

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.

5 Rs of Radiobiology:

Repair of sublethal damage

Reassortment /redistribution of cells within the cell cycle

Repopulation

Reoxygenation

Radiosensitivity

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 (slightly)

Overall treatment time=increased/same

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 practice 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.