Therapeutic ratio
- An Overview

Past Present Future

Prof Ramesh S Bilimaga

Radiation Oncology

Discipline of human medicine concerned with the generation, conservation and dissemination of knowledge concerning the causes, prevention and treatment of cancer and other diseases involving special expertise in the therapeutic applications of ionizing radiation.

Goal of Radiotherapy

- To deliver precisely measured dose of radiation to a defined tumor volume with minimal damage to surrounding normal tissue
- Aims:
  - To eradicate tumor
  - Improve quality of life &
  - Prolongation of survival

History

In the early part of 20th century relationship between dose and lethal effect was described as if they were isolated entities. But in reality everything is dependent on one-another. It was in the early 1940 that Dr Ralston Patterson tried to employ the terminology “therapeutic ratio” in the field of radiation oncology.

NTT : Factors

- Site of tissue – axilla, perineum less tolerant
- Area or volume irradiated
- Vascularity
- Supporting tissues (stroma and parenchymal cells)
- Individual variation of tolerance.

TISSUE TOLERANCE

- Radiation dose that will not produce any appreciable damage to normal tissue irradiated. usually <5% damage to normal tissue is acceptable.
- In RT the success of eradicating tumor depends on radio sensitivity of tumor as well as tolerance of surrounding normal tissue
- NTT limits the max. dose that can be delivered to tumor
- During early years of RT with orthovoltage skin was a limiting factor.
- This was overcome by use of Co - 60 & megavoltage X-rays

TUMOR LETHAL DOSE

- Tumor control is a probabilistic event i.e. for every increment of radiation dose certain # of cells will be killed
- Total no. of surviving cells will be proportional to initial no. of cells present & the # killed after each dose.
- Constant # of cells are killed by each dose #.

TUMOR LETHAL DOSE

- Dose of radiation that produces complete & permanent regression of tumor in vivo in zone irradiated.

- The expression of relationship b/w lethal effect & dose was first propounded by Holthusen

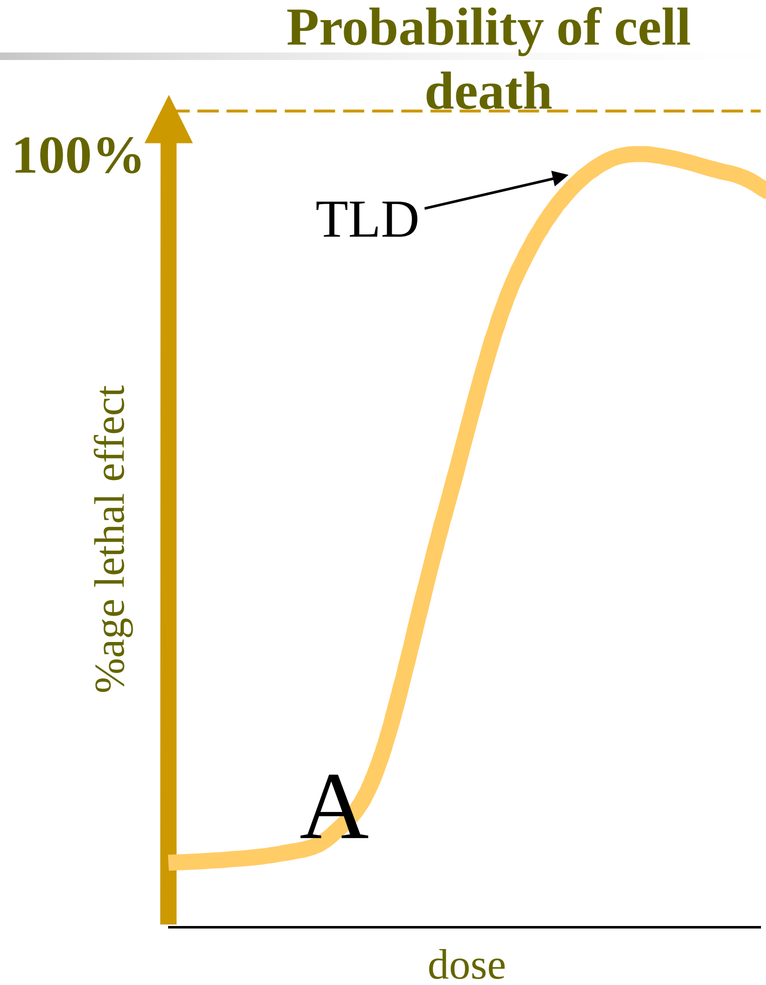
TUMOR LETHAL DOSE

- Consecutive of his working hypothesis are

  There is a dose point A below which there is no appreciable lethal effect
  As dose is increased lethal effect increases

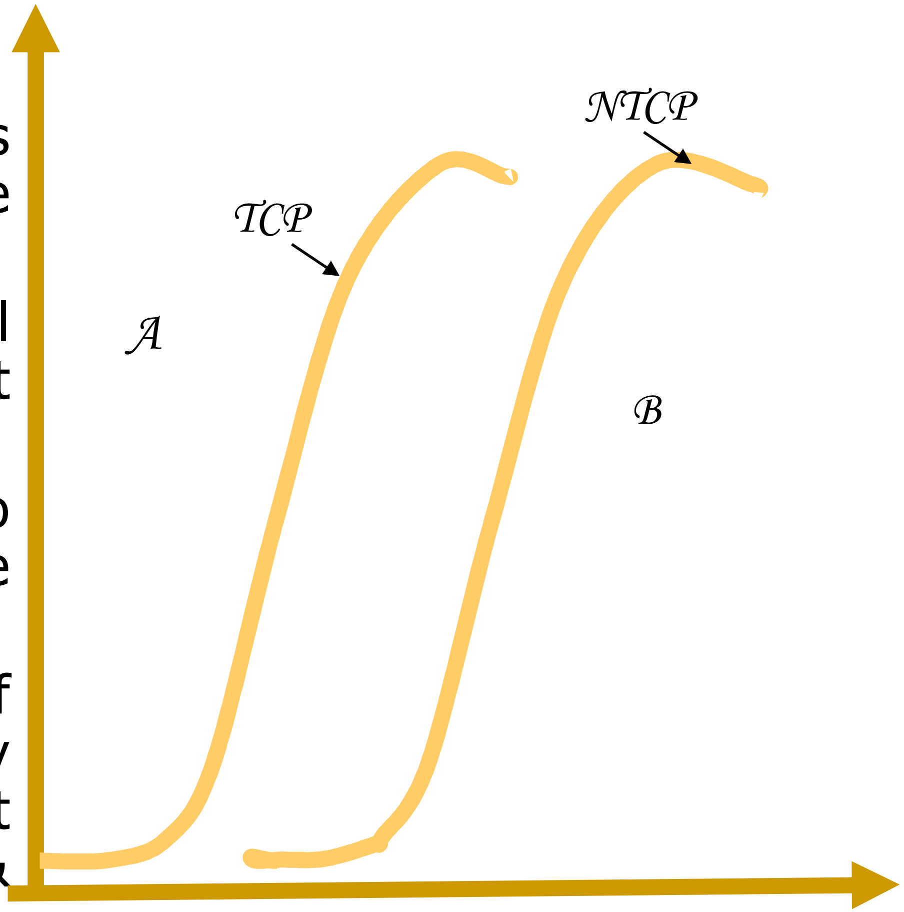
  At upper end of sigmoid curve there is a point TLD at which 80-90% tumor resolves completely

  Above this point dose has to be increased considerably to gain any appreciable rise in lethal effect.

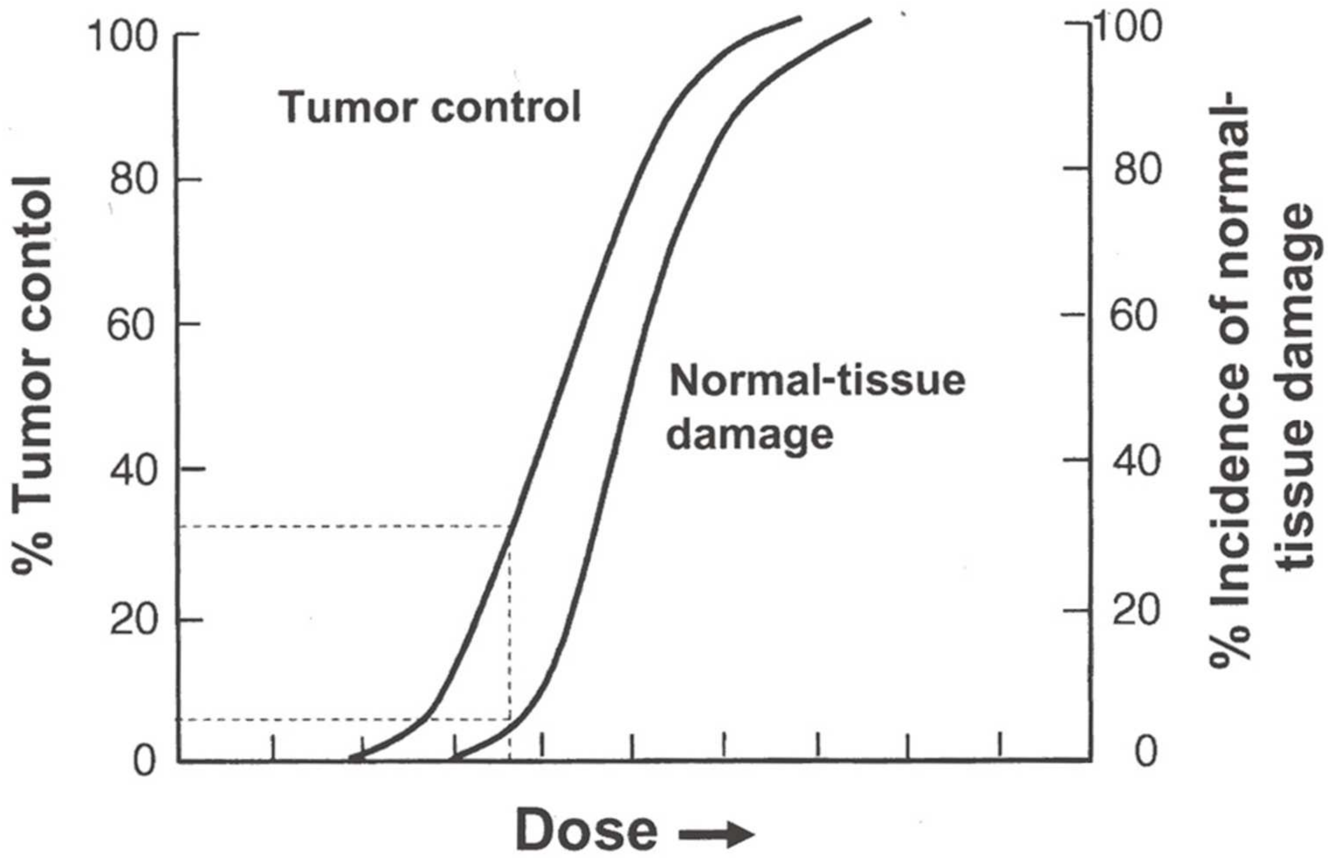


Therapeutic index

- It is ratio of NTT/ TLD.
- This ratio determines whether a particular disease can be treated or not
  - TLD $\geq$ NTT then radical dose of radiation cannot be delivered.
- The more the curve B is to the right of curve A the more is therapeutic ratio
- The optimum choice of radiation dose delivery technique is one that maximizes the TCP & simultaneously minimizes the NTCP



Dose-Response Relationships

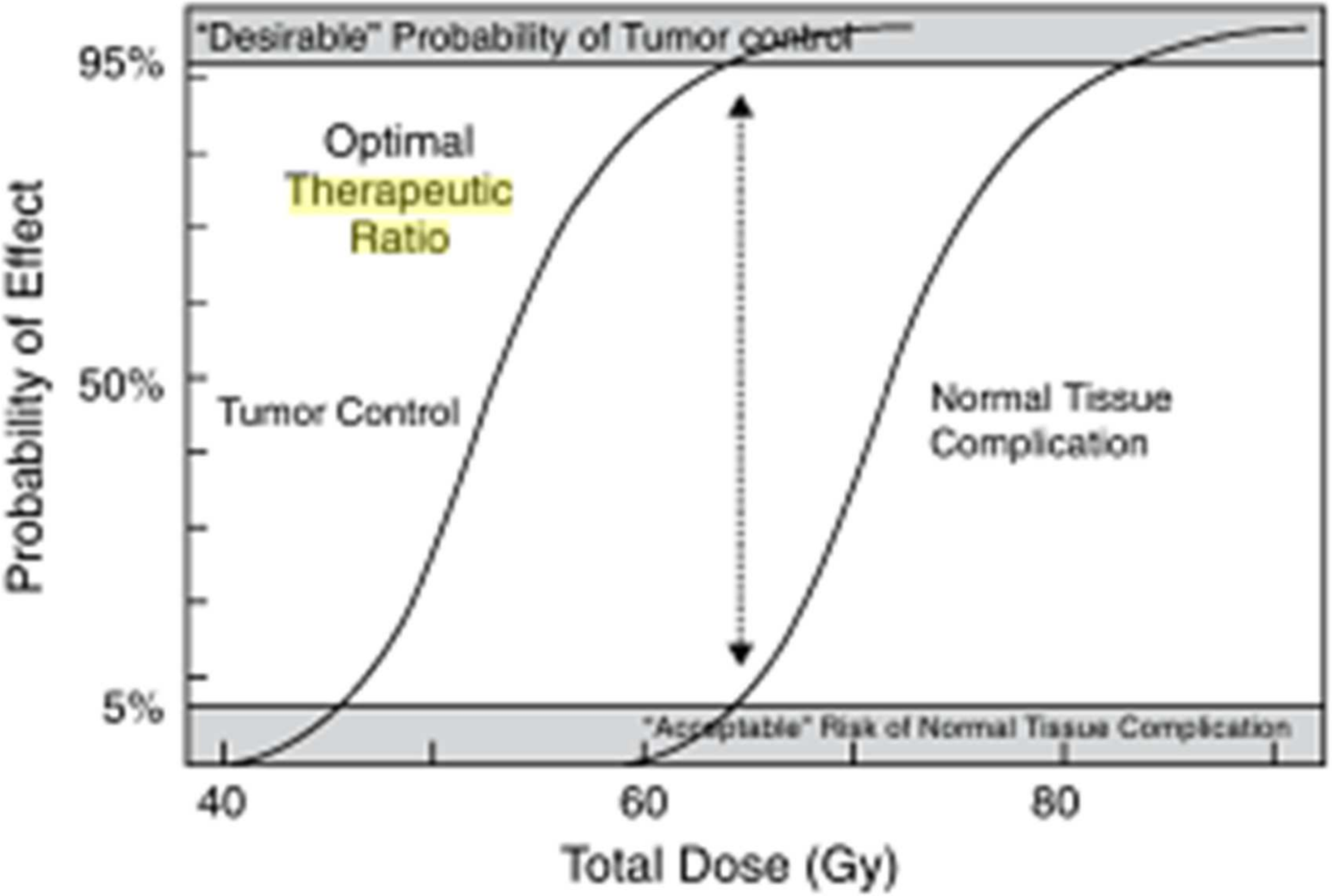


Types

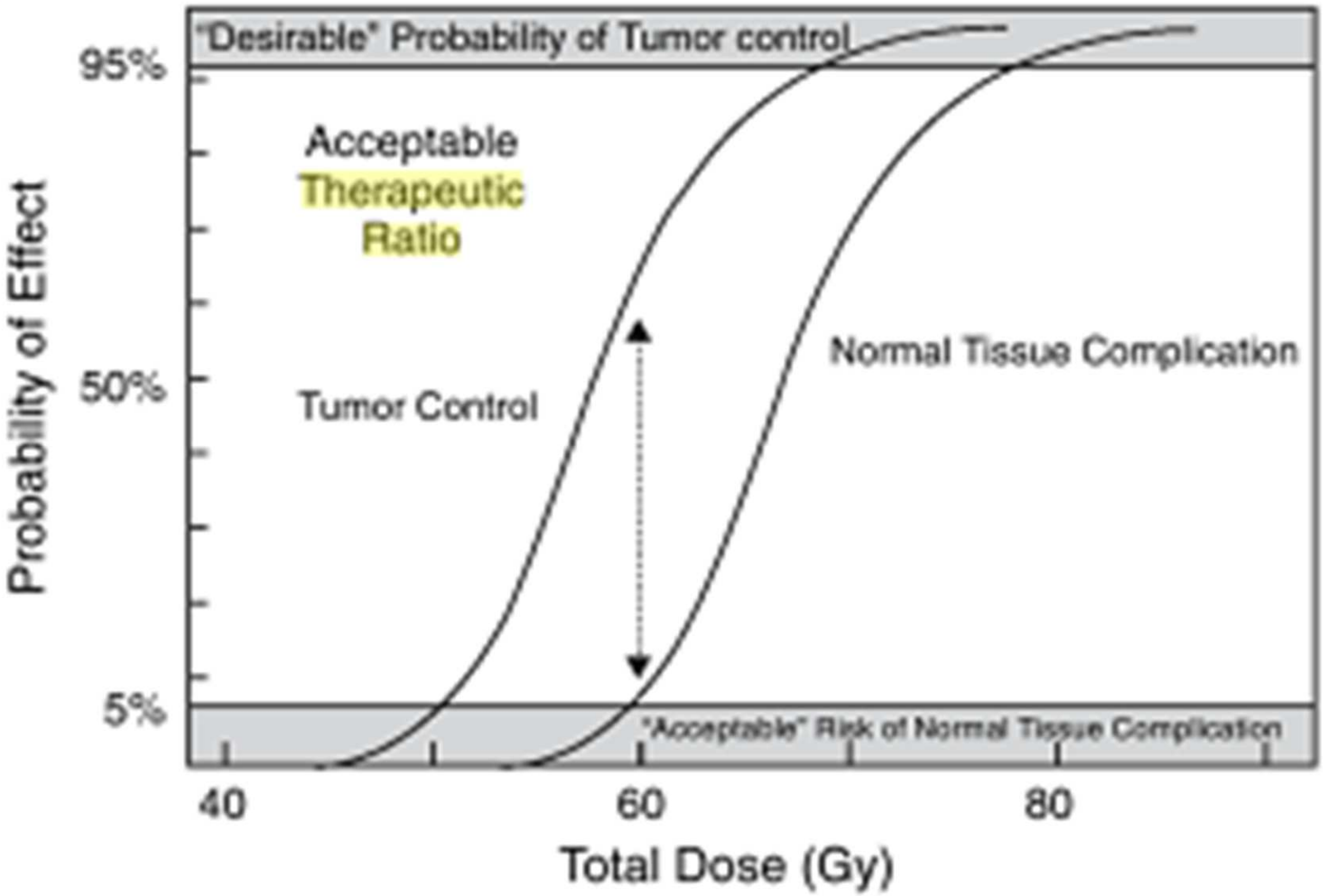
- Optimal – tumour control curve always lies left to the normal tissue complication curve

- Unacceptable – tumour control & normal tissue complication curves are reversed

Optimal Therapeutic Ratio

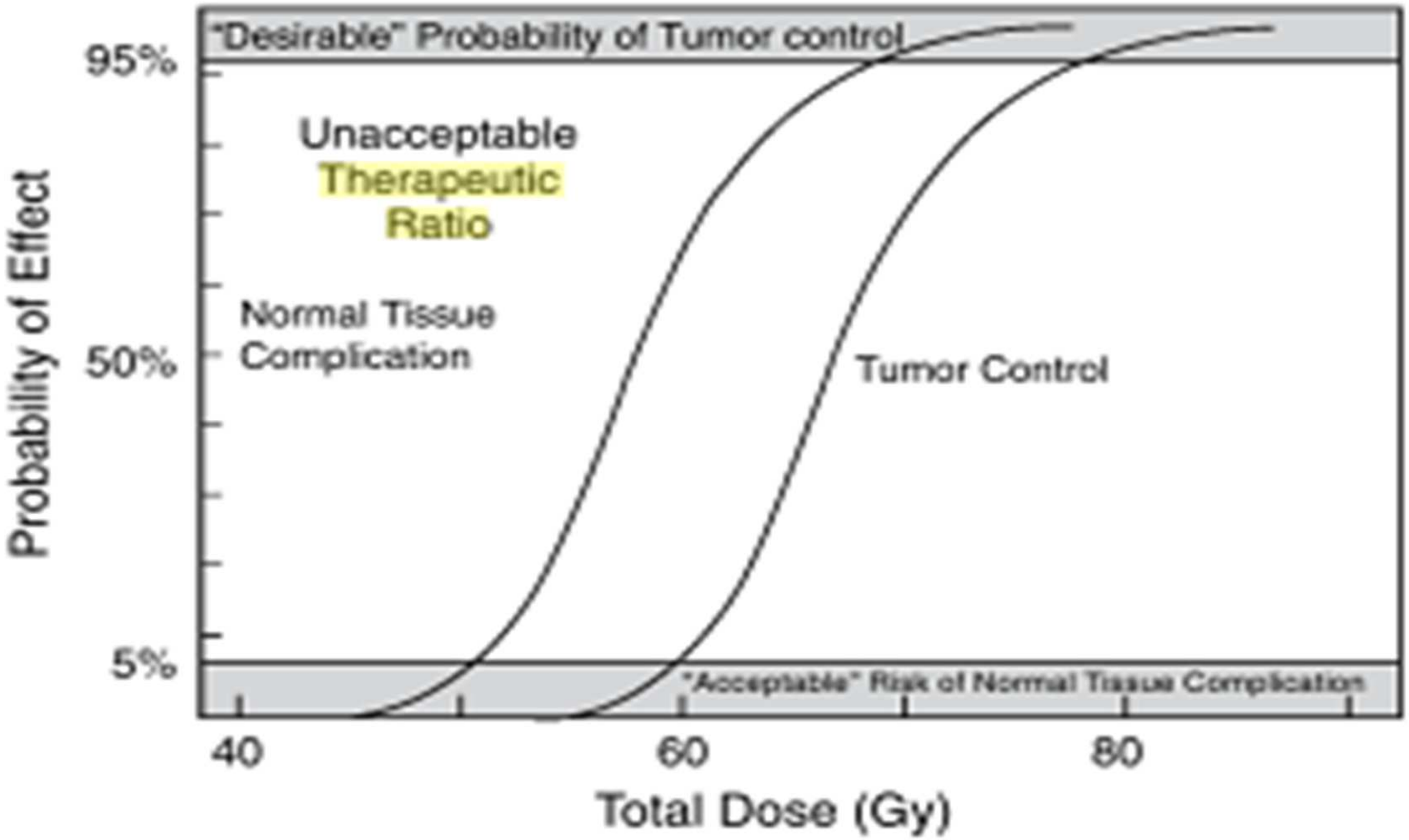


Acceptable



"Desirable" Probability of Tumor control
95%
Acceptable
Therapeutic
Ratio
50%
Tumor Control
Normal Tissue Complication
5%
"Acceptable" Risk of Normal Tissue Complication
Probability of Effect
40
60
80
Total Dose (Gy)

Unacceptable



Factors Influencing TR

- Biological
  - Phases of cell cycle
  - Type of cancer
  - Size of tumor
- Physical
  - LET
  - Fractionation
- Chemical
  - Drugs
  - O2
- Technical
  - Errors in contouring, setup, execution of Rx

To Increase T R

- ↑Total dose
  - Three-dimensional conformal radiation therapy (3D CRT)
  - Intensity-modulated radiation therapy (IMRT)
  - Stereotacticbody radiation therapy (SBRT)
- ↓Overall duration of treatment
  - Altered fractionation
- ↓Hypoxia
- ↑Radiosensitization
- Hyperbaric oxygen
- Chemotherapy
- Molecularly targeted therapy

To Increase T R

- Decrease probability of complications
  - ↑Dose distribution
- Radioprotectors
  - Aminothiols
  - Cytokines
- Spare normal tissues
  - Better immobilization
  - Control organ motion and breathing
  - Optimization of technique
  - ↓Dose/fraction
    - Except with SRS radiation and SBRT
  - ↑Inter fraction interval

Radio sensitivity

- Radio sensitivity expresses the response of the tumor to irradiation.
- Bergonie and Tribondeau (1906): “RS LAWS”: RS will be greater if the cell:
  - Is highly mitotic.
  - Is undifferentiated.
  - Has a high carcinogenicity
- Malignant cells have greater reproductive capacity hence are more radiosensitive.

Radio sensitivity

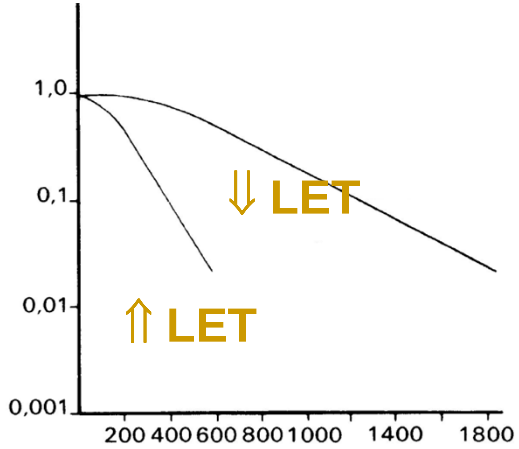
Highly radiosensitive	Moderately sensitive	Resistant
For which therapeutic ratio is high Normal tissue tolerates doses several times magnitude of TLD. e.g. lymphoma, leukemia, seminoma, dysgerminoma Bone Marrow, Spleen, Thymus ,Lymphatic nodes, Gonads, Eye lens, Lymphocytes	Though tumors are more sensitive, therapeutic ratio is low. NTT exceeds TLD by only small #. e.g. sq. cell. ca. & adenoca. Skin, Mesoderm organs (liver, heart, lungs…)	Dose required to produce lethal effect is more than NTT. Hence therapeutic index is very low. e.g. soft tissue & bone sarcoma, melanoma etc. Muscle, Bones, Nervous system

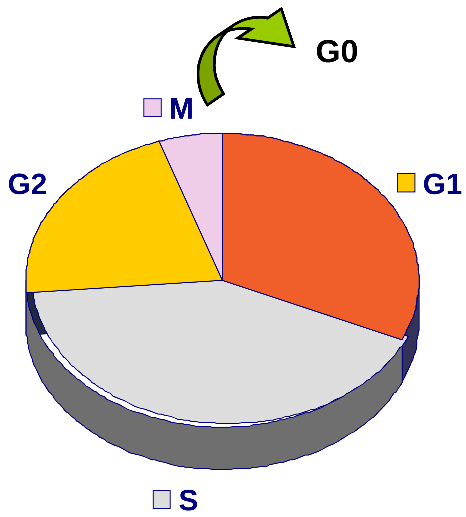
TISSUE CLASIFICATIONS

Very High	Lymphocytes, immature hematopoietic cells, intestinal epithelium, spermatogonia, ovarian follicular cells
High	Urinary bladder epithelium, esophageal epithelium, gastric mucosa, mucous membranes, epidermal epithelium, epithelium of optic lens
Intermediate	Endothelium, growing bone and cartilage, fibroblasts, glial cells, glandular epithelium of breast, pulmonary epithelium, renal epithelium, hepatic epithelium, pancreatic epithelium, thyroid epithelium, adrenal epithelium
Low	Mature red cells, muscle cells, mature connective tissues, mature bone and cartilage, ganglion cells

Factors affecting the radiosensitivity

- Physical
  - LET (linear energy transfer): ▪ RS
  - Dose rate: ▪ RS
- Chemical
  - Increase RS: OXYGEN, cytotoxic drugs.
  - Decrease RS: SULFHYDRL compounds (cys, cysteamine…)
- Biological
  - Cycle status:
    - ▪ RS: G2, M
    - ▪ RS: S
  - Repair of damage (sub-lethal damage may be repaired e.g. fractionated dose)





RADIOCURABILITY

- Eradication of tumor at primary or regional sites & reflects direct effect of irradiation.
- There is no significant relation b/w radio sensitivity & radio curability. A tumor may be radio sensitive yet incurable & vice versa.
- Examples
  - Leukemia is radiosensitive but not radio curable.
  - Seminoma is radiosensitive & radio curable.
  - Sarcoma is not radiosensitive/ radio curable.

TREATMENT FACTORS

- To eradicate a tumor radiation is delivered & factors that play an important role in any treatment are
  - Dose of radiation
  - Time of dose delivery
  - Fractionation of dose

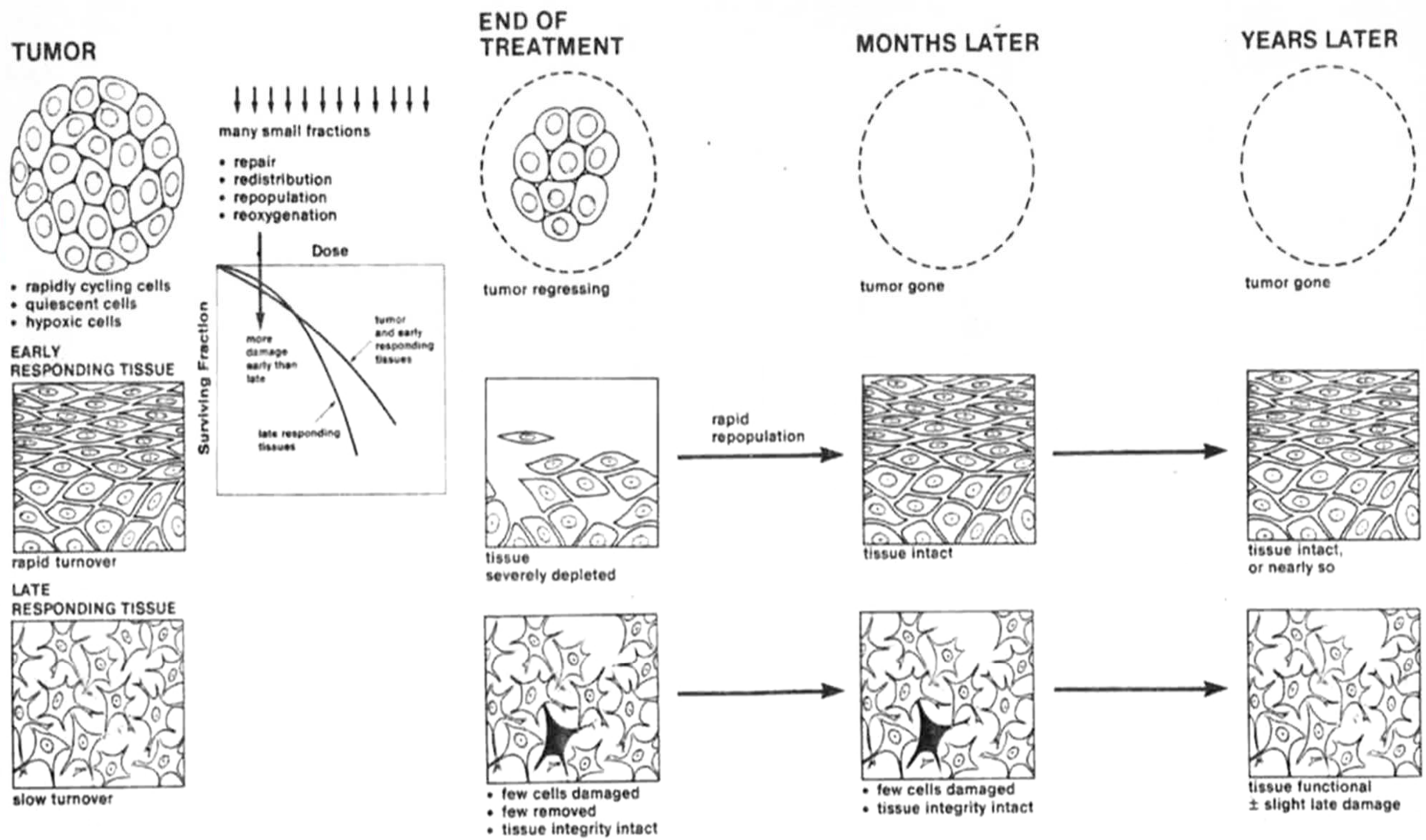


Figure 12–9. The kinetic pattern following irradiation with many small dose fractions. A small dose fraction produces relatively less damage to late-responding than to early-responding tissues because of their curvy dose-response relationship. The tumor regresses and disappears. The early-responding tissues show a **reaction** but repopulate by rapid cell division. The late responding tissues show little damage.

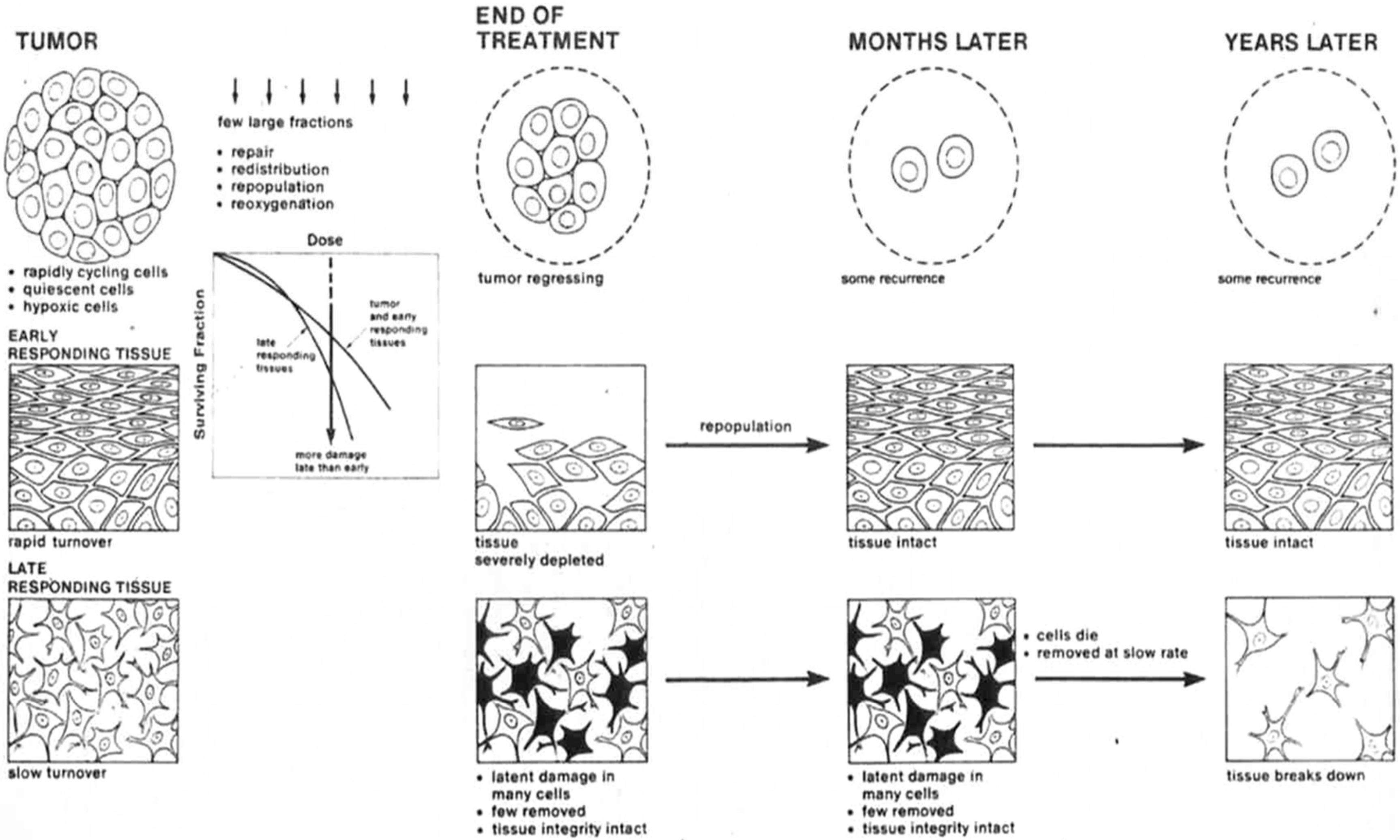


Figure 12–10. The kinetic pattern following irradiation with a few large dose fractions. A large dose fraction produces relatively more damage to late-responding than to early-responding tissues because of the difference in curviness of the dose-response relationship. The tumor regresses and disappears, though there is evidence of a higher recurrence rate after radiotherapy regimens involving a small number of fractions, perhaps because there is less opportunity for reoxygenation. The early-responding tissues show a reaction but repopulate by cell division; this is the same as in Figure 12–9. However, the late-responding tissues carry a large amount of latent damage, which is expressed months or years later when the cells in these tissues begin to turn over.

CHOICE OF DOSE

- In radical radiotherapy choice of dose & fractionation regimen depends on following factors:-
  - **Radio sensitivity of tumor**
    - e.g. radiosensitive tumor such as seminoma can be controlled by total dose of 30Gy/ 4wks
    - While for moderately sensitive sq. cell ca. of head & neck higher doses of the order of 50-60Gy in 5-6wks is used.
  - **Size of treatment volume**
    - smaller the vol. the greater is the dose that can be delivered without exceeding NTT.
  - **Proximity of dose limiting structures**
    - presence of critical st. such as brain stem & spinal chord may limit dose that can be delivered to tumors e.g while treating head & neck cancer & esophagus spinal chord is the critical st.

TIME

- Time factor is overall time to deliver prescribed dose from beginning of course of radiation until its completion.
- Therapy effect varies enormously with time.
- General rule is longer the overall duration of treatment greater is the dose required to produce a particular effect.
- Hence dose should always be stated in relation to time.

TIME

- For curative purposes overall t/t is 5-6wks
  - Better tumor control with minimal morbidity
  - Tumor suppression can be monitored.
  - Radiation reactions can be monitored.
- If treatment time is more than 6wks then dose has to be increased
- Short duration treatment time is justified for
  - Treatment of small lesions
  - To treat aged persons
  - Palliative treatments
  - Tumors with high therapeutic ratio e.g. skin tumors

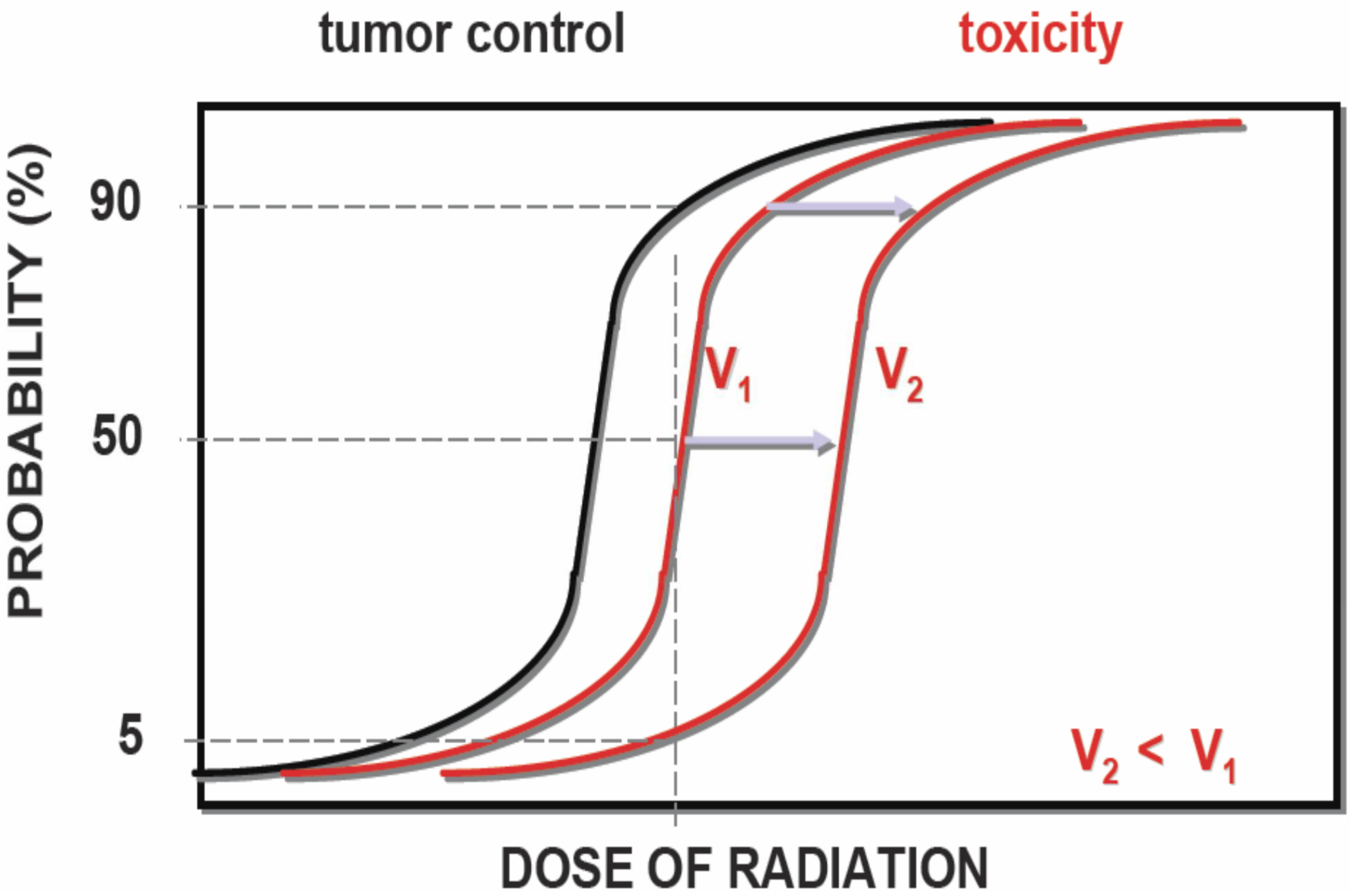
Overall Time Effect

- **Prolonged radiotherapy schedules:**
  - Spare acute reactions and tumors but not late complications
- **Shortened radiotherapy schedules:**
  - Will give more tumor cell kill, but the acute reactions will also be more severe so that total dose must be reduced to some extent. Late reactions should not be worse

Volume Effect

- Clinical tolerance depends strongly on volume irradiated in:
  - Spinal cord, Kidney, Lung
- Skin
  - No well defined FSU but respond similar to where FSUs are in parallel
    - Severity is dose independent
    - Larger area – potentially more problems
      - Infection, prolonged healing time
      - Not based on increased probability of injury

Therapeutic Window: Effect of Reducing Volume of Normal Tissue



Functional Subunits in Tissues

- Can be structurally defined:
  - Survival of unit depends on the survival of one or more clonogenic cells within unit
  - Small units more sensitive to radiation (smaller #s of clonogens)
  - Examples: Kidney nephron, Liver lobule

- Can have no clear anatomic demarcation
  - Clonogenic cells can migrate from one unit to another
  - Tissue-rescue units
  - Examples: Bone marrow, Skin, Mucosa

Clinical Application

- To recommend radiation therapy
- New technological advancements allows the radiation oncologists to change an unacceptable therapeutic ratio to an acceptable one.
- Provides a risk benefit approach to plan a radiotherapy regimen

Future

- Dose escalation
- Image based brachytherapy
- Targeted radiotherapy
- Targeted drug therapies (Gene therapy)
- Advances
  - Imaging , Planning, Technology

Future Directions:
Increase Therapeutic Ratio

- New drugs can potentially decrease the risk of distant metastasis and improve survival
  - carboplatinum, paclitaxel, gemcitabine, docetaxel
- Hypoxic cell sensitizers
  - tirapazamine
- Molecularly targeted therapy
  - C225: cetuximab
  - Cyclo-oxygenase-2 inhibitors: celecoxib
  - Anti-vascular endothelial growth factor: bevacizumab

Future Directions: Increase Therapeutic Ratio (cont.)

- Improved tumor localization and planning
  - Positron emission tomography/computerized tomography simulator
  - Intensity-modulated radiation therapy / image-guided radiation therapy
- Agents to minimize acute and/or late toxicity of chemoradiation
  - amifostine (Ethyol)
  - prostaglandin E analog misoprostol (Cytotec)
  - pentoxifyllin (Trental)
  - pilocarpine (Salagen)

Int. J. Radiation Oncology Biol. Phys., Vol. 46, No. 1, pp. 1–2, 2000

0360-3016/00/$–see front matter

ELSEVIER

PII S0360-3016(99)00495-2

EDITORIAL

A RADIATION BIOLOGIST LOOKS TO THE FUTURE

ERIC J. HALL, D.SC.

Center for Radiological Research, Columbia University, New York, NY

This explosion of knowledge and understanding is very satisfying intellectually, but it has not (to date) done the patient with cancer much good! The vast majority of patients, when diagnosed with cancer, receive surgery and/or radiotherapy and/or chemotherapy just as they did 10, 20, or even 50 years ago! The new biology has yet to make an impact on cancer treatment, unless it is to make some people worry more because of the possibility that they are in a cancer-susceptible group with increased risk of multiple malignancies.

2010. By now 5 genes have been identified in the human population that give rise to increased radiosensitivity. Patients assigned to radiotherapy are routinely screened for these genes; the 5% or so who respond positively receive a reduced radiation dose or are considered for alternative therapy. The remaining 95% can receive an escalated dose with improved local control.

2015. Gene therapy strategies involving new suicide gene constructs are combined with radiation therapy for a variety of malignancies, including carcinoma of the prostate and breast cancer. The rationale is based on combining modalities that both target cancer cells, but have different normal tissue toxicities.

2020. New radioprotectors have been developed which can be delivered locally and topically, in order to protect normal tissues, such as the oral mucosa and salivary glands.