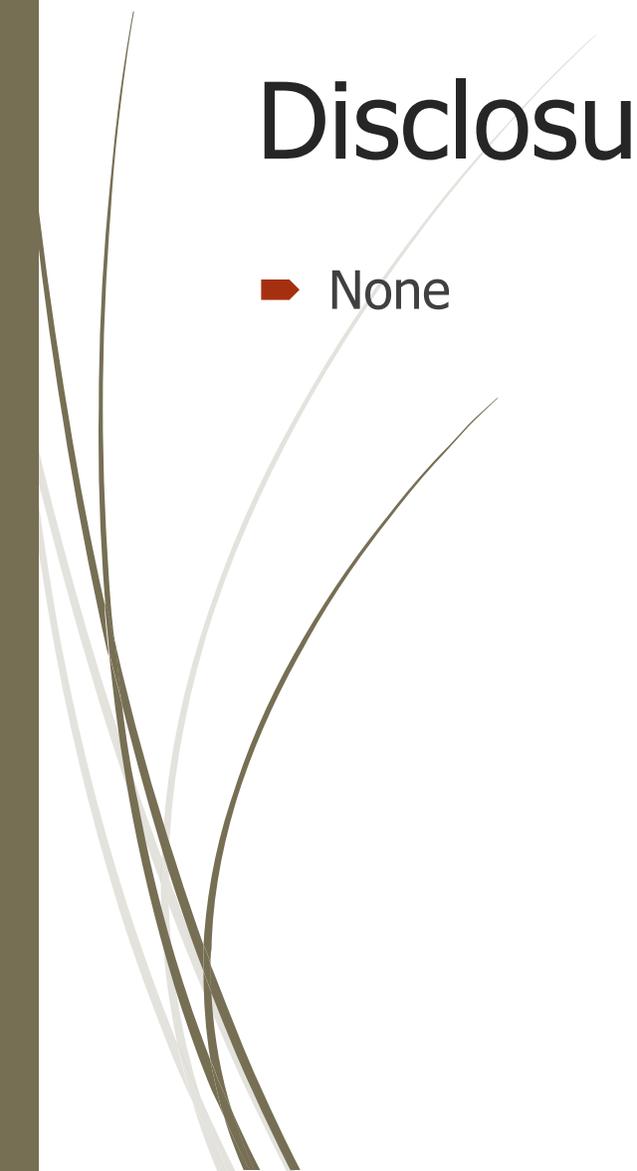




Disclosures

➤ None





Treatment breaks

- ▶ Machine down time (technical/staffing)
- ▶ Patient illness/psychosocial circumstances
- ▶ Holidays

- ▶ Mackillop's ASARA "As Short As Reasonably Achievable"

ChenZ, King W, Pearcey R, Kerba M and Mackillop WJ. The relationship between waiting time for radiotherapy and clinical outcomes: a systematic review of the literature. *Radiother Oncol* 2008; 87(1).

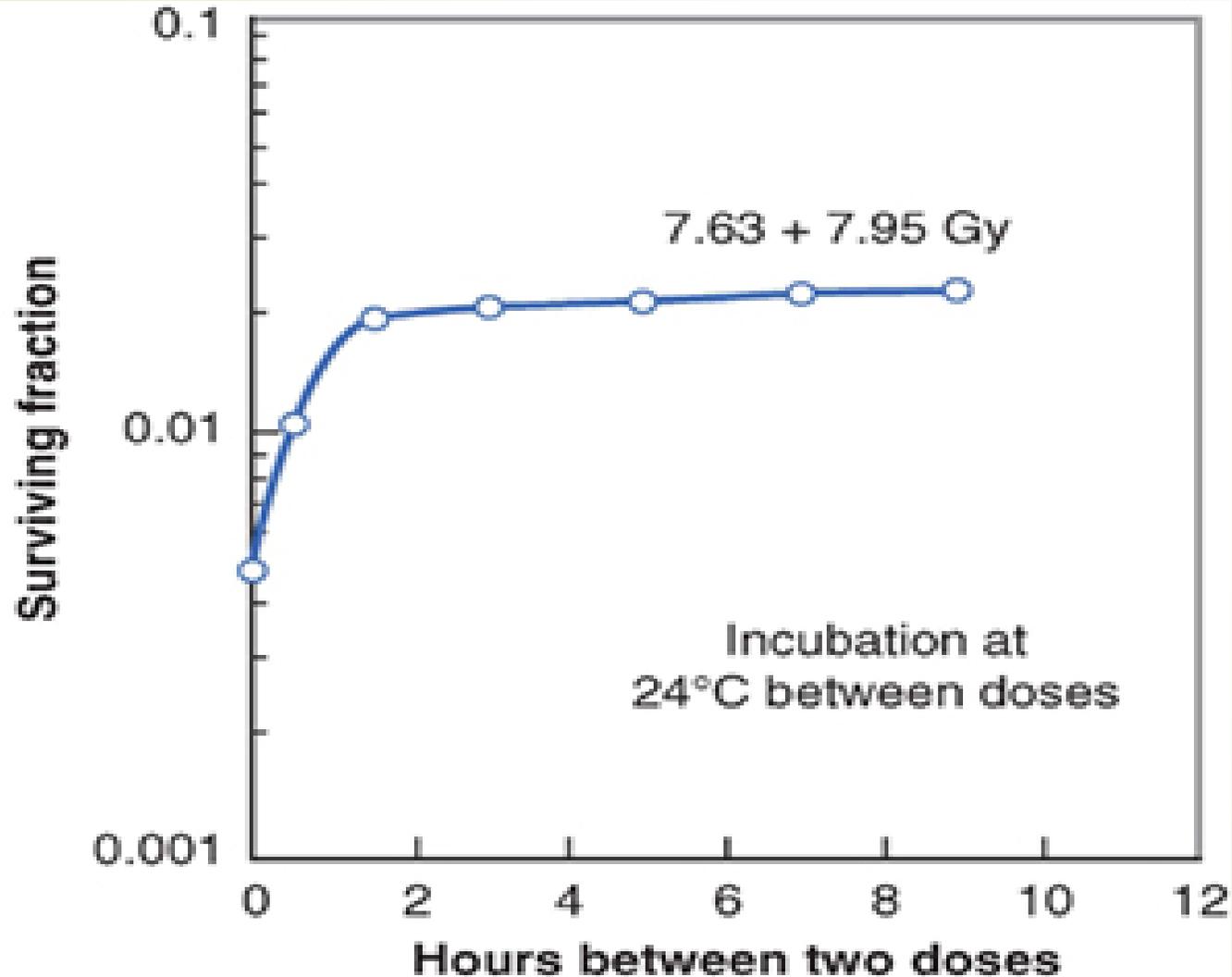
Categories of Radiation Damage

1- Lethal—irreversible, irreparable, leads to cell death

2- Sublethal Damage (SLD)—repaired in hours.

- If a second dose is given before this repair happens, new damage can interact with prior damage to create lethal damage
- Increased survival when a dose is fractionated

“Split-dose” Experiment



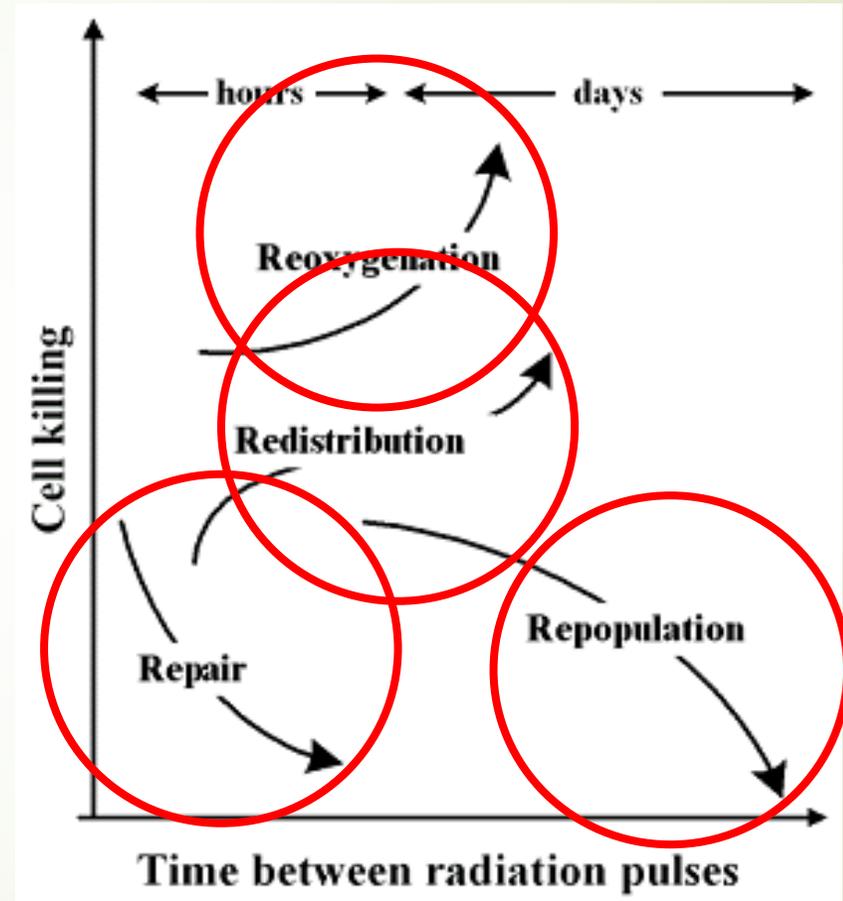
In vitro irradiation of CHO cells

Increased survival when a dose is split into two fractions separated by a time interval

There is a point at which an increase in the time between fractions will no longer increase survival—plateau in the response

4 R's of Radiation Biology

- ◆ Repair of sub-lethal damage between doses
- ◆ Reoxygenation of the tumor
- ◆ Redistribution to a radiosensitive phase of the cell cycle
- ◆ Repopulation of cells



Case 1: COVID-19 infection

- 69 yo woman with stage IB2 squamous cell carcinoma of the cervix.
- Initially diagnosed following post-menopausal vaginal bleeding and found to have a cervical mass. Biopsy confirmed invasive squamous cell carcinoma.
- PE: 3 cm tumor on exam with some tethering anteriorly concerning for possible vaginal involvement.
- PET: no obvious metastatic disease.
- Pelvic MRI: cervical mass measured 3.8 cm maximum dimension, no LAD.
- Treatment plan EBRT CRT followed by T+O brachytherapy boost.
- EBRT started on 1/10/21
- Became COVID+ after first week of tx

“Package-time”

- 1224 pts locally advanced SCC cervix, single-institution retrospective study.
- Definitive radiation with EBRT and brachytherapy boost with 2 intracavitary tx.

	≤7 weeks package-time	>9 weeks package-time	p-value
10 -yr Pelvic Failure Rate	7%	36%	≤0.01
10-yr CSS	86%	55%	≤0.01

- Although all stages were impacted, stage IB were most

“Package-time”

RTOG Report HN trials (fractionation and radiosensitizers)

MVA: Other unacceptable variations, TNM stage, KPS and higher risk primary site (oral cavity and hypopharynx).

	Treatment break ≤14 days	Treatment break >14 days	p-value
3-yr local control rate	27%	13%	≤0.01

Major variations of overall treatment time was found to be a significant detrimental factor

“Package-time”

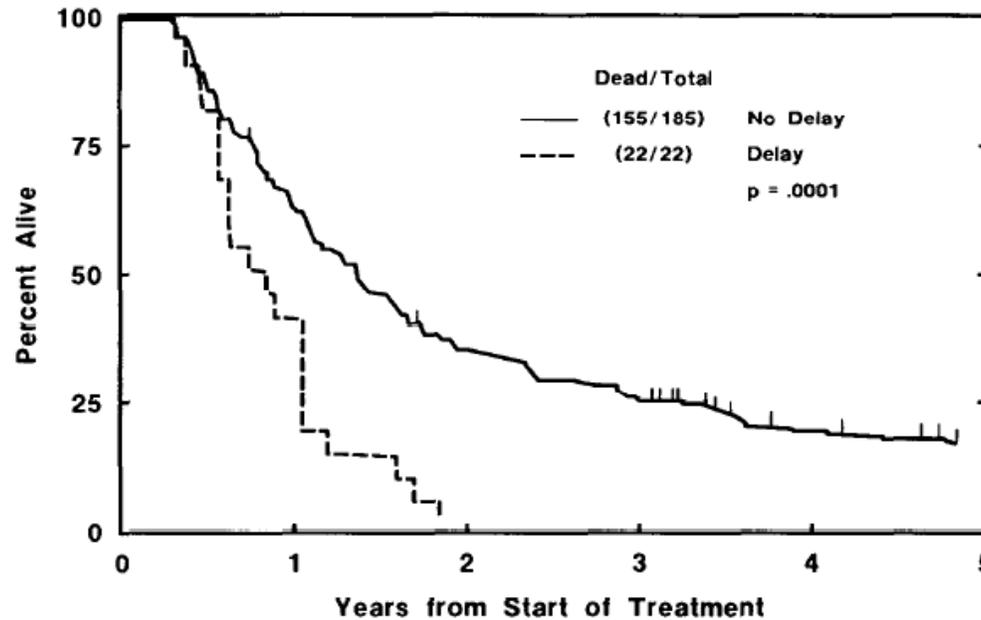


Fig. 2. NSCLC, Stage III, KPS \geq 70, weight loss \leq 5%. Total dose \geq 69.6 Gy (RTOG 8311). Effect of treatment interruptions on survival in high-total dose HFX patients.

- ▶ RTOG metaanalysis: Same delay effect seen in patients irradiated with higher doses (69.6 Gy) for unresectable non-small cell lung cancer.

Cox, J. D., et al. Interruptions of high-dose radiation therapy decrease long-term survival of favorable patients with unresectable non-small cell carcinoma of the lung : Analysis of 1244 cases from 3 Radiation Therapy Oncology Group (RTOG) trials. *Int. J. Radiat. Oncol. Biol. Phys.* 27:493-498; 1993.

Case 1: COVID-19 infection

- COVID-19 symptoms resolved after 2 days (mild fever, fatigue cough)
- Ideally wait 20 days post-symptom onset before lifting quarantine for immunosuppressed patient. But this would result in total treatment course >9 weeks.
- Need to weigh risk to patient and staff (vaccinations available)
- Shorten delay to 1 week after symptoms resolved, total treatment break 7 days
- Time made up by BID tx once per week for the remaining weeks and efforts made to minimize delay in completing her brachytherapy boost to keep total package time to 7 weeks.
 - BID tx should not be used when fraction sizes are > 2.2 Gy
 - Minimum 6 hours between BID treatments

SAM Question #1

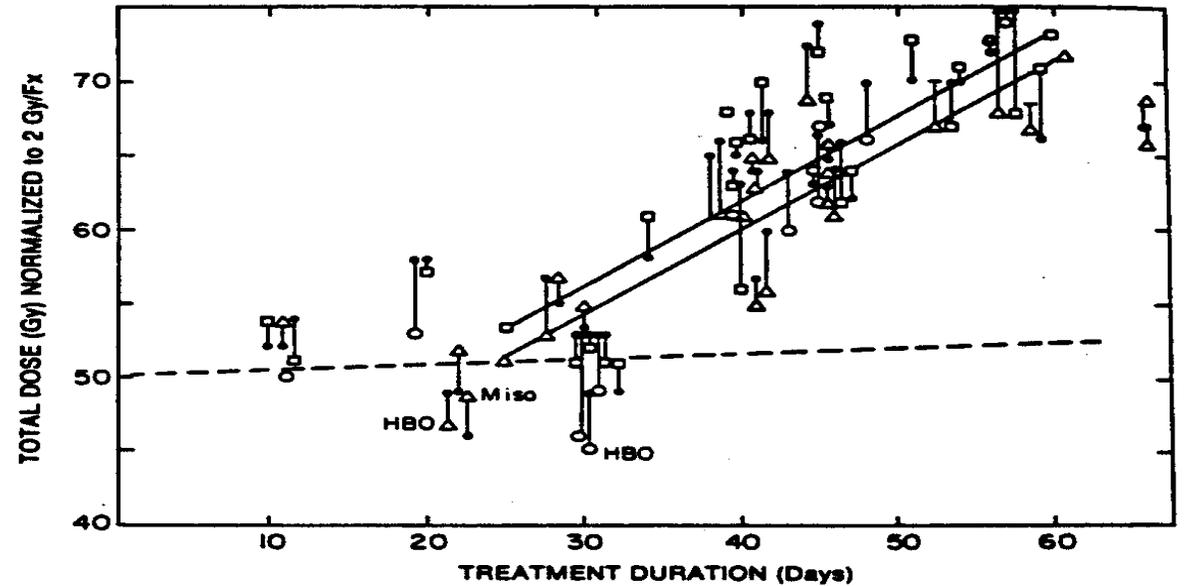
Radiation treatment breaks longer than 2 weeks often:

- A. worsen acute radiation reactions, such as oral mucositis or moist desquamation
- B. worsen local tumor control due to tumor cell repopulation and increased proliferation.
- C. worsen local tumor control due to reoxygenation of the tumor, resulting in decreased tumor radiosensitivity
- D. worsen late radiation reactions, such as soft tissue fibrosis or myelopathy
- E. improve local tumor control due to neovascularization and improved antigen delivery

The Withers “Hockey Stick”

- Doses to achieve TCD50 for human SCC vs. treatment time
- Compensatory dose 0.6Gy/day to achieve same tumor control (modern meta-analysis estimates 0.7-0.9Gy/day)
- Also estimated 1% loss of local control for each day of treatment prolongation

Withers HR, et al. Acta Oncol 27:131, 1988



Data suggest linear time factor -- Proliferative response delayed 2-4 weeks (Roberts, SA, et al. The delay before onset of accelerated tumour cell repopulation during radiotherapy. Radiother. Oncol. 29:69-74; 1993.)



SAM Question #2

Based on experience in head and neck cancers, accelerated repopulation likely begins how long after the start of conventionally fractionated radiation therapy?

- A. <1 week
- B. 2-4 weeks
- C. 3 months
- D. 6 months
- E. None of the above

Case 2: Tx break for skin breakdown

- ▶ 58yo man, never smoker, hx with p16+ HPV associated SCC of the Oropharynx, T3 N3 M0.
- ▶ Definitive concurrent IMRT 70Gy and q3wk high dose cisplatin.
- ▶ Developed G3 skin reaction in 6th week of treatment.

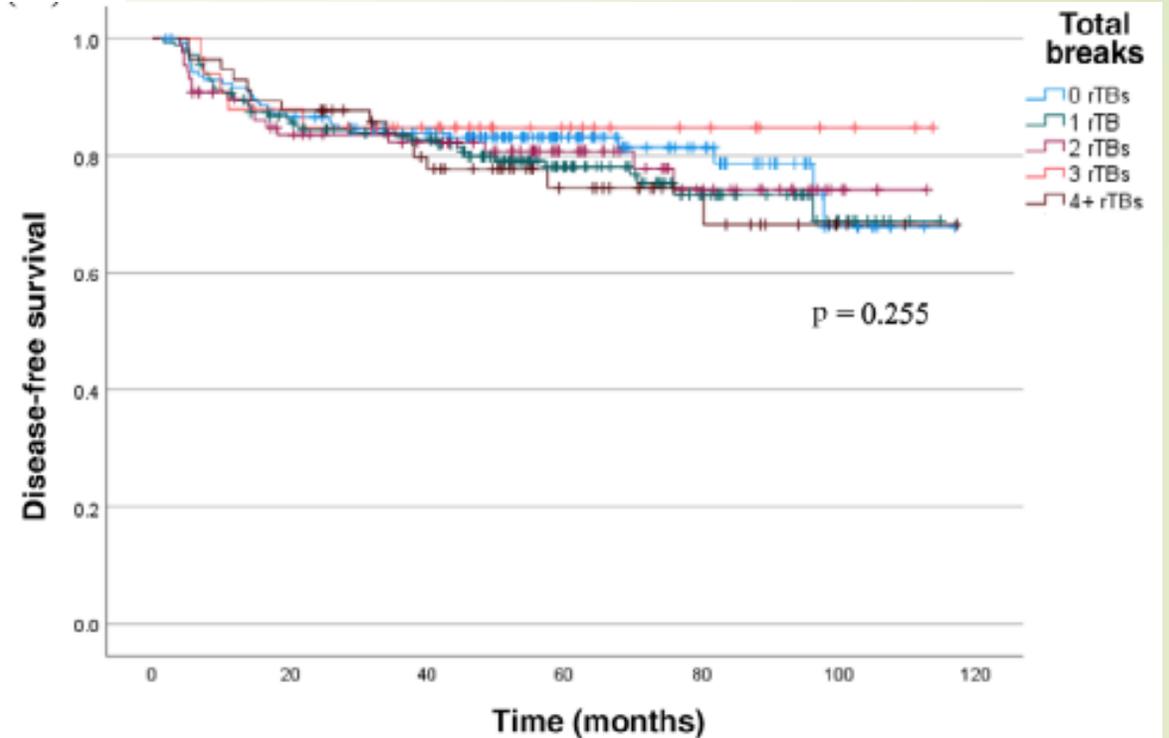


Royal College Radiologists Guidelines

- Category one patients:
 - Rapidly growing tumors (SCC HN, Anus, Lung, Cervix)
 - Tx with radical intent
 - Recommendation: treatment duration not prolonged by more than 2 days
- Category two patients:
 - Slower growing tumors tx with radical intent
 - Adjuvant treatment
 - Recommendation: treatment duration prolonged by more than 5 days may not be deleterious, but avoid more than 2 day breaks when possible.
- Category three patients:
 - Palliative tx
 - Recommendation: treatment duration prolonged by more than 5 days may not be deleterious, but breaks >7 days may require compensation to achieve desired palliative effect

The effect of short radiation treatment breaks on chemo-radiotherapy for oropharyngeal cancers

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- In oropharyngeal SCC patients treated with definitive concurrent chemoradiotherapy, there is no significant association between disease failure and total radiation treatment breaks of ≤ 3 consecutive or scattered days.



Case 2: Tx break for skin breakdown

- Skin wound treated with local care (silvadine, vasoline gauze dressing, saline soaks) and pain management.
- Patient given treatment break for 2 days
- At 2 days, continued severe pain, swelling and areas of spontaneous bleeding within confluent desquamation
- Given 1 more day of scheduled tx break followed by planned weekend 2 day break.
- At 5 days, patient's pain improved, no longer bleeding, skin islands forming.
- Restarted treatment and completed last 5 days of course.
- No modification made for additional compensatory dose given severity of skin reaction and clinical tumor response.



Case 3: Neutropenia

- ▶ 63 yo man with T2N2M0 NSCLC
- ▶ IMRT single-level plan 60 Gy concurrent Carbo/Taxol
- ▶ During the 5th week of tx developed diarrhea and severe neutropenia (ANC=0!)
- ▶ Hospitalized, GM-CSF, Abx, IV hydration, and treatment break
- ▶ Checked ANC daily, 4 days for ANC >500
- ▶ How can you adjust dose to make up for tx prolongation

Linear-Quadratic Model

- ▶ Introduced in the 1980's, the L-Q model initially based on cell survival after radiation exposure became the model of choice to estimate the biological effect of different dose-fractionation schedules.
- ▶ Estimates the contributions of cell killing that have a linear or quadratic relationship to dose
 - ▶ Survival Fraction = $e^{-(\alpha D - \beta D^2)}$
- ▶ $\frac{\alpha}{\beta}$ = "alpha-beta ratio" \approx how much the tissue affected by fractionation

Normalizing dose to “Standard Fractionation”

- ▶ $\frac{\alpha}{\beta} = 8 \text{ to } 10$ Acute normal tissues and most tumors
- ▶ $\frac{\alpha}{\beta} = 1 \text{ to } 3$ Late normal tissues
- ▶
$$\text{EQD2} = dn \cdot \frac{d + \frac{\alpha}{\beta}}{2 + \frac{\alpha}{\beta}}$$
- ▶
$$\text{EQD2} = 4 \times 4 \cdot \frac{4 + 10}{2 + 10} = 18.7 \text{ Gy (early)}$$

$$\text{EQD2} = 4 \times 4 \cdot \frac{4 + 2}{2 + 2} = 24 \text{ Gy (late)}$$
- ▶ $18.7 - 16 = 2.7 \text{ Gy (early)}$ $24 - 16 = 8 \text{ Gy (late)}$

Estimating Dose “lost” to Proliferation

➤ $\text{EQD2}_{\text{break}} = \text{EQD2}_{\text{conv}} - (T_{\text{break}} - T_{\text{conv}}) \cdot D_{\text{prolif}}$

➤ $\text{EQD2}_{\text{break}} = 60 \text{ Gy} - (46 \text{ days} - 40 \text{ days}) \cdot 0.7 \text{ Gy/day}$

➤ $\text{EQD2}_{\text{break}} = 60 \text{ Gy} - 4.2 \text{ Gy}$


$$\text{EQD2} = \text{dn} \cdot \frac{d + \frac{\alpha}{\beta}}{2 + \frac{\alpha}{\beta}}$$

$$\text{Early: } 16 + 4.2 = d \cdot 8 \cdot \frac{d + 10}{2 + 10} = \frac{8d^2 + 80d}{12}$$

$$0 = 8d^2 + 80d - 242$$

$$d = \frac{-b \pm \sqrt{b^2 - 4ac}}{2a}$$

$$d = \frac{-80 \pm \sqrt{80^2 + 4 \cdot 8 \cdot 242}}{2 \cdot 8}$$

$$d = 2.44 \text{ Gy}$$

Normalizing dose to “Standard Fractionation” again

Early ($\frac{\alpha}{\beta} = 10$)

$$\text{EQD2} = 4 \cdot 4 \cdot \frac{4+10}{2+10} = 18.7 \text{ Gy}$$

$$18.7 - 16 = 2.7 \text{ Gy}$$

Late ($\frac{\alpha}{\beta} = 2$)

$$\text{EQD2} = 4 \cdot 4 \cdot \frac{4+2}{2+2} = 24 \text{ Gy}$$

$$24 - 16 = 8 \text{ Gy}$$

$$\text{EQD2} = 2.44 \cdot 8 \cdot \frac{2.44+10}{2+10} = 20.2 \text{ Gy}$$

$$20.2 - 16 = 4.2 \text{ Gy}$$

(Same number “lost” dose)

$$\text{EQD2} = 2.44 \cdot 8 \cdot \frac{2.44+2}{2+2} = 21.6 \text{ Gy}$$

$$21.6 - 16 = 5.6 \text{ Gy}$$



SAM Question #3

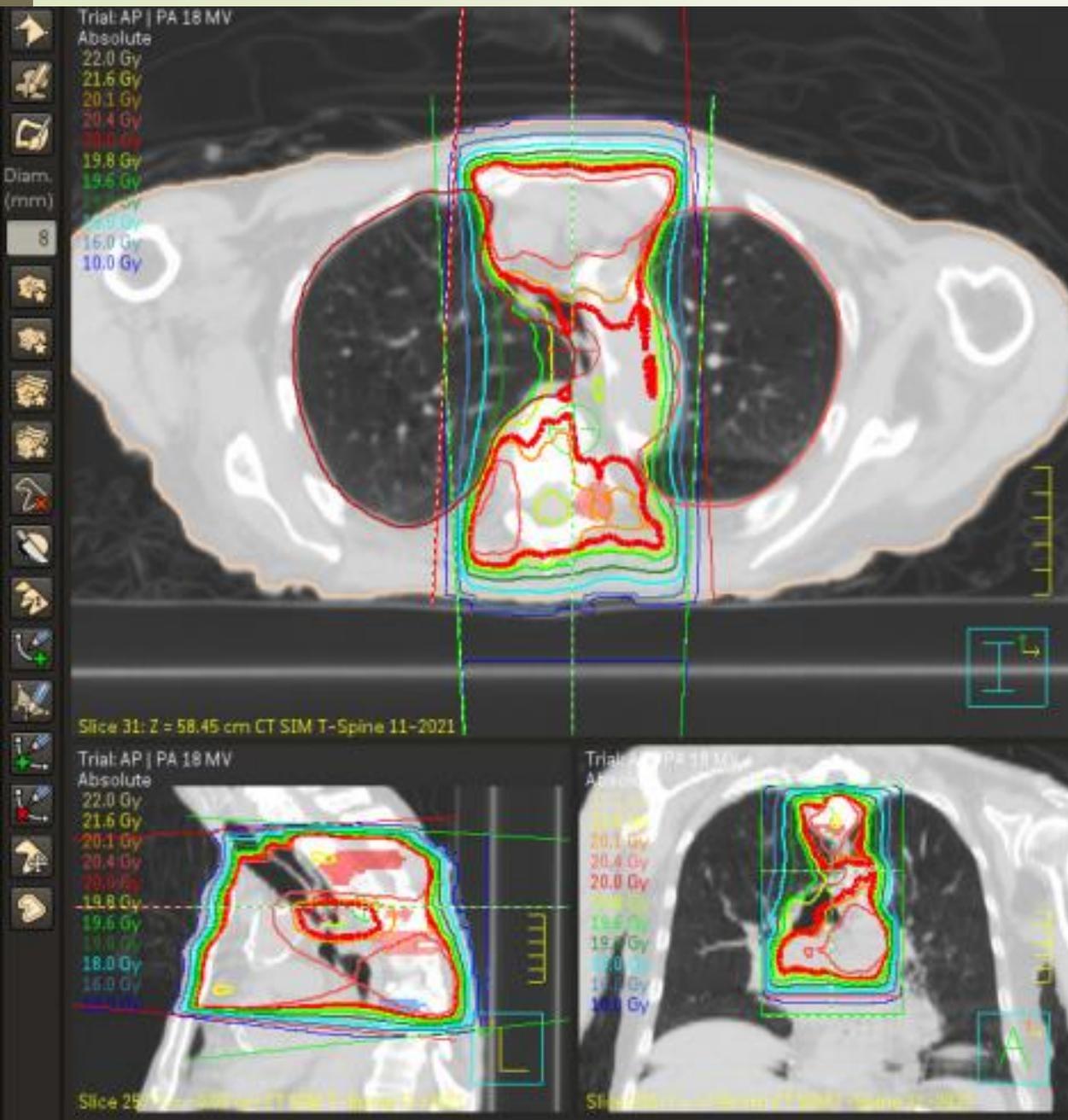
The EQD2 formula, which provides a simple way of calculating radiotherapy schedules with different dose per fraction but the same total effective dose, is based on which model for cell survival after radiation exposure?

- A. Linear-Quadratic Model
- B. Single-hit, Target Cell Model
- C. Linear no-threshold Model
- D. Multi-hit, multi-fraction Target Cell Model
- E. Differential Fractionation Model



Case 4: Emergency Tx on a Friday

- 89 yo man with metastatic prostate cancer presented with progressive lower extremity weakness over the course of a few days.
- MRI demonstrated diffuse metastatic lesions in the thoracic spine and L2, with soft tissue extension with cord compression at T3-T4 and T5-6.
- He was started on dexamethasone 10mg loading dose followed by 4mg Q6H.
- Neurosurgery was consulted and did not recommend surgical intervention.
- PE: Unable to move bilateral lower extremities.



- Recommended palliative radiation to the thoracic spine.
- Start radiation same day as consult.
- Plan 20 Gy (4 Gy x 5) to T2-T7
- 3D conf 18 MV photons AP/PA .



The 5th fx on Holiday Weeks

How? Can be BID on one of the days, or Sat or Sun tx

Who? Rapidly proliferating histology getting definitive treatment (RCR category 1)

SCC HN, cervix, esophagus, anus, vagina, vulva

NSCLC and SCLC

Meduloblastoma and PNETs

High grade lymphoma

Inflammatory breast

Anaplastic Thyroid

Last single fraction remaining after a 3-day weekend for category 2

Clinically critical response time: spinal cord compression, SVC, bleeding, airway compression



Conclusions:

- Clinical decisions are guided by radiobiological principles supported by clinical data
- Mackillop's ASARA "As Short As Reasonably Achievable"
- Early tx breaks can often be made up with BID or weekend tx
- Accelerated proliferation and short amount of catch-up time for prolonged breaks at end of tx require calculations and careful consideration balancing loss of tumor control with late effects.
- Have a policy for prioritizing category 1 patients to received planned 5th fx on holiday weeks