THE RATIONALE BEHIND HYPOFRACTIONATED HIGH-DOSE INTENSITY-MODULATED RADIOTHERAPY IN PATIENTS WITH LOCALIZED PROSTATE CANCER: SHORT REVIEW

ZASADNOŚĆ HIPOFRAKCYJNEJ RADIOTERAPII DUŻEJ DAWKI Z MODULOWANĄ INTENSYWNOSCIĄ U PACJENTÓW Z RAKIEM STERCZA – KRÓTKI PRZEGŁĄD

Streszczenie

Zwiększające się możliwości techniczne spowodowały wzrost zainteresowania napromienianiem hipofrakcyjnym w leczeniu raka prostaty. Radiobiologia komórek nowotworowych raka prostaty pozwala na znaczną eskalację dawki użytego promieniowania.

Celem pracy było podkreślenie zwiększonej skuteczności terapii antynowotworowej przy zastosowaniu napromieniania hipofrakcyjnego.

H a s ł a: radioterapia – frakcjonowana radioterapia – nowotwór – prosta.

Summary

The use of improved technology has fostered increasing interest in hypofractionated radiation therapy for prostate cancer. There also is convincing evidence that an unusual aspect of prostate cancer radiobiology allow a different approach to dose escalation that is radiobiological in nature.

The aim of this paper is to explain the rationale behind hypofractionated high-dose intensity-modulated radiotherapy in patients with localized prostate cancer.

K e y w o r d s: radiation – hypofractionation – cancer – prostate.

Hypofractionation*

Hypofractionation, the delivery of radiation therapy with a dose per fraction > 2.0 Gy, was introduced in radiotherapy treatment in many oncological centres all over the world in the period between 1939 to the 1970’s. However, clinical studies conducted in the 70’s and 80’s revealed that these schedules were often associated with excessive late toxicity compared to standard fractionation schedules and as the result hypofractionation was abandoned in most centres. This negative experience grossly resulted from the over-estimation of tolerance doses in hypofractionated schedules arising from Ellis NSD formula [1].

Based on the improved physical dose distribution achievable with intensity modulated radiation therapy (IMRT),
there now is convincing evidence that biochemical control is improved with higher cumulative doses of radiation to the prostate. There is also a biological rationale for hypofractionation due to an unusual prostate tumour radiobiology that relates to prostate cancer’s high sensitivity to large fractions of radiation [2, 3].

Conventional fractionation schemes employ fraction sizes of 1.8–2.0 Gy based on the hypothesis that tumours typically are less responsive to fraction size (have higher $\alpha/\beta$ ratio) than are late-responding normal tissues (lower $\alpha/\beta$ ratio). The $\alpha/\beta$ ratio is a measure of fractionation response. A low $\alpha/\beta$ ratio is compatible with a greater capacity for repair between fractions, with an associated greater relative sparing with small fraction sizes, than for tumours with their typically higher $\alpha/\beta$ ratios. In those cases an improved therapeutic ratio is obtained with multiple small fractions for most types of tumours. For acutely responding tissues that express their damage within a period of days to weeks after irradiation, the $\alpha/\beta$ ratio values are in the range between 7–20 Gy, while for late responding tissues that express their damage months to years after irradiation, $\alpha/\beta$ ratios vary from 0.5 to 6 Gy [4, 5, 6]. Effective cell cycle time is often associated with fractionation response, with slowly proliferating normal tissues and some slowly proliferating tumours that display stronger fraction size responses (low $\alpha/\beta$ ratios). The reason for this difference might be explained by a hypothesis that the net $\alpha/\beta$ ratio of a cell population is determined by its age distribution. Hence, slowly proliferating tissues with a high preponderance of cells in $G_\text{S}$ will have a lower overall $\alpha/\beta$ ratio (and therefore higher relative sensitivity to large fractional doses) than proliferating tissues containing a significant proportion of cells in $G_\text{S}/M$ [7].

Analyses and reviews of clinical tumour response data revealed that prostate cancers have a higher sensitivity to fraction size, reflected in a low $\alpha/\beta$ ratio, than do late responding organs at risk such as the rectum or bladder [8, 9]. Brenner et al. conducted a study in which patients with prostate cancer were treated with a standard external beam course of treatment followed by high dose rate temporary implant boost doses which were escalated by decreasing fraction number from 3 to 2 and by increasing fraction size from 5.5 to 10.5 Gy [8]. Patients were grouped according to prognostic factors and biochemical control was formed versus equivalent dose as calculated via a linear quadratic model. The authors observed higher biochemical control rates with escalation of hypofractionation, consistent with an $\alpha/\beta$ ratio of 1.2. The advantage of this study was comparing several high dose rate brachytherapy schedules that differed only in the radiation fraction size [8].

Favouring the use of hypofractionation in prostate cancers can be illustrated through the linear quadratic equation that calculates the biologically effective dose (BED) for a given total dose (D), dose per fraction (d) and $\alpha/\beta$ ratio:

$$\text{BED} = D \left[1 + \frac{d}{\alpha/\beta}\right]$$

A low $\alpha/\beta$ ratio for tumour (less than for late responding normal tissue) predicts an improved therapeutic ratio with hypofractionation. If the ratio of biologically effective dose at an $\alpha/\beta$ ratio of 3 for late tissue toxicity versus 1.5 for tumour is considered as a form of therapeutic ratio, in this situation the ratio, readily calculated using the linear quadratic equation, increases significantly with fraction size (fig. 1) [10].

While the relationship is mathematically independent of total dose, the total dose needs to be accordingly limited to prevent excessive toxicities. Furthermore, if $\alpha/\beta$ ratios for prostate cancer and late normal tissue damage were equal, there would be no advantage or loss in predicted therapeutic gain from hypofractionation.

**Hypofractionation in a clinical setting**

Dose-per-fraction escalation schedules, as calculated using the linear quadratic equation, predict increase in tumour control while maintaining a constant, biologically effective Gy3 dose for late responding normal tissue (fig. 2). This type of hypofractionation design exploits the hypothesised radiobiological advantages discussed above. Biochemical freedom from disease (bNED) are estimated by calculating the equivalent doses if delivered in 2 Gy fractions ($\alpha/\beta = 1.5$) and determining the corresponding bNED values from the biochemical control versus dose data derived from Fowler et al. [11]. Total dose delivered decreases with increasing hypofractionation in order to maintain constant late effects [10]. An $\alpha/\beta$ ratio for prostate cancer lower than that for normal tissues provides the basis for improving tumour control without increasing late effect risk. If normal tissue and tumour $\alpha/\beta$ ratios were equal, tumour control would not improve with hypofractionation. However
Incomplete repair

The linear quadratic equation concludes that adequate time is allowed between fractions for complete repair of sublethal damage to take place after each dose. The full repair interval is at least 6 hours. The repair of damage caused by one radiation dose may not be completed before the next fraction is given if the interfraction interval is reduced below 6 hours. In these circumstances interaction between residual unrepaired damage from one fraction and the damage from the next fraction occurs. The influence of incomplete repair is determined by the repair halftime (T½) in the tissue. This is the time required between fractions or during low dose-rate treatment, for half the maximum possible repair to take place. Corrections are required for the consequent loss of tolerance as an incomplete repair reduce the isoeffective dose. The corrections can be achieved by the use of the incomplete repair model that was introduced by Thames in 1985 [4, 12]. In this model, the amount of unrepaired damage is expressed by a function Hm that depends on the number of equally spaced fractions (m), the time interval between them and the repair halftime. For the purpose of calculations the extra Hm term is added to the basic EQD2 formula:

$$\text{EQD}_2 = D \left[ d(1 + H_m) + \frac{\alpha}{\beta}\right] / 2 + \frac{\alpha}{\beta}$$

D is the total dose, d the dose per fraction, m is the number of fractions per day if repair from one day to the next is assumed to be completed [4].

Time factor

An increase in overall duration of fractionated radiotherapy usually causes greater repopulation of the irradiated tissues, both in the tumour and in early-reacting normal tissues. The time factor in radiotherapy is noticed to be more complex than had previously been assumed. For example, Denekamp reported in 1973 that the extra dose needed to counteract proliferation in mouse does not become meaningful until about 2 weeks after the start of daily fractionation [13]. In this situation, the time factor in the old Ellis NSD formula gives a wrong picture as it predicts a large amount of sparing if the overall time was increased from 1 to 12 days. The false time factors also underestimate the dose required to compensate for planned or unplanned gaps in treatment. The use of the linear quadratic equation model in clinical practice with no time factor at all seems to be ideal strategy for late-reacting tissues as any extra dose needed to counteract proliferation does not become meaningful until beyond the overall time of treatment, even up to 6 weeks. However for early reactions (and for tumour response) a correction for overall treatment time should be taken into consideration [4].

Concluding remarks

Specialized radiation therapy that delivers a high dose of radiation directly to the tumor may kill more tumor cells and cause less damage to normal tissue. The outcomes of several hypofractionation trials support the hypothesis that the α/β ratio for prostate cancer is low and that future treatment schedules are expected to emerge, based on the further trials such as randomized phase III trial CHHIP that is studying the side effects of different schedules of intensity-modulated radiation therapy and compares how well they work in treating patients with localized prostate cancer.

References


