Optimization of Functional MRI Techniques for Tumor and Normal Tissue Response to RT

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Acknowledgments

- Radiation Oncology
  - James Baker, Ph.D.
  - Edgar Ban-Hash, MD
  - Andrew Eshagh, MD
  - Mary Huang, MD, Ph.D.
  - Theodore S. Lawrence, MD, Ph.D.
  - Charles Park, MD
  - Samuel Tien, Ph.D.
  - Christine Y.及其 MD
  - Clinical Coordinator
    - Alan Antonuk, BS
    - Chris Chapman, BS
    - Reza Farjam, M.S.
    - Mohammad Najemzadeh, Ph.D.
    - Hesheng Wang, Ph.D.
    - Peng Wang, Ph.D.

- Radiology
  - Thomas L. Downard, Ph.D.
  - Herrmann, Ph.D.
  - Jedd E. Shapiro, M.D., Ph.D.
  - Sunee Mukherji, MD
  - Ru-Min Zhang, MD, Ph.D.

- Radiation staff

- STATISTICS
  - Tim Johnson, Ph.D.
  - Dan Normolle, Ph.D.
  - Matt Schipper, Ph.D.

- NIH grants
  1. R01 CA059827 (Ten Haken)
  2. R01 NS064973 (Cao)
  3. RO1 CA132834 (Cao)

Biological Target Volume, Tx Predictor, Dose Painting and Sculpting

A tumor target volume could be defined and segmented as multiple biological target subvolumes, which are defined based upon multiple functional imaging studies, and each of which could be a prognostic or predictive indicator for radiation response.

A dose sculpting and painting of multiple biological target subvolumes could lead to better outcome.
**Imaging Biomarker for Therapy Assessment**

- Longitudinal study
  - Repeated measures
  - Reliability, reproducibility, robustness
- Sensitive indicator (biomarker)
  - Sensitive to therapy-induced changes
- Prognostic or Predictive biomarker
  - Predict Tx response and outcome
  - Surrogate endpoint

**Physiological MRI**

- Diffusion
- Hepatic Perfusion
- DCE
- CBV
- DTI

**How to Establish a Imaging Biomarker for Therapy Assessment**

- Reproducibility
  - Separation of a true change from variation
- Sensitivity and specificity
  - End points, problem-specific
- Utility
  - Therapy selection
  - Adaptive therapy for intensification or toxicity reduction
Reproducibility

- NCI RIDER project
  - A set of articles describe importance, procedures and statistical analysis for test and re-test (Translational Oncology, 2, 2009)
  - Test and retest data (NBIA database)
- What level of change in parameter should be observed to be confident that there has been a true change in the parameter in an individual patient?

How to determine repeatability from Test and Retest Data

- Within-subject SDw of a parameter
- Repeatability Coefficient of a parameter
  - RC=2.77SDw
  - RC defines 95% confidence interval
  - A true change from a subject has to be
  - |u_post-u_pre| >RC

Barnharts et al, Translational Oncology, 2, 2009

Repeatability of Segmenting Cingulum Fiber Track

- Develop a method for segmenting cingulum, a fiber track connecting to hippocampus, for assessment of radiation-induced cognitive dysfunction
- Evaluate reproducibility of segmented volumes and DTI indices
  - Dice coefficient: overlapped volumes
  - RC: uncertainty of parameters

Nazemzadeh et al, AAPM 2012
Fractional Anisotropy Changes in Patients Received WBRT

How to determine reproducibility of an image parameter

Sensitivity and Specificity

- Endpoints
  - Prognostic or Predictive indicator for tumor response to therapy
  - Clinical outcomes, local control, survival, PFS...
  - Radiographic response
  - Pathophysiology
  - For normal tissue radiation toxicity
  - Clinical outcome (symptom)
  - Radiation dose
  - Independently established measure
Imaging-driven Response-Induced Subvolume of a Tumor

Hypothesis

A heterogeneous therapy response of a tumor could be primarily due to biological heterogeneity in the tumor.
A. The most aggressive or resistant sub-volume in a tumor could predominantly determine therapy response or outcome of a tumor.

Aim

A. Develop a methodology to delineate physiological imaging-driven subvolume of a tumor
A. Predictive for treatment response
A. Highly reproducible
A. Potential candidate to be a boost target

How to identify sub-volumes

- Generate a feature space of tumors defined by a joint histogram of physiological imaging parameters from "training" tumors
- Classify the distribution of tumor features (joint histogram) using fuzzy c-means to determine globally-defined probability membership functions of the classes
- Create the subvolumes (metric and map) of each individual tumor using the probability membership functions and physiological images of the tumor

Brain metastases

Create a single metric, a subvolume of a tumor with high CBV, \( K_{\text{trans}} \), or both, for assessment of response.
Does the tumor subvolume with high CBV predict response?

- **End point**
  - Post-RT radiographic response
  - $\Delta TV_{post} = TV_{post} - TV_{preRT}$
  - Non-responsive: $\Delta TV_{post}$ decreases <25 %

- **Early prediction for non-responsive tumors**
  - A change in the subvolume with high CBV, high $K_{trans}$, or both at the end of WBRT
  - Receiver operating characteristics (ROC)

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**Sensitivity and Specificity**

- **Prediction for non-responsive tumors**
  - ROC curves showing sensitivity and specificity for various parameters.

- **Fujim. et al AAMP 2012**

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**Poorly Perfused Sub-Volumes in Advanced HN Cancers**

- The large sub-volumes of the tumors with low BV (blue color) pre-Tx and during the early course of CRT (2 weeks) are significantly associated with LF, Wang, et al Med Phys 2012.
**Prediction of Local Failure**

![ROC Comparison Graph](image)


**Association with Pattern Failure**

![Images of brain scans](image)

**Subvolumes of a Tumor**

- A physiological imaging defined response-induced subvolume of a tumor could be a candidate for intensified therapy target
- Our approach can be applied to other physiological/metabolic imaging parameters
- Our method does not depend upon the voxel level accuracy of registration of a pair of images acquired over a period of therapy
- Our method produces the metrics robust to image noise and other random factors
How to determine sensitivity and specificity of a parameter

1. Use a clinical end point & ROC analysis
2. Recruit 500 patients
3. Repeat the same study
4. Ask a radiation oncologist
5. Increase signal-to-noise ratio of the image

Normal Tissue Function

- Radiation-induced tissue toxicity is a complex, dynamic and progressive process
- Individual sensitivity to radiation limits the utility of dose-based NTCP models
- Determination of specific risks versus benefits of treatment should be an integral part of clinical decision making for each patient

How to assess normal tissue/organ function

- Assess normal tissue/organ function
  - Dynamic changes in organ function from pre to during and to post RT
  - Spatially resolved volumetric distribution of function
  - Individual sensitivity to dose and pre-RT dysfunction
- Early measures predict organ functional risks of radiation
- Re-optimization of individual patients’ treatment plans and early intervention for tissue/organ protection
MRI Perfusion Imaging to Assess Liver Function

- Patients with high risks or poor liver function
  - HCC with or without cirrhosis
  - Large tumor
  - Previous treatments, TACE, surgery, RT, RFA
- General paradigm
  - DCE MRI scans: pre, during (~50%), 1 month after RT

Individual Perfusion Response

Spatial perfusion changes are related to regional doses

Evaluation of Perfusion with Overall Liver Function

Indocyanine green: Independent measure of overall liver function
Dose-Dependent Spatial Perfusion Changes

Early Prediction of Post-RT Perfusion Change

- Linear mixed effects model to account for individual random effects:
  \[ \log(F_{ij}) = \alpha + a_i + \gamma_{0j}F_{ij} + \beta d_j + \beta_2 F_{ij} + \epsilon_{ij} \]

  - Post-RT perfusion for Subject i in region j received dose d
  - Pre- or during-RT perfusion for Subject i in region j
  - Dose in region j

Model 1: independent variable: pre-RT perfusion, total dose; predictor: total dose (p<.0007)
Model 2: independent variable: pre-RT perfusion, during-RT perfusion, total dose; predictor: pre-RT perfusion (p<.05); during-RT perfusion (p<0.0001)

Liver Perfusion Imaging

- Evaluation of hepatic perfusion imaging using an independent liver function measure
- Perfusion imaging could be used to select "expendable" segments or regions to direct high doses
- Individual patients who show high risk for injury during RT could be selected for lower doses to prevent from liver injury
Localization and Detection of Prostate Cancer Using MRI

- DCE, DW, T2W and MRS
- DCE MRI is superior to diffusion, T2W, and MRS.
- Combining DCE, diffusion, T2W or MRS seem to result in marginal improvement
- A lower rate of localization of cancer is in transition zone than in peripheral zone.

Localization of Prostate Cancer Using DCE MRI

- Overall, sensitivity: 74-93%, specificity: 79-96%
  - Visual inspection and scored by radiologists
  - Depend upon the experience of reading radiologists, imaging acquisition protocol, and the derived parameters from DCE MRI as well as image processing approaches
  - Tell nothing about the impacts of tumor size and tumor density

Pathological Validation for Prostate Cancer Delineation

- Compare DCE MRI and MRS with histological specimens (Schmuecking et al, 2009)
  - DCE MRI parameters are not able to detect the lesions with a size less than 3 mm and/or containing less than 30% of tumor cells.
  - MRS is failed to detect the lesion with a size less than 8 mm and/or containing 50% of cancer cells.
  - DCE MRI defined volumes underestimates the histological volumes, especially in cases with a diffuse tumor growth with low cancer cell density
  - DCE MRI for localization of prostate cancer is equally good as Cho PET/CT
Cancer Detection by DCE MRI

Missed lesion: size < 3 mm and containing < 30% of cancer cells (Schmuecking 2009)

Prostate cancer with a lesion size of 9x3.7 mm and a cancer cell density of >30% was detected by DCE-MRI (orange lesion); but MRS shows a normal spectrum with a low choline peak (Schmuecking 2009)

Summary

- Reproducibility
  - Uncertainty of the methods as a whole
- Sensitivity and specificity
- Automated algorithms for supporting decision making
- Standardizations
  - Imaging protocols, pharmacokinetic models, quantitative metrics for a particular problem
- QC/QA of imaging acquisition and parameter extraction
Pathological Validation for prostate GTV definition

- Prostate GTV delineated by combination of diffusion and DCE MRI by a radiation oncologist compared lesions (22) defined on prostatectomy specimens by a pathologist (Groenendaal 2010)

- Five dominate cancers with the volume greater than 1 cc, and four other smaller ones with a minimum volume of 0.56 cc are able to be detected on MRI

- The GTVs of the five dominant cancers delineated on the MRI cover 44-76% and have 62-174% of the pathologically determined tumor volumes

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General Hypothesis:
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- Dose sculpt and paint of multiple biological target subvolumes could lead better outcome.