Clinical Evidence For Adaptive Radiotherapy

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Disclosures

- Honoraria and travel grants from ViewRay, Inc.

Outline

- Definition of ART
- Clinical evidence for offline ART
- Clinical evidence for online ART
- Summary

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Definition of ART

- Earliest – Soviet paper in 1973
  - Oleinik & Klepper, "Determination of the optimal dynamic conditions for irradiating malignant neoplasms and adaptive radiation treatment" Meditsinskaia Radiologia 18(2):pp.49-54
- Most cited – 1997
  - Di Yan et al Phys. Med. Biol. 42 123

Definition of ART

- General paradigm
  - Identify that there is a clinically-significant change
    - Determine the probable rate of change and potential risk if unmanaged
  - Amend the planned radiation delivery to account for this change
    - Plan to amend as often as necessary based on rate of change and degree of risk optimized for efficiency of delivery
- Goals
  - Ensure treatment plan is being delivered as intended even if patient's anatomy changes
  - Margin reduction and safe dose escalation for possible improvement in treatment outcomes

Definition of ART

- Rate of change defines the categories of ART
  - Slow (over the course of several days to weeks) – Offline
    - General weight change (loss/gain)
    - Bulk tumor change
    - Major bulk organ change (e.g., collapsed lung reinflating)
  - Fast (over the course of several hours) – Online
    - Organ filling (bladder)
    - Daily organ motion with respect to treatment area (e.g., bowels)
  - Continuous – Dynamic
    - Change in position due to breathing (or peristalsis, etc.)

	Offline	Online	Dynamic
When to perform?	Between fractions.	Immediately prior to delivery.	During treatment delivery.
What imaging is required?	May use diagnostic, functional, and any other applicable type.	Volumetric imaging with FOV large enough to encompass area of interest.	Real-time (or near) continuous imaging of either tumor or effective surrogate.
What other technology is required?	Standard treatment planning and fusion tools.	Fast treatment planning system, phantom-less quality assurance process, method for determining or assigning electron density information.	Feedback mechanism for ensuring consistent accuracy during delivery (in-vivo or exit dosimetry, log file analysis), fast MLC and beam control.
What other resources are needed?	Additional simulation, image fusion, contouring, planning, and pre-treatment patient-specific QA.	Additional staff at the machine to do recontouring, planning, and QA.	
Applicable disease sites?	Any; typically head-and-neck, lung, pelvic sites involving nodes.	Abdominal lesions (pancreas, mets), prostate, bladder, cervix, lung.	Lung, abdomen, liver, prostate, cervix.
Available solutions	Standard clinical tools.	MVCT, CBCT, MR-IGRT, in-room MRI, in-room CT.	Dynamic MLC tracking, dynamic aperture tracking
Practical consideration	Easy but time-consuming; potential for interruption.	Difficult but potentially effective, long on-table time.	Difficult to implement, easy to use, limited to tumor only.

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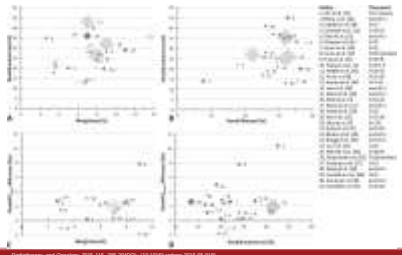
Clinical Evidence for Offline ART – Head & Neck

- Mulitple anatomic changes reported in the literature for HN sites
  - Weight loss
  - Parotid gland volume and density changes
  - CTV changes
- Most published reports focus on dosimetric impacts of these changes
- Several investigate whether the theoretical advantages of better dosimetric distributions actually make a difference for patients

Clinical Evidence for Offline ART – Head & Neck

(A) Parotid volume loss vs. patient's weight loss (22 studies), (B) parotid volume loss vs. planned parotid mean dose (20 studies), (C) parotid mean dose increase (repeat CT – plan CT) vs. weight loss (16 studies), and (D) parotid mean dose increase (repeat CT – plan CT) vs. parotid volume loss (23 studies) during radiotherapy. The size of the data points is proportional to the number of patients included in the study (minimum 10, maximum 87 patients). fx=fraction, tx=treatment. Time point: time of the repeat scan analysed.



Radiotherapy and Oncology 2015 115, 285-294DOI: (10.1016/j.radonc.2015.05.018)

Clinical Evidence for Offline ART – Head & Neck

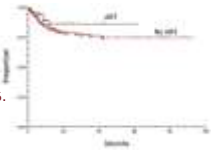
- Clinical outcomes among patients with head and neck cancer treated by intensity-modulated radiotherapy with and without adaptive replanning
  - Chen *et al.*, Head & neck 36.11 (2014): 1541-1546.
- Study Setup:
  - 317 patients with squamous cell carcinoma
  - Prescribed 60-74 Gy depending on operative status
  - 19% underwent adaptation midway through treatment
  - No standardized decision metrics for adaptation
- Treatment Modality:
  - IMRT

Clinical Evidence for Offline ART – Head & Neck

- Clinical outcomes among patients with head and neck cancer treated by intensity-modulated radiotherapy with and without adaptive replanning
  - Chen *et al.*, Head & neck 36.11 (2014): 1541-1546.
- Results:
  - Adaptation occurred in the range of 10-58 Gy, median 40 Gy
  - Predominant indications were weight loss, tumor shrinkage, poorly fitting mask, and prolonged treatment break
  - 30 patients replanned using a new CT scan
  - 21 patients replanned using MVCT data from Tomotherapy
  - Median time to new plan implementation was 3 days (1-7)

Clinical Evidence for Offline ART – Head & Neck

- Clinical outcomes among patients with head and neck cancer treated by intensity-modulated radiotherapy with and without adaptive replanning
  - Chen *et al.*, Head & neck 36.11 (2014): 1541-1546.
- Clinical outcomes:
  - Improvement in 2-year local-regional control for ART (88%) vs no ART (79%)
  - Incidence of grade 3+ acute toxicity was higher for ART (39%) than no ART (30%) but this may have been due to differences in characteristics between the two cohorts



Clinical Evidence for Offline ART – Head & Neck

- Image-guided adaptive radiotherapy improves acute toxicity during intensity-modulated radiation therapy for head and neck cancer
  - Chen et al., Journal of Radiation Oncology (2018): 1-7
- Study Setup:
  - 198 patients
  - 40% underwent ART midway through treatment
  - No standardized decision metrics for adaptation
- Treatment Modality:
  - IMRT

Clinical Evidence for Offline ART – Head & Neck

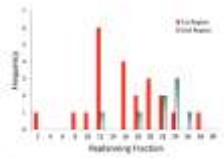
- Image-guided adaptive radiotherapy improves acute toxicity during intensity-modulated radiation therapy for head and neck cancer
  - Chen et al., Journal of Radiation Oncology (2018): 1-7
- Clinical Outcomes:
  - Reduction in grade 3+ skin toxicity (15% with ART vs 35%)
  - Reduction in grade 3+ oral mucositis (15% vs 29%)
  - Both groups had similar local-regional control and overall survival

Clinical Evidence for Offline ART – Head & Neck

- Adaptive radiotherapy for head-and-neck cancer: initial clinical outcomes from a prospective trial.
  - Schwartz, David L., et al., International Journal of Radiation Oncology* Biology* Physics 83.3 (2012): 986-993.
- Study setup:
  - 24 patients prospectively enrolled, 22 analyzed
  - Oropharyngeal squamous cell carcinoma
  - Daily evaluation of in-room CT imaging
  - Gross anatomy changes resulting in suboptimal target coverage or inadequate sparing were triggers for adapting
  - Offline treatment planning, review, and QA process
  - Reduced CTV to PTV margin from 3-4 mm to zero at ART replan
- Treatment modality:
  - IMRT

Clinical Evidence for Offline ART – Head & Neck

- Adaptive radiotherapy for head-and-neck cancer: initial clinical outcomes from a prospective trial.
  - Schwartz, David L., et al., International Journal of Radiation Oncology* Biology* Physics 83.3 (2012): 986-993.
- Results:
  - All patients had at least one replan per protocol
  - 36% (8 patients) required a second replan



Clinical Evidence for Offline ART – Head & Neck

- Adaptive radiotherapy for head-and-neck cancer: initial clinical outcomes from a prospective trial.
  - Schwartz, David L., et al., International Journal of Radiation Oncology* Biology* Physics 83.3 (2012): 986-993.
- Clinical Outcomes:
  - 100% local control at 2 years
  - 95% regional control at 2 years
  - Acute toxicity comparable to average
  - Early chronic toxicity results hint at post-treatment functional recovery but it's too early to determine

Clinical Evidence for Offline ART – Lung

- Local control and toxicity of adaptive radiotherapy using weekly CT imaging: results from the LARTIA trial in stage III NSCLC.
  - Ramella, Sara, et al., Journal of Thoracic Oncology 12.7 (2017): 1122-1130.
- Study design:
  - 217 patients underwent weekly CT simulation
  - 45-75 Gy delivered with standard fractionation and concurrent chemotherapy
  - Trigger for adaptation determined by agreement between two physicians that the tumor change was present and clinically significant (undefined)
- Treatment modality:
  - 3D conformal

Clinical Evidence for Offline ART – Lung

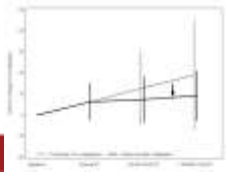
- Local control and toxicity of adaptive radiotherapy using weekly CT imaging: results from the LARTIA trial in stage III NSCLC.
  - Ramella, Sara, et al., Journal of Thoracic Oncology 12.7 (2017): 1122-1130.
- Results:
  - 50 patients were replanned as a result of the weekly CTs
  - Median dose for replanning was 45 Gy (25 fractions at 1.8 Gy day)
- Clinical Outcomes:
  - Low incidence of toxicity – 2 & 4% as compared to RTOG9410 rates of 13 & 17% for Grade 3+ pulmonary or esophageal, respectively
  - Local failure rate (30%) comparable to previous RTOG studies with and without hypofractionation

Clinical Evidence for Offline ART – Liver

- Individualized adaptive stereotactic body radiotherapy for liver tumors in patients at high risk for liver damage: a phase 2 clinical trial.
  - Feng, Mary, et al., JAMA oncology 4.1 (2018): 40-47.
- Study Design:
  - To safely deliver SBRT for HCC patients with compromised liver function via biomarker-based ART
  - Determined extent of liver damage by evaluating indocyanine green (ICG) extraction after first portion of SBRT, used this to adapt treatment for the second portion
- Treatment modality:
  - Either 3D conformal or IMRT (if adjacent organs at risk)

Clinical Evidence for Offline ART – Liver

- Individualized adaptive stereotactic body radiotherapy for liver tumors in patients at high risk for liver damage: a phase 2 clinical trial.
  - Feng, Mary, et al., JAMA oncology 4.1 (2018): 40-47.
- Results:
  - 90 patients with 119 tumors received treatment
  - Treatment adapted for 42% of the tumors
- Clinical Outcomes:
  - Estimated local control at 1 year was 99%
  - (expected 65%)
  - Lower decline in liver function



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Clinical Evidence for Dynamic ART – Bladder

- Prospective phase II study of image-guided local boost using a real-time tumor-tracking radiotherapy (RTRT) system for locally advanced bladder cancer.
  - Nishioka, Kentaro, et al., Japanese journal of clinical oncology 44.1 (2013): 28-35.
- Study setup:
  - 14 patients treated with chemoradiotherapy
  - 40 Gy RT after transurethral tumor resection
  - Marker implantation followed by a 25-Gy boost
- Treatment modality:
  - IMRT
  - Continuous fluoroscopy to visualize markers and make table corrections as necessary during treatment

Clinical Evidence for Dynamic ART – Bladder

- Prospective phase II study of image-guided local boost using a real-time tumor-tracking radiotherapy (RTRT) system for locally advanced bladder cancer.
  - Nishioka, Kentaro, et al., Japanese journal of clinical oncology 44.1 (2013): 28-35.
- Clinical outcomes:
  - All patients preserved native bladder
  - 64% local control at 5 years – comparable to reported outcomes for both combined modality therapy and cystectomy

Clinical Evidence for Online ART – Brachytherapy

- Clinical outcome of protocol based image (MRI) guided adaptive brachytherapy combined with 3D conformal radiotherapy with or without chemotherapy in patients with locally advanced cervical cancer.
  - Pötter R et al., Radiother Oncol 100(1):116-123, 2011
- MRI-guided adaptive radiotherapy in locally advanced cervical cancer from a Nordic perspective.
  - Lindegaard JC et al., Acta Oncol 52(7):1510-1519, 2013
- Study Setup:
  - Cervical cancer patients (Vienna=156, Aarhus=140)
  - Prescribed dose of 80-85 Gy
- Treatment modality:
  - MRI-guided radiotherapy per GEC-ESTRO guidelines combined with definitive 3D conformal radiotherapy and chemotherapy

Clinical Evidence for Online ART – Brachytherapy

- Clinical outcome of protocol based image (MRI) guided adaptive brachytherapy combined with 3D conformal radiotherapy with or without chemotherapy in patients with locally advanced cervical cancer.
  - Pötter R et al., Radiother Oncol 100(1):116-123, 2011
- MRI-guided adaptive radiotherapy in locally advanced cervical cancer from a Nordic perspective.
  - Lindegaard JC et al., Acta Oncol 52(7):1510-1519, 2013
- Results:
  - Dose volume adaptation in >90% of patients
- Clinical Outcomes:
  - 30% improvement in overall survival (as compared to historical controls)
  - Significant reduction in both early and late morbidity

Clinical Evidence for Online ART – Oligometastases

- Phase I Trial of Stereotactic MR-Guided Online-Adaptive Radiotherapy (SMART)
  - Henke LE et al, *Radiother. Oncol.* 2017
- Study Setup:
  - 20 patients with unresectable primary or oligometastatic disease of the liver (n = 10) & non-liver (n=10) abdomen planned for SBRT
  - Prescription: 50Gy/5fx
  - Isotoxicity approach, with dose escalation (or de-escalation) based on hard OAR constraints
- Treatment modality:
  - Tri-cobalt 0.35-T MR-IGRT
    - Daily large-FOV MR imaging
    - Real-time, real-anatomy tracking and gating

Clinical Evidence for Online ART – Oligometastases

- Phase I Trial of Stereotactic MR-Guided Online-Adaptive Radiotherapy (SMART)
  - Henke LE et al, *Radiother. Oncol.* 2017
- Results:
  - 83% (79/95) fxs adapted—all patients had at least 1 adaptation
  - Plans adapted for 64% of liver & 98% of non-liver abdomen fxs
  - Initial plans would have violated OAR constraints in 70/95 fxs
  - 100% of OAR violations resolved with adaptive planning
- Clinical Outcomes:
  - No Grade 3+ toxicity at median 11.8 mo f/u
  - Expected up to 30% based on prior reports accounting for motion (Hoyer, et al. 2005)
  - No change in patient-reported quality-of-life scores (P=0.29)
  - 95% and 90% control of treated lesions at 3 and 6 months by RECIST criteria

Clinical Evidence for Online ART – Pancreas

- Higher Maximum Biological Effective Dose Utilizing Adaptive MRI Guided Radiation Therapy Improves Survival of Inoperable Pancreatic Cancer Patients
  - Rudra, Jiang, Rosenberg, Olsen, Lagerwaard, Bruynzeel, Parikh, Bassetti, Lee, Int J Radiat Oncol Biol Phys. 2017;99:0
- Study Setup:
  - Multi-institutional retrospective analysis of 42 patients
  - Prescription: variable, analyzed as a function of BED10
- Treatment modality:
  - Tri-cobalt 0.35-T MR-IGRT
    - Daily large-FOV MR imaging
    - Real-time, real-anatomy tracking and gating

Clinical Evidence for Online ART – Pancreas

- Higher Maximum Biological Effective Dose Utilizing Adaptive MRI Guided Radiation Therapy Improves Survival of Inoperable Pancreatic Cancer Patients
  - Rudra, Jiang, Rosenberg, Olsen, Lagerwaard, Bruynzeel, Parikh, Bassetti, Lee, Int J Radiat Oncol Biol Phys. 2017;99:0
- Results:
  - All patients with maximum BED > 90 Gy adapted (n=23)

50 Gy / 5 fractions	100 Gy
67.5 Gy / 15 fractions	97.5 Gy
40 Gy / 5 fractions	72 Gy
60 Gy / 30 fractions	72 Gy
55 Gy / 25 fractions	67.1 Gy
33 Gy / 5 fractions	54.5 Gy

Clinical Evidence for Online ART – Pancreas

- Higher Maximum Biological Effective Dose Utilizing Adaptive MRI Guided Radiation Therapy Improves Survival of Inoperable Pancreatic Cancer Patients
  - Rudra, Jiang, Rosenberg, Olsen, Lagerwaard, Bruynzeel, Parikh, Bassetti, Lee, Int J Radiat Oncol Biol Phys. 2017;99:0
- Clinical Outcomes:
  - No acute grade 3+ GI toxicity for BED>90Gy
  - Would normally expect ~22% rate of grade 3 acute GI toxicity with a dose of 55 Gy in 25 fractions
    - Badiyan AJCO 2016

Gr 3+ GI Toxicity	
maxBED$_{10}$>90	0%
maxBED$_{10}$<90	15.8%

Summary of Clinical Evidence

- Offline:
  - Necessary for obvious bulk changes in patient weight or tumor volume
  - Promising in HN to decrease toxicity and preserve function
  - Very promising liver biomarker results
- Online:
  - Brachytherapy – MR-guided adaptation has clear benefit
  - External beam – in its infancy, more trials needed, but promising results
- Dynamic:
  - No extensive trials yet, but promising approach in combination with online ART so as to account for both daily variation in position of normal tissues relative to target as well as continuous target motion during delivery
- Overall:
  - 104 trials for adaptive radiotherapy registered on clinicaltrials.gov, 3 have posted results, awaiting publication

Practical Implementation of ART: Requirements

- Any version of adaptation requires a decision support framework
- Need to have:
  - Trigger for adaptation
    - Offline – weight change, observed bulk tumor change, predetermined biomarkers or other functional changes
    - Online – violation of predetermined daily constraints, changes in anatomy enabling dose escalation
    - Dynamic – observable, trackable motion
  - Efficient process for acquisition of data necessary for adaptation
    - Offline – additional imaging
    - Online – recontouring, new electron density information
    - Dynamic – sufficiently fast acquisition of motion information
  - Analysis of potential failure points to ensure standard of care is maintained
  - Decision regarding dose accumulation

Thank you for your time!

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SCHOOL OF MEDICINE

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