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Comparing Intensity-Modulated Proton Therapy With Intensity-Modulated Photon Therapy for Oropharyngeal Cancer: The Journey From Clinical Trial Concept to Activation

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Intensity-modulated proton therapy minimizes the incidental irradiation of normal tissues in patients with head and neck cancer relative to intensity-modulated photon (x-ray) therapy and has been associated with lesser treatment-related toxicity and improved quality of life. A phase II/III randomized trial sponsored by the US National Cancer Institute is currently underway to compare deintensification treatment strategies with intensity-modulated proton therapy vs intensity-modulated photon (x-ray) therapy for patients with advanced-stage oropharyngeal tumors. After significant input from numerous stakeholders, the phase III portion of the randomized trial was redesigned as a noninferiority trial with progression-free survival as the primary endpoint. The process by which that redesign took place is described here.

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Introduction

Identifying the most appropriate primary endpoint may be the most important feature in the design of any clinical trial. The primary endpoint forms the basis or metric for assessing efficacy within study arms and for planned comparisons of efficacy between study arms. Once that endpoint is established, design considerations ensue in congruence with the various options regarding the phase of the clinical trial.[1] Ideally, the clinical trial design provides investigators with the ability to evaluate their primary objective in an unbiased manner, thus adding confidence to the acquired results.

The Department of Radiation Oncology at The University of Texas MD Anderson Cancer Center, under the aegis of a multi-institutional NIH/NCI-sponsored U19 cooperative agreement (2U19CA021239-35) with the Massachusetts General Hospital and IROC St. Louis, proposed a study to evaluate a potentially less toxic deintensification approach for delivering conformal radiation therapy to patients with cancer of the oropharynx. This approach involves the use of intensity-modulated proton therapy (IMPT), which is thought to reduce or eliminate the incidental irradiation of normal tissues associated with intensity-modulated [photon or x-ray] radiation therapy (IMRT) (Fig. 1).

Preliminary support for this concept came from dose distribution analyses that consistently showed superior dosimetry with IMPT for the treatment of head and neck cancers compared with IMRT[2-4] and from retrospective comparisons suggesting clinical benefits.[5-7] As for prospective evidence, the first 50 patients with oropharyngeal cancer (OPC) treated with IMPT experienced no grade 4 or 5 toxicity, and the 2-year actuarial rates of overall survival (OS) and progression-free survival (PFS) were 94.5% and 88.6%.[8] Also, a 1:2 case-matched control analysis of IMPT vs IMRT for OPC at MD Anderson revealed no significant differences in OS (hazard ratio (HR) = 0.55, 95% CI: 0.12-2.50, $P = 0.44$) or in PFS (HR = 1.02, 95% CI: 0.41-2.54, $P = 0.96$) between patients treated with IMPT vs IMRT. Third, a report of patient-reported outcomes (PROs) after IMPT vs IMRT for OPC,[9] obtained with the MD Anderson Symptom Inventory for Head and Neck Cancer (MDASI-HN) module, compared symptoms before treatment (baseline), during treatment (acute phase), within the first 3 months after treatment (subacute phase), and afterward (chronic phase). The 5 most common symptoms were found to be problems with food taste (mean score 4.91 on a 0-10 scale), dry mouth (4.49), swallowing or chewing (4.26), lack of appetite (4.08), and fatigue (4.00). Among the top 11 symptoms, changes in taste and appetite during the subacute and chronic phases favored the use of IMPT (all $P < 0.05$). During the subacute phase, the mean (±standard deviation) for the top 5 MDASI scores were 22% lower among patients who received IMPT (5.15 ± 2.66 for IMPT vs 6.58 ± 1.98 for IMRT, $P = 0.01$).

Despite this early evidence, irrefutable demonstration of the clinical superiority of proton therapy with level 1 evidence has yet to be accomplished. When the concept for the U19-supported clinical trial comparing IMPT with IMRT for OPC was developed, by consensus the main outcome of interest was the cumulative incidence of late-onset grade ≥3 treatment-related toxicity (scored according to the National Cancer Institute's Common Terminology Criteria for Adverse Events [CTCAE]) during the 2 years after completion of radiation

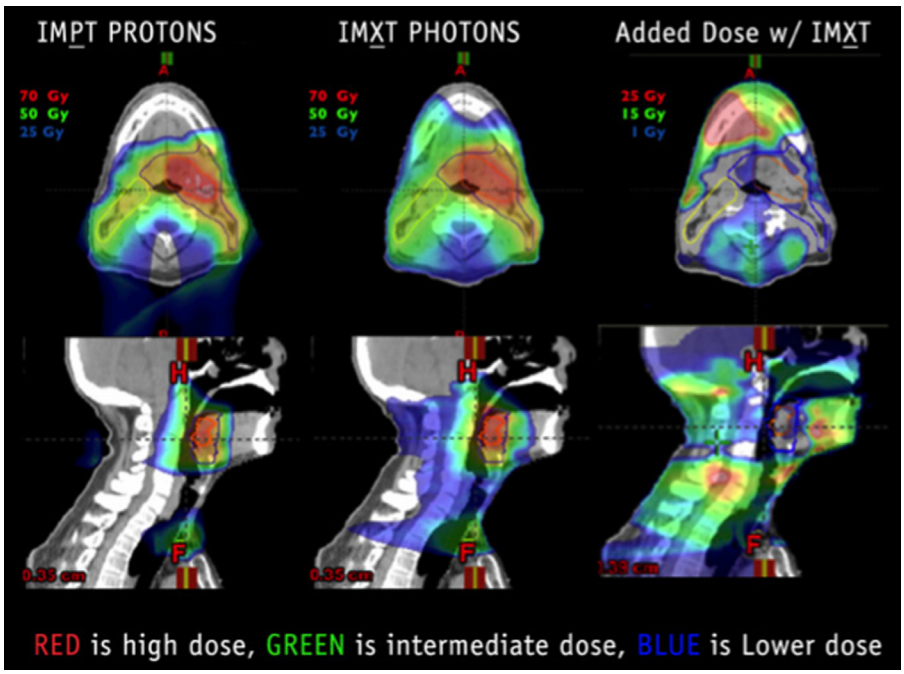

Figure 1 Axial (top) and sagittal (bottom) views of treatment plans used to assess dose distributions associated with intensity-modulated proton therapy (IMPT) (left) and intensity-modulated photon (x-ray) radiation therapy (IMXT) (middle). The images at right illustrate the additional dose associated with IMXT relative to IMPT. (Color version of figure is available online.)