Informatics Challenges in Modeling of IMRT Knowledge for Treatment Planning

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IMRT Treatment Planning

- Time consuming, Iterative process
- Variable quality
  - Knowledge, experience, and resources

Modeling of RT knowledge
Integrated decision support

Higher Efficiency
Better Quality
Knowledge Sources

• Prior plan data
  – Plans, quality assessment, patient and machine features, treatment outcomes

• Published knowledge
  – Guidelines, clinical trials, peer reviewed papers, normal tissue complication models

• Experience
  – In the head of physicians, physicists, dosimetrists, therapists
Informatics Challenges

- Data collection and management
- Data and terminology standardization
- Data modeling and mining
- Knowledge representation and reasoning
- Integrated, intuitive, and interactive interface for decision support
Infrastructure for Data Collection

• Scale
  – Ad hoc, trial-based data collection
  – Large scale, long term data collection

• Purpose
  – Quality assessment
  – Model training and validation
  – Outcomes analysis
  – “Learning Healthcare System”
PCORI CDRN

Patent Centered Outcomes Research Institute

Clinical Data Research Network

Phase 1
$56M
8 networks
18 months
Data Standards

• Common data elements
• Vocabulary/Terminology
• Ontology
Common Data Elements

- Common data element
  - A data element that is common to multiple data sets across different studies
- Data element
  - Information that describes a piece of data to be collected in a study
    - Name, definition, query/instructions, provenance, value set
- Examples
  - caDSR
Data Standards

ACC/AHA/ACR/ASE/ASNC/HRS/NASCI/RSNA/SAIP/SCAI/
SCCT/SCMR/SIR 2008 Key Data Elements
and Definitions for Cardiac Imaging

A Report of the American College of Cardiology/American Heart
Association Task Force on Clinical Data Standards (Writing Committee to
Develop Clinical Data Standards for Cardiac Imaging)

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Terminology / Vocabulary

• A collection of concepts with their corresponding definitions and codes that may include relationships between concepts
  – SNOMED CT
  – CTCAE
  – RTOG Late/Acute Morbidity Scoring

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## Renal and urinary disorders

<table>
<thead>
<tr>
<th>Adverse Event</th>
<th>Grade 1</th>
<th>Grade 2</th>
<th>Grade 3</th>
<th>Grade 4</th>
<th>Grade 5</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acute kidney injury</td>
<td>Creatinine level increase of &gt;0.3 mg/dL; creatinine 1.5 - 2.0 x above</td>
<td>Creatinine 2 - 3 x above baseline</td>
<td>Creatinine &gt;3 x baseline or &gt;4.0 mg/dL; hospitalization indicated</td>
<td>Life-threatening consequences; dialysis indicated</td>
<td>Death</td>
</tr>
<tr>
<td>Bladder perforation</td>
<td>-</td>
<td>Extraperitoneal perforation; indwelling catheter indicated</td>
<td>Intraperitoneal perforation; elective radiologic, endoscopic or operative intervention indicated</td>
<td>Life-threatening consequences; organ failure; urgent operative intervention indicated</td>
<td>Death</td>
</tr>
<tr>
<td>Bladder spasm</td>
<td>Intervention not indicated</td>
<td>Antispasmodics indicated</td>
<td>Hospitalization indicated</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Chronic kidney disease</td>
<td>eGFR (estimated Glomerular Filtration Rate) or CrCl (creatinine clearance) &lt; LLN - 60 ml/min/1.73 m² or proteinuria 2+ present; urine protein/creatinine &gt; 0.5</td>
<td>eGFR or CrCl 50 - 30 ml/min/1.73 m²</td>
<td>eGFR or CrCl 29 - 15 ml/min/1.73 m²</td>
<td>eGFR or CrCl &lt;15 ml/min/1.73 m²; dialysis or renal transplant indicated</td>
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</tr>
</tbody>
</table>

**Definition:** A disorder characterized by the acute loss of renal function and is traditionally classified as pre-renal (low blood flow into kidney), renal (kidney damage) and post-renal causes (ureteral or bladder outflow obstruction).

**Bladder perforation**

**Definition:** A disorder characterized by a rupture in the bladder wall.

**Bladder spasm**

**Definition:** A disorder characterized by a sudden and involuntary contraction of the bladder wall.

**Chronic kidney disease**

**Definition:** A disorder characterized by gradual and usually permanent loss of kidney function resulting in renal failure.
<table>
<thead>
<tr>
<th>Organ</th>
<th>None</th>
<th>Slight epithelial atrophy&lt;br&gt;Minor telangiectasia (microscopic hematuria)</th>
<th>Moderate frequency&lt;br&gt;Generalized telangiectasia&lt;br&gt;Intermittent macroscopic hematuria</th>
<th>Severe frequency and dysuria&lt;br&gt;Severe generalized telangiectasia (often with petechiae)&lt;br&gt;Frequent hematuria&lt;br&gt;Reduction in bladder capacity (&lt;150 cc)</th>
<th>Necrosis/Contracted bladder (capacity &lt;100 cc)&lt;br&gt;Severe hemorrhagic cystitis</th>
</tr>
</thead>
<tbody>
<tr>
<td>BLADDER</td>
<td>None</td>
<td>Asymptomatic&lt;br&gt;No growth retardation&lt;br&gt;Reduced bone density</td>
<td>Moderate pain or tenderness&lt;br&gt;Growth retardation&lt;br&gt;Irregular bone sclerosis</td>
<td>Severe pain or tenderness&lt;br&gt;Complete arrest of bone growth&lt;br&gt;Dense bone sclerosis</td>
<td>Necrosis/Spontaneous fracture</td>
</tr>
<tr>
<td>BONE</td>
<td>None</td>
<td>Mild joint stiffness&lt;br&gt;Slight limitation of movement</td>
<td>Moderate stiffness&lt;br&gt;Intermittent or moderate joint pain&lt;br&gt;Moderate limitation of movement</td>
<td>Severe joint stiffness&lt;br&gt;Pain with severe limitation of movement</td>
<td>Necrosis/Complete fixation</td>
</tr>
</tbody>
</table>
Ontology

• Formal representation for a domain of knowledge
  – Concepts
  – Relationships

• Examples
  – Foundational Model of Anatomy (FMA)
  – SNOMED CT (?)
Knowledge Representation

- Ontology, rules, and instances
  - Clinical trials publications
  - Guidelines
  - Experience
Normal Tissue Toxicity Criteria (1)

• Common Terminology Criteria for Adverse Events (CTCAE)
• Radiation Therapy Oncology Group (RTOG)/European Organization for Research and Treatment of Cancer (EORTC)
  • Acute and late toxicity scoring

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Normal Tissue Toxicity Criteria (2)

- Late Effect Normal Tissue Task Force (LENT)/subjective, objective, management, analytic (SOMA)
- World Health Organization (WHO)
- Eastern Cooperative Oncology Group (ECOG)
- Child-Pugh
- EORTC Quality of Life Questionnaire-Core 30 (EORTC QLQ-C30)

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CTCAE Terminology App

Tinnitus

- Show Definition

Grade 1
- Mild symptoms; intervention not indicated

Grade 2
- Moderate symptoms; limiting instrumental ADL

Grade 3
- Severe symptoms; limiting self care ADL

Grade 4

Matched Name
- Fever

Matched Definition
- Allergic reaction
- Chills
- Enterocolitis

Unc Charlotte
CTCAE Terminology

Class hierarchy: 'Grade 1 Bladder spasm'

- Pregnancy, puerperium and perinatal conditions
- Psychiatric disorders
- Renal and urinary disorders
  - Acute kidney injury
  - Bladder perforation
- Bladder spasm
  - Grade 1 Bladder spasm
  - Grade 2 Bladder spasm
  - Grade 3 Bladder spasm
- Chronic kidney disease
- Cystitis noninfective
  - Hematuria
  - Hemoglobinuria
  - Proteinuria
- Renal and urinary disorders - Other, specify
  - Renal calculi
  - Renal colic
  - Renal hemorrhage
  - Urinary fistula
  - Urinary frequency
  - Urinary incontinence
  - Urinary retention
  - Urinary tract obstruction
  - Urinary tract pain
  - Urinary urgency
  - Urine discoloration
Knowledge in Publications

RECTAL BLEEDING, FECAL INCONTINENCE, AND HIGH STOOL FREQUENCY AFTER CONFORMAL RADIOTHERAPY FOR PROSTATE CANCER: NORMAL TISSUE COMPLICATION PROBABILITY MODELING

Stephanie T. H. Peeters, M.D.,* Mischa S. Hoogeman, P Augustinus A. M. Hart, M.Sc.,* Peter C. M Joos V. Lellesque, M.D.,
*Department of Radiation Oncology, The Netherlands Cancer Institute–The Netherlands; †Department of Radiation Oncology, Erasmus Medical Centre, Rotterdam, the Netherlands

Prostate

prostate only (treatment group I). Acute GI toxicity (RTOG Grade ≥2) was seen in 53% of the patients. After a follow-up of 3 years, 23 of the 468 patients (5%) developed rectal bleeding. 30 (6%) had a high stool frequency, and 32 (7%) experienced fecal incontinence. Of the 23 patients with late rectal bleeding, 14 developed it between the second and third year of follow-up. Only 3 patients experienced bleeding after 3 years of follow-up (11% of all patients with rectal bleeding) and were therefore considered as nonbleeders in the present analysis. This was also the case for 7 patients with a high stool frequency (19% of all patients with high stool frequency) and 10 patients with fecal incontinence (24%).
Renal Genitourinary Endpoints

Urinary Frequency: 5 Grades

The Studies

Other Endpoints
Toxicity Criteria in RT Studies

• Published in past 3 years (2010, 2011, 2012)
• 4 normal tissue toxicity criteria
  • CTC/CTCAE
  • LENT-SOMA
  • RTOG
  • RTOG/EORTC
• 668 articles total
• 531 analyzed

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<table>
<thead>
<tr>
<th></th>
<th>No. of articles</th>
<th>Percent(%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acute and late</td>
<td>201</td>
<td>37.9</td>
</tr>
<tr>
<td>Acute only</td>
<td>137</td>
<td>25.8</td>
</tr>
<tr>
<td>Late only</td>
<td>82</td>
<td>15.4</td>
</tr>
<tr>
<td>Not clear</td>
<td>97</td>
<td>18.3</td>
</tr>
<tr>
<td>Not acquired</td>
<td>14</td>
<td>2.6</td>
</tr>
<tr>
<td><strong>total</strong></td>
<td><strong>531</strong></td>
<td></td>
</tr>
</tbody>
</table>

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## Acute vs. Late by Criteria

<table>
<thead>
<tr>
<th>System</th>
<th>No. of articles</th>
<th>Acute</th>
<th>Late</th>
<th>Acute and Late</th>
<th>Not clear</th>
</tr>
</thead>
<tbody>
<tr>
<td>LENT</td>
<td>28</td>
<td>28</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CTC/CTCAE</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CTC2.0</td>
<td>37</td>
<td>26</td>
<td>1</td>
<td>1</td>
<td>9</td>
</tr>
<tr>
<td>CTCAE3.0</td>
<td>243</td>
<td>77</td>
<td>26</td>
<td>67</td>
<td>73</td>
</tr>
<tr>
<td>CTCAE4.0</td>
<td>32</td>
<td>11</td>
<td>2</td>
<td>11</td>
<td>11</td>
</tr>
<tr>
<td>CTC(no clear)</td>
<td>8</td>
<td>1</td>
<td></td>
<td></td>
<td>7</td>
</tr>
<tr>
<td>RTOG</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>RTOG-Acute</td>
<td>151</td>
<td>151</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>RTOG/EORTC-Late</td>
<td>147</td>
<td></td>
<td>147</td>
<td></td>
<td></td>
</tr>
<tr>
<td>No clear</td>
<td>25</td>
<td></td>
<td></td>
<td></td>
<td>25</td>
</tr>
</tbody>
</table>
### Combined Use

<table>
<thead>
<tr>
<th>Acute side effect</th>
<th>Late side effect</th>
<th>No. of articles</th>
<th>Percent (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CTCAE 2.0</td>
<td>LENT</td>
<td>1</td>
<td>0.4</td>
</tr>
<tr>
<td>CTCAE 3.0</td>
<td>LENT</td>
<td>8</td>
<td>3.8</td>
</tr>
<tr>
<td>RTOG-acute</td>
<td>LENT</td>
<td>9</td>
<td>4.3</td>
</tr>
<tr>
<td>CTC 2.0</td>
<td>RTOG\EORTC</td>
<td>15</td>
<td>7.1</td>
</tr>
<tr>
<td>CTCAE 3.0</td>
<td>RTOG\EORTC</td>
<td>14</td>
<td>6.7</td>
</tr>
<tr>
<td>RTOG-acute</td>
<td>RTOG\EORTC</td>
<td>88</td>
<td>42.1</td>
</tr>
<tr>
<td>CTCAE 3.0</td>
<td>CTCAE 3.0</td>
<td>66</td>
<td>31.6</td>
</tr>
<tr>
<td>CTCAE 4.0</td>
<td>CTCAE 4.0</td>
<td>8</td>
<td>3.8</td>
</tr>
</tbody>
</table>
## Effect of Adding Chemotherapy

<table>
<thead>
<tr>
<th>Treatment</th>
<th>CTC</th>
<th>Not CTC</th>
<th>No. of articles</th>
</tr>
</thead>
<tbody>
<tr>
<td>EBRT and/or BRT</td>
<td>163</td>
<td>170</td>
<td>333</td>
</tr>
<tr>
<td>EBRT and/or BRT + CT</td>
<td>140</td>
<td>58</td>
<td>198</td>
</tr>
</tbody>
</table>

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Conclusions

• PCORI CDRN is a promising platform for large scale data collection
• RT Ontology has potential to capture knowledge in RT treatment
• Toxicity criteria harmonization will be valuable
Acknowledgement

• Collaborators – Duke U.
  – Jackie Wu
  – Yuliang Jiang
  – John Kirkpatrick
  – Lulin Yuan
  – Fangfang Yin

• Support from NIH grant R21CA161389
Thanks!
RT Decision Support User Interface

• Integrated
  – All sources of knowledge

• Individualized
  – Specific patient

• Intuitive and visual
  – Minimal cognitive burden (e.g. nomograms)

• Interactive
  – Zoom in and out, trade-off
Integrated, Individualized, Intuitive, and Interactive DSS

Prediction

QUANTEC Guidelines

Graph showing the LQ equivalent dose in 2 Gy fractions (Gy) against % volume. Various studies are plotted, each with different radiation doses and associated risks.
Radiation Treatment Guideline Ontology

Use the filters below to search for studies matching the desired parameters.
Once the parameters have been entered, click DISPLAY to obtain the results.

DATE RANGE:
From: 2000
To: 2011

STUDY SIZE:
Min Participants: 25
Max Participants: 350

ORGAN:
Rectum

QUANTEC RECOMMENDATION:
Dose Volume Effects
[QUANTEC RECOMMENDATION FOR: Rectum]

STUDIES MATCHING QUERY:
Dose Volume Effects
[ORGAN: Rectum] [DATES: 2000-2011] [STUDY SIZE: 25-350]

VIEW PAPERS:
Choose an author from the list and click "View Paper" or "View Abstract"

- Jackson (2001)
- Jackson (2001)
- Cozzarini (2003)
- Waechter (2001)
- Huang (2002)
- Koper (2006)