OFFLINE
ADAPTIVE
RADIOThERAPY

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ANADOLU
In Affiliation with
JOHNS HOPKINS MEDICINE
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OVERVIEW

▪ Is there a need for adaptation?
  – Clinical rationale
  – Head and neck
  – Lung

▪ The workflow

▪ The uncertainties
  – Deformable registration (DIR)

▪ Cost / benefit

▪ How do we do it?
▪ Important role in cancer management

▪ Improvement is impeded by variability
  – Dosimetric variation by daily set up error
  – Radiation beam placement error
  – Changes of patient anatomical position, shape, and volume (weight loss, tumor response)
  – Biological variation throughout the treatment (the information from the PET images)
ADAPTIVE RADIOTHERAPY

Feedback control strategy to include patient-specific treatment variation in the control of treatment planning and delivery during the treatment course.

- To cope with treatment variation
- Increase of radiation dose delivery accuracy
- Potential improvement in radiotherapy efficacy after patient-specific biological changes

- To date limited to target position or OAR correction alone

Yan et al, 2010
EVOLUTION OF ADAPTATION

- Basic
- Simple replan to respond to the change within the patient
- New treatment plan using the same clinical criteria
- Ad hoc
- No information about the delivered dose, the toxicity rates, and the benefit of adaptation
- Using the clinical resources for non-documented (and probably well-understood) benefits

Subjective

Brook et al, 2019
EVOLUTION OF ADAPTATION

- Increase of technology
- Volumetric imaging and auto segmentation (deformable registration)
- Enables the daily dose calculated
- The decision of adaptation based on dosimetry not geometry
- Outcomes according to the TCP and NTCP

Brook et al, 2019
EVOLUTION OF ADAPTATION

▪ Additional evaluation of functional changes of the patient
▪ Online replanning
▪ Computational advances; artificial intelligence (AI)
▪ Advanced in-room imaging; MR-guided delivery
▪ The increasing amount of data acquired on clinical trials

**Brook et al, 2019**
ARTIFICIAL INTELLIGENCE (AI)

- To decrease the workload
  - Contouring
  - Registration
  - Planning
  - Quality assurance (QA)
  - Decision-making

- Objective

- Time consuming

- To change impossible into probable
Clinical practice - rationale

- Clinical implementation is complex
- Requires fundamental shift of the infrastructure
- No level I evidence to prove the benefit
- No international guidelines
- Clinical data
  - Head-and-neck cancer
  - Lung cancer
  - Cervical cancer
  - Liver cancer
  - Bladder cancer
  - Prostate cancer
ART IN HEAD AND NECK CANCER

- Standard of care in organ sparing treatment
- 7-week period
- Major anatomical changes (weight loss, parotid / tumor shrinkage)
- Under / over dosage of target and OAR
- With the advent of 3D serial imaging
- Customized planning throughout the treatment
- Daily set-up accuracy
### Table 1: Clinical Benefits of ART in Patients With Head and Neck Cancer

<table>
<thead>
<tr>
<th>Author (year)</th>
<th>Nb Patients</th>
<th>Tumor site</th>
<th>Total dose (Gy)</th>
<th>Replanning Strategies</th>
<th>Follow-Up (months)</th>
<th>Locoregional Control and Survival</th>
<th>Acute Toxicity</th>
<th>Late Toxicity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Schwartz et al(^1)</td>
<td>22</td>
<td>OPC</td>
<td>66-70</td>
<td>1 or 2 16th and 22nd fr</td>
<td>31</td>
<td>2-year LRC = 95% G II xerostomia = 55% G III xerostomia = 5%</td>
<td>Full preservation or functional recovery of speech and eating at 20 months</td>
<td></td>
</tr>
<tr>
<td>Kataria et al(^6)</td>
<td>36</td>
<td>LAHNC</td>
<td>70</td>
<td>1 54 Gy</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yang et al(^7)</td>
<td>86</td>
<td>NPC</td>
<td>70-76</td>
<td>1 or 2 15th and/or 25th fr</td>
<td>29</td>
<td>2-year DFS = 72% 2-year OS = 75%</td>
<td>G II-III mucosal = 100% G II xerostomia = 8%</td>
<td>Improvements in quality of life with ART</td>
</tr>
<tr>
<td>Chen et al(^11)</td>
<td>51</td>
<td>LAHNC</td>
<td>60b 70c</td>
<td>1 40 Gy (10-58 Gy)</td>
<td>30</td>
<td>2-year LRC 97.2% (ART) 82.2% (No-ART) (P = 0.04) 2-year OS 89.8% (ART) 82.2% (No-ART) (P = 0.47)</td>
<td>G III: 39% (ART) 30% (No-ART) (P = 0.45)</td>
<td></td>
</tr>
<tr>
<td>Zhao et al(^7)</td>
<td>33</td>
<td>NPC</td>
<td>70</td>
<td>1 15th (≤) or fr</td>
<td>38</td>
<td>3-year LRFS  72.7% (ART) 68.1% (No-ART) (P = 0.3)</td>
<td>G III: 14% (ART) 10% (No-ART) (P = 0.71)</td>
<td>No difference except less xerostomia and mucosal with ART for N2 and N3 patients</td>
</tr>
</tbody>
</table>
# ART IN HEAD AND NECK CANCER

## Table 2: Dosimetric Benefits of ART in Patients With Head and Neck Cancer (From Castelli et al)

<table>
<thead>
<tr>
<th>Author (year)</th>
<th>Nb Patients</th>
<th>Replanning Strategies</th>
<th>Dosimetric Analysis</th>
<th>Dosimetric Benefit</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Nb</td>
<td>Timing</td>
<td>Time Point to Cumulate the Dose</td>
<td>Method to Cumulate the Dose</td>
</tr>
<tr>
<td>Capelle (2012)</td>
<td>20</td>
<td>3rd week</td>
<td>2</td>
<td>Average DVH</td>
</tr>
<tr>
<td>Castelli (2015)</td>
<td>15</td>
<td>Weekly</td>
<td>7</td>
<td>DIR</td>
</tr>
<tr>
<td>Dewan (2016)</td>
<td>30</td>
<td>40 Gy</td>
<td>2</td>
<td>DVH</td>
</tr>
<tr>
<td>Duma (2012)</td>
<td>11</td>
<td>16th (9th-21st) fr</td>
<td>1</td>
<td>DVH</td>
</tr>
<tr>
<td>Jensen (2012)</td>
<td>15</td>
<td>2 to 4</td>
<td>3 to 5</td>
<td>DIR</td>
</tr>
<tr>
<td>Olteanu (2014)</td>
<td>10</td>
<td>–</td>
<td>–</td>
<td>DIR</td>
</tr>
<tr>
<td>Schwartz (2013)</td>
<td>22</td>
<td>16th and 22nd fr</td>
<td>2 or 3</td>
<td>DIR</td>
</tr>
<tr>
<td>Zhao (2011)</td>
<td>33</td>
<td>15th (±) fr</td>
<td>2</td>
<td>DVH</td>
</tr>
</tbody>
</table>
ART IN HEAD AND NECK CANCER

- Majority willing to increase the use of ART in head and neck
  - To improve clinical outcome
  - Improve productivity
  - Improve therapeutic ratio

- Barriers:
  - The lack of equipment
  - Lack of training
  - Lack of tools / support
  - Resource heavy
  - Time consuming

_Krishnatry R et al, 2018_
ART IN LUNG CANCER

- Chemoradiation to 60-70 Gy in locally advanced disease
- 6-7 week period
- The addition of immunotherapy increases survival
- No room for dose escalation
- 30-35% local recurrence
- Lung and heart toxicity effects survival
ART IN LUNG CANCER

− Midtreatment anatomical changes (tumor regression, tumor displacement, pleural effusion, and/or atelectasis)
− Limited consensus

3 philosophy:
– Maintain prescribed dose to the initially defined target volume
– Dose reduction to healthy organs while maintaining initial prescribed dose to a regressing tumor volume
– Dose escalation to a regressing tumor volume with isotoxicity to healthy organs.

**Table 1** Lung Density Changes Observed Across Multiple Large Patient Studies During Radiation Therapy Treatments

<table>
<thead>
<tr>
<th>Study</th>
<th>No. Patients</th>
<th>Tumor Anatomical Shift</th>
<th>Atelectasis</th>
<th>Pleural Effusion</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kwint (2014)</td>
<td>177</td>
<td>27%</td>
<td>19%</td>
<td>6%</td>
</tr>
<tr>
<td>Elsayad (2016)</td>
<td>71</td>
<td>10%</td>
<td>20%</td>
<td>25%</td>
</tr>
<tr>
<td>Moller (2014)</td>
<td>163</td>
<td></td>
<td>15%</td>
<td>8%</td>
</tr>
<tr>
<td>Van Zwienen (2008)</td>
<td>114</td>
<td></td>
<td>29%</td>
<td>13%</td>
</tr>
</tbody>
</table>

**Table 2** Tumor Regression Rates for Patients Diagnosed With Stage III NSCLC Treated With Definitive Radiation

<table>
<thead>
<tr>
<th>Study</th>
<th>No. Patients</th>
<th>Imaging Modality</th>
<th>Volume</th>
<th>Midtreatment Tumor Reduction</th>
<th>Near End of treatment Tumor Reduction</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Median Fraction (Range)</td>
<td>Median Regression (Range)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Median Fraction (Range)</td>
<td>Median Regression (Range)</td>
</tr>
<tr>
<td>Kataria (2014)</td>
<td>15</td>
<td>Helical kVCT</td>
<td>GTVp</td>
<td>22nd-23rd</td>
<td>−34% (−13.8% to −73.0%)</td>
</tr>
<tr>
<td>Spoelstra (2009)</td>
<td>21</td>
<td>Helical kVCT</td>
<td>ITVp</td>
<td>15th (14th-17th)</td>
<td>Not reported (−47% to −25%)</td>
</tr>
<tr>
<td>Berkovic (2015)</td>
<td>41</td>
<td>kV CBCT</td>
<td>GTVp</td>
<td>−</td>
<td>−</td>
</tr>
<tr>
<td>Fox (2009)</td>
<td>22</td>
<td>Helical kVCT</td>
<td>GTVp</td>
<td>15th (4th-20th)</td>
<td>−24.7% (−0.3% to −61.7%)</td>
</tr>
<tr>
<td>Wald (2017)</td>
<td>52</td>
<td>kV CBCT</td>
<td>GTVp</td>
<td>11th</td>
<td>−30% (−24.0% to −84.3%)</td>
</tr>
<tr>
<td>Elsayad (2016)</td>
<td>37</td>
<td>kV CBCT</td>
<td>GTVp</td>
<td>−</td>
<td>−</td>
</tr>
<tr>
<td>Ramella (2017)</td>
<td>50</td>
<td>Helical kVCT</td>
<td>CTV</td>
<td>−</td>
<td>−</td>
</tr>
<tr>
<td>Seibert (2007)</td>
<td>17</td>
<td>MVCT</td>
<td>GTVp</td>
<td>−</td>
<td>−</td>
</tr>
</tbody>
</table>

Studies Include a Combination of Sequential and Concurrent Chemotherapy.

* mean. CBCT, cone beam CT. GTVp, primary gross tumor volume. ITVp, primary internal target volume. CTV, clinical target volume.
ART IN LUNG CANCER

- 125 patient – 20% ART
- 3-4th week
- Daily CBCT
- Dose to PTV and OAR
<table>
<thead>
<tr>
<th>OAR</th>
<th>Constraints</th>
<th>IMRT&lt;sub&gt;In&lt;/sub&gt;</th>
<th>IMRT&lt;sub&gt;Proj&lt;/sub&gt;</th>
<th>IMRT&lt;sub&gt;ADAPT&lt;/sub&gt;</th>
<th>IMRT&lt;sub&gt;In&lt;/sub&gt; vs. IMRT&lt;sub&gt;Proj&lt;/sub&gt;</th>
<th>IMRT&lt;sub&gt;Proj&lt;/sub&gt; vs. IMRT&lt;sub&gt;ADAPT&lt;/sub&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Lung</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>V&lt;sub&gt;5&lt;/sub&gt; (cc)</td>
<td>50</td>
<td>54</td>
<td>40</td>
<td>0.01</td>
<td>0.003</td>
<td></td>
</tr>
<tr>
<td>V&lt;sub&gt;20&lt;/sub&gt; (cc)</td>
<td>24</td>
<td>28</td>
<td>20</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
<td></td>
</tr>
<tr>
<td>D&lt;sub&gt;MLD&lt;/sub&gt; (cGy)</td>
<td>1429.45</td>
<td>1680.66</td>
<td>1167.59</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
<td></td>
</tr>
<tr>
<td><strong>Heart</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>V&lt;sub&gt;20&lt;/sub&gt; (%)</td>
<td>22.37</td>
<td>19.6</td>
<td>13.42</td>
<td>0.166</td>
<td>0.024</td>
<td></td>
</tr>
<tr>
<td>V&lt;sub&gt;60&lt;/sub&gt; (%)</td>
<td>4.03</td>
<td>3.68</td>
<td>1.48</td>
<td>0.751</td>
<td>0.012</td>
<td></td>
</tr>
<tr>
<td><strong>Spinal Cord</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>D&lt;sub&gt;MAX&lt;/sub&gt; (cGy)</td>
<td>4056.06</td>
<td>4527.32</td>
<td>3778.32</td>
<td>0.025</td>
<td>0.007</td>
<td></td>
</tr>
<tr>
<td>D&lt;sub&gt;MLD&lt;/sub&gt; (cGy)</td>
<td>2763.77</td>
<td>2994.32</td>
<td>2290.99</td>
<td>0.076</td>
<td>&lt;0.001</td>
<td></td>
</tr>
<tr>
<td><strong>Esophagus</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>V&lt;sub&gt;40&lt;/sub&gt; (%)</td>
<td>35.12</td>
<td>38.07</td>
<td>27.24</td>
<td>0.146</td>
<td>0.006</td>
<td></td>
</tr>
<tr>
<td>D&lt;sub&gt;MAX&lt;/sub&gt; (cGy)</td>
<td>6681052</td>
<td>6836.35</td>
<td>6815.68</td>
<td>0.009</td>
<td>0.927</td>
<td></td>
</tr>
<tr>
<td><strong>Body</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>D&lt;sub&gt;MAX&lt;/sub&gt; (%)</td>
<td>110.57</td>
<td>114.5</td>
<td>109.76</td>
<td>&lt;0.001</td>
<td>0.001</td>
<td></td>
</tr>
</tbody>
</table>
CLINICAL CHALLENGES FOR LUNG ART

When to adapt?
- At least weekly 3D imaging
- Mid treatment
- 3-4th week (80%)

How to adapt?
- Which philosophy?
KEY TECHNOLOGIES FOR PRACTICAL WORKFLOW

- 3D imaging
- Assessment (manual evaluation to highly automated review of cumulative dose)
- Replanning (standard planning for offline – time!!!)
- QA
THE UNCERTAINTIES

- Deformable registration (DIR)
  - Commissioning
- Auto-segmentation
- Dose accumulation
HOW DO WE DO IT?

- Full neck radiotherapy, head and neck cancer
- Radixact® System
- 10/2018
- Ongoing adaptive workflow for linac treatments
- PreciseART® since mid 2019
HOW DO WE DO IT?

▪ All patients are potential for adaptation
▪ Enroll to PreciseART® during plan approval
▪ Template (OAR and PTV)
▪ Dedicated IGRT dosimetrist from the second week
  – 2 days a week
▪ PreciseART® software check
HOW DO WE DO IT?
Total Planned vs Projected Dose

<table>
<thead>
<tr>
<th>Contour</th>
<th>Constraint Name</th>
<th>Total Planned</th>
<th>Fulfilled</th>
<th>Projected dose</th>
<th>Fulfilled</th>
<th>% Change</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oral Cavity</td>
<td>Oral Cavity Dmax&gt;300 Gy</td>
<td>2991.67</td>
<td>✔</td>
<td>3131.11</td>
<td>✔</td>
<td>4.66</td>
</tr>
<tr>
<td>PTV60rev</td>
<td>PTV60rev, Dmax&gt;60 Gy</td>
<td>6029.11</td>
<td>✔</td>
<td>6031.68</td>
<td>✔</td>
<td>0.02</td>
</tr>
<tr>
<td>PTV60rev</td>
<td>PTV60rev, Dmax&lt;60 Gy</td>
<td>6595.48</td>
<td>✔</td>
<td>7148.27</td>
<td>✔</td>
<td>8.38</td>
</tr>
<tr>
<td>PTV66rev</td>
<td>PTV66rev, Dmax&lt;60.6 Gy</td>
<td>6941.2</td>
<td>✔</td>
<td>7201.51</td>
<td>✔</td>
<td>3.75</td>
</tr>
<tr>
<td>PTV70rev</td>
<td>PTV70rev, Dmax&lt;70 Gy</td>
<td>7182.26</td>
<td>✔</td>
<td>6932.33</td>
<td>✔</td>
<td>-5.72</td>
</tr>
<tr>
<td>R Parotid</td>
<td>R Parotid, Dmax&lt;100 Gy</td>
<td>2812.98</td>
<td>✔</td>
<td>3526.52</td>
<td>✔</td>
<td>21.06</td>
</tr>
<tr>
<td>L Parotid</td>
<td>L Parotid, Dmax&lt;30 Gy</td>
<td>2903.75</td>
<td>✔</td>
<td>3226.55</td>
<td>✔</td>
<td>11.12</td>
</tr>
<tr>
<td>PTV66rev</td>
<td>PTV66rev, Dmax&lt;60 Gy</td>
<td>6606.33</td>
<td>✔</td>
<td>6721.32</td>
<td>✔</td>
<td>1.74</td>
</tr>
<tr>
<td>PTV70rev</td>
<td>PTV70rev, Dmax&lt;70 Gy</td>
<td>7255.56</td>
<td>✔</td>
<td>7455.92</td>
<td>✔</td>
<td>1.56</td>
</tr>
<tr>
<td>Spinal Cord</td>
<td>Spinal Cord, Dmax&lt;50 Gy</td>
<td>3764.6</td>
<td>✔</td>
<td>3886.41</td>
<td>✔</td>
<td>2.71</td>
</tr>
</tbody>
</table>

![Diagram of Total Planned Dose vs Projected Dose]

- **Dose ID**: Line Style
  - **D1**: Total Planned Dose
  - **D2**: Projected Dose

<table>
<thead>
<tr>
<th>Contour</th>
<th>Color</th>
<th>Max Dose</th>
<th>Min Dose</th>
<th>Mean Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>R Parotid</td>
<td>Green</td>
<td>4,935.48</td>
<td>3,270.69</td>
<td>3,921.33</td>
</tr>
<tr>
<td>L Parotid</td>
<td>Blue</td>
<td>6,931.20</td>
<td>6,374.72</td>
<td>6,617.93</td>
</tr>
<tr>
<td>PTV50rev</td>
<td>Cyan</td>
<td>7,355.56</td>
<td>6,228.07</td>
<td>6,745.00</td>
</tr>
<tr>
<td>PTV70rev</td>
<td>Red</td>
<td>7,720.07</td>
<td>8,385.53</td>
<td>7,720.07</td>
</tr>
<tr>
<td>Spinal Cord</td>
<td>Purple</td>
<td>3,764.50</td>
<td>3,806.41</td>
<td>3,845.71</td>
</tr>
</tbody>
</table>
HOW DO WE DO IT?

- DIR
- Auto segmentation
- Setup
SUMMARY...

- Adaptive is in the frame
- More technological evolution
- Workload – time
- Selected patients
- Data!!!