Primary CNS lymphoma (PCNSL)

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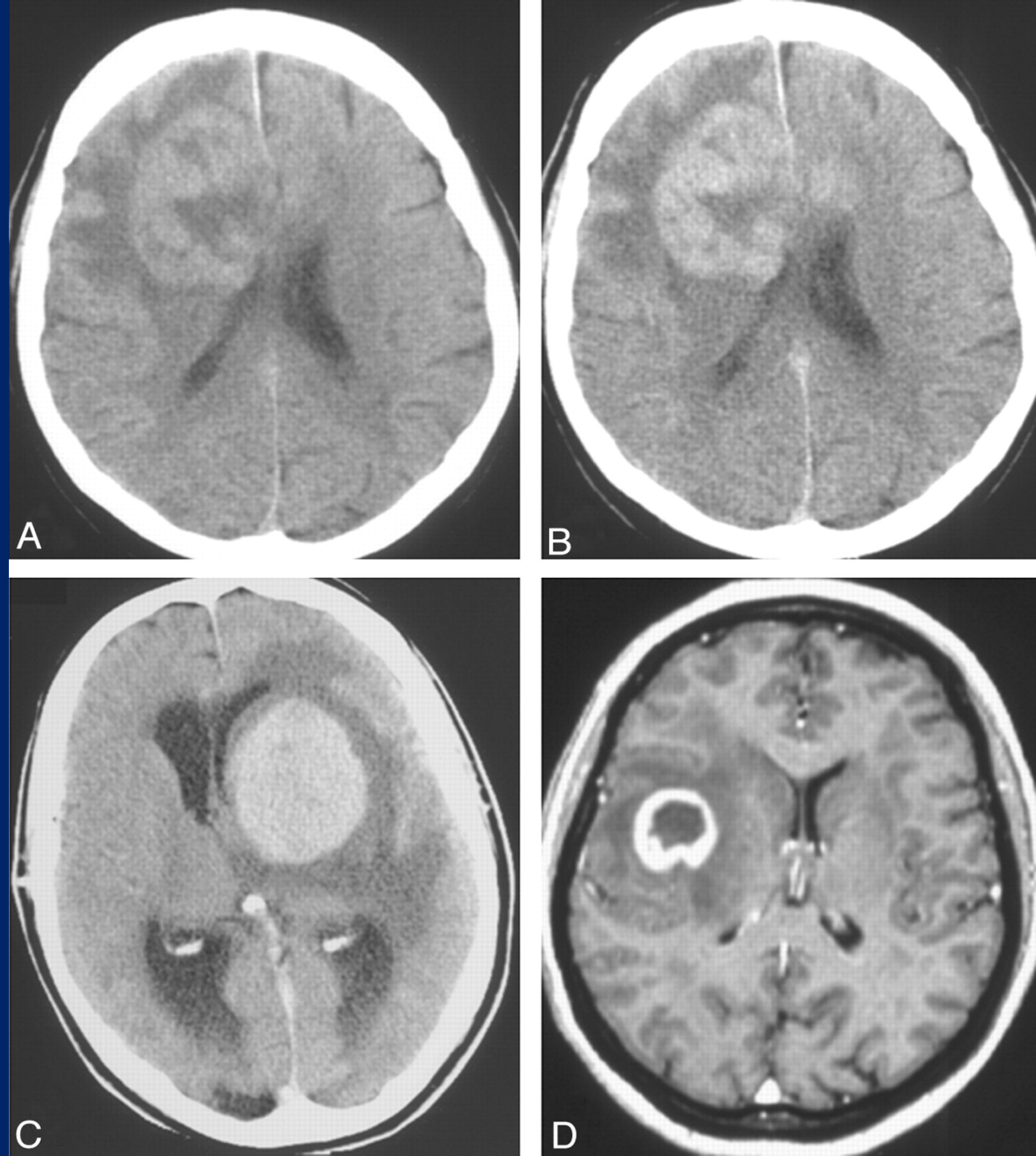
Memorial Sloan Kettering Cancer Center



PCNSL is a highly aggressive NHL confined to the brain, spine, CSF and/or ocular compartments

Epidemiology

- Historically in immunosuppressed (HIV/ post-transplant) population
- Rare in immunocompetent (4-6% of extranodal lymphomas)
- Rising incidence, particularly in elderly

Clinical presentation

- Neurologic symptoms develop over weeks
- Focal neuro deficits (55-70%)
- Altered mental status (40%)
- Symptoms of elevated ICP (30%)
- Seizures (15%)

Pathology and pathobiology

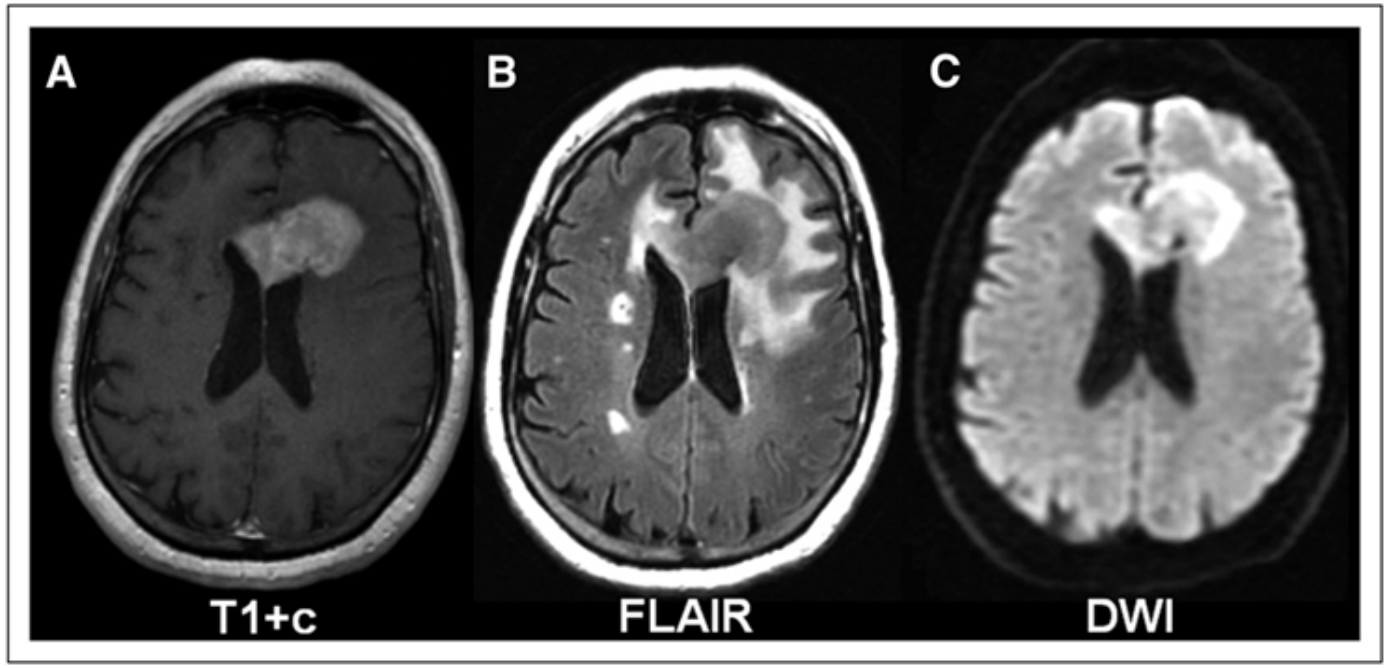
- Most will be DLBCL (90%)
- Vast majority will be non-GCB subtype
- Occasionally other histology (Burkitt, T-cell)
- Typically driven by B-cell receptor signaling and effector NFkB
- Frequent mutations in MYD88, CD79B

Standard workup

- Tissue biopsy (brain biopsy, CSF sampling or vitrectomy)
- MRI w/wo contrast of brain
- LP if safe
- Full ophthalmologic exam including slit lamp
- PET/CT (rule out secondary CNSL)
- LDH, HIV, CBC, COMP

Source: Grommes and DeAngelis, JCO 2017

Typical appearance on imaging



- Most often **solitary brain** lesion (66%)
- Typically **supratentorial** (87%)
- Typically frontoparietal
- Often **periventricular**
- Ocular involvement (15-25%)
- CSF involvement (7-40%)
- Rarely spinal cord

Avoid steroids if possible!

- **T1post:** homogeneous enhancing
- **T2 FLAIR**: significant edema
- **DWI**: restricted diffusion due to cellularity

Source: Grommes and DeAngelis, JCO 2017

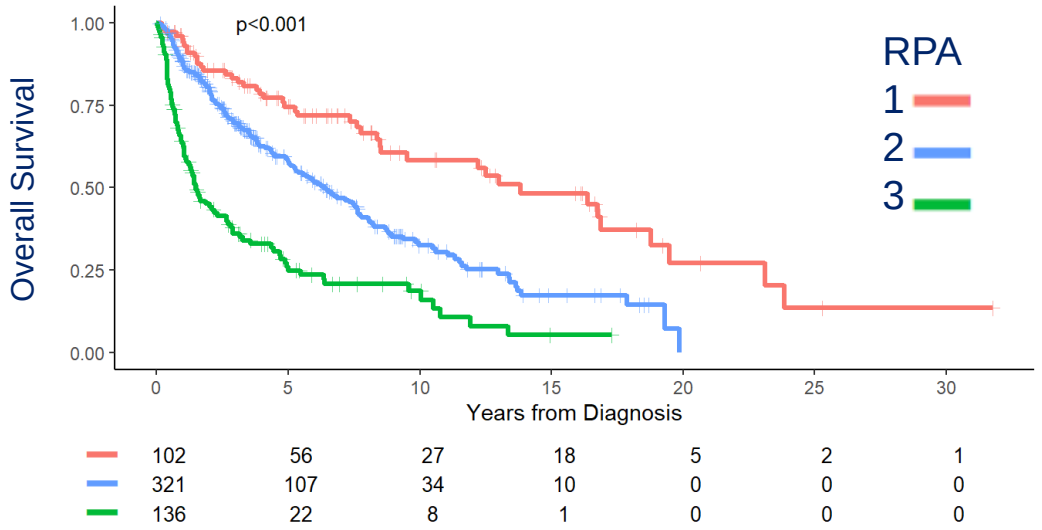
Prognostic scoring systems

MSKCC RPA prognostic score

TABLE 5-3 **The Memorial Sloan Kettering Cancer Center Prognostic Model for Patients With Primary Central Nervous System Lymphoma[a]**

Class	Median Overall Survival (Years)	Median Failure-Free Survival (Years)
1 = Age ≤50	8.5	2.0
2 = Age >50 + Karnofsky Performance Status Scale score ≥70	3.2	1.8
3 = Age >50 + Karnofsky Performance Status Scale score <70	1.1	0.6

[a] Data from Abrey LE, et al, J Clin Oncol.[16] *ascopubs.org/doi/10.1200/JCO.2006.08.2941.*



International Extranodal Lymphoma Study Group (IELSG) score

TABLE 5-2 **International Extranodal Lymphoma Study Group Prognostic Scoring System for Patients With Primary Central Nervous System Lymphoma[a]**

Prognostic Factors	Score 1 for Each Factor Present
Age >60 years	
Eastern Cooperative Oncology Group Performance Status ≥2	
Elevated lactate dehydrogenase	
Elevated CSF protein concentration	
Involvement of the deep structures of the brain	
	Total Score[b]

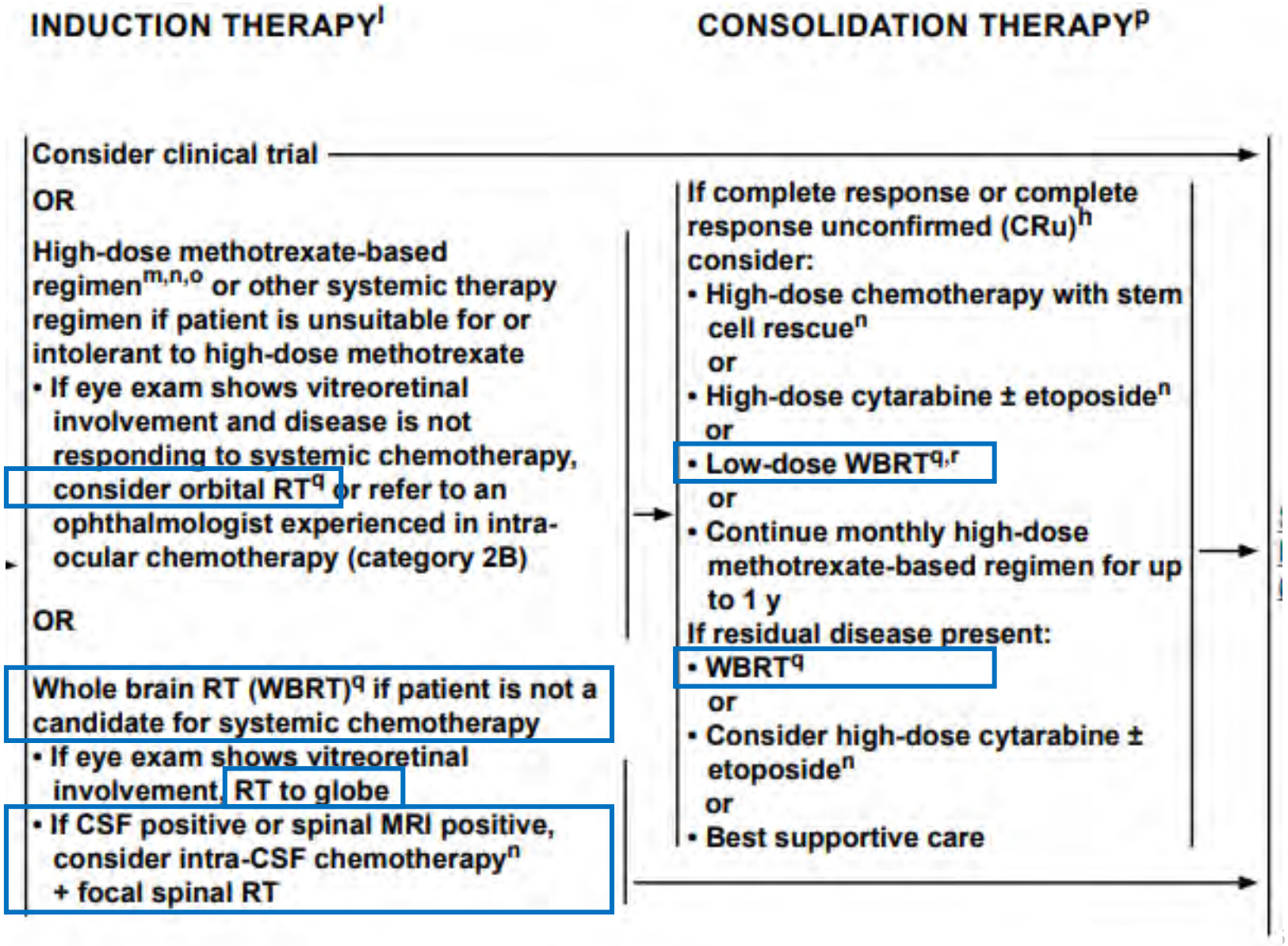
CSF = cerebrospinal fluid.

[a] Data from Ferreri AJ, et al, J Clin Oncol.[15] *ascopubs.org/doi/abs/10.1200/JCO.2003.09.139?journalCode=jco.*
[b] Patients scoring 0–1 prognosticate an 80% 2-year overall survival rate. Patients scoring 2–3 prognosticate a 48% 2-year overall survival rate. Patients scoring 4–5 prognosticate a 15% 2-year overall survival rate.

Source: Han and Batchelor; CONTINUUM 2017

General treatment approach

1. Induction
2. Consolidation
3. Maintenance – typically no role right now



Source: Han and Batchelor; CONTINUUM 2017

Mainstay of induction therapy is high dose MTX

- **Standard of care is high dose MTX based regimens**
  - Dose >= 3.5 g/m2
  - Rapid infusions (e.g., over 2 hours)
- In the US: IV rituximab used in all regimens; G-CSF support
  - **R-MPV**
  - R-M+TMZ (and variations)
- Aim is to achieve response rates >90%, with no toxic deaths

Many regimens are possible!

- MTX alone
- Methotrexate, then Cytarabine & Thiotepa
- Methotrexate, then Cytarabine
- Lomustine, Methotrexate, Procarbazine
- R-MPV: MTX, procarbazine, vincristine
- MBVP: MTX, carmustine, teniposide, prednisone
- MATRix: **M**ethotrexate, **A**ra-C (Cytarabine), **T**hiotepa, **Ri**tu**x**imab
- IT Cytarabine monotherapy
- IT MTX monotherapy

Check out https://hemonc.org/wiki/CNS_lymphoma for good review of chemo regimens

Source: Han and Batchelor; CONTINUUM 2017

Goal of induction is to achieve CR

TABLE 5-4 **International Primary Central Nervous System Lymphoma Collaborative Group Response Criteria[a]**

Response	Brain Imaging	Corticosteroid Dose	Eye Examination	CSF Cytology
Complete response	No contrast-enhancing lesion	None	Normal	Negative
Unconfirmed complete response	No contrast-enhancing lesion	Any	Normal	Negative
	Minimal abnormality	Any	Minor retinal pigment epithelium abnormality	Negative
Partial response	50% decrease in enhancing lesion	Irrelevant	Normal or minor retinal pigment epithelium abnormality	Negative
	No contrast-enhancing lesion	Irrelevant	Decrease in vitreous cells or retinal infiltrate	Persistent or suspicious
Progressive disease	25% increase in enhancing lesion	Irrelevant	Recurrent or new ocular disease	Recurrent or positive
	Any new site of disease: central nervous system or systemic			
Stable disease	All cases not covered by responses above			

CSF = cerebrospinal fluid.

[a] Modified with permission from Abrey LE, et al, J Clin Oncol.[14] © 2005 American Society of Clinical Oncology. *ascopubs.org/doi/10.1200/JCO.2005.13.524*.

If CR is not achieved…

- Switch to different chemo
  - CYVE chemotherapy
- Pivot to targeted therapies
  - Bruton's kinase inhibitors (ibrutinib, zanubrutinib)
  - PI3K inhibitors (Copanlisib)
  - Pomalidomide
- **WBRT or Focal RT?**

Source: Han and Batchelor; CONTINUUM 2017

Options for consolidation therapy

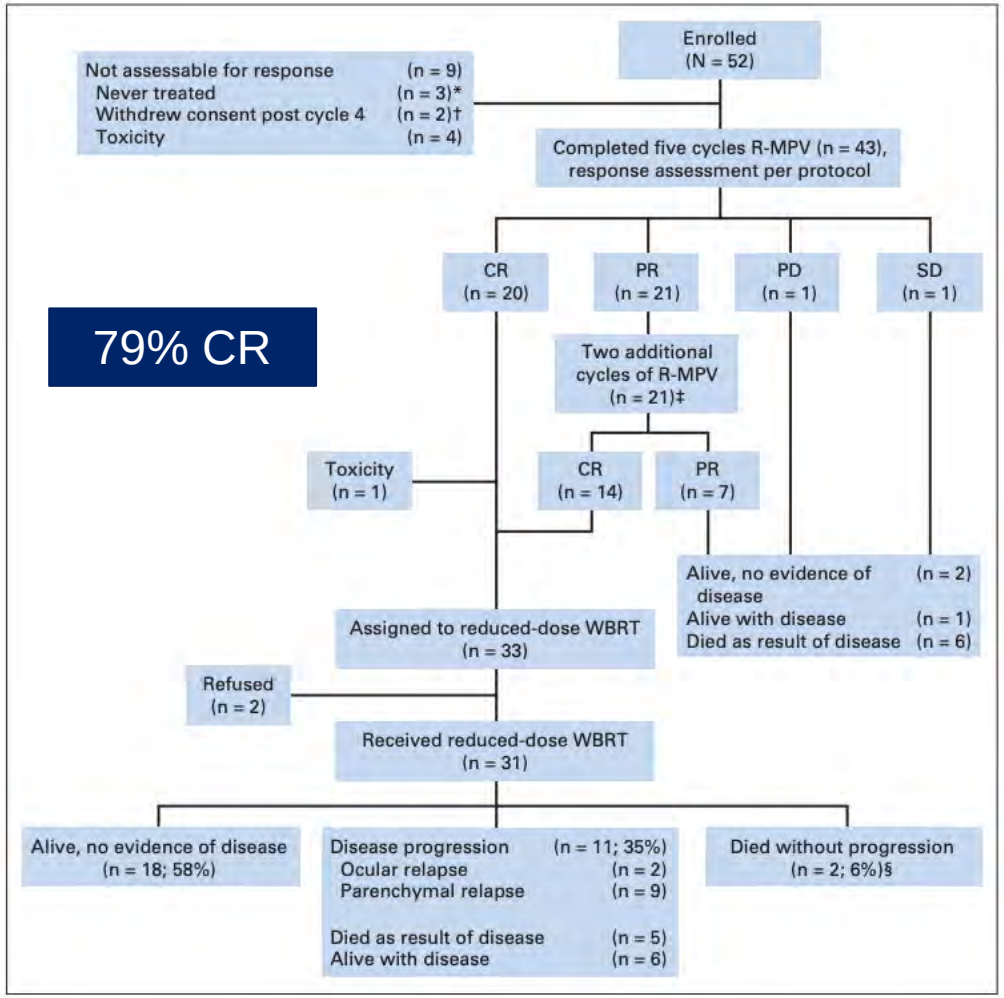
Starting with minimal residual disease is essential!

1. **Radiotherapy:**
   - No role for full dose WBRT (36-45 Gy or higher) due to neurotoxicity risks
   - No established role for focal RT, tumor bed boost or SRS
   - **Reduced dose WBRT 23.4 Gy**

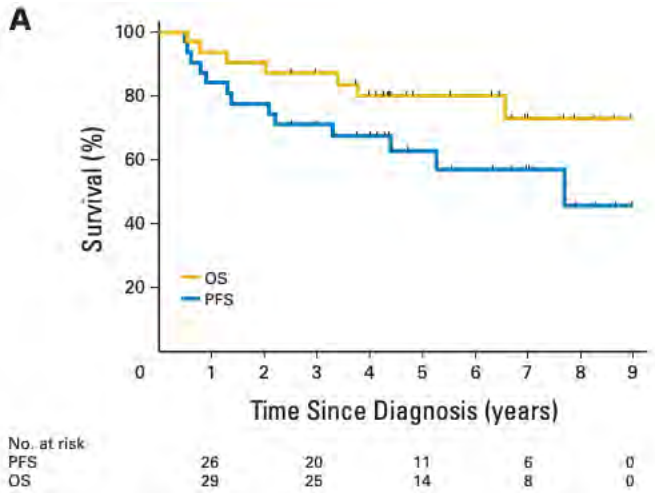
2. **HDT + ASCT rescue:**
   - No role for BEAM
   - TBC: Best phase II results, but can be toxic
   - BCNU/ Thiotepa: Milder but possibly less efficacious

3. **Non myeloablative chemotherapy regimens:**
   - Cytarabine/ etoposide (CYVE): Decent results but toxic
   - HD cytarabine: Not really a consolidation, complement to R-MPV

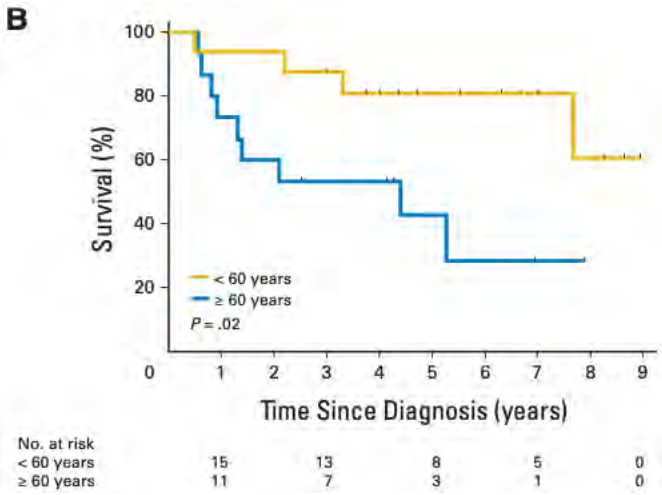
Reduced dose WBRT is a standard of care consolidation



PFS/OS following receipt of rdWBRT



PFS stratified by age



- ORR (95%), intent-to-treat PFS (median, 3.3 years) and intent to-treat OS (median, 6.6 years) were among the highest reported in any PCNSL study to date
- Favorable outcomes compared to MPV + 45 Gy WBRT
- Cognitive assessment showed improvement in executive function and verbal memory after chemotherapy, and follow-up scores remained stable

Morris et al, JCO 2013

Despite promising data, utilization of WBRT is on the decline

PCNSL diagnosed between 1983-2020
N=645

↓

Induction
N=559

↓

Consolidation
N=385 (69%)

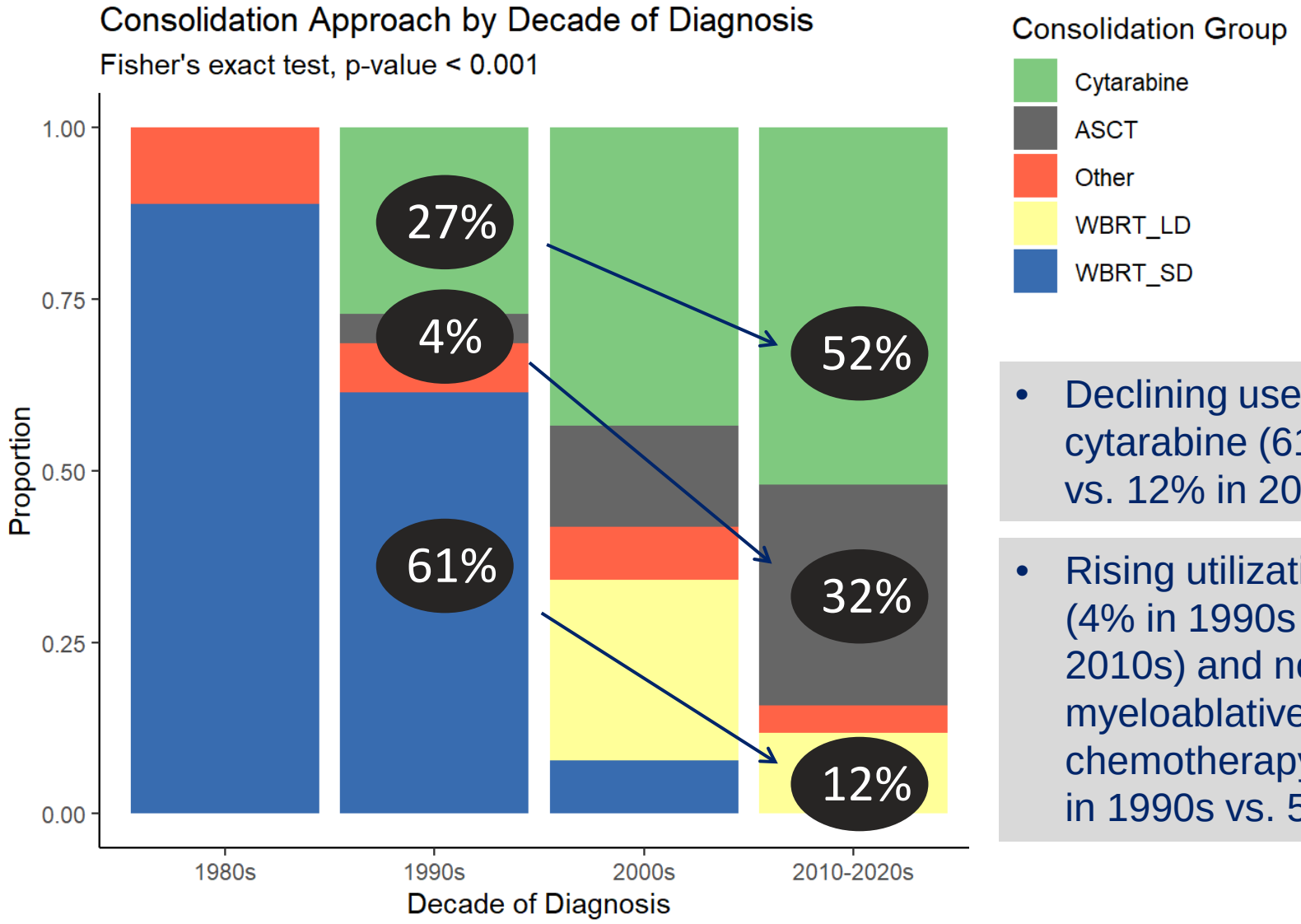
Median age = 63

46.9% female

18.2% RPA 1

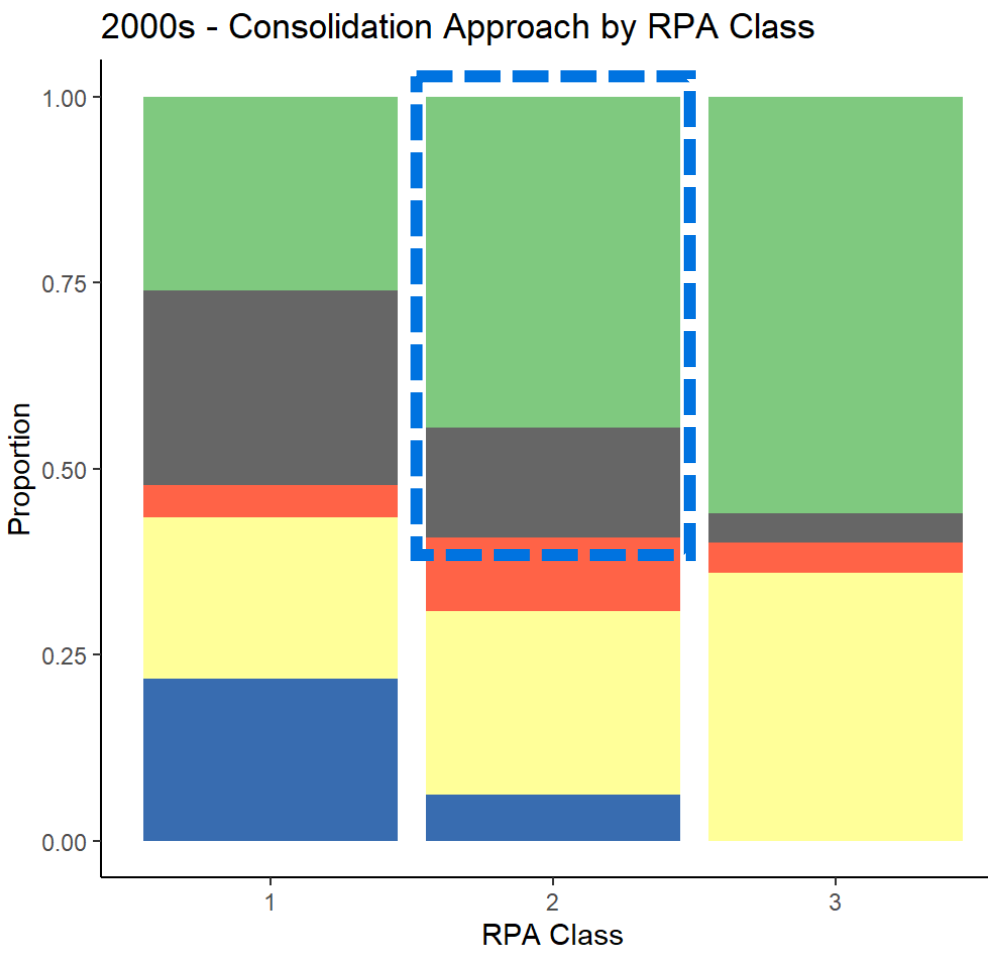
57.4% RPA 2

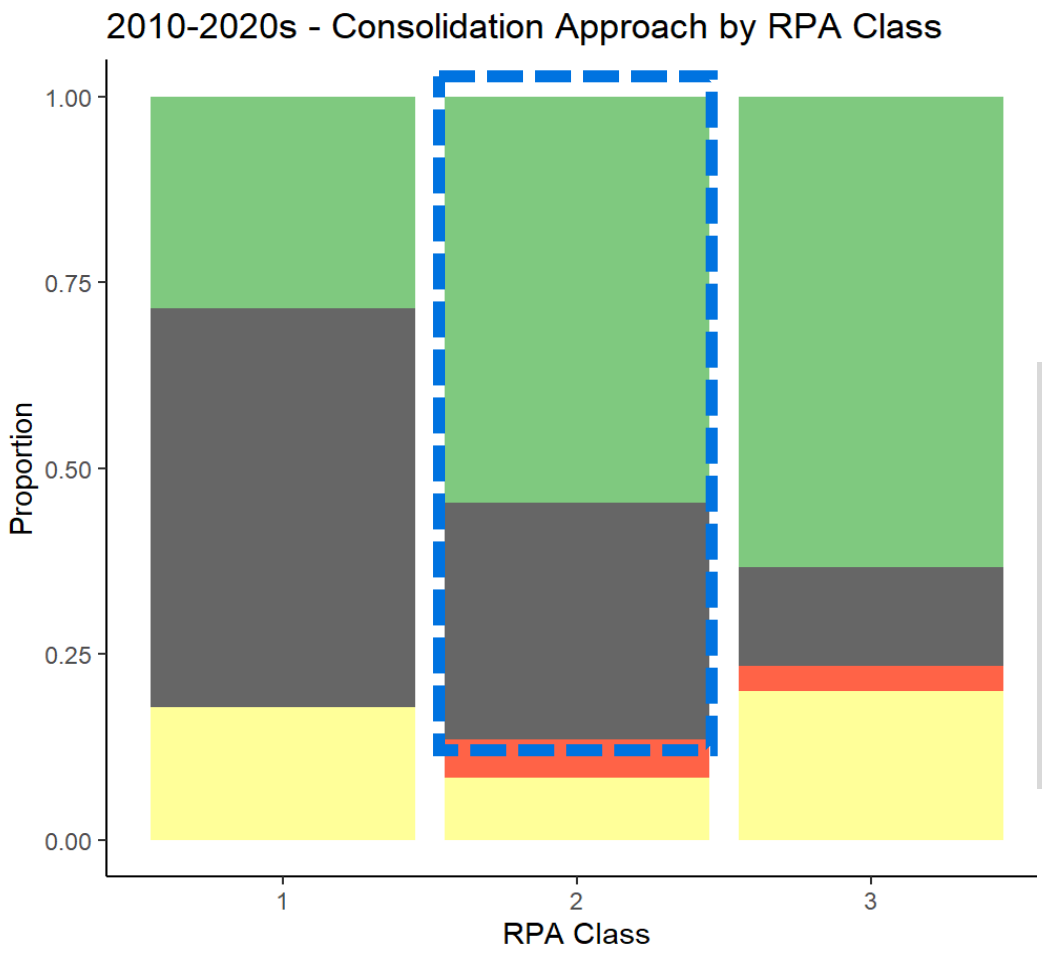
24.3% RPA 3

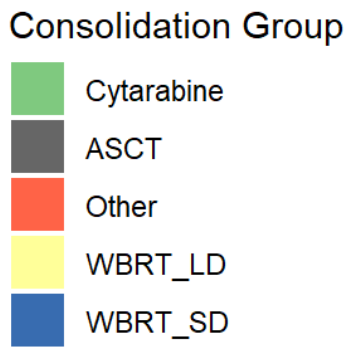


- Declining use of WBRT plus cytarabine (61% in 1990s vs. 12% in 2010s)
- Rising utilization of ASCT (4% in 1990s vs. 32% in 2010s) and non-myeloablative chemotherapy alone (27% in 1990s vs. 52% in 2010s)

Greater utilization of non-myeloablative chemotherapy and ASCT extended across all RPA groups



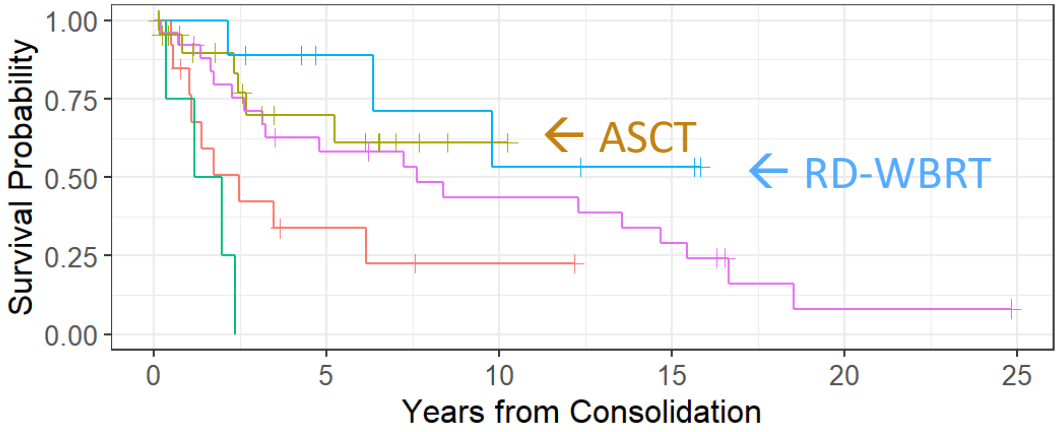




Shift away from WBRT consolidation most prominent in RPA 2 subgroup (age≥50, KPS≥70)

For the fittest patients (RPA 1), RD-WBRT and ASCT were associated with similar best outcomes

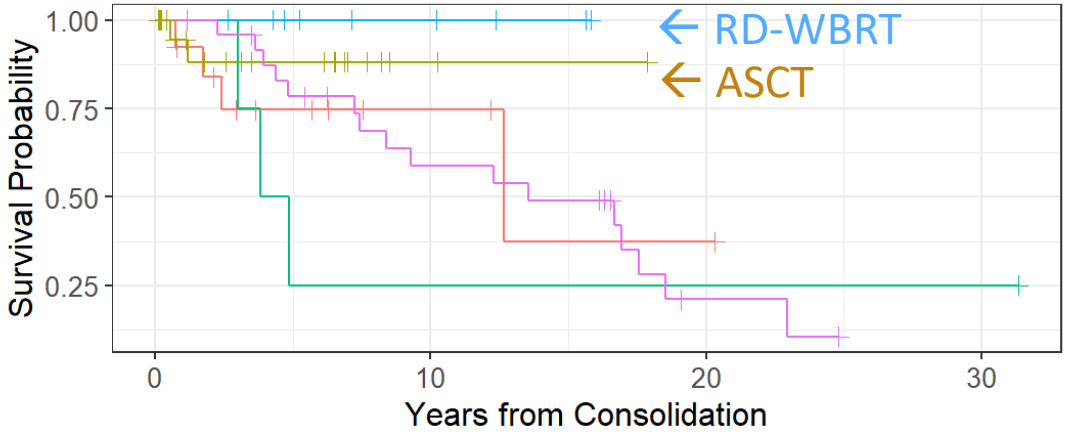
PFS (RPA Class 1)



At Risk

13	3	1	0	0	0
23	8	1	0	0	0
4	0	0	0	0	0
9	5	3	2	0	0
25	13	9	6	1	0

OS (RPA Class 1)



At Risk

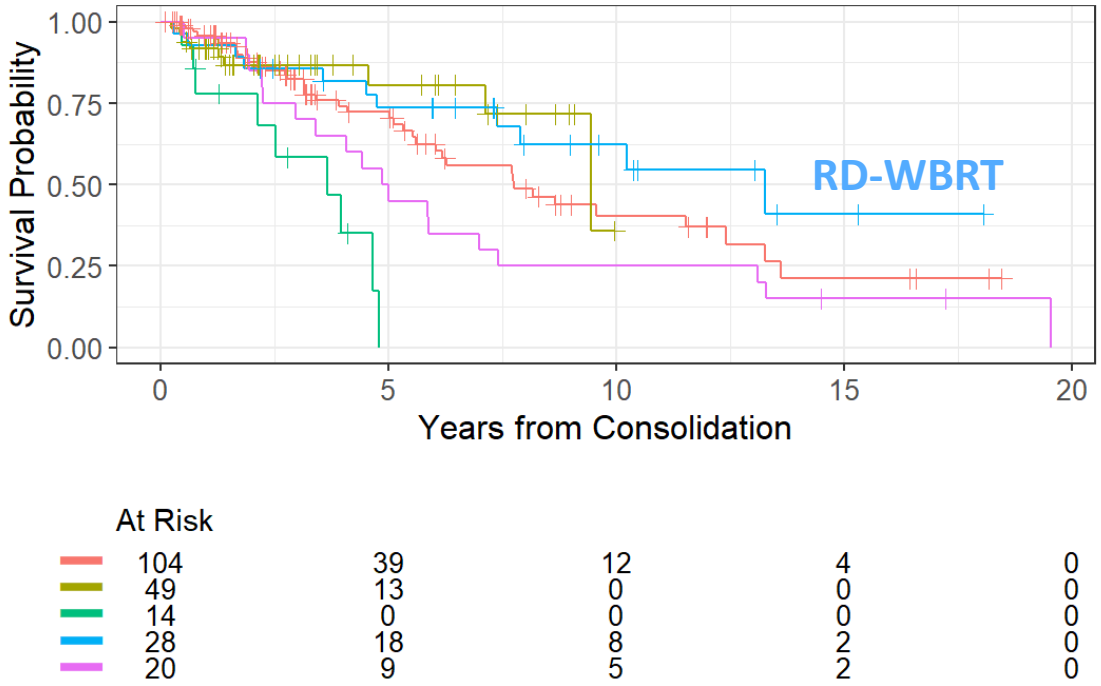
13	3	1	0
23	2	0	0
4	1	1	1
9	4	0	0
25	12	2	0

Cytarabine
ASCT
Other
WBRT_LD
WBRT_SD

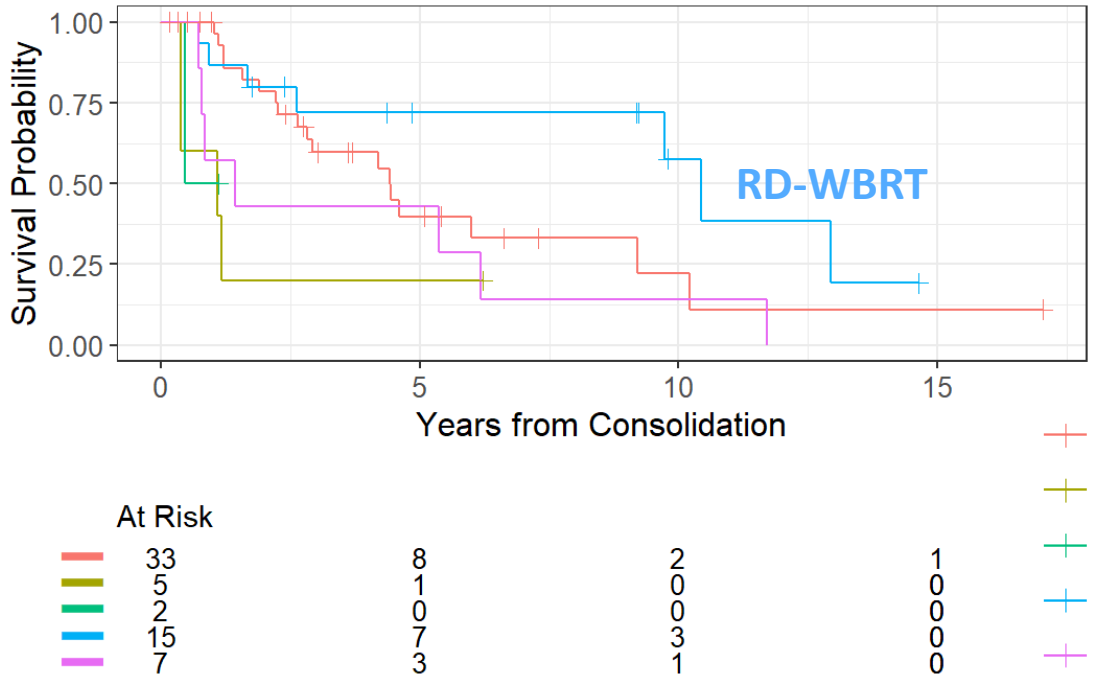
While important to acknowledge decade of treatment, RD-WBRT associated with better PFS and OS versus SD-WBRT

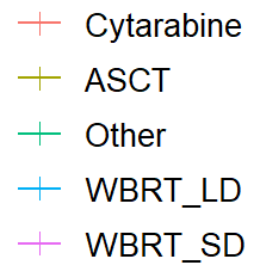
RD-WBRT also associated with strong outcomes for frailer subgroups

OS (RPA Class 2)



OS (RPA Class 3)





Consolidation strategy	Median OS (RPA Class 2)	Median OS (RPA Class 3)
Cytarabine	7.7 y	4.4 y
RD-WBRT	13.0 y	10.0 y
Auto stem cell transplant	9.4 y	1.1 y

RD-WBRT has not been associated with worse neurotoxicity

RTOG 1114: Randomized Phase 2 Study of R-MPV-A with or without reduced dose WBRT

SCHEMA

STRATIFY

RPA Class

Class 1: age ≤ 50

Class 2: age > 50 and KPS ≥ 70

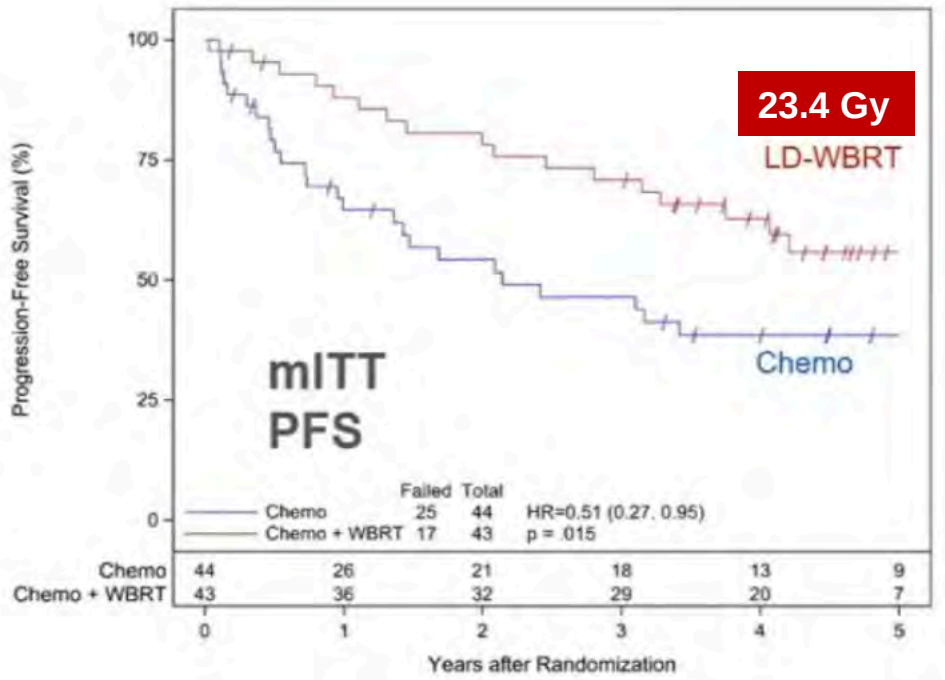
Class 3: age >50 and KPS < 70

RANDOMIZE

Arm A (chemo only)	R-MPV Cycle 1	R-MPV Cycle 2	R-MP Cycle 3 (no vincristine)	R-MP Cycle 4 (no vincristine)		Ara-C Cycle 1	Ara-C Cycle 2
Arm B (chemo + low-dose WBRT)	R-MPV Cycle 1	R-MPV Cycle 2	R-MP Cycle 3 (no vincristine)	R-MP Cycle 4 (no vincristine)	Low-Dose WBRT (13 fx)	Ara-C Cycle 1	Ara-C Cycle 2

23.4 Gy

1 cycle = 28 days
(8 MTX doses total)



- After median follow-up of 55 months
- Median ITT PFS was 25m in the chemo arm and NR in the chemoRT arm (HR 0.51; p = 0.015)
- **No neurotox differences**
- Awaiting OS data…

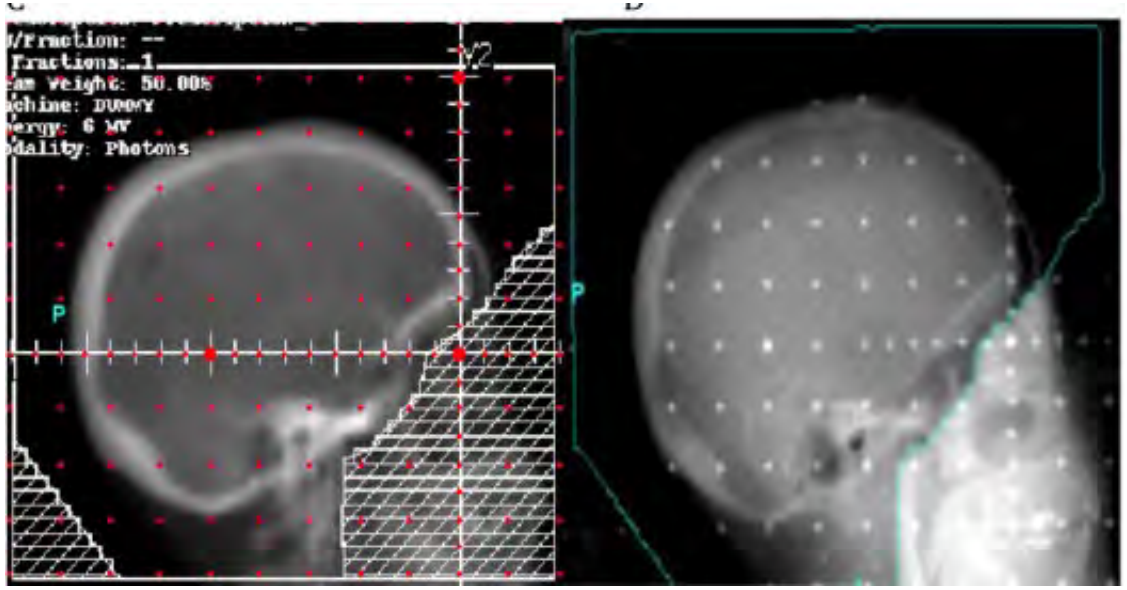
Source: Omuro et al. ASCO 2020

ILROG guidelines for PCNSL

Generally, PCNSL is a multifocal process, with intracranial involvement that is evident even far from radiologically detected sites

Field design (brain involvement)

- CTV: Whole brain including 1 or 2 upper cervical vertebrae and the posterior aspect of the eyes.
- The isocenter is set anteriorly and bisects the bony canthi (to reduce divergence in possible future match to ocular field)
- Alternatively, the anterior border of the PTV is set with the isocenter 5 mm behind the lens
- If eyes were originally involved, both eyes should be included in the WBRT field
- Role of tumor site boost is uncertain and is not recommended by most experts



Consolidation after CR to chemo: **24 Gy**

WBRT after incomplete response to chemo or salvage WBRT: **36-45 Gy (1.5-1.8 Gy/fx)**

WBRT as primary treatment: **40-50 Gy**

Palliation: WBRT to **30-36 Gy in 10-15 fx**

Yahalom et al, IJROBP 2015

ILROG guidelines for primary intraocular lymphoma (PIOL)

- Most patients with PIOL present with pathologic or clinical suspicion of bilateral ocular involvement, and most treatments have included both eyes,
- However, when there is no suspicion of disease in the contralateral eye, it is reasonable to treat only the involved eye

Field design (ocular involvement)

- CTV: the globe of the eye(s), optic nerve (s) to the level of the chiasm
- PTV: 5 mm expansion
- If both eyes involved: opposed lats with isocenter at posterior border to reduce divergence in case need for subsequent WBRT
- If uniocular: IMRT acceptable

Dose: **36 Gy**

Yahalom et al, IJROBP 2015

WBRT can be an effective salvage strategy

Outcomes for n=27 consecutive patients salvaged with WBRT after prior MTX

Table 2. Baseline Characteristics of Patients at Initiation of WBRT

	No. of Patients	%
Age > 60 years	17	63
KPS ≥ 70	14	52
Multiple lesions	17	63
Deep brain* involved	18	67
Months since diagnosis		
Median	5.7	
Range	0.83-64.1	
Cycles of MTX		
Median	8	
Range	3-38	
MTX stopped for progression	17	63
MTX stopped for relapse	10	37
Additional therapy before WBRT?	16	59

NOTE. All percentages are out of 27 patients.
Abbreviations: WBRT, whole-brain radiotherapy; KPS, Karnofsky performance status; MTX, methotrexate.
*Basal ganglia, brainstem, cerebellum, and periventricular lesions.

WBRT dosing

- **No boost**: Median dose of **36 Gy** (28-45)
- **Boost**: Base dose of 36 (19.6-40) and boost of 10 Gy (10-21.6) or SRS boost to 12-16 Gy

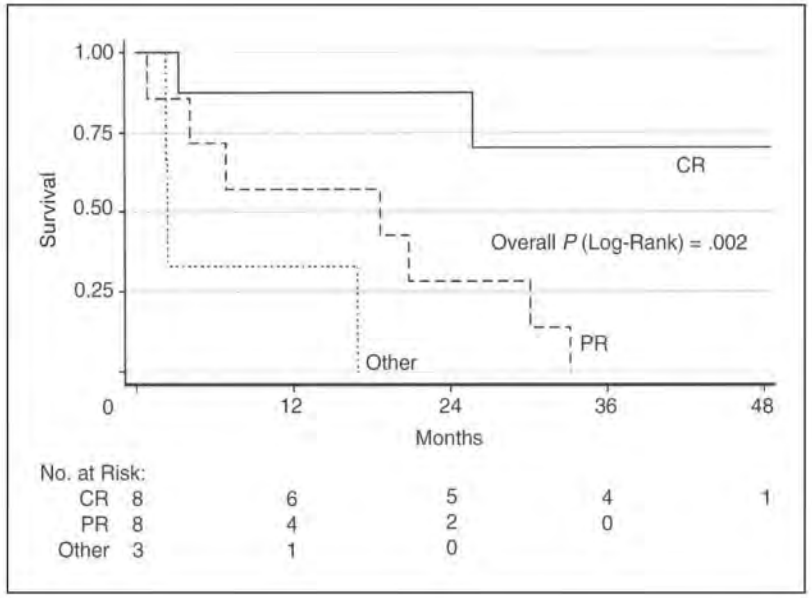
Radiographic response to RT

- Best response of CR: n=10 (37%)
- Best response of PR: n=10 (37%)
- Median time to max response: 2.5m

Other outcomes

- Median PFS: 9.7 months (58m if CR)
- 12m survival of 49%

Landmark survival 4m post WBRT



Source: Nguyen et al. JCO 2005

Potential future directions for CNSL radiotherapy

1. **Standardized radiation paradigms for the treatment of secondary CNSL**

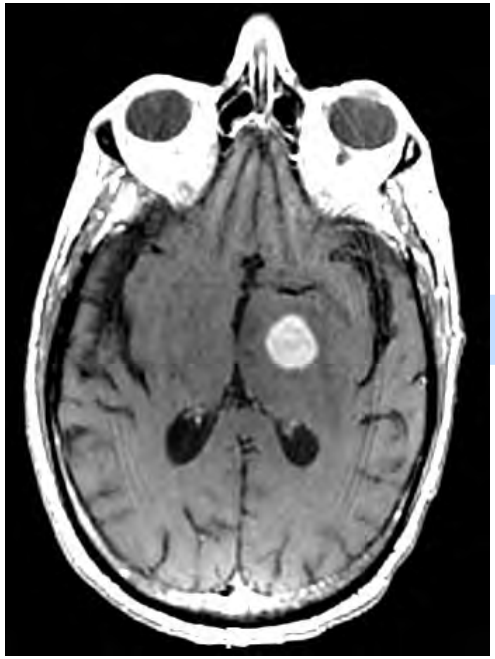
2. **Revisiting focal radiotherapy in an era of better systemic therapies and autologous transplantation**

3. **Exploring radiotherapy as a bridging strategy for CNSL patient planned for CAR T-cells**

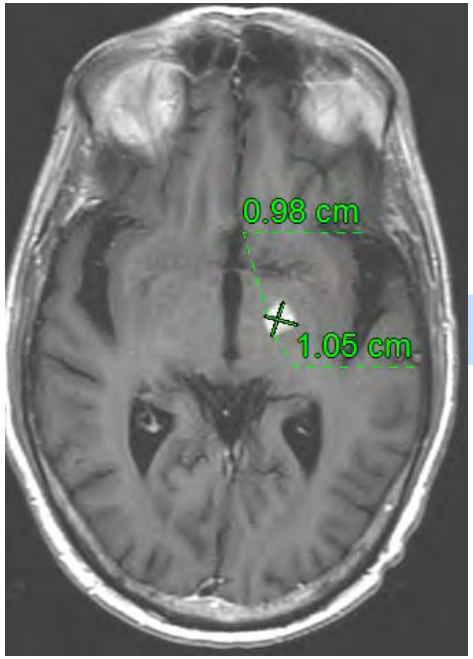
2. Focal RT can rapidly cytoreduce refractory lesions potentially opening doors to more curative options

Case example: 71yo M with relapsed/refractory DLBCL presenting with neurologic symptoms (R-sided weakness, confusion) found to have **a left thalamic lesion**

- s/p IV HD-MTX x2, initially with PR → POD of the left thalamic lesion
- Body PET otherwise negative

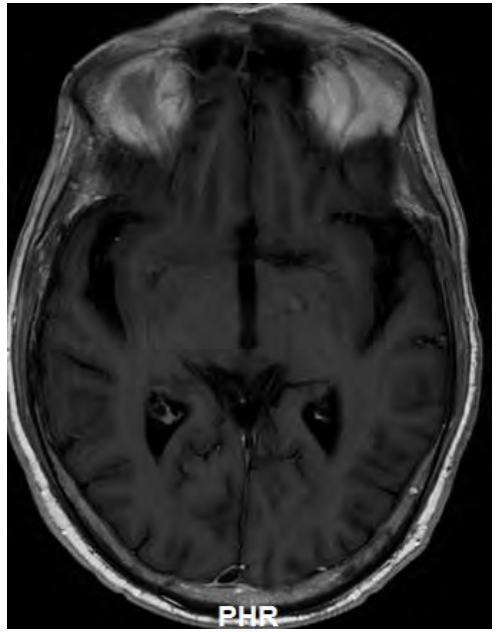


3 Gy x 10



3 days post RT

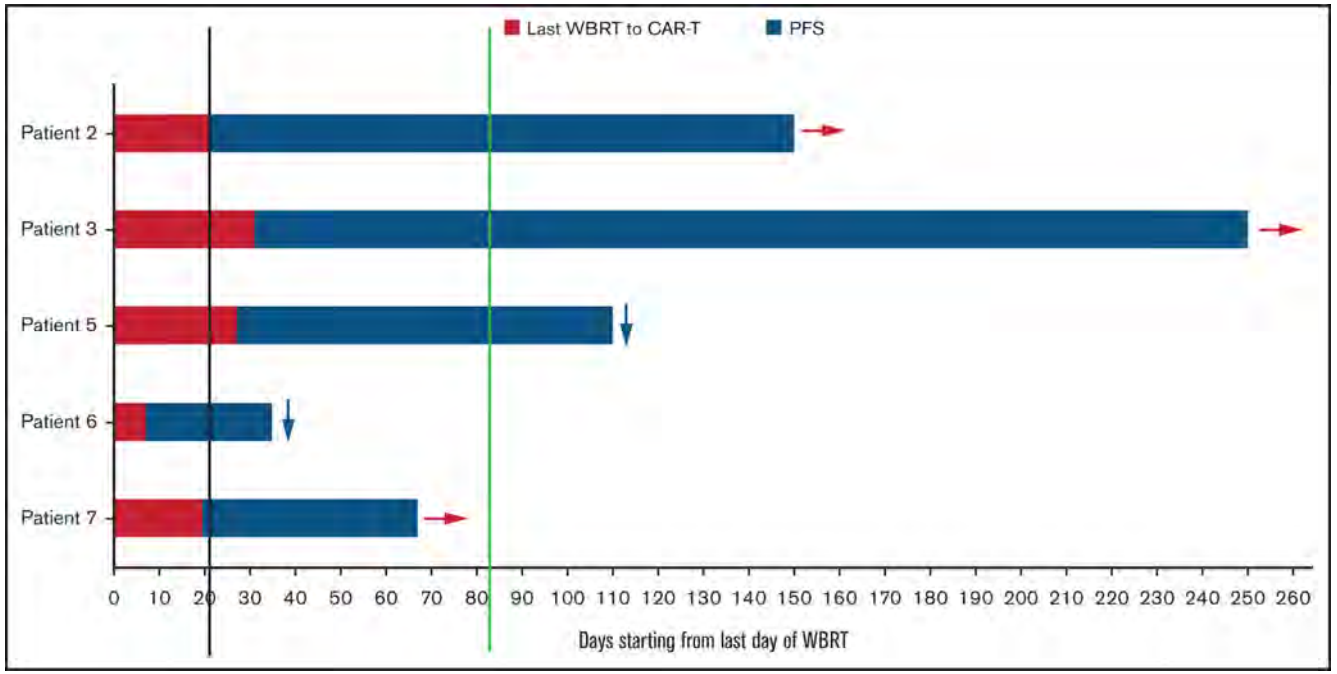
Autologous SCT



6mo post

3. CAR T-cells are under study for CNSL and may also create new indications for RT

7 adult patients with SCNSL who underwent CAR T-cell therapy for their refractory disease, with focus on safety of WBRT as bridging



- WBRT was administered to 5/7 at a median dose of 28 Gy (4-40 cGy) immediately pre-CAR T
- Median of 21days (range: 7-31) from RT to CAR T-cell

CLINICAL TRIALS AND OBSERVATIONS

Safety and efficacy of tisagenlecleucel in primary CNS lymphoma: a phase 1/2 clinical trial

Matthew J. Frigault,[1,2,*] Jorg Dietrich,[3,*] Kathleen Gallagher,[2] Mark Roschewski,[4] Justin T. Jordan,[3] Deborah Forst,[3] Scott R. Plotkin,[3] Daniella Cook,[1,2] Keagan S. Casey,[1,2] Kevin A. Lindell,[1,2] Gabriel D. Depinho,[1,2] Katelin Katsis,[2] Eva Lynn Elder,[2] Mark B. Leick,[1,2] Bryan Choi,[2,5] Nora Horick,[2] Frederic Preffer,[6] Meredith Saylor,[1] Steven McAfee,[1] Paul V. O'Donnell,[1] Thomas R. Spitzer,[1] Bimalangshu Dey,[1] Zachariah DeFilipp,[1] Areej El-Jawahri,[1] Tracy T. Batchelor,[7] Marcela V. Maus,[1,2,*] and Yi-Bin Chen[1,*]

CAR T-cell therapy for secondary CNS DLBCL

Gulrayz Ahmed, Mehdi Hamadani, and Nirav N. Shah

Blood and Marrow Transplant and Cellular Therapy Program, Department of Medicine, Medical College of Wisconsin, Milwaukee, WI

- Of the 5 patients who received WBRT as bridging therapy, 3 had no ICANS, but 2 had grade 1 or 3 ICANS
- No grade 4 ICANS was reported
- All fully recovered with no treatment-related mortalities

Source: Ahmed et al. Blood Advances 2022

Conclusions

- PCSNL has rising incidence and is typically a disease of the elderly
- Full workup is required to understand which CNS reservoirs are affected
- Two prognostic scoring systems can risk stratify and guide treatment decision making
- Induction therapy is typically a high dose methotrexate containing regimen with a goal of attaining complete response
- Consolidation options include reduced dose WBRT, autologous transplantation or non-myeloablative chemotherapy
- Despite declining utilization, rdWBRT may be an attractive option particularly for RPA 2/3 patients with significantly improved PFS vs. chemo alone
- Increased utilization of autologous transplants and CAR T-cells may create new opportunities for RT

Source: Grommes and DeAngelis, JCO 2017