Brain Tumor Treatment Trends

Radiation Treatment

Jonathan Knisely, MD
North Shore-LIJ Health System & Hofstra Medical School
jknisely@nshs.edu

2014 Patient and Family Conference
Providing and Pursuing Answers: Advances in Brain Tumor Research, Treatment & Care
www.abta.org
1-800-886-ABTA (2282)
abtacares@abta.org
#ABTA2014
Disclosure

No commercial ties or funding have influenced either the content or the delivery of this presentation.
“The art of medicine consists in amused the patient while Nature effects the cure.” Voltaire
Radiotherapy Brain Tumor Treatment Trends

“δίς ἐς τὸν αὐτὸν ποταμὸν οὐκ ἂν ἐμβαίης.” (You cannot step in the same river twice.)
—Herakleitos (535-475 BC), quoted by Plato, Cratylus, 402a
Radiotherapy Brain Tumor Treatment Trends

• The goal of radiation therapy remains the same as it has been for the past century
  – Local control of the tumor
  – Acceptably low side-effect profile
  – Preservation of normal tissue functioning

• Brain tumor radiotherapy is evolving along with our understanding of the diseases we treat and concomitant technological advances, both in diagnosis and treatment
Radiation Oncology Roots
Precision Radiotherapy Technology from the 1930s
Stanford University Linear Accelerator (1960s)
Modern Stereotactic Linear Accelerator
(General) Radiotherapy Precepts

• Dimensions and locations of tumors are uncertain

• Accurate treatment delivery (dose, location, etc.) is important

• Normal tissues may be safely treated with the same dose that the tumor receives
  – Increasing the volume treated lowers the risk of missing tumor at the edge of the radiotherapy field
  – Increasing the volume treated increases the risk of complications for normal tissues
Imprecision in Manual Target Delineation

(General) Radiotherapy Precepts

• Repetitive daily treatments permit biological differences between normal and tumor tissue in the volume being irradiated to be manifested, hopefully with improved tumor control.

• Large single doses cannot be used effectively because of difficulties with targeting and with normal tissue exposure.
Radiotherapy is the Most Effective Locoregional Cancer Treatment

• Radiotherapy occupies a middle ground between purely local therapies such as surgery and systemically administered treatments

• How does radiotherapy differ from surgical treatment and from drug treatment?
  – Can treat tissues that cannot be excised
  – Only the part getting radiation is exposed to potential toxicity—the rest of the body is spared
Surgery (on a potato)

• The surgeon’s scalpel blade creates a plane
  – On one side the bad spot comes out
  – On one side the bad spot stays behind
• Complete surgical excision cannot always be achieved
• Apparently complete resections may leave microscopic disease behind
Surgery Can Be Risky
Chemotherapy (on a chicken)

- Injection or oral administration of various compounds
- Distribution throughout the body by the circulatory system
- Normal tissues’ tolerances may limit dosing and thus the curative potential
Radiotherapy (on chicken & potatoes)

- Radiotherapy often follows surgery and chemotherapy
- Radiotherapy treats everything uniformly
- Treatment is carefully calibrated to produce good results
- Large and small targets may be treated at the same time
Radiotherapy vs. Radiosurgery

- Radiosurgery is the most focal external beam radiation treatment
- Crème Brûlée uses intense focal heating to obtain the desired result
Overarching Radiotherapy Trend:

Less Normal Tissue Irradiation

- Automated Rigid 3D Multimodal Image Registration
- 3D Conformal Radiotherapy
- Intensity Modulated Radiation Therapy
- Radiotherapy Dose De-Escalation
- Stereotactic Radiosurgery

• How can we know if these newer approaches are better?
Clinical Trials Will Guide Us

• Radiotherapy plans may look ‘better’, but are better outcomes achieved?

• Clinical trials permit objective evaluation of important endpoints
  – Is local control equal with fewer side-effects?
  – Can dose escalation improve tumor control with the same level of side-effects?
  – Can systemic therapy be more tightly integrated with irradiation for disease that cannot be resected or controlled adequately by systemic therapy alone?
Current Clinical Trials (Pediatric)

**Medulloblastoma Phase III Trials (>3 years old)**

- ACNS 0331 (avg risk patients):
  - Effects on tumor control and survival of chemotherapy dose-intensification* combined with 25% dose-reduction of craniospinal radiotherapy dose (23.4 Gy → 18 Gy)# and 3D conformal radiotherapy or conventional radiation for cerebellar boost volume

- ACNS 0332 (high risk patients):
  - Effects on tumor control and survival of both the addition of concurrent carboplatin to craniospinal radiation and vincristine, as well as maintenance isotretinoin

- Molecular subtyping (WNT, SHH, Groups 3 & 4)
  - *may permit further reduction of radiotherapy in WNT and intensification of therapies for other groups*

*weekly Vincristine followed by 8 cycles of Vincristine, CCNU, and Cisplatin
# for children 3-7 years of age; children >7 years get standard dose CSI
Current Clinical Trials (Pediatric)

**Diffuse Intrinsic Pontine Glioma**
- Phase II Trials of radiotherapy and systemic agents
  - MK-1775 (WEE1 inhibitor)
  - Veliparib (PARP inhibitor)
  - Lenalidomide (angiogenesis inhibitor)

**Malignant Glioma**
- ACNS0822 (Phase II/III trial):
  - radiotherapy + temozolomide, vorinostat, or bevacizumab in anaplastic astrocytoma, glioblastoma, or gliosarcoma

**Atypical Teratoid/Rhabdoid CNS Tumor**
- ACNS 0333 (Phase II trial):
  - Chemotherapy, stem cell transplant, and radiotherapy
Current Clinical Trials (Pediatric)

Primary CNS Germ Cell Tumors

– ACNS 1123 (Phase II trial):
  • NGGCT: IE&CE chemotherapy (x 6) before 3DCRT (30.6 Gy WVI and 23.4 Gy to primary site)
  • Germinomas: CE chemotherapy (x 4) before 3DCRT
    – Better prognosis on repeat surgery (18.0 Gy WVI and 12.0 Gy to primary site)
    – Worse prognosis on repeat surgery (24.0 Gy WVI and 12.0 Gy to primary site)
    – No second look surgery, residual tumor >1.5 cm—off protocol

Side-Effect Management

– ACCL 0922 (Randomized Phase II trial):
  • Modafinil vs. placebo for effects on attention, memory, processing speed, and fatigue
Current Clinical Trials (Pediatric)

Ependymoma

- ACNS 0121 (Phase II trial):
  - Observation or 3DCRT (involved fields only) and/or chemotherapy and second surgery for children as young as 2 (study publication pending)
- ACNS 0831 (Phase III trial):
  - surgery, radiotherapy, chemotherapy +/- maintenance chemo
Current Clinical Trials (Adult)

**Primary CNS Lymphoma**
- RTOG 1114 (Phase II trial):
  - Rituximab, Methotrexate, Procarbazine, Vincristine, and Cytarabine +/- Low-Dose Whole-Brain Radiotherapy (23.4 Gy)

**Meningioma**
- RTOG 0539 (Phase II trial):
  - Low risk: Postoperative observation
  - Intermediate risk: Radiotherapy to 54 Gy (IMRT/3DCRT/Proton)
  - High risk: Radiotherapy to 60 Gy (IMRT only)

Low risk: Grade I meningioma, regardless of degree of resection
Intermediate risk: Completely resected Grade II or recurrent Grade I
High risk: Grade III tumor or recurrent or subtotally resected Grade II
Current Clinical Trials (Adult)

**Low Grade Glioma**
- RTOG 0925 (Phase II trial):
  - Serial neurocognitive testing in patients with low-risk LGG who are being managed with observation after resection or biopsy
  - Evaluation of impact on higher neurocognitive functioning from tumor recurrence

**Anaplastic Glioma**
- RTOG 0834 — CATNON trial (Phase III trial):
  - Non-codeleted anaplastic (Grade III) gliomas treated with radiotherapy +/- concurrent +/- sequential temozolomide
  - European & North American clinical trials groups
  - Overall survival is primary outcome measure
Recent Clinical Trials (Adult)

**Glioblastoma**

- RTOG 0825 (Randomized phase III trial):
  - 60 Gy radiotherapy (Stupp regimen) +/- bevacizumab
  - Nonsignificant progression-free survival increase (7→10m), but worse quality of life and increased symptom burden
    » *No role for bevacizumab with initial treatment of GBM*

- Avaglio (Randomized phase III trial):
  - 60 Gy radiotherapy (Stupp regimen) +/- bevacizumab
  - Significant progression-free survival increase (6→10m), decreased steroid requirements, and preservation of performance status
    » *Bevacizumab has a role in initial GBM treatment*

- The FDA is evaluating raw data from both studies
- Bevacizumab is currently approved only for recurrent GBM
Perplexed? Me too!
Current Clinical Trials (Adult)

Glioblastoma

– RTOG 1205 (Randomized phase II trial):
  • Bevacizumab +/- 35 Gy RT in 10 fractions for recurrent GBM (IMRT, 3DCRT, or protons)

– NRG BN-001 (Randomized phase II trial):
  • Dose-escalated 6 week hypofractionated photon or proton IMRT
  • All arms get concomitant and sequential temozolomide
  • Reference arm:
    – 60 Gy of photon IMRT
  • Experimental arms:
    – 60 Gy of proton IMRT
    – 75 Gy and 50 Gy dose-intensified photon IMRT
    – 75 Gy and 50 Gy dose-intensified proton IMRT
  • ~ 600 patients total
  • Randomization of 2:1 to dose-escalated treatment
Comparison of simultaneous integrated boost (SIB) and dose escalation using IMRT and IMPT

Protons vs. Photons

IMRT-SIB

IMPT-SIB
Are Protons Better? We Don’t Know

Don’t count your chickens before they hatch. They might not turn out to be chickens!
Recent Clinical Trials (Adult)

**Brain Metastases**

– RTOG 0933 (Phase II trial):
  - Neurocognitive endpoints for a novel ‘WBRT’ treatment that minimized dose to the hippocampal regions bilaterally

7% decline in verbal memory (Hopkins Verbal Learning Test) at 4 months

Historical WBRT treatments showed 30% decline in HVLT at 4 months
Recent Clinical Trials (Adult)

**Brain Metastases**

- RTOG 0614 (Phase III trial):
  - Neurocognitive endpoints for a WBRT +/- memantine (a drug approved by the FDA for vascular dementia, which blocks excitotoxic depolarization of neurons)

Significantly reduced rates and pace of cognitive deterioration
Current Clinical Trials (Adult)

**Brain Metastases**

- NCCTG N0574 (Phase III trial):
  - Survival, QOL, neurocognitive/other toxicity, CNS recurrence rates for patients with 1-3 brain metastases treated with SRS +/- WBRT

- NCCTG N107C (Phase III trial):
  - Survival and neurocognitive outcomes with WBRT or SRS after surgery in patients with 1-4 brain metastases

- NAGKC 12-01 (Phase III trial):
  - Neurocognitive outcomes after WBRT or SRS for 5-10 brain metastases

- MRC QUARTZ (Phase III trial):
  - Survival and QALYs in patients with non-small cell lung cancer brain metastases using optimal supportive care +/- WBRT
Recent Meta-Analysis of Clinical Trials Evaluating SRS +/- WBRT for Brain Metastases

• Rigorously conducted meta-analysis of 3 phase III trials comparing SRS to SRS + WBRT
  – Chang (MDACC); Kocher (EORTC); Aoyama (JROSG)
  – 364 patients treated
    • 51% SRS alone
    • 60% had a single brain metastasis
    • 19% were 50 or younger

• *Survival for individuals ≤ 50 who got SRS alone was superior* (Hazard Ratio 0.64 (95% CI 0.42, 0.99))

Sahgal *et al.* ASTRO Plenary Session, 2013
Brain Metastases: Is Metastasis Management a Numbers Game?

- Multi-institutional prospective observational research (JLGK0901) has shown that for patients managed with SRS alone, the number of brain metastases does not predict survival.
- 1194 patients with 1-10 brain metastases (total volume ≤15 mL) enrolled at 23 sites in Japan

<table>
<thead>
<tr>
<th>Number of Brain Metastases</th>
<th>Median Survival [95% CI] in months</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>13.9 [12.0-15.6]</td>
</tr>
<tr>
<td>2-4</td>
<td>10.8 [9.4-12.4]</td>
</tr>
<tr>
<td>5-10</td>
<td>10.8 [9.1-12.7]</td>
</tr>
</tbody>
</table>

67 year old woman with triple-negative breast cancer who got treated with SRS for 11 brain metastases and the co-registered follow-up MRI from 4 months later showing gratifying regression of all metastases—and no new metastases
## Diagnosis-Specific Graded Prognostic Assessment

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>Overall Median Survival (mo)</th>
<th>GPA: 0-1.0 Median Survival (mo)</th>
<th>GPA: 1.5-2.0 Median survival (mo)</th>
<th>GPA: 2.5-3.0 Median survival (mo)</th>
<th>GPA: 3.5-4.0 Median survival (mo)</th>
</tr>
</thead>
<tbody>
<tr>
<td>NSCLC</td>
<td>7.0</td>
<td>3.0</td>
<td>5.5</td>
<td>9.4</td>
<td>14.8</td>
</tr>
<tr>
<td>SCLC</td>
<td>4.9</td>
<td>2.8</td>
<td>4.9</td>
<td>7.0</td>
<td>17.1</td>
</tr>
<tr>
<td>Melanoma</td>
<td>6.7</td>
<td>3.4</td>
<td>4.7</td>
<td>8.8</td>
<td>13.2</td>
</tr>
<tr>
<td>RCC</td>
<td>9.6</td>
<td>3.3</td>
<td>7.3</td>
<td>11.3</td>
<td>14.8</td>
</tr>
<tr>
<td>GI</td>
<td>5.4</td>
<td>3.1</td>
<td>4.4</td>
<td>6.9</td>
<td>13.5</td>
</tr>
<tr>
<td>Breast</td>
<td>13.8</td>
<td>3.4</td>
<td>7.7</td>
<td>15.1</td>
<td>25.3</td>
</tr>
<tr>
<td>Total</td>
<td>7.2</td>
<td>3.1</td>
<td>5.4</td>
<td>9.6</td>
<td>16.7</td>
</tr>
</tbody>
</table>

Breast cancer

Small-cell lung cancer

Renal cell carcinoma

Non-small-cell lung cancer

Melanoma

GI cancers

Trends for the Future?

• “...I hope and expect that our evaluation of patient outcomes will develop in such a way that the extent to which a patient is able to return to a normal life within society and within his/her family is seen as the determinant of success...”

Vladimír Beneš, MD
Professor & Chairman of Neurosurgery,
1st Medical School, Charles University,
Prague, Czech Republic
THANK YOU
Any Questions?

2014 Patient and Family Conference
Providing and Pursuing Answers: Advances in Brain Tumor Research, Treatment & Care
www.abta.org
1-800-886-ABTA (2282)
abtacares@abta.org
#ABTA2014