EXPERIENCE BUILDING A LEARNING HEALTH SYSTEM AND DECISION SUPPORT IN RADIATION ONCOLOGY

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Radiation Oncology
Johns Hopkins University

Disclosures

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Toshiba Medical Systems

as well as

Commonwealth Foundation
Maritz Foundation

Which patient will do better?

85-year-old man with T3 N2b M0 Stage IV A Squamous cell carcinoma, NOS of the Right Malignant neoplasm of larynx

85-year-old man with T3 N2b M0 Stage IV A Squamous cell carcinoma, NOS of the Malignant neoplasm of tonsil
Types of Clinical Data

- Clinician Assessments
  - Quality of life
  - Toxicity and complications
- Patient Reported
  - Quality of life
  - Toxity and complications
- Biospecimen
  - Labs
  - Pathology
- Image derived features
  - Radiomics
- Treatment
  - Radiation Dosimetry
  - Surgery
  - Chemotherapy
- Symptom management
  - Nutritional support
  - Pain medications

Learning health system

- Knowledge Database
- Predictive Modeling
- Presentation of Predictions
- Decision Point
  - Facts
  - Controls
  - Outcomes
  - Time
  - Data Feedback
  - (Facts, Outcomes)

Oncospace Consortium Repository

- It’s all about the data
- Knowledge Base
- Registry
- Quality Reporting
- Decision Support
- Research
- John Hopkins
- U. Washington
- M. Samuels
- Sunnybrook
- U. Virginia
- Johns Hopkins
- Institution X
- N, S, Pt
- $/pt

Quality Reporting

Decision Support

Research
Consortium Status
Michael Bowers MS

University of Washington
Prostate – 1800 Pt
Pancreas - 500 Pt
Thoracic - 720 Pt
Head/Neck - 1300 Pt

University of Virginia
Prostate – 1000 Pt
Pancreas - 500 Pt
Thoracic - 200 Pt

University of Toronto
Head/Neck – 100 Pt

Johns Hopkins SOM
NKI*
Prostate – 20 Pt

Michael Bowers MS

Precision Radiotherapy Treatment

Shape-dose relationship for radiation plan quality

For a selected Organ at Risk and %V, find the lowest dose achieved from all patients whose %V is closer to the selected target volume?

Dose prediction

Decisions:
- Plan quality assessment
- Automated planning
- IMRT objective selection
- Dosimetric trade-offs
Promote Culture of Data Collection
Data collected over entire treatment

At what point do we have enough data to make decisions based on future predictions?

Input Variables => Prediction?

Extract, Transform, Load

- SQL Query
- Lab, Toxicity, Assessments

Head and Neck Inventory
~1000 pts up to 6 yr follow up
Toxicity and Dose Volume Histogram
(Scott Robertson et al...)

The Data Modeling Culture

Statistical Modeling: The Two Cultures
Lee Breiman

The Algorithmic Modeling Culture

Results: Weight loss prediction at planning
Endpoint: > 5kg loss at 3 months post RT

- Predictors:
  - (1) Diagnosis (ICD-9 code)
  - (2) Dosimetry: dose to swallowing muscles, larynx, parotid
  - (3) Patient: age

- Prediction result: High negative predictive value
  - The model can screen out patients without weight loss
  - Physicians can focus on patients with high probability of weight loss

Sierra Zhi Cheng MD MS
Minoru Nakatsagawa PhD

Prediction result

<table>
<thead>
<tr>
<th></th>
<th>AUC</th>
<th>Sensitivity</th>
<th>PPV</th>
<th>NPV</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>0.773</td>
<td>0.768</td>
<td>0.426</td>
<td>0.905</td>
</tr>
</tbody>
</table>
Results: Weight loss prediction during RT

- Predictors:
  - (1): QOL, patient reported oral intake
  - (2): Diagnosis and staging, ICD-9, N stage
  - (3): Dosimetry, dose to larynx, parotid
  - (4): Toxicity, skin toxicity, nausea, pain
  - (5): Geometry, minimum distance b/w PTV, larynx

<table>
<thead>
<tr>
<th>Prediction result</th>
<th>AUC</th>
<th>Sensitivity</th>
<th>PPV</th>
<th>NPV</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>0.821</td>
<td>0.977</td>
<td>0.862</td>
<td>0.986</td>
</tr>
</tbody>
</table>

Results of Decision Support for Weight Loss

Included radiomic features of the parotid glands

Pancreas Resectability

(S. Cheng et al.)
Xerostomia results  

**Study population**

- **N = 319**
- **Age (mean ± sd) = 57.82 ± 11.10**
- **Male: 76.8%**
- **Caucasian: 75.69%**
- **Tobacco use history: 56.84%**
- **Alcohol use history: 48.32%**

<table>
<thead>
<tr>
<th>Chemotherapy</th>
<th>HPV</th>
<th>Weight loss</th>
<th>Parotid D95</th>
<th>Submandibular D70</th>
</tr>
</thead>
<tbody>
<tr>
<td>61.34%</td>
<td>57.99%</td>
<td>9.23 ± 7.42</td>
<td>10.88 ± 6.33</td>
<td>55.72 ± 12.80</td>
</tr>
</tbody>
</table>

**Reference**

- **Severe xerostomia**
  - 125 (39.18%)
  - 194 (60.82%)

- **Chemotherapy**: 80%
- **HPV**: 78.57%
- **Weight loss**: 5.36 ± 5.87
- **Parotid D95**: 6.6 ± 5.03
- **Submandibular D70**: 41.94 ± 23.59

- **Combined parotid volume < 70.2**:
  - **N = 100**
  - **Low grade xerostomia**:
    - **N = 45**
    - 80%
    - **Low grade xerostomia**:
      - **N = 18**
      - 78%
      - **Severe xerostomia**:
        - **N = 56**
        - 53% severe

- **Ever smoker**
  - **N = 26**
  - 62%

- **Low grade xerostomia**
  - **N = 56**

- **Primary tumor stage 0 or 1**
- **Age < 51**
- **KPS < 85**

- **African American, Caucasian, Declined, Unknown or others**
- **Ethnicity**

- **Weight loss < Parotid D95 dose < 9.26 Gy**
- **Parotid mean dose < 9.07 Gy**

**Results**

**ROC curves of prediction using parotid D95 and parotid mean dose**

- **CART with 10-fold cross-validation to compare prediction power using parotid D95 and parotid mean dose**

<table>
<thead>
<tr>
<th>Parotid D95</th>
<th>0.691</th>
<th>0.639</th>
<th>0.640</th>
<th>0.674</th>
</tr>
</thead>
<tbody>
<tr>
<td>Parotid mean dose</td>
<td>0.561</td>
<td>0.561</td>
<td>0.702</td>
<td>0.413</td>
</tr>
</tbody>
</table>

*Accuracy*: the weighted average of a test’s sensitivity and specificity
**Xerostomia prevalence separated by age = 51**

![Xerostomia prevalence graph]

**Parametric Shape-Based Features**

*What are they?*
- Consistently identifiable substructures that characterize a region of interest
- Based on geometric image manipulation

*How are they calculated?*
- Regions of interest are normalized to a common atlas anatomy
- Features are calculated based on predefined parameters, such as expansion/contraction, slicing, etc.

**Defining a Feature**

- Transformations can be composed to create more complicated features

**Shells+Octants Feature**: Defined by expansion, contraction, and partitioning into octants about the origin. Shown here applied to a parotid gland.
Compute Dose to a Feature

• Dose distribution can be mapped onto each sub-structure

Visualization of a parotid gland with dose mapping

Shell created from surface of parotid to 2mm expansion with dose mapping

Spatially dependent features of dose in the structures (F. Marungo et al.)

<table>
<thead>
<tr>
<th>Method</th>
<th>Value distribution</th>
<th>NTCP LKB</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bagged Naive Bayes (1000 Iterations)</td>
<td>0.915</td>
<td>0.743</td>
</tr>
<tr>
<td>Bagged Linear Regression (1000 Iterations)</td>
<td>0.905</td>
<td>0.737</td>
</tr>
<tr>
<td>Naive Bayes</td>
<td>0.900</td>
<td>0.734</td>
</tr>
<tr>
<td>Linear Regression</td>
<td>0.896</td>
<td>0.731</td>
</tr>
<tr>
<td>Random Forest (1000 trees)</td>
<td>0.724</td>
<td>0.683</td>
</tr>
<tr>
<td>WTDCP</td>
<td>0.596</td>
<td>0.700</td>
</tr>
</tbody>
</table>
Needs…

- For the vision of a learning health system, significantly improved user interfaces are required
- In order to present a prediction, we must first present the “quantitative” patient state
- More continuous assessment of patient condition is needed through mobile devices
- Stronger linkages between genomic, pathology and clinical databases

Summary

- We can quantify the patient experience and are improving our capabilities rapidly
- It is possible to collect and house RT data/knowledge in a clinical setting
- Current shape-based auto-planning utilizes a learning health system
- Data science models are maturing that can convert the knowledge to clinical predictions
- Sharing data across institutions allows for experience and expertise sharing

…we have work to do which requires real partnerships between clinicians and informaticists

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**Xerostomia Prediction**

**Study Design**
- **Primary outcome**: Xerostomia grade (CTCAE v4.0) at 90 - 150 days after RT
  - Grade 2 & 3 – severe xerostomia
  - Grade 0 & 1 – reference
- **Confounding factors**
  - **Time-fixed parameters**: age, gender, race, chemotherapy, smoking status, alcohol use, HPV status, tumor stage (T, N, M, overall), Karnofsky Performance Scale (KPS), tumor site, volume of salivary glands, dosimetric factors
  - **Time-varying parameters**: weight, taste function

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**Results**

**Backward stepwise elimination**

<table>
<thead>
<tr>
<th>OR</th>
<th>p-value</th>
<th>95% Confidence Interval</th>
</tr>
</thead>
<tbody>
<tr>
<td>alpha</td>
<td>0.05</td>
<td></td>
</tr>
<tr>
<td>Parotid D95</td>
<td>1.15</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Submandibular D70</td>
<td>1.04</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Submandibular D60</td>
<td>1.05</td>
<td>0.036</td>
</tr>
<tr>
<td>alpha</td>
<td>0.01</td>
<td></td>
</tr>
<tr>
<td>Parotid D95</td>
<td>1.15</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Submandibular D70</td>
<td>1.04</td>
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</tr>
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**Parametric modeling – Univariate Analyses**

<table>
<thead>
<tr>
<th>Parameters</th>
<th>OR</th>
<th>p-value</th>
<th>95% Confidence Interval</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chemotherapy</td>
<td>ref.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>No.</td>
<td>2.52</td>
<td>&lt;0.001</td>
<td>[1.49, 4.26]</td>
</tr>
<tr>
<td>HPV</td>
<td>ref.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>2.67</td>
<td>&lt;0.001</td>
<td>[1.32, 5.38]</td>
</tr>
<tr>
<td>Weight loss at 1st visit</td>
<td>ref.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>0 kg</td>
<td>2.58</td>
<td>&lt;0.001</td>
<td>[1.62, 4.09]</td>
</tr>
<tr>
<td>&gt; 5 kg</td>
<td>1.15</td>
<td>&lt;0.001</td>
<td>[1.09, 1.21]</td>
</tr>
<tr>
<td>Parotid D95</td>
<td>1.04</td>
<td>&lt;0.001</td>
<td>[1.02, 1.06]</td>
</tr>
<tr>
<td>Submandibular D70</td>
<td>1.04</td>
<td>0.033</td>
<td>[1.00, 1.08]</td>
</tr>
<tr>
<td>Parotid mean dose</td>
<td>1.04</td>
<td>0.033</td>
<td>[1.00, 1.08]</td>
</tr>
</tbody>
</table>