The fractionation conundrum: Are we still missing a piece of the puzzle?

Dear Editor,

We read with interest the paper by Majumder *et al.*,[1] on altered fractionation in locally advanced head and neck squamous cell carcinoma (LAHNSCC). The study highlights several day-to-day issues faced in the clinic. The higher incidence of acute toxicities, the resultant reduction in compliance to treatment, and persistent dismal control rates has forced researchers to look beyond the standard of care, concurrent chemo-radiation (CTRT). In spite of the sound radiobiological basis behind the various altered fractionation (AF) schedules, their clinical implementation is arduous, especially in a high volume radiotherapy center.

Although, Majumder *et al.,* should be commended for their efforts; as not many studies have directly compared CTRT with AF; the study is rife with pitfalls. The authors are ambiguous about the statistical basis of selecting the sample size (though they mention this is a pilot study). Absence of data regarding the proportion of individual sub-sites, nodal stage, and relatively lesser stage IV disease (all of which are independent prognostic factors for local control) and the small sample size precludes any significant conclusions from the current study. Also, the authors chose a nonstandard chemotherapy schedule of administering weekly Cisplatin on a weekend. More than half the study population in all the arms had taken a longer time to complete treatment, which might have had an adverse impact on tumor control. The higher incidence of neutropenia in the accelerated fractionation arm in the absence of concurrent chemotherapy is also enigmatic. Comparative response rates at 6-8 weeks (rather than 6 months), differential primary and node response would have been informative.

Both CTRT[2] and AF[3-6] have been proven to be beneficial over conventional radiation alone. Furthermore, as demonstrated by the Meta-Analysis of Radiotherapy in Carcinomas of Head and neck (MARCH) Collaborative Group,[6] the survival benefit due to hyper-fractionated radiotherapy, corresponds to an absolute benefit of 8% at 5 years, and is of the same size as the effect due to the use of concurrent chemotherapy. Also, addition of concurrent chemotherapy to AF schedules has not resulted in gain in therapeutic ratio.[7] A recently published trial[8] compared a hybrid accelerated fractionation schedule (concomitant boost technique) with CTRT; acute toxicity (except for grade 3 mucositis and dermatitis), xerostomia and quality of life were worse in the CTRT arm with similar 2 year disease free survival rates in both the arms.

Given the current evidence, CTRT continues to remain the standard of care in LAHNSCC; patients unsuited for concurrent chemotherapy can be offered radiation therapy alone with one of the AF schedules (hyper fractionation or concomitant boost being preferred). Intensity Modulated RT (IMRT) has been to shown to reduce both acute and late toxicities in comparison to more conventional techniques. As toxicity profile has been the major detriment of combining AF and concurrent chemotherapy, it is to be seen if the combination with IMRT would tilt the balance favorably towards this approach.

Collaborative efforts within the oncology community culminating in larger studies and longer follow-ups are the need of the hour in establishing the optimal treatment of this impasse.

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