THE BRISTOL
GAMMA KNIFE
CENTRE

Treatment of Melanoma Brain Metastases

Dr Chris Herbert
Consultant Clinical Oncologist
University Hospitals Bristol

Introduction

- Common in melanoma
  - 20-25% at diagnosis stage 4 disease
  - 70-80% at post-mortem
  - associated with poor prognosis (4-5 months)

Brain metastases: the goals

- Prolong overall survival
- Preservation or improvement of function
- Reduction or elimination of steroids
- Minimisation of side effects
- Continued treatment of extra-cranial disease

Brain metastases: what do we know?

- Tumours are moderately well circumscribed
- Resection has an important role especially for large tumours
- Survival is related to extra-cranial disease
- Prolonged survival is possible

Options for treatment

- Systemic therapy
  - Immunotherapy
    - Ipilimumab + nivolumab
    - Pembrolizumab/nivolumab
    - Ipilimumab
  - Targeted therapy
    - Dabrafenib/vemurafenib
    - Dabrafenib + trametinib / vemurafenib + cobimetinib
- Focal therapy
  - Stereotactic radiosurgery
  - Surgery
  - ?Whole brain radiotherapy

Systemic therapy

	ACTIVE BRAIN METASTASES		NO ACTIVE BRAIN METASTASES	
	Response	**1 year OS**	**Response**	**1 year OS**
Dabrafenib (n=89+83)	39%	-	53%	68%
Vemurafenib (90+56)	33%	35%	51%	65%
Ipilimumab (n=51+21)	10%	31%	19%	67%
Pembrolizumab (n=14)	22%	-	37%	71%
Dabrafenib / trametinib (n=76+49)	58%	-	67%	74%
Ipilimumab/ nivolumab (n=30+45)	50%	-	58.9%	73%

Stereotactic Radiosurgery

- Definition:

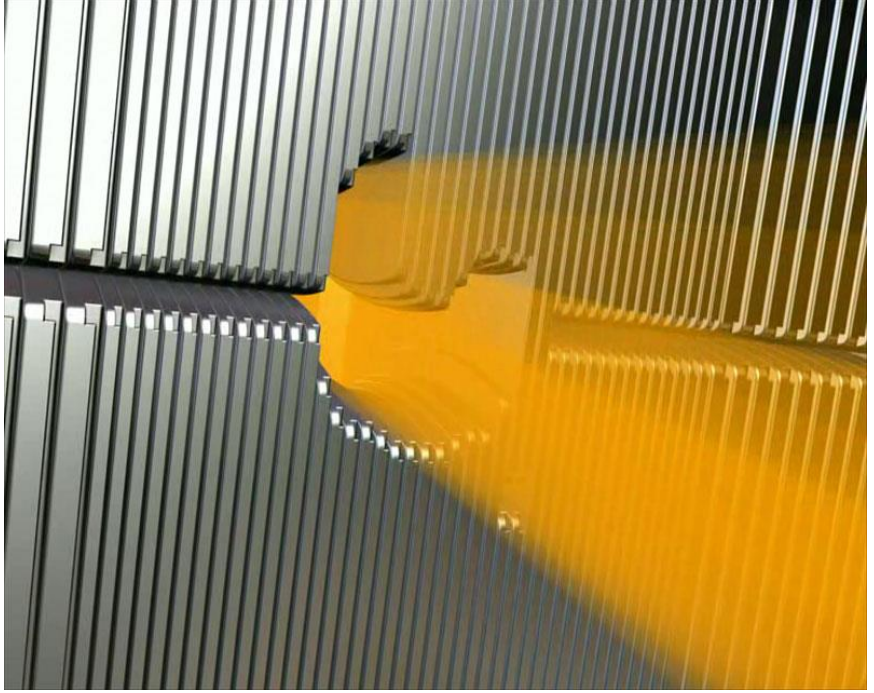
"*The use of external radiation in conjunction with a stereotactic guidance device to very precisely deliver a therapeutic dose to a tissue volume "*

Nuclear Regulatory Commission (NRC)

Definition: Radiosurgery

- Typically performed in a single session, limited to a maximum of five sessions.
- Using a rigid stereotactic guiding device
  - Leksell frame
  - mask

Linac base system:
True Beam STX



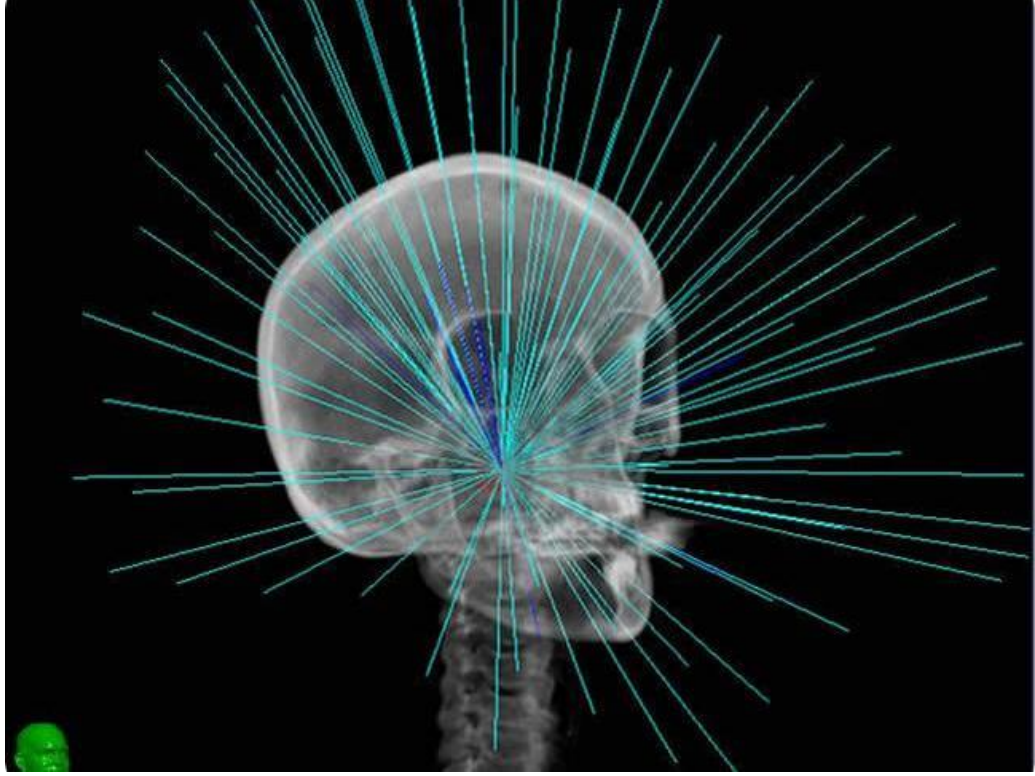
Advantages:
Quick to treat
Can be used for conventional treatment and all parts of the body

Disadvantages:
Less conformal so higher dose to tissue outside the lesion- potentially greater side effects
Longer planning time
Can not treat very small lesions or multiple lesions well
Accuracy of isocentre worse

THE BRISTOL
GAMMA KNIFE
CENTRE

CyberKnife

Advantages:
All of body
No need for fixed frame

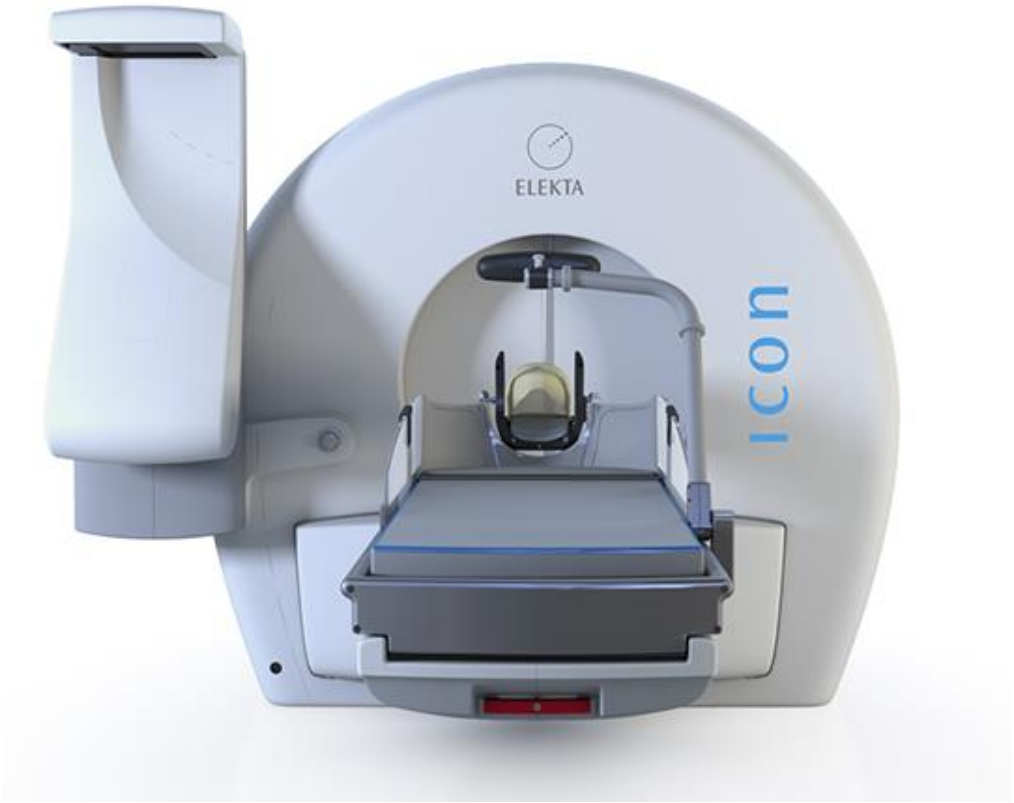


Disadvantages:
Slow to plan and treat
expensive
Big bunker

Advantages:

- Excellent conformity of dose to lesion
- Steep drop of dose outside the tumour
- Quick to plan
- Multiple tumours
- Stereotactic radiotherapy
- Mask or fixed frame

Gamma Knife:
Icon



Disadvantages:

- Can only treat the head

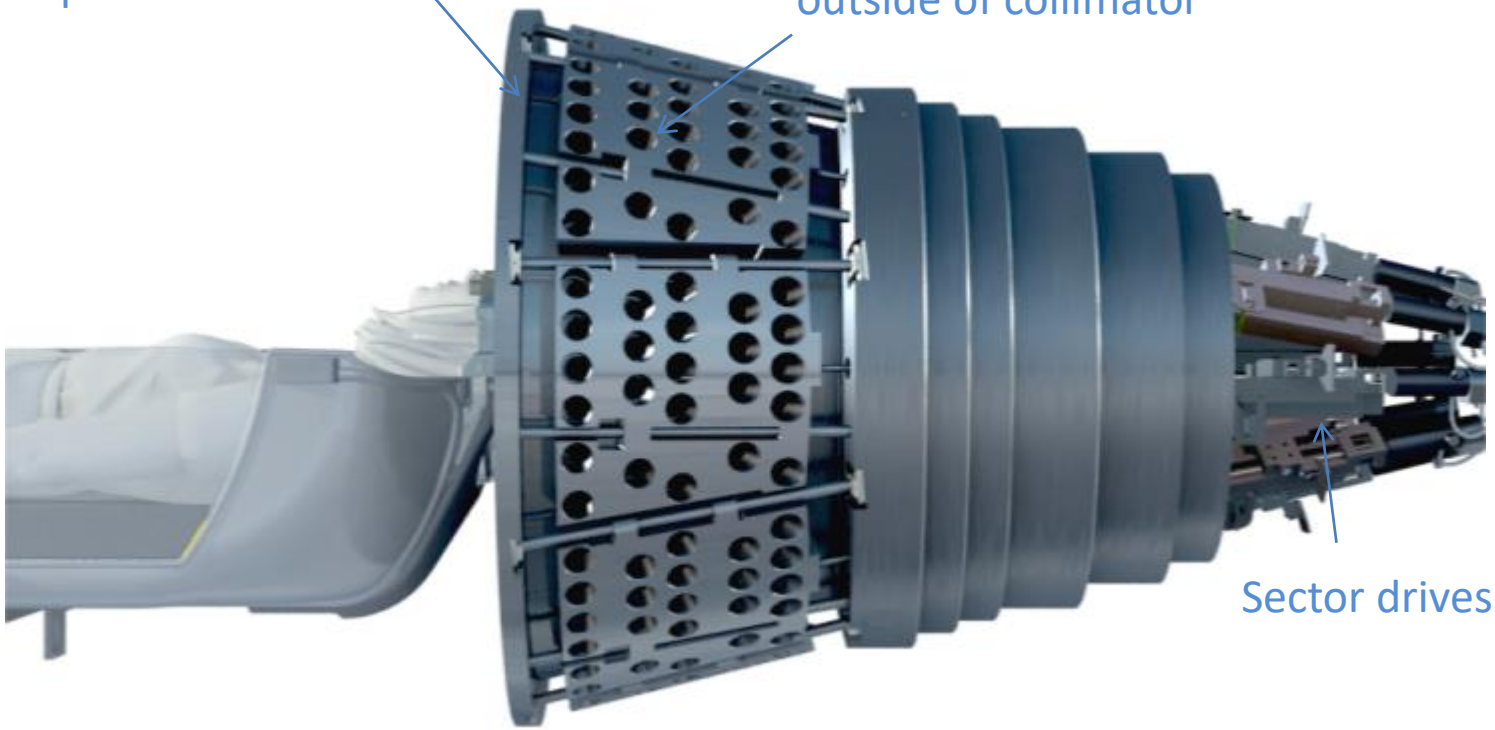
How a Gamma knife works

192 sources in total

8 independent, identical sectors

24 sources per sector

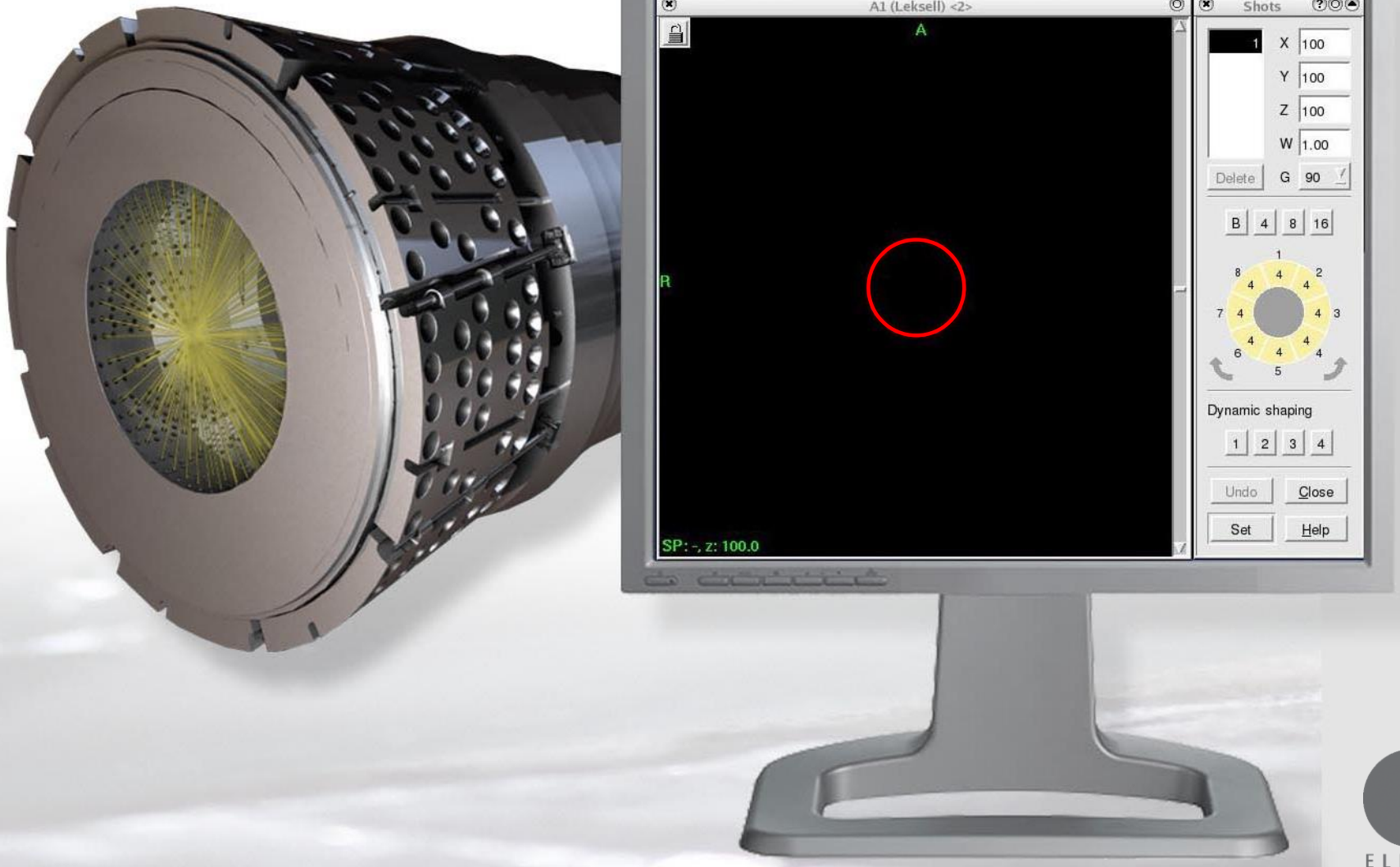
Sectors slide back and forth on outside of collimator



Sector drives

Sources are arranged in 5 rings

Planning- shot size and shape

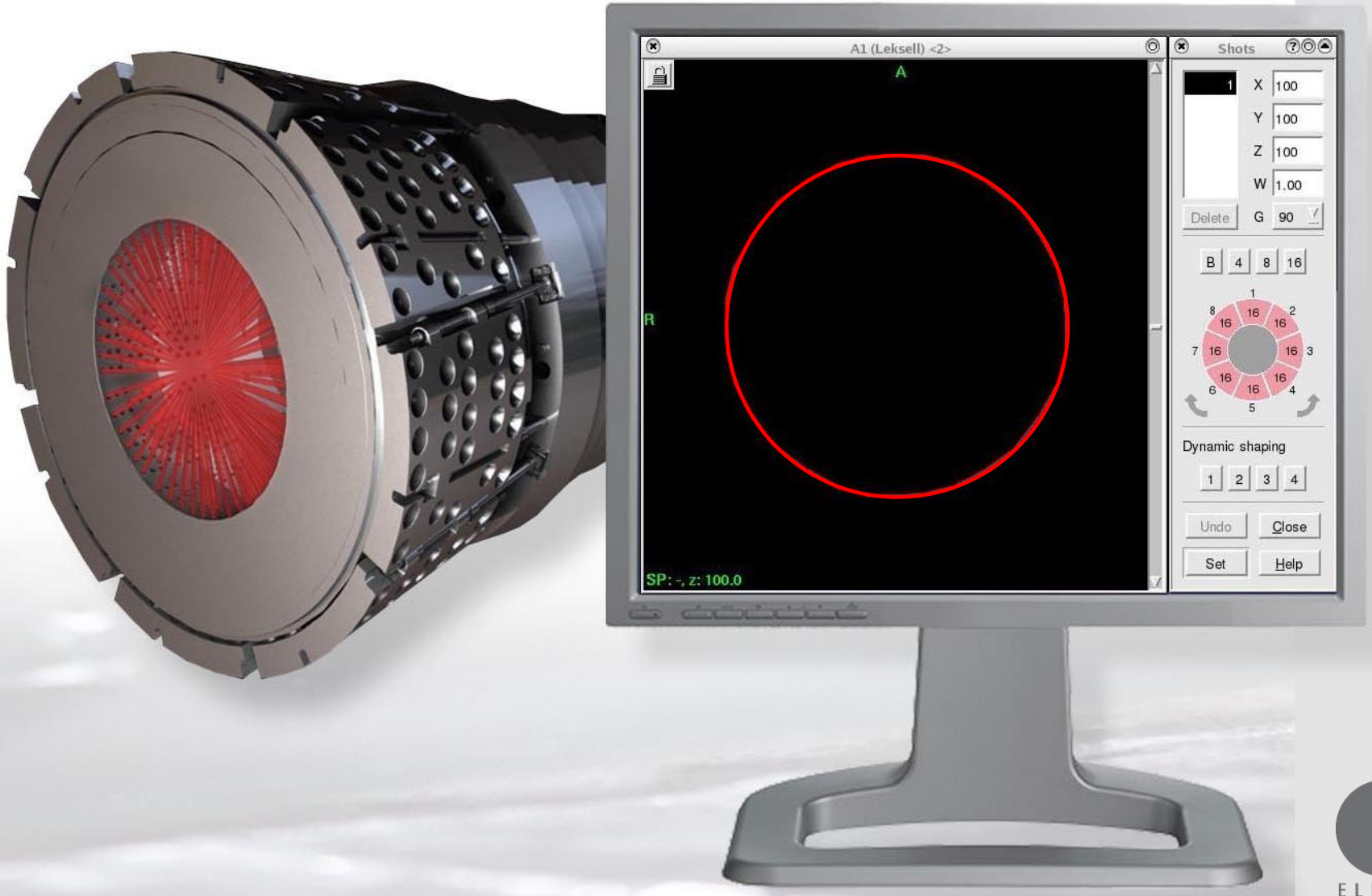


ELEKTA

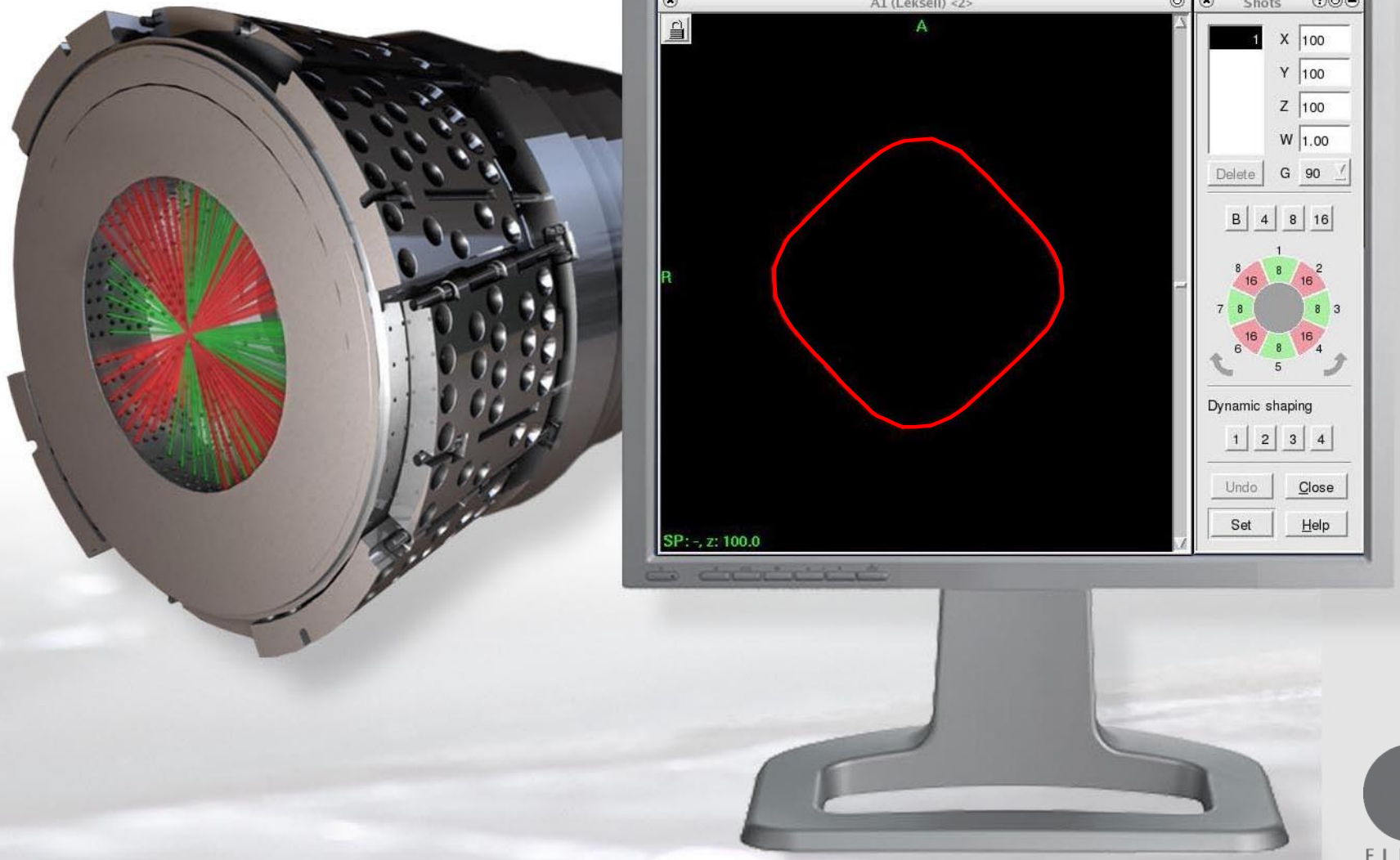
Planning- shot size and shape

ELEKTA

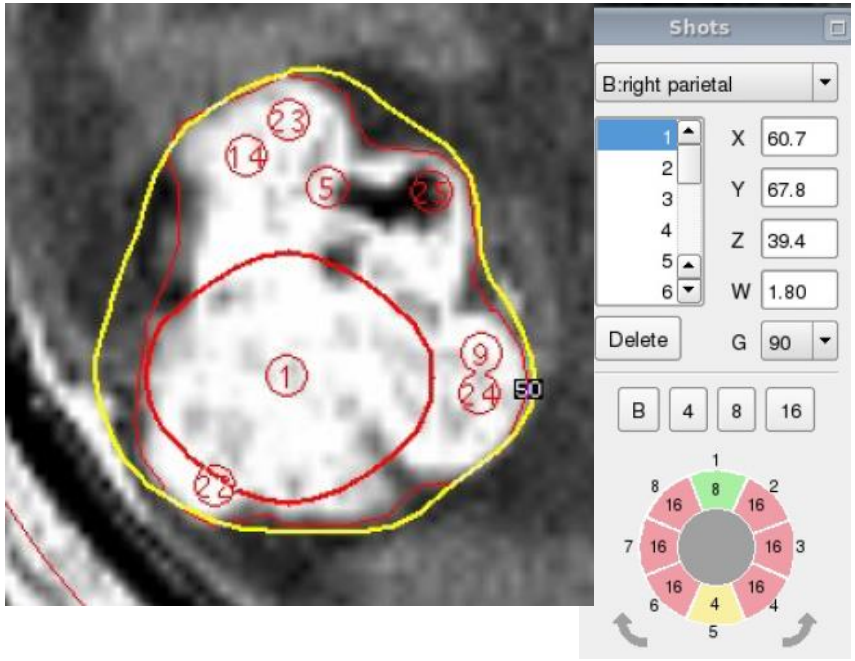
Planning- shot size and shape

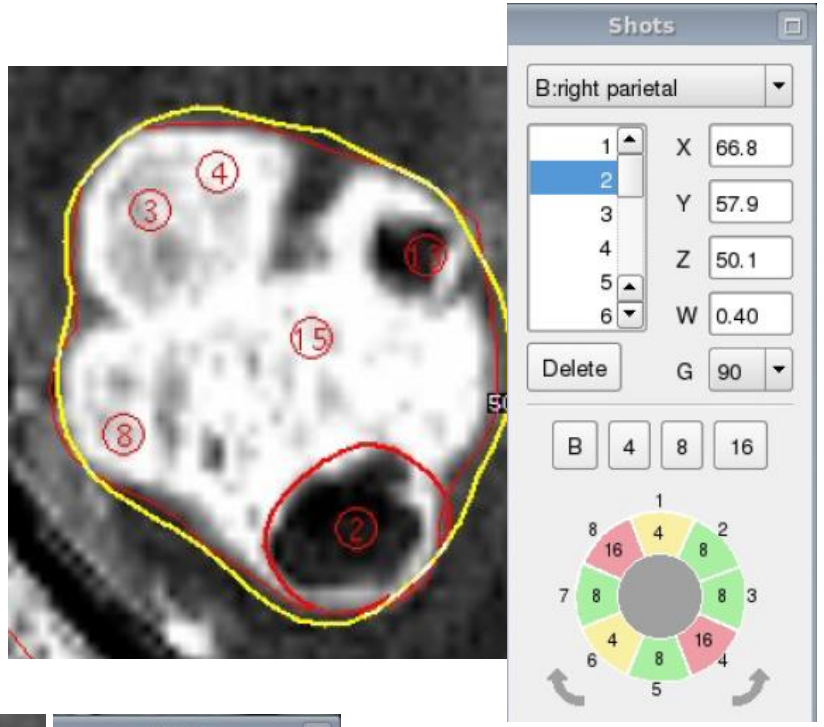


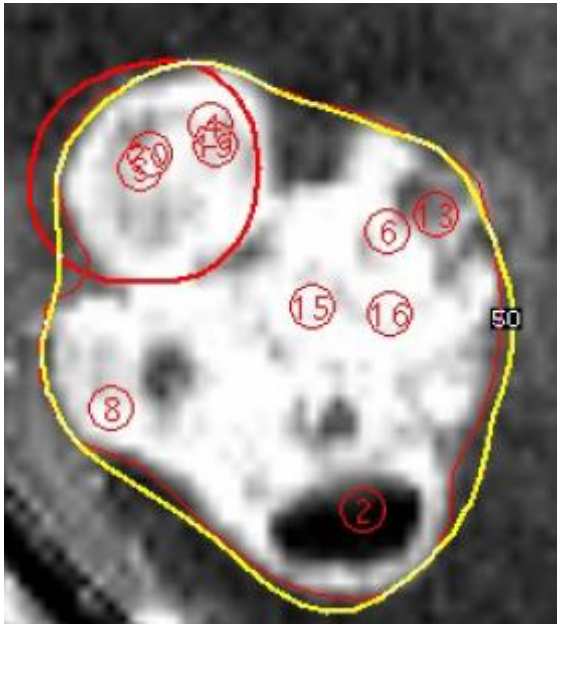
Planning- shot size and shape



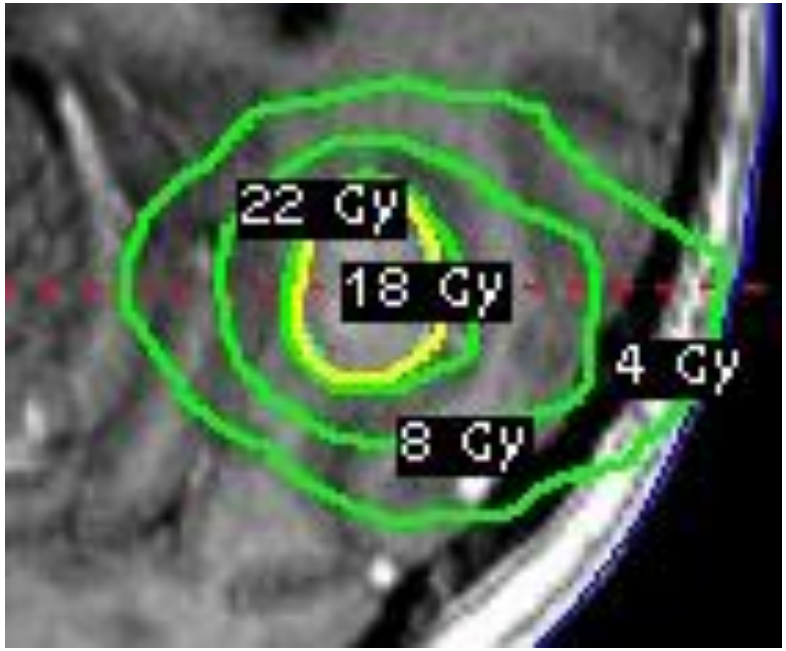
ELEKTA

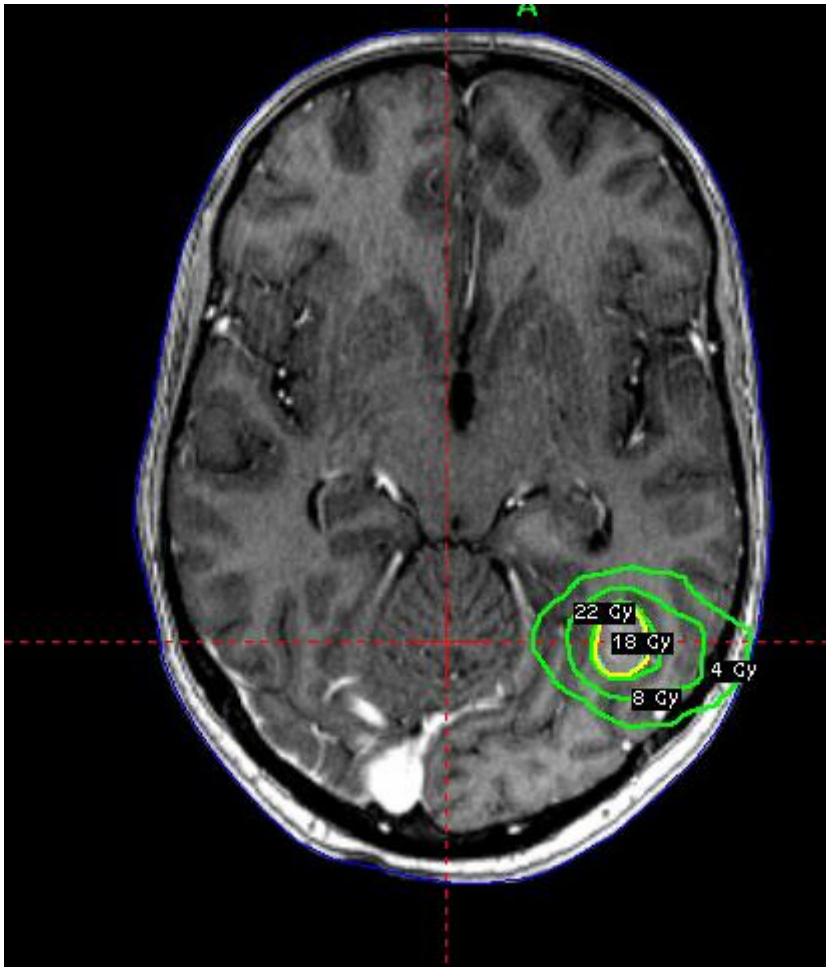

Shots
B:right parietal
1
2
3
4
5
6
X 60.7
Y 67.8
Z 39.4
W 1.80
G 90
Delete
B 4 8 16


Shots
B:right parietal
1
2
3
4
5
6
X 66.8
Y 57.9
Z 50.1
W 0.40
G 90
Delete
B 4 8 16

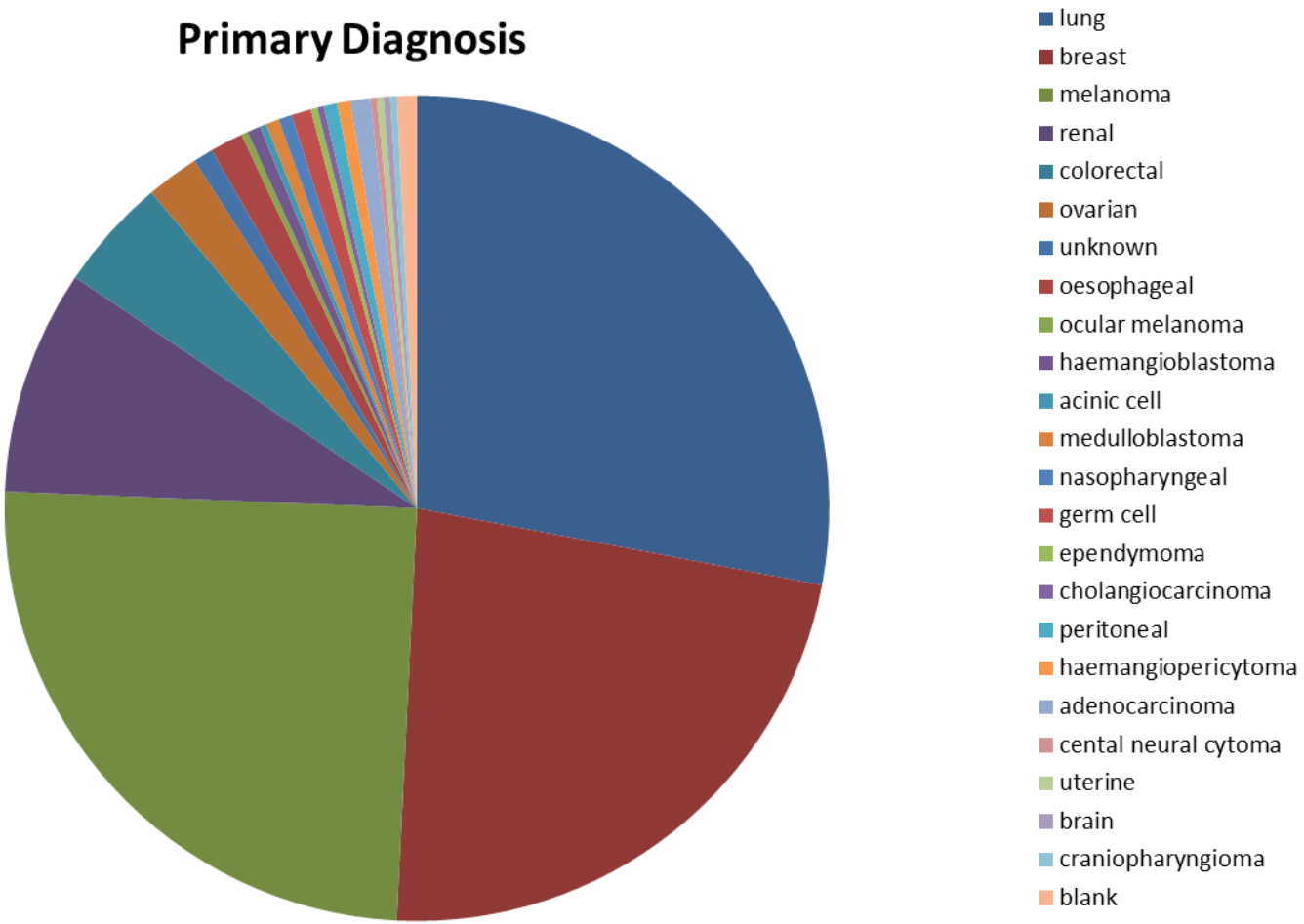

Shots
B:right parietal
1
2
3
4
5
6
X 52.7
Y 80.4
Z 50.7
W 1.01
G 90
Delete
B 4 8 16

Isodoses





648 patients treated
383 brain metastases patients



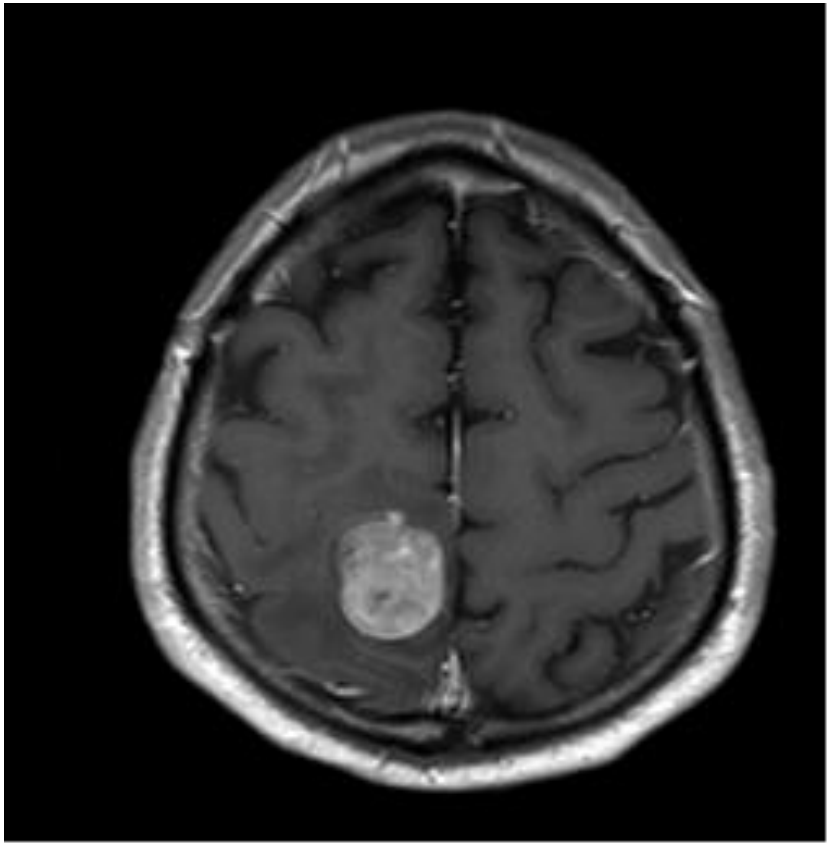
THE BRISTOL
GAMMA KNIFE
CENTRE

- Clearly defined selection criteria
  - Prognosis >6 months
  - Patient must be WHO performance status 0-2
  - ***No*** or ***controlled*** metastatic disease elsewhere
  - Lesions must be less than or equal to 20cc total volume

THE BRISTOL
GAMMA KNIFE
CENTRE

Case history

- April 2015
  - Presents with left leg weakness
- May 2015
  - Resection of 3cm right frontal metastasis
    - Melanoma BRAF +ve
    - No primary



THE BRISTOL
GAMMA KNIFE
CENTRE

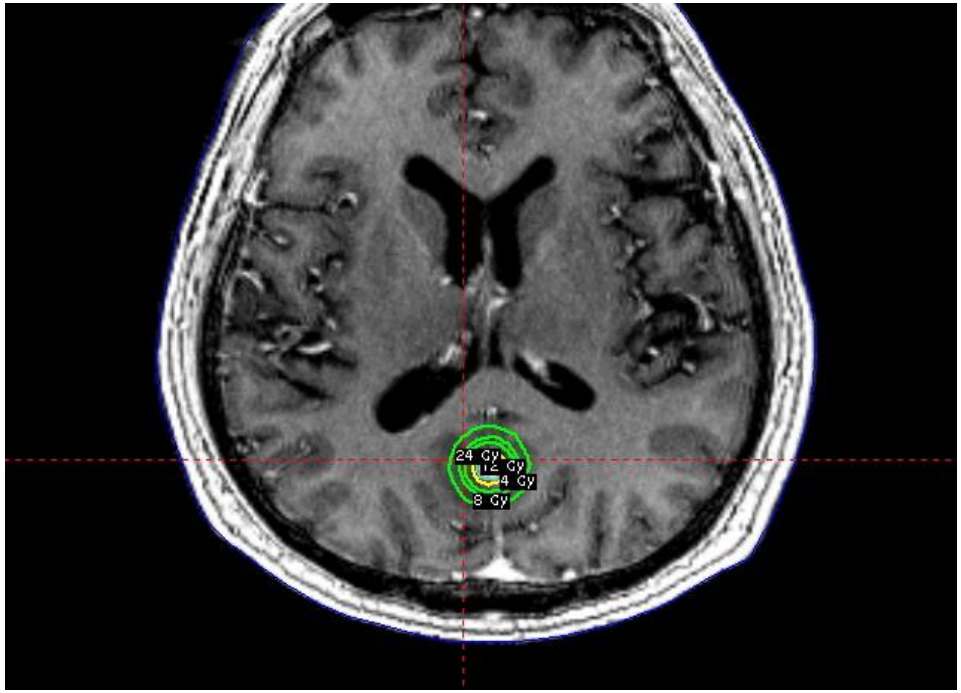
Case history

- July 2015
  - CHECKMATE-238
    - MRI shows recurrence plus 3 new brain metastases
    - No extracranial disease
- Aug 2015
  - BRAF inhibitor
  - SRS to 4 lesions

THE BRISTOL
GAMMA KNIFE
CENTRE

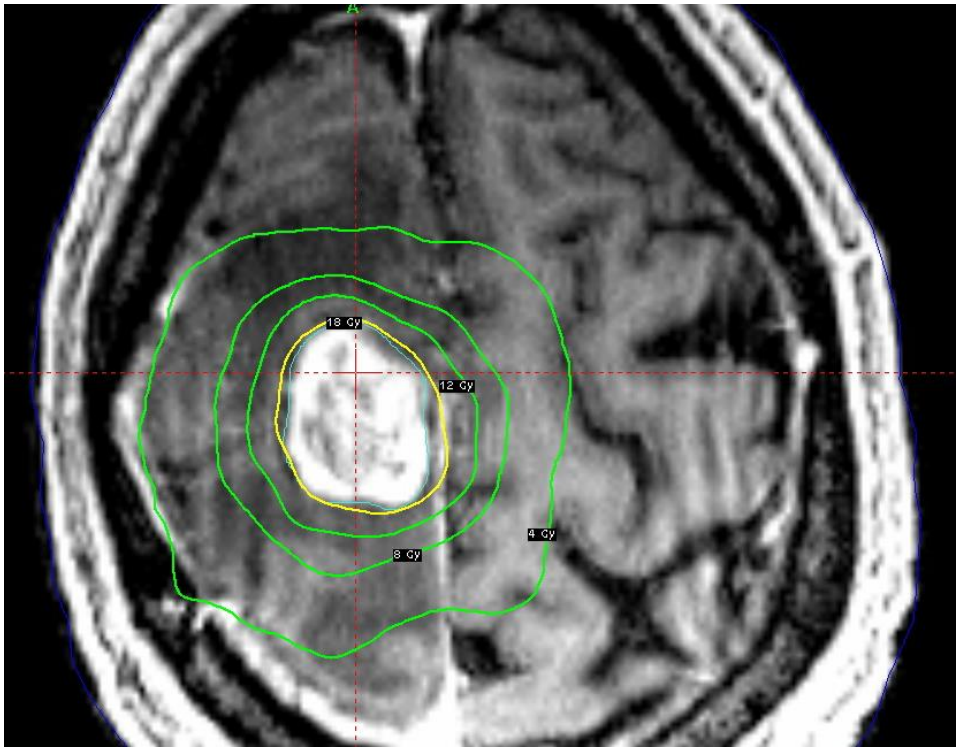
Case history

- Feb 2016
  - Further brain metastasis
  - SRS
  - pembrolizumab



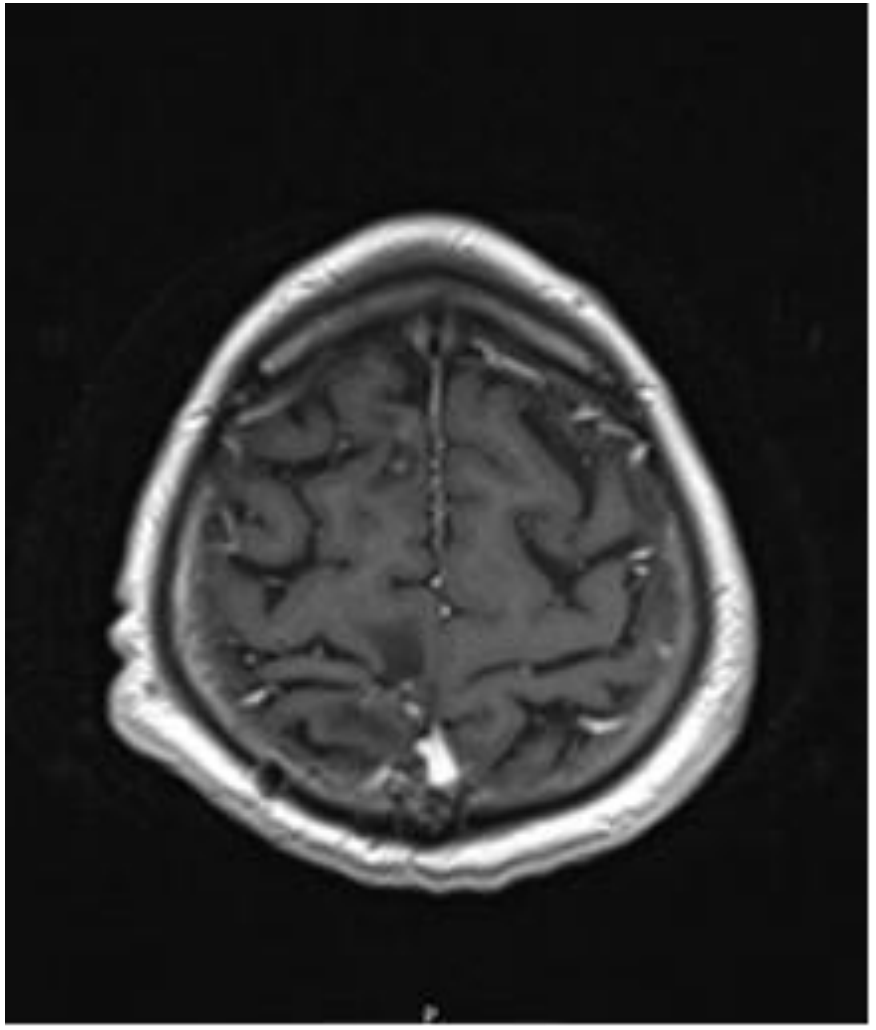
Case history

- July 2016
  - 2 further brain metastases treated SRS
  - Continues pembrolizumab



Case history

May 2017

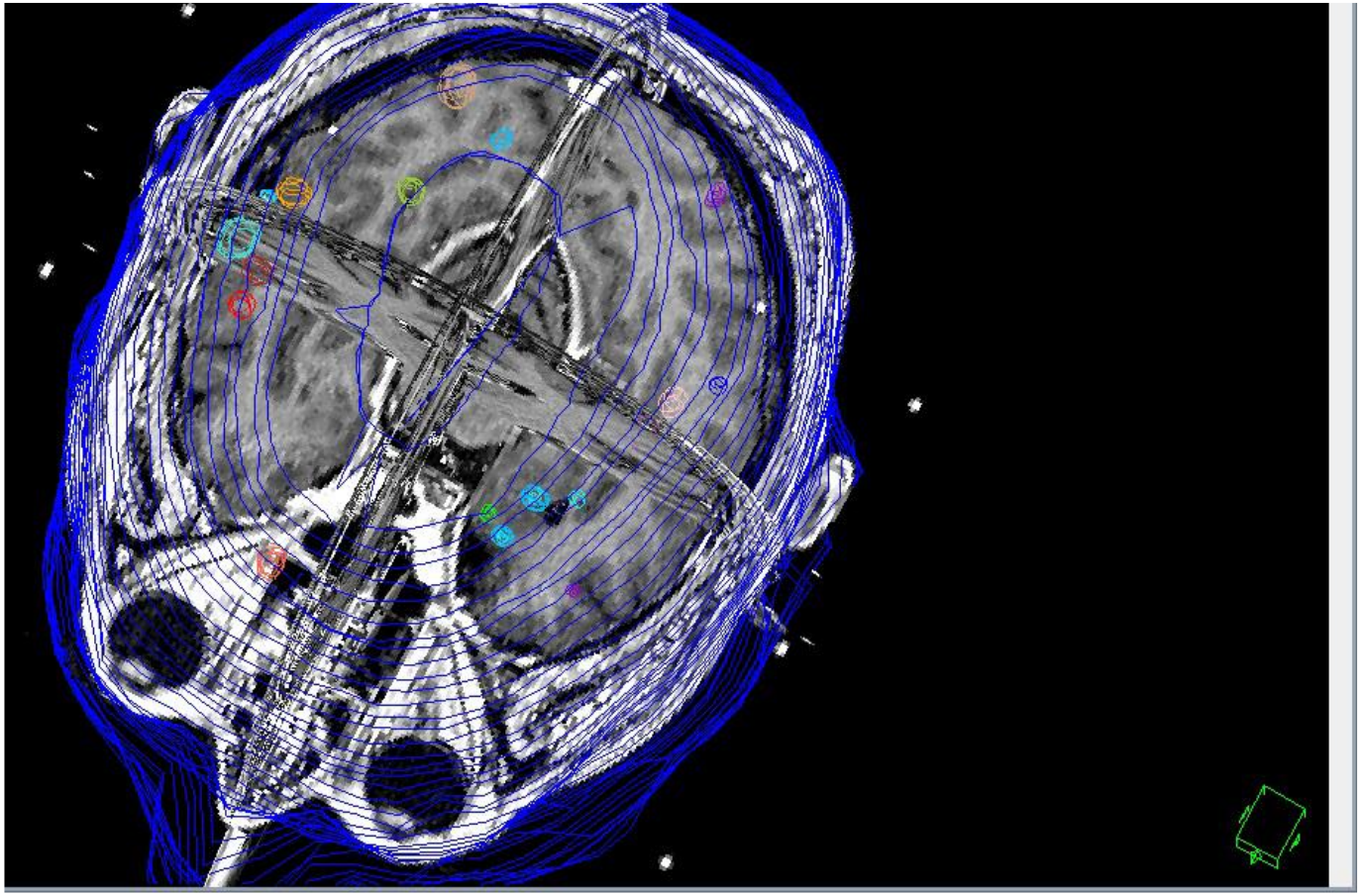


Multiple metastases

- Yamamoto et al.
  - 1194 patients
  - No WBRT
  - Median OS 1 metastasis = 13.9 months
  - Median OS 2-4 metastases = 10.8 months
  - Median OS 5-10 metastases = 10.8 months
- SRS without WBRT in patients 5-10 mets is non-inferior to that in patients with 2-4 mets

Stereotactic radiosurgery for patients with multiple brain metastases (JLGK0901): a multi-institutional prospective observational study

Masaaki Yamamoto, Toru Serizawa*, Takashi Shuto, Atsuya Akabane, Yoshinori Higuchi, Jun Kawagishi, Kazuhiro Yamanaka, Yasunori Sato, Hidefumi Jokura, Shoji Yomo, Osamu Nagano, Hiroyuki Kenai, Akihito Moriki, Satoshi Suzuki, Yoshihisa Kida, Yoshiyasu Iwai, Motohiro Hayashi, Hiroaki Onishi, Masazumi Gondo, Mitsuya Sato, Tomohide Akimitsu, Kenji Kubo, Yasuhiro Kikuchi, Toru Shibasaki, Tomoaki Goto, Masami Takanashi, Yoshimasa Mori, Kintomo Takakura, Naokatsu Saeki, Etsuo Kunieda, Hidefumi Aoyama, Suketaka Momoshima, Kazuhiro Tsuchiya*



Where?

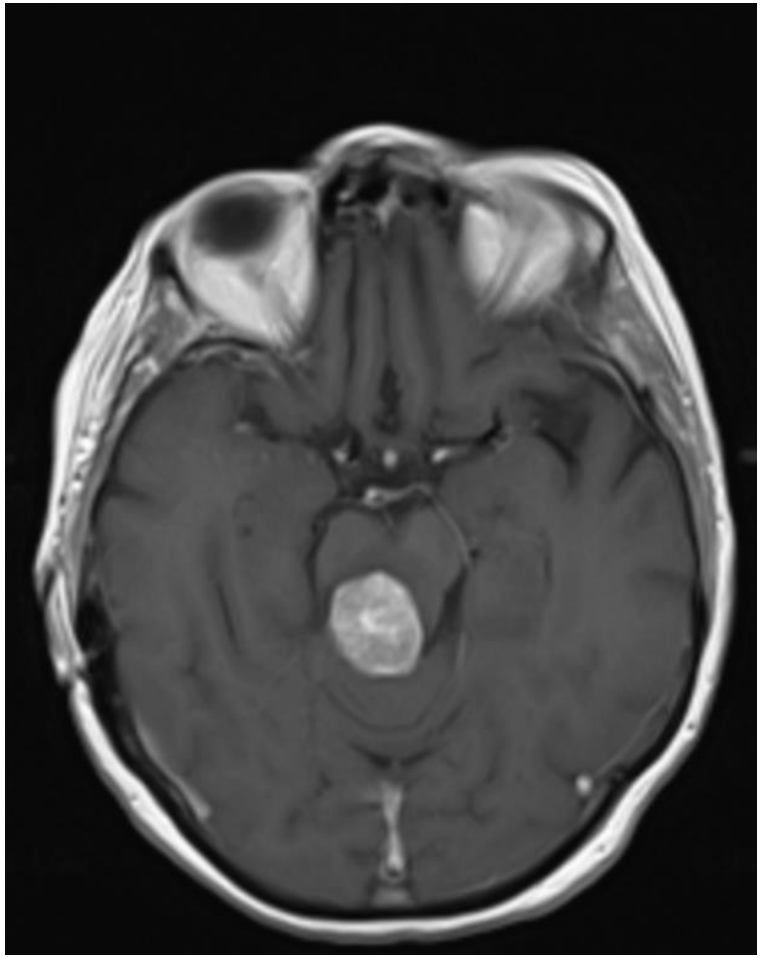
- Anywhere in brain or skull base

- Special considerations
  - Brain stem

Where?

- Case study
  - 69 year old
  - T2 N2 G3 ER +ve, HER-2 -ve breast cancer diagnosed 2008.
  - Treated mastectomy, 6xFEC chemotherapy, chest wall radiotherapy and tamoxifen
  - Presented in March 2012 with dizziness, falls and diplopia
    - Shunt for hydrocephalus

Where? Breast cancer brainstem metastasis



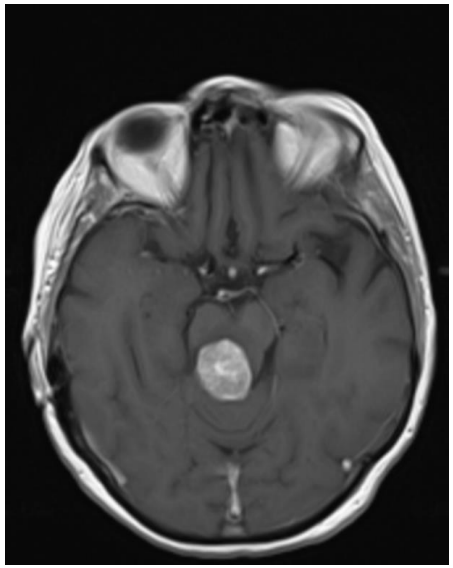
Treated with radiosurgery 12Gy to 80% April 2012

Required prolonged steroid use after treatment

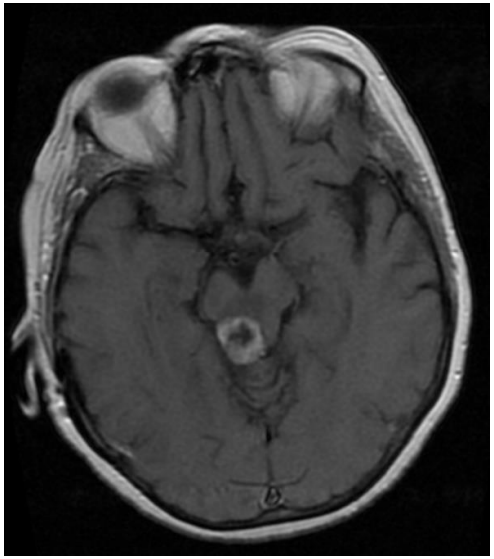
THE BRISTOL
GAMMA KNIFE
CENTRE

Where? Breast cancer brainstem metastasis

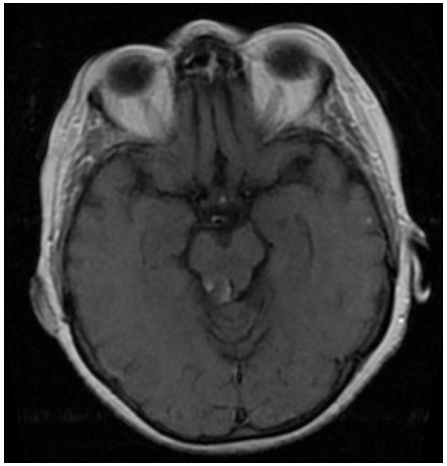
March 2012



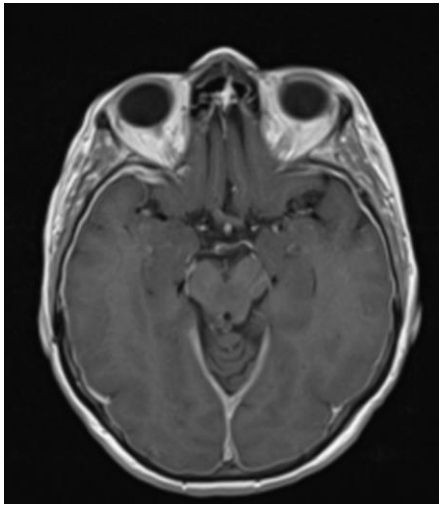
August 2012



March 2013



April 2014



What about large metastases?

- Fractionated treatment of brain metastases
  - Fractionation schedules
    - 24-30Gy 3#
    - **20-30Gy 2-3# with 2 week gap between fractions**
    - Use for volumes >10cc?

Adaptive fractionated treatment

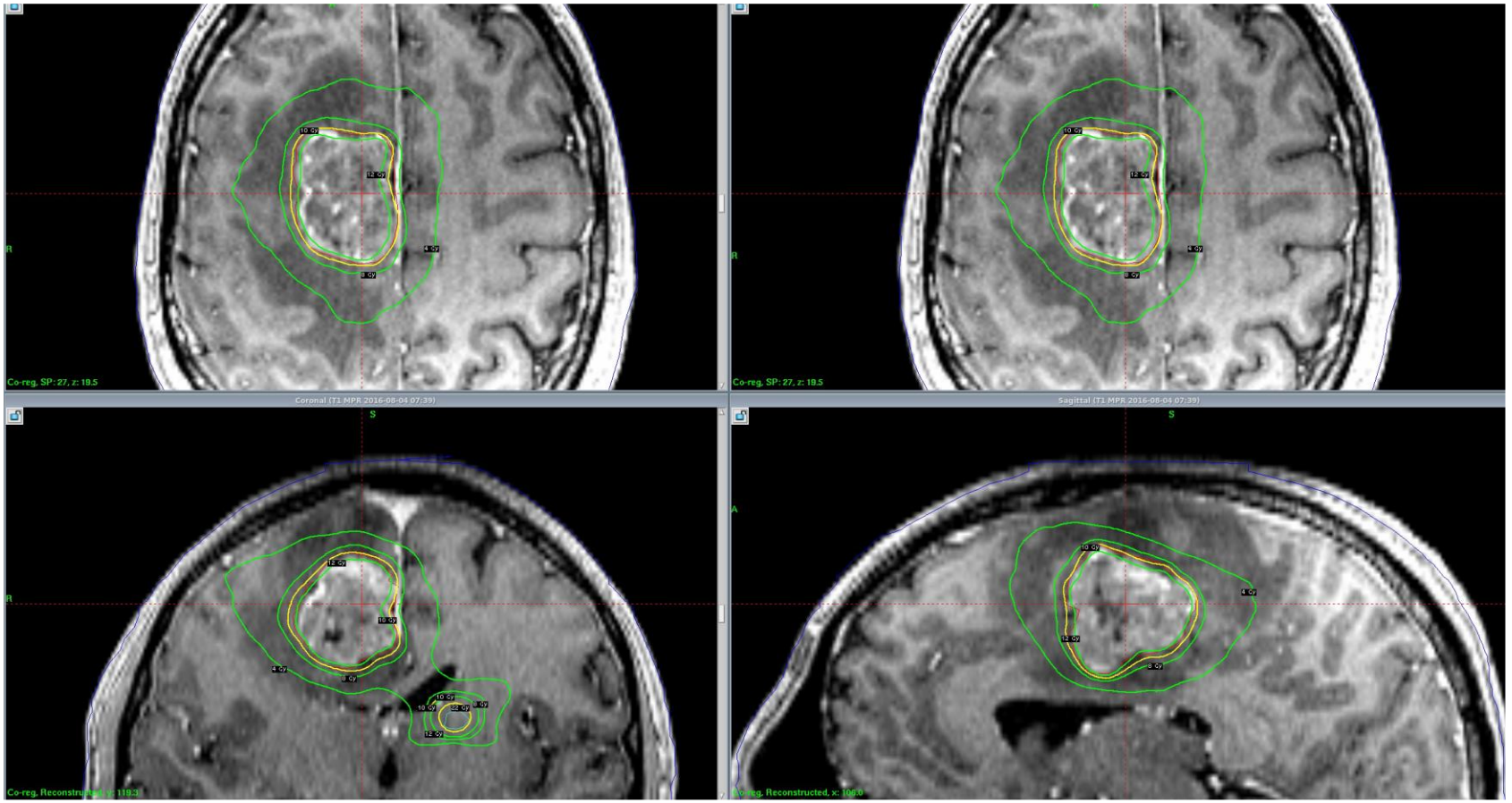
- 54 year old male
- Metastatic oesophageal carcinoma Dec 2014
  - 8 x palliative chemotherapy
- Left-sided weakness July 2016
  - MRI 2 x brain metastases
  - Significant increase in volume on planning scan compared to diagnostic imaging

THE BRISTOL
GAMMA KNIFE
CENTRE

Fraction 1

C = 0.99
S = 0.87
GI = 2.85
PCI = 0.86

Volume = 15.643 cm^3

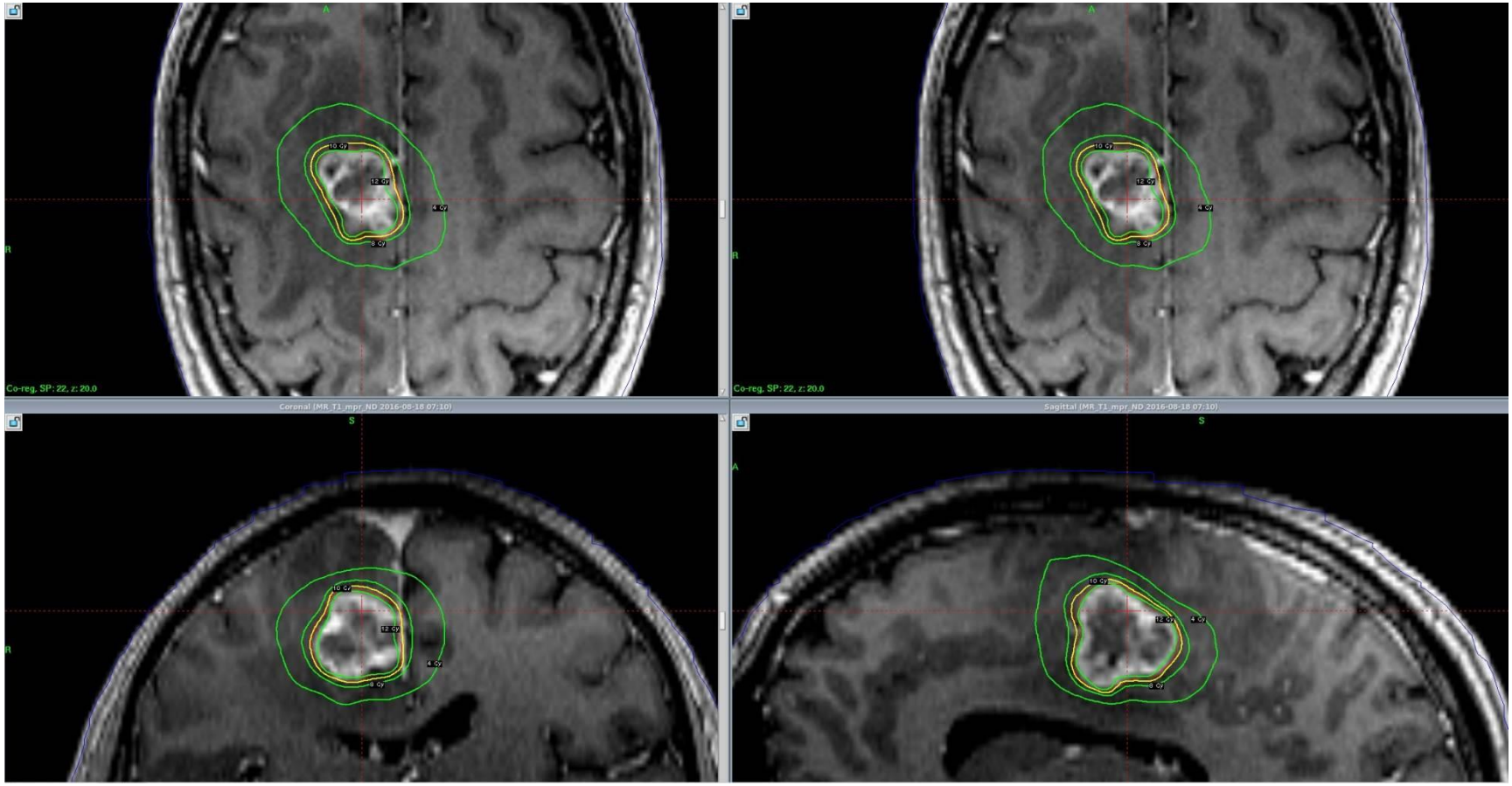


C = 1.0
S = 0.86
GI = 2.64
PCI = 0.86

Fraction 2

Volume = 6.628 cm^3

57.6% reduction in volume



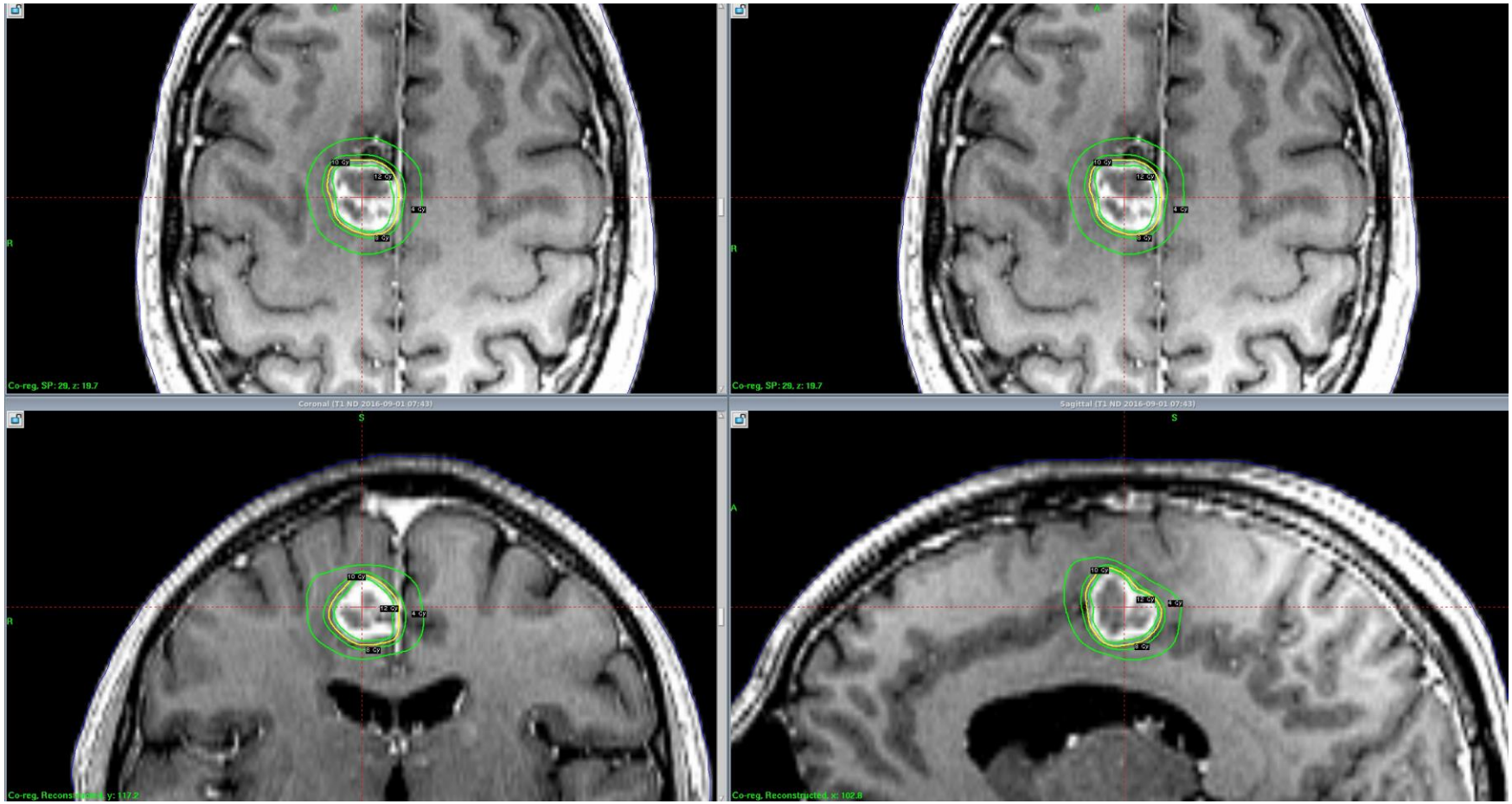
THE BRISTOL
GAMMA KNIFE
CENTRE

Fraction 3

S = 0.86
GI = 2.52
PCI = 0.86

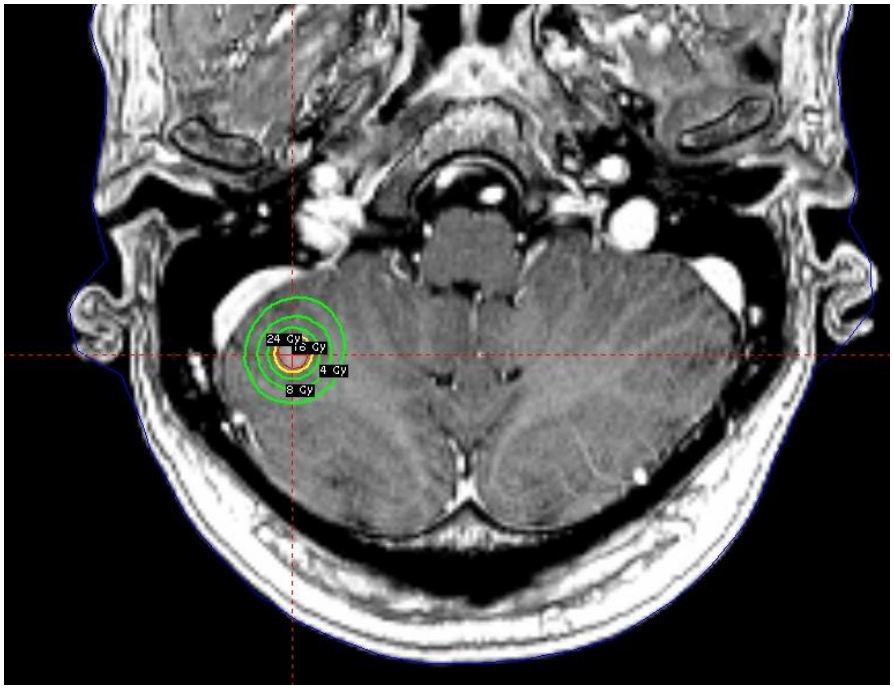
Volume = 2.639 cm^3

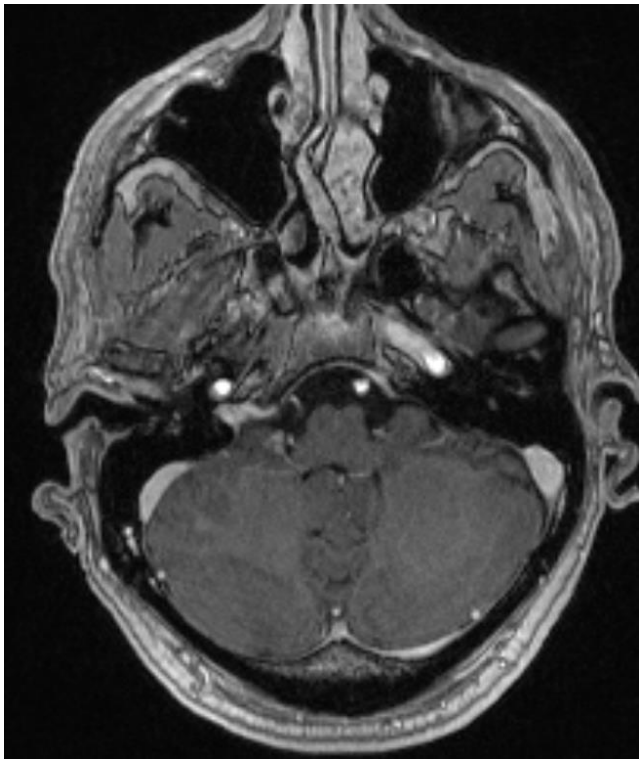
83.1 % reduction in volume



Fraction 3

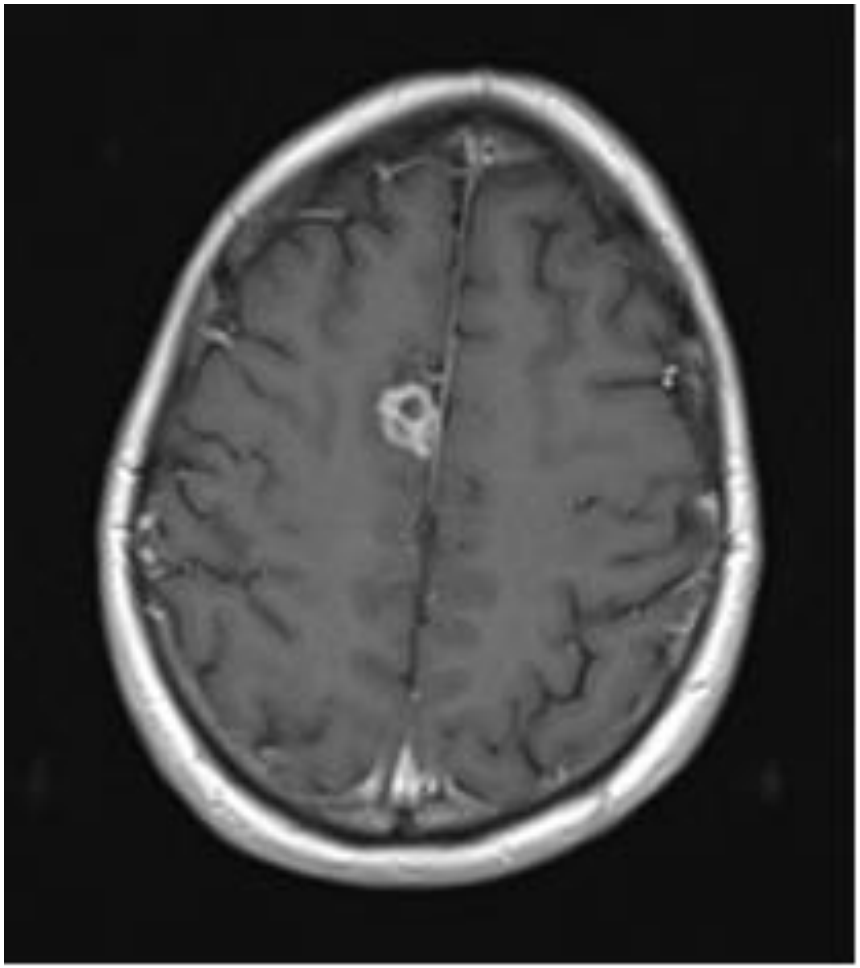
- 3rd metastasis noted cerebellum!





THE BRISTOL
GAMMA KNIFE
CENTRE

3 month follow up scan



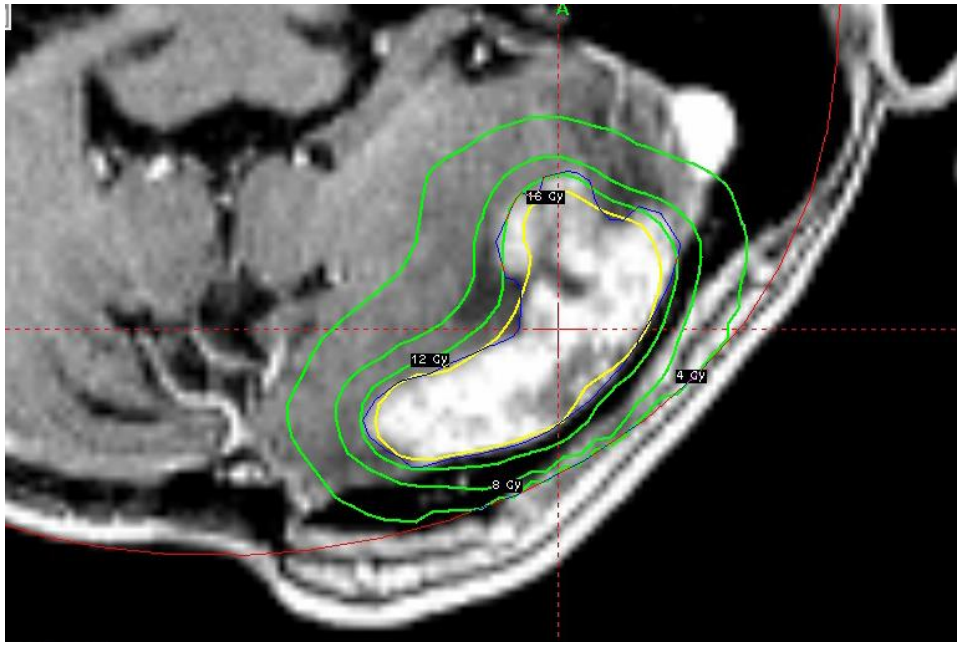
Hazards!

- Radionecrosis
  - ?worse with immunotherapy
- Haemorrhage

THE BRISTOL GAMMA KNIFE CENTRE

What can go wrong - Radiation Necrosis

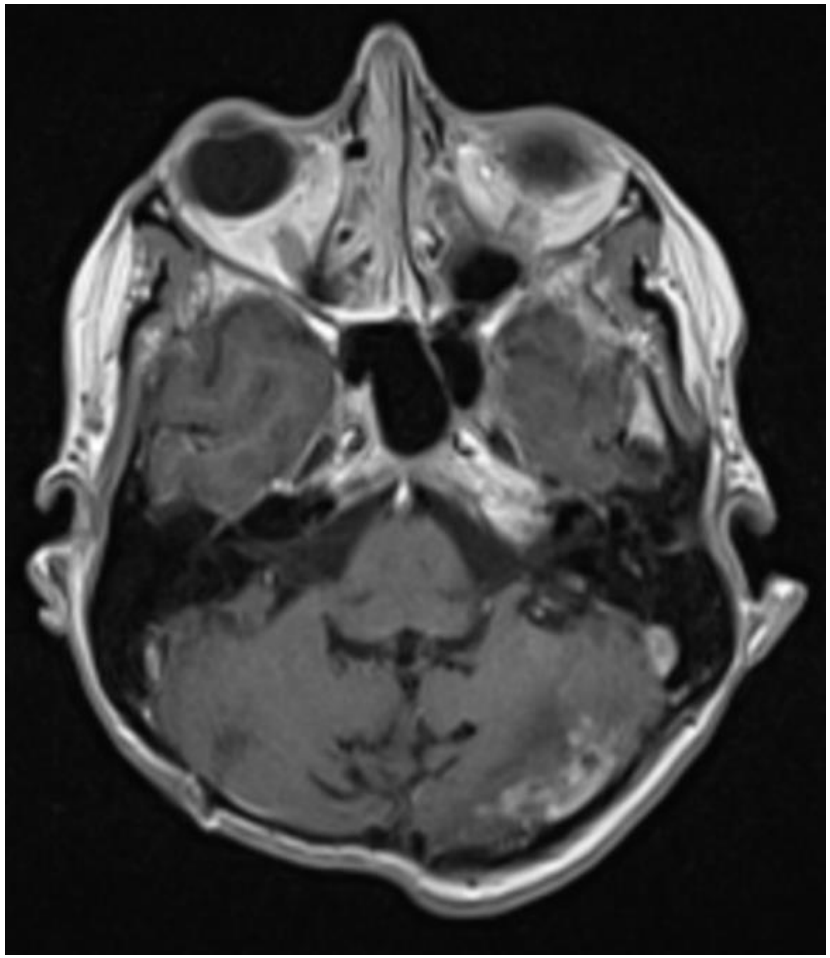
- Case study
  - 51 year old female
  - Metastatic breast ca diagnosed 8 years ago
  - Developed metastatic disease 2009 (lung)
  - 2010 right cerebellar metastasis resected
  - Left cerebellar metastasis December 2013



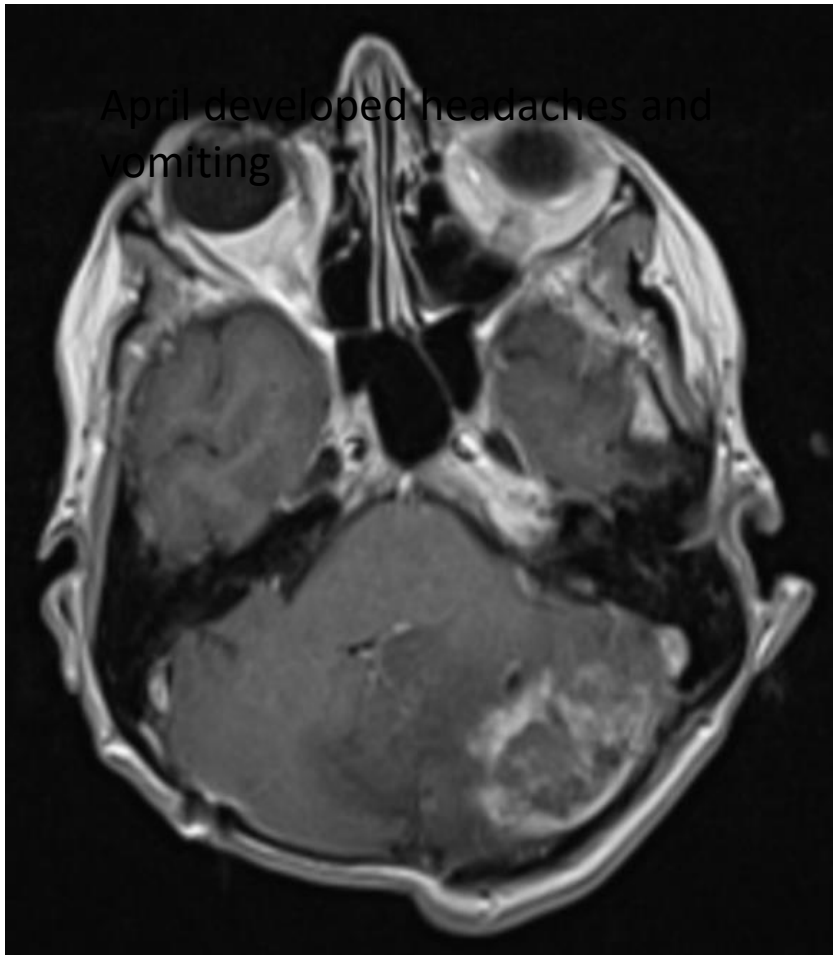
THE BRISTOL
GAMMA KNIFE
CENTRE

Radiation necrosis

10th March



26th April



Conclusions

- Easy to decide what we can treat
- Difficult to decide who we should treat
- But
  - Radiosurgery is a generally safe and effective treatment for patients with limited brain metastases although patient selection is key
  - Is an important adjunct to systemic therapy