Solitary Brain Metastases

Resection or Radiosurgery

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Disclosures

Consultant - Stryker Corp

Consultant - IMRIS, Inc

Disclosures

inherent biases

- Director - FH Gamma Knife Program
- Medical School - UF
  - *Mentor / Advisor - Bill Friedman*
- Residency- Univ. of Pittsburgh
  - *Mentors - Dade Lunsford & Doug Kondziolka*

Solitary Brain Mets

- Extensive literature exists on optimal treatment of solitary mets
- Surgery alone
  WBRT
- Radiosurgery alone
  WBRT
- WBRT alone
  Radiosurgery
- Surgery +
- Radiosurgery +
- Surgery +

Solitary Brain Mets

- No level 1 evidence exists showing a benefit of Radiosurgery over Surgery or Surgery over Radiosurgery, in spite of attempts

Table 5 AANS/CNS evidence classes and levels of recommendation

Evidence classification	
Class I	Evidence provided by one or more well-designed randomized controlled clinical trials, including overview (meta-analyses) of such trials
Class II	Evidence provided by well-designed observational studies with concurrent controls (e.g. case control and cohort studies)
Class III	Evidence provided by expert opinion, case series, case reports and studies with historical controls
Levels of recommendation	
Level 1	Generally accepted principles for patient management, which reflect a high degree of clinical certainty (usually this requires Class I evidence which directly addresses the clinical questions or overwhelming Class II evidence when circumstances preclude randomized clinical trials)
Level 2	Recommendations for patient management which reflect clinical certainty (usually this requires Class II evidence or a strong consensus of class III evidence)
Level 3	Other strategies for patient management for which the clinical utility is uncertain (inconclusive or conflicting evidence or opinion)

Recent trials

- Surgery versus radiosurgery to treat metastatic brain tumors
- Official Title: A Prospective, Randomized Trial Comparing Surgery Versus Radiosurgery for the Treatment of Metastatic Brain Tumors
  Status: Completed Clinicaltrials.gov Identifier: NCT00075166 Location: United States
  Sponsors and Collaborators: National Institute of Neurological Disorders and Stroke (NINDS)

- Surgery versus stereotactic radiosurgery in the treatment of single brain metastasis: a randomized trial
  Official Title: Surgery Versus Stereotactic Radiosurgery in the Treatment of Single Brain Metastasis: A Randomized Trial
  Status: Completed Clinicaltrials.gov Identifier: NCT00460395
  Principal Investigator: Frederick F. Lang, M.D., University Of Texas MD Anderson Cancer Center
  Location: United States Sponsors and Collaborators: M.D. Anderson Cancer Center

- A Trial Comparing Radiosurgery With Surgery for Solitary Brain Metastases
  Official Title: A Randomised Trial of Surgery Plus Whole Brain Radiotherapy (WBRT) Versus Radiosurgery Plus WBRT for Solitary Brain Metastases
  Status: Completed
  Clinicaltrials.gov Identifier: NCT00124761 Principal Investigator: Daniel Roos, FRANZCR, Royal Adelaide Hospital Location: Australia Sponsors and Collaborators: Royal Adelaide Hospital

Problem with existing trials

- Retrospective
- Inhomogeneous groups
  - RPA (Recursive Partitioning Analysis), tumor size, tumor location, tumor histology, single or multifraction radiosurgery, steroids, etc
- Small sample size

Role for Radiosurgery

- In spite of these limitations, existing literature does support the role of radiosurgery for certain patient populations.
  - Tumors in unresectable locations
  - Systemic comorbidities making surgery contraindicated
  - Uncontrolled systemic disease
  - Radioresistant tumors

Solitary Brain Metastasis

- Existing literature is fairly clear that the management of a solitary metastasis is not all surgical or radiosurgical.

- Discuss role of surgery for solitary brain metastasis and consideration for treatment algorithm

The NEW ENGLAND JOURNAL of MEDICINE

A RANDOMIZED TRIAL OF SURGERY IN THE TREATMENT OF SINGLE METASTASES TO THE BRAIN

ROY A. PATCHELL, M.D., PHILLIP A. TIBBS, M.D., JOHN W. WALSH, M.D., ROBERT J. DEMPSEY, M.D., YOSH MARUYAMA, M.D., RICHARD J. KRYSCIO, PH.D., WILLIAM R. MARKESBERY, M.D., JOHN S. MACDONALD, M.D., AND BYRON YOUNG, M.D.

Abstract To assess the efficacy of surgical resection of brain metastases from extracranial primary cancer, we randomly assigned patients with a single brain metastasis to either surgical removal of the brain tumor followed by radiotherapy (surgical group) or needle biopsy and radiotherapy (radiation group). Forty-eight patients (25 in the surgical group and 23 in the radiation group) formed the study group; 6 other patients (11 percent) were excluded from the study because on biopsy their lesions proved to be either second primary tumors or inflammatory or infectious processes.

Recurrence at the site of the original metastasis was less frequent in the surgical group than in the radiation group (5 of 25 [20 percent] vs. 12 of 23 [52 percent]; $P<0.02$). The overall length of survival was significantly longer in the surgical group (median, 40 weeks vs. 15 weeks in the radiation group; $P<0.01$), and the patients treated with surgery remained functionally independent longer (median, 38 weeks vs. 8 weeks in the radiation group; $P<0.005$).

We conclude that patients with cancer and a single metastasis to the brain who receive treatment with surgical resection plus radiotherapy live longer, have fewer recurrences of cancer in the brain, and have a better quality of life than similar patients treated with radiotherapy alone.
(N Engl J Med 1990; 322:494-500.)

Patchell study

- 11% of patients thought to have a solitary brain metastasis on workup from a known primary actually harbored a secondary pathology.
- Did not have a large enough N to comment on histology and outcome
- Recurrence 2.5 times more common in the WBRT group
- Survival 2.5 times longer in the surgical arm (40 vs 15 weeks)
- Functional independence markedly prolonged in surgical group (38 vs 8 weeks)

Patchell study

- Level 1 evidence - surgery + WBRT improves outcome compared to WBRT alone for solitary metastatic disease

Int. J. Radiation Oncology Biol. Phys., Vol. 35, No. 1, pp. 27–35, 1996

0360-3016/96 $15.00 + .00

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SSDI: 0360-3016(95)02259-7

● *Clinical Original Contribution*

A MULTIINSTITUTIONAL OUTCOME AND PROGNOSTIC FACTOR ANALYSIS OF RADIOSURGERY FOR RESECTABLE SINGLE BRAIN METASTASIS

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Purpose: Recent randomized trials of selected patients with single brain metastasis comparing resection followed by whole-brain radiotherapy (WBRT) to WBRT alone have shown a statistically significant survival advantage for surgery and WBRT. A multiinstitutional retrospective study was performed, which identified comparable patients who were treated with stereotactic radiosurgery (RS) and WBRT.

Methods and Materials: The RS databases of four institutions were reviewed to identify patients who met the following criteria: single-brain metastasis; no prior cranial surgery or WBRT; age > 18 years; surgically resectable lesion; Karnofsky Performance Status (KPS) ≥ 70 at time of RS; nonradiosensitive histology. One hundred twenty-two patients were identified who met these criteria. Patients were categorized by: (a) status of the primary, (b) status of non-CNS metastasis, (c) age, (d) baseline KPS (from 70–100), (e) histology, (f) time from diagnosis of primary to the detection of the brain metastasis, (g) gender, and (h) tumor volume. RS was performed with a linear accelerator based technique (peripheral dose range was 10–27 Gy, median was 17 Gy). WBRT was performed in all but five patients who refused WBRT (dose range was 25–40 Gy, median was 37.5 Gy).

Results: The median follow-up for all patients was 123 weeks. The overall local control rate (defined as lack of progression in the RS volume) was 86%. Intracranial recurrence outside of the RS volume was seen in 27 patients (22%). The actuarial median survival from date of RS is 56 weeks, and the 1-year and 2-year actuarial survival rates are 53 and 30%. The median duration of functional independence (sustained KPS ≥ 70) is 44 weeks. Nineteen of 77 deaths were attributed to CNS progression (25% of all deaths). Multivariate analysis revealed the following factors to be statistically significant predictors of survival: baseline KPS ($p < .0001$) and absence of other sites of metastasis ($p = 0.008$).

Conclusion: The RS in conjunction with WBRT for single brain metastasis can produce substantial functional survival, especially in patients with good performance status and without extracranial metastasis. These results are comparable to recent randomized trials of resection and WBRT. The advantages of RS over surgery in terms of cost, hospitalization, morbidity, and wider applicability strongly suggest that a randomized trial to compare RS with surgery is warranted.

Int. J. Radiation Oncology Biol. Phys., Vol. 66, No. 3, pp. 810–817, 2006

0360-3016/06/$–see front matter

doi:10.1016/j.ijrobp.2006.06.003

CLINICAL INVESTIGATION **Brain**

RPA CLASSIFICATION HAS PROGNOSTIC SIGNIFICANCE FOR SURGICALLY RESECTED SINGLE BRAIN METASTASIS

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Departments of *Radiation Oncology, ‡Neurosurgery, and §Biostatistics, Brain Tumor Institute, Cleveland Clinic, Cleveland, OH and †Northwestern University Feinberg School of Medicine, Chicago, IL

Purpose: To retrospectively evaluate prognostic factors that correlate with overall survival among patients with a surgically resected single brain metastasis.

Methods and Materials: An Institutional Review Board–approved database of the Cleveland Clinic Brain Tumor Institute was queried for patients with a single brain metastasis treated by surgical resection between February 1984 and January 2004. The primary endpoint was overall survival from the date of surgery by the Kaplan-Meier method.

Results: A total of 271 patients were included. Statistically significant variables for improved survival on multivariate analysis included age <65 years, lack of extracranial metastases, control of primary tumor, histology (non–small-cell lung carcinoma), and use of stereotactic radiosurgery. The median survival for all patients was 10.2 months. Survival of patients in recursive partitioning analysis (RPA) class 1 was better (21.4 months) than those in RPA class 2 (9.0 months, $p < 0.001$), RPA class 3 (8.9 months, $p = 0.15$), or the combined group of RPA classes 2 and 3 (9.0 months, $p < 0.001$). Patients had a median survival of 10.6 months after documented gross total resection and 8.7 months after subtotal resection, which approached statistical significance ($p = 0.07$). Those who were treated with stereotactic radiosurgery had a median survival of 17.1 months, which was greater than patients who were not treated with stereotactic radiosurgery (8.9 months, $p = 0.006$).

Conclusions: This analysis supports the prognostic significance of the RPA classification in patients with a single brain metastasis who undergo surgical resection and adjuvant therapy. RPA class 1 patients have a very favorable prognosis with a median survival of 21.4 months. © 2006 Elsevier Inc.

Auchter study

- RPA class 1 patients

Recursive Partitioning Analysis Classes for Brain Mets

	Class 1	Class 2	Class 3
Karnofsky performance score	≥ 70	≥ 70	< 70
Primary (systemic) tumor status	controlled	uncontrolled	uncontrolled
Age in years	≤ 65	> 65	> 65
Extracranial metastases	none	present	present

RPA 1 patients

- Surgery + WBRT = 21 months (Tendulkar, et al) (12 months including RPA I & II)
- SRS + WBRT = 12.2 months (Auchter, et al.) Likely involved some RPA II patients

Summary of studies comparing surgery with SRS in the treatment of brain metastases.

Author (year)	Method	Complete resection %	Tumor size	Median survival	Local control	Median time to local failure
Bindal et al. (1996) [63]	SRS ± WBRT	NR	1.96 cm^3	16.4	61%	
	Surgery ± WBRT	NR	NR	7.2	87%	
Schoggl et al. (2000) [66]	SRS ± WBRT	NR	7800 mm^3	52% at 1 year	95%	
	Surgery ± WBRT	NR	12 500 mm^3	44% at 1 year	83%	
O'Neill et al. (2003) [64]	SRS ± WBRT		NR	NR	100%	
	Surgery ± WBRT		NR	NR	42%	
Rades et al. (2009) [68]	SRS + WBRT		NR	61%	87%	
	Surgery + WBRT	84%	NR	53%	56%	
Roos et al. (2011) [69]	SRS + WBRT			6.2 mo	NR	3.1
	Surgery + WBRT		Tumor larger	2.8 mo	NR	1.7
Kocher et al. (2011) [59]	SRS + WBRT	100%		NR	81%	
	Surgery + WBRT		Tumor larger	NR	73%	

NR, not reported; WBRT, whole brain radiotherapy; SRS, stereotactic radiosurgery; mo, months.

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DOI 10.1007/s11060-009-0073-4

INVITED MANUSCRIPT

The role of stereotactic radiosurgery in the management of patients with newly diagnosed brain metastases: a systematic review and evidence-based clinical practice guideline

Mark E. Linskey · David W. Andrews · Anthony L. Asher · Stuart H. Burri · Douglas Kondziolka · Paula D. Robinson · Mario Ammirati · Charles S. Cobbs · Laurie E. Gaspar · Jay S. Loeffler · Michael McDermott · Minesh P. Mehta · Tom Mikkelsen · Jeffrey J. Olson · Nina A. Paleologos · Roy A. Patchell · Timothy C. Ryken · Steven N. Kalkanis

J Neurooncol (2010) 96:33–43
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INVITED MANUSCRIPT

The role of surgical resection in the management of newly diagnosed brain metastases: a systematic review and evidence-based clinical practice guideline

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Eligibility criteria

- Published in English.
- Patients with newly diagnosed brain metastases.
- Fully-published (i.e., not in abstract form) peer-reviewed primary comparative studies. (These included the following comparative study designs for primary data collection: RCTs, non-randomized trials, cohort studies, and case–control studies.
- Study comparisons include one or more of the following (local RT = fractionated radiotherapy localized to the tumor):
  - WBRT vs. WBRT + SRS
  - SRS vs. WBRT + SRS
  - SRS vs. WBRT
  - SRS ± WBRT or local RT vs. Resection ± WBRT or local RT
  - SRS ± Resection vs. WBRT ± Resection
  - Single dose SRS ± WBRT vs. Multi-dose SRS ± WBRT
- Number of study participants with newly diagnosed brain metastases ≥5 per study arm for at least two of the study arms.
- Baseline information on study participants is provided by treatment group in studies evaluating interventions exclusively in patients with newly diagnosed brain metastases. For studies with mixed populations (i.e., includes participants with conditions other than newly diagnosed brain metastases), baseline information is provided for the intervention sub-groups of participants with newly diagnosed brain metastases.

SRS

Eligibility criteria

- Published in English.
- Patients with newly diagnosed brain metastases.
- Fully-published (i.e., not in abstract form) peer-reviewed primary comparative studies (These included the following comparative study designs for primary data collection: RCTs, non-randomized trials, cohort studies and case–control studies).
- Study comparisons include one or more of the following:
  - Surgery versus WBRT
  - Surgery versus surgery + WBRT
  - Surgery ± WBRT or partial brain RT versus SRS ± WBRT or partial brain RT
  - Surgery versus surgery + SRS
  - Surgery + WBRT versus surgery + SRS
    (Where SRS could be single session and fractionated stereotactic radiotherapy)
- Number of study participants with a newly diagnosed brain metastasis ≥5 per study arm for at least two of the study arms.
- Baseline information on study participants is provided by treatment group in studies evaluating interventions exclusively in patients with a newly diagnosed brain metastasis. For studies with mixed populations (i.e., includes participants with conditions other than newly diagnosed brain metastases), baseline information is provided for the intervention sub-groups of participants with a newly diagnosed brain metastasis.

Surgery

Surgery Study Questions

Question
- Should patients with newly-diagnosed metastatic brain tumors undergo open surgical resection versus whole brain radiation therapy (WBRT) and/or other treatment modalities such as radiosurgery, and in what clinical settings?
Target population
These recommendations apply to adults with a newly diagnosed single brain metastasis amenable to surgical resection.

- Does surgical resection in addition to WBRT improve outcomes when compared with WBRT alone?
Target population
This recommendation applies to adults with a newly diagnosed single brain metastasis amenable to surgical resection; however, the recommendation does not apply to relatively radiosensitive tumors histologies (i.e., small cell lung cancer, leukemia, lymphoma, germ cell tumors and multiple myeloma).

15 studies met criteria to address these questions

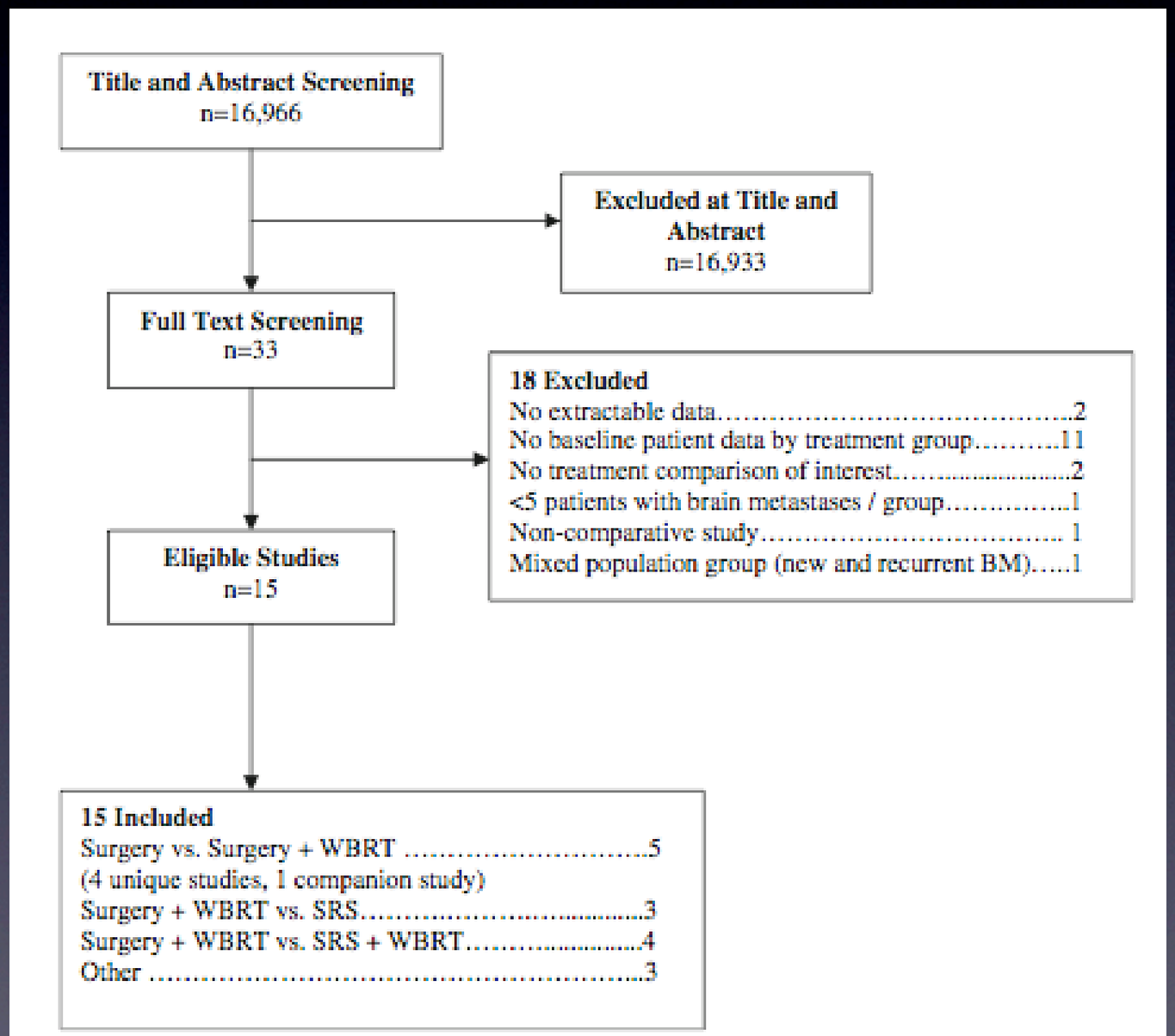


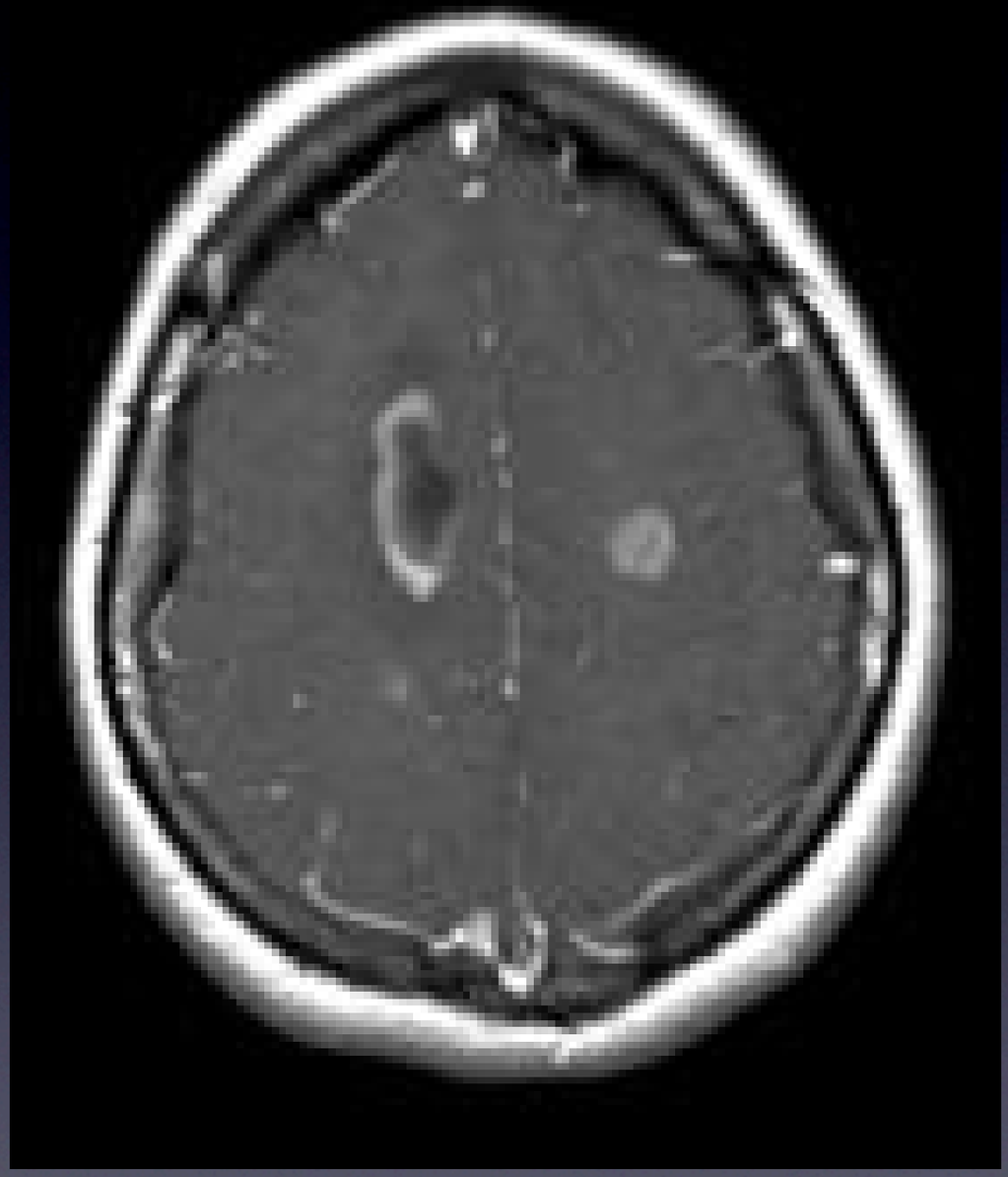
Fig. 1 Flow of studies to final number of eligible studies

Surgical resection ± WBRT or partial brain RT versus stereotactic radiosurgery (SRS) ± whole or partial brain RT

- 1 Randomized Control and 9 Retrospective Cohort Studies

- Surgical Resection + WBRT vs SRS + WBRT
- No prospective studies
- 4 Retrospective Cohort Studies
    - A majority, but not all subjects received WBRT
    - 3 studies showed no difference in survival
    - 1 study showed survival was significantly longer for patients in the surgery + WBRT arm. Freedom from local recurrence was also significantly longer in the surgery arm in this study.
    - 3 other studies, however, showed freedom from local recurrence trended to benefit the SRS arm.
    - Class II evidence exists for these studies, but all are retrospective, each yielded conflicting results in terms of overall survival and duration of freedom from local recurrence.
    - Class II evidence supporting surgery over SRS in solitary mets in the following scenarios
        - ★ Larger lesions (>3cm in max. diameter)
        - ★ Lesions causing significant mass effect (>1 cm shift)
        - ★Lesions causing symptomatic compression
    - Class II evidence supporting SRS over surgery in solitary mets in the following scenario
        - ★ Surgically inaccessible lesions <3cm in max. diameter

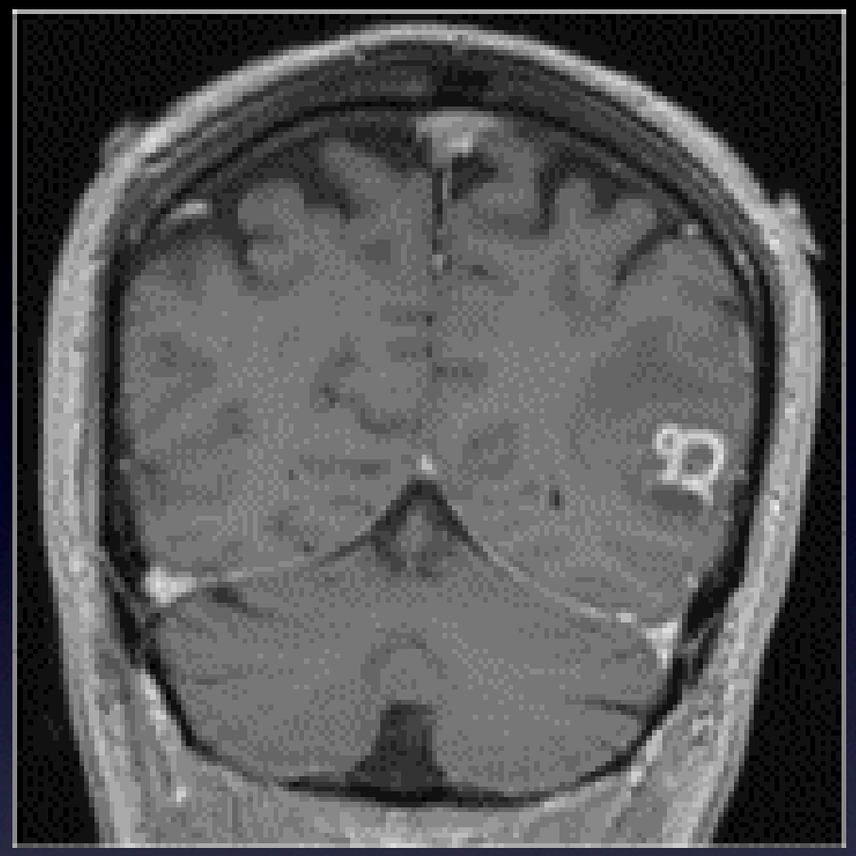
- 40 year-old female diagnosed with Stage IIb (T2, N1, M0) diagnosed 9 months ago.
- Treated with mastectomy and CTX.
- 1 week history of headache and seizure



Diagnosis & Treament ?

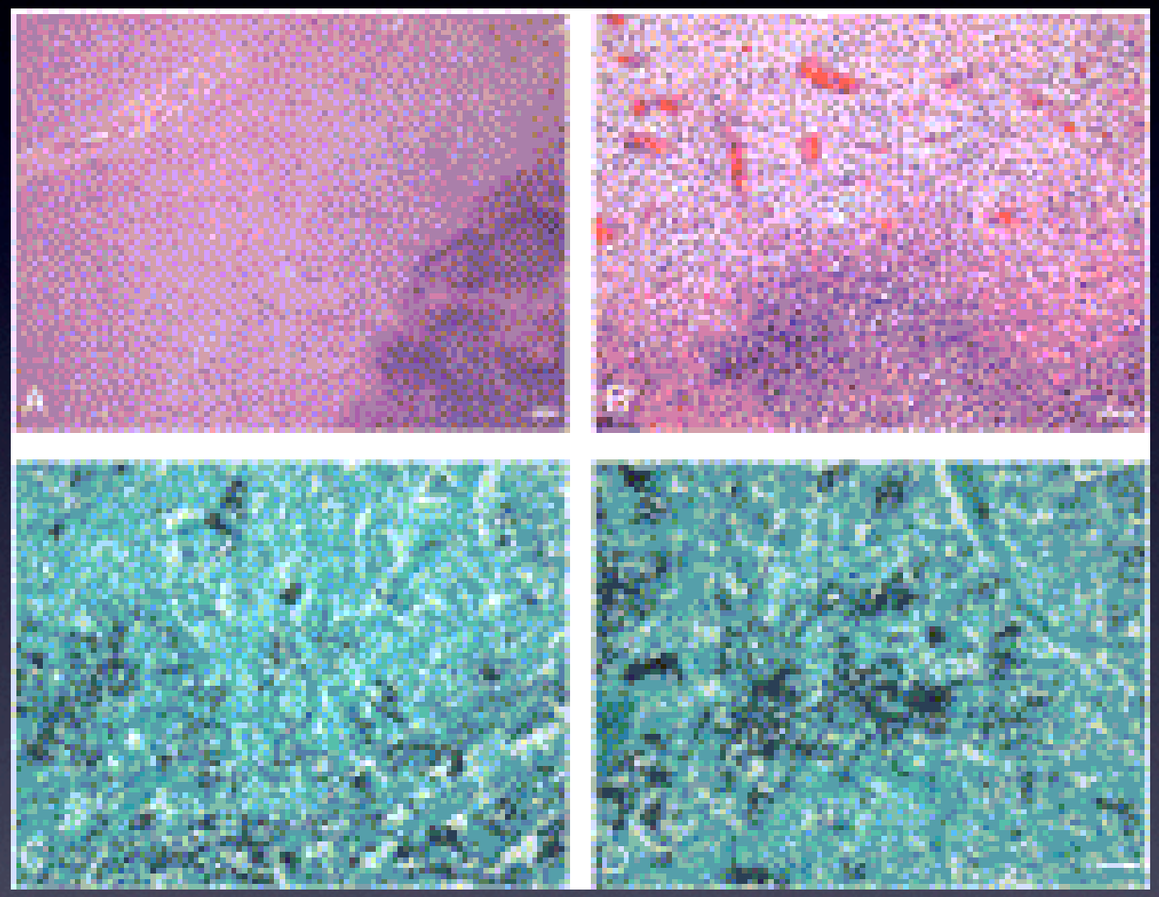
- Acute disseminated encephalomyelitis (ADEM)
- Retrospectively acknowledged flu vaccine 3 weeks prior

- 60 year-old female 3 weeks post-op from robotic hysterectomy, BSO and nodal dissection for newly diagnosed Stage IIIc Ovarian Cancer (T3c, N1, M0)
- Now complaining of headache



Diagnosis and Treatment ?

Brain Abscess



- 75 year-old male with history of Non-small Cell Lung Ca diagnosed 14 months ago as IIb (T2b, N1, M0) treated with resection followed by CTX. 3 months ago noted to have progressive hilar adenopathy. XRT to region administered.
- Presents with aphasia and right-sided weakness that began 4 days ago and hasn’t improved.

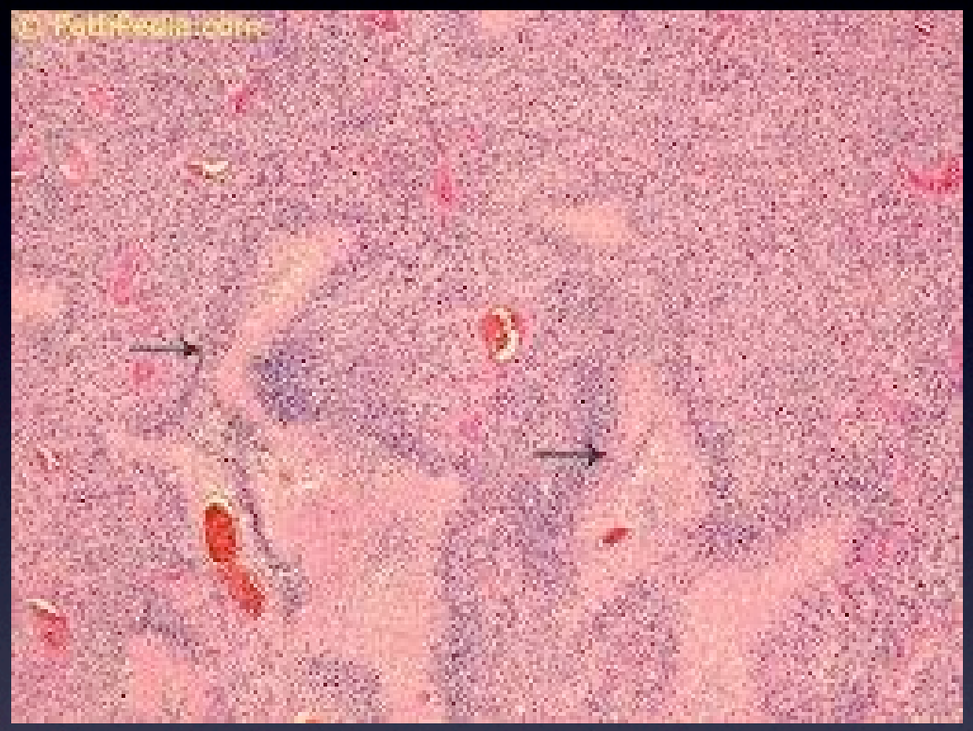
Diagnosis and Treatment ?

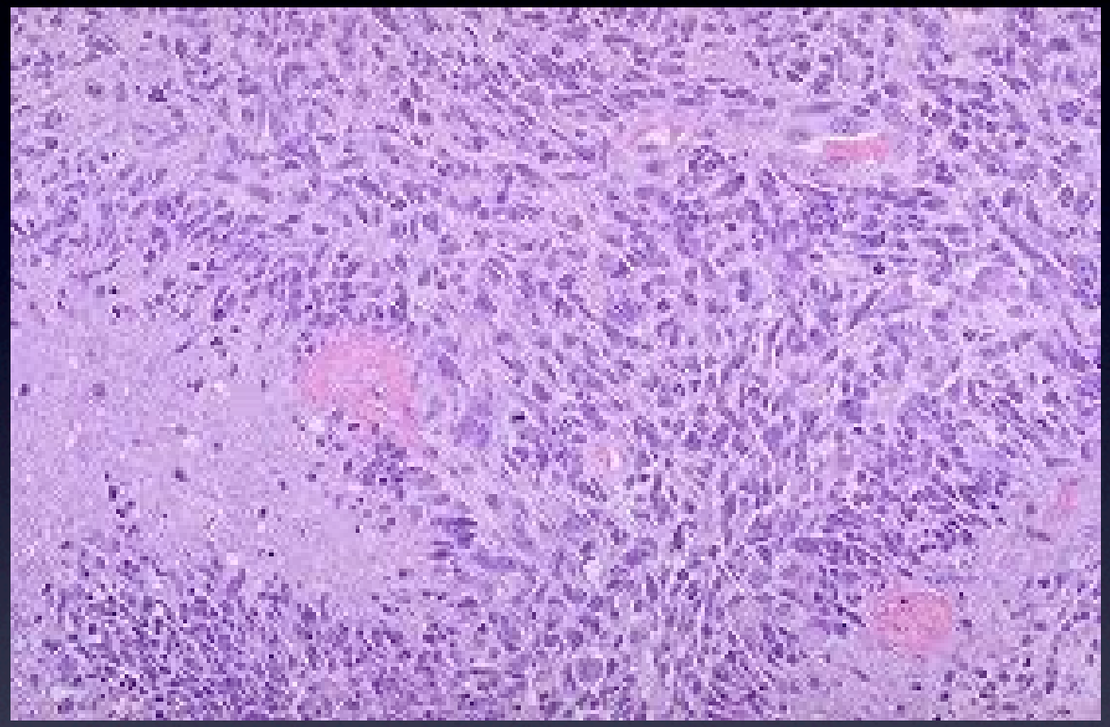
- Stroke

- 65 year-old male diagnosed with renal cell CA 1 year ago. Treated with nephrectomy only (Stage 1 disease).
- 3 months ago found to have a “new spot” in his lungs. Treated with XRT and began CTX and stable on repeat imaging.
- Now presents with a generalized seizure, 3 week headache and Left drift.

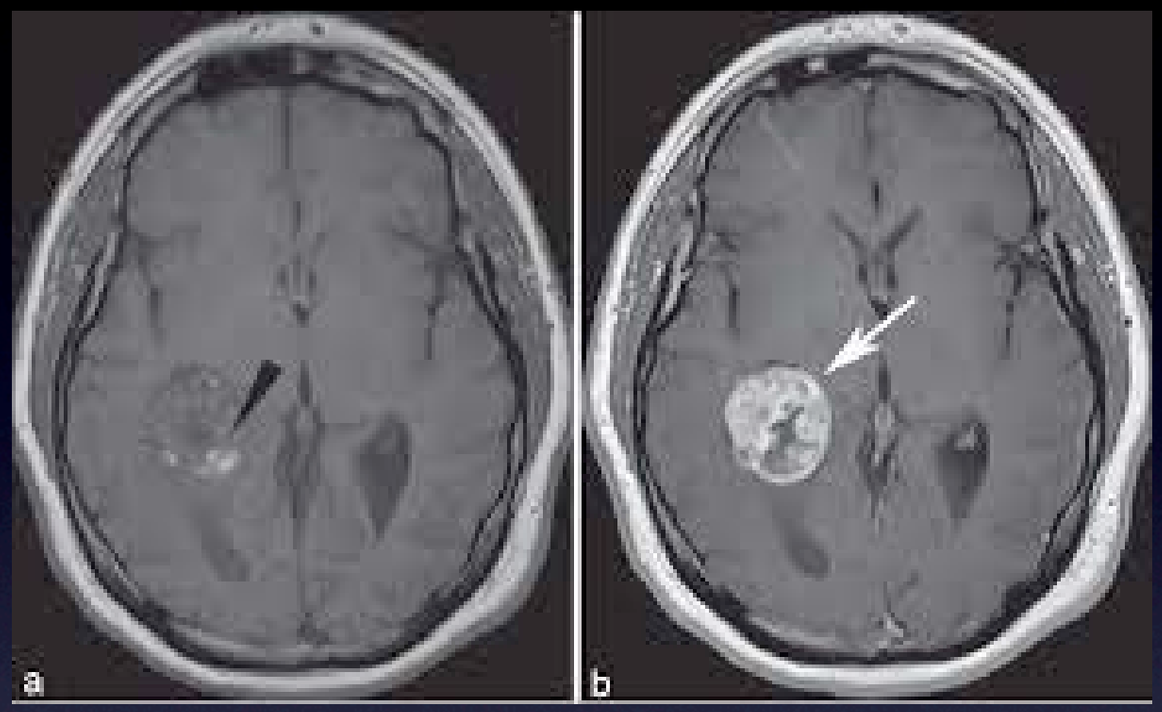
Diagnosis and Treatment?

GBM



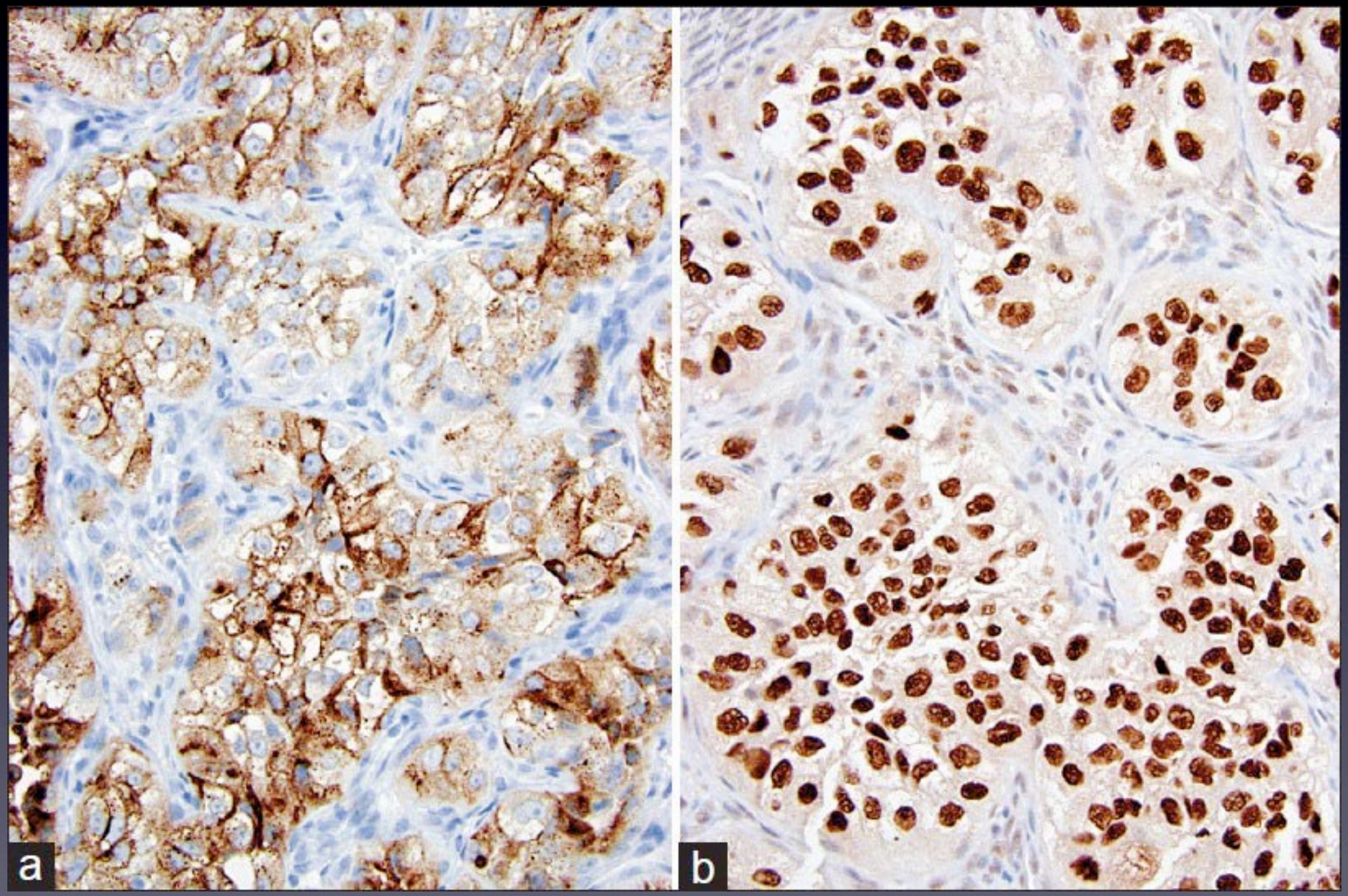


- 50 year-old male diagnosed with Stage IV Renal Cell Ca 6 months ago treated by nephrectomy and CTX. Stable disease with 1 week history of headache.

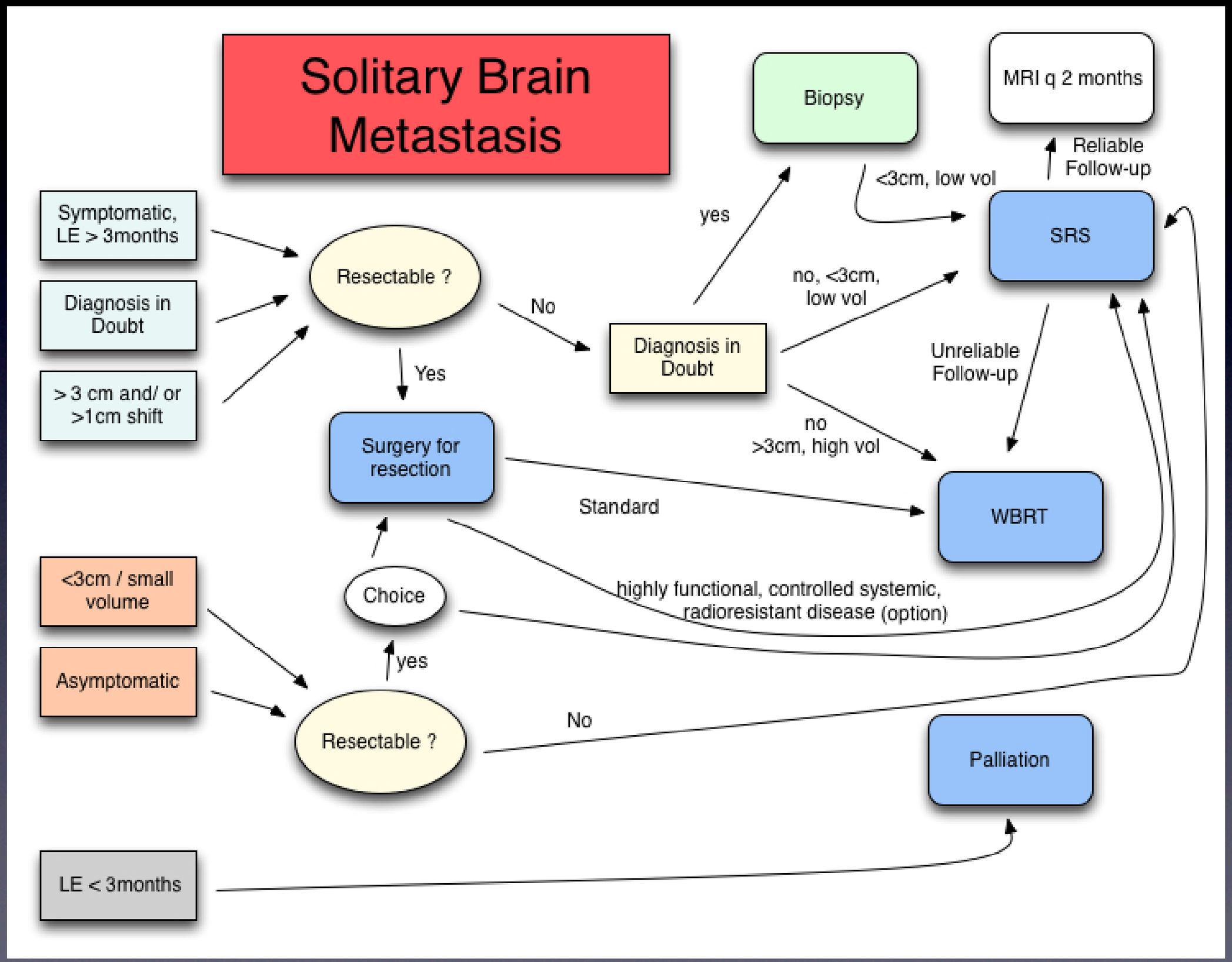


Diagnosis and Treatment ?

Renal Cell Metastasis



Our Algorithm



Summary

- Diagnosis in doubt
- >3cm
- symptomatic mass effect
- > 1cm shift
- ? Role for Rsxn + SRS for solitary disease

RSXN + SRS

- Active NCT01891318 **Neoadjuvant Radiosurgery for Resectable Brain Metastases: Phase I/II Study** **radiosurgery** followed by **surgical** resection Cleveland Clinic Taussig Cancer Institute & Case Medical Center, University Hospitals Seidman Cancer Center Principal Investigator: Andrew Sloan, MD

- Active NCT00950001 Efficacy of Post-**Surgical** Stereotactic **Radiosurgery** for Metastatic Brain Disease: A Randomized Trial evaluate benefit of post-**surgical** stereotactic **radiosurgery** (SRS) on the resection bed in providing 6 month local control (decreasing the risk of local tumor recurrence) when compared to **surgical** resection alone. M.D. Anderson Cancer Center Principal Investigator: Anita Mahajan, MD UT MD Anderson Cancer Center Principal Investigator:Ganesh Rao, MD UT MD Anderson Cancer Center

- Completed NCT00587964 Phase II Trial of Stereotactic **Radiosurgery** Boost Following **Surgical** Resection for Brain Metastases. Surgery followed by SRS 2-8 wks postop as single fraction. 1-2 resected mets Memorial Sloan-Kettering Cancer Center Principal Investigator: Kathryn Beal, MD Memorial Sloan-Kettering Cancer Center

- Active NCT01372774 A Phase III Trial of Post-**Surgical** Stereotactic **Radiosurgery** (SRS) Compared With Whole Brain Radiotherapy (WBRT) for Resected Metastatic Brain Disease North Central Cancer Treatment Group National Cancer Institute (NCI) Principal Investigator: Paul D. Brown, MD M.D. Anderson Cancer Center

- Completed, NCT00814463 Phase II Single-arm Study of Post-operative Stereotactic **Radiosurgery** for Brain Metastases. Duke Comprehensive Cancer Center Principal Investigator: John H. Sampson, MD, PhD Duke University

- Active NCT01395407 Phase I Trial of Stereotactic **Radiosurgery** Following **Surgical** Resection of Intra-axial Brain Metastases Emory University Hospital Principal Investigator: Ian Crocker, MD Emory University

- Active NCT01535209 Phase 3 Study of **Stereotactic Radiotherapy** of the Postoperative Resection Cavity Versus Whole-Brain Irradiation After **Surgical** Resection of Single Brain Metastasis Maria Sklodowska-Curie Memorial Cancer Center, Poland, Principal Investigator: Lucyna Kepka, Prof