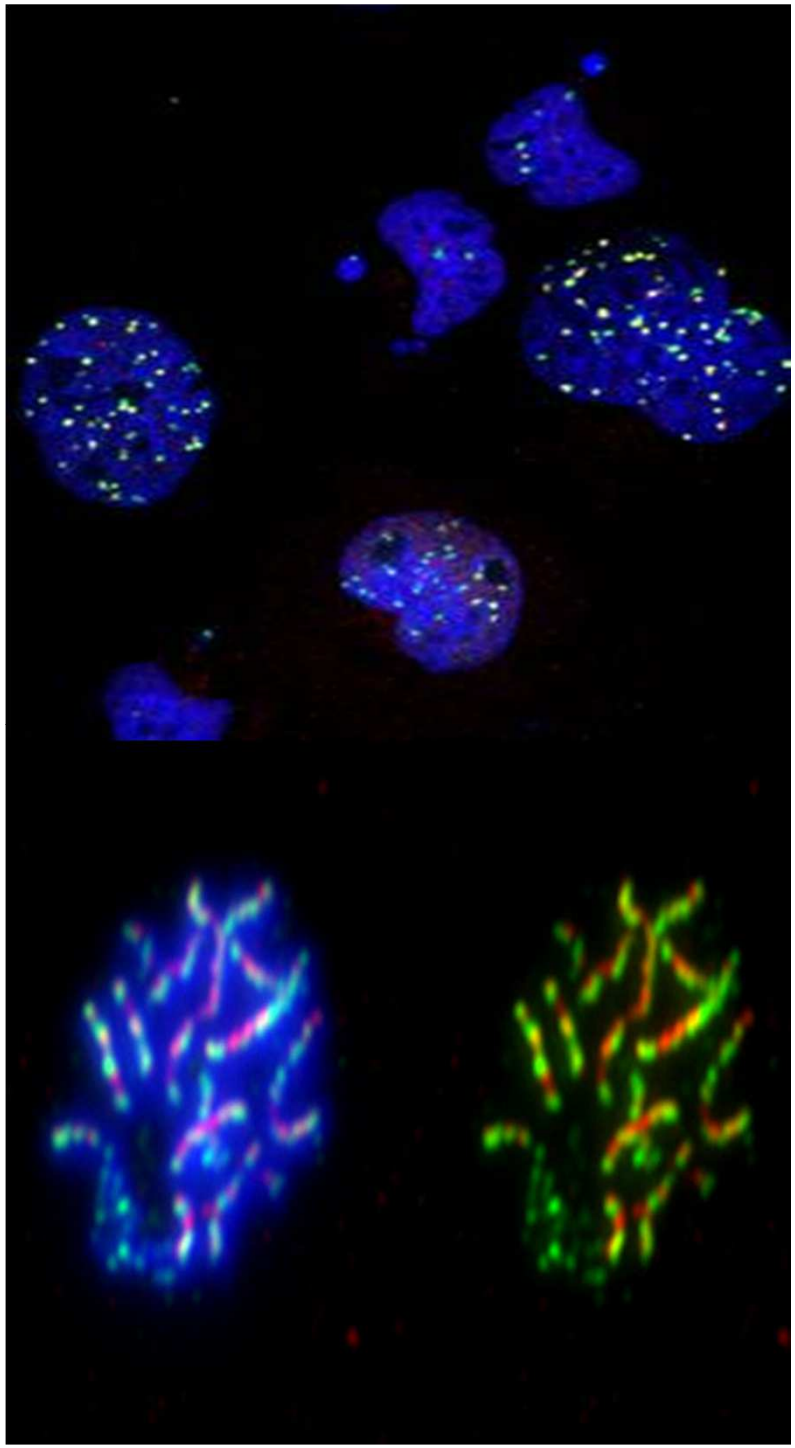

Manipulating Radiation Response – Protectors and Physical Modalities

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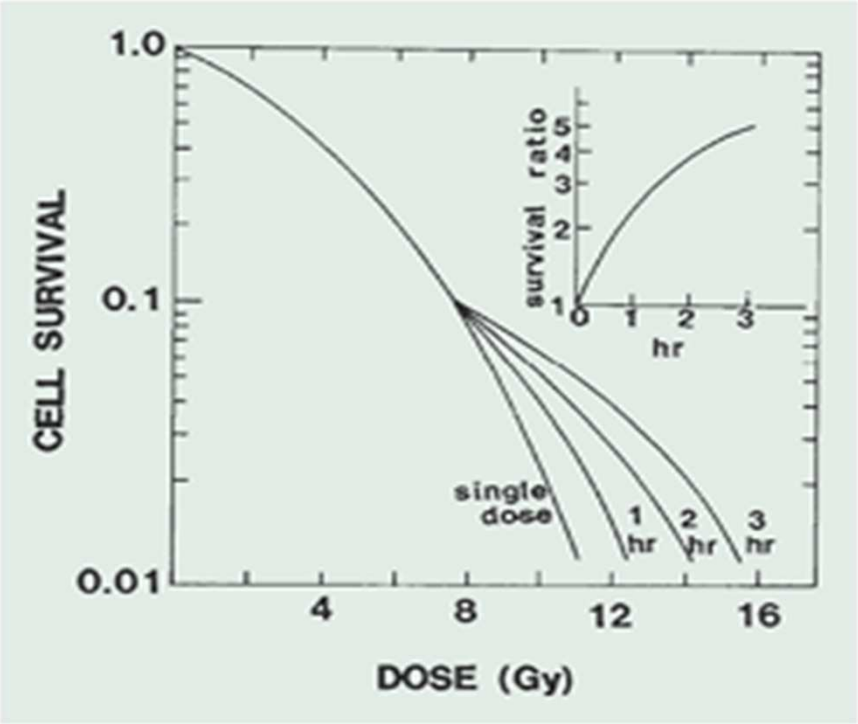
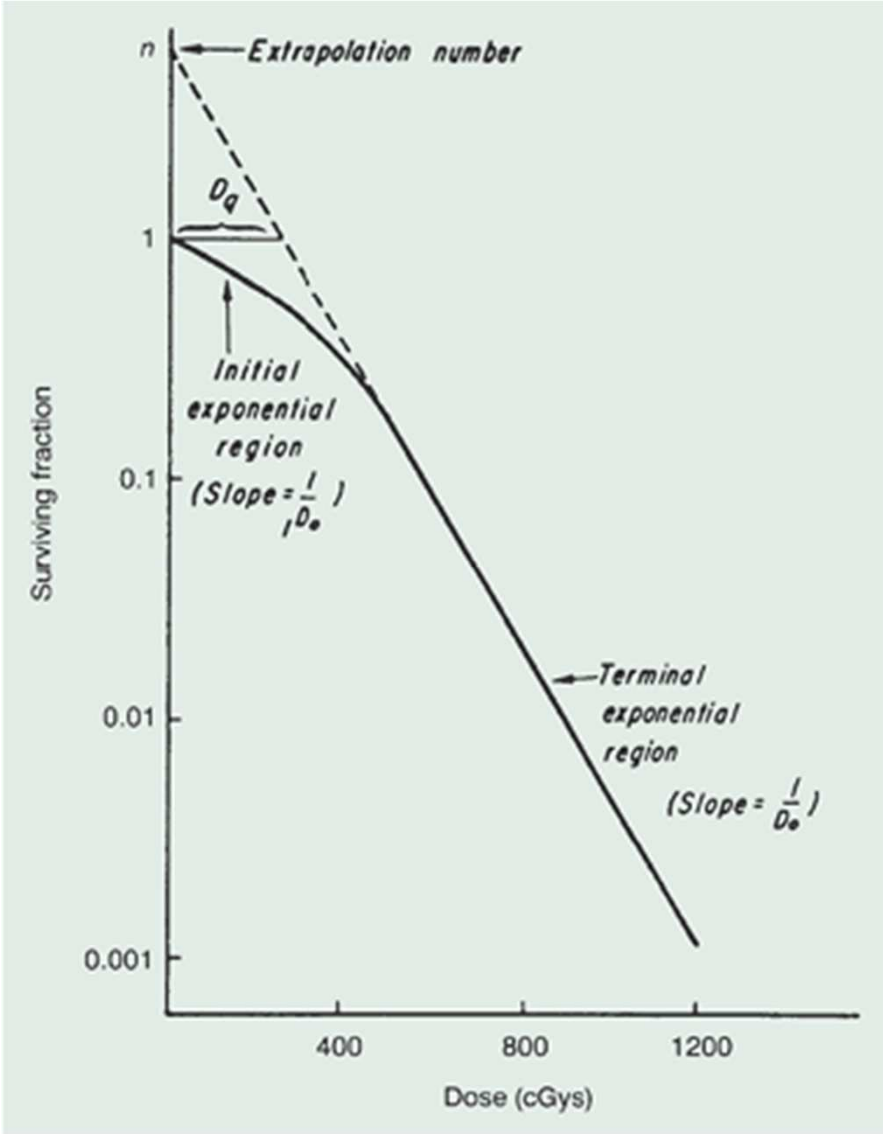
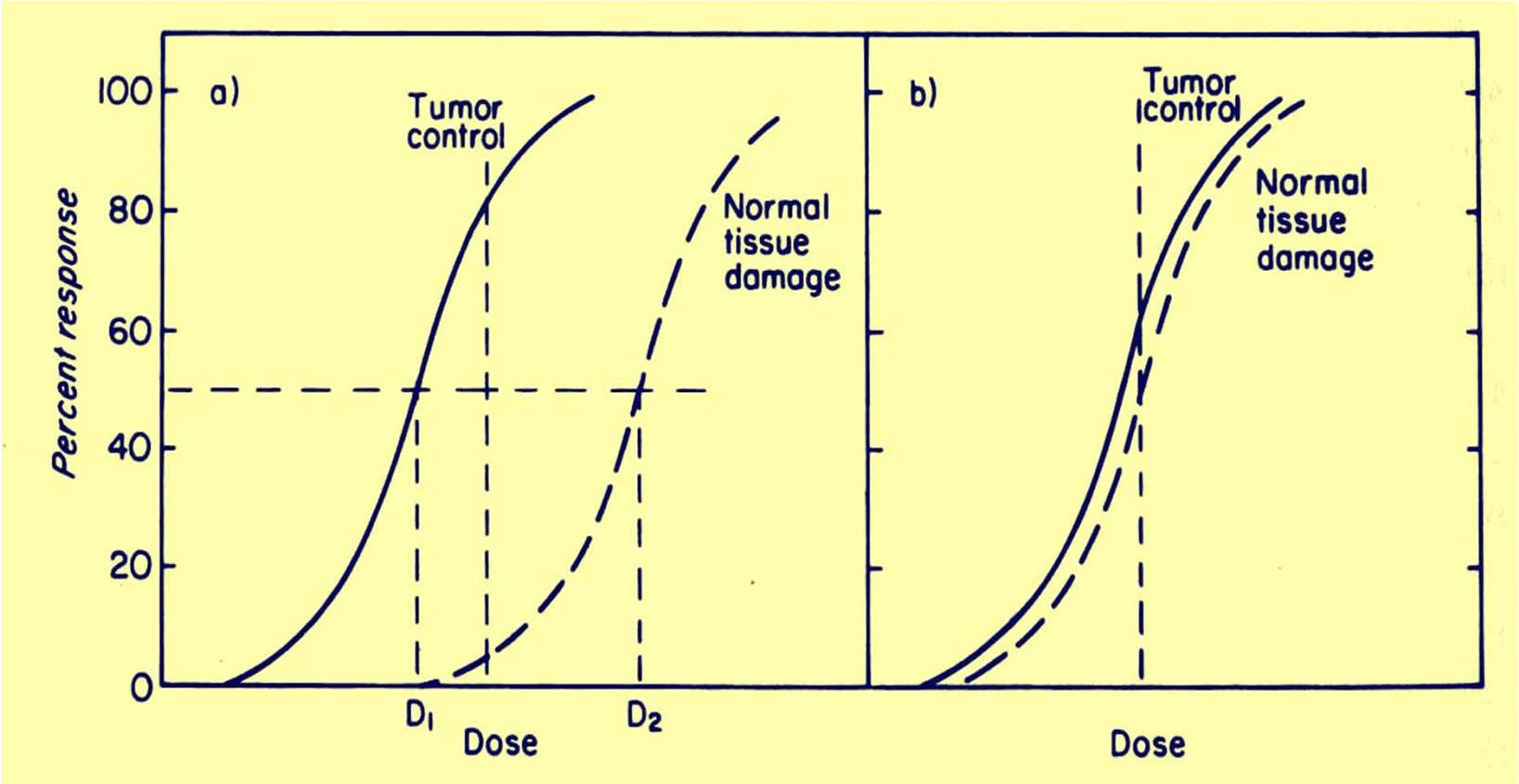


Recovery curves of the type first described by Elkind and Sutton

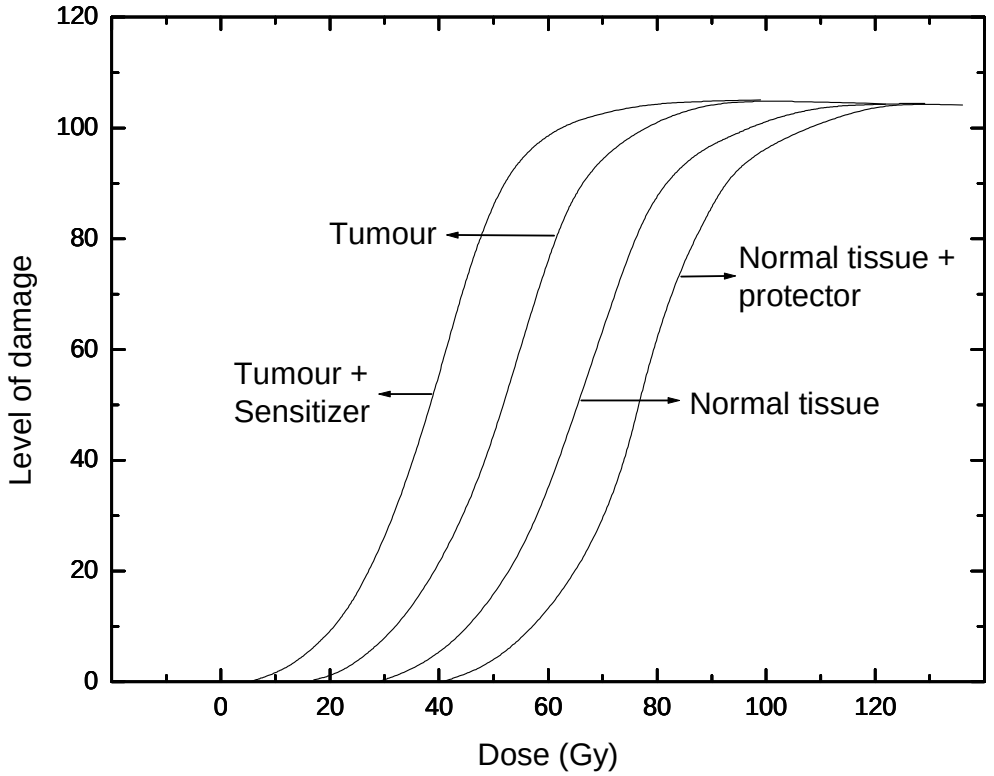


A two-component survival curve for mammalian cells

Illustration of the concept of a Therapeutic ratio in turn of dose response relationships for tumour control and normal tissue damage

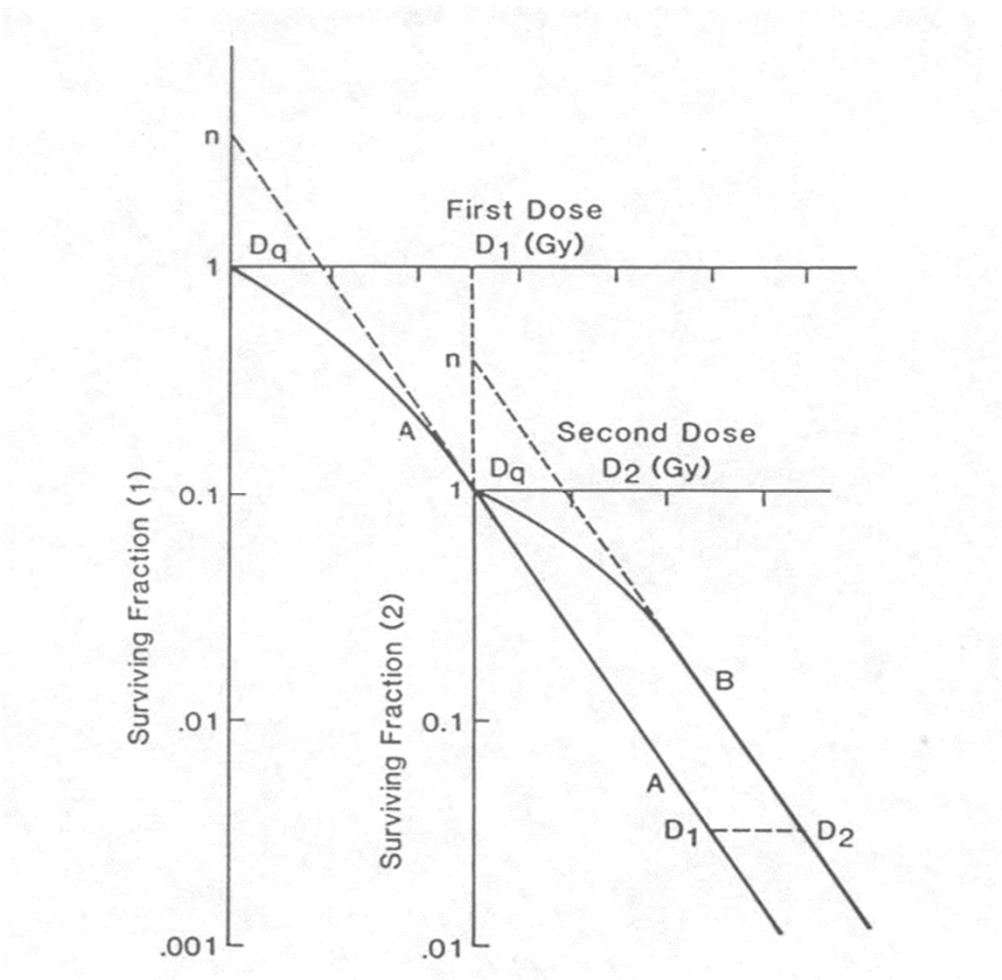


Dose response relationships for normal tissue and tumour.

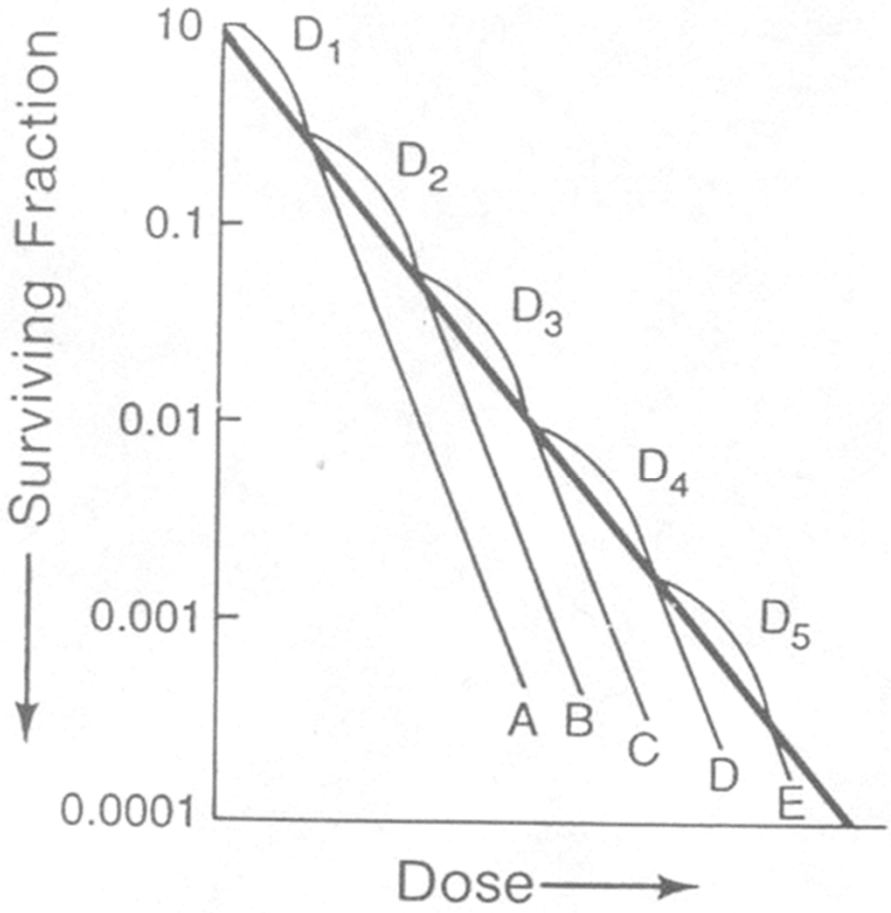


Modification of the response of tumour by radiosensitizers and normal tissue by radioprotectors is also shown.

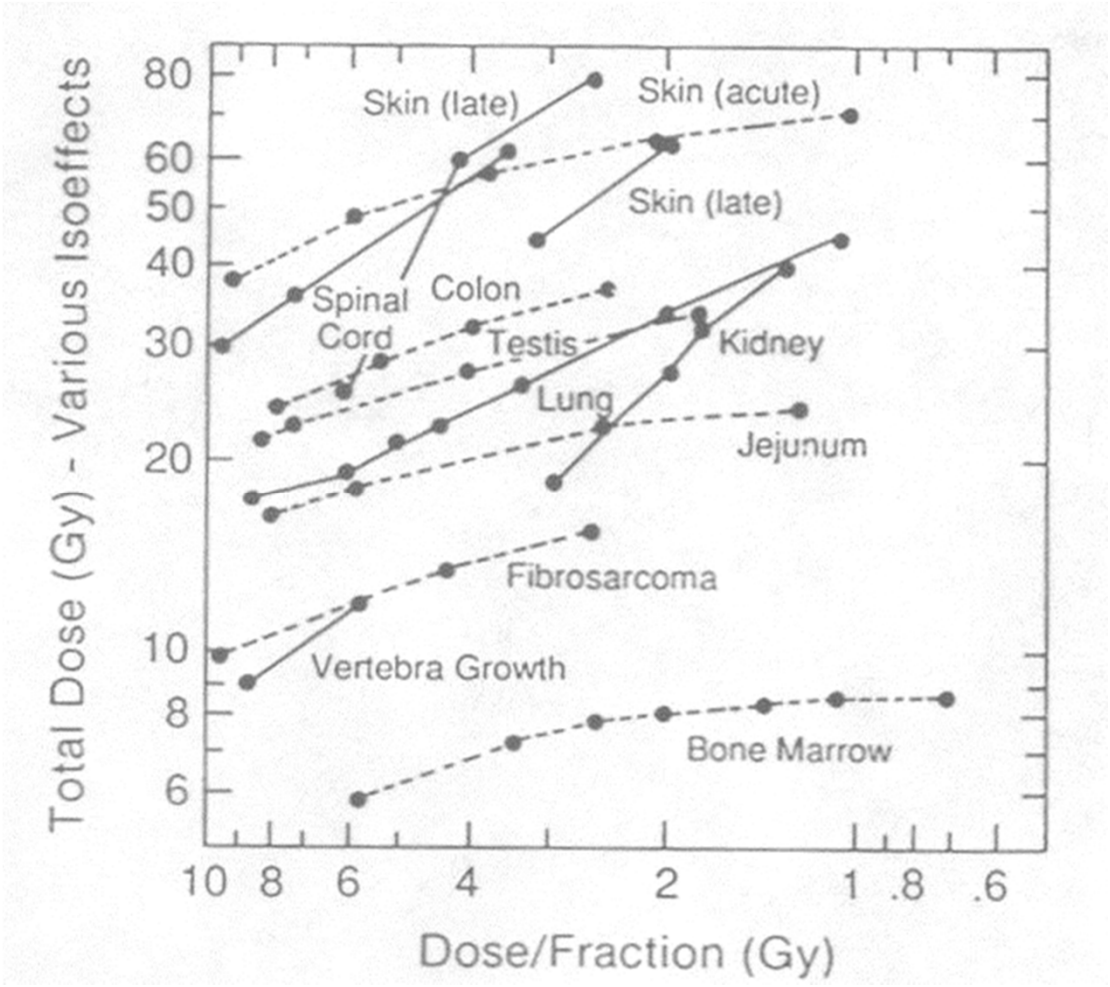
Radiobiological Principals of Radiation Therapy Design



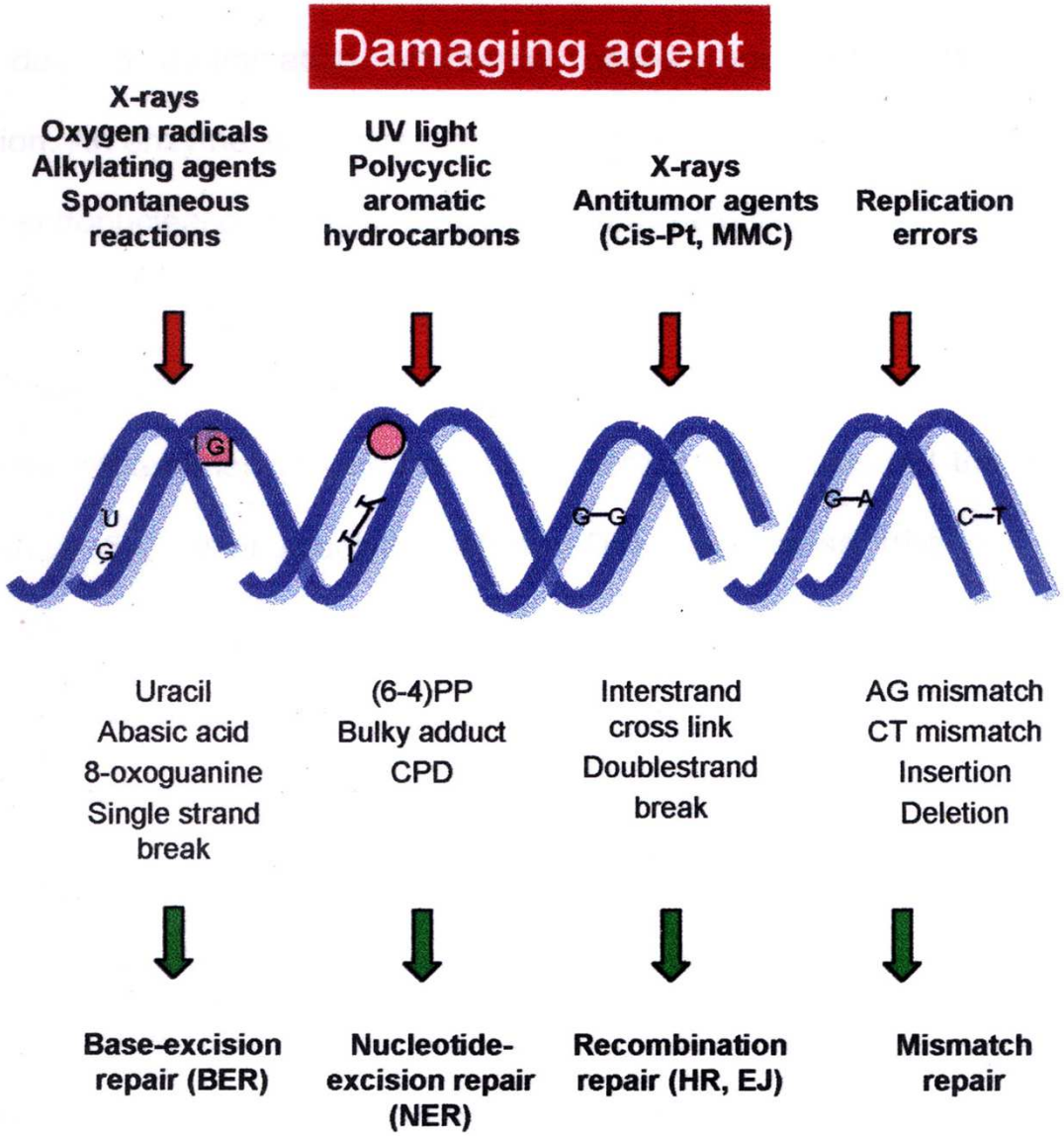
Radiobiological Principals of Radiation Therapy Design

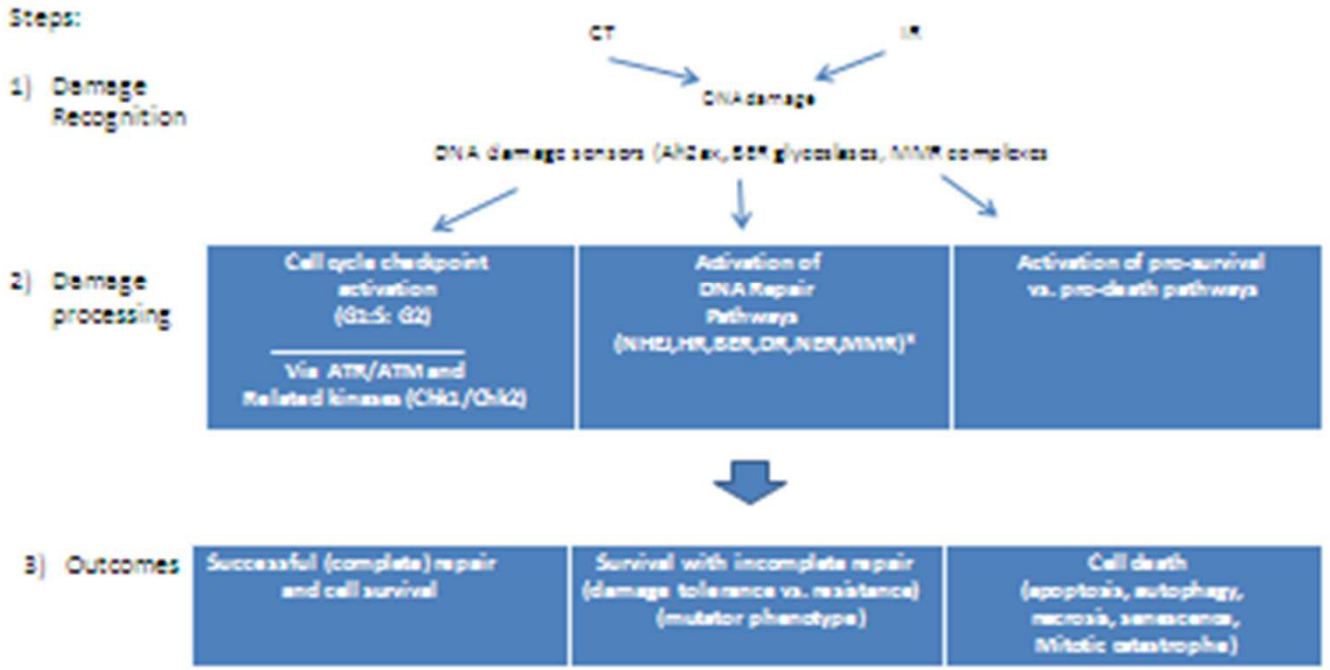


Radiobiological Principals of Radiation Therapy Design



Interaction between DNA damage and repair process





*NHEJ- Non- homologous end joining, HR- Homologous recombination BER- Base excision repair, DR- Direct repair(by MGMT) NER – Nucleotide excision repair; MMR- Mismatch repair; other- see text

Table 1: Cancer Susceptibility Syndromes Linked to Defective DNA Damage Repair Responses

Syndrome	Defects	Tumor Risk
Li-Fraumeni (AD: p53 heterozygote)	Cell cycle regulation, apoptosis	Breast, sarcoma, others
Lynch/HNPCC (AD: 1 D MLH1/MSH2) others	Mismatch repair	Colorectal, uterine,
BRCA1, BRCA2 (AD: gene heterozygote)	HR and other DNA repair pathways	Breast, ovary
Ataxia telangiectasia (AR: AT-mutated [atm]	DSB repair; cell cycle Regulation	Acute leukemia lymphomas
Xeroderma pigmentosum (AR: XP variants or complementation groups)	NER	Skin cancers
Fanconi's anemia (AR: complementation variants)	Cross-link repair	Acute myeloid leukemia

Abbreviations: AD, autosomal dominant: AR, autosomal recessive: DSB, double-strand breaks:HNPCC,hereditary nonpolyposis colorectal cancer: HR, homologous recombination: NER, nucleotide excision repair: XP, xeroderma pigmentosum.

Table 2. DNA Repair Pathways Involved in the DDR to Chemotherapy and Ionizing Radiation

Pathway	Description
• Non- homologous end joining (NHEJ)	• Mediates repair of DNA DSBs without the need for sequence homology.
• Homologous recombination (HR)	• Mediates DNA strand breaks and replication lesions by copying a DNA sequence from intact DNA (often a newly synthesized sister chromatid
• Base excision repair (BER)	• A repair process that replaces missing or modified DNA bases resulting from oxidative stress or cancer treatments (IR, alkylating drugs)
• Direct (enzymatic repair (DR)	• A repair process of alkylated base damage (eg,TMZ treatment via O6-methyguanine-DNA methyltransferase (MGMT)
• Nucleotide excision repair (NER)	• A repair process that removes large DNA adducts or large base Modifications causing DNA helix distortions using the opposite strand as a template for repair
• Mismatch repair (MMR)	• A repair process that functions during DNA replication (S-phase) To correct base-pairing errors made by DNA polymerase (slippage) or exogenously produced by IR and/ or CT.

SITE OF ACTION..

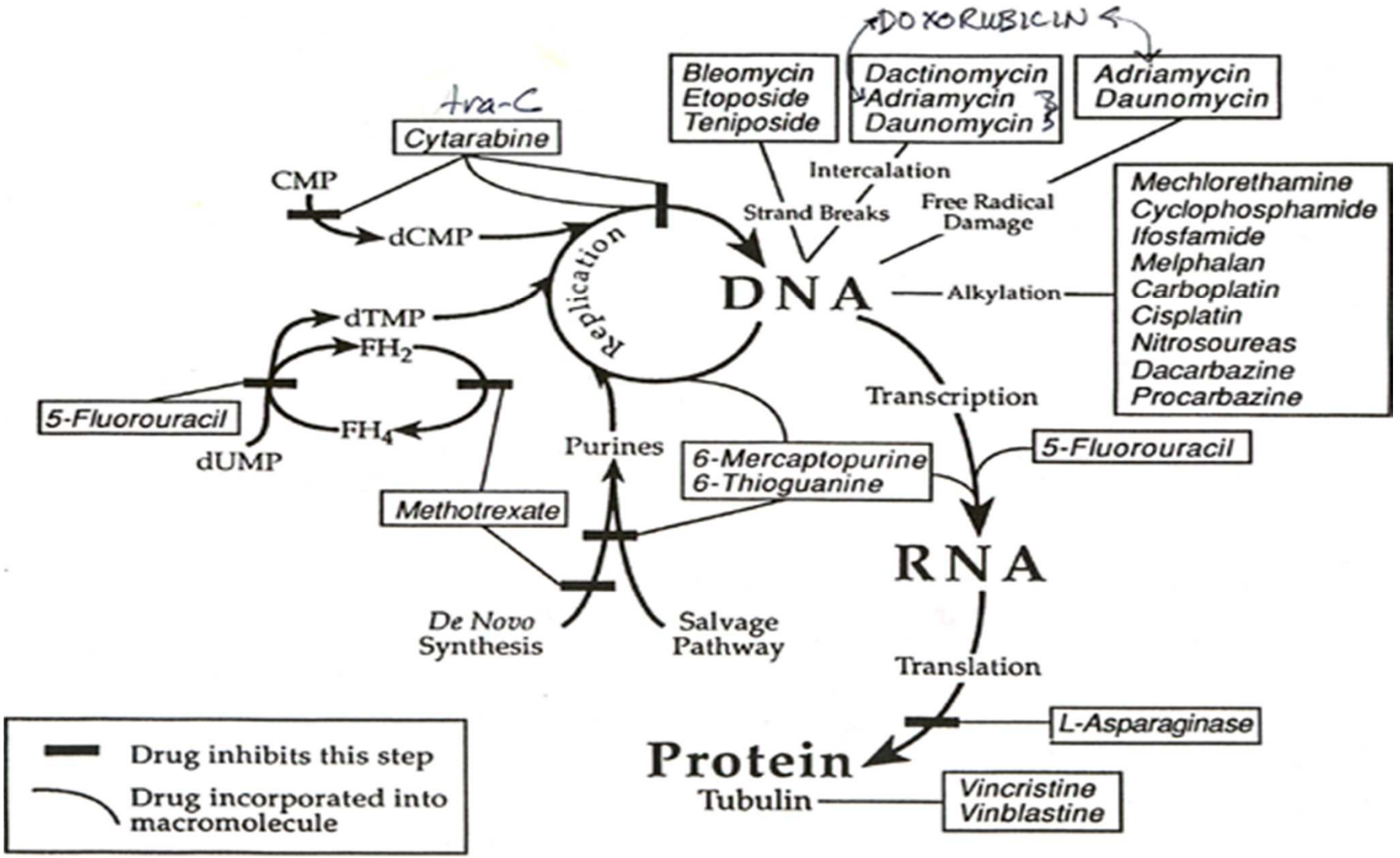


FIGURE 10–2. Sites of action of the commonly used anticancer drugs.

The 4 R’s of Radiation Therapy

- **Restitution**
- **Repopulation**
- **Redistribution**
- **Reoxygenation**

The 4 R’s of Radiation Therapy

- Reassortment (Redistribution)
  - Following a D_0 level radiation event cells die
    - Cells in G_2 and M are most sensitive and more likely to be killed.
    - Cells in S are more resistant and likely to survive
    - A radiation induce mitotic arrest is likely present
  - Cell growth kinetics tend to determine what percentage of the population will be in each phase of the cell cycle

The 4 R’s of Radiation Therapy

- Reassortment (cont.)
  - Following irrradiation the percentage of cycling cells in each phase will be reestablished within 1-2 cell cycle times.
  - Reirradition will then again selectively kill cells in the radiation sensitive portions of the cell cycle
  - Thus reassortment improves chances of cells being irradiated in a sensitive part of the cycle

The 4 R’s of Radiation Therapy

- Reassortment cont.
  - Tumor cells on average have shorter cell cycle times than normal tissues
  - This is especially true for late responding tissue
  - Reassortment then occurs more quickly in tumors.
  - Reasortment favors survival of normal late responding tissues

The 4 R's of Radiation Therapy

- Repair – Following a D_0 level dose there is repair of radiation injury in surviving cells
  - Cells with long cell cycle times generally have a wider repair shoulder on the survival curve
  - Cells with short cell cycle time generally have a narrow repair shoulder.
  - Tumor cells are consdered to have short cell cycle times

The 4 R’s of Radiation Therapy

- Repair – cont.
  - Fractionation will broaden the survival shoulder more for late responding tissue than early responding tissues.
  - At high doses the cell survival curve actually indicates lower survival for late responding cells

The 4 R’s of Radiation Therapy

- Regeneration
  - Following irradiation some cell populations will exhibit increased cell division
    - Usually follows a period of mitotic arrest
  - Repopulation tends to begin more quickly in normal early responding tissues than in tumors
  - Repopulation then favors survival of normal early responding tissues over tumors
  - Opposite is true of late responding tissues

The 4 R’s of Radiation Therapy

- Reoxygenation
  - Hypoxia in many tumors blunts radiation injury
    - 2-3 times as much dose required to kill hypoxic cells
  - Normal tissues are not hypoxic as a rule
  - This markedly favors survival of tumor cells for doses in the D_0 range.
  - However, of the well oxygenated cells in a tumor there is usually a high percentage of cycling cells.

The 4 R’s of Radiation Therapy

- Reoxygenation cont.
  - Large numbers of cycling tumor cells are killed
  - Cells previously of marginal oxygenation survive and move into the oxygenated zone
  - These newly oxygenated cells then start to cycle and are then susceptible to the next dose due to being oxygenated and cycling
  - Theoretically all tumor cells can be reoxygenated this way if enough fractions used

The 4 R’s of Radiation Therapy

- Recruitment
  - Recruitment is the “5th” of the “4 r’s”
  - Cells not previously part of the cycling pool are “recruited” to enter the cycling pool by one of the mechanisms of the 4 r’s
    - Leads to regeneration
    - Can be direct result of reoxygenation
    - Contributes cells to the reassortment process
    - Repair of injury allows cells to enter cycling pool.

Factors Affecting Tumor Growth

- Cell cycle time
  - Cell cycle times vary widely within a given tumor.
  - Some tumor cells may be very slowly cycling
  - Tumors of the same type may have different average cell cycle times
    - Slow is generally equated with benign tumors
    - Fast is generally equated with malignancy

Factors Affecting Tumor Growth

- Growth fraction (fraction of cells in population which are actually cycling)
  - Even in tumors most cells are not cycling
  - Cycling cells are well oxygenated and fed
  - Growth fractions of greater than 10% are unusual.
  - Growth fraction may be less than 1%
  - Large growth fraction will usually result in rapid tumor growth.

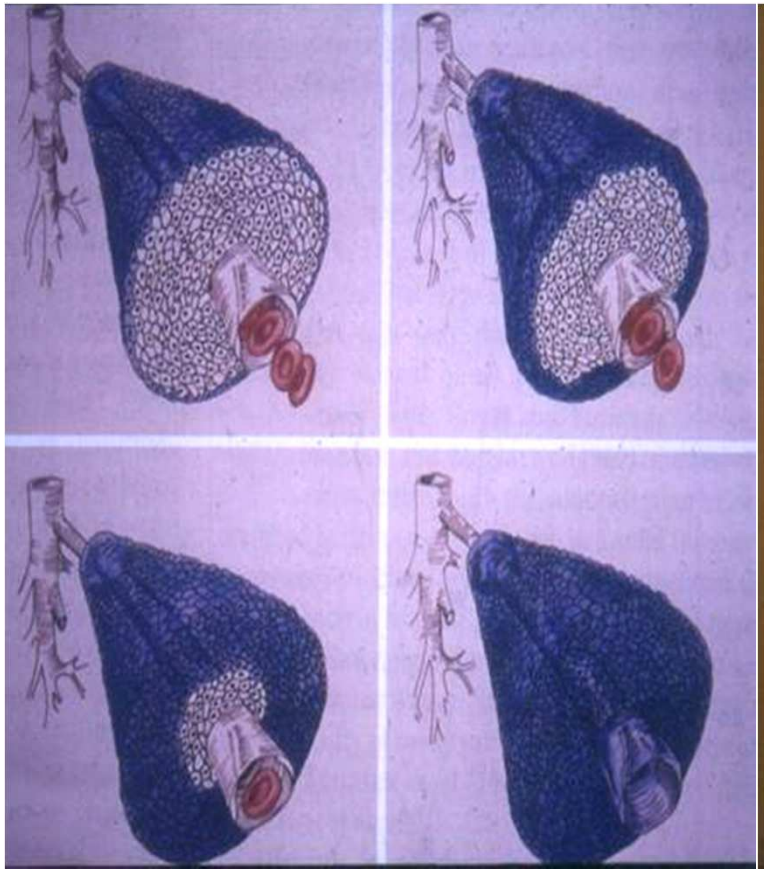
Factors Affecting Tumor Growth

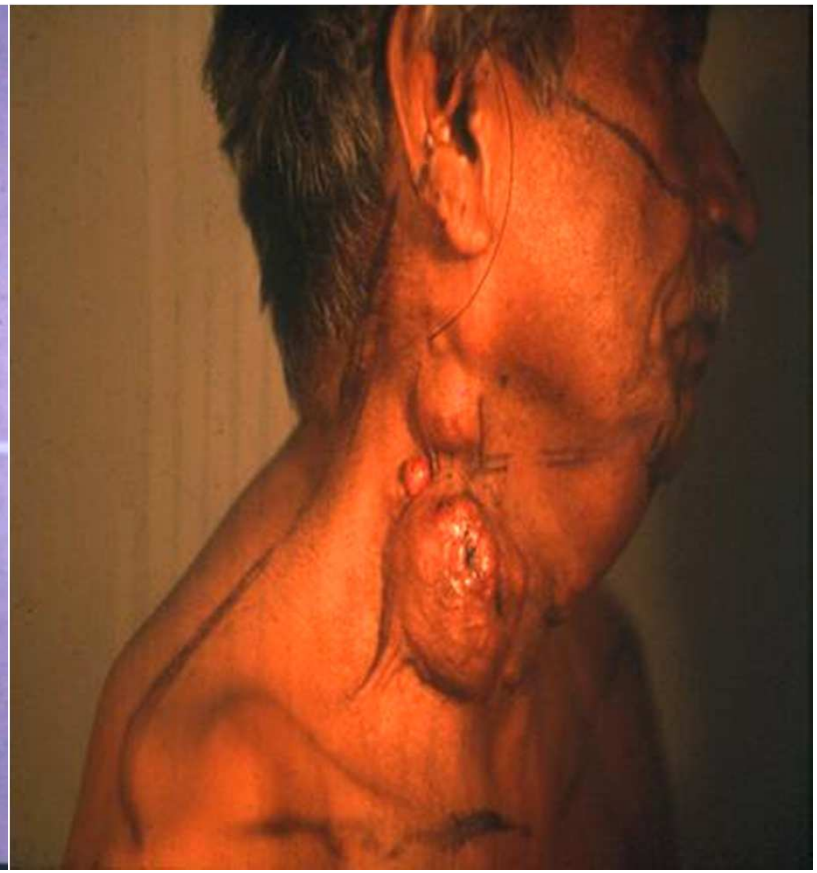
- Cell loss fraction
  - Cells are lost from the tumor population in several ways.
  - Nonviable replication of deranged cells will result in loss of those cells
    - DNA is too altered for a functional cell to exist
  - Anoxia, cell death from poor blood supply
  - Attack of antigentic cells by immune system
  - Metastasis to blood stream > vast majority die

Factors Affecting Tumor Growth

- Tumor oxygenation
  - Poor tumor oxygenation = slow growth
  - Poor tumor oxygenation = increased cell death
  - Tumor oxygenation decreases as size increases
  - Both chronic and transient hypoxia may have effect.

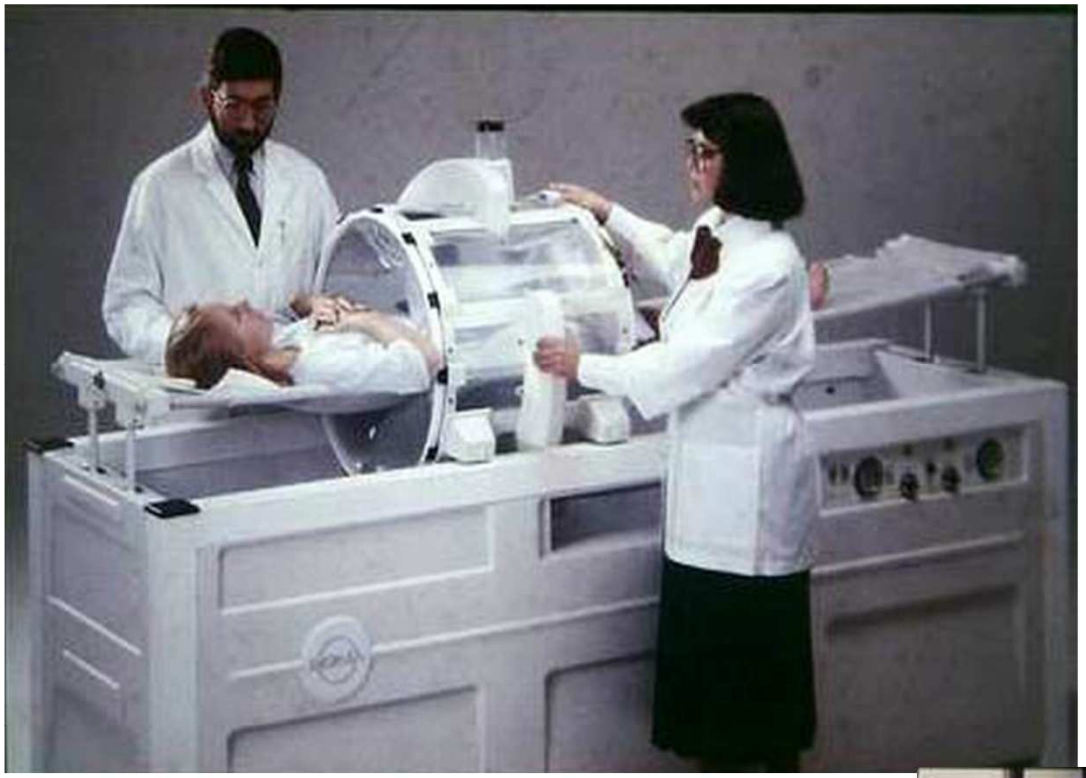
Tumour Hypoxia is One of the Determinant of Poor Outcome Following Radiation

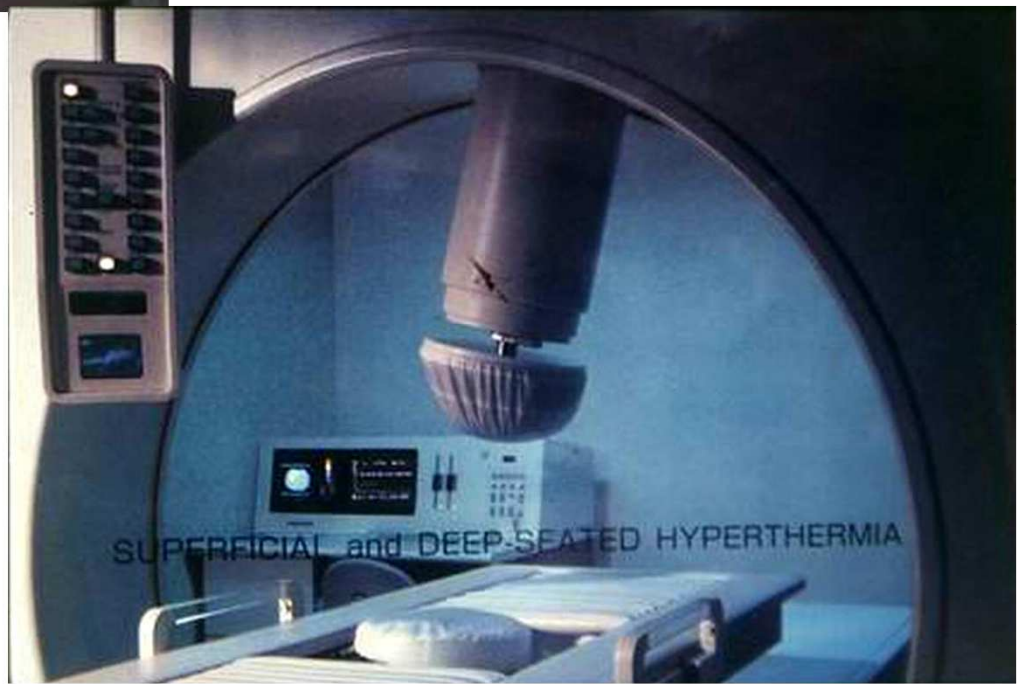




Outcome of Interactions

- *Additive*
- *Supra additive – Sensitization*
- *Sub additive - Protection*




SUPERFICIAL and DEEP-SEATED HYPERTHERMIA

Biological Basis

- Temperature above 41°C is differential to mammalian cells
- Sensitizes cells to ionising radiation
- Can activate 0 and S phase cells
- Preferentially kills hypoxic cells due to pH dependency
- Cell membrane may be the primary target
- Can inhibit DNA repair

Biological Basis for Hyperthermia

- Microenvironment is hostile in tumour to heat, and heat in turn perpetuates the state
- Better thermal washouts in normal tissue reduces the cytotoxic effects.
- A therapeutic window is created

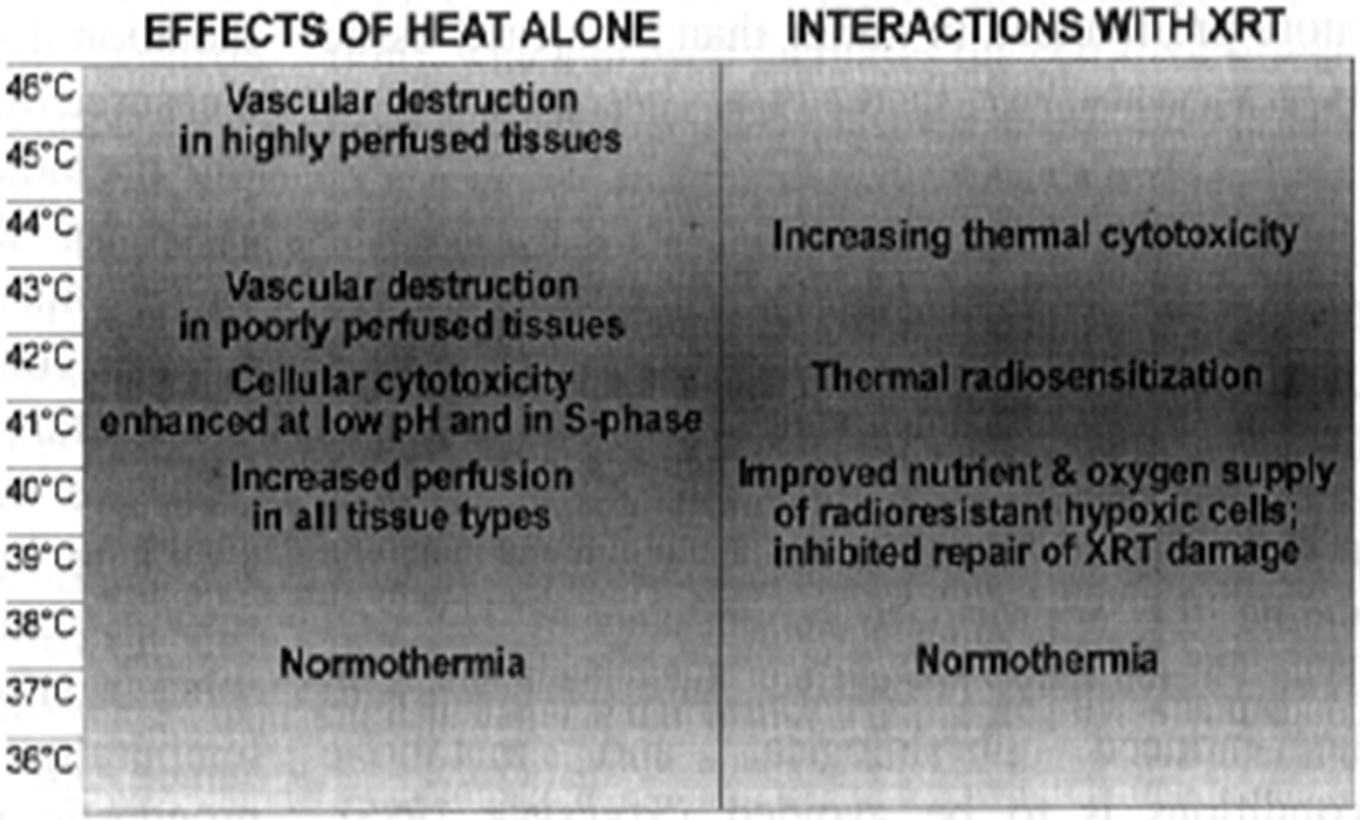
Vascularity - Hypoxia - pH

Hyperthermia can totally occlude tortous

Neo-vascularization with concomitant alterations in oxygenation metabolism.

Leading to hypoxia and low pH

Walenta; Streffer


EFFECTS OF HEAT ALONE
INTERACTIONS WITH XRT
46°C
45°C
44°C
43°C
42°C
41°C
40°C
39°C
38°C
37°C
36°C
Vascular destruction in highly perfused tissues
Vascular destruction in poorly perfused tissues
Cellular cytotoxicity enhanced at low pH and in S-phase
Increased perfusion in all tissue types
Normothermia
Increasing thermal cytotoxicity
Thermal radiosensitization
Improved nutrient & oxygen supply of radioresistant hypoxic cells; inhibited repair of XRT damage
Normothermia

Tissue Oxygenation

Low flow → Further decline

High Flow → Perfusion may go up

Decline in pO2 may last for 24 hours

Targets for Hyperthermia

- Plasma Membrane
- Cytoskeleton
- Nucleus

Changes in Tissue pH

- Accumulation of lactic acids
- Changes equilibrium of intra and extra cellular buffer state
- Increase in ATP hydrolysis
- Increase in pCO^2 level
- Inhibition of the Na^+/H^+ ion pump

Variable to Affect the Outcome

- Heat dose i.e. temperature over a time period
- Thermal gradients
- Sequence and interval between two modalities
- Tumour volume
- Intrinsic sensitivity for heat
- Heating mechanism

Characteristics of Heat Susceptible Tumour

- Nutrient deprived tissue
- Poor perfusion
- Anerobic metabolism
- Lower pH
- Low on energy

Thermal Sensitizers

- Hyperglycemia
- Amiloride
- Hydralazine
- Nitroprusside
- Arsenic Trioxide

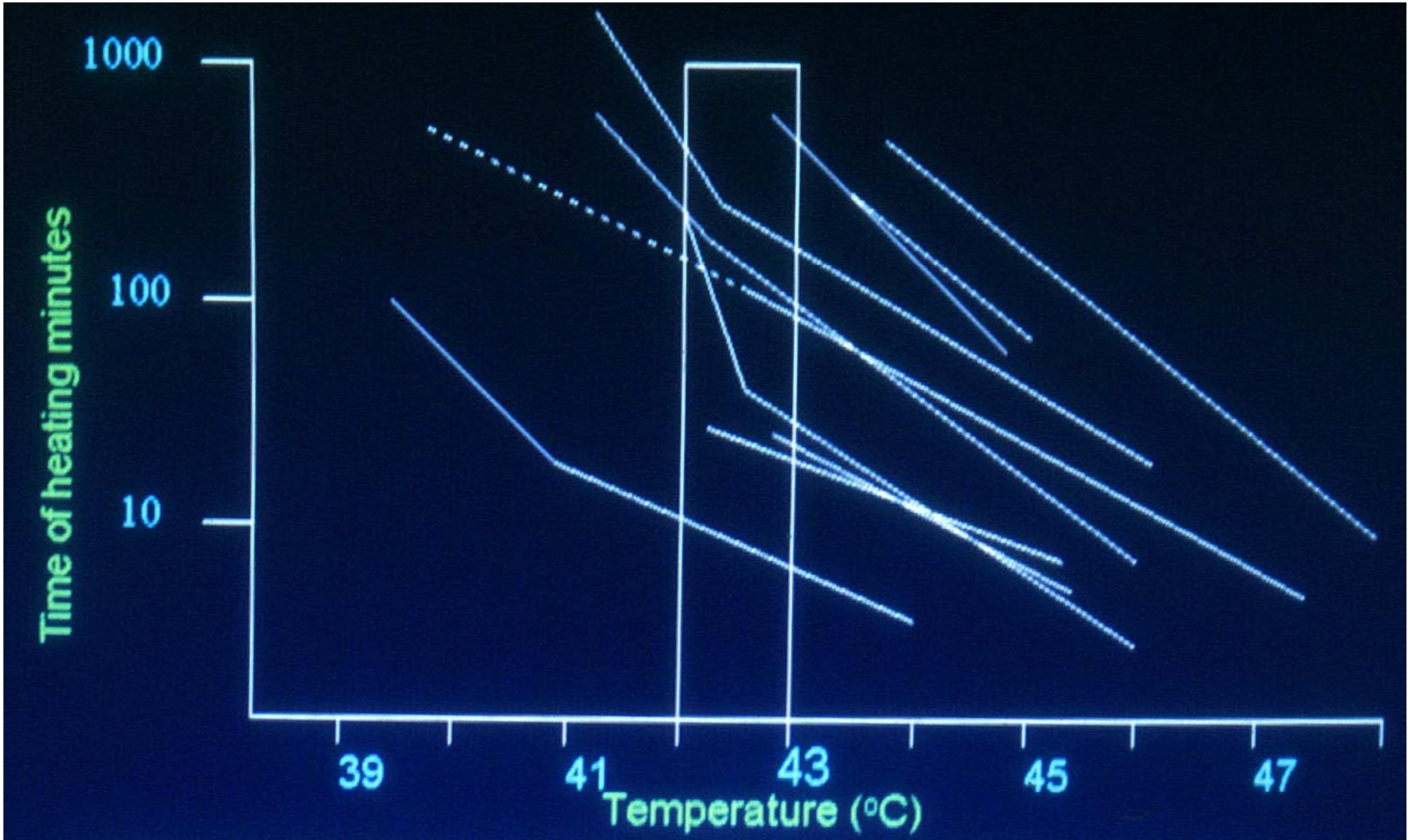
Specification of the RF Heating System

Power Source	Single phase, 200V, 50~60Hz, 30A
Max. Input	4KVA
RF Output	8MHz
Electrode	Twin plate electrodes, ϕ10cm, ϕ14cm, ϕ25cm
Temp. Measurement	Micro thermocouple sensor (0.64mm diameter)
Temperature Control	On-Off control
Heating Method	RF Capacitive coupling heating

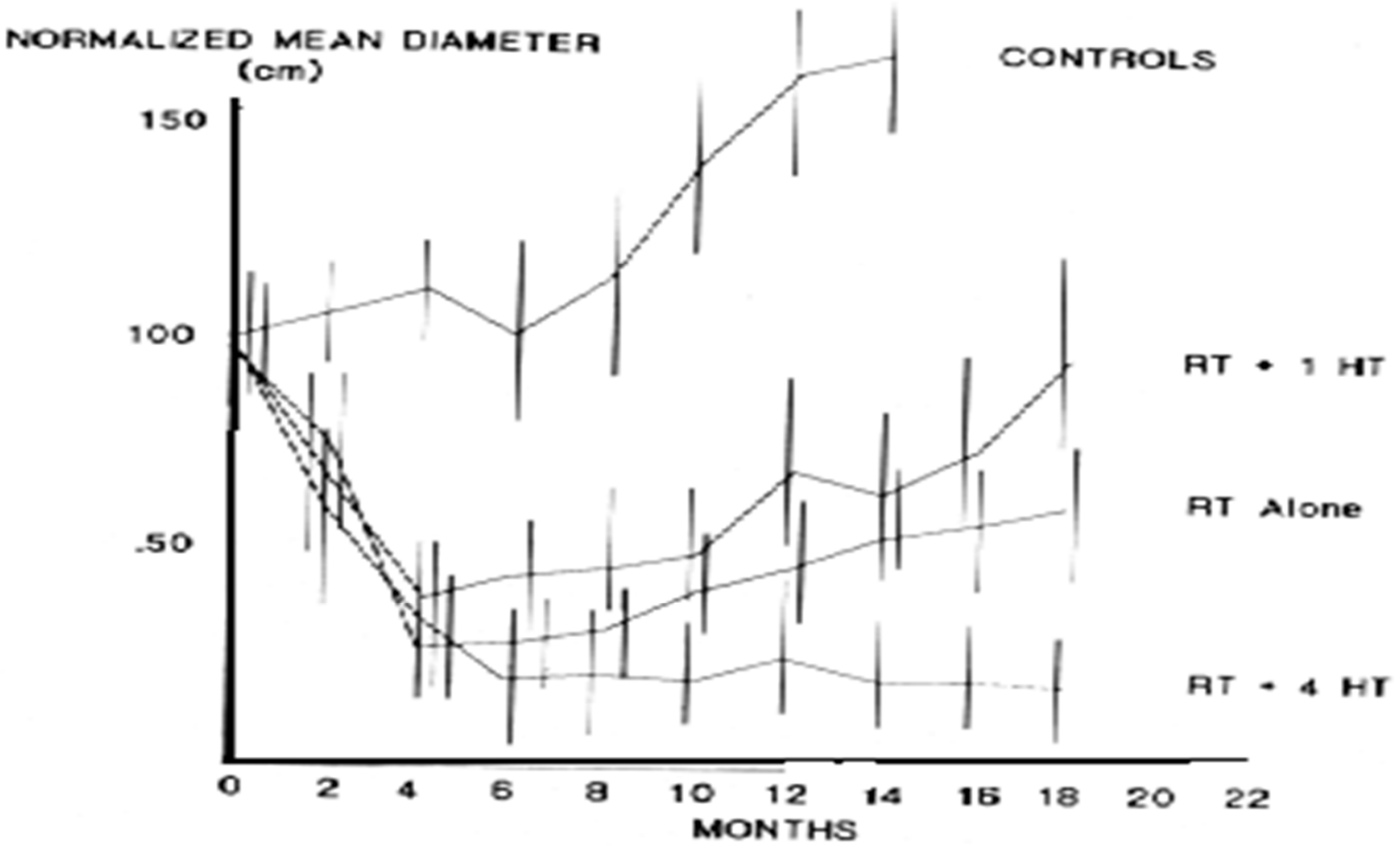
HEATING TECHNIQUE

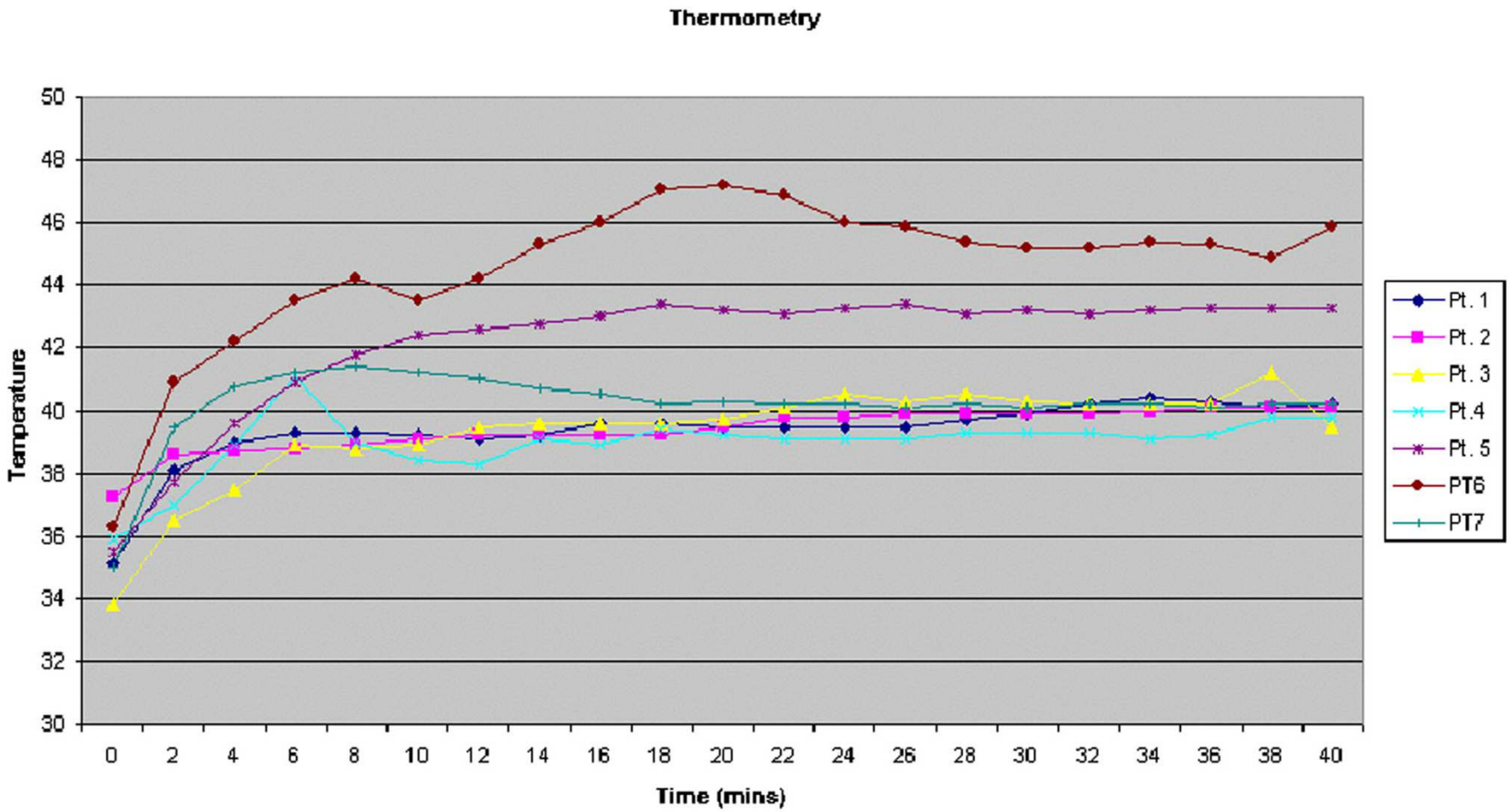
- THERMOMETRY – AT LEAST ONCE, WITH INVASIVE THERMISTOR PROBES
- PRIMARY – HEAD & NECK NOT DONE
- APPROPRIATE ANTENNAE ARE ARRANGED IN PARALLEL WITH ACTIVE

  SIDE TOWARDS THE LESION
- POWER : - 400 – 900 W
- RF – 8 MHz – THERMATRON – CAPCITATIVE HEATING



Relationship between time of heating temperature to produce a given effect in a range of normal tissues and tumours in situ. At temperatures above the break point 1°C is equivalent to a factor of two in heating time: below the break 1°C is equivalent to a factor of six.


NORMALIZED MEAN DIAMETER
(cm)
150
100
.50
CONTROLS
RT + 1 HT
RT Alone
RT + 4 HT
0
2
4
6
8
10
12
14
16
18
20
22
MONTHS


Thermometry
Temperature
50
48
46
44
42
40
38
36
34
32
30
0
2
4
6
8
10
12
14
16
18
20
22
24
26
28
30
32
34
36
38
40
Time (mins)
Pt. 1
Pt. 2
Pt. 3
Pt.4
Pt. 5
PT6
PT7

I C M R – Hyperthermia Trial

Randomized

RT
64 – 70 Gy / 6 – 7 wks
200 cGy / day

N = 14

RT
64 – 70 Gy / 6 – 7 wks
200 cGy / day
+
Weekly Hyperthermia.

N = 14

Exclusion Criteria

Karnofsky's Index <80

Histology other than sq.cell.ca

Early Head & Neck Cancer

Bilateral nodes

Emotionally incompetent

Short Neck

Inclusion Criteria

Squamous cell- carcinoma –confirmed histologically /FNAC

Karnofsky's Index > 70

Loco-regionally advanced H&N cancer T3- 4/ No – N3

Only ipsilateral nodes

Emotionally capable of giving informed consent

Radiation Therapy

-Total dose of 66-70 Gy was given by appropriate portals with daily 200cGy per fraction.

-6 1/2 – 7weeks of treatment

-4-6 MV energy rays used for treatment.

Demographic data

Parameters	RT-Group	RT + HT-Group
No. of Cases	26	28
@Age (yrs) Mean SD Range	58.42 11.39 40-76 yrs	57.71 12.93 31-78 yrs
#Sex (%) Male Female	24(92.3) 02(07.7)	22(78.6) 06(21.4)

@ By Student‘t’ Test
# By Chi-square Test

P > 0.05 Not Significant

TNM staging classification

Response	RT-Group (N=26)		RT + HT-Group (N=28)	
	No	%	No	%
T2N0	01	03.8	01	03.6
T2N1	01	03.8	01	03.6
T2N3	02	07.7	02	07.1
T3N1	02	07.7	03	10.7
T3N2	04	15.4	04	14.3
T3N3	06	23.1	02	07.1
T3NO	04	15.4	07	25.0
T4N0	-	-	03	10.7
T4N1	-	-	02	07.1
T4N2	02	07.7	02	07.1
T4N3	04	15.4	01	03.6

SITES OF DISEASE

Site	RT-Group (N=26)		RT + HT-Group (N=28)	
	No	%	No	%
Oropharynx	17	65.4	10	35.7
Hypopharynx	05	19.2	12	42.9
Oral cavity	04	15.4	06	21.4

RADIATION DOSE IN BOTH GROUPS

Response	RT-Group (N=26)		RT + HT-Group (N=28)	
	No	%	No	%
</=50GY	04	15.4	04	14.3
>70GY	01	03.8	01	03.6
50-60GY	-	-	01	03.6
60-70GY	21	80.8	22	78.5

FOLLOW-UP PERIOD

Durations	RT-Group (N=26)		RT + HT-Group (N=28)	
	No.	%	No.	%
< 6 months	16	61.5	11	39.3
6-12 months	08	30.8	12	42.8
> 12 months	02	07.7	05	17.9

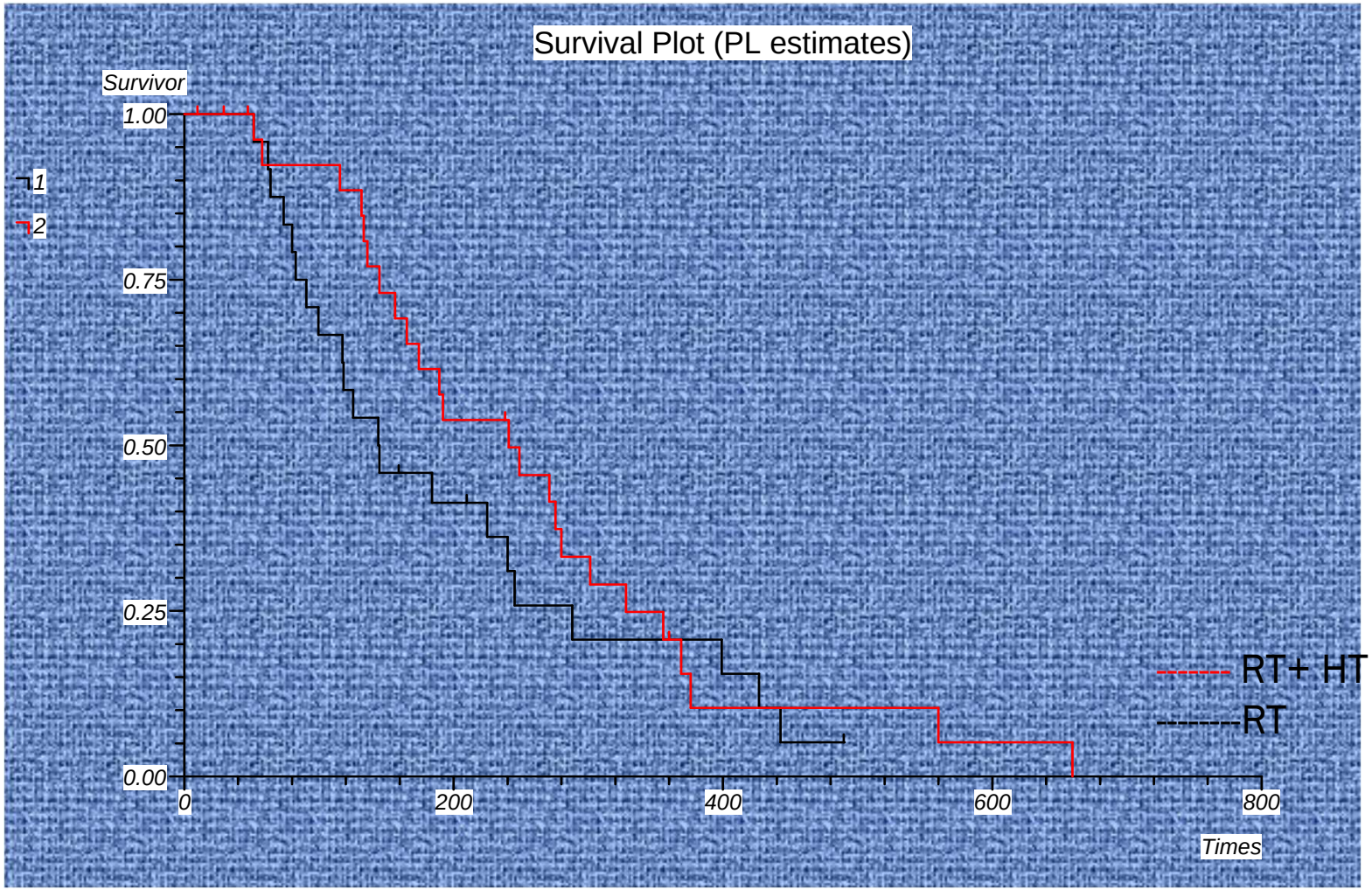
Compliance to Hyperthermia Treatment

No. of hyperthermia treatments	No. of patients
0-1	03
2-4	02
5-7	23

COMPARISON OF RESPONSE BETWEEN TWO TREATMENT GROUPS

Response	RT-Group (N=26)		RT + HT-Group (N=28)	
	No	%	No	%
Complete Response	11	**42.4**	22	**78.6**
Partial Response	13	50.0	03	10.7
No Response	01	03.8	-	-
PD	01	03.8	03	10.7

Kaplan-Meier Survival plot



Mechanisms of Thermal Enhancement

Increase in intracellular drug concentration

Stimulation of drug binding to DNA

Change in the spectrum of adducts formed

Reduction in DNA repair

Increase in perfusion

Chemotherapy

- Concurrent once a week chemotherapy given
- Cisplatin- 30mg/m^2 i/v
- Paclitaxel- 30mg/m^2 i/v

Chemoradiation with hyperthermia in the treatment of head and neck cancer

Nagraj G. Huilgol, Sapna Gupta, Rajesh Dixit
Int.J. Hyperthermia, February 2010; 26(1): 21-25

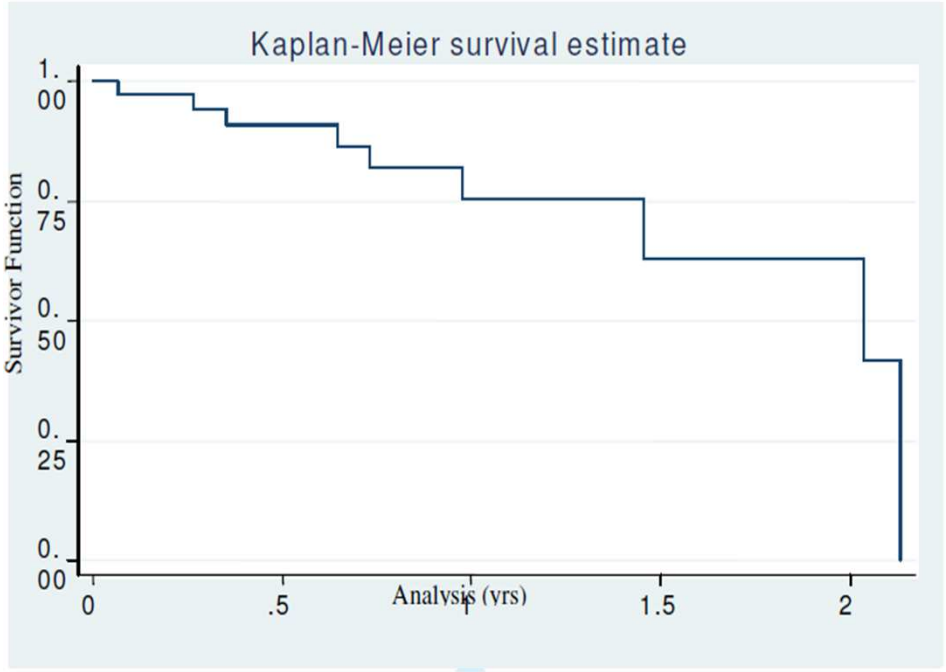
38 patients evaluated at the end of study

Complete response- 29/38 patients

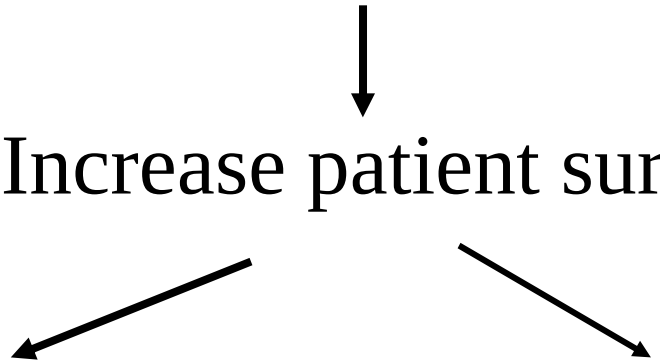
Partial response- 09/38 patients

Mortality- 01/40

Incomplete treatment- 01/40



BASIS OF CHEMORADIATION

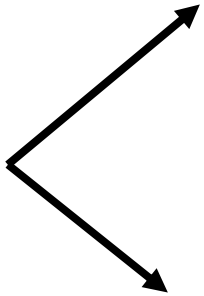


Increase patient survival

improving loco-regional tumor control

decreasing or eliminating distant metastases

SITE OF ACTION



Locoregional

Systemic

Steel and Peckham- strategies of combined modality

- spatial cooperation
- independent toxicity
- enhancement of tumor response
- protection of normal tissues.

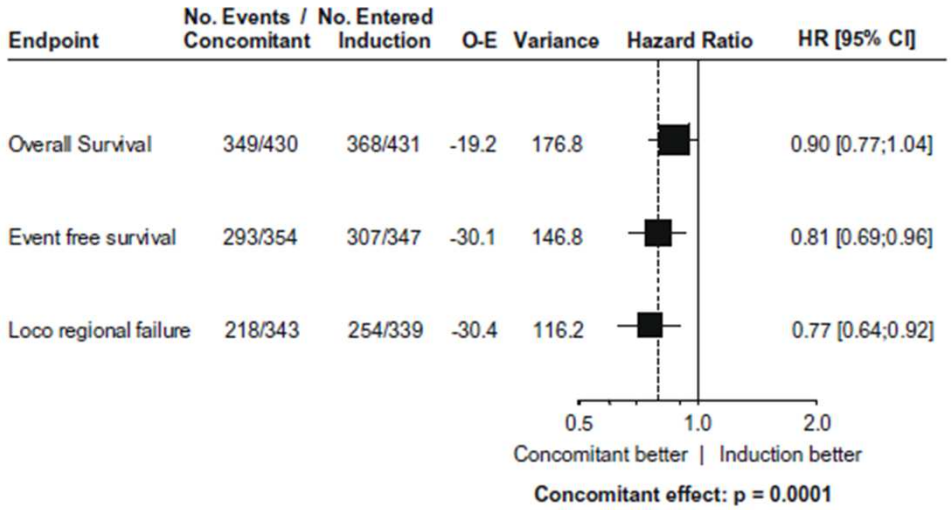
Drug-Radiation Interactions

- Increasing Initial Radiation Damage
- Inhibition of Cellular Repair
- Cell Cycle Redistribution
- Counteracting Hypoxia-Associated Tumor Radio-resistance
- Inhibition of Tumor Cell Repopulation

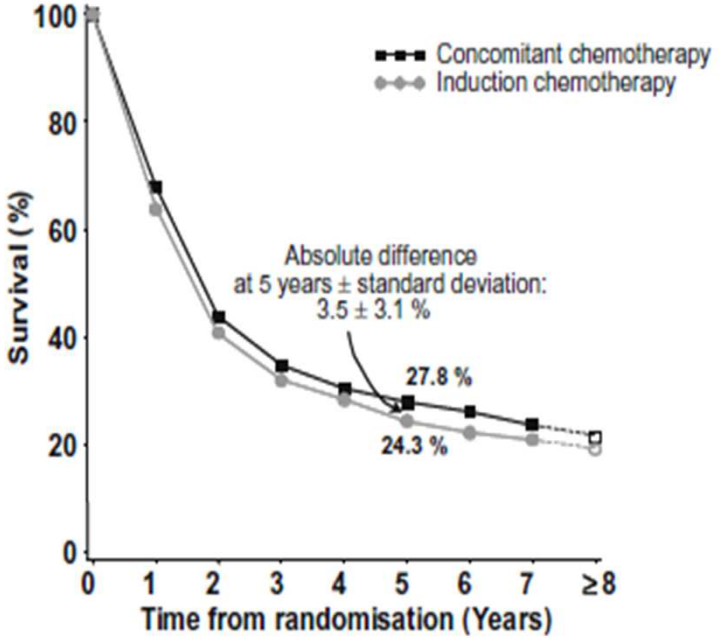
Meta-analysis of chemotherapy in head and neck cancer (MACH-NC): An update on 93 randomised trials and 17,346 patients

Jean-Pierre Pignon a,*, Aurélie le Maître a, Emilie Maillard a, Jean Bourhis b, on behalf of the MACH-NC Collaborative Group

Radiotherapy and Oncology 92 (2009) 4–14



Hazard ratio of different end-points



Overall Survival Curves

EVIDENCE SO FAR ……..!

- Chemoradiotherapy shows equal results of survival with the possibility of laryngeal preservation. It is higher with chemoradiation in laryngopharyngeal malignancies.

- CT+RT should be considered standard of care for small volume stage III/stage IV laryngeal and hypopharyngeal cancers (TMH – EBM)

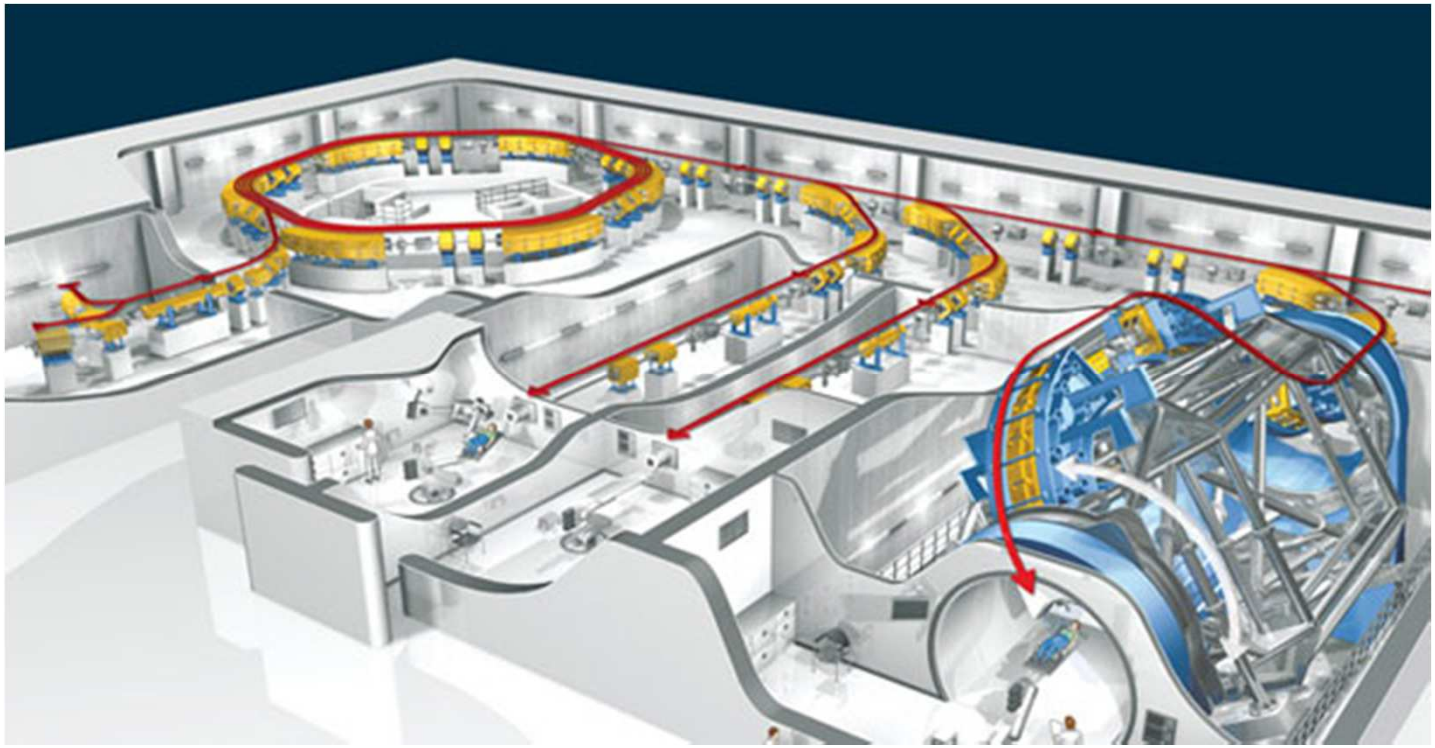
RESULTS OF TREATMENT OF ADVANCED CARCINOMA OF THE LARYNX UTILIZING CHEMOTHERAPY AND RADIATION THERAPY

Author	Year	No.	Type of Therapy	Stage III/IV (%)	2 Year Survival (%)
Veterans Affairs	1987	30	C/RT	100	52
Larynx Group		166	S/RT	100	68
Pfister	1991	13	C/RT	98	77
Karp	1991	14	C/RT	92	50
Urpa	1994	8	C/RT	93	75

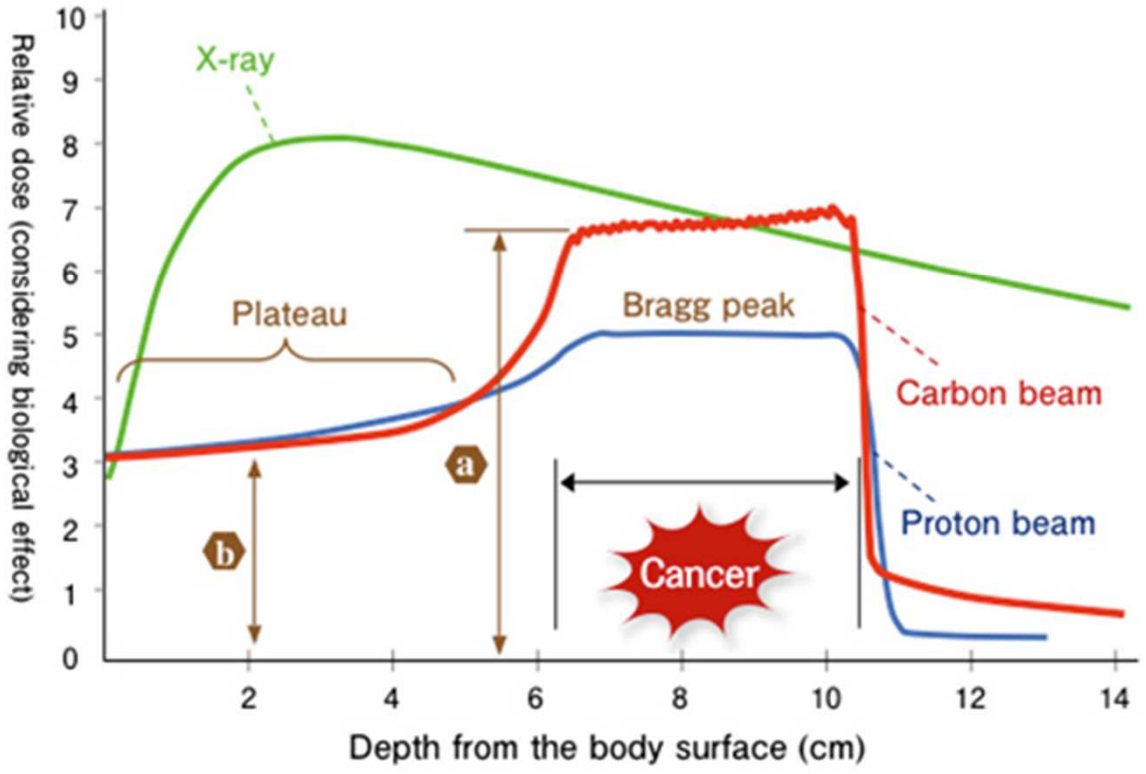
SELECTED RANDOMIZED TRIALS COMPARING COMBINATION CHEMOTHERAPY AND RADIATION THERAPY WITH RADIATION THERAPY ALONE IN PATIENTS WITH LOCALLY ADVANCED HEAD AND NECK CANCERS

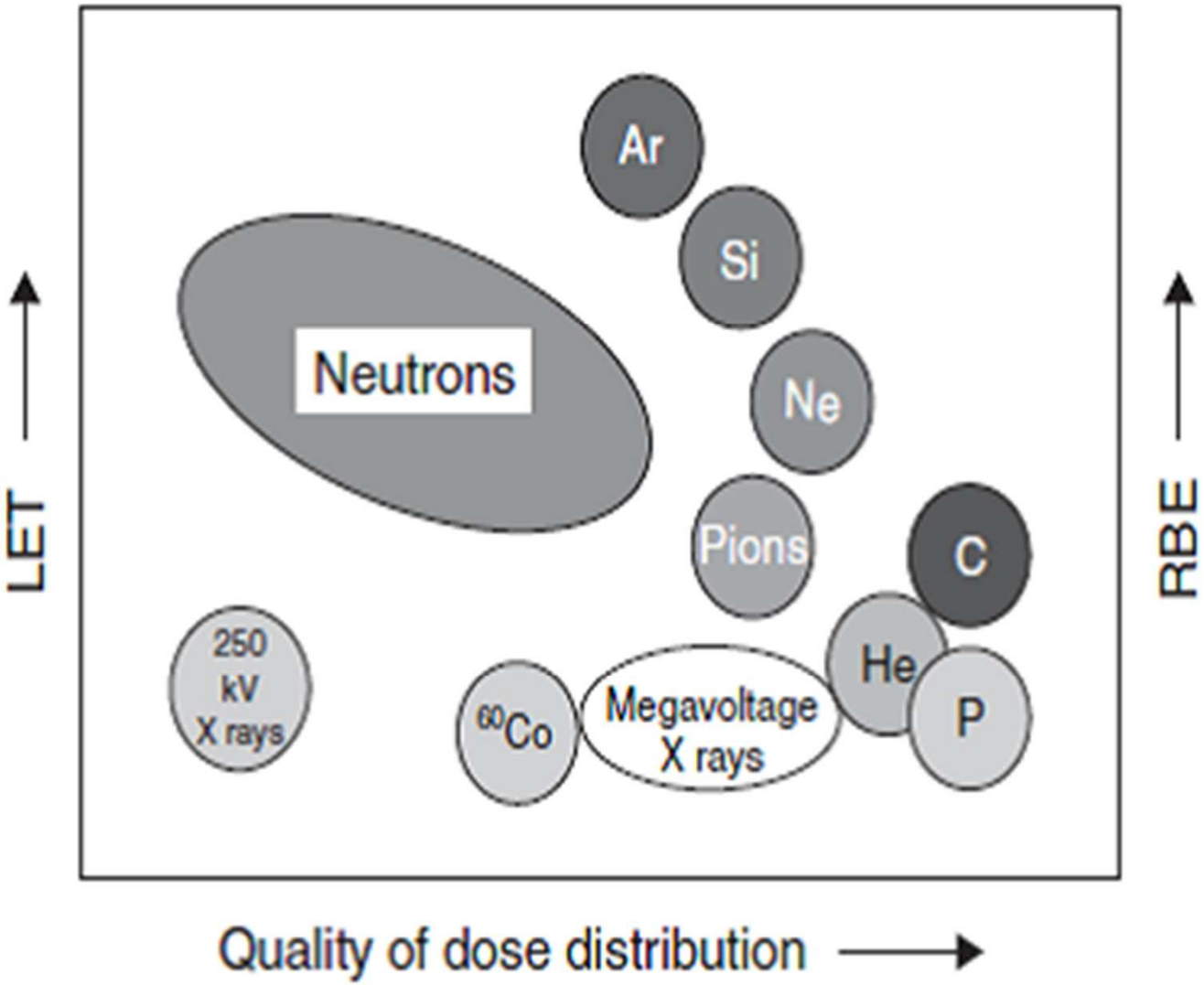
Author	*Total No. of Patients*	*CT/RT Schedule*	*CT Regimen*	*RT Fraction*	*Overall Survival Benefit (p<0.05)*
GORTEC	*226*	*Concurrent*	*CBDCA/5-FU*	*Standard*	*Yes*
Adelsin	*100*	*Concurrent*	*CDDP/5-FU*	*Standard*	*No*
Wendt	*270*	*Concurrent*	*CDDP/5-FU*	*Hyper-fractionated*	*Yes*
Keane	*212*	*Concurrent*	*MMC/5-FU*	*Standard*	*No*
Brizel	*122*	*Concurrent*	*CDDP/5-FU*	*Hyper-fractionated*	*No*
Merlano	*157*	*Alternating*	*CDDP/5-FU*	*Standard*	*Yes*

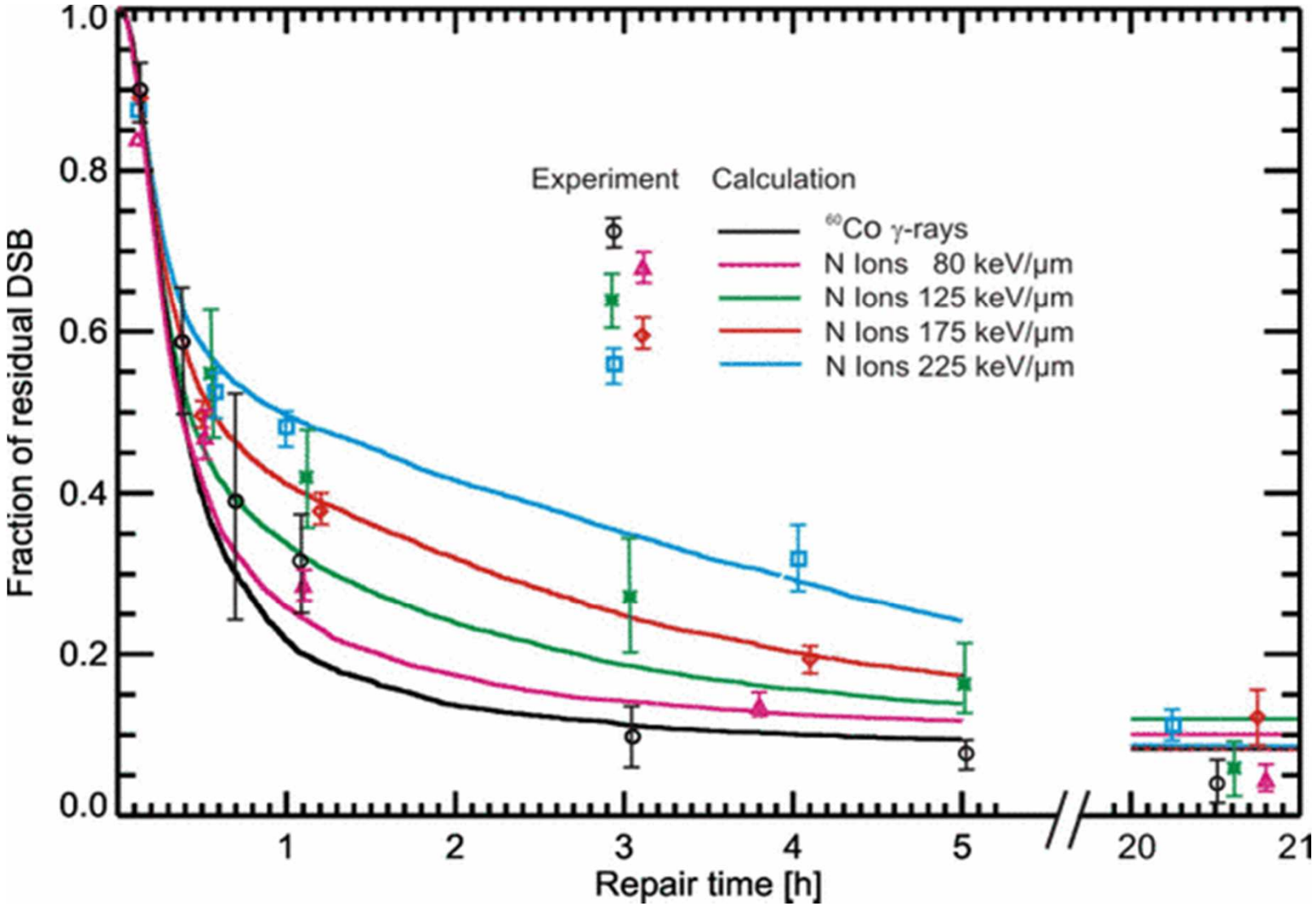
Carbon Ion Accelerator



When the ratios of peak to plateau (a/b) are compared while considering biological effect, the carbon beam has the largest value.




Ar
Si
Neutrons
Ne
Pions
C
He
P
250
kV
X rays
60Co
Megavoltage
X rays
LET
RBE
Quality of dose distribution

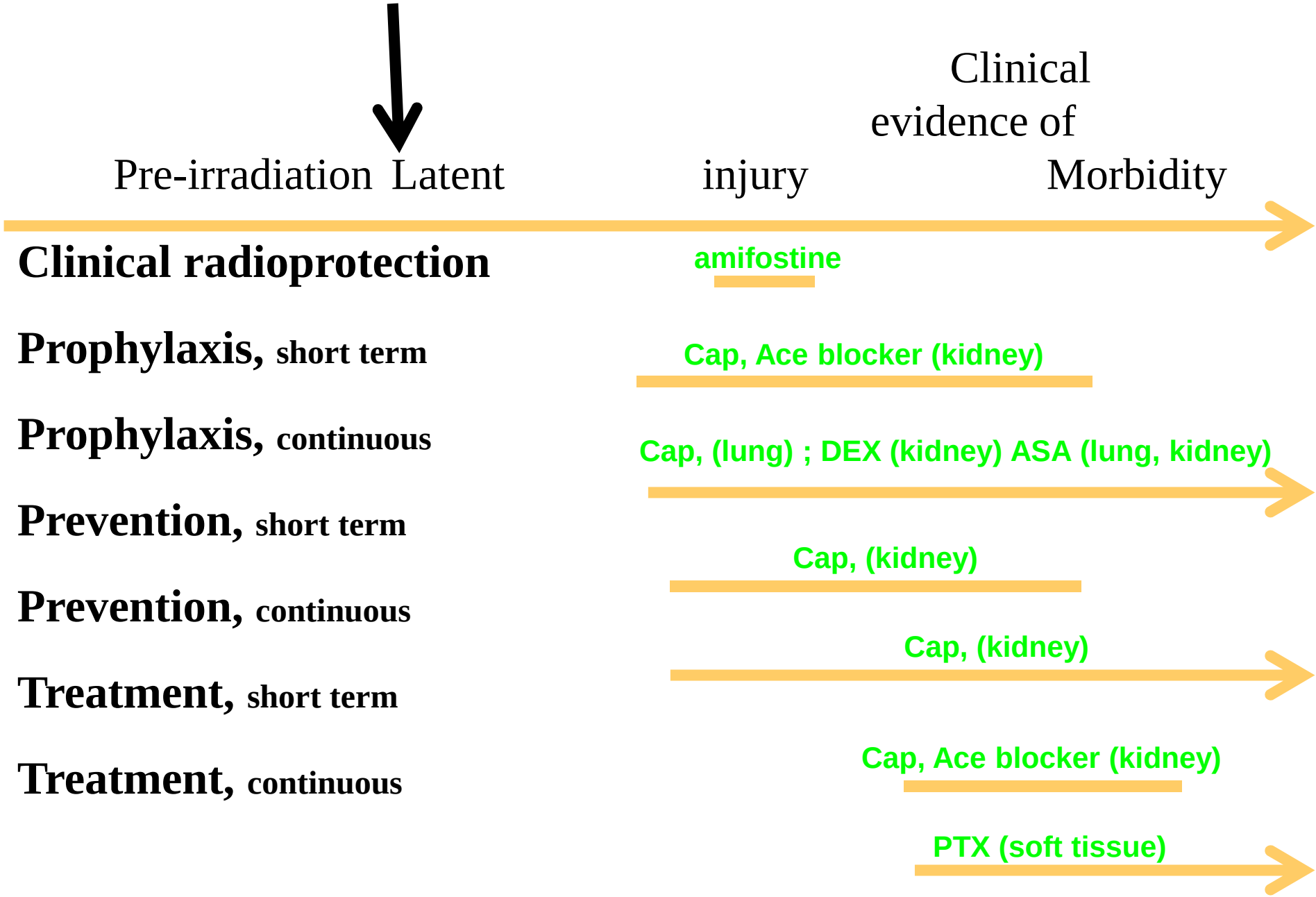

Fraction of residual DSB
1.0
0.8
0.6
0.4
0.2
0.0
Experiment
Calculation
60Co γ-rays
N Ions 80 keV/μm
N Ions 125 keV/μm
N Ions 175 keV/μm
N Ions 225 keV/μm
1
2
3
4
5
20
21
Repair time [h]

IDEAL RADIATION PROTECTOR

- Pre-empt injury
- Promote repair
- High DRF
- Should protect all organ systems
- Should spare tumours
- Least toxic – unlike amifostine
- Compatible with other drugs

Protectors

- Methylene Blue
- Phenobarbitone
- Mannitol
- Antioxidants
- Diethyldithiocarbonate (DDTC)
- Disulfran (dimer of DDTC)
- Sodium thiosulfate
- Mercaptoetahnosulfonate
- (MESNA)


Pre-irradiation
Latent
injury
Clinical evidence of Morbidity
Clinical radioprotection
amifostine
Prophylaxis, short term
Cap, Ace blocker (kidney)
Prophylaxis, continuous
Cap, (lung) ; DEX (kidney) ASA (lung, kidney)
Prevention, short term
Cap, (kidney)
Prevention, continuous
Cap, (kidney)
Treatment, short term
Cap, Ace blocker (kidney)
Treatment, continuous
PTX (soft tissue)

Damage

- Scavangable damage - $OH^{\bullet}$
- Non Scavangable damage
  - Direct ionisation of DNA

    Reaction with H_2O^+

    or non scavangable $OH^{\bullet}$

    Scavangable : 63

    Non Scavangable : 35

Conversion of Amifostine

Amifostine (prodrug)

NH_2-$(CH_2)_3$-NH-$(CH_2)_2$-S-PO_3H_2

↓ Membrane bound alkaline phosphatase

NH_2-$(CH_2)_3$-NH-$(CH_2)_2$-SH

WR-1065 (Active form)

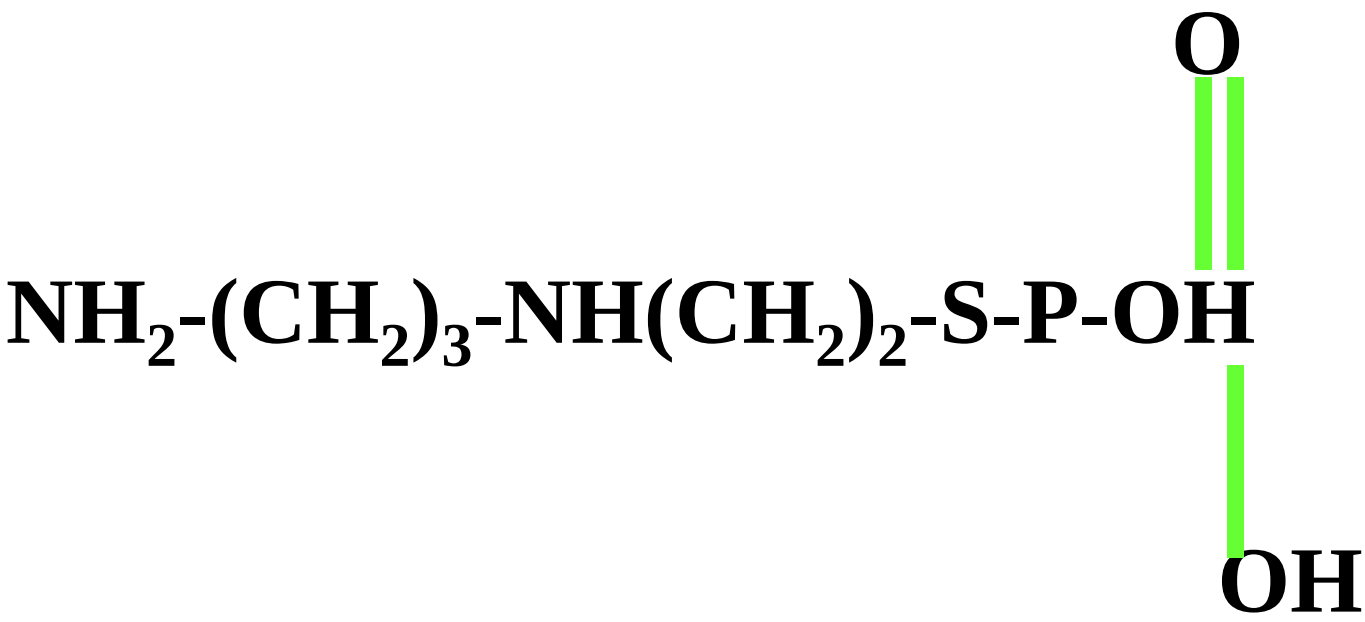
↓ Oxidation

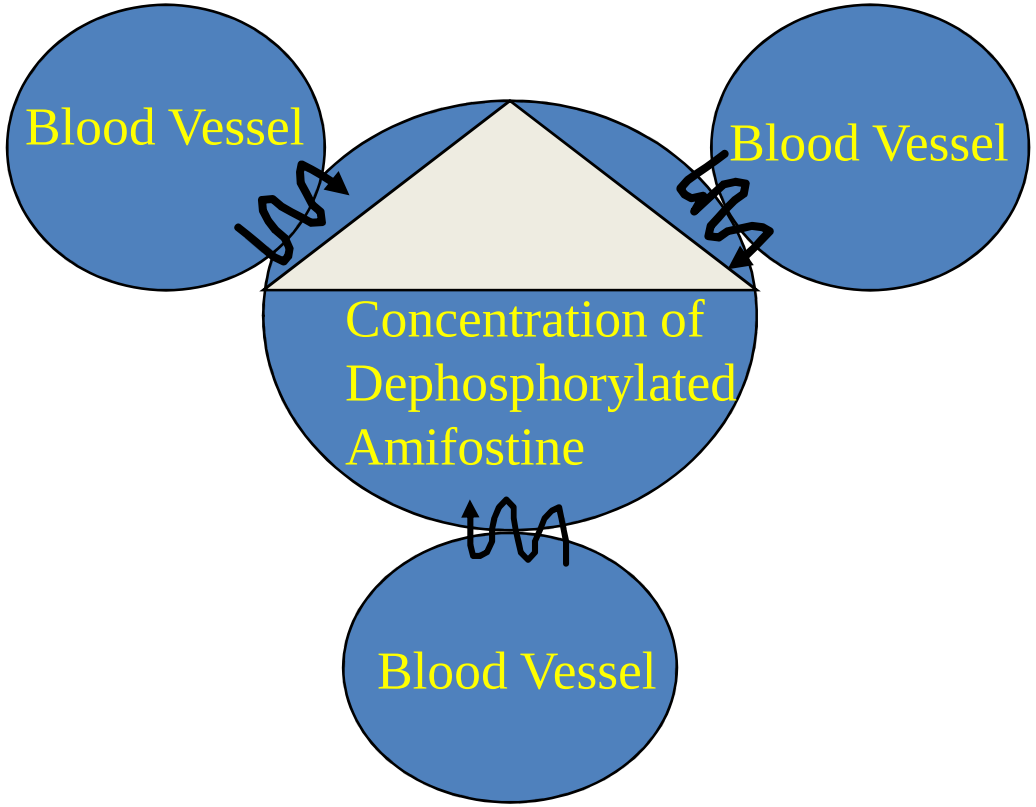
NH_2-$(CH_2)_3$-NH-$(CH_2)_2$-S

HH_2-$(CH_2)_3$-NH-$(CH_2)_2$-S

WR-33278

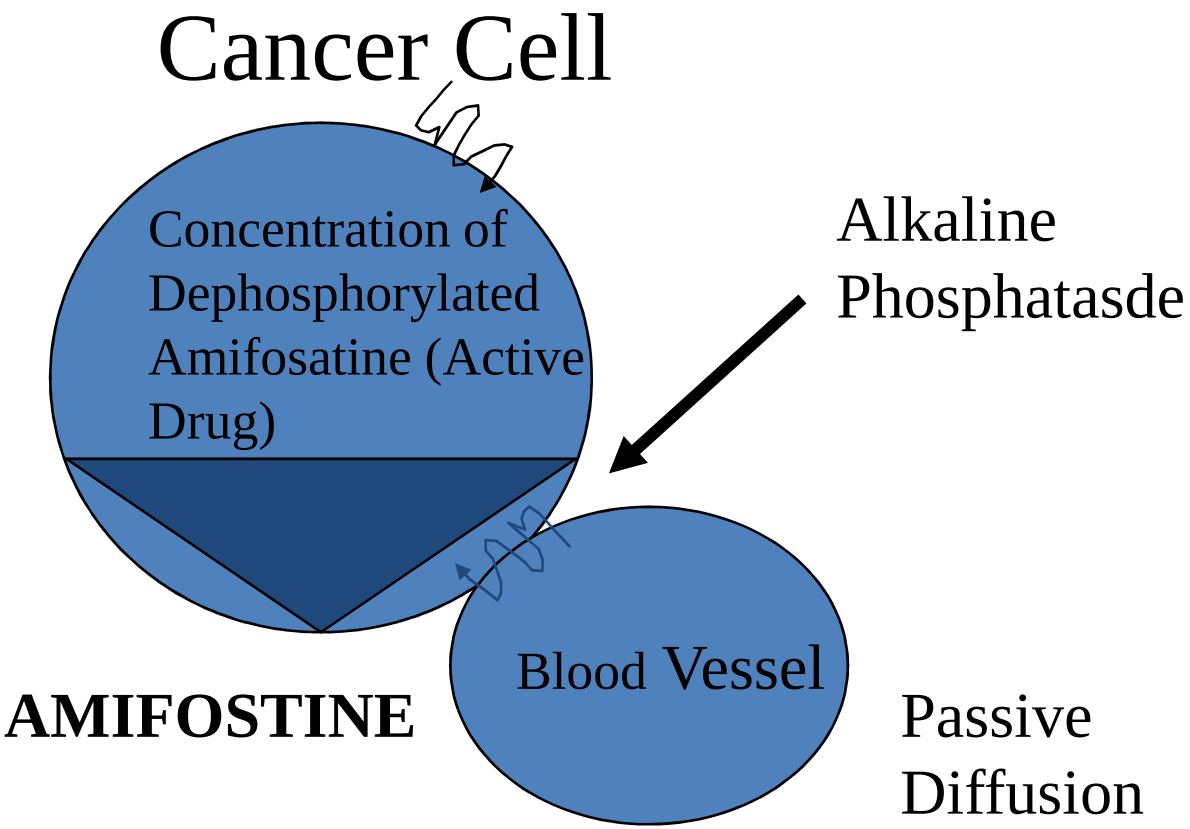
Amifostine – WR2721
“Organic Thiophosphate”
- A Pro Drug



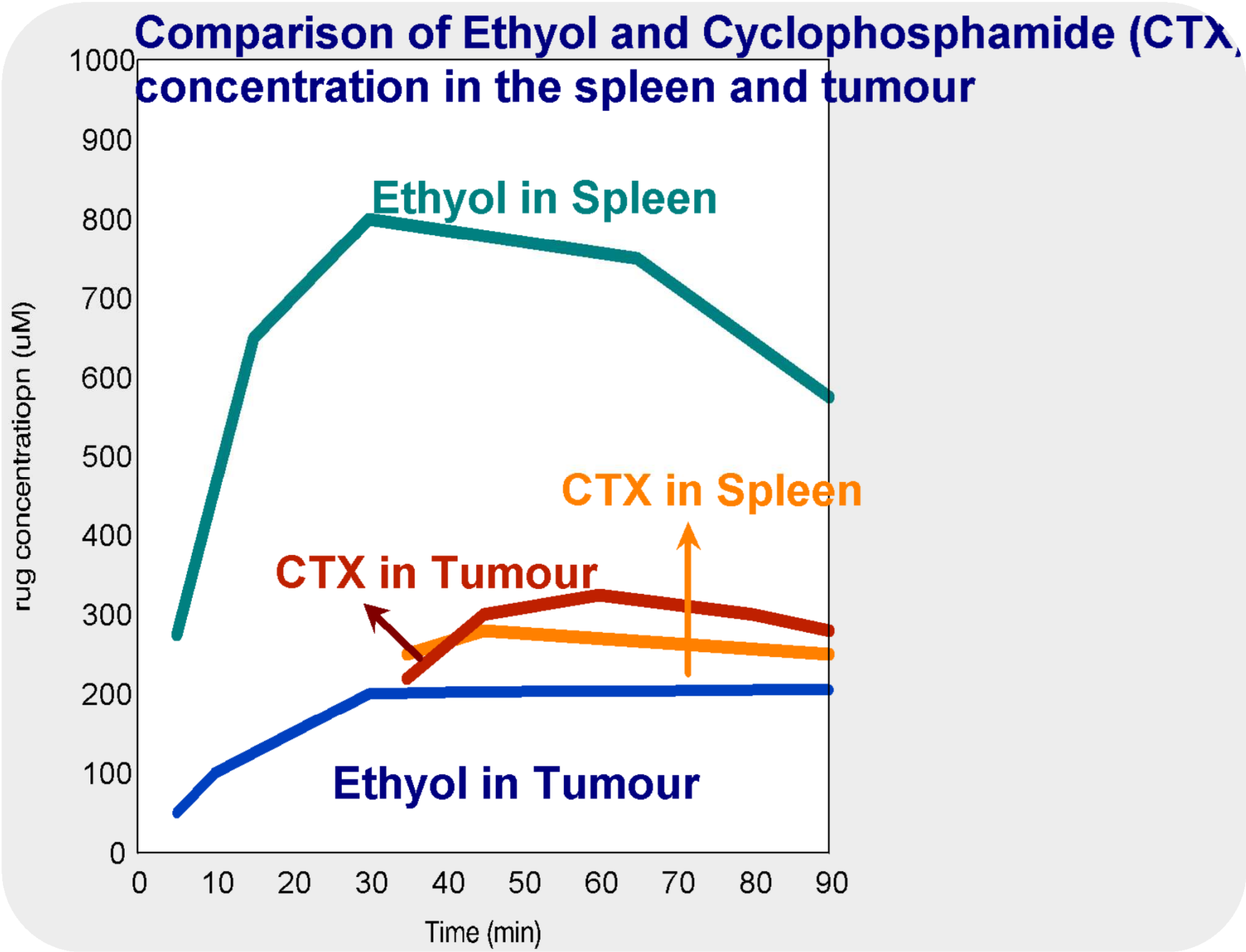


AMIFOSTINE

- High concentration of alkaline phosphates
- Facilatated uptake into normal cell
- High vascularity
- Normal pH



- Low concentration of alkaline phosphatasde
- Passive uptake into cell
- Low vascularity
- Acidic pH

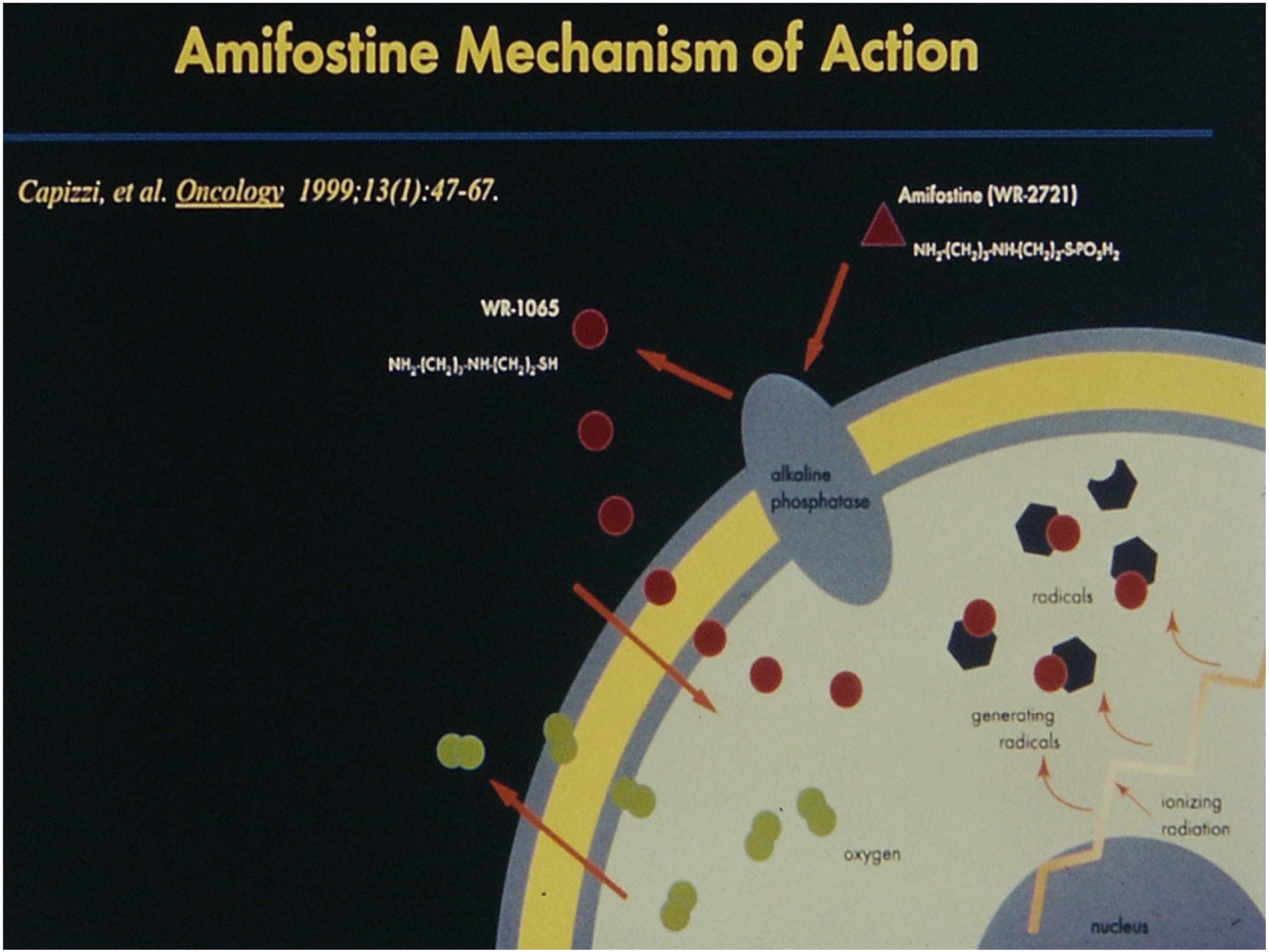

Comparison of Ethyol and Cyclophosphamide (CTX) concentration in the spleen and tumour
1000
900
800
700
600
500
400
300
200
100
0
rug concentratiopn (uM)
Ethyol in Spleen
CTX in Spleen
CTX in Tumour
Ethyol in Tumour
0
10
20
30
40
50
60
70
80
90
Time (min)

Examples of Protection Factors Achieved by Amifostine in Different Normal Tissues and Tumours

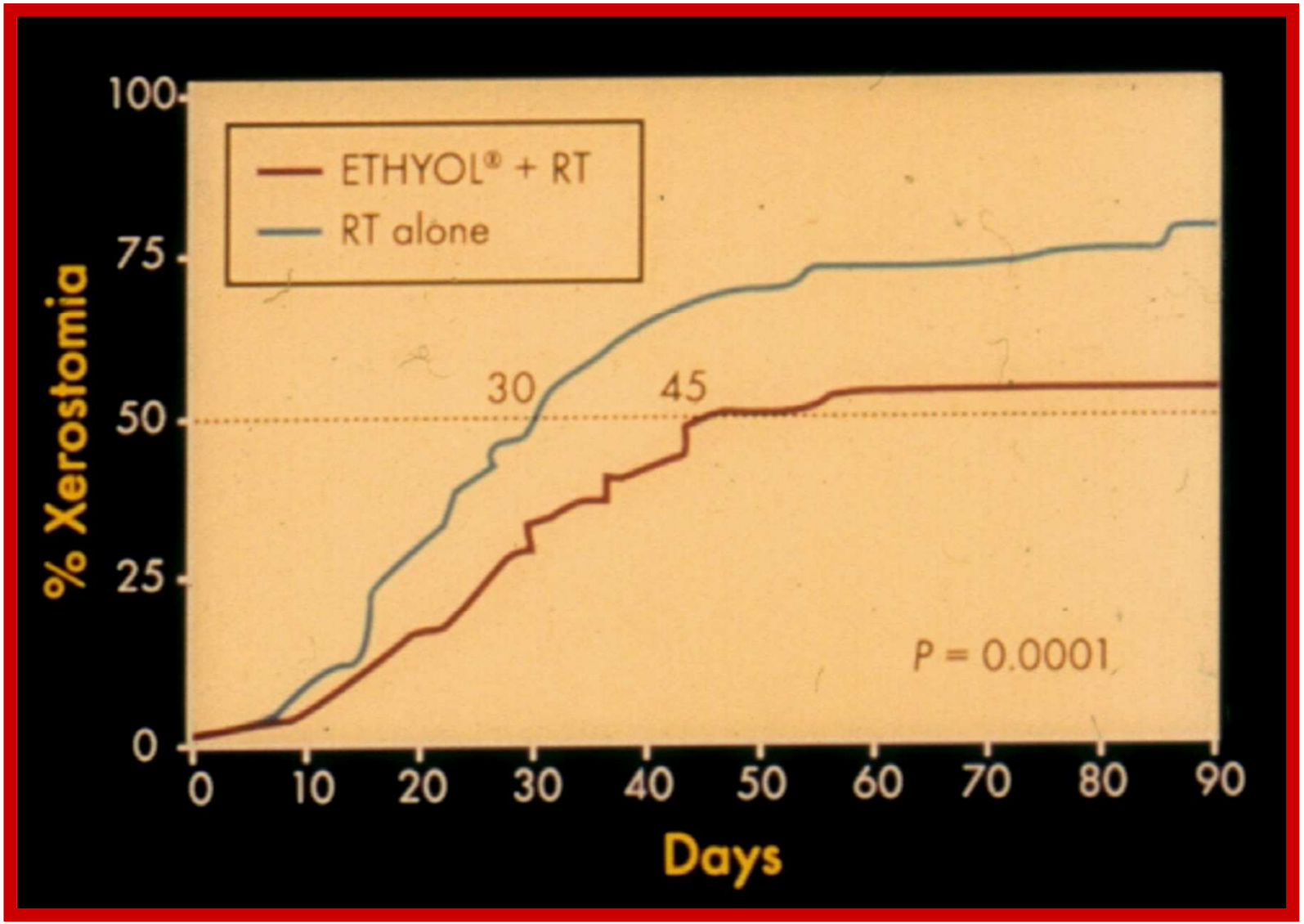
Tissue	Protection Factor
Salivary gland	**2.3-3.3**
Bone marrow	**1.8-3.0**
Jejunum	**1.5-2.1**
Skin	**1.4-2.1**
Testis	**1.5-164**
Lung	**1.2-1.4**
Kidney	**1.3-1.5**
Bladder	**1.3-1.5**
Tumours	**1.0-2.8**

Amifostine Mechanism of Action

Capizzi, et al. Oncology 1999;13(1):47-67.



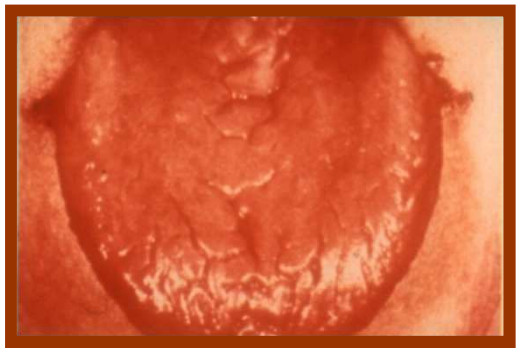
Onset of Xerostomia Significantly Delayed
With Amifostine



Radiation Toxicity

Effects of Xerostomia

- Health
  - Loss of teeth
    - Osteoradionecrosis
    - Oral infections
- Quality of life
  - Eating
  - Sleeping
- Function
  - Speaking



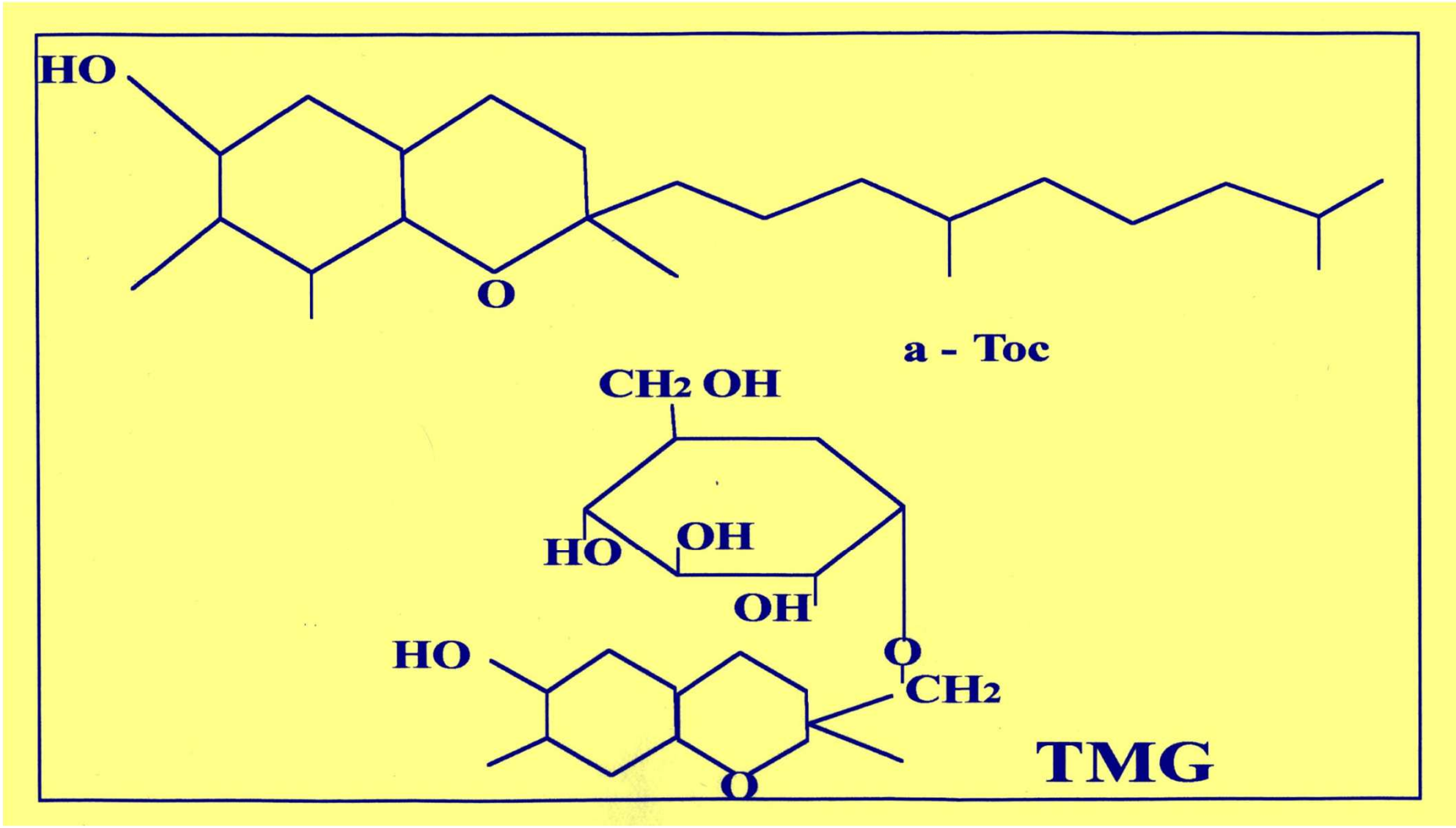
Summary of Pivotal Phase III Study of Amifostine as a Radioprotector

- Amifostine significantly reduced the incidence of ≥ grade 2 xerostomia
  - Acute xerostomia was reduced from 78% to 51% ($p < 0.0001$)
  - Late xerostomia 57% to 34% ($p < 0.002$)

- Improved clinical benefit as assessed by PBQ
  - Mouth dryness ($p < 0.001$)
  - Mean summary score ($p < 0.008$)

Conclusion

Amifostine offers patients with head and neck cancer a new option to protect against long-term complications of xerostomia without affecting efficacy or survival


HO
O
a - Toc
CH2 OH
HO
OH
OH
HO
O
CH2
O
TMG

Structure of various Vitamin E derivatives and their physical properties

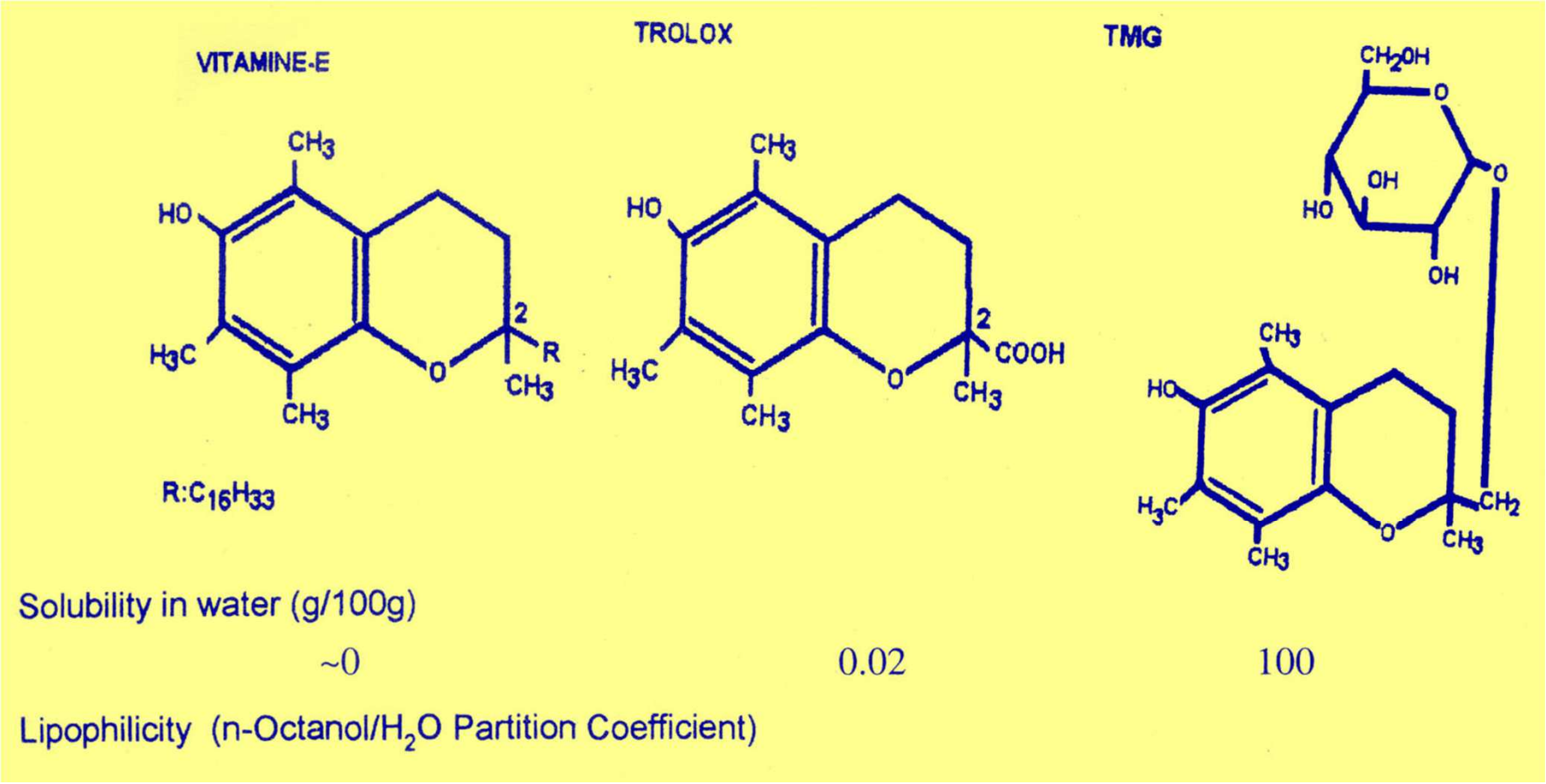
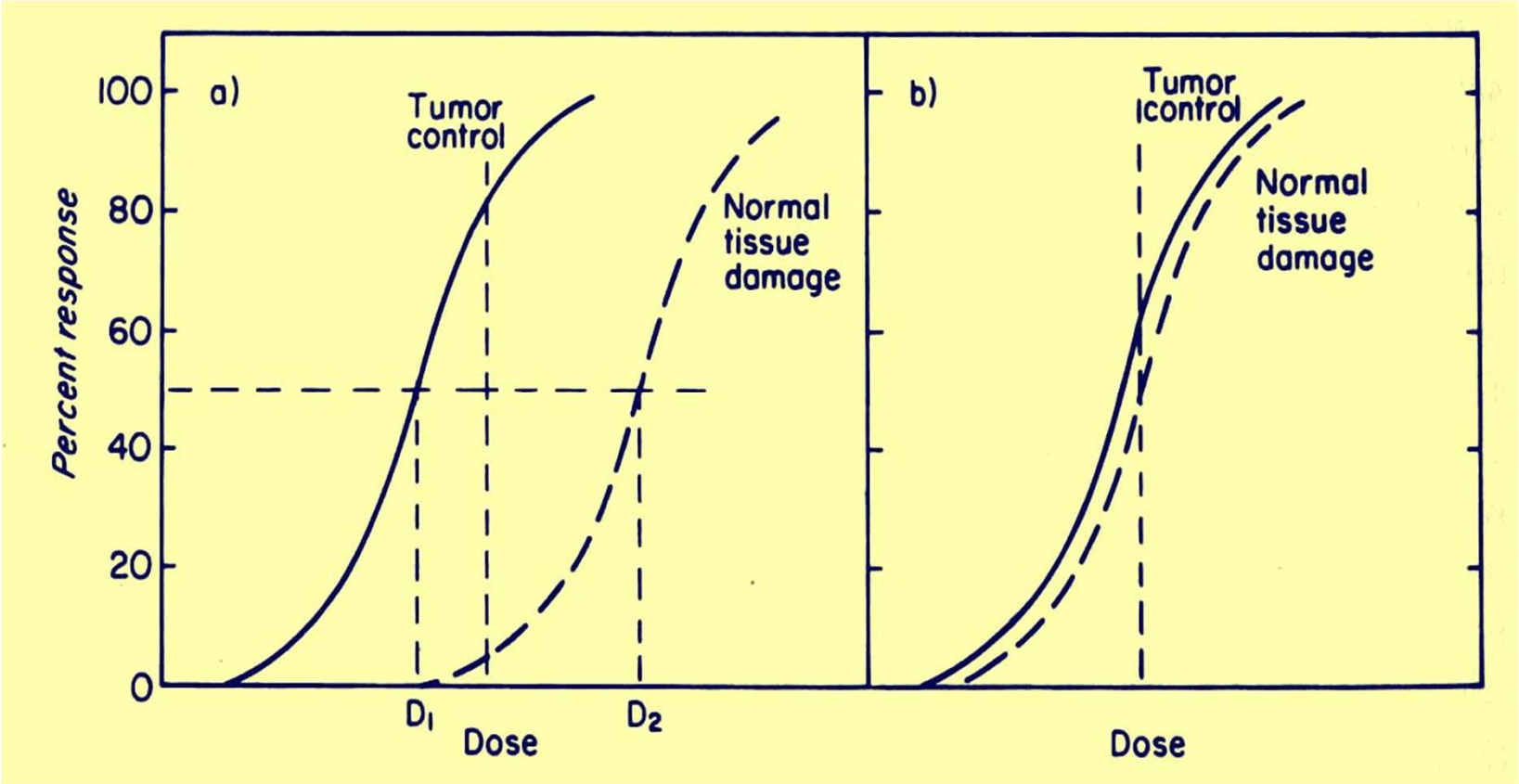
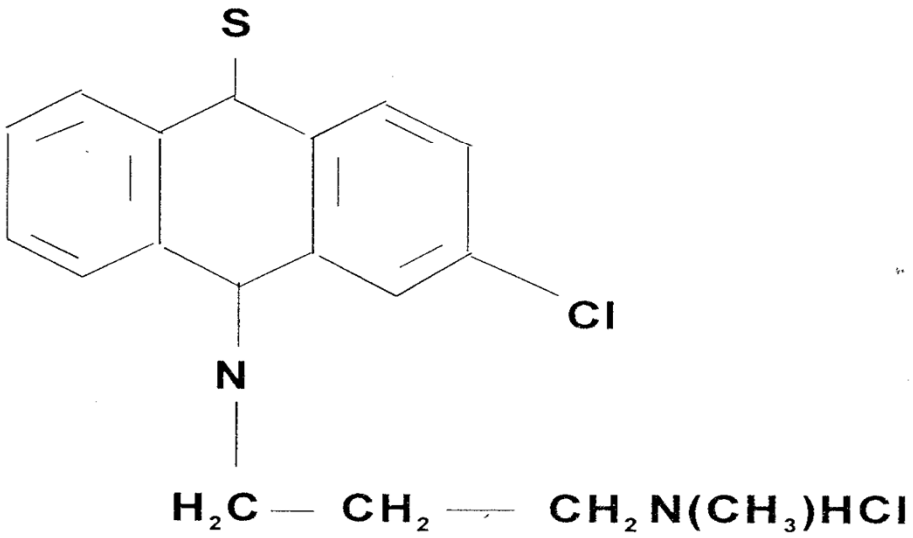


Illustration of the concept of a Therapeutic ratio in turn of dose response relationships for tumour control and normal tissue damage



CHLORPROMAZINE



Calmodulin regulated enzymes and cellular processes

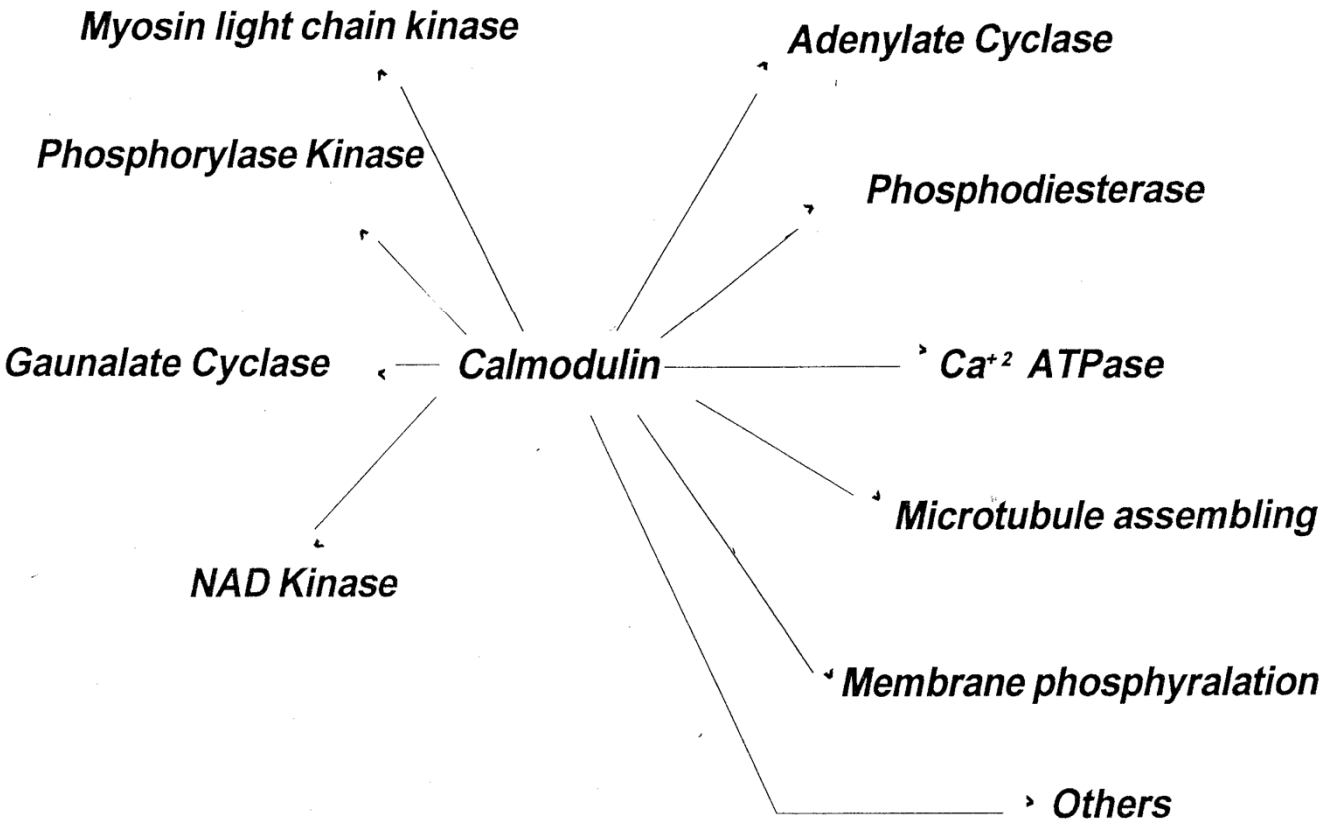


Fig. 1

Inclusion Criteria in Ca. Cervix

- FIGO – STAGE III
- HISTOLOGICAL PROOF OF SQUAMOUS CELL CARCINOMA
- NORMAL RENAL PARAMETERS
- KL – 70 % & ABOVE
- AGE UP TO 70 AND AP/PA > 18 CMS

Biphasic Effects of CPZ

Cation radical of CPZ has marked non-specific inhibitory effects on various emzymatic processes in cells.

CPZ 10^{-6} --10^{-5} → Protective

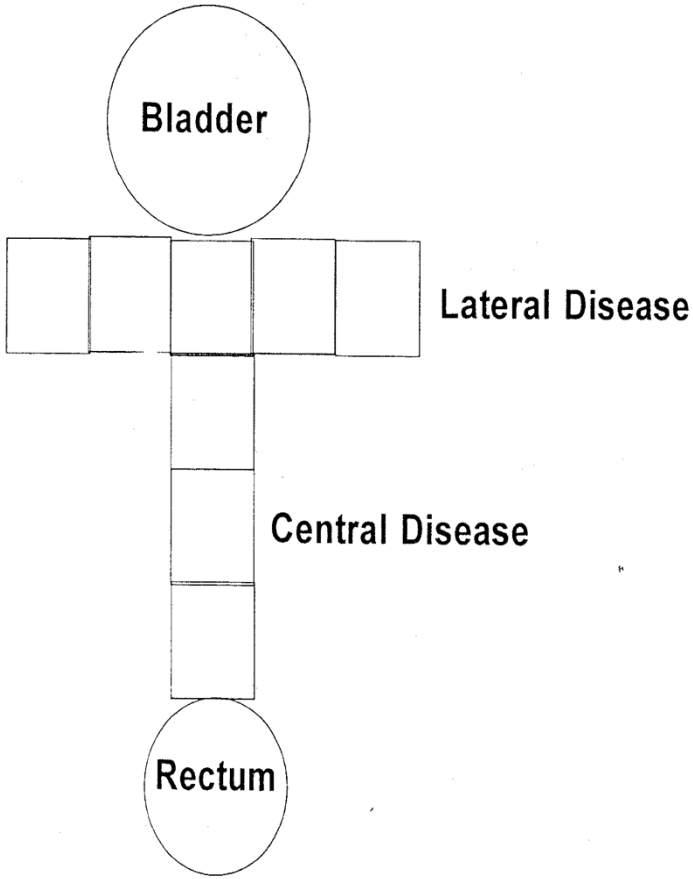
10^{-4}– 10^{-2} → Toxic

Abe. et al

CANCER OF CERVIX

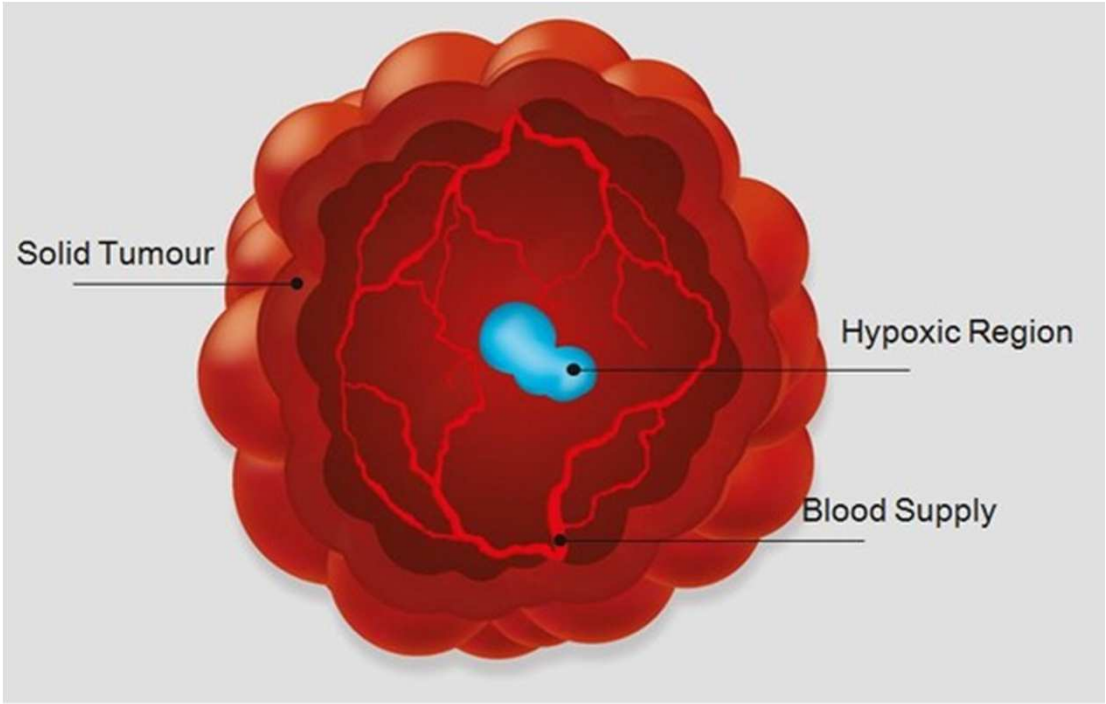
- **FIGO – STAGE III**
- **HISTOLOGICAL PROOF OF SQUAMOUS CELL CARCINOMA**
- **NORMAL RENAL PARAMETERS**
- **KL – 70 % & ABOVE**
- **AGE UP TO 70 AND AP/PA > 18 CMS**

Diagramatic Illustration of Cancer of Cervix

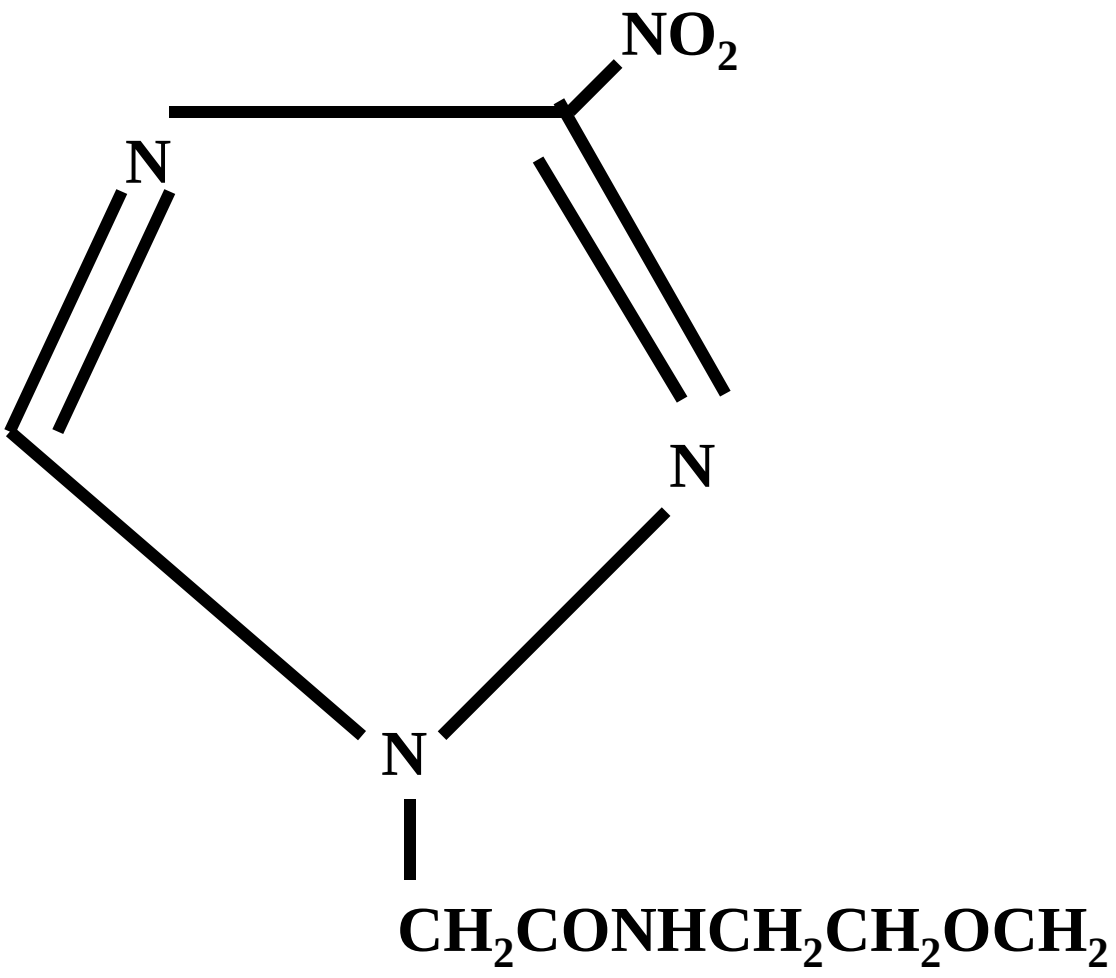


Proctitis

Treatment Group Proctitis	Control No. of Pts. (%) n=15	CPZ No. of Pts (%) n=17
Gr. 0	0(0)	8(47.0)
Gr. I	1(6.66)	2(11.76)
Gr. 2	3(20)	4(23.52)
Gr. 3	10(66.66)	4(23.52)
Gr. 4	1(6.6)	0(0)


Solid Tumour
Hypoxic Region
Blood Supply

Sanazole (AK-2123)



Sanazole (AK-2123) with Accelearated Hyperfrationated Radiotherapy

Groups	Age	Diagnosis	Stage	Initial response	Disease-free-survival1
Control Control	70 65	Ca.larynx Ca.pyriform	T4 N0 M0 T3 N3 M0	PR PR	Lost to FU with disease 7months lost to FU With disease
Control Control Control	67 70 61	Ca. base tongue Ca. base tongue Ca. base tongue	T4 N3 M0 T3 N1 M0 T4 N3 M0	PR CR PR	Lost to FU with disease 18 months died 6 months lost to FU with disease
Control Control Control	25 50 39	Ca. tonsil Ca. pyriform Ca. or pharynx	T4 N3 M0 T3 N0 M0 T4 N0 M0	CR CR CR	Lost to FU 2 years 2 years: recc.after 1 months
Control	42	Ca. tonsil	T4 N3 M0	PR	2 months died with disease
AK-2123 mg/d 880 mg x 9 880 mg x 9 880 mg x 9	 60 25 60	 Ca. pyriform Ca. floor of the mouth Ca.base tongue	 T3 N0 M0 T3 N0 M0 T3 N2 M0	 CR CR CR	 2 year 21 months 1 year, died without disease
880 mg x 9	45	Ca.pyriform	T3 N3 M0	CR	6 months, recc. Lost to FU
990 mg x 9 990 mg x 9 990 mg x 9 990 mg x 9 990 mg x 9	70 50 55 48 50	Ca. pyriform Ca. base tongue Ca. pyriform Ca. base tongue Ca. base tongue	T3 N1 M0 T3 N3 M0 T3 N0 M0 T3 N0 M0 T3 N0 M0	CR CR CR CR CR	21 months 10 months 5 months: ? 2nd neoplasm in esophagus 1 year developed Striders 1 year

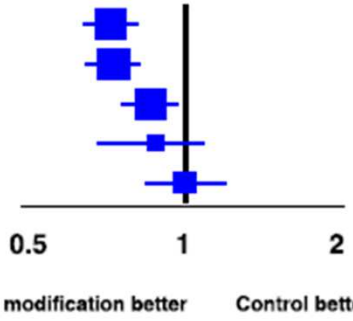
Randomized clinical trials with hypoxic modification of radiotherapy in HNSCC.

References	Trial acronym	Year	No. pts	fx[a]	RT schedule	Hypoxic modification	Endpoint[b]					Obs. time
[21]	van den Brenk	1968	30	HH	7.75 Gy x4vs7.25 Gy x4 with HBO	HBO 4 atm	L	D	S			2 + years
[22]	Evans 1	1970	40	LL	60 Gy/30 fx	Normobaric 02	L	D	S			2 + years
[23]	Tobin	1971	17	LL	60 Gy/30 fx	HBO 3 atm	L	D	S			2–3 years
[24]	Chang	1973	51	HHL	6 Gy x6+ HBO vs 6 Gy x7 or 60 Gy/30 fx	HBO 3 atm	L	D	S	M	C	5 years
[25]	Shigamats u	1973	31	HH	60–79 Gy/10 fx vs. 40–50 Gy/8–10 fx + HBO	HBO	L	D	S			2 + years
[26]	Evans 2	1975	44	LL	60 Gy/30 fx	Normobaric 02	L	D	S	M	C	2 + years
[27]	MRC 1 trial	1977	276	HH	35–45 Gy x10	HBO 3 atm	L	D	S	M	c	4 + years
[26]	MRC 3, trial	1979	24	HL	45–50/15 el 48.5–55/20 air vs. 40–45/10 HBO	HBO	L	D	S		c	5 years
[29]	RTOG 70-02	1979	254	LL	60–70 Gy/30 fx	Carbogen	L	D	S	M	c	2 + years
[30]	Sause	1979	44	HL	48 Gy/12 fx + HBO vs. 62 Gy/25 fx	HBO 3 aim	L	D	S		c	2 + years
[31]	Giaux	1962	56	II	50 Gy/16 fx	MISO	L	D	S			34 months
[32]	Sealy 1	1962	97	HH	36 Gy/6 fx/17 days	MISO	L					>1 year
[33]	B run in	1963	101	LL	72 Gy/36 fx	MISO	L	D	S			2 years
[34]	MRC 10 fx	1964	162	HH	40–45 Gy/10 fx	MISO	L	D	S		c	3 + years
[34]	MRC 20 fx	1964	89	LL	50–57 Gy/20 fx	MISO	L	D	S			3 + years
[35]	Panis	1964	52	MM	Split-course 1.1 Gy x6 daily/ 5 days – 4 weeks split-repeat	MISO	L	D	S		c	2 + years
[36,37]	EORTC 22S111	1966	330	MM	1.6 Gy x3/10 days – 3 weeks split + same to total of 67–72 Gy	MISO	L	D	S		c	5 + years
[38,39]	MRC 2, trial	1966	103	HL	64 Gy/30 fx vs. 41–44 Gy/10 fx + HBO	HBO 3 aim	L	D	S	M	c	4 + years
[40]	Sealy 2	1966	124	HL	63 Gy/30 fx (air); 36 Gy/6 fx (HBO)	HBO/MISO	L	D	S	M	c	1–2-year
[41,42]	IAEA study	1967	36	LL	70 Gy/35 fx	On ids zo e	L	D	S		c	2 + years
[43,44]	RTOG 79-15	1967	297	LL	66–74/33–37 fx	MISO	L	D	S	M	c	2 + years
[45]	Galecki	1969	35	LL	70 Gy/35 fx vs. 66 Gy/30 fx vs. 80.5 Gyx 70 fx	Metronidazole	L	D	S		c	3 + years
[46]	Dahanca 2	1969	622	LL	68-72/34–36 fx eller 61/22/9.5 weeks	MISO	L	D	S	M	c	5 + years
[47]	RTOG 79-04	1969	40	HH	4 Gy 11–13 fx	MISO	L	D	S		c	2 + years
[48]	RTOG 8S-27	1995	504	LL	66–74 Gy/33–37 fx	Etanidazole	L	D	S	M	c	5 + years
[49]	Huilgol	1996	18	LL	54 Gy/45 fx/22 days	AK-2123	L	D	S			2 + years
[50]	European trial	1997	374	LL	66–74 Gy/33–37 fx	Etanidazole	L	D	S		c	5 + years
[51,52]	Dahanca 5	1998	414	LL	66–68/33–34	Nirnorazole	L	D	S	M		5 years
[53]	Haffty	1999	48	HH	12.65 Gy x2 vs. 11.50 Gy x2 + HBO	HB04 atm	L	D		M	c	5 + years
[54]	Mendenhall	2005	101	MM	76 Gy/1.2 Gy fx BID	02 Carbogen	L	D	s	M		5 + years
[55]	Ullal	2006	46	LL	60 Gy/30 fx	AK-2123	L					3 + months
[56]	ARCON	2010	345	LL	64–68 Gy/32–34 fx accelerated fx	Nicotinamide	L	D	s			2 years

[a] H: Hypofract; L: conventional tract; M: hyperfract (multiple fx/day).
[b] L: Loco-regional failure; D: disease specific death; S: overall death; M: distant metastasis; C: complications.

Head and neck cancer - meta analysis - summary

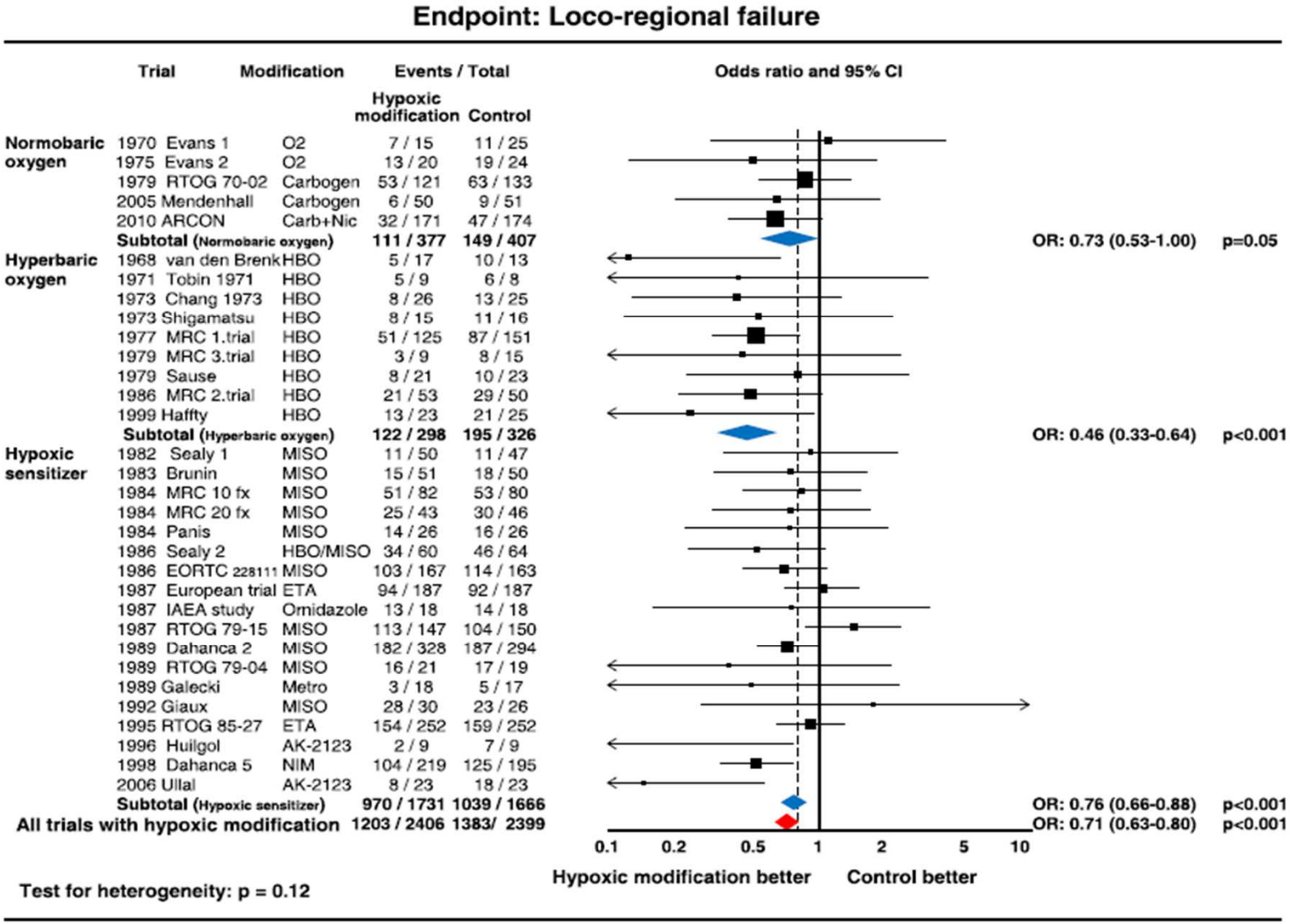
Endpoint	Events / Total		Odds ratio and 95% CI	Odds ratio	Risk Reduction	NNT**
	Hypoxic modification	Control				
Loco-regional control	1203 / 2406	1383 / 2399		0.71 (0.63-0.80)*	8% (5-10%)*	13
Disease specific survival	1175 / 2335	1347 / 2329		0.73 (0.64-0.82)	7% (5-10%)	14
Overall survival	1450 / 2312	1519 / 2305		0.87 (0.77-0.98)	3% (0-6%)	31
Distant metastasis	159 / 1427	179 / 1391		0.87 (0.69-1.09)	2% (-1-4%)	57
Radiotherapy complications	307 / 1864	297 / 1822		1.00 (0.82-1.23)	0% (-3-2%)	>>



Meta Analysis - Hypoxic modification of radiotherapy in HNSCC

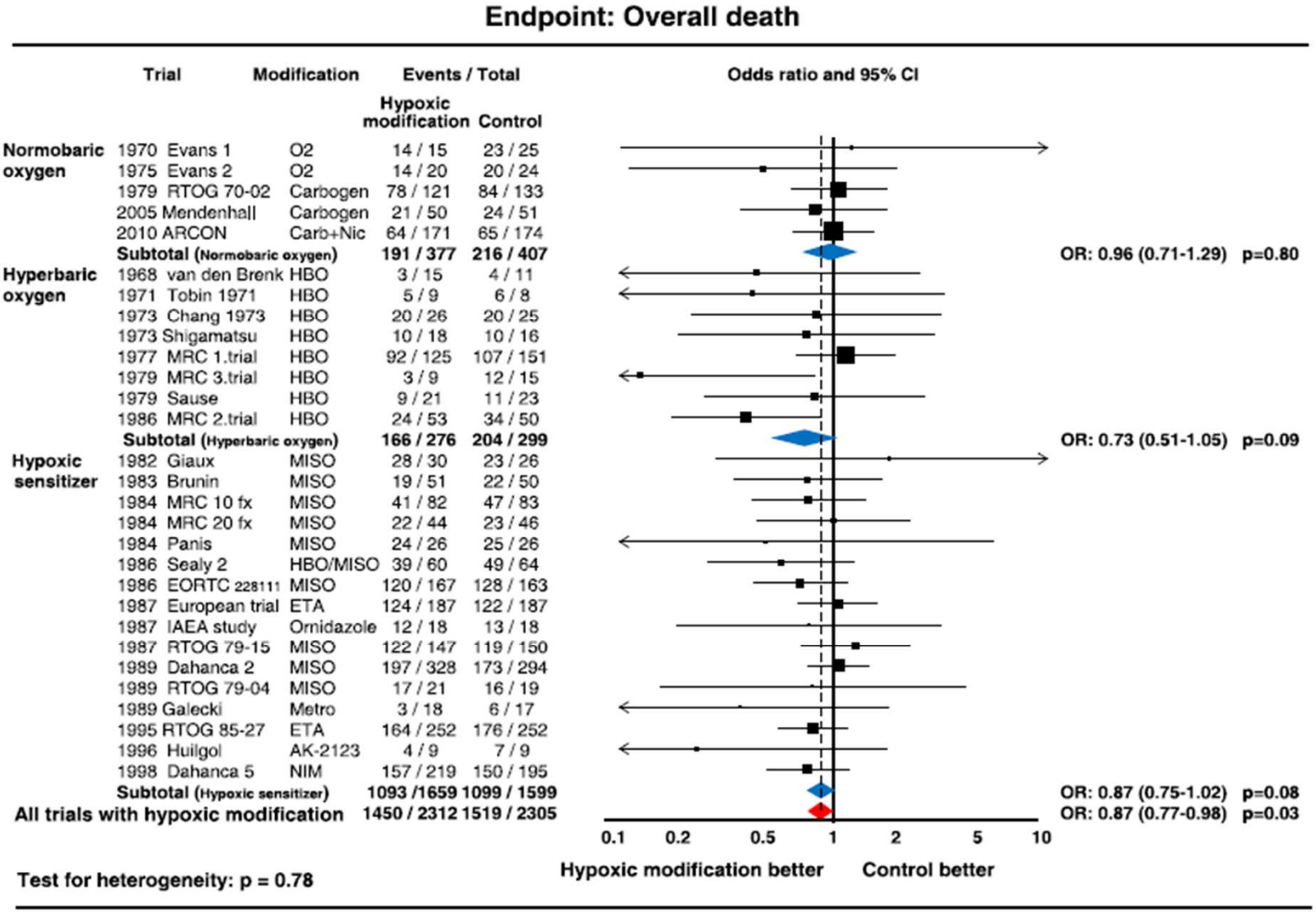
* 95% CI.
** Numbers of patients Needed to Treat to achieve benefit in one patients.

Hypoxia modification of radiotherapy…….Overgaard Jens, 100 (2011); 22-32, Radiotherapy and Oncology



Meta Analysis - Hypoxic modification of radiotherapy in HNSCC

Hypoxia modification of radiotherapy…….Overgaard Jens, 100 (2011); 22-32, Radiotherapy and Oncology



Meta Analysis - Hypoxic modification of radiotherapy in HNSCC

Hypoxia modification of radiotherapy…….Overgaard Jens, 100 (2011); 22-32, Radiotherapy and Oncology

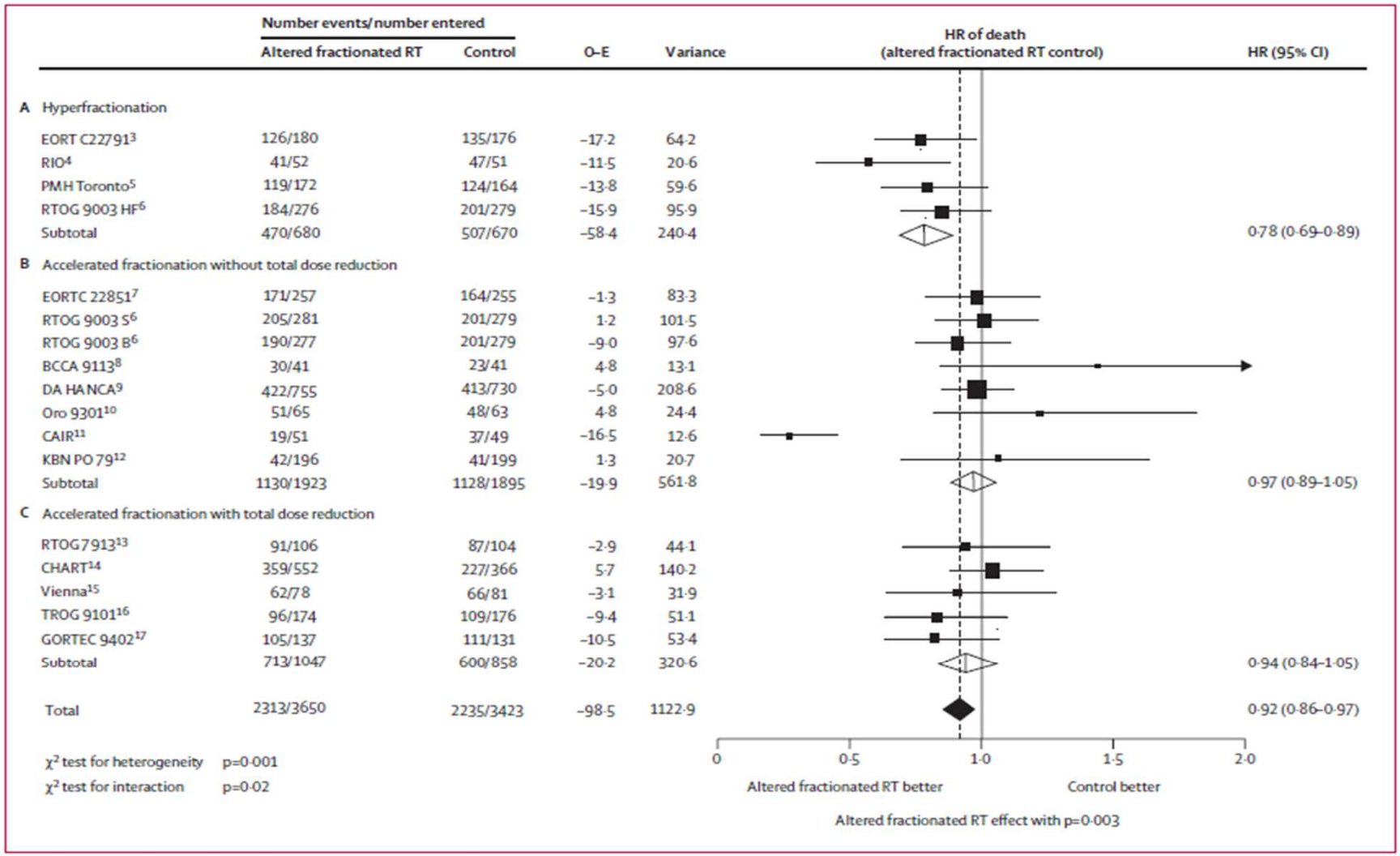


Figure 1: **Hazard ratio of death with altered fractionated radiotherapy versus conventional radiotherapy**

The centre of each square is the hazard ratio (HR) for individual trials and corresponding horizontal line is the 95% CI. The area of the square is proportional to the number of deaths in each trial. The broken line and centre of the black diamond is overall pooled HR and the horizontal tip of the diamond is the 95% CI. Open diamonds are the HR of different types of radiotherapy. BCCA=British Columbia Cancer Agency. CAIR=Continuous Accelerated Irradiation. CHART=Continuous Hyperfractionated Accelerated Radiation Therapy. DAHANCA=Danish Head and Neck Cancer Study Group. EORTC=European Organisation for Research and Treatment of Cancer. GORTEC=Groupe d'Oncologie Radiothérapie Tête et Cou. KBN=Komiet Badan Naukowych (Committee for Scientific Research). O–E=observed minus expected. PMH-Toronto=Princess Margaret Hospital, Toronto. RT=radiotherapy. RTOG=Radiation Therapy Oncology Group. TROG=Trans-Tansman Radiation Oncology Group.

Hypwerfractionated or accelerated radiotherapy…… Bourhis J, Overgaard J. et., Vol. 368: 843-854; Sep 2, 2006, Lancet

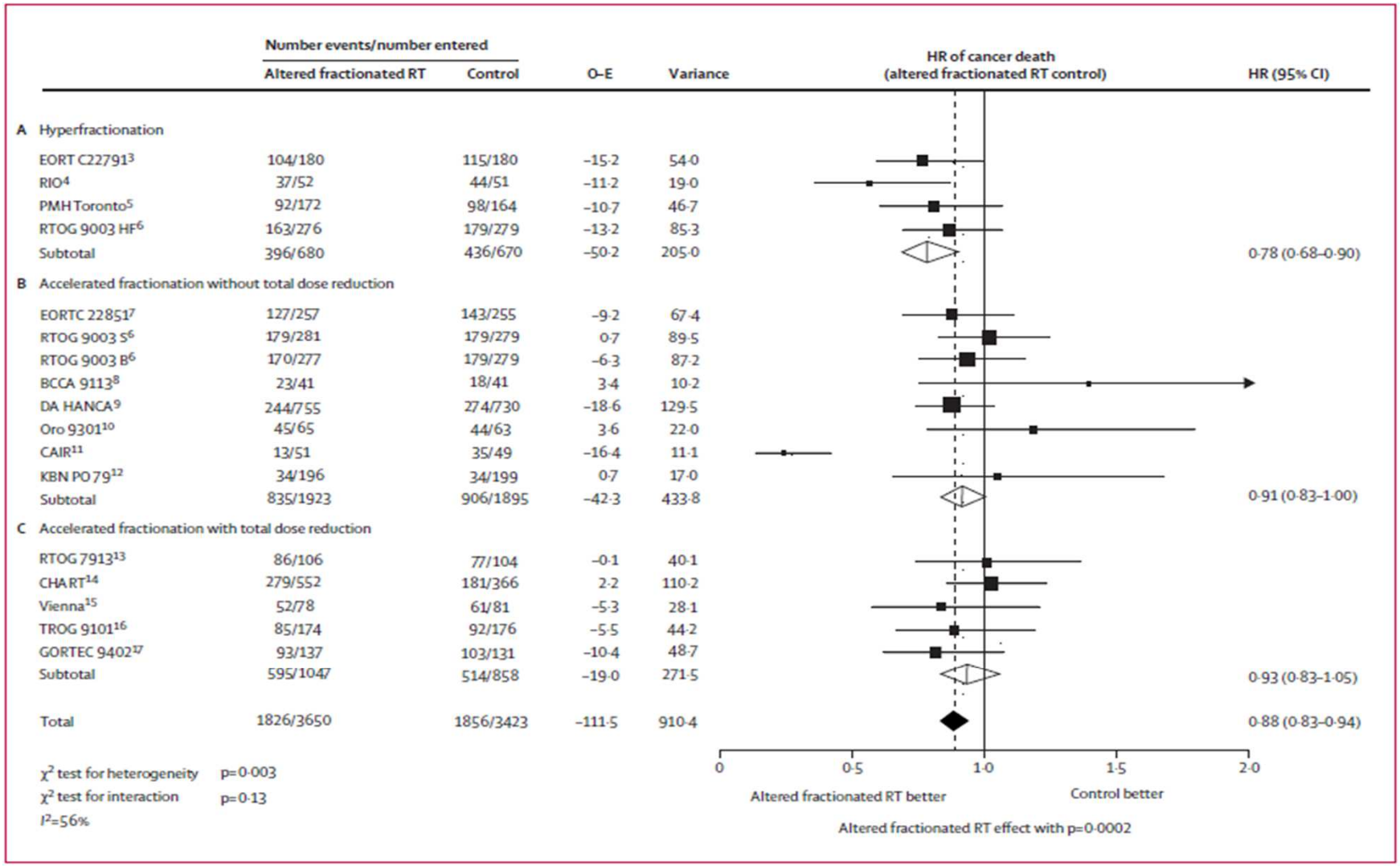


***Figure 3*: Hazard ratio of head and neck cancer death with altered fractionated radiotherapy versus conventional radiotherapy**

The centre of each square is the hazard ratio (HR) for individual trials and corresponding horizontal line is the 95% CI. The area of the square is proportional to the number of events from each trial. The broken line and centre of the black diamond is overall pooled HR and the horizontal tip of the diamond is the 95% CI. Open diamonds are the HR of different types of radiotherapy. BCCA=British Columbia Cancer Agency. CAIR=Continuous Accelerated Irradiation. CHART=Continuous Hyperfractionated Accelerated Radiation Therapy. DAHANCA=Danish Head and Neck Cancer Study Group. EORTC=European Organisation for Research and Treatment of Cancer. GORTEC=Groupe d'Oncologie Radiothérapie Tête et Cou. KBN=Komiet Badan Naukowych (Committee for Scientific Research). O–E=observed minus expected. PMH-Toronto=Princess Margaret Hospital, Toronto. RT=radiotherapy. RTOG=Radiation Therapy Oncology Group. TROG=Trans-Tasman Radiation Oncology Group.

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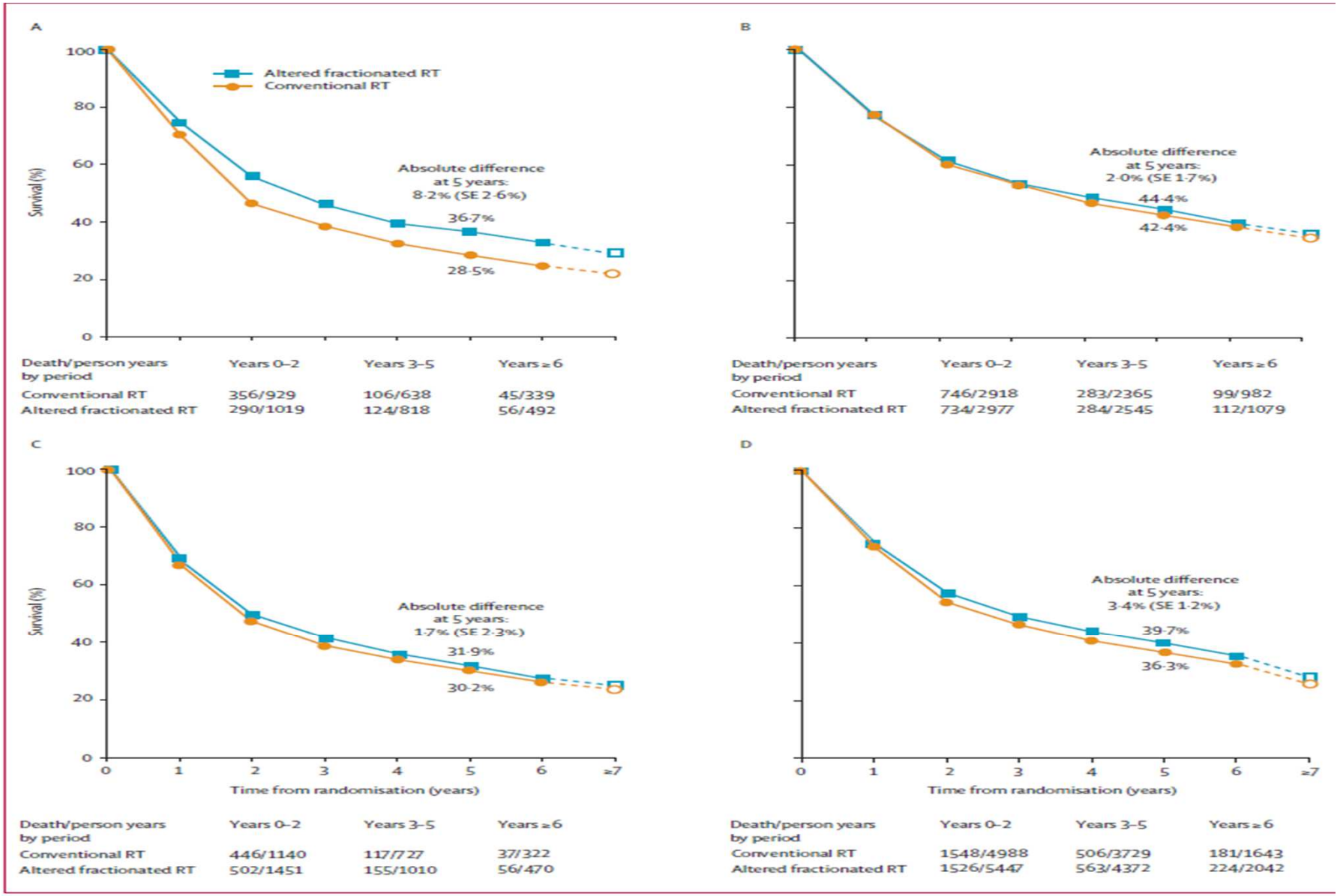

Figure 2: **Survival curves by treatment arm for all trials and for the three groups of trials according to the type of altered fractionated radiotherapy**
(A) Hyperfractionation. (B) Accelerated fractionation without total dose reduction. (C) Accelerated fractionation with total dose reduction. (D) All three groups together. The slopes of the broken lines from year 6 to year ≥7 are based on the overall death rates in the seventh and subsequent years. RT=radiotherapy.

Hypwerfractionated or accelerated radiotherapy…… Bourhis J, Overgaard J. et., Vol. 368: 843-854; Sep 2, 2006, Lancet

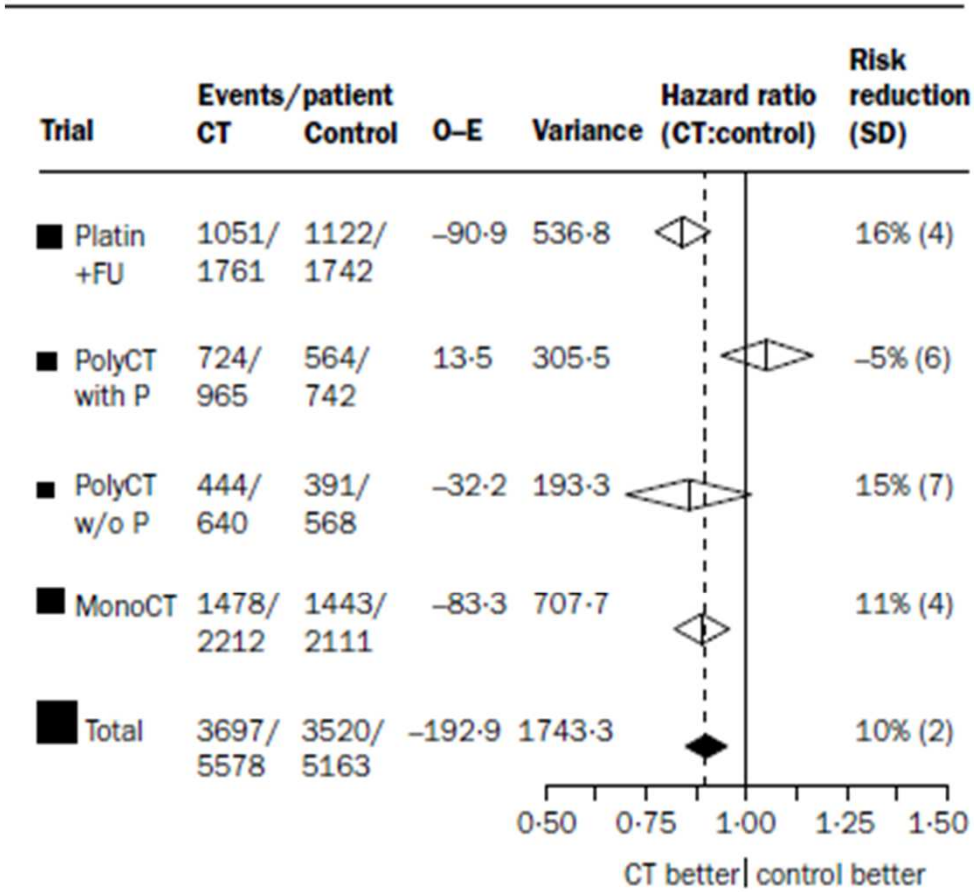

Figure 3: **Hazard ratio of death with locoregional treatment plus chemotherapy compared with locoregional treatment by types of chemotherapy**

Platin (cisplatin or carboplatin)+fluorouracil (FU), combination CT with platin (Poly CT+P), combination CT without platin (Poly CT w/o P), single-agent CT (mono CT) including platin. Test for heterogeneity between types of chemotherapy, p=0·02.

Hypwerfractionated or accelerated radiotherapy…… Bourhis J, Overgaard J. et., Vol. 368: 843-854; Sep 2, 2006, Lancet

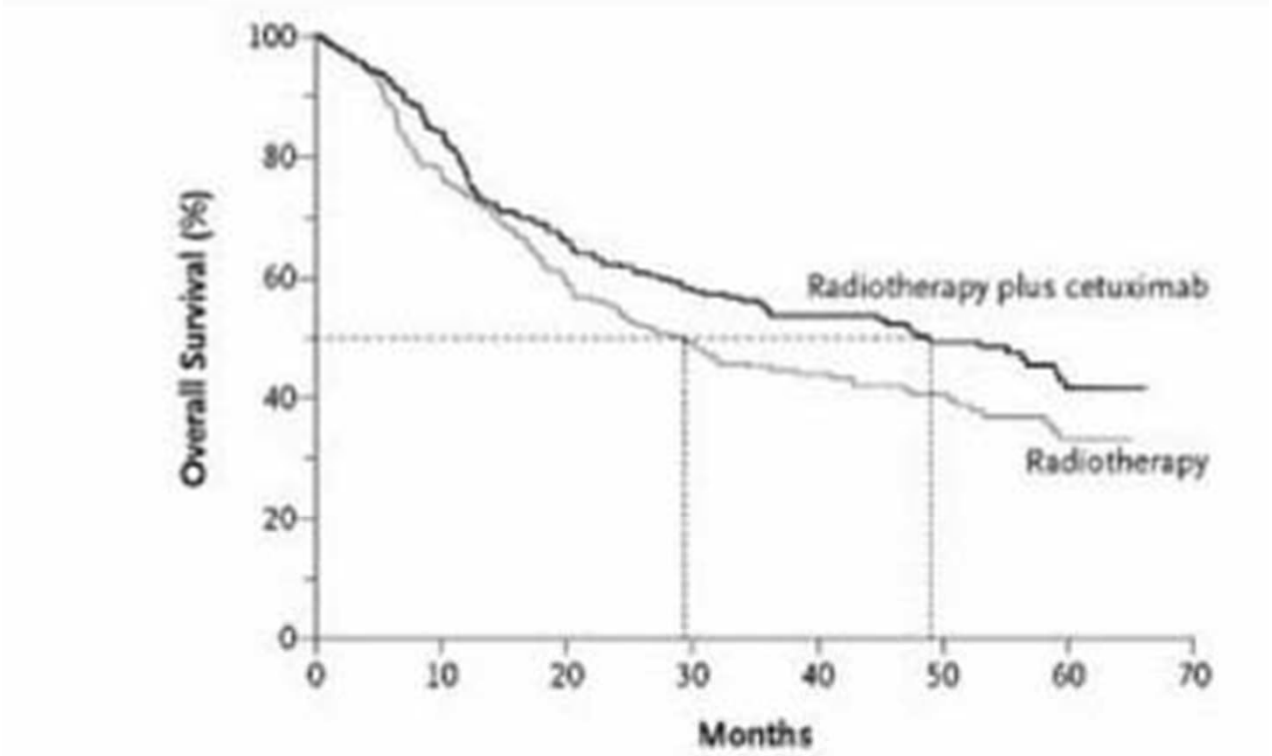

Figure 2

Hypwerfractionated or accelerated radiotherapy…… Bourhis J, Overgaard J. et., Vol. 368: 843-854; Sep 2, 2006, Lancet

Table 1: Randomised Trials in Recurrent/Metastatic Squamous Cell Cancer of the Head and Neck

Study	n	Regimen	Population	RR(%)	OS (months)
EXTREME[11]	442	Carbo/CisE vs Carbo/Cis	1st-line	36 vs 20*	10.1 vs 7.4*
ECOG 5397[10]	117	CisE vs Cis	1st-line	26 vs 10*	9.2 vs 8.0**
IMEX[26]	486	Gefitinib 250mg vs gefitinib 500mg vs methotrexate	2nd-line	2.7** vs 7.6 vs 3.9	5.6** vs 6.0 vs 6.7
ECOG 1302[29]	270	D + Gefitinib vs D	Any line	14** 6	6.8** 6.0

Carbo/Cis = carboplatin or cisplatin; Cis = cisplatin; D = docetaxel; E = cetuximab; OS = overall survival; RR = response rate.
**p<0.05; **Not statistically significant.*