Uncertainties in Radiation Medicine: An Oncologist’s Perspective

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Personalized Radiation Medicine

Anatomic targeting

Molecular targeting

Complementary strategies to improve tumor control and reducing side effects
Uncertainty is Context-Specific

The clinical significance of uncertainties depends on patient, tumor and treatment related factors.

Pelvic IMRT for cervical cancer

MRgBT for cervical cancer
Implications of dosimetric uncertainties for tumor control and toxicity

Tanderup, 2013
Clinical Challenges

• Harmonizing care in the face of uncertainty
  – Target delineation
  – Internal target and OAR motion
  – Tumor regression and deformation
  – CTV margin for subclinical tumor
  – Clinical response to a shrinking tumor

• Measuring and reporting clinical outcomes
  – Harmonization of care improves our ability to demonstrate clinical benefit
Priorities in Radiation Medicine

Clinical work load (Efficiency)

Complexity and innovation

Quality and safety

Resource limitations (costs) impose constraints
Harmonizing Clinical Care

Harmonizing care in the face of uncertainty

- Standardization
- Clinical practice guidelines
- Consensus statements
- Clinical trials
- Peer review
- Education and training
ICRU Target Definitions

ICRU 50 and 62

GTV: Gross tumor volume
- ‘Visible’ tumor

CTV: Clinical target volume
- Microscopic tumor

ITV: Internal target volume
- Target motion

PTV: Planning target volume
- Setup variability
Target Delineation

... the weakest link in the search for accuracy in radiotherapy


Cervix  Uterus  Parametria

19 international experts in GYNE radiation oncology

Lim, 2010
Improving Contour Agreement

• High quality imaging
  – Anatomic, metabolic, multi-parametric
• Contouring guidelines and atlases
• Simplification and automation
• Peer review
  – Radiation oncologists, other specialists
• Education and training
The Importance of Imaging

CBCT  Diagnostic CT  T2-MR

Cervical Cancer

Increasing physician confidence
The Importance of Imaging

FDG PET imaging to guide contouring in lung cancer

CT alone

FDG PET CT

Steenbakkers, 2006
Automated delineation of FDG PET metabolic target volume in lung cancer

Manual contours

Automated contours (40% of $\text{SUV}_{\text{Max}}$)

van Baardwijk, 2007
CONSENSUS GUIDELINES FOR DELINEATION OF CLINICAL TARGET VOLUME FOR INTENSITY-MODULATED PELVIC RADIO THERAPY FOR THE DEFINITIVE TREATMENT OF CERVIX CANCER

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Alexandra Taylor, F.R.C.R.,↑↑ Walter Bosch, Ph.D.,↑↑ Issam El Naqa, Ph.D.,↑↑
and Anthony Fyles, M.D.∗ FOR THE GYN IMRT CONSORTIUM.

Recommendations from Gynaecological (GYN) GEC-ESTRO Working Group* (I): concepts and terms in 3D image based 3D treatment planning in cervix cancer brachytherapy with emphasis on MRI assessment of GTV and CTV

Contouring Guidelines and Atlases

Seroma contouring guideline for partial breast RT

Greater contour agreement with training and adherence to guidelines

<table>
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<th>Case no.</th>
<th>Phase 1 Mean (SD)</th>
<th>Phase 2 Mean (SD)</th>
<th>p</th>
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<td></td>
<td>Trained</td>
<td>Untrained</td>
<td>Doubly trained</td>
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<tr>
<td>1</td>
<td>187.4 (9.8)</td>
<td>207.4 (3.5)</td>
<td>68.6 (6.8)</td>
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<td>2</td>
<td>74.8 (3.9)</td>
<td>100.2 (6.1)</td>
<td>13.5 (4.4)</td>
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<tr>
<td>3</td>
<td>30.4 (2.2)</td>
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<td>150.0 (5.3)</td>
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<td>4</td>
<td>22.6 (4.9)</td>
<td>28.8 (3.8)</td>
<td>14.7 (1.0)</td>
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<td>5</td>
<td>12.8 (5.6)</td>
<td>18.1 (4.8)</td>
<td>63.2 (16.9)</td>
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</table>

Wong, 2006
Peer Review of Treatment Plans

Original plan: Inadequate target coverage

Revised plan after peer review

Lefresne, 2013
# Peer Review of Treatment Plans

### 6.10 Radiation Oncology Peer Review of Treatment Plans

<table>
<thead>
<tr>
<th>Key Indicators</th>
<th>Indicator Range</th>
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<tr>
<td>Percentage of adjuvant or curative radiotherapy treatment plans that undergo radiation oncology peer review at any time.</td>
<td>0-100%</td>
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<tr>
<td>Percentage of adjuvant or curative radiotherapy treatment plans that undergo radiation oncology peer review prior to the start of treatment.</td>
<td>0-100%</td>
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<tr>
<td>Percentage of adjuvant or curative radiotherapy treatment plans that undergo radiation oncology peer review after the start of treatment but before 25% of the prescribed dose has been administered.</td>
<td>0-100%</td>
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</table>

Programmatic Quality Assurance Guidance for Canadian Radiation Treatment Programs

www.cpqr.ca
The Importance of Internal Motion

Failure to compensate for tumor and OAR motion can offset the benefits of dose escalation and increase side effects

Crevoisier, 2005
Population PTVMargins

For Inter-Fraction Motion

For Intra-Fraction Motion

Daily Image Guidance
Cervical Cancer Extreme Motion

Cervix cancer (Week 1)  Cervix cancer (Week 3)

Extreme unpredictable motion
Cervical Cancer Regression

Tumor regression during treatment

50 Gy
Adaptive Radiotherapy

New uncertainties and challenges to assure optimal, safe treatment
MR-gated brachytherapy for cervical cancer: Adapting to tumor regression during EBRT
GEC-ESTRO Cervix Guidelines

Planning constraints

- IR-CTV $D_{90}$ > 60 Gy$_{10}$
- HR-CTV $D_{90}$ > 85 Gy$_{10}$
- Sigmoid $D_{2cc}$ < 75 Gy$_3$
- Rectum $D_{2cc}$ < 75 Gy$_3$
- Bladder $D_{2cc}$ < 90 Gy$_3$

IR-CTV: Tumor volume at diagnosis
HR-CTV: Tumor volume at brachytherapy

New ICRU Definitions

Revision of ICRU Report 38: *Prescribing, Recording, and Reporting Cervical Brachytherapy*

- **CTV-T**: Primary tumor clinical target volume
- **CTV-N**: Lymph node clinical target volume
- **iGTV**: Initial gross tumor volume
- **rGTV**: Residual gross tumor volume
- **aCTV**: Adaptive clinical target volume

A vocabulary for adaptive radiotherapy
Shrinking Tumor Volume?

GEC-ESTRO Target Volumes

- GTV
- HR CTV
- IR CTV
- ADC\text{low}

Restricted diffusion as a function of target volume:

- GTV: 37% low ADC <1.2\times10^{-3}\,\text{mm}^2/\text{s}
- HR CTV: 22%
- IR CTV: 12%
MRgBT for Cervical Cancer

145 patients
- T1b-3b
- RT±CT
- BED 80-85 Gy$_{10}$

Outcome at 3y
- Local control 88%
- Overall survival 58%
- Severe late toxicity 5%

Diagram: Local Control

Potter, 2007
Adaptive EBRT for Cervical Cancer

Weekly (or daily!) dose accumulation with adaptive replanning

Dose-Difference Map

Week 1
Week 2
Week 3
Week 4
Week 5

Kristy Brock, James Stewart, Karen Lim
Harmonized Care Improves Outcome

Effect of protocol compliance in a HN cancer clinical trial

Peter, 2010
Summary

• The clinical significance of uncertainties depends on patient, tumor and treatment factors.

• Uncertainties about target volume, internal motion and response to a shrinking tumor currently limit further advances in tumor targeting (in some sites).

• Advances in biology and technology will enable more personalized radiation treatment, reduce some uncertainties and introduce new challenges.

• In the face of uncertainty, harmonization of clinical care based on expert consensus agreement can improve clinical outcome.