The Future of Radiotherapy

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Financial Disclosure
I am a founder and Chairman of TomoTherapy Inc. (Madison, WI) which is participating in the commercial development of helical tomotherapy.

www.tomotherapy.com

99% of Radiation Therapy Procedures are to Treat Cancer

Diagnostic Planar X-ray of a Crab

Somatic Mutations and Cancer

- Like wrinkles and other aging symptoms, cancer is usually the result of many somatic mutations.
- Reversing cancer is about as likely as reversing aging.
- There is more money spent on wrinkles than cancer, so it is likely that a cure for wrinkles will happen before a cure for cancer.
“It will take another 15 to 20 years for the new biology to revolutionize our concepts of cancer treatment”

E. Hall 1995

Societal Costs

- The direct costs of cancer in the US is about $80B annually.
- Radiotherapy costs about $10B.
- Radiotherapy equipment is about $2B.
- In addition there is over $150B in indirect costs due to disability and premature death.
Radiotherapy Costs in Perspective

<table>
<thead>
<tr>
<th>PROCEDURE</th>
<th>COST ($/yr of life saved)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bone Marrow Transplant</td>
<td>10,000 to 125,000</td>
</tr>
<tr>
<td>Treatment of Heart Disease</td>
<td>10,000 to 100,000</td>
</tr>
<tr>
<td>Kidney Dialysis</td>
<td>20,000 to 50,000</td>
</tr>
<tr>
<td>Societal Acceptance</td>
<td>25,000 – 100,000</td>
</tr>
<tr>
<td>Chemotherapy</td>
<td>4,500 to 50,000</td>
</tr>
<tr>
<td>Radiation Therapy</td>
<td>900 to 3,000</td>
</tr>
</tbody>
</table>

ASCO 1992
Ontario Ministry of Health, Canada
**Perez IMRT, assuming 10 years gained
Adapted from Jerry Battista, London Regional Cancer Centre, Ontario

More Costs in Perspective

<table>
<thead>
<tr>
<th>PROCEDURE</th>
<th>COST ($/yr of life saved)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mine Safety</td>
<td>1,000,000</td>
</tr>
<tr>
<td>Radiation Protection</td>
<td>16,000</td>
</tr>
<tr>
<td>Auto Safety (Air Bags)</td>
<td>8,000</td>
</tr>
<tr>
<td>Traffic Barrier (Median)</td>
<td>5,700</td>
</tr>
<tr>
<td>Radiation Therapy</td>
<td>350 to 1,800</td>
</tr>
<tr>
<td>Feeding the Poor</td>
<td>125</td>
</tr>
</tbody>
</table>

Adapted from Jerry Battista, London Regional Cancer Centre, Ontario

Radiotherapy Timeline

- 1895: 100-400 keV X-Rays, Rotation Therapy
- 1950: Co-60, Low Energy Linacs, Betatrons
- 1965: CT Scanners, 3-D Planning, Accurate Dosimetry
- 1980: Computerized 3-D Planning, Linear Accelerators (Linacs), Simulators
- 1995: MRI, PET, PET-CT, MLCs, Optimization, and IMRT, Image-Guided Radiotherapy

Scientific Forces Behind Our Field

- Nuclear and Particle Physics
- Computer Science
- Imaging
- Biotechnology
2D Treatment Planning

Tumors are hard to see in 2D images, especially port films, and you must rely on "landmarks."

2D simulation films or computer-generated "DRRs" Treatment machine port films

3-D Treatment Planning

Planning workstations use 3D imaging and accurate dose calculations to allow highly "conformal" treatment planning.

CT Slices Forming a Patient Representation is the Modern Basis for Radiotherapy

The Tumor and Sensitive Structures are Outlined
The Beam Directions are Chosen

PET/CT will Become the Main Instrument for Radiotherapy Planning

CT PET CT+PET

Sometimes CT Cannot Provide The Target Location

Use of MRI with Grow

CT: No Target Seen PET Image

Abdominal MRI
Comparison Between CT and MRI

- Axial CT
- Axial MRI
- Coronal CT
- Coronal MRI

Tumor seen only on MRI.

Optimization and Intensity-Modulated Radiotherapy (IMRT)

- Let the computer do the work...

Let the computer optimize the plan, varying the intensity within each beam, to "conform" and "spare" even more.

Tomotherapy IMRT Plan

Head and neck plan with avoidance of the spine and parotids.

Re-Treatments

Re-treatments, using tomotherapy for patients not eligible for conventional photon radiation therapy due to cord tolerance.

Patients courtesy of UAB
Dose Sculpting

2-D Planning

3-D

Conformal

IMRT

Protons and Heavy ("Light") Ions

Will the Long Term Future Be Protons?

Protons stop so integral dose is less.

Not so great lateral penumbra.

Dose Distribution Comparison

Protons

Low integral Dose.

90% line

50% line

Photons

(Tomotherapy)
Why 3D Image-Guided Radiotherapy (IGRT)?

- Eventually most radiotherapy will be IMRT, even many palliative treatments, e.g., re-treatments.
- All IMRT should be image-guided:
  - IMRT is justified by sparing critical tissues (conformal avoidance) which produces higher dose gradients.
  - IGRT enables higher gradients to be delivered safely and effectively.
  - IGRT enables a smaller setup margins to be defined.
- In some radiotherapy sites, e.g., prostate, IGRT may be more important than IMRT.
- 2D imaging is inadequate to obtain volume information.

Setup Alignment with Ultrasound

When contour alignment to ultrasound is satisfactory, shift the patient to the new position.

Using Z-Med’s Ultrasound Localization System
From Dr. Wolfgang Tomé

Pitfall: Pubic Arch Interference

Probe placed over treatment isocenter.
Probe displaced by 1 cm superiorly from treatment isocenter.
From Dr. Wolfgang Tomé, UW-Madison

CT in the Treatment Room

First CT
Then Treat
From Minoru Uematsu et al. IJROBP 48, 432 (2000)
CT in Treatment Room

Siemens Primatom “CT on Rails”
GE CT + Varian Linac

From Tim Holmes, St. Agnes Hospital

Cone Beam Imaging

Elekta Synergy
Varian Trilogy

Helical Tomotherapy

Tomotherapy Scanning With Megavoltage X-Rays

Orange
Parallel Plate Chamber
Gold Seeds
Hip Prostheses
Register Verification CT to Planning CT

Tomotherapy Registration of Lung Case

Adaptive Radiotherapy

Theory of Dose Reconstruction

The leaf $j$ produces a beam intensity $\Psi_j$ which is detected after the patient in detector element $S_i$. 

From Gustavo Olivera, TomoTherapy Inc.
Theory of Dose Reconstruction

Using the same dose calculation algorithm used for planning, the beam intensity $\psi_j$ is used to compute the dose in volume element $D_k$.

Verifying the Dose Delivered

Planned  Actual
PET-CT for In-Vivo Dosimetry

Image of Regret
Adapted Dose Distribution

Dose to deliver to correct regret.

Deformable Registration Will Be a Foundation Technology for Radiotherapy and Radiology

- Deformable registration maps one 3-D distribution to another.
- Enabling technology for use of 4-D imaging.
- Allows anatomy and/or dose to be combined onto one time point to account for motion.
- Makes atlas-based auto-contouring possible.
- Enables longitudinal comparison of anatomy for diagnosis, treatment progress and outcome studies.
Indications for Conformal Avoidance

- The tumor volume may not be visible using 3-D imaging.
- There may be uncertainty in defining the clinical margins.
- There may be suspected regional/nodal involvement.
- The margin to account for setup variation or organ motion may be uncertain.
- The target dose is limited by normal sensitive tissue.

Strategy for Conformal Avoidance Radiotherapy

- Use generous treatment volumes.
- Outline normal sensitive tissues and concentrate on avoiding them.
- Use image-guidance to assure that the normal tissues are being avoided.
- Conformal avoidance radiotherapy is the complement of conformal radiotherapy.

Continuum Between Conformal Tx and Conformal Avoidance Tx

<table>
<thead>
<tr>
<th>Conformal Tx</th>
<th>Conformal Avoidance Tx</th>
</tr>
</thead>
<tbody>
<tr>
<td>Know where tumor is but will not harm sensitive tissue.</td>
<td>Don’t really know where tumor is and may harm sensitive tissue.</td>
</tr>
</tbody>
</table>
With Better Avoidance of Normal Tissue Can We Shorten Courses of Therapy?

- In prostate CA, the tumor may repair even better than the normal tissues.
- In lung CA, rapid proliferation reduces the treatment control probability as the treatment is extended in duration.
- Provided better avoidance of sensitive tissues is maintained, fewer fractions of higher dose/fraction will provide both better tumor control and be less expense to deliver.
- Carefulness can be cost effective.

### Hypofractionation of Lung CA May Yield Much Better Results

Moving to left along any one curve keeps late BED constant, with fewer and larger fractions. Overall time is shorter, so TCP.

### Optimizing Tumor Control

<table>
<thead>
<tr>
<th>Duration in weeks</th>
<th>% Tumor Control Probability (TCP)</th>
</tr>
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<tbody>
<tr>
<td>3</td>
<td>100</td>
</tr>
<tr>
<td>4</td>
<td>90</td>
</tr>
<tr>
<td>5</td>
<td>80</td>
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<td>6</td>
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<td>60</td>
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<td>8</td>
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<td>9</td>
<td>40</td>
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<tr>
<td>10</td>
<td>30</td>
</tr>
<tr>
<td>11</td>
<td>20</td>
</tr>
</tbody>
</table>

\[
\text{BED} = \text{BED} - 0.66 \text{ Gy/day}
\]

\[
\text{BED} = n d (1 + d / a^2)
\]

### Fall of TCP due to decreasing total dose necessary to keep late complications constant

\[
\text{TP} = 3 \text{ days} \quad \text{Tk} = 28 \text{ days}
\]

\[
2 \text{ Gy} \quad 2.23 \text{ Gy} \quad 2.83 \text{ Gy} \quad 3.22 \text{ Gy}
\]

### Fall of TCP due to repopulation

\[
2 \text{ Gy} \quad 2.53 \text{ Gy} \quad 3.22 \text{ Gy} \quad 3.88 \text{ Gy}
\]

\[
60 \text{ Gy} \quad 70 \text{ Gy} \quad 80 \text{ Gy} \quad 90 \text{ Gy}
\]

From Jack Fowler

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From Jack Fowler

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From Jack Fowler

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From Jack Fowler
Image-Guided Radiotherapy of the Future

- Image-based staging of the primary and regional field.
  - Determine hypoxic and highly proliferative regions using bioimaging and paint in higher dose.
  - Conformally avoid sensitive structures in the regional field.
- IMRT with 3-D image verification.
  - Less fraction quantity – greater fraction quality.
  - Adaptive radiotherapy to provide patient-specific QA of the whole course of therapy.

Image-Guided Radiotherapy of the Future (Cont.)

- Image-based monitoring of outcome.
  - e.g., PET scans for regional or metastatic development using a priori information.
- Aggressive treatment of recurrences or distant metastases using conformal avoidance to spare critical structures.
  - Better QA of first treatment will allow safer retreatments.
  - "Weeding the garden" with image-guided radiotherapy and prevent spread with chemotherapy and immunotherapy.

Oligometastases or "Weeding the Garden"

- Following definitive radiotherapy with local control we often have metastatic progression.
- Chemotherapy (analogous to pre-emergent herbicides) may be effective against 100 to 1000 cell tumorlets.
- With PET it is possible to infer the presence of tumorlets with 100,000 to 1,000,000 labeled cells.
- Perform PET scan followups to catch the emergent tumorlets.
- Weed with conformal avoidance hypofractionated radiotherapy before they can seed more metastases.
- Keep careful track of the cumulative dose delivered so the process can be repeated several times if necessary.

Treating Multiple Metastases Determined From PET Scans

- Planned Using PET-CT

PET-CT Scans

Tomotherapy Treatment Plan

Courtesy of Chet Ramsey, Thompson Cancer Survival Center
Tomotherapy Irradiation of Metastases with One Setup

Tomotherapy Irradiation of Metastases with One Setup
What About Targeted Therapies?

- Targeted therapies like radioimmunotherapy and BNCT will unlikely be stand-alone therapies.
- Getting an agent to all of the tumor cells is like committing genocide with letter bombs.
- Before an agent can be a successful therapeutically, it should prove itself a fantastic diagnostic contrast agent.
- NM404 is an example of a “diapeutic” agent.
- Targeted therapies will be useful in conjunction with conventional radiotherapy.

Economic Forces Driving Our Field

- Cost containment.
- Demand for higher quality done more easily.
- Radiotherapy is about 40 times more medical physics intensive than radiology.
- Expect that radiotherapy will be economically driven to be more like radiology where medical physicists are mainly quality assurance experts.
- Much of that QA will be imaging related.
- Like radiology, radiotherapy will specialize around disease sites.

Year 2014 - Merging of Technologies

<table>
<thead>
<tr>
<th></th>
<th>Tomotherapy</th>
<th>Conventional</th>
</tr>
</thead>
<tbody>
<tr>
<td>High Quality Fast Scanning</td>
<td>Faster rotation times for scanning.</td>
<td>Faster rotation will demand a ring gantry.</td>
</tr>
<tr>
<td>High Quality Fast Delivery</td>
<td>Faster delivery times will lead to larger fields and higher outputs.</td>
<td>Faster delivery times will lead to faster leaves and higher linac outputs.</td>
</tr>
<tr>
<td></td>
<td>Multislice detectors using CT electronics.</td>
<td>Limited field cone beam and a translating couch.</td>
</tr>
<tr>
<td></td>
<td>Non-uniform gantry and couch velocities.</td>
<td>More treatment directions.</td>
</tr>
</tbody>
</table>
Change from Individual QA to QA of Automated Processes

- Machine QA processes will be built into the machines.
- QA processes for individual patients will be generated automatically.
- Physicists will be responsible for checking that the automated processes are performing correctly.
- Role will become more like that of a physicist working in radiology.

Radiotherapy and Radiology Futures

- Radiotherapy will employ fewer medical physicists in the future.
- Radiology procedures will be done more and more by other disciplines, e.g., cardiologists, neurologists, oncologists.
- Radiotherapy physicists will require more training in imaging.
- Like radiology physicists, radiotherapy physicists will become QA experts.

Shifting Balance Between Rival Treatment Technologies

- More Precise Tumor Dissection
- Gene and Protein Targets
- Better Regional and Metastatic Tx

Radiotherapy and Surgery with Surgical Precision

- Gene and Protein Targets
- Better Regional and Metastatic Tx

Chemotherapy

- Radiation Therapy

100% - diagnosed with cancer
70% - have loco-regional disease on presentation
30% - have metastatic disease
35% are treated with radiation ± other treatment modality
25% achieve loco-regional control
10% fail with loco-regional recurrence ± metastases
5% fail due to biological causes
50% Patients who will not survive
25% achieve loco-regional control
10% fail with loco-regional recurrence ± metastases
5% fail due to biological causes

Adapted from Jerry Battista, London Regional Cancer Centre, Ontario
Be a Booster for Our Field!

- Remind your colleagues that radiotherapy physics is the basic science behind radiotherapy.
- Radiation therapy has far better quality control as compared to surgery or chemotherapy.
- Question why radiotherapy research (including molecular radiation bioeffects) accounts for less than 3% of cancer research.
- Support research and innovation in our field.
- Encourage your colleagues to partake in prospective random clinical trials.
- Educate your community to be well informed about radiation and radiotherapy.
- Don’t be second class citizens in the cancer establishment.
- Don’t be apologetic about our field, it is currently vital to cancer management and will continue to improve.