International Journal of
Radiation Oncology
biology • physics

www.redjournal.org

EDITORIAL

Acceler-Dated Fractionation: The End of the Era of the Large, "One Size Fits All" Trial for Locally Advanced Head and Neck Cancer

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Received Jan 21, 2014, and in revised form Jan 23, 2014. Accepted for publication Jan 25, 2014.

Repair, accelerated repopulation, reoxygenation, and reassortment (cell cycle) are the 4 tenets of classical radiation biology. They form the cornerstones for designing and optimizing radiation fractionation schemas in head and neck squamous cell carcinoma, particularly locally advanced head and neck cancer (LAHNC), in the past century. Accelerated fractionation targets tumor repopulation, whereas classical hyperfractionation aims to increase the total dose while taking advantage of normal tissue repair. Because of the scientific rationale and positive results reported in the literature (1), the Radiation Therapy Oncology Group (RTOG) launched RTOG 9003, one of the largest randomized trials in LAHNC ever performed. This study tested 3 altered fractionation regimens against standard fractionation RT alone (SFX) (1).

Early results of the trial showed that both hyperfractionation (HFX) and accelerated fractionation with concomitant boost (AFX-C) yielded significantly better locoregional control (LRC) and a trend for improved disease-free survival compared with SFX (1). Both were associated with more acute toxicity but without a significant increase of physician-assessed late effects. In this latest update of RTOG 9003 (Beitler et al, this issue [2]), only HFX remained significantly associated with improved LRC, although a trend for higher LRC was still noted for AFX-C. Composite severe grade 3 to 5 late toxicity appeared to trend higher for 6 versus 7 weeks of treatment, although the difference was not statistically significant. Patient-reported outcomes were not included in RTOG 9003.

What have we learned from the long-term update of RTOG 9003? First, the study confirms that late failures are uncommon in this population. Only 31 additional LRFs were recorded between the last report (data cut-point August 1999) and the current report (October 2012), justifying the practice of censoring the locoregional failure endpoint at 5 years. Beyond 5 years, a large number of deaths occurred from causes other than the original cancer; therefore, overall survival curves showed no significant benefit to altered fractionation over standard fractionation. This confirms data from meta-analyses showing that the benefit from altered fractionation over SFX is modest, smaller than the benefit from concurrent chemoradiation therapy (CCRT), with the exception of pure HFX (3). In an unselected population of LAHNC, accelerated fractionation alone, even with dose escalation, is probably inferior to CCRT; randomized trials from Groupe Oncologie Radiotherapie Tete Et Cou (GORTEC) and the German Cancer Society would appear to confirm that (4, 5). Finally, late toxicity continues to plague our patients. Approximately 8% (13 of 166) of 5-year survivors without disease are dependent on feeding tube use. An exploratory analysis suggested that 6-week (accelerated) treatment courses had greater late toxicity than 7-week

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This work was supported by grants RTOG U10-CA21661 and CCOP U10-CA37422 from the National Cancer Institute. This contents of this article are the sole responsibility of the authors and do not necessarily represent the official views of the National Cancer Institute.

Conflict of interest: none.

Int J Radiation Oncol Biol Phys, Vol. 89, No. 1, pp. 7–9, 2014
0360-3016/$ - see front matter
http://dx.doi.org/10.1016/j.ijrobp.2014.01.045

treatment courses. Although late toxicity in RTOG 9003 appears to be somewhat lower than after CCRT, the rates are still considerable.

Given the LRC benefit of CCRT and altered fractionation and the survival benefit of CCRT, the next question is whether further gains can be achieved by combining both strategies. This was addressed in GORTEC 9902, where accelerated radiation therapy (70 Gy in 6 weeks) plus 2 cycles of concurrent carboplatin-fluorouracil was compared with SFX (70 Gy in 7 weeks) plus 3 cycles of concurrent carboplatin-fluorouracil. AFX plus concurrent chemotherapy was not better; in fact, the highest survival rate was noted for the SFX plus chemotherapy arm (4). Similarly, RTOG 0129 compared SFX plus 3 cycles of high-dose cisplatin to an experimental arm of AFX-C plus 2 cycles of cisplatin (6). At a mean follow-up of 7.9 years, there was no demonstration of improved outcome for any endpoint (7). Although AFX-C for 1 week may have compensated for the lower total cisplatin dose, accelerated RT plus concurrent chemotherapy was not shown to be superior to SFX plus concurrent RT. On the basis of these data, it is unlikely that future trials will compare various radiation fractionation schedules during CCRT in unselected groups of patients. Individual clinicians may opt to use AFX-C with slightly less chemotherapy than SFX plus a full-course chemotherapy, but they should recognize that this is primarily for logistical reasons rather than improved outcomes.

Where are we going from here with regard to LAHNC? Recent advances in molecular biology and next-generation sequencing have taught us much about these tumors. We know now that there is a growing entity of human papilloma virus (HPV)-related oropharyngeal carcinomas (OPC) and that these have a better prognosis than other LAHNC (6). Many HPV-positive OPCs respond well to standard chemoradiation therapy and may warrant treatment deescalation (in the setting of clinical trials). This may include altered fractionation RT alone, or with less intense concurrent systemic therapy.

In addition, analogous to breast cancer, head and neck squamous cell carcinoma (HNSCC) might soon be classifiable into different subtypes (classical, mesenchymal, basal, and atypical) with different behaviors based on their gene expression profiles (8). We are also learning that tumor behavior is often influenced by the tumor microenvironment and the immune function within the tumor and the host (9). Moreover, certain tumors have mutations (such as FGFR2-3 and PIK3K mutations) and aberrant pathway function (such as the PIK3K pathway) that may in the future be successfully targeted pharmacologically (10-12).

On the basis of this newfound knowledge, risk stratification using a combination of clinical and biological features now forms the corner stones of RTOG clinical trials for HNSCC. As previously mentioned, for certain good risk HPV-positive OPCs (small-size T1-T3 tumors with limited nodal involvement in patients with no or minimal smoking history), the goal is for treatment de-intensification to minimize late toxicity while maintaining an outstanding cure rate. Clinical trials are being designed to address this intent. For the intermediate-risk HPV-positive tumors (large T3-T4 tumors or with extensive nodal involvement or in patients with >10 pack-years of cigarette use), the disease progression rate is still high (32% at 5 years for RTOG 0129 and 0522) (6, 13). In these patients, the addition of an immune check point inhibitor (eg, against CTLA4 or PD1) to CCRT has the theoretical benefit of overcoming the immune exhaustion that is often seen in these patients (14) while eliciting antitumor immune response to antigens that are unmasked by RT (15).

Immune checkpoint targeting may likewise benefit patients with HPV-negative LAHNC because immune dysfunction is common in these patients (16). In addition, targeting a specific active pathway or mutation in combination with CCRT may benefit the subsets of patients harboring such defects. Novel approaches at DNA damage, such as poly(ADP-ribose) polymerase inhibition, may be an option for patients who do not have an obviously "actionable" molecular target. However, it must be kept in mind that many HPV-negative HNSCC patients are frail, and any treatment intensification needs to take into account the potential for severe acute and late treatment-related toxicity.

In summary, we are approaching a new paradigm in the management of SCCHN. Altered fractionation alone may continue to play a role in small groups of patients such as those who cannot tolerate concomitant chemotherapy or those with good risk HPV-positive tumor enrolled on clinical trials. The remaining patients will be partitioned into different risk groups on the basis of clinical and biological features and will be treated with different strategies. New treatment paradigms need to take into consideration the late toxicity profile that may be experienced by our patients and new research to mitigate such late toxicity is needed to improve the quality of life in long-term survivors.

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