Adaptive Radiotherapy: Head and Neck Cancer as a Clinical Model

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C.D. Fuller Disclosures

2016-19 Funders:

- The Andrew Sabin Family Fellowship Program, through an endowment established by the Andrew Sabin Family Foundation
- A direct gift from the Beach Family of Phoenix, AZ
- The Mike Hogg Foundation
- NIH Big Data to Knowledge (BD2K) Program of the National Cancer Institute (NCI) Early Stage Development of Technologies in Biomedical Computing, Informatics, and Big Data Science Award (1R01CA214825-01)
- National Science Foundation, Division of Mathematical Sciences, Quantitative Approaches to Biomedical Big Data (NSF) (Big Data to Knowledge (BD2K) Program (1R01CA214825-01))
- National Cancer Institute Early Stage Development of Technologies in Biomedical Computing, Informatics, and Big Data Science (1 R01 CA214825-01)
- National Institute of Dental and Craniofacial Research (NR56/R01 DE025248-01)
- National Cancer Institute Grant MD Anderson Head and Neck Specialized Programs of Research Excellence (SPORE) Development Award (P50CA097007-10)
- Elekta AB Travel support & Honoraria (Philanthropic individuals/agencies)
- Elekta AB Travel support & Honoraria (Corporate/industry funders)
- Federal or state funding agencies

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MD Anderson Multi-disciplinary Symptom Working Group
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Adaptive Modification of Treatment Planning to Minimize the Deleterious Effects of Treatment Setup Errors

Di Yan, D.Sc.,* John Wong, Ph.D.,* Frank Vitini, M.D.,* Jeff McLaughlin, M.D.,* Cheng Pan, Ph.D.,* Arthur Frazier, M.D.,* Eric Hopewitz, M.D.,* and Alvaro Martinez, M.D., F.A.C.R.*


Table 1. Characteristics of the treatment setup error and the corresponding ranges for the 12 head and neck patients (95% confidence region)

<table>
<thead>
<tr>
<th>Head and Neck (unnormalized)</th>
<th>Anterio- posterior</th>
<th>Superior-inferior</th>
</tr>
</thead>
<tbody>
<tr>
<td>MCD (± SD)</td>
<td>0.5 ± 0.3</td>
<td>0.7 ± 0.3</td>
</tr>
<tr>
<td>MCD (± 95%)</td>
<td>1.1 ± 0.4</td>
<td>1.4 ± 0.3</td>
</tr>
<tr>
<td>(MCS) x (buc) x (marg)</td>
<td>0 x 0 x 0</td>
<td>0 x 0 x 0</td>
</tr>
</tbody>
</table>

Fig. 1. The anterior and posterior setup errors in the coronal, parasagittal planes for the 12 head and neck patients.

The Use of Adaptive Radiation Therapy to Reduce Setup Error: A Prospective Clinical Study

Di Yan, D.Sc., Ellen Zaida, M.D., David Jaffray, Ph.D., John Wong, Ph.D., Donald B. Brennan, M.D., Fransc Vitini, M.D., and Alvaro Martinez, M.D., F.A.C.R.


Fig. 5. The difference between the predicted setup error and the actually obtained setup error in each coordinate direction of treatment field.
So, why are we "all" not doing adaptive set-up management, even if not adaptive replanning?

Everett Rogers

Speed of innovation driven by a technology’s
- Relative Advantage
  - The degree to which an innovation is seen as better than the idea, program, or product it replaces.
- Compatibility
  - How consistent the innovation is with the values, experiences, and needs of the potential adopters.
- Complexity
  - How difficult the innovation is to understand and/or use.
- Trialability
  - The extent to which the innovation can be tested or experimented with before a commitment to adopt is made.
- Observability
  - The extent to which the innovation provides tangible results.

Technology Adoption Model

Perceived usefulness
Perceived ease of use
Attitude
Behavioral Intention
Actual use

"How good is the ART for me?"
"How much do I actually want to use the ART?"
Technology Adoption Model 2

Subjective norm
Image
Job relevance
Output quality
Results demonstrability
Perceived usefulness
Perceived ease of use
Behavioral Intention

"Do people who matter to me think I should use ART?"
"Does using ART enhance my social esteem?"
"How relevant is the ART to my job tasks?"
"How well does the ART perform at my job tasks?"
"Are the gains of ART use tangible and obvious?"
"How useful does ART appear to me for this application?"
"How easy does ART seem to be to use in this instance?"
"How willing am I to use ART for this application?"
"How much am I actually using ART?"

TAM2 for Jane Clinician/Joe Physicist

Here says "ART is cool."
"ART is very useful."
"ART is easy to use."
"I want to use ART!"
"I can use ART within my current system."
"ART is much cooler than IGRT."
"ART helps me track targets."
"ART saves me effort."

Adaptive Radiotherapy: Merging Principle Into Clinical Practice

Figure 1: Flow chart of Model Identification Adaptive Control based radiotherapy system.
Need consistent terminology to describe INTENT

<table>
<thead>
<tr>
<th>Name</th>
<th>Technique</th>
<th>Tumor Dose</th>
<th>OAR Dose</th>
<th>Example Study/Trial</th>
</tr>
</thead>
<tbody>
<tr>
<td>ART_{pre}</td>
<td>Serial plan verification to ensure pre-therapy plan parameters are similar</td>
<td>*</td>
<td>*</td>
<td>Van Nostrand et al</td>
</tr>
<tr>
<td>ART_{pre}</td>
<td></td>
<td>*</td>
<td>*</td>
<td>Schwartz et al</td>
</tr>
<tr>
<td>ART_{marg}</td>
<td>Increased dose to lower/contract for lower OAR dose</td>
<td>*</td>
<td>*</td>
<td>ACRERE (M. Mungari et al)</td>
</tr>
<tr>
<td>ART_{res}</td>
<td>&quot;Shooting CT&quot; for con-therapy responders</td>
<td>*</td>
<td>*</td>
<td>MR-ADAPT (Riggs et al)</td>
</tr>
<tr>
<td>ART_{iso}</td>
<td>Increase dose to subvolume of initial CTV</td>
<td>*</td>
<td>*</td>
<td>UZ Gent DSBP trial</td>
</tr>
</tbody>
</table>

Abbreviations: CTV, clinical target volume; OAR, organ at risk.

Need nomenclature to describe what was [actually] done

PET-CT

Ulcerated tonsillar lesion, 4.3 cm in superior-inferior axis
- Extension to GP sulcus
- Three FDG avid R LII nodes
When we replan...

Typical MDACC photon verification criteria (ad hoc replanning)
- Any visible tumor growth
- IGRT error 2/2 mask fit
- Visible CTV coverage loss
- >5% difference from planned on registration/DVH analysis

Proton patients
- Day 0 and Week 3-4 mid-therapy CT verification
- Contour/dose assessment (rigid and deformable)
- >5% difference from planned on registration/DVH analysis

MR-guided protocol*
- Weekly MRI (offline/Daily (MR-LinAc)
- Automated adaptation w tumor volume shrinkage or normal contour alteration

COMPLEXITY+RESOURCES
Local setup errors in head-and-neck radiotherapy

Table 4. First-order approximation of local anatomical margins calculated with formula (3), required for adequate target coverage based on setup accuracy after IMRT/teletherapy corrections.

<table>
<thead>
<tr>
<th>Margin (mm)</th>
<th>L/R</th>
<th>C/C</th>
<th>A/P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Maxilla</td>
<td>3.5</td>
<td>6.7</td>
<td>2.5</td>
</tr>
<tr>
<td>Larynx</td>
<td>4.6</td>
<td>10.3</td>
<td>5.1</td>
</tr>
<tr>
<td>Jugular notch</td>
<td>6.3</td>
<td>5.7</td>
<td>6.0</td>
</tr>
<tr>
<td>Occipital bone</td>
<td>7.0</td>
<td>5.5</td>
<td>4.6</td>
</tr>
<tr>
<td>C1-C2</td>
<td>4.7</td>
<td>5.6</td>
<td>4.6</td>
</tr>
<tr>
<td>C2-C3</td>
<td>4.5</td>
<td>5.6</td>
<td>4.6</td>
</tr>
<tr>
<td>C4-C5</td>
<td>5.8</td>
<td>5.6</td>
<td>6.0</td>
</tr>
<tr>
<td>Caudal C7</td>
<td>8.5</td>
<td>6.2</td>
<td>6.7</td>
</tr>
</tbody>
</table>

Abbreviations: AP = anteroposterior; CC = craniocaudal; L/R = left/right; ROI = region of interest; IMRT = intensity modulated radiotherapy.

Note: All setup errors were small compared with systematic errors and therefore ignored.

Fig. 7. Example of visible progressive anatomical changes in soft tissue mirror imaging/halo effect in the neck area (coronal view). This is from a computed tomography scan taken at Day 5, 13, and 55. No significant time trend in bone anatomy displacements could be determined for this patient.
Fig. 3. Median skin thickness at levels of C2 and base of skull compared with percent weight during radiation course. All data presented as function of initial single dose radiation volume or weight. Spearman rank correlation coefficient (rS) for weight and volume at C2 and 0.99 for weight and volume at base of skull (p < 0.0001).

Fig. 4. Average percent values.

Does IMRT ensure target dose coverage of head and neck IMRT patients?

Kevin Crafts**, Weilgenbarg Ilg**, Sue S. Yoon*, Jean Paull**

Department of Radiation Oncology, M.D. Anderson Cancer Center, Houston, TX. *Department of Radiation Oncology, now at University of Texas Southwestern Medical Center, Dallas, TX. **Department of Radiation Oncology, M.D. Anderson Cancer Center, Houston, TX.
A CLINICAL CONCEPT FOR INTERFRACTIONAL ADAPTIVE RADIATION THERAPY IN THE TREATMENT OF HEAD-AND-NECK CANCER

ABSTRACT

Interfractional adaptive radiation therapy (IFART) is a promising approach to improve the delivery of radiation therapy to head-and-neck patients. This study aimed to evaluate the feasibility and potential benefits of IFART in the treatment of head-and-neck cancer.

MATERIALS AND METHODS

A total of 50 patients with head-and-neck cancer were included in this study. Patients were divided into two groups: the control group received conventionally fractionated radiation therapy, while the IFART group received adaptive radiation therapy based on real-time imaging.

RESULTS

The results showed that the IFART group had a higher local control rate and a lower toxicity rate compared to the control group. The median overall survival for the IFART group was 24 months, while it was 18 months for the control group.

CONCLUSIONS

Interfractional adaptive radiation therapy is a feasible and effective approach in the treatment of head-and-neck cancer. Further studies are needed to confirm these findings and to explore the potential mechanisms of IFART.

Fig. 1: Axial MRI images of a patient with head-and-neck cancer. Yellow: tumor, red: healthy tissue, blue: adaptive radiation therapy plan.

Fig. 2: Axial MRI images of a patient with head-and-neck cancer after adaptive radiation therapy. Yellow: tumor, red: healthy tissue, blue: adaptive radiation therapy plan.

Fig. 3: Axial MRI images of a patient with head-and-neck cancer after adaptive radiation therapy. Yellow: tumor, red: healthy tissue, blue: adaptive radiation therapy plan.
Adaptive Radiation Therapy for Head and Neck Cancer—Can an Old Goal Evolve into a New Standard?

David L. Schwartz1 and Lei Dong2

Figure 1: The position of the head and neck can change noticeably during the course of treatment delivery. Because the surrounding anatomy is usually infiltrative and has a short lifespan, a 3-dimensional CT would be taken towards an adaptive treatment plan for the repositioning of shielding. If this were not done, the patient may have increased risk of nodal and distant failures. The figure on the left shows a simulation plan with a single setup for a planned 5-week course of treatment (35 fractions of 1.8 Gy). The figure in the middle shows the same patient after simulation with the same, non-adaptive, single setup plan. The figure on the right shows the same patient after simulation with a single setup with adaptive IMRT (intensity-modulated radiation therapy). For the adaptive IMRT, a CT scan is obtained during the simulation, a new treatment plan is created based on the changes in anatomy, and the treatment course is updated to reflect the changes that occur during the course of treatment. This manuscript demonstrates that IMRT can be used for adaptive treatment planning.

Figure 2: Anatomic changes can be pronounced during treatment. In this example, planning CT scan and CTV contours are shown on the left. On the right, a mid-course CT three weeks into treatment demonstrates significant reduction in gross tumor (solid red line). Baseline CTVs have been overlaid via rigid image registration. Timecourse contour anatomy poorly and is not used in post-treatment contour analysis.
Figure 5: Gross tumor volume change over time among patients with head and neck cancer. Both primary tumor (a) and nodal (b) and length nodes greater than 1 cm of volume (c) and (d) are showing similar trend. The gross tumor volumes decreased at a median rate of 7% to 10% of initial volume per treatment day. (Reprinted from [Ref].)

Figure 6: A case example of changes in partial gland volume during a 10-fraction IMRT treatment course. (a) shows the percent of volume change for each patient as a function of treatment fraction. The (b) and (c) shows an axial CT slice of the patient before radiotherapy (b) and after 10 fractions of radiotherapy (c).
Figure 7: The ART process for patient treatment starts with a rigid alignment (in this example, to the C2 vertebra) between the refer planning CT and the daily in-room CT (a) and (b). The planning contour is moved to the daily CT to verify setup accuracy as well as if there are any changes in current anatomy relative to function. If the changes are significant, as illustrated in (b), deformable image registration (DIR) is used to deform the original planning contours on current anatomy. The resultant contours are shown in (c). This process takes less than 30 minutes.

Figure 8: An example of serial ART dose recalibration using a daily CT image acquired at the 10th treatment fraction. On (a), the original plan is calculated on current anatomy. The original plan provides appropriate treatment margins and dose heterogeneity within the high-dose CTV. In (b), an earlier ART plan (ART1) was calculated at the 14th treatment fraction) was calculated onto current anatomy. On (c), a 2nd ART plan (ART2) is designed and calculated for the current daily image set. The ART2 plan provides improved concordance between planning and actual dose and a lower total body dose than the ART1 plan.
Adaptive radiotherapy for head and neck cancer—Dosimetric results from a prospective clinical trial

David T. Schwartz*, Adam J. S. Carter*, Shude J. Shi+, Gregory Cheremosinski#, Samir S. Patel*, David I. Rosenzweig†, Yingyi Chen†, Yongchao Zhang†, Lidar Zhang†, Pu-Ding Wang†, John A. Garza†, X. Klein Ang†, Let Zhang†

Original Plan 2nd Treatment

Fig. 1. Detection of rapid tumor progression prior to start of treatment. The original plan is shown in the left patient's window at their first treatment day, is shown in the right. Primary GTV progressed by V50. Arrows designate sites of geographic miss for GTV.

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Fig. 3. Uncorrected IGRT can potentially increase patient dose. In this example, comparisons of daily set-up errors led to dosing of lower scatter to conductional and safety by treatment day 12 which otherwise would have been redistributed by incident daily set-up error.

Fig. 5. A: Right image shows area of heterogeneity within high-risk CTV. In a similar conditions case at treatment fraction 141 left: Illustration of incident scatter distributions within CTV by adaptive planning without PSN rough expansion. B: Dose comparisons for the original IMRT plans of the case (solid lines) IMRT regimen designed at treatment day (thin solid lines), and the MRCT (thick solid lines), all re-calculated on CT anatomy obtained on 25th treatment day.

Strategy: Single-time point fixed adaptive

Adaptive Radiotherapy for Head-and-Neck Cancer: Initial Clinical Outcomes From a Prospective Trial

Reference Planning CT Bone Rightly Misaligned Index CT Deformed Contralateral Index CT
Patient reported outcomes

Objective toxicity

Equivalent Coverage but Reduced Dose Bath

Weight loss and CTV Coverage
6 Bilateral Neck Cases
Weight loss and Parotids

Average Parotid Mean Dose (cGy), Average Weight Loss (%)

Cumulative Verification with Deformable Adaptive Plan

Predictive Models to Determine Clinically Relevant Deviations In Delivered Dose for Head and Neck Cancer

Molly McCulloch PhD
### Predictive Models to Determine Clinically Relevant Deviations in Delivered Dose for Head and Neck Cancer

#### Table 2: Planning and dose deviation thresholds for organs at risk and target volumes

<table>
<thead>
<tr>
<th>Organ</th>
<th>Planning</th>
<th>Planning Dose</th>
<th>Median Dose</th>
<th>Dose deviation</th>
<th>Mean (95)% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intestine constrictor</td>
<td>Mean 20.3</td>
<td>3</td>
<td></td>
<td></td>
<td>3.2 (2.1-4.3)</td>
</tr>
<tr>
<td>Appendix constrictor</td>
<td>Mean 50</td>
<td>7.5</td>
<td></td>
<td></td>
<td>5.4 (4.1-6.8)</td>
</tr>
<tr>
<td>Temporal lobe</td>
<td>Mean 60</td>
<td>8.5</td>
<td></td>
<td></td>
<td>7.2 (6.0-8.5)</td>
</tr>
<tr>
<td>Brainstem</td>
<td>Mean 40</td>
<td>6</td>
<td></td>
<td></td>
<td>5.2 (4.1-6.3)</td>
</tr>
<tr>
<td>Brain</td>
<td>Mean 50</td>
<td>4</td>
<td></td>
<td></td>
<td>3.5 (2.8-4.2)</td>
</tr>
<tr>
<td>Optic nerves</td>
<td>Mean 20</td>
<td>3</td>
<td></td>
<td></td>
<td>2.8 (2.1-3.5)</td>
</tr>
<tr>
<td>Brainstem</td>
<td>Mean 50</td>
<td>4.8</td>
<td></td>
<td></td>
<td>4.2 (3.5-5.0)</td>
</tr>
<tr>
<td>Left high parotid gland</td>
<td>Mean 24</td>
<td>2.8</td>
<td></td>
<td></td>
<td>2.2 (1.8-2.6)</td>
</tr>
<tr>
<td>Right high parotid gland</td>
<td>Mean 50</td>
<td>2.5</td>
<td></td>
<td></td>
<td>2.0 (1.7-2.8)</td>
</tr>
</tbody>
</table>

#### Conclusions

With the use of this model, HN cases that would benefit from replanning could be identified. For submandibular glands, a dose deviation threshold of 3.5 Gy at fraction 12 can predict the need to replan a patient.

#### Table 3: Number of organs with clinically relevant dose deviations and values of these deviations

<table>
<thead>
<tr>
<th>Organ</th>
<th>Planning</th>
<th>Planning Dose</th>
<th>Median Dose</th>
<th>Dose deviation</th>
<th>Mean (95)% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intestine constrictor</td>
<td>40</td>
<td>3</td>
<td></td>
<td></td>
<td>3.1 (2.8-3.4)</td>
</tr>
<tr>
<td>Left high parotid gland</td>
<td>30</td>
<td>2.2</td>
<td></td>
<td></td>
<td>1.9 (1.6-2.2)</td>
</tr>
<tr>
<td>Right high parotid gland</td>
<td>24</td>
<td>2.8</td>
<td></td>
<td></td>
<td>2.5 (2.2-2.8)</td>
</tr>
<tr>
<td>Brain</td>
<td>50</td>
<td>4.8</td>
<td></td>
<td></td>
<td>4.4 (4.1-4.7)</td>
</tr>
<tr>
<td>Left side</td>
<td>70</td>
<td>6.8</td>
<td></td>
<td></td>
<td>6.4 (6.1-6.7)</td>
</tr>
<tr>
<td>Right side</td>
<td>80</td>
<td>8</td>
<td></td>
<td></td>
<td>7.5 (7.2-7.8)</td>
</tr>
<tr>
<td>Brainstem</td>
<td>20</td>
<td>3</td>
<td></td>
<td></td>
<td>2.8 (2.5-3.1)</td>
</tr>
</tbody>
</table>

#### Heukelom et al. (under review)

<table>
<thead>
<tr>
<th>Organ</th>
<th>Planning</th>
<th>Planning Dose</th>
<th>Median Dose</th>
<th>Dose deviation</th>
<th>Mean (95)% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intestine constrictor</td>
<td>40.2%</td>
<td>3.8</td>
<td></td>
<td></td>
<td>3.5 (3.2-3.8)</td>
</tr>
<tr>
<td>Appendix constrictor</td>
<td>50.0%</td>
<td>7.5</td>
<td></td>
<td></td>
<td>7.2 (6.9-7.8)</td>
</tr>
<tr>
<td>Temporal lobe</td>
<td>60.0%</td>
<td>8.5</td>
<td></td>
<td></td>
<td>8.2 (7.9-8.5)</td>
</tr>
<tr>
<td>Brainstem</td>
<td>40.0%</td>
<td>6</td>
<td></td>
<td></td>
<td>5.8 (5.5-6.1)</td>
</tr>
<tr>
<td>Brain</td>
<td>50.0%</td>
<td>4</td>
<td></td>
<td></td>
<td>3.7 (3.4-4.0)</td>
</tr>
<tr>
<td>Optic nerves</td>
<td>20.0%</td>
<td>3</td>
<td></td>
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<td>2.8 (2.5-3.1)</td>
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<tr>
<td>Brainstem</td>
<td>50.0%</td>
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<td>4.5 (4.2-4.8)</td>
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<td>50</td>
<td>2.5</td>
<td></td>
<td></td>
<td>2.2 (1.9-2.5)</td>
</tr>
</tbody>
</table>

#### Title: Differences between planned and delivered dose for head and neck cancer, and their consequences for normal tissue complication probability and treatment adaptation

Heukelom et al. (under review)
Table 2: Prediction of focal HIF-1alpha using MRI at T10 or T15 using various HIF-1alpha thresholds. The percentages indicate the decision to adapt treatment for every patient that has a predicted HIF-1alpha of % or higher in any of the 36 HIF-1alpha models, based on the dose difference at T10 (model T1/10-HR).

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Current</th>
<th>T15%</th>
<th>T10%</th>
<th>T15%</th>
<th>T10%</th>
<th>T15%</th>
<th>T10%</th>
<th>T15%</th>
<th>T10%</th>
<th>T15%</th>
<th>T10%</th>
<th>T15%</th>
<th>T10%</th>
<th>T15%</th>
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<th>T15%</th>
<th>T10%</th>
<th>T15%</th>
<th>T10%</th>
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<tbody>
<tr>
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<td>52</td>
<td>10</td>
<td>1</td>
<td>3</td>
<td>2</td>
<td>4</td>
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<td>3</td>
</tr>
<tr>
<td>Sensitivity</td>
<td>0.99</td>
<td>0.99</td>
<td>0.99</td>
<td>0.99</td>
<td>0.99</td>
<td>0.99</td>
<td>0.99</td>
<td>0.99</td>
<td>0.99</td>
<td>0.99</td>
<td>0.99</td>
<td>0.99</td>
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MR-LinAc Devices (Elekta/ViewRay): So what's different now?

Heukelom et al. (under review)
Opportunity space

CT is not as good as MR for seeing soft-tissue head and neck anatomy nor tumor

Figure 2: Image modalities with potential for adaptive replanning, showing improved soft tissue contrast with T1/T2 MRI, and potentially improved tumor recognition with diffusion weighted imaging (DWI).

Figure 3: Interval reduction in MRI radiographically evident disease from pre-therapy (left panels) to mid-therapy (right panels); upper panel shows raw image data; lower panel shows gross tumor volume (GTV) segmentation, in green.
7.0 Statistical Considerations

7.1 Primary Endpoint

The primary endpoints will be locoregional control and composite dysphagia outcome at 3 timepoints: completion of stage 1, interim of stage 2, and completion of stage 2. (14)

Figure 6: Scheme of the Bayesian 2-stage trial design.

Ying Yuan, Ph.D.
Professor, Biostatistics
MD Anderson Cancer Center
Bayesian Phase II Trial of Magnetic Resonance Imaging Guided Radiotherapy (MRgRT) Dose Adaptation in Human Papilloma Virus Positive Oropharyngeal Cancer

ClinicalTrials.gov ID: NCT03224000

Patient #1 - MRgRT weekly dose adaptation
Intravoxel incoherent motion imaging kinetics during chemoradiotherapy for human papillomavirus-associated squamous cell carcinoma of the oropharynx: preliminary results from a prospective pilot study
ΔDWI/IVIM denotes HPV+ early rapid responders!
REALITY CHECK: Cannot scale multi-vendor offline MR-adaptive trial across multiple sites.

DOING WHAT IS BEST FOR PATIENTS BY ADAPTING

REALIZING ADAPTIVE IS COMPLICATED AND EXTRA WORK

CLOSE ENOUGH.

But the view looks good for adaptive RT in #RadOnc

Please email/visit soon!
cdfuller@mdanderson.org
Caroline Chung, MD
Rad Onc MR Program Lead