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Final Report of Radiation Therapy Oncology Group Protocol 9003: Provocative, but Limited Conclusions From Exploratory Analyses

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It is disconcerting when the benefits seen in a published positive prospective phase 3 randomized controlled trial are not confirmed in longer-term follow-up. The mature results of Radiation Therapy Oncology Group (RTOG) protocol 9003 recently reported by Beitler et al (1) are a case in point. These results have led to ongoing debate about the benefits of different schedules of altered fractionation (AFX) for definitive radiation therapy (RT) in patients with head and neck squamous cell cancer (HNSCC). We suggest that this is due at least in part to overinterpretation of the data from RTOG 9003 in the context of contemporary best practice.

In assessing what conclusions can be drawn from the long-term results of RTOG 9003, a major change that cannot be ignored since the original report was published in 2000 is that we have moved from older 2-dimensional/3-dimensional (2D/3D) treatment planning and delivery to the now gold standard of intensity modulated radiation therapy (IMRT). IMRT is more time consuming and costly to plan, generally requires longer delivery time, and has a higher fractional delivery cost than 2D/3D. Because the hyperfractionation (HFX) schedule used in RTOG 9003 requires 68 fractions per 7 weeks of twice-daily (BID) RT, and AFX-C (continuous) 12 BID days and a second IMRT plan, it is simply not logistically or economically feasible in most centers to use these fractionation schedules routinely in the current context of IMRT. What lessons, then, from RTOG 9003 can we apply to current practice?

In RTOG 9003 the 2-year locoregional control (LRC) was 45.7%, 55.3%, and 53.8% for the standard fractionation (SFX), HFX, and accelerated fractionation-continuous arms, respectively. Long term, the cumulative incidence of 5-year locoregional failure for HFX and accelerated fractionation-continuous schedules was 6.5% and 6.6%, respectively. In the original report both HFX and AFX-C were proclaimed LRC winners over SFX. In the final report the multivariate hazard ratio for the cumulative incidence of locoregional failure was

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0.81 for both HFX and AFX-C, as evidenced visually by superimposed curves in Figure 1a in Beitler et al (1) as compared with the SFX curve. Table 1 in Beitler et al (1) shows that on both univariate and multivariate analysis, neither of these differences remained statistically significant compared with SFX when all follow-up data were analyzed.

The final report also included unplanned statistical analyses and the censoring of events after 5 years, with the justification that 97% of the failures occurred in the first 5 years. When this was done, only the gains with HFX for LRC and overall survival (OS) remained statistically significant compared with SFX. Although censoring at 5 years is reasonable for LRC, it is clearly not for OS, because the survival curves again become superimposed by 7 years (Fig. 2 in Beitler et al [1]). There also seems to be a visual difference between SFX and AFX-C, but disappointingly, the confidence interval for neither study arm is given. The difference in hazard ratio effect size of <3% for each compared with SFX is marginal, representing only approximately 5 events, and is not clinically meaningful.

Our assessment of the presented RTOG 9003 data and related subsequent publications leads to the following observations and conclusions.

1. First, the RTOG began to study AFX, especially HFX, in the 1970s. The group started a prospective, phase 3 study in 1979 (RTOG 7913) in which HFX (albeit limited to a total dose of 60 Gy) was not better than SFX (2). This was followed by a prospective dose-escalation trial, RTOG 8313, that brought to light the importance of the interfraction interval (3, 4). The RTOG then took a cautious, ethical approach in building a sound basis to evaluate AFX safely in its prospective, multi-institution, randomized 9003 trial.
2. Second, RTOG 9003 achieved its planned goal, showing that HFX and AFX-C significantly improved LRC as compared with SFX at 2 years. With longer follow-up, HFX and AFX-C both showed persisting but numerically smaller improvements in LRC, which at best approach statistical significance, compared with SFX, but *only* if long-term (>5-year) data are ignored, and in the context that the confidence intervals include unity (Table 1 in Beitler et al [1]).
3. Third, HFX seems to show a small numerical advantage over AFX-C in OS at 5 years, but the curves rejoin at 7 years.

It is clear that any long-term differences among the AFX regimens studied and SFX in the final report of 9003 are small. Specifically, the surety of the conclusion that HFX significantly improves OS shows an interpretive confidence with which we disagree. Although it is legitimate to truncate data for LRC, we believe it is imprudent to do for survival outcomes *when the actual event data are available*. Although most cancer events occurred by 5 years, deaths attributable directly or indirectly to late toxicities (such as chronic aspiration) may also occur in the next 2 years (5). This is when the curves rejoin.

There is a suggestion that late higher-grade toxicities, including feeding tube requirement, may be worse in both 6-week regimens (accelerated fractionation, continuous [AFX-C] and accelerated fractionation with split [AFX-S]) when pooled together and compared with the 7-week regimens (SFX and HFX) pooled together. The *P* values are not significant, and

pooling introduces potential bias, so this is hypothesis generating. Of course, if accelerated regimens do result in greater late toxicities, then the therapeutic ratio would favor HFX.

In the broader context of the AFX literature, various different schedules of AFX have shown a benefit in local control, and perhaps survival, over SFX. A meta-analysis of trials completed before 2006 favors HFX (6–15). Thus, HFX may be the preferred choice for RT alone using 2D/3D treatment planning and delivery. However, as noted previously, HFX is not logistically or economically feasible for most centers when IMRT is used, as acknowledged by the main protagonists of HFX: “When IMRT is used ... we prefer the concomitant boost schedule for logistical purposes” (16). Although at the MD Anderson Cancer Center we have used the concomitant boost (AFX-C) schedule, we find that the accelerated 6-week Danish Head and Neck Cancer Study Group (DAHANCA) regimen (single plan and only 5 BID days) is the most practical form of IMRT AFX, as demonstrated by the rapid accrual and high compliance in the multi-institutional RTOG 0522 (17) and 1016 trials.

Another significant factor that must be considered in the context of optimized AFX is that the standard of care for treatment of advanced HNSCC is now concurrent chemoradiation therapy. Whether RT fractionation is as relevant in combined treatment remains unclear. The results of Groupe d’Oncologie Radiothérapie Tête Et Cou (GORTEC) 99-02 (11) and RTOG 0129 (18) both showed no benefit or even a worsening of the therapeutic ratio with accelerated fractionation in the concurrent chemotherapy setting for which SFX is standard. Whether the combination of HFX with concurrent chemoradiation therapy would have yielded different results is conjectural. One small study showed a nonsignificant benefit of HFX plus chemotherapy versus HFX alone (19), but no study comparing HFX plus chemotherapy versus SFX plus chemotherapy has ever been done.

The role of AFX alone in the treatment of advanced HNSCC is, therefore, no longer a pressing issue. No additional studies will likely be done to tease out fine differences between LRC, OS, and late toxicity in the AFX regimens studied in RTOG 9003. This study has, however, emphasized the importance of collecting long-term toxicity and functional data. For now, AFX-C, DAHANCA, or HFX all seem to be acceptable alternatives for patients with intermediate-stage tumors who might benefit from the small gains in local control imparted by single-modality AFX. Of these, DAHANCA is most compatible with IMRT, though practitioners who wish to limit toxicity as much as possible may prefer HFX, even though a toxicity benefit is not absolutely proved. Patients with higher-risk, especially P16-negative, cancers require concurrent chemoradiation, in which SFX is the current standard of care (11, 18).

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