Development of 4D-MRI for Radiation Therapy

Wensha Yang Ph.D.

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Disclosure

I do not have financial interest with vendors mentioned in this talk.
• Accuracy of radiation therapy treatment is challenged by respiration-induced tumor and organ motion.
• 4D-CT has shown great potential in lung cancer treatment, but only has limited use in abdominal motion assessment.

Background: CT / 4D-CT

Lung    Liver    Pancreas

• MRI is well known for its ability to display soft tissue contrast as opposed to X-ray imaging.
• X-rays can only discriminate tissues by electron densities, which are not that different between tumor and surrounding soft tissue.
• In MRI, tissue-specific parameters affect the MR signal (T1, T2, proton density).
• The effect of soft tissue contrast in an MR image can be suppressed or enhanced by other parameters (such as TR, TE, and flip angle).

Background: MRI with improved soft tissue contrast

CT      T1 VIBE      T2 HASTE

Background: Imaging dose

<table>
<thead>
<tr>
<th>Organ</th>
<th>Dose (cGy)</th>
<th>Organ</th>
<th>Dose (cGy)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lung</td>
<td>5.7</td>
<td>Lung</td>
<td>1.4</td>
</tr>
<tr>
<td>Thyroids</td>
<td>7.7</td>
<td>Thyroids</td>
<td>0.1</td>
</tr>
<tr>
<td>Breasts</td>
<td>4.8</td>
<td>Breasts</td>
<td>1.0</td>
</tr>
<tr>
<td>Colon</td>
<td>1.1</td>
<td>Colon</td>
<td>5.8</td>
</tr>
</tbody>
</table>

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Associated radiation dose prevents 4DCT to be frequently used in the clinic for motion or treatment response assessments.
Both morphological and functional information can be extracted from MR imaging. Versatile sequence designs allow for quantitative MR imaging biomarker to be explored.

We need to explore 4D-MRI to guide radiation therapy planning and delivery.

Dynamic MRI (or real-time 4D-MRI or time-resolved 4D-MRI):

- Fast 3D MR sequences
- Fast gradient, parallel imaging, multi-coils
- Compromised SNR and spatial resolution (>3mm)
- Post-imaging processing to improve SNR
Background: 4D-MRI based on retrospective sorting/binning

Current CT based radiation therapy planning:
- Planning CT spatial resolution (~1.2 mm in-plane, ~2.5 mm cross-plane)
- For SRS or SBRT cases with small tumor targets, ~1 mm isotropic

To generate 4D-MRI dataset amenable to accurate radiation therapy planning:

4D-MRI from retrospective binning:
- Fast 2D/3D MR sequences, repetitive scans
- Respiratory surrogates for resorting the data in the imaging domain or from k space
- Adequate image quality, high spatial resolution (~2 mm in-plane, ~5 mm cross-plane)
- Unable to reflect inter-cycle variations in the respiration pattern

Background: Respiratory surrogates

Internal surrogates
- Diaphragm motion
- Body area
- Deformable image registration
- Fourier transform of the k space line

External surrogates
- Bellow system from GE (stretch device)
- PMU system from Siemens (pressure belt)
Background: 4D-MRI categorized by sampling trajectories

1. 4D-MRI from resorting images acquired using 2D sampling strategies/sequences; Respiratory phase/amplitude binning happens in the imaging domain after the image reconstruction.

2. 4D-MRI from resorting k space data acquired using 3D MR sampling strategies/sequences; Respiratory binning happens in the k space before the image reconstruction.

4D-MRI strategies similar to 4D-CT.
4D-MRI: Example of internal surrogate (body area, phase sorted)

- \( T2^*/T1 \) TrueFISP/FIESTA on Siemens 1.5T
- Body area as breathing surrogate
- 1.4x1.4x5 mm³


4D-MRI: Example of external surrogate (prospective amplitude gated acquisition)

- TSE (turbo spin echo, T2) on a Philips 1.5T
- Below pressure system to trigger acquisition
- 2-stage process (preparation and acquisition)
- 1.5x1.5x5 mm³


“Snap-shot” 4D-MRI might not reflect the average breathing pattern of an irregular breather.
Intend to solve the problem of “snap-shot” 4D-MRI
- TrueFISP and HASTE on Siemens 1.5T
- PMU, pneumatic device + diaphragm detection
- Phase and amplitude probability based
- 2-pass sorting (1st pass for average 4D-MRI and 2nd pass for deblurred 4D-MRI using a normalized cross-correlation similarity metric)
- 2x2x6 mm³


4D-MRI based on 2D acquisition/sampling strategies: Stitching artifacts

J Yang et al. IJROBP V88, No.4, pp. 907-912, 2014

2. 4D-MRI from resorting k space data acquired using 3D sampling strategies (sequences): Respiratory binning happens in the k space before the image reconstruction.
4D-MRI: k spaced sorted

- bTFE (3D balanced turbo field echo) on Philips 1.5T
- Cartesian or radial in-plane sampling
- Navigator placed on the diaphragm or bellow system
- k space sorting
- 2x2x4 mm³


4D-MRI: k spaced sorted (ROCK)

- bSSFP (balanced steady-state free precession) on Siemens 1.5T
- Novel rotating Cartesian k-space (ROCK) sampling
- Self-gated centerline
- 1.2x1.2x1.6 mm³


4D-MRI: Cedars approach

Respiratory phase/amplitude resolved 4D-MRI
1) 3D radial acquisition
   • 1.6mm isotropic high resolution.
2) Fixed scan time of ~6 minutes
   • Obtaining averaged breathing pattern
3) Self-gating (SG)
   • Direct monitoring of respiratory motion.
4) Retrospective binning of k-space raw data
   • Further enable averaged breathing pattern
4D-MRI: Cedars approach

Spoiled Gradient recalled Echo (GRE) sequence

a. RF pulses:
Self-gating (SG) k-space lines collected in the superior-inferior (SI) direction at every 15 radial projection intervals. Temporal interval of ~98ms between each SG line.

b. K-space:
3D k-space trajectory via radial 2D golden means ordering.

4D-MRI: Cedars approach

SG-KS-4D-MRI: Image Reconstruction

- Respiratory curve was extracted from the time-series SG lines.
- Analyze curve to discard outliers.
- Valid projections were rebinned to 10 phases.
- Reconstruct 4D-MRI using SENSE method.


SG-KS-4D-MRI: Cedars approach
Tumor motion trajectory analysis: 4D imaging (MR or CT)

4D deformable registration

Map contour from phase 1 to other phases

Tumor center of mass from 10 phases

\[(x_1, y_1, z_1), (x_2, y_2, z_2), \ldots, (x_{10}, y_{10}, z_{10})\]

4D-MRI: Validation using 2D cine MRI

Cine 2D-MRI

- Template matching was used to extract tumor motion trajectory from the time-series cine 2D-MRI
- SI and AP motion was extracted from sagittal images
- ML motion was extracted from coronal images

4D-MRI: Evaluation of tumor motion trajectories
4D-MRI: Comparison to 4DCT

4D-MRI: Evaluation of tumor motion trajectories for pancreatic cancer patients

<table>
<thead>
<tr>
<th>Patient</th>
<th>SG-KS-4D-MRI vs. 4DCT</th>
<th>SG-KS-4D-MRI vs. 2D-MRI</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>SI</td>
<td>AP</td>
</tr>
<tr>
<td>1a</td>
<td>0.45</td>
<td>0.23</td>
</tr>
<tr>
<td>1b</td>
<td>1.28</td>
<td>0.55</td>
</tr>
<tr>
<td>2</td>
<td>0.97</td>
<td>0.51</td>
</tr>
<tr>
<td>3</td>
<td>N/A</td>
<td>N/A</td>
</tr>
<tr>
<td>4</td>
<td>1.15</td>
<td>0.43</td>
</tr>
<tr>
<td>5</td>
<td>1.71</td>
<td>0.93</td>
</tr>
<tr>
<td>6</td>
<td>1.72</td>
<td>0.79</td>
</tr>
<tr>
<td>7</td>
<td>1.32</td>
<td>0.29</td>
</tr>
<tr>
<td>8</td>
<td>0.91</td>
<td>0.06</td>
</tr>
<tr>
<td>9</td>
<td>1.02</td>
<td>0.46</td>
</tr>
<tr>
<td>10</td>
<td>0.98</td>
<td>0.01</td>
</tr>
<tr>
<td>Mean</td>
<td>1.09</td>
<td>0.53</td>
</tr>
<tr>
<td>σ</td>
<td>0.43</td>
<td>0.24</td>
</tr>
</tbody>
</table>

- $D_{\text{diff}}$: The difference of the tumor displacements between two imaging modalities calculated for each phase
- Small ($\leq 2\text{mm}$) $D_{\text{diff}}$ was observed comparing SG-KS-4D-MRI to 4DCT/cine 2D-MRI.

4D-MRI: Evaluation of tumor motion trajectories for pancreatic cancer patients

<table>
<thead>
<tr>
<th>Patient</th>
<th>SG-KS-4D-MRI vs. 4DCT</th>
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<tbody>
<tr>
<td></td>
<td>SI</td>
<td>AP</td>
</tr>
<tr>
<td>1a</td>
<td>0.97</td>
<td>0.82</td>
</tr>
<tr>
<td>1b</td>
<td>0.27</td>
<td>0.28</td>
</tr>
<tr>
<td>2</td>
<td>0.94</td>
<td>0.65</td>
</tr>
<tr>
<td>3</td>
<td>N/A</td>
<td>N/A</td>
</tr>
<tr>
<td>4</td>
<td>0.22</td>
<td>0.47</td>
</tr>
<tr>
<td>5</td>
<td>0.22</td>
<td>0.58</td>
</tr>
<tr>
<td>6</td>
<td>0.83</td>
<td>0.45</td>
</tr>
<tr>
<td>7</td>
<td>0.83</td>
<td>0.04</td>
</tr>
<tr>
<td>8</td>
<td>0.83</td>
<td>0.83</td>
</tr>
<tr>
<td>9</td>
<td>0.83</td>
<td>0.73</td>
</tr>
<tr>
<td>10</td>
<td>0.92</td>
<td>0.72</td>
</tr>
<tr>
<td>Mean</td>
<td>0.91</td>
<td>0.72</td>
</tr>
<tr>
<td>σ</td>
<td>0.06</td>
<td>0.16</td>
</tr>
</tbody>
</table>

- $\text{CC}$: Correlation coefficients calculated from tumor trajectories of two imaging modalities
- Good correlations ($\text{CC} > 0.9$) were observed between SG-KS-4D-MRI and 4DCT/cine 2D-MRI in SI direction.
- Correlations between SG-KS-4D-MRI and 4DCT/cine 2D-MRI in AP and ML directions are not as good as those in SI direction, possibly due to smaller motion magnitudes in these two directions.
4D-MRI: Evaluation of tumor volume for pancreatic cancer patients

<table>
<thead>
<tr>
<th>Patient</th>
<th>SG-KS-4D-MRI</th>
<th>4DCT</th>
</tr>
</thead>
<tbody>
<tr>
<td>1a</td>
<td>0.66</td>
<td>0.57</td>
</tr>
<tr>
<td>1b</td>
<td>0.60</td>
<td>0.63</td>
</tr>
<tr>
<td>2</td>
<td>1.71</td>
<td>2.20</td>
</tr>
<tr>
<td>3</td>
<td>0.69</td>
<td>N/A</td>
</tr>
<tr>
<td>4</td>
<td>0.38</td>
<td>0.71</td>
</tr>
<tr>
<td>5</td>
<td>1.73</td>
<td>1.92</td>
</tr>
<tr>
<td>6</td>
<td>1.26</td>
<td>1.67</td>
</tr>
<tr>
<td>7</td>
<td>0.24</td>
<td>0.47</td>
</tr>
<tr>
<td>8</td>
<td>0.09</td>
<td>0.12</td>
</tr>
<tr>
<td>9</td>
<td>0.82</td>
<td>1.02</td>
</tr>
<tr>
<td>10</td>
<td>0.77</td>
<td>0.98</td>
</tr>
</tbody>
</table>

Mean: 0.81
σ: 0.54
p: 0.012*

- GTV_σ: Standard deviation of GTVs calculated from ten phases for each patient
- SG-KS-4D-MRI shows a consistently smaller GTV_σ comparing to 4D-CT for all patients.
- Wilcoxon rank test between the two groups shows a p value of 0.012, indicating a statistically significant difference.
- Possibly due to the stitching artifacts present in 4D-CT resulting a more variable tumor boundary definition.

Initial experience of SG-KS-4D-MRI on pancreatic cancer patients

- Absence of stitching artifacts
- Average motion trajectory agrees well with 2D cine MRI and 4D-CT in SI direction
- Less variation in tumor volumes across ten respiratory bins comparing to 4D-CT.

SG-KS-4D-MRI: Effect of breathing irregularity

- Regular breathing
- Baseline drift
- Irregular breathing
SG-KS-4D-MRI: Effect of breathing irregularity

Regular breathing | Baseline drift | Irregular breathing

Noise: 7.2% | 9.9% | 10.3%

Noise: the standard deviation divided by the average voxel intensities within a selected volume.

4D-MRI: Improving image quality by non-local means denoising

Non-local means denoising: Use the mean values of distant pixels to enhance the signal to noise ratio based on the similarity to the target pixel.

4D-MRI: Improving image quality by block matching 3D (BM3D)
4D-MRI: Improving image quality by block matching 3D (BM3D)

3D wavelet transform and hard thresholding, inverse transform, Second denoising using automated threshold

4D-MRI: Extending BM3D in the space and time domains

The additional space and time domain offers more similar patches for block construction

4D-MRI: Denoise using BM3D
4D-MRI: Comparing BM3D to local denoising method

- Anisotropic diffusion using low diffusion coefficient achieves limited denoising effect; to achieve high degree of noise suppression, details are compromised.
- In comparison, BM3D is able to achieve substantial noise suppression while maximally preserving image details.

4D-MRI: Limitation of BM3D on 4DMRI acquired from 3D sampling

Effective in suppressing random noise but keep artifacts that appear repetitively at the same location

Methods such as principle component analysis (PCA) can be used to remove the banding artifacts.
We hypothesize that the quality of 4D images can be improved without compromising motion information by averaging the undersampled fan images after motion correction (MoCoAve).

Slide courtesy of Xiaoming Bi, Jianing Pang, Zhaoyang Fan

4D-MRI: Two 3D sampling trajectories were tested
Stack-of-stars Koosh-ball

Slide courtesy of Xiaoming Bi and Jianing Pang

4D-MRI: Improving image quality by deformable image registration

Results: GWR Assessment
- GWR measured how 2D image pairs (without and with MoCoAve)

Slide courtesy of Xiaoming Bi, Jianing Pang, Zhaoyang Fan
4D-MRI: Comparison to 4D-CT

4D-MRI: Improving image quality by deformable image registration

Current 4D-MRI techniques:
• Able to provide anatomic motion information.
• Tumor contrast can be enhanced by different MR sequences.
• Imaging quality can be improved by post-imaging processing.
Current 4D-MRI techniques:

• Able to provide anatomic motion information.
• Tumor contrast can be enhanced by different MR sequences.
• Imaging quality can be improved by post-imaging processing.

How do we use it to guide radiation therapy?

1. Incorporating functional MR sequence in 4D-MRI which might give you information differently from anatomy-only imaging.

2. Use the motion model extracted from 4D-MRI to create synthetic 4D-CT

4D-MRI: Cedars effort on pancreatic cancer patients

• Pancreatic ductal adenocarcinoma has the worst outcome of any solid tumor.
• Surgical resection remains the most effective therapy to prolong survival.
• Only 15% of patients present with resectable disease, due to primary tumors encompassing and infiltrating vasculatures.
• Overall survival rates in the patients undergoing margin negative resection after neoadjuvant therapy are 2-3 times that of those who remain unresectable.
• Stereotactic body radiation therapy (SBRT) with simultaneous integrated boost (SIB) to tumor infiltrating blood vessels has the potential to sterilize tumor around the vessels and improve resection rates.
We need to visualize the vessels in the 4D-MRI.
Vessel signals in the 4D-MRI can be enhanced by shrinking the excitation volume.
SS-4D-MRI

nonSS 4D-MRI

Conclusions/Future developments

- Vessel CNR is significantly improved comparing to 4D-CT.
- Tumor motion correlates well with vessel motion for most patients.

<table>
<thead>
<tr>
<th>Patient ID</th>
<th>Gender</th>
<th>Age</th>
<th>GTV (cc)</th>
<th>SI motion (mm)</th>
<th>CNR aorta</th>
<th>CNR IV</th>
<th>SI</th>
<th>AP</th>
<th>ML</th>
<th>ICC (PTV vs. involved vessels)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>M</td>
<td>54</td>
<td>220</td>
<td>3.7</td>
<td>13.2 / 0.7</td>
<td>11.2 / 2.9</td>
<td>0.90</td>
<td>0.54</td>
<td>0.94</td>
<td>0.97 (0.94)</td>
</tr>
<tr>
<td>2</td>
<td>M</td>
<td>68</td>
<td>187</td>
<td>3.3</td>
<td>13.5 / 0.6</td>
<td>11.8 / 3.5</td>
<td>0.90</td>
<td>0.34</td>
<td>0.94</td>
<td>0.97 (0.94)</td>
</tr>
<tr>
<td>3</td>
<td>F</td>
<td>48</td>
<td>248</td>
<td>1.5</td>
<td>30.2 / 0.6</td>
<td>25.1 / 0.9</td>
<td>0.80</td>
<td>0.44</td>
<td>0.80</td>
<td>0.56 (0.54)</td>
</tr>
<tr>
<td>4</td>
<td>M</td>
<td>54</td>
<td>48</td>
<td>8.6</td>
<td>5.0 / 2.5</td>
<td>3.0 / 0.5</td>
<td>0.90</td>
<td>0.90</td>
<td>0.90</td>
<td>0.99 (0.95)</td>
</tr>
<tr>
<td>5</td>
<td>M</td>
<td>57</td>
<td>37</td>
<td>6.8</td>
<td>14.6 / 5.4</td>
<td>13.1 / 7.4</td>
<td>0.90</td>
<td>0.90</td>
<td>0.90</td>
<td>0.99 (0.95)</td>
</tr>
<tr>
<td>6</td>
<td>F</td>
<td>75</td>
<td>165</td>
<td>9.6</td>
<td>15.8 / 1.7</td>
<td>14.9 / 7.6</td>
<td>0.90</td>
<td>0.31</td>
<td>0.90</td>
<td>0.99 (0.95)</td>
</tr>
<tr>
<td>7</td>
<td>M</td>
<td>54</td>
<td>172</td>
<td>7.5</td>
<td>30.2 / 1.3</td>
<td>23.8 / 0.9</td>
<td>0.60</td>
<td>0.40</td>
<td>0.80</td>
<td>0.56 (0.54)</td>
</tr>
<tr>
<td>8</td>
<td>F</td>
<td>74</td>
<td>14</td>
<td>3.0</td>
<td>30.0 / 4.8</td>
<td>28.4 / 6.6</td>
<td>0.80</td>
<td>0.40</td>
<td>0.80</td>
<td>0.56 (0.54)</td>
</tr>
<tr>
<td>Average</td>
<td></td>
<td></td>
<td>65</td>
<td>86</td>
<td>22.3 / 2.1</td>
<td>13.7 / 2.9</td>
<td>0.80</td>
<td>0.90</td>
<td>0.90</td>
<td>0.97 (0.97)</td>
</tr>
</tbody>
</table>

**Notes:**
- GTV = gross tumor volume, SI = superior-inferior, AP = anterior-posterior, ML = medial-lateral, CNR aorta, CNR IV = contrast to noise for aorta, CNR IV = contrast to noise for involved vessel, CC = correlation coefficient.
4D-MRI: Validation using 2D cine MRI

<table>
<thead>
<tr>
<th>Hardware</th>
<th>3T MAGNETOM Verio, Siemens</th>
<th>32 channel surface coil</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sequence</td>
<td>Real-time 2D MRI</td>
<td>3G-KS-4D MRI</td>
</tr>
<tr>
<td>Imaging Protocol</td>
<td>2D Cartesian-sampling</td>
<td>3D radial-sampling with golden-angle</td>
</tr>
<tr>
<td></td>
<td>Spoiled GRE sequence</td>
<td>Spoiled GRE sequence</td>
</tr>
<tr>
<td></td>
<td>Temporal resolution = 351ms/frame</td>
<td>5G lines every ~98ms</td>
</tr>
<tr>
<td></td>
<td>FOV = 300x300mm²</td>
<td>FOV = 300x300x300mm³</td>
</tr>
<tr>
<td></td>
<td>Spatial resolution = 1.6x1.6mm²</td>
<td>Isotropic resolution (1.6x1.6x1.6mm³)</td>
</tr>
<tr>
<td></td>
<td>Slice thickness = 8mm</td>
<td>FA = 10°</td>
</tr>
<tr>
<td></td>
<td>TR/TE = 4ms/1.64ms</td>
<td>TR/TE = 5.8/2.6 ms</td>
</tr>
<tr>
<td></td>
<td>BW = 651Hz/pixel</td>
<td>BW = 399Hz/pixel</td>
</tr>
<tr>
<td></td>
<td>TA = 1 min</td>
<td>TA = 8min</td>
</tr>
</tbody>
</table>

4D-MRI: Comparison to 4D-CT

Case 4

Case 3
a. Stack of stars  
b. Koosh-ball

SS-4D-MRI: Slab-Selective 4-dimensional magnetic resonance imaging; nonSS-4D-MRI: non-Slab-Selective 4D-MRI; 4D-CT: 4 dimensional computed tomography