Multiparametric MRI in Prostate Cancer: Open source tools for quantitative analysis and data standardization

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Prostate Cancer

- 1 in 7 men in USA will be diagnosed over lifetime
- PSA, DRE and sextant biopsy are still first line tests
- Clinical challenges
  - Early detection of aggressive disease
  - Therapy selection and monitoring
  - Early detection of recurrence
- A test to identify fatal disease would spare 80% from treatment
  - $1.3B cost savings annually
- Localized disease: no significant difference between active Tx vs observation

Nuclear Magnetic Resonance Imaging of the Prostate

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Summary—Nuclear magnetic resonance (NMR) imaging of the prostate has been done in 25 patients, using a prototype machine developed in Aberdeen. It is a non-invasive technique which demonstrated the anatomical extent and pathological nature of prostatic lesions. The NMR images in both benign and malignant prostatic disease on this machine are comparable with first generation CT scans.

Materials and Methods

Twenty-five patients planned for prostatic surgery were studied. The clinical features, pathology and NMR diagnoses were correlated. The Aberdeen NMR imager, which has been described in detail elsewhere (Edelstein et al., 1980; Hutchinson et al., 1980), is based on a 4 coil, air cored magnetic ring producing a static field of 0.04 tesla, giving a proton NMR frequency of 1.7 MHz for the hydrogen proton of body tissue. It is capable of imaging the whole human body. Each section of 17.53 mm equivalent thickness requires data to be collected from 128 electrical signals, each signal being collected during a s interval. Thus all the data for each section are collected in just over 2 min.

It is concluded that NMR imaging is a non-invasive technique which shows great promise in improving the anatomical and pathological definition of body lesions. It is a technique that has been developed only recently but has advanced very rapidly, and there can be little doubt that further technical improvements will greatly improve the anatomical display and the pathological accuracy of diagnosis. As improvements occur, the use of NMR imaging in the diagnosis and planning of treatment of neoplastic disease, particularly of organs such as the prostate, will develop greatly. Further work is required but there is clear evidence that this is a very promising field of advance.
Prostate MRI historical perspective

1982-1990
Body coil 1.5T
T2W/T1W

1990-2000 +
E-coil/external
1.5T
T2W/T1W/MRSI

2000-2010
E-coil/external array
2007---3.0T
Multiparametric
T2W/T1W
MRSI
DW/ADC
DCE

ACRIN 6659* MR and MRS
RDOG I * 1988-1991

1982-1990
Body coil 1.5T
T2W/T1W

*NIH/NCI funded multicenter trials of prostate MRI

PI-RADS v2 2015
ACRIN 6701 repeatability

Slide courtesy Clare Tempany, MD - BWH
Prostate Imaging - Reporting and Data System (PI-RADS)

Figure 1. Flowchart showing the PI-RADS version 2 assessment categories. DCE = dynamic contrast-enhanced MR imaging, T2-WI = T2-weighted MR imaging.
PRECISION study

- Multi-center, randomized, non-inferiority trial, 500 biopsy-naive subjects
- Standard biopsy vs MRI w/wo targeted biopsy
- Primary outcome: clinically significant PCa
- Result: MRI and MRI-targeted biopsy is superior to standard biopsy


Figure 3. Percentages of Men with Clinically Significant, Clinically Insignificant, and No Cancer, Identified According to PI-RADS v2 Score.

For men randomly assigned to the MRI-targeted biopsy group, the areas of the prostate were scored with the use of the Prostate Imaging–Reporting and Data System, version 2 (PI-RADS v2). Scores range from 1 to 5, with higher numbers indicating a greater likelihood of clinically significant cancer; a score of 3 indicates equivocal results. 4 results that are likely to be prostate cancer, and 5 results that are highly likely to be prostate cancer. Men who had a score of 3 or higher underwent MRI-targeted biopsy. Clinically significant cancer was defined as the presence of a single biopsy core indicating disease of Gleason score 3+4 (Gleason sum of 7) or greater, and clinically insignificant cancer as a biopsy sample with a Gleason score of 3+3 (Gleason sum of 6). The Gleason score is composed of a primary (most predominant) grade plus a secondary (highest nonpredominant) grade; the range for a primary or secondary grade is from 3 to 5, with the Gleason sum ranging from 6 to 10, and with higher scores indicating a more aggressive form of prostate cancer. Percentages may not total 100 because of rounding.
INDICATION: XXXXXXXX with known prostate adenocarcinoma
Gleason 3 + 4 right lateral apex and another focus at the right medial apex. PSA 5.4.

COMPARISON: MR prostate MM/DD/YY.

FINDINGS: Volume of the prostate measures 34.6 mL. There is enlargement of the central gland nodularity which is likely due to benign prostatic hyperplasia. A tiny punctate focus of T1 hyperintensity in the right peripheral zone is likely due to hemorrhage from recent prostate biopsy. Note is again made of 2 areas of abnormality in the right peripheral zone. The first is a 17 x 4 mm area of T2 hypointensity posterior and midline at 6:00 with enhancement and without restricted diffusion. Second is an area of T2 hypointensity in the right peripheral zone at the mid gland without contrast enhancement or restricted diffusion. No extracapsular, seminal vesicle, or bladder invasion is noted. No retroperitoneal lymphadenopathy. Partially imaged pelvic bone marrow signal appears normal.

IMPRESSION: Unchanged areas of abnormality in the right peripheral zone, one posterior at 6:00 with T2 hypointensity and contrast enhancement without restricted diffusion and one in the right peripheral zone at the mid gland with T2 hypointensity and no enhancement or restricted diffusion.
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Key projects that supported development of the presented tools

- BWH QIN: “Quantitative MRI of Prostate Cancer as a Biomarker and Guide for Treatment” (PI Fiona Fennessy, U01 CA151261, 2010-2016)
- DFCI QIN: “Genotype and Imaging Phenotype Biomarkers in Lung Cancer” (PI Hugo Aerts, U01 CA190234, 2015-2020)
- DFCI ITCR: “Quantitative Radiomics System Decoding the Tumor Phenotype” (PI Hugo Aerts, U24 CA194354, 2015-2020)
- BWH “National Center for Image Guided Therapy” (PI Clare Tempany, P41 EB015898)

QIN as of March 2014

https://itcr.nci.nih.gov/
QI tools delivery platform: 3D Slicer

- Est. 1997
- Free open source
- Research platform, **not** FDA approved
- Visualization, annotation, analysis, IGT
- Extensible
- Broad adoption across QIN and beyond
- Version 4.8 released Oct 2017

Funding: NAC P41 EB015902, NCIGT P41 EB015898, ITCR U24 CA180918, U24 CA194354, QIN U01 CA151261
Diffusion Weighted MRI (DW MRI)

- Surrogate measure of tissue cellularity
- Restricted diffusion of water molecules in densely packed tissue
- Parameterized by the selection of b-values
- Strong correlation with prostate cancer Gleason grade
- Assessed qualitatively in clinic

DW Modeling in 3D Slicer

Models implemented:

- Mono-exponential
- Bi-exponential: models fast and slow diffusion components
- Kurtosis: estimates deviation from plan water diffusion
- Gamma distribution: models continuous distribution of components
- Stretched exponential


More than model fitting

- Parsing of the b-values from vendor-specific DICOM attributes
- Interactive visualization of the signal curves
- Parameter map overlay
- Model fit visualization
- Fit quality diagnostics maps
- Command line interface for batch mode execution
- Pre-built binaries for Windows, Linux, macOS
Validation

- Single site evaluation
- QIN multi-site collaborative evaluation
  - Physical phantom
  - Clinical data


Dynamic Contrast Enhanced MRI (DCE MRI)

- Marker of tissue vascularity
- Increased number and density of small vessels
- Increased permeability of vessel walls
- Treatment response assessment
- Assessed qualitatively in clinic
DCE Modeling in 3D Slicer

- Tofts’ Generalized Kinetic Model
- Individualized or population-averaged Arterial Input Function
- T1 mapping


More details: [http://qiicr.org/tool/PkModeling/](http://qiicr.org/tool/PkModeling/)
Validation

- QIN multi-site collaborative project
- Concordance of QIN DCE MRI analysis
- Phantom and clinical data (breast treatment response assessment)
- Result: good to excellent prediction of pathologic response with $K_{\text{trans}}{\%}$ change

Radiomics analysis

- Pyradiomics: python library for radiomics feature extraction
  - First order statistics, shape, variety of texture features
  - Preprocessing: normalization, LoG, wavelets
  - Command line interface for batch processing
  - Available in Docker, Jupyter examples
  - 3D Slicer extension for interactive usage

More details: https://github.com/radiomics/pyradiomics

Repeatability of mpMRI Radiomics features

- Can be highly sensitive to extraction parameters (normalization, binning, pre-processing)
- Features identified as predictive in the literature may not be reproducible
- Further investigation is needed!

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Deformable image registration

- **Intensity-based**
  - Hierarchical up to b-spline, mutual information, ROI-constrained
  - Evaluated for MR-guided biopsy applications

- **Contour-based**
  - Hierarchical up to b-spline
  - Segmentation distance map
  - Evaluated for MR-TRUS fusion

- **Other tools**
  - Elastix
  - ITK, SimpleITK, itk-python

More details:
https://github.com/SlicerProstate
https://github.com/SlicerProstate/SliceTracker

Validation

A lot more 3D Slicer tools that I did not cover ...

- Annotation tools
- Deep learning models (promising results for automatic prostate segmentation, disease characterization)
- End-to-end solution for targeted in-bore MRI-guided biopsy
- Integration with devices and scanner control

More details:
https://slicer.org
https://discourse.slicer.org
http://deepinfer.org
Data harmonization along the PCa management continuum

*START: Standards of Reporting for MRI-targeted biopsy studies; **PI-RADS: Prostate Imaging - Reporting and Data System; ***PRECISE: Prostate Cancer Radiological Estimation of Change in Sequential Evaluation.
TCIA Collections

TCIA is a service which de-identifies and hosts a large archive of medical images of cancer accessible for public download. The data are organized as “Collections”, typically patients related by a common disease (e.g., lung cancer), image modality (MRI, CT, etc) or research focus. DICOM is the primary file format used by TCIA for image storage. Supporting data related to the images such as patient outcomes, treatment details, genomics, pathology, and expert analyses are also provided when available.

<table>
<thead>
<tr>
<th>Collection</th>
<th>Cancer Type</th>
<th>Modalities</th>
<th>Subjects</th>
<th>Location</th>
<th>Metadata</th>
<th>Access</th>
<th>Status</th>
<th>Updated</th>
</tr>
</thead>
<tbody>
<tr>
<td>National Lung Screening</td>
<td>Lung Cancer</td>
<td>CT</td>
<td>26254</td>
<td>Chest</td>
<td>Yes</td>
<td>Limited</td>
<td>Complete</td>
<td>2013/03/01</td>
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<tr>
<td>CBIS-DDSM</td>
<td>Breast Cancer</td>
<td>MG</td>
<td>6671</td>
<td>Breast</td>
<td>Yes</td>
<td>Public</td>
<td>Complete</td>
<td>2017/09/27</td>
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<tr>
<td>LIDC-IDRI</td>
<td>Lung Cancer</td>
<td>CT, CR, DX</td>
<td>1010</td>
<td>Chest</td>
<td>Yes</td>
<td>Public</td>
<td>Complete</td>
<td>2012/03/21</td>
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<tr>
<td>Colonography</td>
<td>Colon Cancer</td>
<td>CT</td>
<td>825</td>
<td>Colon</td>
<td>Yes</td>
<td>Public</td>
<td>Complete</td>
<td>2011/10/31</td>
</tr>
<tr>
<td>NSCLC Radiomics</td>
<td>Lung Cancer</td>
<td>CT, RSTRUCT</td>
<td>422</td>
<td>Lung</td>
<td>Yes</td>
<td>Public</td>
<td>Ongoing</td>
<td>2016/05/20</td>
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<tr>
<td>PROSTATE</td>
<td>Prostate Cancer</td>
<td>MR</td>
<td>346</td>
<td>Prostate</td>
<td>Yes</td>
<td>Public</td>
<td>Complete</td>
<td>2017/03/30</td>
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<tr>
<td>MyelomaTT3PET</td>
<td>Myeloma</td>
<td>PET</td>
<td>300</td>
<td>Whole Body</td>
<td>Yes</td>
<td>Public</td>
<td>Coming Soon</td>
<td>2016/04/16</td>
</tr>
</tbody>
</table>

https://www.cancerimagingarchive.net/
Research data harmonization

- Images
- Derived data
  - Image-like (e.g., segmentations, parametric maps)
  - Non-image-like - Quantitative, qualitative, categorical (e.g., measurements, impressions)

<table>
<thead>
<tr>
<th>Segment</th>
<th>Mean [SU, V%g/ml]</th>
<th>Minimum [SU, V%g/ml]</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 primary tumor</td>
<td>10.6175</td>
<td>5.0406</td>
</tr>
<tr>
<td>2 lymph node 1</td>
<td>5.18311</td>
<td>3.76263</td>
</tr>
<tr>
<td>3 lymph node 2</td>
<td>8.29498</td>
<td>3.88878</td>
</tr>
<tr>
<td>4 lymph node 3</td>
<td>3.38146</td>
<td>0.353775</td>
</tr>
<tr>
<td>5 lymph node 4</td>
<td>6.27497</td>
<td>3.60357</td>
</tr>
<tr>
<td>6 lymph node 5</td>
<td>8.73281</td>
<td>4.22984</td>
</tr>
<tr>
<td>7 lymph node 6</td>
<td>8.50875</td>
<td>3.00571</td>
</tr>
</tbody>
</table>
Digital Imaging and Communication in Medicine (DICOM) is the standard for communication of medical imaging information and related data.

- Compatibility with acquisition and archival tools
- Harmonized with other standards (HL7, JSON, XML, REST, WADO)
- History of development and adoption since 1983
- Adopted by virtually all manufacturers of medical imaging equipment
- Open international community of stakeholders
- Continuously evolving standard
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- History of development and adoption since 1983
- Adopted by virtually all manufacturers of medical imaging equipment
- Open international community of stakeholders
- Continuously evolving standard
- **Can be used to store images and results of analysis**
  - **clinical and pre-clinical!**
DICOM - preparing for the unknown, since 1983

- **Standard for images and image-related evidence**
- Information object definitions - CT, MR, RT ... SEG, PM, SR!
  - Object type defines required and optional attributes
- For all object types: *Composite context* is formalized and required
  - Dates, patient IDs, study, series - for every object
- Unique identifiers
- References to related evidence
  - Provenance of data acquisition
  - Provenance of data analysis
- Fixed syntax
  - (hierarchical) list of attribute/value pairs
- Normalized semantics
  - Common data elements / lexicons / ontologies
Conversion to DICOM

Composite context is propagated from the source image data

Segmentation image volume in any format readable by ITK (NRRD, NIfTI, Analyze, MHD)

Analysis-specific metadata is defined by the user and parametrized by a JSON-Schema

Source code, binaries for Win/Mac/Linux, Docker

More details: https://github.com/qiicr/dcmqi
Promoting and evaluating adoption of the standard

DICOM4QI: DICOM for Quantitative Imaging

● Demonstration and connectathon at RSNA
● Goals:
  ○ Promote adoption of the DICOM standard for Quantitative Imaging applications
  ○ Develop best practices for storing QI analysis data using DICOM
  ○ Understand and lower adoption barriers
● Educate vendors so they adopt standards
● Educate customers so they demand standards

* This is not an official IHE or DICOM connectathon. We use the word "connectathon" to describe the essence of the activity, and not our affiliation to official connectathons that are already established in the field.
Status

- RSNA Quantitative Imaging Reading Room exhibit since 2015
- RSNA 2017
  - 4 types of QI DICOM objects (segmentations, parametric maps, volumetric measurements, tractography)
  - 11 platforms participated (including 5 commercial)
- Free open source tools that support the standard for QI analysis results
  - 3D Slicer (desktop platform and application)
  - ePAD (browser-based application)
  - MITK (desktop platform and application)
  - OHIF LesionTracker / Cornerstone (browser-based application and toolkit)
  - vtk-dicom (desktop)

More details: [https://qiicr.gitbooks.io/dicom4qi/](https://qiicr.gitbooks.io/dicom4qi/)
Example data collection: Head and neck cancer

- Methods paper: Medical Physics 2016
- Data paper: PeerJ 2016
  - PET SUV, segmentations, measurements, clinical data
- Data: TCIA QIN-HEADNECK collection
- Demonstration/tutorial: http://qiicr.org/dicom4miccai/

Example data collection: Repeatability of mpMRI

- Confirmed or suspected treatment naive PCa
- Quantitative measures: image-based volume and mean Apparent Diffusion Coefficient
- Standard-of-care repeat mpMRI performed within 2 weeks, with e-coil
- 189 men approached, 40 consented, 15 completed the study
- DICOM dataset to be released on TCIA (images, segmentations, measurements, radiomics features later) - under review!

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Conclusions

- mpMRI is a promising biomarker for PCa assessment
- Challenges remain in refinement, validation, deployment of decision support tools
- A spectrum of free open source tools are available for mpMRI analysis of PCa
- Improved data harmonization and management can be enabled by judicious use of standards
  - tools, reference datasets, implementations are available
Acknowledgments

- Ron Kikinis, Clare Tempany, Hugo Aerts
- QIICR and NCIGT teams: David Clunie, Steve Pieper, Christian Herz, Reinhard Beichel, Christian Bauer, Ethan Ulrich, Michael Onken, Jörg Riesmeier, Jayashree Kalpathy-Cramer, Andrew Beers, Fiona Fennessy, Andras Lasso, Csaba Pinter, Kemal Tuncali, Junichi Tokuda, and many more ...
- Collaborators and colleagues beyond immediate team
- NCI for QIN, ITCR, TCIA, and all the collaboration-fostering projects
- Funding: U24 CA180918, U24 CA194354, P41 EB015898, U01 CA151261, U24 Siemens AG

https://radiomics.io
Thank you!

Questions? Comments? Collaborations?

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