RADIOBIOLOGY IN RELATION TO CONCURRENT CHEMORADIOTHERAPY

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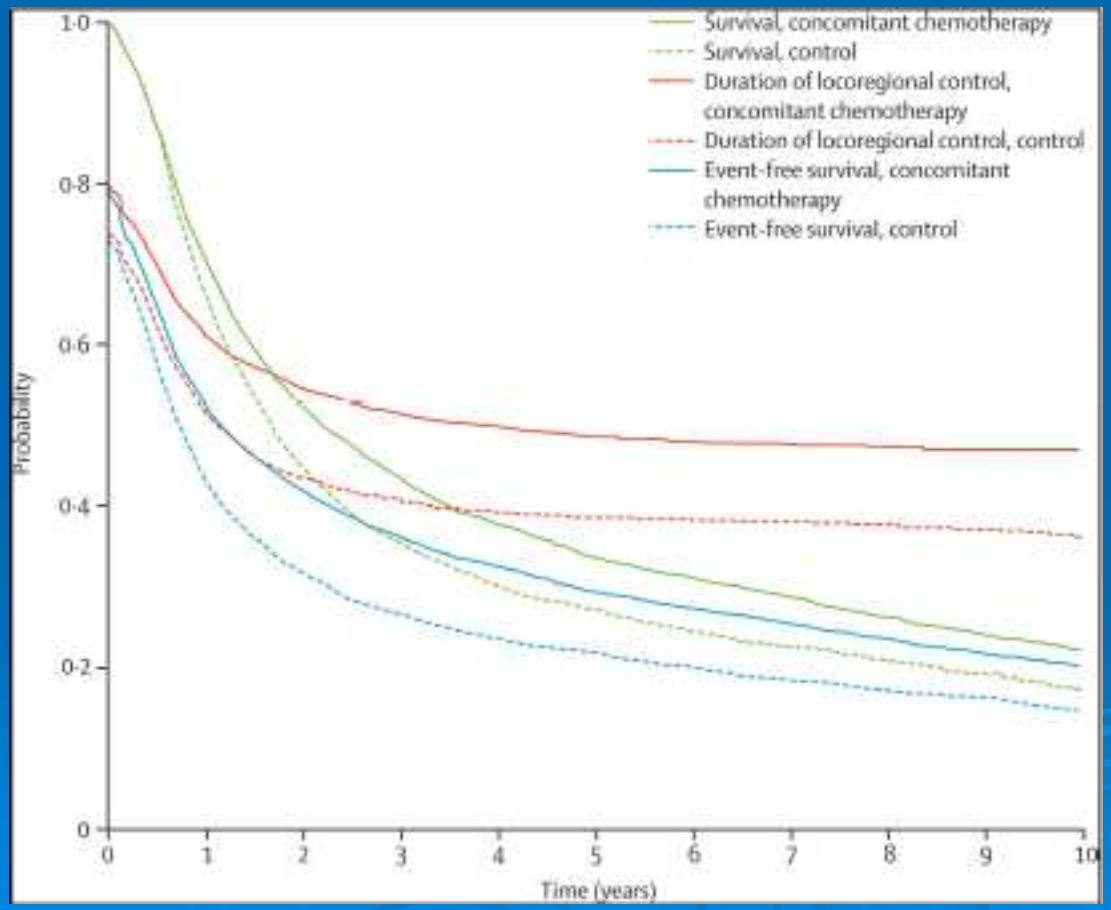
- Combined use of RT and CT in cancer treatment-a logical and reasonable approach-has already proven beneficial for several malignancies.
- Local control of primary tumor mass by RT + Systemic CT to control metastatic disease-effective means to combat the disease.
- Many CT drugs enhance the effects of RT- even more impetus to integrate both modalities.

Biological Basis for Concurrent Chemoradiotherapy

- Chemotherapy may be given neo-adjuvantly, concurrently or adjuvantly
- Used concurrently
  - Advantage: neither modality delayed
  - Disadvantage: risk of increased toxicity
- Biological basis
  - Spatial co-operation: radiotherapy targets local and chemotherapy distant disease
  - Additive independent cell kill with no overlapping toxicity
  - Preferential sensitisation of tumour *vs* normal cells (or protection of normal *vs* tumour cells)

Meta-analysis of Head and Neck Cancer Trials Involving Concurrent Chemoradiotherapy



Michiels *et al* 2009; Lancet Oncol; 10:341-50

- 1950s- Search for chemical agents that might enhance the effects of radiation.
- In1958- Heidelberger *et al* obtained “potentiation of activity” by combining FU with radiation in a preclinical study.
- Pioneering studies later translated into clinical trials-often with contradictory results,(those observed in treatment of lung cancer).
- Major breakthrough in early 1970s-, Nigro *et al*. - Concurrent CT & RT in patients with cancer of anal canal.

Chemoradiation: e.g. Locally advanced NSCLC

- Meta-analysis
- Concurrent chemoradiotherapy *vs* sequential chemotherapy and radiotherapy
- Improved local control
- Significant overall survival advantage of 6.6% at 3 years (24.8% *vs* 18.2%)
- But higher oesophageal toxicity rates (18% *vs* 3%)

Auperin. J Thor Onc 2007; 2: S310

Developments in Radiobiology

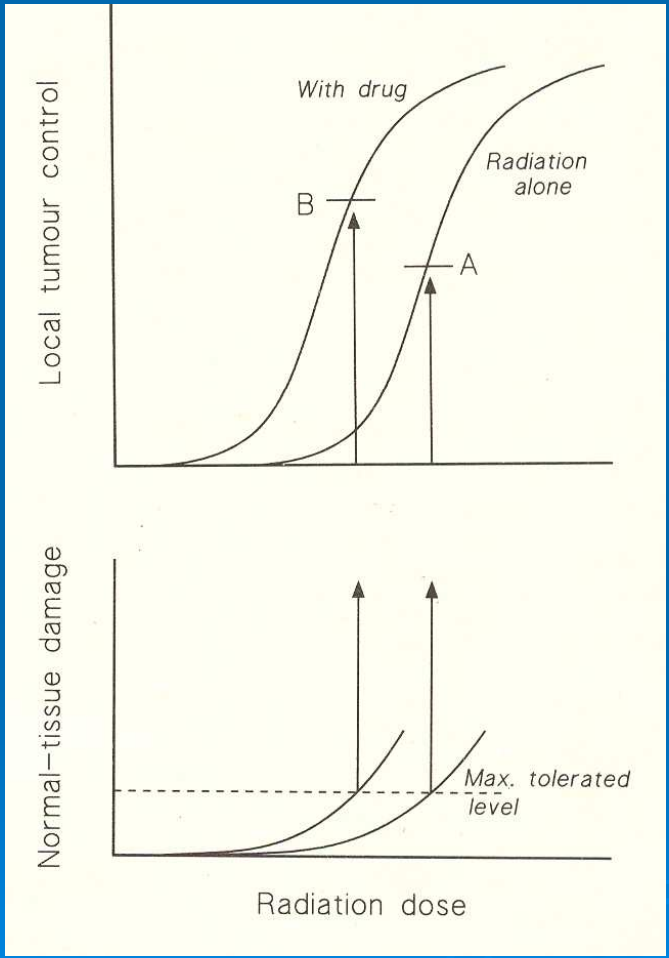
- Developments in biology are increasing our understanding of the complex molecular pathways that control cellular processes
- Our understanding of radiation effects on cells has changed considerably over the past 10 years
- Radiobiology is exploiting these developments to find novel molecular targets for successful chemoradiotherapy approaches

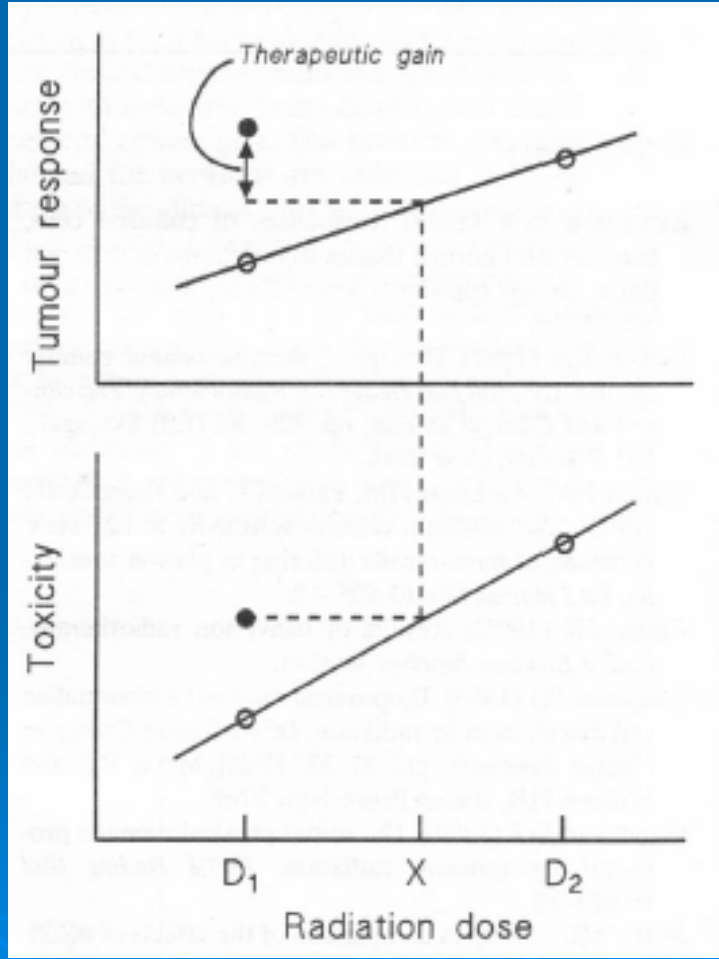
Chemoradiation: e.g. Locally Advanced Head & Neck Cancer

- Meta-analysis
- Significant overall survival advantage with addition of chemotherapy to RT (sequential & concomitant) 4.5% at 5 years
- More pronounced effect with concomitant chemotherapy 6.5% at 5 years

Pignon. Rad Onc 2009; 92(1):4-14

Improvement in Therapeutic Index





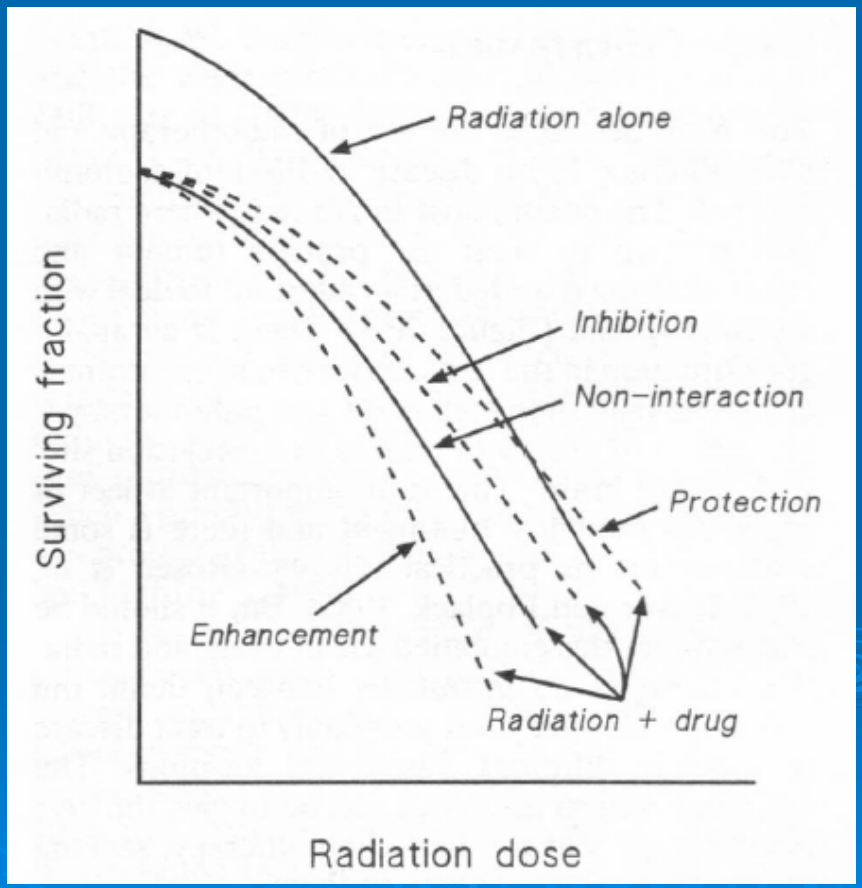
Combining CT with RT

Goals- increase patient survival by:

- Improving local-regional tumour control
- Decreasing or eliminating distant metastases
- Both
- Preserving organ or tissue integrity and function

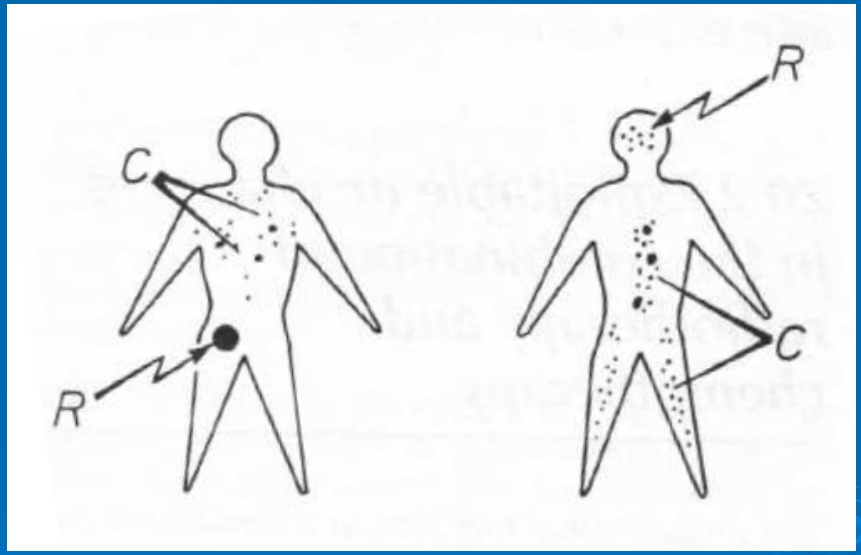
Interaction of Different Modalities

- Noninteractive- each modality appears to exert its own individual effect
- Interactive- situation where one modality modifies the effect of the other



Spatial Cooperation

- Action of RT and CT drugs directed towards different anatomical sites
- Envisages no interaction between the two modalities
- Independent action of the two agents



C= Chemotherapy
R= Radiotherapy

Independent Cell Kill

- Two modalities can both be given at full dose,
- Even in absence of interactive processes, tumour response greater than that achieved with either alone
- Effective antitumour drugs that do not increase radiation damage

	Associated Toxicity			Response of Bronchial tumour
	Intestinal	Bone marrow	Lung	
Radiation	-	-	+++	+++
Drug	+++	+	-	++
Combination	+++	+	+++	++++

Advantages & Disadvantages of Different Chemoradiation Sequencing Strategies

Strategy	Advantages	Disadvantages
Sequential Chemoradiation	•Least toxic •Maximize systemic therapy •Smaller RT fields	•Increased T/t time •Lack of local synergy
Concurrent Chemoradiation	•Shorter T/t time •Radiation enhancement	•Compromised systemic therapy •Increased Toxicity •No cytoreduction of tumour
Concurrent Chemoradiation & Posterior Chemotherapy	•Maximise systemic therapy •Radiation enhancement •Local and systemic therapy delivered upfront	•Increased toxicity •Increased T/t time •Difficult to complete CT after CTRT
Induction Chemotherapy & Concurrent Chemoradiation	•Maximize systemic therapy •Radiation enhancement	•Increased toxicity •Increased T/t time •Difficult to complete CTRT after induction CT

Lung Damage in Mice as a Result of CT+RT

Drug	Drug Administration*			Source**
	Before	Concurrent	After	
Cyclophosphamide	++ -	+++ +++	++ -	C M
Bleomycin	+ - ++	++ +++	++ -	C M S
Adriamycin	- - +	+++ +++	+ -	C M S
Actinomycin-D	- +	+		C S
Methotrexate	+ - -	- -	- -	C M S
5-FU	-	-	-	M
Vincristine	+	+	+	C
CCNU	-	-	+	C
Cis-Platinum	- -	- -	- -	C M
Mitomycin C	-	+	-	M

* Before= 7-28 days before irradiation; After= 7-28 days after irradiation

**C=Collis(1981); Collis & Steel (1983); M=von der Maase (1986); S=Steel *et al* (1979)

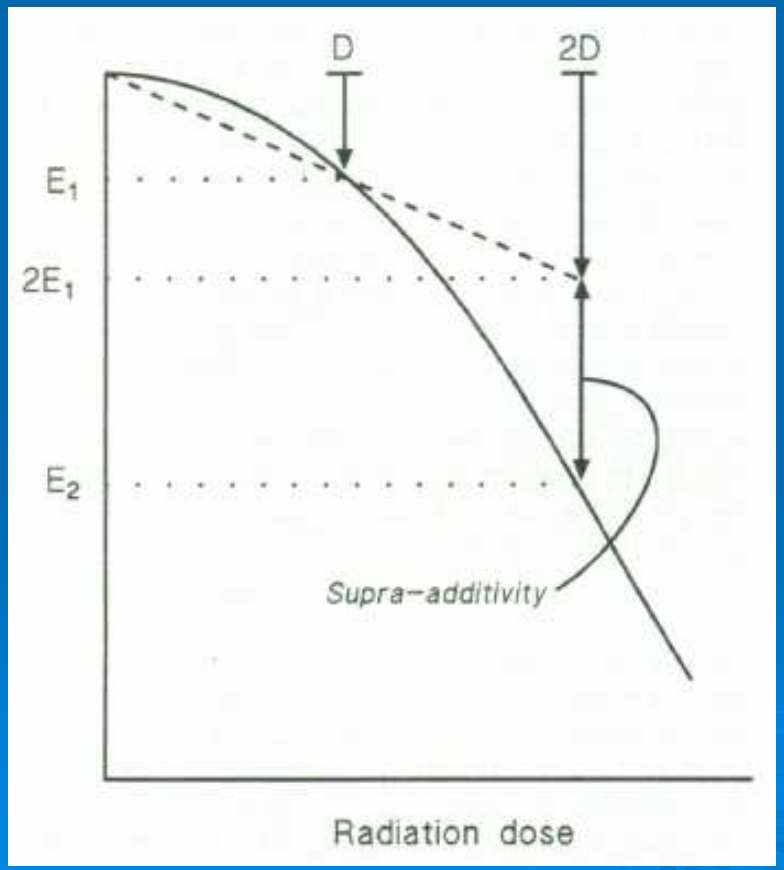
Protection of Normal Tissues

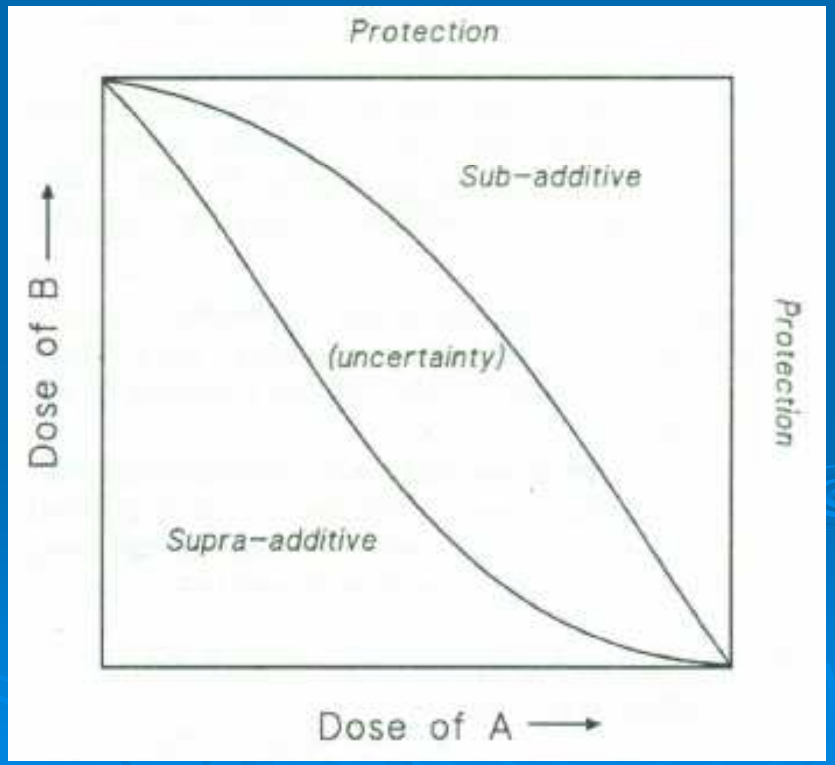
- Well documented situation in experimental animals where certain drugs increase resistance of normal tissues to radiation or second cytotoxic treatment.
- Phenomenon with Colchicine and vinca alkaloids. WW Smith earlier, Millar et al (1978)
- Cyclophosphamide, Cyt Arab., Chlorambucil, MTX- effective radioprotective agents
- Maximal radioprotection- Cyt. Arab 2 days before irradiation . For Cyclophos optimum gap 3 days before
- Priming treatment with one cytotoxic drug can protect against a large dose of another (Millar & McElwain, 1978)

Protection of Normal Tissues

- Cyt Arab- in marrow did not modify stem cell radiosensitivity-stimulated enhanced repopulation by surviving stem cells
- In small intestine- Cyt Arab 12hrs before irradiation increased survival of intestinal stem cells perhaps by repair of radiation damage(Phelps & Blackett,1979)
- Attempts made to exploit this phenomenon in high dose combination CT (Hedley *et al* 1978)- critical dependence on timing precluded use in fractionated RT

Enhancement of Tumour Response- Concept of Supra-additivity





Mechanisms of Interaction between Drug and Radiation

Inhibition of Repair of Radiation Damage:

- Antimetabolites of no interest as cytotoxic agents-3-aminobenzmide, cordyceptin, caffeine etc
- Anticancer agents- Actinomycin D, Adriamycin, Hydroxyurea, Ara-C, Cisplatinum
- Sensitization detected at low radiation dose and at low dose rate (Kelland and Steel, 1988)
- Selectivity for effects on tumours rather than on normal tissues is essential

Mechanisms of Interaction between Drug and Radiation

Cell Synchronization:

- Many cytotoxic drugs- some degree of selectivity in killing cells at certain phases of cell cycle
- Radiation- cell cycle dependence-peaks of resistance in S-phase and in G1
- Attractive possibility of complementary action between drug and radiation
- This approach to synergism works well with rapidly cycling cells
- Slowly growing or resting cells in human tumours – explanation why synchronisation therapy disappointing (Tubiana *et a*l, 1975; Tannock, 1989)

Mechanisms of Interaction between Drug and Radiation

Recruitment:

- Response to therapy can be improved if non-proliferating cells stimulated to come into cycle
- Growth fraction of some experimental tumours is increased by suitable priming treatment
- Resulting therapeutic benefit has not been large

Mechanisms of Interaction between Drug and Radiation

Enhanced Repopulation:

- CT after a few days of RT-greater effect on experimental tumour
- This strategy also damaging normal tissues that repopulate rapidly after irradiation
- Enhanced repopulation may lead to therapeutic detriment in combined modality therapy
- If CT given first it may switch on repopulation during subsequent course of RT-may reduce effectiveness

Mechanisms of Interaction between Drug and Radiation

Reduction of Hypoxic Fraction:

- Debulking of tumour by CT-reduction of hypoxic fraction- improved response to RT
- Little evidence for benefit being achieved this way

Mechanisms of Interaction between Drug and Radiation

Debulking:

- Most promising basis for expecting benefit from combined CT+RT
- Debulking leads to improved O_2 supply or increased proliferation-greater cell kill from subsequent RT

Concurrent CTRT-Summary

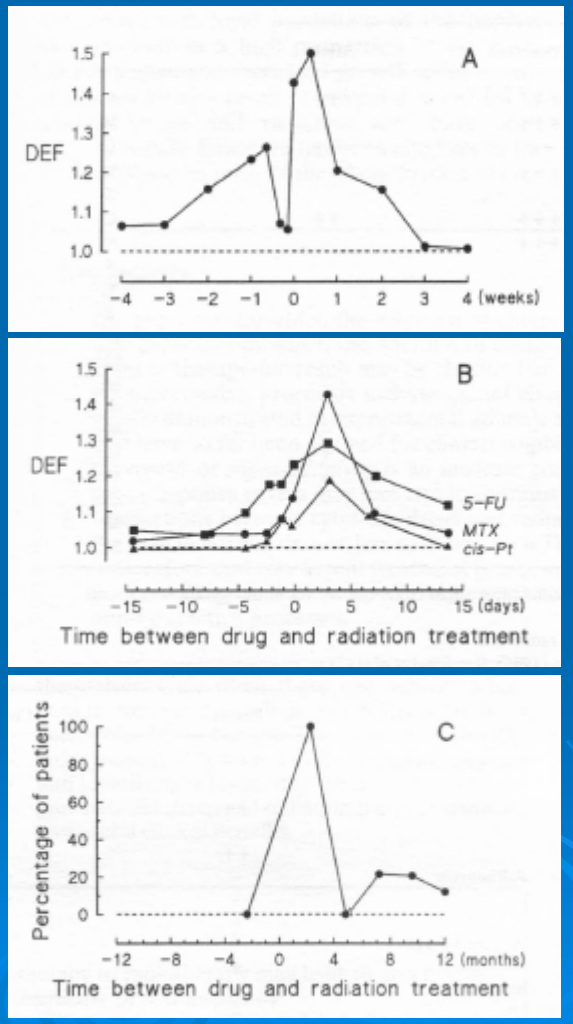
- Concurrent CT & RT- T/t with CT during fractionated course of RT
- Reasoning based on expectation of interaction between the two modalities
- Mechanism:
  - Influence of one modality on intrinsic cellular sensitivity of other modality
  - Indirect interaction such as physiological alteration involving oxygenation or pH status by one modality
- Advantages: Avoids delaying CT or RT
  Least chance of tumour repopulation
- Disadvantages: Increased normal tissue complications-, e.g. Esophageal stricture, Mucositis

Time-dependence of Interactive Effects between Drugs and Radiation

Interaction of Cyclophos. (200mg/kg) and pelvic irradiation in mice

Interaction of 5FU, MTX and cis-platinum and pelvic irradiation in mice

Normal tissue damage in patients treated for testicular teratoma with RT and combination CT



Summary of Evidence for Exploitation of Four Mechanisms in Combination of RT & CT

	Evidence in Mice	Evidence in Man
Spatial co-operation	+++	++
Independent cell kill	+++	+
Protection of normal tissues	++	-
Enhancement of tumour response	+	-

Thank You