Imaging to determine tumor phenotype

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Can we use imaging to understand tumor phenotype?

• Goal: be able to provide patient-specific predictions of their outcome given a specific treatment
  – Treatment choices – dose escalation? Chemo regimen? Etc…..
  – Future planning
  – Monitoring treatment response
An example for overall survival

Advanced NSCLC

Kaplan-Meier Survival Plot

p = 1.4E-8
This is a hot topic in clinical research

• Prominent symposiums at:
  – American Association of Physicists in Medicine (AAPM)
  – Radiological Society of North America (RSNA)
  – American Society for Radiation Oncology (ASTRO)

First.....

• What images do we have available in RT, and how do we use them now, what sort of image variability do we have.......?
First…..

- What images do we have available in RT, and how do we use them now, what sort of image variability do we have…….?
IGRT workflow

Treatment preparation
- Pre-treatment imaging (CT, MRI, PET)
- Image registration
- Delineate targets and normal tissues
- Create treatment plan
- Create reference images (e.g. DRRs)

Treatment
- Position patient in treatment position
- Take images of patient
- Image registration
- Evaluate registration results
- Correct patient position
- Treat
- Evaluate registration results
- Correct patient position
- Treat
- Evaluate registration results
- Correct patient position
- Treat
- Evaluate registration results
- Correct patient position
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- Evaluate registration results
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- Treat
- Evaluate registration results
- Correct patient position
- Treat

Evaluation and verification system
Primary use of images in RT (today)

Treatment preparation
- Delineation (may include PET)
- Determination of extent of respiratory motion
- Dose calculation
- Creation of reference images for patient setup

Treatment
- Patient setup

\[ I = I_0 e^{-\frac{\mu dx}{R^2}} \]

\( I \) = Primary Transmission Fluence
\( I_0 \) = Initial Fluence
\( \mu \) = Linear attenuation coefficient
\( dx \) = Small element of path length
\( R \) = Distance from source to point of interest

Image Cassette

Source

Ray Tracing To Create Digitally Reconstructed Radiographs

Patient's 3D CT data
In-room imaging

CT-on-rails

LINAC

Patient couch

Rails
MRI-guided radiation therapy
Use of contour overlay
Available images

Before coming to radiation oncology
• CT (usually contrast-enhanced)
• PET
• Sometimes MRI

Simulation imaging
• Nearly always CT (usually non-contrast), may be 4DCT

On-treatment imaging
• Daily kV-kV imaging
• Daily CT imaging
• Daily kV-kV, weekly CBCT
• Numerous other alternative imaging schedules
• Sometimes PET mid-treatment (under study)

Follow-up imaging
• Follow-up every 3 months, then reducing frequency
• PET, CT
Now discuss different approaches to using imaging data to determine tumor phenotype.
Imaging features and radiomics

- Radiologists identified 138 different imaging traits on contrast-CT scans of hepatocellular carcinomas (n=28)
- Filtered traits based on reproducibility and independence (->32)
- Searched for associations between expression of 6,732 genes (clustered) (microarray analysis) and combinations of imaging traits.

• Cross-sectional area

• Liver capsule abutment

• Number of regions of necrosis
28 imaging traits could reconstruct 78% of gene expression profile (116 modules)
Imaging traits predict venous invasion and survival

E. Segal et al. Decoding global gene expression programs in liver cancer by noninvasive imaging (2007)
**Radiomics**

**Hypothesis:** Quantitative image features are related to underlying gene expression and phenotype

**Goal:** Be able to provide patient-specific predictions of their outcome given a specific treatment

- Large datasets – need high throughput
- Need to automate the image analysis
- Need quantitative image feature descriptors
- Need consistent imaging
- (I will focus on CT)
What are quantifiable features?

Start with geometric features
**Quantitative Image Features from Texture**

**texture** = visualization of complex patterns composed of spatially organized, repeated subpatterns, which have a characteristic, somewhat uniform appearance.

Texture Quantification

- Histogram
- Gradient
- Co-occurrence matrix (COM)
- Run-length matrix (RLM)
Intensity Histogram

Features
- Mean
- Median
- Variance
- Skewness
- Kurtosis
- Min
- Max
- 99th percentile
- 1st percentile
- Entropy

\[ H = - \sum_{i} p_i \log_2 p_i \]
Tumor heterogeneity $\rightarrow$ overall survival

- NSCLC patients (n=54)
- Filter image to emphasise / de-emphasise different scales (fine to course)
- Tumor uniformity

$$u = \sum_{l=1}^{k} [p(l)]^2$$

- AUC $\sim$0.6

Ganeshan et al 2011
Esophageal cancer

- N=21
- Uniformity and entropy

Ganeshan et al 2012
There are lots of other features out there…

<table>
<thead>
<tr>
<th>Intensity Histogram</th>
<th>Absolute Gradient</th>
<th>Run-Length Matrix</th>
<th>Co-Occurrence Matrix</th>
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<tbody>
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<td>Run Length Nonuniformity</td>
<td>Angular Second Moment</td>
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<tr>
<td>Median</td>
<td>Variance</td>
<td>Grey Level Nonuniformity</td>
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<td>99&lt;sup&gt;th&lt;/sup&gt; percentile</td>
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<td>Entropy</td>
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</table>

**Note:** there are many additional image features which could also be considered (morphometric, fractal dimension, heterogeneity quantifications, wavelet transform, etc.)
Prediction limitations – OS is very stochastic

So let’s try baby steps

- Use image features to predict tumor shrinkage - Luke Hunter
- 66 locally advanced stage II-IIIB NSCLC
  - IMRT (n=36), PSPT (n=30)
- Standardized treatment
  - 74 Gy dose level RT (RBE = 1.1)
  - Concurrent chemotherapy
- Standardized imaging
  - Simulation and weekly 4DCTs
  - Identical CT machine
  - Identical scan parameters
Method for $\text{getMSE}(s, FM)$

Rows = Observations

Columns = Features

Omit row $i$

z-score Transform

Principal Component Transform

Multiple Linear Regression

Hidden Observation

Prediction Model

$\tilde{s} = \{s_1, s_2, \ldots, s_m\}$ Column Selection Vector

$y = \beta_0 + \beta_1 x_{i,1} + \beta_2 x_{i,2} + \cdots + \beta_k x_{i,k} + e_i$

$MSE = \frac{1}{n} \sum (\text{observed}_i - \text{predicted}_i)^2$
Results

- Best results found from 100 searches using the specified feature set

- Each point shown is a leave-one-out cross-validation prediction
Model Validation

\[ MSE = \frac{1}{n} \sum_{i} (observed_i - predicted_i)^2 \]

- Histogram bins indicate the number of times out of 100 runs that the best MSE returned by the search algorithm fell into the indicated MSE range.
- Blue bars have correct relationship between feature matrix and response vector.
- Red bars have randomly permuted relationship between feature matrix and response vector.
### Table 3. Applications of Texture Analysis in Lung Cancer Outcomes or Prognostic Factors

<table>
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<tr>
<th>Author</th>
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Abbreviations: CRT, chemoradiotherapy; PORT, post-operative radiation therapy; CE-CT, contrast enhanced computed tomography; NCE-CT, non-contrast enhanced computed tomography; PET, positron emission tomography
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Image parameters

- 4DCT
- Most on the same CT scanner (GE)
- Same exposure
- 120kVp
- 0.096 x 0.096 x 0.25 – 0.30cm voxels
Freedom from Distant Metastases: Both Texture and Clinical

$p = 1.2E-9$

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</table>
Some discussion of image variability

Internal studies can be done with very consistent data, but.....

Variations in images:

- X-ray energy
- Respiratory motion management
- Contrast-enhanced? Timing of contrast
- Reconstruction algorithm....
- Pixel size
- Slice thickness
- Patient dose
- Artifacts
- Slice tilt
- ..............................
Imaging and treatment variability

Observation: signal is there, but AUCs are not very high

Kumar et al 2012
Tomotherapy: MV CT images
Worse Case – T50 v. average
Worse Case – average vs. CBCT
Better Case – T50 v. average
Better Case – TAvg v. CBCT
Other artifacts
Desirable Feature Properties

- Reproducible
  - Repeat scans yield similar feature values

- Informative
  - Feature is useful for discriminating patients

- Non-redundant
  - Feature value is not strongly correlated with other feature values
What about reproducibility

• Test-retest patients – concordance correlation coefficient

• Test-retest – see how impacts model results

• Inter-scanner variability – phantom tests
Reproducibility Metric

- **Concordance Correlation Coefficient (CCC)**\(^{14}\)
  - Quantifies agreement between two observations \([-1, 1]\)
  - Used to evaluate intra-class reproducibility
  - Literature shows that CCC \(\geq 0.90\) is a useful cutoff\(^{15}\)

\[
CCC \equiv 1 - \frac{\langle (x - y)^2 \rangle}{\sigma_x^2 + \sigma_y^2 + (\mu_x - \mu_y)^2}
\]
Same patient, different time points

Figure 1. Examples of repeat images (patient 1) and images of different patients. When image features are used to understand/predict patient outcomes, it is important that their reproducibility (intra-patient variability) is high compared with the variations that are expected in the patient population.

Figure 2. CT number variance calculated from the CT of the tumor as a function of time after contrast injection. Each line is for a different imaging session (different day). The intra-patient variations (due to timing or session) is smaller than the inter-patient variations.

Figure 3. Skewness (calculated from the absolute image gradient) calculated from the CT of the tumor as a function of time after contrast injection. As with figure 2, each line is for a different imaging session (different day). The intra-patient variations (due to timing or session) is smaller than the inter-patient variations.
Phantom for inter-scanner tests

Phantom features simulated tumors
- different sizes
- different HU number variations

After CT acquired, auto-contour 9 different ROIs using automated contouring parameters in Pinnacle
- 5 lung nodules
- 3 bronchial tree regions
- 1 subcarinal nodal area

Simulated tumors in five-size and three-HU-number variations can be attached to arbitrary position in the lung field.
4 of 9 (44%) phantom ROIs had 75% or more of CT texture values from 10 CT scanners within the range of human data
Results: No significant effect of scanner used on 15 of the 17 CT textures assessed.
Monitoring change through treatment

- Routinely look at tumor shrinkage during treatment
- Mainly focused at the need for adaptive replanning – not actual patient-specific dose response.
- We have just started to look at structural changes through treatment
Fig. 1. Example of rapidly changing anatomy during conformal radiotherapy for head-and-neck cancer. (a) Computed tomography slice taken at treatment simulation; (b) corresponding computed tomography slice taken 3 weeks into radiotherapy.
Fig. 4. Gross tumor volume changes over time among patients with head-and-neck cancer (HNn). Both (a,b) primary tumor and (c,d) lymph nodes >2 cm³ in volume showed similar trend. Gross tumor volumes decreased at a median rate of 0.2 cm³ or 1.8% of initial volume/treatment day.
Change in tumor appearance through treatment

- Is change in tumor appearance related to treatment outcome?

Wk0  Wk2  Wk6
Cavities are often visible in PET images before they are visible in CT.
Result – Pre-PET Early Detection

Pre PET

Mid PET
Summary

• CT texture appears to contain meaningful and useful information
• Patient-specific outcome predictions are extremely useful in the clinic
• There is much variability in imaging
• There is much to be done…….

Possible collaborative projects:
• Modeling to account for mixed inputs and missing data (different image availability….)
• More ways to characterize tumors – shape, etc.
• Noise and artifact reduction in images (esp. retrospective and/or CBCT)
• Better modeling – machine learning, etc…..
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• Francesco Stingo, Ph.D.

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• Patti Chen
• Joey Cheung
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• Xenia Fave
• Mindy Hsieh
• Ashley Rubinstein
• Scott Ingram
• Josh Niedzielski
• Ryan Williamson
• Adam Yock
• Henry Yu