



Radiosurgery in the management of brain metastases (2)

Michael Brada
IAEA NTC Bratislava
21 March 2018

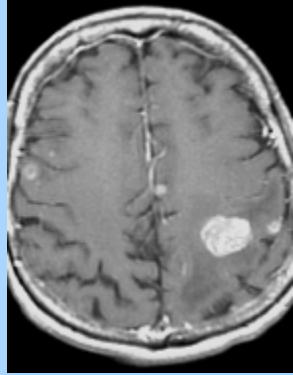
- **Radiotherapy technologies**
- **Context and endpoints**
- **Clinical issues - evidence base**

Radiotherapy in the treatment of brain metastases

- Radiotherapy technologies
- Context and endpoints
- Clinical issues - evidence base

Radiotherapy in the treatment of brain metastases

Context



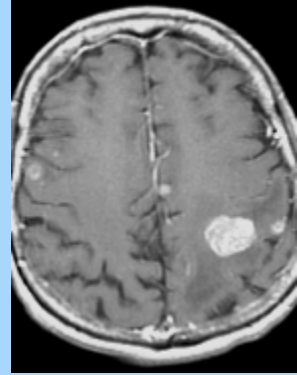
prognosis

primary tumour type

timing in the course of disease

Oncological management options

Context



prognosis

primary tumour type

timing in the course of disease

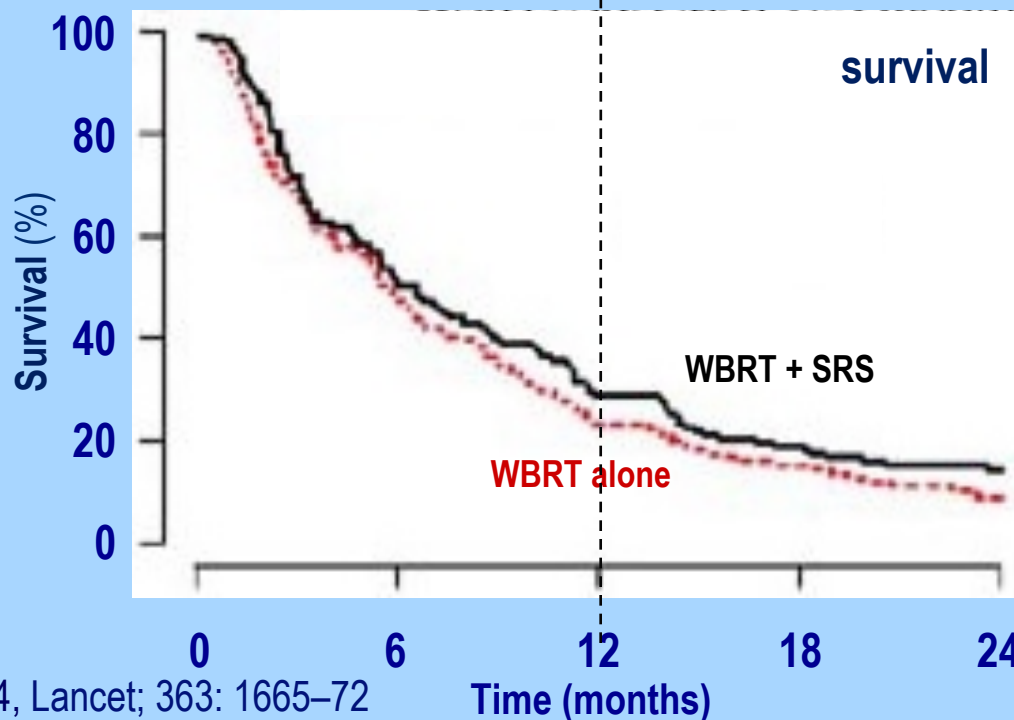
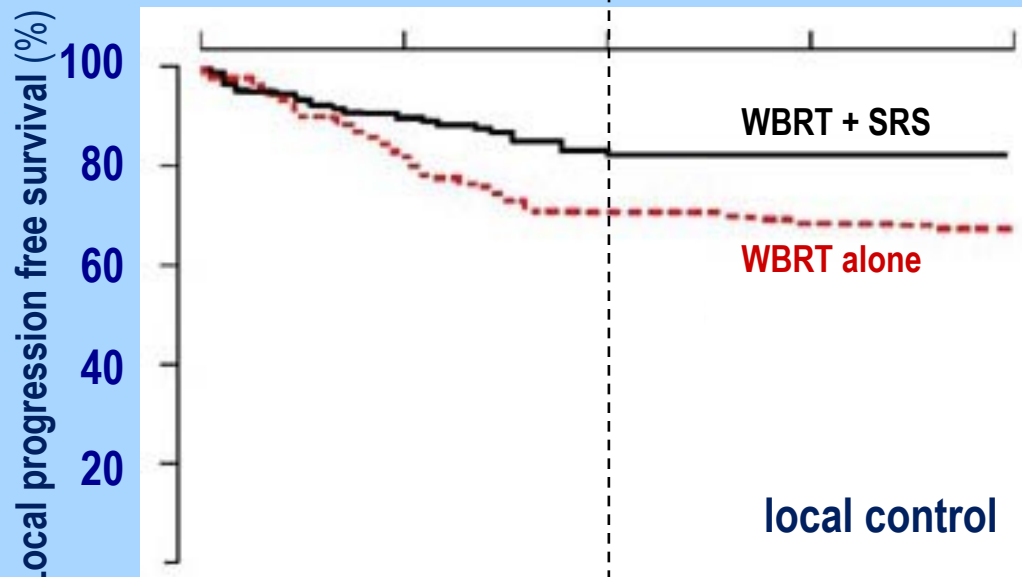
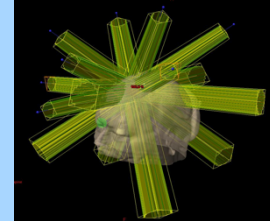
Endpoints

survival

quality of life

Oncological management options

WBRT +/- radiosurgery for brain metastases



RTOG 9508

Andrews et al 2004, Lancet; 363: 1665-72

WBRT whole brain RT
SRS stereotactic
radiosurgery

- Radiotherapy technologies
- Context and endpoints
- **Clinical issues - evidence base**

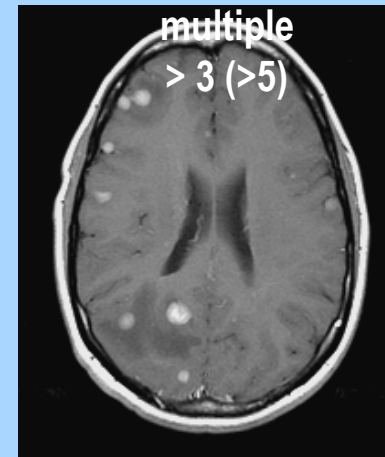
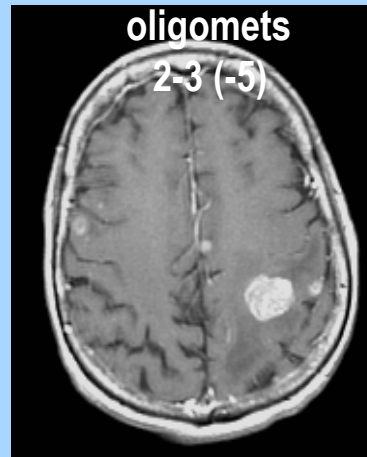
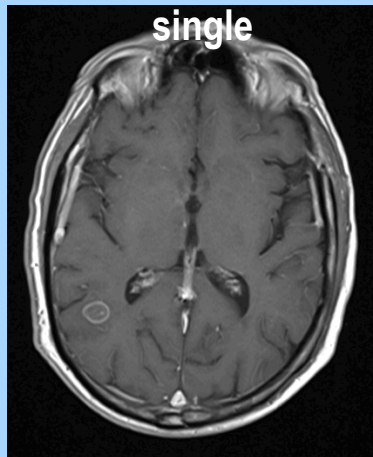
Radiotherapy in the treatment of brain metastases

radiotherapy options

whole brain radiotherapy

partial brain radiotherapy

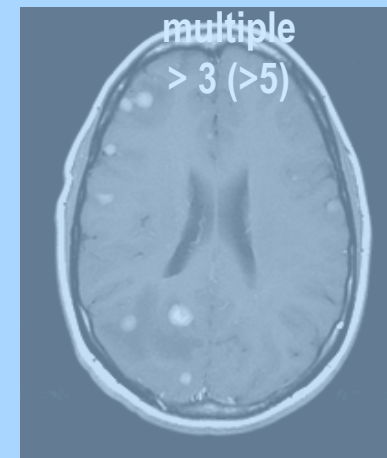
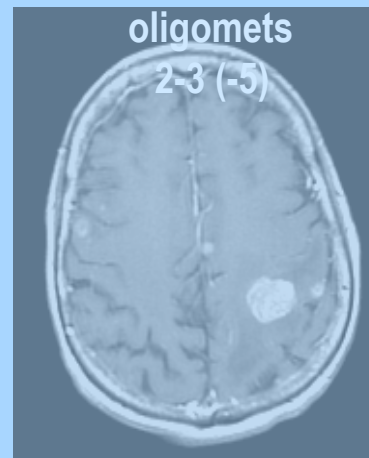
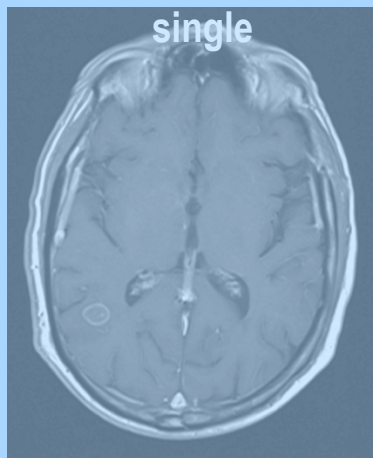
focal radiotherapy & radiosurgery



Evidence base for radiotherapy in the treatment of brain metastases

Matrix - radiotherapy options

No. met's	prognosis	1 ^o tumour	timing
single			
oligomets			
multiple			



Evidence base for radiotherapy in the treatment of brain metastases

Radisurgery plus whole brain radiotherapy compared to whole brain radiotherapy alone for brain metastases

prolongs survival in patients with oligometastases

prolongs time to functional deterioration in patients with oligometastases

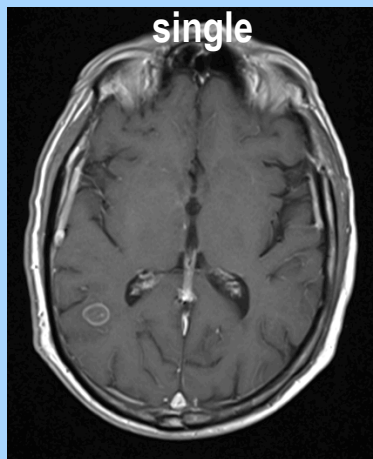
prolongs survival in patients with single brain metastases

none of these

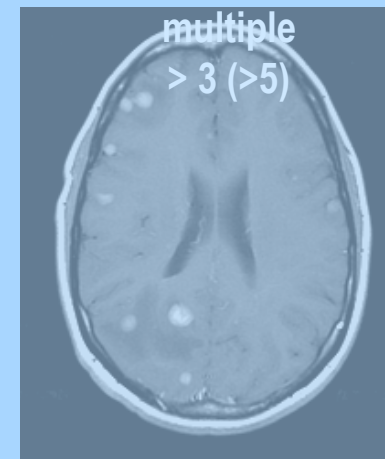
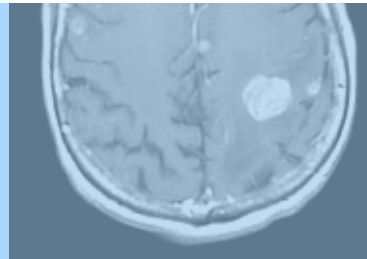
all of these

Matrix - radiotherapy options

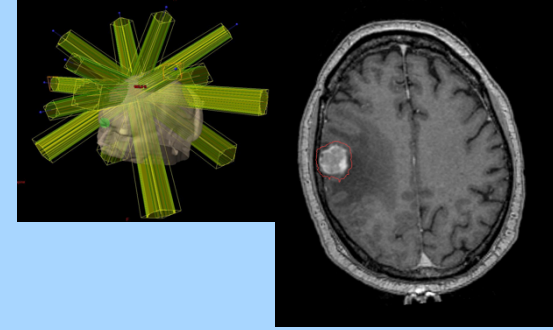
No. met's	prognosis	1 ^o tumour	timing
single	good	any	
oligomet's			
multiple			



surgery
radiosurgery



Evidence base for radiotherapy in the treatment of brain metastases



1 - 3 brain metastases
oligometastases

randomise

**whole brain radiotherapy
& radiosurgery (SRS)**

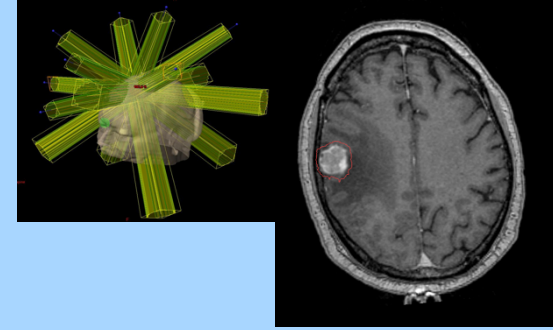
167 patients

**whole brain radiotherapy
(WBRT)**

164 patients

331 patients

Radiosurgery for “solitary” brain metastases



1 brain metastasis

randomise

whole brain radiotherapy
& radiosurgery (SRS)

92 patients

whole brain radiotherapy
(WBRT)

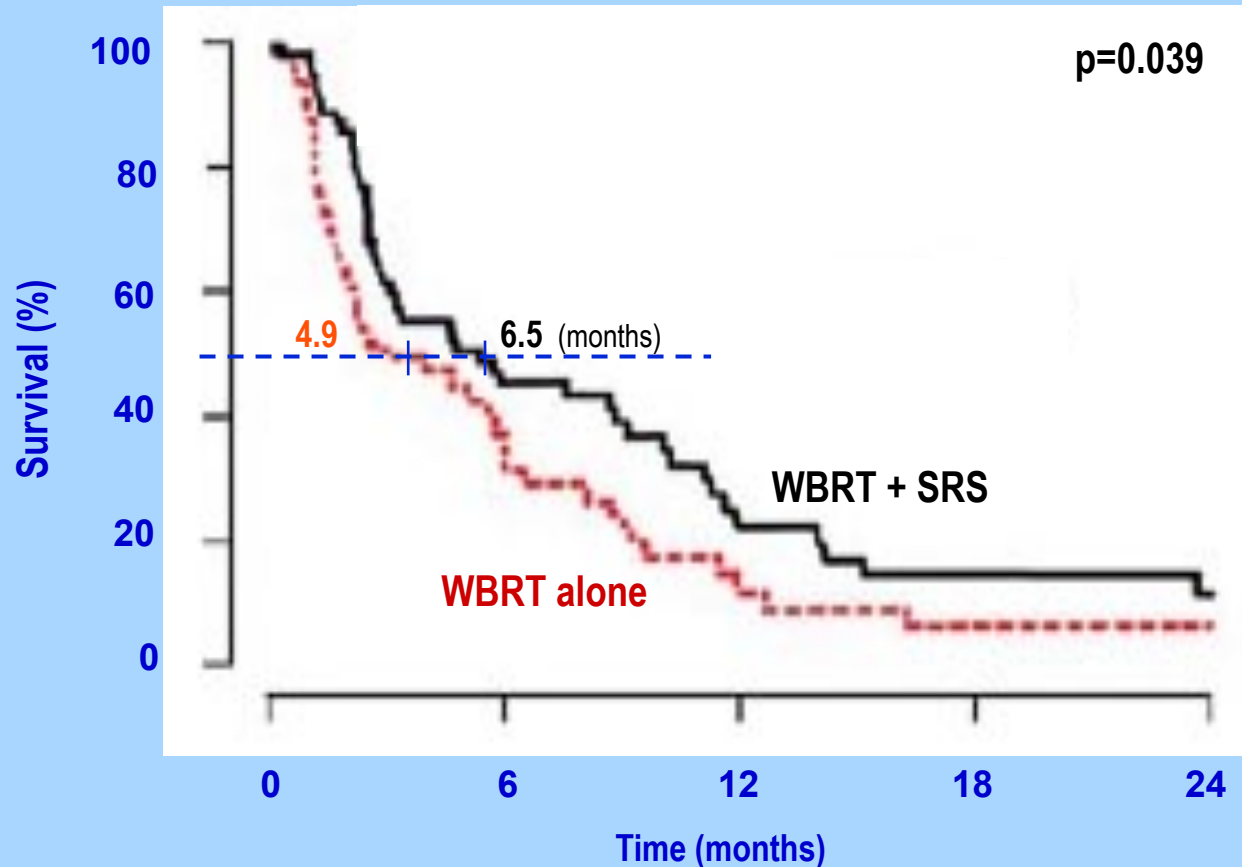
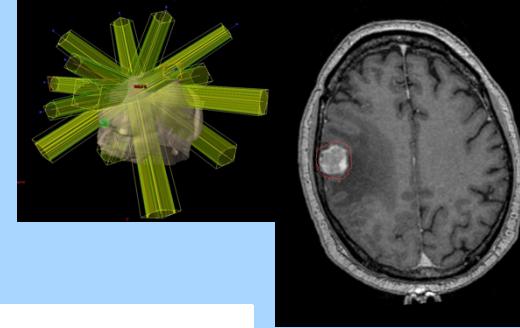
94 patients

186 patients

Radiosurgery for solitary brain metastases

RTOG trial 9508

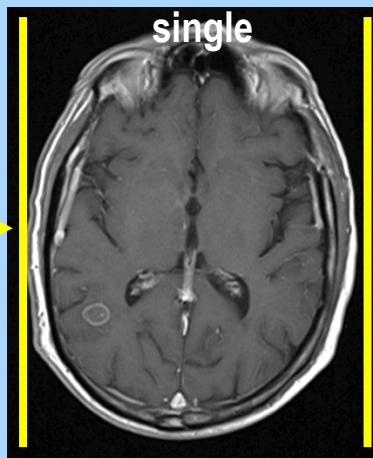
survival – single brain metastases



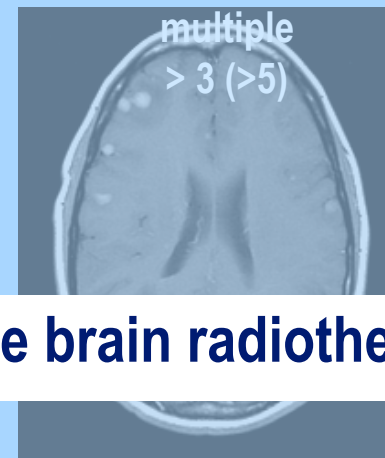
Radiosurgery for solitary brain metastases

Matrix - radiotherapy options

No. met's	prognosis	1 ^o tumour	timing
single	good	any	
oligomet's			
multiple			



surgery
radiosurgery



additional whole brain radiotherapy ?

Evidence base for radiotherapy in the treatment of brain metastases

Whole brain radiotherapy after radiosurgery is important because it

prolongs survival

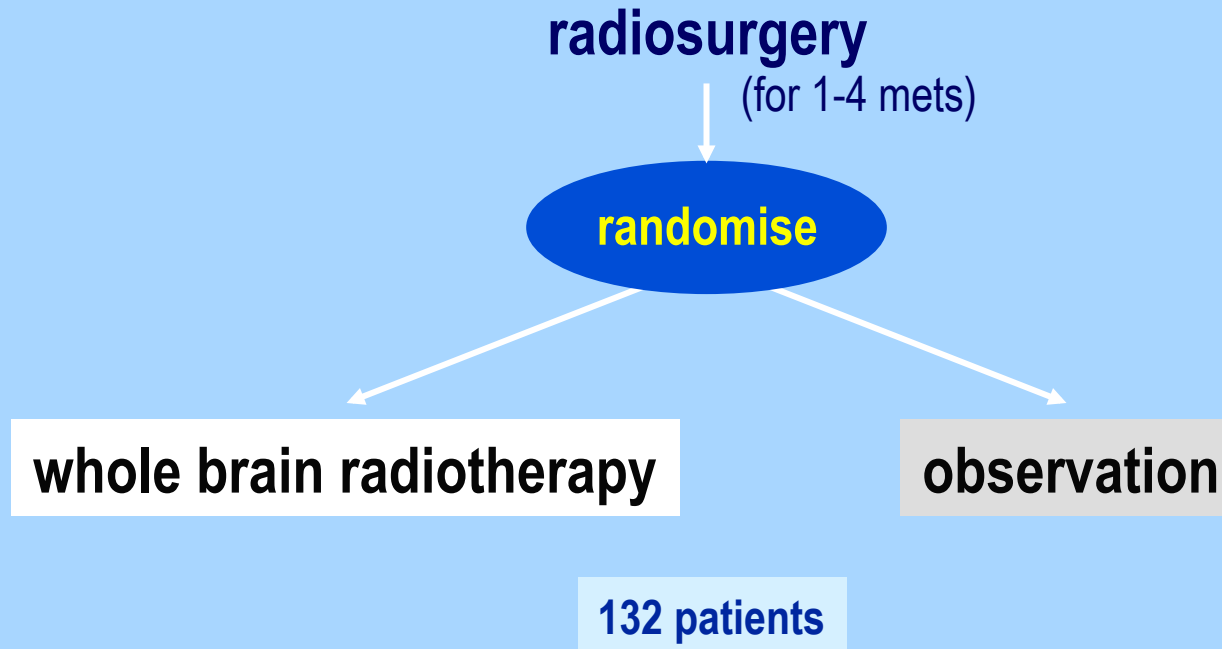
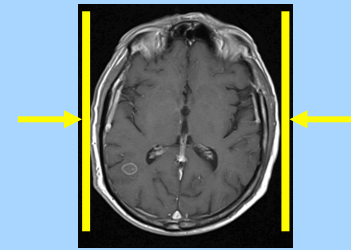
prolongs time to
functional deterioration

prolongs intracranial
tumour control

none of these

all of these

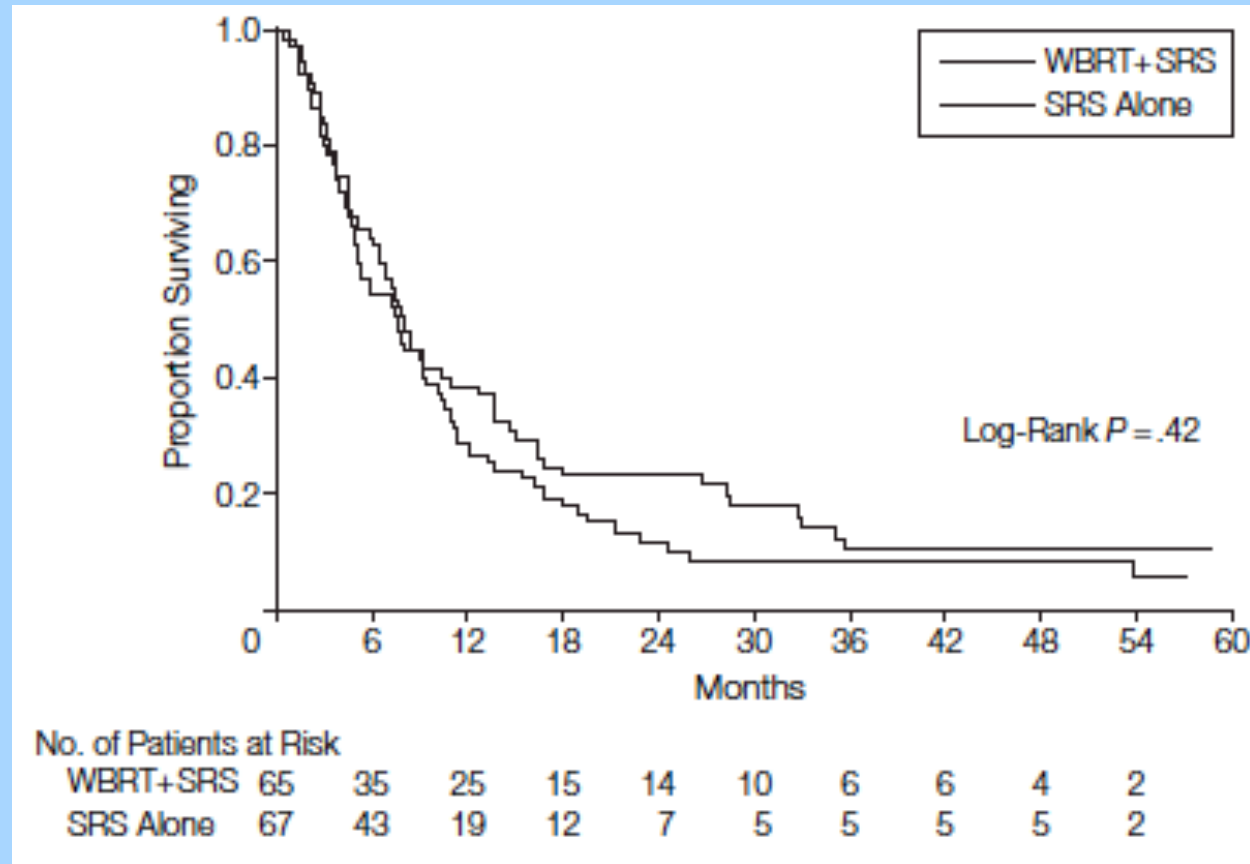
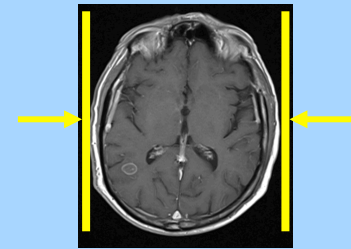
Japanese Radiation Oncology Study Group (JROSG 99-1)



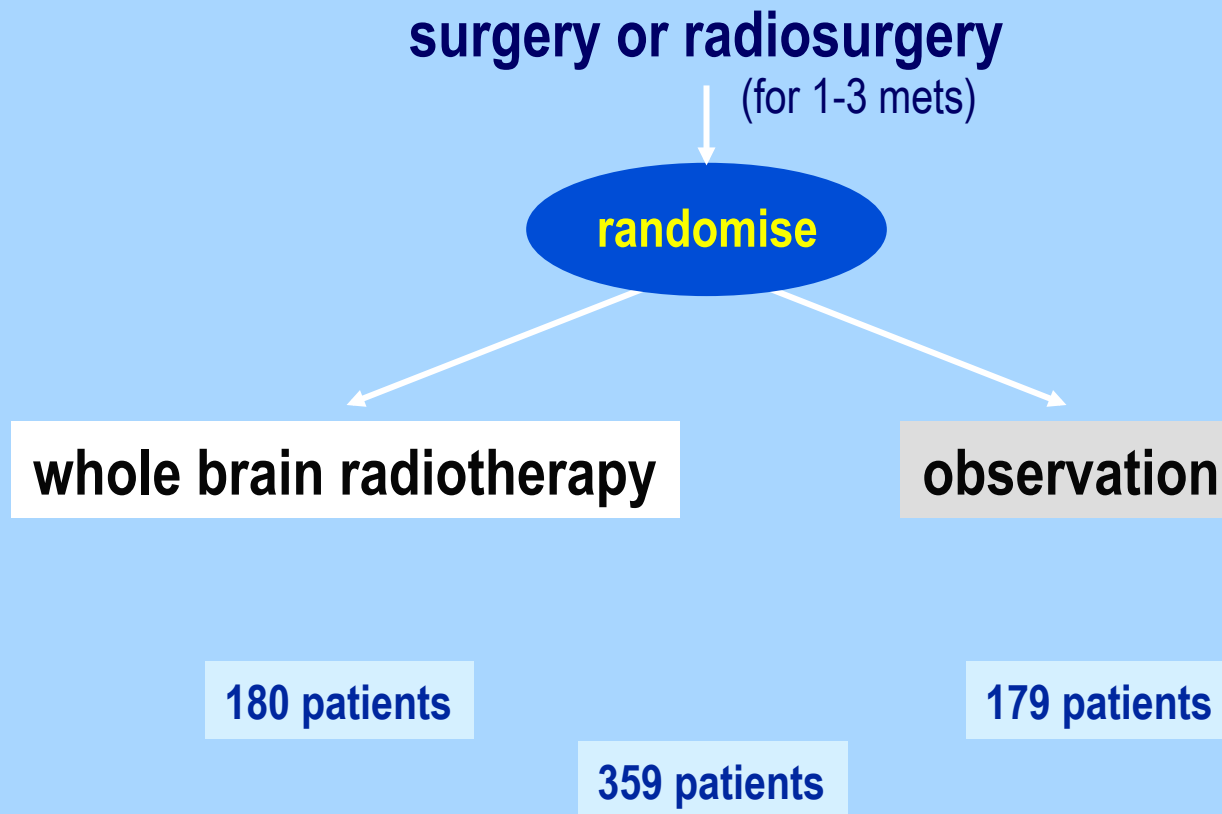
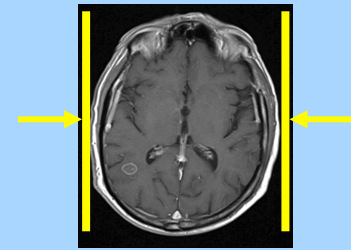
Whole brain radiotherapy following surgery or radiosurgery

Japanese Radiation Oncology Study Group (JROSG 99-1)

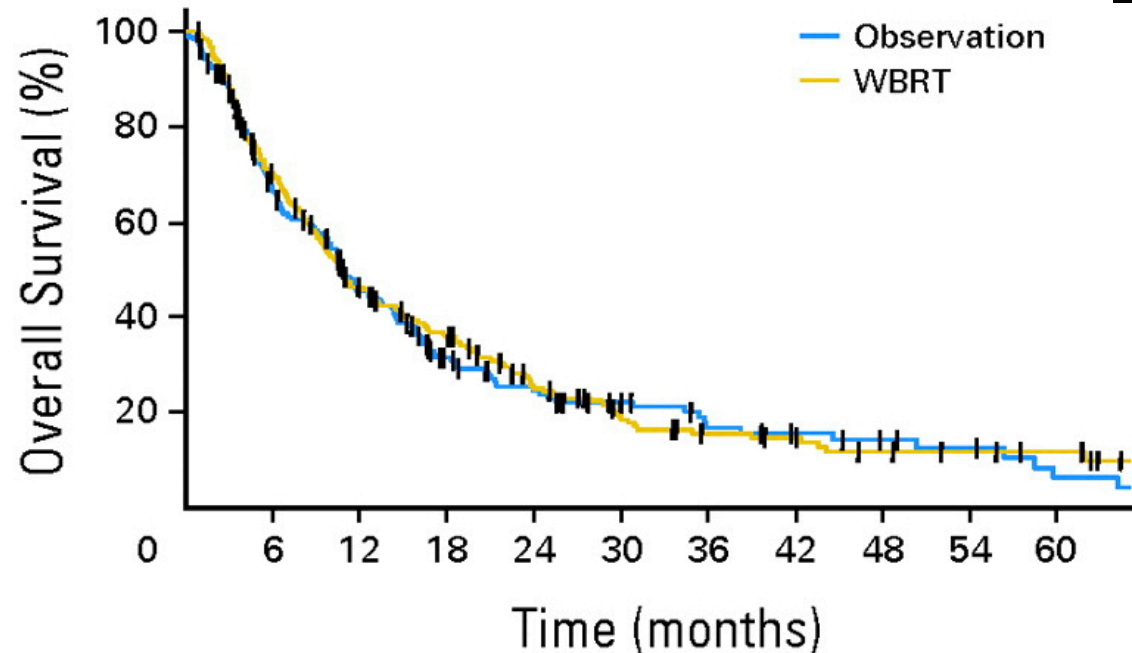
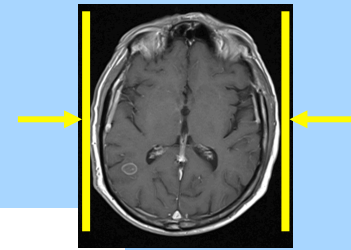
survival



Whole brain radiotherapy following surgery or radiosurgery



Whole brain radiotherapy following surgery or radiosurgery

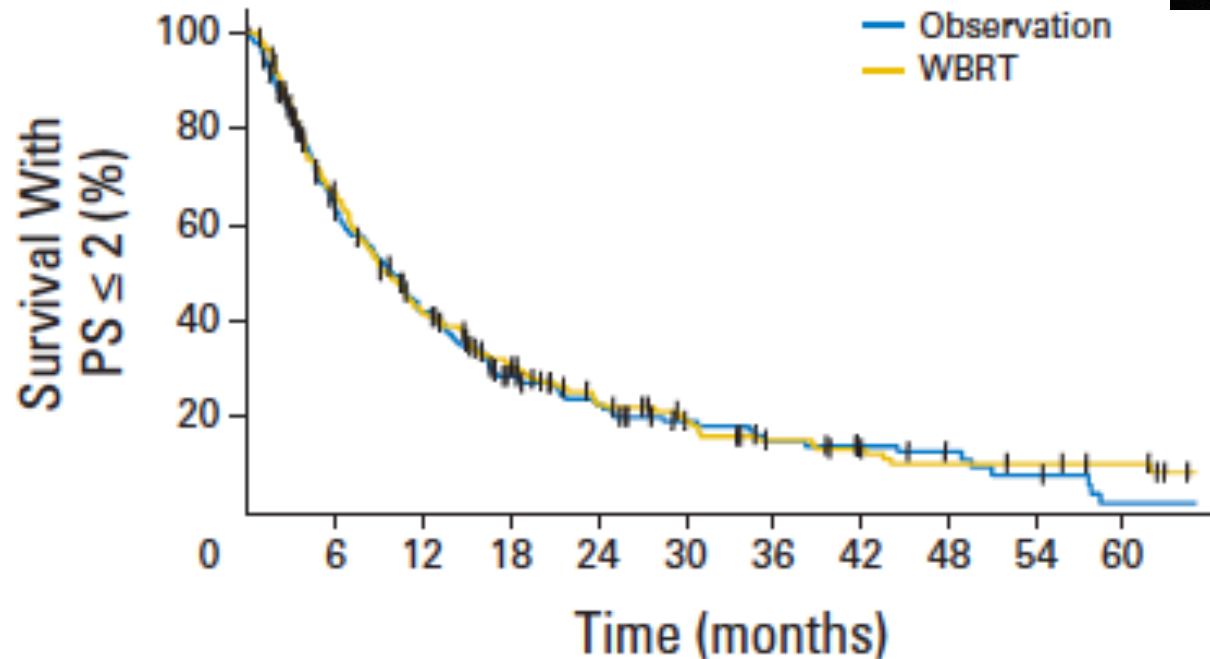
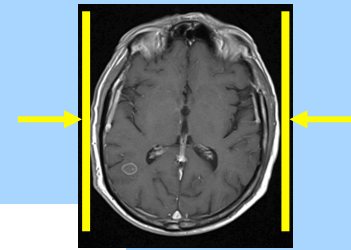


Randomized treatment	0	N	No. of patients at risk									
Observation	143	179	117	75	44	31	22	15	12	9	7	3
WBRT	149	180	124	80	61	38	25	18	15	11	9	7

Whole brain radiotherapy following surgery or radiosurgery

EORTC 22952-26001

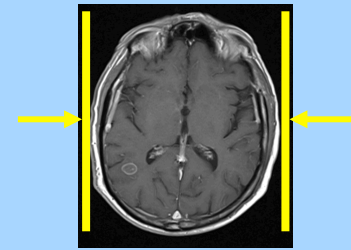
survival with good performance status



Randomized treatment	0	N	No. of patients at risk									
Observation	149	179	112	71	41	29	19	14	11	8	5	1
WBRT	152	180	118	73	52	34	25	17	13	10	9	7

Whole brain radiotherapy following surgery or radiosurgery

NCCTG N0574 (Alliance) trial



1 - 3 brain metastases

randomise

213 patients

radiosurgery &
whole brain radiotherapy

radiosurgery alone

1° endpoint:
2° endpoint

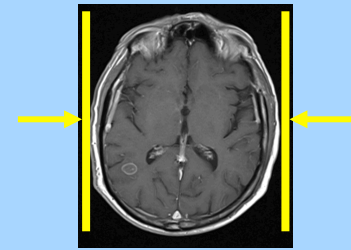
cognitive progression after treatment

Cognitive progression

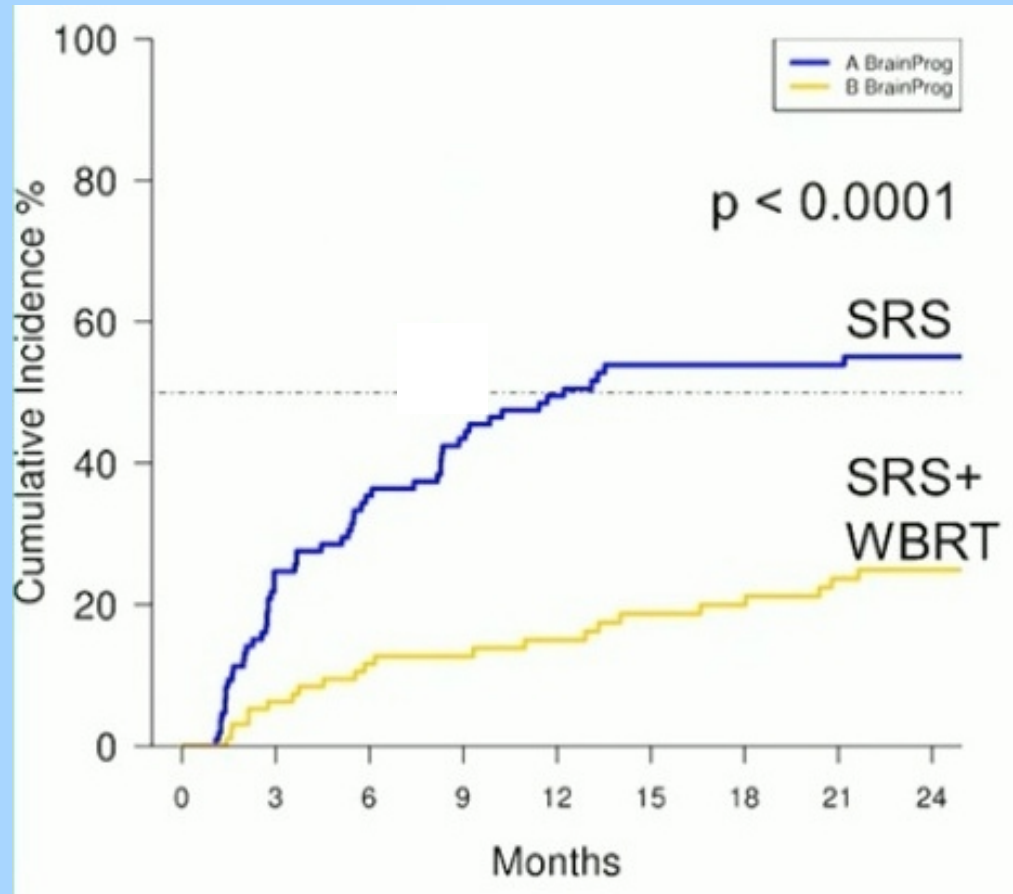
cognitive function tests - drop in 1SD in one test

Whole brain radiotherapy following radiosurgery

NCCTG N0574 (Alliance) trial

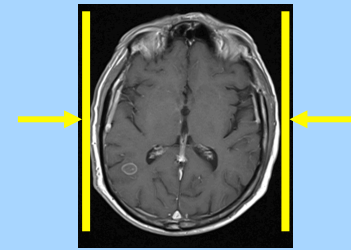


Intracranial progression

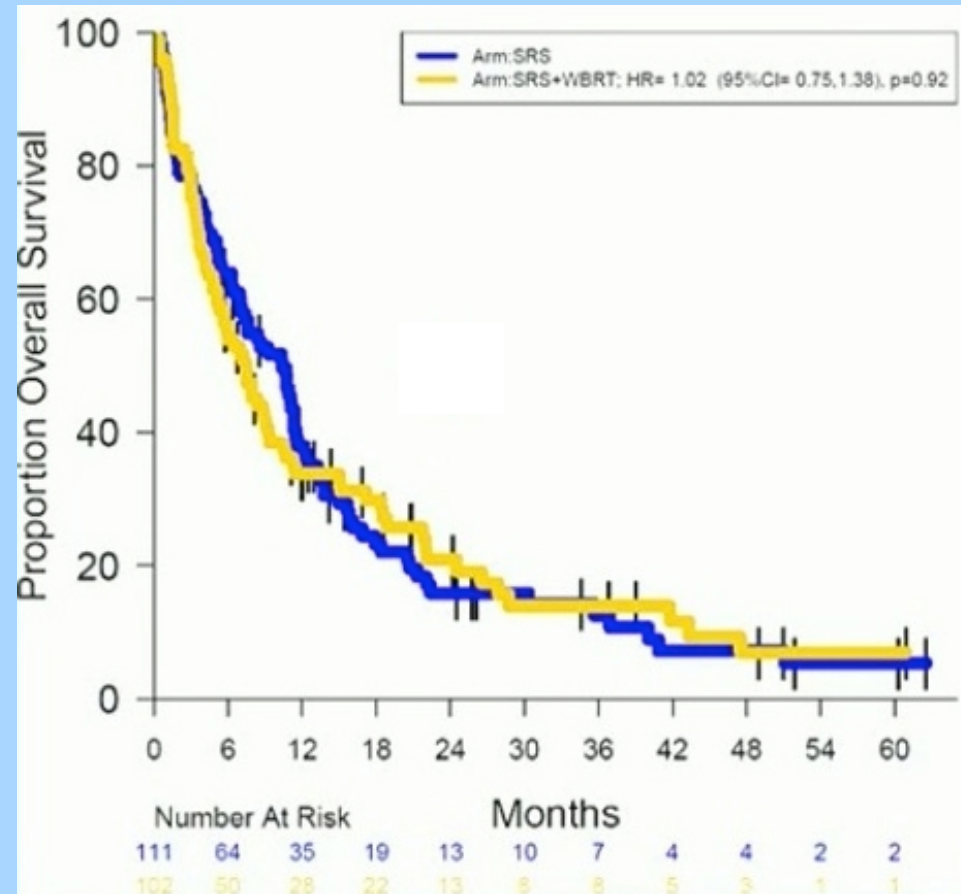


Whole brain radiotherapy following radiosurgery

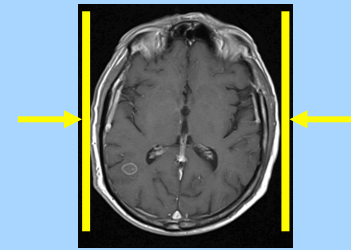
NCCTG N0574 (Alliance) trial



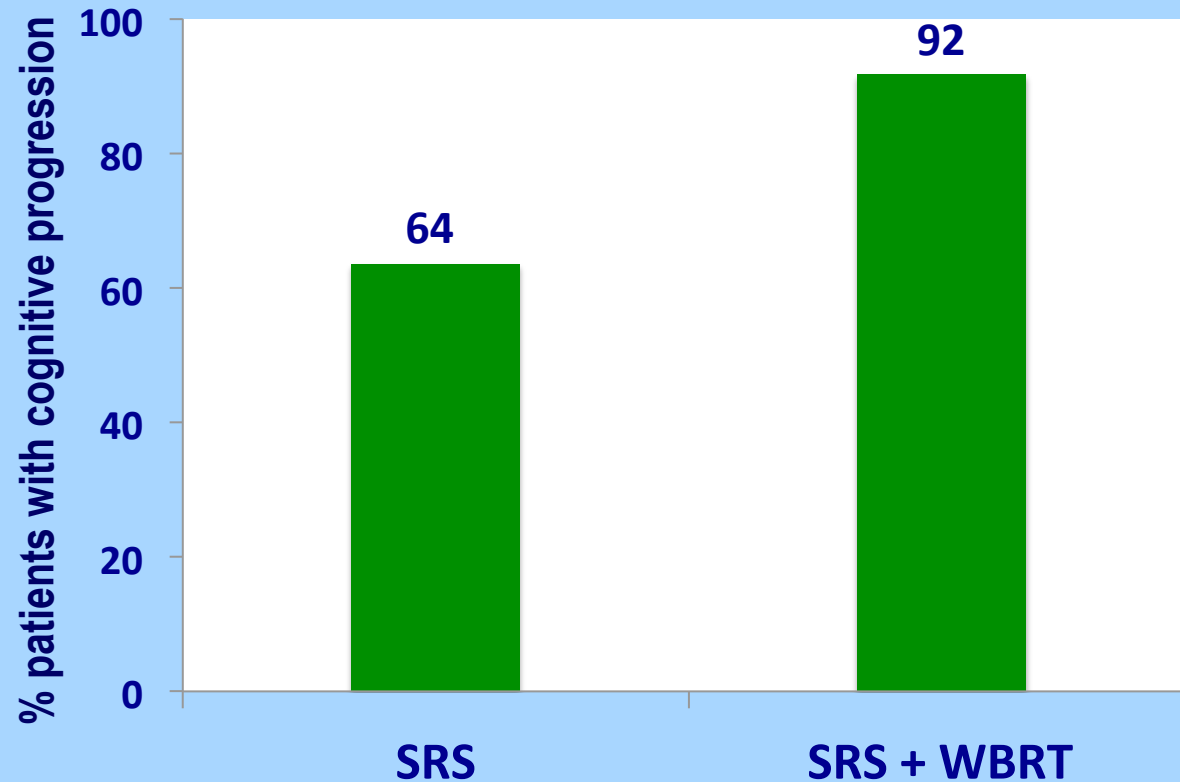
Survival



Whole brain radiotherapy following radiosurgery



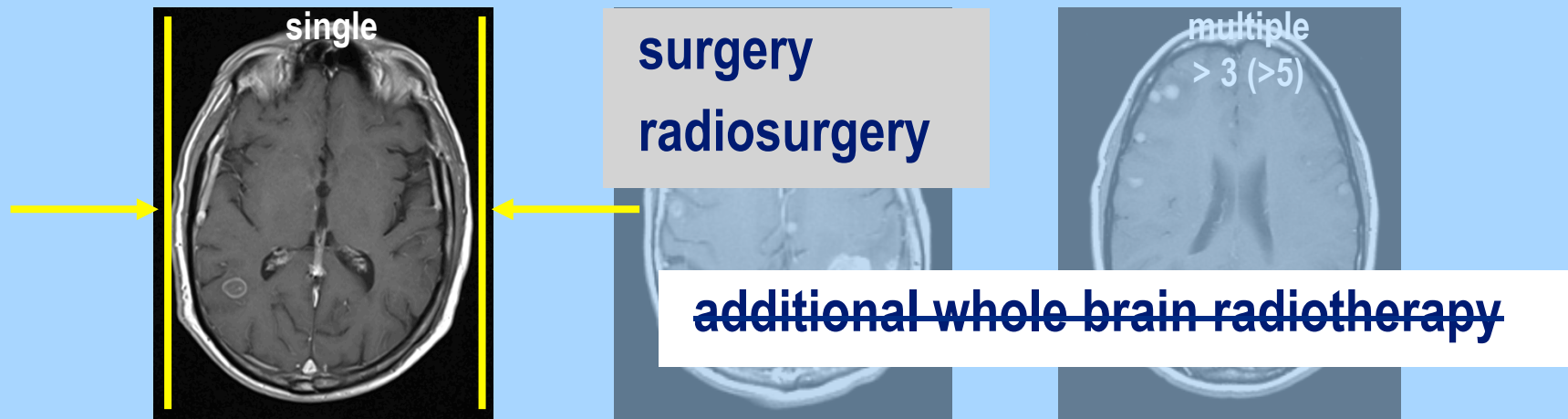
Cognitive progression at 3 months



Whole brain radiotherapy following radiosurgery

Matrix - radiotherapy options

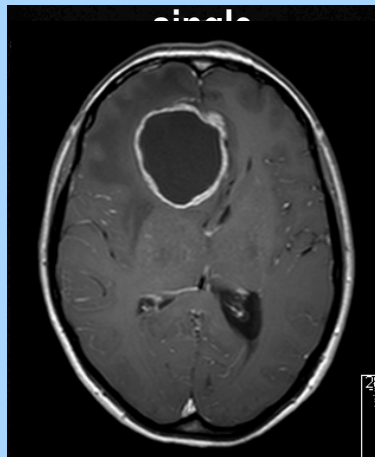
No. met's	prognosis	1 ^o tumour	timing
single	good	any	
oligomet's			
multiple			



Evidence base for radiotherapy in the treatment of brain metastases

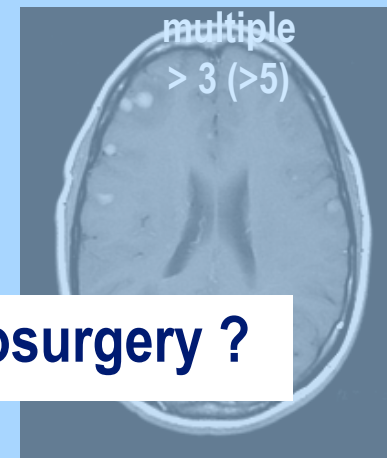
Matrix - radiotherapy options

No. met's	prognosis	1 ^o tumour	timing
single	good	any	
oligomets			
multiple			



surgery
radiosurgery

additional radiosurgery ?



Radiotherapy in the management of brain metastases

radiosurgery after resection of single or oligometastases

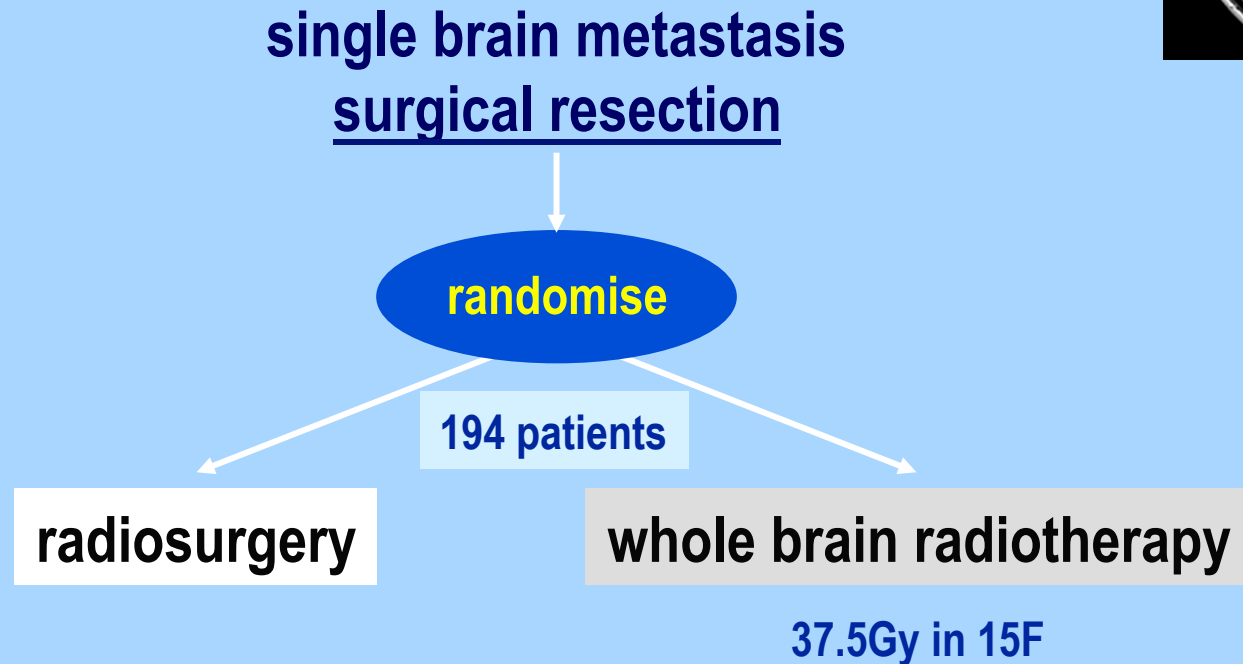
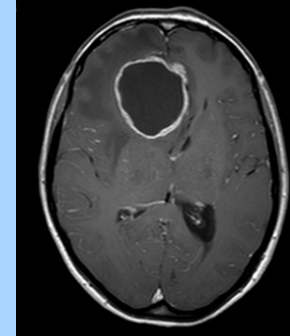
prolongs survival

prolongs time to
functional deterioration

prolongs intracranial
tumour control

none of these

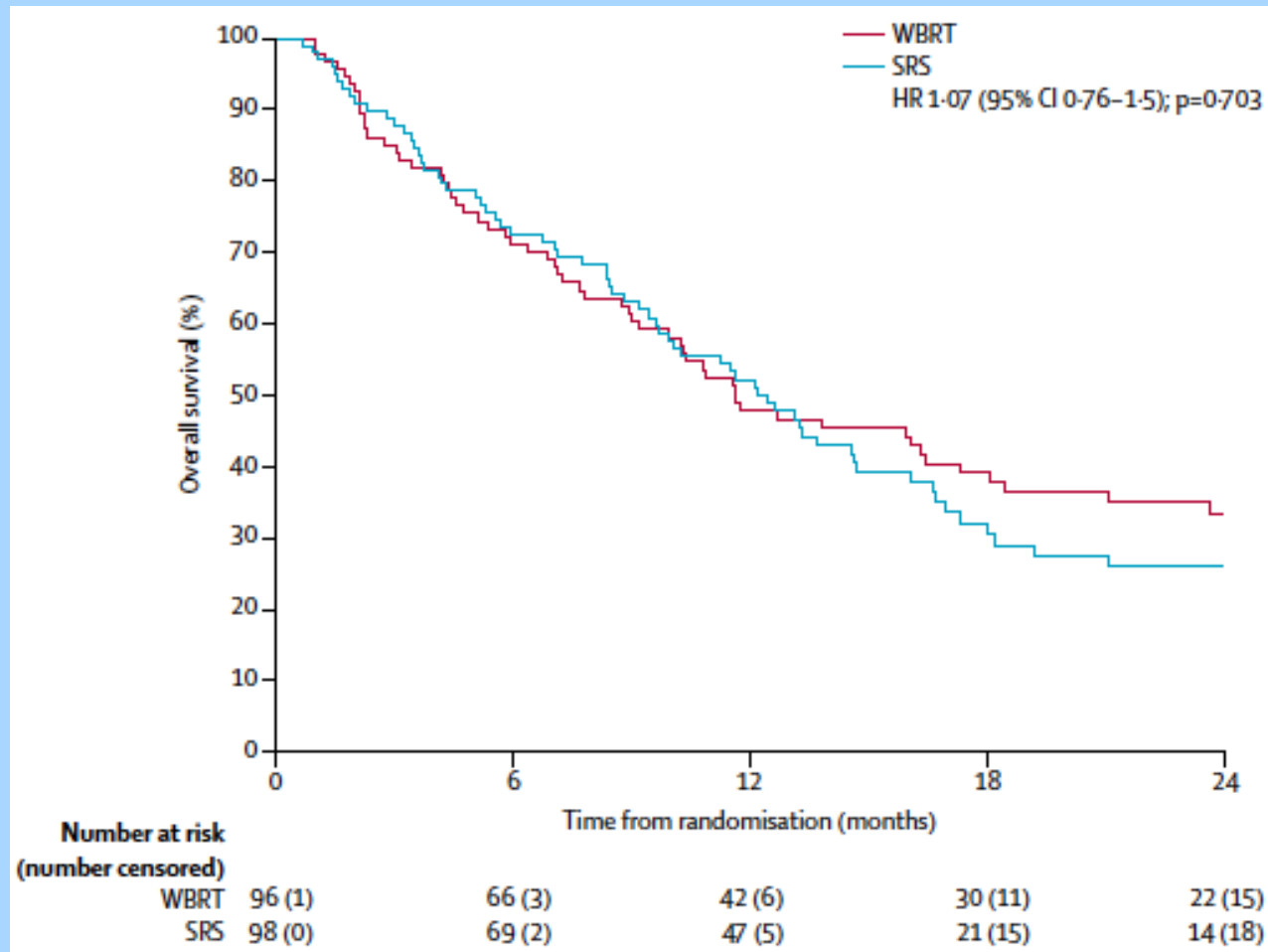
all of these



WBRT vs radiosurgery following resection of solitary metastasis

NCCTG N107C/CEC-3

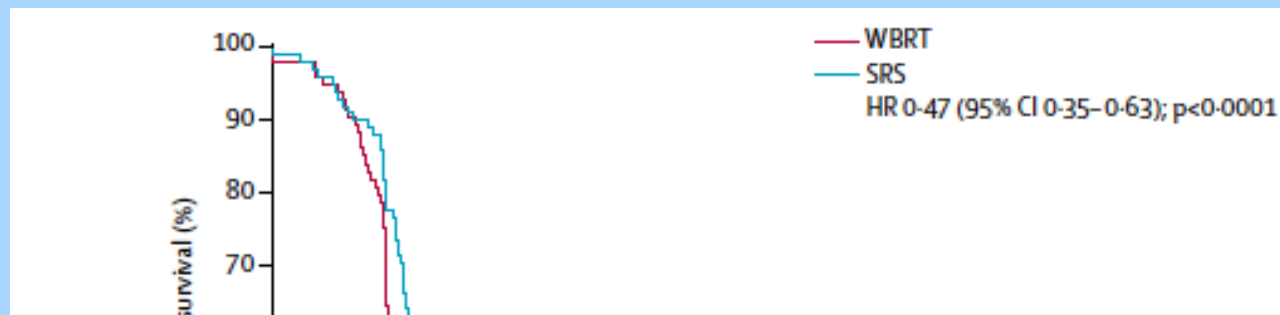
Survival



WBRT vs radiosurgery following resection of solitary metastasis

NCCTG N107C/CEC-3

Cognitive function



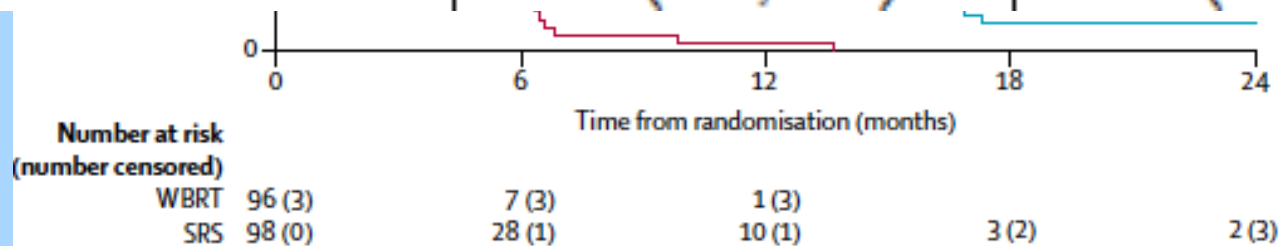
Total Intracranial Brain Control

(based on time to first recurrence of any type)

SRS

WBRT

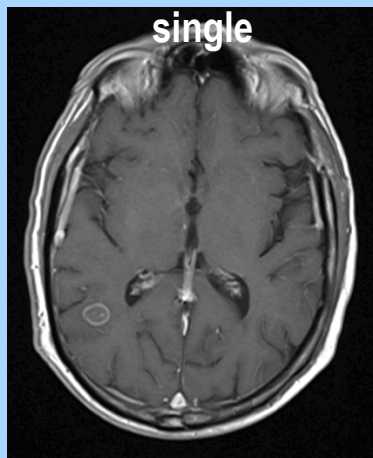
	SRS	WBRT
at 3 months	79.6% (72.0, 88.0)	90.4% (84.7, 96.6)
at 6 months	55.1% (46.1, 65.9)	80.8% (73.1, 89.2)
at 12 months	36.6% (28.1, 47.8)	72.1% (63.6, 81.8)



WBRT vs radiosurgery following resection of solitary metastasis

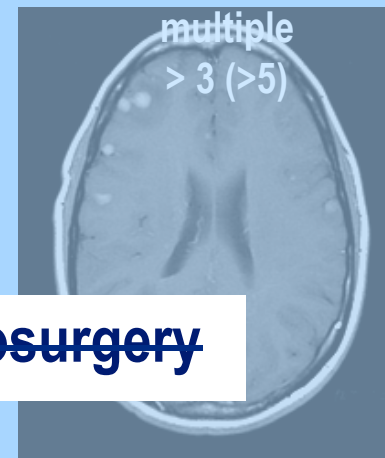
Matrix - radiotherapy options

No. met's	prognosis	1 ^o tumour	timing
single	good	any	
oligomets			
multiple			



surgery
radiosurgery

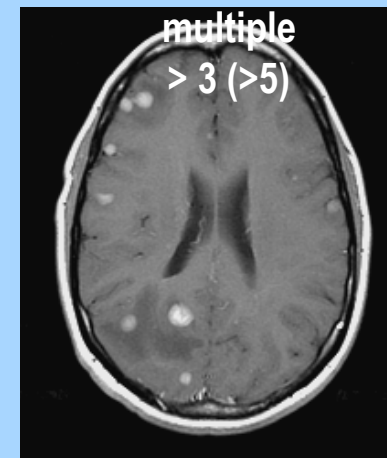
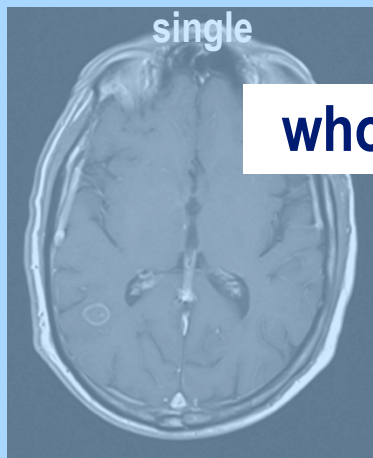
additional radiosurgery



Radiotherapy in the management of brain metastases

Matrix - radiotherapy options

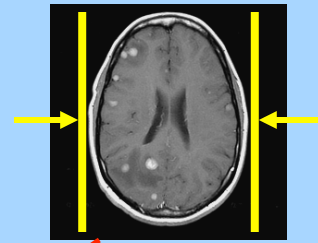
No. met's	prognosis	1 ^o tumour	timing
single			
oligomets			
multiple			



whole brain radiotherapy

Evidence base for radiotherapy in the treatment of brain metastases

whole brain radiotherapy and survival



patients with brain metastases

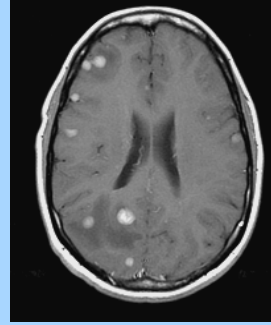
randomise

palliative radiotherapy
& supportive care

supportive care
alone

Effect of whole brain radiotherapy on survival

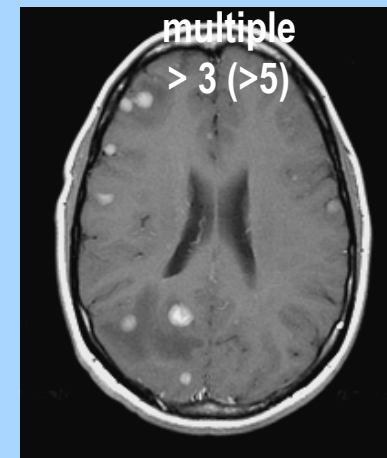
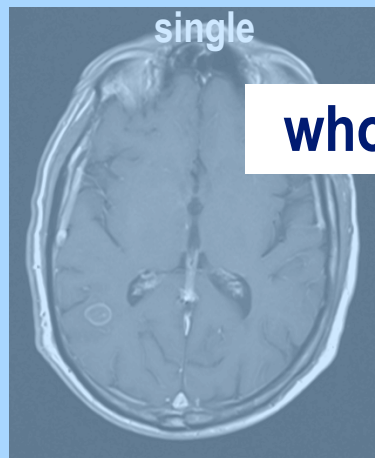
Course of malignant disease



Brain metastases in malignancy

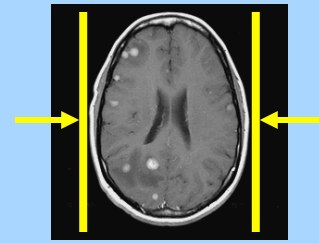
Matrix - radiotherapy options

No. met's	prognosis	1 ^o tumour	timing
single			
oligomets			
multiple	poor		end stage



whole brain radiotherapy

Evidence base for radiotherapy in the treatment of brain metastases



**brain metastases in NSCLC
& poor prognosis**

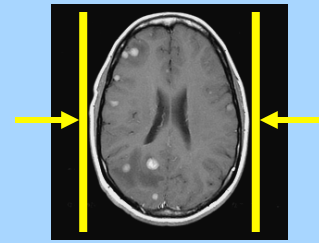
randomise

**palliative radiotherapy
& supportive care**

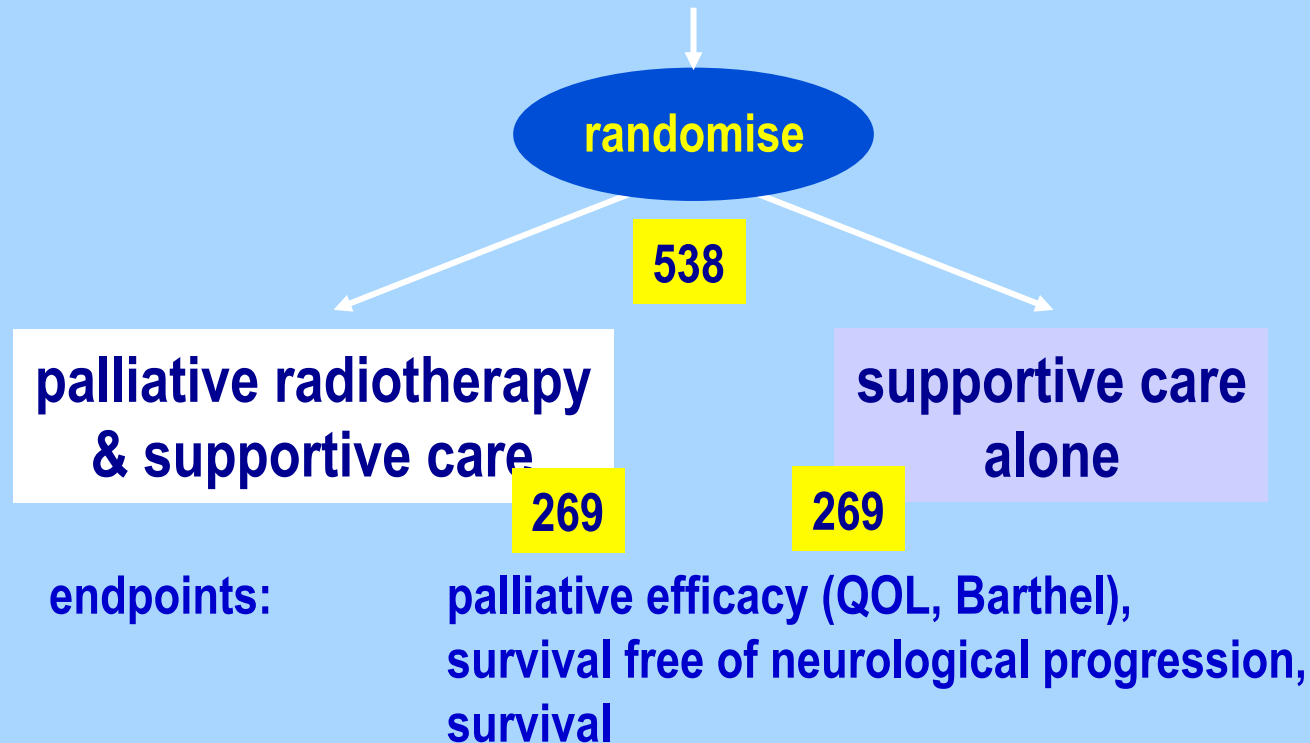
**supportive care
alone**

endpoints: **palliative efficacy (QOL, Barthel),
survival free of neurological progression,
survival**

Effect of whole brain radiotherapy on survival & QOL



**brain metastases in NSCLC
& poor prognosis**

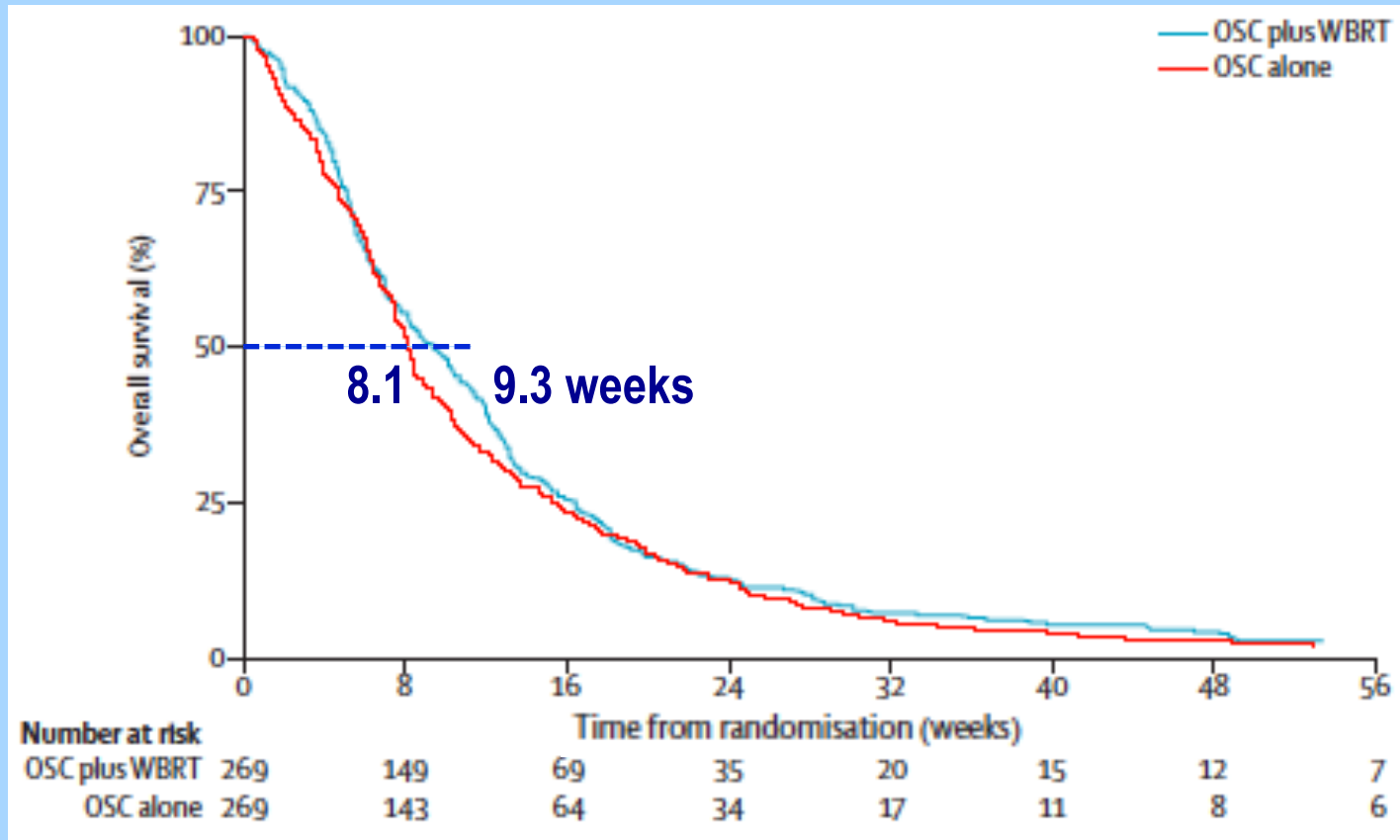
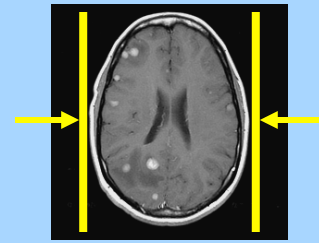


Effect of whole brain radiotherapy on survival & QOL

QUARTZ trial

CR UK & TROG

survival

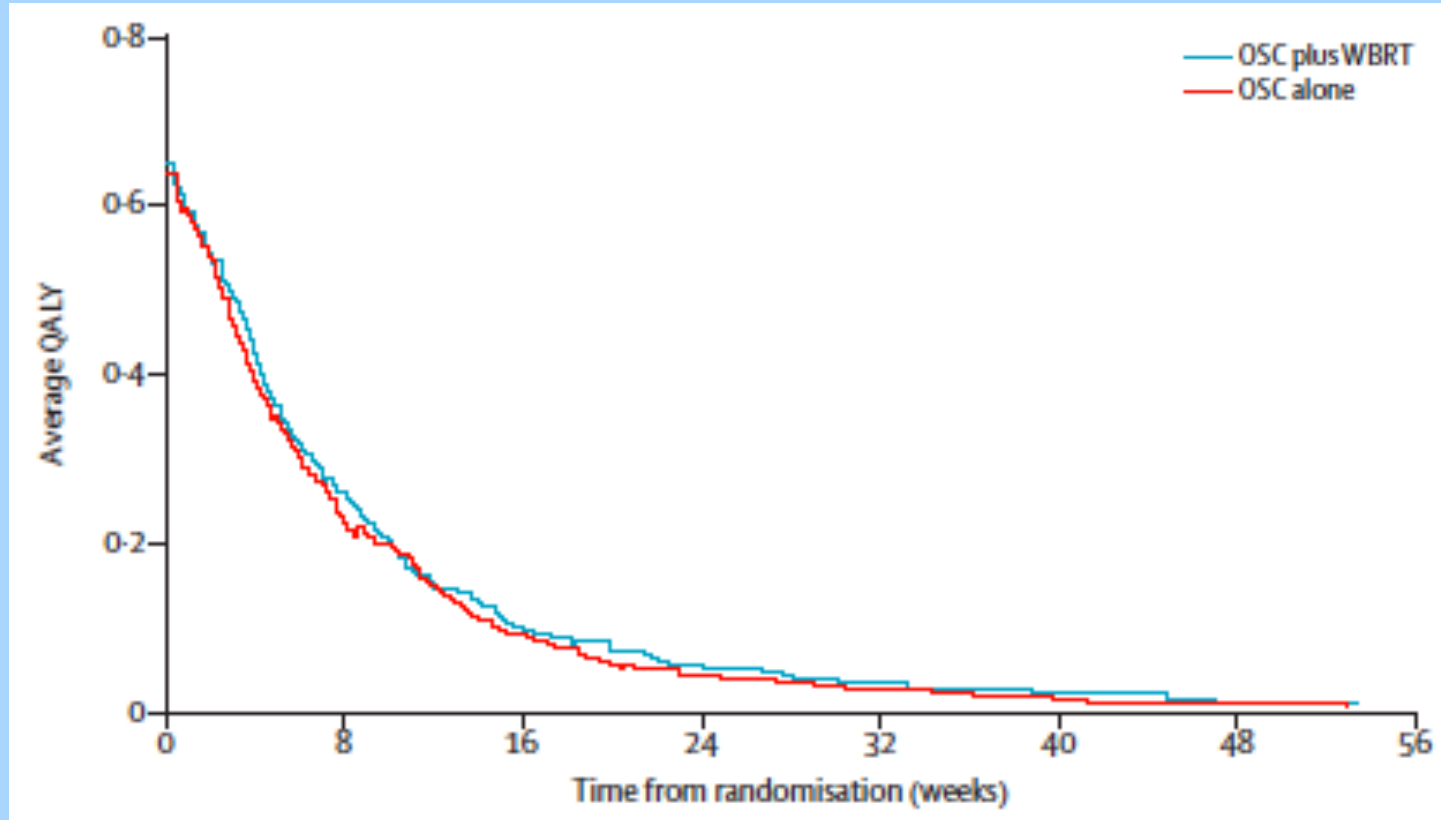
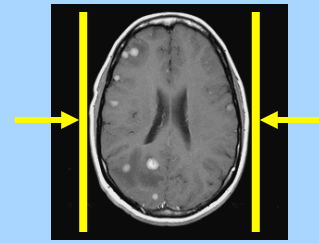


Effect of whole brain radiotherapy on survival & QOL

QUARTZ trial

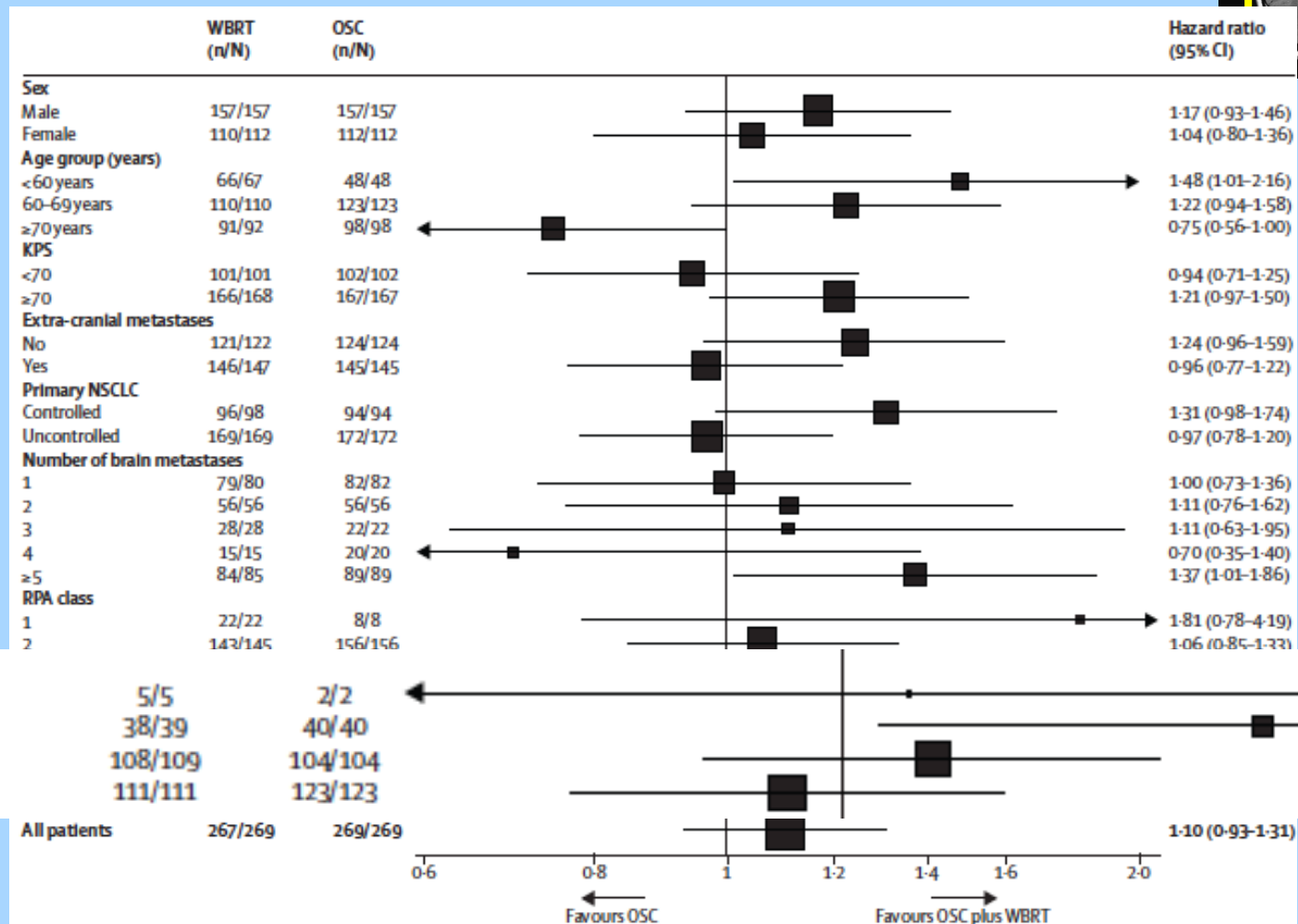
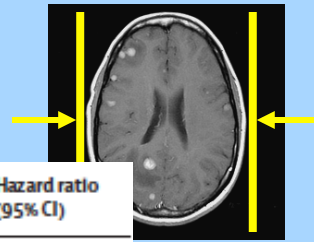
CR UK & TROG

quality adjusted life years (QALY)



Effect of whole brain radiotherapy on survival & QOL

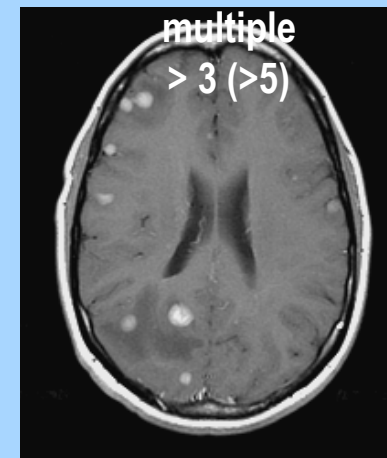
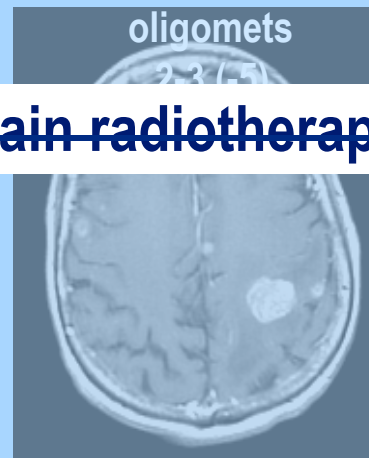
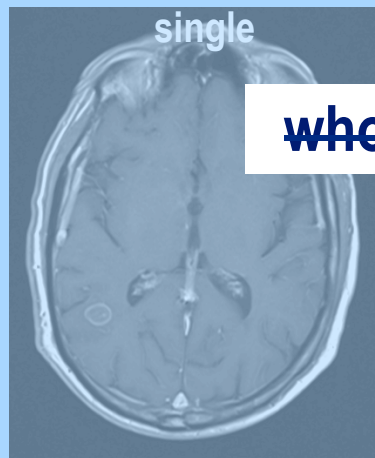
QUARTZ trial CR UK & TROG



Effect of whole brain radiotherapy on survival & QOL

Matrix - radiotherapy options

No. met's	prognosis	1 ^o tumour	timing
single			
oligomets			
multiple	poor		end stage

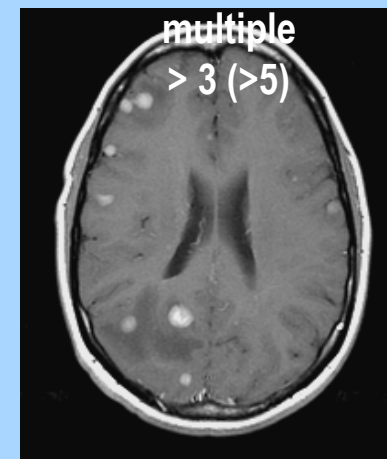
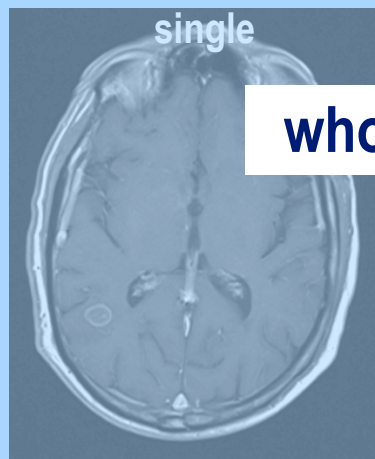


~~whole brain radiotherapy~~

Evidence base for radiotherapy in the treatment of brain metastases

Matrix - radiotherapy options

No. met's	prognosis	1 ^o tumour	timing
single			
oligomets			
multiple			

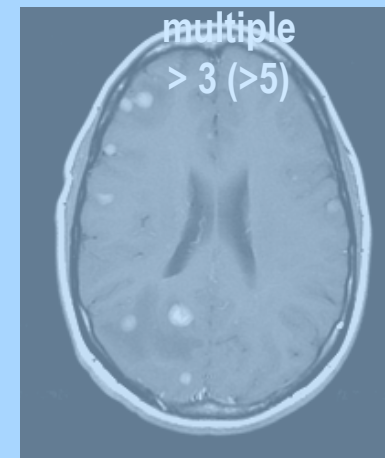
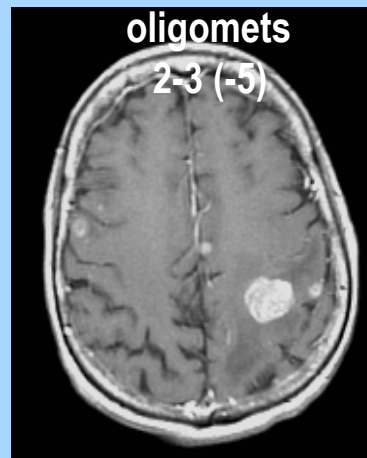
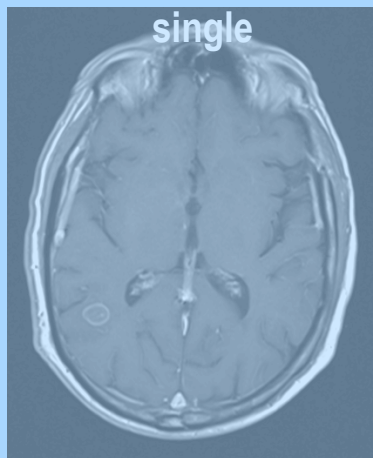


whole brain radiotherapy

Evidence base for radiotherapy in the treatment of brain metastases

Matrix - radiotherapy options

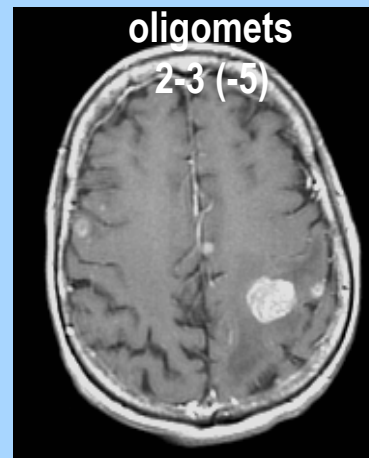
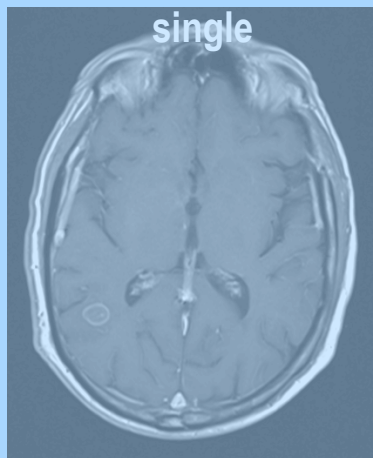
No. met's	prognosis	1 ^o tumour	timing
single			
oligomets			
multiple			



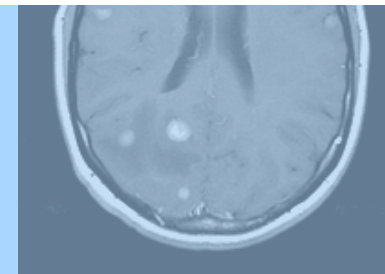
Evidence base for radiotherapy in the treatment of brain metastases

Matrix - radiotherapy options

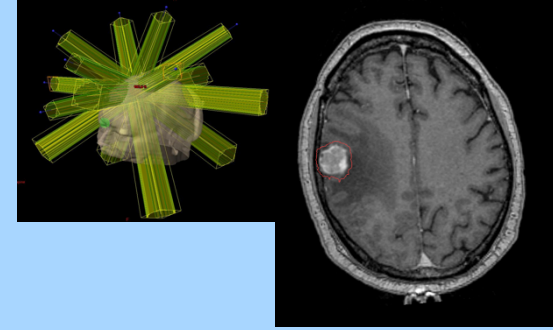
No. met's	prognosis	1 ^o tumour	timing
single			
oligomets	good		
multiple			



**whole brain radiotherapy
or radiosurgery (or both)**



Evidence base for radiotherapy in the treatment of brain metastases



1 - 3 brain metastases
oligometastases

randomise

**whole brain radiotherapy
& radiosurgery (SRS)**

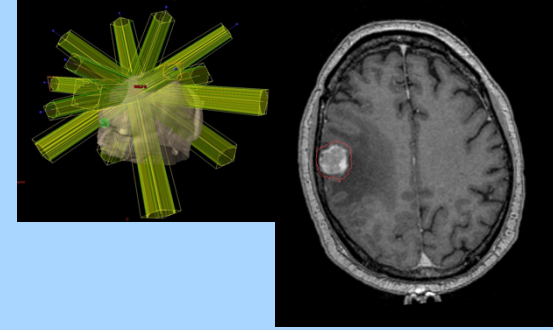
167 patients

**whole brain radiotherapy
(WBRT)**

164 patients

331 patients

Radiosurgery for “solitary” brain metastases



oligometastases
(2-3 mets)

randomise

whole brain radiotherapy
& radiosurgery (SRS)

whole brain radiotherapy
(WBRT)

73 patients

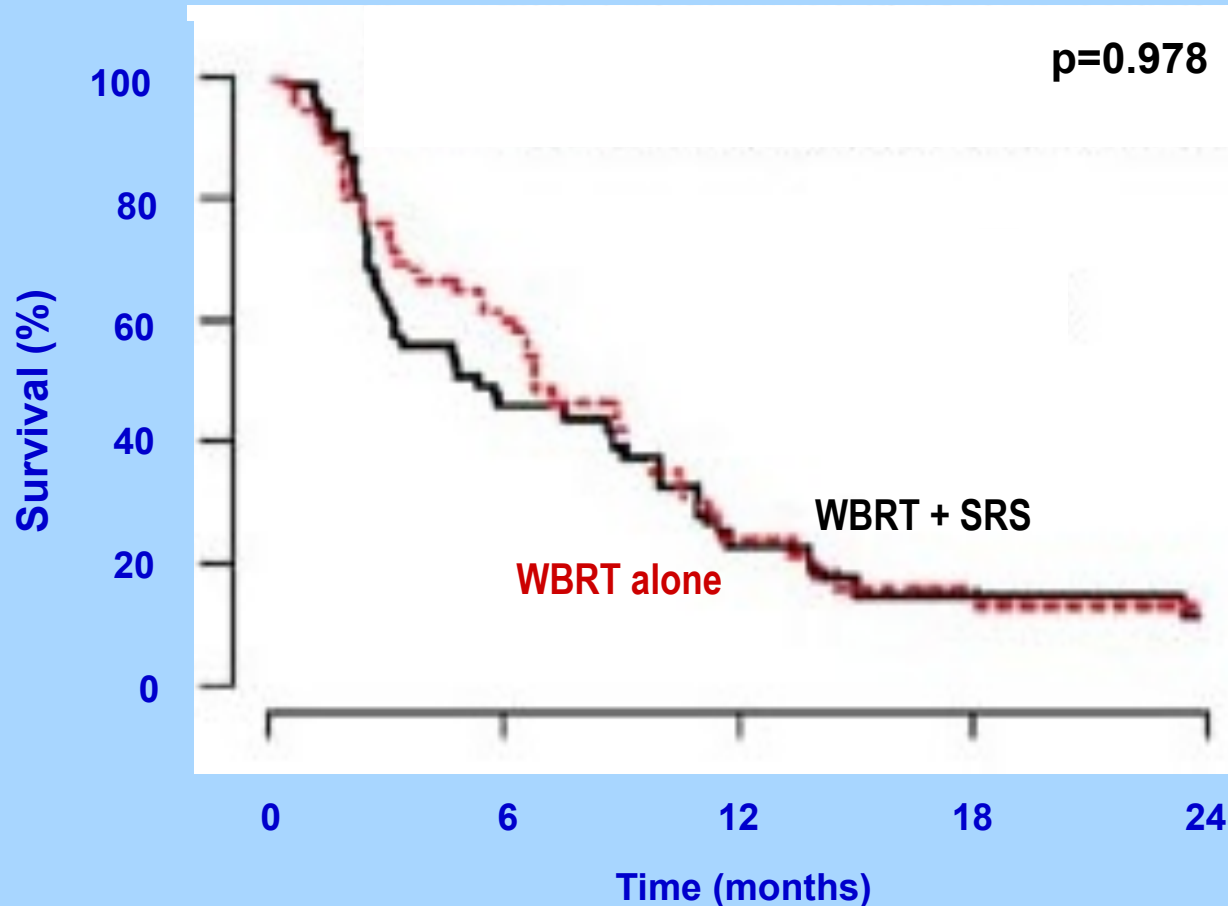
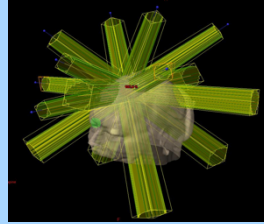
145 patients

72 patients

Radiosurgery for oligometastases in the brain

survival

2 – 3 brain metastases



Radiosurgery for oligometastases in the brain

RTOG 9508

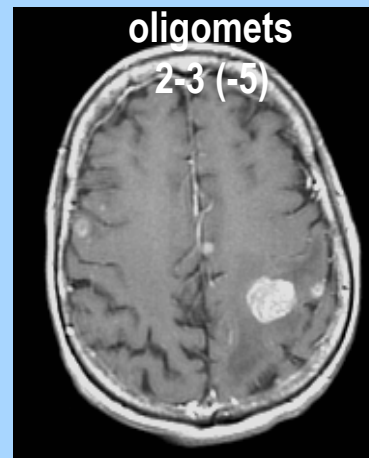
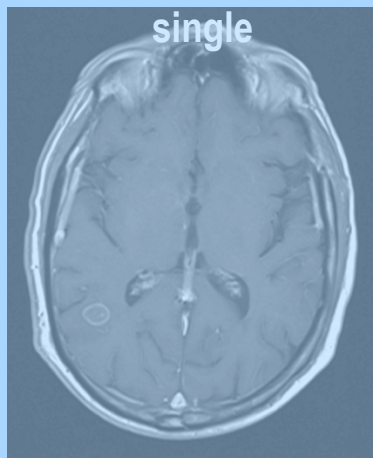
Andrews et al 2004, Lancet; 363: 1665–72

WBRT
SRS

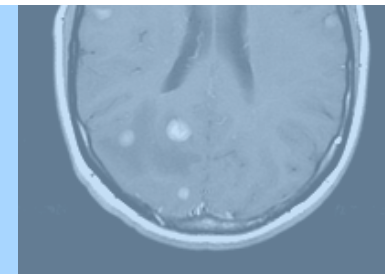
whole brain radiotherapy
stereotactic radiosurgery

Matrix - radiotherapy options

No. met's	prognosis	1 ^o tumour	timing
single			
oligomets	good		
multiple			

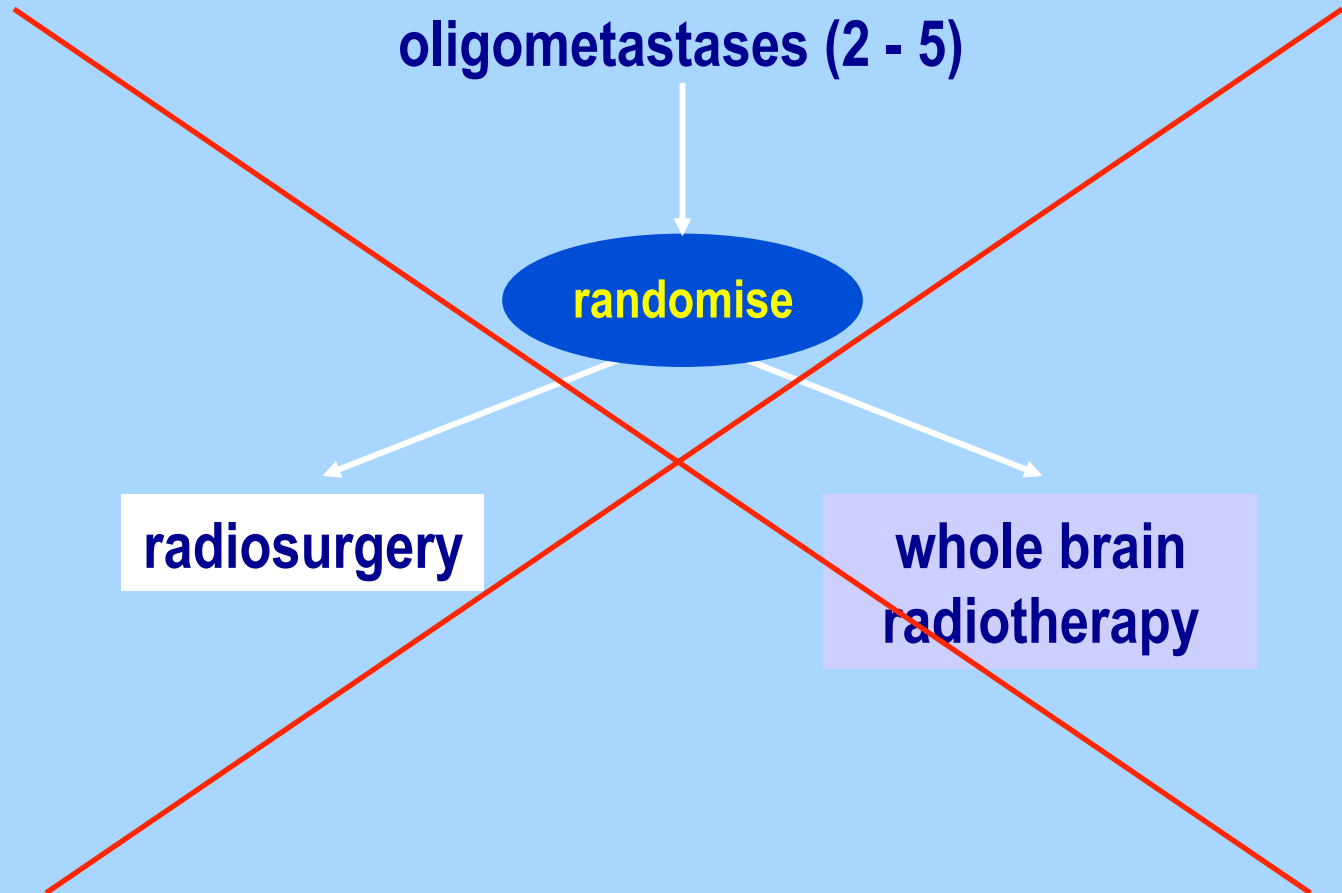


**whole brain radiotherapy
or radiosurgery (or both)**

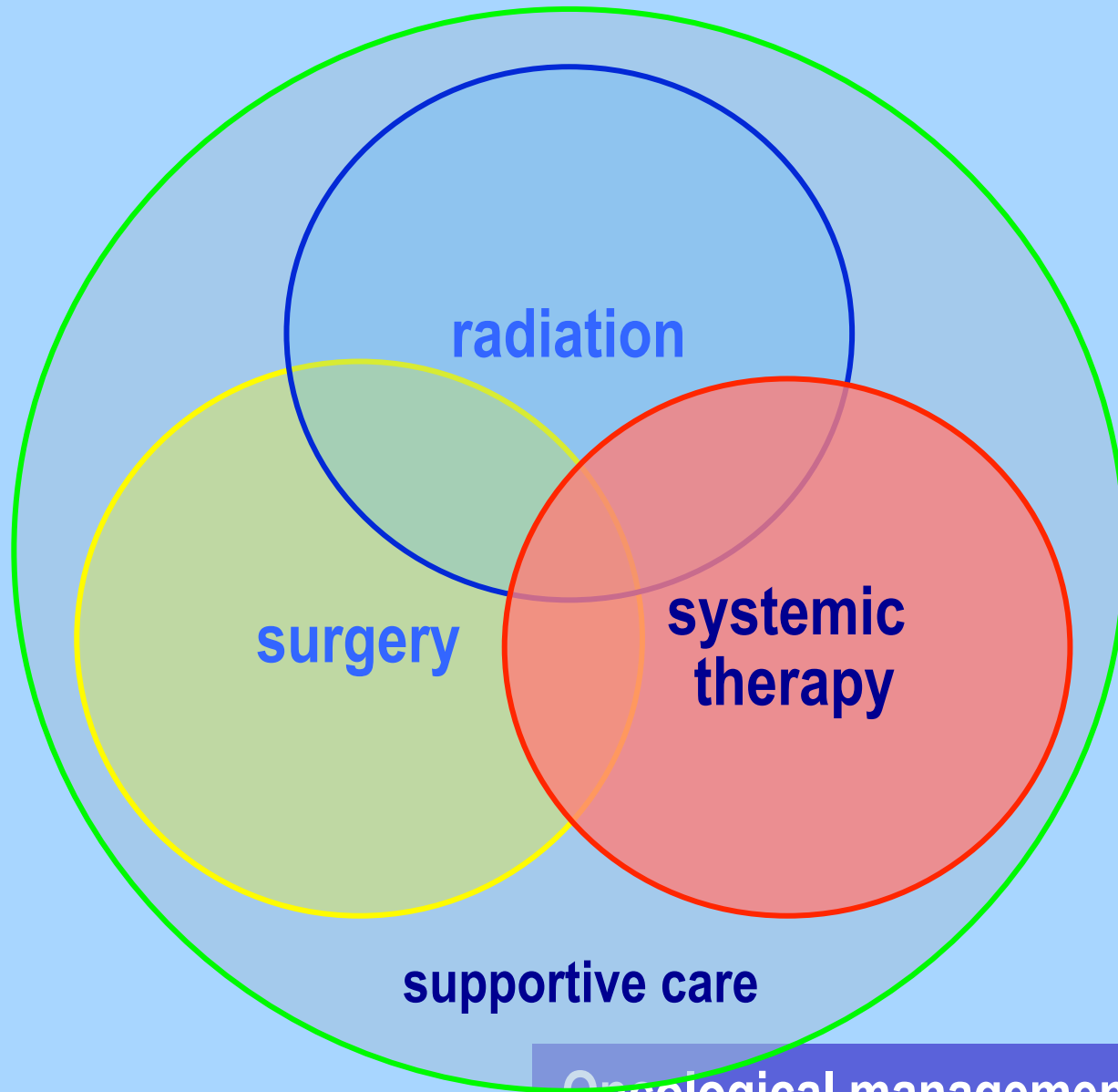
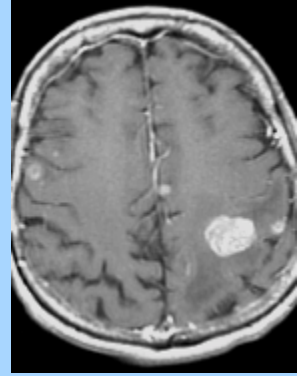


Evidence base for radiotherapy in the treatment of brain metastases

Oligometastases



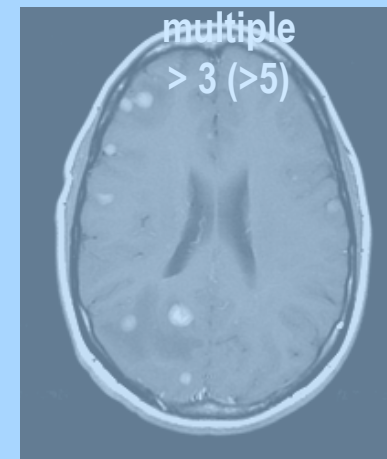
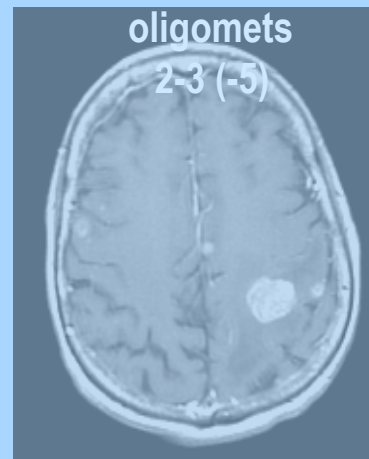
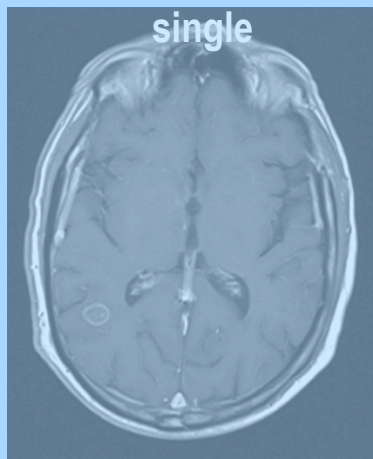
Radiosurgery for oligometastases in the brain



Oncological management options

Matrix - radiotherapy options

No. met's	prognosis	1 ^o tumour	timing
single	responsive to systemic treatment		
oligomets			
multiple			



Evidence base for radiotherapy in the treatment of brain metastases

ER+ metastatic breast cancer



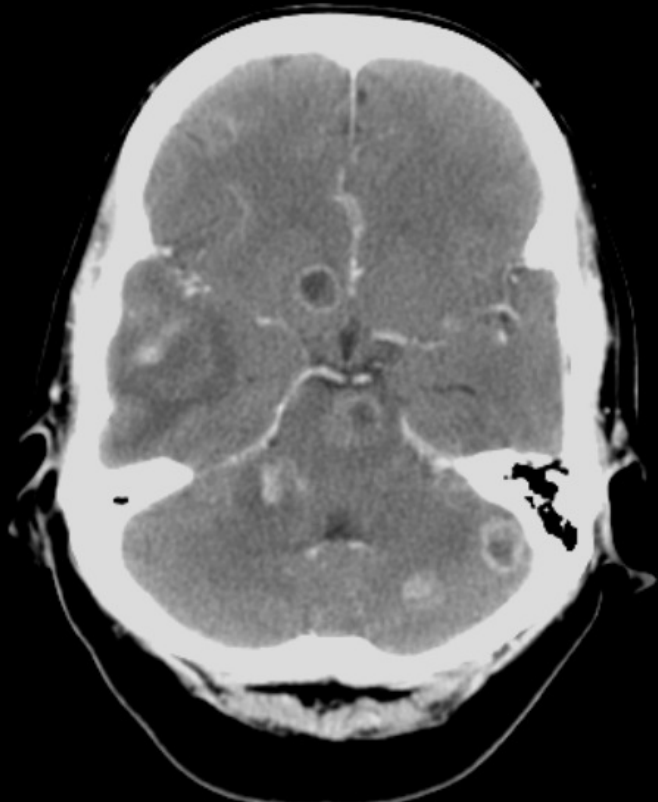
1.6.2011



12.8.2011

response to Anastrozole & Goserelin

lung adenocarcinoma with EGFR mutation



21.5.2010



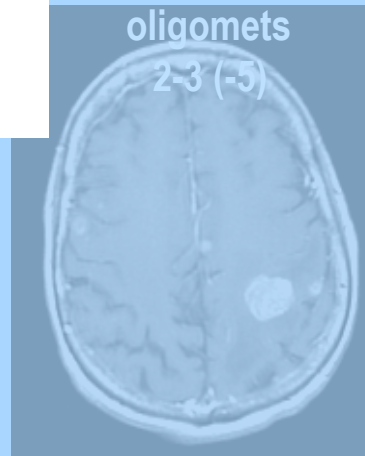
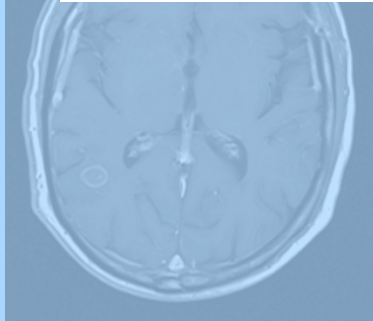
28.10.2010

response to Erlotinib

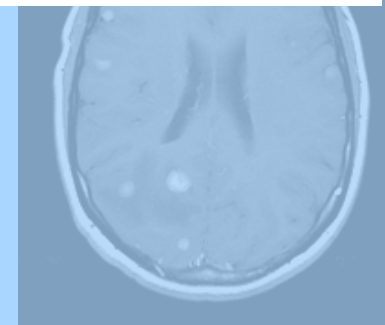
Matrix - radiotherapy options

No. met's	prognosis	1 ^o tumour	timing
single	responsive to systemic treatment		
oligomets			

“activity”
“benefit”



survival
quality of life

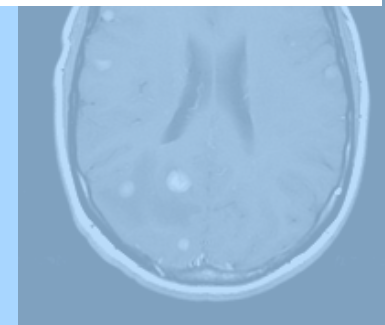
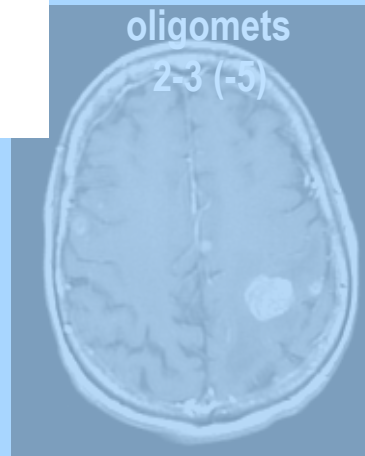
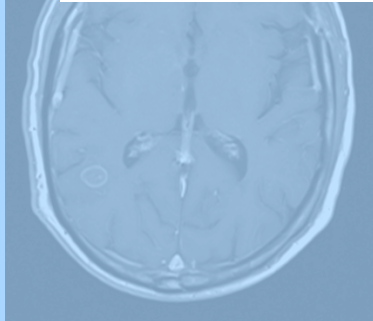


Systemic therapy endpoints

Matrix - radiotherapy options

No. met's	prognosis	1 ^o tumour	timing
single	responsive to systemic treatment		
oligomets			

“activity”
“benefit”



survival
quality of life

Systemic therapy endpoints

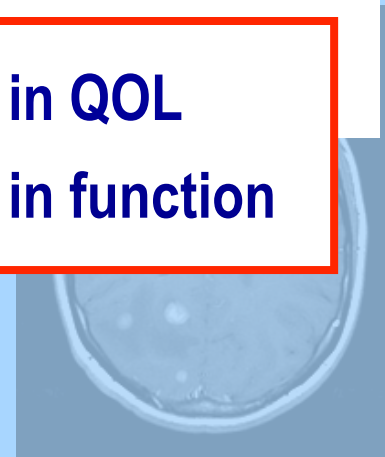
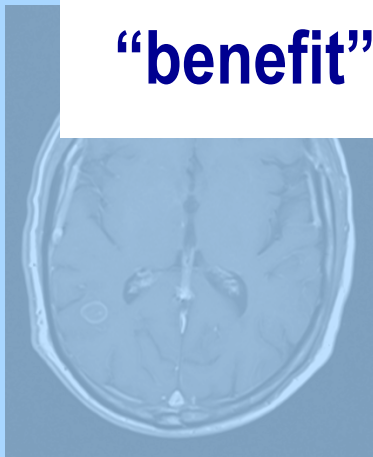
Matrix - radiotherapy options

No. met's	prognosis	1 ^o tumour	timing
single	responsive to systemic treatment		
oligomet's			

“activity”
“benefit”

survival

improvement in QOL
improvement in function



Systemic therapy endpoints

Matrix - radiotherapy options

No. met's	prognosis	1 ^o tumour	timing
single	responsive to systemic treatment		
oligomet's			

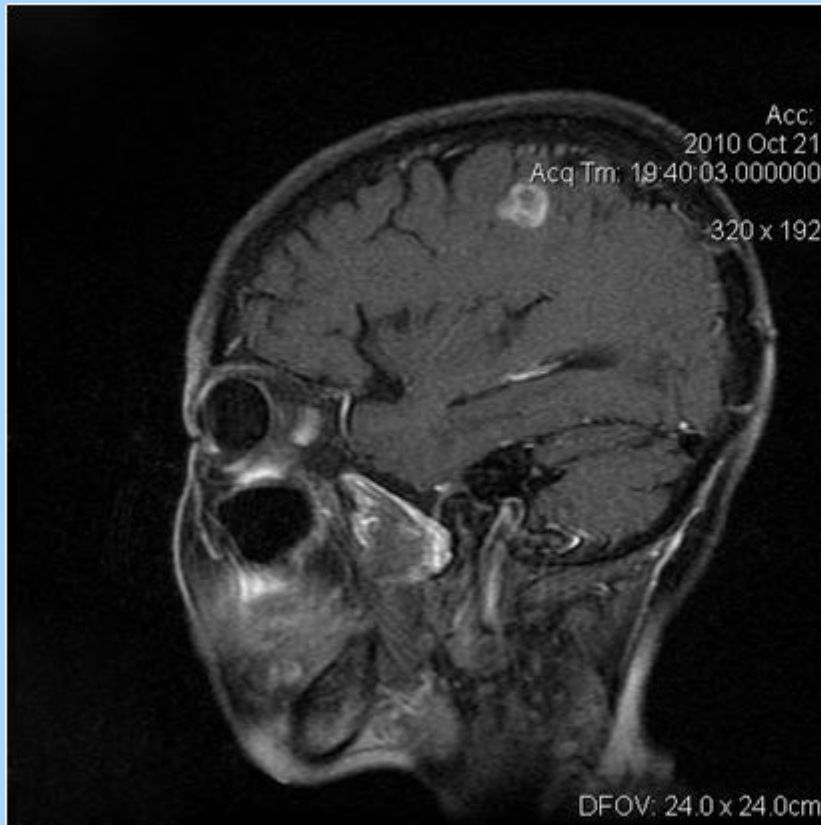
“activity”
“benefit”

survival

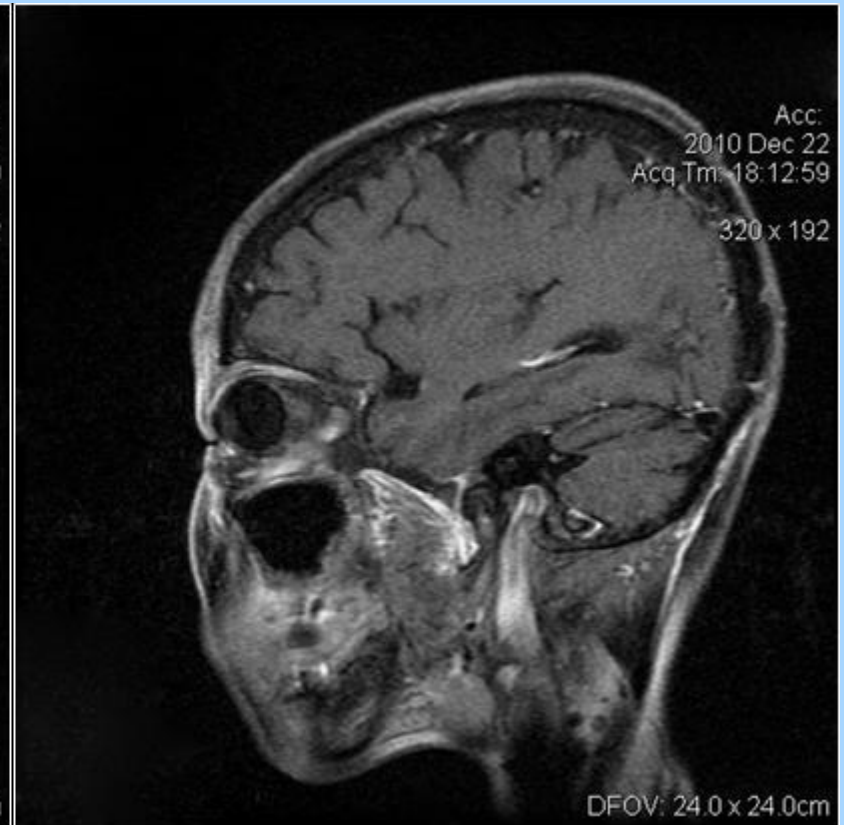
improvement in QOL
improvement in function
long term CNS control

Systemic therapy endpoints

PROFILE trials



Before initiation of crizotinib



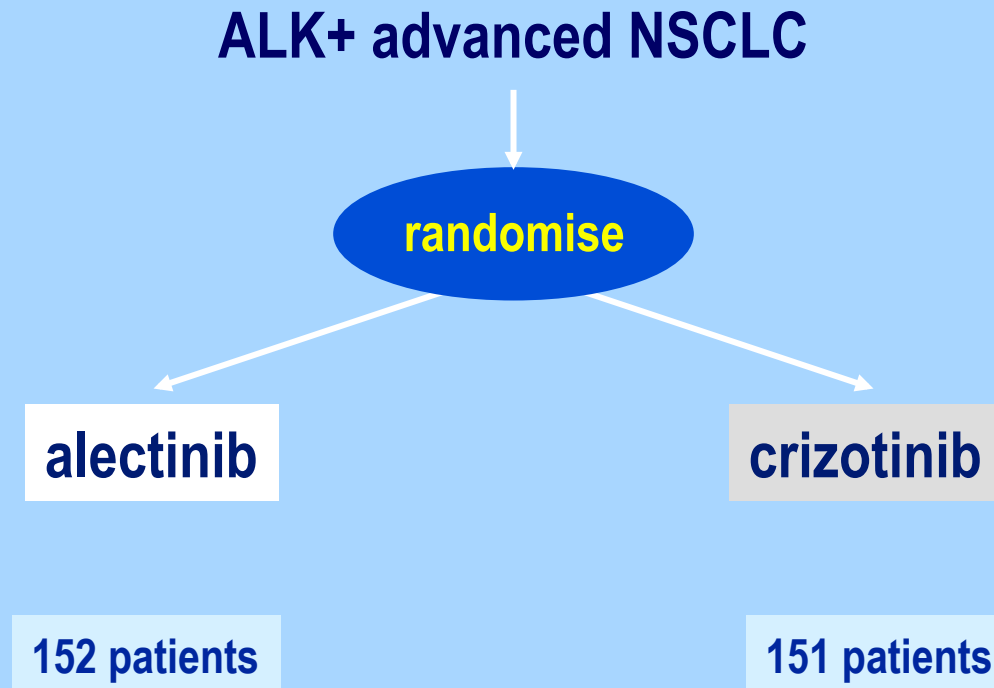
6 weeks after crizotinib

(provided by Pfizer, courtesy of J-Y Han, National Cancer Center, Goyang, South Korea)

Brain metastases in patients with ALK-positive NSCLC

Costa et al 2015, J Clin Oncol; 33 (17): 1881-1888

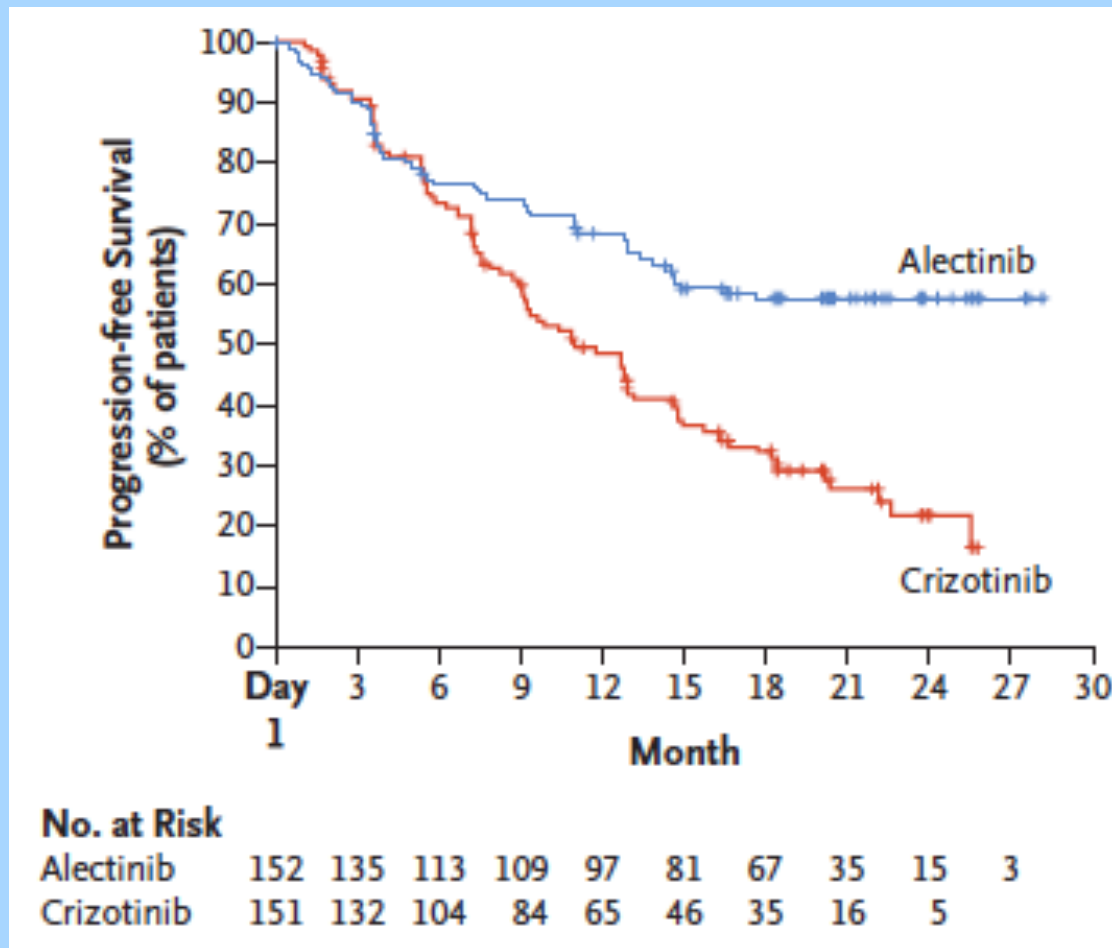
Alectinib vs Crizotinib trial



Brain metastases in patients with ALK-positive NSCLC

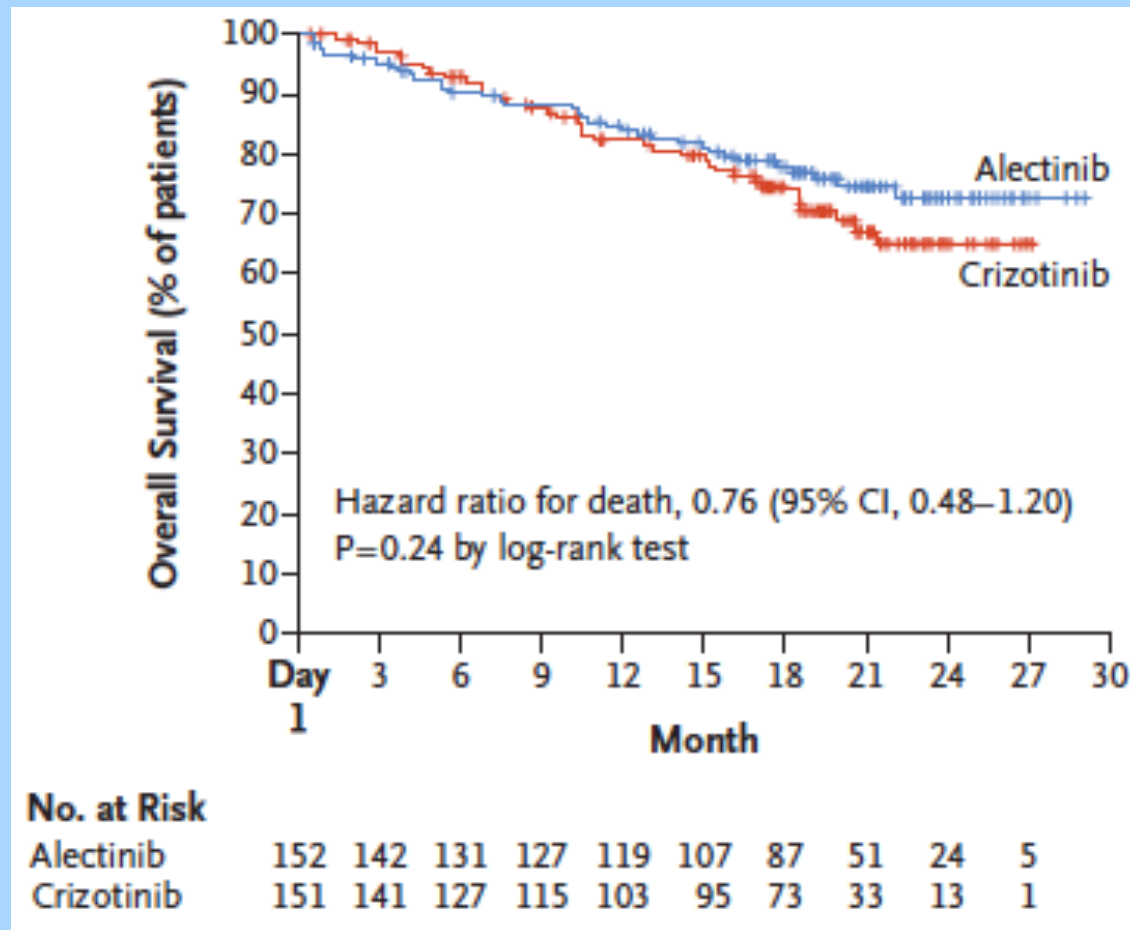
Alectinib vs Crizotinib trial

progression free survival



Brain metastases in patients with ALK-positive NSCLC

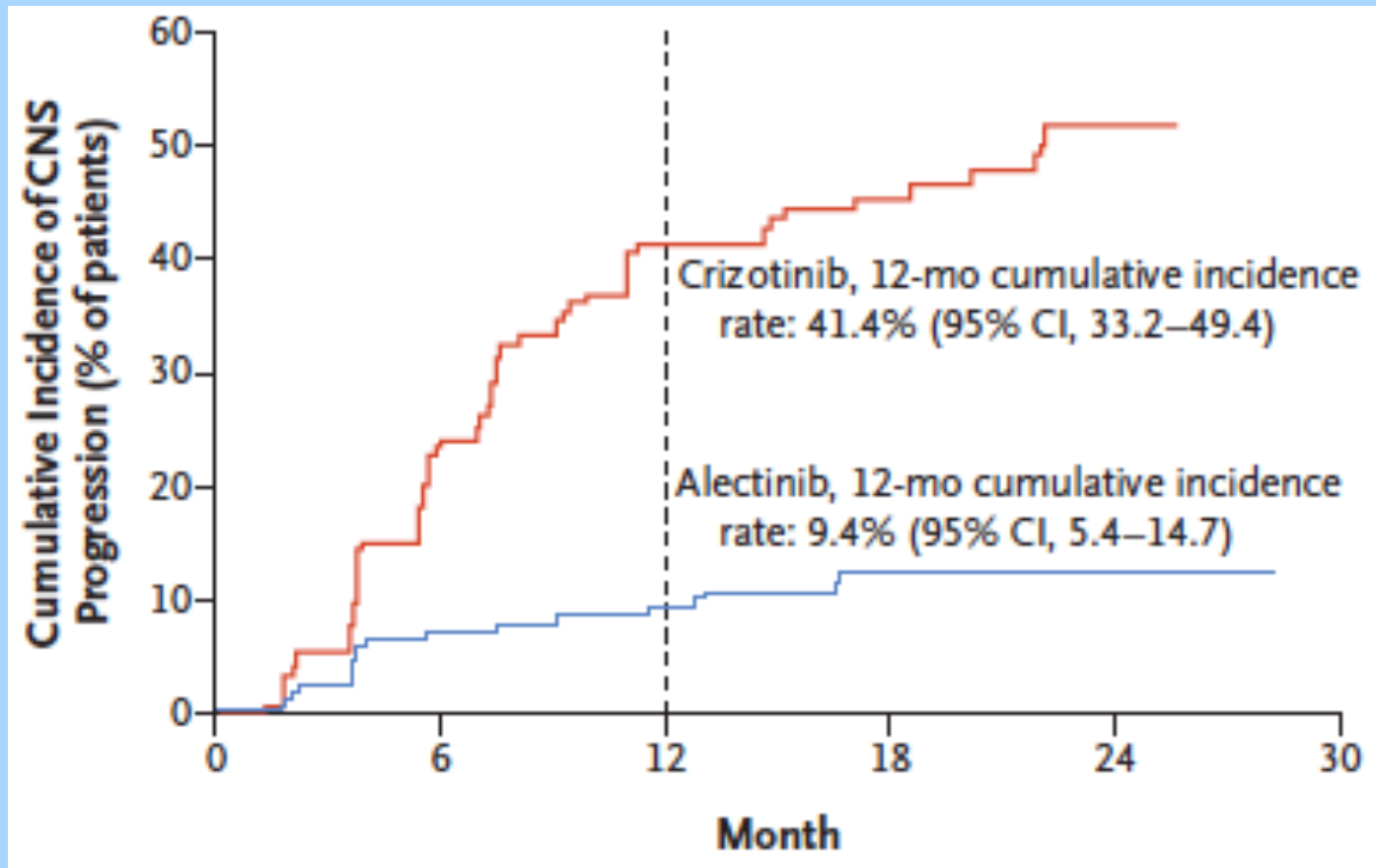
Alectinib vs Crizotinib trial survival



Brain metastases in patients with ALK-positive NSCLC

Alectinib vs Crizotinib trial

cumulative incidence of CNS progression

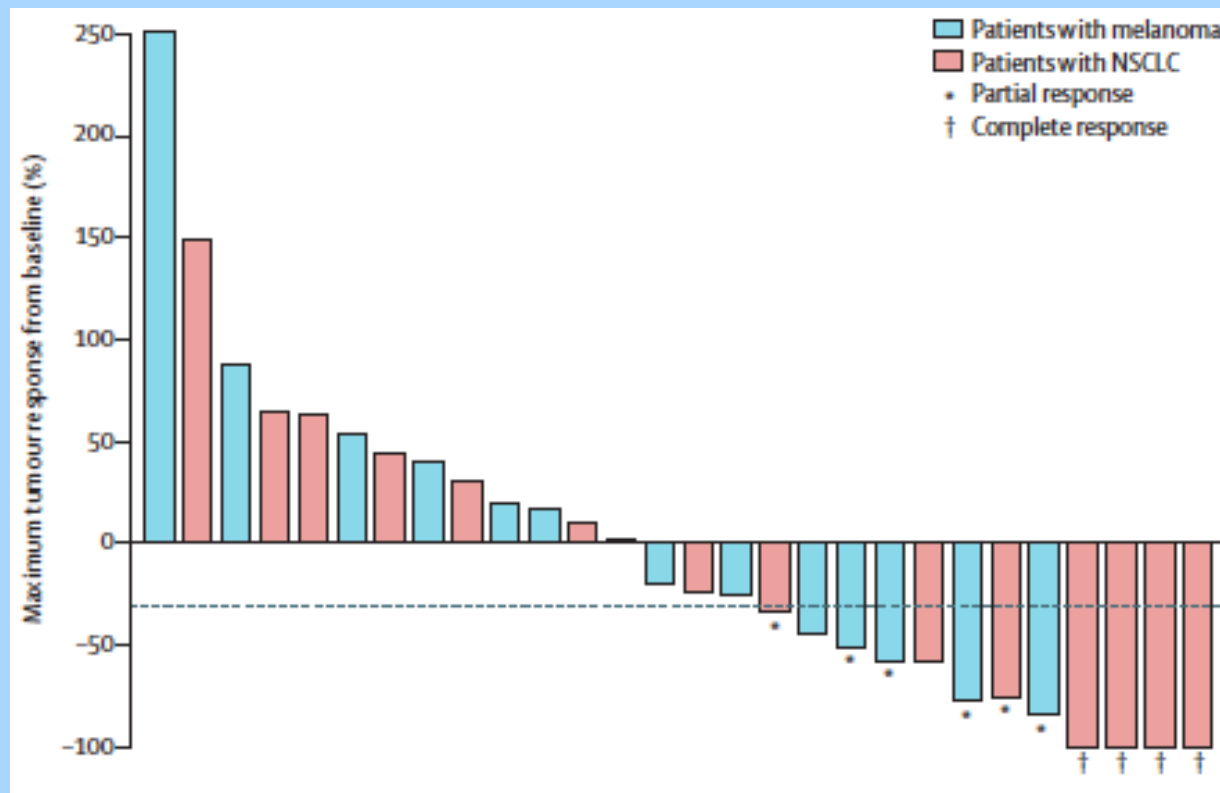


Brain metastases in patients with ALK-positive NSCLC

Pembrolizumab in melanoma

Phase II study

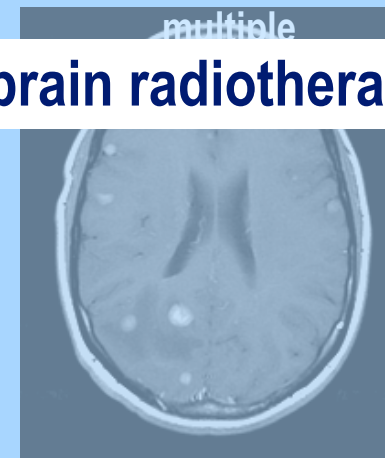
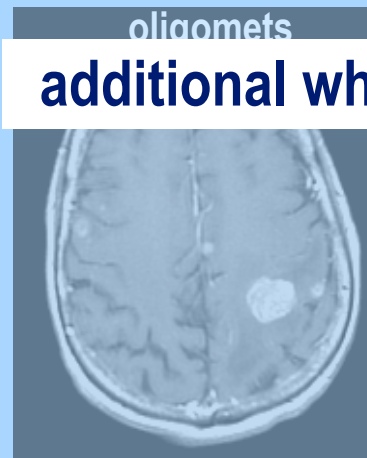
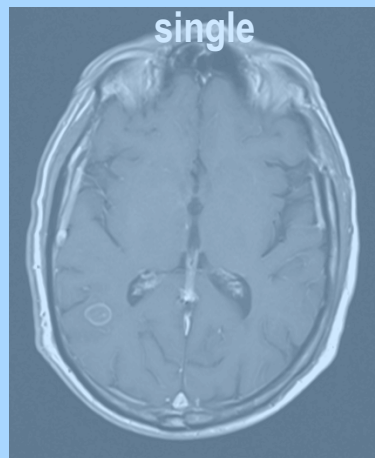
patients with untreated brain metastases from melanoma (18) & NSCLC (34)



Immune checkpoint inhibitors in patients with brain metastases

Matrix - radiotherapy options

No. met's	prognosis	1 ^o tumour	timing
single	responsive to systemic treatment		
oligomets			
multiple			



additional whole brain radiotherapy?

Radiotherapy in the management of brain metastases

Whole brain radiotherapy after systemic therapy in responders

prolongs survival

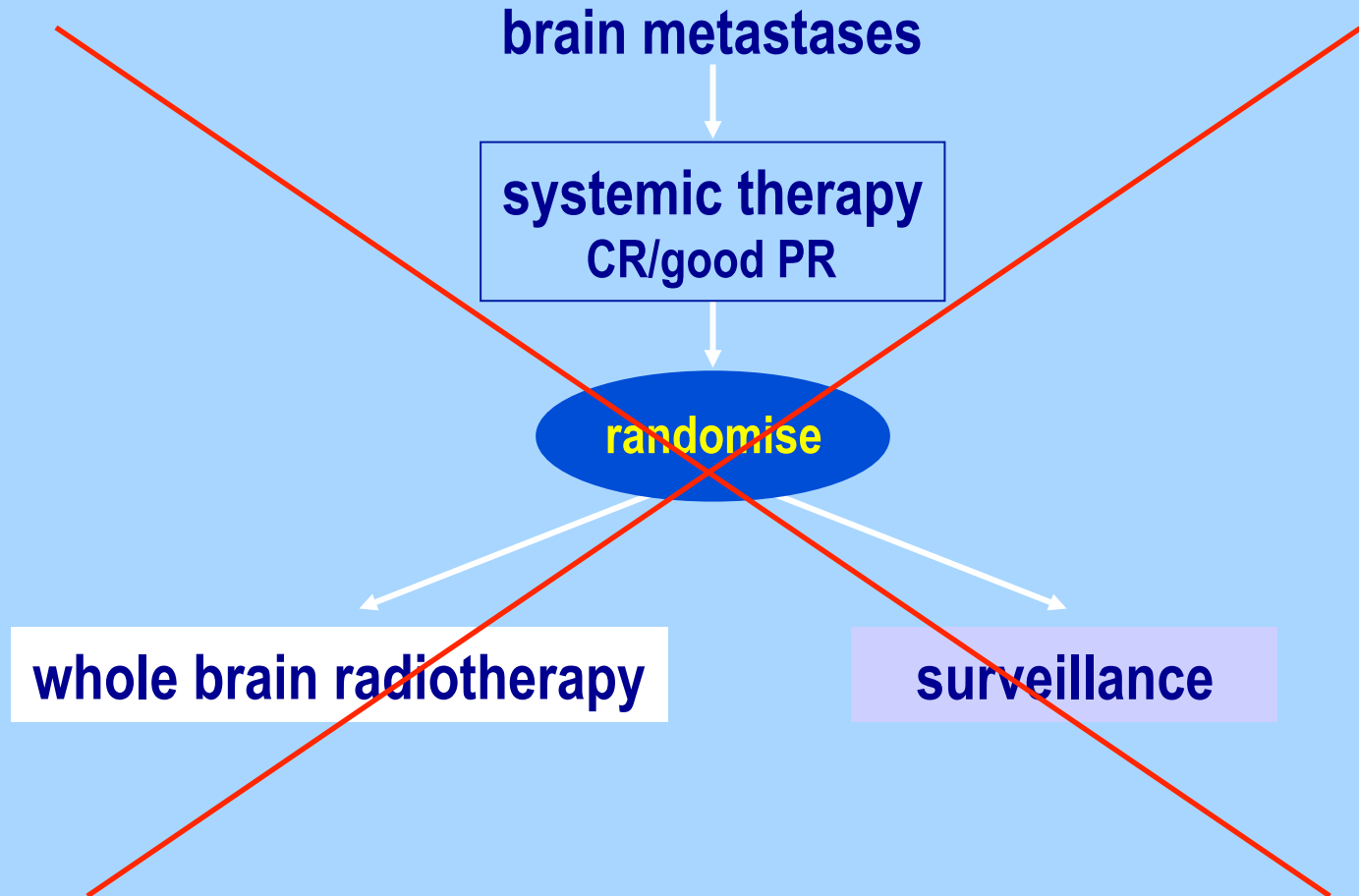
prolongs time to
functional deterioration

should be used shortly
after achieving CR

should be used at the
time of progression

should never be used

Tumours responsive to systemic treatment

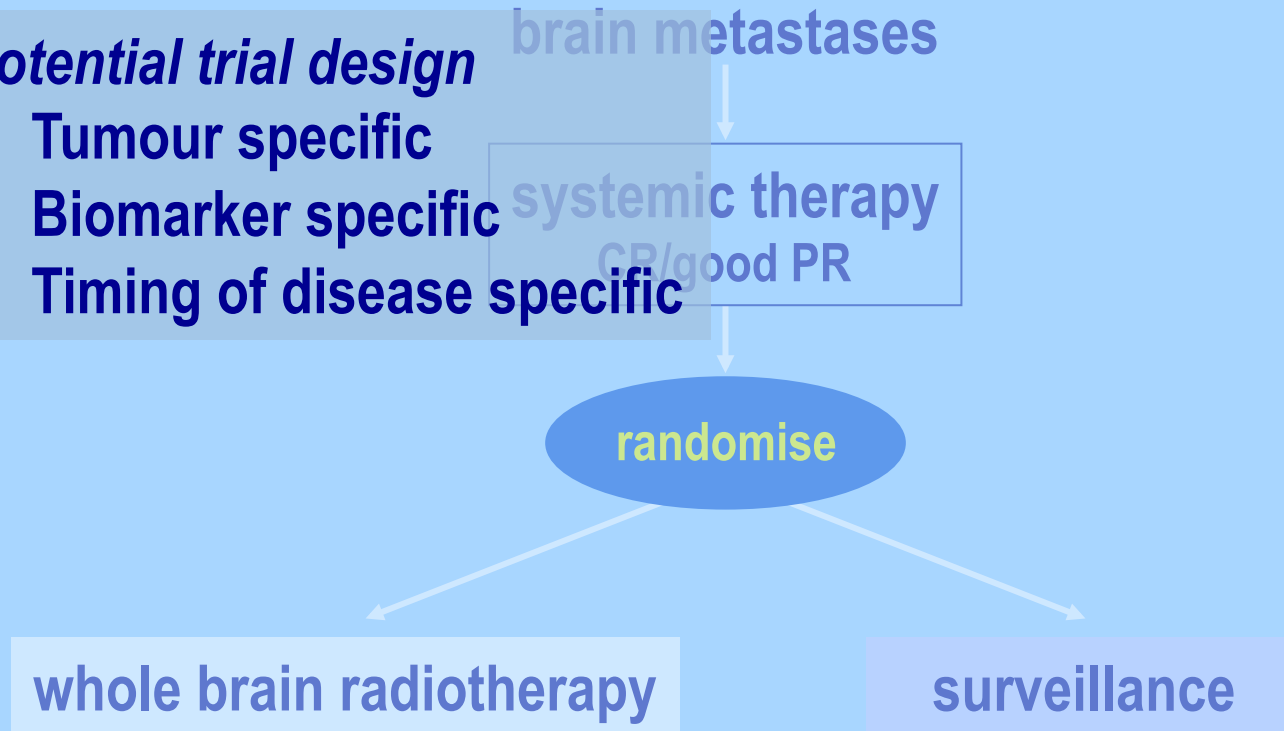


Role of radiotherapy in responsive tumours

Tumours responsive to systemic treatment

Potential trial design

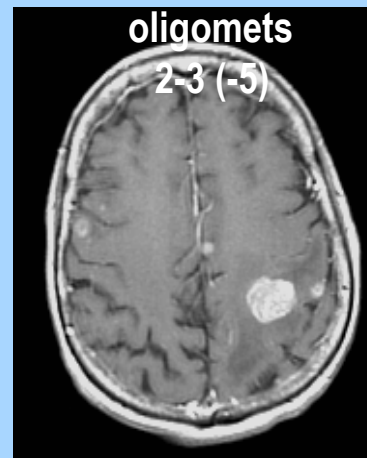
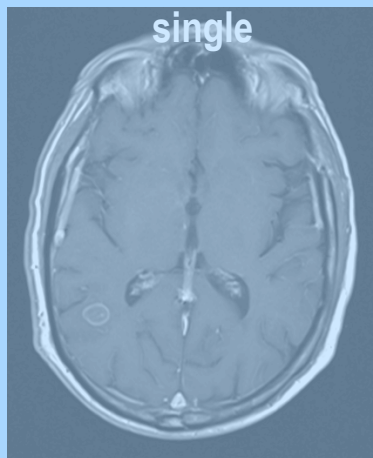
- Tumour specific
- Biomarker specific
- Timing of disease specific



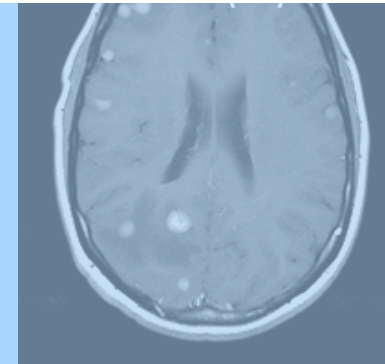
Role of radiotherapy in responsive tumours

Matrix - radiotherapy options

No. met's	prognosis	1 ^o tumour	timing
single			
oligomets	responsive to systemic treatment		
multiple			

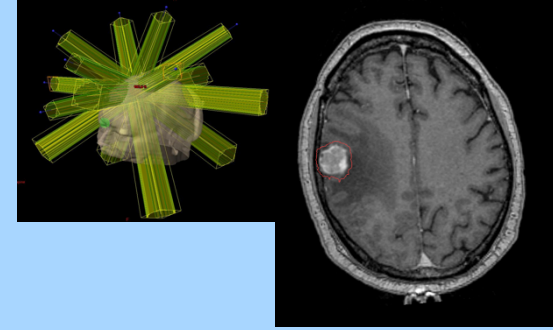


additional radiosurgery ?



Radiotherapy in the management of brain metastases

Synchronous oligometastases in non-small cell lung cancer



1 - 4 brain metastases
oligometastases

randomise

radiosurgery (SRS) (49)

chemotherapy (49)

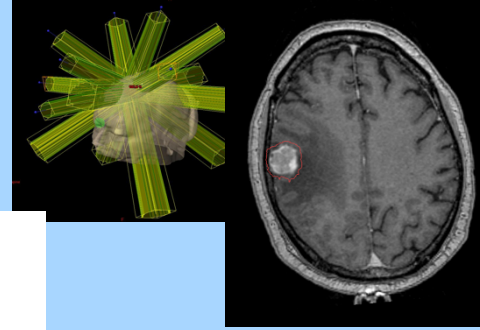
chemotherapy

98 patients - synchronous asymptomatic brain metastases

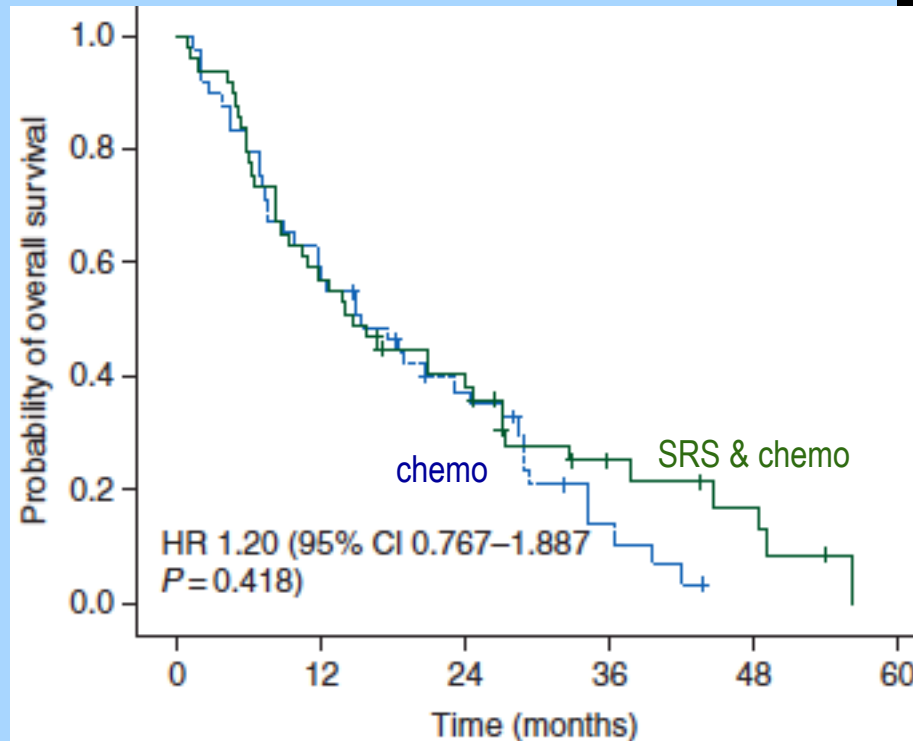
Samsung Medical Centre, Seoul 2008 - 13

Radiosurgery for synchronous brain oligometastases

Synchronous oligometastases in NSCLS



survival



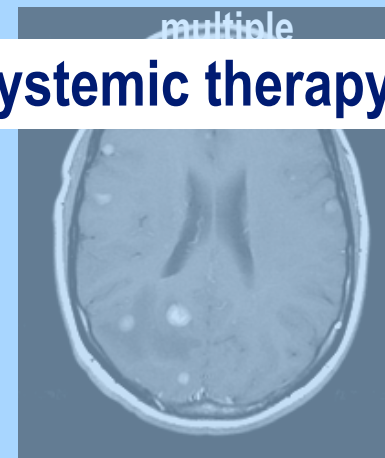
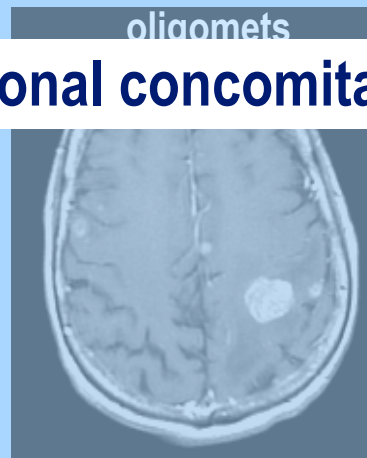
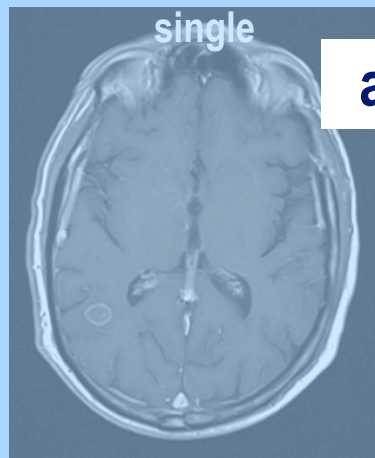
Number at risk

GKS	49	31	20	10	6	2
Upfront chemotherapy	49	31	19	7	2	0

Radiosurgery for synchronous brain oligometastases

Matrix - radiotherapy options

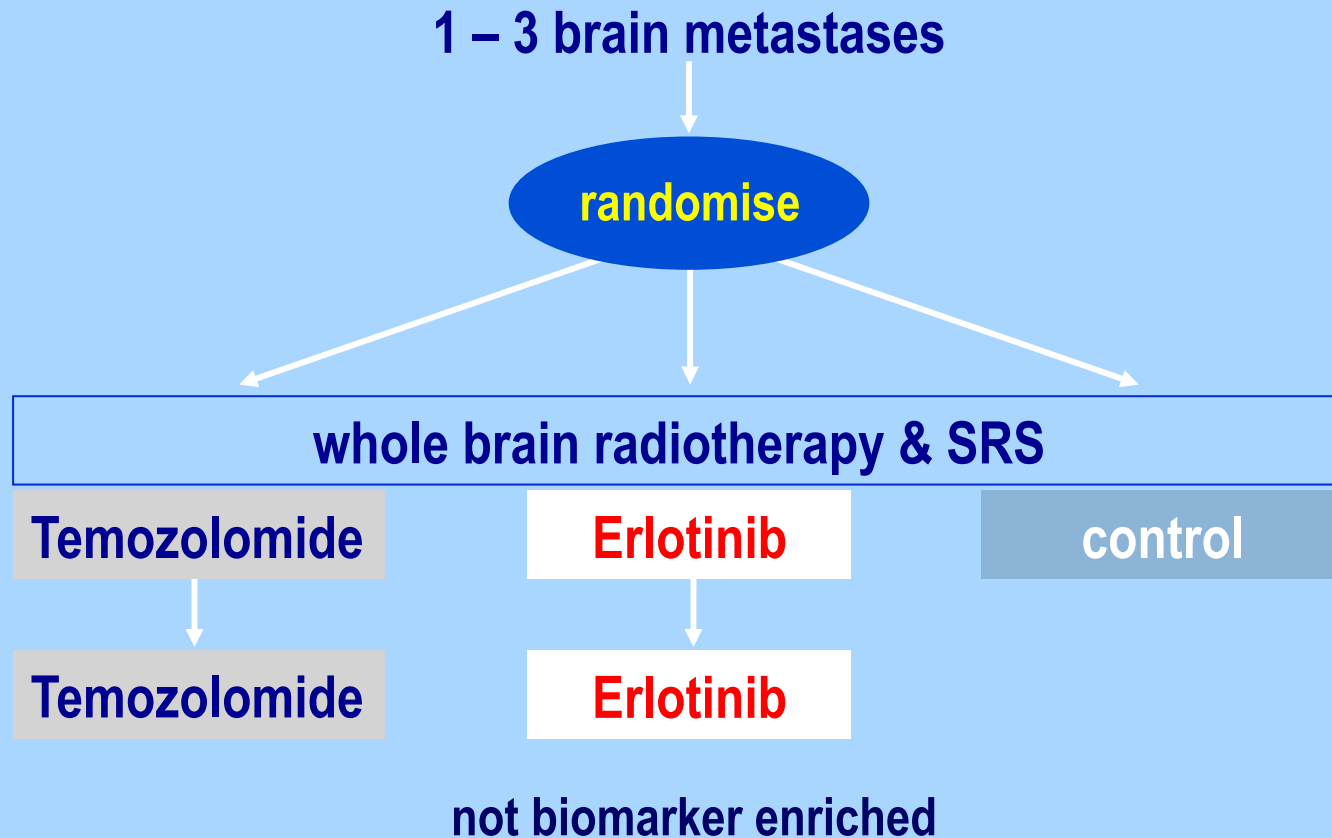
No. met's	prognosis	1 ^o tumour	timing
single	treated with radiotherapy		
oligomets			
multiple			



additional concomitant systemic therapy ?

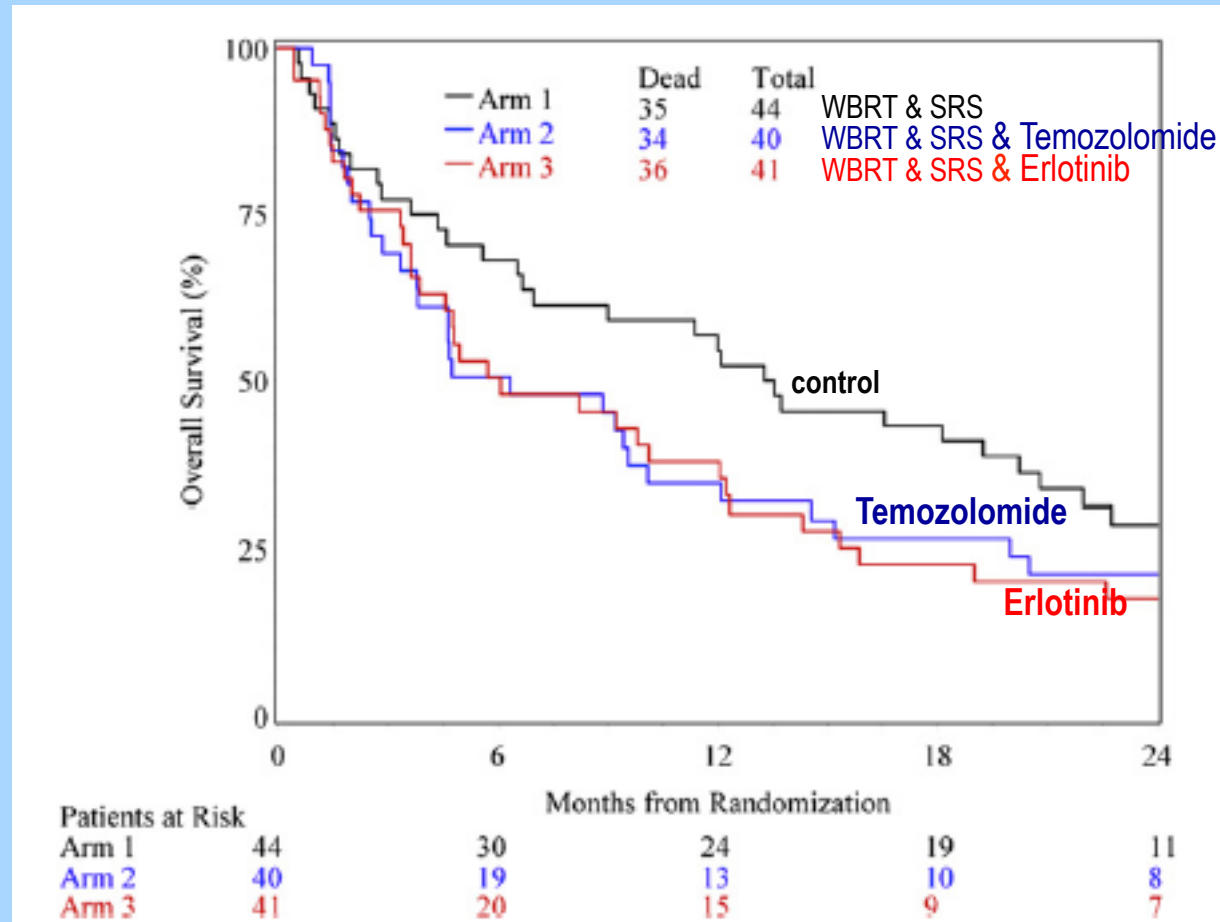
Radiotherapy in the management of brain metastases

non-small cell lung cancer brain metastases RTOG 0320



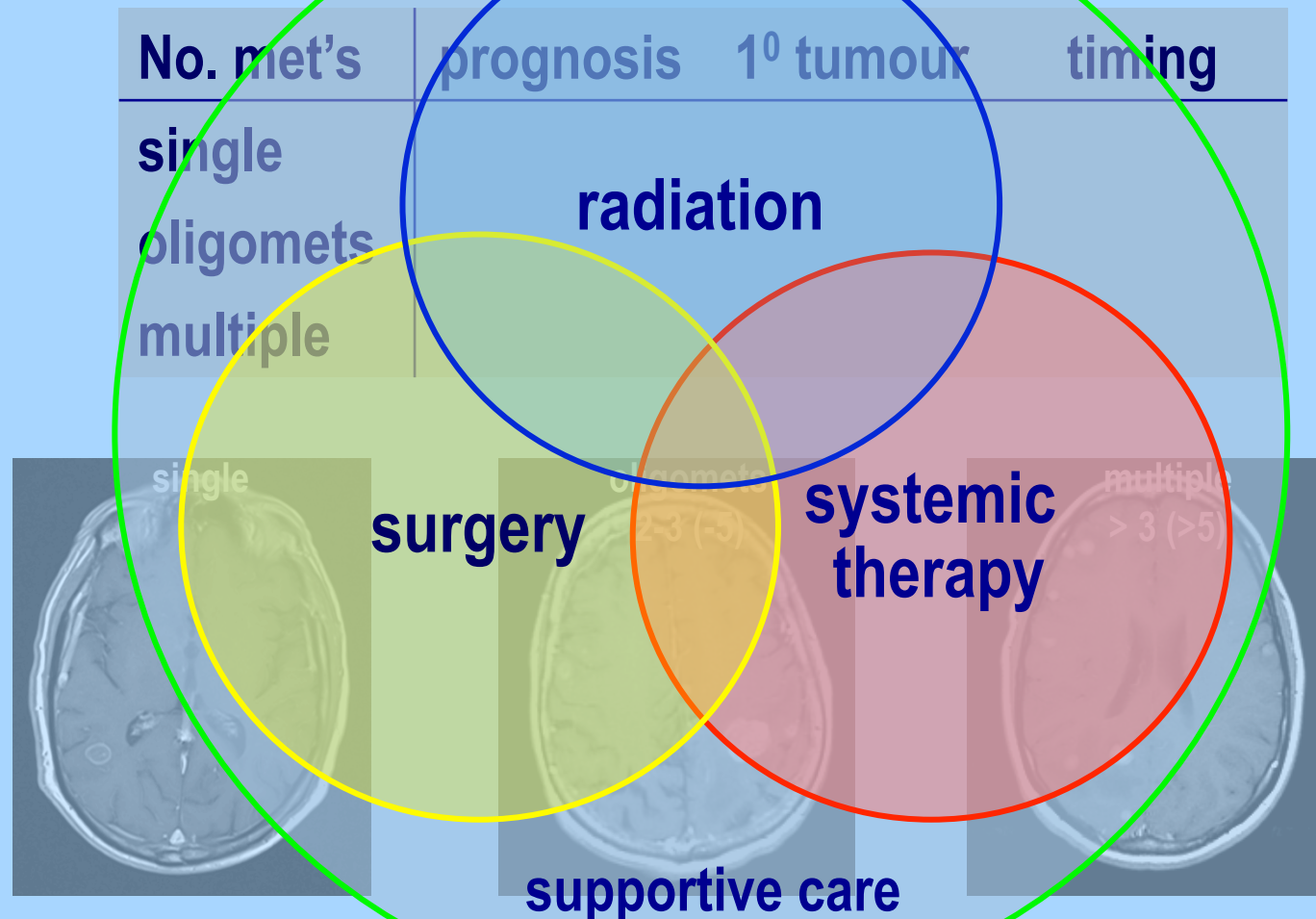
Additional systemic therapy in NSCLC brain metastases

non-small cell lung cancer brain metastases RTOG 0320



Additional systemic therapy in NSCLC brain metastases

Matrix - radiotherapy options



Evidence base for radiotherapy in the treatment of brain metastases



Radiosurgery in the management of brain metastases (2)

Michael Brada

University of Liverpool

Department of Molecular and Clinical Cancer Medicine
& Department of Radiation Oncology

Clatterbridge Cancer Centre NHS Foundation Trust
Bebington, Wirral, CH63 4JY

michael.brada@liverpool.ac.uk