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ALTERED FRACTIONATION RADIOBIOLOGICAL BASIS IMPROVING THERAPEUTIC RATIO

What to Discuss

- Altered Fractionation
- Radio sensitivity
- 4 R's of Radiobiology
- Cell survival Curve
- L-Q Model
- Radiobiological Basis
- Clinical Experience
- Conclusion

History

- Jan.29,1896: 18 daily 1-hr RT fractions in Ca Breast: June ,1899:50 # in ca cheek,at Stockholm, curative
- 1920s :Ram's Experiment by Regaud in Paris
- 1932:Coutard published results and established Fractionation as standard of Practice
- Radiobiological basis recent

What is Fractionation

- Required Radiation Dose for Cure /Adjuvant /Palliation
- Total dose divided into several smaller parts,called fractions

- Total Dose – D in Gy
- Dose per fraction—d Gy
- No. of Fractions—N
- Total treat time—T days
- Inter fract time—t hrs
- D d
- N
- T t

Conventional

- d 1.8-2.2 Gy
- #/wk 5
- D 60-70 Gy
- N 30-35 #
- T 6-7 wks

- Used for most patients Worldwide
- Established clinical experience
- Reached a plateau 60-70Gy/ 30-35#/ 6-7 wks

Altered

- What is Altered
- N
- d
- T
- t
- D

- Hyper #
- Hypo #
- Accelerated
- Accelerated Hyper/Hypo
- CHART/CHARTWEL
- Dynamic #

Main characteristics of the conventional and altered fractionation schedules.

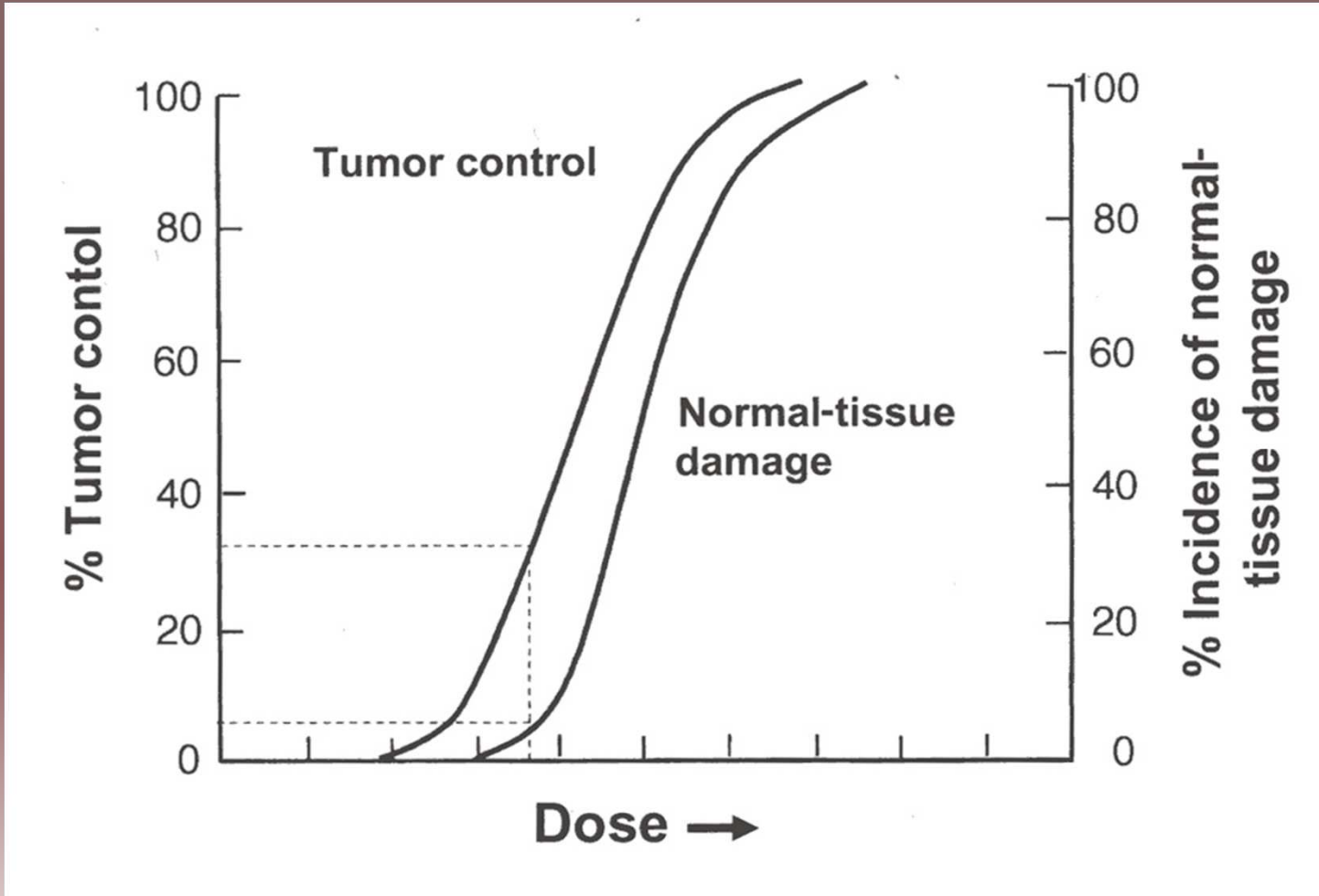
Fractionation regimen	Conventional	Hyperfractionated	Accelerated
Aim	To control the tumour through redistribution and reoxygenation at the same time as sparing normal tissue through repair and repopulation	To exploit the differences in radiosensitivity of tumour and healthy cells	To overcome tumour repopulation during treatment
Dose/fraction	2 Gy	<2 Gy	⩾2 Gy
Number of fractions/day	1	2–3	1
Days of treatment/ week	5	5	6
Overall dose	70 Gy	⩾70 Gy	<70 Gy
Overall treatment time	7 weeks	7 weeks	5 weeks

Radiosensitivity

- Therapeutic Ratio
- TR= Tissue Tolerance / Tumor Lethal Dose
- > 1- radiosensitive
- < 1 - radioresistance
- ~ 1 - tumor of limited sensitivity

- Sensitive- Seminoma Lymphoma
- Resistant – Sarcoma Melanoma
- Limited Sensitivity- Carcinomas
- Majority tumors of limited sensitivity

Dose-Response Relationships



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4 R's of Radiobiology

- Repair of Sub Lethal Damage
- Repopulation
- Reoxygenation
- Redistribution

- Saves normal tissue Vs Cancer
- Saves Cancer
- Increase cancer kill
- Increase Cancer kill

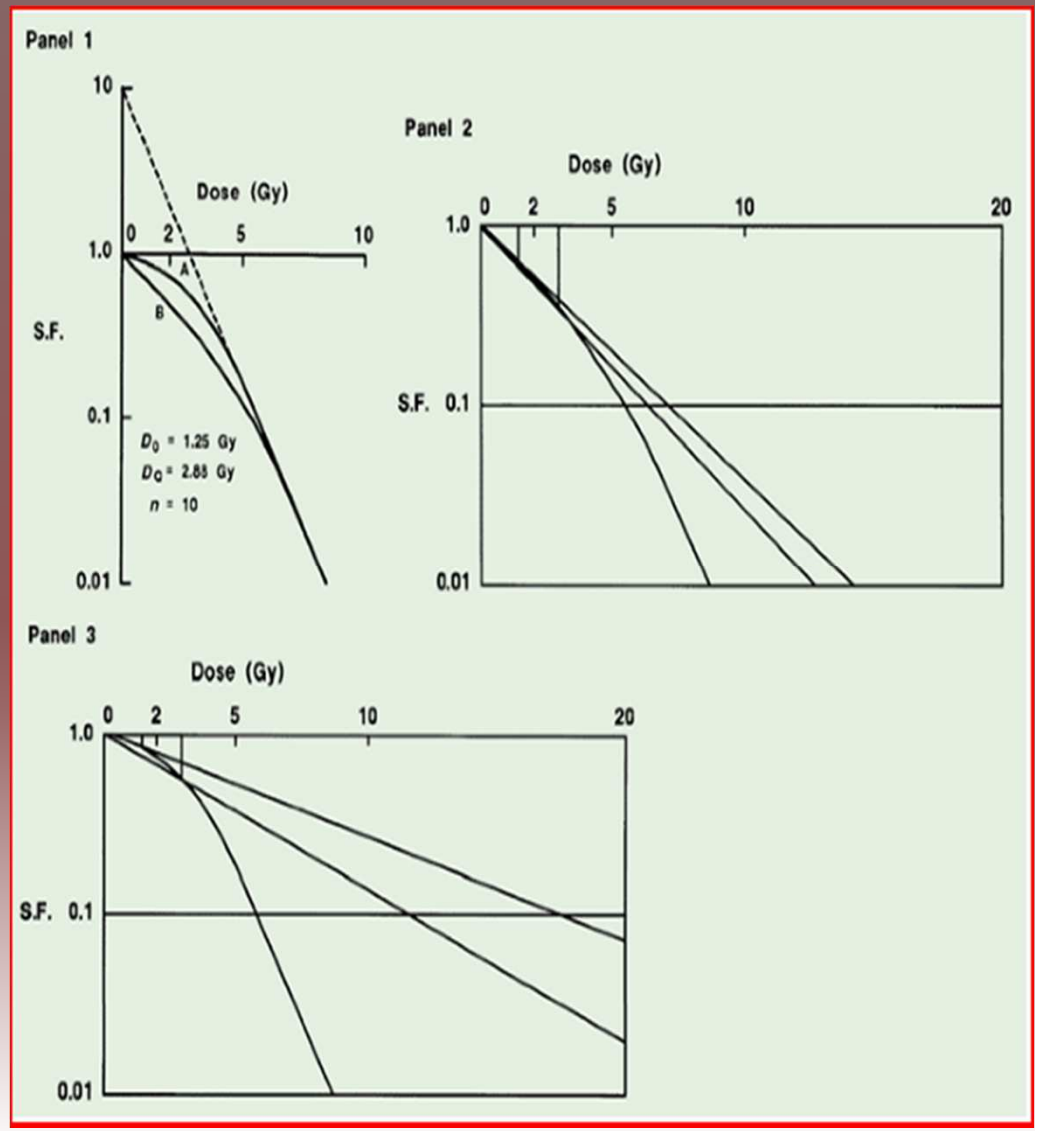
Cell survival curve

- For Single # dose vs
  Survival Fraction

Initial slope –single particle event/single hit single target

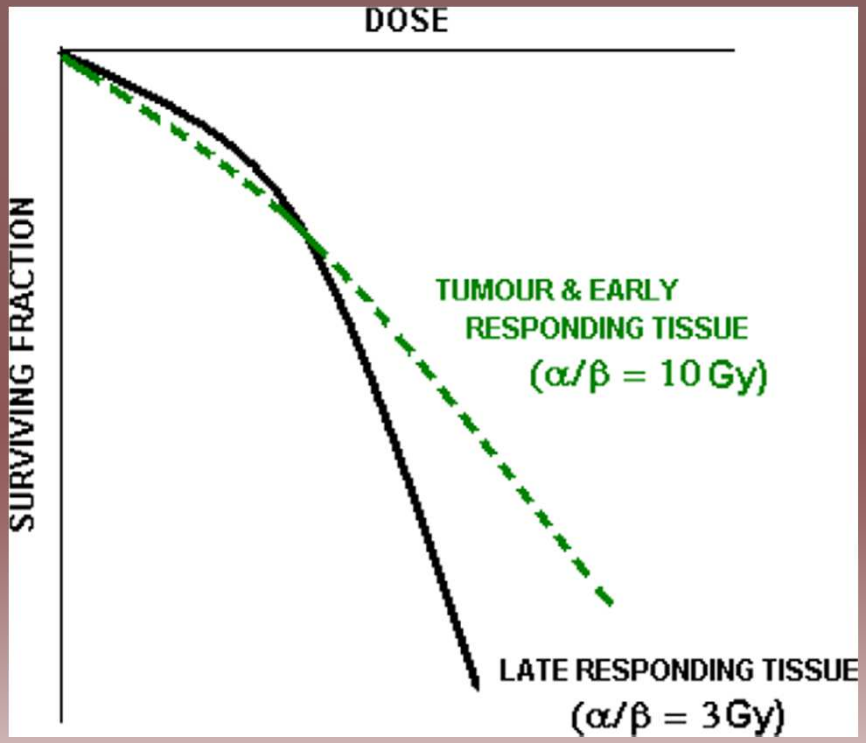
Shoulder- Repair SLD

Subsequent linear curve



Cell survival curve
single # dose vs survival

- L-Q Model
- Irreparable damage
- alpha d-A
- Reparable damage
- beta d2-B
- Alpha/beta= dose in Gy at which A=B
- For cancer -5-20Gy
- Normal tissue-1-4 Gy



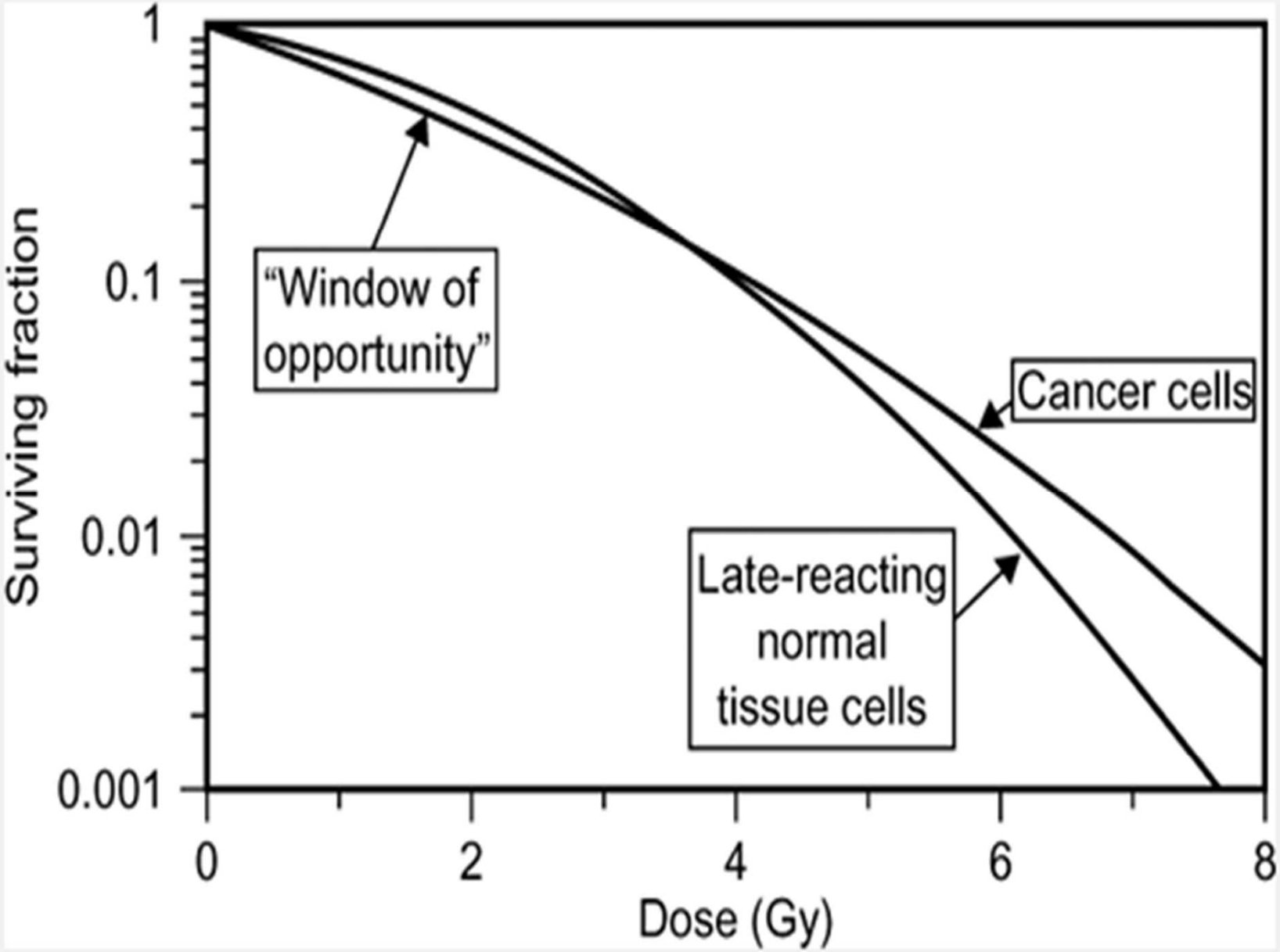
Survival for cancer cells and late responding normal tissue

Cross over point / Window of Opportunity- 3-5 Gy
normal tissue survival is higher than cancer cells

For cure of cancer ,higher dose is required

Solution:

1. Fractionation within window of opportunity
2.geometrical sparing factor in conformal/IMRT/IGRT


1
0.1
0.01
0.001
Surviving fraction
"Window of opportunity"
Cancer cells
Late-reacting normal tissue cells
0
2
4
6
8
Dose (Gy)

Survival curve for fractionated RT

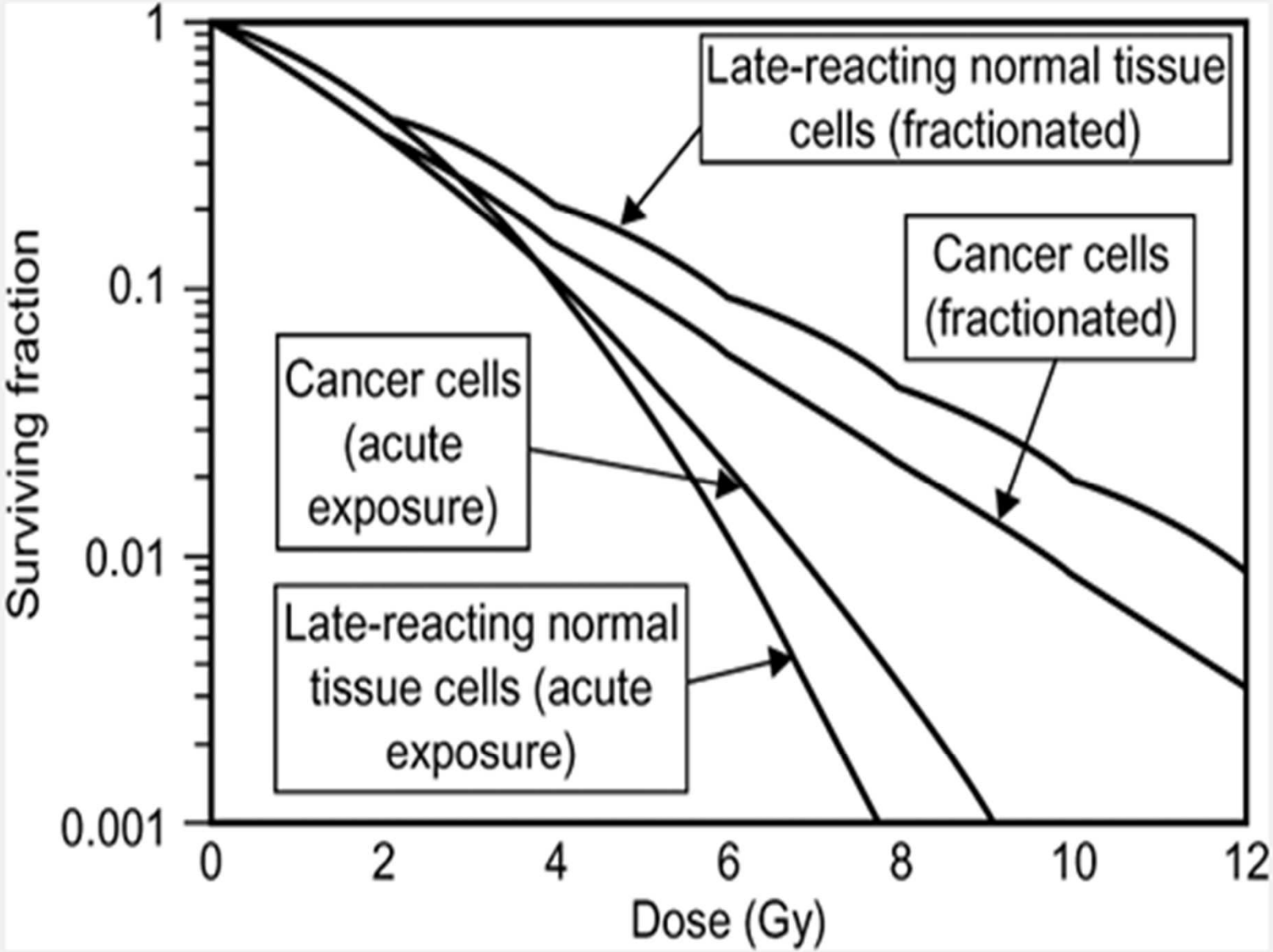
- # RT within WOO will separate the survival curves for cancer cells and normal tissue with cancer cells suffer more damage.
- LQ model suggests infinite no. of #-not realistic
- Optimal dose per #
- Where the rate of increase in separation of 2 curves per # is a maximum,occurs at the point of maxm sep bet two acute exposure curves
- = 1.5-2.5 Gy

Survival curve

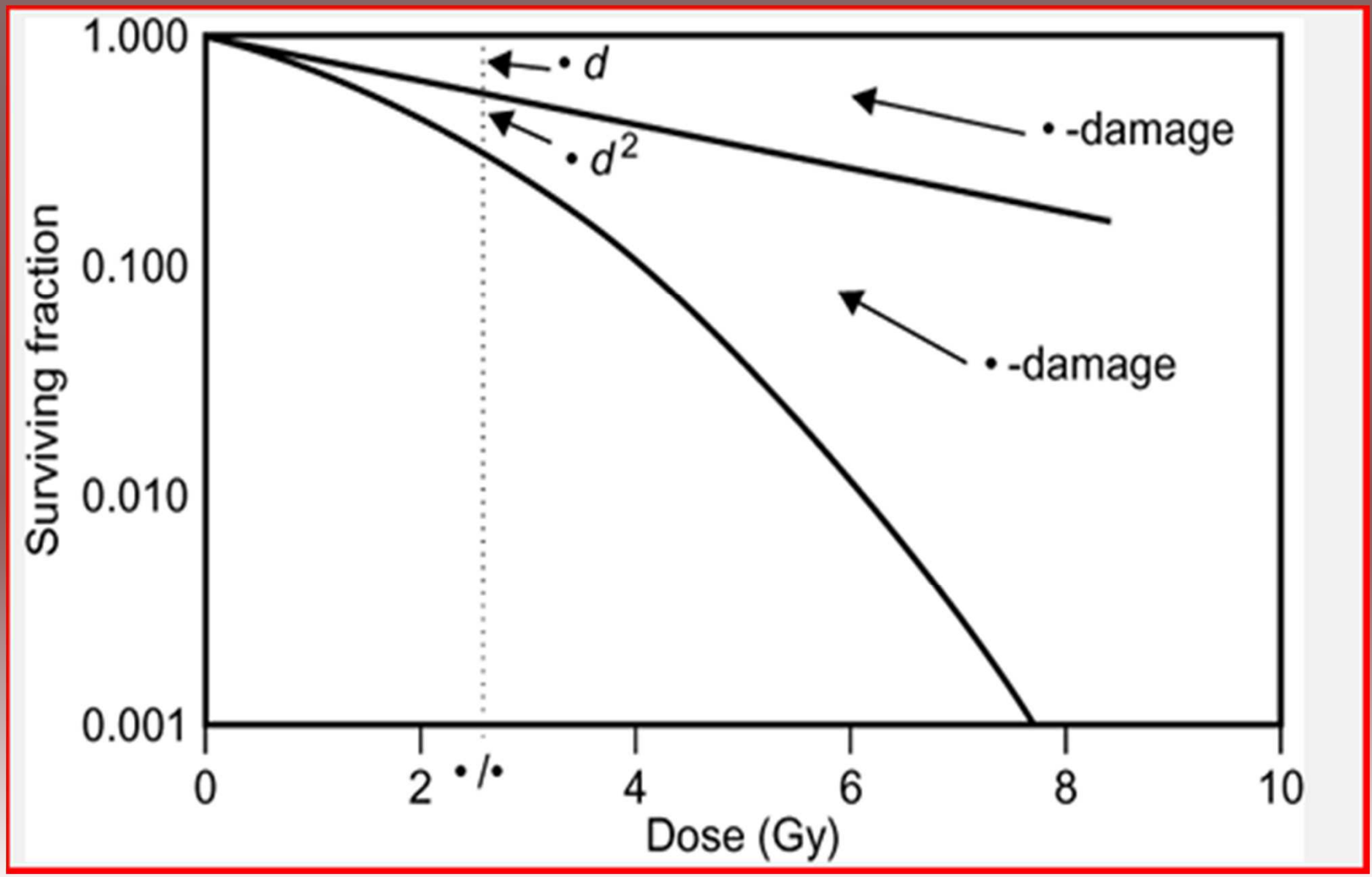
- **Effective Dose-** dose if delivered uniformly to the tissue in question,would result in the same probability of local control / complications as the actual inhomogeneous dose distribution in that tissue-DVH
- **Geometrical sparing Factor(f)**

  ED in normal tissue / ED in tumor

modest sparing f=0.8—increase cross over point from 3.8 to 14,and optimal dose of 7 Gy, Stereotactic RT,f=0.6—20 Gy SF are used; large tumor with f>0.6,#RT better


Late-reacting normal tissue cells (fractionated)
Cancer cells (fractionated)
Cancer cells (acute exposure)
Late-reacting normal tissue cells (acute exposure)
Surviving fraction
1
0.1
0.01
0.001
0
2
4
6
8
10
12
Dose (Gy)

LQ Model


1.000
0.100
0.010
0.001
Surviving fraction
• d
• d²
• -damage
• -damage
0
2
• /•
4
6
8
10
Dose (Gy)

LQ model :

- Conventional: 70 Gy/35 #/7 weeks,d=2Gy,5 #/wk
- α/β=10,for tumor and acutely responding normal tissue
- α/β=2.5,for late responding normal tissue
- E/ α=Nd(1+d/ α/β)
- BED

$$\frac{E}{\alpha} = (nd)\left(1 + \frac{d}{\alpha/\beta}\right) - \frac{0.693}{\alpha}\frac{t}{T_{pot}}$$

- BED=Nd(1+d/ α/β)-kT
- =Nd(1+d/ α/β)-k(T-Tk)
- k= repopulation rate parameter(estimated from loss of local control with prolongation with RT)
- K=0.6BED units per day for rapidly repopulating tumor
- 0.1BED for slow proliferating cells ex.prostate
- K=0 for late responding tissue
- 0.2-0.3 for acutely responding normal tissue

- LQ Model to compare different fractionation
- $BED = D2(1 + 2/\ \alpha/\beta) = Dd(1 + d/\ \alpha/\beta)$
- Therefore, $D2/Dd = (1 + d/\ \alpha/\beta)/\ (1 + 2/\ \alpha/\beta)$

Radiobiological Basis of Altered

Hyper

- Large no. of #
- Smaller d
- Similar T
- Slightly higher D
- =
- Late respond tissue spared
- Acute toxicity –higher but can be managed
- Higher separation of curves for cancer cells and normal tissue
- TG achieved for HNC

Hypo#

- Smaller no. of #
- Larger d
- Similar T
- Slight reduction of D
- =
- More damage to normal tissue
- Acute toxicity -not
- Used for Palliation
- **OR CURATIVE in Ca Prostate or highly conformal therapy**

Radiobiological Basis of Altered

Accelerated

- T is reduced
- d may be reduced or conventional or increased
- D may be reduced
- # per week may be increased to 5-10
- Higher acute toxicity
- Late toxicity may be similar
- Reduced Repopulation of cancer cells

Accelerated Hyper

- T reduced
- N increased
- d may be reduced

- CHART-Continuous Hyper #
- Accelerated RT
- 54Gy/36#/15 days,3#/day,d=1.5 Gy
- CHARTWEL,week End Less

Dynamic

- 1.2Gy,bd/20#/2 wks
- 1.4 Gy,bd/20#/2 wks
- 1.6 Gy,bd/10 #/1 wk
- =
- 68Gy/50 #/5 wks

Fractionation scheme	Dose/fraction (Gy)	Fractions/week	Total dose (Gy)	Comments
Conventional	1.8â€"2.0	5	~60	Used for most patients
Hyperfractionation	1.1â€"1.3	10	~70	Allows higher doses to tumors without increased late complications
Accelerated fractionation 2â€"2.2 2.2â€"2.4 1.4â€"1.6	 7 5 10	 ~60 ~50 ~50	Used for rapidly proliferating tumors Increased risk of acute complications
Hyperfractionated accelerated radiotherapy	~1.5	15 (CHARTWEL) 21 (CHART)	~54	Used for rapidly proliferating cancers High risk of severe acute complications
Dynamic fractionation	1.2â€"2.0	10	~75	For rapidly proliferating tumors Gradually increasing the intensity of treatment in order to minimize acute reactions
Hypofractionation	3â€"10	1â€"5	10â€"30 (palliation) 40â€"60 (â€œcureâ€)	For palliation Potential use for â€œcureâ€ with highly conformal radiotherapy

Head & Neck Ca

- Options:
- 1. hyper# ,to exploit the diff.in radiosensitivity to increase TR
- 2. Accelerated #,to overcome repopulation
- 3. Combined = 2 or more # on all or some trt days

6 days / wk

CHART

- 54Gy/36#/12 days,d=1.5 Gy
- Results similar to conventional ?
- Low total dose delivered
- Increasing the D will increase late toxicity
- Similarly Trans-Tasman Oncology Group(TROG):reported no difference
- 59.4Gy/33#,d=1.8,bd/24 days
- TD WAS MOST SIGNIFICANT FACTOR

HNC –Altered

- Best results obtained with regimens delivering conventional D with modest redn in T with fractions 6 days/wk.mod acc elerated RT offers improved TR
- Bourhis et al,2006
- Meta analysis
- 15 trials,N6515,FU 6 yrs:Alt# improves survival,locoregional control,Hyper#-greatest advantage
- Conventional Rt is not standard care

Phase III randomised clinical trials of accelerated radiotherapy regimens for head and neck cancer: great versus modest acceleration and associated therapeutic gains.

Trial/reference	Regimens compared	Overall dose (Gy)	Treatment duration (weeks)	Local tumour control (%)	Therapeutic gain
DAHANCA (Overgaard et al., 2003) [22]	Accelerated Conventional	66 66	6 7	70 60	Yes
RTOG (Fu et al., 2000) [23]	Accelerated-with concomitant boost Hyperfractionated Conventional	72 81.6 70	6 7 7	54.5 54.4 46	Yes Yes
Skladowski et al. (2000) [24]	Accelerated Conventional	70 70	5 7	82 37	Yes
TROG (Poulsen et al., 2001) [20]	Accelerated-hyperfractionated Conventional	59.4 70	3.5 7	No difference	No
EORTC (Horiot et al., 1997) [25]	Accelerated-hyperfractionated Conventional	72 70	5 7	59 46	No (late toxicity nullified gain in tumour control)
CHART (Dische et al., 1997) [19]	Accelerated-hyperfractionated Conventional	54 66	1.7 6.5	No difference	No

Ca Prostate

- Low alpha/beta ratio vs late rectal toxicity
- Case for Hypo #
- d=2.7 Gy-4.5Gy
- Livsey et al ,2003:hypo#,conformal Rt,N-705, 50 Gy/13 #/22 days,d-3.13 ,similar tumor control,toxicity,as 65-70 Gy/d-1.8-2 Gy.
- Arcangeli et al,2010: prospective, phase III,randomised trial ,N-168,62 Gy/20#/5 wks,4 # per wk,d-3.1 Gy,vs 80 Gy/40 #
- Achieved TG,reason higher dose

Calculated α/β ratios for prostate carcinoma and late rectal toxicity, respectively.

α/β (Gy) Prostate carcinoma	α/β (Gy) Late rectal toxicity	References
1.5 (assumed)	2.3	Marzi et al. (2009) [40]
–	5.4	Brenner (2004) [41]
3.1 (1.7–4.5)	–	Wang et al. (2003) [42]
1.2	–	Brenner et al. (2002) [43]
1.49 (1.25–1.76)	–	Fowler et al. (2001) [33]
1.5 (1.4–1.7)	–	Brenner and Hall (1999) [32]
–	3.87	Deore et al. (1993) [44]

Breast Ca

- Larger pDouble Time 10.4 d
- Alpha/beta ratio -4 Gy,similar to healthy normal tissue
- Hypo#,Better cosmesis,though no TG achieved

- IMRT-SIB
- Smaller double time for younger <50yrs
  & early breast ca? Accelerated Hypo#
- Accelerated Partial Breast Irradiation

Lung Ca

- Doubling time ,adenoca-222d,nonsmall cell ca-46-81 days
- High repopulation during trt
- CHART trial,Saunders et al,1999;vs 60 Gy/30 #
- N-563,TG achieved,2 yr survival-20 to 29%,reducing relative risk of local progression by 27%,similar toxicity
- HICHART ,unresectable tumor,phaseI/II
- 68.4 Gy/38#/28d-2 yr survival 36%(=80Gy)
- Increase TD in CHART,CHARTWEL

Conclusion

- Low survival and high l-r trt failure led to modification of conventional RT
- Advanced HNC –hyper# RT better than accl RT

  =TG achieved

Ca Prostate-Hypo # IMRT

Promising,TG might be achieved

- Ca lung- CHART improved survival
- CHARTWEL with CTH might improve trt efficacy=TG might be achieved
- Ca breast=TG might be achieved
- Gliom= no benefit

Conclusion

- Rapidly proliferating tumors
  - Aggressive trt-AcceleratedRT
    - hyperfractionation RT
- Slowly growing Tumors
  - Hypofractionation

THANK YOU