Difficulties, Uncertainties and Concerns of IMRT

Luis Souhami, MD
Professor
Department of Radiation Oncology
McGill University, Montreal, Canada
Goal of Radiotherapy

- Maximize dose to tumor site
- Minimize dose to normal tissue

THERAPEUTIC INDEX

Holthusen – Strahlentherapie 1936
Inverse Planning

CT Scan → Geometry → Planning Constraints

Optimization → Calculation → Beam Modulation → IMRT Treatment
IMRT Publications

Year: 1994 to 2008

Number of Publications:
- 0 in 1994
- 100 in 1996
- 200 in 1998
- 300 in 2000
- 400 in 2002
- 500 in 2004
- 600 in 2006
- 700 in 2008

McGill
Fact:
A given RT dose causes less toxicity in a smaller volume

Principle of Conformal Therapy (3DCRT)

- Improved conformality \(\rightarrow\) ↑dose without increase in toxicity
- Increased dose \(\rightarrow\) ↑tumor control
- Increased tumor control \(\rightarrow\) ↑survival
Tumor Control vs. Complication

Hypothetical Model
Tumor Control vs. Complication

Human Tumor Model
Planning Systems Evolution

Clinical positioning

2D Planning (X-rays)

2.5D Planning (X-rays + CT)

3D Planning (CT)

IMRT (CT)
# 2D vs. 3D Treatment Planning

<table>
<thead>
<tr>
<th>2D</th>
<th>3D</th>
</tr>
</thead>
<tbody>
<tr>
<td>Contours</td>
<td>Volumes</td>
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<tr>
<td>Beam data</td>
<td>Beam models</td>
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<tr>
<td>Simulation film</td>
<td>BEV/DRR</td>
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<tr>
<td>Wedges</td>
<td>Intensity modulation</td>
</tr>
<tr>
<td>Isodose curve</td>
<td>Isodose surface</td>
</tr>
<tr>
<td>Isodose distribution</td>
<td>DVH</td>
</tr>
</tbody>
</table>
Cost and Effort vs. Benefit

- Conventional simulation
- CT + conventional simulation
- 3D conformal radiotherapy
- IMRT
- Protons, heavy ions ???
Imaging, imaging, imaging!!!
Comparison of radiation side-effects of conformal and conventional radiotherapy in prostate cancer: a randomised trial

David P Dearnaley, Vincent S Khoo, Andrew R Norman, Lesley Meyer, Alan Nahum, Diana Tait, John Yamold, Alan Horwich

Summary
Background Radical radiotherapy is commonly used to treat localised prostate cancer. Late chronic side-effects limit the dose that can be given, and may be linked to the volume of normal tissues irradiated. Conformal radiotherapy allows a smaller amount of rectum and

225 pacientes - 64 Gy/2 Gy fx dia

Grau I  Grau II

<table>
<thead>
<tr>
<th></th>
<th>2D</th>
<th>3D</th>
<th>2D</th>
<th>3D</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>56%</td>
<td>37%</td>
<td>15%</td>
<td>5%</td>
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</tbody>
</table>

p=0.004  p=0.01

Introduction
The dose of radiation that can be given in clinical practice is usually limited by the need to restrict the number and severity of side-effects. Late side-effects, defined as those that develop or persist more than 3 months after completion of treatment, are more “dose-limiting” than
IMRT decreases complications

• Kam et al ASCO 2005  IMRT vs 2/3DRT
• Small study 28 pts in each arm
• Less xerostomia at 6 weeks (p=0.0019)
• Less xerostomia at 6 mos (p=0.068)
• SPFR at 6 wks (p=0.0001)
• SPFR at 6 mos (p=0.0001)

Local control???
IMRT: The Inverse, the Converse, and the Perverse
Glatstein Sem Rad Oncol 2002

• “The present euphoria surrounding IMRT is difficult to dissect. IMRT has been heavily touted by both vendors and investigators, although actual clinical data for analysis have so far been sparse.”
Why do we need IMRT?

- Better results?
- Practical – increases efficiency?
- Institutional competition?
- Financial stimulus?
Radiation Treatment Delivery: Total Medicare Payments by Selected CPT Codes
2000-2005 ($ millions)
Transition from 2-D Radiotherapy to 3-D Conformal and Intensity Modulated Radiotherapy
Rectal Sparing

Table 1. Acute toxicity IMRT (n = 772)

<table>
<thead>
<tr>
<th>Toxicity grade</th>
<th>Gastrointestinal</th>
<th>Genitourinary</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>568 (74%)</td>
<td>258 (33%)</td>
</tr>
<tr>
<td>1</td>
<td>169 (22%)</td>
<td>296 (38%)</td>
</tr>
<tr>
<td>2</td>
<td>35 (4%)</td>
<td>217 (28%)</td>
</tr>
<tr>
<td>3</td>
<td>0</td>
<td>1</td>
</tr>
</tbody>
</table>

Zelefsky et al. IJROBP 53, 2002

Zelefsky et al. J Urol 166, 2001
<table>
<thead>
<tr>
<th>Dose %</th>
<th>Gy</th>
<th>Volume IMRT</th>
<th>Volume 3D CRT</th>
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<tbody>
<tr>
<td>30</td>
<td>15</td>
<td>92</td>
<td>91</td>
</tr>
<tr>
<td>50</td>
<td>25</td>
<td>73</td>
<td>85</td>
</tr>
<tr>
<td>90</td>
<td>44</td>
<td>28</td>
<td>52</td>
</tr>
<tr>
<td>100</td>
<td>49.3</td>
<td>17</td>
<td>47</td>
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</table>
## Bone marrow DVH

<table>
<thead>
<tr>
<th>Dose %</th>
<th>Gy</th>
<th>IMRT</th>
<th>3D CRT</th>
</tr>
</thead>
<tbody>
<tr>
<td>20</td>
<td>10</td>
<td>95</td>
<td>94</td>
</tr>
<tr>
<td>50</td>
<td>25</td>
<td>46</td>
<td>86</td>
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<td>90</td>
<td>45</td>
<td>6</td>
<td>35</td>
</tr>
<tr>
<td>100</td>
<td>49.3</td>
<td>1</td>
<td>24</td>
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</table>

## Rectum DVH

<table>
<thead>
<tr>
<th>Dose %</th>
<th>Gy</th>
<th>IMRT</th>
<th>3D CRT</th>
</tr>
</thead>
<tbody>
<tr>
<td>30</td>
<td>15</td>
<td>94</td>
<td>95</td>
</tr>
<tr>
<td>50</td>
<td>25</td>
<td>91</td>
<td>94</td>
</tr>
<tr>
<td>90</td>
<td>45</td>
<td>56</td>
<td>82</td>
</tr>
<tr>
<td>100</td>
<td>49.3</td>
<td>39</td>
<td>71</td>
</tr>
<tr>
<td>105</td>
<td>52</td>
<td>14</td>
<td>23</td>
</tr>
</tbody>
</table>
Anatomical certainty

Physical or biologically needed margin

Conservative approach

“geographical miss”
Planning Technique

Differences in shape of dose distribution

3 DCRT

IMRT
Who should be treated?

- Several reports show better dosimetric results (IMRT vs 3DCRT)
  - Irregularly-shaped targets
  - Concave targets
  - Critical organs adjacent to target volume
  - Previously irradiated tissues
Is it all rosy with IMRT?

• Treatment Precision
• Treatment Duration
• Dose Rate
• Integral Dose
• Cost
• Quality Control
Volume Definition

ICRU 29

ICRU 50

ICRU 62

Purdy Sem Radiat Oncol 2004
Volume Definitions (ICRU 62)

• Organs at risk (OAR) – normal tissues whose radiation sensitivity may significantly influence treatment planning and/or prescribed dose
• Internal target volume (ITV) – takes in account variations in internal margin and set-up margin
• Planning risk volume (PRV) – margin added around OAR to compensate for organ geometrical uncertainties
MRI vs. CT: Prostate Apex
Target Delineation
CT vs MR

Average CT/MR volume: 1.24 (Kagawa, 1997)
Average CT/MR volume: 1.3  (Roach, 1996)
Average CT/MR volume: 1.4  (Rasch, 1999)
MRI vs. CT: Hip Replacement
Target Volume Delineation

• Important variation in target delineation
  – Central Nervous System
  – Head & Neck
  – GU
  – Lung, etc

• Set-up uncertainty
Target Volume Variation

8 radiation oncologists
2 radiologists
2 neurosurgeons

Leunens Radioth Oncol 1993
Target Volume Variation

- 20 centers: US, Europe, Asia
- T2N1M0 (stage III), tonsil carcinoma
  - Virtual tumor 3 cm
  - Ipsilateral 2 cm node, level II
- Participants: CTV and PTV

Tong et al IJRBOP 2004
Target Volume Variation

- 2/3 – primary tumor & nodes bilaterally
- 1/3 – primary tumor & nodes unilaterally
- 1/3 – significant variation in CTV volume
- Median time: 1h 40 min (60-210 min)

Tong et al IJRBOG 2004
Target Volume Variation

Tong et al Br J Cancer 2005
Prostate volume: Variation

5 “experts” in prostate cancer

Table 1. Prostate volumes according to each reviewer

<table>
<thead>
<tr>
<th>Case</th>
<th>R1</th>
<th>R2</th>
<th>R3</th>
<th>R4</th>
<th>R5</th>
<th>Mean</th>
<th>Median</th>
<th>SD</th>
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</thead>
<tbody>
<tr>
<td>Case 1</td>
<td>71.83</td>
<td><strong>88.11</strong></td>
<td>52.71</td>
<td>80.21</td>
<td>67.33</td>
<td>72.038</td>
<td>71.83</td>
<td>13.42452</td>
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<tr>
<td>Case 2</td>
<td>39.35</td>
<td>35.61</td>
<td>33.34</td>
<td>50.79</td>
<td>41.32</td>
<td>40.082</td>
<td>39.35</td>
<td>6.748761</td>
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<tr>
<td>Case 3</td>
<td>35.57</td>
<td>40.81</td>
<td>27.39</td>
<td>40.31</td>
<td>37.17</td>
<td>36.25</td>
<td>37.17</td>
<td>5.410305</td>
</tr>
<tr>
<td>Case 4</td>
<td>55.81</td>
<td>61.49</td>
<td>46.94</td>
<td>69.28</td>
<td>56.92</td>
<td>58.088</td>
<td>56.92</td>
<td>8.180249</td>
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<tr>
<td>Case 5</td>
<td>47.52</td>
<td>57.41</td>
<td>36.91</td>
<td>57.35</td>
<td>38.08</td>
<td>47.454</td>
<td>47.52</td>
<td>9.951192</td>
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<tr>
<td>Case 6</td>
<td>50.94</td>
<td>56.63</td>
<td>37.76</td>
<td>57.73</td>
<td>40.59</td>
<td>48.73</td>
<td>50.94</td>
<td>9.150063</td>
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<tr>
<td>Case 7</td>
<td>55.98</td>
<td>67.27</td>
<td>51.66</td>
<td>60.53</td>
<td>48.26</td>
<td>56.74</td>
<td>55.98</td>
<td>7.475617</td>
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<tr>
<td>Case 8</td>
<td><strong>42.02</strong></td>
<td>37.01</td>
<td><strong>23.41</strong></td>
<td>39.56</td>
<td>28.14</td>
<td>34.028</td>
<td>37.01</td>
<td>7.917984</td>
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<tr>
<td>Case 9</td>
<td>50.74</td>
<td>50.04</td>
<td>43.88</td>
<td>54.33</td>
<td>43.42</td>
<td>48.482</td>
<td>50.04</td>
<td>4.704447</td>
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<tr>
<td>Case 10</td>
<td>59.13</td>
<td>59.79</td>
<td>46.16</td>
<td>56.9</td>
<td>44.01</td>
<td>53.198</td>
<td>56.9</td>
<td>7.521647</td>
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<tr>
<td>Mean</td>
<td>50.889</td>
<td>55.417</td>
<td>40.016</td>
<td>56.699</td>
<td>44.524</td>
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<tr>
<td>Median</td>
<td>50.84</td>
<td>57.02</td>
<td>40.82</td>
<td>57.125</td>
<td>42.37</td>
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<tr>
<td>SD</td>
<td>10.6167</td>
<td>15.791</td>
<td>9.95446</td>
<td>12.157</td>
<td>10.94937</td>
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</tr>
</tbody>
</table>

*Abbreviations: R = reviewer; SD = standard deviation.
Data presented as cubic centimeters.*

Lee et al. IJROBP 2002
Physiologic Maps: RT Planning
Inadequate Target Definition?

Based on concentrations of various metabolites, color maps highlighting possible areas at increased risk of relapse could be identified & selectively boosted.
The uterine cervix is approximately 2.5 cm in length and consists of the hollow, narrow, cervical part of the cervix, distal to the isthmus which terminates by producing into the upper vagina. It can be divided into epicervical and infracervical parts. The posterior portion of the cervix lies in the cervico-vaginal space which communicates with the vagina through the external cervical os, situated on the surface of the exocervix on speculum examination.

The blood supply of the cervix is derived from the uterine arteries which arise from the common iliac arteries. The uterine artery branches into the ovarian and the vaginal arteries. These vessels form the main arterial supply to the cervix. The lymphatic drainage of the cervix is similar to the uterine and involves the deep lymph nodes which drain into the iliac nodes. The uterine cervix has a rich vascularity, and the lymphatics drain into the pelvic lymph nodes.

The nerve supply to the cervix is provided by the pelvic plexus, which is a network of nerves supplying the pelvic organs. The cervical plexus provides sensory innervation to the cervix and vagina. The cervical plexus is formed by the anterior branches of the sacral plexus and the posterior branches of the lumbar plexus. The cervical plexus provides motor innervation to the muscles of the cervix and vagina.
Uncertainties in target volume definition

- Organ motion
- Changes in organ shape/size during RT
- High conformality may lead to “geographical misses”
- Larger margin may lead to unacceptable high dose to normal critical structure
Issues with PTV

• Consider set-up variation and organ motion
• Under dose to CTV or overdose to OAR
• PTV and PRV overlap
• Wide variation in recommended “adequate” margins
• “The conventional approach of creating a PTV by assigning a uniform margin around the CTV is no longer adequate for IMRT” (IMRT CWG 2001)*

* IJROBP 2001
Set-up Variation & Organ Motion

• **Systematic Errors** (treatment preparation)
  – Average error from planned set-up position
  – Systematic for a single RT course of a single patient
  – Shift of the cumulative dose distribution

• **Random Errors** (treatment execution)
  – Day to day variation
  – Blurring of the dose distribution

• **Margin Recipes?**

Van Herk et al Radiat Oncol 2000
PTV Margin Recipe

Van Herk Sem Radiat Oncol 2002

Margin = 2.5 Σ + 0.7σ

Σ - systematic error
σ - random error
## Set-up Accuracy (1SD, mm)

<table>
<thead>
<tr>
<th>Tumor Type</th>
<th>Systematic</th>
<th>Random</th>
</tr>
</thead>
<tbody>
<tr>
<td>Head &amp; neck</td>
<td>1.6 - 4.6</td>
<td>1.1 - 2.5</td>
</tr>
<tr>
<td><strong>Prostate</strong></td>
<td>1.0 - 3.8</td>
<td>1.2 - 3.5</td>
</tr>
<tr>
<td>Pelvis</td>
<td>1.1 - 4.7</td>
<td>1.1 - 4.9</td>
</tr>
<tr>
<td>Lung</td>
<td>1.8 - 5.1</td>
<td>2.2 - 5.4</td>
</tr>
<tr>
<td>Breast</td>
<td>1.0 - 4.7</td>
<td>1.7 - 14.4</td>
</tr>
</tbody>
</table>

Hurkmans et al Radiot Oncol 2001
Do we want to do IMRT?

• IMRT can be worse than conventional treatments
  – Margins of error are small
  – Complex isodose volumes and high dose gradients mean patient setup errors can result in a geographical miss of the target or overdosing of critical structures

Langer, AAPM SS, 2003
The most resistant tumor is the one outside the irradiation field!
Dose conformality vs. uniformity

- Can we accept hotspots of up to 25%?
- Do you want to prescribe to the 75-85% isodose?

conformality = uniformity
Effect of OAR constraint

115%
110%
100%
70%
50%

OAR at 70% 
conformality

OAR at 50% 
uniformity
Evaluation Tools: DVH?
Trying too hard?

structure at 10%

structure at 2%
Do we want to do IMRT?

- IMRT can be worse than conventional treatments
  - “dose dumping” can put areas of high dose outside the target when dose constraints for non-target regions are, for various reasons, unspecified.
Dose Dumping
Evaluation Tools

“Cold spot in the target”    “dose dumping”

Review every single slice!!!!
Uncertainties in DVH Evaluation

$V_{40} = 20\%$
PTV Margins

5 mm PTV

10 mm PTV

15 mm PTV
Filling Effects on Rectal DVH Parameters

- 70 Gy line
- V70 = 25% for Ischial Tuberosities
- V70 = 10% for Sigmoid Flexure

McGill
Repair of Sublethal Damage

• Is the duration of treatment important?
  – 1960s – Elkind et al
  – surviving fraction ↑ if interval between fractions ↑

• Treatment time ↑ with IMRT
Repair of Sublethal Damage
Shibamoto et al IJROBP 2004

Murine EMT6 ($\alpha/\beta=3.3$ Gy) and SCCVII ($\alpha/\beta=1.7$ Gy) cells
Survival by colony assay

<table>
<thead>
<tr>
<th>Experiment 1</th>
<th>Experiment 2</th>
<th>Experiment 3</th>
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<tr>
<td>8 Gy/ 2 fxs</td>
<td>8 Gy/ 2 fxs</td>
<td>8 Gy/ 5 fxs</td>
</tr>
<tr>
<td>15min – 6h</td>
<td>1 – 10 min</td>
<td>1-5 min</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Experiment 4</th>
<th>Experiment 5</th>
<th>Experiment 6</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.2 – 2 Gy</td>
<td>2 Gy/ 5 fxs (0.4 Gy)</td>
<td>2 Gy/ 10 fxs (0.2 Gy)</td>
</tr>
<tr>
<td>No interruption</td>
<td>1-15 min</td>
<td>0.5 – 3 min</td>
</tr>
</tbody>
</table>
EMT 6 cells after 8 Gy/5 fx

SCC VII cells after 8 Gy/5 fx

Shibamoto et al. IJROBP 2004
Prolonged Dose Delivery Time

Human HCC HepG2 - HepG3b cell lines

Zheng et al World J Gastro 2005
Repair of Sublethal Damage

- Total dose RT – 20-30 min
- Biological effect reduced by 9-14%
- Increase of 8-16% in planned dose is necessary
Average Treatment Times: MIR


- Conventional: 10 min
- 3D CRT: 18 min
- IMRT - MiMiC: 30 min
- IMRT - SMLC: 19 min

Gillin: AAPM Summer Course 2003
Average Treatment Times
UT MDACC

Prostate
• Conventional 10 min
• 3D-CRT 15 min
• IMRT - SMLC 20 min

Head and Neck
• Conventional 15 min
• 3D-CRT 20 min
• IMRT - SMLC 25 min

Gillin: AAPM Summer Course 2003
## Average Treatment Times

**McGill**

### Prostate
- Conventional: 10 min
- 3D-CRT: 15 min
- IMRT: 20 min

### Head and Neck
- Conventional: 15 min
- 3D-CRT: 15-20 min
- IMRT: 20-30 min
1.3 Gy/fx

GTV = 76 Gy/ 38 fxs
LN = 50 Gy/ 38 fxs

Dose-Rate Effect
Low Dose Hypersensitivity

- Several lines have exhibited decrease in survival at doses < 0.1 Gy
- 0.4 Gy TID may be more cytotoxic than 1.2 Gy OD (Joiner et al IJROBP 2001)
- Damage to G2-phase cells (Marples et al Radiat Res 2004)
- Bystander effect
Taxol Sensitization with Fractionated RT (Low Dose)

Colorectal tumor cell lines

Head & Neck cancer cell lines

Chendil et al Cancer 2000

Dey et al Clin Cancer Res 2003
Higher Integral Dose

- IMRT
  - Larger number of fields
  - Larger volume of normal tissues exposed to lower doses
  - More monitor units (2-6 times)
    - Larger body dose (“leakage”)
    - Body dose 8X higher than 3D CRT in Head & Neck tumors (1969 vs 242 mSv)*

*Verellen & Vanhavere Radioth Oncol 1999
Increased Risk of 2nd Cancer

• Hall, Wuu IJROBP 2003
  Risk
  Conventional RT 1%
  IMRT 1.75%

• Kry et al IJROBP 2005
  Risk
  Conventional RT 1.7%
  IMRT 6 MV 2.9%
  IMRT 10 MV 2.1%
  IMRT 18 MV 5.1%
Conclusions

• New paradigm. IMRT may improve results
  – ($\uparrow$ dose = $\uparrow$ local control, $\downarrow$ toxicity)

• Greater complexity
  – Different concept
  – Requires experience (learning curve)
  – Requires sound anatomical knowledge and proper imaging capability
  – Advanced and reliable treatment planning software
  – Accurate treatment delivery
Conclusions

• Organ motion & set-up uncertainty remains a problem
• Rigid quality control
• Unpredictable biological outcomes

Ting and Scarbrough 2006