Stereotactic Radiotherapy for Metastatic Cancer – Adding to Survival?

NOSCM 2019

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Local Therapy for Advanced Disease

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Disclosures:

None

Historical Dogma for Stage IV Cancers:

Systemic Therapy

Radiation Therapy for Palliation

This dogma has begun to change because data suggests that local therapies can improve survival in metastatic solid tumor patient populations.

Areas of Greatest Research Efforts into Local Therapy Benefits for Stage IV Disease

1. Brain Metastases treated with radiation or/and surgery

2. Oligometastatic Colorectal Cancer, Sarcoma, etc. treated with radiation or/and surgery

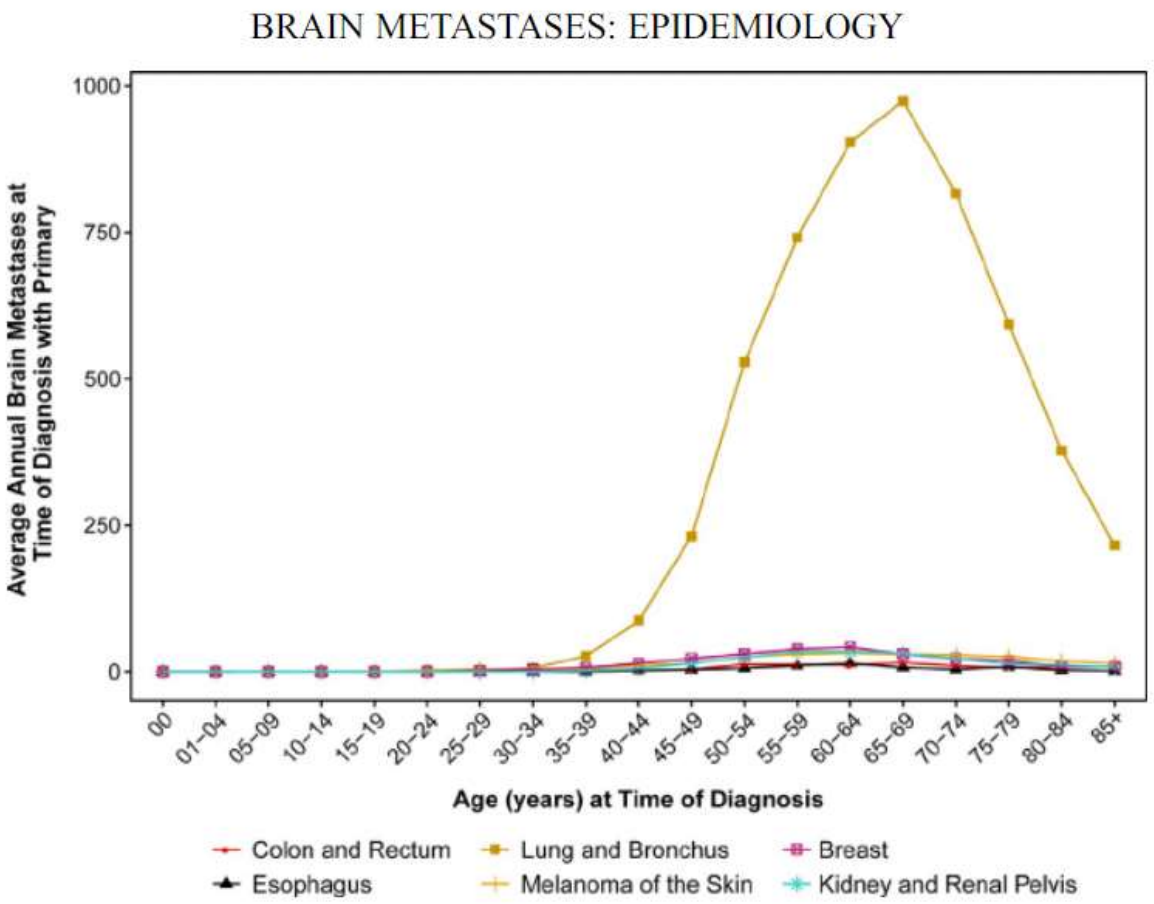
3. Oligometastatic NSCLC treated with radiation
    a. Consolidation
    b. Oligoprogression
    c. Abscopal Response

Brain Metastases

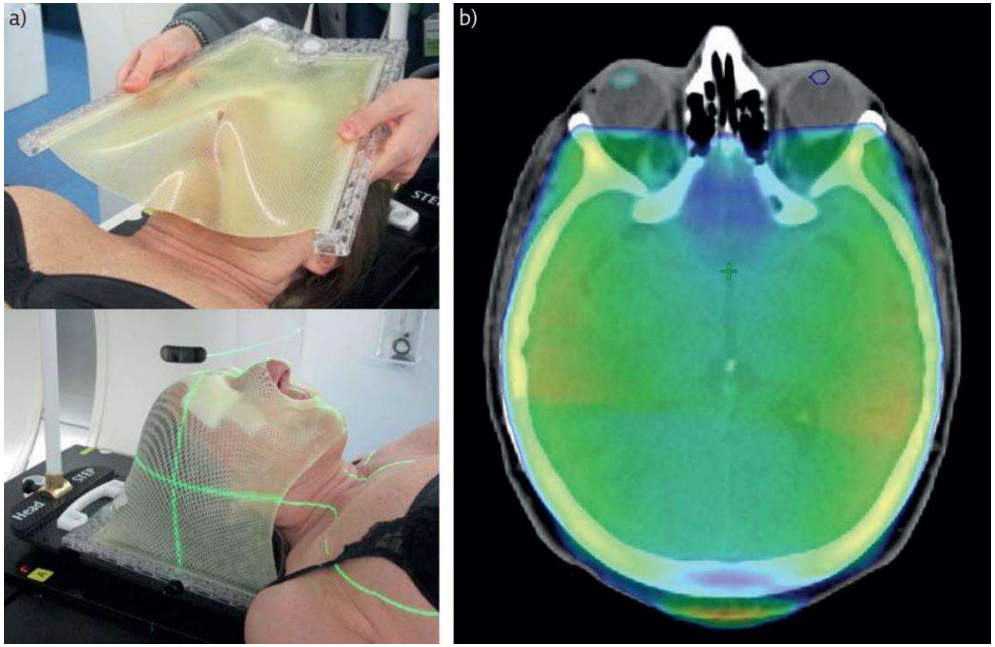
Incidence & Epidemiology

- Brain metastases most common intracranial malignancy
- ~200,000 cases annually and rising
- Disproportionately affects older population
- Intracranial control will become more important as extracranial treatments improve

Incidence & Epidemiology



Whole brain radiation therapy (WBRT) for palliation (avoid brain tumor morbidity) and to improve intracranial brain dx control



WBRT ± Surgery

- Entry criteria: single brain met, h/o systemic ca ≤5yrs of dx, KPS≥70
- Exclusion criteria: unresectable brain lesions, leptomeningeal mets, h/o CrI, need for immediate tx to prevent acute neuro deterioration, or radiosensitive tumors (SCLC, GCTs, lymphoma, leukemia, MM)
- Intracranial w/u: HCT and MRI
- systemic w/u: CXR, heme/chem labs, CT a, radionuclide liver-spleen scan, bone scan
- Decadron 4mg Q6 throughout course of WBRT
- Stratified by location of tumor (supratentorial vs infratentorial), extent of dz (brain met, brain met + primary site, brain met + primary site + ≥1 additional site), type of primary
- S: total resection confirmed by contrast HCT postop d 2-5 (none)
- WBRT: 36 Gy/12 fxns – stereotactic bx of supratentorial lesions to confirm ca
- F/U: Q3mo neuro exam, MRI/contrast CT

Patchell et al. NEJM 322(8):494-500

WBRT ± S

- Conclusion: S+WBRT results in longer survival and QOL than WBRT alone as a result of better LC translating into a decrease in neurologic morbidity/mortality
- No excess mortality due to S over WBRT alone (4%)
- Comment: only 20% of brain mets are single and only 50% of those are surgically accessible
- Pts most likely to benefit from S have a single met w/ no systemic dz, and life expectancy ≥2mo

Patchell et al. NEJM 322(8):494-500

Neurotoxicity of WBRT

- Retrospective report of 12,370 pts who developed delayed complications of WBRT w/o evidence of intracranial dz
- 7pts died of progressive neuro deterioration

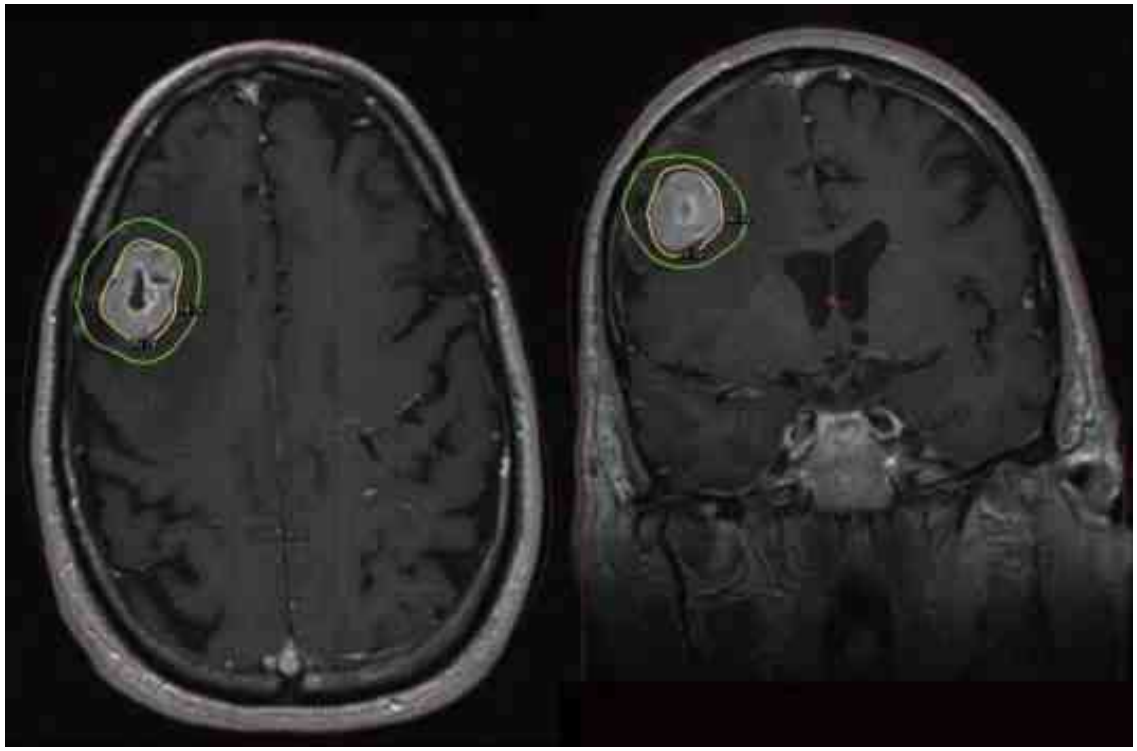
Number of patients	Total dose (cGy)	Fractionation (cGy × days)	NSD	Neuret
1	2,500	500 × 5	1,423	1,151
1	3,000	500 × 3, 300 × 5	1,414	1,046
6	3,000	600 × 3, 400 × 3	1,552	1,204
2	3,000	300 × 10	1,313	938
1	3,600	300 × 12	1,462	1,021
1	3,900	500 × 3, 300 × 8	1,606	1,146

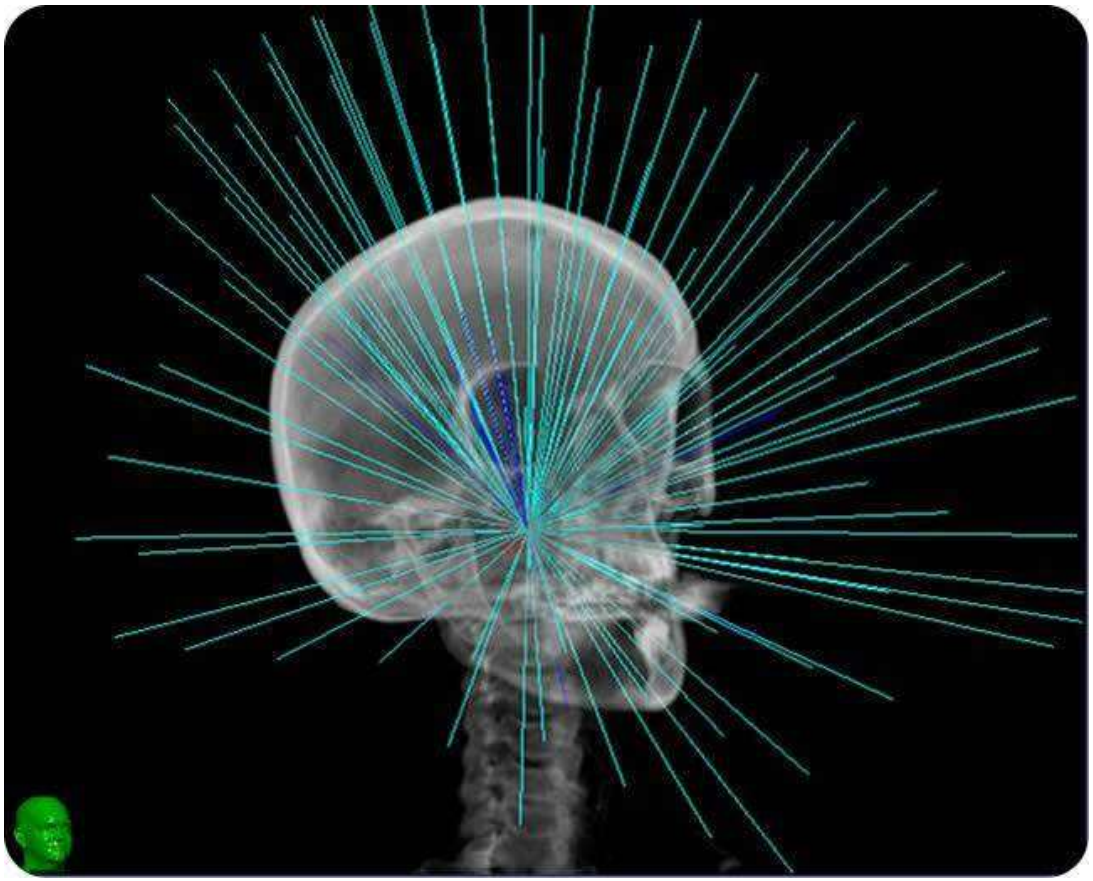
DeAngelis et al. Neuro 39:789-96

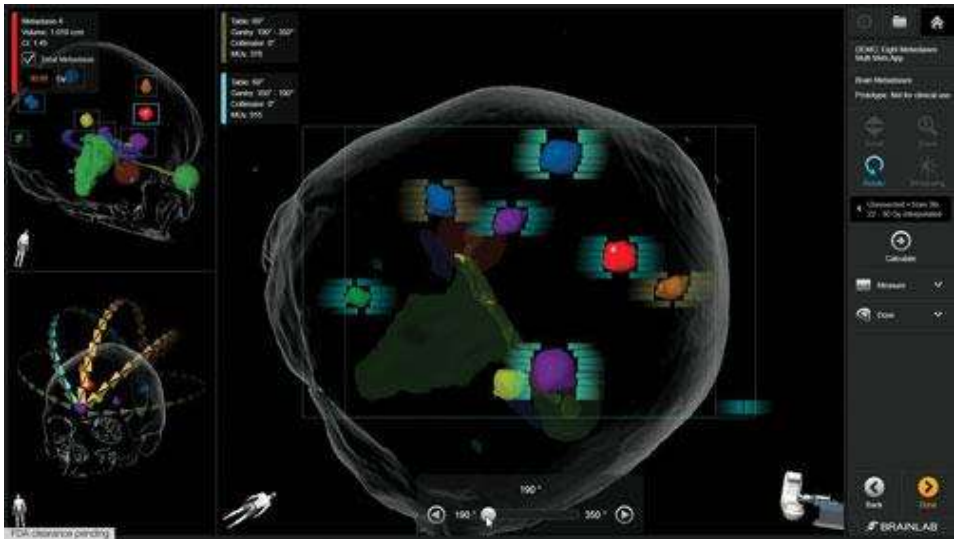
WBRT Summary

- WBRT improves both local and distant brain control
- WBRT is associated with neurocognitive decline and decreased quality of life
- No evidence that WBRT improves overall survival
  - If extracranial disease controlled, intracranial control more important

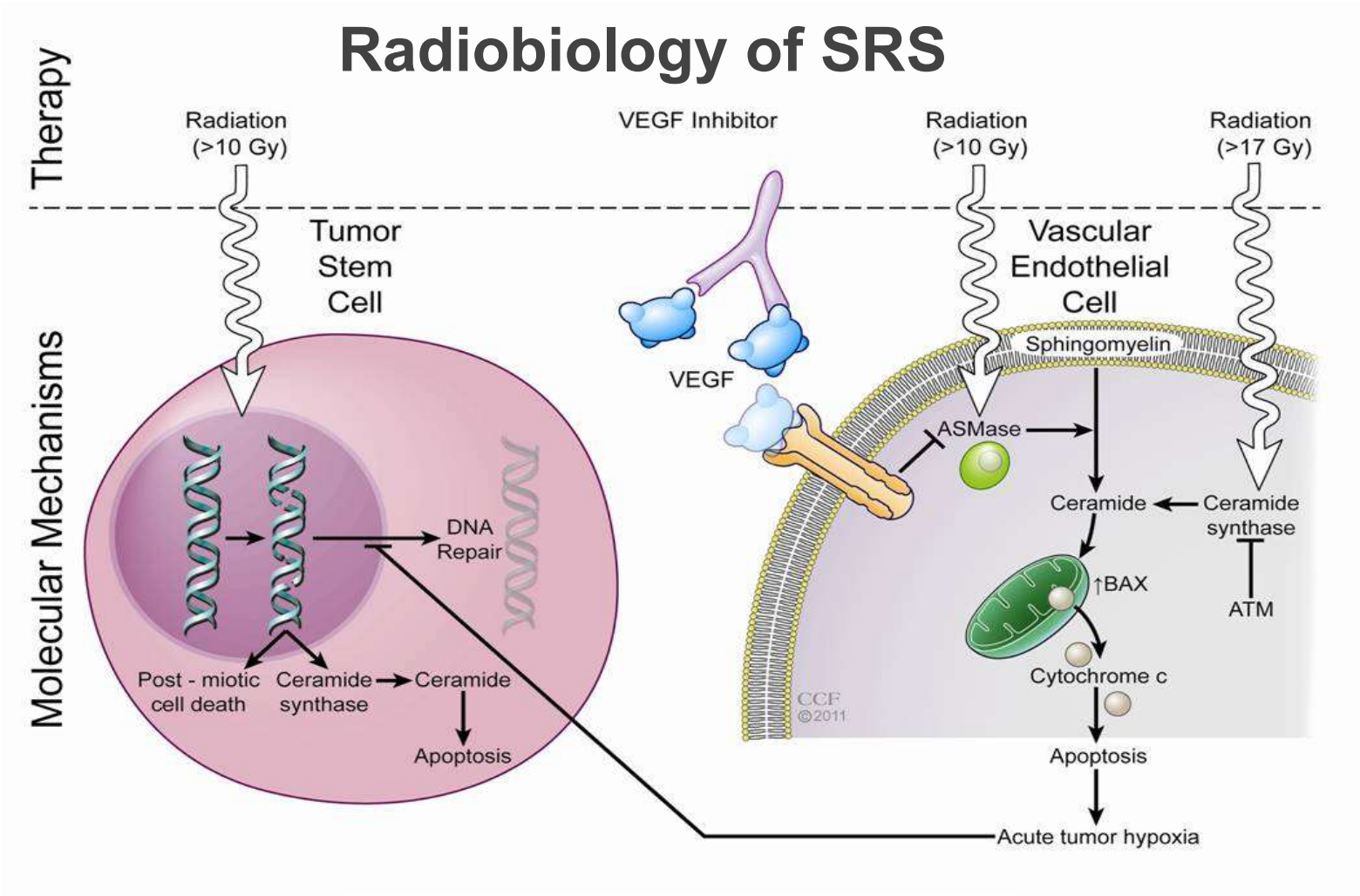
The Rise of Stereotactic Radiation (SRS)






BRAINLAB

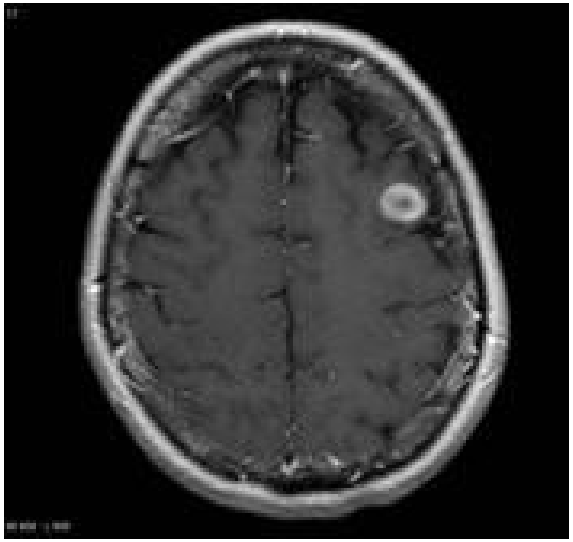
Radiobiology of SRS



Balagamwala E, Chao S, Suh J. Tech Ca Res Treat 2012

Optimal Characteristics of patients eligible for SRS

- Controlled extracranial disease, life expectancy >3 months
- Radiographically distinct on T1 post contrast
- No implanted devices
- Non-infiltrative
  - Clear border between tumor and normal brain
- Distant to sensitive brain structures
  - Chiasm, optic nerves, brainstem
- Size at presentation ≤3 cm
- Pseudospherical shape?
  - Surface area adjacent to normal brain



Treatment options for Brain Metastases

- Supportive care
  - Corticosteroids alone (QUARTZ)
- Radiation therapy
  - Whole brain RT
  - SRS
  - Whole brain + SRS
- Surgical Resection
- Systemic therapy

JAMA Oncology | Brief Report

Estimating Survival in Patients With Lung Cancer and Brain Metastases

An Update of the Graded Prognostic Assessment for Lung Cancer Using Molecular Markers (Lung-molGPA)

Old GPA

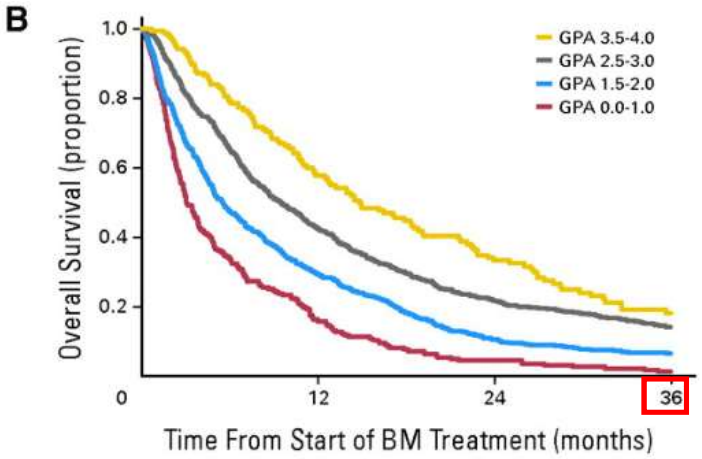


Table 2. Updated DS-GPA for NSCLC With Brain Metastases (Lung-molGPA) Scoring Chart and Worksheet to Estimate Survival

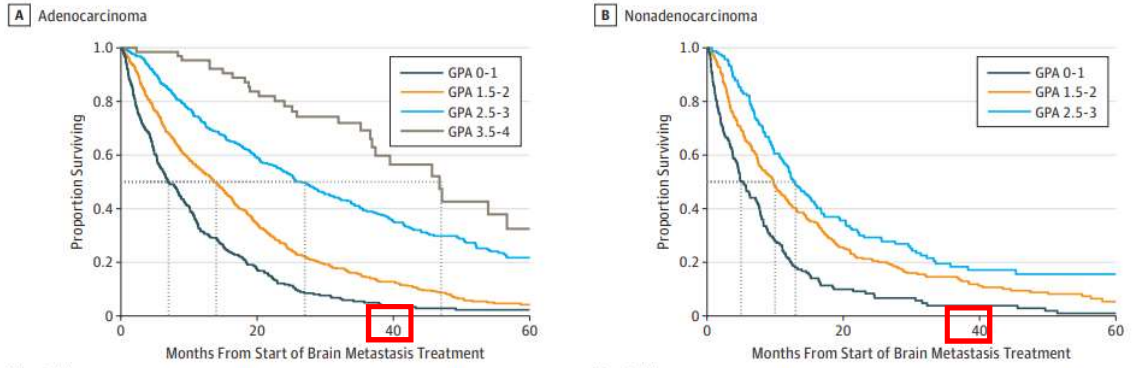
	GPA Scoring Criteria[a]			
Prognostic Factor	0	0.5	1.0	Patient Score[b]
Age, y	≥70	<70	NA	___
KPS	<70	80	90-100	___
ECM	Present		Absent	___
Brain metastases, No.	>4	1-4	NA	___
Gene status	*EGFR* neg/unk and *ALK* neg/unk	NA	*EGFR* pos or *ALK* pos	___
Total	NA	NA	NA	___

Abbreviations: DS, diagnosis-specific; ECM, extracranial metastases; GPA, graded prognostic assessment; KPS, Karnofsky Performance Status; MS, median survival; NA, not applicable; neg/unk, negative or unknown; NSCLC, non–small-cell lung cancer; pos, positive.

[a] Adenocarcinoma MS in months by GPA: 0-1.0 6.9; 1.5-2.0, 13.7; 2.5-3.0 ,26.5; and 3.5-4.0, 46.8; nonadenocarcinoma MS in months by GPA: 0-1.0, 5.3; 1.5-2.0, 9.8; 2.5-3.0, 12.8.

[b] Evaluating clinician completes this column.

Figure. Kaplan-Meier Curves Showing Survival by the Lung-molGPA for Non–Small-Cell Lung Cancer



Sperduto PW et al., JCO 2012; Lin X et al., IJROBP 2015

Dose escalation trial: RTOG 90-05

- N=156, non-brainstem brain tumor ≤4cm diameter, 36% with recurrence primary tumor (median prior dose 60Gy);64% recurrent brain metastasis (median prior dose 30Gy);
- Dose escalated in 3Gy increments providing Grade 3-5 toxicities <20% in 3 months.
- Results:

Size (mm)	Initial dose	MTD (Gy)
<20	18 Gy	**24 (not true MTD)**
21-30	15 Gy	18 Gy
31-40	12 Gy	15 Gy

- The MTD for tumors <20 mm was actually not reached, but investigator did not increase the dose beyond 24 Gy;
- 2 yr incidence of local progression was 50% and radio-necrosis was 11%;
- Grade 3-5 neurotoxicity is associated with tumor size, dose and KPS.

Table 5. Incidence of Grade 3, 4, and 5 CNS toxicity by tumor size and treatment arm

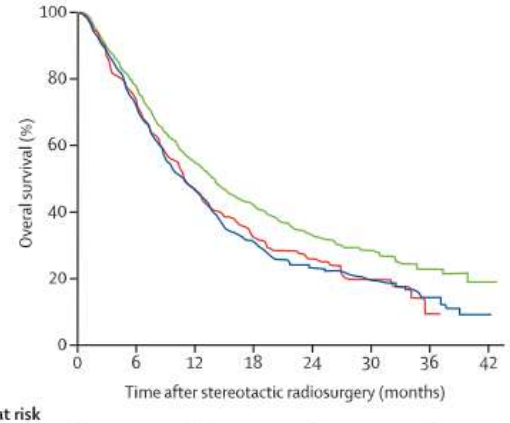
				Incidence of Grade 3, 4, and 5 CNS Toxicity		
				% of Patients With Toxicity		
Tumor size*	Arm	Dose	No. of patients	Acute	Chronic	Total
≤ 20 mm (3.6 cc)	1	18 Gy	12	0	8	8
	4	21 Gy	18	0	11	11
	7	24 Gy	10	0	10	10
21–30 mm (6.6 cc)	2	15 Gy	15	7	7	13
	5	18 Gy	15	0	20	20
	8	21 Gy	13	8	31	38
	11	24 Gy	12	33	25	58
31–40 mm (17.9 cc)	3	12 Gy	21	5	5	10
	6	15 Gy	22	0	14	14
	9	18 Gy	18	17	33	50

* Maximum tumor diameter.

IJROBP, 2000 May 1;47(2):291-8

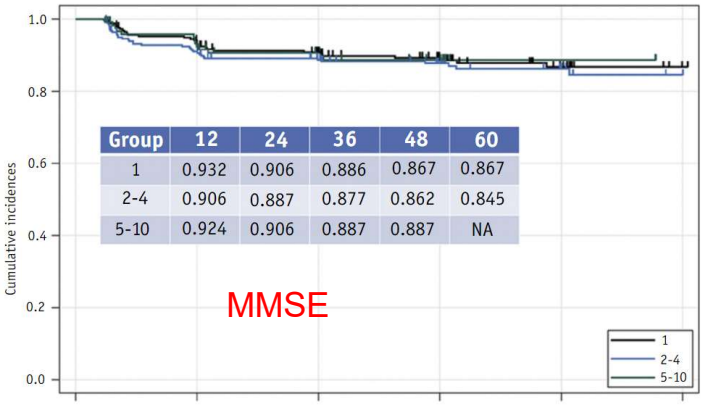
A Multi-institutional Prospective Observational Study of Stereotactic Radiosurgery for Patients With Multiple Brain Metastases (JLGK0901 Study Update): Irradiation-related Complications and Long-term Maintenance of Mini-Mental State Examination Scores

Group	Median overall survival, months (95% CI)	HR (95% CI)	p value
1 tumour	13·9 (12·0–15·6)	0·76 (0·66–0·88)	0·0004
2–4 tumours	10·8 (9·4–12·4)	Reference	
5–10 tumours	10·8 (9·1–12·7)	0·97 (0·81–1·18)	0·78



Number at risk				
1 tumour	455	234	97	22
2–4 tumours	531	215	61	16
5–10 tumours	208	84	31	1

B

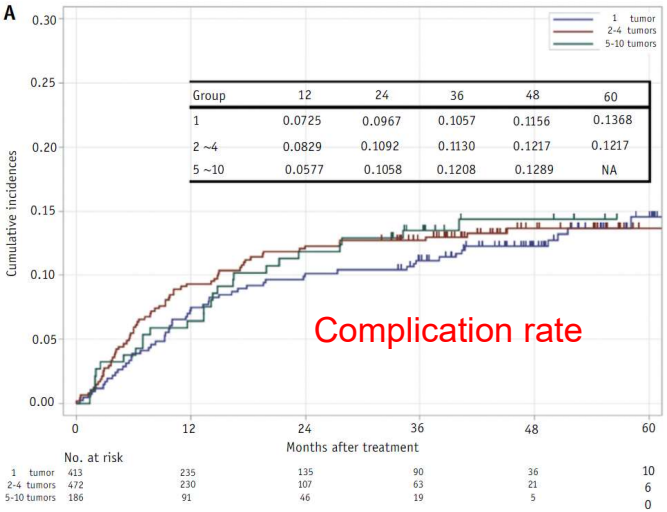


Group	12	24	36	48	60
1	0.932	0.906	0.886	0.867	0.867
2-4	0.906	0.887	0.877	0.862	0.845
5-10	0.924	0.906	0.887	0.887	NA

MMSE

No. at risk						
1	256	106	61	30	10	1
2-4	281	92	50	20	7	1
5-10	122	46	22	8	2	0

A

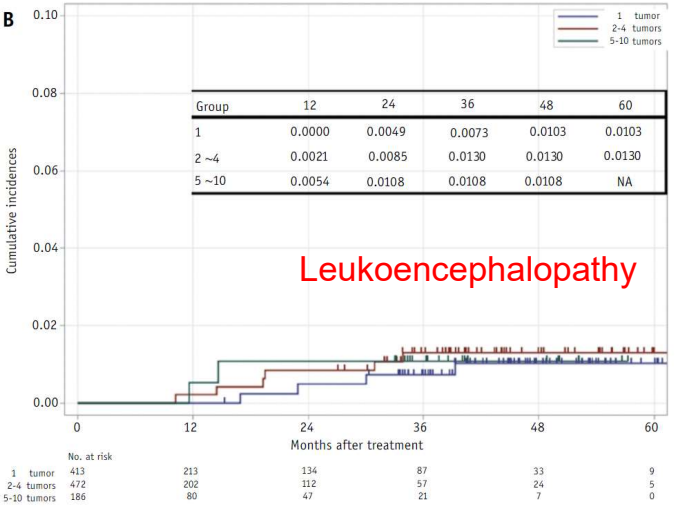


Group	12	24	36	48	60
1	0.0725	0.0967	0.1057	0.1156	0.1368
2 ~4	0.0829	0.1092	0.1130	0.1217	0.1217
5 ~10	0.0577	0.1058	0.1208	0.1289	NA

Complication rate

No. at risk						
1 tumor	413	235	135	90	36	10
2-4 tumors	472	230	107	63	21	6
5-10 tumors	186	91	46	19	5	0

B



Group	12	24	36	48	60
1	0.0000	0.0049	0.0073	0.0103	0.0103
2 ~4	0.0021	0.0085	0.0130	0.0130	0.0130
5 ~10	0.0054	0.0108	0.0108	0.0108	NA

Leukoencephalopathy

No. at risk						
1 tumor	413	213	134	87	33	9
2-4 tumors	472	202	112	57	24	5
5-10 tumors	186	80	47	21	7	0

Ultimately, every conceivable combination was tested with SRS on brain mets:

1) In dose escalation (as shown previously in one of earliest papers)

2) WBRT -/+ SRS

3) SRS -/+ WBRT

4) Surgery/SRS -/+ WBRT

5) Surgery -/+ SRS

6) SRS for Multiple Mets (previous slide)

Higher biological WBRT doses versus control

The HR for OS with higher biological WBRT doses as compared with control (3000 cGy in 10 daily fractions) was 0.97 (95% CI 0.83 to 1.12; P = 0.65; moderate-certainty evidence). The HR for NFI was 1.14 (95% CI 0.92 to 1.42; P = 0.23; moderate-certainty evidence).

WBRT and radiosensitisers

The addition of radiosensitisers to WBRT did not confer additional benefit for OS (HR 1.05, 95% CI 0.99 to 1.12; P = 0.12; moderate-certainty evidence) or for brain tumour response rates (odds ratio (OR) 0.84, 95% CI 0.63 to 1.11; P = 0.22; high-certainty evidence).

Radiosurgery and WBRT versus WBRT alone

The HR for OS with use of WBRT and radiosurgery boost as compared with WBRT alone for selected participants was 0.61 (95% CI 0.27 to 1.39; P = 0.24; moderate-certainty evidence). For overall brain control at one year, the HR was 0.39 (95% CI 0.25 to 0.60; P < 0.0001; high-certainty evidence) favouring the WBRT and radiosurgery boost group.

Radiosurgery alone versus radiosurgery and WBRT

The HR for local brain control was 2.73 (95% CI 1.87 to 3.99; P < 0.00001; high-certainty evidence)favouring the addition of WBRT to radiosurgery. The HR for distant brain control was 2.34 (95% CI 1.73 to 3.18; P < 0.00001; high-certainty evidence) favouring WBRT and radiosurgery. The HR for OS was 1.00 (95% CI 0.80 to 1.25; P = 0.99; moderate-certainty evidence). Two trials reported worse neurocognitive outcomes and one trial reported worse quality of life outcomes when WBRT was added to radiosurgery.

Overall Survival is never improved with SRS or WBRT. Better brain tumor control with treatment.

If survival is the same what is more likely to affect QOL?

SRS alone	Whole Brain
Morbidity of new brain mets (new mets can be symptomatic – may lead to more steroid use, anticonvulsants, etc)	Neurocognitive decline, side effects, more fractions
Requires more follow up MRIs, “Scan Anxiety”	Worse control of larger mets, certain histologies
Possible delay in radiation	Possible delay in systemic therapy

Areas of Greatest Research Efforts into Local Therapy Benefits for Stage IV Disease

1. Brain Metastases treated with radiation or/and surgery

2. Oligometastatic Colorectal Cancer, Sarcoma, etc. treated with radiation or/and surgery

3. Oligometastatic NSCLC treated with radiation
    a. Consolidation
    b. Oligoprogression
    c. Abscopal Response

Current Statistics

An estimated 230,000 new cases of lung cancer are expected in 2019 in the United States

Approximately 50-60% of patients with NSCLC present with stage IV disease

SOC (at least FDA approval) now encompasses multiple regimens (20% vs 20% vs 60%?):

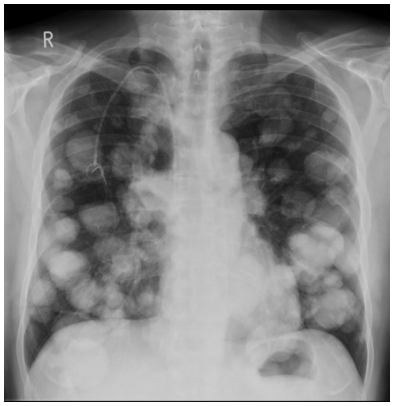
- Cytotoxics: 4-6 cycles, traditional OS of approx 1 year
- Single Agent IO: Pembro
- IO + Cytotoxics – Pembro + Pem/Platinum

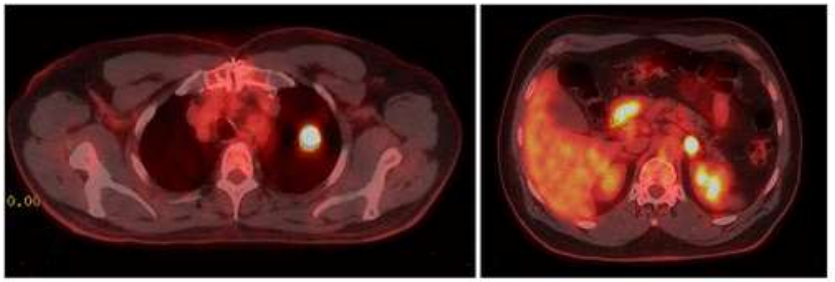
Always trying to improve OS in these patients!!!!!

Limited Metastatic Disease

"The evolution of metastatic capacity has intermediate states in which spread may be limited to specific organs and metastases might be present in limited numbers."

Hellman and Weichselbaum, 1990's





Biology

We know that biology effectuates NSCLC outcomes:

EGFR/ALK positive disease vs wild type
KRAS vs non-KRAS
Adeno vs Squam
PD-L1 expressing vs non-expressing
Resistance Mechanisms and Patterns
Limited metastatic vs widely metastatic?

Rationale – Local Tx for Mets

Development and widespread availability of modern systemic therapies

Systemic therapies are improving outcomes but cannot stand alone

Modern diagnostic tools allow the detection of early metastatic disease

Is there a "potentially chronic or curable" subset?

Rationale – Local Tx for Mets

Up to 70% of patients with stage IV NSCLC achieve either a partial response or stable disease to first line systemic therapy (Capuzzo et al).

Progression occurs within median of 3-4 months after last cycle.

In those patients who do show progression of disease, up to 64% progress only at sites present prior to the start of first line chemotherapy (Mehta et al, Rusthoven et al).

There similar patterns of failure for IO-treated patients.

Limited Metastatic Disease

Data Suggest:

1. Metastases are not always widely disseminated

2. Metastases do not always progress in multiple sites

3. Patients with limited sites of metastases may not progress or progress only in sites of initial disease

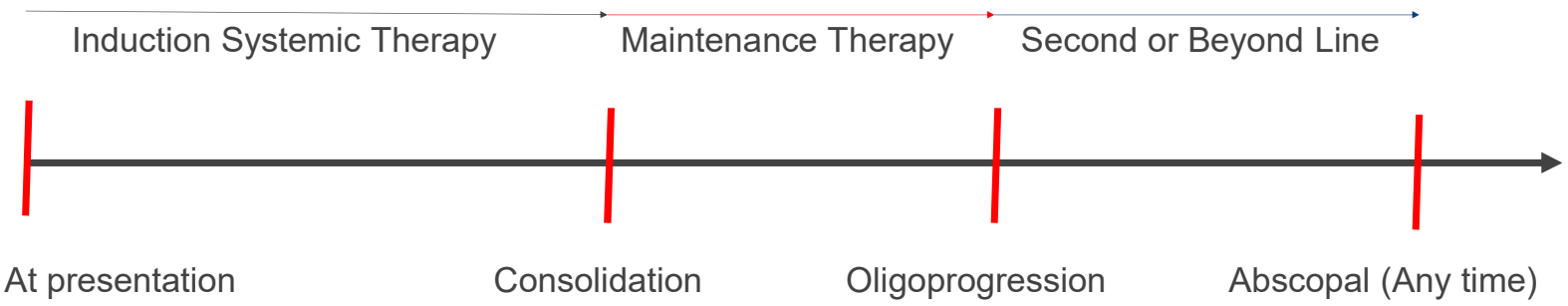
4. Therefore there may be a role for local therapy in these selected patients

Indications/Timing for Local Therapy

1) Consolidation

2) Oligoprogression

3) Abscopal Effects



Consolidation for NSCLC

1) Retrospective/Single arm prospective evaluations – **too many to review**

1) Earliest prospective randomized attempts – **2 failed to accrue**

2) Smaller randomized efforts – Canada/Europe
MDACC/W Ontario/U of Colo
UTSW

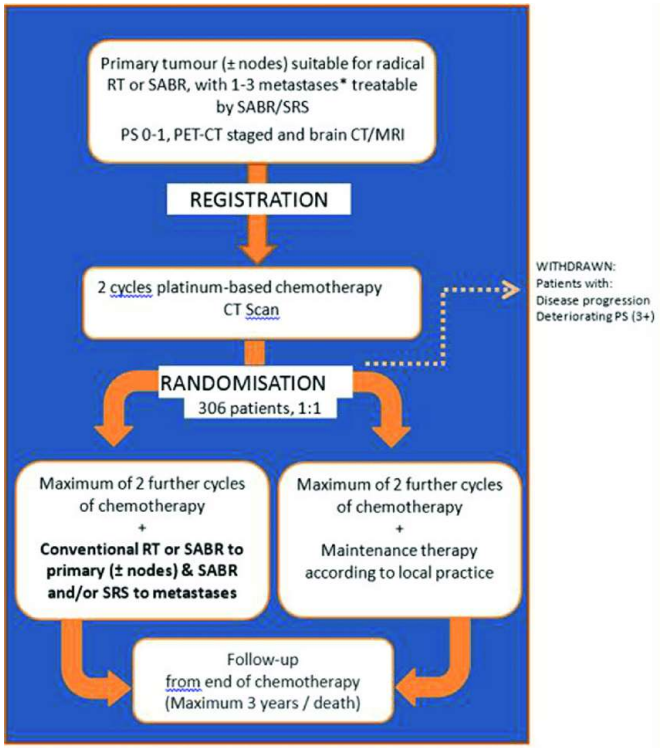
PFS good, what about OS in homogenous NSCLC pt population?

3) NRG LU002 (International) and SARON (UK) - **We will see**

Study Authors	Year	Type of Study	Patient Eligibility	Arms of Study	Primary Endpoint
De Ruysscher et al.	2012	Single Arm Ph2 CON	Oligometastatic NSCLC <5 mets	Chemo with Surgery or Radiation for Mets	Median OS 13.6 months
Collen et al.	2014	Single Arm Ph2 CON	Oligometastatic NSCLC <=5 mets	Chemo followed by SBRT or SBRT alone	Median OS 23 months
Iyengar et al	2014	Single Arm Ph2 SALVAGE	Limited Metastatic NSCLC <= 5 mets, failed at least one line of systemic therapy	Erlotinib with SBRT	OS 20.4 months Median PFS 14.7 months
Palma/Senan	2016 – Closed to Accrual	RPh2 CON	Oligometastatic Cancers	Chemo vs SBRT + Chemo	Median OS 28 months vs 41 months
Gomez et al	2016	RPh2 CON	Oligometastatic NSCLC (Mut Pos or Neg) <=3 mets	Chemo/Obs vs XRT/Surgery + Chemo/Obs	Median PFS 3.9 months vs 11.9 months Median OS 17 months vs 41 months
Iyengar et al	2017	RPh2 CON	Oligometastatic NSCLC <=5 mets	Chemo vs SBRT + Chemo	Median PFS 3.5 months vs 9.7 months

Study	Year	Type of Study	Patient Eligibility	Arms of Study	Primary Endpoint
NRG LU 002 NCT03137771	2017 CON	RPh3	Oligometastatic NSCLC <= 3 mets	Systemic Therapy vs SBRT + Systemic Therapy (IO Permitted)	OS
SARON NCT02417662	2016 CON	RPh3	Oligometastatic NSCLC <= 3 mets	Chemo vs SBRT + Chemo	OS

Schema of Phase III Study SARON



*Brain metastases can be included if at least one extra-cranial metastasis is also present.

NRG-LU002

Maintenance Systemic Therapy Versus Local Consolidative Therapy (LCT) Plus Maintenance Systemic Therapy For Limited Metastatic Non-Small Cell Lung Cancer (NSCLC): A Randomized Phase II/III Trial

Puneeth Iyengar MD, PhD, *UT Southwestern*	PI
Daniel Gomez MD, *MDAnderson Cancer Center (MDACC)*	Co-PI
Robert Timmerman MD *UT Southwestern* **Hak Choy MD, *UT Southwestern*** **Clifford Robinson MD, *Washington University of St. Louis*** **Charles Simone MD, *Maryland Proton Center***	Co-Chairs
David Gerber MD, *UT Southwestern* **Saiama Waqar MD, *Washington University of St. Louis***	Med Oncology
Michael Weldon MSc, DABR, *Ohio State University* **Jackie Wu PhD, *Duke***	Physics
Ben Movsas MD, *Henry Ford Hospital*	Quality of Life
Kirk Jones MD, *University of California at San Francisco*	Pathology
Adam Dicker MD, PhD, *Jefferson* **Max Diehn MD, PhD, *Stanford*** **John Heymach, MD, MDACC**	Translational
Chen Hu, PhD, *Johns Hopkins University/NRG Oncology*	Statistics

UT Southwestern Medical Center

Schema of Phase II/III Study

Patients with metastatic NSCLC having completed 4 cycles or courses of first-line/induction systemic therapy Restaging studies reveal no evidence of progression and limited (≤ 3 discrete sites) metastatic disease, all of which must be amenable to SBRT +/- Surgery	**S** **T** **R** **A** **T** **I** **F** **Y**	**Histology:** Squamous vs. Non-squamous **Systemic Therapy:** Immunotherapy* vs Cytotoxic Chemotherapy	**R** **A** **N** **D** **O** **M** **I** **Z** **E**	**Arm 1**: Maintenance systemic therapy alone** **Arm 2:** SBRT or SBRT and Surgery to all sites of metastases (≤ 3 discrete sites) plus irradiation (SBRT or hypofractionated RT) of the primary site followed by maintenance systemic therapy. All Arm 2 patients, even if treated with Surgery, must have one site of disease (metastasis or primary) treated with radiation.** **** As noted in Section 5**

* Acceptable immunotherapy for LU002 is pembrolizumab.
** Randomization will be 2:1 between Arm 2 and 1.

Indications for Local Therapy

1) Consolidation

2) Oligoprogression

3) Abscopal Effects

Oligoprogression

1)UTSW/U Colorado experience

2) Canadian/David Palma study

3) HALT Study – Fiona McDonald

SBRT for Oligoprogression

VOLUME 32 · NUMBER 34 · DECEMBER 1 2014

JOURNAL OF CLINICAL ONCOLOGY

ORIGINAL REPORT

Phase II Trial of Stereotactic Body Radiation Therapy Combined With Erlotinib for Patients With Limited but Progressive Metastatic Non–Small-Cell Lung Cancer

Puneeth Iyengar, Brian D. Kavanagh, Zabi Wardak, Irma Smith, Chul Ahn, David E. Gerber, Jonathan Dowell, Randall Hughes, Ramzi Abdulrahman, D. Ross Camidge, Laurie E. Gaspar, Robert C. Doebele, Paul A. Bunn, Hak Choy, and Robert Timmerman

Survival

Iyengar

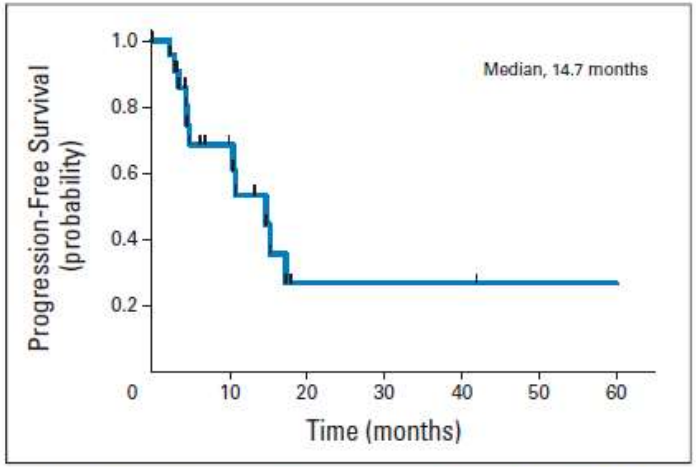


Fig 1. Kaplan-Meier analysis of progression-free survival (PFS) in months for all 24 patients enrolled on the study.

PFS 14.7 months

OS 20.4 months

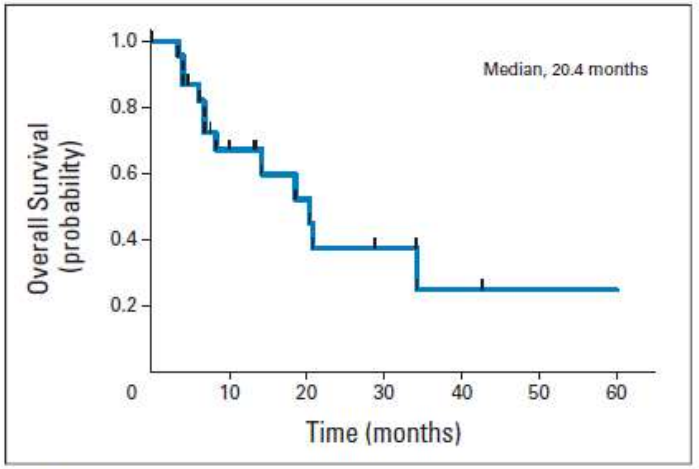
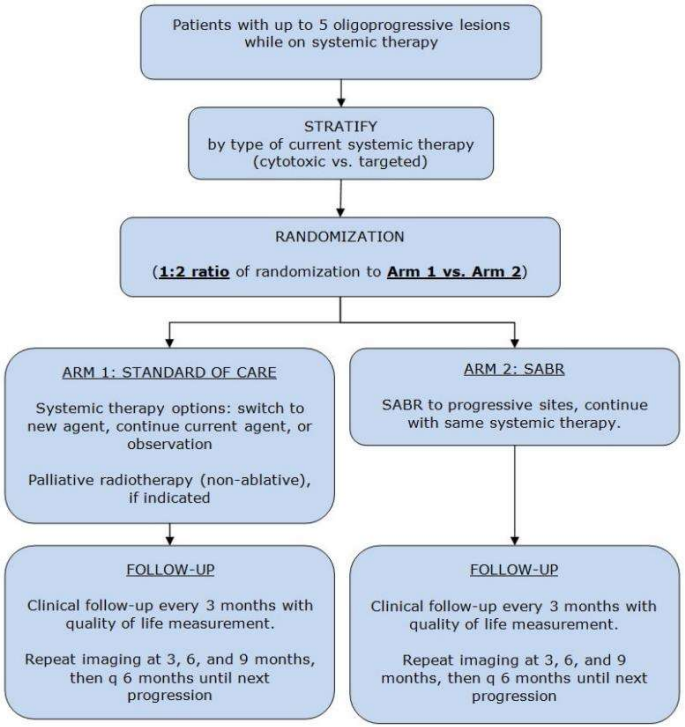
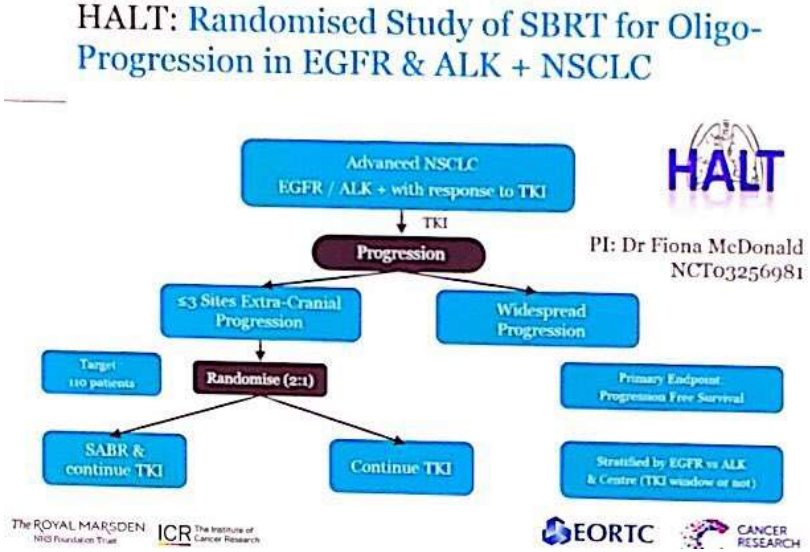


Fig 2. Kaplan-Meier analysis of overall survival (OS) in months for all 24 patients enrolled on the study.

RCT for NSCLC
Oligo-progression



STOP-NSCLC



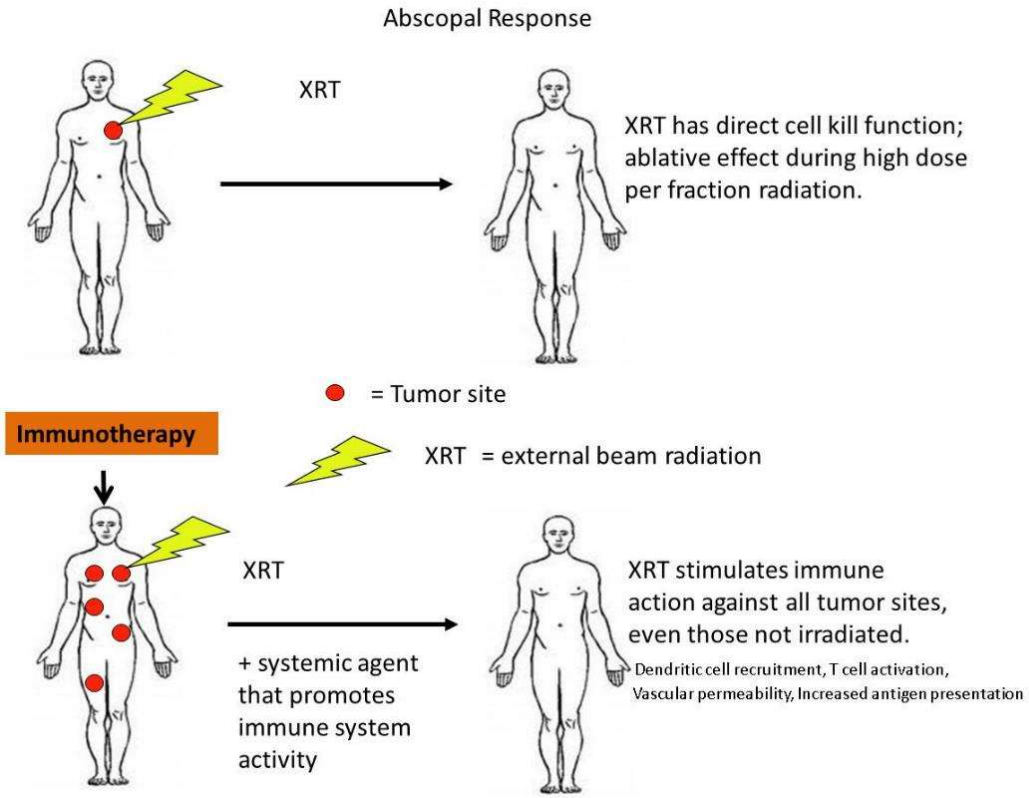
Indications for Local Therapy

1) Consolidation

2) Oligoprogression

3) Abscopal Effects

Abscopal Effect



UT Southwestern Medical Center

Abscopal Response

Historically agreed that widely metastatic NSCLC would only receive local treatment in the form of radiation as palliation.

Should we be reassessing this view in light of abscopal responses in other disease sites

1) NEJM case report for melanoma
2) Abscopal responses from RCC
3) An increased interest in this phenomenon
4) Formenti trial
5) Science Translational Medicine study

How should we really define oligometastatic disease?

3 mets vs 5 mets vs 1 met?

Locations of mets matter?

Volume/Size of mets matter?

Should patients with N1 or N2 disease be included?

Don’t know when optimally to use local therapy? **(sequence vs disease burden)**

Up front

Consolidation

Oligoprogression

In abscopal state

At multiple time points

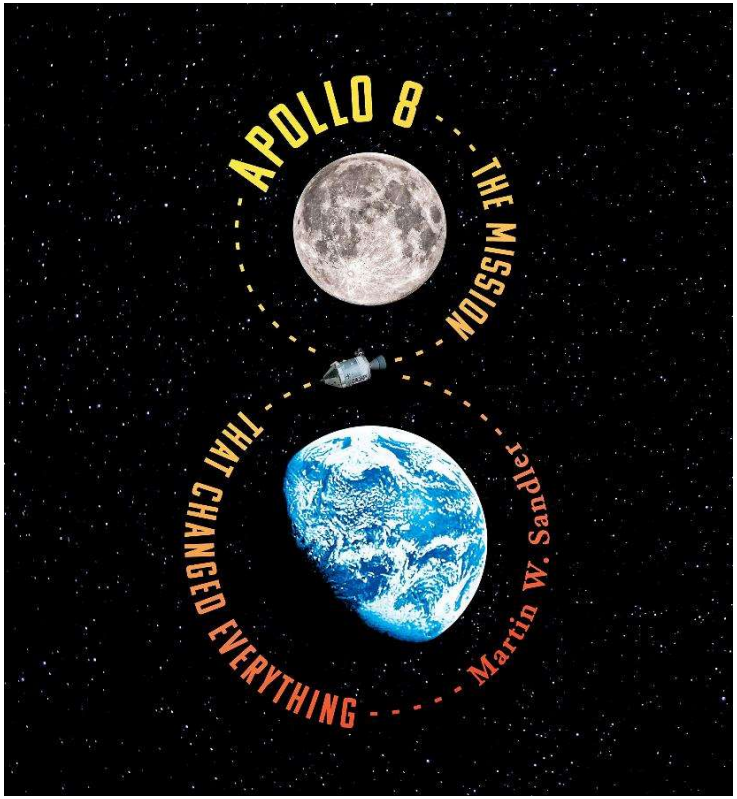
After other metrics are established – tumor burden by imaging, tumor activity by imaging, after certain finding in circulating tumor DNA values, etc.

Conclusion

Local therapy is being added to stage IV pts for:

1. Controlling brain mets
2. Extracranially to improve OS at
   a) initial diagnosis/up front, b) in consolidation, c) oligoprogression – all for oligometastatic dx, or d) abscopal

Whole Brain Radiation Therapy Systemic Therapy



SBRT SRS Systemic Therapy