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Head and neck cancer

Adaptive radiotherapy for head and neck cancer—Dosimetric results from a prospective clinical trial

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ABSTRACT

Purpose: To conduct a clinical trial evaluating adaptive head and neck radiotherapy (ART).
Methods: Patients with locally advanced oropharyngeal cancer were prospectively enrolled. Daily CT-guided setup and deformable image registration permitted mapping of dose to avoidance structures and CTVs. We compared four planning scenarios: (1) original IMRT plan aligned daily to marked isocenter (BB); (2) original plan aligned daily to bone (IGRT); (3) IGRT with one adaptive replan (ART1); and (4) actual treatment received by each study patient (IGRT with one or two adaptive replans, ART2).
Results: All 22 study patients underwent one replan (ART1); eight patients had two replans (ART2). ART1 reduced mean dose to contralateral parotid by 0.6 Gy or 2.8% (paired *t*-test; $p = 0.003$) and ipsilateral parotid by 1.3 Gy (3.9%) ($p = 0.002$) over the IGRT alone. ART2 further reduced the mean contralateral parotid dose by 0.8 Gy or 3.8% ($p = 0.026$) and ipsilateral parotid by 4.1 Gy or 9% ($p = 0.001$). ART significantly reduced integral body dose.
Conclusions: This pilot trial suggests that head and neck ART dosimetrically outperforms IMRT. IGRT that leverages conventional PTV margins does not improve dosimetry. One properly timed replan delivers the majority of achievable dosimetric improvement. The clinical impact of ART must be confirmed by future trials.

Intensity modulated radiotherapy (IMRT) techniques can spare normal head and neck tissues such as salivary glands, larynx, oral cavity, and spinal cord [1,2]. Emerging institutional data suggest promising locoregional tumor control, as well as potential preservation of salivary function, swallowing, and quality-of-life [3–6]. IMRT utilizes 3D anatomic information extracted from imaging acquired days prior to treatment. However, the geometry of tumor and normal structures changes significantly during treatment due to positioning uncertainties and tissue responses [7–9].

Our clinical experience has taught us that IMRT continues to cause severe acute oral and pharyngeal side effects [10]. It is reasonable to conclude that much of IMRT's potential ability to reduce toxicity remains unrealized if it is statically guided by pre-treatment imaging.

Adaptive radiotherapy (ART) is a conceptually attractive approach to correct for daily tumor and normal tissue variations. Current ART approaches depend on in-room megavoltage CT [11], CT-on-rails [7,12], or cone-beam CTs [13] obtained prior to daily treatment. Limited preclinical work exists to guide development for head and neck ART, and little practical experience in patients has been described.

This report presents dosimetric analysis from a recently reported pilot clinical trial prospectively evaluating clinical delivery of head and neck ART [14], with direct comparison of ART to standard image-guided IMRT.

Methods

Patient cases

Nineteen patients with histologically proven squamous cell carcinoma of the oropharynx were enrolled between 10/2007 and 9/2009 onto a prospective clinical trial approved by the M.D. Anderson Cancer Center Investigational Review Board (#2006-0947). Three additional patients treated off-protocol with identical daily imaging and off-line ART during a run-in period were also included in this dosimetric analysis.

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IMRT planning

Baseline planning was performed on an ADAC Pinnacle[3] (Philips Medical Systems, Andover, MA) system as described previously [14] using our institutional standard for volumetric CTV-to-PTV expansion of 3–4 mm.

Hybrid online IGRT-offline ART

Our in-room image-guided ART system had two levels of adaptation. First, on-line correction was performed prior to each treatment to align target volumes relative to treatment beams using simple couch shifts. A total of 722 daily CT-on-rails image sets were taken, as well as 2 cone-beam CTs acquired when the CT-on-rails scanner required maintenance [15]. Original IMRT contours (or replanned contours if a new plan was used) were overlaid onto each daily CT to verify couch correction for setup errors. Therapists performed the routine IGRT alignment procedure and informed supervising physicists when mismatches occurred. This contour overlay also indicated changes in current anatomy. The original IMRT plan was re-calculated at least weekly, or as indicated by IGRT. Deformable image transformation procedures mapped baseline anatomic contours to the new CT for replanning [16,17]. The supervising attending reviewed the deformably mapped contours and the adapted IMRT plan design. All patients had at least one ART replanning (ART1) procedure. Eight patients were determined by the supervising attending physician to require a second ART replan (ART2) to maintain intended treatment dosimetry. Zero-mm PTV margins were used for all ART plans [12]. Once the ART plan was approved, QA and data transfer to the treatment unit were identical to our conventional procedures.

Retrospective dose evaluation

ART dose distributions were compared to the dose distributions predicted from the unmodified IMRT plan using dose-volume histograms (DVHs). The initial IMRT plan reflected original treatment intent. Four planning scenarios were compared: (1) the original IMRT plan aligned to the marked isocenter (BB); (2) the original plan aligned according to daily bone alignment without plan modification (IGRT); (3) IGRT combined with one mid-treatment adaptive replan (ART1); and (4) actual treatment received by each study patient (IGRT with one or two adaptive replans—ART2).

A dose accumulation procedure calculated the cumulative total delivered dose for each scenario based on a deformable dose mapping technique, as described previously [12]. In-house software was developed to load the cumulative dose distribution into the treatment planning system as a separate trial. DVHs were then compared using the same set of original contours defined on the baseline planning CT. Because the same contours were used for evaluation, differences elicited by DVH comparisons resulted entirely from different dose delivery strategies. Paired *t*-tests determined the statistical significance of differences among different treatment strategies.

Results

Study cohort

Study cohort characteristics and treatment planning statistics are summarized in Table 1. The cohort was composed of 20 males and two females; median age was 54 (range: 42–75 years). Primary site was base of tongue in 14 patients, tonsil in 7, and glossopharyngeal sulcus in 1. Three patients had AJCC stage III disease and 19 patients had stage IVA disease, 18 of whom had N2 disease. Nine patients had T3-4 disease. Twenty-one (95%) patients received concurrent systemic therapy with radiation. Sixteen patients received cisplatin either weekly or every 3 weeks; one of these patients was switched to paclitaxel/carboplatin mid-treatment because of unfavorable early disease response. Four patients received weekly single agent cetuximab, while one patient received combination cisplatin/cetuximab.

High-risk target coverage

Complete BB, IGRT, and ART dosimetric results were available for the first 17 patients; ART2 planning took place for four of these patients. The original high-risk CTV coverage ranged from 94% to 99.9% in original treatment plans with a PTV margin of 3–4 mm.

Two patients had >5% loss in the high-risk CTV coverage (ranging from −7.1% to −5.5%) with reference to the prescription isodose line with BB-alignment alone due to daily setup errors. Underdosing (e.g. greater than 5% loss in high-risk CTV) did not occur with bone-aligned (IGRT) or ART1 treatments, confirming clinical benefit from use of IGRT as well as the adequacy of our PTV expansion margin widths for our ART approach.

Only one patient in the ART2 group had technically deficient high-risk target coverage at −5.6%. This patient suffered brisk tumor progression prior to treatment start (Fig. 1). The first two treatment fractions were severely under-dosed by the original IMRT plan before a prompt ART1 plan could be implemented. Thus, the first two treatment fractions played a significant role in the overall cumulative dose distribution; adaptive replanning was unable to compensate for GTV dose deficiencies. Since our ART2 plans were extremely conformal, they were acutely sensitive to dosimetric deficiencies from prior planning.

Parotid sparing

IGRT delivered higher contralateral parotid doses relative to standard IMRT in 10 of 16 cases. As a group, mean parotid dose for IGRT increased by 0.4 Gy ($p = 0.55$; paired sample *t*-test). IGRT increased ipsilateral parotid dose in 8 of 16 cases; mean ipsilateral parotid dose increased by 0.1 Gy ($p = 0.83$). Given unpredictable setup errors, there were large individual differences in parotid sparing between conventional treatment and IGRT. IGRT provides no clear parotid sparing if improved target coverage is not leveraged toward smaller PTV margin expansions. IGRT, in fact, may degrade dose sparing to bystander structures due to focusing of incidental dose which otherwise would be distributed more widely by daily set-up error (Fig. 2).

ART1 reduced mean doses to contralateral parotid by 0.6 Gy or 2.9% (*t*-test; $p = 0.003$) and ipsilateral parotid by 1.3 Gy or 3.8% ($p = 0.002$) versus IGRT. ART1 improved parotid sparing by 2.9% for the contralateral parotid and 3.8% for the ipsilateral parotid. In an exploratory comparison between the ART2 group (4 cases) and the same patients planned with ART1 only, ART2 reduced the mean contralateral parotid dose by 0.8 Gy (paired *t*-test; $p = 0.026$) and ipsilateral parotid by 4.1 Gy ($p = 0.001$) versus IGRT alone. This translated into improved parotid sparing of 3.8% for the contralateral parotid and 9.0% for the ipsilateral parotid.

Recalculating and replanning on daily CT images

Uncompensated anatomic changes resulted in larger hot spots than intended. Fig. 3A demonstrates a tonsillar carcinoma case where significant dose heterogeneity emerged within the high-risk target volume by the 11th treatment fraction (left). Restoration of dose homogeneity within this GTV required adaptive replanning without PTV margin expansions (right). Representative DVHs of the baseline IMRT plan, ART1 plan (from treatment day 15), and ART2 plan (from treatment day 25) recalculated on CT anatomy from treatment day 25 are shown in Fig. 3B.