# CHEMORADIOTHERAPY

**Goals:**

(1) To increase patient survival by improving locoregional tumor control
(2) To decrease of eliminate distant metastasis
(3) To preserve organ and tissue integrity and function.

**Strategies:**

(1) Spatial co-operation
(2) Independent toxicity
(3) Enhancement of tumor response
(4) Protection of normal tissue

***Spatial co-operation*** implies that actions of radiation and chemotherapeutic drugs are directed at different anatomic sites,with radiation targeting the localized tumor and chemotherapy targeting disseminated micrometastasis.This was the initial rationale for combining chemotherapy and radiotherapy and is still the basis for adjuvant chemoradiation therapy where radiation is given first to control the primary tumor and chemotherapy is given later to cope with the micrometastasis.

***Independent toxicity*** is important to increase the therapeutic ratio due to better tolerance of regimes which combine radiation with drugs whose toxicities to specific cell types and tissues do not overlap with or minimally add to,radiation-induced toxicities.

***Enhancement of tumor response*** to radiation by use of chemotherapy can be brought about by various mechanisms :

(1) Increasing initial radiation damage
(2) Inhibition of cellular repair
(3) Cell cycles redistribution
(4) Counteracting hypoxia-associated tumor radioresistance
(5) Inhibition of tumor cell repopulation

*Increasing initial radiation damage* Certain drugs such as halogenated pyrimidines,incorporate into DNA and make it more susceptible to radiation damage.

*Inhibition of cellular repair* Halogenated pyrimidines inhibit cellular repair.Nucleoside analogues like Gemcitabine, inhibit the repair of radiation-induced DNA and chromosome damage,

*Cell cycles redistribution* Taxanes can block transition of cells through mitosis with the result that the cells accumulate in the radiosensitive G2 and M phases of the cell cycle.Radiation delivered at the time of significant accumulation of cells in both these phases results in enhanced radioresistance of cells.

Elimination of the radioresistant S-phase cells by the chemotherapeutic agents may be another cell cycle redistribution strategy in chemoradiation therapy.Nucleoside analogues such as Gemcitabine incorporate into S-phase cells and eliminate them by inducing apoptosis.They thus induce the surviving cells to undergo parasynchronous movement to accumulate in the G2-M phases of the cell cycle between 1-2 days after drug administration.a time when the highest enhancement of tumor radioresponse is observed.

Tumors with a high cell growth fraction are likely to respond to cell cycles redistribution strategy.

*Counteracting hypoxia-associated tumor radioresistance* Most chemotherapeutic drugs preferentially kill proliferating cells ,which are primarily found in well-oxygenated regions of the tumor.Destruction of tumor cells in these areas leads to increased oxygen supply to hypoxic regions and hence reoxygenates hypoxic tumor cells.Massive loss of tumor cells after chemotherapy lowers the interstitial pressure which then allows re-opening of previously closed capillaries and re-establishment of blood supply.It also causes tumor shrinkage so that previously hypoxic areas are closer to capillaries and thus accessible to oxygen.Finally,by eliminating oxygenated cells,more oxygen becomes available to cells that survive chemotherapy.

Tumor reoxygenation is a major mechanism underlying the enhancement of tumor radioresponse induced by taxanes.

Another approach is use of bioreductive drugs like Tirapamazine that selectively kill hypoxic cells.

Agents like Misonidazole are also effective as they mimic the effect of oxygen and therby radiosensitize the hypoxic cells.

*Inhibition of tumor cell repopulation* Chemotherapeutic drugs can reduce the rate of repopulation when given concurrently with radiation therapy and thereby increase the effectiveness of the treatment.This is however limited by the poor specificity of most chemotherapeutic agents which causes enhanced toxicity of rapidly dividing normal tissues as well.

**ADVANTAGES AND DISADANTAGES OF DIFFERENT CHEMORADIATION SEQUENCING STRATEGIES:**

**Sequential chemoradiation:** It has least toxicity and maximizes systemic therapy.It allows smaller radiation fiels due to shrinkage of the tumor.On the other hand,it may lead to accelerated repopulation of tumor cells,leading to loss of therapeutic gain during radiotherapy.It also results in increase of total treatment time.

**Concurrent chemoradiation:** It shortens the treatment time and allows radiation enhancement by counteracting tumor cell hypoxia or cell cycles redistribution.On the other hand ,systemic therapy is compromised and there is also increased toxicity.

**Concurrent chemoradiation & adjuvant chemotherapy:** It maximizes systemic therapy and allows radiation enhancement.On the other hand,it leads to both increased toxicity and increased total treatment time.

**Induction chemotherapy & concomitant chemoradiation:** It maximizes systemic therapy and allows radiation enhancement.On the other hand,it leads to increased treatment time and also causes increased toxicity.

## EMERGING STRATEGIES FOR IMPROVEMENT OF CHEMORADIATION THERAPY:

(1) Increasing the anti-tumor efficacy of chemotherapy drugs
(2) Incorporation of molecular targeting
(3) Normal tissue protection

## MECHANISMS OF CHEMOTHERAPY-INDUCED RADIATION SENSITIZATION:

### *Platinum agents:*

(1) Inhibition of DNA synthesis
(2) Inhibition of transcription elongation by DNA interstrand cross-links
(3) Inhibition of repair of radiation induced DNA damage.

### *Taxanes:*

(1) Cellular arrest in G2-M phase of the cell cycle
(2) Induction of apoptosis
(3) Reoxygenation of tumor cells

### *Antimetabolites:*

(1) Nucleotice pool perturbation
(2) Lowering apoptotic threshold
(3) Cell cycles redistribution
(4) Tumor cell reoxygenation

### *Topoisomerase I inhibitors:*

(1) Inhibition of repair of radiation-induced DNA strand breaks
(2) Redistribution into G2 phase of cell cycles
(3) Conversion of radiation-induced single-strand breaks into double-strand breaks

***Gemcitabine:***

It is S-phase specific and its biological effect is almost completely due to its effects on DNA metabolism.It acts as follows:

(1) Decreases the amount of proliferation that can occur during fractionated radiotherapy
(2) By direct incorporation into DNA,they trigger the apoptotic response
(3) Inhibit cellular repair of radiation-induced damage
(4) By purging cells in the S-phase ,augments redistribution of cells into the radiosensitive G2 and M phases of the cell cycles.