Radiation Oncology
Recent Advances & New Challenges

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Medical (Radiological) Physics

- An applied branch of physics concerned with the application of the concepts and methods of physics to the diagnosis and treatment of human disease.

- ~5000 medical physicists in North America
  - **Therapeutic Radiological Physics** (Radiation Oncology – 76%)
  - **Diagnostic Radiological Physics** (Radiology ~11%)
  - **Medical Nuclear Physics** (Nuclear Medicine ~7%)
  - **Medical Health Physics** (Radiation Safety ~6%)
Therapeutic Radiological Physics

- Introduction and Basics of Radiation Oncology (Physics, Biology)
- Recent Advances: IMRT, IGRT, SBRT
- Challenges
Radiation Physics

- Basis – ionizing particles interact with cellular molecules
- Relies on transfer of energy created by secondary charged particles (usually electrons)
- Break chemical bonds
- External beam vs. Brachytherapy
External Beam Irradiation

- Dual-energy linear accelerators generate:
  - Low energy megavoltage x-rays (4-6 MV)
  - High energy x-rays (15-20 MV)
  - Electrons (4-23 MeV)
- Particle Radiation (electrons, protons, neutrons)
- Photon therapy advantages
  - Skin sparing, penetration, beam uniformity
- Head and Neck sites – 4-6 MeV x-ray or Co60 gamma ray radiation
FIGURE 31-1  Central axis percent depth dose curves of x-rays and protons (A) and electron beams (E) of different energies and those of 200-MeV proton beams with or without modulation (C). The x-ray beams fall off exponentially after the initial build-up whereas the dose for proton beams rises slowly to reach the Bragg peak (BP) where the protons stop. When the proton is modulated the Bragg peak spreads out (SOBP) but the superficial dose also increases. The advantage of the proton beam is the absence of dose beyond the Bragg peak and lower surface dose. Electron beams have characteristics similar to those of protons except that the dose fall-off is not as sharp owing to the light mass of electron and the surface dose is relatively high (no skin-sparing effect).
Linear Accelerator
Brachytherapy

- Radioactive source in direct contact with tumor
  - Interstitial implants, intracavitary implants or surface molds
- Greater deliverable dose
- Continuous low dose rate
- Advantage for hypoxic or slow proliferators
- Shorter treatment times with high dose rate
Brachytherapy
Cancer treatment using radioactive materials

Intracavitary
Brachytherapy

Interstitial
Radiobiology
Dose-Response Curves

![Graph showing dose-response curves for aerated and hypoxic conditions.](image-url)
Rediosensitivity and Cell Cycle

![Graph showing single-cell survival vs. dose for different phases of the cell cycle.](image)

- M
- G2
- G1
- ES
- LS
- M x 2.5
4 R’s of radiation biology

- Repair of cellular damage
- Reoxygenation of the tumor
- Redistribution within the cell cycle
- Repopulation of cells
Goals of Radiation Therapy

- Eradication of the tumor.
- Avoidance of damage to healthy tissue and organs near the tumor.

Search for the highest therapeutic ratio
Fractionation

- Allow normal tissue to repair sublethal damage
- Allow tumor cells in S phase to progress to G2-M
- Allow reoxygenation to hypoxic regions in tumor
- Tumor also has chance to repair sublethal damage
- Accelerated proliferation

**Figure 31-5** Survival curves of fractionated radiation delivered in equal doses per fraction separated by time interval, allowing complete repair from SLD to clapse. The curves become exponential as a function of radiation dose. The slope of each curve is defined by the respective “effective” $D_e$ [$D_{eq}(n)$] for a particular fraction size. The $D_{eq}(n)$ can never exceed $D_e$, because this denotes single-hit killing that results from irreparable damage.
Fractionation Schedules

- **Conventional**
  - 1.8 to 2.0 Gy given 5 times/week
  - Total of 6 to 8 weeks
  - Effort to minimize late complications

- **Accelerated fractionation**
  - 1.8 to 2.0 Gy given bid/tid
  - Similar total dose (less treatment time)
  - Minimize tumor repopulation (increase local control)
  - Increased acute complications
The Linear-Quadratic model

\[ E = n(\alpha d + \beta d^2) \]
\[ E/\alpha = nd(1 + d/(\alpha/\beta)) \]
Therapeutic Radiological Physics

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- **Recent Advances: IMRT, IGRT, SBRT**
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Goals of Radiation Therapy

- Eradication of the tumor.
- Avoidance of damage to healthy tissue and organs near the tumor.

Search for the highest therapeutic ratio
How to achieve the goal

1. Better treatment design
2. Improve the radiation machine to provide greater degrees of freedom in plan design
3. Use heavy particles (Protons, light ions – different physics of interactions)
4. Improve geometric accuracy using imaging guidance
5. Reduce dosimetric uncertainty
Technology of the ‘80s
Intensity Modulated Radiotherapy?
Intensity Modulated Radiotherapy?
“The Age of Gizmos”

- MLC (1990)
- Inverse planning (1990)
- IMRT (1993)
- Tomotherapy (1993)
- Cyber Knife (1992)
- CBCT (2000)
- Novalus (2000)

- IGRT (2004)
- Clypso (2004)
- MammoSite (2005)
- Synergy (2006)
- Trilogy (2006)
- Protons (1990 - )
- ......
Muli-Leaf Collimator
Intensity Modulated Radiation Therapy (IMRT)

- Computer optimization of beam intensities – *shaping the dose from 2D to 3D*
- Proposed in 1983 by Anders Brahme
- More research work on computer optimization started in 1990
- First delivery to phantoms - 1994
Conventional Treatment with limited number of beams
Increase beam direction and optimize beam weighting
Intensity Modulated

NNPSS 2008
For example:
Capabilities of IMRT

IMRT
Intensity-modulated arc therapy with dynamic multileaf collimation: an alternative to tomotherapy

Cedric X Yu
William Beaumont Hospital, Royal Oak, MI, USA

Received 9 February 1995, in final form 20 April 1995
GBM – 4 Non-coplanar Arcs
DVHs for Brain

Solid lines: Tomotherapy
Dashed lines: IMAT with Axial arcs
Dotted lines: IMAT with non-coplanar arcs

Normalized Volume (%)

Dose (cGy)

Optical nerve

Brainstem

PTV
Multi-arc to Single arc

ARC 1
ARC 2
ARC 3

ARC 1
ARC 2
ARC 3
Stacked -> Spaced
Image guided Radiation Therapy (IGRT)

- A new trend of the field
- Broad definition with multiple flavors
- Clinical implications are significant

The use of three- and/or four-dimensional multi-modality images to guide target delineation, localization, treatment positioning, verification, and/or continuous adjustment of radiation therapy.
Elekta’s Synergy
Varian’s OBI and Trilogy
On-Board Imager
Sample images

Images courtesy of Karolinska Medial Center
Sample images

Images courtesy of Karolinska Medical Center
Sample CBCT image
How to use the images?

- Simple shift of the patient
  - Cannot handle deformation
  - Cannot handle organ rotation
  - Cannot consider changes in surrounding structures
To Handle Target Deformation

- Re-plan requires 3D target delineation for each CBCT (re-contour) – not realistic if done manually.
- On-line correction – an UMD scheme
- Fast deformable registration as the cornerstone to the effective use of CBCT
auto contouring
Collapsing the 3D vector to 2D
Morphing the Aperture
Intra-treatment Motion
Dynamic Tumor Tracking
Protons
Proton Site

Single Proton Beam Feeds Multiple Treatment Rooms

- Beam transport line
- Particle accelerator
- Gantry treatment rooms
Physics

Protons Deliver More Targeted Dose

Much of dose absorbed by tissue in front of target

Maximum dose delivered at proper tumor depth

Dose

Photon
Protons

NNPSS 2008
Proton Marketing

Protons

Photons

Unintended dose delivered to critical

Source: Massachusetts General Hospital

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Therapeutic Radiological Physics

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New Challenges

- **Geometric uncertainty**
  - Geometric uncertainties are far greater.

- **Biological uncertainty**
  - Biological understanding of radiotherapy falls far behind physics.

- **New treatment techniques** based on new biological understanding and new imaging capabilities hold the key to cure.
New Challenges

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- **New treatment techniques based on new biological understanding and new imaging capabilities hold the key to cure.**
“Patient repositioning and patient motion have been a problem in radiation therapy since its inception,”

Connor et al, IJROBP 1975
Table 1. Summary of Published Data on Patient Setup Errors

<table>
<thead>
<tr>
<th>Patients</th>
<th>Fields</th>
<th>&gt;10mm</th>
<th>St. Deviation (mm)</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Head and Neck</td>
<td>434</td>
<td>9.6%</td>
<td>4.5 (approximate)</td>
<td>Bihardt et al [7]</td>
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<tr>
<td>17</td>
<td></td>
<td></td>
<td></td>
<td>Halverson et al [17]</td>
</tr>
<tr>
<td>22</td>
<td>138</td>
<td></td>
<td>5.6</td>
<td>Huizenga et al [18]</td>
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<tr>
<td>10</td>
<td>168</td>
<td></td>
<td>4.0</td>
<td>Kihlen and Ruder [24]</td>
</tr>
<tr>
<td>25</td>
<td>172</td>
<td></td>
<td>16.0%</td>
<td>Marks and Haus [40]</td>
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<tr>
<td>Breast</td>
<td>8</td>
<td>80</td>
<td>3.4%</td>
<td>Jacobsen et al [22]</td>
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<tr>
<td>21</td>
<td>128</td>
<td>.9%</td>
<td>3.0</td>
<td></td>
</tr>
<tr>
<td>Pelvis</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>153</td>
<td></td>
<td>23%</td>
<td>6.7 (total)</td>
<td>Byhard et al [7]</td>
</tr>
<tr>
<td>23</td>
<td>25</td>
<td>24%</td>
<td></td>
<td>Rabinowitz et al [48]</td>
</tr>
<tr>
<td>6</td>
<td>111</td>
<td>5.0</td>
<td></td>
<td>Kihlen and Ruder [24]</td>
</tr>
<tr>
<td>Mantle/thorax</td>
<td>317</td>
<td>8%</td>
<td></td>
<td>Byhard et al [7]</td>
</tr>
<tr>
<td>19</td>
<td>171</td>
<td>11%</td>
<td></td>
<td>Griffiths &amp; Pearcey [16]</td>
</tr>
<tr>
<td>102</td>
<td>216</td>
<td>7%</td>
<td></td>
<td>Hulshof et al [19]</td>
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<tr>
<td>1</td>
<td>15</td>
<td>3.0</td>
<td></td>
<td>Kihlen and Ruder [24]</td>
</tr>
<tr>
<td>99</td>
<td>902</td>
<td>37% clin sig</td>
<td></td>
<td>Marks et al [41]</td>
</tr>
<tr>
<td>16</td>
<td>22</td>
<td>32%</td>
<td>6.7 (total)</td>
<td>Rabinowitz et al [49]</td>
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</table>
Liver Motion

<table>
<thead>
<tr>
<th>Study: first author (ref)</th>
<th>No. of patients</th>
<th>Patient position</th>
<th>Normal breathing PTT (mm)</th>
<th>Deep breathing PTT (mm)</th>
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<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>Avg ± SD</td>
<td>Range</td>
</tr>
<tr>
<td>Weiss (40)</td>
<td>25</td>
<td>Standing</td>
<td>8 ± 2</td>
<td></td>
</tr>
<tr>
<td></td>
<td>25</td>
<td>Supine</td>
<td>11 ± 3</td>
<td></td>
</tr>
<tr>
<td>Harauz (41)</td>
<td>51</td>
<td>Standing</td>
<td>12</td>
<td></td>
</tr>
<tr>
<td></td>
<td>51</td>
<td>Supine</td>
<td>14</td>
<td></td>
</tr>
<tr>
<td>Suramo (42)</td>
<td>50</td>
<td>Supine</td>
<td>25</td>
<td>10–40</td>
</tr>
<tr>
<td>Davies (43)</td>
<td>9</td>
<td>Supine</td>
<td>10 ± 8</td>
<td>5–17</td>
</tr>
<tr>
<td>Balter (44)</td>
<td>9</td>
<td>Supine</td>
<td>17</td>
<td></td>
</tr>
<tr>
<td>Shimizu (45)</td>
<td>1</td>
<td>Supine</td>
<td>21</td>
<td></td>
</tr>
</tbody>
</table>

PTT = peak-to-trough.

Diaphragm

<table>
<thead>
<tr>
<th>Study: first author (ref)</th>
<th>No. of patients</th>
<th>Patient position</th>
<th>Normal breathing PTT (mm)</th>
<th>Deep breathing PTT (mm)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>Avg ± SD</td>
<td>Range</td>
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<tr>
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<td>10</td>
<td>Standing</td>
<td>16 ± 2</td>
<td></td>
</tr>
<tr>
<td></td>
<td>10</td>
<td>Supine</td>
<td>17 ± 3</td>
<td></td>
</tr>
<tr>
<td>Weiss (40)</td>
<td>30</td>
<td>Standing</td>
<td>8 ± 4</td>
<td></td>
</tr>
<tr>
<td></td>
<td>30</td>
<td>Supine</td>
<td>13 ± 5</td>
<td></td>
</tr>
<tr>
<td>Korin (47)</td>
<td>15</td>
<td>Supine</td>
<td>13</td>
<td></td>
</tr>
<tr>
<td>Davies (43)</td>
<td>9</td>
<td>Supine</td>
<td>12 ± 7</td>
<td>7–28</td>
</tr>
<tr>
<td>Hanley (48)</td>
<td>5</td>
<td>Supine</td>
<td>26.4</td>
<td>18.8–38.2</td>
</tr>
<tr>
<td>Balter (49)</td>
<td>12</td>
<td></td>
<td>9.1 ± 2.4</td>
<td></td>
</tr>
</tbody>
</table>

PTT = peak-to-trough.
Gated RT

Non-Gated

Gated
Limitations of Imaging

- Tumors consist of $<10^5$ cells cannot be imaged or palpated
- Experience involved in the “guessing game”

Large variations among physicians!
Example of difficulty and risk of disagreement when delineating the Gross Tumor Volume. Schematic drawings on lateral radiographs for two patients with brain tumors, where the Gross Tumor Volume was delineated by:

- 8 radiation oncologists (----), - 2 radiologists (········),
-- 2 neurosurgeons (- - - -).

*Adapted from Leunens et al., 1993.*
New Imaging Tools May Help

Glioma T2 weighted MRI (a),
IMT(I-123-alpha-methyl tyrosine)-SPECT (c)

In 4 cases of T3 bladder cancer:

RESULTS: There was a maximum variation ratio (largest to smallest volume outlined) of the GTV in the four cases of 1.74 among radiologists and 3.74 among oncologists.
New Challenges

- **Geometric uncertainty**
  - Geometric uncertainties are far greater.

- **Biological uncertainty**
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- **New treatment techniques**
  - New treatment techniques based on new biological understanding and new imaging capabilities hold the key to cure.
'When I came into radiotherapy in 1950, I was puzzled that some patients were treated to 3000 rads (cGy) in 3 weeks but others received 4000 in 5 or 6000 in 6 weeks. When I asked why, there were no convincing answers given, except ‘this is what we usually do’.

--- Jack Fawler, Phys Med Biol. 51, 2006
The LQ model – Fowler et al

\[ E = n(ad + \beta d^2) \]
\[ E/\alpha = nd(1 + d/\alpha/\beta) \]
Actual $\alpha/\beta$ is unknown

Using the same clinical data set, similar methods, we derived an $\alpha/\beta$ of 3.1 for prostate cancer, Branner and Fowler gave an $\alpha/\beta$ of 1.5
Reason: Uncertainty of Analysis
Our Method: Add a control
Practical Impact

- Design clinical trials with different fractionation schemes.
- Predicting TCP and NTCP
Practical Impact

- RTOG 0415: A Phase III study of hypofractionated 3D-CRT/IMRT (70Gy in 28 fractions) v.s. Conventionally fractionated (73.8 Gy in 41 fractions) 3D-CRT/IMRT in patients with favorable risk prostate cancer
  - BED to prostate:
    if $\alpha/\beta = 1.5$, 187Gy v.s. 162Gy BED
    if $\alpha/\beta = 3.1$, 126Gy v.s. 117Gy BED
  - BED to Rectum:
    if $\alpha/\beta = 6.0$, 99.2Gy v.s. 95.9Gy BED
Grid Therapy

• Open-to-Closed Ratio
  = 1:3 (~25% open)

• Typical Dose 15 – 20 Gy
Spatially Fractionated (Grid) Field on Skin

Courtesy of the University of Kentucky
Line Dose Profiles of the 1cm x 1cm Grid

Relative Dose to Open Field [%]

Horizontal Scan [cm]

Peak-to-Valley Dose Ratio [%]

Horizontal Scan [cm]

1.5 cm
5 cm
10 cm
Clinical Study of Grid Therapy Conducted by the University of Kentucky

- 71 Patients were admitted in the clinical trial;
- 16% show a complete clinical response;
- 62% show at least a partial clinical response;
- Head and Neck has the most successful rate.

What makes it work?

- No explanation on the lack of normal tissue damage.
  - Different apoptotic pathway with single high dose?
  - Different mechanisms exist between tumor and normal structure in the repair of small regions of damage.
  - Cell mobility and “system control” may play a role.
Experimental Setup
Experimental Setup
Two Groups

- Group 1: Open irradiation of 13 Gy x 4 days

- Group 2: Grid irradiation of 52 Gy, shifting 4 times to unirradiated areas in 4 days
## Results

<table>
<thead>
<tr>
<th>Description</th>
<th>Image 1</th>
<th>Image 2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Open Exposures (13 Gy x 4 daily), 36 days</td>
<td><img src="image1.png" alt="Image" /></td>
<td><img src="image2.png" alt="Image" /></td>
</tr>
<tr>
<td>Grid Exposures (52 Gy x 4 quarters), 36 days</td>
<td><img src="image3.png" alt="Image" /></td>
<td><img src="image4.png" alt="Image" /></td>
</tr>
</tbody>
</table>
### Hair Counts

<table>
<thead>
<tr>
<th></th>
<th>Open</th>
<th>Grid</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Entry side</td>
<td>452</td>
<td>860</td>
<td>0.0003</td>
</tr>
<tr>
<td>Exit side</td>
<td>223</td>
<td>730</td>
<td>0.0001</td>
</tr>
</tbody>
</table>

- By fractionate spatially, tumor get a more intense assault while normal tissue had less collateral damage.
New Challenges

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- Biological uncertainty
  - Biological understanding of radiotherapy falls far behind physics.

- New treatment techniques based on new biological understanding and new imaging capabilities hold the key to enhance cure.
Breast Cancer

- Pathology
  - DCIS, LCIS
  - Medullary
  - Tubular
  - Lymphatic status
- Hormonal
  - ER, PR
  - Menstrual status
- Other
  - Familial history
  - Age
  - Obesity
- Genetics
  - HER-2
  - P53
  - Basal phenotype
  - Luminal A or B
Radiation Therapy

- It is proven that BCT is as effective as mastectomy
- Very high cure rate (95-97%) and very low complication rate
- Dose-fractionation schemes for all comers (BCT) are the mostly the same
- Treatment techniques for all comers are mostly the same
- Distribution of residual tumor foci and the probability of recurrence location is well known, however, dose uniformity remain a dosimetric goal.
What could make a difference?

- Imaging (diagnosis)
  - From mammography to dedicated 3D MRI imaging
- New treatment techniques that can make use of the new diagnostic and delivery capabilities
New MRI capable of fat suppression
MRIs with better resolution
Image guided interventions

- Radiation therapy does not take advantage of these new 3D imaging capabilities
- MRI-guided interventions include RF ablation, and cryosurgery
- There is room for radiotherapy improvement
Lung Cancer

- Poor prognosis for non-operable patients
  - About 30% 3-5 year survival (radiation therapy)

- Conventional radiation therapy
  - 45-55 Gy in 1.8 – 2.0 Gy fractions
New Directions


“All 70 patients enrolled completed therapy as planned and median follow-up was 17.5 months. The 3-month major response rate was 60%. Kaplan-Meier local control at 2 years was 95%”.

In late 2004, RTOG 0236 using SBRT for medically inoperable patients with clinical stage I non-small cell lung cancer (NSCLC) was activated for accrual.
Japanese SBRT Experience


“In tumors which received a BED of more than 100 Gy, overall survival at 3 years was 91% for operable patients, and 50% for inoperable patients.”
What make this possible

- Imaging guidance
  - On-board fluoro and x-ray imaging
- New delivery techniques
  - Gating
  - IMRT
  - Stereotactic localization
- Most importantly: New thinking based on new biological understanding and new technological capabilities.
Using New biological understanding

- Some exciting new biological understandings:
  - By-stander effect
  - Tumor stem cells
  - Effects of single high dose
  - Different responses by tumor and normal structures on small fields - high doses
MRSI for Detecting Cancer in Prostate

T2-weighted axial MR image obtained by using an endorectal coil
Preferential Dose Escalation

- For fixed TCP

- $\alpha/\beta = 1.5$ Gy
- $\alpha/\beta = 3.1$ Gy
- $\alpha/\beta = 8$ Gy

Relative Density of Tumor Burden vs. Dose/frac. for Burden (Gy)
Status

- New trial 1: HDR brachy
- New trial 2: EXRT with target in target
Conclusion

- Accelerated technical advancements in last 20 years
- Dosimetric < Geometric < Biological
- New treatment techniques based on new biological understanding and new imaging capabilities hold the key to enhance cure.