Epidemiology

At diagnosis: Jemal et al: CA Cancer J Clin J ‘09

- Localized disease: 82 to 85%
- Regional disease: 10 to 13%
- Non-regional metastases: 2 to 5%

Prognosis: Homer: SEER Cancer Statistics R/V

- Localised: 98%
- Regional: 62%
- Metastatic: 15%
- OS over the decades: 1977 (82%) 2004 (92%)

Josh Dass
Myth: Radiation Effect

- Radiotherapy
  - Cook
  - Sizzle
  - Burn
  - Microwave
  - Electrocute
  - Nuclear holocaust

Josh Dass
Principles of Quantum Physics

Wave Theory

Quantum
Principles of Quantum Physics

Electromagnetic radiation

Particles called photons
Target: DNA

Indirect Route

radiation → water → free radical → DAMAGE

Direct Route

radiation → DAMAGE

Josh Dass
The Principles

- High Dose
- Low Dose
- Delivery
- Cancer
- Normal Tissue
EBRT = Linear Accelerator
Radical
- Definitive
- Adjuvant

Palliative
- Definitive
- Symptom control

Stereotactic
- ?Radical
Adjuvant to primary skin melanoma

Local control factors

- Close/positive margins
- Early/multiple recurrences
- Extensive satellitosis: 12 to 14% recur
- Desmoplasia: 11 to 48% recur
- Neurotropism

Not clearly established role
### Radical Adjuvant

<table>
<thead>
<tr>
<th>Regional Nodal Involvement</th>
<th>Size &gt; 3cm</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number</td>
<td></td>
</tr>
<tr>
<td>1 parotid</td>
<td></td>
</tr>
<tr>
<td>2 Head and neck/Axillae</td>
<td></td>
</tr>
<tr>
<td>3 Inguinal</td>
<td></td>
</tr>
<tr>
<td>ECE = extracapsular</td>
<td></td>
</tr>
<tr>
<td>extension</td>
<td></td>
</tr>
<tr>
<td>ENE = extranodal</td>
<td></td>
</tr>
<tr>
<td>extension</td>
<td></td>
</tr>
</tbody>
</table>
Radical Definitive

Radiotherapy alone

- Unresectable
- Not suitable for systemic therapy
- Patient preference
- Co-morbidities
Palliative Radiotherapy

- Prevent symptoms
- Progression on systemic therapy
- Symptomatic
  - Compression
  - Spinal cord
- Bleeding
- Pain
- Fractures (after fixation)
Conspiracy Theory

MacKee 1946: Xrays & Radium in Rx of Skin

- Irradiation alone by any technique should not be relied on for the cure of these lesions
- Based on orthovoltage radiotherapy and radium experience

Today questioned

- Million et al 1984: Mx of HN Ca: A MDM approach
- Jenrette 1996: MM: the role of RT revisited
  - Seminars Oncology 1996
- Stevens et al: Dispelling the Myths of RT for MM
  - Lancet Oncology 2006; 7:7:575
- Overgaard: important factors in treatment of MM
  - RO 1986; 5:183
- Rofstad: Radiation biology of malignant melanoma
  - Acta Radiol Oncol
Radioresistant Theory

Cell Culture Studies
- Barranco et al. *Cancer Res.* 1971; 31:830
- Dewey *Br J Radiol.* 1971; 44:816
- Fertil et al. *IJROBP.* 1985; 11:1699
- Doss et al. *IJROBP.* 1982; 8:1131

Broad shoulder on survival curve
- High repair capacity

Hypofractionation more effective
- Rofstad *Acta Radiol Oncol.* 1986; 25:1

Graph showing surviving fraction vs. radiation therapy dose (Gy). Other tumor types and melanoma differentiated.
<table>
<thead>
<tr>
<th>Study</th>
<th>Journal</th>
<th>Year</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bentzen et al</td>
<td>Rad Onc</td>
<td>1989; 16:169</td>
</tr>
<tr>
<td>Overgaard</td>
<td>IJROBP</td>
<td>1986; 12:867</td>
</tr>
<tr>
<td>Chang et al</td>
<td>IJROBP</td>
<td>2006; 66:1051</td>
</tr>
<tr>
<td>RTOG</td>
<td>Phase III metastatic melanoma</td>
<td></td>
</tr>
<tr>
<td>Sause et al</td>
<td>IJROBP</td>
<td>1991; 20:429</td>
</tr>
<tr>
<td>32Gy/4#/4wk @ 8gpf</td>
<td>vs. 50Gy/25#/5wk @ 2.5gpf</td>
<td></td>
</tr>
<tr>
<td>Complete response similar</td>
<td>24 vs 23%</td>
<td></td>
</tr>
<tr>
<td>Partial response similar</td>
<td>36% vs 34%</td>
<td></td>
</tr>
<tr>
<td>However increased toxicity in the hypo# arm</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Josh Dass
Emerging paradigm shift

- brain mets
- High risk nodal disease
- High risk nodal disease
- head and neck
- uveal melanoma
- Plaque brachytherapy
- IMRT/VMAT
- Adjuvant radiotherapy
- Radiosurgery
Hypofractionated

**Bentzen:**
RO 1989; 16:169-182
- Retrospective studies showing improved outcome

**Konefal:**
Radiology 1987; 164:607
- For fraction size > 5 Gy, 50% CR, vs 9% for < 5 Gy/fx.
  Local control @ 1 yr 25% vs 7%

**Ang & Peters:**
Arch Otol H N Surg 199; 116:169
- 2 yr LRC 95% in HN Melanoma node negative neck
- 24 – 30Gy in 4 to 5# in 5 – 6 gpf

**Burmeister:**
RO 2006 TROG 96:06
- Increased progression free survival

**Henderson:**
JCO 2009
- RT reduced the risk of Ly Node Field relapse by 52%
3D – CRT vs. IMRT

Equal Intensity Across Field

Intensity is modulated across field
3D – CRT vs. IMRT

Equal Intensity Across Field

Intensity is modulated across field
VMAT

Continuous Arc Modulation

Josh Dass
**NEW ERA – STEREOTACTIC RADIOTHERAPY**

<table>
<thead>
<tr>
<th>Single very high dose radiotherapy</th>
<th>Typically 2 to 8 high dose radiotherapy fractions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pin point accuracy</td>
<td>Pin point accuracy</td>
</tr>
<tr>
<td>Almost total avoidance of normal tissue</td>
<td>Almost total avoidance of normal tissue</td>
</tr>
<tr>
<td>Brain Mets</td>
<td>Increased Risk a/w:</td>
</tr>
<tr>
<td>------------</td>
<td>---------------------</td>
</tr>
<tr>
<td></td>
<td>(Sampson J Neuro 1998; 88: 11)</td>
</tr>
<tr>
<td>Skibber: Ann Surg Oncol 1996: Cranial Rt after Sx</td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td></td>
</tr>
<tr>
<td>Head and Neck mucosal melanoma</td>
<td></td>
</tr>
<tr>
<td>Nodal mets &gt; 2 nodes</td>
<td></td>
</tr>
</tbody>
</table>
Table 2
Role of linear accelerator stereotactic radiosurgery in the treatment of melanoma brain metastases

<table>
<thead>
<tr>
<th>Study</th>
<th>Patients (n)</th>
<th>One-year LC</th>
<th>One-year OS</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mori et al34</td>
<td>60</td>
<td>90%</td>
<td>7 months</td>
<td>Improved survival on multivariate analysis included lack of active systemic disease and at least one metastasis.</td>
</tr>
<tr>
<td></td>
<td>51 (WBRT + SRS)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Selek et al35</td>
<td>103</td>
<td>49%</td>
<td>6.7 months</td>
<td>75% LC for tumors &lt; 2 cm with initial SRS alone</td>
</tr>
<tr>
<td></td>
<td>61 (SRS)</td>
<td>60%</td>
<td>7.5 months</td>
<td></td>
</tr>
<tr>
<td></td>
<td>12 (SRS +</td>
<td>0%</td>
<td>3.7 months</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
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</tr>
</tbody>
</table>
Uveal Melanoma

Location

- Choroid, Ciliary Body, Iris

83% have mutation in GNA11 or GNAQ loci

- Heterotrimeric G proteins upregulate MAPK

Treatment

- COMS – Collaborative Ocular Melanoma Study
  - 1317 pts enucleation vs. Plaque I-125 BT
    - 5 yr survival 81% vs. 82%
    - 2.5 to 10mm in apical height
    - 5 to 16 mm largest basal diameter
Patient moves

Organs move – lung, liver, etc...

Tight radiotherapy field = geographical miss
  • Make field larger = more normal tissue damage

Need 4D capability
  • Hit a moving target including changing shape
Josh Dass, Sir Charles Gairdner Hospital, Perth

OAR = Organ at risk
Original Plan

Make the radiation field bigger to allow for movement

Josh Dass
Introducing CyberKnife M6 system

- Only one in Australia
- Only 4 M6 systems in the world
- Advantage
  - 4D capability
  - Irregular shape targeting
  - Multiple targets in one session
CyberKnife in Action

Inter target motion tracking
- Tract detect and correct

Non co-planar = not single plane but any angle

Fudicial Marker tracking
- Orthogonal KV imaging systems
- Fudicial Markers
  - Gold seeds
  - Calypso

Stereotactic radiotherapy—shorter course with higher dose