Use + Share + Adapt

{ Content the copyright holder, author, or law permits you to use, share and adapt. }

- **Public Domain – Government:** Works that are produced by the U.S. Government. (17 USC § 105)
- **Public Domain – Expired:** Works that are no longer protected due to an expired copyright term.
- **Public Domain – Self Dedicated:** Works that a copyright holder has dedicated to the public domain.
- **Creative Commons – Zero Waiver**
- **Creative Commons – Attribution License**
- **Creative Commons – Attribution Share Alike License**
- **Creative Commons – Attribution Noncommercial License**
- **Creative Commons – Attribution Noncommercial Share Alike License**
- **GNU – Free Documentation License**

Make Your Own Assessment

{ Content Open.Michigan believes can be used, shared, and adapted because it is ineligible for copyright. }

- **Public Domain – Ineligible:** Works that are ineligible for copyright protection in the U.S. (17 USC § 102(b)) *laws in your jurisdiction may differ

{ Content Open.Michigan has used under a Fair Use determination. }

- **Fair Use:** Use of works that is determined to be Fair consistent with the U.S. Copyright Act. (17 USC § 107) *laws in your jurisdiction may differ
  
  Our determination DOES NOT mean that all uses of this 3rd-party content are Fair Uses and we DO NOT guarantee that your use of the content is Fair.
  
  To use this content you should **do your own independent analysis** to determine whether or not your use will be Fair.
Who Cures Cancer?

- Surgery - 150,000 patients per year
- Radiation - 85,000 patients per year
- Chemotherapy - 15,000 patients per year!

Vincent DeVita, NCI Grant Rounds, 1983
Standard radiation alone can cure

- Brain tumors (low grade)
- Head and neck cancers (early stage)
- Skin cancers (all)
  - Especially lip, eyelid, nose, and ear
- Lymphomas (all but advanced stage)
- Seminoma (all but advanced stage)
- Soft tissue sarcoma (any stage)
- Lung cancer (early stage)
- Cervix and endometrial cancer (early stage)
Treatment of Skin Cancer
And has an important role in palliation

- Brain metastases
- Lung metastases
  - Producing airway obstruction or superior vena cava syndrome
- Bone metastases
  - Producing spinal cord compression
- Esophageal obstruction
- Bile duct obstruction
Improving outcome: Individualizing Therapy

• By improving our ability to hit the tumor and miss the normal tissue

• By customizing combinations of radiation with chemotherapy or molecularly targeted therapy

• By assessing tumor and normal tissue response during treatment and tailoring therapy to these responses
Radiation therapy: *The process*

- **Treatment planning**
  - Determine 3D orientation of tumors and normal tissues
  - Planning radiation
    - Conformal treatment
    - Tools to quantify dose (dose-volume histograms)

- **Position patient and tumor**
  - Localize patient on treatment machine
  - Account for organ motion

- **Treatment delivery**
“Standard” Radiation Therapy

- Treatment based on population estimate of what might control a tumor
- Estimate the risk of normal tissue damage base on the most sensitive 5% of the population
- Treatment delivered to initially prescribed dose
  - Stop only for unacceptable acute toxicity
- Emphasis making isodose lines conform more tightly to the tumor
Partial Parotid Gland Sparing:

Conformal Techniques in Patients Undergoing Bilateral Neck Neck Irradiation

NODE PTV

ORAL CAVITY

RT PAROTID

TUMOR PTV

SPINAL CORD

Source Undetermined
Target Volumes and Normal Structures
Intensity Modulated Radiation Therapy (IMRT)
62-70 Gy
58-63 Gy
51-57 Gy

Parotids
Oral Cavity

Spinal Cord
95% Isodose Surface, PTV54

Sources Undetermined
MR-CT Registration

Move info between MR and CT

regions

doses

Kessler, University of Michigan
Target Volume Definition

Define volumes on MR data

Axial “Target”

Coronal “Target” + Optic Structures
Target Volume Definition

Map to CT data and combine

MR-derived CT target volume!

Kessler, University of Michigan
Brain Example
Brain Example
Six Field Prostate

Kaplan-Meier FFF curves for all patients by dose randomization (70 Gy vs. 78 Gy)

Pollack, et al., IJROBP, 53:5, 2002
Prostate Motion

Inhale

Exhale

Source Undetermined

Source Undetermined

Radiation Oncology
Dose Volume Histogram (DVH)

- Tumor
- Normal Organ
- 63% Volume
- 50% Dose

Volume (%) vs. Dose (%)

T. Lawrence
Two hypotheses

• Unresectable intrahepatic cancer could be cured by radiation (± chemotherapy) if a high dose could be given

• A high dose could be safely given if we
  – Limited the dose to the normal liver
  – Understood how much of the liver could be irradiated safely

• Requires knowing the relationship between the risk of complication and the DVH of the normal liver
Retrospective Analysis of RILD

• Dose prescribed by volume of normal liver irradiated
  – Of 9 of 79 patients developed radiation-induced liver disease (RILD)

• Fit data to an NTCP model
  – Clinical guesses greatly overestimated the risk of partial liver radiation
  – Recalculated the parameters and fit the data to the model

New Dose Escalation Trial

- Designed a prospective trial to test the model parameters
- We were able to deliver a median dose of 57 Gy
- The actual rate of complications (1/21 patients or 4.8%) was close to the calculated rate (9%)

Radiographic Response

Pre-radiation

6 months post-radiation

Source Undetermined
Overall Survival of Patients by Dose Quartile

Ben-Josef E., et al., J Clin Oncol 23:8747, 2005
## Improvements Over 2D Produced by Highly Conformal Therapy: 2007

<table>
<thead>
<tr>
<th>Organ</th>
<th>2D Max dose (Gy)</th>
<th>3D Max dose (Gy)</th>
<th>Benefit</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lung</td>
<td>60-70</td>
<td>102</td>
<td>1%/Gy 2 yr PFS</td>
</tr>
<tr>
<td>Prostate</td>
<td>68-70</td>
<td>78-86.4</td>
<td>1-2%/Gy increase in 5 year PFS</td>
</tr>
<tr>
<td>Liver</td>
<td>30</td>
<td>90</td>
<td>24 vs 6-10 mos OS for ≥70 Gy vs less</td>
</tr>
<tr>
<td>Head &amp; Neck</td>
<td>70-76</td>
<td>70-76</td>
<td>↓ Xerostomia</td>
</tr>
</tbody>
</table>
Improving outcome: Individualizing Therapy

• By improving our ability to hit the tumor and miss the normal tissue

• By customizing combinations of radiation with chemotherapy or molecularly targeted therapy

• By assessing tumor and normal tissue response during treatment and tailoring therapy to these responses
Chemotherapy with Radiation is Superior to Radiation Alone

- High grade glioma
- Locally advanced head and neck cancer
- Stage III non-small cell lung cancer
- Esophageal cancer
- Pancreas cancer
- Cervix cancer
- Adjuvant therapy
  - Rectal cancer
  - Stomach cancer
Chemotherapy with Radiation Permits Organ Conservation

- **Concurrent**
  - Locally advanced laryngeal cancer
    - Avoids laryngectomy
  - Anal cancer
    - Avoids colostomy

- **Sequential**
  - Breast cancer
  - Extremity sarcoma (± chemotherapy)
• Address both local and distant disease

• Full dose gemcitabine with concurrent dose escalating radiation
  – To do this safely, needed to decrease the irradiated volume
  – Radiation dose escalation trial
Treatment Volumes with Concurrent Full Dose Gemcitabine

Prophylactic irradiation

No prophylactic irradiation
Response to Gem-RT

Gemcitabine + Cisplatin + Radiation

Growth Factor Receptors

Phase III Study Design

Stratify by
- Karnofsky score: 90-100 vs. 60-80
- Regional Nodes: Negative vs. Positive
- Tumor stage: AJCC T1-3 vs. T4
- RT fractionation*: Concomitant boost vs. Once daily vs. Twice daily

* Investigators’ choice

Arm 1
Radiation therapy

Arm 2
Radiation therapy + Cetuximab, weekly**
Cetuximab + RT vs RT Alone

**Locoregional Control**

- Cetuximab + RT
- RT

\[ P = 0.02 \]

**Overall Survival**

- Cetuximab + RT
- RT

\[ P = 0.02 \]

**Time (months)***

T. Lawrence
Improving outcome: Individualizing Therapy

- By improving our ability to hit the tumor and miss the normal tissue
- By customizing combinations of radiation with chemotherapy or molecularly targeted therapy
- By assessing tumor and normal tissue response during treatment and tailoring therapy to these responses
Normal Tissues

- TGFβ1 is a marker for lung damage
- Prospective trial to select patients for dose escalation
  - Eligibility escalate dose above 73.6 Gy only if TGFβ1 level suggested they were not experiencing lung damage
- Only 2/14 patients treated at 80 Gy or above developed dose limiting toxicity (at 86.4 Gy)
- Further follow-up, grade 4 and 5 complications occurred, but only in patients who were NOT dose escalated (because of high TGFβ1)

Cu-ATSM PET to Image Hypoxia

Chao, IJROBP 2001; 49(4): 1171-1182
Change in Hypoxic GTV During RT

Before Radiation

After 20 Gy

Chao et al., IJROBP 54:72, 2002 (Both images)
DCE-CT to predict liver injury

- Radiation-induced liver disease (RILD) occurs 2 weeks to 3 months after treatment
  - Too late to adjust radiation dose
- RILD is caused by veno-occlusive disease
- Hypothesis: can decreased blood flow during a course of radiation be detected?
  - Dynamic contrast-enhanced CT
Time Courses of Contrast Uptake

- CTV
- 70 Gy
- 60 Gy
- 4 Gy
- 12 Gy
- 24 Gy
- 30 Gy

Hounsfield Units

- artery
- portal vein
- liver

Cao Y et al., Medical Physics (accepted) 2006 (Both images)
Predicting Changes in Portal Venous Perfusion

Change after 45 Gy vs. Total RT dose

Cao Y et al., Medical Physics (accepted) 2006

Change 1 month after treatment
Functional lung DVH

- Lung cancer typically occurs in patients with damaged lungs due to smoking.
- In contrast to liver, in which volume can act as a surrogate for function, not all parts of the lung may be equal.
- “Functional lung DVH” - take into account which parts of the lung work.
Functional normal lung DVH

APPAs

Obliques

Ventilation changes after 50 Gy

Kong F, unpublished, 2005
Diffusion MRI predicts brain tumor response

• Diffusion MRI measures water mobility
• Hypothesis
  – In a responding tumor
    • Mobility could increase when cells die
    • Mobility could decrease if cells shrink before dying
  – In a non-responding tumor
    • No change in mobility
• Tumors were imaged pretreatment and again 3 weeks into treatment
  – How did the change in mobility correlate with response?
Diffusion MRI predicts response

Hamstra DA et al, Proc Nat Acad Sci USA 102: 16759, 2005
RT affects brain tumor blood flow

• MRI can measure brain tumor blood flow
• Although high grade brain tumors show regions of increased blood flow, some parts have little flow
• Hypothesis
  – Radiation might increase blood flow to regions with poor initial flow
  – If this were true, radiation might increase delivery of systemic chemotherapy into a tumor
    • Might partially explain why concurrent chemotherapy and radiation benefits patients with glioblastoma
Blood-Brain/Tumor Barrier Opening During RT

Pre RT

Week 3 during RT

Red: initially enhanced region; Yellow: initially non-enhanced tumor region

Cao, Y. et al J Clin Oncol 23: 4127, 2005
“Standard” Radiation Therapy

- Treatment based on population estimate of what might control a tumor
- Estimate the risk of normal tissue damage based on the most sensitive 5% of the population
- Treatment delivered to initially prescribed dose
  - Stop only for unacceptable acute toxicity
- Emphasis making isodose lines conform more tightly to the tumor
New Radiation Therapy

- Treatment based on molecular targeting of aberrant growth pathways
- Estimate the risk of normal tissue damage base on the individual patient using functional and metabolic imaging with adjustments during treatment
- Emphasis on
  - Multimodality research
  - Multimodality therapy
  - Continued technical advances, but in a broader context
Additional Source Information
for more information see: http://open.umich.edu/wiki/CitationPolicy

Slide 4: Source Undetermined
Slide 9: Source Undetermined
Slide 10: Source Undetermined
Slide 11: Source Undetermined
Slide 12: Source Undetermined
Slide 13: Sources Undetermined
Slide 14: Kessler, University of Michigan
Slide 15: Kessler, University of Michigan
Slide 16: Kessler, University of Michigan
Slide 17: Kessler, University of Michigan
Slide 18: Kessler, University of Michigan
Slide 19: Kessler, University of Michigan
Slide 21: Pollack, et. al., IJROBP, 53:5, 2002
Slide 22: Sources Undetermined
Slide 23: Theodore Lawrence
Slide 27: Source Undetermined
Slide 28: Ben-Josef E., et.al, J Clin Oncol 23:8747, 2005
Slide 29: Theodore Lawrence
Slide 34: Sources Undetermined
Slide 36: Source Undetermined
Slide 38: Nyati MK et al Nature Reviews Cancer Nov 2006
Slide 40: Theodore Lawrence
Slide 43: Chao, IJROBP 2001; 49(4): 1171-1182
Slide 44: Chao et al., IJROBP 54:72, 2002 (Both images)
Slide 46: Cao Y et al, Medical Physics (accepted) 2006 (Both images)
Slide 47: Cao Y et al, Medical Physics (accepted) 2006
Slide 50: Kong F, unpublished, 2005
Slide 54: Cao, Y et al J Clin Oncol 23: 4127, 2005