



ESMO PRECEPTORSHIP PROGRAMME
BRAIN TUMOURS

Multidisciplinary management, standards of care, therapeutic targets
and future perspectives

Athens, Greece
28-29 September 2018

Brain metastases: standards of care

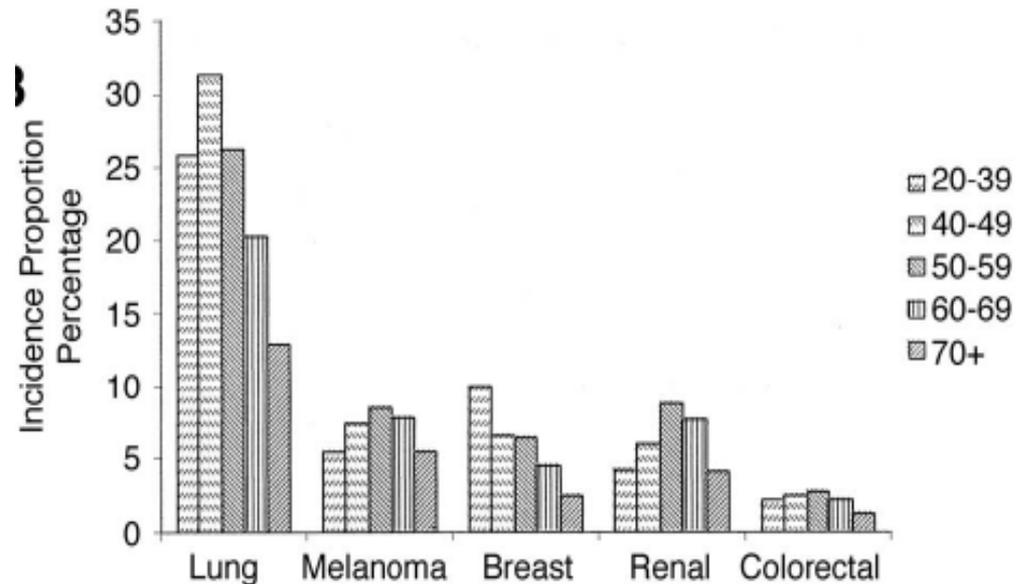
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Disclosures

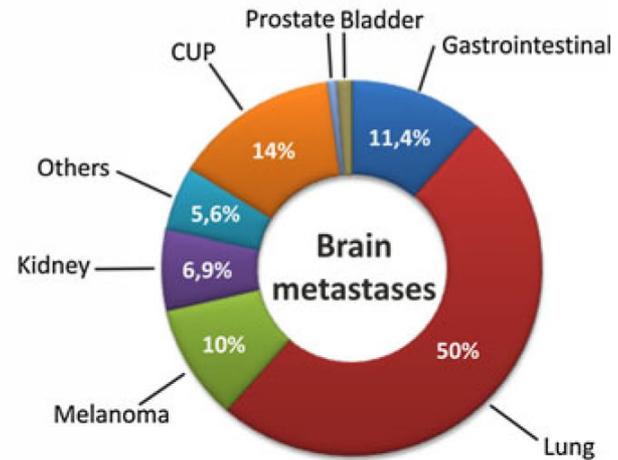
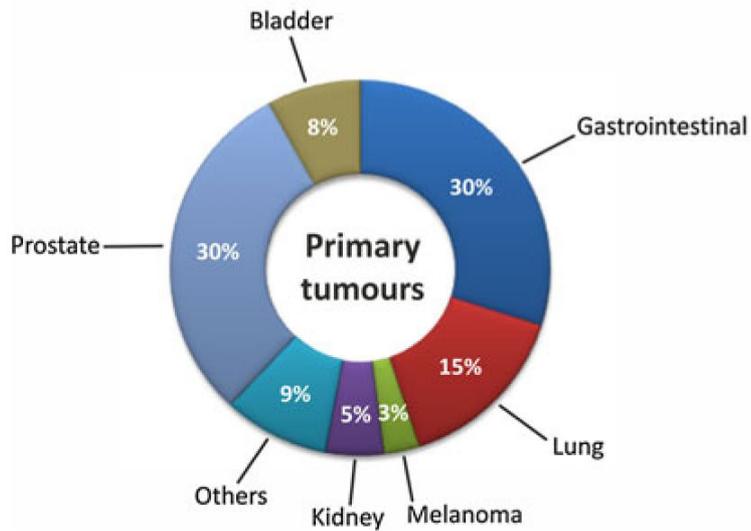
MP has received research support from Böhringer-Ingelheim, GlaxoSmithKline, Merck Sharp & Dome and Roche and honoraria for lectures, consultation or advisory board participation from Bristol-Myers Squibb, Novartis, Gerson Lehrman Group (GLG), CMC Contrast, GlaxoSmithKline, Mundipharma, Roche, Astra Zeneca, AbbVie, Lilly, Medahead, Daiichi Sankyo, Merck Sharp & Dome.

Incidence of brain metastases

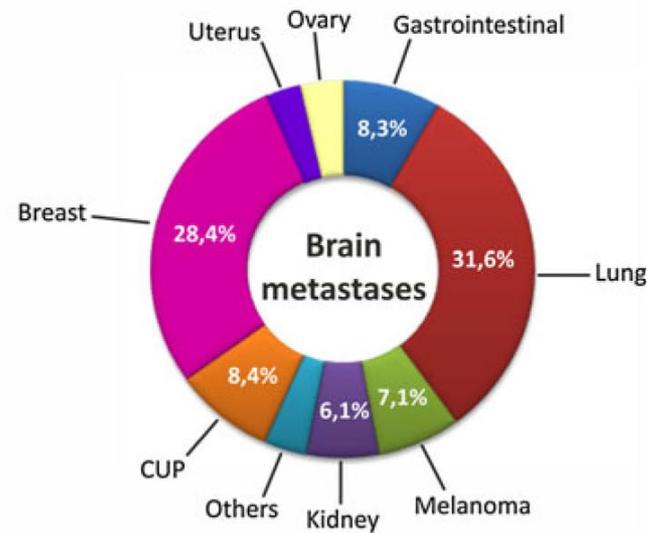
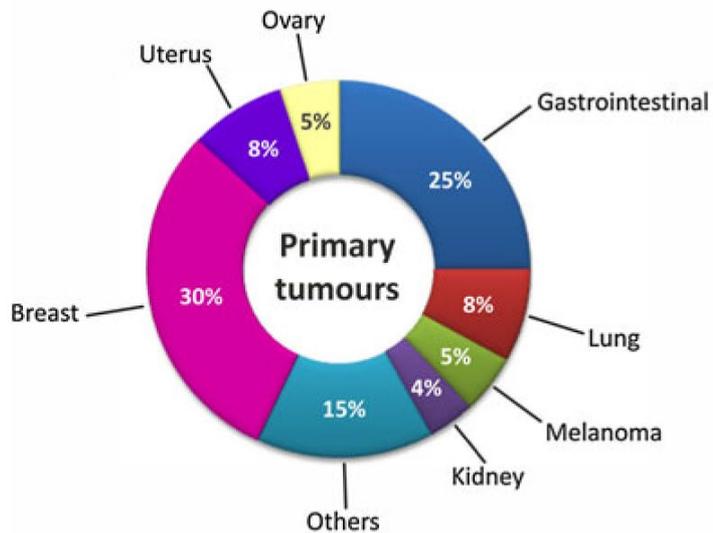
- Occur in 10-30% of all adult cancers
- Approx. 10 times more frequent than primary brain tumors
- Relative incidence increasing, due to
 - Effective systemic treatments → with longer survival
 - Improved imaging techniques and their increased availability
- Approx. half of all brain mets due to NSCLC, others:
 - Breast cancer
 - Melanoma
 - Unknown primary
 - Renal cell carcinoma



Relative frequencies of tumour types in males



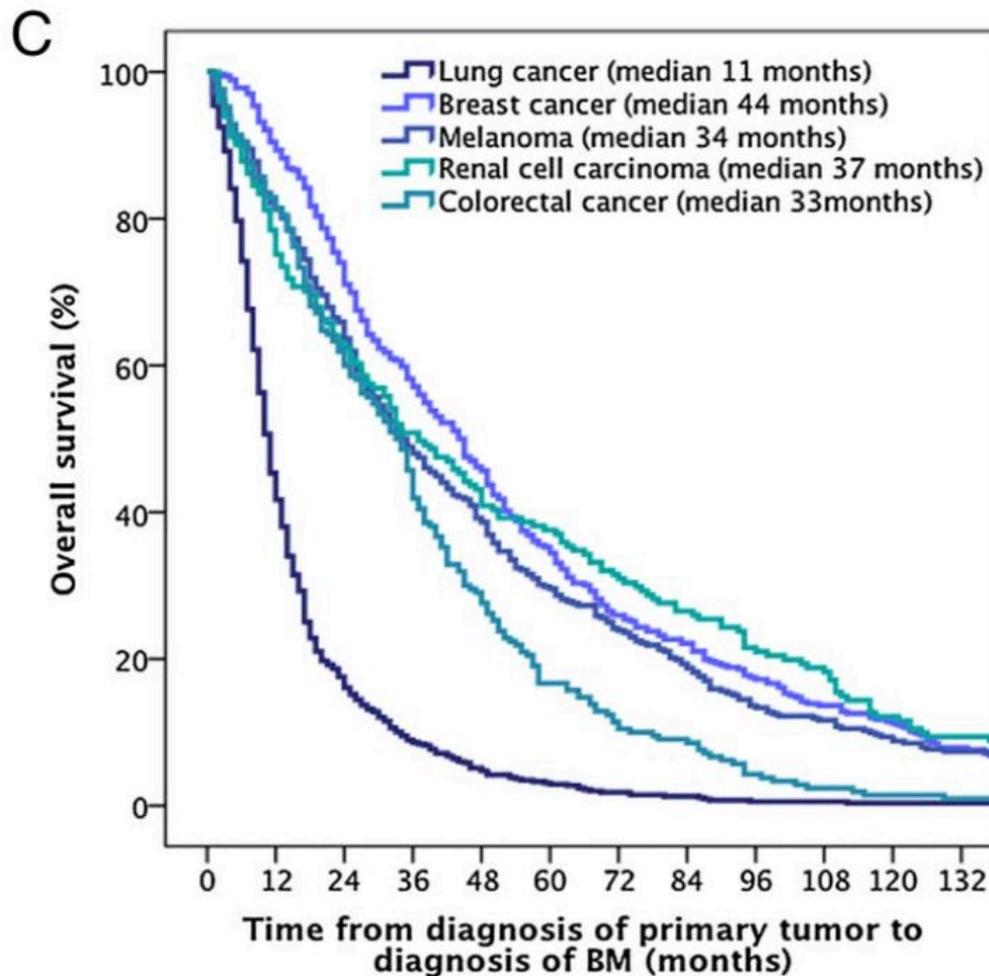
Relative frequencies of tumour types in females



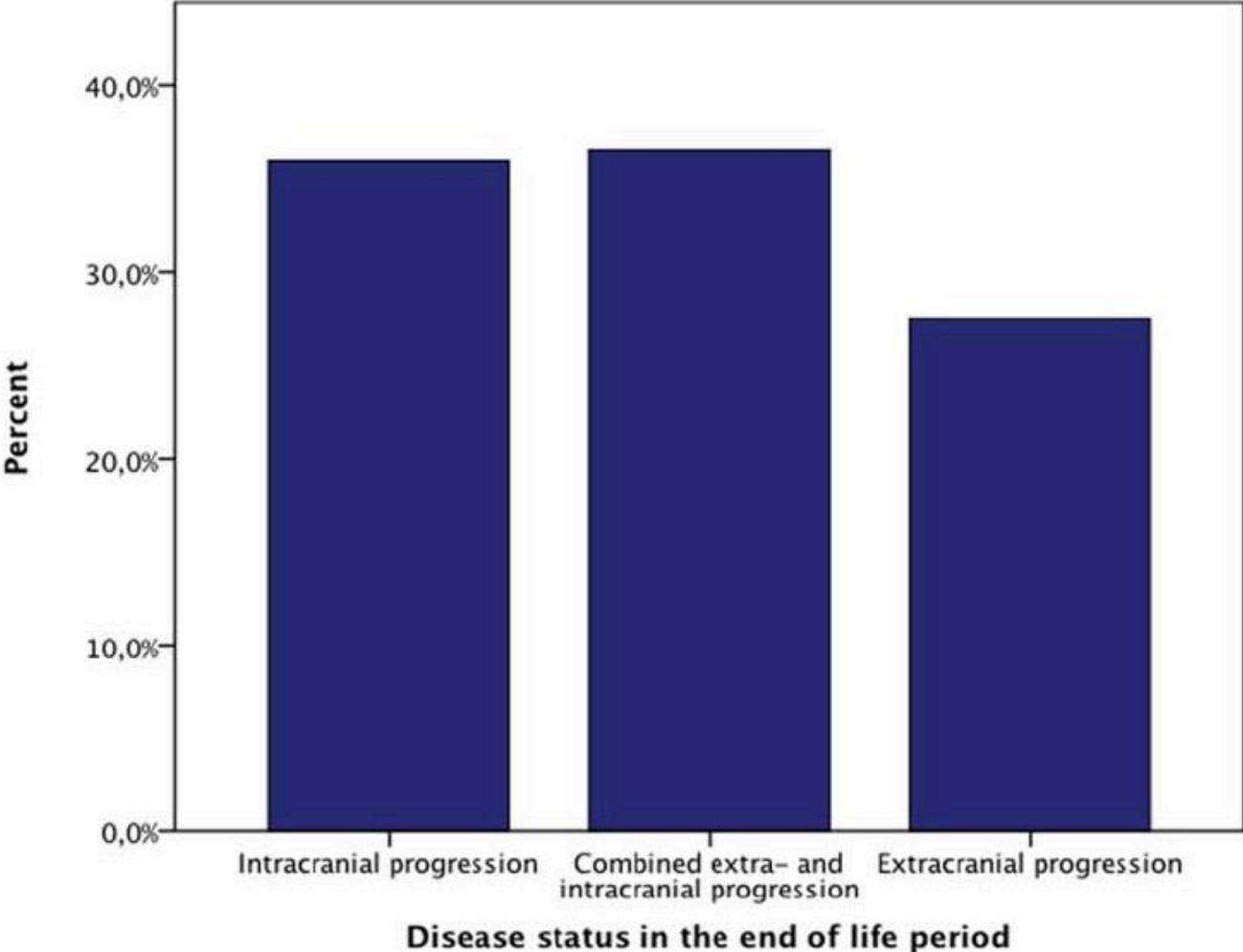
Descriptive statistical analysis of a real life cohort of 2419 patients with brain metastases of solid cancers



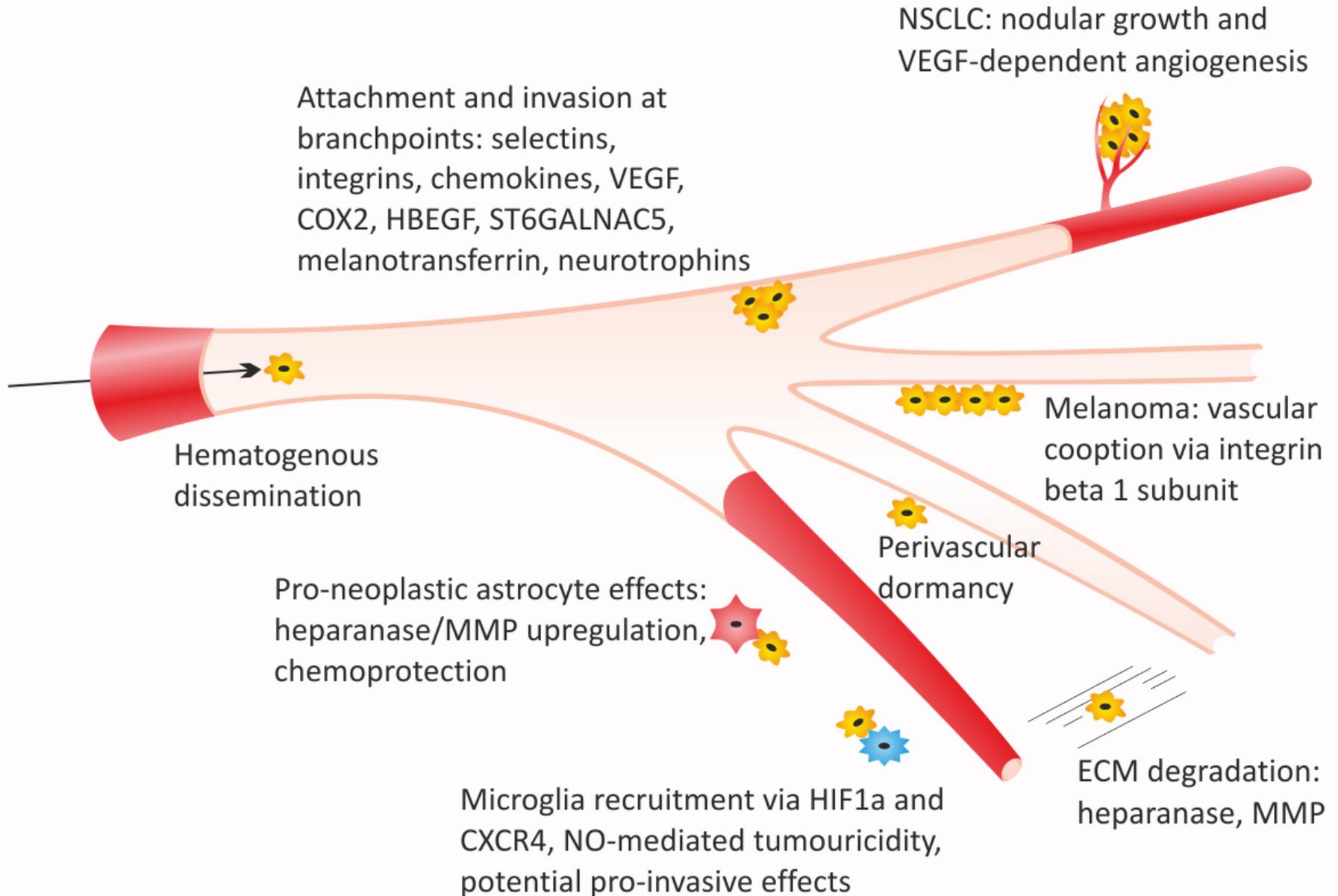
Anna S Berghoff,^{1,2} Sophie Schur,^{1,2} Lisa M Füreder,^{1,2} Brigitte Gatterbauer,^{2,3}
Karin Dieckmann,^{2,4} Georg Widhalm,^{2,3} Johannes Hainfellner,^{2,5}
Christoph C Zielinski,^{1,2} Peter Birner,^{2,6} Rupert Bartsch,^{1,2} Matthias Preusser^{1,2}



What do brain metastasis patients die of?

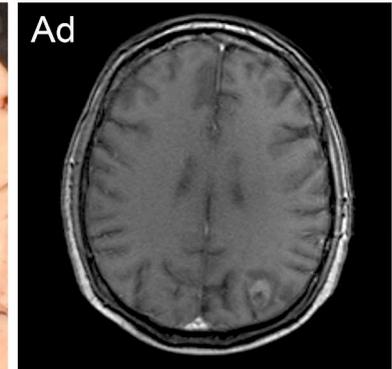
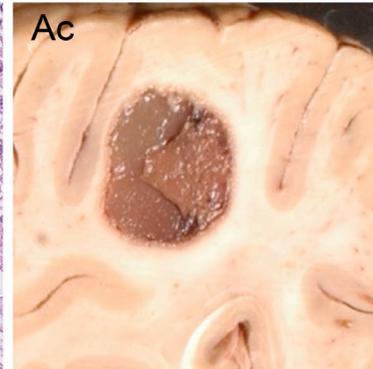
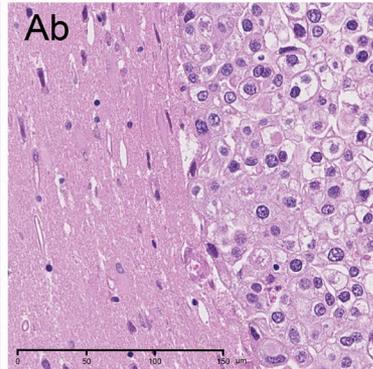
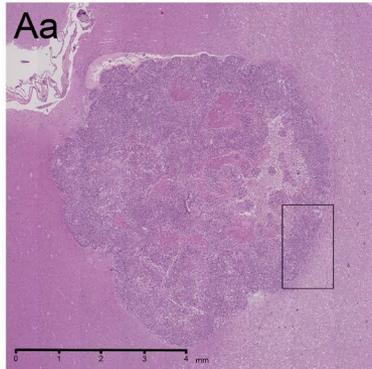


Brain-metastatic cascade

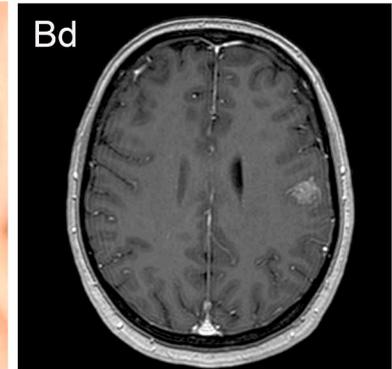
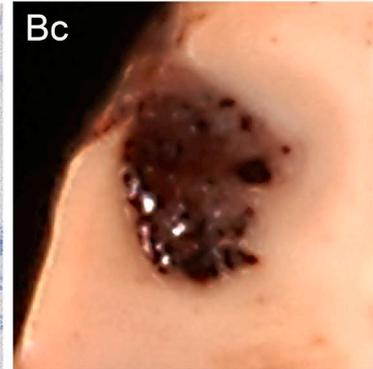
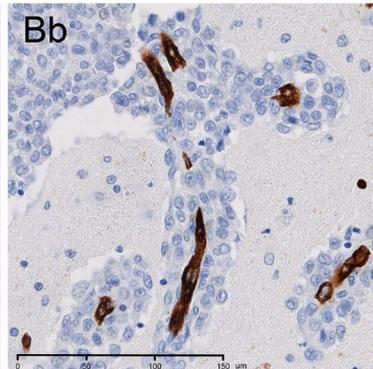
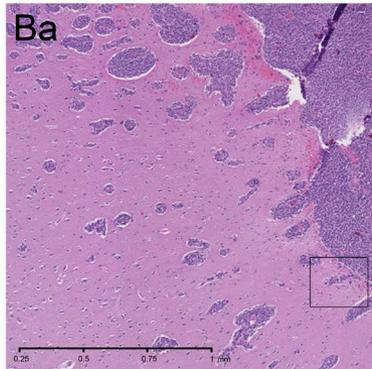


Infiltration patterns in brain metastases

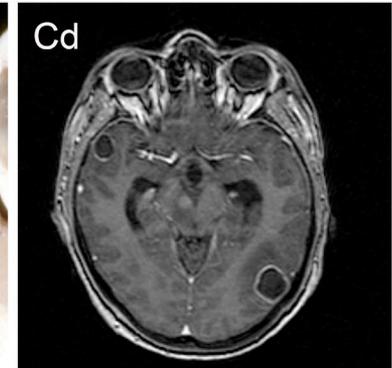
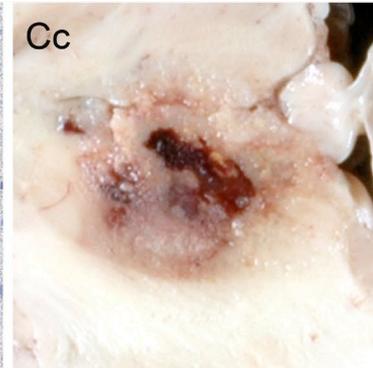
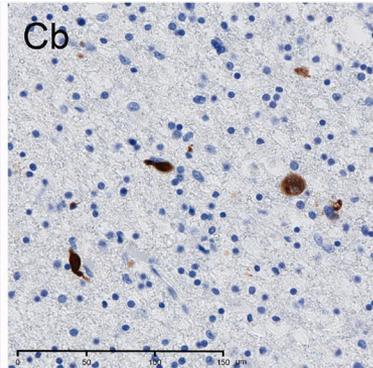
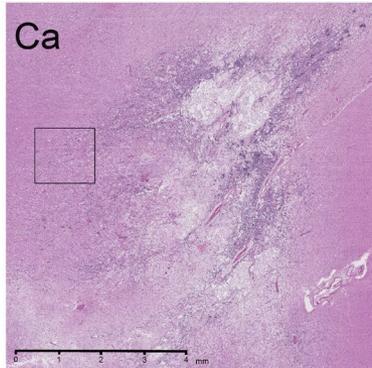
Delineated
51%



Perovascular
18%



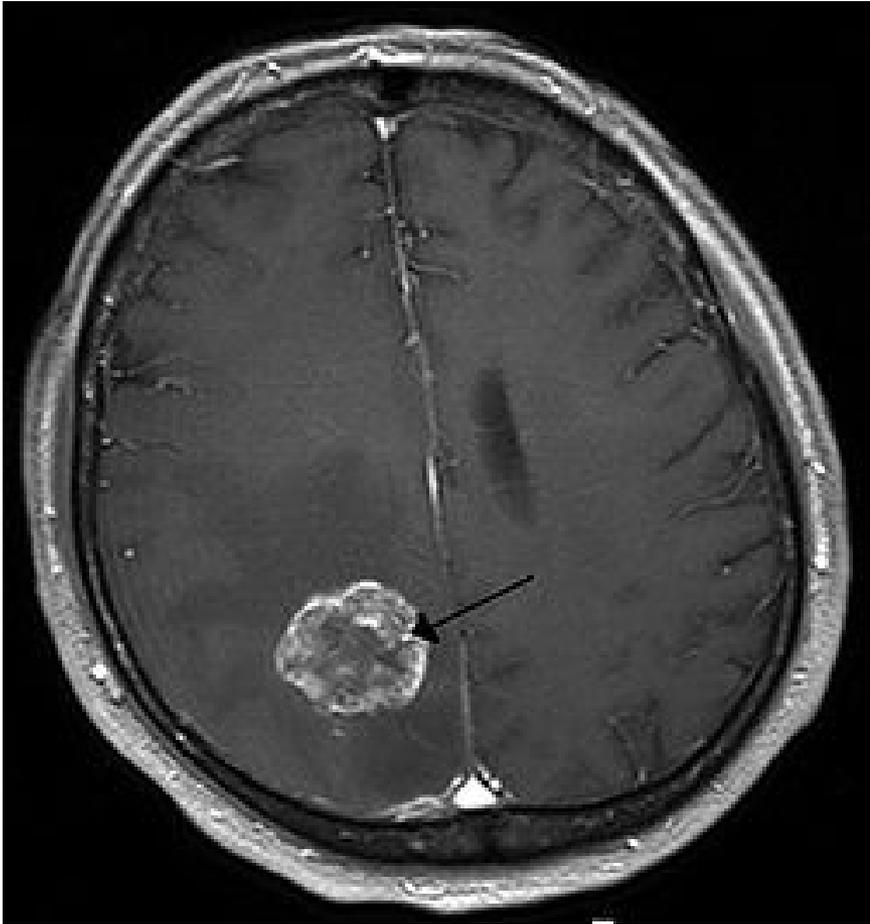
Diffuse
32%



Symptoms and clinical presentation

- High variability in clinical presentation of brain metastases
- Symptoms depend on the localization of the cerebral lesions
 - focal neurological deficits
 - aphasia,
 - epileptic seizures
 - signs of increased pressure (headache, nausea)
 - personality changes
- Brain metastases may be asymptomatic over longer periods of time

Diagnosis



Contrast-enhanced MRI

Treatment approaches

- Neurosurgery
- Radiotherapy
 - Whole brain radiotherapy (WBRT)
 - Stereotactic radiosurgery/radiotherapy (SRS/SRT)
- Systemic therapy
 - Chemotherapy
 - Targeted therapies, e.g. tyrosine kinase inhibitors, antibodies
- Supportive therapy
 - Edema control
 - Anticonvulsants
 - Pain

Neurosurgery

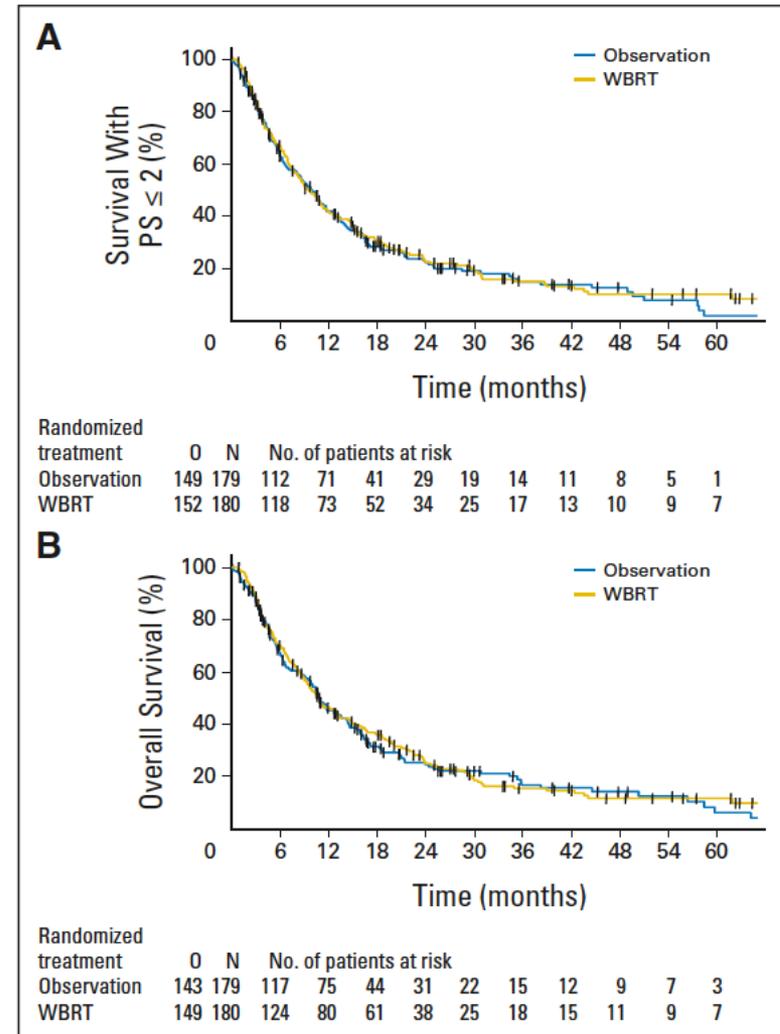
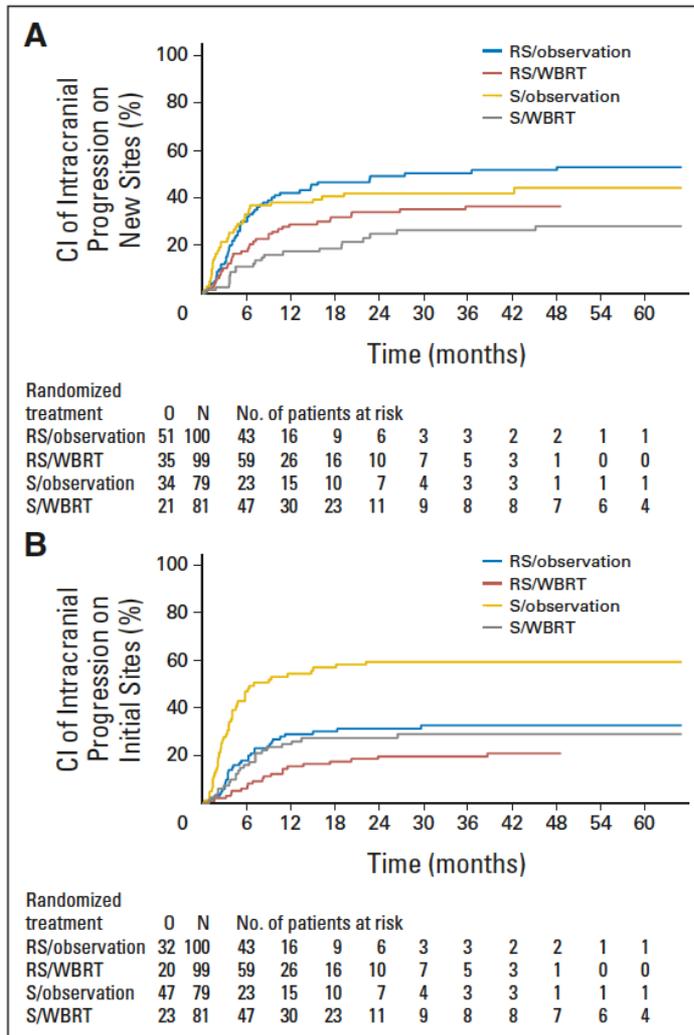
Typical indications:

- Patients with surgically accessible single brain metastases, no or controlled extracranial tumor burden and good performance status
- Acute decompression on patients with significant mass effect from one or more brain metastases
- Patients with an unknown primary tumor to obtain tissue for histopathological and molecular tumor (sub-)typing

Note: unresolved issue of whether or not perform adjuvant irradiation after neurosurgical resection; possible strategies:

- WBRT
- SRS
- Wait and see

Adjuvant WBRT after surgery/radiosurgery



Adjuvant SRS vs WBRT after surgery

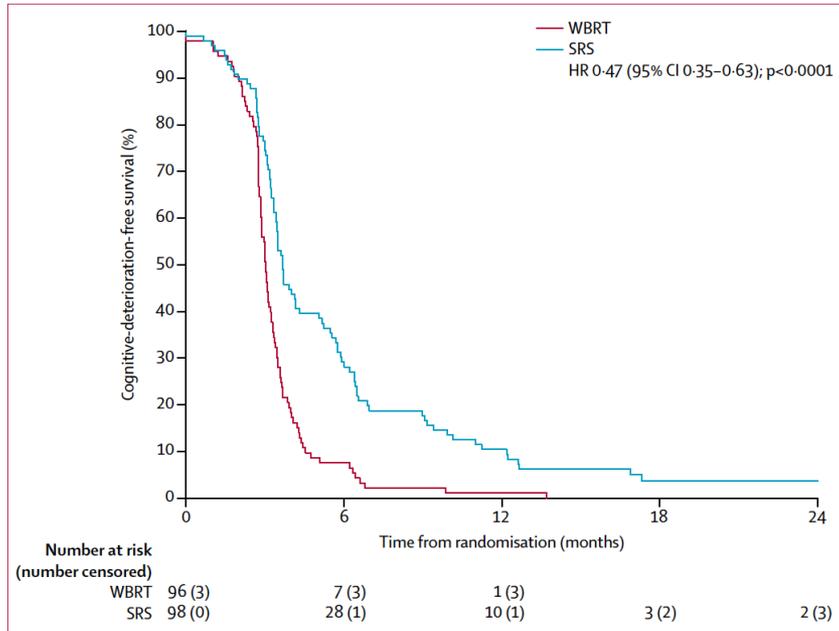


Figure 2: Cognitive-deterioration-free survival
WBRT=whole brain radiotherapy. SRS=stereotactic radiosurgery.

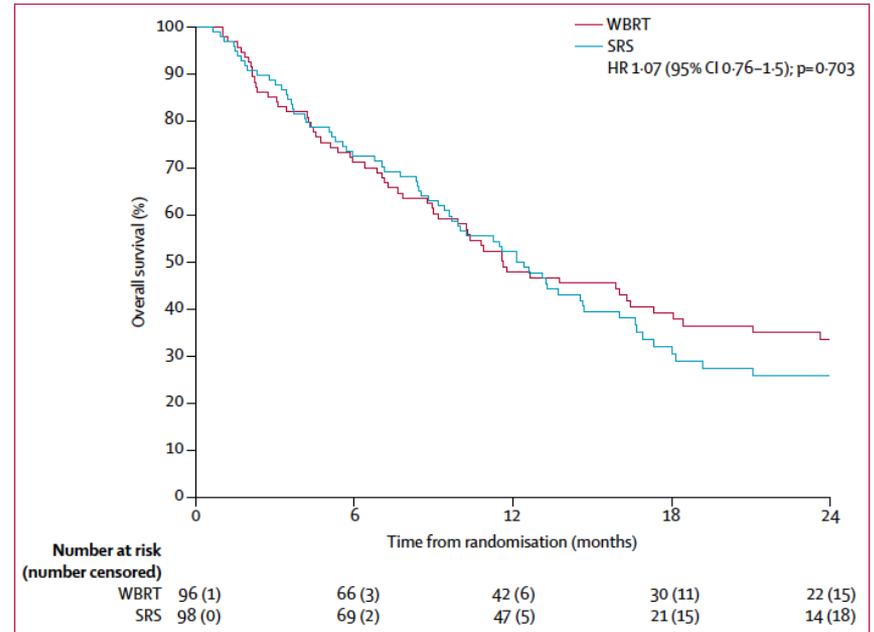
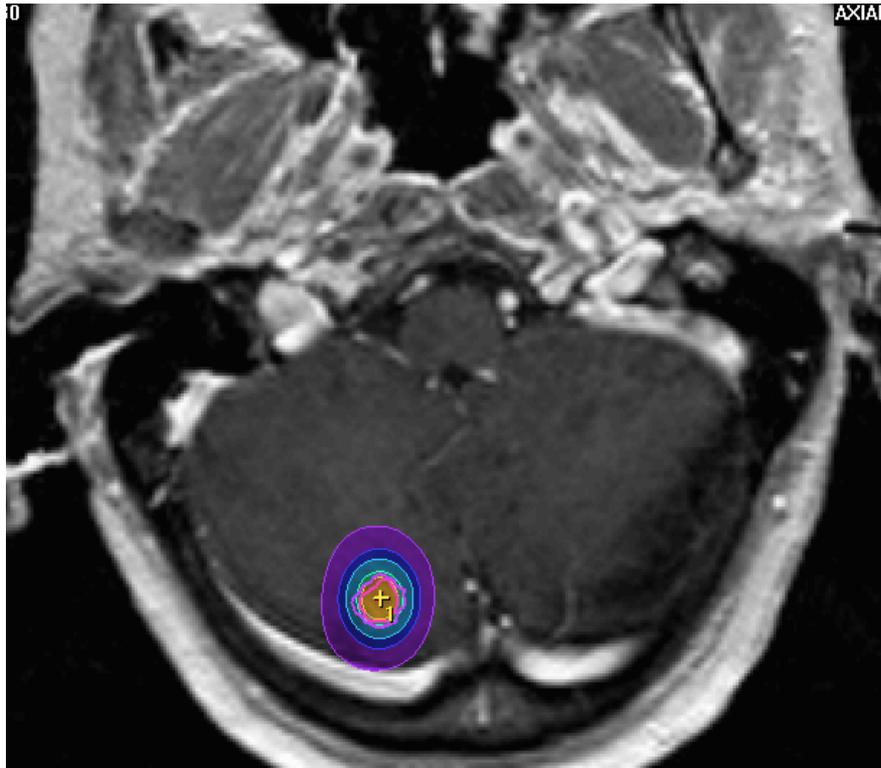


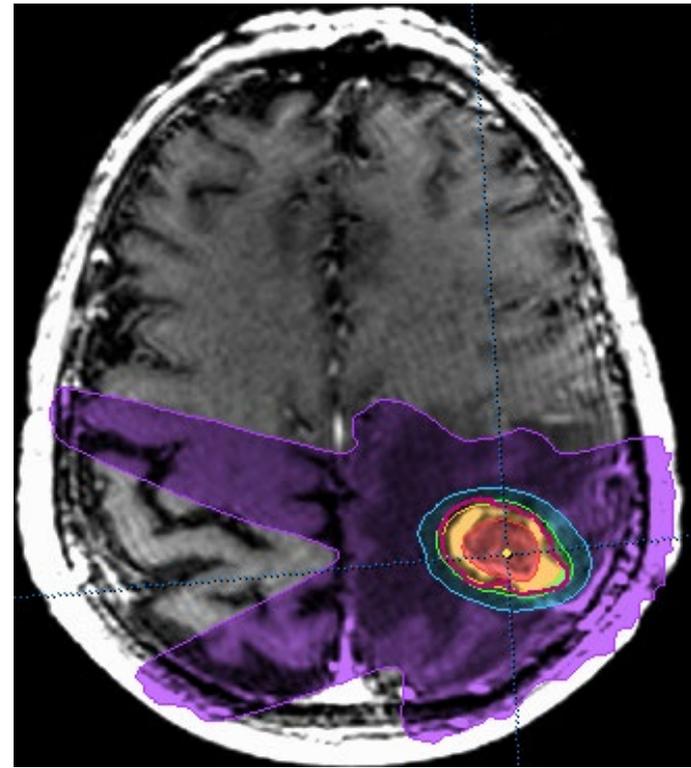
Figure 3: Overall survival
WBRT=whole brain radiotherapy. SRS=stereotactic radiosurgery.

Radiotherapy: SRS

SRS: single-dose high-precision focused radiotherapy, utilizes convergent beams or arcs to irradiate in a single fraction circumscribed lesions with a high dose in the planning target volume (PTV) and a steep dose gradient at the margin.



„Gamma-knife“



Arc technique

Light blue color: high dose area
Purple color: low dose area

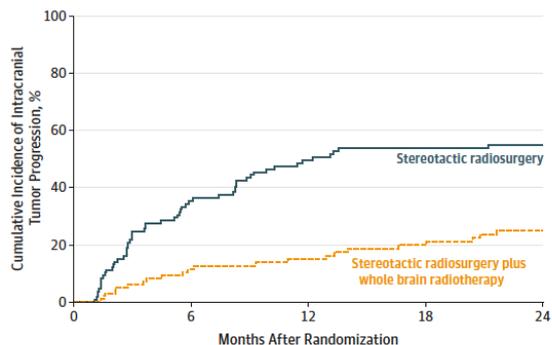
Radiotherapy: SRS/SRT

- Typical indication: small (maximal diameter of up to 3 cm) and of limited number (less than 3 to 4) of brain metastases
- Advantages
 - Better preservation of neurocognitive function due to sparing of non-affected brain areas
 - SRS is delivered in a single fraction in an outpatient setting and may thus be more convenient for many patients in this palliative disease setting
 - Feasible also in lesions not amenable to resection due to sensitive localization in the CNS (e.g. brain stem, eloquent area)
 - Doable in patients that cannot be operated on due to co-morbidities
- Disadvantages
 - SRS/SRT will not be able to treat microscopic tumor manifestations escaping detection by neuroimaging
 - No tumor tissue collection

Note: increasingly, SRS is utilized to treat multiple brain metastases

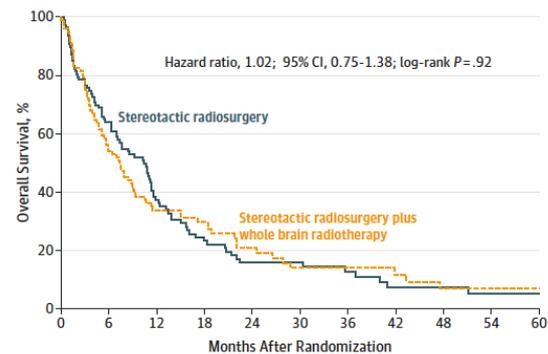
SRS +/- WBRT of 1-3 brain metastases

Figure 2. Cumulative Incidence of Brain Tumor Progression (Local and/or Distant) After Correcting for the Competing Risk of Survival According to Treatment Group



No. at risk	0	6	12	18	24
Stereotactic radiosurgery	111	35	12	5	1
Stereotactic radiosurgery plus whole brain radiotherapy	102	43	24	16	9

Figure 3. Kaplan-Meier Estimates of Overall Survival According to Treatment Group



No. at risk	0	6	12	18	24	30	36	42	48	54	60
Stereotactic radiosurgery	111	64	35	19	13	10	7	4	4	2	2
Stereotactic radiosurgery plus whole brain radiotherapy	102	50	28	22	13	8	8	5	3	1	1

SRS of multiple brain metastases

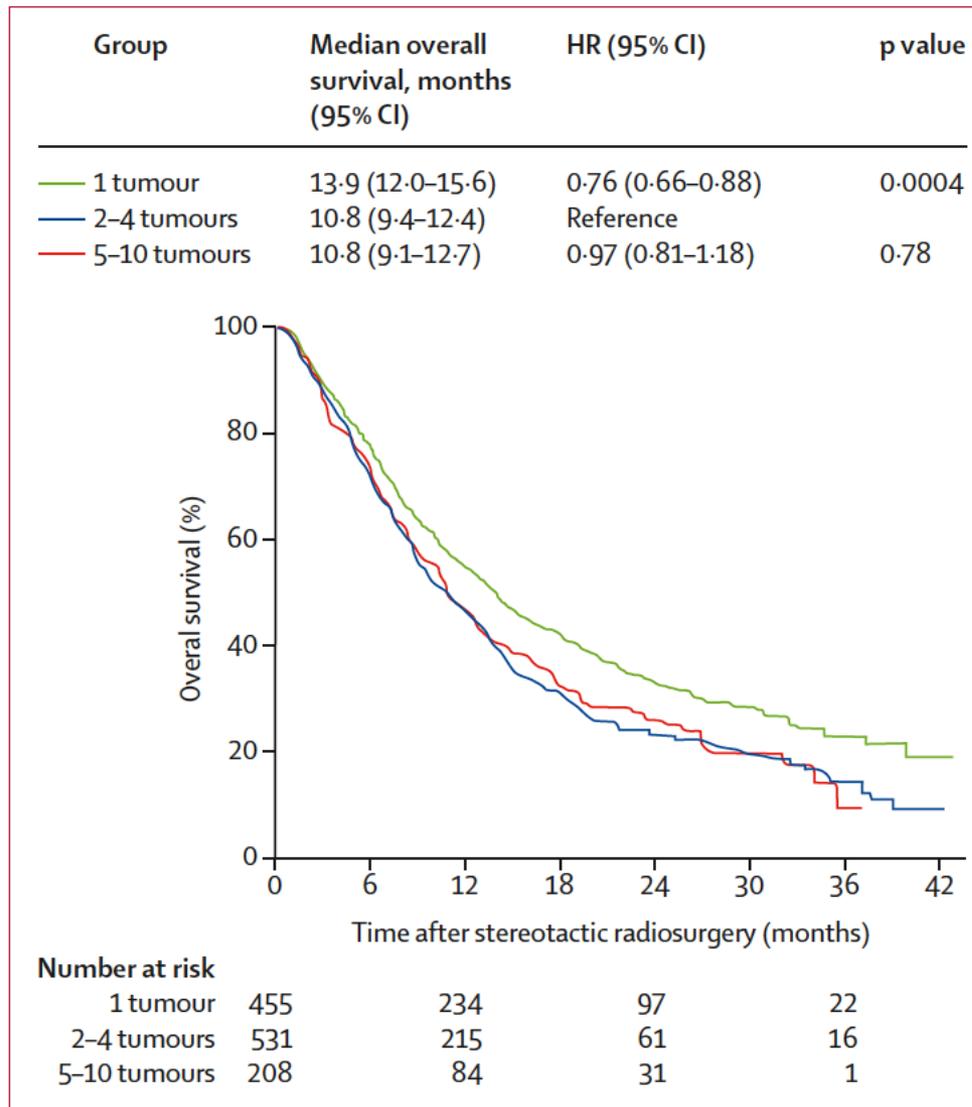


Figure: Kaplan-Meier curves of overall survival
HR=hazard ratio.

Radiotherapy: WBRT

- Typical indication: multiple brain metastases
- Significant risk for neurocognitive decline due to damages to the brain parenchyma or induction of intracerebral vascular changes
 - Hippocampal-sparing radiotherapy
 - Memantine and other drugs may help to protect neurocognition
- Hair-sparing WBRT
- Prophylactic cranial irradiation (PCI)
 - Recommended for SCLC patients with extensive disease achieving a complete or partial response to first-line chemotherapy and for patients with localized disease with stable disease

Prophylactic cranial irradiation (PCI) in stage III NSCLC

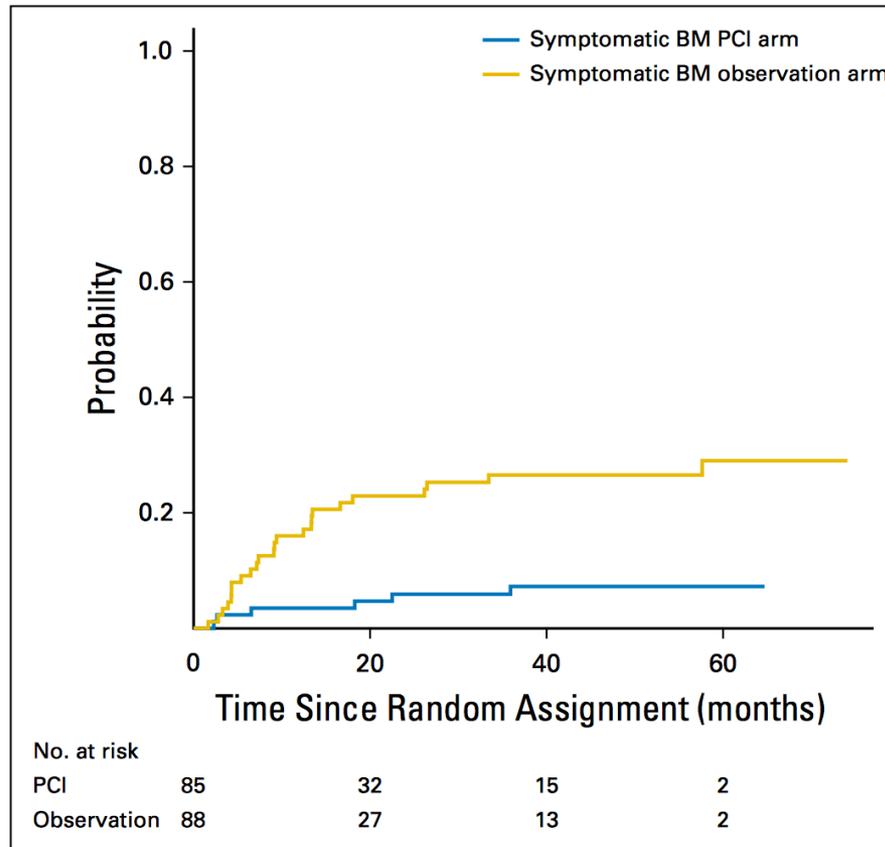


Fig 2. Cumulative incidence of symptomatic brain metastases (BM) by arm (solid lines) with death as a competing risk. Prophylactic cranial irradiation (PCI) increased the time to symptomatic BM (hazard ratio, 0.23 [95% CI, 0.09 to 0.56]; $P = .0012$). PCI, prophylactic cranial irradiation.

Hippocampal avoidance WBRT

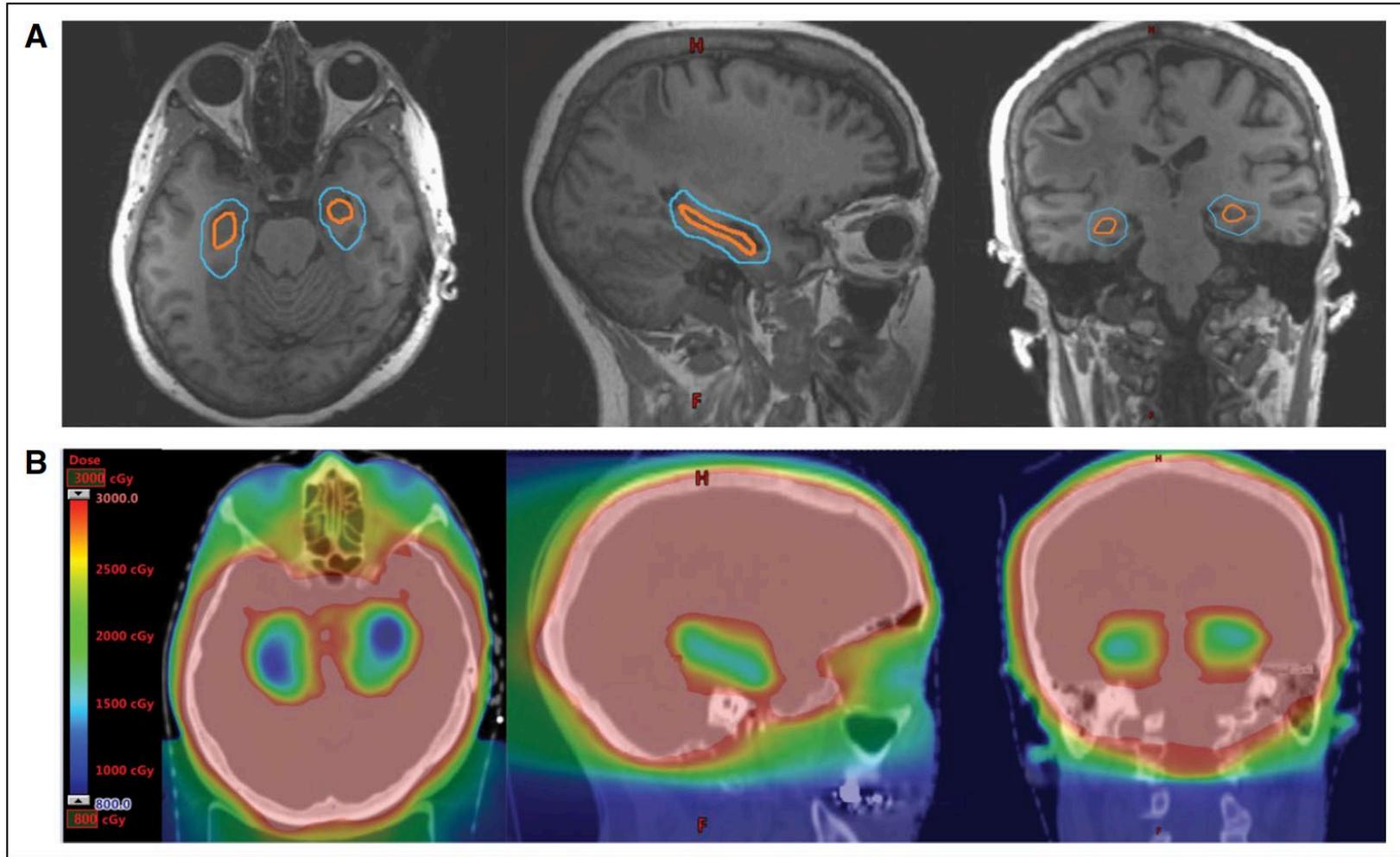


Fig 2. (A) The hippocampal avoidance region (blue) is generated by expanding the hippocampal contour (orange) by 5 mm. (B) Color wash dose distributions for hippocampal-avoidance whole-brain radiotherapy are shown on representative axial, sagittal, and coronal images.

NMDA antagonist memantine and WBRT

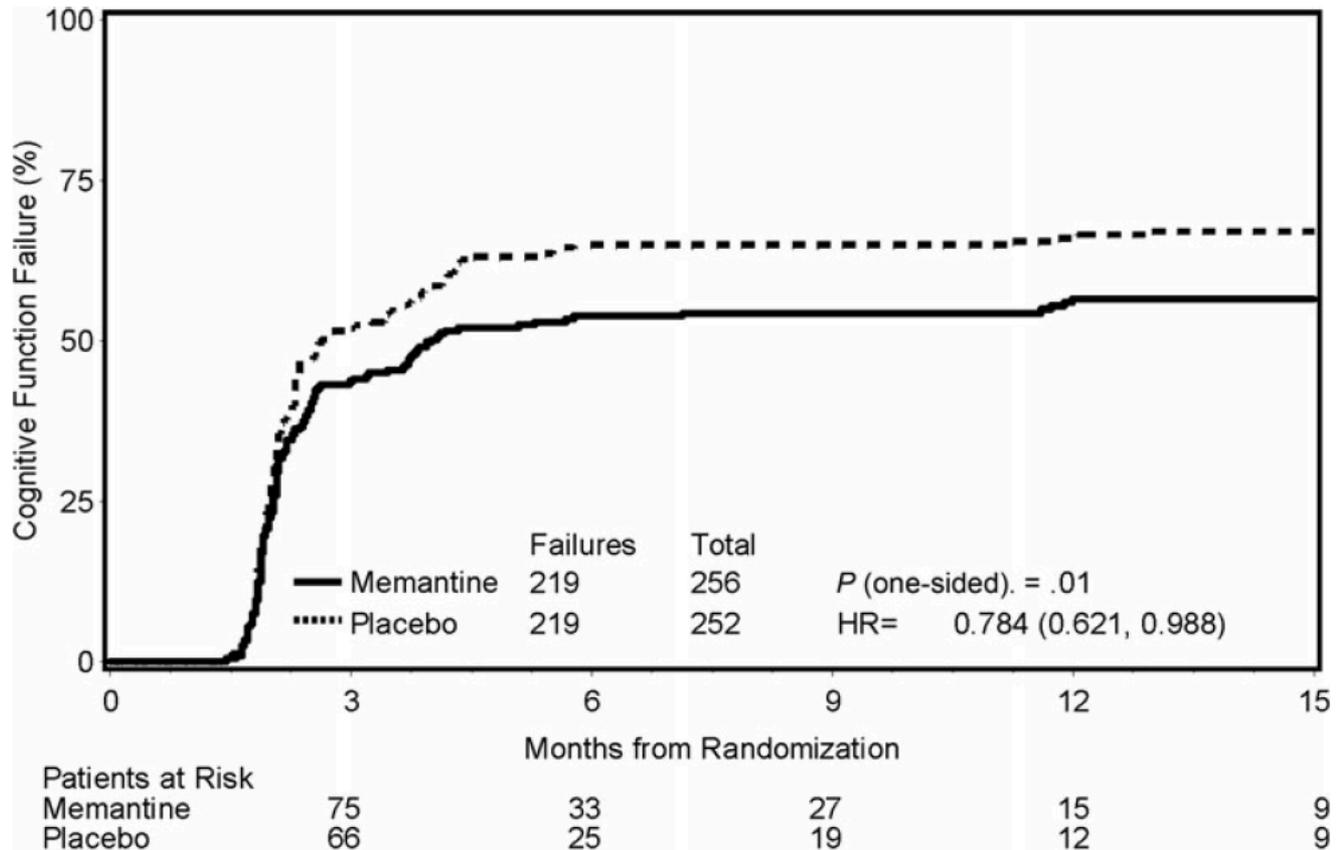
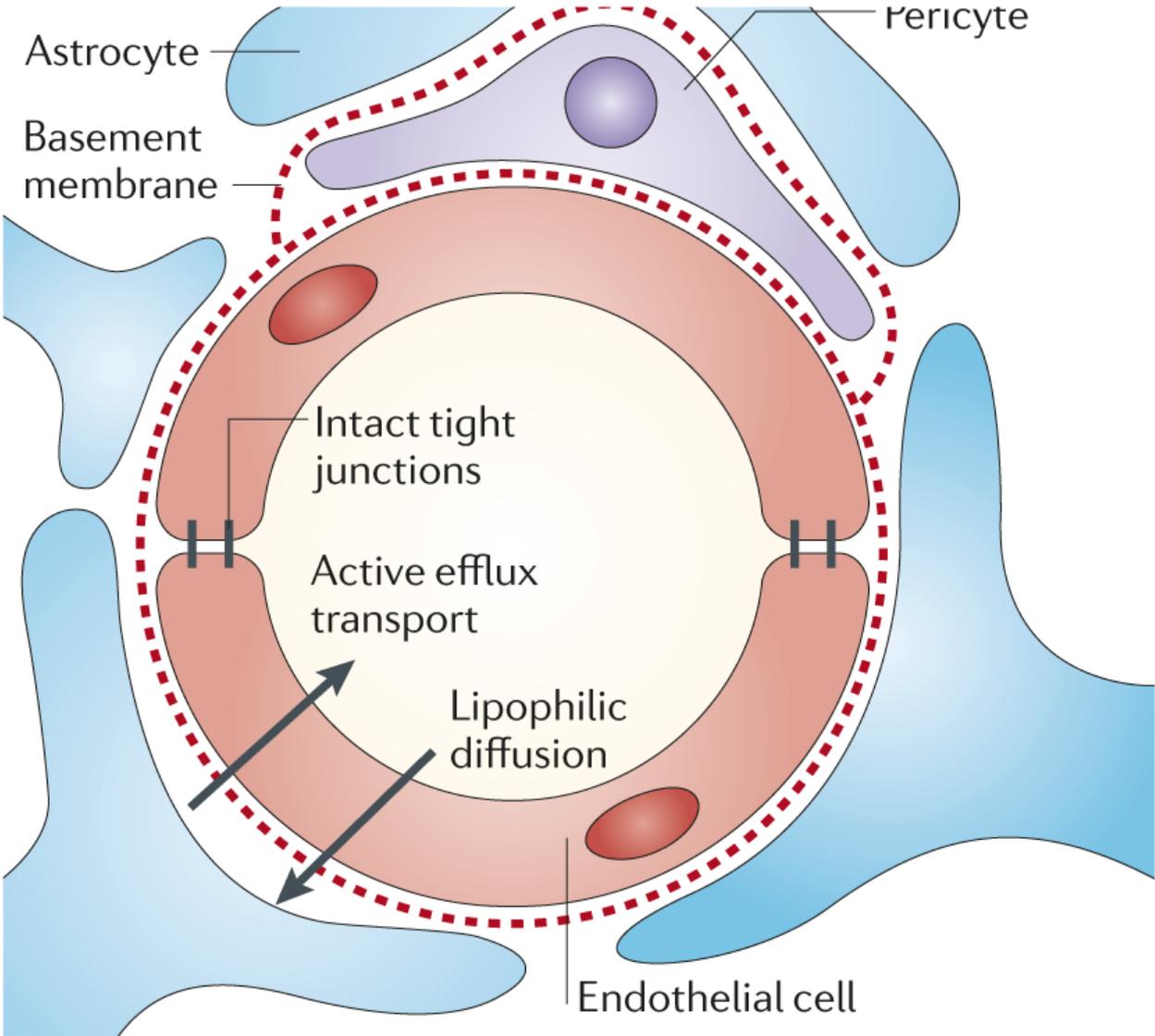


Fig. 2. Cumulative incidence of cognitive function failure according to treatment arm.

CYTOTOXIC CHEMOTHERAPY





Zytostatikum	Liquorpenetration
Nitrosoureas (ACNU, BCNU; CCNU, Fotemustine)	++
Procarbacin	++
Thiotepa	+
Dacarbacin	(+)
Temozolomide	++
Cyclophosphamid, Ifosfamid	+/-
Cytosinarabinosid	++
Methotrexat	-/+
5-Fluorouracil	(++)
Anthracyclins	-
Liposomal doxorubicine	++
VM26	-/+
Etoposid	-/+
Vincaalkaloids, Taxanes	-
Topotecan	++
Cisplatin, Carboplatin	-
Cytokines	-

++ : Liquorkonzentration 20-30% der Sermukonzentration

+ : Liquorkonzentration 10% der Sermukonzentration

- : Liquorkonzentration <5% der Sermukonzentration

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

10 Included

WBRT vs. WBRT + chemotherapy.....	5
Chemotherapy vs. chemotherapy + WBRT.....	3
WBRT + concurrent chemotherapy vs. WBRT + delayed chemotherapy.....	1
Upfront chemotherapy + WBRT vs. upfront WBRT + chemotherapy.....	1

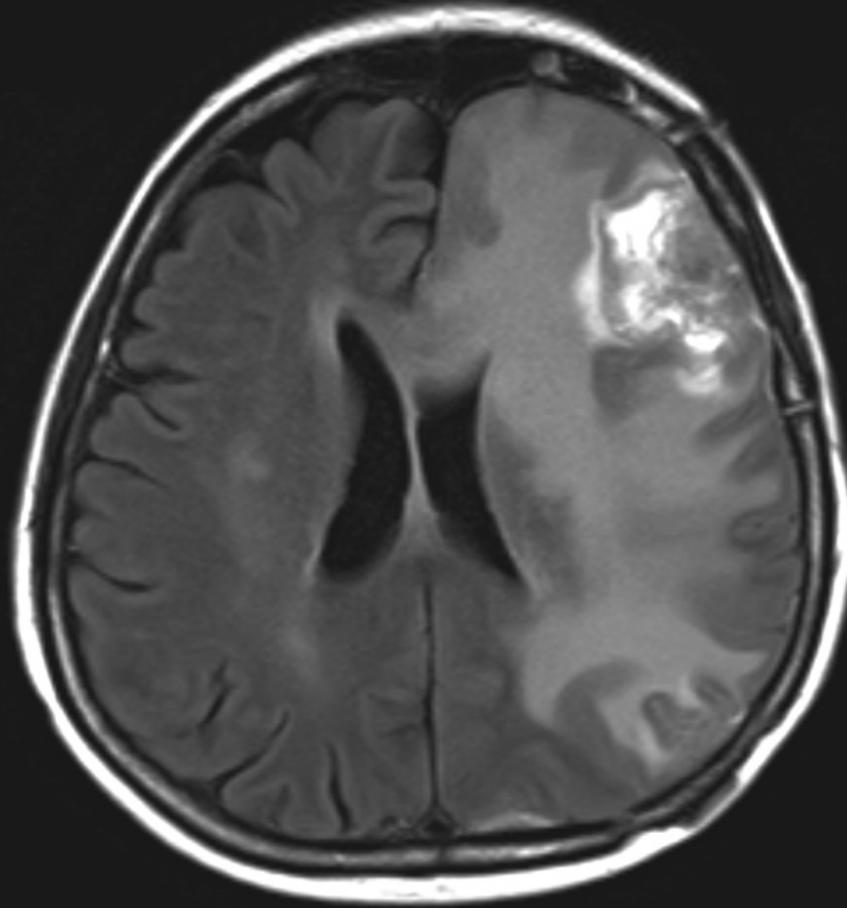
1. The lack of clear and robust survival benefit with the addition of chemotherapy to WBRT.
2. Enhanced response rates, specifically in NSCLC with the addition of chemotherapy to WBRT.
3. In terms of secondary endpoints such as time to neurologic progression, steroid dose, etc., the data and results are mixed and do not permit robust conclusions.
4. In at least one trial, time to progression was improved by the addition of WBRT to chemotherapy as compared to chemotherapy alone; however, the evidence to corroborate this study is sparse.
5. A single trial provides evidence that outcome is similar whether WBRT is delivered upfront with chemotherapy or delayed by up to 2 cycles, but the data remains too limited to support definitive recommendations for the delay of radiation therapy, especially given the lack of any known survival advantage with chemotherapy.
6. Similarly, the sequencing question (does it matter if chemotherapy precedes WBRT or vice versa?) has been inadequately addressed and the data are too sparse to make definitive conclusions.

Are there druggable targets in brain mets?



Brain edema

16



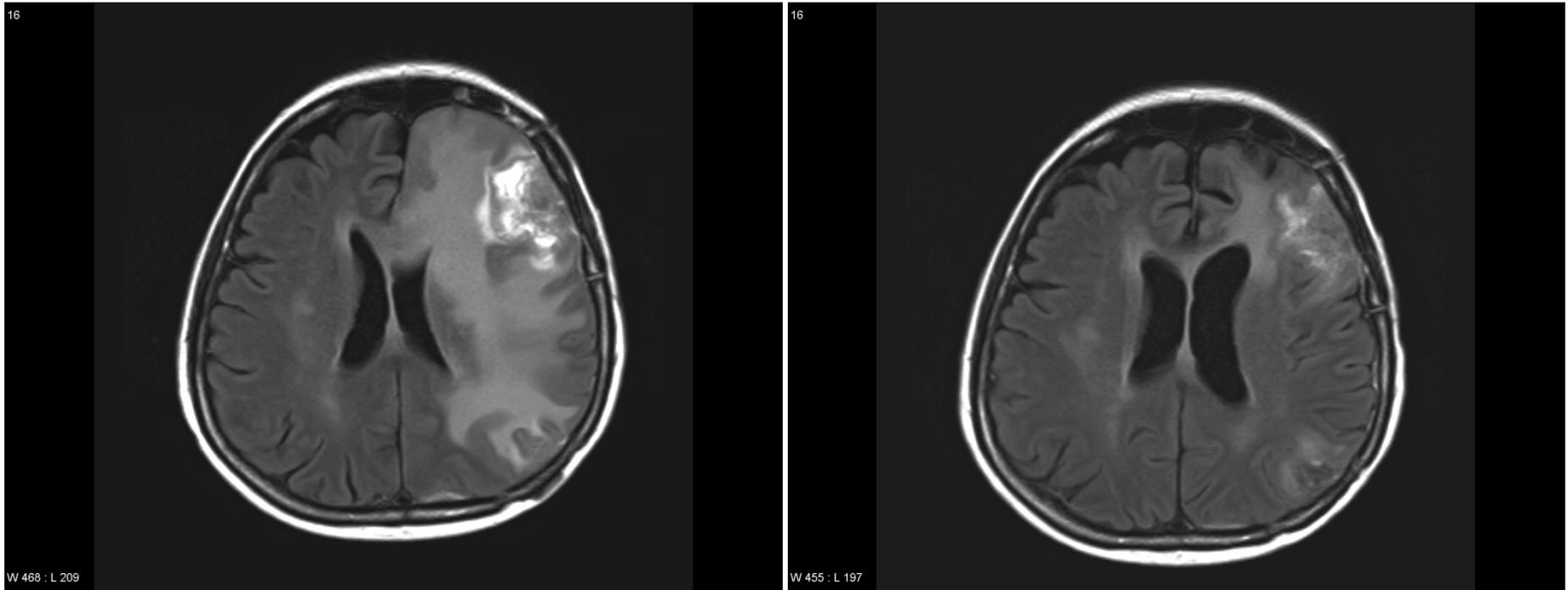
W 468 : L 209

Anti-oedema therapy

- Results from leakage of plasma into the tissue through disrupted BBB
- Detectable on T2-weighted and FLAIR MRI images
- Increased intracranial pressure with headache, vertigo, nausea/vomiting
- May lead to life-threatening brainstem compression and herniation
- Drug of choice: Dexamethasone
 - Initial daily dose usually 12-16 mg
 - Steroid dose should be rapidly reduced and tapered to individual need (“as much as needed, as little as possible”)
 - Withhold corticosteroid in asymptomatic patients and when lymphoma or inflammatory lesion can not be ruled out
- Dexamethasone may be combined with osmotic agents such as mannitol or glycerol
- Obstructive hydrocephalus may be treated with CSF shunt
- Bevacizumab may reduce brain oedema and is associated with decreased corticosteroid need

Bevacizumab for brain edema and radionecrosis

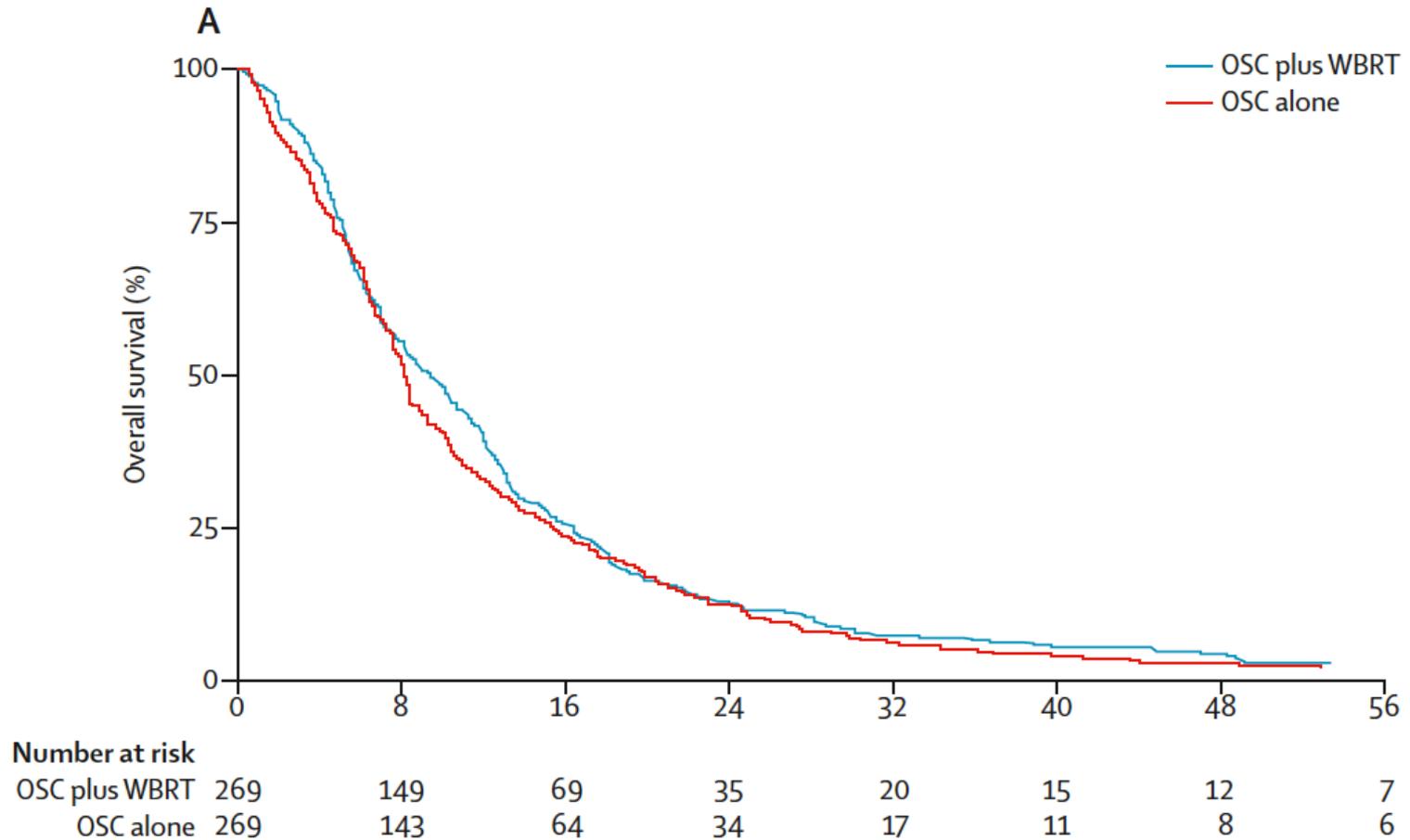
FLAIR



01.12.2012
Before bevacizumab

01.03.2013
After 4x bevacizumab

WBRT vs. Dexamethasone in NSCLC (QUARTZ trial)



B

Conclusions

- Brain metastases are common and a clinical challenge
- Radiotherapy/SRS and surgery are established treatment options
- Brain mets are a promising target for prophylactic and therapeutic intervention based on molecular insights, some mechanisms and drug targets identified and treatments emerging
- Many open questions that require specifically designed trials (e.g. sequencing/combination strategies)

Thank you!

