MODIFIERS OF RADIATION RESPONSE

Sri Aurobindo Institute of Medical Sciences

Dental College | Medical College | Hospital

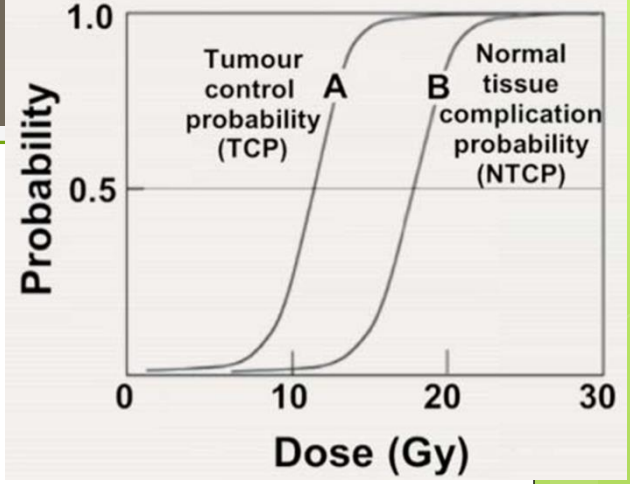
DR.VIRENDRA BHANDARI

M.D., FELLOW UICC, FELLOW ICRO

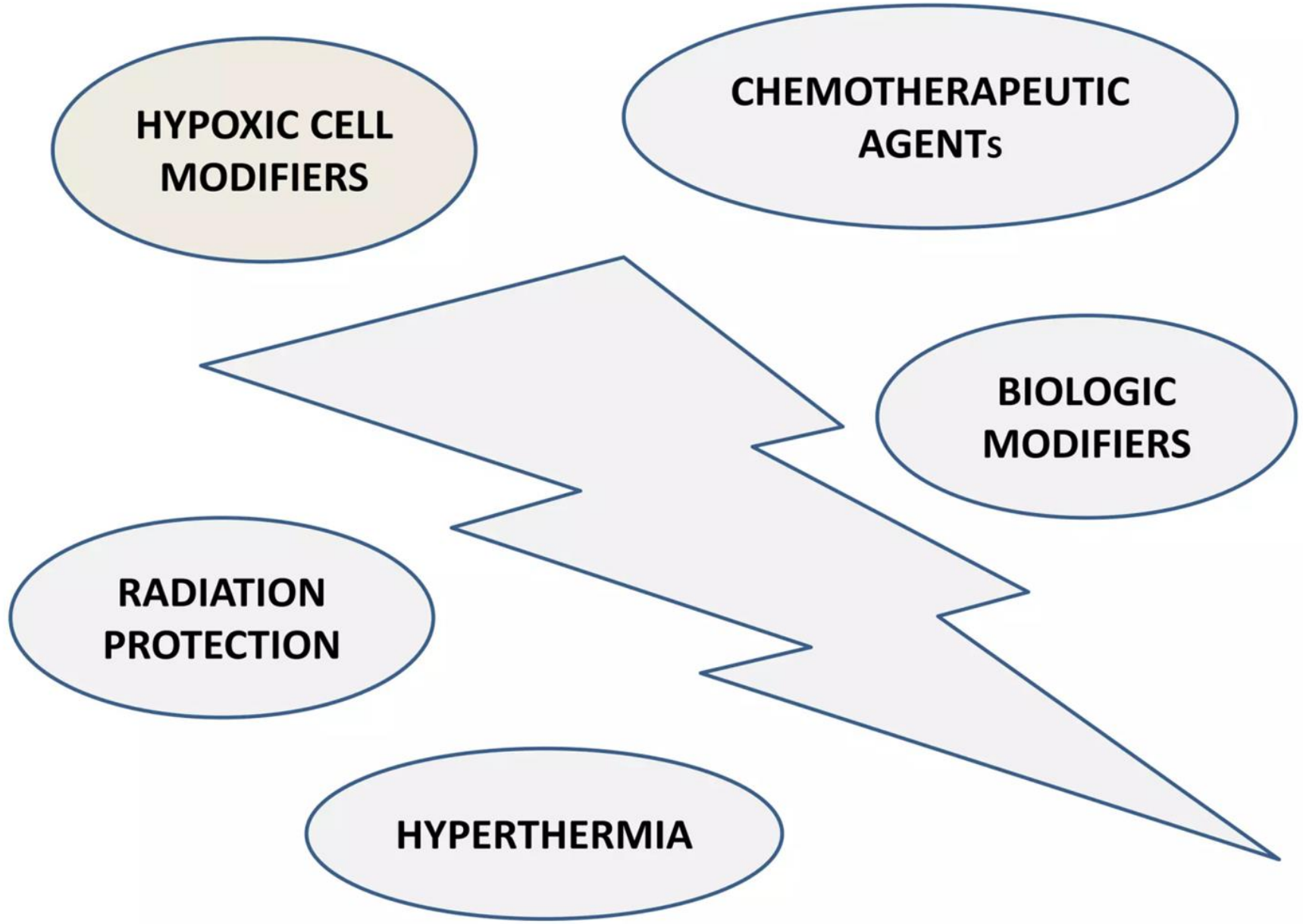
Prof & Head, Radiation Oncology

Indore-Ujjain State Highway, Gram Bhanwarasala, Sanwer Road , Indore, Ph. 0731-4958888

Introduction



- There is a clear Dose Response relationship while we execute radiation therapy.
- Unfortunately the damage to normal tissues also increases as we increase the total radiation dose to tumor.
- There has been a wide variety of changes and development in technology to modify this dose response relationship by trying to increase the seperation between tumor tissue and normal tissue dose response curves.


HYPOXIC CELL MODIFIERS
CHEMOTHERAPEUTIC AGENTs
BIOLOGIC MODIFIERS
RADIATION PROTECTION
HYPERTHERMIA

• Radiosensitivity

- Relative susceptibility of cells,tissues,organs or organisms to the harmful effect of ionizing radiation
- **Bergonie** and **Tribondaeu**'s law:

Tissues will be more radiosensitive if:

I. The cells are undifferentiated

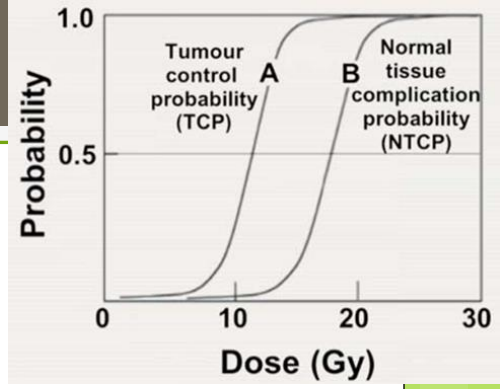
II. They have greater proliferative capacity

III. They divide more rapidly

Jean Alban BERGONIE
(1857-1925)

Louis TRIBONDEAU
(1872-1918)

Radiosensitization



- Is a physical, chemical or pharmacological intervention that increases the lethal effect of radiation when administered with radiation by making the tumor more sensitive.
- To be clinically effective it should improve the Therapeutic Ratio ie TCP/NTCP, because if an intervention equally increases the effect and side effect it is not useful.
- A radiosensitizer may or may not have any lethal effect against tumor when given without radiation.

Mechanisms of radiosensitization

⇧ DNA sensitivity→ direct & indirect	Modulate biological response of irradiated cells
• Counteracting tumour hypoxia	• Inhibition of cellular repair
• Increase in initial radiation damage	• Overcoming accelerated repopulation
• Cell cycle redistribution	• Targeting molecular events assosciated with radiation response

Characters of an Ideal radiosensitiser

- Lack of Toxicity
- Potent radiosensitizing effect
- Non cell cycle specific
- Amenable to dose intense or prolonged infusion schedules
- Adaptable to convenience out patient administration

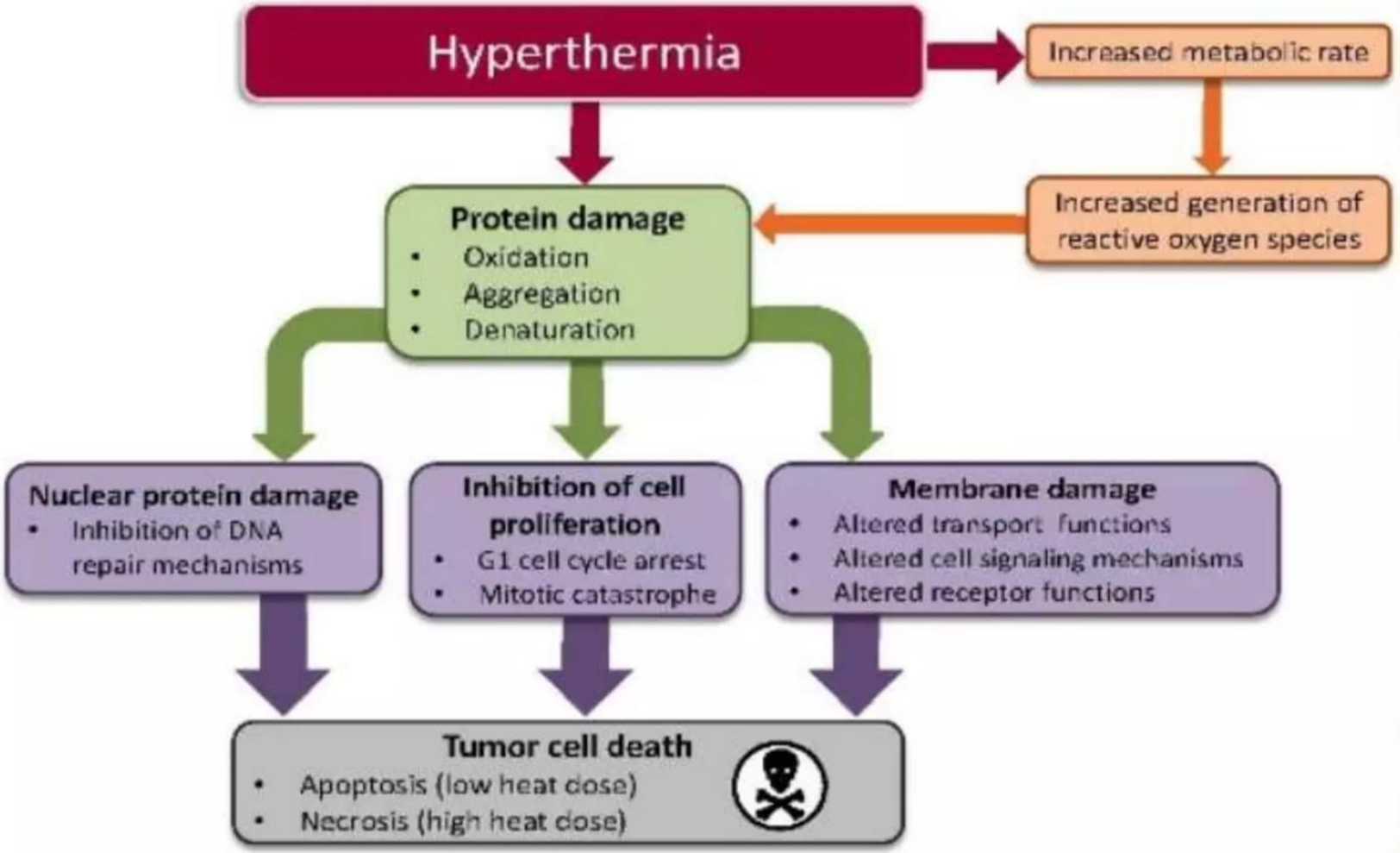
Types of radiosensitisers

PHYSICAL	CHEMICAL
• HYPERTHERMIA	• MODIFIERS OF HAEMOGLOBIN
• HYPERBARIC OXYGEN	• NON HYPOXIC CELL SENSITISERS
• CARBOGEN+/- NICOTINAMIDE	• HYPOXIC CELL SENSITISERS
• ARCON	• HYPOXIC CYTOTOXINS
	• BIOLOGICAL MODIFIERS
	• CHEMOTHERAPEUTIC DRUGS

Hyperthermia

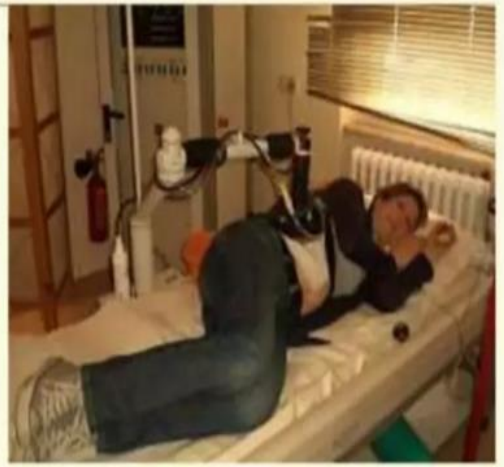
- Tumors are heated using exogenous energy source
- Heat directly kills the cancer cells but also synergizes with radiotherapy /chemotherapy to increase the Therapeutic gain.
- Temperature 39-45^{0}c

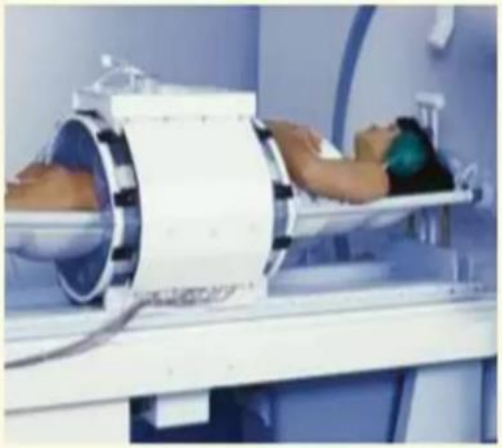
Hyperthermia – mechanism of action



Hyperthermia therapy can be delivered;

- **Local hyperthermia**: Heat is applied externally with high-frequency waves to a small area or directly to a tumor through the use of implanted microwave antenna, radiofrequency electrodes or probes, and ultrasound. Mostly used for solid tumors.
- **Regional (Perfusion) hyperthermia**: Heat is applied to large tissue areas or body cavity where the entire area or region is targeted and treated using microwave or radiofrequency energy that raises the temperature to the area.
- **Whole body hyperthermia**: Done for patients with metastatic cancer. Heat is given at 41.8 to 42°C.





Hyperthermia and Radiation

Rationale for combining the two:

- Radioresistant cells in s phase are more sensitive to Hyperthermia
- Hypoxic cells are not resistant to Hyperthermia
- Killing of hypoxic cells leads to re oxigenation leading to increased radiosensitivity
- Inhibits the repair of both sub lethal and potentially lethal damage increasing the cell kill.

Hyperthermia

- Interection of RT and HT is described by TER Thermal Enhancement ratio which is the doses of radiation producing similar biological effect with and without heat.
- Maximum interection occurs when given simultaneously.
- TER reduces with increasing time interval between HT and RT.
- When RT preceeds HT- no sensitisation after two hours of RT
- When HT preceeds RT cells can be sensitized for upto several hours.

Prospective randomized trials

Trial	n	CR for RT	CR for RT +HT	p value
Advanced H & N cancer				
Datta et al	52	13%	46%	**<0.05**
Valdagni et al	40	41%	83%	**0.016**
ESHO-2 et al	62	53%	50%	NS
Advanced Breast Cancer				
MRC et al	143	64%	71%	NS

Prospective randomized trials

Trial	n	CR for RT	CR for RT + HT	p value
Advanced Cervix/Rectal/Bladder Cancers				
DDHG	143(rectal)	15%	21%	**NS**
	114(cervix)	57%	83%	**0.003**
	101(bladder)	51%	73%	**0.01**
Harima	40	50%	80%	**0.048**

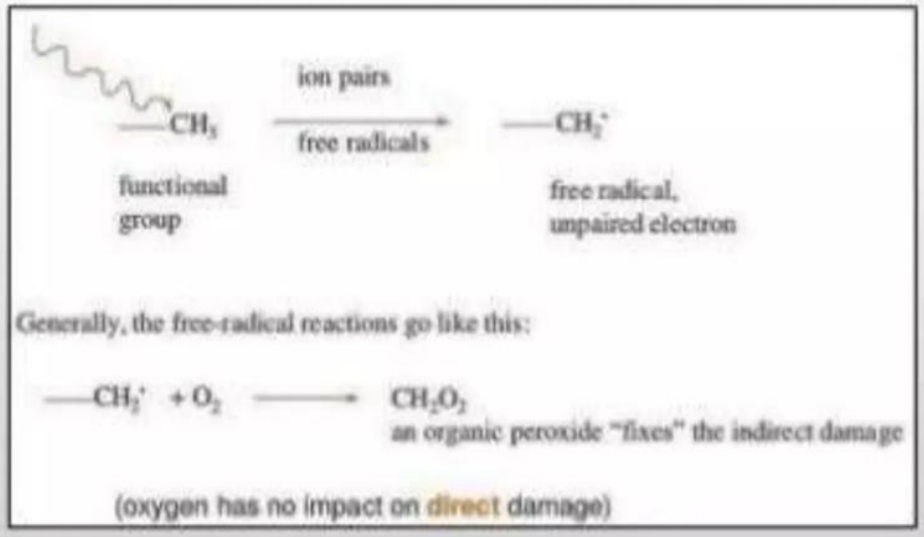
Hypoxia

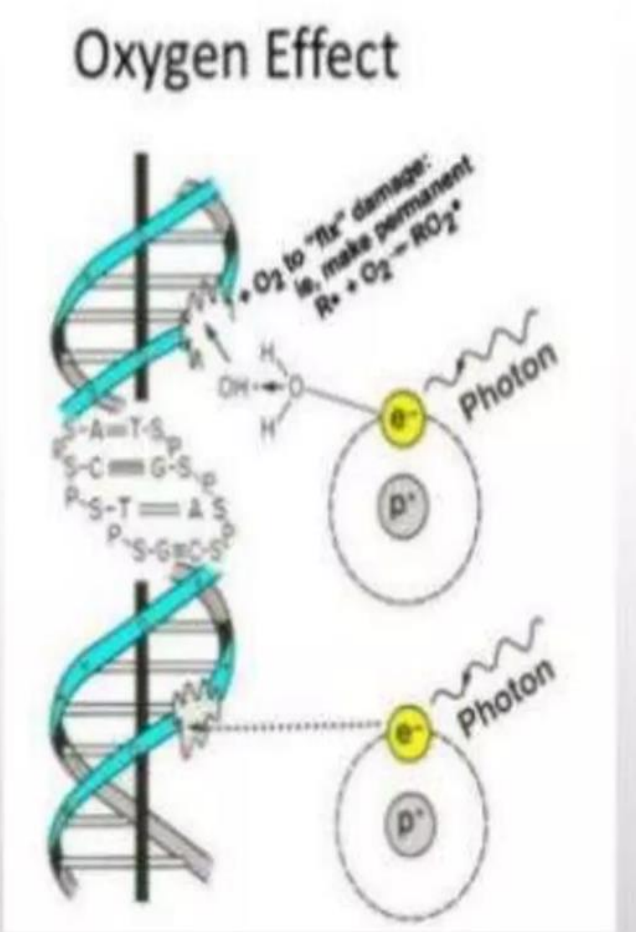
- Tumor Vasculature
- Slow rate of proliferation → decreased sensitivity to RT and CT
- Concentration of anticancer drugs is lesser in cells away from blood vessels leading to less killing of hypoxic cells similar to radiation resistance in hypoxic cells.

The Oxygen fixation hypothesis.

Oxygen "fixes" (i.e. makes permanent) the damage produced by free radicals.

The formation of RO2,an organic peroxide, represents a non restorable form of the target material; ie.the reaction results in a change in the chemical composition of the material exposed to the radiation.





Oxygen Effect

- Oxygen acts at level of free radicals
- Oxygen sensitization occurs as late as 0.01 msec after radiation
- Rapidly growing cells have an OER of 2.5
- Cells in G1 phase (2.5) have lower OER than cells in S phase (OER- 2.8)
- G2/M phase have 2.3-2.4
- Because G1 are more radiosensitive they dominate the low dose region of the servival curve.

Methods to sensitize or Eliminate Hypoxic cells

1. Physical:

- Overcoming hypoxia by eliminating it with treatment that increases delivery of oxygen to tumor ie increases the oxygen carrying capacity of blood and increasing the tumor blood flow
- a. Hyperbaric Oxygen
- b. Carbogen with or without nicotinamide

Hyperbaric Oxygen

- An increase in barometric pressure of the gas breathed by patient dyuring RT is termed as hyperberic Oxygen Therapy.
- Pioneered by Churchil and Davidson in 1968
- Increases plasma and tissue oxygen 10 times
- Increases VEGF secretion as well as secretion of matrix by fibroblasts

- Placing the patient in a compression chamber, increasing the environmental pressure within the chamber, and administering 100% oxygen for respiration
- Tumour o2 sensitisation involves pressurisation to between 2 to 4 atmospheres absolute for periods of 20 to 30 minutes, following which radiation therapy is delivered

Meta analysis

Site	Patients	Endpoints	HBO(%)	Air (%)	p
H&N, 1977	294	Control, 5 y	53	30	<0.01
H&N, 1986	106	Control, 5 y	60	41	<0.05
Uterine cervix, 1978	320	Control, 2 y	67	47	<0.01
Bronchus, 1978 (60 Gy/40 fx)	51	Survival, 2 y	15	8	NS
Bronchus, 1978 (30 Gy/6 fx)	123	Survival, 2 y	25	12	<0.05
Bladder, 1978	291	Survival, 5 y	28	30	NS

Advantages

- HBO Stimulates oxygenation leading to increased radiosensitivity
- Promotes growth of new cappillaries and blood vessels thus increasing perfusion leading to increase in chemosensitivity also
- Supports wound healing and used in treatment of cerebral radionecrosis
- Used in treatment of radiation induced bone and soft tissue necrosis

Disadvantages

- Patient has a feeling of Claustrophobia
- Cumbersome logistics associated with delivery

SIDE EFFECTS:

- Barotrauma in Ears, sinuses and lungs due to high pressure
- Temporary worsoning of Myopia
- Oxygen Toxicity Seizuers

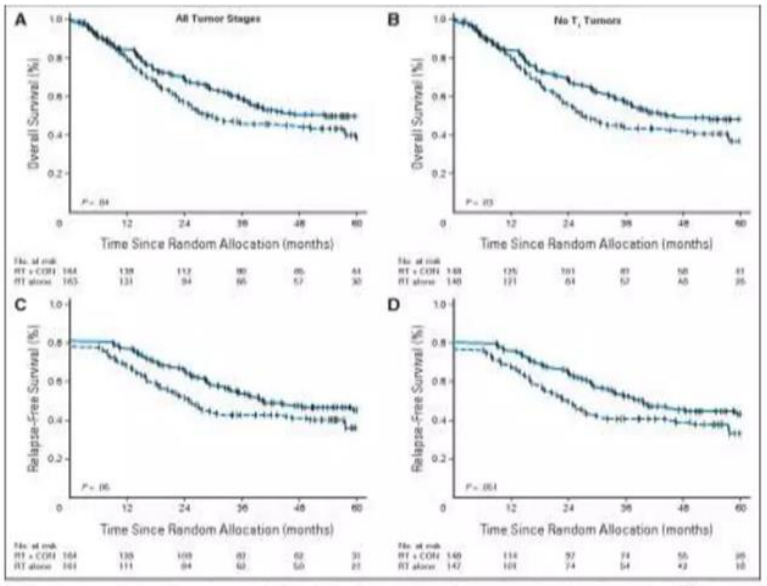
CARBOGEN

- Carbogen – 95% Oxygen + 5% CO_2
- Pure oxygen breathed leads to vaso constriction due to closing of some blood vessels
- Rationale:
- Addition of CO_2 to pure Oxygen facilitates unloading of O_2 into most hypoxic cells and can be given with or without nicotinamide.

Nicotinamide

- Vitamin B3 or nicotinamide
- Co factor of NADPH oxidase 2 angiogenesis
- prevent fluctuation in tumor blood flow
- preventing acute hypoxia
- Inhibition of PARP leading to inhibition of DNA Repair
- 60-80 mg/kg, to be given 1 to 1 ½ hours before radiation

- Phase II study by Hoskin et al
- 335 patients with locally advanced bladder cancer randomly assigned to RT alone versus RT with carbogen and nicotinamide
- 55Gy in 20#/4weeks are given
- OS → 59% vs 46%
- RFS → 54% vs 43%



Modifiers of Haemoglobin

ANAEMIA:

- Is an adverse prognostic factor and is the first investigation in all cancer patients
- Transfusion in patients with low haemoglobin increases tumor oxygenation and radiosensitisation
- Hb 11gm% or higher gives improved survival
- Erythropoetin does not help in increasing Hb but may also increase the tumor growth

PERFLUOROCARBONS

- Artificial blood substances
- These are small particles capable of carrying more oxygen or manipulating oxygen unloading capacity of blood
- Potential usefulness in radio sensitization is uncertain.

Non Hypoxic Cell Sensitizer

- Halogenated Pyrimidines = sensitize cells to degree dependent on amount of analogue incorporated
- Has diffrential effects as tumor cells cycles faster and therefore incorporates more drug than normal tissues.
- Drugs like 5-bromodeoxyuridine and 5-iododeoxyuridine.
- These are incorporated in DNA in place of Thymidine and has cell cycle specific radiosensitisation.
- Tumor response is good but normal tissue damage is unacceptable.

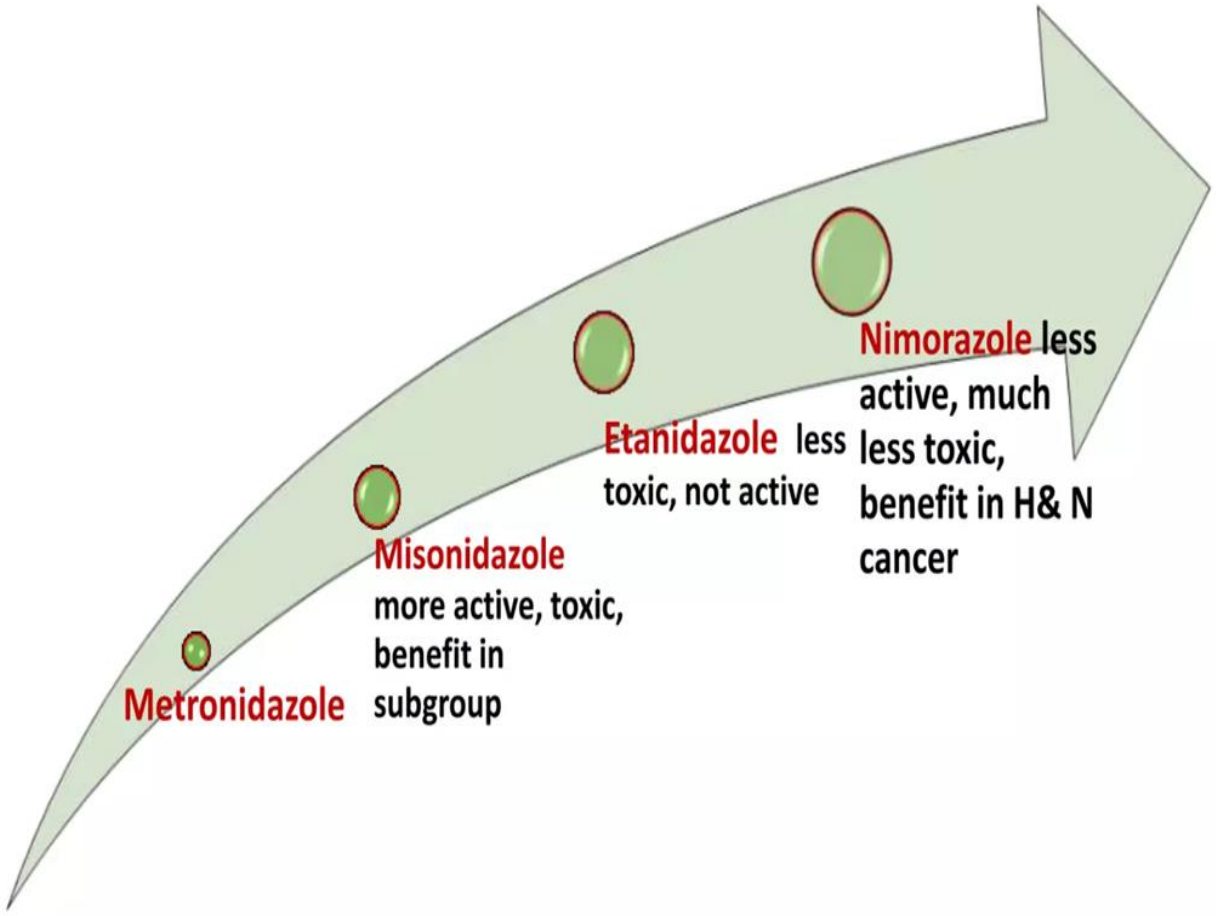
Hypoxic Radiosensitizers

- These compounds selectively activated in the hypoxic environment of tumor cells
- These are electronic affinic compounds which oxidise radiation induced free radicle damage in the cell to produce increased cell kill.
- Useful in hypoxic tumor microenvironment

Properties of Clinically Useful Hypoxic Cell Sensitizer

- They selectively sensitize hypoxic cells at a concentration which does not affect normal tissue toxicity.
- They are chemically stable
- Should be water and lipid soluble and must be capable of diffusion in a nonvascularised cell mass to reach the hypoxic cell.
- Should be effective at low dose

Development of nitroimidazoles



Metronidazole

- First generation 5- nitroimidazole
- Sensitizer enhancement Ratio of 1.2
- Half Life of 9.8 hours
- Total cumulative dose should not increase 54gm/m2
- Optimal time for administration – 4 hours before Radiation
- Dose: 6gm/m2 3 time a week for 3-4 weeks.
- Dose Limiting Toxicity:

  Gastro intestinal

  Sensory peripheral neuropathy

Misonidazole

- Second Generation 2- nitroimidazole
- Has higher electron effinity
- Sesitizer enhancement Ratio:

  1.4 with multiple dose of 2gm/m2

  1.15 with 0.5gm/m2

Given once or twice a week and total cumulative dose should not exceed 12gm/m2

Given 4 hours before radiation

Toxicity:

Gastro intestinal

Sensory peripheral neuropathy which may progress to central nervous system toxicity

Etanidazole

- Third generation
- SER is 2.5 – 3with a dose of 12gm/m2
- Has shorter half life
- Lower lipid solubility and is less neurotoxic
- Arthralgia is more
- 1000mg in 19.4 ml saline solution
- Total Dose: 40.8 gm/m2 at 1.7-2 gm/m2 3 times a week
- Give 30 minutes before radiation

Pimonidazole

- Fourth Generation 4-nitroimidazole
- More Potent then Misonidazole
- Maximum tolerated dose is 750mg/m2
- Toxicity: CNS menifesting as disorientation and Malaise
- No benefit seen in a randomised trial on Cancer Cervix

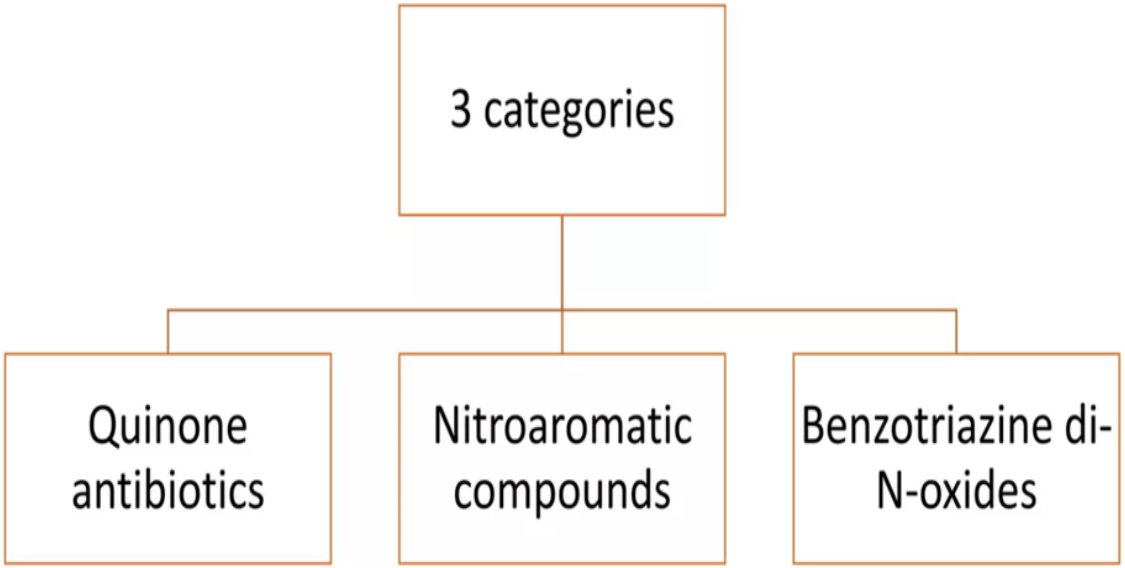
Nimorazole

- Is a 5-nitroimidazole, has same structure as metronidazole
- Administered orally as 500mg capsules. Daily dose 1200mg/m2 daily
- Given 30 minutes before radiation
- Total dose not to exceed 75gm
- Less toxic with no cumulative neuropathy
- Less effective than Misonidazole.

Summary of efficacy of clinical trials with nitroimidazoles

Compounds	Trials (n)	Significant benefit	No benefit
Metronidazole	1	1	–
Misonidazole / Nimorazole	38	5	33
Etanidazole	7	–	7
Pimonidazole	1	–	1

Hypoxic cytotoxins...



Quinone Antibiotic- Mitomycin-C

- Is a Prototype bioreductive drug
- Used as chemotherapy agent in SCC
- It is cytotoxic to relative radioresistant Hypoxic cells
- Differential Cytotoxicity between Hypoxic and Oxygenated cells is very less
- Myelosupression is main limiting toxicity

Tirapazemine (sr 4233)

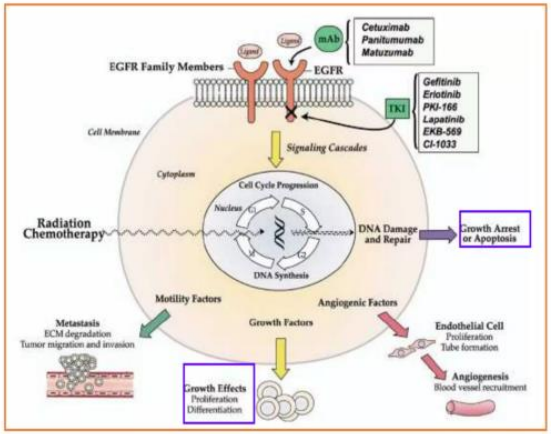
- Highly selective against Hypoxic cells
- This bioreductive agent in itself is cytotoxic to hypoxic cells
- **MOA**: Drug is reduced by intracellular reductases to form highly reactive radicle which produces both single strand and double strand breaks in DNA leading to cell death.
- Efficacy depends on number of courses given during radiotherapy
- Nausea and muscle cramps are main side effects
- Can be given before or after radiation
- Tirapazemine also enhances cytotoxicity of Cisplatin.

Tirapazemine (sr 4233)

- A phase III trial was conducted in H&N cancers to validate concept of targeting hypoxic cells
- Concurrent radiation (70GY) and chemotherapy with Cisplatin or Tirapazemine was given in 880 patients
- Three year loco regional failure free survival was 55% and 44% in TPC and Cisplatin respectively.
- Compliance was satisfactory in both arms
- More febrile neutropenia and mucosal toxicity was observed.

Biologic Modifiers of Radiation Response

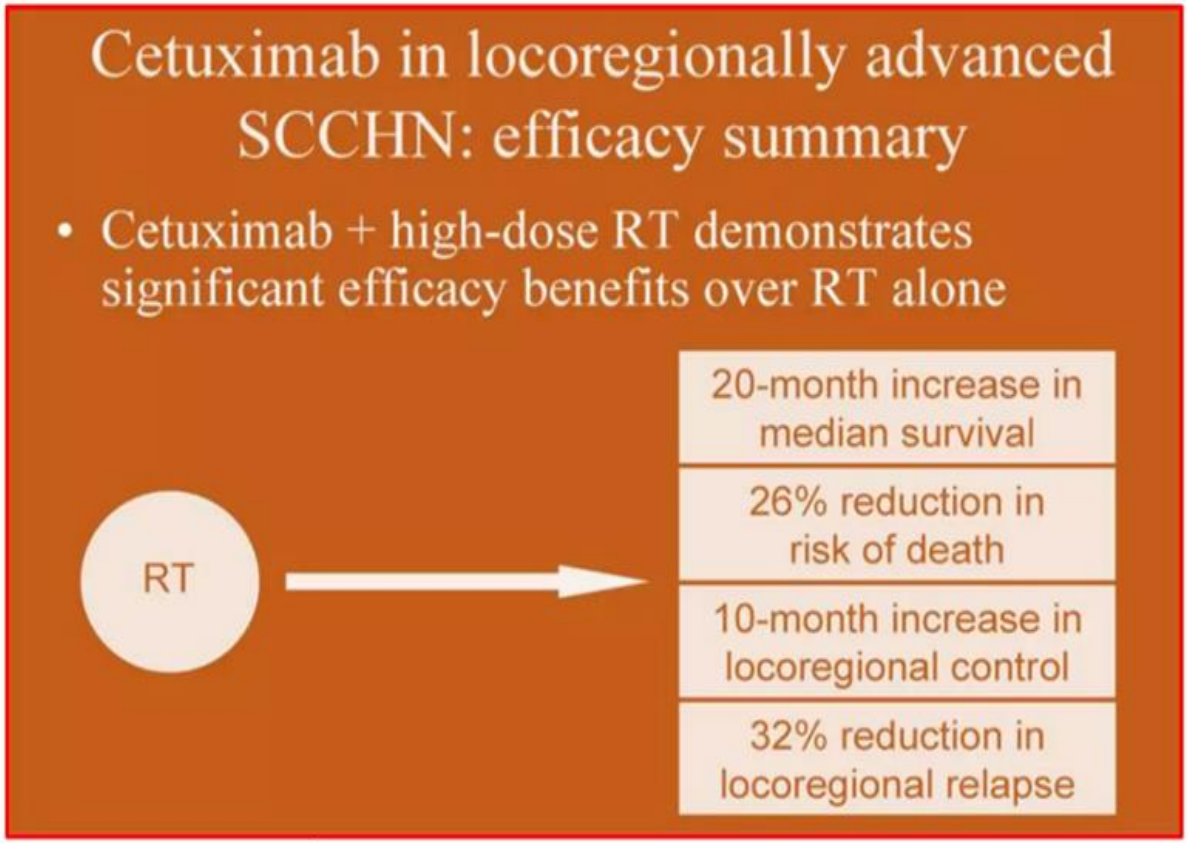
-EGFR is a promising therapeutic target as it is usually overexpressed in H&N cancers and is a predictor of clinical outcome.
-Several studies have reported that repopulation of epithelial tumor cells after radiation exposure is related to activation and expression of EGFR.
-Blockade of EGFR may be important in reducing tumor cell repopulation by modulation of cellular proliferation and enhancement of tumor radioresponse.



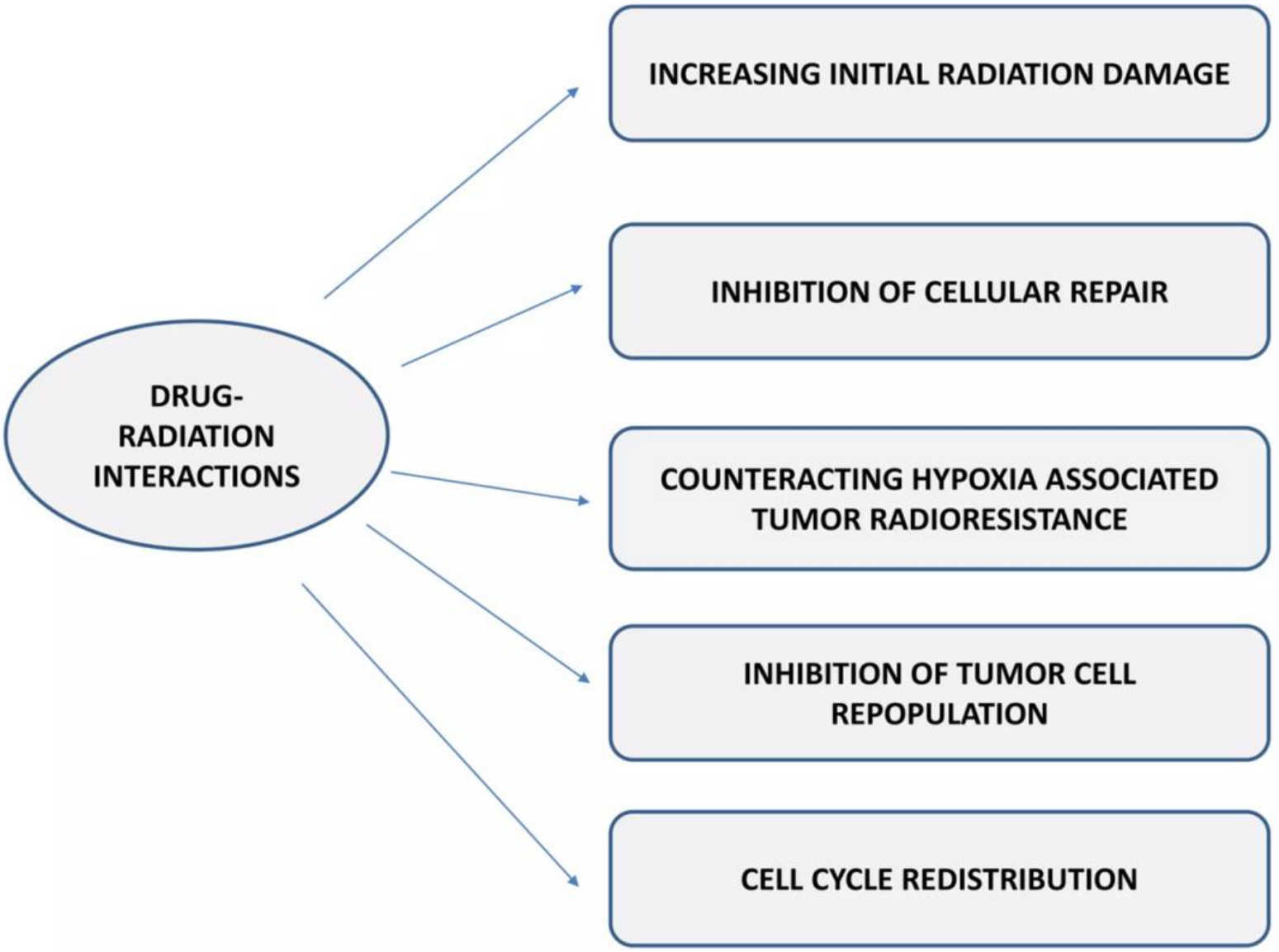
Cetuximab

- It specifically targets EGFR with high affinity & blocks ligand binding
- Enhances antitumor activity of both radiotherapy as well as cisplatin
- This has shown activity in patients of SCCHN and also known platinum resistance.
- Intravenous Cetuximab given one week before RT. Loading dose of 400mg in two hours along with premedications followed by weekly dose of 250mg over one hour.
- SIDE EFFECTS: angioedema, urticaria, hypotension, bronchospasm.

Results contd...



Bonner , Harari, Giralt etal N Engl J Med 354;567-78. 2006


DRUG-
RADIATION
INTERACTIONS
INCREASING INITIAL RADIATION DAMAGE
INHIBITION OF CELLULAR REPAIR
COUNTERACTING HYPOXIA ASSOCIATED
TUMOR RADIORESISTANCE
INHIBITION OF TUMOR CELL
REPOPULATION
CELL CYCLE REDISTRIBUTION

5-fluorouracil (5-Fu)

- Gets incorporated in RNA and distrupts its functions
- Inhibits DNA synthesis by inhibition of Thymidylate synthetase and results in accumulation of cells in early S phase
- Causing Radiosensitising effects
- RT and 5Fu are being used concurrantly in GI tumors and improvement in locoregional control and survival is seen.

Cisplatinum

- Is cell cycle non specific
- More toxic to hypoxic cells than aerated cells
- Radiation induces increased cellular cisplatin uptake hence when used with radiation causes enhanced cell kill .
- Coughlin, Richmond and Douple suggested two mechanisms of Radiosensitivity:

a. Free radicals with altered binding of platinum to DNA are formed in Hypoxic cells during radiation

b. This interaction inhibits repair of SLD and PLD thereby increasing cell kill.

Taxanes

- Are Mitotic spindle inhibitors
- Causes cellular arrest in G2/M phase which are highly radiosensitive
- Induces apoptosis
- Causes reoxygenation

ALKYLATING AGENTS

TEMOZOLOMIDE

2nd generation orally acting
Unique in its ability to cross BBB.
Radiosensitization- inhibition of DNA repair
1st line therapy in GBM concurrent with RT

TOPOISOMERASE I INHIBITOR

TOPOTECAN,IRINOTECAN

MECHANISMS-1. Inhibition of Repair
2. Redistribution ino G_2 phase.
3.Conversion of RT induced SSBs into DSBs.

CHEMORADIATION THERAPY AS STANDARD OF CARE

HEAD & NECK (LOCALLY ADVANCED)	CISPLATIN,5FU, CARBOPLATIN, CETUXIMAB	DEFINITIVE/ POST-OP. CONCURRENT	LRC/DFS,OS BENEFIT ORGAN PRESERVE
GLIOBLASTOMA MULTIFORME	TEMOZOLOMIDE	DEFINITIVE/ POST-OP. CONCURRENT	OVERALL SURVIVAL
LOCALLY ADVANCED NSCLC	CISPLATIN,CARBOPLATIN, ETOPOSIDE,PACLITAXEL	DEFINITIVE CONCURRENT, SEQUENTIAL	OVERALL SURVIVAL
LIMITED STAGE SMALL CELL LUNG CA	CISPLATIN/ETOPOSIDE	DEFINITIVE CONCURRENT	OVERALL SURVIVAL
ESOPHAGEAL CA.	CISPLATIN/5FU	PRE-OP./ DEFINITIVE CONCURRENT	LOCAL CONTROL,OS

CHEMORADIATION THERAPY AS STANDARD OF CARE

GASTRIC CA.	5FU	POST-OP. CONCURRENT	OVERALL SURVIVAL
PANCREATIC CA.	5FU,GEMCITABINE	POST-OP./ DEFINITIVE CONCURRENT	LOCOREGIONAL CONTROL,POSSIBLY SURVIVAL
LOCALLY ADVANCED RECTAL CANCER	5FU,CAPECITABINE	PRE-OP. CONCURRENT	IMPROVED SPHINCTER PRESERVATION,OS
ANAL CA.	5FU,MITOMYCIN C	DEFINITIVE CONCURRENT	IMPROVED COLOSTOMY FREE SURVIVAL
CA. CERVIX	CISPLATIN,5FU	DEFINITIVE CONCURRENT	OVERALL SURVIVAL
BLADDER CA.	CISPLATIN,5FU	DEFINITIVE CONCURRENT	BLADDER PRESERVATION

CTRT IN HEAD & NECK CANCER

INT 0099, 1998	RT(70Gy) vs. RT(70Gy) + Cisplatin(100mg/m^2) with adj. cisplatin+5-FU	At 5 yr PFS(58% vs 29%), DFS(74% vs 46%), OS(67% vs37%) favours CT/RT arm. $p<0.001$
RTOG 9111, 2003	3 ARM-(Glottic & supraglottic) –RT vs sequential CT/RT vs concurrent CT/RT	NO Diff. in OS, but Concurrent arm had superior local control & highest organ preservation
EORTC 22931, 2004	Post-op. RT(66Gy) vs. post-op. CTRT (66Gy+cisplatin)	5 yr OS(53% vs 40%), PFS (47% vs. 36%), LRC (82% vs. 69%) $p<0.05$
MACH-NC Meta analysis	93 randomised trials in Head & Neck- 17,346 Patients	CT/RT Provides absolute 5-yr OS BENEFIT OF 6.5%, whereas induction CT showed only 2.4%

CTRT IN CARCINOMA CERVIX

GOG-120, 1999	IIB-IVA; 3 ARMS; RT+ CISPLATIN vs. RT+CISPLATIN/5FU/HU vs. RT+HU	IMPROVED PFS & OS IN BOTH CISPLATIN ARMS P<0.005
GOG-123, 1999	IB(TUMORS ≥4cm.) RT vs. RT+ cisplatin	IMPROVED PFS(P<0.001) & IMPROVED OS(P<0.008) IN CISPLATIN ARM
INTERGROUP 0107, 2000	I-IIA(POST HYSTERECTOMY) WITH HIGH RISK, RT vs. RT+CISPLATIN/5FU	IMPROVED PFS (P=0.003) & IMPROVED OS(P=0.008) IN CTRT ARM
RTOG 9001, 1999	IB-IIA(≥5cm. Or +ve pelvic nodes), IIB-IVA EFRT vs CTRT	IMPROVED 5 yr DFS (P<0.001)& IMPROVED 5 yr OS(P=0.004) IN CISPLATIN ARM

Radioprotectors

Rationale for using Radioprotectors

- Reducing the Normal tissue complication probablity without affecting tumor control.
- Agents which reduce radiation toxicity but will reduce efficacy against tumor also

Ideal Radioprotector

- Should preserve the antitumor efficacy of radiation
- Provide wide window of protection for all other tissues
- Should have high therapeutic ratio
- Easy and comfortable administration
- Reasonable cost - effectiveness

- After World war II a development program was initiated in 1959 by US Army to identify and synthesize a drug capable of protection of individuals in a radiation environment

- Over 4000 compounds were synthesized out of which only two compounds were of practical use.

Two Radioprotectors in Practical Use

Compound	Dose (mg/kg)	Dose reduction factor		Use
		7 days (GI)	30 days (Haematopoetic)	
WR-638 Cystaphos	500	1.6	2.1	Carried in field pack by Russian army
WR-2721 Amifostine	900	1.8	2.7	Protector in radiotherapy and carried by US astronauts on lunar trips

- This was the first breakthrough to reduce toxicity by covering the SH group with a Phosphate.

- Toxicity of compound reduced because the phosphate group is stripped inside the cell and the SH group begins scavanging for free radicals.

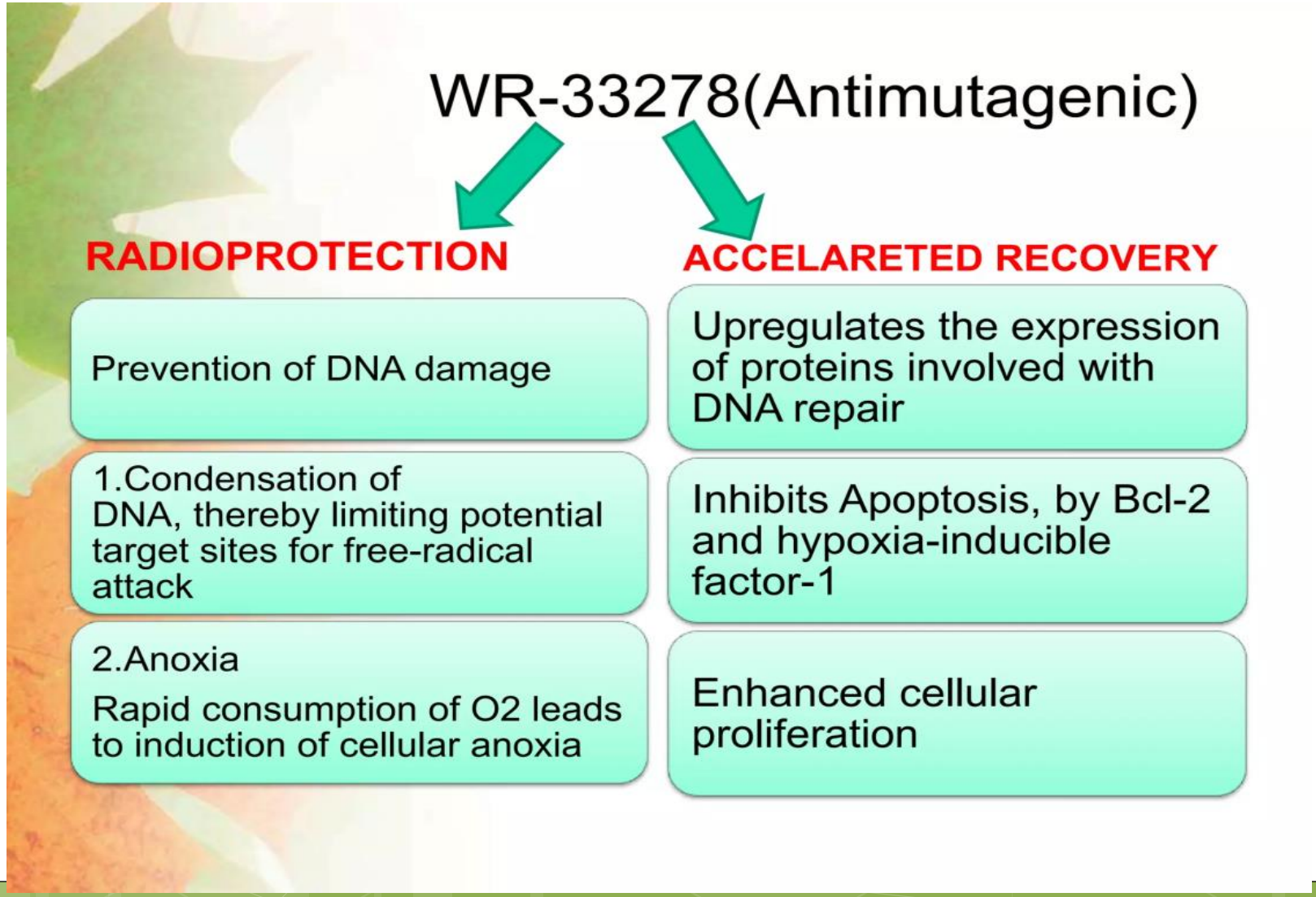
CLASSIFICATION

1. Free radical scavenging and cellular detoxification
   - Amifostine (WR2721, Ethyol)
   - Superoxide dismutase
   - Selenium

2. Modification of normal tissue oxygen levels
   - Systemic hypoxia
   - Local hypoxia

3. Epithelial cell-specific growth factors
   - Keratinocyte growth factor (Dorr et al., 2001)

Amifostine


WR-33278(Antimutagenic)
RADIOPROTECTION
ACCELARETED RECOVERY
Prevention of DNA damage
1.Condensation of DNA, thereby limiting potential target sites for free-radical attack
2.Anoxia
Rapid consumption of O2 leads to induction of cellular anoxia
Upregulates the expression of proteins involved with DNA repair
Inhibits Apoptosis, by Bcl-2 and hypoxia-inducible factor-1
Enhanced cellular proliferation

Diffrential Uptake

Extensive uptake is seen in:

- Salivary Glands
- Kidneys
- Intestinal mucosa

- Where as markedly low uptake is seen in the tumor tissue.
- Amifostine do not cross the BBB

Timing of Administration

- To be given 30 minutes prior to RT for optimal cyto protection.
- Single Morning dose provides superior radioprotection than afternoon dose
- Can be given as IV infusion, subcutaneous or orally also.
- Dose 900 mg/kg as infusion

Table 1. Clinical trials of amifostine therapy during radiation therapy or chemoradiotherapy for head and neck cancer

Study	*n* of patients	Treatments	Key findings
RT			
McDonald et al. (1994) [60]	9	RT + i.v. amifostine, 100 mg/m^2	Flow rates of unstimulated whole saliva recovered to 20% of baseline at 12 mos post-treatment
Wagner et al. (1998) [61]	14	RT + i.v. amifostine, 200 mg/m^2	i.v. amifostine treatment led to significant reduction in oral symptoms and duration of mucositis
Bourhis et al. (2000) [62]	26	RT + i.v. amifostine, 150 mg/m^2, versus RT alone	i.v. amifostine treatment led to significant reduction in duration of acute mucositis and duration of feeding tube use compared with RT treatment alone
Koukourakis et al. (2000) [20]	40	RT + s.c. amifostine, 500 mg, versus RT alone	s.c. amifostine led to significant reduction in severity of oral mucositis compared with RT treatment alone
Brizel et al. (2000) [26]	315	RT + i.v. amifostine, 200 mg/m^2, versus RT alone	i.v. amifostine led to significant reduction in acute and chronic xerostomia versus RT alone and increased saliva production versus RT alone; no significant reduction in grade ≥3 mucositis versus RT
Wasserman et al. (2005) [30]	315	2-yr follow-up of Brizel et al. (2000) [26]	i.v. amifostine led to significant decrease in severity and duration of xerostomia at 2 yrs post-treatment without compromising tumor control

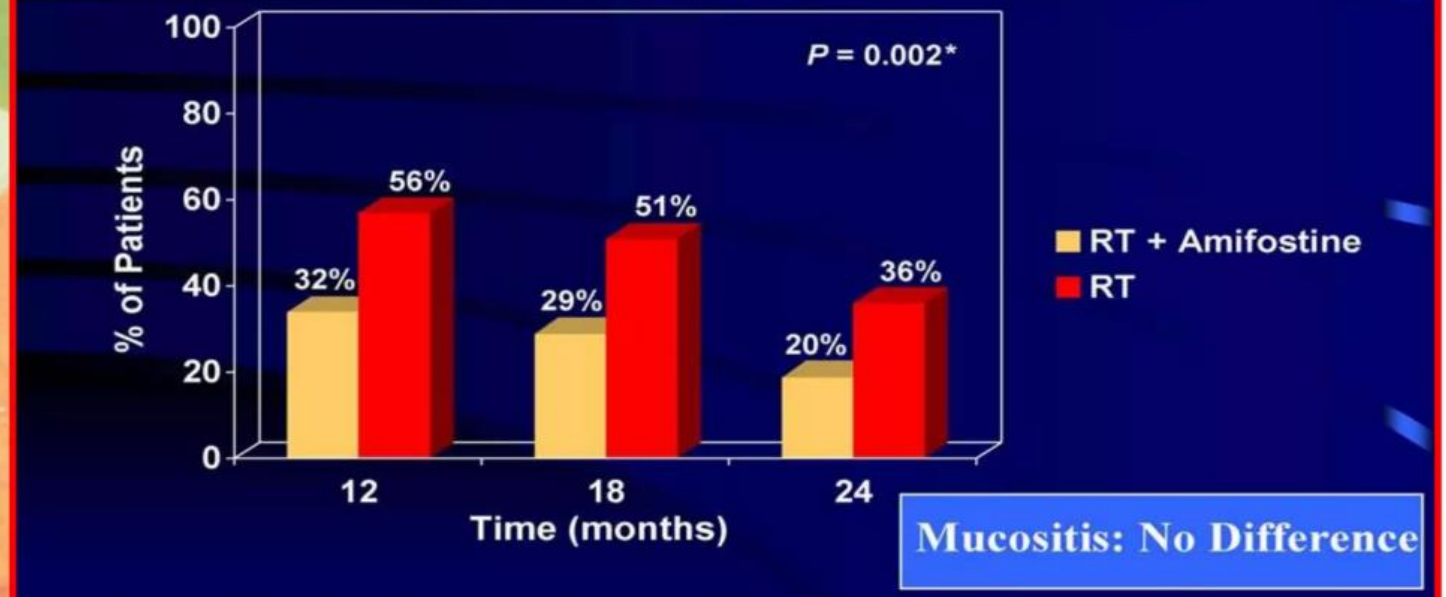
<30 min--- Difference present

Side Effects

- Nausea, Vomitting and other GI Symptoms
- Transient Hypotension seen in 60% patients
- Flushing, feeling of warmth, chills, dizziness, somnalence
- Hypocalcaemia in < 1%
- Metallic taste during infusion
- Allergic reactions

RT ± Amifostine

Randomized Phase III Trial



Mucositis: No Difference

Brizel DM, Wasserman T. Poster presented at: Annual Meeting of the American Society of Clinical Oncology. June 6, 2004; New Orleans, LA.

Issue of Tumor Protection

A meta analysis by Sasse et al in 2006 concluded:

- Amifostine does not affect the efficacy of radiation
- Amifostine arm received slightly higher CR due to low toxicity and less interruption in treatment.

Take Home Message

- The chemical modification,for enhancing treatment efficacy and reducing toxicity remains an area of investigation.
- All Preclinical and early and phase III trials have not shown promising results
- Attempts to improve treatment efficacy by augmenting tumor oxygen delivery have a mixed record of success.
- Use of drugs that are cytotoxic to hypoxic cells holds promise.

Cont.

- Apart from use of radiosensitizer Nimorazole in Denmark, none of the treatments have become a standard part of RT
- Use of radio protectors is also more contraversial. As there is radioprotection in tumor cells also.
- The combination of chemotherapy and radiation is more common strategy which has shown good results in radiosensitization when used concurrantly.

Cont

- In the era of new RT technologies, monoclonal antibodies and novel chemotherapeutic agents are associated with significant cost profiles. In this regard HYPERTHERMIA is relatively inexpensive and has given promising results and needs further investigations.

THANK YOU