IMRT Evolution and Hypothesis

IMRT Implementation Issues
- Workload, Cost?, Carcinogenesis?
- IMRT Technology Strategies
  - Cones, Fans, and Pencils of X-rays
  - Hi-LET particle beams
The Adaptive Radiotherapy Process
- 3D and 3D+ Imaging
- Dose Reconstruction and Dose Imaging
- Biological Advances
- Future Outlook for IMRT

**Outline**

**Beam Delivery Evolution**

- Megavoltage Isocentric Setup
- Blocks Wedges Comps
- MLC Dynamic Wedge Dynamic DMLC

**Image Guidance Evolution**

- Portal Imaging (Film)
- Portal Imaging (Electronic)
- Biplanar Radiography
- Ultrasound
- Video Tracking
- CT Imaging
  - CT scanner in room
  - CT scanner "on board"
  - Kilovoltage versus Megavoltage
  - Cone Beam versus Fan Beam

**Hypothesis for IMRT**

- Inadequate loco-regional control of tumors is a significant barrier to cancer survival
- Better dose distributions translate into better clinical outcomes
  - "Herman Suit Credo"
- Goals:
  - To achieve greater differential effects between tumor and normal tissue, through stronger dose gradients
  - To exploit dose escalation
  - To optimize TCP (1.0 – NTCP)
**Tumour Strategies**

- **Local** – solid, localized, GTV
  - Surgery or radiation
- **Regional** – nodes in healthy tissue matrix, CTV
  - Surgery, radiation, chemotherapy
  - Conformal avoidance
- **Systemic** – lymph, blood, marrow, CTV+
  - Chemotherapy, radio-nuclides

Strategic “juggling” is often used:
- As better systemic agents become available, loco-regional control will gain more importance
- 3DCRT and IMRT needed in the future

**IMRT - Scale of Benefits**

- **Individual Patient**
  - Probability of success = TCP(1 - NTCP)
  - For one patient, however, it is a binary outcome
  - Fractionation schedule and convenience
- **Select Cohort of Patients**
  - Clinical Trials (Phase, I, II, III)
  - Find the “niche” for new techniques
  - Patterns of success and failure
- **Populations**
  - Phase III – attitude is IMRT better/cheaper than surgery?
  - Socio-economics
  - Significant gain factors

**IMRT Strategy**

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Response
IMRT
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**IMRT in Perspective**

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Benefit
IMRT
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**Is 5 % significant?**

- US population is 287 million
- 1.28 million/yr will be diagnosed with cancer
- 555,000/yr will succumb
- 5 % corresponds to saving over 64,000 lives/yr
- Extendable to world population?
- Repeat algorithm for each tumour site
IMRT QA Escalation

- 3D Geometry
  - Multi-Modality images (CT, PET, MRI)
  - Complex beam shaping
  - Portal Imaging
- 3D Imaging
  - CT (planning and verification)
  - Functional data (e.g., hypoxia)
- 2D and 3D Dosimetry
  - Smaller fields - calibration
  - 3D dosimetry, integrating
  - 3D dose reconstruction (*in-vivo*)

3D Geometrics

- Multi-Modality images (CT, PET, MRI)
- Complex beam shaping
- Portal Imaging

2D and 3D Dosimetry

- Smaller fields - calibration
- 3D dosimetry, integrating
- 3D dose reconstruction (*in-vivo*)

Dosimetry (SiMAT)

- E. Wong et al., LRCC

3D Densitometry

- First Generation Optical CT Scanner (LRCC model)

IMRT Staff Escalation

- Requirements*
- Retention
- Recruitment
- Residency Programs

* Ontario Standard:
  1 physicist per 300 RT cases
IMRT Cost Escalation

- Prostate (Perez et al., 1997)
  - Standard RT Revenue $10,900
  - 3D-CRT Revenue $13,800
  - RT Failure (with hormones) $40,800
- Prostate (Perez et al., 2001)
  - Standard RT Revenue (prostate) $10,800
  - 3D-CRT Revenue (prostate) $15,600
  - IMRT Revenue (head & neck) $18,100

Break-Even Condition

- Standard Radiotherapy
  \[
  \Delta C = C_{RT} + \Delta F (1 - TCP_{RT})
  \]
- New and Improved Radiotherapy
  \[
  \Delta C = C_{RT} + \Delta F (1 - TCP_{RT}) + \Delta TCP
  \]

Equilibrium condition yields...

\[
\Delta C = \Delta TCP \times \Delta F
\]

3D-CRT Example

- Prostate (Perez et al., 1997)
  - \(\Delta C = \$3,000\) incremental cost of 3D-CRT
  - \(\Delta F = \$27,000\) incremental cost of failure
  - \(\Delta TCP = 3/27 = 0.11\)
- \(\Delta C = \Delta TCP \times \Delta F\)
- Break Even if \(TCP\) climbs from 80% to 91%

IMRT Peripheral Dose

- Fluence (MUs) is increased
- modulation factor
- Dose Escalation
- escalation factor

- a) Primary Head Leakage
- b) Field Shaper Scatter
- c) Field Shaper Transmission
- d) In-Patient Scatter

A Hidden Cost?

Secondary Carcinogenesis

- Hodgkin’s Disease (Cellai et al., 2001)
  - 16% lifetime risk of secondary cancers at 15 years post-radiotherapy
  - Double the baseline risk
- (Hall EJ, 2000)
  - Breast cancers following RT
  - Risk enhancement factor of 2.24
  - Solid tumours following RT of prostate
  - bladder, rectum, lung, sarcomas
  - 34% increase in risk

Secondary Radiation

<table>
<thead>
<tr>
<th>In-Field Dose</th>
<th>Out-of-Field Dose</th>
<th>Standard RT 6 MV</th>
<th>3D-CRT MLC 6 MV</th>
<th>IMRT DMLC 6 MV</th>
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<tbody>
<tr>
<td>Primary Collimator Leakage</td>
<td>Not Applicable</td>
<td>Far Zone</td>
<td>0.1%</td>
<td>0.1%</td>
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<tr>
<td>Field Shaper Scattering and Leakage</td>
<td>Small relative to target dose</td>
<td>Near and Intermediate Zones</td>
<td>0.1% to 0.5% from field edge</td>
<td>0.02 to 0.07% (Mutic)</td>
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<td>Field Shaper Transmission</td>
<td>Significant for small relative</td>
<td>Not Applicable</td>
<td>&lt; 0.5%</td>
<td>&lt; 2.5%</td>
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<td>In-Patient Lateral Scattering</td>
<td>Significantly for</td>
<td>Near and Intermediate Zones</td>
<td>Typically 5-10 MV</td>
<td>Reduced with smaller fields</td>
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<tr>
<td>Modulation Factor</td>
<td>More &quot;beam on&quot; time (MUs)</td>
<td>Mainly affects A, B, C</td>
<td>2X (wedges)</td>
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<tr>
<td>Dose Escalation Factor</td>
<td>Prescription Dose</td>
<td>Affects A, B, C, D</td>
<td>1.0</td>
<td>1.1</td>
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</table>
**IMRT Risk Estimates**

- Followill et al., (1997)
  - Peripheral dose increases from 76 mSv to 190 mSv for 70 Gy IMRT with 6 MV x-ray beam.
  - Excludes dose escalation factor ($1.3 \times 190 = 247$ mSv)
  - Lifetime increase in cancer risk* is 1%
  - 8-fold higher for 25 MV x-rays (neutrons)

- Compare to natural lifetime risk of
  - 8% for lung cancer
  - 13% for breast cancer
  - 40% for incidence of any type of cancer

* $4 \times 10^{-2}$ /Sv

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**Imaging Complementary Principle**

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<tr>
<th>Feature</th>
<th>Simulator</th>
<th>CT</th>
<th>MRI</th>
<th>MRS</th>
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<td>3D Dose Intensity</td>
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<td>(x)</td>
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(x) Partially in development

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**PET-CT Fusion**

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**Imaging for Hypoxia**

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**Structure without function is a corpse:**

**function without structure is a ghost**
Biological Target Volumes

CT, US | PET/SPECT, MRLUS | PET, PET/SPECT, fMRI

Density

Tumour Cells

Hypoxia

PET/SPECT, MRS

Proliferation

CTV

On-Line Imaging

Composite

Adapted from C. Ling et al.

PET-CT Planning and In-Vivo Dosimetry

On-Line Imaging

PET-CT, PET/SPECT, fMRI

PET-CT Planning and In-Vivo Dosimetry

PET-CT, PET/SPECT, fMRI

image dating back to 2003 by Brahme et al.

Image –Guided IMRT

Pencil Beam

Fan Beam

Cone Beam

AccuRay

TomoTherapy

Varian

Cone Beam Delivery

Cone Beam CT Imaging

• Elekta SL-20

• X-ray Tube:
  • 600 kHU
  • 85 kW X-ray Generator
  • Retractable Mount
  • SAD: 100 cm

• Flat-panel Imager:
  • 41 × 41 cm²
  • 1024x1024 @ 400 μm
  • Gd₂O₂S:Tb (133 mg/cm²)
  • Removable Mount
  • SDD: 155 cm
Transverse Coronal Sagittal

kV CT of Head Phantom
320 Projections; 120 kVp, 200 mA; 180 s.
(0.25 x 0.25 x 0.25) mm³ voxels

Tomotherapy Unit

MVCT of a Lung Cancer Patient at 3 cGy
Soft Tissue Window
Lung Window
Future HiART II will capture 24 images/minute

Hip Prosthesis

MVCT Densitometry

Co-MVCT: CT Number Linearity

Beam on Time is 19 min for 5 cm Slice Width and 1.2 Gy/fix

TomoTherapy Inc.

Courtesy Tim Schultheiss, Ph.D.
City of Hope
Tomotherapy Update

- ISO 9001, FDA 510(k) cleared
- Megavoltage CT scans of humans 2002.
- First patient treated August 21, 2002.
- Two units in Canada Dec 2002.
- Two units in USA 2003.

Tomo Bicycle?

Adaptive Radiotherapy

3-D Imaging
Deformable Dose Fusion
Optimized Planning
MV CT + Image Fusion

Dose Reconstruction
Helical Tomotherapy
Modify Setup

Patient Anatomy Changes from Plan Day to First Treatment Day

Planning kV CT
MVCT @1.5 cGy on Fraction #1
Inter-Fraction Deformations

The slices were registered to bony anatomy

Courtesy Di Yan, William Beaumont and Marcel Van Herk, Amsterdam

PTV Changes

3D Deformation Field

Deformable Registration

CT Plan

CT Fraction n

Mapped 0 and n
1:1 Mapping of Tissue Voxels

Dose Warping

In Vivo “Dose of the Day”

Schaly et al.
**Warped Dose - Multi-Fraction**

- Planned dose $d_0$
- $D_0$
- Planned dose $d_1$
- $D_1$

**Dose Error - Multi-Fraction**

- Referenced to Planning Scan
- $\Delta D_5 (+23\%)$
- $\Delta D_{15} (+23\%)$

**Adaptive Dose Algorithm**

- Adaptive Dose Algorithm
- $D_{ijk}(n) = \sum \Delta D_{ijk}(n)$
- If $D_{i,j,k}(n)$ is not converging quickly to $D_{i,j,k}(0)$, re-optimize plan and beams for $f_{n+1}$
- Adjust for remaining dose fractions $f_{n+1}$ (Radiobiology Model)
- Reset Reference Plan to $f_n$
- Repeat as needed

**Moving Tumours**

- Moving Tumours
- Respiratory Motion
- Gate the Beam
  - Respiratory Monitoring
  - Direct (e.g. pneumo)
  - Indirect (e.g. chest movement)
  - Fluoroscopic Tracking of the target
- Gate the Patient
  - Breathing control
  - Voluntary
  - Forced (e.g. ABC)

"If you can't see it, you can't hit it. If you can't hit it, you can't cure it"  
H.E. Johns or W. Powers

"If it's moving, you can't hit it. If you can't hit it, you can't cure it"  
J. Battista
**Active Breathing Control (ABC)**

**Cones, Fans, and Pencils**

<table>
<thead>
<tr>
<th>Traditional Linear</th>
<th>Beam Geometry</th>
<th>Country Design</th>
<th>Degrees of Freedom</th>
<th>Beam Gating Potential Capability</th>
<th>Imaging</th>
</tr>
</thead>
<tbody>
<tr>
<td>Case beam</td>
<td>Co-Planar</td>
<td>Non-coplanar</td>
<td>Breath Hold or Beam Trigger</td>
<td>Fluoroscopy KiloVoltage CT</td>
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<table>
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<th>Helical Tomotherapy</th>
<th>Beam Geometry</th>
<th>Country Design</th>
<th>Degrees of Freedom</th>
<th>Beam Gating Potential Capability</th>
<th>Imaging</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fan beam</td>
<td>Co-Planar</td>
<td>Non-coplanar</td>
<td>Breath Hold with Interleaved Helices</td>
<td>Megavoltage CT</td>
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<th>Serial Tomotherapy</th>
<th>Beam Geometry</th>
<th>Country Design</th>
<th>Degrees of Freedom</th>
<th>Beam Gating Potential Capability</th>
<th>Imaging</th>
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<tbody>
<tr>
<td>Fan beam</td>
<td>C-Arm</td>
<td>Co-Planar</td>
<td>Breath Hold during single slice</td>
<td>Portal Imaging</td>
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<table>
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<th>Robotic Linear</th>
<th>Beam Geometry</th>
<th>Country Design</th>
<th>Degrees of Freedom</th>
<th>Beam Gating Potential Capability</th>
<th>Imaging</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pencil beam</td>
<td>Robotic Arm</td>
<td>Non-coplanar</td>
<td>Gated beam</td>
<td>Bipolar Radiography</td>
<td></td>
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</table>

**Summary**

- **Fan-beam versus Cone-Beam for Adaptive Radiotherapy**
  - CT image guidance
  - kV and MV image quality (noise, scatter rejection, dose)
  - Beam delivery process
    - efficiency of photon production and "waste"
    - peripheral dose levels
  - Gated Radiotherapy Capability
    - Tracking, Beam gating, or Lung gating
  - Dose distributions (DVHs) will likely be competitive
  - The key will therefore be:
    - "On-Board" Image and Dose Verification (CT, PET-CT ?)
    - Streamlining of new adaptive radiotherapy processes
    - (Beam delivery technology will become secondary)
Particle Beam IMRT

- Scan
  - position (2D raster)
  - energy (depth 3D)
  - intensity

A Research Breakthrough?

DNA
Radiobiology Strategy

Response
IMRT gradients

Tumour
Critical Organ

Dose

Current Trends
- Imaging and Therapy are on convergent paths
- Imaging techniques are rarely used “solo”
  - Need sensitivity and specificity
  - Image fusion is available
- IMRT requires multi-modality imaging
  - BTV concept and molecular imaging
  - Gating
- Biology Research
  - Molecular mechanisms uncovered
  - Gene expression/imaging in small animals (micro-imaging)
- Clinical Research
  - Patterns of success and failure
  - Fractionation manipulation

Conclusions
- Radiotherapy is a proven “curative” agent that can reach its full potential through IMRT
- Radiotherapy is non-invasive; toxicity can be reduced further using IMRT techniques
- Long term carcinogenic effects are a concern for IMRT, especially with higher energy x-ray beams (e.g. > 10 MV x-rays)
  - Higher energy not needed for IMRT but needed for PET dosimetry
Conclusions

- Ultimate advances in IMRT will hinge upon better imaging of the Biological Target Volume, to be treated effectively in space and in time.
- Clinical trials are showing early advantages for IMRT both in terms of tumour control by dose escalation and reduced toxicity.
- Positive results will impact the general cancer population, but the magnitude of the effect is still debated, relative to cost and complexity escalation.
- Efficiency and cost-effectives of IMRT will naturally evolve as this form of treatment becomes more widely adopted.

Outlook

- IMRT will continue to complement new "avant garde" therapies, including those based on molecular targeting.
- Radiation will continue to play a unique role as an agent that is especially efficient at killing tumour cells that find refuge in tumours that are not approachable through systemic channels.
- IMRT has produced an exciting technological milieu that enhances the retention and recruitment of a future generation of radiation specialists in our evolving field.

The End

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