Modern Radiotherapy in Melanoma

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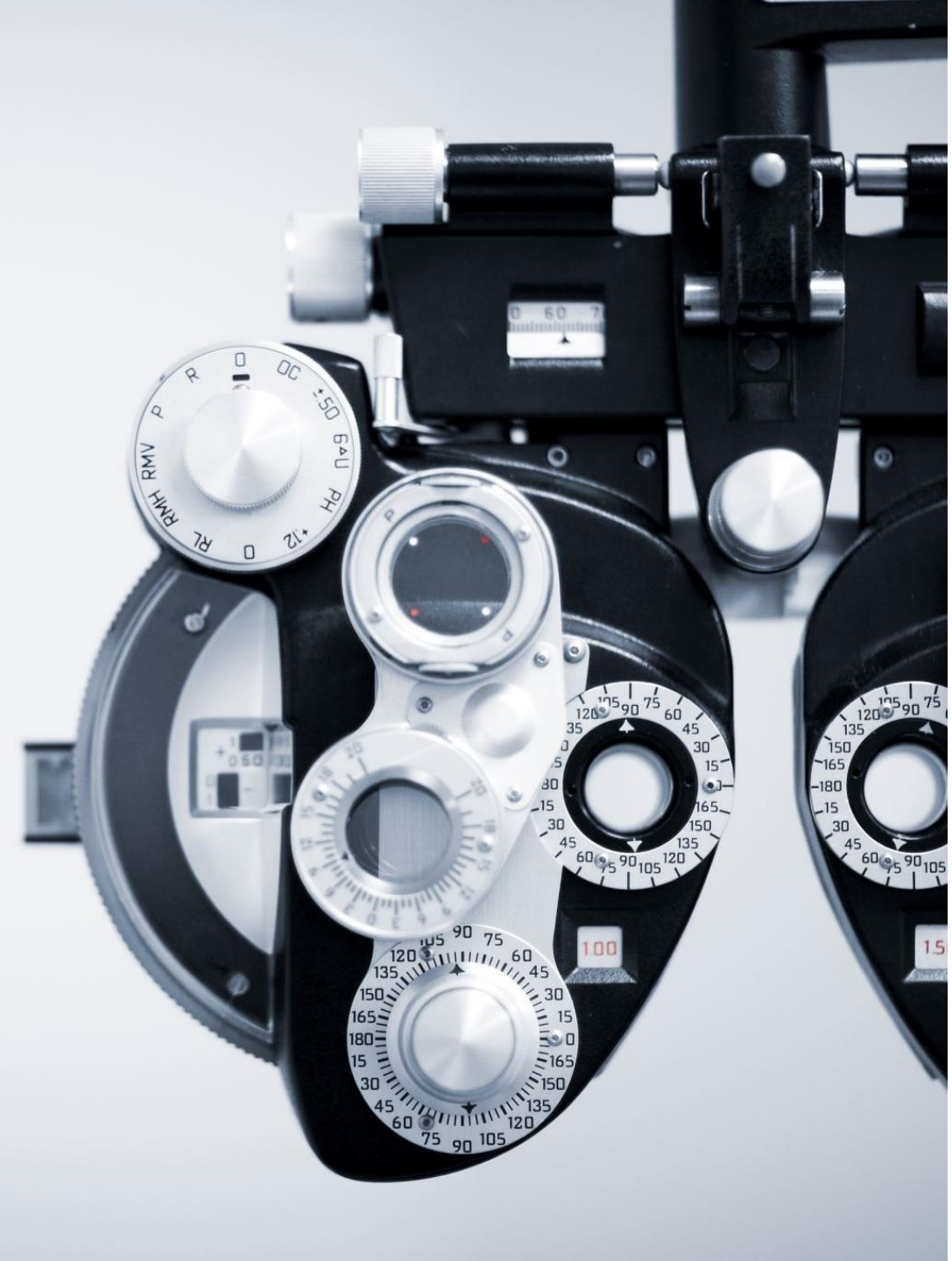


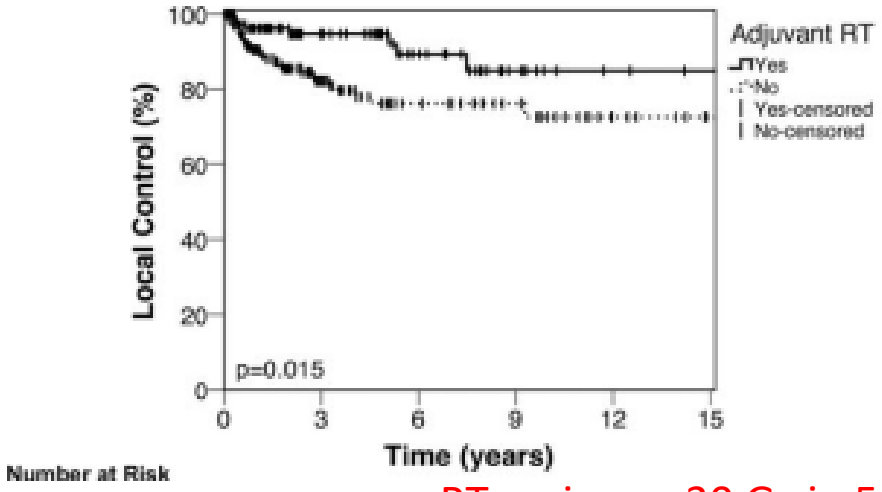
Modern Indications for Radiotherapy in Melanoma

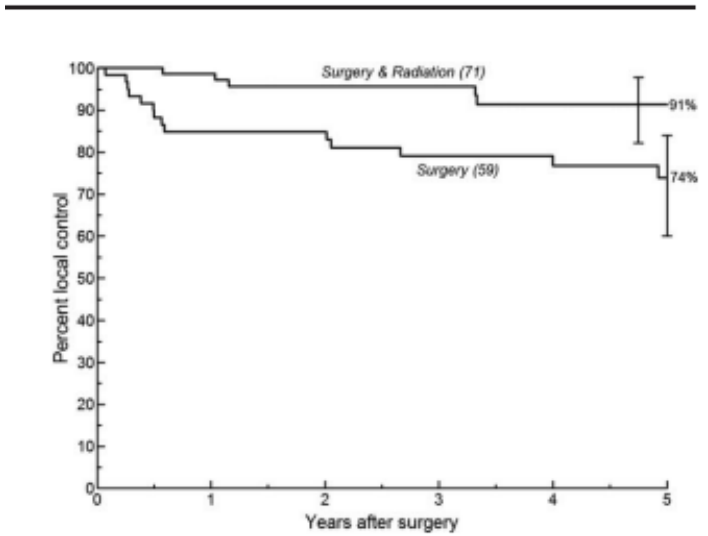
- Local Disease
  - Primary
    - Uveal Melanoma (I-125 eye plaque brachytherapy ~ 85 Gy vs. protons ~ 60 Gy in 4 fractions) for medium and large sized lesions; LC 90-95%; enucleation for toxicities ~ 3-5%
    - Lentigo Maligna
  - Adjuvant
    - Recurrent in-transit disease (30-36 Gy in 5-6 fractions, twice a week)
    - Desmoplastic melanoma (30-36 Gy in 5-6 fractions, twice a week)
    - Mucosal Melanoma (48-60 Gy in 20 fractions over 4 weeks)

Desmoplastic Cutaneous Melanoma

Strom et al. Cancer 2014 (Moffitt); Guadagnolo et al. Cancer 2013 (MDACC)

- Pattern of Failure
  - Primarily Local & Perineural >>> Regional or Distant
    - Local Recurrence Rates ~ 20-60%
    - Higher risk in select anatomic sites, advanced T stage, + margins
    - Neurotropic by definition





RT regimen: 30 Gy in 5 twice a week en face electrons; brachytherapy: 40 Gy in 10 BID

Desmoplastic Cutaneous Melanoma

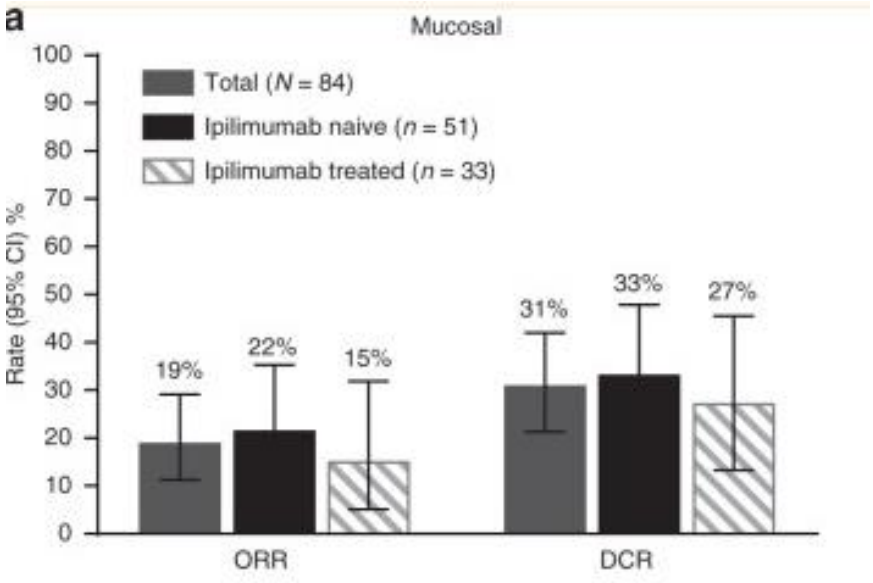
- TROG trial on adjuvant RT for desmoplastic melanoma has been completed (08.09)
  - Surgery + RT vs. Surgery alone
  - RT: 48 Gy in 20 fractions over 4 weeks
- Important to stage these patients with MRI evaluating CN for HN cutaneous lesions

Mucosal Melanomas

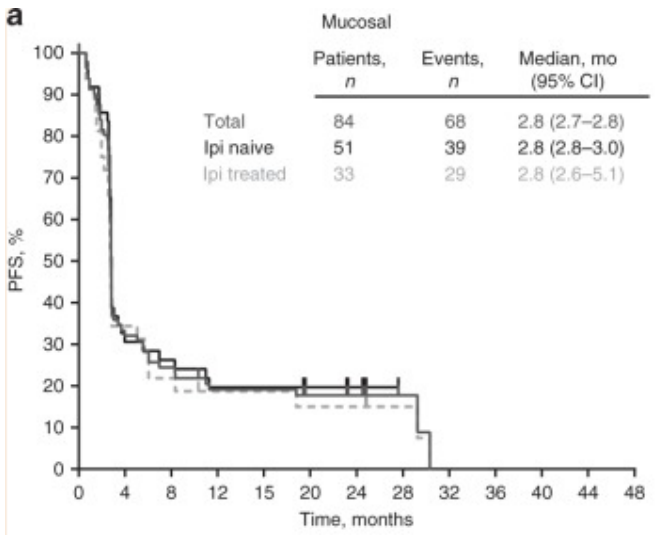
- Overall survival in lower than cutaneous melanoma
  - Location matters: HN does better than GI/GU/Gyn locations
- Lower response rate to immunotherapy (~ 10-25%)
  - Unlikely to have BRAF mutation
- Local relapse can be clinically and functionally devastating
- Local RT has been shown to significantly decrease risk of local relapse

Immunotherapy in Mucosal Melanoma

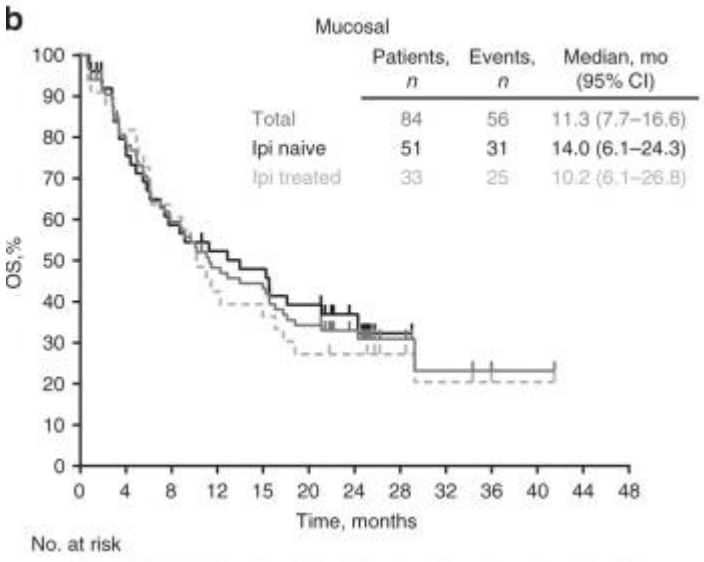
Hamid et al. Br J Cancer 2018



ORR 19%



Median PFS 2.8 m



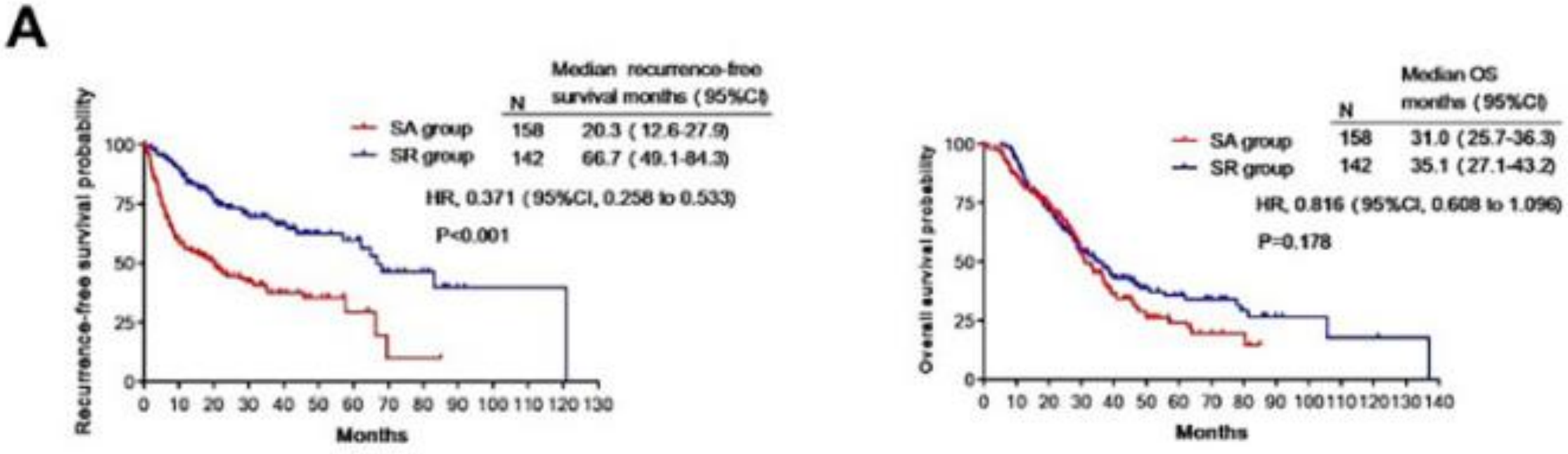
Median OS 11.3 m

Adjuvant RT in Mucosal Melanoma

- Treat primary site only in absence of nodal involvement
  - ENI no longer recommended
- RT choices
  - Sino-nasal: EBRT 48 Gy in 20 (TROG) → 60 Gy in 20-30 fractions (modest dose escalation with VMAT/Protons); 30 Gy in 5 (MDACC)
  - Ano-rectal, Vagino-Vulvar
    - EBRT alone 48 Gy in 20 fx,
    - Brachytherapy alone 30 Gy in 5 fx
    - EBRT+ brachytherapy boost

Adjuvant RT in HN Mucosal Melanoma

Lian et al. IJROBP 2024



>3 fold improvement in LRC

No improvement in OS

Brain Metastases

- Should you offer surgical resection?
  - Remains a consideration in large or symptomatic metastases prior to IO
  - If going to resect, strongly consider neo-adjuvant SRS/SRT
- Should you offer SRS to all brain metastases?
  - Historically yes, modern era… nuanced
  - Asymptomatic IO naïve patients in non-eloquent locations can safely start with IO
    - SRS upon progression
  - Symptomatic patients have significantly lower likelihood of response to IO alone
  - Anatomically High Risk or Eloquent Sites
    - Brainstem
    - Motor Cortex, Visual Cortex
    - Thalamus

Symptomatic vs. Asymptomatic

Tawabi et al. CheckMate 204 Lancet 2021

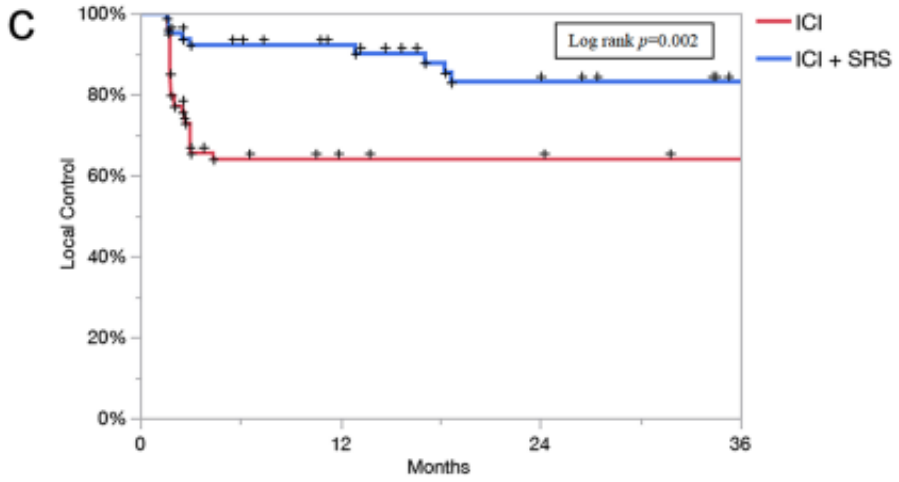
- Immunotherapy Response Rates
  - Asymptomatic Lesions ~ 50%
    - 3 y intra-cranial PFS 53.4%; OS 71.9%
  - Symptomatic Lesions ~15-20%
    - 3 y intra-cranial PFS 16.7%; OS 36.6%

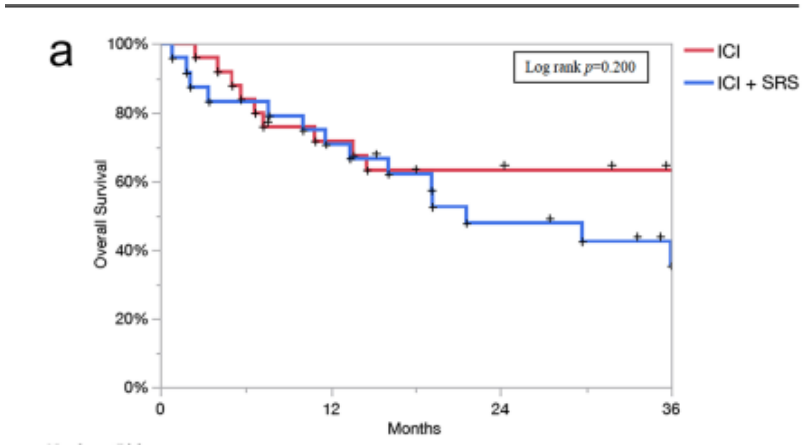
	Asymptomatic patients (n=101)			Symptomatic patients (n=18)		
	Intracranial	Extracranial	Global	Intracranial	Extracranial	Global
Best overall response*						
Complete response	33 (33%)	16 (16%)	17 (17%)	3 (17%)	1 (6%)	1 (6%)
Partial response	21 (21%)	33 (33%)	35 (35%)	0	3 (17%)	3 (17%)
Stable disease ≥6 months	4 (4%)	5 (5%)	4 (4%)	0	0	0
Progressive disease	30 (30%)	17 (17%)	26 (26%)	11 (61%)	7 (39%)	10 (56%)

ICI +/- SRS in symptomatic patients

Dang et al. JNO 2024

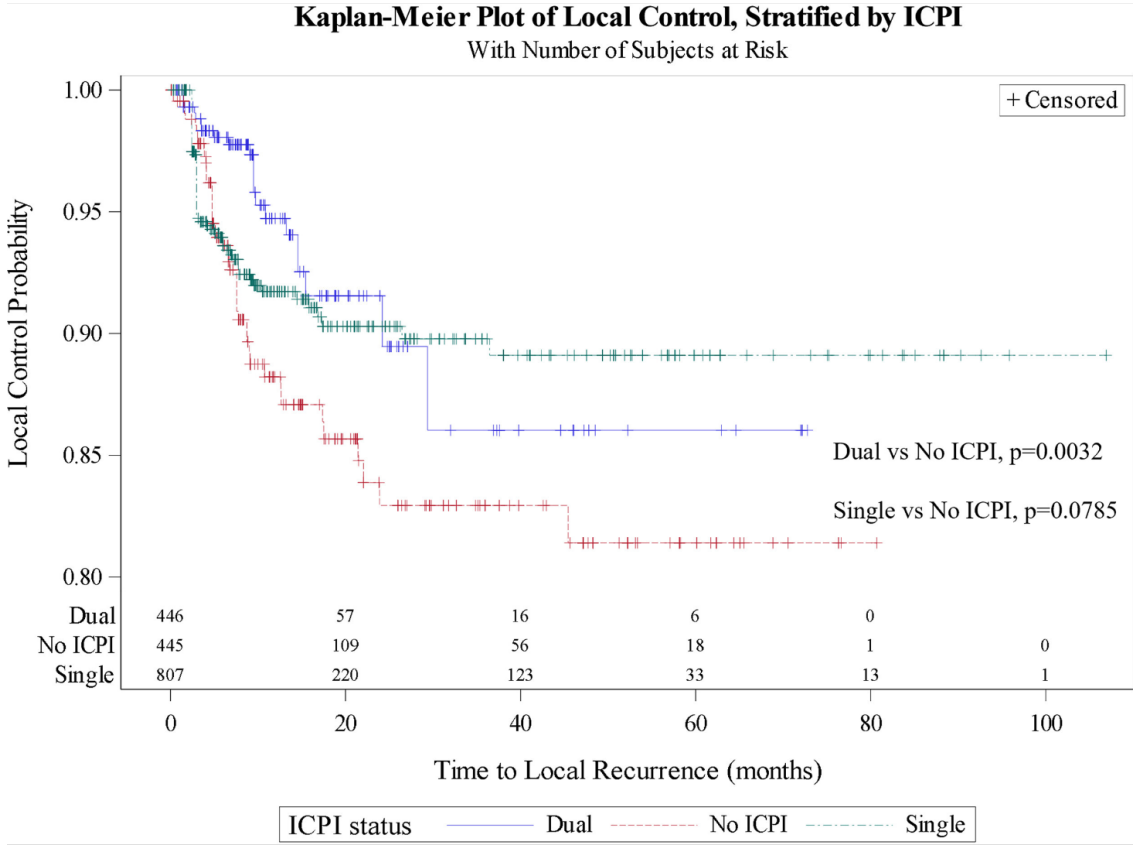
Moffett Experience – SRS added only for symptomatic or anatomically unfavorable lesions

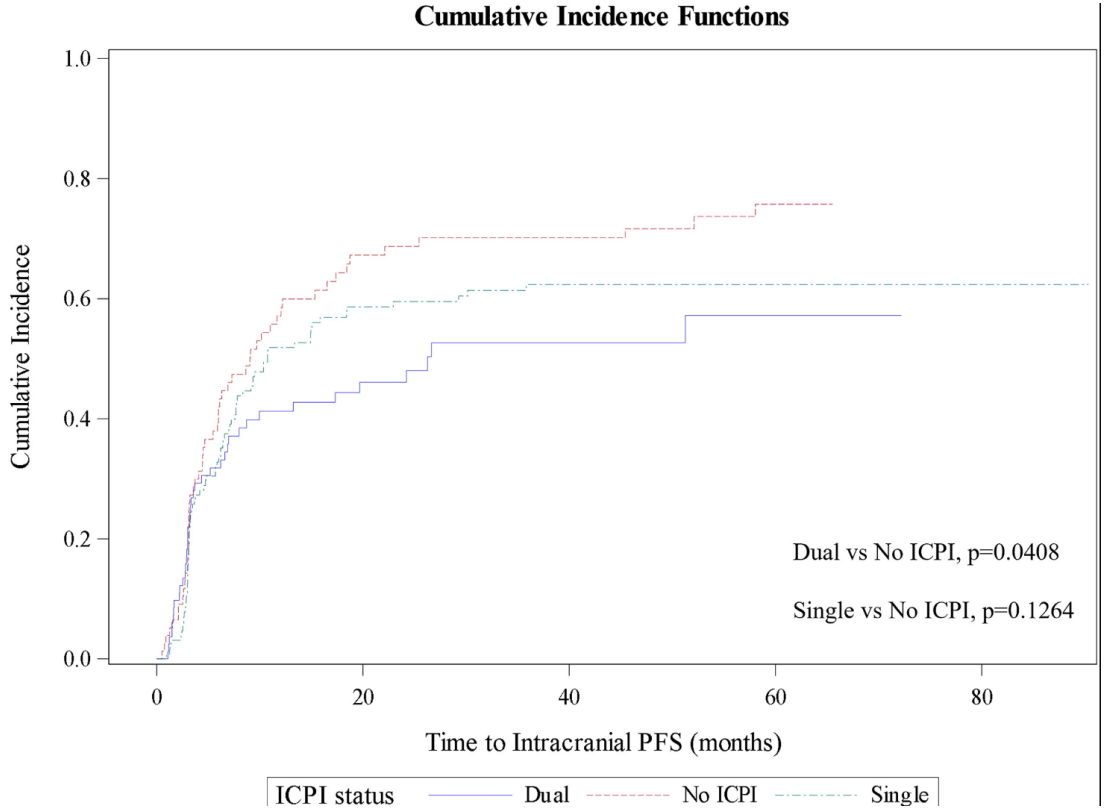




Dual ICB+ SRS

Vaios et al. IJROBP 2024



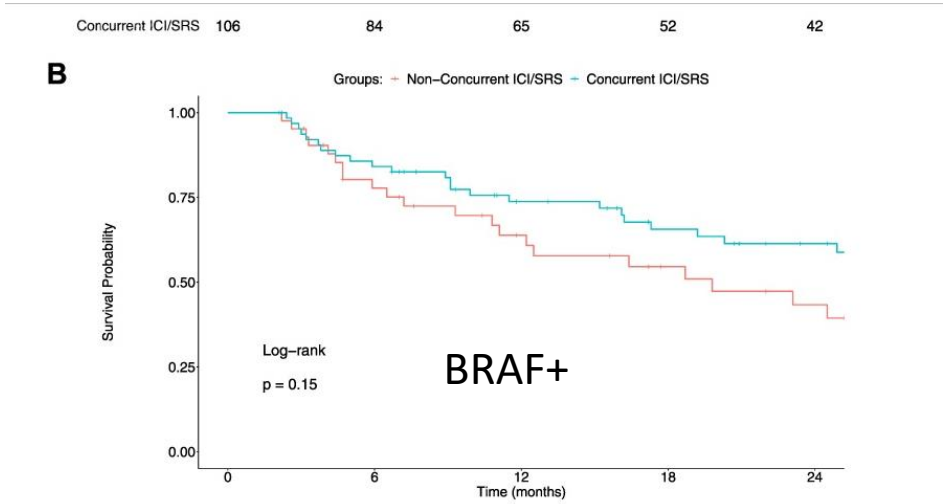


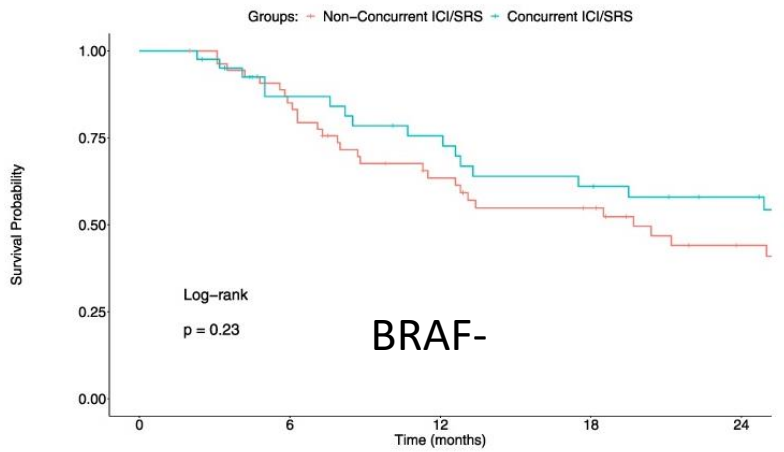
>1700 brain metastases melanoma/lung

Considerations when doing IO

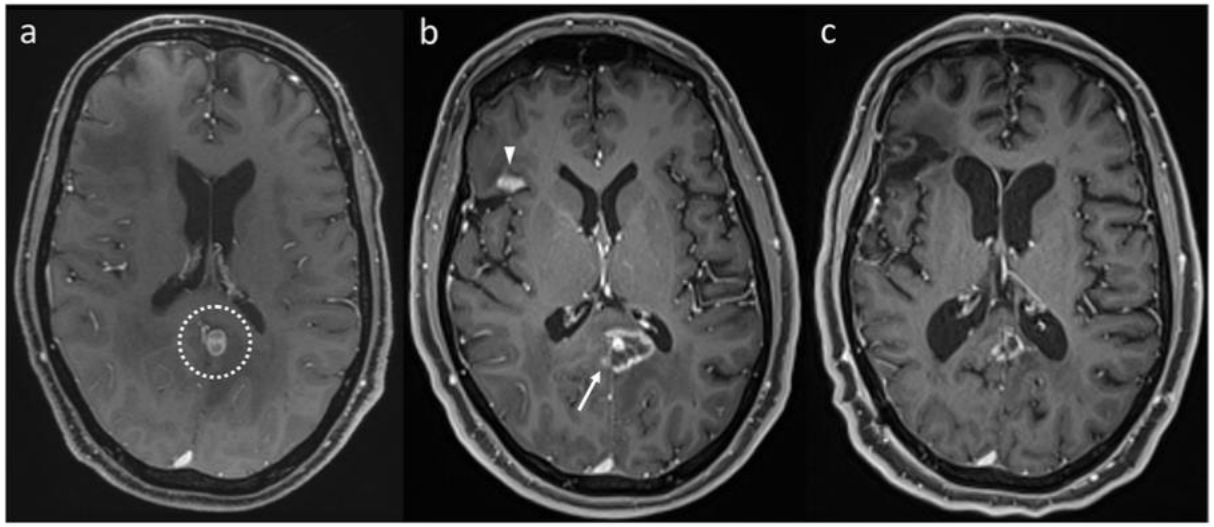
Jablonska et al. J NeuroOnc 2023; Lehrer et al. Neurosurgery 2022

- Increased risk of symptomatic RN/IH when SRS done with IO
  - Hemorrhage ~ 10-25%
    - Incidental in most patients, symptomatic in ~ 5%
  - Radionecrosis
    - G2 or higher ~ 10%
- Should NOT stop IO during SRS

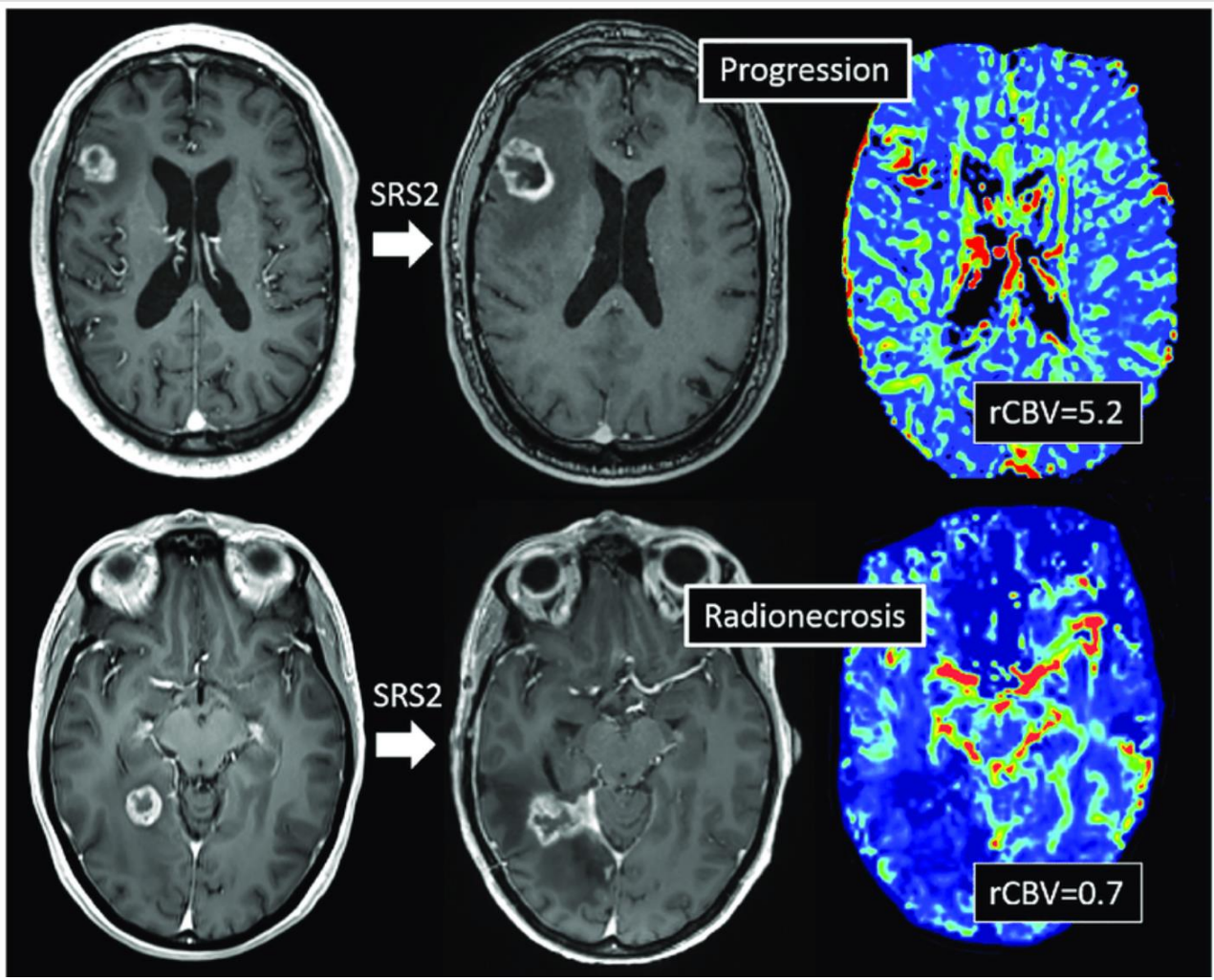




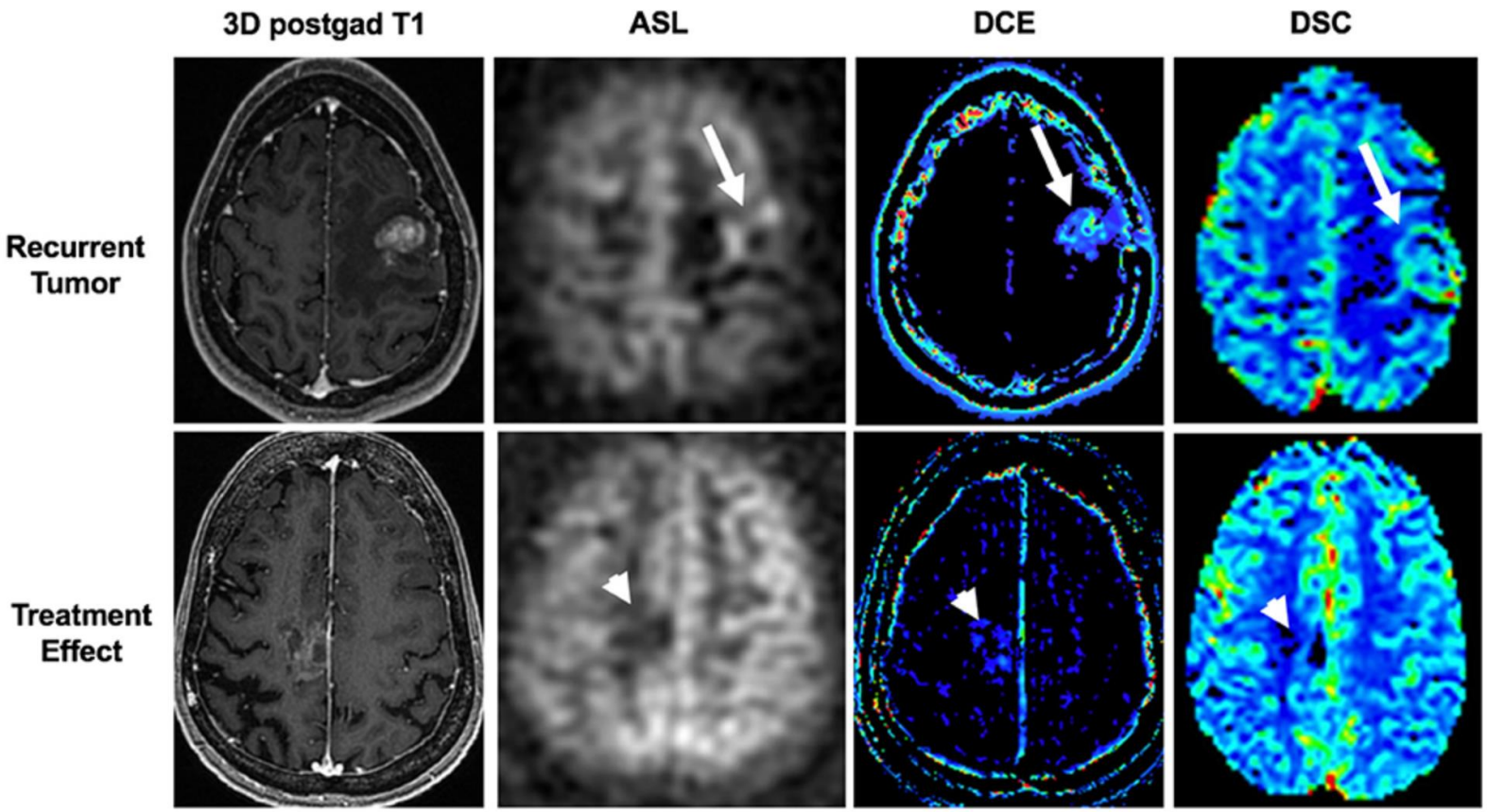
How to detect RN



- MRI with contrast
  - Add Perfusion sequences (Cerebral Blood Flow, Cerebral Blood Volume)



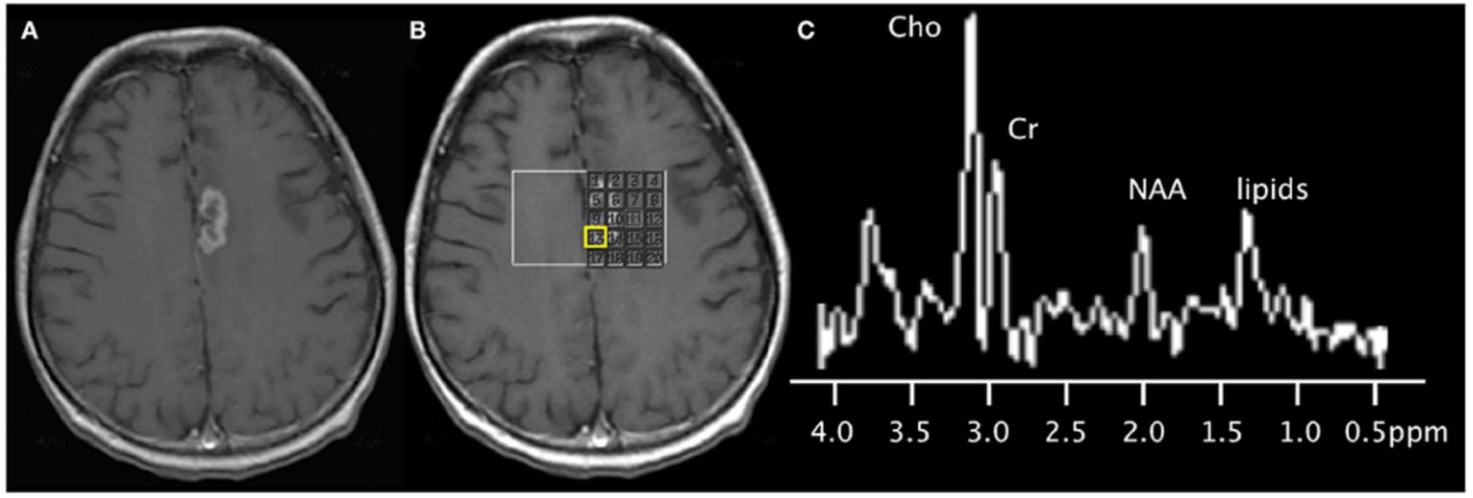
How to detect RN



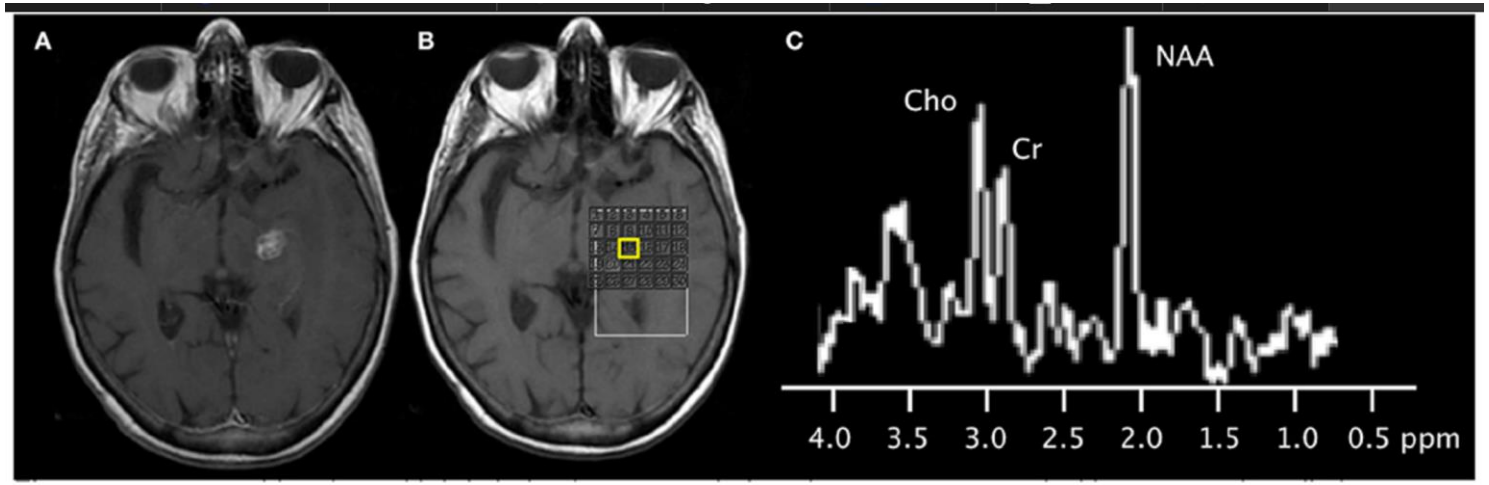
Special MR sequences

- Arterial Spin Labeling
- Dynamic Contrast Enhancement
- Dynamic Susceptibility Contrast

How to detect RN

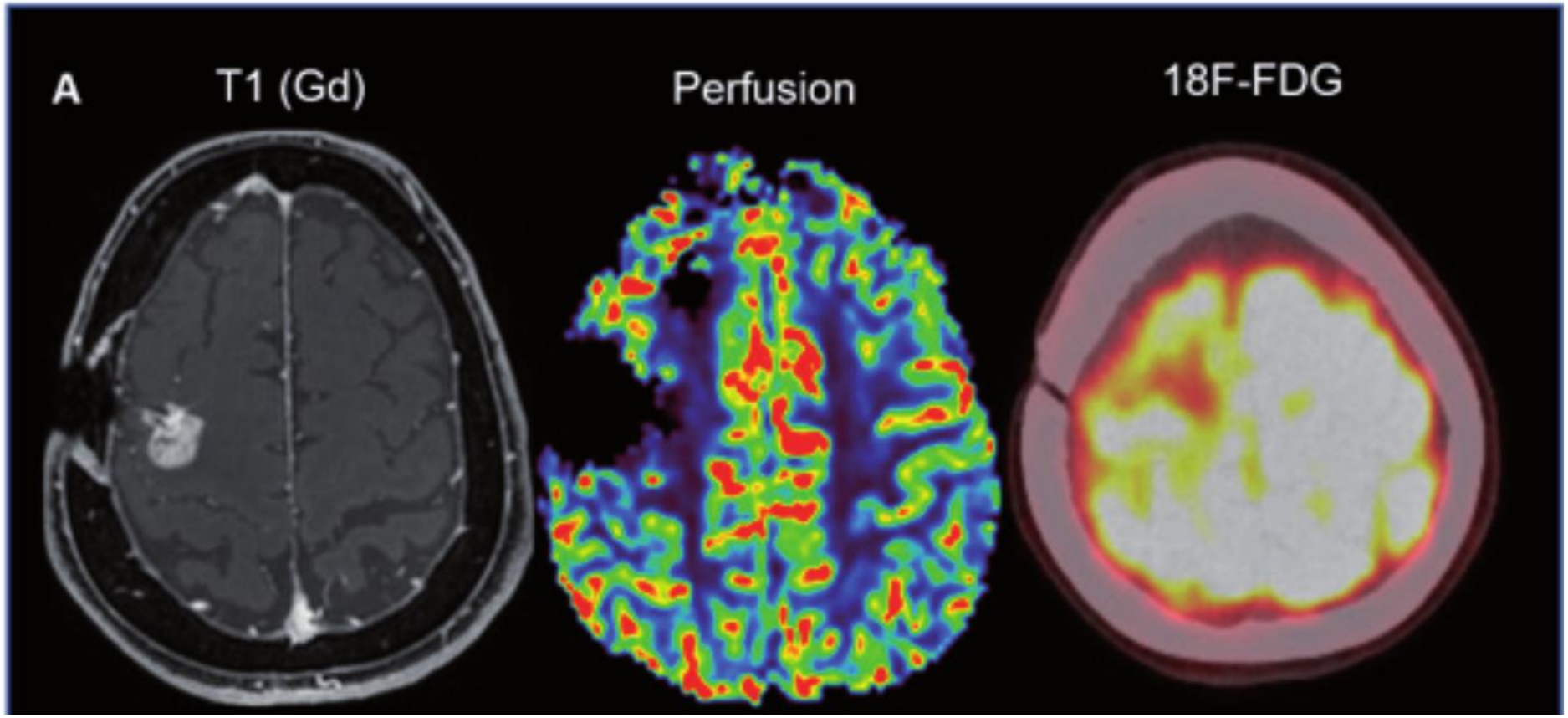


High NAA/Cho and NAA/Cr ratio suggestive of tumor progression



Slight Cho/Cr, Cho/NAA suggestive of RN

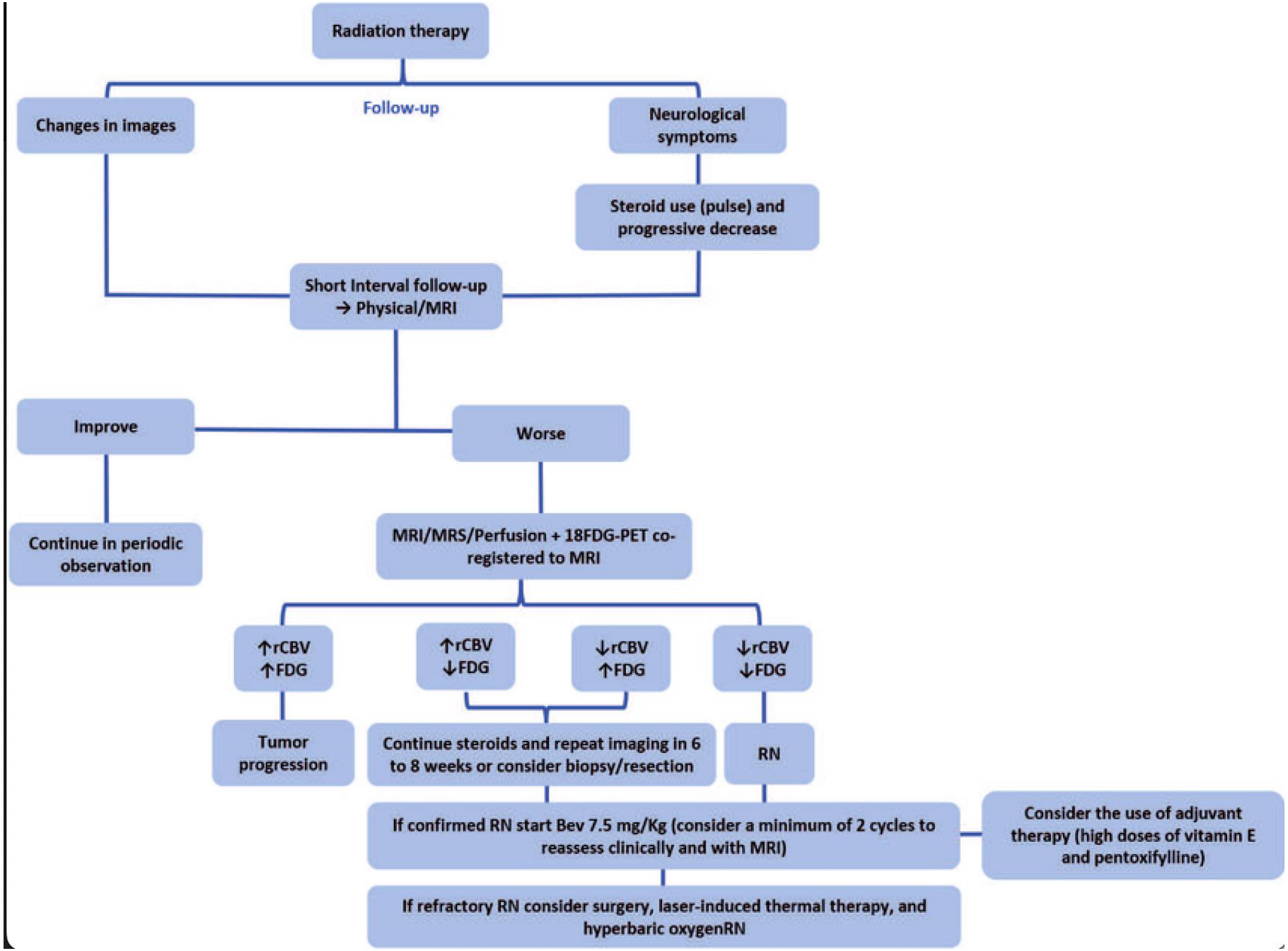
How to detect RN



FDG pet – showing decreased glucose metabolism

How to treat RN

- Asymptomatic (Incidentally Found)
  - Observe
- Symptomatic
  - Mild --> Steroids → If can’t wean off → Avastin
  - Moderate → Avastin
  - Severe → Surgery


Radiation therapy
Follow-up
Changes in images
Neurological symptoms
Steroid use (pulse) and progressive decrease
Short Interval follow-up → Physical/MRI
Improve
Worse
Continue in periodic observation
MRI/MRS/Perfusion + 18FDG-PET co-registered to MRI
↑rCBV ↑FDG
↑rCBV ↓FDG
↓rCBV ↑FDG
↓rCBV ↓FDG
Tumor progression
Continue steroids and repeat imaging in 6 to 8 weeks or consider biopsy/resection
RN
If confirmed RN start Bev 7.5 mg/Kg (consider a minimum of 2 cycles to reassess clinically and with MRI)
Consider the use of adjuvant therapy (high doses of vitamin E and pentoxifylline)
If refractory RN consider surgery, laser-induced thermal therapy, and hyperbaric oxygenRN

Take Away Points

- Add adjuvant local RT in
  - Recurrent in-transit disease (30-36 Gy in 5-6 fractions)
  - Desmoplastic melanoma (30-36 Gy in 5-6 fractions or brachytherapy)
  - Mucosal Melanoma (48-60 Gy in 20 fractions)
- Asymptomatic brain metastases in IO naïve patients can be on active surveillance → treat at time of progression
- Symptomatic brain metastases benefit from SRS+IO
- Be aware of increased risk of radionecrosis and intra-lesional hemorrahage after SRS with IO
- Asymptomatic RO – observe
- Symptomatic RO – steroids → Avastin → Resection

Thank You

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