See NCTN Trial Portfolios by Disease Site: [Brain].

Brain Mets | Palliative | Oligo | Immuno

StatPearls: Anorexia and Cachexia *Last update: 8/3/2019.*
StatPearls: Bone Metastasis *Last update: 11/8/2019.*
StatPearls: Brain Metastasis *Last update: 3/13/2019.*
StatPearls: Heterotopic Ossification *Last update: 6/4/2019.*
StatPearls: Radiation Therapy for Heterotopic Ossification Prophylaxis *Last update: 6/3/2019.*
StatPearls: Spinal Metastasis *Last update: 12/3/2019.*

- **GCG- Benign Disease Patterns of Care** [Kriz ARO '18]
  - Questionnaire mailed to all RT institutions in Germany, Austria, and Switzerland in 2015
  - Of 54k patients receiving RT in 2014, 37k (68%) had benign disease!
  - Nearly half treated for degenerative disease, 40% treated for OA, 4% treated for hyperproliferative disorders, 7% treated for functional disorders, 2% received SRS to the CNS.
  - It is estimated that 1/3 of patients in Germany are treated for benign disease.

Speaking with Patients

See the [Palliative Care] section for more.

- Don't initiate non-curative RT without defining the goals of treatment with the patient and considering palliative care referral [ASTRO Choose Wisely #8]
- Try to incorporate the Best Case/Worst Case scenario when counseling patients [video here].
- Earlier conversations about goals of care reduce anxiety and depression [Bernacki JAMA Int Med '19]
- **Serious illness conversation guide** [Here]: SPIKES [Baile Oncologist '00].
  - SETTING UP the interview.
  - Assess understanding/PERCEPTION.
  - Ask permission/Obtain INVITATION.
  - Three headlines to choose from to impart KNOWLEDGE: Time in ranges, Uncertainty (gentlest), function. *For Rad Onc, consider "We hope you have improvement with XRT, but worry that you may have persistent symptoms." Pairing hoping/worrying works well together.*
  - Respond with EMOTION: Explore hopes, worries, strengths, trade offs.
  - STRATEGIZE and SUMMARIZE and plan.
- Be aware of potential detrimental responses
  - The Emotional Hijacker/Terminator: "Don't cry…", "Things are going to be okay"
  - The Vulcan (only using cognitive skills): "It's not your fault"
  - The Strategist (only wanting to have an agenda): "Let's talk next steps"
- Ask - tell - ask. "Tell me more". Respond to emotions with empathy.
- ADAPT: A framework for discussing prognosis. *Taken from ASTRO Refresher 2020: Kavita V. Dharmarajan MD MSc*
  - Ask (what the patient knows/wants to know): "What have other doctors told you?"
  - Discover (what information about the future is helpful): "What have you been thinking about? Statistics? Average time? Living until a certain date?"
  - Anticipate (ambivalence): "Can be scary, may be helpful to discuss why we review prognosis"
  - Provide (information): Best/worst/average scenario, ranges.
  - Track (emotion): "I can't imagine how hard this must be". "I wish I had better news…"
- Responding to emotions with empathy: NURSES. *Taken from ASTRO Refresher 2020: Kavita V. Dharmarajan MD MSc*
  - Name: "You seem worried"
  - Understand: "I can't imagine how difficult it must be to face this uncertainty"
  - Respect: "I'm so impressed at how dedicated you've been to your mother"
  - Support: "My team and I will be here for you to get you through this"
  - Explore: "Tell me more about what you mean when you say…"
  - Silence.
- Addressing goals of care: REMAP. *Taken from ASTRO Refresher 2020: Kavita V. Dharmarajan MD MSc*
  - Reframe: "We're in a different place now."
  - Emotion: Expect it, and respond with empathy: NURSE.
  - Map goals, values, preferences: "Given this news, what's most important to you?"
  - Align with the patient: "It sounds like x, y, and z are most important. Is that right?"
  - Plan: "From what you've told me about x, y, and z being most important to you, I recommend"
- **When nothing is the right thing to say** [Morgan BMJ '20]: The most difficult moments in medicine are those when there are no solutions. When faced with a moment where we cannot fix something, our role as doctors is to simply "sit in the rubble" with our patients. "As someone who has been taught, mentored, and motivated to build answers out of rubble, sitting in it can be uncomfortable. But sometimes it is more important than making structures that will simply fall to the ground." Beautifully said.
- **'An Emotional Slap in the Face': The Language of Cancer** [Dizon and Prowell Medscape '19]:
  TBL [QS]: Oncologists are particularly notorious at forgetting that even our most educated patients don't speak doctor. Here is a painfully relatable discussion on the many oncologic faux paus we are all guilty of making, and it's worth a read / listen if only to avoid reducing your next patient to tears by walking in the room to alarmingly pronounce: "Your scans are negative!"
- **For patients who present with cord compression or metastatic disease**:
  - Start with the Best Case/Worst Case scenario when counseling patients [video here].
  - Hopefully Palliative Care has been introduced to the patient [video here].
- **Radiation Oncologists' Role in End-Of-Life Care: A Perspective From Medical Oncologists** [QS] [Gross PRO '19]:
  - Rad oncs may not counsel their patients in regard to palliative care due to a fear of losing referrals.
  - See Table 5 for interesting quotes "I think [rad oncs] should be scared of the medical oncologist"

Palliative

ASCO/SNO Guideline: Anticonvulsant Ppx and Steroid Use in Adults w Metastatic Brain Tumors *March 18, 2019*
- ➢ Prophylactic antiepileptic drugs are not recommended for routine use.
- ➢ Dexamethasone recommended for temporary sx relief in patients with neuro symptoms.

ASCO Guideline: Recommendations on Dz Mgmt for Pts w Advanced HER2+ BrCa and Brain Mets *June 25, 2018*
- ➢ Clinicians should have a low threshold for MRI of the brain due to high incidence of brain mets for HER2+.

ASCO Guideline: Integration of Palliative Care Into Standard Oncology Care *October 31, 2016*

See the [Speaking with Patients] section above.
ASCO Educational Book: Palliative Care Skills and New Resources for Oncology Practices [QS] [Back EduBook '20]
Center to Advance Palliative care: www.capc.org

- Palliative Care Is a Bridge: Great video to introduce your patients to Palliative Care [video here].
- Around 1/3 of pts treated with RT are palliative intent.
- State of palliative care services at US cancer centers: An updated national survey [Hui Cancer '20]: 2009 vs. 2018.
  - Among NCI-designated cancer centers: Outpatient palliative care 59→ 95% with no significant changes in inpatient consult teams ~90%, palliative care units ~26→ 40% (p=.17) or institution-operated hospices ~31→ 18% (p=.14).
  - Among non-NCI: There was no significant changes in outpatient palliative care ~22→ 40% (p=0.07), inpatient consult teams ~60%, palliative care units ~20% or institution-operated hospices ~42→ 23% (p=0.05).
  - The median interval from outpatient palliative care referral to death increased significantly, particularly for NCI-designated cancer centers (90 vs. 180 days).
- **Temel** [NEJM '10]: **Standard of care ± palliative care**.
  There is a survival benefit with early palliative care!
  - 151 newly dx metastatic NSCLC pts.
  - Better QoL, less depression, longer MS.
  - Aggressive end of life: 54→ 33%, documented resuscitation: 53→ 28%.
  - MS 8.9→ 11.6 mo.
- **Cost reductions with early palliative care consult** [May JCO '15]:
  - Savings attributable to reduced level of service and reduced intensity of hospital stay.
  - Consult within 2 days with a reduced cost of 24%.
  - Consult within 6 days with a reduced cost of 14%.
- **ENABLE III** [Bakitas JCO '15]: **Early vs. 3 mo delayed palliative care**.
  Equivalent patient reported outcomes and resource utilization, but 1y OS improved!
  - 207 pts with oncologist determined prognosis of 6-14 months.
  - 1y OS 48→ 63% with early palliative care.
- **Patient Reported Outcomes** system may prolong survival by 5 mo in patients receiving palliative chemo [Basch JAMA '17]
  - Consider systems that can alert nurses when patients are having difficulties.
- **VA Population Study: Advanced lung cancer** [Sullivan JAMA Onc '19]: **Early Palliative Care**.
  There is an association with early palliative care and improved overall survival.
  TBL [QS]: Early integrated palliative care should still be the go-to for patients with terminal metastatic disease.
  - Demonstrates facilities have variable usage of early palliative care, ranging from 5-95%.

Prognostication

KPS remains the best prognosticator.
- KPS and ECOG. KPS is the most accurate predictor of survival [Benson IJROBP '20].
- **Validation of the Surprise Question in Gyn Onc** [Rauh Gyn Onc '20]:
  "Would you be surprised if this patient died within the next year?"
  The surprise question is a simple, one question tool that effectively identifies gyn onc patients increased risk of 12 month mortality, and could be used to identify patients for early referral to palliative care and initiation of advanced care planning.
  - 32 providers provided 942 surprise question assessments for 358 patients. 57% had ovarian cancer and 54% had recurrent disease. 24% of patients died within a year.
  - Overall RR of 12 month mortality for "No" was 3.8.
  - Among statistically significant predictors of 12 mo mortality (including recurrent disease and >2 prior lines of chemo), the surprise question had the highest RR.
- **Chow** ['02, '08]: **Prognostic model for survival in metastatic cancer patients attending outpatient palliative RT clinic**.
  - Earlier (6 factors): primary cancer site, site(s) of mets, KPS, fatigue, appetite, and shortness of breath from ESAS.

    - Later looked at a more simplified model, using three instead of six factors (does not account for symptoms).
        - Primary cancer site (breast vs. non-breast), site(s) of metastasis (bone only vs. other) and KPS < 70.
        - From 0-3 points, MS decreases from ~15 mo to ~2.5 mo.
- **NEAT Predictive model for Survival** [Zucker CRT '18]:
  Helps differentiate < 2 mo vs. > 2 y life expectancy.
    - 280 pts. 2012-2015.
        - **N**umber of active tumors: > 5 (1).
        - **E**COG: 2 (1), 3+ (2).
        - **A**lbumin: 2.4-3.3 (0.5), < 2.4 (1).
        - **T**umor primary site: Non-breast/kidney/prostate (1).
    - MS for VLR (0-1) / LR (1.5-2) / IR (2.5-3.5) / HR (4-5) of 25→ 15→ 4→ 1.2 mo.
- **BMET Decision Support Platform** [Alcorn IJROBP '19]
    - Bone Mets Ensemble Trees for Survival.
    - Uses 27 covariates and random survival forests to predict time from RT consultation to death.
- **TEACHH prognostic groups for palliative RT** [Krishnan Cancer '15]:
  Helps differentiate < 2 mo vs. >1 y life expectancy.
    - 862 pts. 2008-2011. On MVA, 6 things affect life expectancy:
        - **T**umor primary site: Lung and other (1) vs. breast and prostate (0).
        - **E**COG: ≥ 2 (1).
        - **A**ge: > 60y (1).
        - **C**hemotherapy: ≥ 2 palliative courses (1).
        - **H**epatic mets: (1).
        - **H**ospitalization: 1+ within the past 3 mo (1).
    - MS for Group A (0-1) / Group B (2-4) / Group C (5-6) of 19.9→ 5 → 1.7 mo.
- **Brain mets**:
    - [DS-GPA]: **www.brainmetGPA.com**
- **Cord compression:**
    - **Rades score** [Cancer '07, '10]: 6 month survival ranges from 1 in 8 to 8 in 10!
      This nomogram helps guide treatment options, including supportive care, surgery, and RT.
        - There is a range of survival in cord compression.
        - There is a benefit for laminectomy and stabilization followed by RT for all groups.
        - Six factors: Tumor type, dx interval, other bone/visceral met, ambulatory status, duration of motor deficit.
        - Scores range from 20-45 with 31 and 36 as divider between groups.
        - 6mo OS 14→ 56→ 80%. MS 2→ 6→ 24 mo.
    - **Prognosis for spine met patients** [Tokuhashi WJO 2014]:
        - Revised tokuhashi score (2005)
        - Tomita score (2001)
        - Modified Baur score: No visceral mets, no lung cancer, primary tumor (breast, kidney, lymphoma, MM), solitary skeletal mets with MS 28 mo. MS for 0-1 / 2 / 3-4 points of 4.8→ 18.2→ 28.4 mo.
        - Predict survival using [Rades] cord compression nomogram.

Palliation in Head and Neck

See [Reirradiation] in the H&N section.
ARRO: [Palliative advanced non-melanoma skin cancer].

- **Palliative radiation therapy for H&N cancer** [Grewal IJROBP '19]
  Patients with 4-12 mo MS and with few prior therapies desiring durable palliation and comfort and avoiding severe toxicity from treatment should consider 30/5. For MS < 4 mo, QUAD Shot or 20/5 appears reasonable with minimized risk of new toxicity. See Figure 1 for the decision tree.
    - Best supportive care is associated with a MS between 3-5 months, shorter if prior therapy has been received.
    - The [EXTREME] regimen is associated with a MS of 10 mo, while Pembro adds 4 mo to that [KEYNOTE 048].
    - Re-irradiation is typically 60 Gy for PORT, while 66 Gy for intact. Traditionally, G4 late effects approached 25%, while modern numbers suggest < 5% chance of late side effects. Tumors less than 25 cc may be considered for SBRT to 40/5, so long as no organ dysfunction. See the [Re-irradiation] section for more.
    - The QUAD shot regimen is based off of [pelvic data], but is below the threshold which causes mucositis. QUAD shot is 3.7 Gy BID x 2 days (14.8 Gy) repeated 2-4 weeks later up to a total dose of 44.4 Gy. Around 80% of patients treated in this manner for H&N cancer will have both response and symptomatic improvement. MS 5 mo.

Concurrent Carboplatin AUC 2 or cetuximab 250 prior to each Shot appears safe. There is only 9% G3 toxicity associated with this regimen.

- **Largest QUAD shot H&N report** [Fan Oral Onc '20]: Retro. **3.7 Gy BID over 2 consecutive days q1m x1-4c**. Palliative QS is an effective last-line local therapy with minimal toxicity in patients with previously irradiated H&N cancer. Administration of 3-4 QS cycles predicts palliative response, improved PFS, and improved OS.
  - 166 pts. 2011-2018. Prior H&N RT. Median age 66y. MFU 6 mo overall, 10 mo for living patients.
  - More than 1 recurrence in 75%, and 43% of patients had end organ dysfunction. 60% KPS ≤ 70
  - 25% completed 1 / 2 / 3 / 4c. Concurrent chemotherapy in 50%.
  - Predictors of palliative response were > 2y interval from prior RT and 3-4 QS cycles.
  - Palliative response for 1-2 / 3-4c of 45→ 83%.
  - Symptom relief for 1-2 / 3-4c of 46→ 73%.
  - MLPFS 5 mo, 1y LPFS 18%.
  - MS 6 mo, 1y OS 25%.
  - On MVA, proton RT, KPS >70, presence of palliative response and 3-4 QS cycles were associated with improved LPFS and improved OS.
  - Overall G3 toxicity 11%. No G4-5 toxicities observed.
- 30/5 appears safe and effective [Hypo Trial Porceddu Rad Onc '07].
- 24/3 q1w appears effective, but toxicities were not reported.
- 20/5 has a lower ORR than 25/5.
- 30/10 appears safe. Commonly used for dysphagia.
- 40/10 split-course or biw is associated with 20% G3 mucositis.
- 37.5/15 is associated with 30% G3 toxicity.
- 40-50 Gy in 16 fractions is associated with > 50% G3 mucositis.

	Palliative reirradiation EQD2	Palliative de novo RT EQD2
Spinal Cord	60 Gy	50 Gy
Brain stem	60 Gy	54 Gy
Carotid artery	ALARA	ALARA
Mandible	ALARA	ALARA
Optic nerve	60 Gy	54 Gy
Optic chiasm	60 Gy	54 Gy
Constrictors	Mean dose ALARA	Mean dose < 50 Gy
Brachial plexus	70 Gy	60 Gy
*There may be situations when it is appropriate to exceed the cumulative constraint, such as recurrent disease involving the plexus and prior full dose had been received. Clinical discussion between provider and patient is recommended, with clinical decision making depending on the results of discussion.		

Palliation of Dysphagia

- Consider chemo alone with diet changes as indicated.
- Brachytherapy has more durable dysphagia relief, fewer complications vs. stenting [Homs Lancet '04]
  - Stents have less durable response and can migrate, cause pain, reflux etc.
- RT (mainly 20/5) decreased dysphagia in 75%, duration of response ~5 mo [Murray PRO '12].
- **AIRO: Palliative BT in esophageal cancer** [Lancellotta BT '19]: Meta. **EBRT/APC/Stent/Laser vs. BT**.
  External beam = standard of care in the USA. The Italians may be on to something with BT, though.
  - 905 pts from 7 randomized studies evaluated.
  - MS 6 mo. Duration of dysphagia relief 3 mo.
  - G3-4 fistula 8%, G3-4 stenosis 12%.
- **Palliation of dysphagia** [Vermeulen PRO '19]: Retro. **20/5 vs. (30/10 or 12/1 BT**).
  High dose RT was associated with better long term relief of dysphagia, suggesting high dose RT to be considered for patients with longer life expectancy.
  - 144 pts, matched. Inoperable or metastasized esophageal cancer.
  - Improvement in dysphagia at 6w of ~50→ 66% (p=0.07).
  - Persistent/recurrent dysphagia in 64→ 42%.

- No differences in severe adverse effects.
- Median survival 88→ 177 days.

Palliation of the Lung

- RT takes a median of 7 days.
- Dyspnea and cough response ~50% of the time.
- Hemoptysis is most likely to improve, ranging from 70-92% of the time.
- Accepted doses include: 10/1, 17/2 (1 week apart), 20/5, 30/10, 37.5/15.
- Around 2/3 of patients will complete 5 fraction regimens, while 1/3 for 10 fraction regimens [Fraser Lung Ca '19]
- For ICU patients, ~30% will be extubated and ~25% will be discharged home [Louie JTO '13]
- **ASTRO Guideline: Palliative thoracic RT in lung cancer** [Rodrigues PRO '11]:
  - 30/10 is associated with modest improvements in OS and total symptom score at the cost of increased esophagitis.
  - Consider 20/5, 17/2 q1w, or 10/1 for patients requesting shorter treatment courses or with poor PS.
    - For 17/2, keep spinal cord dose < 11 Gy.
    - Slightly prolonged durability and survival with 30/10 vs 16/2 [Kramer JCO '05].
  - There is no role for routine endobronchial brachytherapy in routine initial palliative treatment, but is reasonable for obstructive symptomatology including lung collapse, or for hemoptysis after EBRT failure.
- **ASTRO Guideline: Palliative thoracic RT in lung cancer update** [Moeller PRO '18]
  - Patients with stage III NSCLC deemed unsuitable for curative therapy but who are candidates for chemotherapy, have an ECOG PS 0-2 and have a life expectancy of at least 3 mos, administration of a platinum-containing chemotherapy doublet concurrently with moderately hypofractionated palliative thoracic radiation therapy over treatment with either modality alone.
  - In patients with stage IV NSCLC, routine use of concurrent thoracic CCRT is not recommended.
  - Poland [Nawrocki JCO '10] Phase II. **30/10 ± CDDP/Vinorelbine** x3c. RT given concurrently with cycle 3.
    Longer courses of RT appear superior to 10/1 or 16/2. Chemotherapy appears helpful.
    - 99 patients. "Incurable" stage III NSCLC (FEV1 ≤ 40% predicted or GTV > 8 cm). ECOG 0-2.
      - CDDP 80 d1, Vinorelbine 25 d1, 8. RT given concurrently with cycle 3.
    - MS 9→ 13 mo.
    - 1y OS 25→ 57%, 2y OS 6→ 24%.
    - MPFS 5→ 7 mo.
    - Response rate ~27→ 53%.
  - Norweigan [Strøm BJC '13]: **Carboplatin/Vinorelbine** x4c ± **42/15**. RT given concurrently with cycle 2.
    Longer courses of RT appear superior to 10/1 or 16/2. Chemotherapy appears helpful.
    - 191 pts. Incurable stage III NSCLC (GTV ≥ 8 cm, ECOG ≥ 2, or 10% weight loss in 6 mo).
      - Carboplatin AUC 5 d1, Vinorelbine 60 d1,8.
    - MS 9.7→ 12.6 mo.
    - 1y OS 34→ 53%.
    - HRQoL declined during treatment with CCRT, but then evened out over time.
- **IAEA** [Jeremic ASTRO '17, Rathod ASTRO '17]: **± 10/1 or 16/2 q1w→ Plt chemo x3**.
  Short course thoracic RT prior to chemo improves QoL. Effect is sustained over time.
  No impact on palliative RT in outcomes or toxicity.
  - 185 pts. Advanced NSCLC IIIB-IV.
  - RT improved global HRQoL, role and social functioning, pain, dyspnea, N/V, and lung-specific symptoms.
  - QoL improved at 2 weeks and was maintained.
  - ITT MS ~6 mo.
  - 1y OS 19→ 33%. 2y OS ~6→ 16% (p=0.19).
  - 1y LRPFS 12→ 20%, 2y LRPFS ~3→ 9% (p=0.52).

Palliation of the Liver

- **RTOG Palliation of Liver Mets** [Borgelt IJROBP '81]: **WLI 30/15, 26.5/15, 20/10, 21/7**.
  Around a quart of patients did not finish RT. All but one patient on 21/7 finished. Are short courses more attractive?
  - 109 pts. RT AP/PA WLI with 2 cm to field edge.
  - MS 11w. 22% died prior to 1 mo. 20% lived > 6 mo.
  - Pain response 55%.
  - Liver mass response in 50%.
  - N/V developed or exacerbated in 16%.
- **RTOG Palliation of Liver Mets** [Leibel IJROBP '87]: **WLI 21/7 ± misonidazole**.

    - 214 pts. Misonidazole did not improve any study parameter.
    - MS ~4.2 mo.
    - Any pain response ~80%. *This is way higher than other studies.*
    - Complete pain response ~50%.
    - Duration of response ~2.5 mo.
    - RINV ~22%.
- **Short-fraction RT for Palliation of Liver Mets** [Bydder Australas Rad '03]: **WLI 10/2**.
  All patients completed planned radiotherapy.
    - 28 pts. RT AP/PA WLI with 2 cm to field edge.
    - MS 2.5 mo.
    - Pain response 65% by two weeks.
    - Distension response 60% by two weeks.
    - 1 pt G3 nausea, 1 pt G3 diarrhea.
- **Palliation of Liver Mets and HCC** [Soliman JCO '13]: Phase II. **WLI 8/1**.
    - 41 pts. 8/1. RT AP/PA or opposed obliques. CTV = whole/near-whole liver. PTV ≥ 1 cm.
    - 3 mo OS 63%, 6 mo OS 26%.
    - 1 mo pain response 55%.
    - 1 mo improvement in QoL in 25%.
    - G3 nausea in 2.4% (n=1).
- **CCTG HE.1** [NCT02511522]: **Best supportive care ± 8/1**.
    - HCC or liver mets assessed for pain or discomfort at baseline, 30d and 90d.
    - Crossover allowed at 30d.
- Clinical approach:
    - Confirm liver as source of pain. Correlate symptoms with imaging.
    - Initial analgesics: Opioids ± 2-4 mg dexamethasone PO QD.
    - Consider RT if persistent pain despite optimal management and expected survival ≥ 1 mo.
    - Latency to response appears to be 2-4 weeks.
- Treatment Planning
    - NPO 2h prior.
    - Supine, arms up on the lung board.
    - No abdominal compression.
    - No contrast unless necessary to define partial liver volume.
    - Free-breathing or 4DCT.
    - GTV: not needed if whole/near whole liver disease.
    - CTV: Areas of symptomatic disease. Includes extrahepatic extension.
    - PTV: 1-1.5 cm if 4D, or 1.5-2 cm CC with 1-1.5 cm radial without motion estimation.
    - 95% of PTV receives 8 Gy (7 Gy).
    - Max point dose to stomach / duo / small bowel / spinal canal of 9 Gy.
    - Mean dose to bilateral kidneys < 4.5 Gy.
    - If mean dose to ipsi kidney > 6 Gy, mean dose to contra < 3 Gy.
    - Supportive care: Zofran 2h prior to RT, BID on day of RT, BID day 2. Dex 4 mg po 2h prior, again in the morning next 4d. PPI (takes 2w to work) or H2 blocker (more immediate) for RT and steroid-induced gastritis. Sucralfate prn for odynophagia. Pain flares occasional. Cramping and diarrhea are usually limited to a few days. Fatigue is common and can last weeks.

SVC Syndrome

LearnOncology.ca: SVC Syndrome [YouTube]

- Most frequently seen in lung cancer: 50% NSCLC, 25% SCLC, 10% NHL.
- Presents with cough, dyspnea, dysphagia, swelling or discoloration of neck, face, upper extremities.
- Pleural effusions in 60% of cases due to backflow.
- Accepted doses include: 30/10, 20/5, 37.5/15.
- Expect relief in 3-14 days, depending on histology.

Gyn/Abdominal/GI bleeding

- Vaginal packing, cauterization, IR embolization, TAH.
- Accepted doses include: 30/10, 20/5, 37.5/15 or "Quad Shot" 3.7 Gy BID x 2 days (14.8 Gy) repeated 2-4 weeks later up to total dose of 44.4 Gy.
- Bleeding typically stops 12-48h after initiating RT.

- **RTOG 8502** [Spanos IJROBP '89, '93, '94]: Phase II: 3.7 Gy BID x2d q2-4w up to 3x (44.4 Gy). Phase III: 2w vs. 4w interval.
  The "Quad Shot" regimen leads to favorable outcomes and low toxicity.
  - 152 pts. Advanced pelvic malignancies.
  - Patients completing 3 courses: CR 14%, PR 31%, no change 40%, progression 7%.
  - Rest interval of 2w led to more compliance over 4w. No benefit in LC or toxicity.
  - Estimated 1.5y late toxicity 7% (versus 49% with 30/10 historical control).

Brain Metastases

ASCO/SNO Guideline: Anticonvulsant Ppx and Steroid Use in Adults w Metastatic Brain Tumors *March 18, 2019*

- ➢ Prophylactic antiepileptic drugs are not recommended for routine use.
- ➢ Dexamethasone recommended for temporary sx relief in pts w neuro symptoms.
  - ○ 4-8 mg/d for mild sx.
  - ○ 16 mg/d for severe sx.
- ➢ Insufficient evidence to comment on the use of steroids for asymptomatic pts without mass effect.

Current multidisciplinary management of brain metastases [Moravan Cancer '20]

See the [when to utilize single vs. multi-fraction SRS] and [evaluating radiation necrosis] sections.

- ➢ Brain metastases are the most common adult intracranial malignancy.
- ➢ ~200-300k brain metastasis pts per year, occurring in 20-40% of cancer pts.
- ➢ Lung (50%), breast (15%), RCC (10%), melanoma (9%) and colorectal cancers make up the majority of brain metastases.
- ➢ Historically, the OS of untreated brain metastasis is around 1-2 months and WBRT extended this to 4-6 mo. Modern systemic therapies, supportive care, and early palliative intervention has extended this to ~7-8 months.
- ➢ Although [prognostication] is important, performance status tends to drive clinical management.
- ➢ Dexamethasone 10 mg loading→ 4-6 mg q6h. Lower doses (4-8 mg po qday) can achieve symptom control.
- ➢ Baseline steroids appear to be a [relative contraindication] to immune checkpoint inhibition (ICI), although patients on steroids at baseline for non-cancer reasons still [appear to benefit] from ICI. According to Nivolumab data for melanoma, overall response rate [may not be affected] by the use of steroids.
- ➢ Patients with seizures should receive anticonvulsants.
- ➢ Surgical resection can provide rapid symptom relief secondary to mass effect and/or CSF obstruction, provides tissue for pathology, and is appropriate for large symptomatic (e.g., ≥ 3 cm) tumors.
- ➢ SRS appears to have superior local control versus surgery for lesions < 3.5 cm [EORTC 22952].
- ➢ The addition of WBRT to SRS appears to improve OS for patients with a single brain metastasis [RTOG 95-08], but does not appear to decrease distant brain metastasis in patients under the age of 50 [Sahgal Meta].
- ➢ One year local failure after surgery alone is ~60%. This risk is cut in half with postoperative SRS [MDACC].
- ➢ Surprisingly, local control with post-operative WBRT is superior to postoperative SRS [N107C]. Therefore, postoperative [guidelines] recommend 2-3 mm margins on the surgical cavity, consideration of multi-fraction SRS for surgical beds > 3 cm, and increased margins for lesions with dural contact preoperatively. Or... should we be doing [pre-op]?
- ➢ New targeted therapies with better systemic and [CNS activity]: Osimertinib (EGFR exon 20), Alectinib (ALK), Tucatinib (HER2+). SRS in combination with these agents may eliminate the need for WBRT and improve cognitive outcomes.
  - ○ Generally speaking, omission of upfront local therapy for melanoma, NSCLC, and breast cancer brain mets are experimental, and optimal sequencing remains unknown. Ensure lesions are ≤ 1-1.5 cm, asymptomatic, and do not require steroids before agreeing with close observation. Median progression free survival is commonly on the order of 6 months, so q2-3m MRI is reasonable. Why delay therapy if treatment may be inevitable?
- ➢ An analysis recently suggested 30/10 is superior to 37.5/15 WBRT [N107C].
- ➢ SRS is an established way to treat previously irradiated brains [RTOG 90-05].
- ➢ SRS in addition to WBRT may be of benefit for NSCLC patients with good prognosis or lesions > 2 cm [RTOG 95-08].
- ➢ WBRT in addition to SRS demonstrates a higher incidence of neurocognitive deterioration at 3 and 12 mo [Chang, N0574]
- ➢ Most studies omitting WBRT from SRS only included patients with limited size (< 4 cm) and number (1-4) brain mets, so the benefit of omitting WBRT in patients with >4 BMs is unclear.
- ➢ It has been suggested that SRS may be "reasonable" for up to 10 brain metastases [JLGK0901], and [repeat salvage SRS] may be reasonable especially if brain metastasis velocity is low (e.g. ≤ 3 brain mets per year). There is suggestion of repeat salvage SRS having a lower rate of [neurological death] than WBRT.
- ➢ [NCCTG CE.7] is investigating SRS vs. HA-WBRT for patients with 5-15 brain metastasis, with dual primary endpoints of OS and neurocognitive PFS.
- ➢ Consider [hypofractionated RT] for lesions >2-3 cm or when single fraction OARs cannot be respected.
- ➢ [Single isocenter multitarget SRS] (e.g. ≥ 5 lesions) is also reasonable to avoid long treatment times for sequential treatment. Be sure to use algorithm-based SRS for this, which is now [arguably equivalent] to gamma knife SRS.
- ➢ Laser interstitial thermal therapy (LITT) is recommended for radionecrosis or recurrent BMs for lesions up to 3-4 cm. Residual disease is left along ventricles or near critical structures. Consider 25/5 adjuvantly if residual present [Ali NSF '16].
- ➢ The addition of memantine to WBRT appears to significantly increase time to neurocognitive decline [RTOG 06-14].
- ➢ The use of HA-WBRT appears to significantly decrease neurocognitive decline [NRG CC001].
- ➢ See [Tips on how to keep asymptomatic radionecrosis] rates less than 10%.

Current approaches to the management of brain metastases [Suh NRCO '20]

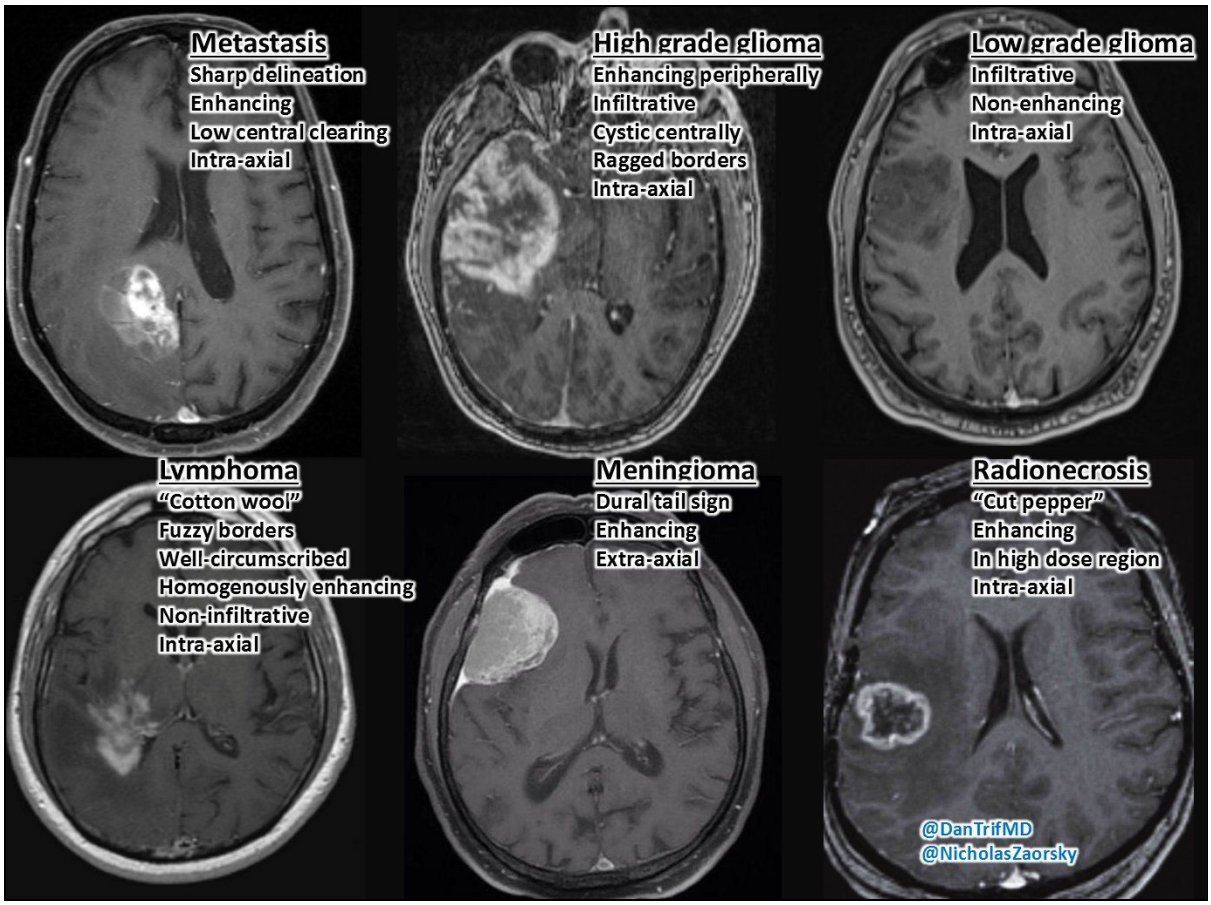
- Another great paper summarizing the best evidence to date.
- See Table 4 for ongoing trials involving ICI in patients with brain metastases.
- Chemical exchange saturation transfer (CEST) has shown promise in differentiating radiation necrosis from progression, and is becoming more widely available [Mehrabian Clin Cancer Res '17].

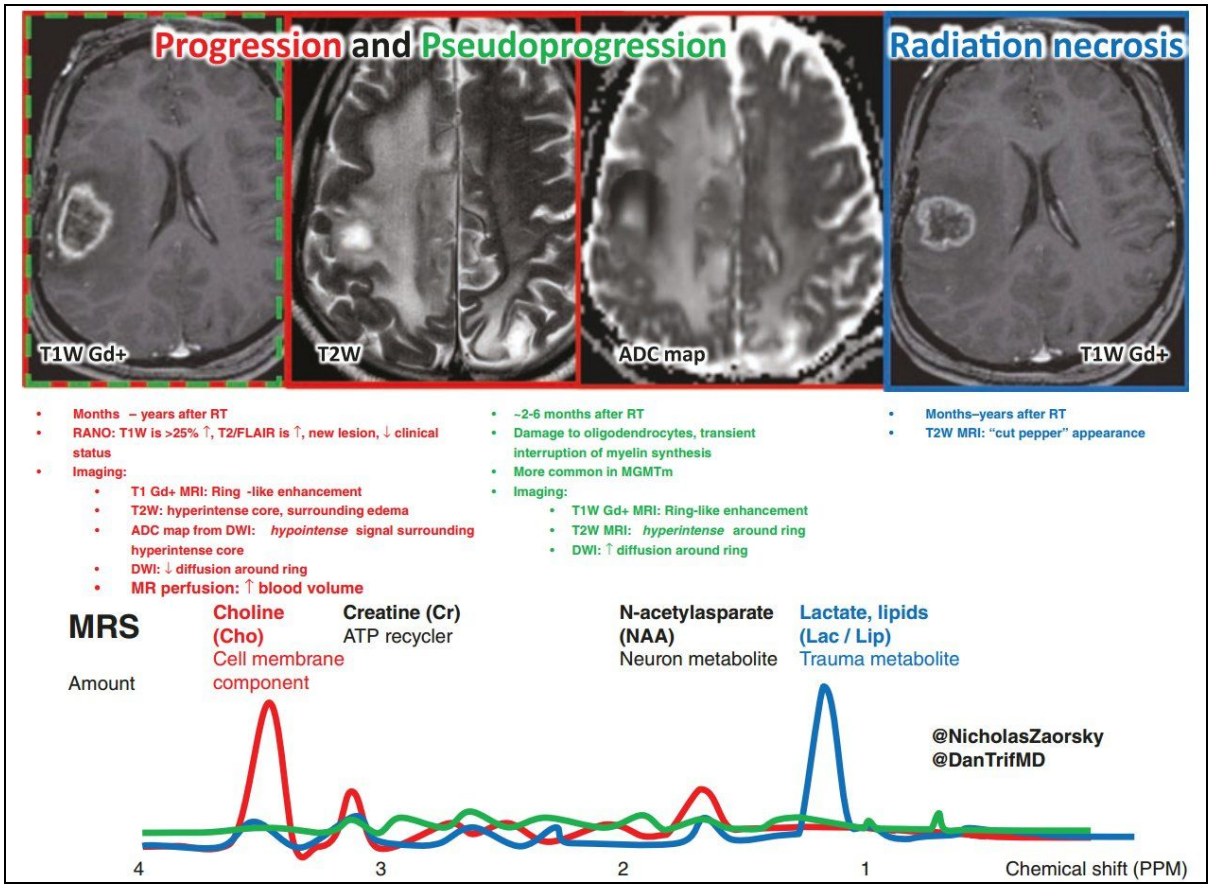
Comparison of SRS modalities [Vergalasova Fronteirs Oncology '19]: Advantages change with advancing technology. There is little difference with GammaKnife versus extensive non-coplanar VMAT. Radionecrosis [appears to be more prominent] with GK-based SRS than LINAC-based SRS.

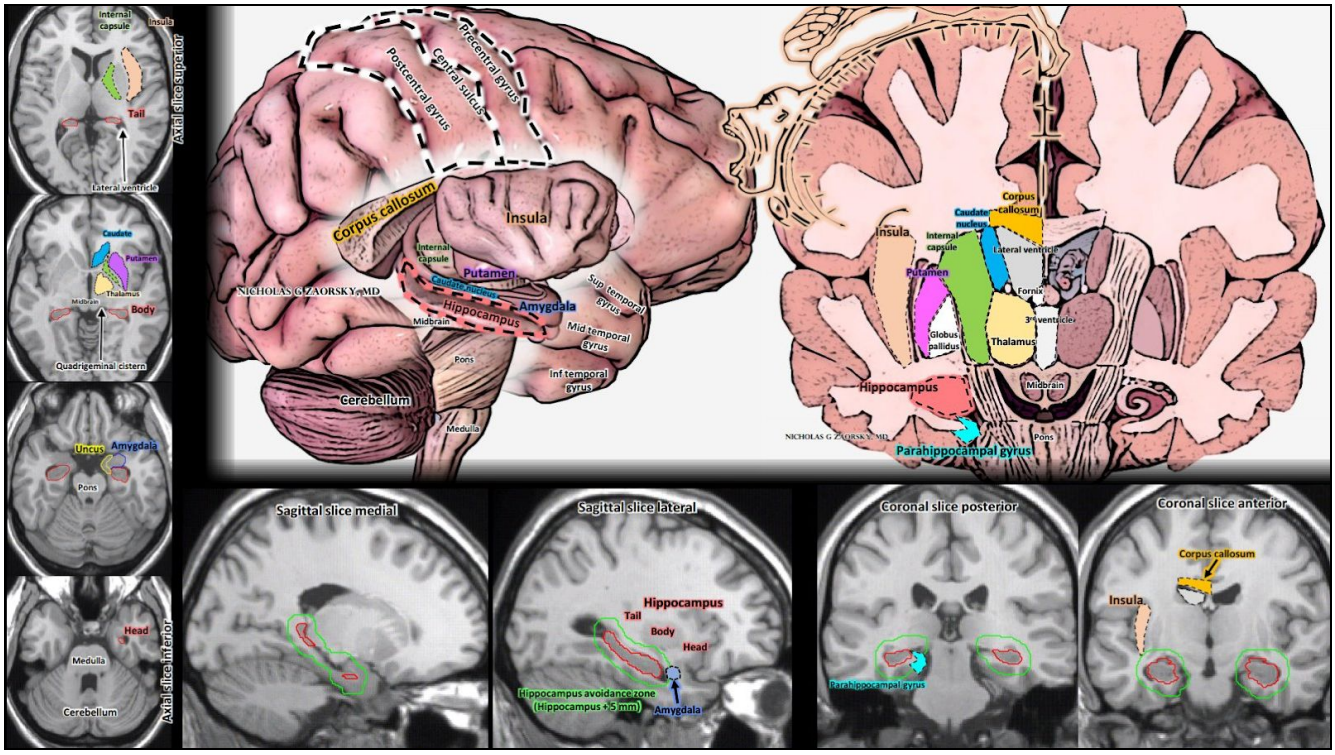
StatPearls: Brain Metastasis *Last update: 3/13/2019.*

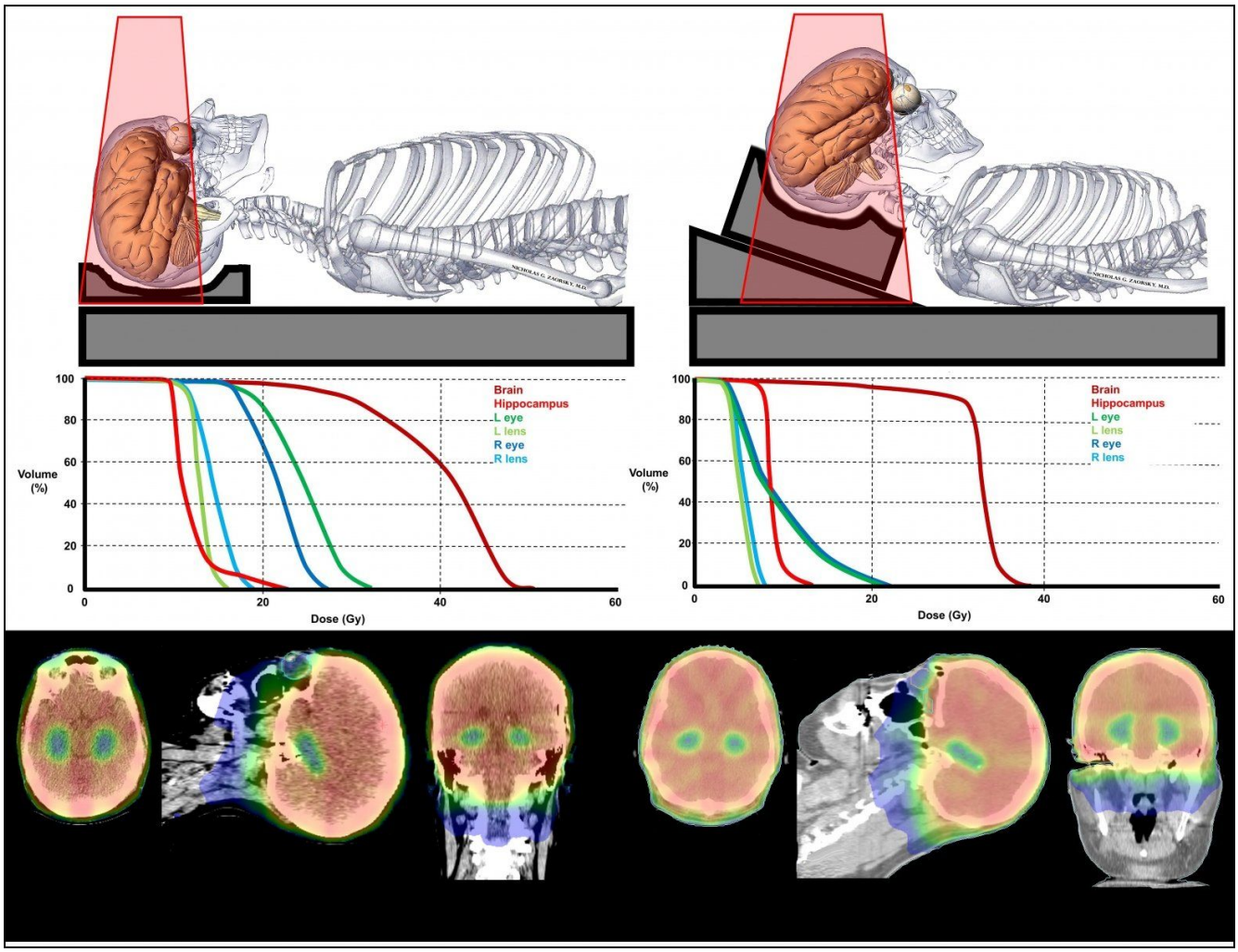
LearnOncology.ca: Brain Metastases [YouTube]

Zaorsky: [General MRI characteristics of brain lesions], [Pseudoprogression vs. radiation necrosis], [For HA-WBRT, use an inclined headboard at 30 degrees to minimize dose to orbits], [HA-Atlas and relevant landmarks].









- About half and half single vs. multiple brain mets. About 33% to 50% of pts die from CNS dz.
- **Solitary**: *No* extracranial metastatic disease.

- **Singular**: Brain met in setting of metastatic disease elsewhere.
- In pts with multiple lesions: Supratentorial (70%) > supratentorial + CBL (26%) >>> CBL (3%) > brainstem (1%).
- Location: Frontal, watershed (G-W junction, vessel dia decreases therefore traps cells), cerebellum (more likely GI/colon).
- Most common sx are HA, AMS and focal weakness in 33% to 50% with seizures and gait ataxia in 10-20%.
- **Hemorrhagic, peripherally enhancing without contrast on CT**: Melanoma, RCC, thyroid, choriocarcinoma.
    - Non-seminomatous tumors spread to the brain 2-3% vs. 10%.
- **Systemic therapy**: Response rate for chemo alone 15-30%. Molecule has to be < 400 dalton.
    - Small, asymptomatic lesions treated with chemo:
        - SCLC, Lymphoma, germ cell, GTD, breast, EGFR+ AC (TKIs = low MW. Non smokers RR = 70-80%).
- **Workup**
    - MRI brain.
    - Mets are typically spherical, ring-enhancing lesions with surrounding vasogenic edema located at the grey-white junction.
    - Typically iso or hypointense on T1 and hyperintense on T2. Some can be hyperintense on T1 if hemorrhagic or of certain histology.
    - If new dx, systemic imaging and biopsy.
    - If new brain mets dx and solitary, biopsy.
    - If suspect LMD, MRI spine and obtain CSF in a patient with symptoms but negative MRI.
        - Three negative LP's required to be a "true" negative. High protein, lymphocytosis, low glucose is suggestive. But, will results change management?
        - Obtaining an MRI post-LP increases risk of false positive from low pressure.
- **Key points**
    - 1y LF with GTR 55-65% *⅔*.
    - WBRT- no trials powered for OS. Increased LC vs. SRS alone, decreased DBM.
        - No WBRT has a 50% chance of new metastasis at 1 year.
        - 1 to 3 mets < 3.5 cm surgery alone have 60% LF (30% with SRS) [EORTC 22952]
    - WBRT improves neurological death in 2 of 3 trials: 44→ 14-28%.
        - Death from neurological disease ~20% of the time. Potential exception: melanoma, with neurological cause of death reported up to 80% of the time.
    - Local intensification (SRS/Surgery) with WBRT: Increased OS in 1 BM or good KPS.
- **Decadron dose**: 1 RCT. 96 pts.
    - 8 vs 16 mg: No difference in KPS increase, around 8 points in each arm.
    - 16 vs 4 mg: 6.7→ 9.1 at 1w, but 7.1→ 5.6 at 4w. 4 mg per day better at 4 weeks, and 16 mg more toxic.
    - Therefore, if a high dose is needed, do 8 mg BID x1 week then can usually drop to 2 mg BID in most patients.

Clinical Pearl: GPA Index. www.brainmetgpa.com. **The most up to date values!**
Bookmark this app on your phone. Looks like the last update in 2017.

- ➢ **All sites now stratify for age** (except RCC).
- ➢ **All sites now stratify for the presence of extracranial metastasis**.
- ➢ **All sites now stratify for number of brain mets**:
    - Lung cancer and RCC now 1-4 / 5+ BM.
      Lung cancer and RCC share a MS of 14.8 mo for GPA 4 as per above.
    - Melanoma and GI now 1 / 2-3 / 4+ BM.
      Melanoma and GI now share a MS of 13.2 mo for GPA 4 as per above.
    - Breast now 1 / 2+ BM.
- ➢ **Lung cancer** now includes histology (AC including EGFR/ALK vs. SqCC), # BM now (1-4 / 5+)
    - **MS up to 4y if EGFR/ALK+**, 1-4 BM only, any age KPS 90+.
      Note: These numbers likely do not reflect Osimertinib as first line!
    - **MS up to 2y if non-targetable AC**, 1-4 BM only, any age KPS 90+.
    - **MS up to 1y if SqCC**, 1-4 BM only, any age KPS 90+.
- ➢ **RCC** now includes Hgb (> 12 g/dL), # of BM now (1-4 / 5+).
  Note: The only DS-GPA not accounting for age.
    - **MS up to 3y** if 1-4 BM only, Hgb ≥ 11.5, KPS 90+.
- ➢ **Melanoma** now includes BRAF positive, # of BM (1 / 2-3 / 4+) and presence of extracranial dz.
    - **MS up to 3y** if solitary brain met and BRAF positive.
- ➢ **Breast cancer** now includes number of brain mets (1 / 2+) and presence of extracranial dz.

- **MS up to 3y for HER2+**/LumB/TP if solitary brain met, any age KPS 90+.
- **MS up to 2y for LumA** if solitary brain met, any age KPS 90+.
- **MS up to 2y for TN** if solitary brain met, < 60y and KPS 70+.
- MS up to 1y for TN if solitary brain met and any age KPS 70+.

➢ **GI** now includes number of brain mets (1 / 2-3 / 4+) and presence of extracranial dz.

- **MS up to 1.5y** for solitary brain met and KPS 90+.

Prognostication

See the Summary Box above for more on DS-GPA. See the [General Prognostication] section.

- Historically, the OS of untreated brain metastasis is around 1-2 months and WBRT extended this to 4-6 mo. Modern systemic therapies, supportive care, and early palliative intervention has extended this to ~7-8 months.
- **Recursive partitioning analysis** (**RPA**): [Gaspar IJROBP '97].
  - From 3 RTOG brain mets trials from 1979-1993.
  - KPS, age, control of primary and "control of extracranial disease" (not in GPA).
  - 1200 pts. **MS for RPA I/II/III of 7→ 4→ 2 mo**.
    - RPA-1: **< 65y**, KPS ≥ 70, solitary mets→ 7.2 mo.
    - RPA-2: All others→ 4.2 mo.
    - RPA-3: **KPS < 70→** 2.3 mo
- **Grading partitioning analysis** (**GPA**): From 5 phase III RTOG trials.
  - Imaging based prognostic factors, such as midline shift and post-WBRT may influence outcomes.
- **DS-GPA** [Sperduto JCO '12]:
  The tables below are to see how different disease sites are stratified. This information is now out of date.
  See [www.BrainMetGPA.com] for the most up to date references - 10 new Sperduto papers have come out since 2012!

NSCLC	0	0.5	1
KPS	< 70		≥ 90
# Brain mets	> 3		1
Age	≥ 60		< 50
Extracranial dz	+		-
MS 14.8→ 9.4→ 5.5→ 3 mo			

RCC	0	1	2
KPS	< 70		≥ 90
# Brain mets	> 3		1
Updated RCC is the only DS-GPA not accounting for age (Hgb).			
MS 14.8→ 11.3→ 7.3→ 3.3 mo			

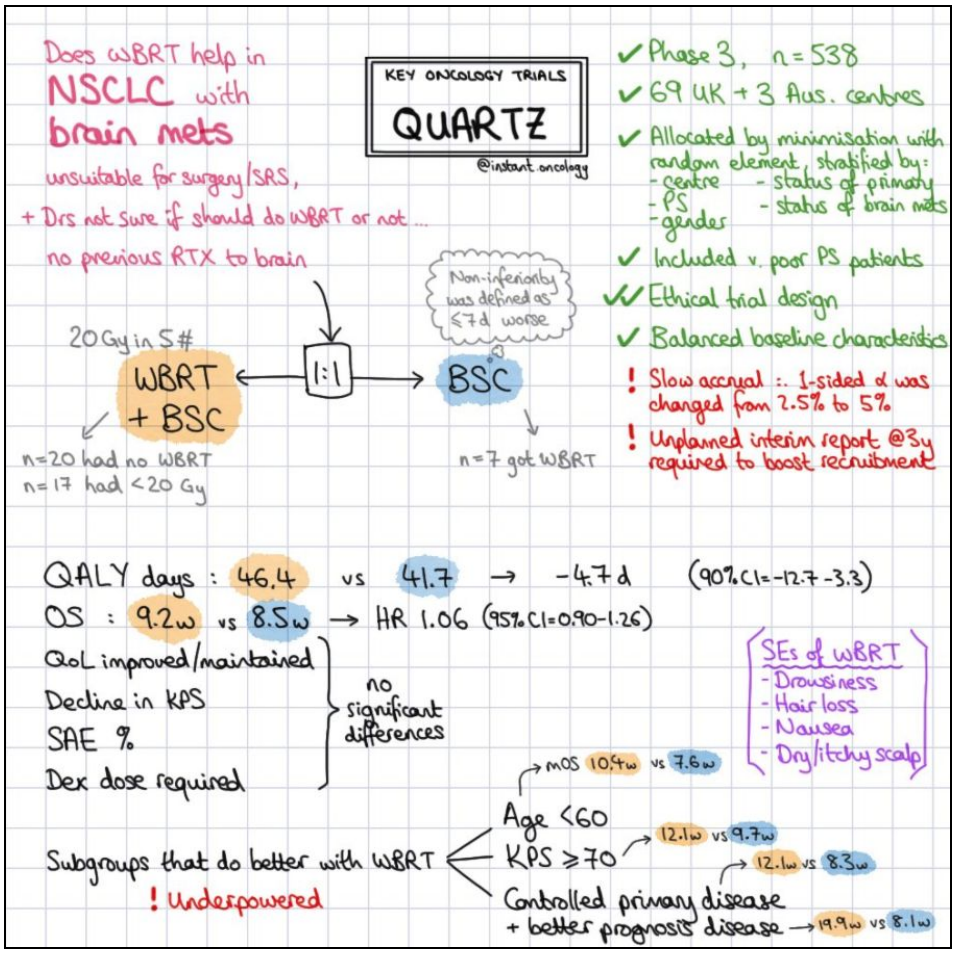
Melanoma	0	1	2
KPS	< 70		≥ 90
# Brain mets	> 3		1
Update includes BRAF+ and singular BMs: MS 34 mo.			
MS 13.2→ 8.8→ 4.7→ 3.4 mo			

Breast	0	0.5	1	1.5	2
KPS	≤ 50	60	70-80	≥ 90	-
Subtype	TN	-	LumA	HER2	TP/LumB
Age	≥ 60	< 60	-	-	-
MS 25.3→ 15.1→ 7.7→ 3.4 mo.					

GI	0	1	2	3	4
KPS	< 70	70	80	90	100
Update includes number of brain mets and presence of extracranial dz.					
MS 13.2→ 8.8→ 4.7→ 3.4 mo					

Key: MS for score of ≥ 3.5 / ≥ 2.5 / ≥ 1.5 / ≥ 0. Think of it as grade point average cutoffs (~A/B/C/F).

Omission of Radiation



- **QUARTZ** [Mulvenna Lancet '16]: **Dexamethasone ± 20/5 WBRT** in inoperable/non-SRSable BM from NSCLC.
  QUARTZ = QoL after Treatment of BM.
  The QUARTZ study only had less than a QUARTer of patients with good prognosis, therefore WBRT demonstrated no OS advantage. Subanalysis demonstrated OS favoring WBRT for patients < 60y or ≥ 5 mets.
  - 538 pts. Non-inferiority study. ~50% RPA 2 (MS 4 mo), while ~40% RPA 3 (MS 2 mo) with 80% DS-GPA 0-2.
    - This means most all pts were > 65y with > 1 brain met (or poor KPS,~40% with KPS < 70%).
  - OS benefit for age < 60y, with trend observed for good GPA/KPS.
    - Subanalysis demonstrated OS benefit in patients with ≥ 5 brain metastasis receiving WBRT.
  - MS ~9w. No difference in QALY. Significantly more drowsiness, hair loss, nausea, and dry/itchy scalp.
- Recall: SRS has an intracranial response rate ~80-90%.
- **Omission of RT for Melanoma brain mets**
  See [Brain Mets and Systemic therapy] in the Melanoma section for more.
  Current Treatment of Melanoma Brain mets [Rishi Curr Treat Options Onc '20]
  Asymptomatic brain mets from melanoma respond to ipi + nivo or BRAFi/MEKi ~50% of the time! [QS]
  Like Alectinib (ALK) or Crizotinib (EGFR), there is a ~50% intracranial response rate for asymptomatic BM.
  - Nivo or Pembro alone has around 20-25% intracranial response rate. Nivo/Ipi→ Nivo has ~50% intracranial response rate. BRAFi/MEKi has around 50% intracranial response rate, but MPFS is only around 6 months therefore Nivo/Ipi followed by maintenance Nivo is the first line for asymptomatic brain metastases.
  - There appears to be no utility for WBRT in the setting of local treatment of 1-3 melanoma BM [ANZMTG 01.07].
- **Omission of RT for NSCLC brain mets**
  See [Targeted therapy] in the NSCLC section for more.
  Like Nivo/Ipi→ Nivo or BRAF/MEKi for melanoma, there is a ~50% intracranial response rate for asymptomatic BM.
  Cut this number in half for PD-1 inhibition alone [QS] [Goldberg Lanc Onc '20].

- ALK: Only present in 5% of NSCLC, but around 33% will present with brain metastases. Crizotinib has poor intracranial response, but alectinib and brigatinib have approxiately 50% intracranial response rate with MPFS over one year. This includes patients previously treated with crizotinib.
  - Alectinib or brigatinib are reasonable for upfront treatment of asymptomatic brain metastasis.
- ROS1: Only present in around 1-2%. Crizotinib and ceritinib are first line, while Entrectinib just received FDA approval. CNS-only progression rates on Crizotinib are as high as 63%. There is little data on intracranial activity with ceritinib or entrectinib.
  - Upfront brain metastasis directed therapy recommended.
- Lorlatinib overcomes the G1202R mutation (occurs in ALK and ROS1), and has promising intracranial activity.
- EGFR: Osimertinib has around 50% intracranial response rate when used for upfront asymptomatic brain metastases. For patients with LMD, there is a ~40% chance of intracranial response! [BLOOM study] It is also reasonable to re-challenge patients who develop LMD with a higher dose or different EGFR inhibitor. QS
  - Osimertinib is reasonable for upfront treatment of asymptomatic brain metastases, and possibly even LMD.
  - Deferring radiotherapy reports commonly exclude patients who received first line osimertinib [Magnuson JCO '17, Miyawaki IJROBP '19].
  - Two ongoing trials looking at deferring SRS with Osimertinib [NCT03769103, NCT03535363].
- Non-targetable NSCLC: Platinum-based chemotherapy has 30-50% overall CNS response rates. Carboplatin and paclitaxel with pembrolizumab trials included patients with untreated brain metastases ≤ 1.5 cm who did not require steroids but these patients have not been reported separately [KEYNOTE 189, KEYNOTE 407].
  - Intracranial ORR is lower for platinum-based chemotherapy regimens than all other agents discussed above. Tread carefully when recommending upfront systemic therapy for non-targetable NSCLC.

- **Omission of RT for breast brain mets**
  See [brain metastasis] in the breast section for more.
  Up-front capecitabine + neratinib for HER2+ disease appears to be the most reasonable option if planning to defer local therapy with intracranial ORR ~50%, although MPFS is only around 6 mo (similar to BRAF/MEKi for melanoma).
  - Incidence of brain mets is highest in TNBC and HER2(+) disease [Darlix BJC '19].
  - CNS ORR for Capecitabine + Neratinib (HER2/erbB) appears to be around 50% if lapatinib-naive [TBCRC 022], while ~30% if ≥ 2 prior HER2/neu therapies [NALA trial].
  - Trastuzumab/Capecitabine + Tucatinib (HER2) appears to have 1y PFS of 25% for patients with brain mets who have progressed on the big HER2-three (Herceptin, Perjeta, Kadcyla) [HER2CLIMB].
  - For ER(+) disease, abemaciclib (CDK 4/6) appears to have an intracranial clinical benefit of around 25% [Anders JCO '19].
  - For TNBC, intracranial response for immunotherapy remains unknown [IMpassion130].
  - Palbociclib in progressive brain metastases [NCT02896335].
  - Abemaciclib in participants with breast cancer, NSCLC or melanoma [NCT02308020].
  - THP ± Atezolizumab for asymptomatic brain mets [NRG-BR004 NCT03199885]:
- Patients with any other primary histology should receive upfront brain metastasis directed therapy.

Surgery

There is no comparison for single met versus SRS (Surgery is superior to WBRT alone for single met per Patchell #1).
Death primarily due to extracranial disease. RoR Potential exception: Melanoma, nearly half of deaths neurological? ANZMTG 01.07
Surgery likely means a higher risk of carcinomatosis (piecemeal resection, location by dura, breast or NSCLC, posterior fossa).
Adding a 2 mm margin in the post-op setting appears wise [Choi ± 2 mm study], more if dural contact. RoR
Hot spots in the surgical cavity appear not to matter. Watch dose to PTV margin (i.e., normal brain) carefully. RoR

- Surgery vs. SRS:
  - No large phase III RCT for single BM.
  - For tumors > 4 cm, surgery wins especially if symptomatic.
  - SRS appears superior to surgery for lesions < 3.5 cm [EORTC 22952].
  - Surgery for mass effect or pathologic con\firmation. Also, KPS >70, age < 60y, life expectancy > 2 mo.
  - Consider RT instead if brainstem lesion would not allow for waiting for two weeks after surgery to start RT.
- SRS to resection cavity:
  - Until 2018, there were no full manuscripts from RCTs available which compared adjuvant WBRT to SRS [NCCTG N107C, JCOG 0504]. Prior studies demonstrated small sample sizes of retrospective nature using a wide range of SRS dosing and schedules. SRS has equivalent rates of distant brain mets to surgery alone.
  - Range of studies demonstrate 1y LC around 60-70% for SRS, while ~80% for WBRT.
  - Roughly 3% of pts need surgery for radiation necrosis [Choi ± 2 mm study].
- Long term survival after surgery or SRS: Generally, 5y OS 2.5-6%, although some pts live > 10y.

- Two of three trials have demonstrated a benefit in surgical resection + WBRT (not Mintz).
    - **Noordijk** [IJROBP '94]: 40/20 BID **WBRT ± pre-RT surgery**.
        - 63 pts. MS 6→ 10 mo, longer functional independence 3.5→ 7.5 mo (p=0.06).
    - **Patchell #1** [NEJM '90]: **Singular BM**: (**Biopsy vs. Surgery**)→ **36/12 WBRT**.
      Surgical resection improves overall survival over biopsy alone in the context of WBRT
        - Of 54 pts, **11%** excluded for unexpected pathology: 3 primaries, 3 inflammatory/infectious processes.
        - MS 4→ 10 mo, crude LR 52→ 20%.
        - Longer fxnal independence 8→ 38w, MPFS 5→ 14 mo, time to death from neuro cause 26→ 62w.
    - Vecht [Ann Neuro '93]: MS 6→ 10 mo single met (7→ 12 controlled systemically, 5→ 5 uncontrolled).
    - Mintz [Cancer '96]. No OS with surgery but worse KPS and not controlled systemically.
        - OS ~6m, not even QoL improvement with omission of surgery!
- **Patchell #2** [JAMA '98]: **Singular BM**: **R0 ± <u>50.4</u> WBRT**.
  We know surgery benefits patients from Patchell #1, so the control arm in this study was R0 resections.
  WBRT improves local control and decreases neurological death, but has the same time to functional decline.
  There is a 50% failure rate after R0 surgery alone.
    - 95 pts. GTR by MRI. > 70 KPS. MFU nearly 1y.
        - RT dose chosen to achieve a 90% microscopic disease control probability.
        - Issue: Roughly 60% on obs got RT.
    - MS ~45 wks, time to recurrence 27→ >57w.
    - 1y LR 46→ 10%, D_BM 37→ 14%, LRR 70→ 18%.
    - **Neuro death 44→ 14%**, systemic death 46→ 84%.
- **MDACC** [Mahajan Lanc Onc '17]: **Surgery ± Postoperative SRS** (12-14-16 Gy).
  Local control improved with postoperative SRS after resection, although 1y distant brain metastasis in over half of patients.
  Unexpected finding: 1y LC with postoperative SRS was only 70%.
    - 131 pts. 1-3 BM with R0 of at least one lesion. ~60% single brain met.
        - Unresected lesions treated with SRS in both arms.
        - SRS: 16 Gy for ≤ 10 cc, 14 Gy for ≤ 15 cc, 12 Gy for > 15 cc.
    - Perioperative tumors > 3 cm has worse LC.
    - 6 mo LC 57→ 83%, 1y LC 43→ 72%.
    - 1y D_BM ~60%.
    - MS ~17 mo.
    - No radiation necrosis events with SRS.
- **NCCTG N107C/CEC.3/RTOG 1270** [Brown Lanc Onc '17, Trifiletti IJROBP '19]: **Single resection→ WBRT vs. SRS**.
  SRS has better cognition than WBRT (still, half of patients treated with SRS had cognitive deterioration, suggesting intracranial progression may lead to cognitive deterioration). This is a similar finding to [NCCTG N0574]. Also, keep in mind this trial only demonstrated median cognitive-free survival increase from 3 mo to 3.7 mo with SRS (disappointing).
  Unexpectedly, WBRT has better LC than SRS. The thought is that 3-5 fx would be better for LC than SRS. Also, variations in cavity target delineation might have led to inferior local tumor bed control with SRS then with WBRT.
  Recall [RTOG 95-08] suggested utility of SRS boost for lesions > 2 cm in the setting of 37.5/15 WBRT. However, this trial demonstrated no advantage with 37.5/15 in terms of surgical bed control, intracranial tumor control, or OS but there are increased adverse effects with the lengthened course of RT. For patients where WBRT is recommended, shorter course WBRT remains the standard of care.
    - 194 pts. **1-4 BM**. Singular resected BM with resection cavity < 5 cm. Up to three < 3 cm unresected allowed.
        - WBRT 30/10 or 37.5/15, Postop SRS 12-20 Gy if up to 5 cm, while unresected lesions SRS 20-24 Gy.
        - Bed: 20 Gy if ≤ 4.2cc, 18 Gy if ≤ 8cc, 17 Gy if ≤ 14.3cc, 15 Gy if ≤ 20cc, 14 Gy if ≤ 30cc, 12 Gy if < 5 cm.
            - SRS not recommended if bed > 5 cm, but off protocol may consider 24-27/3 or 25-35/5.
        - Unresected lesions: 24 Gy if ≤ 1 cm, 22 Gy if ≤ 2 cm, 20 Gy if < 3 cm.
            - SRS not recommended if > 4 cm, but off protocol may consider 24-27/3 or 25-35/5.
        - For both study groups, the SRS dose was prescribed to the highest isodose line encompassing the target.
    - Cognitive progression (CP) defined as decline >1 SD from baseline in any of the 6 cognitive tests at 3 mo.
        - Includes HVLT-R (immediate, delayed, recognition), COWAT, TMT-A (processing speed), TMT-B (executive function), which basically all add up to an objective version of the MMSE.
    - 6 mo cognitive deterioration-free survival of 15→ 50%; Median cognitive-deterioration-free survival of 3→ 3.7 mo.
    - TTLRF 27.5→ 6.4 mo
    - 6 mo bed control 87→ 80%, 1y bed control 81→ 61%.
    - 1y intracranial tumor control 82→ 41%.
    - 1y cognitive deterioration-free survival of 9→ 40%.
    - MS ~11.5 mo.

- 30/10 preferred over 37.5/15. At least one G3+ event for 30 / 37.5 Gy of 31→ 54%.

- **JCOG 0504** [Kayama JCO '16, '18]: **Surgery→ WBRT** (37.5/15) **vs. SRS**.
  Salvage SRS is non-inferior to WBRT for four or fewer brain mets.
  SRS for STR only in resected brain mets has decreased local control versus WBRT, although no difference in OS.
  - 271 pts. 1-4 BM with only one lesion >3 cm having been resected. ~75% single brain met. MFU 1y.
    - All brain mets resected. SRS for STR (40%), observe for GTR (60%) ("salvage SRS").
    - SRS dose: 24 Gy for ≤ 4 cc, 18 Gy for > 4 cc.
  - MS ~15.6 mo.
  - Cavity local control 78→ 51%.
  - Time to intracranial tumor progression 10→ 4 mo.
  - G2-4 cognitive dysfunction at 90 days 16→ 8%.
  - Neurological death ~20%.
  - MMSE no difference.

RT Overview

- WBRT alone for SCLC, leukemia, lymphoma and germ cell tumors.
- About 33% to 50% of pts die from CNS dz.
- **No WBRT trials are powered to detect OS**. WBRT does improve LC.
- **After SRS (or surgery), WBRT improves LC and D_BM, reduces neuro death, but no OS benefit**.
  - WBRT with same **duration of functional independence** as surgery alone [Patchell #2, EORTC 22952].
  - WBRT less **neurological death** in 2 of 3 trials: **44→ 14-28%** [Patchell #2, EORTC 22952, not Aoyama].
- Local intensification (SRS/Surgery) to WBRT: Increased OS in 1 BM or good KPS. *RPA Class I per RTOG 95-08.*
- **SRS improves KPS and reduces the need for steroids.**
- SRS will fail in the brain 50% of the time, or 25% of the time when WBRT is given.
- Dose used for single BM is based mainly on studies performed in pts with mult brain mets.
- 30/10 and 37.5/15 most common. Prospective phase III RCTs: 10/1, 12/2, 18/3, 20/5, 30/10, 36/6, 37.5/15, 40/20, 50/20, 54.4/34 (160 cGy BID) with equivalent OS/efficacy.
  - ~50% have improvement in neurological symptoms.
  - RTOG 6901 and 7361: 40/20, 40/15, 30/15, 30/10, 20/5 MS ~4 mo.
  - RTOG 6901 10/1 and 12/2 RTOG 7361 worse toxicity and time to neurologic progression.
  - No MS advantage with 50/20 (RTOG 7606) or 54.4/34 BID (RTOG 9104) with MS 4.5 mo both arms.

- Mehta [JCO '03, '09]: **30/10 ± motexafin gadolinium** (novel radiation sensitizer).
  - 401 pts of any histology in first publication, 554 pts of NSCLC in second publication.
  - **Baseline impairment of NCF in > 65% of patients**. Initial study of all histologies suggested benefit for NSCLC.
  - Further analysis of the 208 pts receiving WBRT demonstrated WBRT-induced tumor shrinkage correlated w ↑ OS and NCF. Also, NCD preceded QoL declines, which suggests that strategies that delay NCD seem worthwhile.
    - Good response in tumor shrinkage of > 45% tumor volume reduction at 2 mo.

Adjuvant SRS after WBRT

There is a suggestion of an OS benefit to adjuvant SRS after WBRT for patients with one brain metastasis [RTOG 95-08].
Consider the addition of SRS to WBRT for lesions > 2 cm per unplanned subset on [RTOG 95-08].

- **Pittsburgh** [Kondziolka IJROBP '99]: **30/12 WBRT ± 16 Gy SRS**.
  This is the first RCT of WBRT ± SRS boost!
  Trial closed early due to significant differences in brain control.
  - 27 pts 2-4 BM ≤ 25 mm at least 5 mm from chiasm. KPS ≥ 70.
  - 1y LC 0→ 92%. MS 7.5→ 11 mo.
  - Time to LF 6→ 36 mo, longer time to any brain failure 5→ 34 mo but ~OS 7.5→ 11mo (p=0.11)
- **RTOG 9508** [Andrews Lancet '04]: **37.5/15 WBRT ± SRS** 18-24 Gy within 1 week.
  Addition of SRS to WBRT improved LC and KPS, but no change in overall survival.
  Prespecified subgroup analysis demonstrating OS benefit for patients with 1 BM. However, MVA demonstrated no benefit with SRS. MVA of all patients demonstrated RPA class I patients and NSCLC had better overall survival.
  The addition of SRS to WBRT may benefit patients with tumors > 2 cm.
  There appears to be no control advantage and increased toxicity with 37.5/15 per [N107C], while an [interesting report] in 2020 combined HA-WBRT to 30/15 with an SIB to 37.5/15. This advanced technique needs to be evaluated in the prospective setting.

- 333 pts. **1-3 BM**, < 4 cm. KPS ≥ 70. RPA I (25%) and II (75%). 19% dropout in SRS group.
  - SRS dosing per [RTOG 90-05]: **24 Gy** if < 2 cm, **18 Gy** if 2-3 cm, **15 Gy** if 3-4 cm.
  - LINAC and gamma knife outcomes curves were superimposed.
- 1y LC 71→ 82%. 6m stable/improved KPS 27→ 43%.
- Prespecified subgroup analysis of **1 BM with MS 4.9→ 6.5 mo**, otherwise OS 6 mo.
- 37.5/15 control arm designed based on a 1989 retro report of 12 pts with dementia and long survival suggesting that 300 cGy per fraction would have greater likelihood of late effects was highly criticized for reported radiation total doses and fractionation schemes.
  - Reported 11% (5 pts) risk of radiation induced dementia in long-term survivors (>12 mo) based on retro review of 47 pts tx w WBRT. 3 pts nonstandard, 1 pt rc concurrent adriamycin, 1 pt 30/3 w radiosensitizer. Of 15 pts < 3 Gy/fx without systemic therapy, 0 developed severe dementia or neurocognitive sx.
- Unplanned subset of RTOG RPA class 1 pts (MS 9.6→ 11.6 mo) and those with tumors >2 cm (MS 5.3→ 6.5 mo).

SRS dose escalation

- **RTOG 9005** [Shaw IJROBP '00]: Phase I. **Dose escalation study**. **24 Gy** if < 2cm, **18 Gy** if 2-3 cm, **15 Gy** if 3-4 cm.
  This established SRS dosing for later trials. On MVA, increasing dose was not associated with LC.
  This is not a radiation necrosis trial! It defined toxicity with 3 months of SRS.
  Lesions ≥ 2.1 cm obtained a local control rage just under 50%. This is why [multifraction SRS] is considered for lesions > 2 cm as opposed to 18 Gy in one fraction. 20 Gy to periphery of PTV (GTV + 1-2mm) on EORTC 22952, even if up to 3.5 cm.
  - 158 pts. **All recurrent**, 64% BM (30 Gy), 36% primary brain tumor (60 Gy). Average 17 mo prior to SRS.
  - Started at 18 / 15 / 12 Gy and concluded lesions < 2 / 2-3 / 3-4 cm should be treated to 24→ 18→ 15 Gy.
    - Based on CNS toxicity < 20% within 3 mo of SRS.
    - However, for tumors < 2 cm, reluctance to escalate to 27 Gy rather than excessive toxicity determined max.
    - GTV = tumor. No PTV. Rx to 50-90% IDL.
  - Actuarial risk of radionecrosis of 11% at 2y.
  - Radionecrosis requiring reoperation in 9%. MTTRN 5 mo (range 4-27 mo).
- **University of Kentucky** [Regine IJROBP '01]: Retro. **20 Gy SRS ± WBRT**.
  1) For brain metastases ≤ 2 cm, 20 Gy of SRS is highly effective when combined with planned WBRT. 2) For patients being treated for recurrences and/or for which WBRT is not planned, metastases should be treated with 24 Gy as determined by [RTOG 90-05].
  - 234 patients. 1992-2000.
  - 1y LC 79→ 94%.
  - Optimal control of brain mets ≤ 2 cm with 20 Gy SRS + WBRT. If > 20 Gy, then ↑ G3/4.
  - G3/4 toxicity 6%.

Role of WBRT: SRS ± WBRT Trials			
		Outcome	**OS**
[JROSG 99-1]	1-4 mets	1y local and regional control 73→ 89%.	No difference in OS or neurologic death.
[MDACC]	1-3 mets	1y brain control 27→ 73%.	Worse OS for WBRT patients. Worse learning/memory deterioration 24→ 52%.
[EORTC 22952]	1-3 mets	2y local failure around 50→ 25%. 2y distant mets around 50→ 25%. Improved LC with SRS over surgery?	No difference in OS or functional independence. Less neurological death but worse QoL with WBRT.
[Alliance N0574]	1-3 mets	Brain control 75→ 97%	No difference in OS. Worse cognitive deterioration at 3 mo 64→ 92%.
Role of WBRT: Post-op SRS vs. WBRT.			
[Alliance N107C]	1-3 mets	1y LC 60→ 80%. 1y brain control 60→ 85%.	Worse cognitive deterioration at 6 mo 50→ 85%. Worse QoL with WBRT. No difference in OS.
[Meta Analysis] of the first three trials demonstrated an OS detriment when WBRT was utilized for patients < 50y. However, local control and distant brain metastasis was favored in the WBRT arms.			

Adjuvant WBRT after local treatment

See the Summary Box above.

Adjuvant WBRT after local treatment improves local control, but results in neurocognitive decline at 3-4 months.
In the setting of limited brain metastasis (1-4), WBRT in general should be omitted in favor of SRS alone.

- JROSG 99-1 [**Aoyama** JAMA '06, '15]: **SRS ± 30/10 WBRT**.
  Addition of WBRT with marginally slows time to NCD and increases local control over SRS alone.
  - 132 pts, > 18y. **1-4 BM** (< 3 cm), KPS > 70. RPA II 85%. 1999-2003.
    - SRS (18-25 Gy) ± 30/10 (SRS dose ↓ by 30%).
    - First trial to assess the effect of delaying WBRT after SRS! MRI q3 mo.
      - 21% in the obs arm got salvage WBRT (compared to 31% in EORTC 22952).
      - Primary endpoint OS, but closed early.
    - For SRS alone: < 2 cm 18-20 Gy, < 2 cm 22-25 Gy.
  - TT NCD marginally prolonged with WBRT.
  - 3 point deterioration on MMSE from baseline at 12 mo of 24→ 41%.
  - MS ~7.5 mo. Equivalent neurological death of 20%. 1y LC 73→ 89%, 1y D_BM 64→ 42%.
    - Secondary analysis: MS 10→ 17 mo for DS-GPA 2.5-4.
  - 1y brain tumor recurrence (distant and local) 76→ 47%.
- **MDACC** [**Chang** Lanc Onc '09]: 15-24 Gy **SRS ± 30/12 WBRT** within 3 weeks.
  HVLT decline doubled at 4 mo with the addition of WBRT.
  Controversial as unexpected OS difference favoring SRS arm and neurologic assessment at only one time point.
  Stopped to accrual after 58 pts enrolled based on early stopping rules, remains controversial as MS and 1y OS was higher for SRS alone than for patients in SRS + WBRT. Suggested that advantage in SRS group due to an imbalance in prognostic factors between arms and differences in salvage therapy.
  - 58 pts. **1-3 BM** (58% single, < 4 cm), KPS > 70. RPA II 83%. 2001-2007. MFU 10 mo.
  - 4 mo decline in HVLT and memory of **24→ 52%**. Increased PFS but MS 15.2→ 5.7 mo.
  - 1y LRR 27→ 73%. 1y LC 67→ 100%.
  - 1y D_BMC 45→ 73%, salvage 90→ 11% with 61% of SRS pts not having WBRT by 1 year.
  - OS 15→ 6 mo and 1y OS 63→ 21%. *Why was there a worse OS in the WBRT group?*
- **EORTC 22952** [Kocher JCO '11, Churilla Ann Onc '17, JAMA Onc '18]: **Surgery or SRS→ ± 30/10 WBRT**.
  No difference in time to WHO PS >2 (Primary endpoint).
  Neurological death improved with WBRT.
  Interestingly, local control *appears* to be a little better with SRS (LF < 50%) than with Surgery (LF > 50%).
  - 359 pts. **1-3 BM** < 3.5 cm, or 2.5 cm if multiple. Stable systemic dz. WHO PS 0-2.
    - 71% LINAC-based SRS. 96% of surgery pts had 1 BM, compared with 73% of SRS pts.
    - PTV = GTV + 1-2 mm. Rx 25 Gy to center, while 20 Gy at minimum to PTV surface.
      Recall: RTOG 9005 with 24 Gy if < 2 cm, 18 Gy if 2-3 cm, 15 Gy if 3-4 cm.
  - Time to WHO PS >2: ~10 mo. MS ~11 mo.
  - 2y LF 59→ 27% (surgery), 31→ 19% (SRS); 2y D_BM 42→ 23% (surgery), 48→ 33% (SRS).
    Surgery group more likely to have larger brain met, only one, and posterior fossa location.
    - Unadjusted 2y LF 60% after surgery alone and 40% after SRS alone. WBRT 2y LF 20-30%.
    - Adjusted risk of LF overall is no different between surgery and SRS, although surgery patients are more likely to fail early (HR 5.9, 0-3 mo) and SRS patients are more likely to fail late (HR 2.8, > 9 mo).
    - 21% of the observation arm got salvage WBRT (compared to 31% in Aoyama).
  - **Neuro death 44→ 28%**. Decreased neurological death with WBRT, like Patchell #2 but not Aoyama.
  - HRQoL improved with observation-only arm, so close observation is warranted in limited brain disease.
- **Meta of JROSG 99-1, MDACC, and EORTC 22952** [Sahgal IJROBP '15]: **SRS ± WBRT**.
  SRS alone appears to be favored for younger patients. Addition of WBRT decreases OS in patients less than the age of 50y.
  There appears to be no difference in distant brain failure for patients ≤ 50y of age.
  - 364 pts. All trials comparing SRS ± WBRT, with individual patient data.
  - If ≤ 50y, SRS alone had better survival. These pts also had similar rates of D_BM with or without WBRT.
  - Pts >50 had no difference in survival, while WBRT decreases D_BM.
  - Local control significantly favored additional WBRT in all age groups.
- **Alliance NCCTG N0574 / RTOG 0671** [Brown JAMA '16]: **SRS ± 30/12 WBRT**.
  Addition of WBRT worsens the degree of cognitive decline at 3 months.
  Addition of WBRT increases local control without improving OS.
  SRS alone has better cognition than WBRT, but nearly 2/3 of patients treated with SRS had cognitive deterioration, suggesting intracranial progression may lead to cognitive deterioration. This is a similar finding as in [NCCTG N107C].
  - 213 pts. **1-3 BM** < 3 cm. **Primary endpoint: Neurocognitive decline** (Cognitive progression). 2002-2013.
    - SRS alone (20-24 Gy) vs. SRS (18-22 Gy) + WBRT 30/12.

        - Cognitive progression (CP) defined as decline >1 SD from baseline in any of the 6 cognitive tests at 3 mo.
            - Includes HVLT-R (immediate, delayed, recognition), COWAT, TMT-A (processing speed), TMT-B (executive function), which basically all add up to an objective version of the MMSE.
    - 3 mo CP 64→ 92% with improved QoL. 12mo CP 60→ 94%. There was more deterioration in immediate recall, DR, and verbal fluency.
    - Time to intracranial failure HR 3.6 when excluding WBRT.
    - 3 mo LC 75→ 94%, OS ~10.4→ 7.4 mo (p=0.92).
    - Salvage therapy 32→ 7.8%.

Prevention of neurocognitive decline

Zaorsky: [For HA-WBRT, use an inclined headboard at 30 degrees to minimize dose to orbits], [HA-Atlas and relevant landmarks].

- **Memantine** is a non-competitive NMDA receptor antagonist that retains activated NMDA receptors in an open-chanel state, thus preserving long-term potentiation (it blocks excessive stimulation of NMDA receptors) [Suh NRCO '20]. Generally speaking, it is around $100 per month through Walgreens. Coupons from GoodRx and Honest Discounts insurance knock the price down to around $20/month (except at Walgreens), regardless of insurance.
- **WBRT Cochrane Review** [Tsao '18]: **20/5 vs. 30/10 WBRT with no difference in cognitive decline**.
    - No difference in OS, neuro function, or symptom control with either dose.
- **RTOG 0614** [Brown NeuroOnc '13]: **37.5/15 WBRT ± memantine**. Primary endpoint delay HVLT-R at 6 mo.
  Overall, memantine appears to delay time to cognitive decline and the rate of decline in memory, executive fxn, and processing speed in pts receiving WBRT. Notably, 34% of patients died before completing the 24 week assessment and were not included in the analysis. This large number of deaths along with non-compliance or withdrawal might help to explain why this study barely lacked statistical significance. Patients undergoing WBRT with a predicted survival of at least 3 mo should receive memantine.
    - 508 pts. 149 pts analyzable @ 6 mo (expected 442). MS 7 mo.
    - Time to NCF defined as the first cognitive failure on any of the neurocognitive tests.
        - Memantine 20 mg/d vs placebo for 24 weeks.
            - Week 1: 5 mg/day.
            - Week 2: 5 mg BID.
            - Week 3: 5 mg AM, 10 mg PM.
            - Week 4: 10 mg BID→ week 24.
        - TMT-A/B and MMSE at 2,4,6, 12 mo.
    - Rate of decline slowed by 4 mo in both arms, more so in memantine. 6 mo NCF ~65→ 54% (p=0.059).
        - 6m HVLT-R improved but p=0.059. Only 35% statistical power due to greater than expected pt loss rates.
    - Time to NCF HR 0.78.
    - Improved controlled word association test at 16w (verbal fluency) and Trail Making Test A (executive function) at 24w with memantine.
- 3 dose levels related to particular mechanistic features important to cognition [Peiffer Neuro '13]
    - 57 pts who rec'd conventional partial brain RT to 60 Gy.
    - **10 Gy→ NSC reduction** (e.g. **hippocampus**); 40 Gy→ prominent white matter dz; 60 Gy→ necrosis.
- **RTOG 0933** [Protocol, Gondi JCO '14, HA Atlas]: Phase II. **30/10 HA-WBRT**.
  Requires 5 mm from lesion to hippocampus. There is less decline from baseline HVLT-R at 4 mo vs. historical WBRT cohort.
    - 113 pts. Primary endpoint cognition via HVLT-R at 4 mo. Avoids NSC. NSCLC with 2+ extracranial sites excluded.
        - **Hippo D100** < 9 Gy (**10 Gy**), Dmax < 16 Gy. Hippocampus PRV + 5 mm.
        - RT volume to the bottom of C1, unless posterior fossa mets are present (C2).
    - Three pts (4.5%) with new brain mets in hippocampal avoidance region.
    - Decline from baseline HVLT-R at 4 mo for historical WBRT / HA-WBRT of 30→ 7%.
    - Over 2/3 of patients developed intracranial progression.
- **NRG CC001** [Gondi ASTRO '19, (Protocol) Brown JCO '20]: Phase III. 6 mo **Memantine + 30/10 ± HA**.
  For brain mets pts whose survival is expected to be 4 mo or longer, hippocampal avoidance with IMRT should be standard. There are no increased hippocampal region relapses with hippocampal avoidance.
  TBL [QS]: The authors (and editors) are so bold as to conclude a hippocampal avoidance technique should now be the standard for care for patients with good performance status receiving whole brain radiation—we'll see what the payers think.
  TBL [QS]: If embracing HA-WBRT in your practice, get used to a whole new way to evaluate whole brain plans.
    - 518 pts. 85% RPA class II (MS 4 mo). Brain-only mets ~40%. Hydrocephalus excluded. MFU 8 mo.
        - All > 5 mm from hippocampus, KPS ≥ 70, MRI, baseline NCF testing. Ventricular distortion excluded.
        - RT brain volume to bottom of foramen magnum.

        - PTV D90-95 ≥ 30 Gy, PTV D98% ≥ 75% (22.5 - 25 Gy), PTV D2% < 125% (37.5 - 40 Gy).
        - Hippocampal D100 < 9 Gy (10 Gy), Dmax < 16 Gy (17 Gy).
    - Primary endpoint NCD on HVLT-R, TMT-A/B, COWA.
    - Hypothesis: HA will increase 6 mo TTF from 54% to 65%.
    - Tsien of Wash U [2018]: Cognitive impairment is observed in more than 50% of pts who receive WBRT, and 20% of cancer pts overall. HA-WBRT appears to be cost-effective only in pts with longer prognoses (≥ 12 mo) according to 2014 Medicare costs: WBRT alone $6,513. WBRT-HA $9,905. SRS $9,183. Follow-up MRI $646.
        - One third of patients died before 4 months (expected MS with RPA II). Perhaps these patients may not benefit from HA-WBRT, as you have to be alive to benefit from preventing cognitive decline.
    - Between 2 and 4 months, over half of patients in each arm had cognitive decline.
    - 6 mo cognitive failure of 63→ 55% (**HR 0.74**).
        - Differences at 4 mo driven by TMTB (executive function) deterioration of 40→ 23%.
        - Differences at 6 mo driven by HVLT-R (learning) deterioration of 25→ 12%.
        - Differences at 6 mo driven by HVLT-R (memory) deterioration of 33→ 16%.
        - The beneficial effect of HA did not differ by age ± 61y. 6 mo cognitive failure for ± 61y [HR 0.61].
        - Combined HR for memantine + HA of 0.78 * 0.75 = 0.58. *Comparable HR to SRS trials in lieu of WBRT.*
    - At 6 mo, patients who received HA-WBRT reported less fatigue, less difficulty with remembering things and less difficulty with speaking. Imputed data reported less interference of neuro sx with ADL and fewer cognitive symptoms.
    - Intracranial MPFS ~5.3→ 5 mo (p=0.076).
    - MS ~7.6→ 6.3 mo (p=0.242)
    - HA region relapses 17→ 11 patients.
    - G3+ toxicity ~20%.
- **HA-WBRT with SIB** (2014-2018) [Lebow JNO '20]: Retro. **30/15 HA-WBRT with 37.5/15 SIB**.
  Recall [RTOG 95-08] suggested utility of SRS boost for lesions > 2 cm in the setting of 37.5/15 WBRT, while [N107C] demonstrated no control advantage and increased toxicity with 37.5/15 over 30/10. This report provides an interesting middle ground, and this technique needs to be evaluated in the prospective setting. For patients with many brain metastases, it is likely quite reasonable to deliver 30/10 for multiple brain metastasis, and follow lesions > 2 cm closely for consolidative SRS within a year or so after WBRT in order to allow for tumor regression.
    - 32 patients. Median number of brain mets 4 (1-15). MFU nearly 1y.
    - Median freedom from intracranial progression 11 mo. MS 20 mo.
- **HA-WBRT with SIB** (2011-2016) [Westover Neuro Onc '20]: Phase II. **20/10 with 40/10 SIB** (**HSIB-WBRT**).
    - 50 patients. Up to 8 brain mets. GTV + 2 mm. Average lesion size 0.8 cc. MFU 11 mo.
    - MPFS 3 mo . MS 9 mo.
    - 1y cumulative incidence of LF / Distant brain mets of 9→ 21%.
    - 3 mo HVLT-DR for historical WBRT cohort [Chang] / HA-WBRT with SIB of 60→ 11%. *7% at 4 mo on 0933.*
- [NCCTG CE.7] is investigating SRS vs. HA-WBRT for patients with 5-15 brain metastasis, with dual primary endpoints of OS and neurocognitive PFS.

Multiple Brain Mets (> 4)

See Single Isocenter Multitarget SRS in the [SRS Treatment Planning] section.

- JLGK0901 [**Yamamoto** Lanc Onc '14]: Prospective observational. **SRS may be reasonable in up to 10 mets**.
  Patients with 2-4 mets vs. 5-10 mets have similar overall survival.
  The vast majority of patients died from systemic dz, not brain dz.
    - 1194 pts. 1998-2017. 20-22 Gy SRS alone, 1-10 BM, < 3 cm (largest lesion < 10 cc, total cumulative volume ≤ 15 cc), KPS ≥ 70; Primary endpoint OS, non-inferiority margin for comparison of pts with 2-4 BM vs. 5-10 BM was set as HR 1.3. ~OS between comparators, HR 1.18. MFU among the 30% of survivors of 21 mo.
        - RT to 22 Gy for < 4 cc, while 4-10 cc with 20 Gy.
        - RT: Brainstem for < 1 / 4 / 10 cc of 20→ 18→ 16 Gy.
        - Cumulative tumor volume for 1 / 2-4 / 5-10 tumors of 2.3→ 3.1→ 3.5 cc. *This is low volume disease*.
        - There is no detailed follow up of radiation necrosis, but most patients only live one year anyway.
    - Overall rate of salvage SRS 38%, a little higher for 5-10 brain mets. Only 9% had salvage WBRT.
    - MS for 1 / 2-4 / 5-10 tumors of 14→ 11→ 11 mo.
    - 2y development of new lesions for 1 / 2-4 / 5-10 tumors of ~48→ 66→ 72% (p=0.07).
    - 2y development of LMD for 1 / 2-4 / 5-10 tumors of 11→ 13→ 22%.
    - Grade 3 toxicity ≤ 3%.
    - Only 1 patient developed radionecrosis (?!).

- Cause of death was extracranial 92% of the time.
- MMSE was utilized for neurologic assessment.

- **Yamamoto repeat SRS** [IJROBP '19]: Repeat SRS appears feasible, especially for patients with low brain mets velocity. Brain metastasis velocity ≤ 3 BM within a year still has an OS greater than 1 year.
  - 833 patients from the above trial. 250 of these 3rd SRS, 88 of these 4th SRS. Around 6 mos between procedures.
  - Analyzed patients by brain metastasis velocity, or cumulative number of brain mets since initial SRS.
  - Second SRS group (n=833): MS for ≤ 3 / 4-13 / ≥ 14 BM developing within a year of 13→ 7.5→ 5 mo. MFU 16 mo
  - Third SRS group (n=250): MS for ≤ 3 / 4-13 / ≥ 14 BM developing within a year of 13→ 8→ 5.7 mo. MFU 4 mo.
  - Fourth SRS group (n=88): MS for ≤ 3 / 4-13 / ≥ 14 BM developing within a year of 16→10→ 5 mo. MFU 22 mo.
  - Salvage WBRT in 5%.
  - No mention of necrosis.
- **Impact on brain metastasis velocity and neurologic death after SRS** [LeCompte JNO '20]: Retro. **WBRT vs. SRS**. Repeat SRS appears to have less neurologic death than salvage WBRT. The association between brain metastasis velocity and neurological death remains strong for patients treated in the immunotherapy era.
  - 440 pts treated with SRS and progressed to have distant brain failure. 87 pts in the immunotherapy era.
  - 287 pts received salvage SRS, 91 pts received salvage WBRT, and 64 pts received no salvage RT.
  - 1y neurologic death for ≤ 3 BM developing within a year of 23→ 15%.
  - 1y neurologic death for 4-13 BM developing within a year of 37→ 30%.
  - 1y neurologic death for ≥ 14 BM developing within a year of 48→ 31%.
  - On MVA, salvage WBRT was associated with higher incidence of neurologic death compared to repeat SRS.
  - In the immunotherapy era, 1y neuro death for ≤ 3 / 4-13 / ≥ 14 BM developing within a year of 9→ 38→ 38%.
- **Initial SRS for patients with 5-15 brain mets** [Hughes IJROBP '19]: Multi-institutional. **1 vs. 2-4 vs. 5-15 brain mets**.
  - 2,089 pts. 1991-2013. 1 BM in 47%, 2-4 BM in 42%, 5-15 BM in 10% (n=212).
  - MS 15→ 10→ 8 mo.
  - 1y distant brain failure 30→ 41→ 50%. At the time of DBF, median BMV 4→ 6→ 12.
  - 2y salvage SRS 21→ 19→ 13%.
  - No difference in salvage WBRT was observed.
- **Does the number of brain metastasis matter? Yes, but volume seems to matter more.**
  - SRS reports of up to 15 lesions up front have been reported.
  - However, risks of radiation necrosis with SRS is not insignificant, even with the most skilled hands.
  - Interval to additional treatment prolonged with WBRT.
  - Do not offer HA-WBRT for patients with MS 4 months or less.
  - Reserve SRS for recurrence after WBRT.
- **Volume not number of metastasis** [Izard RTO '19]: GK-managed tumors. 80% single fraction.
  Survival outcomes in 180 cases with a median 5.5 (range 1–47) lesions were examined.
  Total tumor volume was more effective in predicting outcome than tumor number.
  A tumor volume index is encouraged for predicting stereotactic treatment outcomes.
  - 180 pts. 2010-2017. Half received prior treatment: 20% surgery, 20% WBRT, and 15% both. MFU nearly 1y. Median of 5.5 and mean of 8.5 mets at presentation (range 1-47 lesions). Total volume 0.57cc (up to 5.44 cc). Data on concurrent chemotherapy or immunotherapy was not collected.
    - RT: No margins added to contoured volume.
    - Lesions < 1.5 cm received 20 Gy, while 18 Gy if 2-3 cm, 15 Gy if 3-4 cm.
  - OS at 1y / 2y of 37→ 21%.
  - At the time of death, 40% had progressing intracranial disease.
  - Long term toxicity due to suspected radionecrosis in 12%.
  - There were no differences in survival for 1-3 / 4-9 / > 9 brain metastasis.
  - MS for volume < 3.2 cc / > 9.1 cc of 11.4→ 5.2 mo.
- **Italian** [Giuseppe JNO '20]: Retro. **Frameless LINAC-based SIMT SRS for 10+ brain mets**.
  Single isocenter multitarget SRS is safe and feasible for patients with many brain metastases. Overall V12 was not significant, while single target V12 > 8 cc predicted for radiological necrosis [Blonigen, Minnitti].
  DCA appears to have a lower V12 per target with SIMT, VMAT may require additional optimization [Cui JACMP '20]
  - 40 pts. 10+ BM < 3 cm in maximum size. Brain tumor volume < 15 cc. 2017-2018. MFU nearly 1y.
    - RT: 22 Gy for lesions < 2 cm, 16-18 Gy for those ≥ 2 cm in size. PTV = GTV + 1 mm.
    - Maximum translation error of 0.5 mm and/or rotation error of 0.5 degrees allowed.
    - Median total GTV and PTV were 4.7 and 7.3 cc, respectively.
  - 1y OS 65%.
  - 1y LC 86%. 1y DBF 70%.
  - 1y LF for lesions ≥ 2 cm of 22%. *Suggests multi-fractionation may be beneficial for lesions > 2 cm.*

    - 1y radiological necrosis in 21%. *Would this have been lower if 20 Gy was used?*
    - V12 was 24cc and V10 was 32cc, which is much higher than single target appearing safe. Individual target V12 > 8.5 cc and tumors ≥ 2 cm were significantly associated with radiologic RN.
    - Three months after SRS, the mean relative decline was 14% for HVLT-R delayed recall, 12% for HVLT-R recognition, and 10% for HVLT-R total recall.
    - Activities of daily living scale (ADLS) declined over time, but scores were not significant.
- **LINAC-based SRS is associated with less radionecrosis than GK SRS** [Sebastian RTO '20]: Retro. **GK vs. LINAC**.
  TBL [QS]: Higher central doses with GK may result in higher rates of radionecrosis than increased lower dose distributions with LINAC-based radiosurgery. P.S. Can someone please popularize a catchier name?
  See also the randomized Gadget trial [Navarria ASTRO '18]
  Critique: LINAC patients were more likely to be multifraction (54% vs. 0% for GK) and able to receive less than 27/3, and 30/5 (lower doses than typically recommended 3 and 5 fraction regimens of [27/3] and 30/5).
    - 391 pts treated to ≥ 2 lesions over 527 courses for 2,699 lesions total. 2015-2018. MFU 16 mo.
        - LINAC: 18-24/1, 21-27/3, or 25-30/5 for lesions < 2 cm, ≥ 2 cm, and ≥ 3 cm, respectively. *PTV margins of 2-3 mm were added for both intact and postoperative brain lesions.*
        - GK: Typically 20/1 prescribed to the 50% IDL. *No PTV margins were added.*
    - Prior WBRT in 7→ 18%. Prior surgery in ~8→ 14% (p=0.05), Multifraction in 0→ 54%.
    - V12 0.9→ 12 cc, but this was calculated as per-plan including multi-fraction. Per lesion V12 matters more. [RoR]
    - Intact lesion radionecrosis 4→ 1%, postoperative radionecrosis of ~5%.
    - G3 radionecrosis 1→ 0%.
    - After propensity score matching, GK was associated with a similar OS and higher rate of radionecrosis (HR 3.8).
    - Second propensity score for single-fraction still demonstrated higher incidence of rad necrosis with GK (HR 4.4).
- **Germany** [Popp Cancer '20]: Feasibility. **WBRT** (historic) **vs. HA-WBRT + SIB for 4-16 brain mets**.
    - 66 pts. 2012-2016. Treated as per HIPPORAD. 4-16 brain mets, ≥ 7 mm from hippo. No LMD. MFU ~7 mo.
        - RT: HA-WBRT (30/12) + SIB (42-51/12).
        - PTV mets = GTV + 1 mm (intact) or + 2 mm (post-op, up to 2 lesions resected).
        - Hippocampus D98% ≤ 9 Gy, D2% ≤ 17 Gy, mean ≤ 10 Gy. See Table 1 for OAR constraints.
    - 1y LC 82→ 98%.
    - 1y no new brain lesions or LMD 82→ 69%.
    - MS 6→ 10 mo.
    - Intracranial PFS 6→ 13 mo.
    - Hippocampal metastasis 5→ 6.5%.
- **SIMT SRS Outcomes Study** [NCT02886572]: **Single isocenter multi-target SRS** for 4-10 brain metastases.
    - Prospective trial at Duke. Nearing completion.
- **CCTG CE.7** [NCT03550391]: **SRS vs. HA-WBRT + memantine** for 5-15 brain metastases.
  See NCTN Trial Portfolios by Disease Site: [Brain] and the [Future Directions] section.
    - Co-primary endpoints: OS and neurocognitive PFS. Total volume < 30 cc (this is a large burden!)
    - There is a lower hippocampal dose with radiosurgery for 10-30 brain mets [Nguyen IJROBP '19].
- **MDACC** [NCT015992968]: **WBRT vs. SRS** for 4-15 brain metastases.
    - Primary endpoint: Local control and cognitive function.
- **Netherlands** [NCT02353000]: **WBRT vs. SRS** for 4-10 brain metastases.
    - Primary endpoint: QoL.
- **BRAIN METS SRS** [Tsien NCT03775330]: **SRS ± WBRT** for 5-20 brain metastases.
    - Utilizes the SPARE technique described in the Nguyen paper above.

Large brain metastasis

[RTOG 90-05] demonstrated a local control rate just under 50% for lesions ≥ 2.1 cm treated with 18/1. Therefore, 27-30/3 is considered for lesions of this size as a viable alternative option with less toxicity.

- There appears to be an approximate 70% rate of local control for lesions > 3 cm treated with 25-30/5, with an apparent increase in LMD for lesions treated with surgery and SRS compared to SBRT. [RoR]
- **Intact MSKCC** [Patel ASTRO '19]: Retro. **27/3 or 30/5 for intact, smaller** brain metastasis
  Either 27/3 or 30/5 are reasonable for intact brain metastasis, with very low rates of radionecrosis.
    - 113 pts with 187 brain mets. 2016-2018. Immunotherapy within 3 mo in 40%. Average 1.6 cm. MFU 13 mo.
        - PTV = GTV + 2 mm.
        - Only 30% > 2 cm, while only 4% > 3 cm.
        - Around 10% had either prior or post-SRS WBRT. Over half in frontoparietal lobes.
    - 2y radiographic radiation necrosis of 4.3%.
    - 2y radiographic PFS of 88%. There were no differences between 27/3 vs. 30/5.

- MS 1y.

- **Intact Italian** [**Minniti** IJROBP '16]: Retro. **Single fraction vs. 27/3 for intact >2 cm** brain mets.
  Better LC and less radionecrosis with 3 fractions.
  Suggested to limit normal brain V18 < 30.2 cc if possible for three fraction to intact brain metastasis.
  - 289 patients. SRS 18 Gy if 2-3 cm, or 15-16 Gy for ≥ 3 cm. No prior WBRT. MFU 2.5y.
    - PTV = GTV + 2 mm. Dose prescribed to 80-90% IDL, ensuring coverage of 95% of PTV.
  - 1y LC 77→ 90%, 1y LC 54→ 73% for tumors ≥ 3 cm.
  - 1y radionecrosis 18→ 9%, for ≥ 3 cm 33→ 14%.
  - Median time to progression 10→ 12 mo.
  - 1y OS ~54%, D_BM ~40%. Around 20% died from neurological death, while 80% died from systemic dz.
  - Radionecrosis for 27/3 normal brain V18 ± 30.2 cc of 5→ 14%.
  - Radionecrosis for 27/3 GTV < 22.8 / < 30.2 / < 41.2 / > 41.2 cc of 0→ 6→ 13→ 24%.
- **3 fraction dose escalation** [Kim JNS '19]: **24 - 27 - 30/3**.
  27/3 is the optimal regimen, as 30/3 has unacceptable rates of radionecrosis. 24/3 has unacceptable local failure. Instead of 24/3, consider 30/5 if not meeting 27/3 [constraints].
  - 60 pts. 2016 - 2018. MFU 10 mo.
  - 6 mo radiation necrosis 0→ 13→ 37%.
  - 1y LC 65→ 80→ 75%.
- **Multi-fraction meta** [Lehrer IJROBP '19]: **Single fraction vs. 27/3** for >2 cm (4-14 cc) brain mets.
  TBL [QS]: For brain mets >2 cm, hypofractionated radiosurgery achieved numerically better local control and minimized rates of radionecrosis across tumor size and setting compared to single-fraction treatment.
  For intact lesions > 3 cm, there appears to be no LC benefit for 27/3, although there is a trend towards decreased RN.
  For post-op lesions > 3 cm, there appears to be a trend to LC benefit for 27/3 and no benefit in rate of RN.
  Across the board, symptomatic radionecrosis with 27/3 and 30/5 appears to be in the single digit percentage range.
  - Meta of 24 studies with 1,887 brain mets. SRS 18 Gy if 2-3 cm, or 15 Gy for post op.
    - Single fraction intact: 18 Gy (15-20 Gy), Post Op 15 Gy (12-15 Gy).
    - Multifraction 27/3 intact and postop. Wide range, delivered from 2-5 fractions.
      - In general, 24-27/3 (BED10 43.2-51.3) and 27.5-30/5 (BED10 42.6-48)
  - For intact lesions 2-3 cm (4-14 cc): 1y LC ~78→ 93% (p=0.18). Radionecrosis 23→ 7%.
  - For intact lesions >3 cm (> 14cc): 1y LC ~78%, radionecrosis ~12→ 7% (p=0.29).
  - For post-op lesions > 3 cm (> 14cc): 1y LC ~62→ 86% (p=0.13), radionecrosis ~7%.

<u>Post-operative SRS</u>

- **French study** [Keller IJROBP '17]: Retro. **Surgery→ 23.1/3** (33/3).
  - 189 pts. Prior WBRT excluded. MFU 15 mo.
    - CTV = surgical cavity. PTV = CTV + 2 mm.
    - 70% IDL encompassed PTV, or 23.1/3 to the PTV.
  - LC at 6 mo / 1y of 93→ 88%.
  - Radionecrosis in 19%. MTTRN of 15 mo.
- **Post-operative Italian** [**Minniti** IJROBP '13]: Retro. **Surgery→ 27/3** for > 3cm resection cavities.
  Suggested to limit normal brain V24 to < 16.8 cc for three fraction postoperative SRS.
  For 5 fraction postop constraints, see [Tannenbaum].
  - 101 pts. 2005-2012. Single brain metastasis. Median cavity size 17.5cc. MFU 16 mo.
    - CTV = cavity. PTV = CTV + 2 mm. Dose prescribed to 80-90% IDL, ensuring coverage of 95% of PTV.
  - OS at 1 / 2y of 69→ 34%.
  - LC at 1 / 2y of 93→ 84%. DBM at 1 / 2y of 50→ 66%.
  - Radionecrosis in 9%, with 5% symptomatic.
  - Radionecrosis for normal brain V24 ± 16.8cc of 2→ 16%.
- **Post-operative Multi-fraction meta** [Akanda RTO '19]: **Single fraction vs. 27/3**
  - Meta of 50 studies with 3,458 brain mets. No prior WBRT allowed. MFU 1y.
  - 1y LC 80→ 87%.
  - There was no improvement in 1y local control with the addition of a margin.
  - 1y D_BM of 53%.
  - LMD 13%.
  - Radiation necrosis 7%.
- **Post-operative Italian** [Navarria IJROBP '19]: Phase II. **Surgery→ 30/3**.
  Hypofractionated SRS after surgery is safe and effective with acceptable toxicity, though higher radionecrosis rates than 27/3.

    - 101 pts. 2015-2018. Oligomets = ≤ 5 extracranial mets. Lesions ≥ 2.1 cm, or ≤ 2 cm with symptoms. MFU 26 mo.
        - Median pre-op size 3.7 cm, median cavity size 31 cc.
        - Prior WBRT excluded. 1-3 brain metastasis. Half received systemic therapy, including immunotherapy.
        - CTV = surgical cavity. PTV = CTV + 3 mm.
    - 2y LR 6%.
    - LC at 6 mo / 1y / 2y of 100→ 99→ 86%.
    - New brain mets in 40% of patients. MTTDBM of 39 mo. Most received salvage focal RT.
    - 2y OS nearly 50%! 20% of patients died from neurological causes, while 80% died from systemic dz.
    - G2+ radionecrosis in 25%. MTTRN of 15 mo.
    - NCF remained stable or in some cases improved.
- **Stanford** [Shi IJROBP '19]: Retro. Most received 27/3 (75%)
  TBL [QS]: This large series confirms an overall low rate of LMD recurrence and favorable rate of local control with SRS to brain met resection cavities.
    - 442 pts with 501 resected brain mets. 2007-2018. MFU 10 mo.
        - CTV = Cavity + T1c + 0-2 mm. No additional margin for PTV.
    - 1y LF 7%. 1y adverse radiation effect 9%. 1y symptomatic ARE 5.5%.
    - 1y distant intracranial failure 44%. 1y distant parenchymal failure 37%.
    - 1y LMD 13%. Just over half of LMD recurrences were [nodular].
- **Alliance A071801** [NCT04114981]: **Single fraction vs. fractionated SRS** (3-5 fractions).
  See NCTN Trial Portfolios by Disease Site: [Brain] and the [Future Directions] section.
    - 1-4 BM. Singular resected BM > 2 cm in size with resection cavity < 5 cm. Up to three < 4 cm unresected allowed.
    - Primary endpoint: Surgical bed RFS.
- **MDACC** [Yeboa NCT03741673]: **Pre-operative vs. Post-operative SRS**.
  See the [Future Directions] section for more ongoing trials.
    - 1 surgically resectable brain metastasis. Single fraction for < 4 cm, multifraction for < 7 cm.
    - Primary endpoint: Leptomeningeal disease-free survival at 1 year.
- **Mayo** [Yan NCT03750227]: **Pre-operative vs. Post-operative SRS**.
  See the [Future Directions] section for more ongoing trials.
    - Primary endpoint: Time to first CNS event.

LMD

- Radiographic LMD develops in up to 30% of patients following postoperative SRS for brain mets.
- Prabhu [NO '19]: Retro. At least **one resected BM→ Adjuvant SRS** who developed LMD. **nLMD vs. cLMD**.
    - 147 pts classified as nodular (nLMD) or classical ("sugarcoating", cLMD). 60% symptomatic.
    - Symptomatic LMD for nLMD / cLMD of 51→ 71%.
        - Salvage with WBRT alone (50%), SRS (27%), CSI (10%) and other. Most (60%) also received WBRT.
    - Second LMD recurrence for focal / whole brain RT of 68→ 40%.
    - MS for nLMD / cLMD of 8.2→ 3.3 mo.
    - On MVA, the pattern of initial LMD was significant, but the type of salvage RT was not.
- **Post-surgical LMD predictors** [Press NS '19]: Retro. Brain metastases→ Surgery→ SRS.
  TBL [QS]: Pre-op radiosurgery prior to brain met resection is gaining favor in certain circles, and these characteristics may point to populations who especially benefit from such a strategy.
    - 134 pts. MFU is just over 1y.
    - Association with post-op LMD: Breast histology (HR 3.2), cystic or hemorrhagic features (HR 2.3) or multiple brain mets (HR 2.1).
- **Post-surgical LMD for mets ≥ 3 cm** [Marcrom ARO '19]: Retro. **Surgery→ SRS vs. FSRS**.
  TBL [QS]: Notwithstanding the uncontrollable biases here, skipping surgery when symptoms allow and going straight to hypofractionated SRS for brain mets >3 cm may minimize LMD without sacrificing local control.
    - 125 pts from UAB. 2:1 surgery/SRS or FSRS. 2004-2017. MFU 7 mo.
        - Stringent definition of LMD: Any LM enhancement from the brain to cauda that was at least 5 mm from the index lesion.
        - Post-op SRS: Median 16/1. Cavity was contoured without a margin.
        - FSRS: 25-30/5. Optional PTV margin from 1-3 mm.
    - Post-treatment LMD 45→ 19%. 1y LC ~70%.

Toxicity

- **RTOG 0320** [Sperduto IJROBP '13]: Phase III **SRS ± WBRT with TMZ or Erlotinib**.
    - 1-3 NSCLC brain mets. Closed secondary to poor accrual.

    - No difference in OS and possible deleterious effect.
- Acute toxicity: HA, N/V, fatigue, hair loss, sore throat, xerostomia, skin irritation.
    - Ear fullness and hearing loss ~1-2% of patients.
    - Tighten up the MLCs around the mandibular condyle to decrease chances of xerostomia [QS] [Wang JAMA Onc '18].
    - Tighten up the MLCs around the lacrimal gland to decrease chances of dry eyes [QS] [Wang IJROBP '19].
        - V20 ≥ 79% is associated with significantly higher rates of dry eyes after WBRT.
        - 1 mo increased DES for V20 ± 79% of 15→ 46%.
- Late toxicity: Radiation necrosis, cognition, memory, cataracts.
    - Cognitive progression occurs in 60% of patients after SRS and approaches 95% after WBRT [N0574].
        - There is more deterioration in immediate recall, delayed recall, and verbal fluency.
- **Normal pressure hydrocephalus**: "Magnetic gait", urinary urgency/incontinence, short term memory/multitasking deficit. Confusion. Compare pre-RT and post-RT third ventricle volume. Shunt may be warranted.
    - See [Life NPH] for more. There is an 80% chance of improvement with a shunt.
- Whole brain: Lens < 7 Gy.
- SRS limits:
    - Cord 14 Gy.
    - Brainstem 12.5 Gy.
    - Optic chiasm or nerves 8 Gy (10 Gy - ballsy).
    - Other cranial nerves 12 Gy.

Clinical Pearl: Evaluating Radiation necrosis
See [Use of multi-fraction SRS and other tips on how to keep asymptomatic radionecrosis] rates less than 10%.
Zaorsky: [General MRI characteristics of brain lesions], [Pseudoprogression vs. radiation necrosis].

- Ensure adequate follow up of studies: At least 1y of follow up is ideal, as the median time to radiation necrosis is around 1 year. Be wary of studies that include patients with only 6 months of follow up.
- A V12 above 8-8.5cc is associated with asymptomatic RN above 10%, and should be considered for multi-fraction SRS [Bloningen IJROBP '10, Minitti Rad Onc '11].
- The best data is from [Flickinger IJROBP '00], which is for AVMs. According to this study, it appears as if location matters more than V12.
- Be wary delivering > 20 Gy for tumors > 1 cm [Kohutek JCO '15].
- MR spectroscopy and amino acid tracers with PET/CT may be of use diagnostically, but no consensus exists on which imaging modalities are best.
- Chemical exchange saturation transfer (CEST) has shown promise in differentiating radiation necrosis from progression, and is becoming more widely available [Mehrabian Clin Cancer Res '17].

Radiation Necrosis

See [Use of multi-fraction SRS and other tips on how to keep asymptomatic radionecrosis] rates less than 10%.
Zaorsky: [General MRI characteristics of brain lesions], [Pseudoprogression vs. radiation necrosis].

- **Diagnosis and Management of Radiation Necrosis in Patient with Brain metastasis** [Vellayappan FRO '18].
- Laser interstitial thermal therapy is recommended for radionecrosis or recurrent BMs for lesions up to 3-4 cm. Residual disease is left along ventricles or near critical structures. Consider 25/5 adjuvantly if residual present [Ali NSF '16].
- Patients biopsied ± 9 mo after SRS had radionecrosis 50→ 94% of the time [Narloch Neuro Onc '17].
    - Median time to radionecrosis is just under one year for most studies.
- **Adverse radiation effects (ARE) after SRS: Incidence, time course and Risk factors** [Sneed JNS '15]:
  ARE risk after SRS was low overall, but increases rapidly with size and volume, leveling off at a 1y incidence of 13-14%.
    - 435 pts with 2200 brain mets. MFU 10 mo.
    - Treatment failure 9%. ARE 5%. Concurrent failure and ARE 1%.
    - Among 118 cases of ARE, ~60% were symptomatic and 85% occurred 3-18 mo after SRS (median 7 mo).
    - Among 99 pts not treated with surgery or bevacizumab, imaging improvement at 6 / 12 / 18 mo of 40→ 57→ 76%.
    - 1y symptomatic ARE for repeat SRS of 20%. Prior WBRT with 4% symptomatic ARE, double if concurrent.
    - 1y symptomatic ARE for tumor ≤ 1.5 / 2 / ≤ 5.1 cm of 3→ 10→ 14%.
    - 1y symptomatic ARE of 13-14% for brain mets > 2.1 cm, target volume 1.2cc, Rx IDV 1.8cc, V12 3.3cc, V10 4.3cc.
- **Risk of necrosis is related to volume receiving 12 Gy** [Flickinger IJROBP '00]: Median 20 Gy to 3.5cc.
  This data is from AVMs! Includes GTV in volume.
    - 85 AVM pts who developed symptomatic complications after GK SRS, 337 pts without complications.
        - 38 of 85 pts had permanent symptomati sequelae of necrosis.

        - 10-35 Gy to lesions 0.26-48 cc. Median V12 7.39cc.
    - V12 (RR 1.08), SPIE score (RR 2.12).
        - Pons/midbrain, Basal ganglia, thalamus w rad necrosis risk ≥ 10% even for 5cc (pons is 40%!)
        - Suggestion of lower necrosis in frontal lobe and possibly temporal lobe.
- **Risk of necrosis is related to volume receiving 10 and 12 Gy** [Blonigen IJROBP '10]: LINAC based SRS (18/1).
  Data from cerebral mets. Includes at least 6 months of imaging follow up.
  Recommend patients with V10 > 10.5 cc or V12 > 8 cc to be considered for hypofractionated treatment.
    - 63 patients with 173 lesions. 63% of patients received prior WBRT. MFU 14 mo.
        - Radionecrosis: Any pt requiring steroids with MRI changes, characteristic MRI changes persisting on two consecutive scans, MRS findings consistent with necrosis, or histologic evidence of necrosis.
        - Range of dose from 12-22 Gy, with mean dose prescribed of 18 Gy.
    - Symptomatic RN in 10%, asymptomatic RN in 4%.
    - Median time to necrosis 10.5 mo (3-19 mo) for asymptomatic, while 11.5 mo (2-41 mo) for symptomatic.
    - V8 to V14 were statistically significant.
        - Rate of radionecrosis for V10 < 2.2 / 2.2-6.3 / 6.4-14.5 / >14.5 cc of 5→ 12→ 35→ 69%.
        - Rate of radionecrosis for V12 < 1.6 / 1.6-4.7 / 4.8-10.8 / >10.8 cc of 5→ 12→ 35→ 69%.
- **Risk of necrosis is related to volume receiving 10 and 12 Gy** [Minniti Rad Onc '11]: LINAC based SRS.
  This data is from cerebral mets. Includes GTV in volume. Includes patients with at least 4 mo of follow up.
  Risk of radionecrosis for V12 > 8.5cc of > 10%, while risk for V12 > 10.9cc of nearly 50%.
    - 206 pts with 310 cerebral mets. 1-3 BM, each < 3.5 cm. MFU 9 mo.
        - For volume ≤ 4.3 cc / 4.3-14.1cc / > 14.1cc, dose 20→ 18→ 15/16 Gy.
    - LC at 1 / 2y of 92→ 84%. OS at 1 / 2y of 58→ 24%.
    - G3/4 toxicity 5.8%.
    - Brain radionecrosis in 24%, less than half (only 10%) symptomatic.
- **Risk of necrosis is related to tumors ≥ 1 cm** [Kohutek JNO '15]: Single institution retro. **21-22 Gy SRS** (75%).
  Patients surviving less than 6 months were excluded. Great MFU of 1.5y.
  On UVA, radionecrosis (including asymptomatic) was associated with maximum tumor diameter (HR 3.55), prior WBRT (HR 2.21), and lower prescription dose (HR 0.56).
  There appears to be a high rate of symptomatic radionecrosis in thyroid, ovarian and SCLC histology.
  This study associated prior WBRT with radionecrosis, but does not tease out the time frame from WBRT to SRS.
    - 271 pts. Diagnosed radiographically in 2/3, pathologic confirmation in 1/3. MFU 1.5y.
        - Added 2 mm margin around GTV for PTV.
        - SRS: 21/1 up to 2 cm, with smaller tumors receiving 22 Gy. 18/1 for 2-3 cm, while 15/1 for > 3cm.
        - **MRI brain at 2 months, then q3mo thereafter**.
        - Radiation necrosis: pathologic diagnosis or MRI changes consistent with necrosis in the setting of new neurologic symptoms or a new steroid requirement. For asymptomatic patients, radionecrosis was based on MRI (including DWI and MR spectroscopy) and FDG-PET. Treatment change consistent with radionecrosis was diagnosed if patients had either two consecutive MRIs with evidence of necrosis or MRI accompanied by advanced MRI and/or PET imaging suggestive of necrosis.
            - MRI must lack evidence of distant intracranial progression and contain hallmark characteristics of necrosis including central hypodensity and peripheral enhancement on T1c with edema on T2.
    - Radionecrosis in 26% (17% symptomatic). 1y symptomatic radionecrosis 12%.
    - MTT radionecrosis 10.7 mo (range 3 months - 4 years).
    - Radionecrosis requiring surgical resection of 5.5% at one year.
    - Actuarial incidence of radiation necrosis at 6 / 12 / 24 mo of 5→ 17→ 34%.
    - Maximum tumor diameter HR 3.1 Gy. *The greatest risk appears to be for lesions > 1 cm.*
    - Actuarial incidence of radiation necrosis for 0-0.5 / 0.6-1.0 / 1.1-1.5 / > 1.5 cm of 3→ 7→ 19→ 38%.
    - Symptomatic radiation necrosis:
        - Tumor diameter: >1 cm (HR 2.74).
        - Prior WBRT: (HR 2.09).
        - Other histology: (HR 2.75). *Driven by thyroid, ovarian and SCLC histology.*
        - Margin dose: HR for < 21 Gy / 21+ Gy with HR for < 21 Gy of 0.75 (p=0.37).
            - Average tumor size for < 21 Gy / 21+ Gy of 0.9→ 1.8 cm.
            - The risk of radionecrosis associated with a larger tumor size may outweigh any potential mitigating effect of a lower radiation dose.
- **Brainstem risk of necrosis** [Trifiletti IJROBP '16]: Retro. **GK-SRS delivered to the brainstem**.
  The largest risk appears to be associated with tumor volumes between 1-2cc. Doses greater than or equal to 20 Gy along with prior WBRT, especially within 4.5 mo prior to SRS, were also factors for symptomatic radiation necrosis.

- 547 pts with 596 brainstem mets.
- MS only 5.6 mo. 1y OS 33%. 2y OS 17%.
- G3+ radiation toxicity of 7.4%.
  - Only related to increasing tumor volume, margin dose, and previous WBRT.
    - Tumor volume: 1-2 cc (OR 14.4), >2 cc (OR 11.7).
    - Margin dose: 16-19.9 Gy (OR 3.8), ≥ 20 Gy (OR 5.8).
    - Prior WBRT (OR 4.5). Median interval between WBRT and SRS of 4.5 mo.
      - Odds ratio 0.116 for interval between WBRT and SRS of ± 4.5 mo.
  - No effect of brainstem tumor location (p=0.30) or V12 (p=0.06) on toxicity.
    V12 included tumor and surrounding brain outside tumor.
- 1y LC 82%. 1y OS 33%

- **Brainstem risk of necrosis** [Lehrer RTO '20]: Retro. **GK-SRS delivered to the brainstem**.
  Increasing D05% to the brainstem is associated with an increased risk of clinical complications. This parameter, in addition to MF-SRS, should be considered when well-established dose constraints are not met.
  - 61 patients. 2007-2019. Brain mets (n=45) or AVM (n=16). Median 18 Gy. MFU only 6 mo.
    - 27 patients underwent prior RT to the brainstem (including 17 WBRT).
  - Clinical / Radiographic complications in 16→ 28%. Most common clinical complication of CN dysfunction (12%).
  - Median D05% ± any complications of 6.3→ 10.1 Gy.
  - Median D95% ± any complications of 0.24→ 0.3 Gy.
  - Logistic regression demonstrated D5% to be associated with an increased probability of developing clinical complications post-SRS (OR 1.18).
- **Immunotherapy and Radiation necrosis** [Martin JAMA Onc '18]: Retro. **Brain SRS/SBRT ± Immunotherapy**.
  - Single institution. 480 patients, 115 of which rec'd immunotherapy for a median of 14 weeks. MFU 2y.
    - SRS: 18-20/1 Gy for 0-2 cm lesions, 18/1 for 2-3 cm lesions, and 25-30/5 for >3 cm lesions.
    - Histology: Mostly NSCLC (n=294), melanoma (n=145), rest were RCC (n=41).
    - Symptomatic radiation necrosis by pathology, PET-CT, or serial MRIs.
  - Incidence of symptomatic radiation necrosis 7→ 20%.
- **Radionecrosis for resected brain metastases** [Tanenbaum PRO '19]: **30/5 to resected brain metastases**.
  Suggested to limit dose to PTV margin (typically 1.5-2 mm) to < 33.5 Gy.
  Includes pts with a minimum of 3 months of F/U. Issue: MFU appears to be < 1y, radionecrosis median ~1y to develop.
  Hot spots within CTV were not predictive for radionecrosis.
  For 5 fraction intact constraints, see [Faruqi]. Minnitti has 3 fraction [intact] and [postop] constraints.
  TBL [QS]: When doing 5 fx post-op SRS for brain mets, keeping the volume receiving 33.5 Gy (or 111% of Rx) to ≤ 0.05 cc outside the cavity lowers the risk of radiation necrosis, a goal made easier without constraining the hotspot within the cavity.
  - 55 resected brain metastasis. 2008-2016. 25-35/5. Median CTV 17.5cc.
    - RN is defined as development of contrast-enhancing mass within previous RT fields and conventional imaging features including feathery enhancement and T2 hyperintensity. Advanced imaging when necessary. Resolution with observation or steroids assisting further.
  - Median PTV expansion 2 mm. Median max hotspot 111%.
  - 1y cumulative radiographic RN of 18%.
  - 1y radiographic RN for ± 33.5 Gy Dmax in PTV margin of 5→ 35%.
- **Radionecrosis for resected and intact brain mets** [Faruqi IJROBP '20]: Retro. **30/5 to intact and resected brain mets**.
  Suggested to limit dose to the brain minus GTV receiving 30 Gy to 10.5cc.
  For 5 fraction postop constraints, see [Tanenbaum]. Minnitti has 3 fraction [intact] and [postop] constraints.
  - 187 pts with 118 surgical cavities (25cc) and 132 intact (8cc) brain mets. GTV + 2 mm for PTV. MFU 1y.
    - Rx 30 Gy (20-35 Gy)
    - 80% of patients only had one brain metastasis.
  - Asymptomatic / symptomatic ARE of 21→ 11%.
  - MTT ARE 8 mo.
  - Time to ARE < 6 / 6-12 / > 12 mo in 38→ 43→ 19%.
  - MVA demonstrated intact brain metastasis OR 3.7 as a predictor of symptomatic ARE.
  - For cavity SRS, prior WBRT OR 7.7 and prior SRS OR 8.7 to be significant predictors of symptomatic ARE.
  - For intact brain metastasis, whole brain minus GTV receiving 30 Gy (BMV30) was a significant predictor of ARE, and a volume based BMC30 threshold of 10.5cc may guide treatment planning.
  - 1y symptomatic ARE for normal brain V30 ± 10.5 cc of 13→ 61%.
- **Necrosis**:
  - Does not extend to the cortex! *This is questionable.*
  - Differs from true progression in that less perfusion present.

- Radionecrosis: Central hypodensity, ring enhancement, edema, and low PET avidity if >6 mo post RT.
- For SRS, V12 < 10cc for radiation necrosis. *Depends on location. See Flickinger AVM study above.*
  - SRS necrosis rate 20-30%, 10-15% symptomatic.
    - Asymptomatic: Observe.
    - Symptomatic or progression:
      - High dose steroids 4 mg BID x4-6w then taper before MRI.
      - Avastin 7.5 mg/kg q3w x2. Durable, high rate of clinical and radiographic response.
      - HBO.
      - Surgery/laser coagulation: Can be diagnostic and therapeutic, high complication.
- Differences in fractionation:
  - BID RT has a steep toxicity curve when BED_3 >80Gy.
  - >2.5 Gy/fx, incidence and severity of toxicity is unpredictable.
  - For fractionated RT with fraction size of < 2.5 Gy:
    - **Incidence of radiation necrosis < 3% for < 60 Gy**.
    - 5% at BED_3= 120 Gy (range 100-140): 72/36.
    - 10% at BED_3= 150 Gy (range 140-170): 90/45.
- Emami: $TD_{5/5}$ radionecrosis = 60/30 to ⅓ of brain.
- Radiation induced brain tissue necrosis was found to occur NTDcumulative >100 Gy.
- 3 dose levels related to particular mechanistic features important to cognition [Peiffer Neuro '13]:
  - 57 pts who rec'd conventional partial brain RT to 60 Gy.
  - 10 Gy→ NSC reduction (Hippocampus); 40 Gy→ prominent white matter dz; 60 Gy→ necrosis.
    - Think: Hippo + 5mm 100% < 9 Gy (10), Dmax < 16 Gy (17) on 09-33 (HA-WBRT).

- Treatment of radiation necrosis
  - Time for asymptomatic patients.
  - Steroids.
  - Bevacizumab may lead to radiographic and clinical responses in all patients [Levin IJROBP '11].
  - Cox-2 inhibitors. 100-200 mg po BID. Caution: Sulfa allergies, renal function, More CV events? [Khan JPHO '04]
  - Surgical resection.
  - Laser interstitial thermal therapy.

This Summary Box was made possible by the ACRO Resident Committee.
A more comprehensive collection of resources for all disease sites may be found at http://www.acro.org/

Zaorsky: [General MRI characteristics of brain lesions], [Pseudoprogression vs. radiation necrosis], [For HA-WBRT, use an inclined headboard at 30 degrees to minimize dose to orbits], [HA-Atlas and relevant landmarks].
eContour: [Intact brain mets].
Contouring
- Hippocampal sparing [RTOG Contouring Atlases]
- Consensus Contouring Guidelines for Post Op Completely Resected SRS for Brain Metastases [Soliman IJROBP '18] RoR
- DEGRO working group on SRS: Treatment of Brain metastasis [Kocher STO '14]

Review Articles
- Current multidisciplinary management of brain metastases [Moravan Cancer '20]. RoR
- Current approaches to the management of brain metastases [Suh NRCO '20] RoR
- Comparison of SRS modalities [Vergalasova Fronteirs Oncology '19] RoR
- Molecular Subtypes and Breast Brain Metastases [Darlix BJC '19]: Retro. HER2(-)HR(+) / TP / TN / HER2(+)HR(-). RoR

Society Guidelines
- ASCO/SNO Guideline: Anticonvulsant Ppx and Steroid Use in Adults w Metastatic Brain Tumors *March 18, 2019* RoR
- ASCO Guideline: Recommendations on Dz Mgmt for Pts w Advanced HER2+ BrCa and Brain Mets *June 25, 2018* RoR

Relevant Accessible Radiation Protocols
- NRG CC001 [Protocol Brown JCO '20]: 6 mo Memantine + 30/10 WBRT ± HA. RoR

Quality of Life/Toxicity
- Risk of necrosis is related to V12 [Flickinger IJROBP '00]: Median 20 Gy to 3.5cc AVMs. RoR

Treatment planning

See the Summary Box above and the [SRS Summary Box] below.
Hippocampal Avoidance Atlas [RTOG 09-33]. See [Zaorsky] tweet concerning the HA-Atlas and relevant landmarks.

- **Solitary / limited brain mets**: Surgery + SRS or WBRT, SRS alone, or WBRT + SRS.
  - Do surgery for large tumors causing mass effect or midline shift, or if diagnosis in doubt.
  - NCCN: After surgery, WBRT is preferred one if disseminated systemic disease with poor systemic treatment options. A volume of less than 9 cc may be considered limited [Izard RTO '19].

- **Multiple mets (2-4), or tumor volume < 9 cc** [Izard RTO '19]: SRS alone, WBRT + SRS, WBRT.
- **Multiple mets > 4 or KPS < 70%**: WBRT.
    - Consider HA-WBRT if lesions > 5 mm from hippocampus and patient is not RPA II
- **Leptomeningeal disease**: RT to bulky or symptomatic sites. If good PS, low tumor volume, few sx: Intrathecal chemo.
    - MS for nodular / diffuse LMD of 3→ 8 mo [Prabhu NO '19].

WBRT

SRS is preferred for patients with 1-4 lesions and a MS greater than 4 months (e.g., KPS > 70). See www.BrainMetGPA.com.

- Bottom of field at the foramen magnum, inferior to C1, or inferior to C2.
- A variety of fractionation schemes have been employed (e.g. 30/10, 37.5/15, 40/20).
- **WBRT**: **30/10 (**or 37.5/15) **with memantine** for good PS (KPS > 70), stable systemic disease.
    - Memantine dosing: 5 mg wk 1, 10 mg wk 2, 15 mg wk 3, 20 mg wk 4 x6 mo. Check CMP weekly.
    - 37.5/15 has loosely fallen out of favor due to increased grade 3 toxicity, but keep in mind this study only looked at 1-4 brain metastasis [N107C]. Consider 30/10 WBRT and following up lesions > 2 cm for SRS, as regression of lesions would allow for either single fraction radiotherapy or less development of radionecrosis while potentially avoiding the increased toxicity of 37.5/15. This is a hybrid model loosely based on the > 2 cm subset analysis from [RTOG 95-08].
- Tighten up the MLCs around the mandibular condyle to decrease chances of xerostomia [QS] [Wang JAMA Onc '18].
- Tighten up the MLCs around the lacrimal gland to decrease chances of dry eyes [QS] [Wang IJROBP '19].
    - V20 ≥ 79% is associated with significantly higher rates of dry eyes after WBRT.
    - 1 mo increased DES for V20 ± 79% of 15→ 46%.
- For HA-WBRT, use an inclined headboard at 30 degrees to minimize dose to orbits [Zaorsky tweet].
- TBL [QS]: If embracing HA-WBRT in your practice, get used to a whole new way to evaluate whole brain plans.

Stereotactic Treatment of Brain metastases: Optimize local control while keeping late asymptomatic radionecrosis ≤ 10%.
See [Current Mult-D management of brain metastases] and the [evaluating radiation necrosis] sections for more information.
Generally speaking, of all patients who develop radiographic RN, around half are symptomatic. However, [location matters]!
See details on [Single Isocenter Multitarget SRS] (SIMT SRS).

- Lesions < 2 cm may have adequate control with 20/1, with around 20% failing at 1 year [UK].
- Over half of lesions > 2 cm treated with 18/1 (for 2-3 cm) or 15/1 (for 3-4 cm) will fail [RTOG 90-05].
    - Lesions > 2 cm treated with single instead of multi-fractions have 2x risk of RN [Minitti intact].
- Therefore, many physicians prefer to utilize single fraction radiation for lesions up to 2 cm, and will consider fractionated regimens such as 27/3 or 30/5 for lesions above 2 cm.
- We believe it is reasonable to consider 27/3 for lesions above [1 cm] or lesions in critical regions such as the motor strip, especially with a suggestion of late radiographic RN of around 5% at long term [MSKCC].

Key points for intact lesions

- Lesions treated with single fraction SRS appear to have > 10% radiographic RN with a brain V12 > 8-8.5cc, and should be considered for multi-fraction SRS [Bloningen IJROBP '10, Minitti Rad Onc '11].
- Lesions greater than [1 cm] treated with single fraction SRS > 20 Gy appear to have > 10% rate of radiographic RN.
- Lesions 1-2 cm treated with 27/3 appear to have a 2y radiographic RN rate of ~5% [MSKCC].
- Lesions 2+ cm treated with 27/3 appear to have a 2y radiographic RN of 5% if V18 < 30.2 cc, otherwise twice that for all comers [Minitti intact].
    - Normal brain V18 < 30.2 cc should lead to late radiographic RN rate to ~5% [Minitti intact].
- Lesions 3+ cm treated with 27/3 appear to have a late radiographic RN rate of at least 10% [Lehrer].
- Treatment with 30/5 appears to have a late *symptomatic* ARE rate of ~10% for normal brain V30 < 10.5cc [Faruq '20]

Key points for postoperative lesions

- Hot spots in the surgical cavity do not appear to matter [Tanenbaum post-op].
- See [N107C] for single fraction postoperative dosing schedule. Consider fractionation above 3 cm cavity.
- For 27/3 to > 3 cm resection cavities, normal brain (PTV margin) V24 < 16.8 cc should lead to late radiographic RN of < 5% [Minitti post-op].
    - 30/3 appears to have a higher rate of radiographic RN than 27/3 [Navarria].
      It may be reasonable to attempt to deliver 30/3 so long as V24 < 16.8 cc is maintained as per Minitti.
- For 30/5 to resection cavities, normal brain (PTV margin) dmax < 33.5 Gy should lead to radiographic RN of ~5% [Tanenbaum post-op].

SRS

SRS is preferred for patients with 1-4 lesions and a MS greater than 4 months (e.g., KPS > 70). See www.BrainMetGPA.com.

See [Use of multi-fraction SRS and other tips on how to keep asymptomatic radionecrosis] rates less than 10%.
Use of 1 mm margin appears legit for intact brain mets (consider 2-3 mm for SIMT lesions farther away from the isocenter), while a minimum of 2 mm appears legit for post-op brain mets (add up to 1 cm of dura if preoperative contact). [RoR]

- **SRS**: Lesions < 2 / 2-3 / 3-4 cm should be treated to 24→ 18→ 15 Gy according to [RTOG 90-05].
    - However, lesions > 2 cm treated with these doses have 50% failure.
    - See the [Stereotactic Treatment of Brain Metastases] summary box above.
- **Conformality index** (CI) = PIV / TV. PIV = Prescription isodose volume.
    - 1 is perfect, higher is worse. CI should be < 2 for radiosurgery.
- **Heterogeneity index** = Max/ Rx.
    - < 2 is ideal.
    - HI 1.25 for Rx to 80% IDL.
- **Consensus Contouring Guidelines for Post Op Completely Resected SRS for Brain Metastases** [Soliman IJROBP '18]
  Local recurrence patterns for postoperative SRS appear to support a [3 mm expansion] of the postoperative cavity.
    - Fuse Pre-op MRI.
    - Contour the entire surgical tract.
    - Extend CTV 5-10 mm along dura overlying bone flap to account for microscopic disease extension in cases with preoperative dural contact.
    - Create a margin ≤ 5 mm into the adjacent sinus when preoperative venous sinus contact is present.
- **SRS for Resected Brain mets - Does the Surgical Corridor need to be targeted?** [Shi PRO '20]: Retro. **± Corridor**.
  Omitting the surgical corridor in post-op SRS was not associated with statistically significant differences in local or corridor failure. The dominant pattern of progression is within the resection cavity. Patients who did not have the surgical corridor targeted were at higher risk of tumor progression. Non-targeting of corridor was associated with breast cancer and infratentorial location, which are known risk factors for LMD. Therefore, omission of the corridor might yield an SRS volume that could allow for dose-escalation to potentially improve local cavity control.
  TBL [QS]: The overall risk of surgical tract failure for deep brain metastases is low when omitted from the SRS target volume so balancing the risk of toxicity should be a careful consideration.
    - 64 patients with 66 "deep" brain metastases ≥ 1 cm from the pial surface prior to resection. Corridor target in 43.
    - 1y LF ~9→ 2% (p=0.25). 1y corridor failure ~9→ 0% (p=0.06). 1y cavity failure ~2→ 0%.
    - 1y ARE 13→ 5%. 1y LMD 26→ 7%. 1y nLMD 13→ 2%.
- **Cancer Care Ontario Organizational Guidelines for Delivery of SRS** [Sahgal PRO '19]:
    - MRI should be within 7 days, certainly no more than 14 days prior to treatment.
    - Follow up: q2-3mo x1y, then q3-4mo for years 2-3.
- **LINAC based SRS for multiple brain mets: Guidance for clinical implementation** [Hartgerink Acta Onc '19]
  Single-isocenter multitarget SRS typically requires all lesions to be of the relatively same size (e.g. all less than 1 cm) and all lesions to be within around 4 cm of the isocenter [Palmer ARO '20].
    - Interval between planning MRI and treatment should be kept as short as possible, e.g. < 2 weeks.
    - Single isocenter non-coplanar VMAT is preferred.
    - Spatially Partitioned Adaptive Radiosurgery (SPARE) [Nguyen IJROBP '19].
        - There is a lower hippocampal dose with radiosurgery for 10-30 brain mets
    - SIMT has better CI and GI than multi-isocentric plans [Kuntz Cancer Radiotherapie '20]
- **Single-Iso Multitarget (SIMT) SRS is Safe & Effective** [Palmer ARO '20]: Retro. **18-24/1, 21-27/3, 25-30/5**.
    - 173 pts with 1,014 brain metastases. Intact mostly < 1 cm, operative bed < 3 cm. MFU 13 mo.
        - Intact and post-op brain mets with 2-3 mm GTV to PTV margin, favoring 2 mm expansions for the isocentric lesion and 3 mm margins for the other lesions to account for added possibility of rotational error with distance from the isocenter.
        - Lesions treated with a single isocenter were no more than 4 cm apart, although size of respective targets were also taken into consideration (e.g. lesions with a large range in sizes were typically excluded from single isocenter treatment due to distinct MLCs required were better suited for multi-iso treatment).
    - Median dose to brain 2.2 Gy.
    - MS 13 mo, freedom from intracranial progression 6 mo.
    - LC at 1 / 2y of 99→ 95%.
    - G2 radionecrosis 1.4%, G3 radionecrosis 1%.
- Frameless: SRS mask, sim with locator box, CT with 1 mm slice, MR within 10 days, no GTV margin. Winston-Lutz daily for isocenter accuracy. RapidArc/Cone based SRS.
    - On average, there is around 1.5 mm of displacement between the frame and the bony anatomy. Do frames move…?
    - Accuracy of frameless appears to be ~0.5 mm [Seneviratne J SRS SBRT '20], less with OSMS [Li Med Phys ‘11].
    - Inaccurate CBCT to CT registration is the #1 cause of mismatch, ensure QA is optimal [Manger Med Phys ‘15].

- Gamma Knife: Place frame. Double gad MRI obtained. 1 mm expansion on tumor. Can use multiple isos. Normalized to IDL best covering, usually 50% IDL.

Follow up

- **RANO Response assessment for brain metastases** [Lin Lanc Onc '15]:
  - Measurable contrast-enhancing lesions ≥ 1 cm in diameter. Criteria for response is based on the sum of the longest diameter of the target lesions (up to five lesions). Response criteria for non-target lesions include mets with a longest diameter < 1 cm, lesions with borders that cannot be reproducibly measured, dural mets, bony skull mets, cyst-only lesions and LMD were also defined.
  - The limits of measurable disease can be lowered to a longest diameter of 5 mm if the slice thickness of the MRI is ≤ 1.5 mm thick, although the committee recommended against this given concerns regarding the reproducibility and interpretation of small changes on follow up scan.
- SRS alone LC:
  - < 2 cm > 90%.
  - 2-3 cm 80-90% if multi-fraction.
  - 3-4 cm 60-70%, potentially higher if multi-fraction.
- **Local recurrence patterns after intact SRS** [Noël RTO '03]: Retro. **± 1 mm CTV margin**.
  Consider a 1 mm margin for intact brain mets. An autopsy series later suggested 1 mm is legit [Baumert IJROBP '06].
  Another study demonstrated no difference for ± 2 mm margin [Nataf IJROBP '08]
  - 61 pts, only 50 with response assessed. 1-2 brain mets. ≤ 3 cm. 1994-2000. MFU 11 mo.
  - Mean minimum dose to GTV of 14.6→ 16.8 Gy.
  - 2y LC 51→ 90%.
  - MVA demonstrated the 1 mm margin to be an independent prognostic factor for local control.
- **Stanford patterns of recurrence after postoperative SRS** [Choi IJROBP '12]: Retro. **± 2 mm PORT margin**.
  Additional margin provides increased local control in the postoperative setting.
  - 120 cavities from 112 patients. 54% D_BM overall.
  - 12 mo LF 16→ 3%.
  - 12 mo toxicity ~3→ 8% (p=0.27).
  - Only 4 patients (3%) required surgery for radionecrosis
- **Local recurrence patterns after postoperative SRS to resected brain metastasis** [Gui PRO '18]: Retro. **Post-op SRS**.
  [N107C] unexpectedly demonstrated better local control for postoperative WBRT over SRS.
  A 3 mm expansion for SRS is recommended, while preoperative dural contact may warrant [larger expansions].
  Choi (above) suggests a 2 mm expansion on the postoperative cavity is warranted for increased local control.
  - 173 pts, 18 of whom experienced local failure.
  - The original SRS volume overlapped with a median of 70% of the recurrence tumor. When the entire preoperative tumor was included, the overlap with the recurrent tumor increased to a median of 77%.
  - Recurrent tumors were closer to the meninges than the corresponding preoperative tumors.
  - Increases in overlap with the recurrent tumor were achieved most efficiently by expanding the contoured cavity, and a median 2.8 mm expansion covered 90% of the recurrent tumor.

Future Directions - Brain Metastases

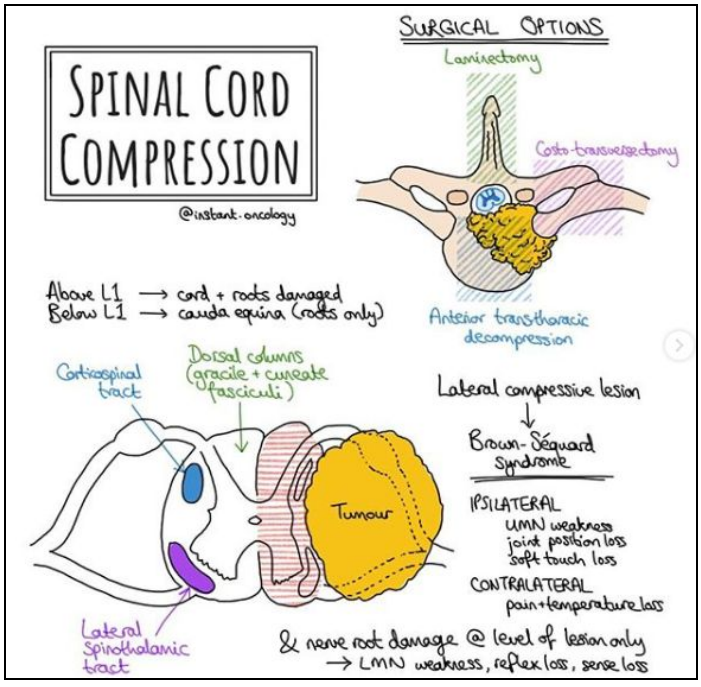
See NCTN Trial Portfolios by Disease Site: [Brain].

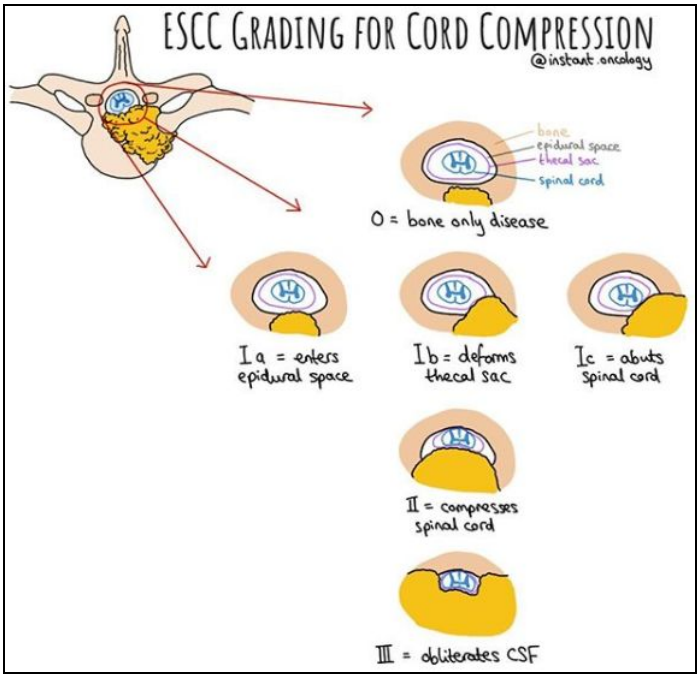
- See [**CCTG CE.7**]: Phase III. **SRS vs. HA-WBRT + memantine** for 5-15 brain metastases.
  - Co-primary endpoints: OS and neurocognitive PFS. Total volume < 30 cc (this is a large disease burden!)
  - There is a lower hippocampal dose with radiosurgery for 10-30 brain mets [Nguyen IJROBP '19].
- See [**A071801**]: Phase III. **Single fraction vs. fractionated SRS** (3-5 fractions).
  - 1-4 BM. Singular resected BM > 2 cm in size with resection cavity < 5 cm. Up to three < 4 cm unresected allowed.
  - Primary endpoint: Surgical bed RFS.
- **A071701** [NCT03994796]: Phase II. Genomically guided Treatment Trial in Brain mets
  - NTRK, ROS1, CDK, or PI3K pathway alterations.
- See [Pre-operative vs. Post-operative SRS] trials.

Cord Compression

StatPearls: Spinal Metastasis *Last update: 12/3/2019.*
Predict survival using [Rades] cord compression nomogram.
LearnOncology.ca: Cord Compression [YouTube]

- Start with the Best Case/Worst Case scenario when counseling patients [video here].
    - Hopefully Palliative Care has been introduced to the patient [video here].
- **Ambulatory status** is the most important prognostic factor, but this **is subjective** as on many trials it is defined as "ambulatory with assistance". **3 out of 5 strength is a more objective measure**, as patients at this level may actually be able to ambulate on their own after treatment.
- Extradural tumors are most commonly metastasis. Intradural/intramedullary primary tumors. Intradural/extramedullary 50/50.
- Maximum safe debulking with spine stabilization followed by EBRT is tx of choice for pts w single region of cord compression and life expectancy > 3 mo.
    - **Laminectomy is not an equal alternative to maximal safe debulking** bc studies report minimal neurological benefit. Commonly the tumor lies ventral to the thecal sac which makes meaningful decompression difficult, and laminectomy can cause or worsen pre-existing spinal instability.
- Radio/chemosensitive - hematologic, GCT, small cell. Level one evidence otherwise for surgery→ EBRT.
- **Workup**
    - MRI C/T/L spine.
    - Start steroids for pain or cord compression.
    - Neurosurgical consult.
- **ASIA International Standards for Neurological Classification of Spinal Cord Injury** [Kirshblum JSCM '11]:
    - **E**: **Normal**.
    - **D**: **Motor incomplete**. Motor fxn preserved below the level, but more than half of key muscle **strength > 3/5**.
    - **C**: **Motor incomplete**. Motor fxn preserved below the level, but more than half of key muscle **strength < 3/5**.
    - **B**: **Sensory incomplete**. Sensory intact but motor fxn is not preserved.
    - **A**: **Complete**. No sensory of motor function is preserved in sacral segments S4-S5.





- **Bilsky Radiographic grades (0-III)** [Bilksy JNS '10]:
  See the Neurologic portion of the NOMS framework below.
    - **0**: spine **bone** involvement only.
    - **I**: **epidural impingement**, but no spinal cord compression.
        - **Ia**: epidural impingement with no deformation of thecal sac.
        - **Ib**: deformation of thecal sac, <u>no cord abutment</u>.
          For up to Ib w/o mechanical instability, consider RT as initial Tx as opposed to surgery.

        - **Ic**: deformation of thecal sac with cord abutment w/o displacement or compression.
          1c role of surgery vs. SRS unclear, as ≥ 15 Gy SRS rec [1] but 14 Gy is cord limit. Hypofrac?
    - **II**: Cord displacement with **CSF still visible**.
    - **III**: Cord compression with **CSF not visible**.
      Grades II-III require surgical decompression prior to RT unless radiosensitive.
        - **Separation surgery**: only minimal tumor resection is carried out to separate tumor margin from spinal cord, leaving the bulk of tumor to be treated with RT.
- **Radiosensitivity varies by histology** [Gerszten Spine '09]:
    - Radiosensitive: Lymphoma, seminoma, myeloma.
    - Moderately radiosensitive: Breast, Prostate.
    - Radioresistant: Sarcoma, Melanoma, GI, NSCLC, Renal.
    - For sensitive and moderately radiosensitive: Median response duration 11 mo, 2y LC 86%.
    - For radioresistant: Median duration of response 3 mo. 2y LC 30%.
    - Pain control for RCC, breast, lung and melanoma above 90% for SBRT. Imaging local control appears to be less than 90% for RCC and melanoma.

NOMS Framework

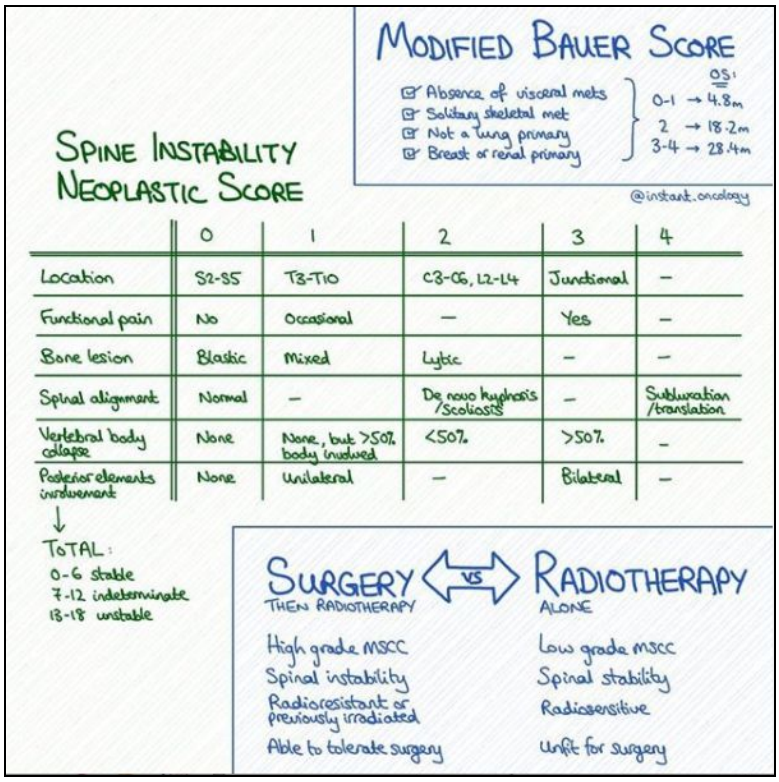
NOMS framework: **Guiding Surgery, RT or Chemotherapy for cord compression** [Laufer Oncologist '13, IAEA ppt]
See the [Spine SBRT/SRS] section for more information.
Summary: Current RT technology allows only pts with radioresistant tumors and high-grade cord compression to require surgery prior to RT unless there is progression of tumor or neuro deficit during RT, prior EBRT/overlapping ports or spinal instability. The type of RT offered depends on tumor histology, with evidence supporting cEBRT for radiosensitive tumors (e.g. 30/10) or SRS/SBRT for radioresistant histologies (24/1 or 27/3).

- **Three predominant pain syndromes**: *Each has significant treatment implications.*

Type	Notes	Treatment
Biologic	Typically **most pronounced at night or early in the morning** when adrenal steroid secretion is lowest. No good position to be comfortable.	Usually responds to Steroids / RT.
Mechanical	Pain with movement, decreased in the morning.	Utilize [SINS] score. Open surgery/PMMA augmentation, percutaneous pedicle screws→ RT.
Radiculopathy	Indicative of neural foraminal disease.	Depends on tumor histo and degree of compression, often RT in absence of instability.
Myelopathy	Indicative of high grade epidural cord compression (e.g. incontinence).	Depends on the radiosensitivity of the tumor. If there is no tissue, then surgery.

- **Neurologic**: Myelopathy, Functional radiculopathy, degree of cord compression [Bilsky].
    - I: Epidural impingement, but no spinal cord compression.
    - II: Cord displacement with CSF still visible.
    - III: Cord compression with CSF not visible
- **Oncologic**: Radiation sensitivity.
  [Histology] might not matter for SRS, while for 30/10 it does.
  For 24/1 SRS, there is evidence that there is a 9% rate of recurrence at 5y, regardless of histology [Yamada IJROBP '11].
  No melanoma patients who received less than 24/1 relapsed [Thiagaragan JCO ‘10].
    - **Sensitive**: Myeloma, Lymphoma, Seminoma.
        - Treatment: For sensitive histologies, consider 30/10 regardless of degree of compression.
    - **Moderately sensitive**: Breast, Prostate, Ovarian, neuroendocrine
        - Treatment: For sensitive histologies, consider 30/10 regardless of degree of compression.
    - **Moderately resistant**: Colon, NSCLC, HCC.
        - Treatment: For resistant histologies, consider 24/1 or 27/3 for up to Grade Ib (no cord abutment). For cord abutment (≥ Grade Ic), consider separation surgery followed by SRS.
    - **Highly resistant**: Thyroid, Renal, Sarcoma, Melanoma (all can be hemorrhagic, and may peripherally enhance on CT without contrast).
        - Treatment: For resistant histologies, consider 24/1 or 27/3 for up to Grade Ib (no cord abutment). For cord abutment (≥ Grade Ic), consider separation surgery followed by SRS.

- **Mechanical Stability**: Is there any pain with movement? If so, then likely needs surgical intervention.
    - Surgery if unstable or if there is high grade cord compression.
    - Use [SINS score]: Refer to neurosurgery if SINS > 7 (potentially unstable), > 12 is unstable.
- **Systemic disease and Medical comorbidity**
    - Less invasive options if high burden of disease or unable to tolerate surgery.

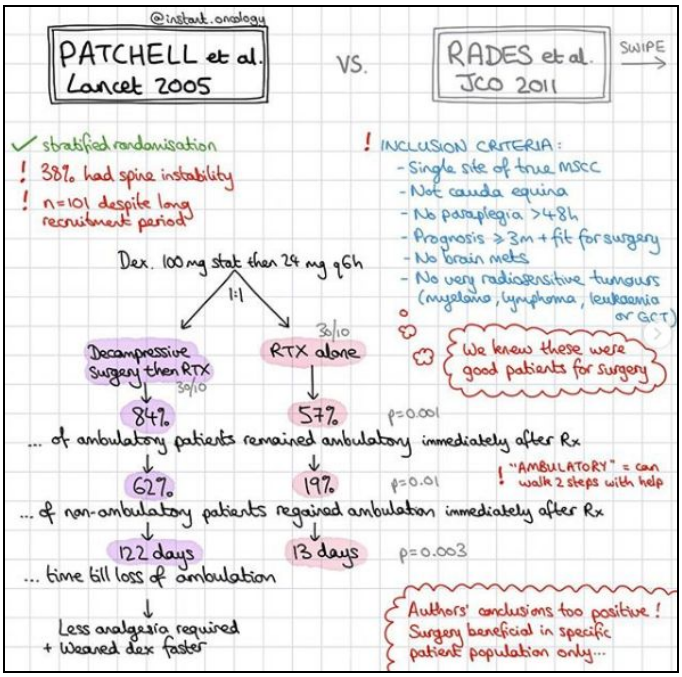


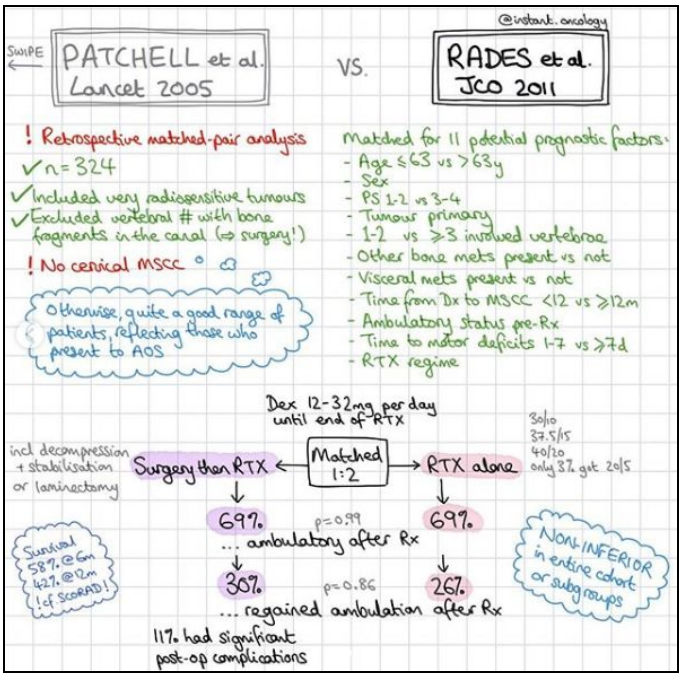
Spinal Instability Neoplastic Score

Spinal Instability Neoplastic Score (SINS) [Fisher Rad Onc '14, Spine '10]: 0-18 points total. Takes into account six clinical and radiographic factors. **≥ 7 warrants neurosurgery referral** (potentially unstable). **> 12 is unstable**.
Many surgeons consider mechanical pain to be the most important factor.

- Global location of tumor. *Junctional location is 3 points: Occiput-C2, C7-T2, T11-L1, L5-S1.*
- Type and presence of bone pain: *Pain w mvmt?*
- Bone lesion quality*: Blastic 0, mixed 1, lytic 2.*
- Spinal alignment.
- Extent of vertebral body collapse.
- Posterolateral spinal element involvement.

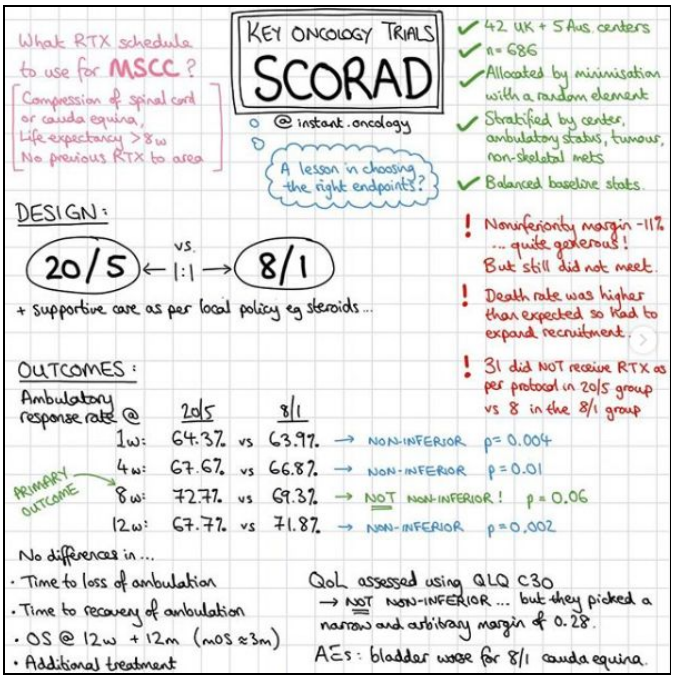
Clinical Trials

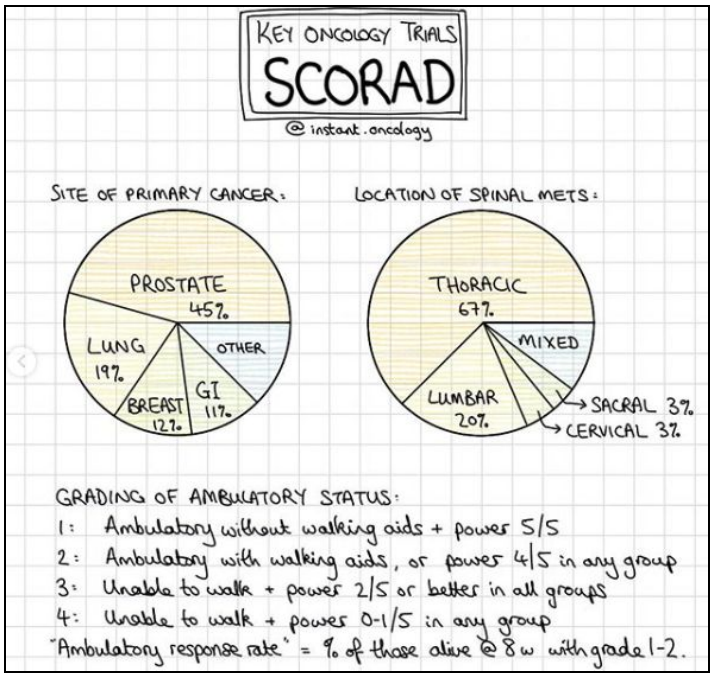




- **Patchell** [Lancet '05]: **± Surgery→ 30/10**.
  Improvement in ambulatory rate and OS with surgery, but this used an anterior approach surgery (uncommon).
  - 101 pts. 70% able to walk at Dx, the rest were with paraplegia for less than 48 hours. Excludes MS < 3 mo.
    - Able to walk = at least four steps unassisted with or without a cane/walker.
    - **Mostly anterior approach surgery** (**corpectomy**). This surgery is better than laminectomy!
    - Lymphoma, myeloma, leukemia, GCT excluded.
    - 20% in the RT group clinically deteriorated and required surgery.
    - This study included spinal instability (~40%), which arguably should have been excluded from the study (these patients automatically go to surgery per the [SINS] algorithm, which came out in 2010).
  - Retained ability to walk 13d→ 113d w surgery. Surgery did not result in increased length of hospital stay.
  - Post-treatment ambulation for no surgery / surgery of 57→ 84%.
    - Of 32 pts unable to walk, **19→ 62% regained ability to walk with surgery**.
  - MS 100→ 126 days.
- **Short vs. long course** [Rades IJROBP '11]: Prospective. (**8/1 or 20/5**) **vs.** (**30/10, 37.5/15, or 40/20**).
  Even though longer courses had better PFS, LC and OS, it still doesn't tell us that 30/10 is better than 20/5.
  - 265 pts. Metastatic spinal cord compression. Primary PFS. MFU 13 mo or death.
  - 1y PFS 55→ 72%. 1y LC 61→ 81%. 1y OS ~23→ 30% (p=0.28). Improved motor function ~38%.
  - MVA: Better OS w improved KPS, no visceral mets, 1-3 vertebrae, ambulatory status and bisphosphonate.
- **SCORE-2** (ARO 2009/01) [Rades JCO '16, IJROBP '19]: Non-inferiority. **20/5 vs. 30/10**.
  Short course (20/5) is non-inferior for pts with ≤ 3 mos prognosis in terms of ORR, ambulatory status, local PFS, or OS.
  Median survival was only 3 months in this study, so meaningful comparisons are not possible.
  TBL^{OS}: In patients with poor or intermediate prognosis and metastatic spinal cord compression, 20/5 is just as effective as 30/10 at relieving patient reported pain and distress.
  - 203 pts. Poor to intermediate expected survival. Pts w motor deficits of LE, no prior surgery or RT to area, not surgical candidates. All RPA Group I or II. 60% able to walk before RT, including with assistance.
  - 1 mo ORR/SD ~90%, split half between groups.
  - 1 mo ability to walk ~70% with nearly half requiring aid.
  - Equivalent 6m response rate, improvement, stability, progression, or ambulatory status.
  - 6 mo local PFS ~80%. 6 mo OS ~40%. MS ~3 mo.
  - 2019 update: Overall pain relief 50-60% with complete pain relief in 20-25%.
    There is no difference in distress relief and pain relief between groups. MS too short for meaningful comparison.
- **Rades** [IJROBP '15]: Matched pair **8/1 vs. 20/5**.
  8/1 is okay with limited survival (3 mos MS).
  - 121 pts in each arm. Limited survival prognosis. MFU 6 mo.

        - Treatment volume 1 VB above and below the metastatic lesion. If lesions extended to the C-spine, then two normal vertebrae above the metastatic lesions were included.
    - ~6 mo in-field re-irradiation 18→ 9% (p=0.11), 12m in-field re-irradiation ~30→ 22% (p=0.11).
    - MS ~3 mo, similar Post-RT motor function with improvement in ~17→ 23% (p=0.21).





- **SCORAD-III** [Hoskin JCO Abstract '17, JAMA '19]: **8/1 vs. 20/5**.
  8/1 is okay with limited survival, however, it just missed reaching non-inferiority criteria. No difference in toxicity, OS, or ambulatory status at 8 weeks. Pain response not assessed.
  TBL [QS]: There is no clinically significant difference after five versus one conventional radiation treatment for non-surgical solid tumor cord compression...other than the number of days a patient comes for treatment.
    - 688 prostate, breast, lung GI pts with cord compression. 66% ambulatory ± aid at enrollment.
        - Limited survival prognosis (>8 weeks - likely KPS < 70), no prior RT.
        - Primary endpoint: Ambulatory status at 8 weeks, if within 11% then non-inferior.
    - MS ~13 weeks. Less than half of patients made it to follow-up at 8 weeks as over one-third had already died.
    - Ambulatory status at 1 / 4 / 8 / 12w of ~64→ 68→ 70→ 70%. *Non-inferiority criteria was barely missed.*
    - G3-4 AE 20%.
- **Ireland ICORG 05-03** [Thirion BJC '20]: Phase III. **10/1 vs. 20/5** not proceeding with surgical decompression.
  For mobility preservation, 10/1 is non-inferior to 20/5 in patients not proceeding with surgical decompression.
    - 112 pts, 73 evaluated for primary. Non-inferiority with detrimental change in mobility of -0.4 mean difference.
        - Modified Tomita score: 1 = walking unaided, 2 = walking with aid, 3 = bed bound.
    - 95% CI for difference in mean change in mobility score between arms was -0.12 to 0.6. Since -0.4 is not in the interval, there is evidence that 10/1 is not inferior to 20/5.
    - MS 6 mo.
    - G2-3 in ~11→ 26% (p=0.09).
- **Rades** [Strahlenther Onkol '11]: **30/10 vs. (37.5/15 or 40/20)**.
    - 203 pts. Favorable survival prognosis.
    - 2y LC 71→ 92%, 2y PFS 58→ 90%, 2y OS 53→ 68%.
- **Italian** [Maranzano JCO '05]: 15/3→ (**16/2 vs. 15/5**).
    - 276 pts. Short life expectancy due to unfavorable histo or good histo with motor deficits or low KPS.
        - RT: 6 day break for the former, 4 day break for the latter.
    - ~60% relief of back pain, ~70% able to walk, ~90% good bladder fxn.
    - MS ~4 mo.
- **Italian** [Maranzano TRO '09]: **8/1 vs. 16/2**.
    - 303 pts.
    - No difference in response or duration.
    - MS ~4 mo both arms.

- **Time from motor deficit development to RT** [Rades '02]:
  Slower development of motor deficits with better outcomes.
  - Subgroups of < 8 days and > 14 days based on time from motor deficit to start of RT.
  - Improvement in symptoms: < 8 days / >14 days of 10→ 89%.
  - Ambulatory rate: < 8 days / >14 days of 35→ 86%.
- **Treat over the weekend?** [Rades PRO '17]: **No benefit!**
  - Overall treatment time for 20/5: 5 vs. 7 days with no difference.
- **PRE-MODE** [Rades IJROBP '19]: Phase II. **20/5** (Historical cohort) **vs. 25/5**.
  There appears to be a benefit in local control with 25/5 versus 20/5, but no difference in motor function.
  - 40 pts received 25/5 and compared to the historical cohort receiving 20/5.
    - 25/5 is theoretically equivalent to 30/10, meaning it should have better results than 20/5.
    - Maximum spinal cord dose was 101.5% (myelopathy risk < 0.03%).
  - 6 mo LPFS 95%. 6 mo OS 43%.
  - Improvement of motor function in 60%.
  - 33 patients (83%) were ambulatory following radiotherapy.
  - Eight of sixteen (50%) with sensory deficits improved.
  - 25/5 was significantly superior regarding LPFS, but not regarding motor function or OS.

Toxicity

- **Re-irradiation for in-field recurrence of cord compression** [Rades Cancer '08]: Retro. Re-irradiation (various).
  Re-irradiation appears to be effective and safe when cumulative BED2 is ≤ 120 Gy.
  - 124 pts. Both courses of RT assumed an $\alpha/\beta = 2$.
    - RT: Mixed bag of 8/1, 15/5, 20/5, 21/7, 20-24/2, 30.6/17.
    - Cumulative BED ≤ 120 Gy in 92% of patients, but >100 Gy in 24% of patients.
  - Motor function improved in 36%, stable in 50%, and deteriorated in 14% of patients.
  - Recurrence at 6 / 12 mo of 52→ 79%.
  - Remaining ambulatory at 6 / 12 mo of 67→ 43%.
  - No RT myelopathy at 11 mo.
  - MVA demonstrated effects of re-irradiation on motor function to be significantly associated with: ECOG, time to development of motor deficits to re-irradiation, and visceral metastases.
  - The re-irradiation schedule had no significant impact on motor function or overall survival.
- **Spinal cord reirradiation** [Nieder IJROBP '06]: **Radiation Myelopathy risk**.
  If using this study, use α / β of 2 even though 3 is used for cord in the modern era.
  Keep cumulative BED2 ≤ 135.5 Gy. No single course with BED2 ≥ 102 Gy. Re-RT interval ≥ 6 mo. If cord compromise imminent, can consider > 2 mo.
  - 38 pts from 5 institutions. A large variety of fractionation schedules with varying BED was used.
    - This study used α / β of 2 for the cervical cord, and 4 for the thoracic cord.
    - Median interval to treatment of 30 mo. MFU 8 mo.
  - No reported radiation myelitis at BED2 < 120, interval > 6 mo, and neither course BED2 > 98.
  - Only 3% radiation myelitis at combined BED2 ≤ 135.5 (up to BED2 150 still was only 3%).
- **HyTEC Spinal cord dose tolerance to SBRT** [Sahgal IJROBP '19]:
  Keep cumulative BED2 ≤ 135.5 Gy. No single course with BED2 ≥ 102 Gy. Re-RT interval ≥ 6 mo. If cord compromise imminent, can consider > 2 mo.
  Initial SRS/SBRT constraints were based off of 45 Gy conventional fractionation to the cord. This is despite Quantec data that demonstrates ≤ 1% RM for cord Dmax ≤ 54 Gy with conventional fractionation.
  "It is important to understand that there may be patients where the risk of spinal cord damage from not achieving tumor control is higher than the risk of RM, therefore clinical judgement is required, alongside such data, to inform practice."
  Moving forward, uniform Reporting Standards for a number of factors are essential to more clearly define constraints!
  Also see: Cord in the Constraints section.
  TBL [QS]: Here's your go-to paper for spinal cord max dose constraints when doing spine SBRT.
  - Cord contours: PRV for T-spine ~1.5 mm, while in C-spine may be 2-3 mm. L-spine may include the entire canal. Be aware of heterogeneous reporting of PRV versus cord with constraints.
  - For de novo SBRT, limit cord Dmax to 12.4-14/1, 17/2, 20.3/3, 23/4, 25.3/5 for 1-5% risk of RM.
    - One example of higher dose levels SRS suggest up to 22.7/1 may be acceptable. Use extreme caution.
  - MTTRM after de novo / re-irradiation conventional RT of 18→ 11 mo.
  - MTTRM after de novo / re-irradiation SBRT of 12→ 6 mo.

- For re-irradiation, suggested to limit thecal sac EQD2 using α/β of 2 to Dmax < 70 Gy, SBRT thecal sac EQD2 Dmax ≤ 25 Gy, thecal sac SBRT EQD2 Dmax / cumulative EQD2 Dmax ratio ≤ 0.5, and a minimum time interval to re-irradiation of ≥ 5 mo.
    - Spinal cord Dmax low RM risk for 3 / 5 fractions of 14.5→ 18 Gy, but depends on prior dose.
    - See Table 4 for further details, and pay attention to ground rules above.
    - There are no guidelines for SRS after 40/20, 45/25, or 50/25. Prior 50/25 should be limited to 15.5/5.

Bone Metastases

StatPearls: Bone Metastasis *Last update: 11/8/2019.*
StatPearls: Lytic Bone Lesions *Last update: 4/4/2019.*

ASTRO palliative guidelines for bone metastasis [Lutz PRO '17].

Fractionation in uncomplicated bone mets
- ➢ No prospective data for optimal dose scheme (8/1, 20/5, 24/6, 30/10 acceptable).
- ➢ EBRT with at least PR of pain in 60-80% of patients, most series suggesting CR in 1/3 of patients.
- ➢ Single fraction with 20% retreatment as opposed to 8% retreatment for prolonged schemes (30/10, 24/6, 20/5).
- ➢ 8/1 is effective and preferred for poor prognosis pts.

Reirradiation of bone mets (non-spine and spine)
- ➢ Only consider retreatment after one month.
- ➢ May reconsider treatment if prior RT was of low dose intensity.
- ➢ EBRT Re-tx w 30-60% pain response [Chow Lanc Onc '14], favoring 60% if 8/1 initially [Huisman IJROBP '12]. Around 40% of patients will not benefit from re-irradiation if treated with EBRT.
- ➢ Suggestion of response >80% at 1y when spinal SBRT is utilized for re-irradiation [Canada Hashmi JNS '16]. Around 20% of patients will not benefit from re-irradiation if treated with SBRT.
- ➢ Need more data if prior RT was higher dose intensity.

SBRT for bone mets
- ➢ The use of advanced RT for painful bone mets or re-tx should be done on clinical trials or prospective registries.
- ➢ Single and multiple fraction regimens routinely used (16-18/1, 24/2, 30-35/3-5).
- ➢ Potential increased risk of VCF, pain flare, and radiation myelopathy for ≥ 20/1.
- ➢ Fractionated SBRT may be more appropriate for larger volumes, or in post-op/reirradiation settings.
- ➢ [RTOG 0631] req'd > 3mm from epidural tumor and cord and < 5 cm of soft tissue extension.

Use of non-RT modalities (plasty, radionuclides, surgery)
- ➢ These techniques do not obviate the need for palliative RT.
- ➢ 24 Gy followed by planned vertebroplasty at one month appears to have excellent results for local control [Wardak]

Complicated bone metastases
- Spinal cord or cauda equina syndrome.
- Impending or existing pathologic fracture.
- Nerve root compression.
- Prior full dose radiation to the spinal cord at that bone.

Uncomplicated bone metastases
- No pathological / impending fracture
- No cord compression
- No prior RT

- Cancer that frequently metastasizes to bone = "PB KTL": **P**rostate, **B**reast, **K**idney, **T**hyroid, **L**ung.
- Most bone mets trials for breast, prostate and lung, so unsure about melanoma. *Use a larger dose per fraction?*
- Acute toxicity worse in multiple fraction regimens, single fraction non-inferior.
- Single fraction with 20% retreatment as opposed to 8% retreatment for prolonged schemes (30/10, 24/6, 20/5).
- Overall rate of pain flare from single fraction 8/1 is 30-40%, while up to 70% for SRS!
  - Consent your steroid-naive pts undergoing SBRT/SRS about pain flare, typically 1 day post-RT.
  - Give dex 4 mg 1 hr prior to SBRT and for four days thereafter.
- **Bone remineralization after RT** [Koswig SRO '99]: **8/1 vs. 30/10**.
  - 107 pts. Pain status and recalcification assessed at baseline, day after, 6w, 3 and 6 mo after RT.
  - ORR ~80%. Complete response in ~33%.
  - Recalcification on 6 mo CT scan of 120→ 173%.
- **NCIC QoL** [McDonald JAMA Onc '17]: 8/1 to answer how soon RT can help improve QoL for painful bone mets.
  - 238 pts. Evaluated pain relief and QoL 10 and 42 days after RT.
  - 40% response rate at 10 days.
- **Dutch bone metastasis trial** [Steenland Rad Onc '99]: **8/1 vs. 24/6**.
  See [Van der Linden's] analysis of pathologic fractures of the femur (13% rate, n=14/110).
  - 1171 pts. Included impending bone fracture.
    - Prior RT, cord compression, C-spine mets, RCC and melanoma excluded.

    - Acute side effects equivalent.
    - Pain ORR 70%.
    - Retreatment 25→ 7%. Path fractures 4→ 2%.
- **TROG 96.05** [Roos RTO '05]: **8/1 vs. 20/5** for neuropathic spinal pain.
  There is a relatively small trend towards inferiority with 8/1 versus 20/5 for neural foraminal involvement.
    - 272 pts. Bone metastasis causing pain with neuropathic components. Spinal in 90%. 1996-2002.
        - Treatment failure defined as: Increased pain score ≥ 1, significant increase in analgesia, re-irradiation, progression or development of fracture, clinical cord or cauda equina compression.
    - Pain response at 2 mo ~53→ 61% (p=0.16). Complete response ~25%.
    - Time to treatment failure ~2.4→ 3.7 mo (p=0.06).
    - MS 5 mo.
    - There were no statistically significant differences in rates of re-treatment, cord compression, or pathologic fracture.
- **EPOSO Cohort: Treatment of Cervical Spine Metastases** [Bond Global Spine '20]: Prospective. **Surgery vs. RT**.
  This is not a comparative study. The two groups must be looked at individually as there were baseline differences in groups. Patients who have worse pain scores and baseline disease-specific and generic HRQOL scores typically go to surgery.
    - 55 pts, 38 underwent surgery + RT and 17 received RT alone. 2013-2017.
        - Most commonly in cervicothoracic junction, with 64% of pts having disease between C6-7.
        - Surgery: Posterior surgical approach in 60% (n=23), anterior in 24% (n=9) and combined in 16% (n=6).
        - RT: Half of the 17 pts had conventional (20/5), half with SBRT (24/2).
    - Presented with mechanical neck pain before intervention in 90→ 38%.
    - [SINS] score of 13→ 8. Surgery arm also had higher pain scores and lower HRQOL scores.
    - From baseline to 6 mo post-treatment, surgically treated patients had improvements in pain score, EQ-5D, and SOSGOQ2.0 scores compared with non-significant improvements in the radiotherapy alone group.

RTOG 9714 [Hartsell JNCI '05]: **8/1 vs. 30/10**.
Around 2/3 of patients have response with 8/1 or 30/10, while 8/1 appears equivalent to 30/10.
Single fraction and 10 fraction RT were equivalent at 3 mo with few AE.
There were more retreatments with single fraction arm but less toxicity.

- 898 pts. KPS ≥ 40. Breast or prostate with 1-3 painful bone mets and mod to sev pain.
- 3 mo ORR 66%, with ~15% CR. At 3 mo, 33% no longer need narcotics.
- **3y re-treatment 18→ 9%**. Potentially biased due to increased likelihood to treat after 8/1.
- G2-4 toxicity 10→ 17%.
- Subgroup of painful vertebral body with essentially the same findings.

Meta for bone metastases [Chow JCO '12, Lanc Onc '14]: **Single vs. multi-fraction RT**.
There were no significant differences between single fraction and multi-fraction in overall or CR rates.

- 5,617 pts from 25 RCTs.
- ORR ~60% with ~24% CR.
- There was no difference in pathologic fractures.
- Overall pain relief ~50% for either 8/1 or 20/5.
- Trend for reduced risk of cord compression with multi fraction RT.
- There is a 2.6x increased retreat event rate with single-fraction RT. Potentially biased due to increased likelihood to treat after 8/1.

Surgery

- **Balloon Kyphoplasty**:
    - Minimally invasive technique where intervertebral cavity is opened and filled with PMMA cement, restoring VB height.
    - RCT with compression fracture observed or treated with kyphoplasty with improved QoL, KPS and activity at 1 mo.
    - No consensus on the utility of kyphoplasty prior to RT.
- **Vertebroplasty**: Percutaneous injection of cement into compromised VB. [RTOG 06-31] only allowed up to 10% of vertebral body involvement, while this study suggests up to 20-40% VB involvement or even higher may be reasonable, identifying high-risk patients who would benefit from prophylactic vertebro or kyphoplasty. The [Wardak] study demonstrated improved local control *and* pain scores with prophylactic vertebroplasty 1 month after 24/1: Caution should be practiced when considering vertebroplasty in the presence of epidural tumor extension and/or significant lytic destruction of the posterior vertebral body, particularly in the setting of retropulsion of tumor or bone from the involved vertebral body. Although significant neurologic toxicities from vertebroplasty are rare, they have been reported. Localizing the delivery of

the PMMA mixture to the anterior third of the vertebral body may minimize this complication. It has been shown that adequate augmentation of the vertebral body compression can be obtained as long as the cement crosses midline.

When is intervention/prophylactic fixation needed?

- **Mirels criteria for long bones** [CORR '89]: A score of 9 or more requires prophylactic fixation prior to RT.
  12 point scoring based on conventional x rays (3 points each). Scores of 10-12 have a 72-100% risk of bone fracture.
  1. Site: UE, LE, peritrochanteric.
  2. Pain: mild, mod, functional.
  3. Lesion: blastic, mixed, lytic.
  4. Size: < 1/3, 1/3 to 2/3, > 2/3 diameter of bone involved.
- **Van der Linden for femur** [JBJS '04]: **8/1 or 24/6→ follow for development of fractures**.
  Return to the [Dutch bone metastasis] trial.
  Mirel's is insufficient to predict fractures when receiving RT! Use [30 mm] axial cortical involvement on plain films instead.
  Mirel's scoring system appears to overestimate actual occurrence of pathological fractures of the femur.
  Axial cortical involvement is measured in the craniocaudal direction on plain X-ray.
  - 102 pts with 110 femoral lesions. Only 14 fractures occurred during follow up.
    - Studied Mirels, site, increasing pain, size of lesion, type of lesion, and involvement of cortex.
  - Mirel's scoring system was insufficient to predict for fracture (p=0.36).
  - Only axial cortical involvement > 3 cm and circumferential cortical involvement > 50% were predictive for fracture.
  - Mirels 9+ (p=0.36): Sn 100%, Sp 13%, PPV 14%, NPV 100%.
  - Circumferential cortical involvement > 50% (subjective on Xray): Sn 43%, Sp 82%, PPV 26%, NPV 91%.
  - Axial cortical involvement ≥ 3 cm: Sn 86%, Sp 58%, PPV 23%, NPV 97%.
- **Femoral fracture risk** [van der Wal RTO '19]: **RT for pain→ ± 30 mm of axial cortical involvement on plain films**.
  Mirel's is insufficient to predict fractures when receiving RT!
  Recommend prophylactic fixation for axial cortical destruction ≥ 3 cm.
  Mirel's scoring system overestimated actual occurrence of pathological fractures of the femur.
  Axial cortical involvement is measured in the craniocaudal direction on plain X-ray.
  Lesions with axial cortical involvement ≥ 3 cm are at 20% risk of fracture.
  - 100 pts with 110 lesions. Only 13% developed fractures during follow up. MFU 2y.
  - Patients with lesions ≥ 3 cm had 5.3x higher fracture risk than patients with smaller lesions.
  - Axial cortical involvement > 3 cm: Sn 86%, Sp 50%. PPV 20%, NPV 96%.
  - Mirels 9+ (p=0.10): Sn 77%, Sp 45%, PPV 17%, NPV 93%.
  - Judgement of impending fracture based on clinical experience (p=0.13): Sn 43%, Sp 78%, PPV 22%, NPV 90%.
- **Harington's criteria** [Orthobullets]:
  - > 50% destruction of diaphyseal cortices.
  - >50-75% destruction of metaphysis (> 2.5 cm - appears to be > 3 cm as per Van der Linden and van der Wal)
  - Permeative destruction of subtrochanteric femoral lesions.
  - Persistent pain following RT (disproved per Van der Linden)

- **Hyperthermia** Taiwanese RCT [Chi IJROBP '18]: Phase III. **30/10 ± hyperthermia**.
  TBL [QS]: Over one third of pts achieved complete pain response, although most interestingly over half of the patients received hyperthermia achieved re-ossification at the tumor site, which the authors attribute to thermo-stimulation of osteoblast activity. There's no proof, but re-ossification theoretically contributes to longer pain control and mechanical stability--two real problems in this population. But because haters gonna hate, pain control in the radiation-alone arm was pretty bad (7% CR vs 18% in RTOG 97-14), and SBRT could arguably do better. So while this adds fodder to rad bio lunchroom convos, it's unlikely to become the next hot trend anytime soon.
  - 57 pts. Painful bony mets, mainly spine.
    - Thermotron RF-8: maintenance target temperature (40-43C) for 40 min per treatment within 2 hours after RT, twice weekly for two weeks.
  - CR pain 7→ 38%.
  - Median time to pain progression 55d→ NR in 24 week follow-up.

Retreatment

- **Retreatment**
  - EBRT Re-tx w 30-60% pain response [Chow Lanc Onc '14], favoring 60% if 8/1 initially [Huisman IJROBP '12]. Around 40% of patients will not benefit from re-irradiation if treated with conventional EBRT.

    - Suggestion of response >80% at 1y when spinal SBRT is utilized for re-irradiation [Canada Hashmi JNS '16]. Around 20% of patients will not benefit from re-irradiation if treated with SBRT.
- **SBRT/SRS Re-tx** [Canada Hashimi JNS '16]: Retro. **The only multi-institution analysis on SBRT retreatment.**
  Note: Single fraction SRS appears superior to multi-fraction SBRT according to the available data.
  Note: Consider up-front SRS to 24 Gy as opposed to conventional for radioresistant histology.
    - 215 pts w 247 **spinal** targets. Median initial 30/10, subsequent median SRS 16.6/1 or 24/3 SBRT. MFU 8mo.
    - MS 12 mo w 1y OS 48%. *Single fraction regimen appears superior.*
    - LC at 6 / 12 mo of 93→ 83%.
    - Toxicity limited (no myelopathy) with **VCF rate of 4.5%**.
    - Of note, single fraction found to predict better LC despite similar equivalent 2 Gy doses in both regimens.

Spinal SRS
Improved pain score and maximize local control for 24 Gy in 1 fraction! However, VCFs are not insignificant. Prophylactic vertebro or kyphoplasty should be considered. PTV should be trimmed out of the spinal canal or cauda. For patients with spinal cord abutment and radioresistant histology (e.g. Melanoma, RCC, sarcoma), separation surgery should be performed prior to radiosurgery. Otherwise, 30/10 is acceptable for radiosensitive histologies with cord compression [NOMS framework].

- ➢ Yamada from MSKCC has paved the way to demonstrate 24/1 leads to optimal local control, with < 5% local failure regardless of histology. Considering 27/3 may also be reasonable.
- ➢ Caution with 24/1: Suggestion of 40% vertebral compression fractures [Sahgal, Rose]. This is 20% for 20-23 Gy [Sahgal].
- ➢ [RTOG 06-31] only allowed up to 10% of vertebral body involvement, while the [Rose] study suggests up to 20-40% VB involvement or even higher may be reasonable, identifying high-risk patients who would benefit from prophylactic vertebro or kyphoplasty.
- ➢ [RTOG 06-31] protocol allowed 16 Gy in 80% coverage, which probably equates to ~10-12 Gy to D95 (insufficient Rx?).
- ➢ The [Wardak] study demonstrated improved local control *and* pain scores with prophylactic vertebroplasty 1 month after 24/1: Caution should be practiced when considering vertebroplasty in the presence of epidural tumor extension and/or significant lytic destruction of the posterior vertebral body, particularly in the setting of retropulsion of tumor or bone from the involved vertebral body. Although significant neurologic toxicities from vertebroplasty are rare, they have been reported. Localizing the delivery of the PMMA mixture to the anterior third of the vertebral body may minimize this complication. It has been shown that adequate augmentation of the vertebral body compression can be obtained as long as the cement crosses midline.

Spine SBRT/SRS

See the [NOMS framework] in the cord compression section.
See why the Summary Box above for why 24/1 makes a lot of sense.
SBRT for spinal mets: Defining the zones of treatment [Zaorsky tweet].

- Generally reserved for disease in 1-2 spinal segments (**at most, 3 spinal segments**) and SINS 0-6.
- **Not indicated for true cord compression, need at least 2-3 mm from cord to create PRV** [Weksberg].
    - Disease compressing cord with CSF still visible around the cord is a relative contraindication.
- **MDACC** [Garg MDACC '11]: Prospective. **Spinal reirradiation. 30/5 or 27/3**.
  Initial surgery should be considered for tumors within 5 mm of the spinal cord.
    - 59 pts with 63 tumors of the spine. 2003-2009. Prior RT dose to cord < 45 Gy. MFU 1.5y.
        - RT: Interestingly, utilized mean dose constraints to the cord (mean 10 Gy).
    - 1y radiographic LC/OS 76%.
    - Of the tumors that progressed, 81% (n=13) had tumors within 5 mm of spinal cord, and 6 of them eventually developed spinal cord compression.
    - 1y freedom from neurologic deterioration of 92%.
- **SBRT is an effective treatment in reirradiation of spinal metastases** [Masucci Expert Rev Anticancer Ther '11]:
    - Meta. MFU nearly 12 mo. Local control 79%. Local failures post-SBRT 21%.
- **SBRT in the re-irradiation setting: A review** [Mantel Rad Onc '13]
- Literature suggests a local control benefit with SBRT/SRS, but mostly retrospective data.
    - LC generally exceeds 80% at 1 year, up to 95% at 18 mo [Huo SNI '17].
        - Favor around 80% for PORT, 90% for upfront RT due to uncertainties of tx volume after surgery.
    - Doses most commonly 15-24 Gy/1 to 27-30 Gy in 3 fractions.
- Huo [SNI '17]: **Spine SRS: Review of safety and efficacy with respect to dose and fractionation**.

- Gersten [Spine '07]: **Prospective** single arm. **12.5-25 Gy SRS** (Mean 20 Gy).
  SRS to spinal metastases results in favorable outcomes, with at leaset 90% local control. Caution applying local control data to melanoma metastases. Fortunately, BRAFi and ICI (Nivo 3 + Ipi 1 q2w) have significant intracranial responses.
  - 500 pts, 344 with previous EBRT. MFU 21 mo.
    - RT: Maximum tumor dose ranges from 12.5 - 25 Gy.
  - Long term pain improvement and radiographic control in > 85%
    Histology dependent? Melanoma has ~75% long term radiographic control. Is there a role for 24/1 for Melanoma?
- **MSKCC LC** [Yamada ASTRO '11]: 18-**24 Gy SRS**.
  >90% LC for SRS upfront, a benefit regardless of histology or tumor size.
  Caution with 24 Gy: Suggestion of 40% vertebral compression fractures. This becomes 10% for < 20 Gy.
  - 410 lesions in 372 pts. 2003-10. Prior surgery or RT excluded. MFU 16 mo.
  - 5y LC 91%.
  - LC for 18-23 Gy / 24 Gy of 74→ 91%.
- **MSKCC RCC/Melanoma** [Thiagaragan JCO Abstract '10]: Prospective. **Spine SRS**.
  - 50 RCC, 30 melanoma. 2004-2008. Imaging and Eval q3-4 mo til death.
  - MS 9 mo. 90% w durable pain control.
  - Durable LC for 18-22 / 24 Gy of ~77→ 96% (p = 0.12).
  - All Melanoma pts who rec'd less than 24 Gy experienced local relapse.
- **MSKCC Long term LC for RCC** [Zelefsky IJROBP '12]: Retro. **20-30/3-5 vs. 24/1 for RCC**.
  Consider 24/1 for RCC. Caution with 24 Gy: Suggestion of 40% vertebral compression fractures.
  While reported LC is 30-40% with conventional [Amini PRO '15], there is nearly 90% 3y PFS with 24/1 for RCC!
  - 105 pts. Single dose IGRT to 24/1 (~75%), range 18-24 (15% 21 Gy) vs. 3-5 fx to 20-30 Gy. MFU 12 mo.
  - 3y PFS 44%.
  - **3y PFS for** Hypofractionated (n=46) / < 24/1 (n=14) / **24/1** (n=24) **of** 17→ 21→ **88%**.
    - For < 24/1, 2 were 18 Gy, 9 were 21 Gy and 3 were 22 Gy.
  - MVA w 24/1 and single dose vs. hypofractionation independent predictors.
- **SAFFRON** [Singh RTO '20]: Meta. **Conventional vs. MF-SRS vs. SF-SRS**.
  TBL [QS]: Pooling multiple studies, single-fraction SRS results in superior local control at the expense of a fairly high rate of vertebral compression fracture.
  There may be a role for [prophylactic vertebroplasty] after SRS due to the high risk of VCF.
  - 37 studies. 3,237 pts with 4,911 spinal mets. Primary outcomes 1y LC and acute/late G3-5 toxicities.
  - 1y LC 81→ 82→ 93%.
  - 1y LC for de novo spinal mets of 84→ 83→ 96%.
  - 20-24/1 is associated with excellent local control and pain control, perhaps consider 24/1 for RCC.
  - Some studies report excellent control for 24/2, 27-30/3, and 30/5, but MF-SRS still appears inferior to SF-SRS. Correlation with poorer local control was noted for 16-18/1 and 24-27/3.
  - There was great heterogeneity in reports especially for MF-SRS. More homogeneous fractionation schemes should be compared prospectively with single fraction SRS.
  - Overall G3-5 toxicity < 1%.
  - MTT VCF ranged from 5 - 16 mo.
  - VCF for MF-SRS / SF-SRS of 10→ 20%.
  - For lesions treated with SRS, a 4.7% increase in LC was noted for every 10 Gy increase in BED 10:
    - BED10 of 50 Gy appears to be associated with 1y LC of 80% (e.g., 18/1, 24/2, 27/3, 30/5).
    - BED10 of 80 Gy appears to be associated with 1y LC of 90% (e.g., 24/1, 32/2*, 36/3*, 42.5/5*).
  - *Caution applying these doses. The most commonly investigated multi-fraction doses appear to be 24/2, 27-30/3 and 30/5. Some institutions dose-paint VB GTV up to 39/3 using protons, with 21/3 to remainder of VB.
- **MSKCC Long term LC** [Yamada Neurosurg Focus '17]: **24/1** (16 - 26 Gy), allowing 30% hotspot.
  - 811 lesions in 657 patients. 2003-2015. MFU 2y.
    - Volumes per [Cox IJROBP '12]. (Figure 2) [Zaorsky tweet].
    - PTV constricted to a 2-3 mm margin around the CTV, but never allowed to transgress the cord/cauda.
  - There was no difference in local failure by histology subtype.
  - Aim for median GTV D95 of 23.56 Gy (minimum 18.3 Gy) and PTV D95 of 22.33 Gy (minimum 17.4 Gy).
  - Patients in the high dose cohort had a 2% cumulative incidence of local failure.
- **German** [Sprave RTO '18]: **30/10 vs. 24/1**.
  - 55 pts. Primary outcome pain response. Baseline VCF in 29%.
    - 24/1 Rx to 80% IDL. Same constraints as RTOG 06-31.
  - VCF at 3/6 mo for SBRT of 9→ 28%.
  - No difference in pain analogue score at 3 mo, though pain values decreased faster in SBRT arm.

    - SBRT with better pain control at 6 mo.
    - No differences in opioid consumption at 3 or 6 mo.
    - No patients in the SBRT arm experienced G3+ toxicity.
- **German** [Guckenberger Cancer '18]: Long survival expectancy **48.5/10**, intermediate survival expectancy **35/5**.
    - 57 patients with 61 lesions. 2012-2015.
    - 3 mo pain response of 87%, remaining stable for at least 12 mo.
    - 1y OS 61%.
    - 1y LC 86%.
    - Risk factors for VCF after spine SBRT [Mantel RTO '19]: Phase II. MFU 16 mo, median radiological FU 8 mo.
        - 8 mo LC 82%.
        - VCF in 34%, with only 5% symptomatic.
        - Relative VB involvement (>34%), osteolytic volume and pre-SBRT VCF are significant RF on MVA.
- **RTOG 0631** [Ryu PRO '14, Ryu ASTRO '19, van de Ven IJROBP '20]: Phase II/III. **8/1 vs. 16/18 SRS**. V16 > 80-90%.
  Recall: VCF rates for ≤ 19 Gy of 10%.
  Insufficient dose? Protocol allowed 16 Gy in 80% coverage, which probably equated to ~10-12 Gy to D95.
  There was a lower rate of pain control than expected in the SRS. Hypothesis that the SRS dose may not have been adequate.
  TBL [QS]: We're gonna shoot straight here: it just got more difficult to justify upfront spine SRS for most spine mets.
  TBL [QS]: Pain control alone isn't an indication for using SBRT techniques for a bone met.
    - Eligibility: Localized spine metastasis in 1-3 sites, where two contiguous spines treated as one site. Subclinical metastasis in < 10% of each VB were also allowed, usually incidentally detected by MRI.
        - Radioresistant histologies included: RCC, melanoma and STS.
    - Ineligibility: VCF with > 50% loss of VB height, prior RT, bony retropulsion, < 3 mm gap from cord, > 5 cm paraspinal mass.
        - Radiosensitive histologies excluded: Myeloma and lymphoma.
    - RT volumes: 8/1 treated 1 VB above and below, SRS included involved spine segment only.
    - Cord contours 5-6 mm above and 5-6 mm below target spine.
        - Cord limits: V14 < 0.03 cc, V10 < 0.35 cc. V10 < 10%.
        - Cauda limits: V16 < 0.03 cc, V14 < 5 cc.
        - Sacral plexus: V18 < 0.03cc, V14.4 < 5 cc.
    - Early report: 46 pts. 33 pts evaluated for toxicity. 4/33 (12%) with increased back pain, but not closely monitored in the first 10d.
    - 215 pts. Up to 5 cm paraspinal mass: solitary, 2 contiguous spine levels, up to 3 separate sites.
        - This trial has exemplary QA for SBRT. Around 50/50 got 16 or 18 Gy in the SRS arm.
        - RT volumes: SRS treated the affected VB, while 8/1 treats one VB above and below as well.
    - 3 mo pain response ~58→ 40% (p=0.99). 6 mo pain response nearly no difference at ~62→ 56%.
    - MPFS 5→ 12 mo.
    - Metastasis control and re-irradiation rates were better after SBRT, however.
- **MDACC** [Nguyen JAMA Onc '19]: Phase II. **30/10 vs. 12/16 Gy SRS**.
  For non-spine bone metastasis, higher dose SBRT demonstrates a higher rate of pain response, and should be considered for patients with longest expected survival.
    - 160 pts. Mostly non-spine bone mets. 12 Gy for ≥ 4 cm lesions, 16 Gy for < 4 cm lesions.
        - Primary pain response: Worsening pain score of ≥ 2 or 50% increase in morphine equivalent.
        - The SBRT group all received dexamethasone at the time of treatment to reduce pain flair.
    - Pain response at 2 weeks of 36→ 62%.
    - Pain response at 3 mo of 49→ 72%.
    - Pain response at 9 mo of 46→ 77%.
    - 1y LC ~80→ 100% (not powered for local control).
    - No differences in QoL.
- Wardak [IJROBP '19]: Phase II. **SABR 20 Gy to GTV, 14 Gy to VB→ prophylactic vertebroplasty** at 1 mo.
  Single fraction SABR followed by prophylactic vertebroplasty improves pain response compared with conventional RT while providing long term pain control and structural stability of the treated spine.
  Caution should be practiced when considering vertebroplasty in the presence of epidural tumor extension and/or significant lytic destruction of the posterior vertebral body, particularly in the setting of retropulsion of tumor or bone from the involved vertebral body. Although significant neurologic toxicities from vertebroplasty are rare, they have been reported. Localizing the delivery of the PMMA mixture to the anterior third of the vertebral body may minimize this complication. It has been shown that adequate augmentation of the vertebral body compression can be obtained as long as the cement crosses midline.
    - 29 patients. No prior RT to VB. Excluded myeloma and lymphoma. Up to 2 contiguous levels or up to 3 noncontiguous single VBs eligible. VCF defined as > 20% VB height loss. No baseline VCF allowed. MFU 10 mo.

- 3 mo pain response on RTOG 97-14 / Wardak of 51→ 95%.
- 3 mo complete pain response on RTOG 97-14 / Wardak of 17→ 57%.
- 10 mo LC of 92%.
- 1y VCF 10%.
- No G2+ toxicity.

- **JHH** [Redmond IJROBP '19]: **Surgery→ 30/5**.
  - 35 pts. KPS ≥ 40. Spine mets from solid tumors, no prior overlapping RT. ≤ 3 consecutive VB levels.
    - See postoperative planning guidelines [Redmond].
  - 1y LC 90%. MTTR 3.5 mo.
- **Toronto** [Tseng IJROBP '18]: Prospective. **24/2** de novo to spine.
  There is around a 20% chance of failure at 4 years with 24/2.
  - 279 de novo spinal mets in 145 patients. MFU 15 mo.
    - Volumes per [Cox IJROBP '12]. (Figure 2) [Zaorsky tweet]. PTV = CTV + 2 mm.
    - Cord PRV = 1.5 mm. Cord limited to 17 Gy in 2 fractions.
  - OS at 1 / 2y of 73→ 61%.
  - Presence of epidural disease, lung, RCC and baseline diffuse metastasis were significant prognostic factors for OS.
  - LF at 1 / 2y of 10→ 18%. MTTLF 9 mo. Only the presence of epidural disease predicted for local failure.
  - VCF at 1 / 2y of 9→ 14%. Lytic components, spinal malalignment, and PTV D90% were predictive for VCF.

Toxicity

Vertebral compression fractures

- **Vertebral compression fractures after SBRT** [Sahgal JCO '13]:
  Most VCFs occur within the first 4 months.
  - 252 pts, 410 spinal segments. Multi-institution retro. MS 16 mo.
  - **14%** developed VCF (57/410). 47% new (27/57) and 53% fracture progression (30/57).
    - Median time to VCF: 2.5 mo with 65% within the first 4 months.
    - Conventional RT with ~3% rate of VCF.
  - 1/2y cumulative incidence of VCF of 12 and 13%, respectively.
  - **1y compression fracture for ≤ 19 / 20-23 / 24+ Gy of ~10→ 20→ 40%**. Know this cold!
  - MVA greatest risk for ≥ 24 Gy vs. 20-23 Gy vs. ≤ 19 Gy, baseline VCF, lytic tumor, and spinal deformity.
- **Vertebral fracture risk after Spine SRS** [Lee ASTRO '19]: Median 18/1.
  - 85 patients. 173 VBs. Prior VCF if 22%. Epidural disease in 40%. MFU 14 mo.
  - All patients prescribed 16 or 18 Gy in 1 fraction.
  - 1y OS 66%. 2y OS 43%.
  - Crude incidence of fracture of 12%. Half progressive and half de novo.
  - Limit vertebral V20 < 24% for 90% sensitivity for VCF.
  - Limit vertebral V24 to 0%.
- **Vertebral compression fracture risk after spine SRS** [Rose JCO '09]: Retro. **18-24/1**.
  [RTOG 06-31] only allowed up to 10% of vertebral body involvement, while this study suggests up to 20-40% VB involvement or even higher may be reasonable, identifying high-risk patients who would benefit from prophylactic vertebro or kyphoplasty. The [Wardak] study demonstrated improved local control *and* pain scores with prophylactic vertebroplasty 1 month after 24/1.
  - 71 sites in 62 patients.
  - Fracture progression was noted in 40% of vertebrae. MTT fracture 25 mo.
  - Lesions between T10 and the sacrum were 4.6 times more likely to fracture than lesions above T10.
  - Lytic lesions were 6.8 times more likely to fracture than sclerotic or mixed lesions.
  - As percent vertebral body involvement increased, odds of fracture also increased. Among the 13 lesions which were lytic and occupied 40-80% of the VB, 11 showed evidence of fracture progression.
  - Patients with fracture progression have significantly higher narcotic use, change in KPS, and strong trend towards higher pain scores.

Steroid naive pts should be consented for pain flare, typically occurring the first day after SBRT/SRS. Give 4 mg Dex 1h prior to RT and for four days after SBRT.

Pain flare

Pain flare is reported in 30-40% of steroid-naive pts for 8/1.
Pair flare is reported in up to 70% of steroid-naive pts for SRS, with SBRT having lower rates.

- **NCIC CTG SC23 Dexa study** [Chow Lanc Onc '15]: **8/1→ Placebo vs. 8 mg Dex x5 (day 0,1,2,3,4)**.
  Pain flare is decreased with steroids. Even with steroids, around 20-25% of patients will experience pain flare with single fraction 8/1.
  - 298 pts. Monitored at baseline and post-RT days 1-10. One-sided alpha, power 90%.
    - Pain flare: +2 pain score or 25% increase in opioid intake with no decrease in worst pain score.
  - Pain flare (PF) 35→ 26%. Sensitivity analysis 25→ 18%.
  - Proportion of pain flare in days 0-5: 31→ 20%. No difference in days 6-10.
- **Dutch DEXA study** [van der Linden IJROBP '20]: **Placebo vs. 8 mg Dex x1** (day 0) **vs. 8 mg Dex x4** (day 0,1,2,3).
  Lower power than the NCIC study, failed to demonstrate improvement with dex. However, pain flares were delayed.
  TBL [QS]: A second large phase 3 trial failed to confirm a significant advantage in pain flare prevention with prophylactic dex given with conventional palliative radiation for painful bone mets.
  - 295 pts. Monitored at baseline and post-RT days 1-14. Uncomplicated. 2012-2016. Two-sided, power 80%.
    - RT: 8/1 or 20/5. Rarely 24/6.
    - PF = +2 pain score or 25% increase in opioid intake with no decrease in pain score with return to baseline.
  - Pain flare (PF) ~39→ 27→ 38% (p=0.07). Sensitivity analysis PF ~25→ 16→ 25 (p=0.09).
  - Mean duration of pain flare ~3.3→ 4.5→ 2.1 days (p=0.06).
  - Pain flare occurrence on day 2-5 of 99→ 73→ 52%. *Dexamethasone postponed pain flare occurrence.*
  - Patients given four days of dex reported lower mean pain scores on days 2-5 than in B or C.
  - No PF or pain progression 37→ 50→ 48%. Sensitivity analysis 51→ 61→ 61%.
  - PF after 8 / 20 Gy of 36→ 27%. Sensitivity analysis PF of 23→ 22%. *There appears to be no differences in RT dose.*
- **Pain flare with SBRT** [Chiang IJROBP '13]: Prospective. Steroid-naive pts.
  - 41 pts. 2010-2012. Pain assessed at baseline, during, and for 10d after SBRT.
    - Nearly 50% got 20-24/1 SRS, while over 50% got 24-35 Gy in 2-5 fractions.
    - Pain flare is 2 point increase in worst pain score vs. baseline with no decrease in analgesic intake, a 25% increase in analgesic intake as compared to baseline with no decrease in worst pain score, or if corticosteroids were initiated at any point during or after SBRT due to pain.
  - Pain flare in 68%. Typically (30%) occurs on day 1.
    - MVA for pain flare: HR for Lumbar / Cervical / KPS of 29→ 11→ 1.2.
- **Pain flare with SBRT** [Khan Supp Care Cancer '15]: Prospective. **Historical vs. 4 mg vs. 8 mg Dex** qd x5d.
  4 mg qday has similar results to 8 mg qday.
  - 47 pts (4 mg vs. 8 mg) compared to 41 steroid naive patients (historical).
    - Dex given 1h prior to RT and for four days after SBRT. Pain at baseline and days 1-10 after SBRT.
    - RT for steroid cohort: 24-30 Gy in 2-5 fractions (80%), 20-24/1 SRS (20%).
    - RT for historical cohort: Nearly 50% of historical got 20-24/1.
  - Pain flare for historical (no dex) vs any dex of 68→ 19%.
    - Pain flare for 4/8 mg of ~25% (n=6/24)→ 13% (n=3/23) (p=0.46).
    - 4 mg with better QoL: Better walking ability, relationships with others.

<u>Cord tolerance</u>

Cord tolerance for SBRT in the reirradiation setting is one of the biggest controversies.

- **HyTEC Spinal cord dose tolerance to SBRT** [Sahgal IJROBP '19]:
  Initial SRS/SBRT constraints were based off of 45 Gy conventional fractionation to the cord. This is despite Quantec data that demonstrates ≤ 1% RM for cord Dmax ≤ 54 Gy with conventional fractionation.
  "It is important to understand that there may be patients where the risk of spinal cord damage from not achieving tumor control is higher than the risk of RM, therefore clinical judgement is required, alongside such data, to inform practice."
  Moving forward, uniform Reporting Standards for a number of factors are essential to more clearly define constraints!
  Also see: Cord in the Constraints section.
  TBL [QS]: Here's your go-to paper for spinal cord max dose constraints when doing spine SBRT.
  - Cord contours: PRV for T-spine ~1.5 mm, while in C-spine may be 2-3 mm. L-spine may include the entire canal. Be aware of heterogeneous reporting of PRV versus cord with constraints.
  - For de novo SBRT, limit cord Dmax to 12.4-14/1, 17/2, 20.3/3, 23/4, 25.3/5 for 1-5% risk of RM.
    - One example of higher dose levels SRS suggest up to 22.7/1 may be acceptable. Use extreme caution.
  - MTTRM after de novo / re-irradiation conventional RT of 18→ 11 mo.
  - MTTRM after de novo / re-irradiation SBRT of 12→ 6 mo.
- **Spinal cord reirradiation** [Nieder IJROBP '06]: **Radiation Myelopathy risk**.
  If using this study, use α / β of 2 even though 3 is used for cord in the modern era.

- No reported radiation myelitis at $BED_2 < 120$, interval > 6 mo, and neither course $BED_2 > 98$. Only 3% radiation myelitis at combined BED ≤ 135.5 (up to BED 150 still 3%).
- This study used α / β of 2 for cervical cord, and 4 for thoracic cord.

- **Sahgal** [IJROBP '11]: **Spinal Cord Tolerance for SBRT**.
  - See table 4 for details.
- **Sahgal** [IJROBP '12]: **Reirradiation Human Spinal Cord Tolerance for SBRT**.
  For re-irradiation, suggested to limit thecal sac EQD2 using α/β of 2 to Dmax < 70 Gy, SBRT thecal sac $EQD2_2$ Dmax ≤ 25 Gy, SBRT thecal sac EQD2 Dmax / cumulative EQD2 Dmax ratio ≤ 0.5, and a minimum time interval to re-irradiation of ≥ 5 mo.
  - 14 controls with 16 treated spinal segments without RM vs. 5 cases with RM.
  - All were G4 RM.
  - First course thecal sac $EQD2_2$ Dmax 18.3-52.5 Gy, SBRT re-irradiation thecal sac $EQD2_2$ Dmax 44.1 - 104.9 Gy.
  - RM cohorts: med SBRT $EQD2_2$ Dmax 62 Gy (44-105 Gy), cumulative $EQD2_2$ 100 Gy (77-155 Gy).
  - No RM cohort: med SBRT $EQD2_2$ Dmax 12.5 Gy (2-59 Gy), cumulative $EQD2_2$ 52 Gy (39-111 Gy).
  - Spinal cord Dmax low RM risk for 3 / 5 fractions of 14.5→ 18 Gy, but depends on prior dose.
  - See Table 4 in Sahgal HyTEC '19 for further details, and pay attention to ground rules above.
  - There are no guidelines for SRS after 40/20, 45/25, or 50/25. Prior 50/25 should be limited to 15.5/5.
- **Sahgal** [IJROBP '13]: **Probabilities of Radiation Myelopathy Specific to SBRT to Guide Safe Practice**.
  - Thecal sac dmax for 2y myelopathy ≤ 5% for 1 / 3 / 5 fractions of 12.4→ 20.3→ 25.3 Gy.
  - Guidelines: BED up to 140 Gy_2 (normalized 2 Gy equivalent 70 $Gy_{2/2}$ with certain caveats, in particular, SBRT component cannot exceed 50 $Gy_{2/2}$ - normalized 2 Gy equivalent 25 $Gy_{2/2}$).

This Summary Box was made possible by the ACRO Resident Committee.
A more comprehensive collection of resources for all disease sites may be found at http://www.acro.org/

Zaorsky: [SBRT for spinal mets: Defining the zones of treatment]

Contouring

- International Spine Radiosurgery Consensus Guidelines for CTV definition in spinal SRS [Cox IJROBP '12] RoR
- Consensus Contouring Guidelines for Postop SBRT for solid metastatic spinal tumors [Redmond IJROBP '17] RoR
- International consensus recommendations for target volume delineation specific to sacral mets [Dunne RTO '19] RoR
- International Practice Patterns for Non-Spine Bone Mets [Nguyen PRO '20] RoR

Relevant Accessible Radiation Protocols

- RTOG 0631 SRS procedure [Ryu PRO '14]: Phase II/III. Spinal mets for pain control. 8/1 vs. 16/18 SRS. V16 > 80-90%. RoR

Treatment Planning for SBRT

See [Treatment Planning] in the Oligometastatic disease section.

- Spinal cord PRVs are NOT static - they depend on prescription dose and cord limits (e.g. 14 Gy). PRV's are best designed when based on maximum achievable dose gradient [Weksberg]
- Spine radiosurgery CTV should include immediate adjacent spinal compartments [Cox IJROBP '12].
  SBRT for spinal mets: Defining the zones of treatment (Figure 2) [Zaorsky tweet].
- Spine radiosurgery PTV can be as small as 1 mm.
- For myelomas and solitary plasmacytomas, classical field placements based on 1 VB above and below are obsolete [ILROG]
- Reasonable prescription doses: 18-24/1, 24/2, 24-27/3, 30-40/5.
- Ensure complete coverage of GTV. Aim to have around 85% coverage of PTV.
- Thecal sac dmax for 2y myelopathy ≤ 5% for 1 / 3 / 5 fractions of 12.4→ 20.3→ 25.3 Gy. 14/1 appears acceptable [HyTEC]
- **Generalizable class solutions for Treatment Planning of Spinal SBRT** [Weksberg IJROBP '11]
  Multicriteria optimization may overcome the need for differential PRVs based on maximum achievable dose gradients.
  - The PRV margin on the spinal cord is *not* necessarily a static expansion!
  - It should be designed based off of maximum achievable dose gradient.
  - For example, if attempting to prescribe 24/1 to a VB lesion and your cord tolerance is 14/1, then a larger PRV (based on maximum achievable dose gradient) must be generated.
    - DG_cord expansion = 2.916 * ln(DRx - Dcordmax) + 0.044.

	Cord PRV	
Rx dose	**12.4 Gy** cord limit	**14 Gy** cord limit
24/1	**7**.2 mm	6.8 mm
22/1	6.6 mm	**6**.1 mm

20/1	6.0 mm	5.3 mm
18/1	**5**.1 mm	**4**.1 mm
16/1	**3**.8 mm	**2**.1 mm

  - TL;DR: At least 4 mm separation between the cord and the GTV is required if delivering 18/1 and your cord tolerance is 14/1. The PRV for the cord should not be a static expansion, but should depend on maximum achievable dose gradient.
  - Some physicians prefer to use a 2 mm PRV regardless of prescription dose and cord tolerance of choice.
- **ILROG Guidelines: RT for Solitary Plasmacytoma and Multiple Myeloma** [Tsang IJROBP '18]
  Field placement based on anatomic landmarks (e.g. 1-2 normal VB above and below) are obsolete.
  - Dosing for MM:
    - 30/10, 20/5, 8/1 reasonable. There is no definitive evidence for more durable control with 30/10 over 20/5, although 8/1 is less durable and preferred for patients who are [poor prospects] for survival.
    - ILROG prefers 30/10 over 20/5 for epidural disease with cord compression, large volumes, or retreatment.
    - Dex 4 mg for cases with nerve root or cord compression to prevent pain flair, consider QID for symptoms.
  - GTV: Field placements based on anatomic landmarks (e.g. 1-2 normal VB above and below) are obsolete.
  - CTV for MM: No CTV margin is necessary in the setting of systemic disease. Whole bone coverage is not required, especially if receiving systemic therapy.
- **International Spine Radiosurgery Consensus Guidelines for CTV definition in spinal SRS** [Cox IJROBP '12]:
  In summary, treat the gross disease and the immediately adjacent spinal compartment.
  - Exception: if disease is just in the anterior VB, then may treat just the body itself (no need to treat adjacent pedicles).
  - Spinal compartments: Body, pedicle, TP and lamina, and spinous process.
  - CTV should include abnormal marrow signal suspicious for microscopic invasion and an adjacent normal bony expansion to account for subclinical tumor spread in marrow space.
  - No epidural CTV expansion recommended without epidural disease, and a donut shaped CTV should only be used when VB, bilateral pedicles/lamina, and spinous processes are all involved or if there is extensive metastatic dz along the circumference of the epidural space.
- **Consensus Contouring Guidelines for Postop SBRT for solid metastatic spinal tumors** [Redmond IJROBP '17]
  There appears to be a 90% local control for lesions treated with 30/5 after surgery [Redmond IJROBP '19]
  - Essentially, treat pre-op gross disease and the immediately adjacent spinal compartment just as in pre-op SBRT.
  - If hardware in place which obscures MRI, consider a CT myelogram to be able to discern cord contours.
  - Recs for CTV include tx of the entire pre-op extent of bony and epidural dz, plus immediately adjacent bony anatomic compartments at risk of microscopic disease extension.
  - Utilize a "donut shaped" CTV for all cases of pre-op circumferential epidural extension, regardless of post-op imaging.
  - Otherwise, more conformal CTVs are described (See Table 4).
  - Special post-op considerations [Wang Phys Med Biol '13]:
    - Electron backscatter may cause ~6% increase in dose in front of titanium.
    - Photon attenuation may underdose the tumor behind hardware by ~7%.
    - Must account for hardware in selecting beam angles and use density overrides!
- **International consensus recommendations for target volume delineation specific to sacral mets** [Dunne RTO '19]:
  - Interesting CTV divisions were developed based on embryological remnants of fused intervertebral disc spaces, seen as transverse fibrocartilage in the sacrum (See Figures 1 and 2 for examples).
- **International Practice Patterns for Non-Spine Bone Mets** [Nguyen PRO '20]:
  Dosing schemes of 35-40/5 appear to be the most widely accepted.
  TBL [QS]: Non-spine bone SBRT deserves just as much care in planning and delivery as other targets.
  - 9 international rad oncs with expertise on non-spine bone mets SBRT.
  - Most (56%) routinely fused MR imaging with planning CT images.
    - RT: 18-24/1, 24/2, 28-30/3, 30-50/5, and 42-50/10.
    - While doses varied considerably, all had BED10 $\leq$ 100 Gy.
    - The most widely used schemes were 20/1, 30/3, and 35/5 (Figure 1).
  - 35/5 was most common in 29% of cases, with most (56%) recommending this dose fractionation in at least one case.
  - Other dose fractionations used by at least 3 experts were 20/1, 30/3, and 30/5.
  - Three experts prescribed two dose volumes using a SIB (e.g., 30/3 and 15-24/3 was used in 50%).
  - Dose de-escalation was recommended by all experts in the setting of previous SBRT and by most in the context of previous conventional radiotherapy or in weight-bearing bones, especially if moderate to severe cortical erosion was present.
  - Case 1 (scapula) was the only case where each dose fractionation scheme was deemed acceptable.

    - Case 2 (humerus), 3 (acetabulum) and 10 (pubic symphysis) had the greatest number of dose fractionation schemes that were not recommended by a majority of experts.
    - The most widely accepted dose was 40/5 which experts unanimously (n=9) or near-unanimously (n=8) considered acceptable in all cases where it had been listed.
- **Inter-observer agreement in GTV delineation of bone mets** [Gerlich RTO '18]: **CT ± MRI**.
    - 20 cases, contoured by individuals from two institutions.
    - MRI with larger volumes but more consistency between observers.
- **Patterns of intraosseous recurrence after SBRT for coxal bone mets** [Ito IJROBP '18]: **30-35/5**.
    - 17 pts. Targets mainly delineated by CT with 0.5-1 cm CTV margin and 0.3 cm PTV margin. MFU 13 mo.
    - There were 7 (41%) marginal/OOF recurrences with MTTR 10 mo.

Future Directions

- **SC.24** [Sahgal NCT02512965]: Phase II/III. **CRT 20/5 vs. SBRT 24/2**.
    - 228 pts anticipated. Endpoint: Pain response in the spine three months after treatment.
        - Excludes seminoma, SCLC, metastasis from lymphoma/myeloma.
    - Pain requiring treatment, ≤ 3 spinal segments.

Radiopharmaceutical therapy

- Best for pts w multiple lesions on bone scan. Do not use it for fractures, cord/nerve compression, or lesions with large extraosseous extension.
- Adequate blood counts, typically no myelosuppressive chemo for 4w prior, 6-8w after tx = **Follow CBC for 3 mo**.
- **Ra-223** (α emitter): for CRPC, symptomatic bone mets and no known visceral metastasis (now visceral is OK). Targets OB bone mets by acting as calcium mimetic.
    - OS advantage with CRPC, though no OS advantage w visceral mets or bulky nodal dz (e.g. >3-4 cm). This differs from Strontium 89 and Samarium 153, which are palliative and have not been shown to extend OS.
    - G3-4 heme (2% neutropenia, 3% thrombocytopenia, 6% anemia).
    - Predominantly excreted in stool, therefore mild N/V/D may occur.
    - Administered once monthly x6 months. Ra-223 should be discontinued if counts do not normalize in 6-8w.
    - **ALSYMPCA** [Parker NEJM '13]: **± Xofigo q4w x6c**.
      Better QoL, MS, and decreased skeletal events.
        - 921 CRPC pts who had previously received docetaxel with 2+ bone mets and no known visceral mets or bulky nodal disease (>3 cm).
            - Requires **ANC ≥ 1500**, **Plt ≥ 100**, **Hgb ≥ 10** before first administration.
            - Subsequent administration: **ANC ≥ 1000** and **Plt ≥ 50**.
            - D/c Xofigo if hematologic values do not recover within 6-8 weeks after last administration despite supportive care.
            - AE for Xofigo: Bone pain, N/V/D, constipation, anemia (2%), hematologic.
        - **MS 11→ 15 mo**.
        - MTT first sx skeletal event 10→ 16 mo. Better QoL in Ra-223 arm.
        - MTT increased PSA 3.4→ 3.6 mo.
    - **ERA-223**: **Abiraterone + Ra-223 - currently on hold due to increased rate of bone fractures**.
- **Strontium 89** (β emitter) and **Samarium 153** (β and emitter) are associated with myelosuppression. Self-limiting bone pain in 36-72h post-tx common. Since Ra-223 is an α emitter, there is a theoretical benefit in more rapid cell killing and less marrow toxicity as compared to β emitters.
    - **Strontium**: response rates 40-95%, pain relief at 1-4w, lasting 18 mo. Improved response rate and duration with low dose platinum.
    - **Samarium**: response rates 70-95%, pain relief at 1-2w, lasting up to 4 mo.
        - [Double blinded trial]: Up to 70% can have pain relief w Samarium, w 31% marked or complete pain relief.
- **Lutetium 177** (β emitter): Can be tagged with somatostatin analogue (neuroendocrine) or even PSMA (prostate specific membrane antigen). Approved by FDA January 2018 for gastrointestinal neuroendocrine tumors.
    - **NETTER-1** [Strosberg NEJM '17]: 229 pts. Well-differentiated, metastatic midgut NET. Lutetium 177 somatostatin analogue vs. octreotide. Four doses of Lu-177.
        - 20 mo PFS 11→ 65%. CR/PR 3→ 18%
            - No other therapy for this pt population has demonstrated CR/PR >5%!
        - Toxicity is acceptable with <10% of clinically significant myelosuppression.
    - **Baseline 68Ga DOTATATE PET/CT predicts for response to Lutathera** [Sharma RTO '19]
- Pharmacologic therapies
    - Pooled analysis of phase III studies of denosumab vs. zometa demonstrated RR of 0.82 with denosumab for delaying time to subsequent skeletal related events.

SBRT and Oligomets

The abscopal effect [Zaorsky tweet]
ACR-ASTRO Practice Parameter for the Performance of SBRT [Revised '19]
ACR-ASTRO Practice Parameter for IGRT [Revised '14]
Quality and safety considerations in SRS and SBRT: Executive summary [Solberg PRO '12]

History

- **Stereotactic Radiotherapy of Malignancies in the Abdomen** [Lax Acta Oncologica '94]
  The first report of extracranial SBRT! The liver was chosen as a first site due to low radiation tolerance of the liver to fractionated radiotherapy and the fact a large part of the liver can be inactivated by irradiation without hazarding the life of the patient.
  - Without immobilization, diaphragmatic movements were found to be between 1.5 - 2.5 cm. Slight, constant pressure on the abdomen displaces the diaphragm in the cranial direction about 1.5 cm, and the diaphragmatic movements were reduced to 0.5 - 1.0 cm.
  - Abdominal compression led to transverse deviation ≤ 5 mm in 93% while no case was larger than 7 mm.
  - Abdominal compression led to craniocaudal deviation ≤ 8 mm in 88%, while no case was larger than 10 mm.
  - A margin on the tumor of 5 mm in the transverse plane and 8 mm in the craniocaudal plane will be equal to the prespecified dose in 90% of cases.
- **Stereotactic High Dose Fraction RT of Extracranial Tumors using an Accelerator** [Blomgren Acta Oncologica '95]
  SRS was first delivered to brain mets in 1975. The Swedish were the first to do it.
  - This is a report of the first 31 patients treated with extracranial SBRT.
  - Abdominal compression led to transverse deviation ≤ 5 mm in 95% and CC deviation ≤ 8 mm in 89% of cases.
  - A fascinating read! The first description of liver and lung SBRT.
- **"Oligometastases" is coined!** [Hellman and Weichselbaum JCO '95]
- **Radiobiology of SBRT** [Park Rad Research '12]: Single dose survival curve for SRS with < 5 Gy killing oxygenated cells, > 5 Gy killing hypoxic cells, > 12 Gy causing radiosensitive endothelial damage and > 17 with radioresistant endothelial damage (See Figure 7). Damage to endothelium is from indirect effects.
  - 18 Gy SRS leads to necrosis, apoptosis, and decreased microvessel density implying direct vascular and DNA damage mechanisms for SRS [Steverink IJROBP '18]. No increased necrosis if surgery performed on the same day.
- **Radiation and ICI: Radiosensitization and potential mechanisms of synergy** [Sharabi Lanc Onc '15] [RoR]
- **Oligometastases: History of a hypothesis** [Milano Ann Palliative Medicine '20]

Definitions

- **The Dandelion Dilemma for Oligoprogression: Treat the Whole Lawn or Weed Selectively?** [Patel Clin Onc '19]
  - Excellent summary of oligometastatic, oligoresistant, oligopersistant and oligoprogressive disease.
- **ASTRO-ESTRO Consensus classification of oligometastatic disease** [Lievens RTO '20]:
  - At a minimum, oligometastatic disease is the ability to deliver safe and clinically meaningful radiotherapy with curative intent to all metastatic sites.
- **Proceedings of the ASTRO-RSNA Oligometastatic workshop** [Yu IJROBP '20]
- **ESTRO and EORTC classification of oligometastatic disease** [Guckenberger Lancet Onc '20]:
  TBL[QS]: Using a common framework for classifying OMD will help us generate and interpret more meaningful data as we venture further into a new era in cancer therapy.
  - Induced oligometastatic disease: History of polymetastatic disease.
  - Genuine oligometastatic disease: No history of polymetastatic disease.
    - Repeat vs. De-novo oligometastatic disease.
    - For De-novo disease: Metachronous if > 6 mo after primary cancer diagnosis, otherwise synchronous.
    - For metachronous: Oligoprogression if on-therapy, oligorecurrence if off-therapy.
  - They do not use an arbitrary number of lesions to define oligometastatic disease, instead basing oligometastatic disease on the feasibility to treat all sites of disease.
- **SABR-COMET** (2012-2016) [Palma IJROBP '18, (Protocol) Lancet '19, JCO '20]: Phase II. **Standard of care ± SABR**.
  TBL [QS]: This trial provides the best evidence to date for consolidative treatment of oligometastatic disease in patients who do well with upfront systemic therapy - and to be clear, the treatment is SBRT.
  TBL [QS]: Recognizing the numbers here are small, particularly per disease site, great gain is likely achievable with subsequent trials investigating consolidative treatment for oligomets in the appropriate populations.
  OS results are not definitive. Is the PFS benefit enough to treat? [ASTRO Video Summary]
  - 99 pts. Controlled primary with no primary progression x3 mo. **No crossover**. Mostly 1-3 sites (n=92). MFU 2y.

        - 1-5 lesions amenable to SBRT, no more than 3 mets in one organ.
        - Most were breast, CRC, lung or prostate cancer. Prostate heavily randomized to SABR arm: 6→ 21%.
        - Median time from cancer diagnosis two years. Life expectancy > 6 mo.
        - Exclusion: Non-SBRTable lesions (e.g. ≤ 3 mm to cord), prior RT in irradiate site, malignant effusion, 1-3 brain-only mets, and bone mets in a femoral bone.
        - RT schema dependent on tumor size and location (Table 1) [Protocol].
        - PTV compromise when needed.
    - MS 28→ 50 mo. 5y OS 18→ 42%.
    - 5y OS in post-hoc excluding prostate cancer of 16→ 33%.
    - Progression at sites present at the time of enrollment of 45→ 12%. MPFS 6→ 12 mo. 5y PFS 3→ 17%.
        - 21 of 33 pts in control arm rec'd "palliative, non-ablative" radiation to symptomatic sites.
    - G2+ 9→ 29%. 5% chance of treatment related death (n=3: 1 pneumonitis, 1 pulmonary abscess, 1 SDH after SABR-related perforated gastric ulcer).
    - SABR is not associated with decline in QoL.

NSCLC

See NCTN Trial Portfolios by Disease Site: [Thorax] and the [Future Directions] for NSCLC section for a multitude of studies.

- **Definition of synchronous oligo-metastatic NSCLC** [Dingemans JTO '19]:
  Patients with NSCLC with 5 or fewer metastases in 3 or fewer organs can be considered oligometastatic after staging with PET/CT and MRI brain. TBL [QS]: A European consensus statement on the definition of synchronous oligo NSCLC has been created, which will potentially inform future clinical trial design, appropriate patient selection for local therapy, and (when we get American definitions) payer coverage.
- **Oligo Review of NSCLC Oligometastases** [Giulani IJROBP '20]: No study below is in the era of immunotherapy.
    - "Oligomez" was a phase II trial of patients with 1-3 NSCLC mets treated with initial systemic therapy without progression at 3 mo. PFS was tripled with LCT, and OS was at least doubled (caution interpreting OS results). Treatment of lung primary for oligo persistent disease (counted as "0 mets") was allowed. Unlike SABR-COMET, crossover was allowed. There appeared to be a detriment in OS for delayed LCT [RoR]
    - Iyengar was a phase II trial from UTSW of patients with mostly 1-3 NSCLC mets treated with initial systemic therapy without progression after around 3 months. PFS and OS were (caution interpreting OS results) more than doubled with SBRT. [RoR]
    - SABR-COMET was a phase II trial of patients with mostly 1-3 mets from various solid tumors treated with initial systemic therapy without primary progression at 3 mo. PFS was doubled with SBRT, with near-significant improvement in OS (caution interpreting results). Patients with prostate cancer were heavily randomized to the SBRT arm (6→ 21%), which may have influenced results favorably towards the SBRT arm. Subgroup analyses excluded prostate cancer patients, and results remained favorable. [RoR]

Prostate Cancer

See NCTN Trial Portfolios by Disease Site: [GU] and [Future Directions] section for details on studies such as the TRAP study.

Oligo Review of Prostate Oligometastases

No trial has looked into treatment of the primary and oligomets in the de novo setting, although treatment of the primary and treatment of oligometastatic disease have been looked at independently:

- Low metastatic burden: Definitions vary, but essentially all exclude patients with visceral mets. Simple definition: ≤ 5 bone or nodal mets, no visceral disease. CHAARTED/STAMPEDE H definition states < 4 bone-only mets anywhere or *any number* of spine/pelvis-only mets. [RoR]
- Treatment of the primary in metastatic disease: The HORRAD trial had a small number of patients with low metastatic burden, and failed to meet statistical significance with 70/35 or 57.76/19 to the prostate only in regards to OS when patients with < 5 lesions were evaluated. STAMPEDE arm H investigated the addition of 55/20 qday or 36/6 weekly to the prostate only and found a significant improvement in overall survival for patients with low metastatic burden. Well over three quarters of patients were alive at 3 years! The STOPCAP meta analyzed both trials and found a statistically significant overall survival advantage at 3 years for patients with < 5 bone mets, and three quarters of patients were alive at 3 years. [RoR]
- Metastasis Directed Therapy: Two trials looked at ADT-free survival for patients with oligometastatic disease (STOMP and ORIOLE). STOMP treated to 30/3 and required primary prostate cancer treatment with curative intent and ≤ 3 extracranial mets on choline PET (MFU of 3 years). ORIOLE treated to mainly 27-30/3 or 35-40/5 and required primary prostate cancer treatment with curative intent and 1-3 asymptomatic mets on CT imaging, although PSMA was obtained and blinded to the investigators (MFU of 1.5 years). ORIOLE demonstrated a very promising 6 month progression for ±

incidental total consolidation of PSMA disease to be 63→ 16%, however, had too short of follow up to reliably predict outcomes past 1.5 years (Figure 2c). The STOMP trial demonstrated 80% of patients still have some kind of progression by 2-3 years (Figure 4c). Notwithstanding the promising (albeit immature) results of total PSMA consolidation on the ORIOLE trial, is ADT-Free Survival an appropriate endpoint? The Spanish SBRT-SG 05 trial went the opposite route of ADT-free survival, instead *mandating* delivery of 2 years of ADT. This trial included men with 1-5 lesions which were treated with SBRT, and had a bcPFS not surprisingly approaching 100% at a MFU of nearly 2 years. Knowing a little over half of men will recover their testosterone after even 1.5 years of ADT at a median of 2.1 years (at least 3.6 years from the initial injection) per [Nabid], the MFU on the Spanish trial will have to reach at least 4 years to allow for some testosterone recovery in order to provide more meaningful results. The Johns Hopkins report provides an interesting middle ground on the ADT dilemma, with a subgroup analysis of 28 men who received consolidation to 1-5 metastatic sites who had received a median of 4 mo of peri-RT ADT and recovered testosterone (MFU nearly 3y). At two years, only 20% of men (1 in 5) had some kind of progression, suggesting there may be a role for a single 3-month Lupron injection. Recall: 80% of men (4 in 5) have some kind of progression by 2-3 years as demonstrated by STOMP, which consolidated all choline PET lesions. We believe it is reasonable to either withhold ADT ± (abiraterone or docetaxel) until PSA progression or deliver one three month injection upon shared decision making discussions with your patients, depending on the desires of your medical oncologist. Either way, there is a paucity of data in this area and you will see a dog's breakfast of clinical practice patterns in this scenario. Fortunately, prostate cancer typically takes many years to progress from oligometastatic disease to produce fulminant metastasis and death (unless [PSA-DT < 3 mo]), so no matter how you feel about a peri-SBRT three month Lupron injection in the setting of total PSMA consolidation, ADT-free survival certainly isn't a wrong answer! [RoR]

Other Sites

See NCTN Trial Portfolios by Disease Site: [GU] and [Future Directions] in the RCC section for studies such as OZM-053.
See NCTN Trial Portfolios by Disease Site: [Breast], [Future Directions] in the Breast section or [BR002] below.
See the [Brain Metastases] section and [Bone Mets SBRT Treatment Planning] for more.

- The first study to demonstrate aggressive local therapy for oligometastatic disease was the CLOCC trial for metastatic colorectal cancer to the liver (2002-2007). It demonstrated an overall survival advantage of chemotherapy and aggressive RFA and surgical resection if possible, and half of patients are alive at 5 years [RoR]
- **According to ESPAC-4, pancreatic cancer which was previously resected (R0/R1) will have 70% of first failures as local-only and/or oligometastatic liver-only metastasis** (Table 2) [Jones JAMA Surg '19]
  Unfortunately, pancreatic cancer is still thought of as a systemic disease. We know 30% of patients die of local failure. [RoR]
  - According to PRODIGE-24, nearly half of failures included a local component of failure. More detailed reporting of patterns of failure on PRODIGE-24 is necessary (i.e., commentary on oligo-hepatic failures ± LRF). [RoR]
  - If more detailed patterns of failure continue to demonstrate a large component of distant metastases to be oligometastatic disease in the liver as first failures, then maybe this "rule out blooming metastases" paradigm is ripe for a change, and we should be doing up-front consolidation of oligometastatic disease so long as there is no delay to systemic therapy known to provide an overall survival benefit.
- **Oligometastatic esophageal cancer** [Shanghai Liu ASTRO '19]: Phase II. **SABR to oligometastases**.
  SBRT is a safe and well tolerated treatment modality of oligometastatic ESCC.
  - 34 patients. 1-4 oligometastases (mostly 1), controlled primary. Mostly lung or abdominal LN. MFU just over 1y.
    - Half previously resected. Half received combined chemotherapy.
    - RT mostly 50/5 or 48/6.
  - MPFS 14 mo.
  - PFS at 1y / 2y of 72→ 41%.
  - OS at 1y / 2y of 78→ 66%.
- **Definition of OligoRecurrence in Biliary Tract Cancer** [Morino ASO '20]: Retro. **R0/1→ Recurrence ± Local Therapy**.
  - 232 pts. 1996-2015. Propensity Score-Stratified analysis. Primary outcome was length of survival after recurrence.
  - MVA: CA 19-9 > 50, multiorgan recurrence, >3 tumors, > 3 cm, and ≤ 1y TTR independently predict poor SAR.
  - Median survival after recurrence of 14→ 49 mo for patients with single-organ recurrence with at most three tumors and late onset recurrence (> 1 year).
- **SBRT for Adrenal Metastases** [Chen IJROBP '20]: Meta. **Median BED10 67 Gy**.
  BED10 of 100 appears to be an excellent regimen, and treatment to this area is safe.
  - 39 studies from 2009-2019. 1,006 pts. MFU 1y.
  - Pooled ORR 55%.
  - Pooled LC at 1 / 2y of 82→ 63%.
  - Pooled OS at 1 / 2y of 66→ 42%.

- There was a strong positive association between SBRT dose and LC and OS.
- 1y LC for BED10 of 60 / 80 / 100 Gy of 71→ 85→ 93%
- 2y LC for BED10 of 60 / 80 / 100 Gy of 48→ 70→ 86%.
- Overall G3+ toxicity 2%

➢ **Stereotactic MR-guided adaptive RT (SMART) for tx of oligo or unresectable primary abdominal dz** [Henke RTO '18]:

- 20 patients. 50/5. At 1y, 9 pts NED with 75% alive.
- 81/97 fractions (84%) of adaptive plans were generated.
  - 61/81 (75%) due to OAR constraint violation.
  - 20/81 (25%) opportunity for PTV dose escalation.
- After adoption, no constraints were violated.
- No G3+ toxicity observed.
- Time cost for on-line adaptive therapy:
  - Median time of table 79 minutes (36-160 min).
  - Median re-contour time 9 min (2-24 min).
  - Median re-plan time 10 min (1-19 min).
  - Median QA time 4 min (1-14 min).
- 6 mo LRPFS 89%.

Toxicity

- Lung SBRT and Concurrent Immunotherapy [Tian IJROBP '20]: SBRT ± ICI. RoR
- Radiation and ICI: Radiosensitization and potential mechanisms of synergy [Sharabi Lanc Onc '15] RoR

Treatment planning

MRI-Based Upper Abdominal Organs-at-Risk Atlas for Radiation Oncology [eContour, Lukovic IJROBP '20]
Zaorsky: [SBRT for spinal mets: Defining the zones of treatment]
International Spine Radiosurgery Consensus Guidelines for CTV definition in spinal SRS [Cox IJROBP '12]
Consensus Contouring Guidelines for Postop SBRT for solid metastatic spinal tumors [Redmond IJROBP '17]
International consensus recommendations for target volume delineation specific to sacral mets [Dunne RTO '19]
International Practice Patterns for Non-Spine Bone Mets [Nguyen PRO '20]
See the [SBRT Treatment Planning for Bone Metastases] section.
See the [Master Constraints] section for 1, 3, 5, 8, 10, and 15 fraction constraints with clinical correlates for toxicity outcomes.

- **NRG-LU002** [NCT03137771]: Phase II/III. **Maintenance systemic treatment ± SBRT for up to 3 mets**. RoR
  See NCTN Trial Portfolios by Disease Site: [Thorax] or the [Future Directions] for NSCLC section.
  Based off of dosing from [Iyengar] at UTSW.
  - Pts who completed 4c of first line chemotherapy or immunotherapy. Requires treated brain lesions.
    - Excludes targetable mutations, untreated brain mets and metastatic disease to esophagus, stomach, intestines or mesenteric lymph nodes.
    - 21-27/1. *Acceptable deviation ≥ 16 Gy.*
    - 26.5-33/3. *Acceptable deviation ≥ 24.5 Gy.*
    - 30-37.5/5. *Acceptable deviation ≥ 28 Gy.*
    - Fifteen fraction: 45 Gy for disease not amenable to SBRT in ≤ 5 fractions.
  - No evidence of progression and ≤ 3 sites of mets amenable to surgery or SBRT plus irradiation (SBRT or hypofractionated RT) of the primary site followed by maintenance therapy. Protocol allows up to 20 Mets at Dx.
  - EGFR or ALK patients are excluded.
- **NRG BR002** [Pending, Protocol]: Phase II/III. **Standard of care and tx of symptomatic mets vs. LCT**. RoR
  See NCTN Trial Portfolios by Disease Site: [Breast] or the [Future Directions] for breast cancer section.
  - New diagnosis breast cancer. May receive up to 12 mo of first line systemic tx without progression.
  - Nonosseous sites:
    - 30/1 (28-30.3): Only single liver and peripheral lung.
    - 45/3 (42.5-45.5): Preferred for peripheral lung, liver, and abdominal pelvic mets.
    - 50/5 (48-50.5): Preferred for central lung, mediastinal/cervical lymph nodes.
  - Osseous sites:
    - 20/1 (14-20.2): Spinal mets.
    - 30/3 (27-30.3): Non-spinal mets.
    - 35/5 (30-35.4): Thoracic/Cervical spine.
- Intact extracranial mets

- Spine: 16-24/1 (20), 20-24/2, 24-27/3 (30), 30-35/5.
- Body: 16-24/1, 40-60/4-5, 48-60/3.

Immunotherapy

Immune Checkpoint Inhibitors (ICI)

See [Zaorsky] simplified diagram. Upregulation of the PD-1 pathway can promote the development of T-cell exhaustion, characterized by reduced T-cell effector function and proliferation.

- **PD-1** is located on the surface of T cells, while PD-L1/2 is located on many different types of cancer cells. **Nivolumab**, **pembrolizumab, and Cemiplimab**: IgG4 inhibits PD-1 receptor, suppressing inhibition on T-cells. **Atezolizumab**, **Durvalumab and Avelumab**: IgG1 inhibits PD-L1 on tumors cells.
  - PD-1 is expressed on multiple immune cells, including T, B and NKT cells. PD-L1 expression is stimulated by IFN-□ which is produced by activated T and NK cells. PD-1 signaling inhibits previously activated T cells in circulation. Inhibition of these ligands allows T cells to attack.
  - PD-L2 is expressed primarily on hematopoietic stem cells.
  - Dosing frequency: Durvalumab **10** mg/kg q2w up to 12 mo. Nivo q2w, pembro q3w.
- **CTLA-4** is expressed on the surface of CD4 and CD8 lymphocytes, competing with the T-cell costimulatory factor CD28. **Ipilimumab** (IgG1) **and tremelimumab** (IgG2 - lower incidence of complement cascade activation).
  - T-cell co-stimulatory factors are expressed on the surface of APCs in the early phase of immune response (i.e., CTLA4 works largely in lymph nodes and Tregs).
  - CTLA-4 serves to down-regulate pathways of T-cell activation. It binds to CD80 and CD86 (B7) with a greater affinity than CD28. CD28 serves to activate T-cells. Blocking CTLA-4 takes the "brakes" off the immune system.
  - CTLA-4 binding reduces IL-2 and T-cell proliferation.

RT blockade and ICI: Radiosensitization and potential mechanisms of synergy [Sharabi Lanc Onc '15].

The Promise of Combining RT with Immunotherapy [Jagodinsky IJROBP '20]:

- The Steel hypothesis was first conceptualized in the 1970s and described mechanisms where combined modality drug and RT approaches could improve treatment outcomes.
- Radiated tumor cells can upregulate Tregs, which can dampen the immune response. Immunotherapy agents can block this negative feedback and reinvigorate the immune response.
- Immunotherapy has the potential to promote normal tissue protection by antibody-mediated blocking of radiation induced fibrosis by targeting TGF-β.
- High dose RT is associated with increased MHC-I expression and death receptors such as Fas. Moderate fractional doses of 8-12 Gy may be optimal for activating a type I IFN response by causing cytoplasmic leakage of DNA from micronuclei, which activates the cGAS/STING pathway. At higher doses, radiation-induced STING activation may decline at least in part due to induced expression of Trex1 endonuclease. Activation of the cGAS/STING pathway appears to be essential for generating radiation-induced adaptive immune response, as it may require dendritic cell intrinsic STING activation by sensing tumor derived DNA in the cytoplasm in exosomes containing tumor cell DNA fragments. Low dose RT induces cytokine release and can modulate the tumor microenvironment by ablating radiosensitive cells such as Tregs which may temporarily deplete exhausted and suppressive T cells from the tumor microenvironment.
- IFN- β after radiotherapy may be a predictor for response to ICI (Figure 1) [Vidotto BJC '20].
  - STING translocation into the nucleus requires the presence of PTEN. Therefore, PTEN deficiency is also associated with impaired activation of the type I IFN and NF-κB pathway which could be highly favorable for tumor progression due to an immunosuppressed tumor microenvironment (Figure 2). PTEN normally regulates several mechanisms that maintain genome stability in the nucleus, so PTEN-deficient tumors are associated with high rates of chromosome rearrangements that are usually associated with increased mutational load.
  - STING deficiency, such as in patients with PTEN mutations or SKT11 mutations, is associated with low PD-L1 expression. This is especially true for STK11 and KRAS mutated tumors, whereas the opposite is true for mutated STK11 and TP53 [de Miguel JTO '20].
- Despite the success of PACIFIC, < 1% of early phase trials are investigating a combination of RT and immunotherapy in the non-metastatic setting. [RoR]

A Review of Cancer Immunotherapy toxicity [Kennedy CA Can J Clin '20]

Generally speaking, blocking CTLA-4 affects *early* T-cell activation (lymph nodes/APCs) while blocking PD-1 signaling is more relevant *later* (tumor site), which helps to explain why there is greater toxicity with CTLA-4 inhibition.

Pneumonitis: There is [suggested increased in-field grade 3 toxicity] if SBRT to the lung is given concurrently with ICI. Although the overall rate of toxicity as compared to ICI alone, it appears to correlate with the area irradiated.

- Generally speaking the majority of toxicity occurs around the same time as the median time to response (MTTR), which is around 2-3 months. Dermatologic side effects peak early at around 1 month [Weber JCO '17].
- Toxicities for immunotherapy have been associated with improved overall survival.
- Cytokines such as IL-2 can cause capillary leakage and sepsis-like syndrome, which, in severe cases, can lead to multiorgan failure. This has historically limited the usefulness of cytokine therapy.

- ➢ PD-1/L1 and CTLA-4 inhibitors have unique side effect profiles.
- ➢ CAR T cell therapy's most common toxicities for heme malignancies are cytokine release syndrome and ICANS. CAR NKT cell therapy appears to have no major side effects [Liu NEJM '20]
    - Severe CRS occurs in up to 30% of patients.
    - The incidence of CRS is higher is ALL compared to NHL or CLL.
    - CRP, ferritin, and other markers for inflammation are increased (IFN-□, IL-6, IL-10).
    - Tocilizumab (IL-6 receptor antagonist).
    - Immune Effector Cell-Associated Neurotoxicity (ICANS): Expressive aphasia develops in patients with severe neurotoxicity. Patients initially develop tremor, dysgraphia, mild expressive aphasia, apraxia and impaired attention.
- ➢ Toxicity related fatality for PD-1/ PD-L1 / CTLA-4 / combined ICI of 0.4→ 0.4→ 1.1→ 1.2%.
- ➢ CTLA-4 inhibition is more associated with colitis (70% of deaths) and hypophysitis (up to 15% if 10 mg/kg).
- ➢ PD-1/PD-L1 inhibition is more associated with pneumonitis, hepatitis, or neurotoxicity.
- ➢ Combined ICI is more associated with colitis and myocarditis.
- ➢ Fatal toxic events most often occur at a median of 14 days with combined ICI while 1 month with single agent ICI.
- ➢ **Colitis**: IL-17 is a cytokine upregulated in IBD, which may correlate with G3 diarrhea.
    - Persistent G2 should lead to the stoppage of ICI and consideration of infliximab within 3-5 days.
    - Refractory may consider vedolizumab, an anti-integrin α4β7 Ab with gut-specific effects.
- ➢ **Hypophysitis**: CTLA-4 is associated with normal pituitary function.
    - Around 6% incidence with ipilimumab, lower with tremelimumab as less likely to activate complement cascade.
    - There is an around 15% incidence with ipi 10 (low dose ipi 1, intermediate dose or 3).
    - Easily missed as [nonspecific], with nausea, fatigue, headache, or weakness.
    - As is easily missed, recommended to check TSH and free thyroxine at baseline and during ICI.
    - Endocrine AE are almost always permanent and require lifelong hormone replacement.
- ➢ **Thyroid**: Antithyroid antibodies are common.
- ➢ **Dermatologic**: Reported in up to 50% of patients, usually 14 days with combined ICI or 1 mo with single agent ICI.
    - Vitiligo has only been reported in melanoma patients.
    - Both vitiligo and dermatological effects are associated with an improved PFS and OS.
- ➢ Around 33% of patients receiving ipilimumab require steroids, while 10% of these patients require additional systemic immunosuppression. Some propose the use of IL-6 receptor blockade (tocilizumab). IL-6 expression has been shown to promote tumor growth and metastasis, therefore, IL-6 blockade might treat irAE while maintaining efficacy.

Predictors of response to Immunotherapy, from most to least important [Lee JAMA Onc '19]
TBL [QS]: It's likely we'll see more complex "triple axis" immunotherapy panels in the future that more accurately predict ICI response. Triple axis = immune cell infiltrate, tumor neoantigens, and checkpoint targets.

1. **Tumor microenvironment** (**pretreatment CD8+ T cells**) within the tumor.
    - Patients on steroids at baseline will have a low burden of pretreatment CD8+ T cells.
    - Therefore, steroids at baseline is a relative contraindication to ICI.
    - There is no clear evidence that steroids mid-treatment leads to decreased ORR.
2. **Tumor neoantigens** (**High mutational burden**) also portends to better response.
3. **Checkpoint targets** (**PD-L1 protein expression**) alone is a poor predictor of response to ICI.

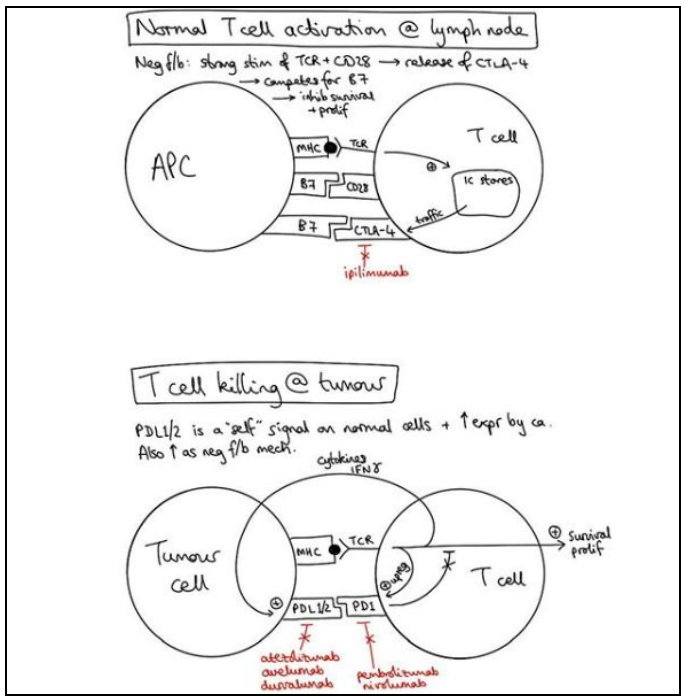
Tumor mutational burden: Current data and emerging concepts [Fumet EJC ' 20]

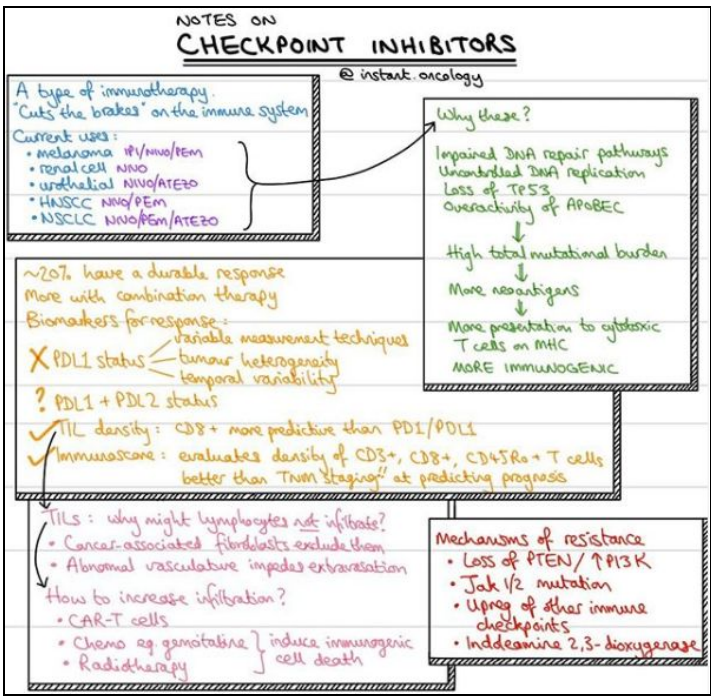
Estimated Dose to the Immune System correlates with lymphopenia and worse OS [Xu RTO '20]:
Generally speaking, conventional fractionation exposes more of the immune system to radiation. Chalk this up as another win for hypofractionation in the era of immunotherapy (Depletion of pre-treatment CD8s is less with hypofractionation).
TBL [QS]: EDIC again appears to be a modifiable measure of radiation's crucial impact on patient immune systems.

ASCO Guideline: Mgmt of Immune-Related AE in Pts Tx with Immune Checkpoint Inhibitor Tx *February 14, 2018*

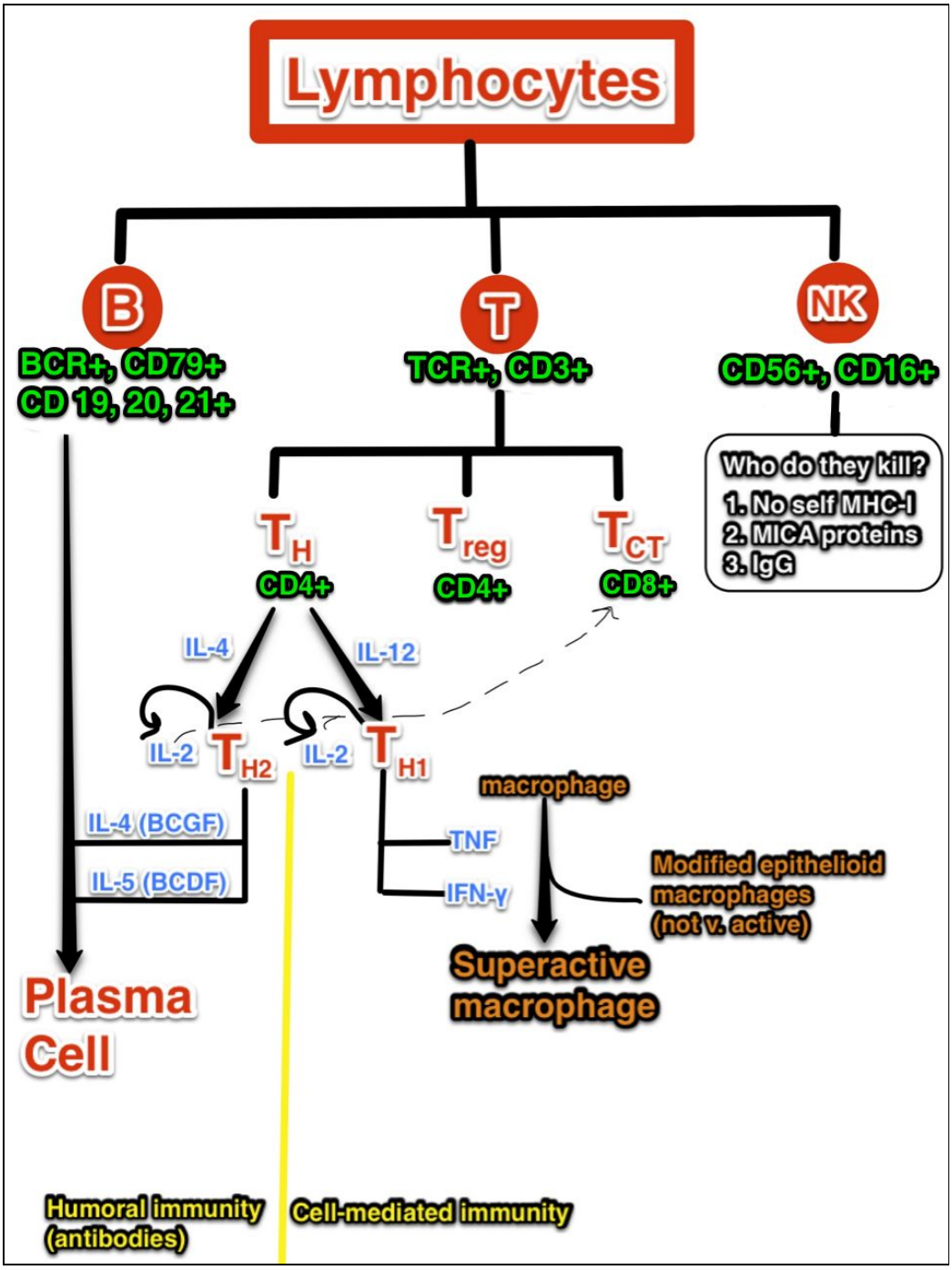
- ➢ Immunotherapy may be held for most G2 toxicities until it becomes G1 (except derm). May give corticosteroids.
- ➢ G3 generally warrants holding immunotherapy and starting pred 1-2 mg/kg/d or methylprednisolone 1-2 mg/kg/d.
- ➢ Corticosteroids should be tapered over the course of at least 4-6 weeks.
- ➢ Some refractory cases may require infliximab or other immunosuppressive therapy.
- ➢ In general, permanent discontinuation of immunotherapy recommended if G4, with the exception of endocrinopathies that have been controlled by HRT.

Radiation and ICI: Radiosensitization and potential mechanisms of synergy [Sharabi Lanc Onc '15]





- **Innate immune system**: Initial, rapid response. No long lasting immunity.
    - Recruits immune cells (cytokines), activates complement cascade, removal of foreign substances by WBCs, APCs (recruits adaptive immune system), provides physical and chemical barriers to infectious agents.
- **Adaptive immune system**: Requires days to respond initially, but more brisk response subsequently.
    - Antibody and cell-mediated.
    - **Th2 cells**: Activate maturation of B cells. IL-4 autocrine stimulation of GATA3.
    - **Th1 cells**: Activates macrophages. IL-12 or IFN□ autocrine stimulation of T-bet. Release TNFα, IFN□.
        - **Superactive macrophages**: activated with low levels of IFN□.
        - **Modified epithelioid macrophages** (granulomas): activated with medium levels of IFN□. Release TNFα.
        - **Giant cells**: Fusion of modified epithelioid macrophages. Activated with high levels of IFN□.
    - **CD8 T cells**: Also release IFN□.
        - LAG-3, TIM-3, PD-1, and CTLA-4 are immune checkpoint receptors.
    - **Treg**: TGFβ autocrine stimulation on FoxP3 receptor. *Cyclophosphamide might deplete Tregs in humans.*
    - **TGF β**: "the anticytokine". Turns off inflammation, fibrosis dominates.
    - **IL-10**: "the lesser anticytokine".
- **Evasion of the immune system**: Reduced expression of tumor antigens, downregulation of MHC-I/II, immunosuppressive cytokines (e.g. TGF-β), induction of immunosuppressive cells (e.g. Tregs or MDSCs - such as seen with PTEN deficiency [Vidotto BJC '20]), overexpression of immune checkpoint ligands.



- **Four major types of immunotherapy**: Checkpoint inhibitors, Adoptive cell transfer, Ab-based therapies, Vaccines.
- **RT may promote immune-mediated killing by**: Release of DAMPs (e.g., HMGB1 - activates dendritic cells most likely by binding to TLR4), Enhancement of FAS surface expression (Caspase 8), increased tumor-specific Ag presentation, upregulation of MHC-I (mTOR mediated), decreased (or increased) expression of PD-L1, upregulation of proteins that support T-cell adhesion (calreticulin - prophagocytic signals), enhancement of TILs (changes in vascular endothelium enhancing immune cell extravasation and increased expression of chemokine attractants).
    - Conversely, RT might lead to substantial increases in the immunosuppressive TGFβ.
- **Smokers have improved ICI response?** [Gainor Ann Onc '20]: Retro. **PD-L1 ≥ 50%**. **Never vs. light vs. heavy smoker**. TBL [QS]: Smoking status may need to be factored into the decision on when to add chemo for NSCLC with higher PD-L1 expression, as never smokers appear to derive less of a benefit from ICI monotherapy.
    - 315 pts with NSCLC. 75% heavy smokers (> 10 py), 13% light (≤ 10 py) and 11% never.
    - ORR 25→ 40→ 40%.
    - Median DOR 7→ 11→ 18 mo.
    - MPFS 3→ 4→ >5 mo.

- Interestingly, subgroup analyses of larger RCTs such as KEYNOTE-042 demonstrated no improvement in OS with pembro among never smokers, even though with PD-L1 expression > 50%.

- **Impact of <u>baseline</u> steroids on efficacy on PD-(L)1 blockade** [Arbour JCO '18]: **PD-L1 ± baseline prednisone ≥ 10 mg**.
  TBL [QS]: Notwithstanding the causation versus correlation question mark, patients who require steroids at initiation of immunotherapy have worse response to therapy and worse survival.
  - 640 advanced NSCLC pts from MSKCC and Gustave Roussy cancer center.
    - Ninety (14%) pts were on ≥ 10 mg prednisone at baseline (i.e., 1.6 mg dex).
  - ORR around 20→ 10%, MPFS 2.6→ 1.9 mo, MS around 10→ 5 mo.
- **Impact of <u>baseline</u> steroids on efficacy of ICI** [Ricciuti JCO '19]: **PD-1 with 0 - 10 mg vs. ≥ 10 mg prednisone**.
  TBL [QS]: The relationship between steroid dose, ICI efficacy, and oncologic outcomes may simply be that patients with worse disease require more steroids.
  - 650 advanced NSCLC pts from Harvard.
    - Ninety-three (14%) pts were on ≥ 10 mg prednisone at baseline (i.e., 1.6 mg dex).
    - Cancer related palliative intent (anorexia, dyspnea, pain, brain mets).
  - mPFS 3.4→ 2.0 mo.
  - MS 11→ 5 mo.
  - MPFS for ≥ 10 mg prednisone for cancer-unrelated vs. palliative indications of 5→ 1 mo.
  - MS for ≥ 10 mg prednisone for cancer-unrelated vs. palliative indications of 11→ 2 mo.

Combining PD-1 with CTLA-4
- ➢ **Ipilimumab alone appears to be more toxic than Nivolumab alone.**
- ➢ **The most effective and most tolerable dose appears to be <u>Nivo 3</u> mg/kg + <u>Ipi 1</u> mg/kg q3w x2c** (See OpACIN-neo)

- **Checkpoint inhibitors**: Checkpoint ligands act to protect against excessive inflammatory response, and tumor cells take advantage of this.
  - Tumor cells expressing **PD-L1** promote T-cell exhaustion (slow T-cell proliferation, poor function).
  - Tumor cells expressing **CTLA-4** can upregulate regulatory T cells (inhibits effector T-cells).
- Improved ORR (and potentially OS) with the addition of CTLA-4 to Nivolumab:
  - **The most effective and most tolerable dose appears to be Nivo 3 mg/kg + Ipi 1 mg/kg q3w x2c**.
  - **CheckMate 067** [Larkin NEJM '17, Wolchuck '17]: **± Nivo ± Ipi**, but no obs. 1:1:1 randomization.
    - 945 pts. Tx-naive metastatic melanoma.
      - Nivo alone: 3 mg/kg q2w.
      - Ipi alone: 3 mg/kg q3w x4c.
      - Combo: Nivo 1 mg/kg + Ipi 3 mg/kg q3w x4c→ Nivo 3 mg/kg q2w.
    - 3y OS for ipi / nivo / combo of 34→ 52→ 58%.
    - G3-4 toxicity for ipi / nivo / combo of 28→ 21→ 59%. *More toxicity w ipi.*
  - **OpACIN-neo** [Rozemann Lanc Onc '19]: Phase II. **HD-Ipi→ HD-Nivo vs. Nivo/HD-Ipi vs. HD-Nivo/Ipi**.
    TBL [QS]: Two cycles of neoadjuvant ipilimumab (1 mg/kg) and nivolumab (3 mg/kg) appear to be both effective and tolerable for patients with resectable stage III melanoma.
    - 89 pts. Resectable stage III melanoma involving lymph nodes only. MFU 32 mo.
      - C HD-Ipi→ HD-Nivo: Ipi 3 mg/kg q3w x2c→ Nivo 3 mg/kg q2w x2c.
      - A Nivo/HD-Ipi: Ipi 3 mg/kg + Nivo 1 mg/kg q3w x2c.
      - B HD-Nivo/Ipi: Ipi 1 mg/kg + Nivo 3 mg/kg q3w x2c.
    - G3-4 toxicity 50→ 40→ 20%.
    - pCR 23→ 47→ 57%. No patients with pCR had relapse over a relatively short follow up period.
- Checkpoint inhibitors work best in tumors with high mutational burden. They require high recognition potential, or the likelihood Ags will be presented by MHC and recognized by T cells.
  - **Metastatic SqCC** [Migden NEJM '18]: Phase 1. **Cemiplimab** (PD-1).
    Methodology: most metastatic SqCC's are immunosuppressed and often hypermutated.
    - ORR nearly 50% w durable response.

Toxicity of Immunotherapy

See the [Summary Box] in the Immunotherapy introduction section.

Nivolumab AE [Weber JCO '17]: **Pooled review of melanomas**. **Nivo 3 mg/kg q2w**.
Excellent reference for AE of Nivolumab.

Most side effects are primarily low grade, resolving with established safety guidelines. Use of systemic suppressive immune-modulating (e.g. corticosteroid) agents did not affect ORR.

- ➢ 576 pts. Melanoma. 54% prior ipilimumab. Median 9 mo nivolumab.
- ➢ 70% overall, **10% G3-4**. Tx-related AE leading to discontinuation in 3% (any grade), most commonly colitis, increased AST, increased lipase, and pneumonitis.
- ➢ GI 2-3%. Hepatic 1% (peri-portal, mostly T cells). Colitis. Dermatitis. Neuro 1%.
- ➢ Median time to onset of AEs range from 5w (skin) and 15w (renal).
- ➢ Around 24% (n=114) rec'd corticosteroids. **ORR for ± corticosteroids ~30%**.

Adverse events in Immunotherapy: ***X*-itis** [Postow NEJM '18]:

- ➢ Most commonly colitis, hepatitis, dermatitis, endocrine abnormalities.
- ➢ Hypophysitis: Persistent HA, sudden loss of libido, persistent fatigue.
  - Suppression of multiple hormones, particularly hydrocortisone. Image with MRI. Treat early and aggressively for best results. EASILY MISSED but < 1% although ipilimumab may be around 5%.
- ➢ Cytokine release syndrome: Treat with infliximab.

Immune-related events portend to better response? [Eggermont JAMA Onc '19]: KEYNOTE 054. **± Pembro**.
TBL [QS]: There should probably be a high threshold for discontinuing immune checkpoint inhibitors due to an immune-related adverse event since that may be a clear signal that the drug is working.

- ➢ 1,019 pts with high risk stage III melanoma. 2015-2017.
- ➢ Immune related AE (irAE) of 9→ 37%.
- ➢ Most common side effects of hyper or hypothyroidism or vitiligo. Less than 20% of pts discontinued tx due to irAE.
- ➢ For patients with irAE, death HR after irAE of 0.37 with RFS HR after irAE of 0.37.

Immunotherapy events are likely overstated [Rodrigo JAMA '18 [QS], Moreau-Bachelard, Coquan, Le Tourneau NEJM '19]
TBL [QS]: Previous reporting indicates rates of adverse events with immune checkpoint inhibitors may be overblown. That's because most patients enrolled in relevant trials (e.g., for refractory metastatic disease) are pretty prone to adverse events at baseline. This Parisian group does a quick tally among 51 recent placebo-controlled trials of anti-cancer agents to determine that more than a quarter of grade 3+ toxicities attributed to anti-cancer drugs also occur in the placebo arm.

Targeted therapy with SBRT: **Reviews here** [Simone TLCR '15, Kroeze CTR '17, Zeng Lancet '14].

- ➢ Awaiting RTOG 1306.
- ➢ Brief summary:
  - VEGF is associated with fatal hemoptysis for lung SBRT or bowel perforations for abdominal SBRT.
  - BRAF V600E is associated with severe dermatitis with SBRT.
    Consider holding BRAF and/or MEK inhibitors ≥ 3d around RT, while only ≥ 1d for SRS or SBRT.
  - TKIs can lead to higher rates of pneumonitis with SBRT.

Pembro with RT [Luke/Lemons JCO '18]: Phase I. **Pembro within 7d after the end of SBRT**.
This toxicity isn't really different from Pembro alone, but seems to correlate to area irradiated. Also see [KEYNOTE 001] and [Tian IJROBP '20], the latter of which suggests up to 30% G3 pneumonitis if SBRT to the lung is given concurrently with ICI.

- ➢ 73 Stage IV patients progressing on prior tx. 2016-2017. Target volumes < 65 mL (5 cm tumor). MFU 5.5 mo.
  - SBRT to 2 sites in 69/73 pts. Treated 2-4 metastatic sites.
  - 30/3 for bone/spinal.
  - 45/3 for peripheral lung/liver/abd/pelvis.
  - 50/5 for central lung/mediastinal/cervical.
- ➢ 6 G3 toxicity (3 pneumonitis, 2 colitis, 1 hepatitis). 10% dose limiting toxicity.
- ➢ G3 RP in 13% of pts (n=3/23) receiving lung SBRT.
- ➢ Objective response 13.5% (2 CR, 8 PR, 21 SD, 38 PD).

- **Radiation + Immunotherapy induced lymphopenia?** [Pike NEJM '18]
- **Pembro-RT Trial** [Theelen ASCO '18, JAMA Onc '19]: Phase II. **± SBRT→ Pembro within 7d after the end of SBRT**.
  TBL [QS]: Inserting a quick shot of SBRT prior to pembro for refractory NSCLC is clearly safe and may double response rates, suggesting it is more practical than not to extrapolate Gomez data in the setting of pembro.
  - 76 pts. ≥ 2nd line chemo for advanced NSCLC. Bx of tumor at baseline and after 2c pembro.
    - Pembro 200 q3w. PD-L1 ≥ 50% in 13→ 29% (control arm had less PD-L1).
    - SBRT 24/3 within 7 days prior to the first cycle.
  - 12w ORR ~18→ 36% (p=0.07). MPFS ~1.9→ 6.6 mo (p=0.19), MS ~7.6→ 15.9 mo (p=0.16).
    - Improvements in ORR with SBRT are most marked in patients who have a PD-L1 of 0%.
    - PD-L1 was not balanced between groups, which may have confounded outcomes.
  - G3+ in ~20%. Most commonly fatigue, nausea, fever, hypothyroidism.
- **SBRT prior to ICI may be superior for resected melanoma brain mets** [Pomeranz Krummel IJROBP '20]: Retro.

TBL QS: Radiation to melanoma brain mets induces changes in the NF-kB signaling pathway that appear to prime a response to subsequent ICI.
    - Only 17 patients. RT→ ICI is associated with better survival than ICI→ RT.
- **Colitis and Immunotherapy** QS [Abu-Sbeih JCO '19]: Retro. What happens if ICI is re-initiated?
    - 167 patients. CTLA-4 in 32 pts, PD-(L)1 in 135 pts. Re-started immune checkpoint inhibition at median of 49d.
    - Recurrent colitis in 1/3 of patients at a median of 53d, mostly G1-2.
    - Risk of immune mediated diarrhea and colitis lower if resuming PD-(L)1 than resumption of CTLA-4 therapy.
- **Colitis in patients with IBD** QS [Abu-Sbeih JCO '20]: Retro. ± **IBD**.
    - 102 pts, only 17 pts CTLA-4 while remainder PD-1 or PD-L1 monotherapy.
        - Half Crohn's, half UC. Median time from the last active IBD episode to immunotherapy was 5y.
        - Nearly half of pts were not receiving treatment for IBD.
    - GI AE in 11→ 41% of patients after a median of 62 days.
    - G3-4 diarrhea in 21% of patients with IBD.
    - No G5 AE.
    - Anti CTLA-4 therapy was associated with increased risk of GI AE on UVA, but not MVA.

CAR T-Cells

- **CAR T Cells: Continuation in a revolution of immunotherapy** QS [Singh Lanc Onc '20]:
- **Adoptive cell transfer**: Removes immune cells from pt, potentially altering them to target a cancer, growing *ex vivo* and re-infusing to the patient. There are three main sources of tumor-specific immune cells: 1) TILs 2) Antigen-specific cells through adaptive immune system and 3) Antigen-specific cells which were genetically engineered.
- **Chimeric antigen receptor (CAR) T-cell therapy**
  Tisagenlecleucel - Refractory B-ALL, Axicabtagene ciloleucel - approved for relapsed DLBCL.
  A type of adoptive cell transfer where T cells are engineered to target tumor Ags expressed on the membrane of cancer cells. Chimeric receptors are formed by fusion of extracellular tumor specific Abs, a transmembrane and intracellular portion that stimulates T-cell activity when an Ag binds to the extracellular Ab. CAR T-cell not dependent on MHC neoantigen presentation, therefore can be effective even with MHC downregulation by the tumor.
    - Autologous stem cells are extracted from the patient and manufactured ex-vivo and then re-infused into the patient.
    - Cell killing mechanism independent of MHC I.
    - Takes 2-5 weeks. Trafficking of CAR T to tumor cells is a major issue (decreased activated T cell adhesion)
        - RT can upregulate ICAM1 and VCAM1.
        - RT enhances chemotaxis.
    - Impractical for patients with rapid progression.
    - Not always possible to generate CAR T cells in heavily pretreated patients.
    - Radiation might have a role after leukapheresis. Perhaps there may be a beneficial effect if RT is delivered during the 2-5 week process where CAR-T cells are manufactured and the patient is being lymphodepleted.
    - Generally speaking, CAR-T may be effective in around 50% of the time (at least for RR HL), so RT also may be used for consolidation after CAR-T.
- **Patterns of failure following CAR-T therapy** [Figura ASTRO '19]
    - Nearly all recurrences for refractory B-cell lymphomas are in the areas of previously involved disease sites by 6 months. Disease sites with high metabolic activity and lesions ≥ 2cc in cross sectional area or ≥ 20cc in metabolic volume are at increased risk of progression following CAR-T therapy. All necrotic lesions progressed at the time of failure.
- NKT cells are an alternative [Liu Leukemia '18] without significant side effects [Liu NEJM '20].
- **ELIANA** [Maude NEJM '18]: Phase 1-2a. **Tisagenlecleucel** (CAR T-cells engineered to react to CD19)
    - 75 pts. CD 19+ relapsed / refractory B-ALL. CAR T cells were engineered to react to CD19. MFU 13 mo.
    - 3 mo ORR 81% w all pts found to be negative for minimal residual dz.
        - Median remission duration NR. Persistence of tisagenlecleucel in blood seen as long as 20 mo.
    - EFS at 6 / 12 mo of 73→ 50%.
    - OS at 6 / 12 mo of 90→ 76%.
    - G3-4 73%. Cytokine release syndrome in 77%, 50% of whom rec'd tocilizumab.
    - Neurological events in 40% of pts managed with best supportive care, no cerebral edema reported.

Sipuleucel T and PROSTVAC

- **Sipuleucel-T**: A therapeutic vaccine/**adoptive cell transfer** to prostatic acid phosphatase (PAP), which helps APCs mature.
    - **IMPACT** [Kantoff NEJM '10]: **Placebo vs. Sipuleucel-T immunotherapy** q2w x3c.
      MS benefit of 4 mo, though interestingly no effect on time to dz progression noted.

        - 512 CRPC pts.
        - MS 22→ 26 mo. 3y OS 23→ 32%. Death RRR 22%.
        - No effect on time to progression was observed.
- **PROSTVAC** ^{qs} [Gulley JCO '19]: **Placebo vs. PROSTVAC ± GM-CSF**.
    - 1297 pts. Chemo-naive mCRPC newly progressed on anti-androgens. MFU 33 mo.
    - MS ~34.5 mo. 6 mo alive without events ~30%. 60% of the events were radiographic only.

Misc

- Anatomy and levels:
    - C3: Hyoid.
    - C3-C6 Larynx.
    - C5-6: TVC.
    - T4-5: Carina
    - T10-11: Diaphragm
    - T12/L1: Celiac
    - L1: SMA
    - L1-L2: Pancreas. *Left crus.*
    - L3: IMA. *Right crus.*
    - Right crus L3, Left crus L2. Lowest point of pleural space can be L4.
- Level 1 - prospective, Level 2 - retrospective, Level 3 - case
- Translocations:
    - t(1;13) ARMS. Fusion between FKHR gene on 13 and PAX7 on chromosome 1. t(2;13) can also be seen in ARMS (FKHR, PAX3)
    - t(9;22) Philadelphia. BCR on 22 and Abl1 on 9. CML, GIST. Abl1 is TK. Imatinib.
    - t(11;22) Ewings. EWS on 22 and FLI1 on 11.

Board pearls

- "I would have a balanced discussion"
- "Even though this is 3D, I would contour all targets and adjust fields to have a margin on PTV"

<u>Drugs</u>

- Dasatinib and imatinib for philly chromosome
- Pazopanib can inhibit angio in STS and RCC (PDGFR, VEGFR, FGFR, c-kit)
- Sunitinib for PDGFR, VEGFR and c-kit
- Erlotinib for EGFR