The Role of Radiation in Symptom Palliation

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PGY3 Resident Physician
Roswell Park Cancer Institute
• No financial disclosures
Definition

from late Latin, *pallium* ‘cloak.’

-hide, cover or disguise
Traditional oncological care (curative, life-prolonging, palliative)

Focus of care

Diagnosis
Symptom burden
6-month prognosis
Death

Palliative care
Hospice
Bereavement

Time
Approximately 50\% of RT is delivered with palliative intent

Guadagnolo JCO 2013
“When the initial objective of radiation therapy is palliation, new ground rules must be applied.
Possible serious complications or even slowly self limiting adverse effects of treatment are no longer acceptable. Overall treatment time must be short. Cost must be minimized. Convenience of treatment must be considered.”

- Robert G. Parker, MD
JAMA 1964
Outline

• Quad Shot
• High Yield
  – Bone Metastases
  – Brain Metastases
• Cases
  – Lymphomas
  – Graves Ophthalmopathy
  – SVC Syndrome
  – Hemostasis
  – Lightning Round
Why do we use radiation for palliation?
Because it works!
Quad Shot

1 cycle = 3.7Gy per fraction, twice daily for 2 days

2-4 week break

2\textsuperscript{nd} cycle

2-4 week break

3\textsuperscript{rd} cycle

Total 44.4Gy in 12 fractions

Spanos IJROBP 1989
• RTOG 7905
  – 10Gy x 3fx (4 week breaks)
  – Response Rate 41%
  – G3-4 Toxicity 45%

Spanos IJROBP 1989
Quad Shot

- RTOG 8502- palliation for advanced pelvic ca.
  - Phase II (n=148)
    - 45% response, only 5% late complication
- Australia
  - HNSCC (n=30)
    - 53% response, 44% improved QOL
- WashU
  - HNSCC (n=20), with chemo
    - 90% response, no late toxicity
- MSKCC
  - HNSCC (n=75)
    - 65% response, 5% G3 toxicity
    - Number of cycles predictive of response
    - OS 5.7mo

Spanos IJROBP 1989
Corry Radiother Oncol 2005
Carrascosa J Palliative Med 2007
Lok Oral Oncology 2015
Quad Shot

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Spanos IJROBP 1989
Corry Radiother Oncol 2005
Carrascosa J Palliative Med 2007
Lok Oral Oncology 2015
Pre Treatment
DON’T MISS!
After 2 Cycles
After 3 Cycles
High Yield
Bone Metastases

- 400,000 cases annually
- Breast + Prostate + Lung = 50-80%
- 70% involves axial skeleton
- 75% painful

Yu Cancer Control 2012
Maurer Nature Reviews 2016
Mechanism of RT

• Pain relief
  – Reduction of cytokine release
  – Direct damage to osteoclasts
  – Effect/damage to nerve endings
  – Remineralization for lasting effects

Mercadante Pain 1997
Dose

• RTOG 9714
  • N=897 with painful *uncomplicated* bone mets from breast or prostate
  • Randomize to 30Gy/10fx or 8Gy/1fx

Hartsell WF, J Natl Cancer Inst. 2005
<table>
<thead>
<tr>
<th>Parameter</th>
<th>No. of patients (%)</th>
<th></th>
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<tr>
<td></td>
<td>8-Gy arm (n=288)</td>
<td>30-Gy arm (n=285)</td>
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<tr>
<td>Overall response type</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Complete</td>
<td>44 (15)</td>
<td>51 (18)</td>
<td>.6</td>
</tr>
<tr>
<td>Partial</td>
<td>143 (50)</td>
<td>137 (48)</td>
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<tr>
<td>Stable</td>
<td>74 (26)</td>
<td>69 (24)</td>
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<tr>
<td>Progressive</td>
<td>27 (9)</td>
<td>28 (10)</td>
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</table>
**Overall Response Rate:**

60% SF vs. 61% MF

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Single Fraction</th>
<th>Multiple Fraction</th>
<th>Risk Ratio M-H, Random, 95% CI</th>
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<tbody>
<tr>
<td></td>
<td>Events Total</td>
<td>Events Total</td>
<td>Weight</td>
</tr>
<tr>
<td>Price</td>
<td>29 140</td>
<td>34 148</td>
<td>0.7%</td>
</tr>
<tr>
<td>Cole</td>
<td>12 16</td>
<td>13 14</td>
<td>0.7%</td>
</tr>
<tr>
<td>Kagel</td>
<td>12 13</td>
<td>12 14</td>
<td>2.0%</td>
</tr>
<tr>
<td>Gaze</td>
<td>108 151</td>
<td>99 144</td>
<td>6.2%</td>
</tr>
<tr>
<td>Nielsen</td>
<td>52 122</td>
<td>56 119</td>
<td>1.8%</td>
</tr>
<tr>
<td>Foro</td>
<td>19 25</td>
<td>25 25</td>
<td>1.8%</td>
</tr>
<tr>
<td>Foro*</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Koswig</td>
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<tr>
<td>BPTWP</td>
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<tr>
<td>Kirkbride</td>
<td></td>
<td></td>
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<tr>
<td>Ozsaran*</td>
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<tr>
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<tr>
<td>Sarkar</td>
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<tr>
<td>Altundag*</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Altundag</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Badzio</td>
<td>53 72</td>
<td>52 74</td>
<td>3.4%</td>
</tr>
<tr>
<td>van der Linden</td>
<td>395 579</td>
<td>396 578</td>
<td>22.5%</td>
</tr>
<tr>
<td>Roos</td>
<td>73 137</td>
<td>83 135</td>
<td>3.3%</td>
</tr>
<tr>
<td>Hartsell</td>
<td>187 455</td>
<td>188 443</td>
<td>5.8%</td>
</tr>
<tr>
<td>El Shenshaw*</td>
<td>39 50</td>
<td>40 50</td>
<td>3.4%</td>
</tr>
<tr>
<td>El Shenshaw</td>
<td>39 50</td>
<td>39 50</td>
<td>3.2%</td>
</tr>
<tr>
<td>Hamouda</td>
<td>42 56</td>
<td>46 55</td>
<td>4.4%</td>
</tr>
<tr>
<td>Safwat*</td>
<td>14 20</td>
<td>20 19</td>
<td>0.8%</td>
</tr>
<tr>
<td>Safwat</td>
<td>14 20</td>
<td>15 19</td>
<td>0.9%</td>
</tr>
<tr>
<td>Amouzegar-Hashemi</td>
<td>21 36</td>
<td>20 34</td>
<td>0.9%</td>
</tr>
<tr>
<td>Foro Amalot</td>
<td>59 78</td>
<td>71 82</td>
<td>6.0%</td>
</tr>
<tr>
<td>Total (95% CI)</td>
<td>2818</td>
<td>2799</td>
<td>100.0%</td>
</tr>
<tr>
<td>Total events</td>
<td>1696</td>
<td>1711</td>
<td></td>
</tr>
</tbody>
</table>

Heterogeneity: $\tau^2 = 0.00$; $\text{Chi}^2 = 11.55$, df = 25 ($P = 0.99$); $I^2 = 0\%$

Test for overall effect: $Z = 0.91$ ($P = 0.36$)

Fig 1. Overall response rates for single versus multiple fractions for intention-to-treat patients. References for studies included in the 2007 systematic review can be found in [4]. *Three-arm trials.

Chow Clinical Oncology 2012
Pain Control

8Gy/1fx $\equiv$ 30Gy/10fx
Retreatment

8Gy/1fx $\neq$ 30Gy/10fx

20% 8%
Why more retreatment?

• Dutch Bone Metastasis Study (n=1200)
  – 4X as many retreatments in SF
  – Retreatment following SF occurred sooner **despite less pain**

Steenland Radiother Oncol 1999
Van Der Linden IJROBP 2004
Retreatment

• Meta-analysis
  – Pain response 58%

Huisman IJROBP 2012
Retreatment

- Meta-analysis
  - Pain response 58%
- Secondary analysis of NCIC CTG SC.20
  - QOL analysis

Retreatment is Effective

Huisman IJROBP 2012
Chow JCO 2014
Retreatment

- Meta-analysis
  - Pain response 58%
- Secondary analysis of NCIC CTG SC.20
  - QOL analysis
- Toxicity

No acute or late G3
0-2% fracture

Retreatment is Safe

Jeremic Radiother and Oncology 1999
Van der Linden IJROBP 2004
Palliative radiation therapy for bone metastases: Update of an ASTRO Evidence-Based Guideline

Stephen Lutz MD a,*, Tracy Balboni MD MPH b, Joshua Jones MD c, Simon Lo MB ChB d, Joshua Petit MD e, Shayna E. Rich MD PhD f, Rebecca Wong MB ChB g, Carol Hahn MD h

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bDepartment of Radiation Oncology, and Department of Psychosocial Oncology and Palliative Care Brigham and Women’s Hospital and Dana-Farber Cancer Institute, Boston, Massachusetts
cDepartment of Radiation Oncology, University of Pennsylvania Health System, Philadelphia, Pennsylvania
dDepartment of Radiation Oncology, University of Washington School of Medicine, Seattle, Washington
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gDepartment of Radiation Oncology, Princess Margaret Hospital, Toronto, Ontario, Canada
hDepartment of Radiation Oncology, Duke University Medical Center, Durham, North Carolina

Practical Radiation Oncology (2017) 7, 4-12

Lutz et al, Pract Radiat Oncol 2017
Summary of Guidelines

• 8Gy/1fx
  – Similar to MF for pain control
  – Effective for spinal bone metastases
  – Toxicity rates similar
  – Consider retreatment at 1 month if no pain improvement

Lutz et al, Pract Radiat Oncol 2017
SBRT for Metastases

• Can be used for retreatment to reduce toxicity
• High BED
  – Oligometastatic disease control?
• ASTRO guidelines recommend clinical trial
Spinal Cord Compression

• Radiation Emergency!
• Tumor entering epidural space
• 5-10% pts will experience
• Symptoms
  – Back pain
  – Weakness/Paralysis
  – Numbness/Parasthesias
  – Cauda Equina Syndrome
• Survival est. few months

Klimo Oncologist 2004
Francel Peds Review 1998
Direct decompressive surgical resection in the treatment of spinal cord compression caused by metastatic cancer: a randomised trial


Surgery+RT vs. RT Alone

• Randomized Trial
• ≥1 neurological symptom
• Good PS, more favorable survival prognosis
• Surgery+RT (n=50) vs. RT Alone (n=51)
  – 30Gy in 10 fx

Patchell Lancet 2005
Surgery+RT vs. RT Alone

- Closed Early due to stopping rule
- Post-treatment ambulatory rate
  - 84% Surgery+RT vs. 57% RT alone
  - Also able to maintain ambulatory state longer

Patchell Lancet 2005
Why RT Alone

• Equally effective for pain control
• Surgical Risks
  – Perioperative complication rate 11-38%
  – 5% postoperative mortality
Dose

• SCORE-2 Trial
  – 30Gy/10fx vs. 20Gy/5fx
  – No difference

• SCORAD III
  – Multicenter Phase III randomized non-inferiority trial
  – Abstract from ASCO 2017
  – N=688
  – 20Gy/5fx vs. 8Gy/1fx

Rades JCO 2016
Hoskin ASCO 2017 Abstract
SCORAD III abstract

- Good Ambulatory Status at week 8
  - 73.3% vs. 69.5% walking or using an aid
  - No difference in OS or toxicity

8Gy/1fx \( \lessdot \) 20Gy/5fx

Hoskin ASCO 2017
Brain Metastases

- Occur in 20-40% of patients
- 97-170K cases/year
- Increasing incidence due to more MRI and increased survival with improving chemotherapy
- Common Primary:
  1. Lung (50%)
  2. Breast (15-20%)
  3. Unknown (10-15%)
  4. Melanoma (10%)
  5. Colorectal (5%)

Mehta IJROBP 2005
Nayak Curr Oncol Rep 2012
Brain Metastases: Symptoms

- 2/3 develop neurological symptoms
  - Headaches
  - Cognitive dysfunction
  - Focal neurological signs
  - Seizures
  - Strokes due to tumor emboli or hemorrhagic lesions
- Due to progressive edema, symptoms worsen without treatment
Brain Metastases: Treatment

- Steroids
Brain Metastases: Treatment

• Steroids
• Surgery
Brain Metastases: Treatment

- Steroids
- Surgery
- WBRT
Brain Metastases: Treatment

- Steroids
- Surgery
- WBRT
- SRS
WBRT

• WBRT+ Steroids
  • 74% improvement in neurological symptoms
    • Majority having durable relief

• OS benefit *(beyond the scope of this presentation)*

Cairncross Ann Neuol V7, p529-41, 1980
Patchell JAMA 1998
WBRT Toxicity

• Acute
  – Fatigue, hair loss, somnolence, n/v, HA
• Subacute
  – Short term memory loss, somnolence
• Delayed Injury (>6 months)
  – Attention and memory impairment
  – IQ decline
  – Dementia

DeAngelis Neurology 1989
Roman and Sperduto IJROBP 1995
RTOG 0933

• Phase II trial
• Hypothesis: Sparing hippocampus may mitigate radiation-induced neurocognitive toxicity
• IMRT or Tomotherapy
  – Contour subgranular zone of the hippocampus

Mehta, Gondi, et al.
RTOG 0933- Contouring Atlas

Mehta, Gondi, et al.
SRS

- Stereotactic Radiosurgery
  - Uses 3D coordinate system
  - Highly focused, precise beam
  - Higher doses, less normal tissue radiated
  - Delivery
    - Linac-based, Gamma Knife or CyberKnife
<table>
<thead>
<tr>
<th></th>
<th>Stereotactic radiosurgery plus whole-brain radiotherapy (N=11)</th>
<th>Stereotactic radiosurgery alone (N=20)</th>
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<tbody>
<tr>
<td>Total recall</td>
<td>52%</td>
<td>24%</td>
</tr>
<tr>
<td>Delayed recall</td>
<td>22%</td>
<td>6%</td>
</tr>
<tr>
<td>Delayed recognition</td>
<td>11%</td>
<td>0%</td>
</tr>
</tbody>
</table>
Quad Shot is not the only catchy name...
“Boom-Boom”

2Gy 2Gy
Lymphomas

- Radiosensitive
- Can be indolent or aggressive
**FORT Trial**

- Phase III Non-inferiority Trial
- Follicular and Marginal Zone Lymphoma
- 2Gy x 2 vs. 24Gy/12fx

<table>
<thead>
<tr>
<th></th>
<th>24 Gy</th>
<th>4 Gy</th>
<th>p value*</th>
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<tbody>
<tr>
<td>Complete</td>
<td>Complete response plus partial response</td>
<td>Complete response (%)</td>
<td></td>
</tr>
<tr>
<td>response</td>
<td>(%)</td>
<td>(%)</td>
<td></td>
</tr>
<tr>
<td>(%)</td>
<td>176/260 (68%)</td>
<td>137/281 (49%)</td>
<td>0.0095</td>
</tr>
<tr>
<td></td>
<td>236/260 (91%)</td>
<td>227/281 (81%)</td>
<td></td>
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</tbody>
</table>

Hoskin Lancet Oncol 2014
Cutaneous T Cell Lymphoma

7-8Gy x1

94% complete response

Thomas IJROBP 2012
Orthovoltage (superficial)
Mycosis Fungoides/Sezary Syndrome

Before

After TSEI

Buder ActaDV 2013
Hauswald Radiation Oncology 2012
Graves’ Ophthalmopathy

- Inflammation of extraocular muscles due to antibodies
- Can threaten eyesight with corneal ulceration
- Treatment
  - Tx underlying hyperthyroidism
  - Steroids
  - Surgery or RT
    - Common Dose: 20Gy in 10fx
A Randomized Controlled Trial of Orbital Radiotherapy Versus Sham Irradiation in Patients with Mild Graves’ Ophthalmopathy

MARK F. PRUMMEL, CAROLINE B. TERWEE, MARTIN N. GERDING, LELIO BALDESCHI, MAARTEN P. MOURITS, LEO BLANK, FRIEDO W. DEKKER, AND WILMAR M. WIERSINGA

Departments of Endocrinology and Metabolism (M.F.P., M.N.G., W.M.W.), Clinical Epidemiology and Biostatistics (C.B.T., F.W.D.), and Radiotherapy (L.Ba.) and Orbital Center (L.Bl.), Academic Medical Center, University of Amsterdam, 1105 AZ Amsterdam, The Netherlands; and Donders Institute of Ophthalmology (Orbital Unit), University Medical Center (M.P.M.), 3584 CX Utrecht, The Netherlands

The Journal of Clinical Endocrinology & Metabolism 89(1):15–20
TABLE 2. Treatment efficacy after 12 months of follow-up in patients treated with radiotherapy and in sham-irradiated patients with mild GO

<table>
<thead>
<tr>
<th>Response</th>
<th>Sham irradiation (n = 44)</th>
<th>%</th>
<th>Radiotherapy (n = 44)</th>
<th>%</th>
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</thead>
<tbody>
<tr>
<td>Very good</td>
<td>1</td>
<td>12</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Good</td>
<td>7</td>
<td>27</td>
<td>8</td>
<td>52</td>
</tr>
<tr>
<td>Fair</td>
<td>4</td>
<td>3</td>
<td></td>
<td></td>
</tr>
<tr>
<td>No change</td>
<td>25</td>
<td>59</td>
<td>15</td>
<td>34</td>
</tr>
<tr>
<td>Worse</td>
<td>7</td>
<td>16</td>
<td>6</td>
<td>14</td>
</tr>
</tbody>
</table>

By $\chi^2$, $P = 0.02$. 

Prummel JCEM 2004
Superior Vena Cava Syndrome

Wilson NEJM 2007
SVC Syndrome

- Impaired venous drainage from head, neck, upper extremities due to obstruction of superior vena cava (SVC)
- 75% due to lung cancer (more often small cell)
- 15% Lymphoma

Talaptra J Can Res Ther 2016
SVC Syndrome

• Symptoms
  – Face/neck swelling
  – Upper ext. swelling
  – Distended neck/chest veins
  – Cough
    – Shortness of breath
    – Headache
    – Confusion
    – Dizziness
    – Obtundation
SVC Syndrome

• **Treatment**
  – Elevate head of the bed
  – Steroids
  – Chemo for lymphoma and small cell

  – **Endovascular stenting**
    • No biopsy needed

  – **Radiation**
    • 78% small cell and 63% NSCLC have relief by 2 weeks
    • Clinical improvement by 72 hours

Armstrong IJROBP 1987
SVC Syndrome
SVC Syndrome

- Consider high dose per fraction initially (3-4 Gy/fx)
- Can transition to definitive treatment +/- chemo (1.8-2 Gy/fx)
Hemostasis

• Bleeding occurs in 10% of patients with advanced cancer
  – Hematemesis
  – Melena/hematachezia
  – Hemoptysis
  – Hematuria
  – Epistaxis
  – Vaginal bleeding
  – Ulcerated skin (breast ca.)
Symptoms

• Fatigue
Symptoms

- Fatigue
- Hypovolemic Shock
RT for Hemostasis

• Better for “oozing” blood, not arterial bleeding
• Hemostasis occurs at ~6Gy
• Dose Range
  • 8Gy/1fx, 3Gyx3, 20Gy/5fx

Tey IJROBP 2007
52 y/o progressive pancreatic cancer p/w black stools and HgB=6.

CT showing invasion into the duodenum.

3Gy x 3

Limit side effects
60 y/o with metastatic esophageal adenoca p/w black stools. HgB=6.5

6Gy x 1
Lightning Round
Brachial Plexopathy

72 y/o metastatic serous carcinoma p/w Pain and Parasthesias right hand

37.5Gy in 15fx
Recurrent Tumor

Metastatic giant cell tumor of bone p/w fungating recurrence

30Gy/10fx
Airway Obstruction

Metastatic NSCLC p/w SOB

20Gy/5fx
Impending Fracture

Metastatic SCC H/N p/w hip pain and impending fx of the femoral neck

8G/1fx
Lower Ext Lymphedema

Metastatic sarcoma p/w worsening LE edema

20Gy/5fx
Radiation Indications for Palliation cont’d

• Bowel or Biliary obstruction
• Urinary retention
• Pelvic recurrence
• Dysphagia
• Abdominal pain
• Recurrent primary brain tumors
• Inflammatory breast disease
• Etc.
Summary

• Palliative radiation is effective
• Delivery should be safe
• ASTRO Guidelines recommending 8Gy/1fx
• Spare healthy tissue when possible
• Consider each patient individually
Questions?