Advances in Meningioma Management

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Disclosures

• None relevant

• Others:
  • UpToDate, writer
  • prIME Oncology, symposium speaker
  • Cleveland Clinic, expert consultant
Outline

• The problem of meningiomas
• Overview of standard of care
• Update on benign meningiomas
• Update on high grade meningiomas
• Imaging, pathology and genetics
Meningiomas

- Most common primary brain tumor, ~37%
- Range from “benign” to aggressive
- Variety of locations along lining of brain
- Risk factors: hormones, radiation
Meningiomas: A Variety of Shapes & Sizes
Distribution of Meningioma by Grade

Using WHO 2000 criteria

**Grade 1**
Benign

**Grade 2**
Atypical

25-30%

**Grade 3**
Anaplastic or Malignant

2-3%

**Grade 1**
Benign

70-75%

Pearson BE et al. Neurosurg 2008
Survival of Meningioma Patients

NCDB 2004-2014:
62,867 meningioma patients

Benign 86%
Atypical 11%
Malignant 3%

Rydzewski NR et al. Cancer 2018
Health Related Quality of Life (HRQoL)

291 patients, all benign meningiomas
455 EORTC QLQ-C30 completed postop annually to 10 years
181, 71, 28, 11 completed 1, 2, 3, 4 times, respectively

Nassiri F et al. Neuro-Oncol 2019
STANDARD OF CARE FOR MENINGIOMAS
Standard of Care for Meningiomas

- **Do nothing**: if not causing symptoms, not growing, and likely benign
- **Surgery**: take out as much as possible if causing symptoms or growing
- **Radiation therapy**:  
  - After surgery if at risk of causing symptoms or of growing back  
  - Alone if small or if surgery not possible
- **No good drugs**
Benign (Grade I) Meningiomas: Surgery and Radiation Define Standard Treatment

- Complete resection (Gross total resection)
- Partial resection + Radiation therapy
- Partial resection (Subtotal total resection)

Soyuer S et al. Radiother Oncol 2004
Atypical (Grade 2) Meningiomas: Radiation Therapy after Surgery Reduces Tumor Recurrence

- 68 atypical meningioma
- All complete surgical removal
- Some with postoperative radiation (RT)

Aizer AA et al. NeuroOncol 2014 BWH
High Grade (Grade 2-3) Meningiomas: Do Better with Higher Radiation Dose

- Local control
  - >60 Gy
  - <60 Gy

- Cause specific survival
  - >60 Gy
  - <60 Gy

McDonald MW et al. JNO 2015 Indiana
22 pts, all Grade 2

Boskos et al. IJROBP 2009 CPO
24 pts, 19 Grade 2, 5 Grade 3
UPDATE ON BENIGN MENINGIOMAS
Proton Radiation

• A radiation beam that stops
• A radiation beam that concentrates the radiation dose at the end of the beamlength
• As compared to standard (photon) radiation, protons may be able to achieve both:
  – Higher dose to tumor target and
  – Lowest dose to normal tissues
Protons vs Photons

Proton beam

Radiation dose vs Depth into tissue

Photon beam

Radiation dose vs Depth into tissue

Note: The graphs illustrate the comparison between proton and photon beams in terms of radiation dose distribution. Protons deposit a higher dose in a smaller volume, which can be beneficial for targeting tumors.
Second Tumor Risk after Radiation Therapy for Meningioma: Always Lower with Protons

Photon

Proton

Arvold N et al. IJROBP 2011 MGH
First Prospective Randomized Study on Benign Meningiomas

Benign meningioma
47 subjects
1991-2000

80/20 protons/photons
Median follow up 14.8 years

55.8 Gy(RBE)
63.0 Gy(RBE)

Local recurrence:
10y LR 2%
15y LR 10%

Sanford NN et al. IJROBP 2017 MGH
Recognizing a Long-Term Risk of Radiation: Stroke

• Cumulative stroke risk at 15 years of 20%

• All cases with tumor encasing middle cerebral artery or close branch

Sanford NN et al. IJROBP 2017 MGH
Multiple Meningiomas: Protons Spare Normal Brain Radiation Exposure Which Increases Safety & Opportunity for Re-Treatments
50 year old woman with multiple meningiomas with multiple recurrences

Doing well after 2 courses of protons separate by 10 years
UPDATE ON HIGH GRADE MENINGIOMAS
US Study NRG Oncology/ RTOG 0539: Intermediate Risk Meningiomas

Phase II Trial of Observation for Low-Risk Meningioma and of Radiotherapy for Intermediate and High-Risk Meningioma

- **Group 1 (Low Risk)**: Observation
- **Group 2 (Intermediate Risk)**: 54 Gy in 30 fractions
  - Recurrent benign (Grade 1)
  - Completely resected atypical (Grade 2)
- **Group 3 (High Risk)**: 60 Gy in 30 fractions
  - Any WHO Grade III, GTR or STR
  - Recurrent WHO Grade II, GTR or STR
  - New WHO Grade II, STR

Opened June 19, 2009
- Required Sample Size: 165
  - 55 for each group
- Patients enrolled:
  - Group 1: 65 (closed 9.29.2010)
  - Group 2: 56 (closed 5.12.2011)
- Average Monthly Accrual:
  - Group 1: 4.2
  - Group 2: 2.5
  - Group 3: 1.5

Group 2:
- Recurrent benign (Grade 1)
- Completely resected atypical (Grade 2)

Rogers L et al. JNS 2018
RTOG 0539: Intermediate Risk Meningiomas Do Well at 3 Years after Radiation Therapy

Progression free survival

Overall survival

Rogers L et al. JNS 2018
US Study NRG Oncology/RTOG 0539: High Risk Meningiomas

Phase II Trial of Observation for Low-Risk Meningioma and of Radiotherapy for Intermediate and High-Risk Meningioma

- **Group 1**: Observation
- **Group 2**: 54 Gy in 30 fractions
- **Group 3**: 60 Gy in 30 fractions

**Group 3**:
- Recurrent atypical (Grade 2)
- Incompletely resected atypical (Grade 2)
- Any anaplastic (Grade 3)

Rogers L et al. ASTRO 2017

Opened June 19, 2009

Required Sample Size: 165
55 for each group

Patients enrolled:
- Group 1: 65 (closed 9.29.2010)
- Group 2: 55 (closed 5.12.2011)

Average Monthly Accrual:
- Group 1: 4.2
- Group 2: 2.5
- Group 3: 1.5
NRG Oncology / RTOG-0539, Group 3

Primary Endpoint: 3y PFS

Progression-Free Survival (%)

Patients at Risk  

0 1 2 3 4 5

Years After Registration

Rogers L et al. ASTRO 2017
European Study EORTC 22042: High Grade Meningiomas

- Fully accrued
- First report of Arm 1
  - 56 patients with grade 2 meningiomas with complete resection
  - All received 60 Gy

Weber D et al. Radiother Oncol 2018
EORTC 22042: Grade 2 Meningiomas
Complete Resection + Radiation Do Well

Complete surgical resection + RT 60 Gy
3 year data:
- Recurrence 89%
- Survival 98%
- Severe side effects 14%

Weber D et al. Radiother Oncol 2018
ROAM/EORTC 1308: Atypical Meningioma with Complete Resection: Radiation or Observation

- Atypical meningiomas
- Gross total resection
- From: UK, Ireland, mainland Europe
- 190 target

Randomize

- RT 60 Gy, 30 fx
- Surveillance

Local Recurrence
Quality of Life
Adverse Events

Jenkinson MD et al. Trials 2015
US Study NRG BN003: Atypical Meningioma with Complete Resection: Radiation or Observation

GTR* WHO Grade II
Newly Diagnosed Only

Randomize

Observation

RT (IMRT or Protons)
59.4 Gy (1.8 Gy x 33)

Rogers L et al. ASTRO 2017
Recurrent Atypical Meningioma: VMAT Photons

Volumetric Modulated Arc Radiotherapy: Fast, highly conformal, much better skin sparing
Malignant (Grade 3) Meningioma

Photons

Protons

Photons
Atypical (grade 2) meningiomas

<table>
<thead>
<tr>
<th>Microscopic disease</th>
<th>Visible tumor</th>
</tr>
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<tbody>
<tr>
<td>59.4 Gy(RBE)</td>
<td>66 Gy(RBE)</td>
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</tbody>
</table>
MORE ON MENINGIOMAS: IMAGING, PATHOLOGY & GENETICS
Meningioma Model for Recurrence

Risk factors:
• Surgery: Incomplete resection (non-Simpson grade I)
• MRI: Low ADC

Hwang WL et al. Neuro Onc 2015 MGH
Brain and/or Bone Invasion is Associated with Recurrence

Kim D et al. JNS 2017

![Graph showing cumulative incidence of progression/recurrence over time for different invasion statuses: No invasion, Brain OR Bone, Brain AND Bone. The log-rank test shows a significant difference with P < 0.0001.](image-url)
More Atypia Features is Associated with Recurrence

Atypia features (AF):
- High cell density
- High nuclear:cytoplasmic ratio
- Prominent nucleoli
- Sheeting
- Necrosis
Benign Meningiomas Treated with Radiation Vary in Local Control by Anatomical Location

Solda F et al. Radiother Oncol 2013
68% of AKT1- and 64% of SMO-mutated meningiomas are in the skull base

Clark et al. Science 2013
Abedalthagafi et al. NeuroOncol 2016
Specific Mutations Occur in Meningiomas

Brastianos P et al. Nature Genet 2013
Targeted Therapy Studies for Meningioma

• mTORC1/2 inhibitor (AZD2014/vistusertib)
  – For recurrence after surgery/RT

• Alliance Oncology, 3 arm mutation specific trial, any tumor, upfront or recurrence:
  – SMO inhibitor (vismodegib)
  – FAK inhibitor (GSK2256098)
  – AKT1 inhibitor (Afuresertib)
Immunotherapy Studies for High Grade Meningioma

• PD-1 inhibitor pembrolizumab
  – For any recurrence

• PD-1 inhibitor nivolumab
  – For recurrence after surgery/RT
Meningioma Key Points

- Span a range of indolent to aggressive behavior
- Small to large, round to flat, & variety of locations and symptoms
- Maximal safe surgical resection is the single most important factor for tumor control
- Radiation therapy improves tumor control
  - More effective with less residual disease
  - For high grade tumors, higher doses are associated with higher control
  - Late side effects such as stroke can likely be minimized with reducing collateral dose to major blood vessels
  - Proton therapy reduces normal tissue radiation exposure and may be helpful
Meningioma Key Points

- Imaging & pathological features will increasingly help in guiding treatment
- Molecular genetics will offer further understanding of tumor variations
- Targeted therapies and immunotherapy may provide for new treatments