Published in final edited form as:

Int J Radiat Oncol Biol Phys. 2014 October 01; 90(2): 253–254. doi:10.1016/j.ijrobp.2014.07.022.

RTOG 90-03: Legacies of a Landmark Trial

Andy Trotti, MD [Professor] and

College of Medicine, University of South Florida, Senior Member, Moffitt Medical Group,
Department of Radiation Oncology, H Lee Moffitt Cancer Center, 12902 USF Magnolia Drive,
MCC-RAD ONC, Tampa, FL 33612. Phone: 813-745-3547 FAX: 813-745-7231
andy.trotti@moffitt.org

Mitchell Machtay, MD [Professor and Chair]

Department of Radiation Oncology, Case Western Reserve University School of Medicine,
Seidman Cancer Center, University Hospitals Case Medical Center, 11100 Euclid Ave.,
Cleveland, OH 44106. Phone: 216-844-2530 FAX: 216-844-4799,
Mitchell.machtay@uhhospitals.org

Designed almost 20 years ago, the RTOG 90-03 head and neck fractionation trial is an important accomplishment that continues to influence current practice and current trial design.

RTOG 90-03 compared conventional fractionation to 3 altered fractionation schemas: concomitant boost (AFX-C), developed by Fletcher and colleagues at MD Anderson, split-course accelerated, by C.C. Wang at Mass General, and hyperfractionation (HFX). Hyperfractionation originated in Paris by Regaud [2]. It was tested by a number of centers and organizations including the EORTC and RTOG. Marcial and Cox conducted the first prospective clinical trials (RTOG 79-13 and 83-13) of (HFX) [3,4].

The hyperfractionation schedule used in 90-03 contains as much acceleration as several other altered schedules that do not use lower dose per fraction. It has an added feature of 6–12% total dose escalation. This extra dose may explain why HFX has a slightly better hazard ratio (0.79) than AFX-C (0.82) in the 9003 analysis. It should be noted that RTOG 90-03 was not designed for a direct statistical comparison between HFX and AFX-C. However, considered within the contemporary context of IMRT, cost, convenience, statistical design and power, we believe both are acceptable schedules in 2014.

A clinical trial tests a specific hypothesis. The outcome is a rigorously tested treatment which may or may not be clinically practical or preferred at the time the data are published. RTOG also tested HFX in T2 vocal cord cancer [5]. Once again, HFX was the "winner", but

Correspondence to: Andy Trotti.

Publisher's Disclaimer: This is a PDF file of an unedited manuscript that has been accepted for publication. As a service to our customers we are providing this early version of the manuscript. The manuscript will undergo copyediting, typesetting, and review of the resulting proof before it is published in its final citable form. Please note that during the production process errors may be discovered which could affect the content, and all legal disclaimers that apply to the journal pertain.

Conflict of Interest: none

a more practical hypofractionation schedule (225 cGy per fraction) has been adopted by practitioners [6].

RTOG has also tested sensitizers with accelerated fractionation by concomitant boost (RTOG 9914, 0129). In 2006, meta-analyses of fractionation indicated several different schedules of altered fractionation could produce similar superior results [8]. The DAHANCA schedule of six fractions per week was adopted for RTOG 0522 as the new standard altered fractionation backbone of RTOG trials [9]. It is IMRT-adaptable, facilitates sensitizers, convenient and less costly than hyperfractionation. Thus, altered fractionation is now fully integrated into combined modality trials of unresected disease.

All RTOG trials are designed and conducted foremost with the ethical and scientific principle of equipoise: we have no a priori knowledge of the outcome. Distinct from single institution retrospective chart reviews, our trials and data are prospectively vetted by numerous scientific and ethics bodies at a national and local level. We conduct our studies in a completely open and broad scientific forum. No one person or group controls the data or interpretation thereof. Any member of RTOG can propose and potentially lead a trial that addresses important questions regarding fractionation or combined modality treatments.

The long-term outcomes of RTOG 9003 affirms RTOG contributions to the evolution of fractionation in both clinical practice and trial design. This is accomplished through the efficient use of resources provided largely by a system of highly dedicated volunteers. Landmark trials like RTOG 9003, 91-11 (larynx preservation) and 0129 (AFX-C with sensitizer) have helped define today's standards of care for the majority of H&N cancers in the US and abroad [10]. We continue to conduct innovative trials fully integrating altered fractionation including the current trial for HPV-related cancers [11].

References

1. Feigenberg S, Patel K, Amdur RJ, et al. Rtog 90-03: The untold story. Red. In Press.
2. Foray N. Claudius regaud (1870–1940): A pioneer of radiobiology and radiotherapy. Cancer radiotherapie : journal de la Societe francaise de radiotherapie oncologique. 2012; 16:315–321. [PubMed: 22818408]
3. Marcial VA, Pajak TF, Chang C, et al. Hyperfractionated photon radiation therapy in the treatment of advanced squamous cell carcinoma of the oral cavity, pharynx, larynx, and sinuses, using radiation therapy as the only planned modality: (preliminary report) by the radiation therapy oncology group (rtog). Red. 1987; 13:41–47.
4. Cox JD, Pajak TF, Marcial VA, et al. Dose-response for local control with hyperfractionated radiation therapy in advanced carcinomas of the upper aerodigestive tracts: Preliminary report of radiation therapy oncology group protocol 83-13. Red. 1990; 18:515–521.
5. Trotti A, Zhang Q, Bentzen SM, et al. Randomized trial of hyperfractionation versus conventional fractionation in t2 squamous cell carcinoma of the vocal cord (rtog 9512). Red. In Press.
6. Chera BS, Amdur RJ, Morris CG, et al. T1n0 to t2n0 squamous cell carcinoma of the glottic larynx treated with definitive radiotherapy. International journal of radiation oncology, biology, physics. 2010; 78:461–466.
7. Newlin HE, Amdur RJ, Riggs CE, et al. Concomitant weekly cisplatin and altered fractionation radiotherapy in locally advanced head and neck cancer. Cancer. 2010
8. Bourhis J, Overgaard J, Audry H, et al. Hyperfractionated or accelerated radiotherapy in head and neck cancer: A meta-analysis. Lancet. 2006; 368:843–854. [PubMed: 16950362]

9. Overgaard J, Hansen HS, Specht L, et al. Five compared with six fractions per week of conventional radiotherapy of squamous-cell carcinoma of head and neck: Dahanca 6 and 7 randomised controlled trial. *Lancet*. 2003; 362:933–940. [PubMed: 14511925]
10. Network NCC. Nccn guidelines. 2014.
11. Trotti, A., Gillison, ML. Radiation Therapy Oncology Group. 2013. Phase iii trial of radiotherapy plus cetuximab versus chemoradiotherapy in hpv-associated oropharynx cancer, vol. 2013. RTOG 1016 Protocol