Altered Fractionation

Benefits, Pitfalls With IMRT Dosimetry, and Combined Gains With Molecular Targeting

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1. INTRODUCTION

Fractionation deserves a second look in light of the explosive growth and development of radiation therapy. With the progress we have just seen in the manipulation and delivery of cytotoxic agents in conjunction with radiotherapy, there are now new avenues to explore as the classical dose and fraction size limits may no longer apply. Technological developments in physics, computing, and imaging over the past three decades culminated at the end of the 1990s in the ability to deliver elaborate 3D high-dose volumes to precisely defined targets. The traditional dose limits that are based on the tolerated dose to surrounding normal tissues may no longer be limiting since normal tissues are now avoided to a large extent. Can dose now be safely escalated using altered fractionation? Will the reduced toxicity also permit further exploration of concurrent chemotherapy with altered fractionation? Will molecular image-guided boosts to smaller subvolumes improve tolerance of “hotter” fractionation regimes? Breakthroughs in tumor biology have opened exciting new opportunities to develop specific molecularly targeted strategies to selectively enhance tumor response to radiation. With the nonoverlapping set of toxicities of these agents, can they be safely administered concurrently with more intense radiotherapy fractionation regimes?

To address these questions, a review of the results and indications of altered fraction would be useful. A survey of the key lessons may not only provide new ideas for combining these modalities to further improve the therapeutic ratio but should also underscore the key radiobiological principles that remain valid and useful in guiding everyday clinical decision making. This is especially pertinent in avoiding the potential disadvantage of the inevitable alteration of fractionation to some targets with the use of intensity-modulated radiation therapy (IMRT). Specifically, this review will summarize:

• The biological basis of altered fractionation: the reason(s) to expect an improved therapeutic ratio.
• The benefit of accelerated radiotherapy regimens.
• The benefit of hyperfractioned radiotherapy regimens.
• The combination of altered fractionation with concurrent chemotherapy.
• Critical fractionation issues to consider when IMRT is used:
  • Delivery of lower biologically effective dose to targets and lower probability of cure.
  • Prospect for improving the therapeutic ratio: dose escalations to targets without increased
dose to normal tissues.
  • Current standard of care.
  • Future directions: combining the gains of molecular imaging and molecular targeting with
  altered fractionation.

2. THE BIOLOGICAL BASIS OF ALTERED FRACTIONATION

Until a few years ago, the standard dose-fractionation schedule for primary treatment of
head and neck cancers in the United States was 70 Gy in 35 fractions once daily, 5 d per week
over 7 wk. Accelerated radiotherapy regimens administer the entire course in less than the
standard (7-wk) overall treatment time. Hyperfractioned radiotherapy regimens administer
a smaller dose (<2 Gy) per fraction over the same overall treatment time, usually by delivering
more than one fraction per day. Both regimes improve locoregional control in head and neck
squamous cell carcinoma (HNSCC). The biological mechanism of this is explained in Sub-
headings 2.1. and 2.2.

2.1. Accelerated Fractionation

Accelerated fractionation shortens the overall treatment time and improves outcome by
counteracting the “hazard of accelerated tumor clonogen repopulation during radiotherapy”
(1). As tumor regresses during the course of radiation, the clonogenic surviving cells begin to
proliferate more rapidly and reduce the overall net cytotoxicity of a fractionated course of
radiation. This is well described in an analysis by Withers et al. (1), who correlated tumor
control with overall treatment time in head and neck cancer. As duration of radiotherapy is
prolonged beyond 3–4 wk, the probability of local control decreases. Beyond this time the
effect of each additional day is equivalent to a loss of dose effectiveness of approx 0.6 Gy. This
was confirmed by a later analysis (2), which showed that the lag before accelerated tumor
clonogen may be less than 3 wk and that an extra 0.48 Gy/d is needed to compensate for this
effect. Conversely, if the treatment duration can be reduced from the classical 7 wk, an
improvement in outcome can be expected. However, to deliver treatment in less than 7 wk,
it is not possible to simply give the dose in larger daily fractions because of the adverse effect
of large fraction-size normal tissue late effects. Such effects on surrounding normal tissue are
dose limiting in radiation therapy. To keep the level of late effects acceptable, either the total
cumulative dose needs to be decreased, or a smaller dose per fraction may be given, as in the
concomitant boost schema. The improvement in the therapeutic ratio by accelerated fraction-
ation regimes is owing to the administration of the course of treatment in a time period short
enough to avoid the effect of accelerated clonogenic proliferation. The probability of tumor
control increases for a given total dose delivered in shorter treatment time. This leads to a
therapeutic gain since overall treatment time has little influence on the probability of late
normal tissue injury (when the fraction size is not increased and the interval between dose
fractions is adequate for repair of sublethal DNA injury) (3). However, when the overall
duration of treatment is markedly reduced, acute reactions become intolerable, and it is nec-
essary to reduce total dose or fraction size. Under these circumstances, a therapeutic gain is
realized only if the dose equivalent of regeneration of tumor cells exceeds the actual reduction
in dose required to keep acute reactions at a tolerable level (4).