Learning objectives

- **Review**: Review published data regarding the incidences, dose-volume relationships, and underlying mechanisms of acute and late effects.
- **Explore**: Explore techniques for minimizing acute and late effects.
- **Address**: Address issues of brain reirradiation.
Acute and late effects

- Vision loss
- Hearing loss
- Hair loss
- Brain Injury
- Neurocognitive decline
- Hypopituitarism
- Vascular anomalies
- Secondary malignancy

Agenda

- Anatomy/contouring pearls
- Dose volume data (QUANTEC)
- Effects of the toxicity
- Treatments
- Examples of strategies to decrease late effects
How do we decrease toxicity?

- Patient selection
- Dose
- Medications
- Immobilization
- Accurate imaging
- Planning approaches
- Proton therapy

Anatomy

- Premotor
- Motor
- Productive speech area of Broca
- Acoustic area
- Somatomotor
- Reading comprehension
- Sensory speech area of Wernicke
Anatomy

FRONTAL
TEMPORAL
PARIETAL
OCCIPITAL
CEREBELLUM


Trim CTVs based on natural barriers

Consensus contours with trimming from averaged CTV1

Kruser T et al. J NeuroOnc 2019
Anatomy

Corpus callosum

Anterior commissure

Fornix


Tumors cross the corpus callosum

Consensus CTV_4600 trimming from averaged CTV1

Kruser T et al. J NeuroOnc 2019
Anatomy

- CN I Olfactory tract
- CN II Optic chiasm and infundibulum
- CN III Oculomotor nerve
- CN IV Trochlear nerve
- CN V Trigeminal nerve
- CN VI Abducens nerve
- CN VII and VIII Facial and vestibulocochlear nerves
- CN IX Glossopharyngeal nerve
- CN X Vagus nerve
- CN XI Accessory nerve
- CN XII Hypoglosa nerve

Vision loss

Contouring optic nerves and chiasm

Soft tissue window  Bone window  Brain window

Chiasm is above the sella, right under the brain
Radiation induced optic neuropathy

- Usually presents with painless rapid visual loss
- Vasculature injury may contribute significantly
- Generally 10-20 months after RT
  - Sometimes occurs after multiple years
- No good treatments


QUANTEC: Optic Nerve Tolerance

Risk of optic neuropathy
- Dmax < 55Gy: unusual
- 55-60 Gy: 3-7%
- >60 Gy: 7-20%

Mayo C et al. IJROBP. 2010
Other risk factors

• Tolerance for pituitary tumors may be lower
  • Seen as low as 46 Gy
  • Prior injury to optic nerve?

• Fraction size
  • Parsons et al. reported for 60-70 Gy rates of 50% vs. 11% at 15 years for ≥1.9- vs. <1.9-Gy dose/fraction, respectively.

• Volume component?
• Increasing age
• Reirradiation
  • Unclear what the tolerances are
  • BID may help

QUANTEC: Optic Nerve Tolerance for SRS

Risk of optic neuropathy
• Dmax < 8 Gy: rare
• 8-12 Gy: low
• 12-15 Gy: >10 %

Mayo C et al. IJROBP. 2010
Radiation Induced Retinopathy

- Risk increases substantially after 45 Gy
- Treatments available
  - Laser treatment panretinal photocoagulation and/or focal macular laser
  - Injections of anti-VEGF medications or triamcinolone
- Risk factors besides dose
  - Diabetes, hypertension, simultaneous chemotherapy, pregnancy

Parsons JT et al. IJROBP Vol 30, NO 4, 1994

Dry eye

- 78 patients receiving head and neck radiation therapy
- Rate of severe dry eye syndrome
  - Affecting vision
  - Associated with higher fraction size and higher dose
- 5% risk at 34 Gy
  - 10% risk at 38 Gy
- Difficult to treat

Bandaree N et al. 82(4); 15 March 2012, Pages 1501-1508
Lacrimal gland contouring

Lacrimal gland tolerance

- 78 patients receiving head and neck radiation therapy
- Rate of severe dry eye syndrome
  - Affecting vision
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Bandaree N et al. 82(4); 15 March 2012, Pages 1501-1508
Lens tolerance

- Threshold dose for cataract formation about 0.5 Gy
- Emami 10 Gy -> 5% at 5 years
  - 18 Gy -> 50% at 5 years
- From treatment of eye tumors, 35 CGE in 5 fractions -> 80%

- Cataracts are treatable


Hearing loss

Bhandare N et al UROBP 2010
QUANTEC: Cochlear tolerance

Cochlear tolerance for SRS

- Conflicting data mostly from treatment of vestibular schwannoma
- QUANTEC: keep prescription dose to 12-14 Gy
- Other series suggest mean 4.2 Gy or 5.3 Gy as threshold for increased hearing loss

Bhandare N et al IJROBP 2010
Immobilization devices

- Invasive frames
- Masks
- Bite blocks
- Intrafraction imaging
- Motion tracking

Permanent hair loss

- Grade 1: none
- Grade 2: minimal
- Grade 3: moderate
- Grade 4: severe

Decreasing risk of permanent alopecia

- Scalp DVH for hippocampal avoidance IMRT whole brain RT
  - Compared to opposed laterals
- 6 patients did not have alopecia after 30 Gy in 10 fractions


Brain injury: Challenges

- Definition is varied
  - Radiation Necrosis
  - Adverse Radiation Treatment Effect
  - Symptomatic vs imaging findings
- Diagnosis is difficult
  - Rarely biopsied
  - Difficult to distinguish from disease on imaging
Brain injury: Treatment

- Observation
- Steroids
- Bevacizumab
- Surgery

QUANTEC: Brain

- 5% risk
  - BED ($\alpha/\beta = 3$) 120 Gy
  - 60 Gy
- 10% risk
  - BED ($\alpha/\beta = 3$) 150 Gy
  - 90 Gy
- Unclear for fractions > 2.5 Gy
- Risk factors: chemotherapy, age, diabetes, and spatial factors.

Lawrence YR et al. IJROBP 2010.
QUANTEC: Brain SRS

- V10-12 Gy correlated with radionecrosis for single session
- Multisession (2-5 fractions) stereotactic radiation therapy data very limited

QUANTEC: Brainstem

With ≤ 2 Gy per fraction
- Entire brainstem: 54 Gy
- 1-10 cc: 59 Gy
- Risk much greater at > 64 Gy

SRS
- < 12.5 Gy = < 5% risk
How do we get away with high dose to the brainstem?

- Keep the center much cool
- Anterior brainstem more tolerant than posterior brainstem
- Good MR imaging
  - Or CT myelogram

Reirradiation: Challenges

- Many retrospective series
  - Glioma, Meningioma, Ependymoma, Medulloblastoma
- Follow-up often short given patients have poor prognosis
- Preclinical data suggests 50% recovery in 1-2 years
  - In practice, concern for brain injury still high after years

Reirradiation principles

- Reviews suggest tolerated if cumulative dose < 100 Gy
- Risk of injury decreased with:
  - Smaller volumes
  - More time since initial RT
  - Lower doses
- Utilize highly conformal therapies

Neurocognitive decline

Trail Making Test A

Trail Making Test B
Neurocognitive outcomes

• Low grade glioma
  • 195 LGG pts compared to 100 low grade hematological patients and 195 healthy controls
  • LGG had lower cognitive domains
  • Worse memory if fractions > 2 Gy
• Meningioma
  • 30% have significant neurocognitive sequelae

Klein et al. Lancet 2002
Duchstein S et al. Strahlenther Onkol 2003
Dufour H et al. Neurosurgery 2001

Long-term impact of neurocognitive outcomes

• 65 LGG pts
• Clinical and radiographic stability
• Mean 12 y to 2nd assessment
  • Patients treated with RT had worse neurocognitive functioning
  • Associated with white matter hyperintensities and brain atrophy

Douw et al. Lancet 2009
Importance of hippocampal dose

NRG-CC001: Hippocampal avoidance WBRT

- Cognitive function failure
  - Reliable change index defined decline on one or more tests)
  - 6 months:
    - HA-WBRT+Mem: 59.5%
    - WBRT+Mem: 68.2%
  - Hazard ratio = 0.76 \( p=0.033 \)
  - Separation of the curves starting at 3 months and maintained through the follow-up period
  - Median follow-up for alive patients: 7.90 months

Slide courtesy of Vinai Gondi
Presented at ASTRO and SNO
Hippocampal contouring

- [https://www.rtog.org/CoreLab/ContouringAtlases/HippocampalSparing.aspx](https://www.rtog.org/CoreLab/ContouringAtlases/HippocampalSparing.aspx)
- 3D-SPGR MRI: 1.25 mm slices
- Treatment-planning CT: 12.5-1.5 mm slices
- Subgranular zone targeted in protocol
- T1 hypointense signal medial to the temporal horn
Hippocampal avoidance WBRT with VMAT

Hippocampal sparing with proton therapy
RTOG 0614: WBRT + memantine vs placebo

- 508 patients with brain metastases
  - WBRT (37.5 Gy) + placebo
  - WBRT (37.5 Gy) + memantine x 6 months
- Primary endpoint: HVLT-R DR at 6 mo better with memantine
  - p = 0.059
- Overall survival: 7 vs 8 months (p=0.28)

Cognitive function failure = Failure in any of the tests

Brown Neuro-Onc 15, 2013

Hypopituitarism

Proton therapy can avoid dose to the pituitary

- 222 patients
  - <26 years old
- Median follow up 4.4 years
- Dependent on pituitary and hypothalamus dose

Vatner RE et al. JCO 2018
Treatment of hypopituitarism

- Routine surveillance to detect
- Replacement with thyroid, cortisol, growth hormone, testosterone.

Vascular toxicities

- Cerebrovascular accident
  - On trial, 9 meningioma pts (20%) had CVA
    - 7 possibly attributable to RT
    - Median time to CVA was 5.6 years (range, 1.4-14.0 years)
- Radiation induced cavernomas
- Bleeding risk
- Moyamoya

Secondary malignancy

- Data on pituitary adenomas treated with EBRT
  - Minniti et al: 426 pts with 5749 person year follow up
    - 2.4% at 20 years (half meningioma)
  - Breen et al: 120 pts with median 9 year follow up
    - 2.7% at 10 and 30 years

Risk of Radiation-Induced Tumors

- 1837 patients at Mayo, 11264 patient years
  - 1990-2009
- Risk of radiation-induced tumor after SRS
  - 0.0% at 15 y
- Risk of malignant transformation
  - 2.2% meningiomas
  - 0.3% vestibular schwannoma
  - 2.4% at 15 y, median 4.9 years
  - None for pituitary adenomas or glomus tumors
Conclusion: Acute and late effects

- Vision loss
- Hearing loss
- Hair loss
- Brain Injury
- Neurocognitive decline
- Hypopituitarism
- Vascular anomalies
- Secondary malignancy

Thank you