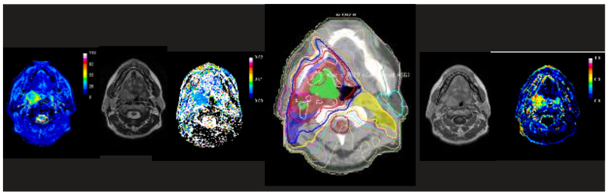

THE UNIVERSITY OF TEXAS MD Anderson Cancer Center Making Cancer History®

Adaptive Radiotherapy: Head and Neck Cancer as a Clinical Model

AAPM 2019 JUL 14–18 BUILDING BRIDGES. CULTIVATING SAFETY. GROWING VALUE. 61ST ANNUAL MEETING & EXHIBITION | SAN ANTONIO, TX

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C.D. Fuller Disclosures

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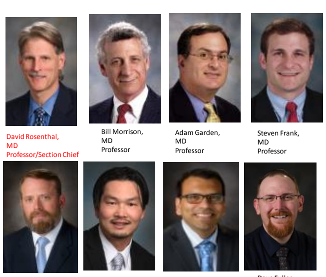
Radiation Oncology Head and Neck Section



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MDACC Head and Neck Team

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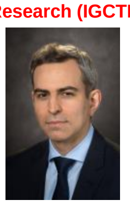

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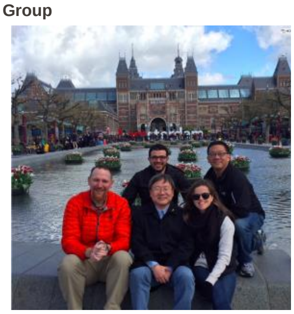

"Interdisciplinary Approaches to Biomedical Data Science Challenges" Team

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-2016 Joint NIH/NSF Division of Mathematical Sciences Initiative on Quantitative Approaches to Biomedical Big Data (QuBBD) Grant, *"Spatial-nonspatial Multidimensional Adaptive Radiotherapy Treatment"* (NSF 1557679)
- 2017-2020 Early Stage Development of Technologies in Biomedical Computing, Informatics, and Big Data Science Grant, *"SMART-ACT: Spatial Methodologic Approaches for Risk Assessment and Therapeutic Adaptation in Cancer Treatment"* (R01 CA214825-01)

National Science Foundation
WHERE DISCOVERIES BEGIN

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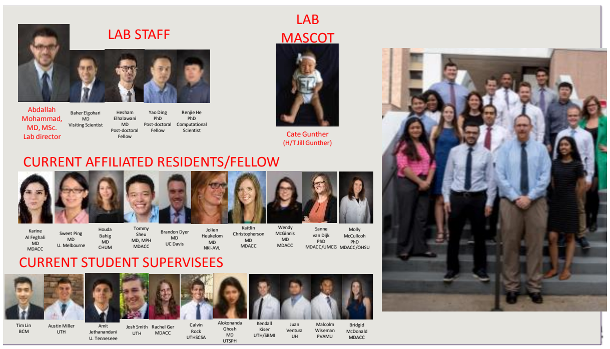

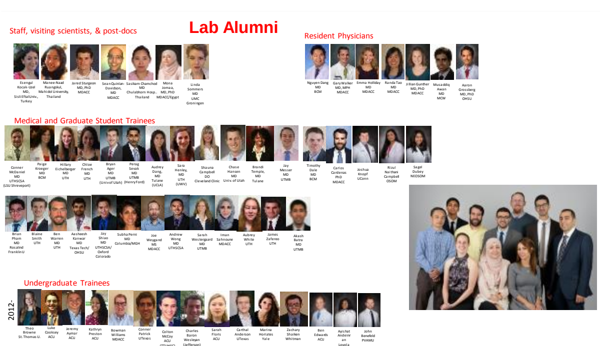

The Home Team

ADAPTIVE MODIFICATION OF TREATMENT PLANNING TO MINIMIZE THE DELETERIOUS EFFECTS OF TREATMENT SETUP ERRORS

Di Yan, D.Sc.,* John Wong, Ph.D.,* Frank Vicini, M.D.,* Jeff Michalski, M.D.†
Cheng Pan, Ph.D.,* Arthur Frazier, M.D.,* Eric Horwitz, M.D.*
and Alvaro Martinez, M.D., F.A.C.R.*

Int. J. Radiation Oncology Biol. Phys., Vol. 38, No. 1, pp. 197–206, 1997

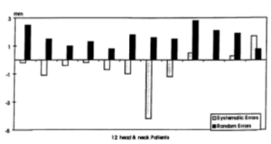

Fig. 1. The systematic and random setup errors in the anterior–posterior direction for the 12 head and neck patient

Table 1. Characteristics of the treatment setup error, and the corresponding margin for the 12 head and neck patients (192 daily portal images)

Head and Neck (immobilized)	Anterior–posterior (mm)	Superior–inferior (mm)
$M(m_i) \pm \sigma(m_i)$	-0.5 ± 1.3	0.5 ± 2.0
$M(\sigma_i) \pm \sigma(\sigma_i)$	1.7 ± 0.6	1.4 ± 0.4
$Mp \pm \sigma p$	-0.5 ± 2.1	0.5 ± 2.4
$\|Mp\| + \lambda\sigma p$ = margin	($\lambda = 2.1$)	($\lambda = 2.3$)
λ was calculated to cover 95% of setup errors	margin = 5	margin = 6

THE USE OF ADAPTIVE RADIATION THERAPY TO REDUCE SETUP ERROR: A PROSPECTIVE CLINICAL STUDY

Di Yan, D.Sc., Ellen Ziaja, M.D., David Jaffray, Ph.D., John Wong, Ph.D.,
Donald Brabbins, M.D., Frank Vicini, M.D. and Alvaro Martinez, M.D., F.A.C.R.

Int. J. Radiation Oncology Biol. Phys., Vol. 41, No. 3, pp. 715–720, 1998

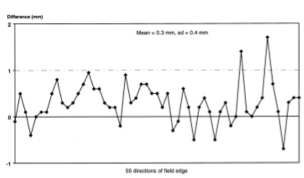

Fig. 5. The difference between the predicted setup margin and the actually calculated setup margin on each coordinate direction of treatment field.

So, why are we *all* not doing adaptive set-up management, even if not adaptive replanning?

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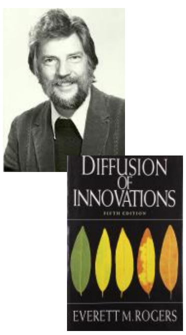
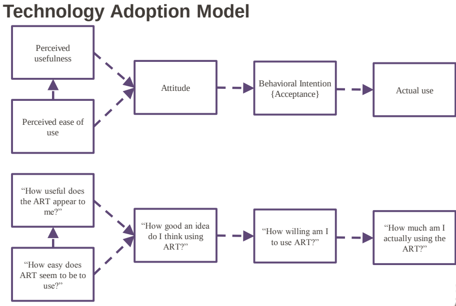
Everett Rogers



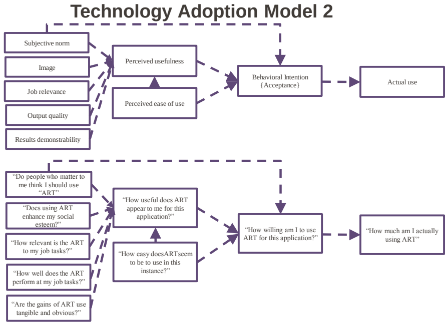
Speed of innovation driven by a technology's

- 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.
- Triability
  - 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



Technology Adoption Model 2



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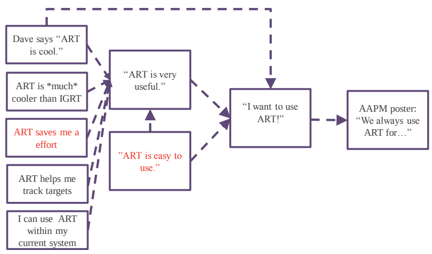
TAM2 for Jane Clinician/Joe Physicist



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Adaptive Radiotherapy: Merging Principle Into Clinical Practice

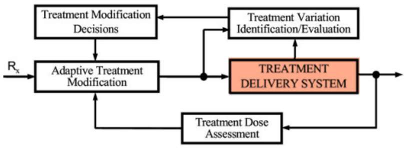

Figure 1 Flow chart of Model Identification Adaptive Control based radiotherapy system.

Seminars in RADIATION ONCOLOGY April 2010

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Need consistent terminology to describe INTENT

Table 3 ART Terminology

Name	Technique	Tumor Dose	OAR Dose	Example Study/Trial
ART_{ex_aequo}	Serial plan verification to ensure pre-therapy plan parameters are stable	=	=	Van Kranen et al[78]
ART_{OAR}	Reduced OAR dose; pre-therapy CTV is conserved	=	↓	Schwartz et al[11,31]
ART_{amplio}	Increased dose to tumor; isotoxic (or lower) OAR dose	↑	=	ADMIRE (Al Mamgani et al[79])
ART_{reduco}	"Shrinking CTV" for on-treatment responders	=	↓	MR-ADAPTOR (Bahig et al[29])
ART_{totale}	Increase dose to subvolume of initial CTV	↑	↓	UZ Gent DBPN trials[77,80-84]

Abbreviations: CTV, clinical target volume; DBPN, dose painting by numbers; OAR, organ at risk.

Seminars in RADIATION ONCOLOGY

Jolien Heukelom MD NKI-AVL

Head and Neck Cancer Adaptive Radiation Therapy (ART): Conceptual Considerations for the Informed Clinician

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Need nomenclature to describe what was [actually] done

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Jolien Heukelom MD NKI-AVL

Figure 1 Possible typologies of ART implementation. A: fixed interval approach; B: 'triggered' ART; C: serial ART; D: cascade ART. ART, adaptive radiation therapy.

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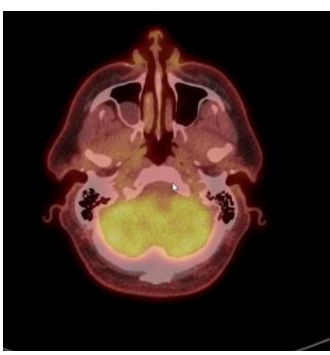
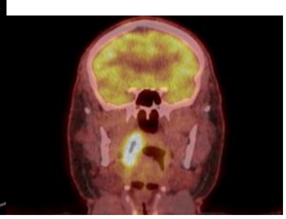
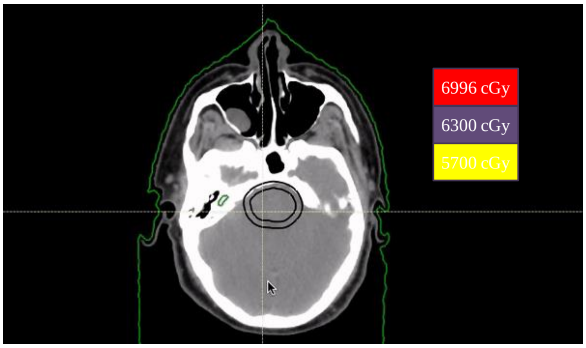


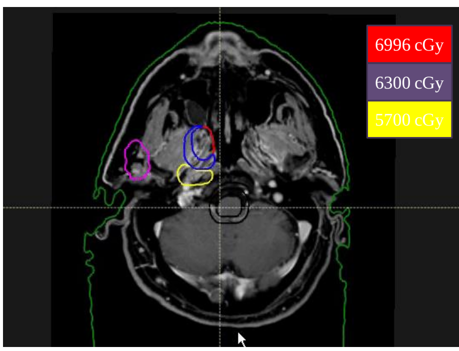
PET-CT

Ulcerated tonsillar lesion; 4.3 cm in superior-inferior axis

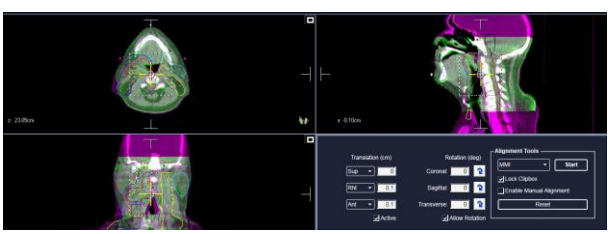
- Extension to GP sulcus
- Three FDG avid R LII nodes



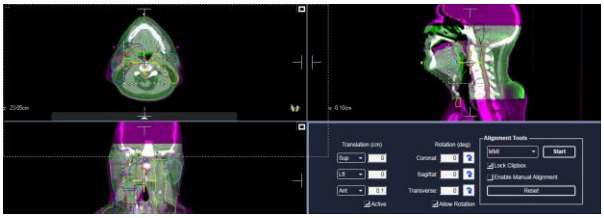




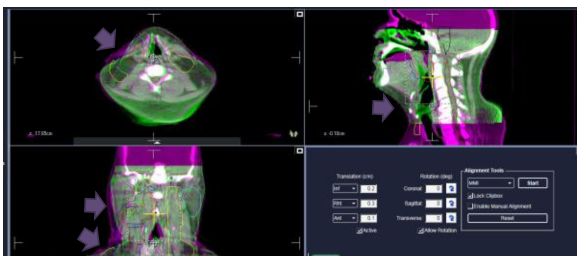
- IGRT Day 0 (aligned to C2)



IGRT Week 2



IGRT Week 4



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 assesment (rigid and deformable)
- >5% difference from planned on registration/DVH analysis

MR-guided protocol*

- Weekly MRI (offline)/Daily (MR-LinAc)
- Automated adapation w tumor volume shrinkage or normal contour alteration

COMPLEXITY+RESOURCES

SETUP UNCERTAINTIES OF ANATOMICAL SUB-REGIONS IN HEAD-AND-NECK CANCER PATIENTS AFTER OFFLINE CBCT GUIDANCE

Simon van Kranen, M.Sc.,* Suzanne van Beek, R.T.T.,* Coen Rasch, M D., Ph.D.,* Marcel van Herk. Ph.D.,* and Jan-Jakob Sonke, Ph.D*

doi:10.1016/j.ijrobp.2008.11.035

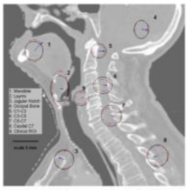


Fig. 3. Error map of local regions of interest (ROIs) in the sagittal plane. Group mean errors are indicated with vectors, systematic and random errors with dotted and straight ellipse (semimajor and semiminor axes correspond to 1 SD). The picture in the background serves as a map showing the approximate position of the different ROIs. Errors were scaled by a factor 5.

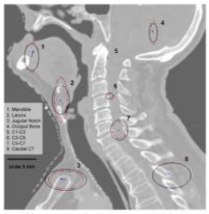


Fig. 5. Error map of deformations with respect to the reference region of interest, vertebrae C1-C3, in the sagittal view. Note the increased motion with longer distances from the reference.

Local setup errors in head-and-neck radiotherapy ● S. van Kranen *et al.*

Table 4. First-order approximation of local anisotropic margins calculated with formula (2), required for adequate target coverage based on setup accuracies after SAL offline corrections

	Margins (mm)		
	LR	CC	AP
Mandible	3.9	6.7	5.5
Larynx	4.6	10.3	5.1
Jugular notch	6.3	5.7	6.0
Occiput bone	7.0	5.5	4.6
C1-C3	4.7	3.8	4.2
C3-C5	5.1	4.0	4.8
C5-C7	5.9	5.4	6.0
Caudal C7	8.3	6.2	6.7
Clinical ROI	4.0	3.7	4.0

Abbreviations: AP = anteroposterior; CC = craniocaudal; LR = left-right; ROI = region of interest; SAL = shrinking action level.

Group mean errors were small compared with systematic errors and therefore ignored.

Local setup errors in head-and-neck radiotherapy ● S. van Kranen *et al.*

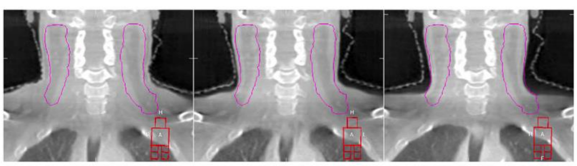


Fig. 7. Example of visible progressive anatomical changes in soft tissue: tumor shrinkage/weight loss in the neck area (coronal view). The cone beam computed tomography scans were taken at Day 1, 18, and 55. No significant time trends in bony anatomy displacements could be determined for this patient.

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Yang *et al.*: Variable planning margins for logoregional variations

Med. Phys. 39 (8), August 2012

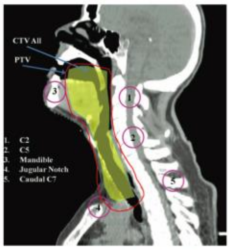

FIG. 1. Approximate locations of the five landmark ROIs and prescribed CTV displayed in the sagittal plane. This CTV is a diagram of the combination of all treatment CTVs. The PTV is a projected expansion with local variable margins, which are larger for the lower neck area than for the upper neck area.

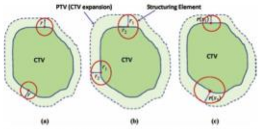

FIG. 2. Illustration of Different margin expansion methods: (a) global uniform margin expansion using a spherical SE of radius r; (b) global nonuniform margin expansion using a SE with different radii in all six directions; and (c) local variable margin expansion with variable radii at different expansion locations.

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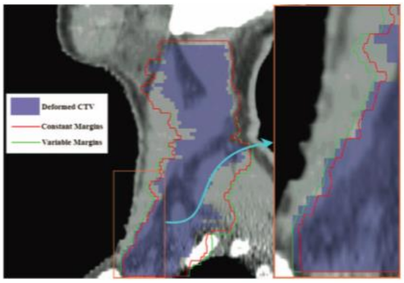

FIG. 7. The advantage of local variable margins in the lower neck region. Global constant margins are not able to cover some parts of CTV in this area, but the local variable margins enclose most CTV. The lower neck region is magnified for a better visualization of the difference between these two approaches.

Medical Physics, Vol. 39, No. 8, August 2012

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QUANTIFICATION OF VOLUMETRIC AND GEOMETRIC CHANGES OCCURRING DURING FRACTIONATED RADIOTHERAPY FOR HEAD-AND-NECK CANCER USING AN INTEGRATED CT/LINEAR ACCELERATOR SYSTEM

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I. J. Radiation Oncology ● Biology ● Physics Volume 59, Number 4, 2004

Fig. 2. Integrated CT/linear accelerator system (EXaCT) that allows computed tomographic imaging at daily radiotherapy sessions while patient remains immobilized in treatment position.

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I. J. Radiation Oncology ● Biology ● Physics Volume 59, Number 4, 2004

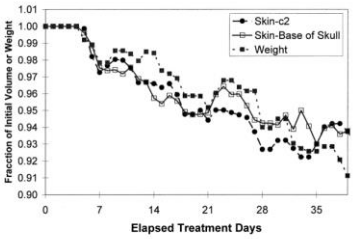

Fig. 3. Median skin contours at levels of C2 and base of skull compared with patient weight during radiotherapy course. All data presented as fraction of initial single-slice contour volume or weight (Spearman two-tailed correlation coefficient 0.917 for weight and contour volume at C2 [p <0.001] and 0.936 for weight and contour at base of skull [p <0.001]).

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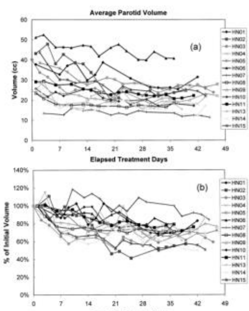

Fig. 7. Parotid glands also decreased in volume during treatment. (a) Change in average parotid volume and (b) percentage of change relative to initial volume. Median volume loss was 0.2 cm^3/d or 0.6%/d of initial volume. HNn = patient number.

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IGRT in head and neck cancer

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

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Radiotherapy and Oncology 104 (2012) 83–90

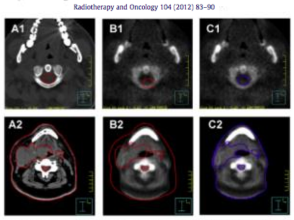

Fig. 1. Process used for the transposition of volumes of interest from the planning kVCT to MVCBCT images. Column A: initial volumes (red) as delineated by the treating physician on the planning kVCT. Column B: initial volumes (red) projected on a registered MVCBCT image (the registration between the MVCBCT and the planning kVCT was the one used to position the patient on the day of treatment). Column C: volumes of interest adapted to MVCBCT images (blue). Line 1 (C1): spinal cord shifted on MVCBCT image to be relocated in its original position within the medullar canal as observed on the planning kVCT. Line 2 (C2): conformation of GTV to new patient's external limits on the MVCBCT image (automatic generation of patient's external contours; automatic exclusion of all parts of GTV located – 3 mm under the external contours; removal of all parts of GTV that projected in air cavities).

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LOCAL ANATOMIC CHANGES IN PAROTID AND SUBMANDIBULAR GLANDS DURING RADIOTHERAPY FOR OROPHARYNX CANCER AND CORRELATION WITH DOSE, STUDIED IN DETAIL WITH NONRIGID REGISTRATION

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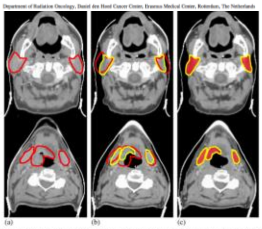

Fig. 5. Example of observed shape and position changes for head-and-neck patient (bilateral neck treatment). (Upper) Parotid glands and (Lower) submandibular glands and primary tumor. (a) Planning computed tomography (CT) scan and delineated structures in red. (b) Post-external beam radiotherapy (EBRT) CT scan with planning (red) and post-EBRT CT scan (yellow) delineations. (c) Post-EBRT CT scan with delineated structures (yellow) and transformed planning structures (red shadow). See colors in electronic version.

doi:10.1016/j.ijrobp.2007.10.063

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PAROTID GLAND DOSE IN INTENSITY-MODULATED RADIOTHERAPY FOR HEAD AND NECK CANCER: IS WHAT YOU PLAN WHAT YOU GET?

Jennifer C. O'Daniel, Ph.D.,* Adam S. Garden, M.D.,† David L. Schwartz, M.D.,† He Wang, Ph.D.,* Kian K. Ang, M.D., Ph.D.,† Anesa Ahamad, M.D.,† David I. Rosenthal, M.D.,† William H. Morrison, M.D.,† Joshua A. Asper, P.A.C.,† Lifei Zhang, Ph.D.,* Shih-Ming Tung, M.S.,* Radhe Mohan, Ph.D.,* and Lei Dong, Ph.D.*

doi:10.1016/j.ijrobp.2007.07.2345

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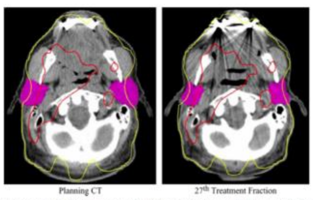

Fig. 5. Weight loss, parotid gland shrinkage, and parotid gland center-of-volume medial displacement during a course of radiation therapy leads to an increase in the parotid gland mean dose. Red denotes 63 Gy and yellow 26 Gy.

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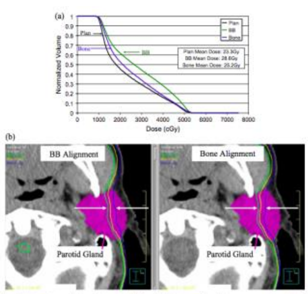

Fig. 6. Parotid gland sparing with bone alignment for Patient 2. (a) Dose–volume histogram comparison of a 3-Gy parotid gland mean dose reduction. (b) Dose distribution comparison of a 3-Gy parotid gland mean dose reduction. Green denotes 30 Gy; yellow, 26 Gy; and blue, 20 Gy.

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A CLINICAL CONCEPT FOR INTERFRACTIONAL ADAPTIVE RADIATION THERAPY IN THE TREATMENT OF HEAD-AND-NECK CANCER

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doi:10.1016/j.ijrobp.2010.10.072

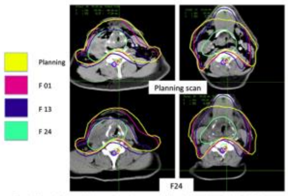

Fig. 1. 62 y old male with laryngeal carcinoma requiring 4 adaptations for the IMRT plan.

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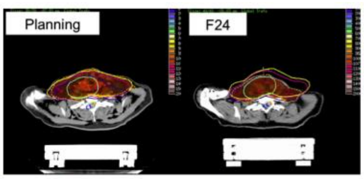

Fig. 2. Inital target volumes and dose distribution on the planning scan (BPL), adapted volumes and dose distribution (F24).

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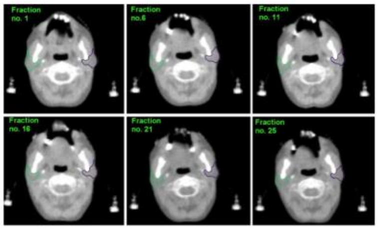
PHYSICS CONTRIBUTION

COMPARATIVE ANALYSIS OF AN IMAGE-GUIDED VERSUS A NON-IMAGE-GUIDED SETUP APPROACH IN TERMS OF DELIVERED DOSE TO THE PAROTID GLANDS IN HEAD-AND-NECK CANCER IMRT

Marciana Nona Duma, M.D.,* Severin Kampfer, M.Sc.,* Jan Jakob Wilkens, D.Sc.,* Tibor Schuster, M.Sc.,† Michael Molls, M.D.,* and Hans Geinitz, M.D.*

1268 I. J. Radiation Oncology ● Biology ● Physics Volume 77, Number 4, 2010



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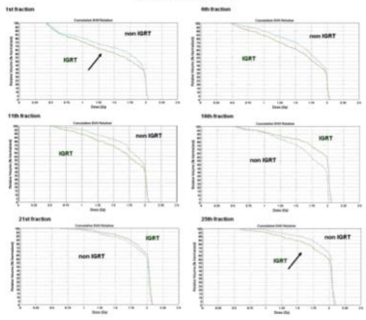
DVHs- Left Parotid Gland



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Adaptive Radiation Therapy for Head and Neck Cancer—Can an Old Goal Evolve into a New Standard?

doi:10.1155/2011/690595

David L. Schwartz[1] and Lei Dong[2]

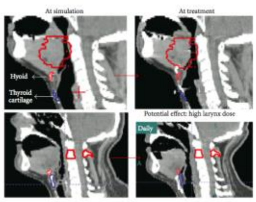

Figure 1: The positions of the hyoid and thyroid cartilages can change noticeably during the simulation or treatment delivery. Because the swallowing action is usually infrequent and has a short duration, a simulation CT could be biased towards an infrequent anatomical pose by the consequence of swallowing. If the hyoid and thyroid cartilages are captured at their most inferior positions (top row), the larynx may receive higher dose during treatment. In the converse situation, if the hyoid and thyroid cartilages are captured at their most superior positions during CT simulation (bottom row), a primary target near the base of tongue could be underdosed during treatment.

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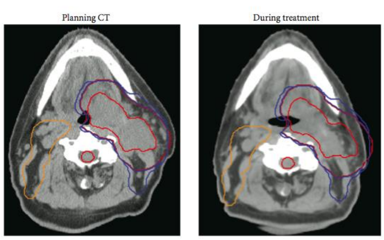

Figure 2: Anatomic changes can be pronounced during treatment. In this example, planning CT scan and CTV contours are shown on the left. On the right, a mid-course CT (three weeks into treatment) demonstrates significant reduction in gross tumor (thick red line). Baseline CTVs have been overlaid via rigid image registration. These match current anatomy poorly and in fact extend past the skin contour into air.

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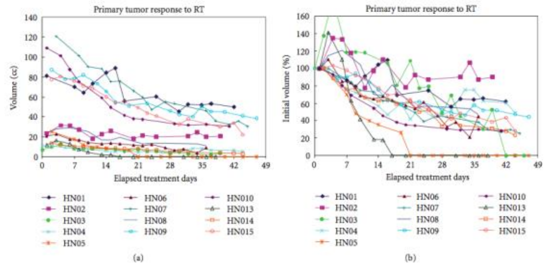

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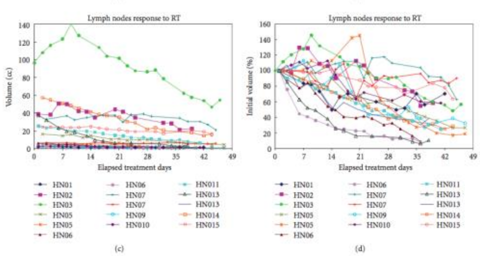

FIGURE 3: Gross tumor volume changes over time among patients with head and neck cancers. Both primary tumor (a) and (b) and lymph nodes greater than 2 cc of volume (c) and (d) are showing similar trend. The gross tumor volumes decreased at a median rate of 0.2 cc or 1.8% of initial volume per treatment day. (Reprinted from [8]).

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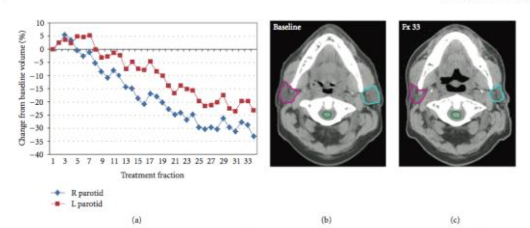

FIGURE 4: A case example of changes in parotid gland volume during a 33-fraction IMRT treatment course. (a) shows the percent of volume change for each parotid as a function of treatment fraction. The (b) and (c) shows an axial CT slice of the parotid before radiotherapy (b) and after 33 fractions of radiotherapy (c).

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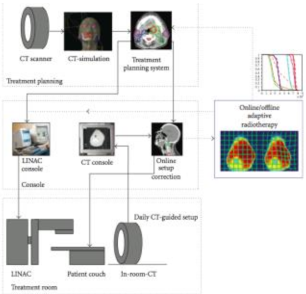

Figure 6: A workflow diagram for in-room CT or CBCT-guided adaptive radiotherapy. The first level of treatment modification is a simple couch shift to correct for daily setup errors (CT-guided IGRT). Nonrigid changes in tumor volumes and normal organs can then be corrected via an online or offline adaptive replanning process (dotted lines).

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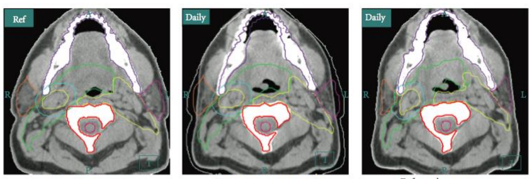

Reference planning CT (a) | Bone rigidly aligned daily CT (b) | Deformed contours to match with the daily CT (c)

Figure 7: The ART process for patient treatment starts with a rigid alignment (in this example, to the C2 vertebra) between the refere planning CT and the daily in-room CT ((a) and (b)). The planning contours are overlaid to the daily CT to verify setup accuracy anc evaluate if there are changes in current anatomy relative to baseline. If the changes are significant, as illustrated in (b), a deformable im registration can be performed to propagate original planning contours onto current anatomy. The resultant contours are shown on (c). T process takes less than 30 seconds

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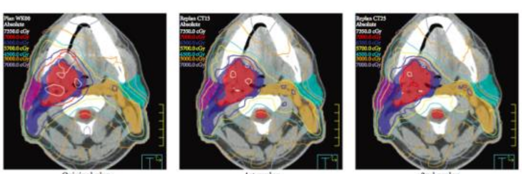
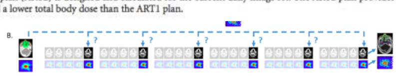


Original plan (a) | 1st replan (b) | 2nd replan (c)

Figure 8: An example of serial ART dose recalculation using a daily CT image acquired at the 25th treatment fraction. On (a), the original plan is calculated on current anatomy. The original plan provides inappropriate treatment margins and dose heterogeneity within the high-dose CTV. In the (b), an earlier ART replan (ART1, designed at the 15th treatment fraction) is calculated onto current anatomy. On (c), a 2nd ART replan (ART2) is designed and calculated for the current daily image set. The ART2 plan provides improved contralateral parotid sparing and a lower total body dose than the ART1 plan.



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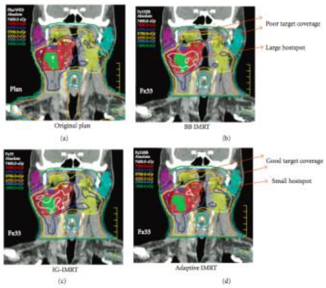

Figure 9: An example of cumulative dose evaluation for IMRT treatments without daily image guidance (alignment to the surface markers or "BBs"on the immobilization device) (BB-IMRT), image-guided IMRT (IG-IMRT), and image-guided adaptive IMRT described in this investigation (adaptive IMRT). Due to setup error, BB-IMRT has a tendency to underdose CTV.

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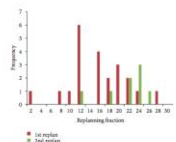

Figure 10: A histogram plot of the timing of the triggering fraction for replanning for the 1st replan and 2nd replan.

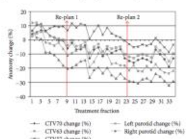

Figure 11: Volumetric changes for high-risk CTV (CTV70), intermediate-risk CTV (CTV63), low-risk CTV (CTV57), and parotid gland in a patient who had two replans performed during the course of treatment. The first replan occurred at the 9th treatment fraction, and the second replan was designed at the 23rd treatment fraction.

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

David L. Schwartz [a,b,c,*], Adam S. Garden [c], Shalin J. Shah [c], Gregory Chronowski [c], Samir Sejpal [c], David I. Rosenthal [c], Yipei Chen [d], Yongbin Zhang [d], Lifei Zhang [d], Pei-Fong Wong [c], John A. Garcia [c], K. Kian Ang [c], Lei Dong [d,e] http://dx.doi.org/10.1016/j.radonc.2012.10.010

Fig. 1. Detection of rapid tumor progression prior to start of treatment. The original plan is shown to the left; patient's anatomy on first treatment day is shown on the right. Primary GTV progressed by >50%. Arrows designate site of geographic miss for CTV1.

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Fig. 2. Uncorrected IGRT can potentially intensify bystander dose. In this example, correction of daily set-up error led to focusing of dose scatter to contralateral oral cavity by treatment day 12 which otherwise would have been redistributed by random daily set-up error.

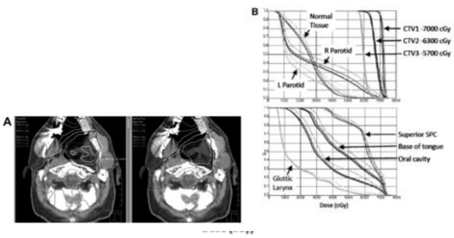
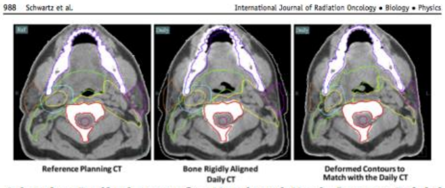


Fig. 3. (A) *Right:* Emergence of dose heterogeneity within high-risk CTV1 in a tonsillar carcinoma case at treatment fraction #11; *Left:* Restoration of intended dose distribution within CTV1 by adaptive replanning without PTV margin expansions. (B) DVH comparison for the original IMRT plan of this case (dotted lines), ART1 replan designed on treatment day 15 (thin solid lines), and the ART2 replan (thick solid lines), all re-calculated on CT anatomy obtained on 25th treatment day.

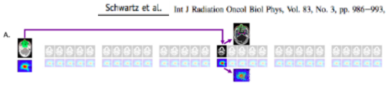
Strategy: Single-time point fixed adaptive

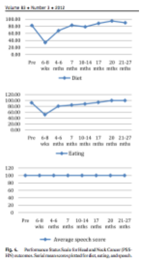
988 Schwartz et al. International Journal of Radiation Oncology • Biology • Physics

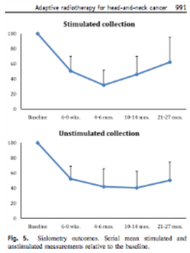


Adaptive Radiotherapy for Head-and-Neck Cancer: Initial Clinical Outcomes From a Prospective Trial

Schwartz et al. Int J Radiation Oncol Biol Phys, Vol. 83, No. 3, pp. 986–993, 2012



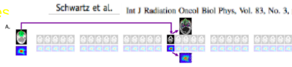




Patient reported outcomes

Objective toxicity

Schwartz et al. Int J Radiation Oncol Biol Phys, Vol. 83, No. 3, pp. 986–993, 2012



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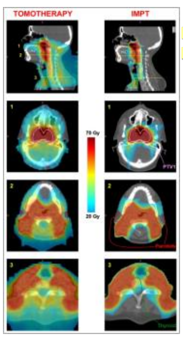
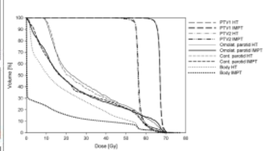


Equivalent Coverage but Reduced Dose Bath



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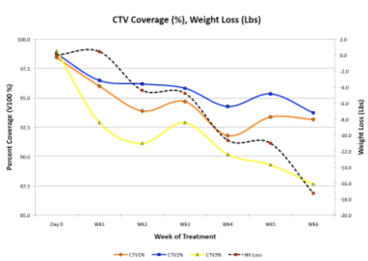
Weight loss and CTV Coverage

6 Bilateral Neck Cases



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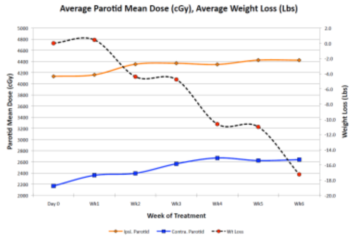
Weight loss and Parotids



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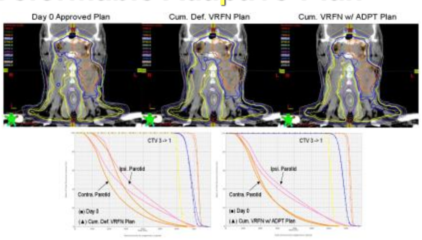
Cumulative Verification with Deformable Adaptive Plan



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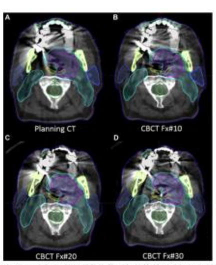
Predictive Models to Determine Clinically Relevant Deviations in Delivered Dose for Head and Neck Cancer

Practical Radiation Oncology (2019) **9**, e422-e431

63



1 Example of contours at planning, fraction 10, fraction 20, and fraction 30 of 1 patient, showing the deformed structures.

Table 1 Patient characteristics for original patient cohort and independent evaluation cohort

Original patient cohort	
Patients, n	100
Sex (male/female), n	80/20
Diagnosis site, n	
Pharynx	58
Larynx	21
Lip and oral cavity	16
Other	5
HPV status (positive/negative/unrecorded), n	59/13/28
CTV, mean (range), cm^3	154 (1-725)
CTV to PTV margin, mm	3
Prescribed dose, mean (range), Gy	68 (60-72)
Fractions (35/30/other), n	66/17/17
Patients with boost, n	10
Patients with replans, n	16
Elapsed treatment time, median (range), d	49 (39-74)
Intravenous contrast used in CT (Y/N), n	78/22
≥10% Weight loss over entire treatment, n	25
≥5% Weight loss over entire treatment, n	67
Patient characteristics − independent evaluation set	
Patients, n	52
Sex (male/female), n	36/16
Diagnosis site, n	
Pharynx	27
Sinonasal	12
Oral cavity	5
Larynx	1
Other	7
HPV status (positive/negative/unrecorded), n	10/10/32
GTV, mean (range), cm^3	45 (4-171)
Prescribed dose, mean (range), Gy	67 (60-70)
Fractions (35/33/32/30), n	14/27/1/10
Patients with boost, n	13
Patients with replans, n	13

Abbreviations: CT = computed tomography; CTV = clinical target volume; GTV = gross tumor volume; HPV = human papilloma-virus; PTV = planning target volume

Molly McCullcoh PhD

MD Anderson Cancer Center

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

Practical Radiation Oncology (2019) **9**, e422-e431

64

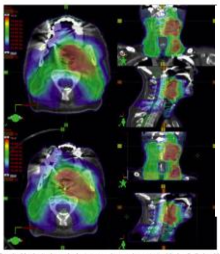
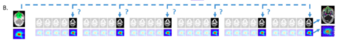


Figure 2 Example of the planning dose on the planning computed tomography scan (top) and the dose distribution of the sum calculated on the fraction 30 cone beam computed tomography scan (bottom).

Table 3 Planning and dose deviation thresholds for organs at risk and target volumes

Organ	Dose metric	Planning constraint, Gy	Dose deviation threshold, Gy
Inferior constrictor	Mean	20	3
Superior constrictor	Mean	50	7.5
Spinal canal	Max	45	3
High-risk CTV	D95%	±7% of Rx	4.10-5.18
Intermediate-risk CTV	D95%	±7% of Rx	2.83-5.17
Larynx	Mean	20	3
Oral cavity	Mean	30	4.5
Left/right parotid glands	Mean	24	3.6
Left/right submandibular glands	Mean	30	4.5



Molly McCullcoh PhD

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

Practical Radiation Oncology (2019) **9**, e422-e431

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Table 5 Number of organs with clinically relevant dose deviations and values of those deviations

Organ	Planning constraint, Gy	Dose deviation threshold, Gy	Total number of organs	Organs included in model	Organs exceeding deviation	Maximum deviation at completion of treatment, Gy	Minimum deviation by fraction 15, Gy
Spinal canal	45	3	99	99	1	3.1	NA
Left/right submandibular glands	30	4.5	176	85	7	8.22	3.5
Superior Constrictor	50	7.5	100	60	0		
Oral cavity	30	4.5	100	56	1	5.18	0.81
High-risk CTV	±7% × Rx	4.10-5.18	103	43	0		
Left parotid	24	3.6	100	37	1	3.77	3.08
Right parotid	24	3.6	99	34	0		
Intermediate-risk CTV	±7% × Rx	2.83-5.17	101	17	1	−6.65	−4.84
Inferior constrictor	20	3	97	12	1	5.62	5.86

Molly McCullcoh PhD

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 15 can predict the need to replan a patient.

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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)

Delta dose: (Delivered – Planned dose)

Structure	N (Manual)	Delta mean dose (Gy) Median	Range	P	Delta D1 (Gy) Median	Range	P
Brainstem	52 (50)	0.25	-3.92 – 3.78	0.14	1.03	-4.72 – 0.59	<0.001
Chiasm	31 (31)	0.62	-12.67 – 5.72	0.95	1.07	-8.20 – 9.67	0.71
Esophagus	52 (7)	0.00	-4.90 – 4.44	0.29	0.00	-8.25 – 6.29	0.85
Larynx	50 (12)	0.94	-8.14 – 10.93	0.006	0.10	-21.79 – 9.94	0.36
Mandible	51 (18)	-0.53	-6.24 – 2.93	0.001	-0.49	-8.26 – 6.28	0.001
Parotid Gland Contralateral	52 (49)	-0.21	-5.42 – 7.05	0.31	-0.47	-11.52 – 4.21	0.04
Parotid Gland Ipsilateral	50 (43)	0.01	-6.90 – 5.63	0.82	-0.44	-5.91 – 4.09	0.01
Spinal_cord	51 (51)	0.71	-1.62 – 4.09	<0.001	0.96	-3.20 – 8.09	<0.001
Submandibular Gland Contralateral	52 (15)	-0.010	-5.38 – 5.15	0.69	-0.14	-13.29 – 9.05	0.15
Submandibular Gland Ipsilateral	52 (6)	-0.003	-4.78 – 7.37	0.99	-0.25	-18.45 – 7.72	0.14

Jolien Heukelom MD NKI-AVL

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Table 2 | Prediction of final NTCP using NTCP at F10 or F15 using various ΔNTCP thresholds. The percentages indicate the decision to adapt treatment for every patient that has a predicted ΔNTCP of x% or higher in any of the four NTCP models, based on the dose difference at Fx, scaled to a full-treatment length.

7

	NTCP whole treatment	Clinical	F10 1%	F10 2%	F10 3%	F10 4%	F10 5%	F10 6%	F10 7%	F10 8%	F10 9%	F10 10%	F10 11%	F10 12%
ART for # patients	9	13	26	19	15	9	7	5	5	4	4	4	3	2
True positive		5	8	8	8	7	6	4	4	3	3	3	2	2
False positive		8	18	11	7	2	1	1	1	1	1	1	1	0
True negative		35	25	32	36	41	42	42	42	42	42	42	42	43
False negative		4	1	1	1	2	3	5	5	6	6	6	7	7
Sensitivity		0.56	0.89	0.89	0.89	0.78	0.67	0.44	0.44	0.33	0.33	0.33	0.22	0.22
Specificity		0.81	0.58	0.74	0.84	0.95	0.98	0.98	0.98	0.98	0.98	0.98	0.98	1.00
PPV		0.38	0.31	0.42	0.53	0.78	0.86	0.80	0.80	0.75	0.75	0.75	0.67	1.00
NPV		0.90	0.96	0.97	0.97	0.95	0.93	0.89	0.89	0.88	0.88	0.88	0.86	0.86
			F15 1%	F15 2%	F15 3%	F15 4%	F15 5%	F15 6%	F15 7%	F15 8%	F15 9%	F15 10%	F15 11%	F15 12%
ART for # patients			29	21	12	10	8	7	6	4	4	4	2	1
True positive			9	9	8	8	6	5	4	3	3	3	2	1
False positive			20	12	4	2	2	2	2	1	1	1	0	0
True negative			23	31	39	41	41	41	41	42	42	42	43	43
False negative			0	0	1	1	3	4	5	6	6	6	7	8
Sensitivity			1.00	1.00	0.89	0.89	0.67	0.56	0.44	0.33	0.33	0.33	0.22	0.11
Specificity			0.53	0.72	0.91	0.95	0.95	0.95	0.95	0.98	0.98	0.98	1.00	1.00
PPV			0.31	0.43	0.67	0.80	0.75	0.71	0.67	0.75	0.75	0.75	1.00	1.00
NPV			1.00	1.00	0.98	0.98	0.93	0.91	0.89	0.88	0.88	0.88	0.86	0.84

Abbreviations: ART: adaptive radiotherapy; F: fraction; NPV: negative predictive value; NTCP: normal tissue complication probability; PPV: positive predictive power; #: number of;

Jolien Heukelom MD NKI-AVL

Heukelom et al. (under review)

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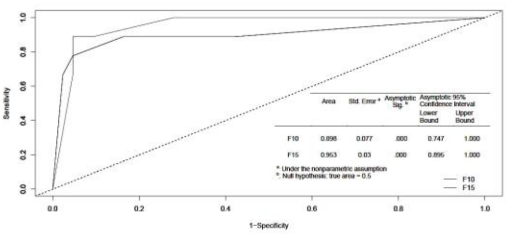
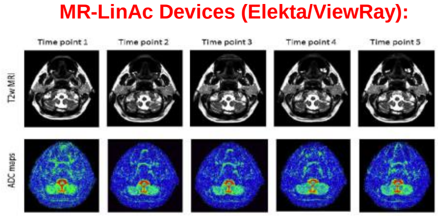
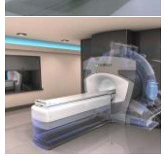


Jolien Heukelom MD NKI-AVL

So what's different now?

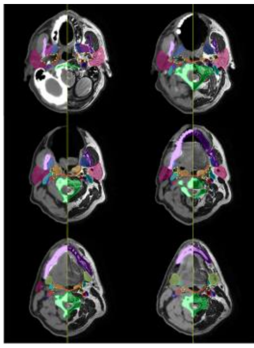
MR-LinAc Devices (Elekta/ViewRay):





Opportunity space

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



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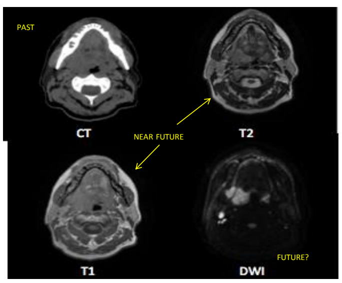

Figure 2: Image modalities with potential for adaptive replanning, showing improved soft-tissue contrast with T1/T2 MRI, and POSSIBLE improved tumor recognition with diffusion weighted imaging (DWI)

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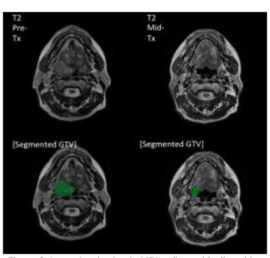

Figure 3: Interval reduction in MRI radiographically evident disease from pre-therapy (left panels) to mid-therapy (right panels); upper panel shows raw image data; lower panel shows gross tumor volume (GTV) segmentation , in green.

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Predicate Data

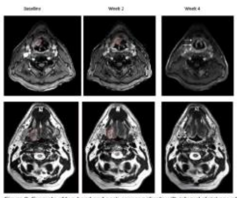

Figure 2: Example of two head and neck cancer patients with interval shrinkage of MRI radiographically evident growth tumor volume at week 2 of radiation treatment (dotted red contours) and complete response at week 4 (white arrows).

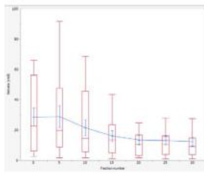

Figure 7: Boxplots of tumor regression kinetics in a subset of 26 patients with HPV+ oropharyngeal cancer treated with IMRT and received daily CT-on-rails

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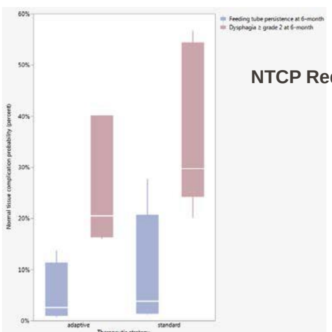

NTCP Reduction

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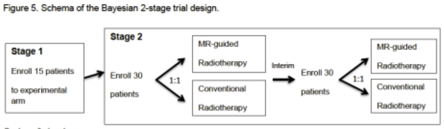
7.0 Statistical Considerations

7.1 Primary Endpoint

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

Figure 5. Schema of the Bayesian 2-stage trial design.



Ying Yuan, Ph.D
Professor,
Biostatistics,
MDACC

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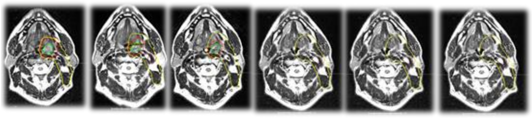
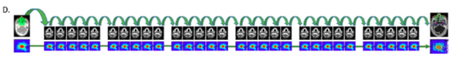
Bayesian Phase II Trial of Magnetic Resonance Imaging Guided Radiotherapy (MRgRT) Dose Adaptation in Human Papilloma Virus Positive Oropharyngeal Cancer

ClinicalTrials.gov ID: NCT03224000

Week 0 (sim)	Week 2	Week 3	Week 4	Week 5	Week 6



Patient # 1- MRgRT weekly dose adaptation



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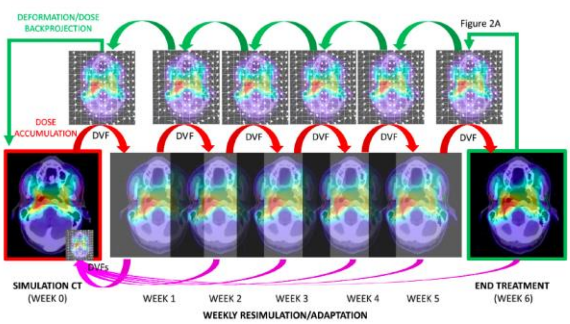

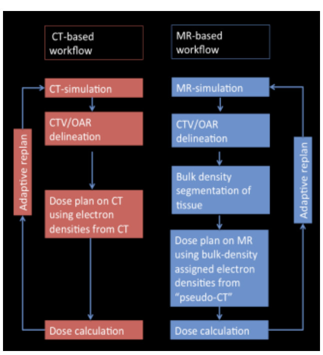

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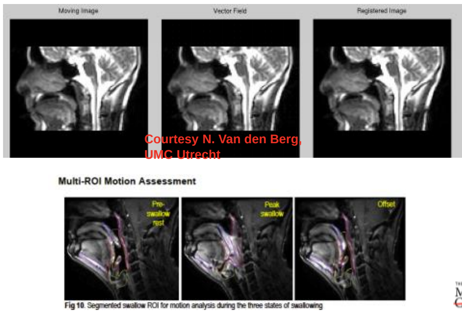

Fig 10. Segmented swallow ROI for motion analysis during the three states of swallowing

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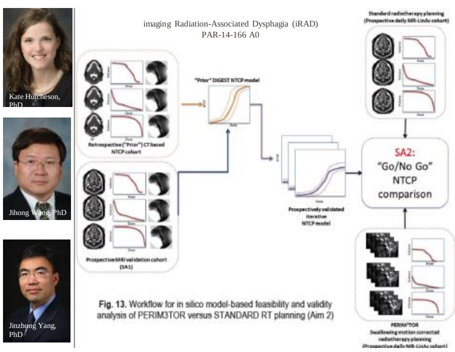

Fig. 13. Workflow for in silico model-based feasibility and validity analysis of PERIM3TOR versus STANDARD RT planning (Aim 2)

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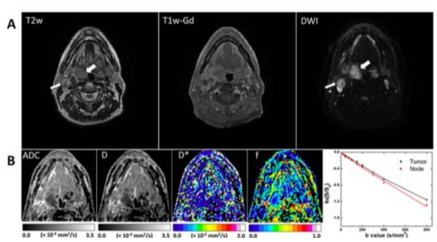
Intravoxel incoherent motion imaging kinetics during chemoradiotherapy for human papillomavirus-associated squamous cell carcinoma of the oropharynx: preliminary results from a prospective pilot study

NMR IN BIOMEDICINE



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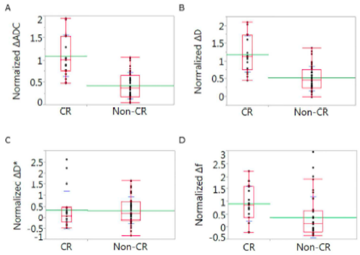

A box-plot depecting the differences between complete response (CR) and non-CR lesions in terms of normalized ΔADC (A), ΔD (B), ΔD* (C), and Δf (D).

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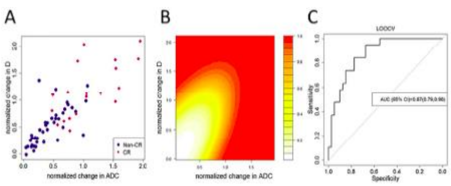
ΔDWI/IVIM denotes HPV+ early rapid responders!



(A) shows a scatterplot depicting mid-therapy changes in ΔADC and ΔD for patients experiencing presence/absence of complete response (CR). (B) shows a Contour plot depicting the posterior probability of observing complete response as a function of mid-therapy changes in ΔADC and ΔD obtained from analysis using Bayesian QDA. (C) shows a Receiver operating characteristics curve obtained from the Bayesian model for predicting complete response using mid-therapy changes in ΔADC and ΔD using leave-one-out cross-validation. Combined the parameters attained an AUC=0.87 (95% CI: 0.79, 0.96) with sensitivity=0.63, specificity=0.85, and accuracy=0.78.

NMR IN BIOMEDICINE MDAnderson Cancer Center

NIH Academic Industrial Partnership Award (1 R01 DE028290-01)

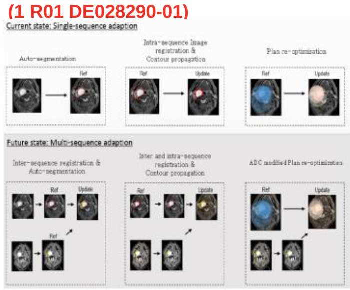


Figure 8: Diagram illustrating the conceptualized Elekta software development pipeline.

Fuller/Christodouleas/Kadbi

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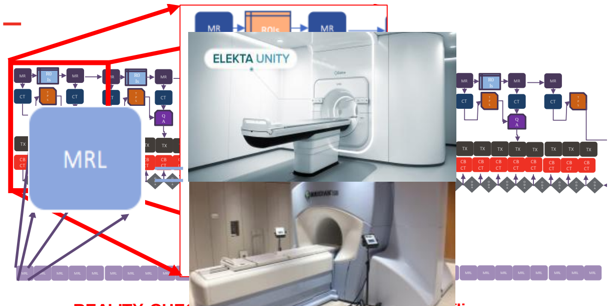

REALITY CHE ... line
MR-adaptive trial across multiple sites.

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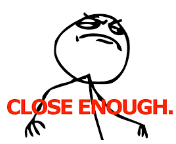
DOING WHAT IS BEST FOR PATIENTS BY ADAPTING

REALIZING ADAPTIVE IS COMPLICATED AND EXTRA WORK



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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.

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