

ROLE OF ALTERED FRACTIONATION & CHEMORADIATION IN HEAD AND NECK CANCER

What is conventional fractionation?

Radiation is given at doses of 1.8 to 2.0 Gy delivered once daily, 5 days weekly for 6 to 7 weeks.

4 Rs of Radiobiology:

Repair of sublethal damage
Reassortment of cells within the cell cycle
Repopulation
Reoxygenation

Basis of fractionation in radiotherapy:

Dividing a dose into a number of fractions spares normal tissues because of repair of SLD between dose fractions and repopulation of cells if the overall time is sufficiently long. At the same time dividing a dose into a number of fractions increases the damage to the tumor because of reoxygenation and reassortment of cells into radiosensitive phases of the cell cycles between dose fractions. The advantages of prolongation of treatment are to spare early reactions and to allow adequate reoxygenation in tumour. Excessive prolongation allows surviving tumor cells to proliferate during treatment.

Early responding tissues like skin, mucosa and intestinal epithelium, are triggered to proliferate within a few weeks of the start of a fractionate regime so that the extra dose to counter proliferation increases with time. On the other hand, conventional RT regimes are never long enough to allow the triggering of proliferation in late-responding tissues such as spinal cord. Therefore prolonging overall time within the normal radiotherapy range has little sparing effect on late reactions but a large sparing effect on early reactions.

Dose response curves for late responding tissues are more curved=shoulder is broader=repair capacity for early effects is more=higher α/β for early as compared to late effects.

This difference in response is due to the fact that in late responding tissues, fewer cells are in the radiosensitive G2-M phase or not in cycle at all whereas in early responding tissues many cells are in cycle and they rapidly cycle to G2-M phase.

Fraction size is the dominant factor in determining late effects and overall treatment time has little influence. By contrast fraction size and overall treatment time both determine the response of acutely responding tissues.

This is why hyperfractionation can be successful in H+N Ca because by breaking total dose into more fractions it ensures less late toxicity while allowing a larger tumoricidal dose (albeit at the expense of more acute toxicity).

Accelerated repopulation:

Treatment with any cytotoxic agent including RT can trigger surviving cells (clonogens) in a tumour to divide faster than before. This is known as accelerated repopulation. In H+N Ca, accelerated repopulation starts at 28 days after the initiation of fractionated RT. Normal clonogen doubling time is about 60 days which accelerates to 4 days only. A dose increment of 0.6 Gy per day is required to compensate for this repopulation. This is why accelerated RT is indicated in H+N Ca as accelerated repopulation can be prevented leading to greater local control (albeit at the expense of more acute toxicity).

Hyperfractionation:

In pure hyperfractionation the total dose and overall treatment time are unchanged but twice as many fractions are delivered by treating twice daily. This is unsatisfactory as reducing the dose per fraction would require increase in total dose. Hence impure hyperfractionation is more commonly practiced.

Here Total dose=increased

Overall treatment time=increased

Number of fractions=increased

Aim of hyperfractionation:

- (1) To reduce the late effects
- (2) To achieve same or better tumor control
- (3) To achieve same or slightly increased early effects.

Trial of hyperfractionated RT in H+N Ca (EORTC 22791):

Compared 80.5 Gy in 70 fractions (1.15 Gy twice daily) in 7 weeks with 70 Gy in 35 fractions in 7 weeks.

Local control was significantly improved from 40% to 59%.

Survival was also significantly improved.

There was no increase reported in late effects.

It was concluded that hyperfractionation confers an unequivocal advantage in treatment of oropharyngeal cancer.

Accelerated fractionation:

In pure accelerated fractionation total dose remains the same while overall treatment time is halved by giving twice the number of fractions by treating twice daily. In practise this is never possible as acute toxicities are limiting.

Hence impure accelerated fractionation is practiced either by giving a break during treatment or by reducing the total dose.

Aim of accelerated fractionation:

- (1) To reduce repopulation in rapidly proliferating tumors
- (2) To achieve little or no change in late effects.

Trial of accelerated fractionation in H+N Ca(EORTC 22851):

Compared 72 Gy in 45 fractions (1.6 Gy per fraction thrice daily) in 5 weeks with 70 Gy in 35 fractions in 7 weeks.

Locoregional control was increased 15%

Acute effects were increased (expected)

Late effects like myelopathy were also increased (unexpected)

Problem with accelerated fractionation:

- (1) If acute effects are very severe they may give rise to consequential late effects
- (2) If the gap between fractions is too small then there will be incomplete repair between fractions. This is basically because the time for SLD repair is largely hypothetical and cannot be accurately determined for individual tumours.

CHART

- Aims :** (1) To minimize late effects by using low dose per fraction
(2) To minimize tumor proliferation by using very short overall treatment time

In the 1st trial of CHART at Mount Vernon Hospital UK, 50.4 to 54 Gy were delivered in 36 fractions (1.4-1.5Gy per fraction thrice daily at 6 hour intervals) over 12 consecutive days.

Local control was good

Acute reactions were brisk but compliance was good as the acute effects peaked after completion of treatment. Also the acute reactions did not translate into late sequelae as the total dose was low.

Late effects did not in general increase and in some cases, were decreased.

An exception was the spinal cord. Severe myelopathies occurred at 50 Gy probably because the time between fractions (6 hours) was too short.

Why chemoradiation?

In the RTOG 90-03 trial the hyperfractionated and accelerated RT arms both gave a LC of 54% with no significant differences in DFS and OS.

Even the most effective RT regimes result in LC of 50-70% and DFS of 30-40%. This circumstance stimulated the investigation of treatments combining RT with chemotherapy.

CHEMORADIOTHERAPY

Goals:

- (1) To increase patient survival by improving locoregional tumor control
- (2) To decrease or 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 thereby 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 DISADVANTAGES OF DIFFERENT CHEMORADIATION SEQUENCING STRATEGIES:

Sequential chemoradiation: It has least toxicity and maximizes systemic therapy. It allows smaller radiation fields 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 cycle 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) Nucleotide pool perturbation
- (2) Lowering apoptotic threshold
- (3) Cell cycle 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.

Review of literature of chemoradiotherapy in H+N Ca:

Induction chemotherapy:

Induction chemotherapy was shown to be useful in achieving organ preservation without compromising overall survival in case of Ca larynx in the Veterans Administration Cooperative Group and EORTC studies.

However the biggest meta-analysis of chemotherapy in H+N Ca, namely the MACH-NC meta-analysis by Pignon et al showed that induction chemotherapy followed by definitive locoregional treatment provides no survival benefit compared with locoregional treatment alone. This was confirmed by the RTOG Intergroup trial R91-11. The Pignon meta-analysis also showed an overall benefit of using combined modality treatment of 8% particularly for use of concurrent multi-agent chemotherapy with EBRT.

Concurrent chemotherapy:

Summary of trials of single-agent chemotherapy synchronously with radiation:

Bleomycin was shown to significantly improve LC, DFS and OS in the NCOG but there was no improvement in the EORTC trial.

Methotrexate was shown to improve LC (significantly) and OS (NS) in the Christie Hospital study, particularly for Ca.Oropharynx.

Continuous infusion 5-FU was shown to improve LC ,DFS and OS (all NS) in the NCI Canada trial.

MMC was shown to improve LC (significantly) and survival (NS) in the Princess Margaret Hospital trial.

Summary of trials of multi-agent chemotherapy synchronously with radiation:

CDDP+ 5-FU improved the 3-year DFS (significantly) and OS (NS) in the Cleveland Clinic trial.

MMC+5-FU did not improve either LC or survival in the Princess Margaret Hospital study.

In a Spanish randomized trial PFS and OS were significantly worse for conventional RT alone as compared to conventional RT+5-FU or hyperfractionated RT (which were equally efficacious).

Alternating Radiation & Chemotherapy:

The NICT trial showed significantly improved 5-year DFS ,OS and LC in patients of unresectable H+N Ca treated by alternating CT+RT compared to conventional RT. There are no other randomized trials of alternating CT and RT.

Summary of trials of Altered Fractionation RT & Concomitant Chemotherapy:

The combination of 5-FU and Leucovorin with continuous RT significantly improved the LC and survival compared to alternating CT+RT in the University of Munich study.

MMC+ V-CHART significantly improved the LC and survival compared to V-CHART alone or conventional RT in the University of Vienna study.

Daily Cisplatin was shown to significantly improve the LC,DFS and OS compared to hyperfractionated RT alone in an Yugoslavian study.

MMC+5-FU was shown to significantly improve LC and survival in a German study.

CDDP+5-FU significantly improved the LC and OS compared to hyperfractionated RT alone in the Yale University study.

Summary of trial of Post-operative Chemoradiation:

NCI trial showed no benefit in terms of LC or OS from the addition of sequential CDDP+Bleo to EBRT in post-op patients of head and neck ca.

Intergroup study 0034 also showed no significant benefit in LC or OS in adding sequential CDDP+5-FU to EBRT in post-op patients of head and neck ca.

On the other hand the EORTC 22931 showed significantly improved DFS and OS in patients of post-op head and neck ca who received 3-weekly CDDP concomitantly with EBRT as compared to those who received EBRT alone.

CA oropharynx:

EORTC trial 22791 showed significantly improved LC (59% vs 40%) and overall survival in patients of CA.Oropharynx treated by hyperfractionated RT (115 cGy twice daily to 80.5 Gy in 7 weeks) compared to conventionally fractionated RT (200cGy daily to 70 Gy in 7 weeks).

Ca larynx:

In the Intergroup trial 91-11 induction CT-RT was compared with concomitant CT-RT and RT alone in patients of potentially resectable locally advanced Ca.larynx. No significant differences in laryngectomy-free survival or overall survival rates were seen in any arm. The time to laryngectomy was significantly better for the concomitant CT-RT arm compared with the induction CT-RT arm.

This confirms that concurrent chemoradiation therapy is the preferred therapy for potentially resectable locally advanced Ca. larynx when organ preservation is desired.

Ca nasopharynx:

In the Intergroup trial by Al-Sarraf et al patients of locally advanced Ca NPX received RT alone, RT + concomitant 3-weekly CDDP followed by adjuvant CDDP + continuous infusion 5-FU. In the concomitant arm the 3-year PFS (69% vs 24%) and OS (78% vs 47%) were significantly better.

Hence the recommended standard of care in treating patients with more advanced CA NPX has become concomitant chemoradiation.

Problems in comparing concomitant CT and/or altered fraction RT with conventional fractionated RT alone:

- (1) Trial of concomitant CT+RT have often used sub-optimal doses of EBRT in the control arm
- (2) It is difficult to quantify the contribution provided by concurrent CT in terms of delivery of an equivalent dose of RT.
- (3) It is difficult to compare trials of altered and conventionally fractionated RT as the durations of treatment are often very different ,hence the role of accelerated repopulation will vary.