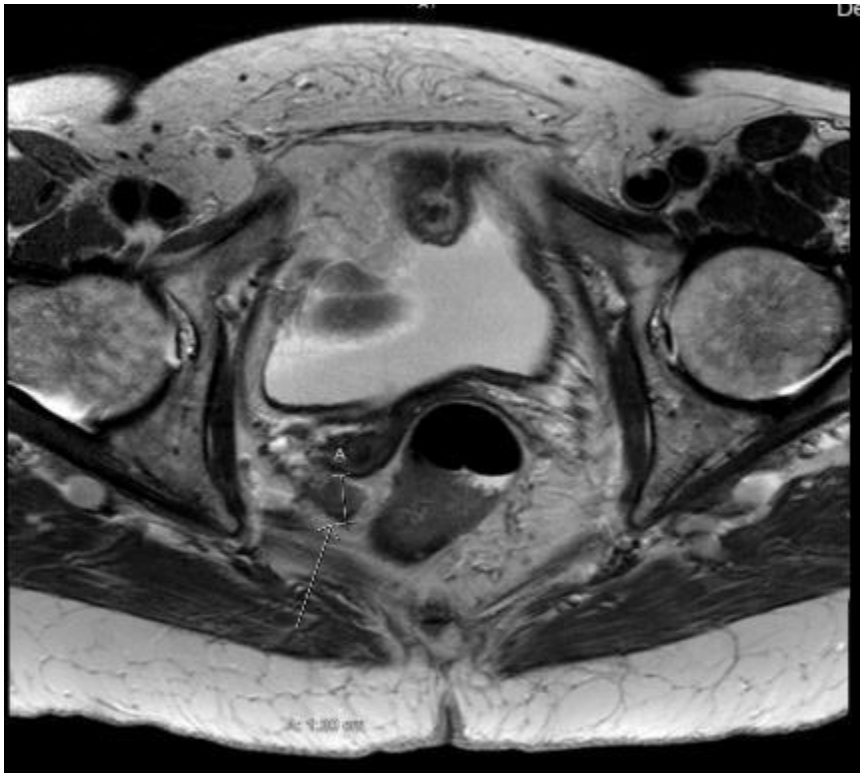
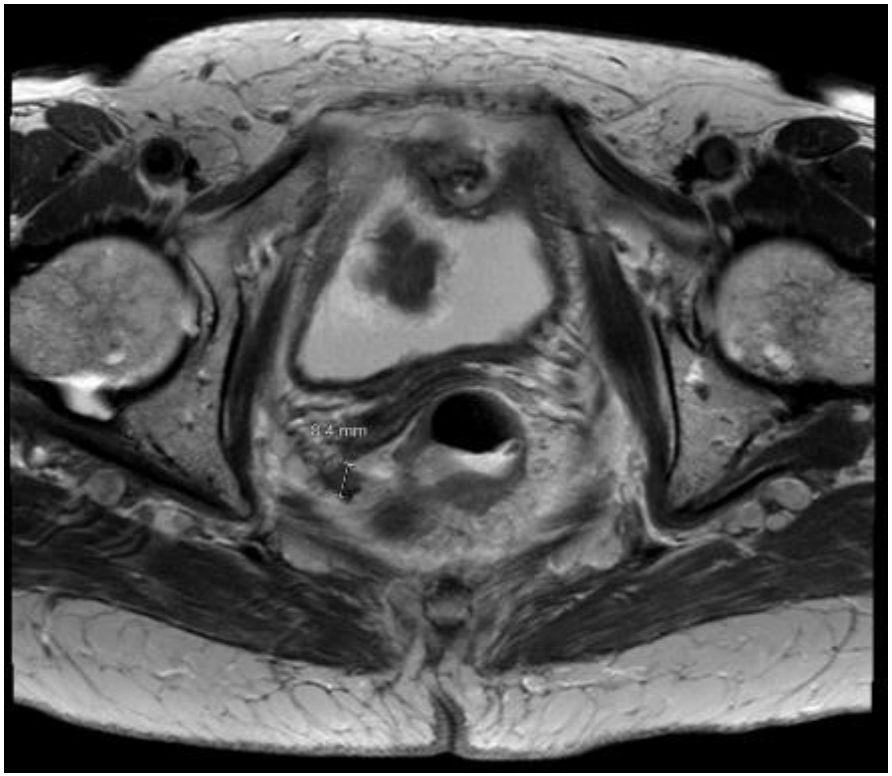
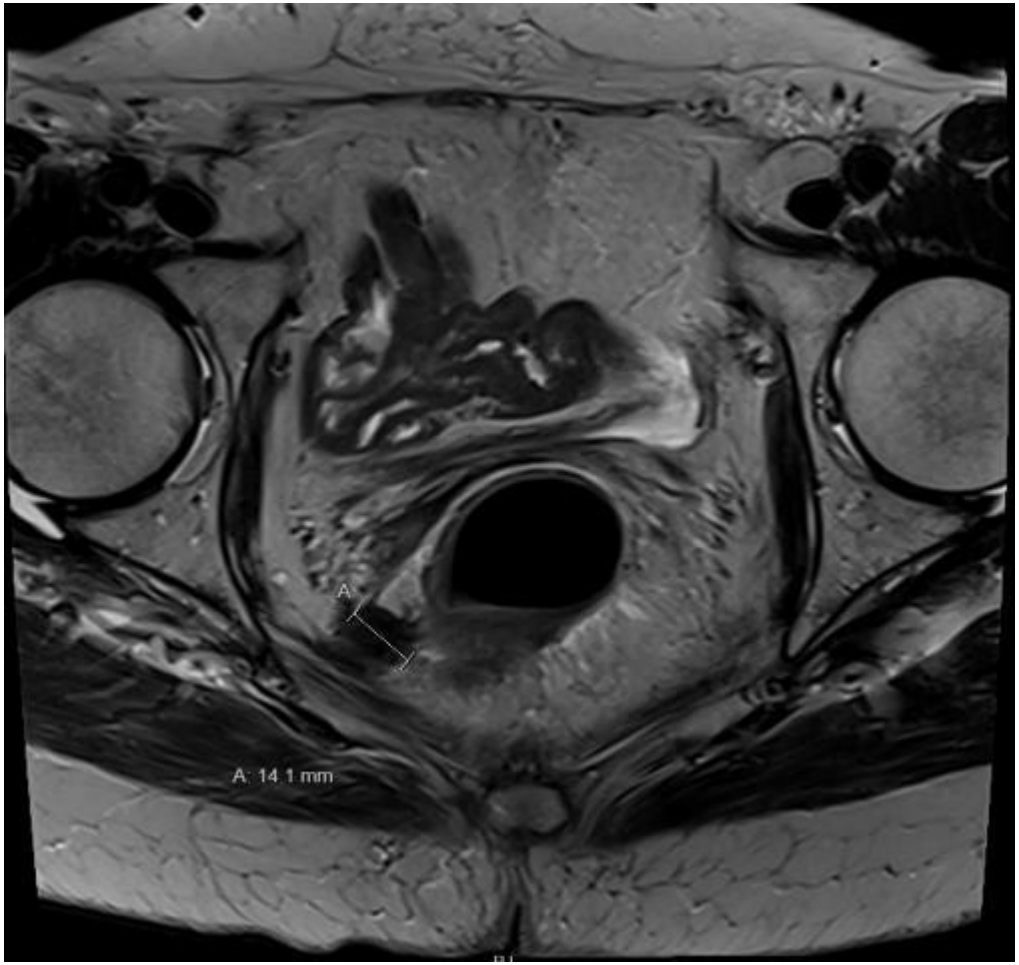


2 months post chemoRT



- Surgery was recommended; patient declined
- Stable appearance of mesorectal lymphadenopathy x 2 yrs

- 2020: Progression of mesorectal lymphadenopathy invading right pelvic side wall and vaginal vault



- Staging CT CAP showed no distant metastasis

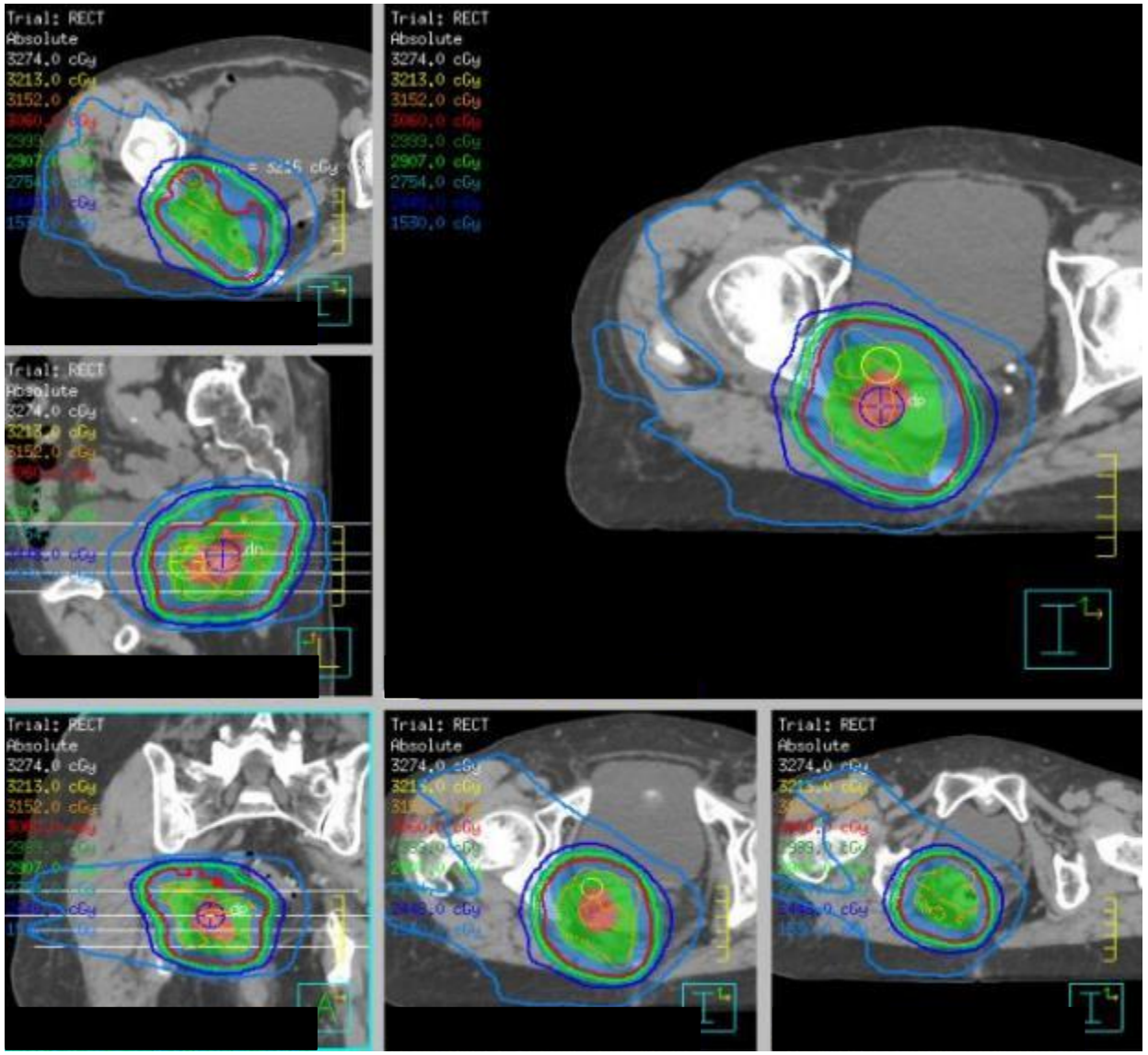
Clinical considerations

- Intent of treatment: curative; no distant metastasis on restaging, disease felt to be resectable
- Options: upfront surgery vs. re-irradiation +/- chemo followed by surgery
- Patient factors: excellent PS, asymptomatic, no late side effects from previous RT; 2 yrs of PFS

Radiobiologic considerations

- Initial RT dose fractionation: 50.4 Gy/28 fr in 2018
- Interval prior to re-RT: >2 yrs
- OARs: small bowel, nerves, bone, bladder

2nd course (2020): Pseudoneoadjuvant chemoRT 30.6 Gy/17 fr + capecitabine



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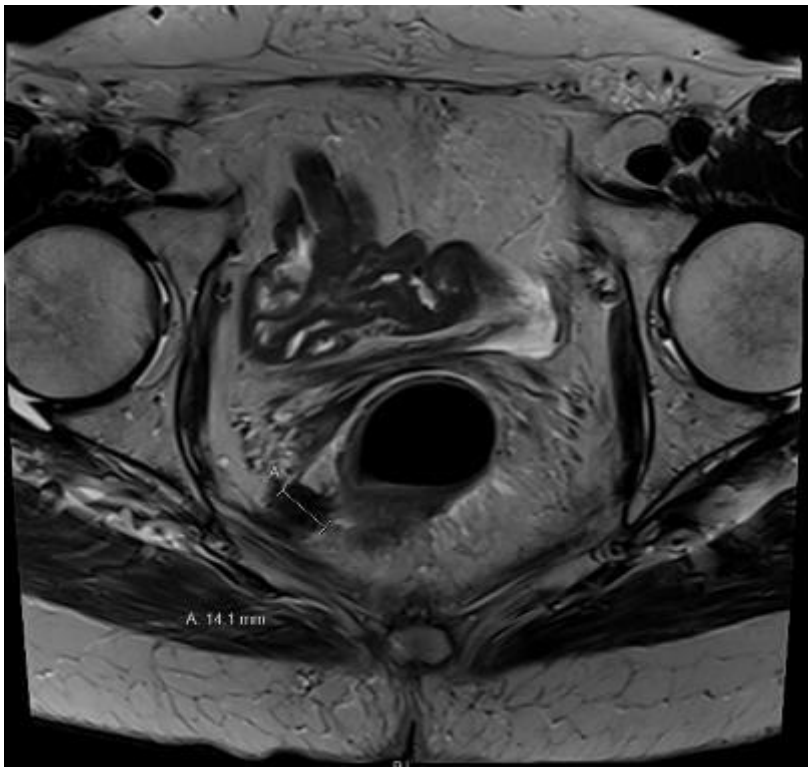
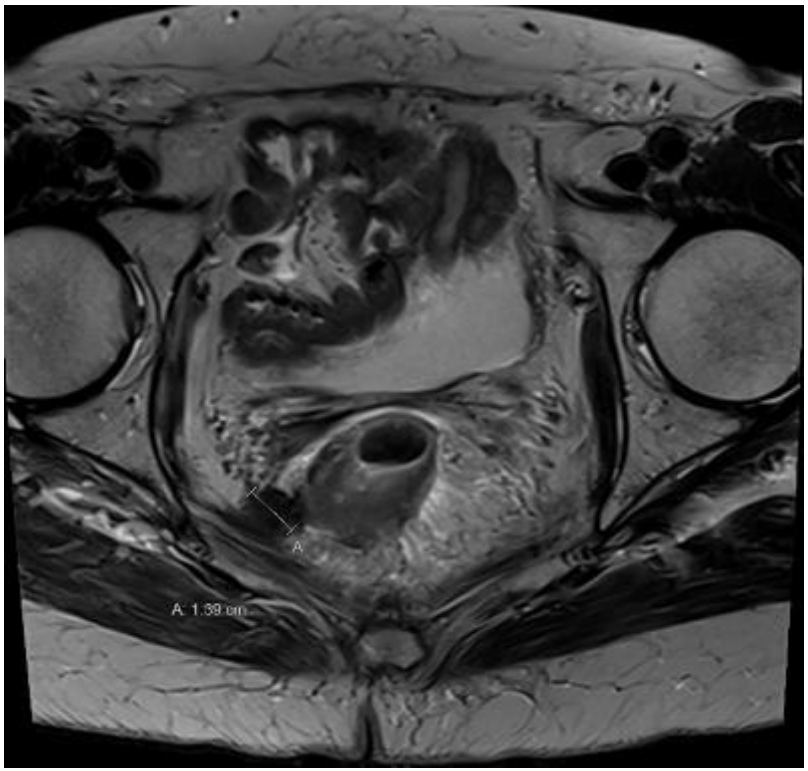


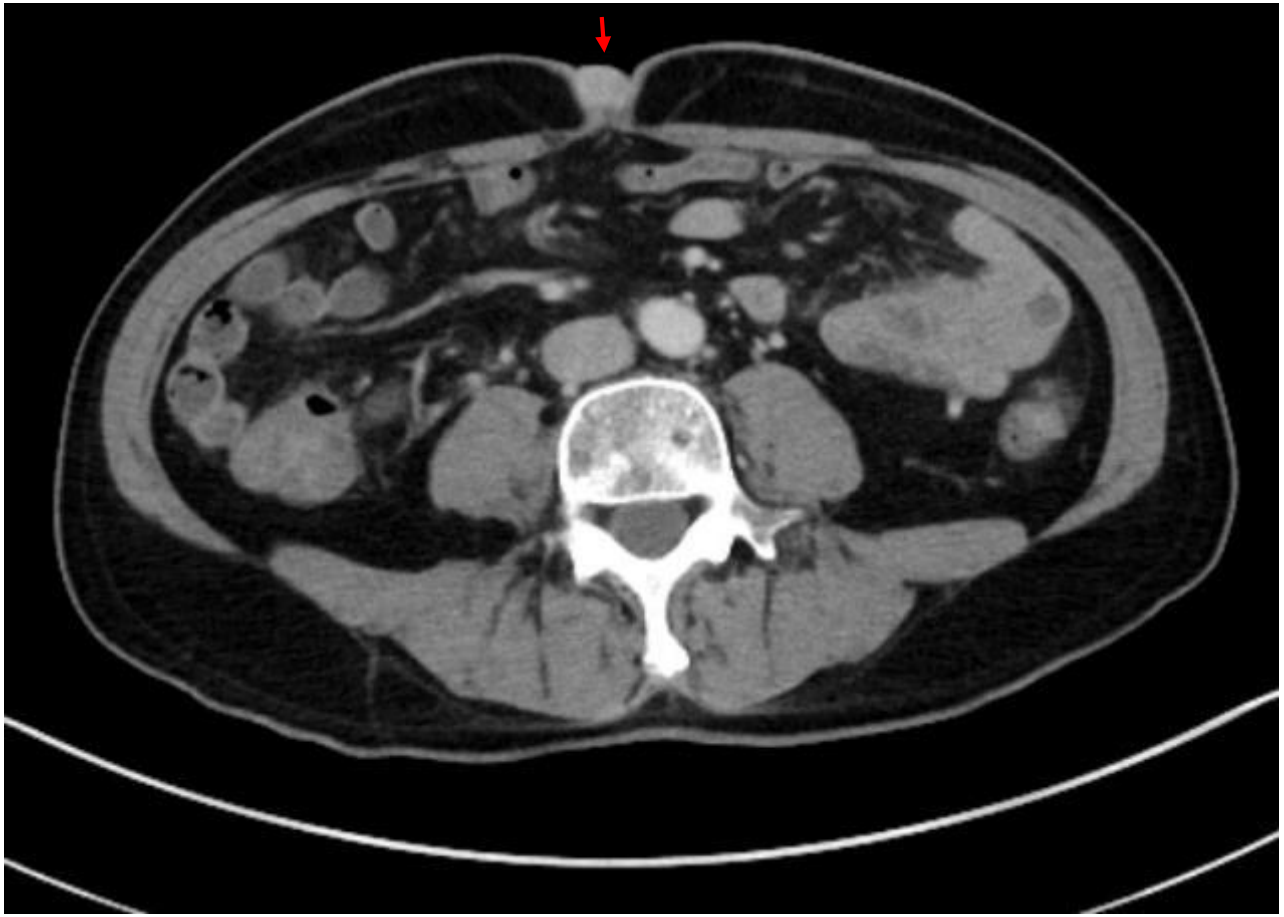
3 months post re-RT



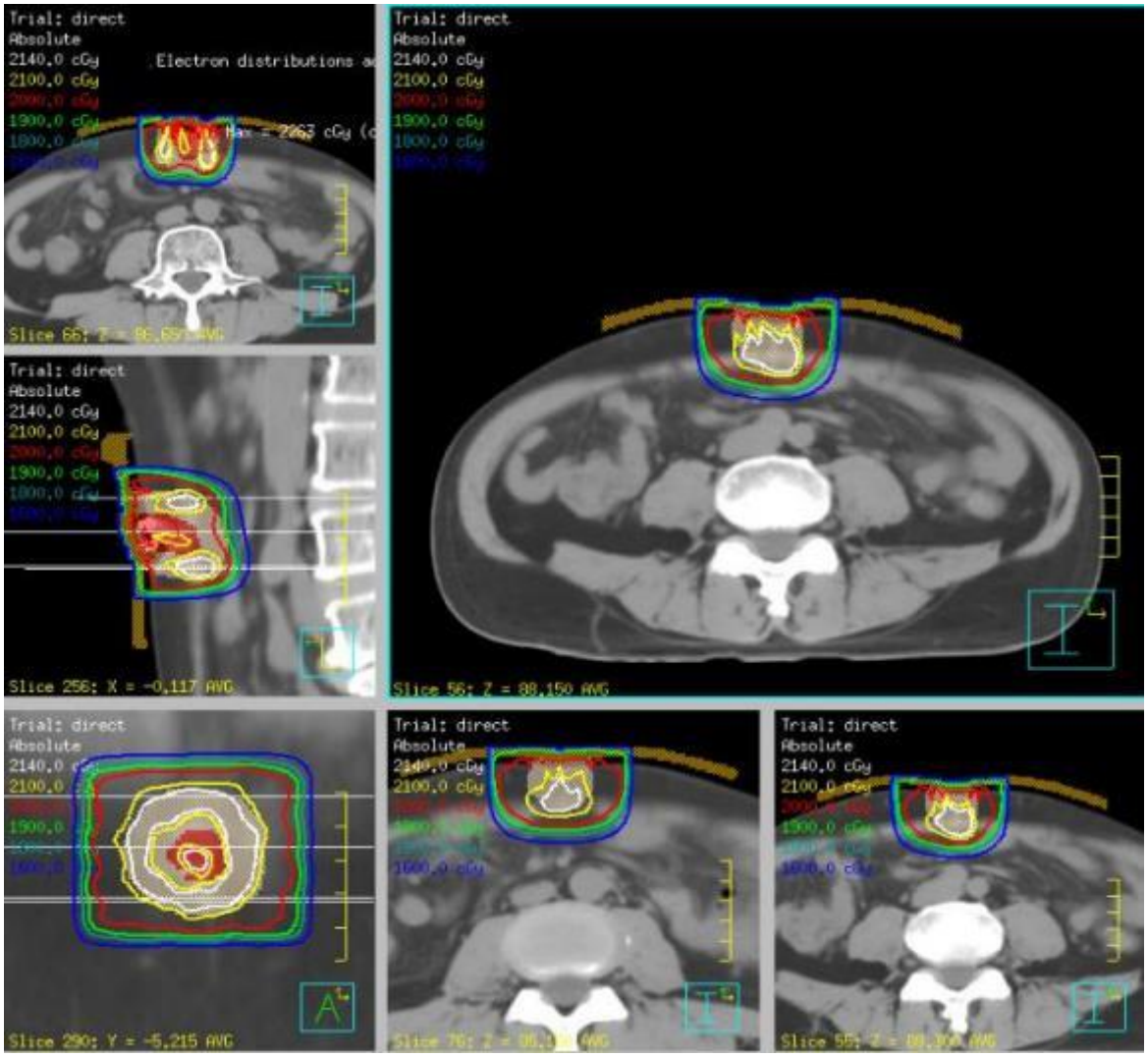
- Surgery was strongly recommended; patient declined
- Developed lung and liver mets; declined chemo; liver mets treated with SBRT
- Achieved 15 months of local control

Scenario 2 (local progression)

- De novo metastatic gastric cancer on first-line chemotherapy
- New umbilical soft tissue met with pain



1st course (Sep 2020): 20 Gy/5 fr



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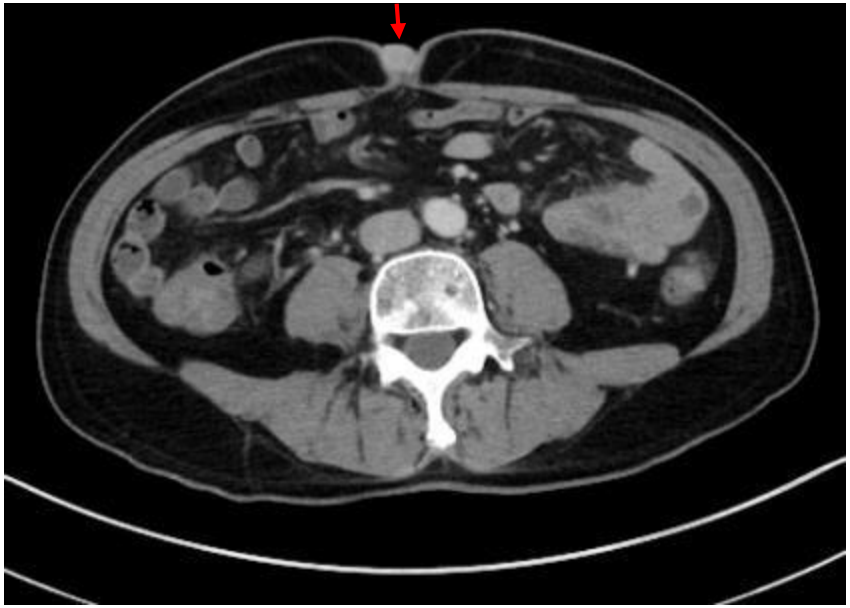
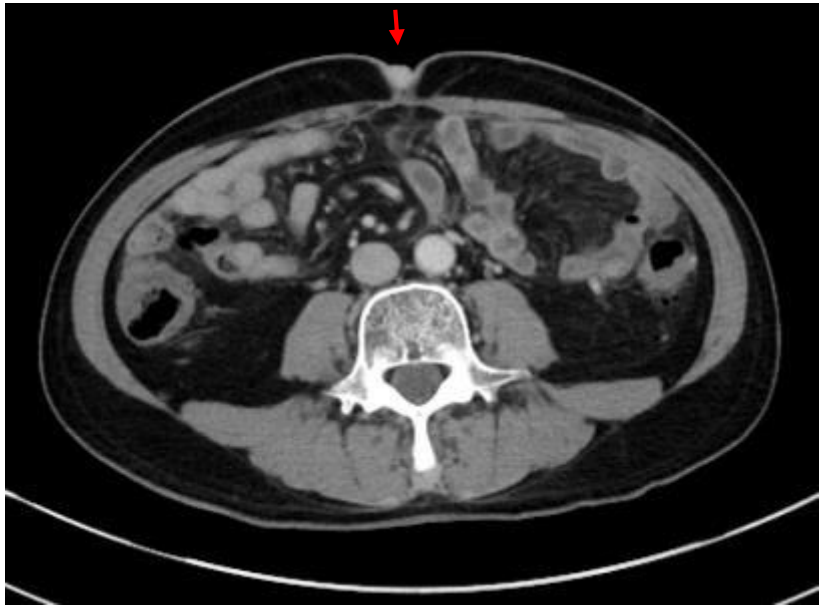
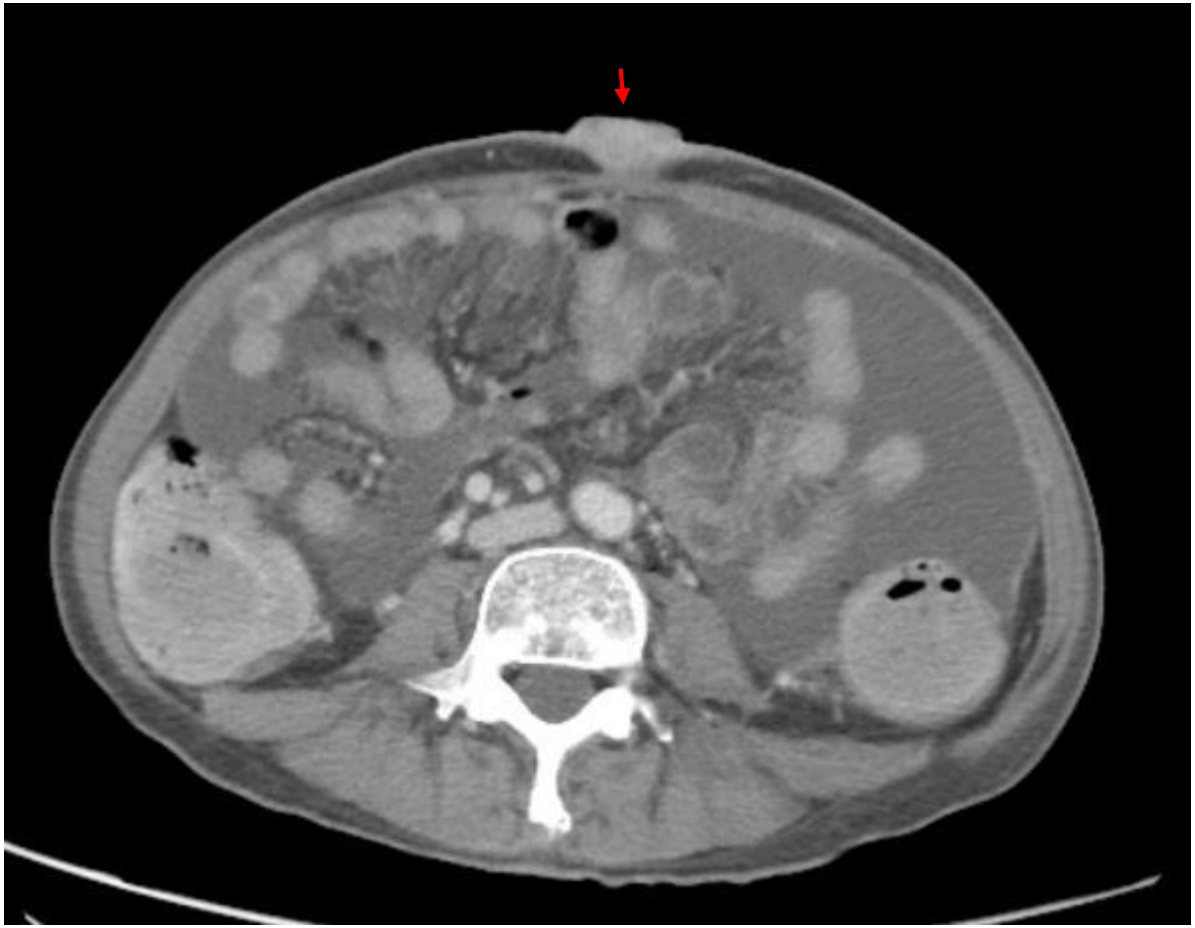


2 months post RT



- Pain improved

- 6 months following 1st course of RT with significant recurrent local pain refractory to opioids and adjunct analgesics



- Also systemic progression with worsening carcinomatosis and ascites

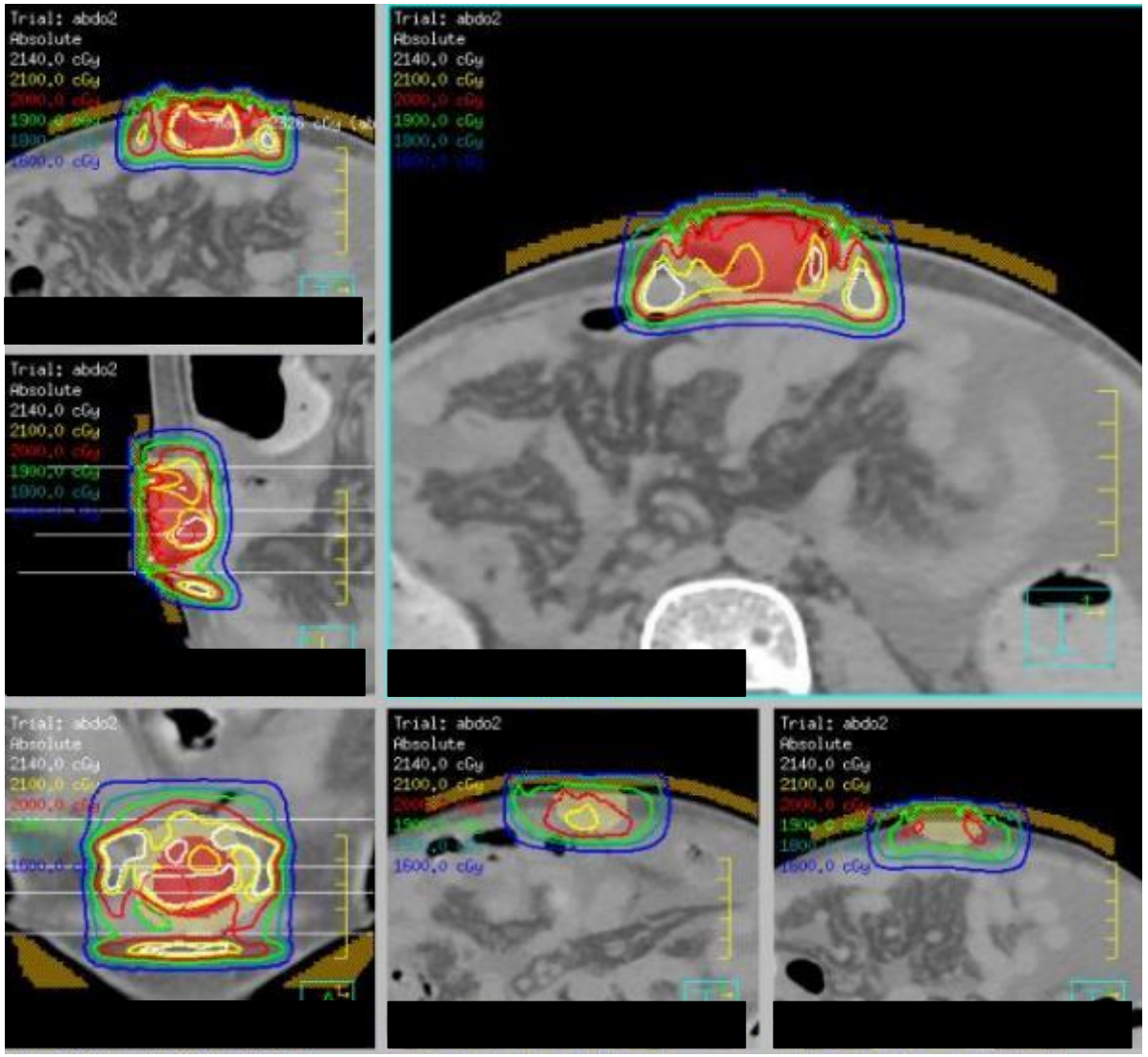
Clinical considerations

- Intent of treatment: palliative
- Options: increase opioid dose, switch opioids, add adjunct analgesics
- Patient factors: poor PS, symptomatic, had good pain control and no side effects from previous RT

Radiobiologic considerations

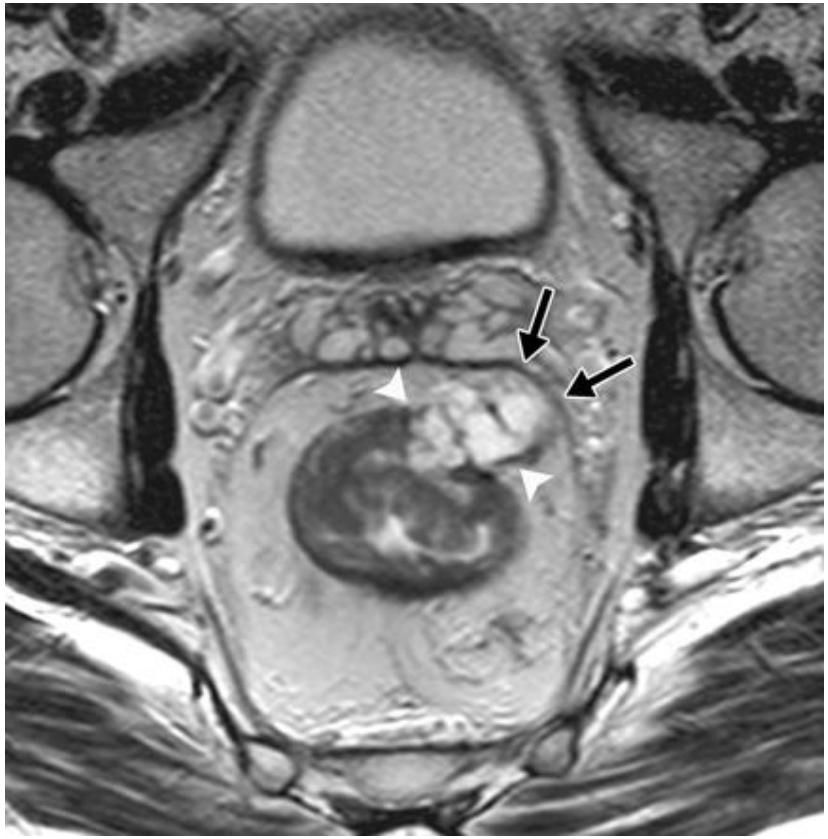
- Initial RT dose fractionation: 20 Gy/5 fr
- Interval prior to re-RT: 6 mo
- OARs: small bowel

2nd course (Mar 2021): 20 Gy/5 fr



Scenario 3 (second primary cancer)

- 45 y.o. with locally advanced rectal cancer
- Previous RT for neuroblastoma 12 Gy/18 fr at the age of 6 months



Clinical considerations

- Intent of treatment: curative
- Options: upfront surgery vs. neoadjuvant chemoRT surgery
- In this case, CRM compromised without neoadjuvant chemoRT
- Patient factors: young, good PS, no late side effects from previous RT (growth/development)

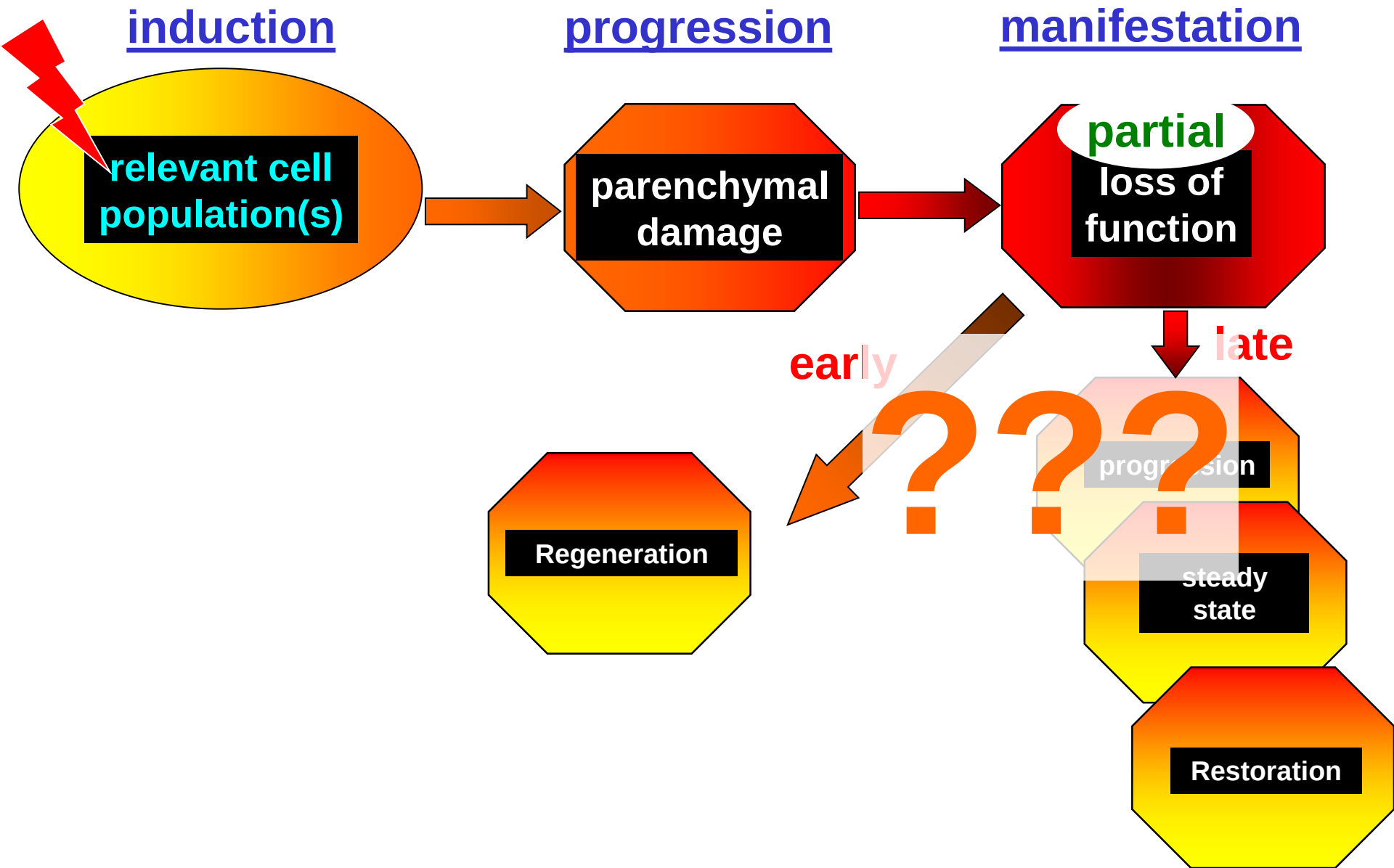
Radiobiologic considerations

- Initial RT dose fractionation: 12 Gy/18 fr
- Long interval to re-RT (4+ decades), previous side effects of RT likely completely recovered
- OARs: small bowel, large bowel, rectum, bladder

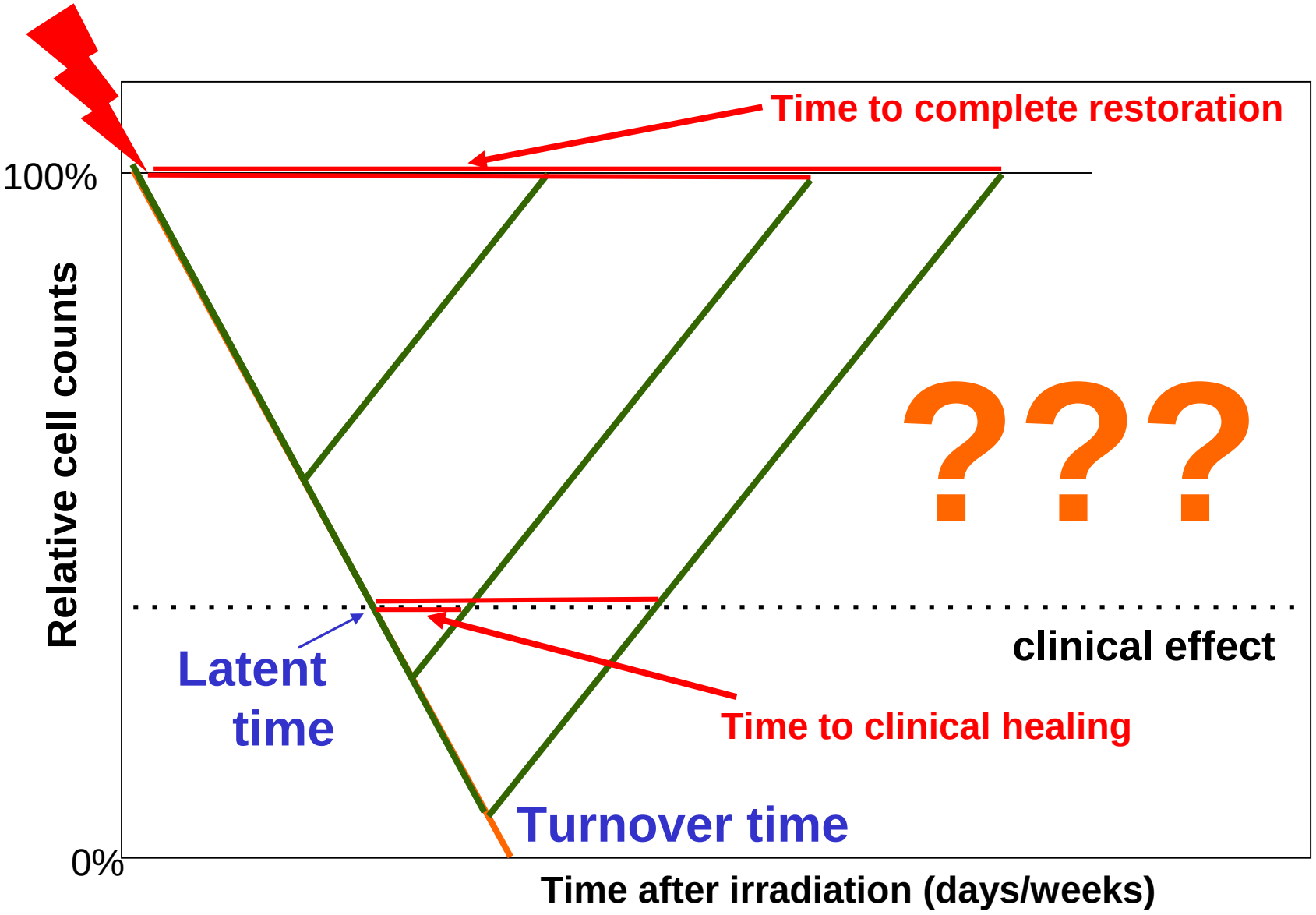
Clinical Data for Re-irradiation

- Virtually all retrospective data
- Extremely heterogeneous populations
- Curative and palliative intent
- Evolving RT techniques over time
- Uncertainties in dosimetric data
- Variations in normal tissue toxicity scoring
- Influence of disease/co-morbidities and other treatments on normal tissue complications

Retreatment Radiobiologic Model



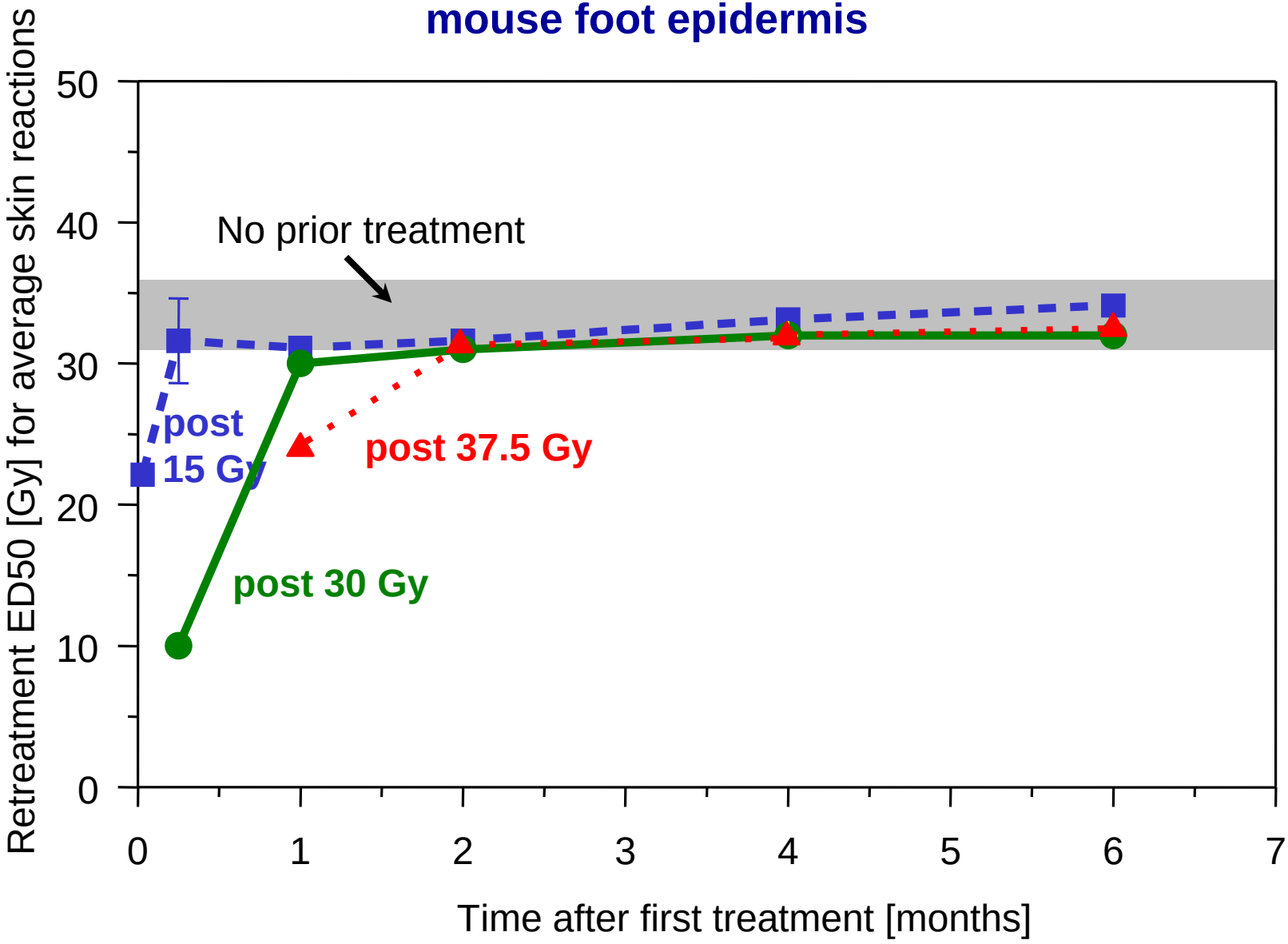
Turnover tissues: changes in cell numbers



Radiobiological Factors for Consideration

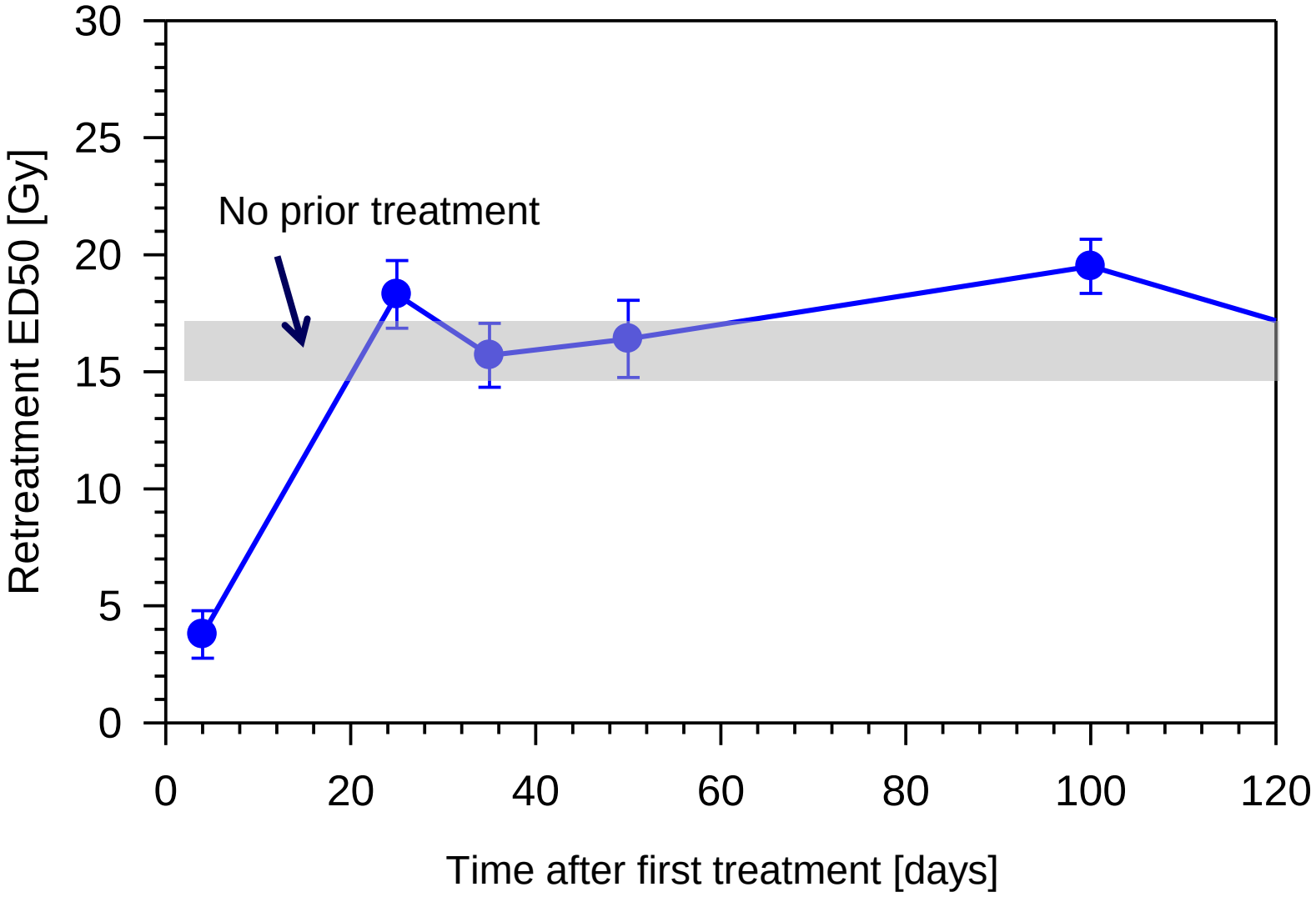
- Dose fractionation
- Volume irradiated during previous RT
- Time interval from previous RT
- Radiobiology (long term recovery) of OARs

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 of Retreatment

- If time interval is allowed before retreatment, the skin and mucosa could be re-irradiated as if it were previously untreated

- Time interval is tissue type dependent:
  *oral mucosa: 3-4 weeks
  *epidermis: 2-3 months

Clinical Implication
Early effects of Retreatment

- Provided sufficient time interval is allowed before retreatment, acute reactions (skin and mucosal reactions) are not expected to alter compared to de novo treatment

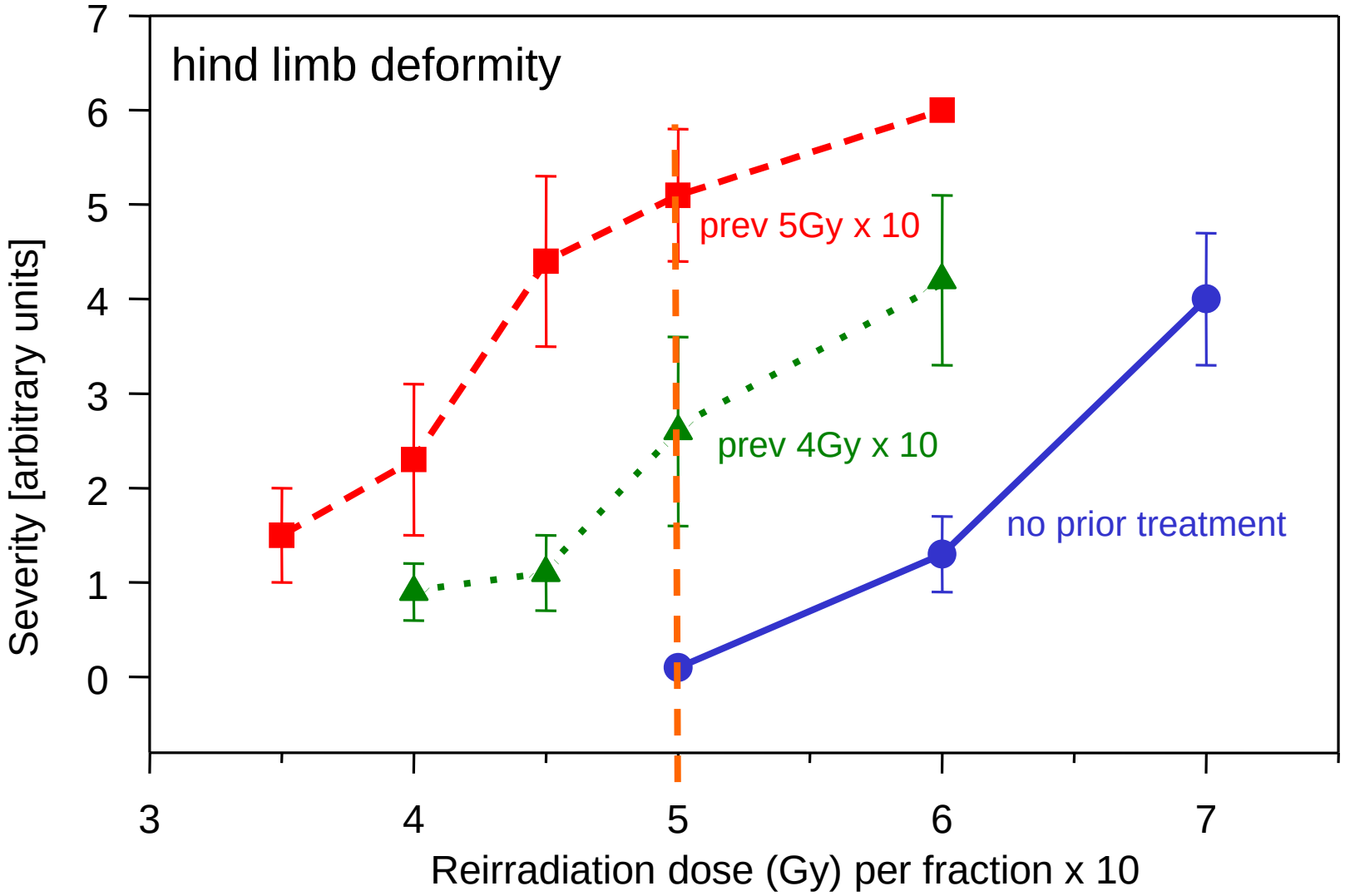
Late Effects of Retreatment

- Recovery of occult damage and hence retreatment tolerance is tissue/organ specific

- Retreatment tolerance dependent on multiple factors:
  *initial dose
  *time to retreatment

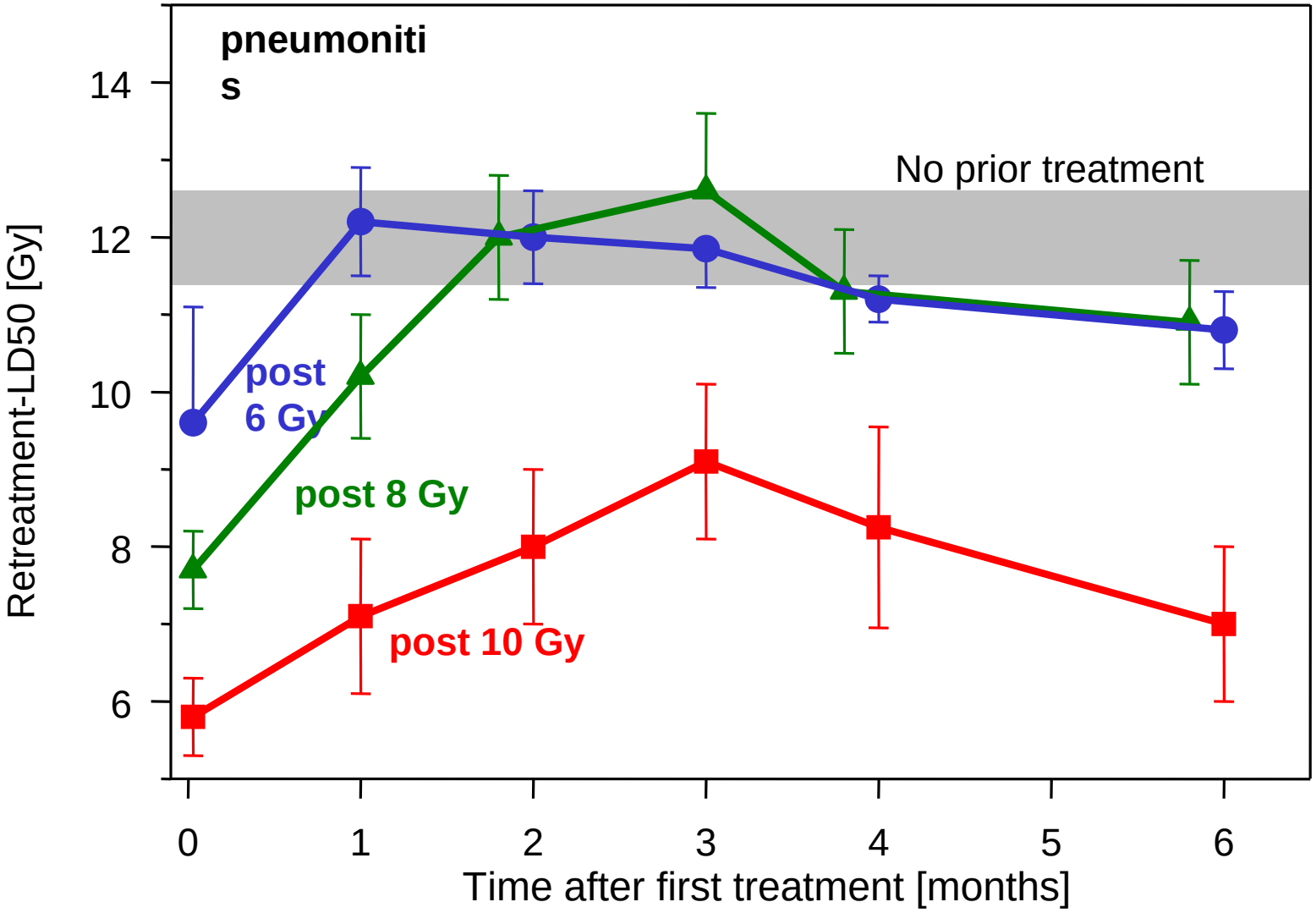
- Latent time to expression of late effects is decreased after retreatment

Late effects – soft tissues



Modified from: Brown and Probert, Radiol. 1975

Late effects - lung



Modified from: Terry et al., IJROBP 1988

Late effects - lung

Pneumonitis:

initial dose <50% tolerance:

full recovery, 2 months (mouse)

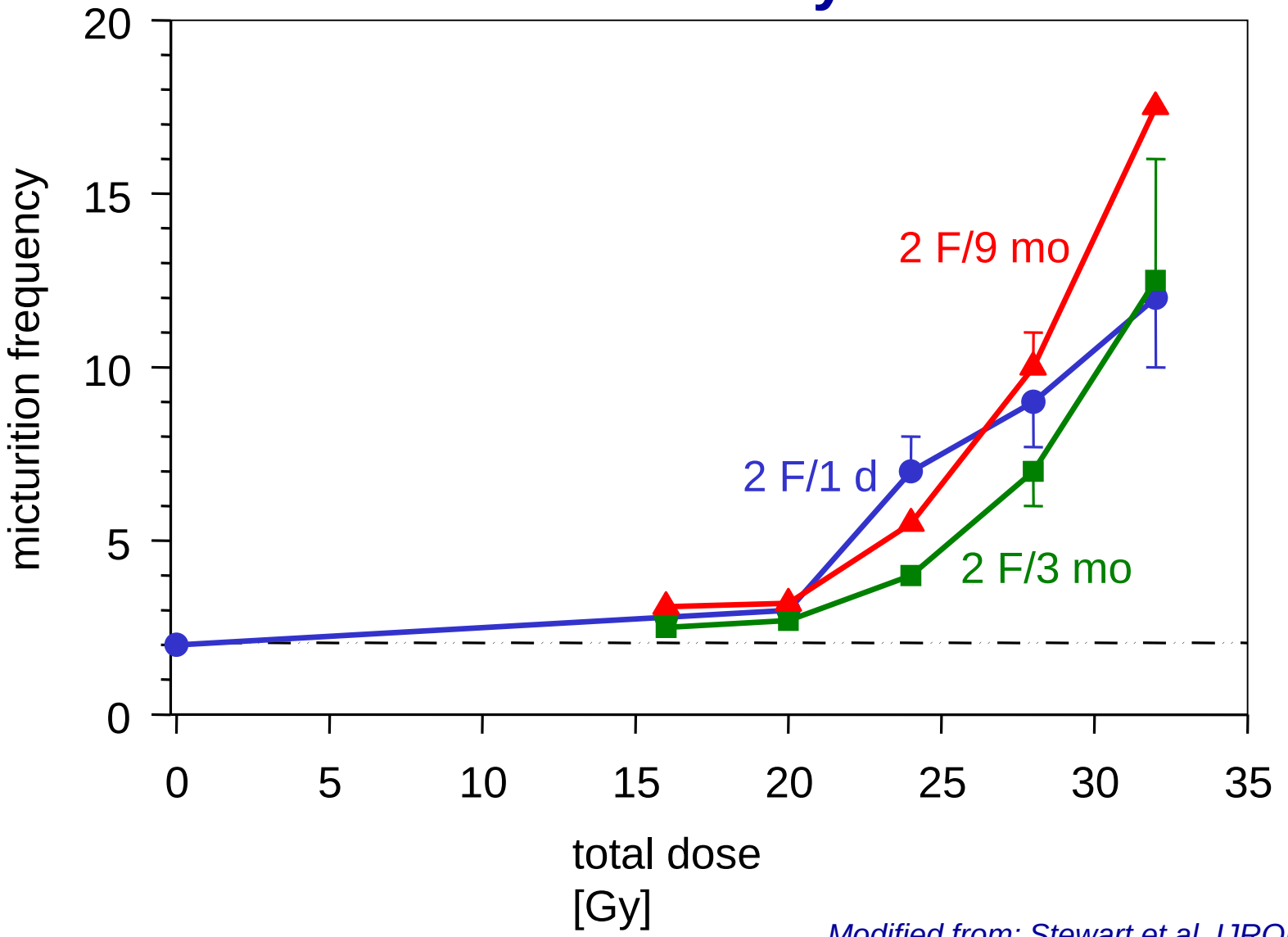
higher initial doses:

partial recovery, 3 months (mouse)

Fibrosis: ????

(retreatment tolerance < pneumonitis)

Late effects – urinary bladder

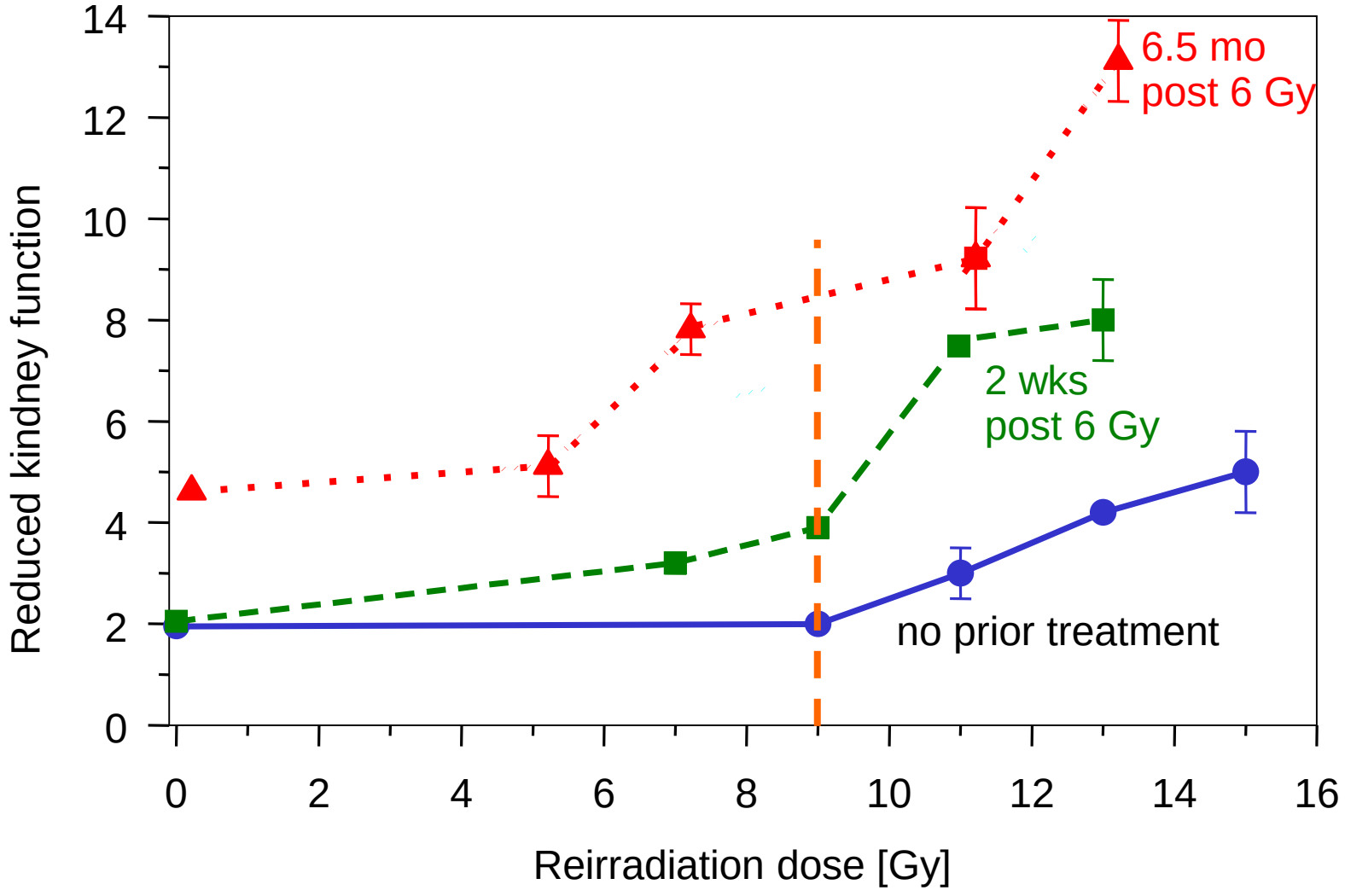


Modified from: Stewart et al. IJROBP 1990

Late effects – urinary bladder

- no recovery between 1 day and 9 months (mouse)
- progression of (subclinical) damage results in shortening of latent times after retreatment

Late effects – kidney

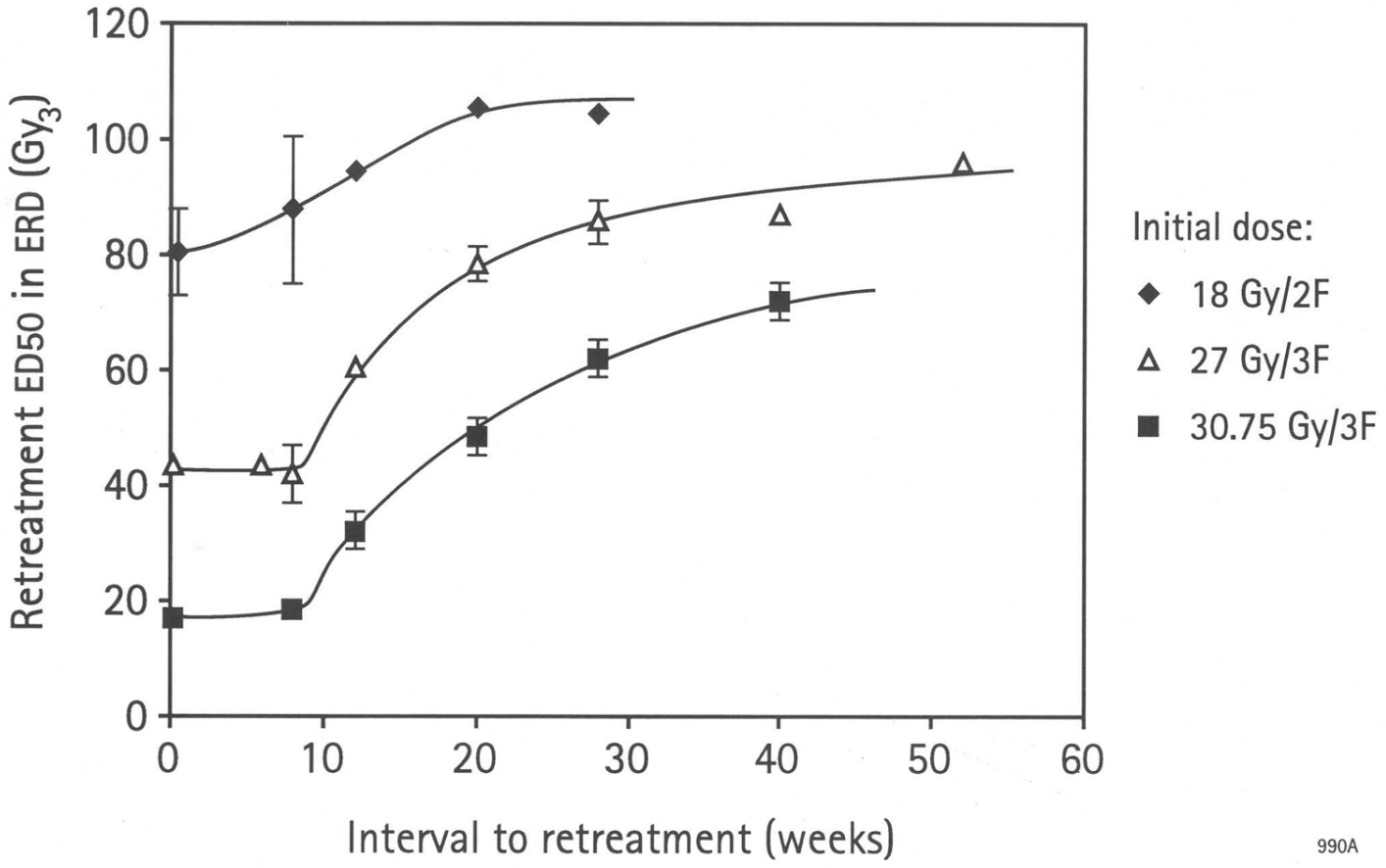


Modified from: Stewart et al. IJRB 1989

Late effects – kidney

- no recovery between 1 day and 6 months (mouse)
- progression of (subclinical) damage
- retreatment tolerance decreases with time

Retreatment tolerance: rat spinal cord



- 18 Gy/2F, 27 Gy/3F, and 30.75 Gy/3F equivalent to 72 Gy_3, 108 Gy_3, and 123 Gy_3, or 47, 71, and 89% of tolerance

Hao & Wong, 1997

Retreatment tolerance: rat spinal cord

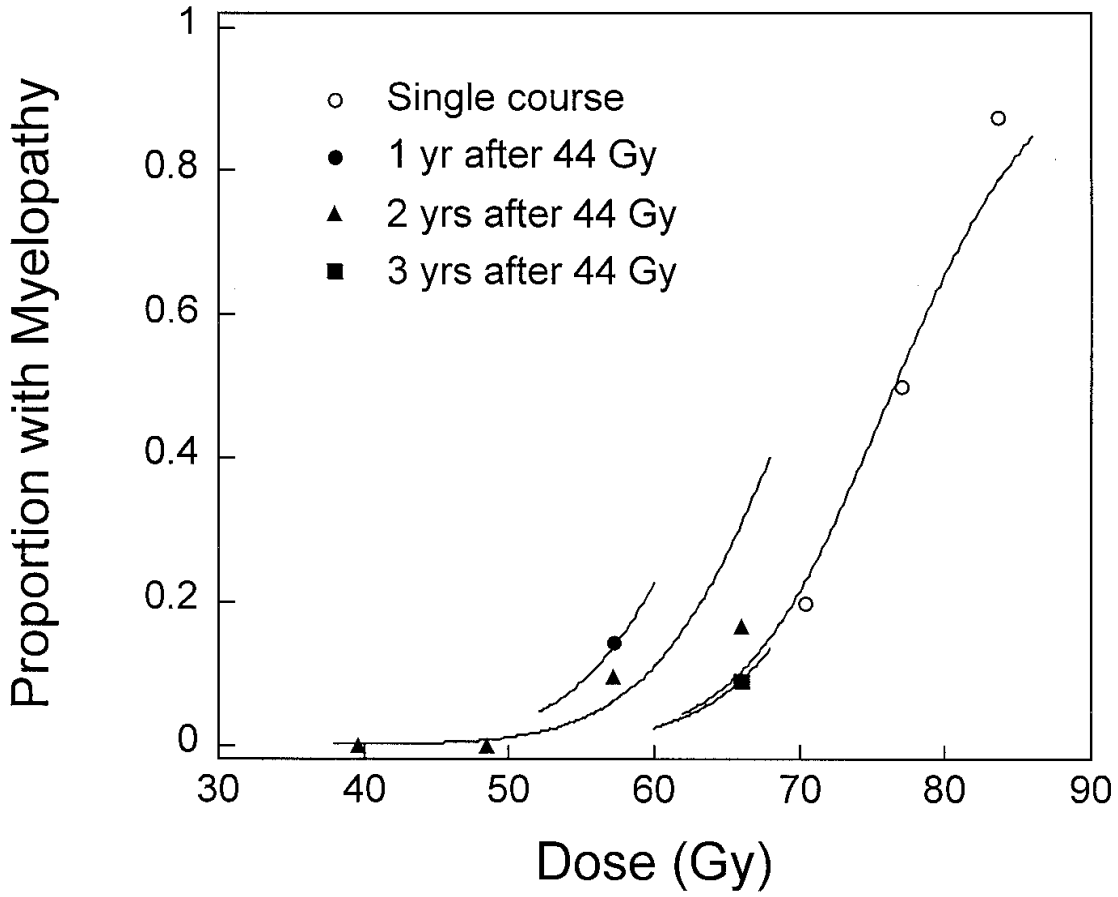
Initial RT: 9 Gy x 3 F ~ 75% tolerance
Fractionated retreatment at 20 wks: 15.5 Gy to 0.4 Gy/fraction (x 1 to 20 daily fractions)

α/β value
de novo treatment: 2.4 Gy
Retreatment: 3 Gy

Previous treatment does not alter retreatment fractionation sensitivity of rat spinal cord

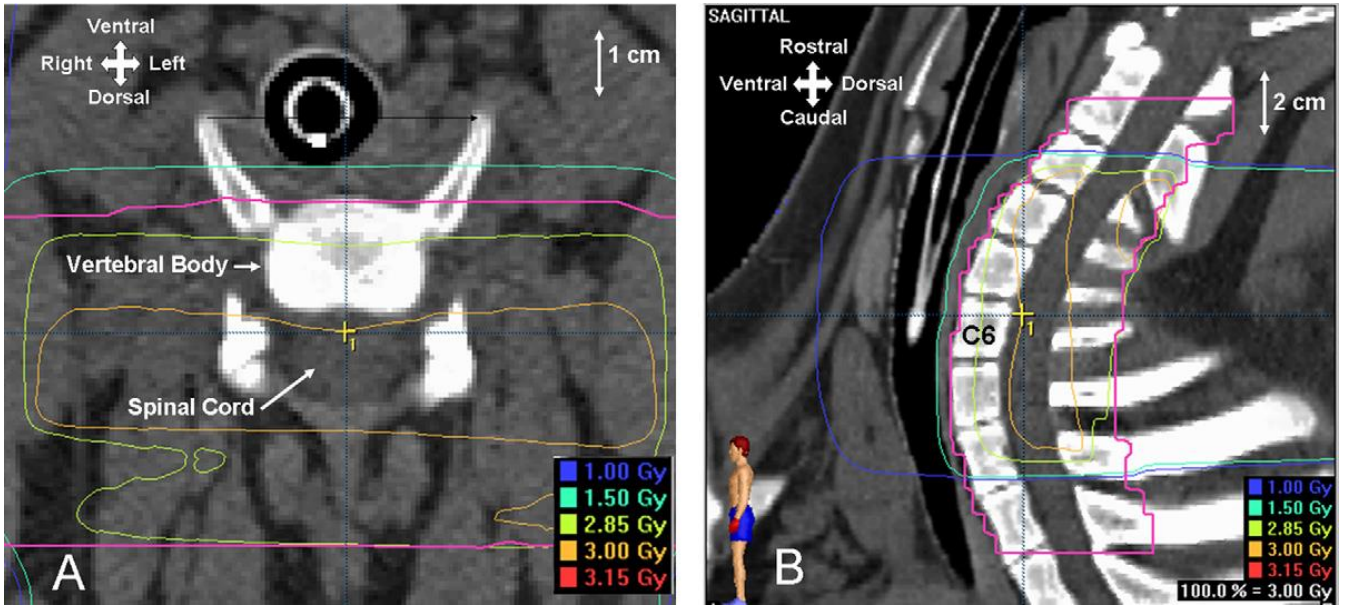
Wong et al, Radiother Oncol,1993

Retreatment tolerance: monkey spinal cord

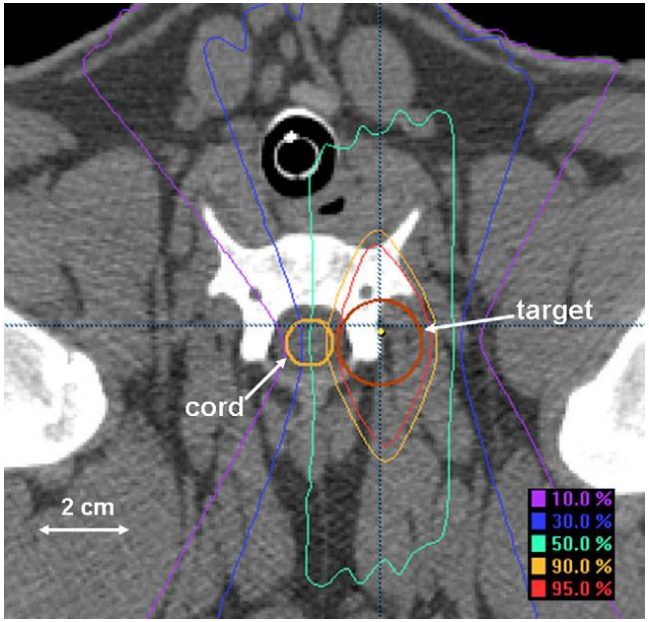


Ang et al, Red J, 2001

Retreatment tolerance: swine spinal cord



Initial RT 30 Gy/10



Retreatment after 1 yr
SBRT: 14-24 Gy in 1 fr
Dmax to cord: 14.9-25.4 Gy in 1 fr

Medin et al, 2012

Retreatment tolerance: swine spinal cord

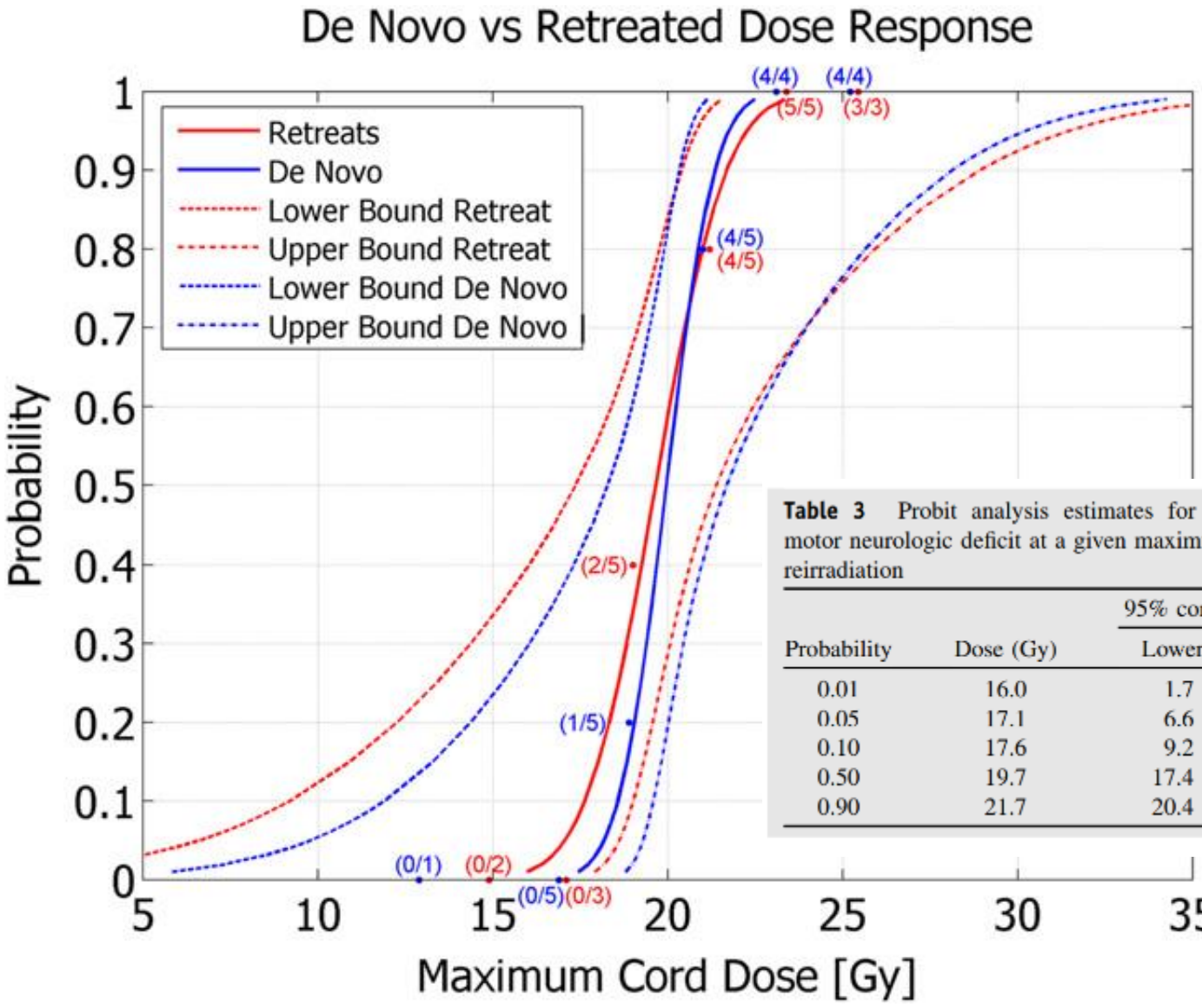


Table 3 Probit analysis estimates for the probability of motor neurologic deficit at a given maximum point dose after reirradiation

		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

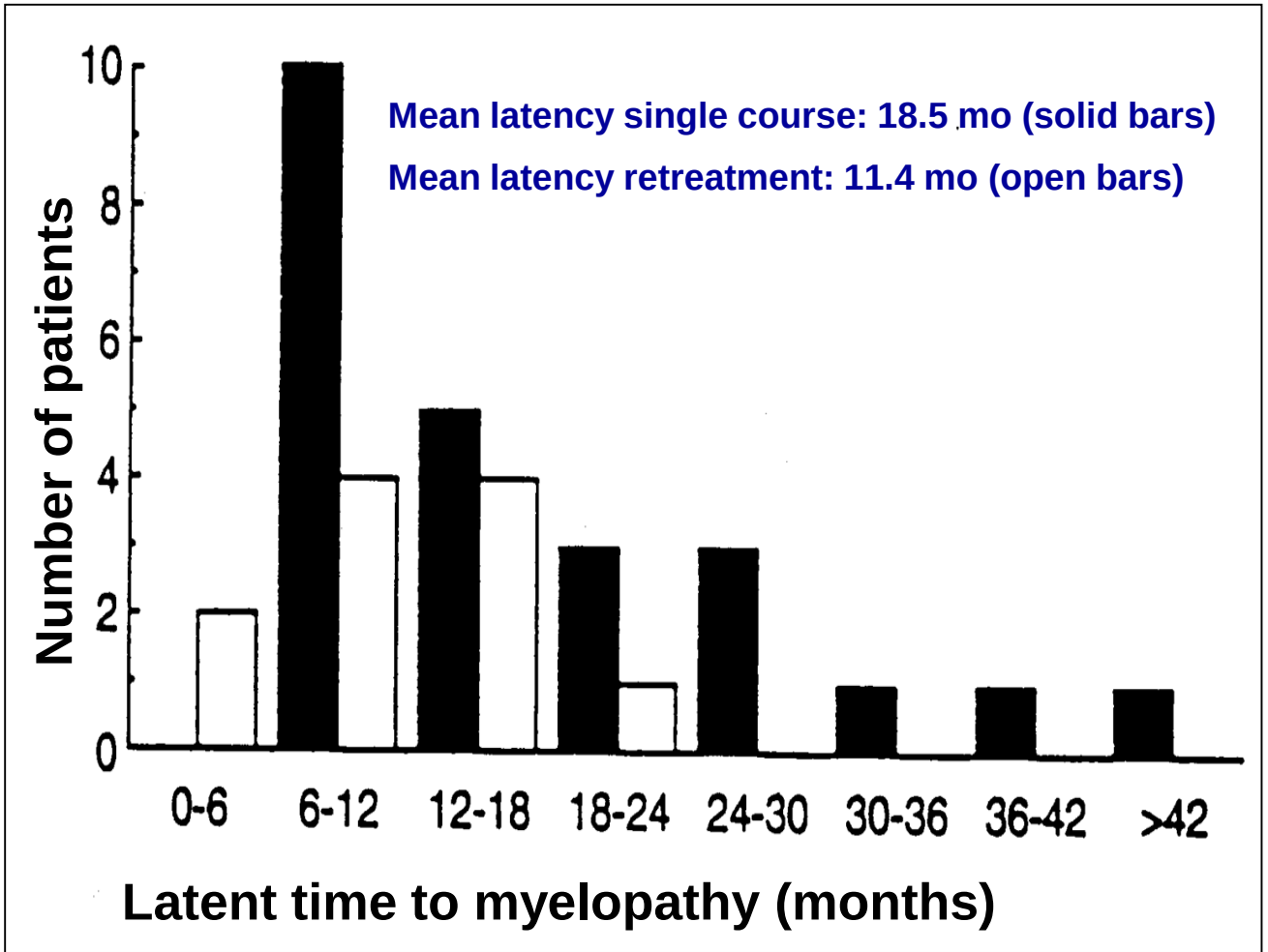
Medin et al, 2012

Summary of factors affecting spinal cord re-treatment tolerance (experimental data)

- Latent time to paralysis decreases with increasing dose of re-irradiation
- Latent time to paralysis decreases with increasing size or total dose of the initial treatment
- Large capacity for recovery of occult injury
- Retreatment tolerance increases with increasing time between initial treatment and re-irradiation
- Size of initial dose or injury influences the extent of recovery
- There is no difference in subsequent fractionation sensitivity with retreatment

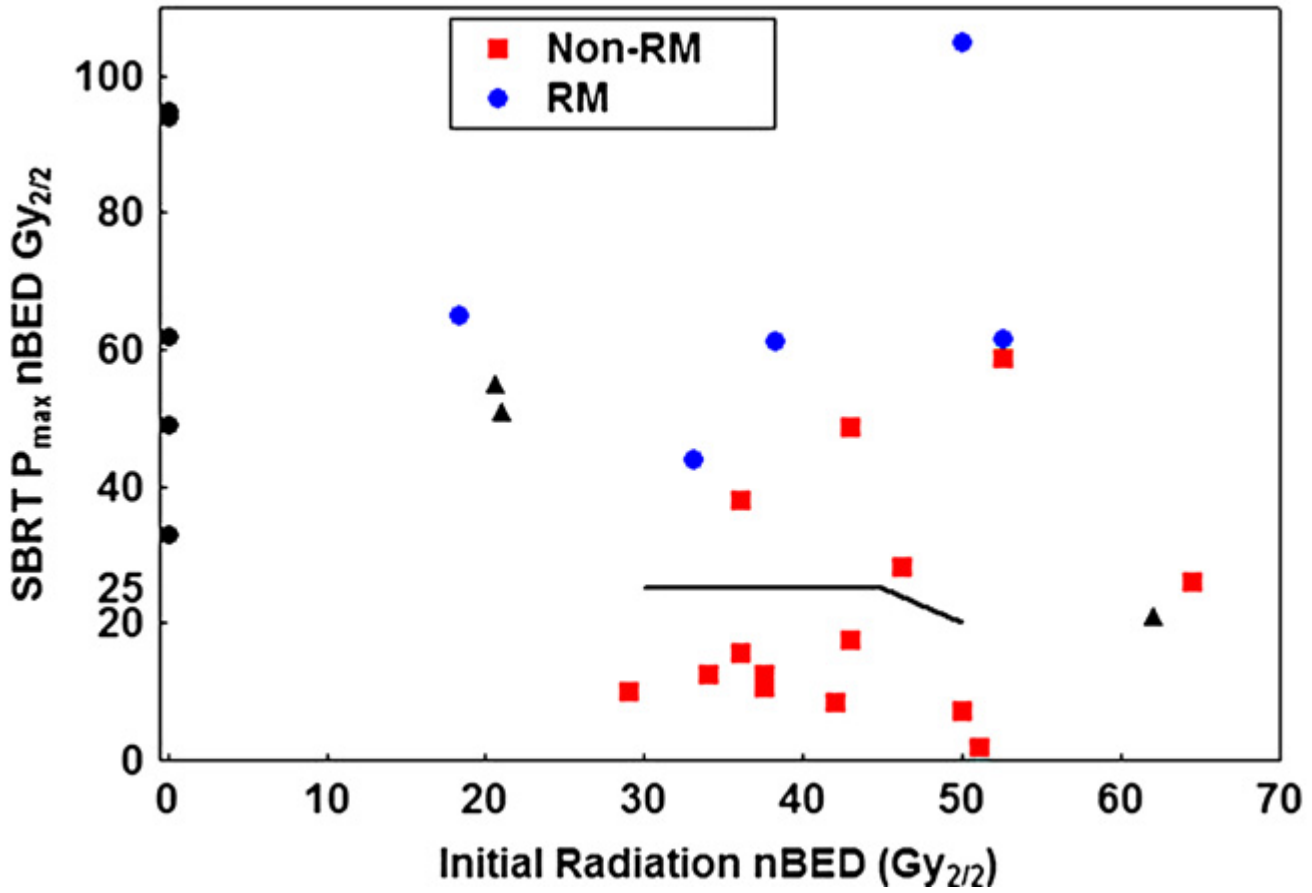
Human Data

- Retrospective only
- Latent time to myelopathy following a single course of treatment (19 mo) were significantly longer than those after re-irradiation (11 mo) *(Wong, 1994)*



Human Data

- 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



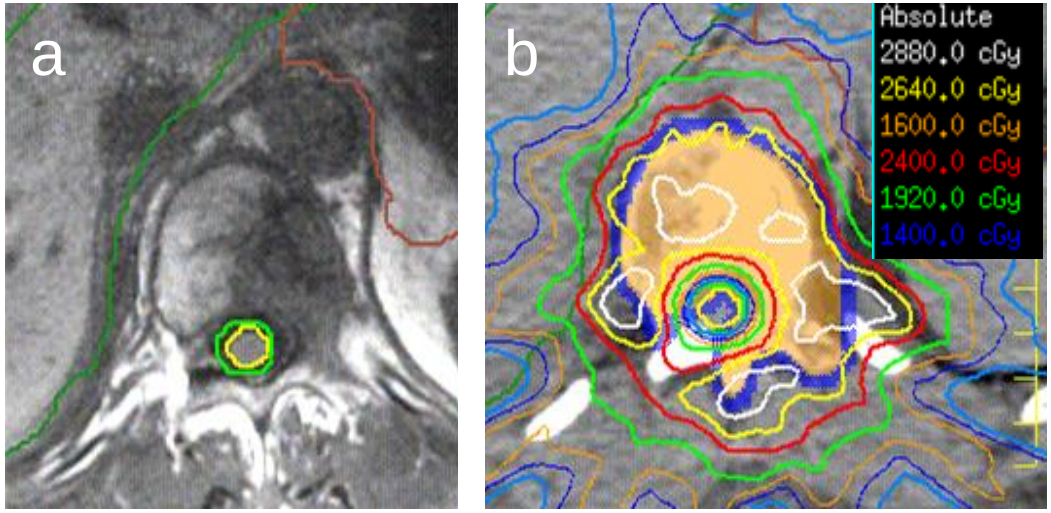
▲ RM cases, non-SBRT, *Wong 1994*

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

- Re-irradiation thecal sac P_{max} nBED <25$Gy_{2/2}$
- Total thecal sac P_{max} nBED <70$Gy_{2/2}$
- Interval to re-irradiation >5 mo

Sahgal A, Wong CS et al, Red J, 2012

Reported SBRT point maximum dose limits to the thecal sac



Prior Radiation	1 fx SBRT P_{max} limit	2 fx SBRT P_{max} limit	3 fx SBRT P_{max} limit	4 fx SBRT P_{max} limit	5 fx SBRT P_{max} limit
None	12.4 Gy	17 Gy	20.3 Gy	23 Gy	25.3 Gy
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

Wong CS et al, Spinal Cord, 2015

Clinical Implications

- There is recovery of occult injury (how much?) in spinal cord
- It may be reasonable to accept a higher tolerance for retreatment as dictated by clinical situation; patient input is important

Retreatment: Late effects

- Recovery of occult damage and hence retreatment tolerance is tissue/organ specific

- Retreatment tolerance dependent on multiple factors:
  - initial dose
  - time to retreatment

- Latent time to expression of late effect is decreased after retreatment

Questions?