Innovations in Radiation Therapy, including SBRT, IMRT, and Proton Beam Therapy

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• ImClone: research support
• Plexxikon: research support
Outline

• Why innovate in radiation oncology?
• 3D conformal radiation therapy
• SBRT
• IMRT
• Proton therapy
• The role of imaging
Radiation Therapy

- Fact: it is effective
- Fact: it produces durable response
- Fact: it is “targeted”

- The physics and dosimetry of radiation oncology DEEPLY affect the immediate wellbeing of our lung cancer patients.
Incestuous Nature of Radiology/Radiotherapy Advances

- 3D – invention of CT scanner
- IMRT – innovations in CT planning
- 4D/motion study – ultrafast helical CT
- SBRT – in-room image guidance
- Proton – commercial development of charged particle delivery and image QA
- IGRT – imaging very often, assessing and manipulating all imaging available
“Treatment with 4DCT/IMRT was at least as good as that with 3DCRT …. There was a significant reduction in toxicity and a significant improvement in OS.”

Reasons??? Improved staging? Reduction of elective coverage? Or, reduced toxicity from conformal therapy?

Is there truly a globalized “technology effect”? Does it apply to ALL new technologies?
Dr. Yom’s “Iron Triangle” of Radiotherapy Innovation

- High Dose
- Low Toxicity
- Workflow Efficiency
Hypofractionated SBRT: Stereotactic Body Radiation Therapy

- 1950-1970s: Stereotactic therapy highly effective in brain metastases
- Led to exploration for small extracranial malignancies
- Ability to deliver hypofractionation with less toxicity
Stereotactic Body RT (SBRT)

- Curative intent
- Very large doses to small area
- Minimal falloff to normal lung
- Sub-cm (“stereotactic”) confirmation of position
  - WORK INTENSIVE, HIGH QA
- Typical course of 1-5 treatments
Physical advantages of SBRT

- Hypofractionation → superior local control
  - And shorter course of treatment

- Sharper dose fall-off gradients
  - Reduced toxicity to normal lung

- Omission of elective nodal coverage
  - Very low rates of regional failure
RTOG 0236

- Phase II Trial of SBRT for Medically Inoperable Stage I/II Non-Small Cell Lung Cancer

- 55 patients
  - ≤ 5 cm, N0, M0

- SBRT dose
  - 20 Gy in 3 fractions
  - over 1.5 to 2 weeks

91% control of tumor + lobe at 3 yrs, locoregional control 87%, distant failure 22%

Where to go from here?

- SBRT for operable stage I lesions
  - randomized trials vs wedge (ACOSOG Z4099/RTOG 1021) or lobectomy (Accuray STARS, initiating RTOG Foundation study 3502)
  - Dutch ROSEL trial closed
- Alternative dosing schedules
  - RTOG 0915 – randomized ph II 34 Gy single fraction vs 12 Gy x 4 fractions
- Safe dosing for central lung tumors
  - RTOG 0813 – currently finishing highest dose level 60 Gy
Out of the Box! New Roles for SBRT

- Brain, lung, liver, and adrenal metastases
- Multiple lung targets
- Recurrent nodal disease
- Small primary tumors discontinuous from mediastinal disease
- Boosting/dose escalation to specific targets
IMRT for Lung Cancer

- Multiple beam, intensity varies
- Usually for large lesions
- Advantages
  - Highly conformal
  - Dose escalation to tumor
  - Decrease toxicity?
- Disadvantages
  - Long treatment duration
  - Steep fall off, more sensitive to organ motion
  - Low radiation doses to large areas of lung
- Indications
  - Bulky bilateral disease, unable to encompass safely using 3D conformal therapy
Typical IMRT case - bilateral hilar nodes. V20 < 35% and isodose away from spinal cord.

63 Gy in 35 fractions.
6 beams, prescribed to 94% isodose line.
Concurrent cisplatin and docetaxel.
Often reduce V20 by 10% in this type of case.
Single-institution direct comparison

Yom et al., IJROBP 2007
Indications and caveats

• **IMRT was originally used for tumors that could not be treated optimally with 3D**
  
  – large, bilateral tumor volumes
  – large GTV, advanced stage, worse KPS
  – history of prior treatment

• IMRT is an option for complex cases that cannot be managed with 3D
IMRT and motion

Static  4 sec period

Extra Dose
Smeared Dose
The effect of multiple treatments

Variations in target dose tend to “smooth out” over 3-4 fractions – clinical relevance unclear

George, Med Phys 2003;552-62; Chui, Med Phys 2003;1736-46
3D vs IMRT: No change in the rate of freedom from distant metastasis

Liao Z, IJROBP 2010
Directions for Lung IMRT

• Dose escalation
  – RTOG 0617 allowed IMRT

• Integrated boosts to hypermetabolic/hypoxic regions
  – PET or FMISO directed

• ? Is it feasible/ethical to compare to 3D conformal or protons – primary benefit will be toxicity/QOL
Protons for Radiation Therapy

• Protons for radiotherapy were introduced by Robert Wilson in 1946.

• The first proton beam treatment in humans took place at the University of California at Berkeley during the mid-50’s.
  – Treated the pituitary gland to suppress hormone secretion
  – Treatments with Helium, Carbon and Neon were developed.

• First treatment in Europe at Uppsala, Sweden for malignant tumors.
  – Stereotactic radiosurgery for Parkinson dz
Proton Centers Worldwide

ICRU 78
Proton Therapy USA

This slide is outdated!
Proton therapy overview

• Advantages
  ✓ finite range
  ✓ straight trajectory
  ✓ good conformality
  ✓ improved dose distributions

• Disadvantages
  ✗ Secondarily produced neutrons can increase the overall patient dose and pose room shielding concerns.
  ✗ Proton delivery may not be robust if there are anatomical changes.
  ✗ Proton therapy is expensive to build and maintain.
Proton sensitivity to air/density changes

Week 1

Week 2
Proton uses in lung cancer

- Used for small tumors like SBRT
- For large tumors, claims of early use for “challenging situations”
  - No level 1 comparison data
  - Early analysis of trial of IMRT vs passive scattering proton therapy was equivocal
    - V20 was better for IMRT

Acta Oncologica, 2011; 50: 745–756
Neither proton nor carbon ion therapy is better than SBRT for 5-year DSS or OS.

<table>
<thead>
<tr>
<th>Treatment</th>
<th>5-year overall survival</th>
<th>(95% CI)</th>
<th>p-Value*</th>
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<tbody>
<tr>
<td>CRT</td>
<td>0.195</td>
<td>(0.148–0.242)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>SBRT</td>
<td>0.421</td>
<td>(0.341–0.501)</td>
<td>0.014</td>
</tr>
<tr>
<td>Protons</td>
<td>0.397</td>
<td>(0.245–0.550)</td>
<td>0.782</td>
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<tr>
<td>Carbon-ions</td>
<td>0.421</td>
<td>(0.322–0.520)</td>
<td>&lt;0.001</td>
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<tr>
<td>5-year disease-specific survival</td>
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<td></td>
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<tr>
<td>CRT</td>
<td>0.435</td>
<td>(0.311–0.559)</td>
<td>0.045</td>
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<tr>
<td>SBRT</td>
<td>0.627</td>
<td>(0.500–0.754)</td>
<td>0.471</td>
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<tr>
<td>Protons</td>
<td>0.521</td>
<td>(0.319–0.724)</td>
<td>0.389</td>
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<tr>
<td>Carbon-ions</td>
<td>0.643</td>
<td>(0.486–0.801)</td>
<td>0.051</td>
</tr>
</tbody>
</table>
What role for proton therapy?

• ‘our professional responsibility to critically examine the value of the new technologies we employ’

• ‘vigilant not to “conflate new with innovative and latest with best” [Emanuel 2007]. Newer is not necessarily better, and indeed may be worse.’

• “an intervention's value resides in its ability to reduce mortality, morbidity, or save money, not in its unique mechanism of action”

“Everyone wants the best available care, especially for life-threatening diseases like cancer. But that doesn’t mean Americans should pay exorbitant costs for treatments that can’t be shown to be better than other, cheaper, options. If the United States is ever going to control our health care costs, we have to demand better evidence of effectiveness, and stop handing out taxpayer dollars with no questions asked.”
“Image Guided RT” = using imaging

- High quality imaging for treatment planning
- Imaging during treatment for accurate positioning
- Imaging for quality assurance/dose confirmation
- Imaging for replanning or altering treatment plan
“Biologic” treatment planning: PETCT

“SMART” boost: dose painting, simultaneous delivery
IGRT “In-Room” or “On-Board” Positioning Techniques

- Electronic MV portal imaging
- CT-on-rails
- MV or KV conebeam CT
- Helical MV conebeam CT
- Orthogonal x-rays
Conebeam CT as a trigger for adaptive replanning

Radiation usually lasts 3-7 weeks with the same plan
Image-guided adaptive RT

Aerts, De Ruysscher, IJROBP 2008
The Primary Endpoint: 2 year local regional control rate
*1:2 randomization.

A trial of individualized RT and modern RT.
Conclusions

• SBRT is a game changing technology proven to be effective in inoperable early lung cancer, now being tested against surgery
• IMRT and proton therapy have reduced toxicity but are highly complex, rapidly evolving, and untested in randomized trials
• Advances in imaging are pushing radiotherapy forward; but meaningful and efficient integration needed for progress