Proton Therapy for Brain Tumors

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UC San Diego
Moores Cancer Center

Disclosures

- Employment - University of California, San Diego
    - California Protons Cancer Therapy Center

- Industry
  - Bristol Meyers Squibb – Consultant

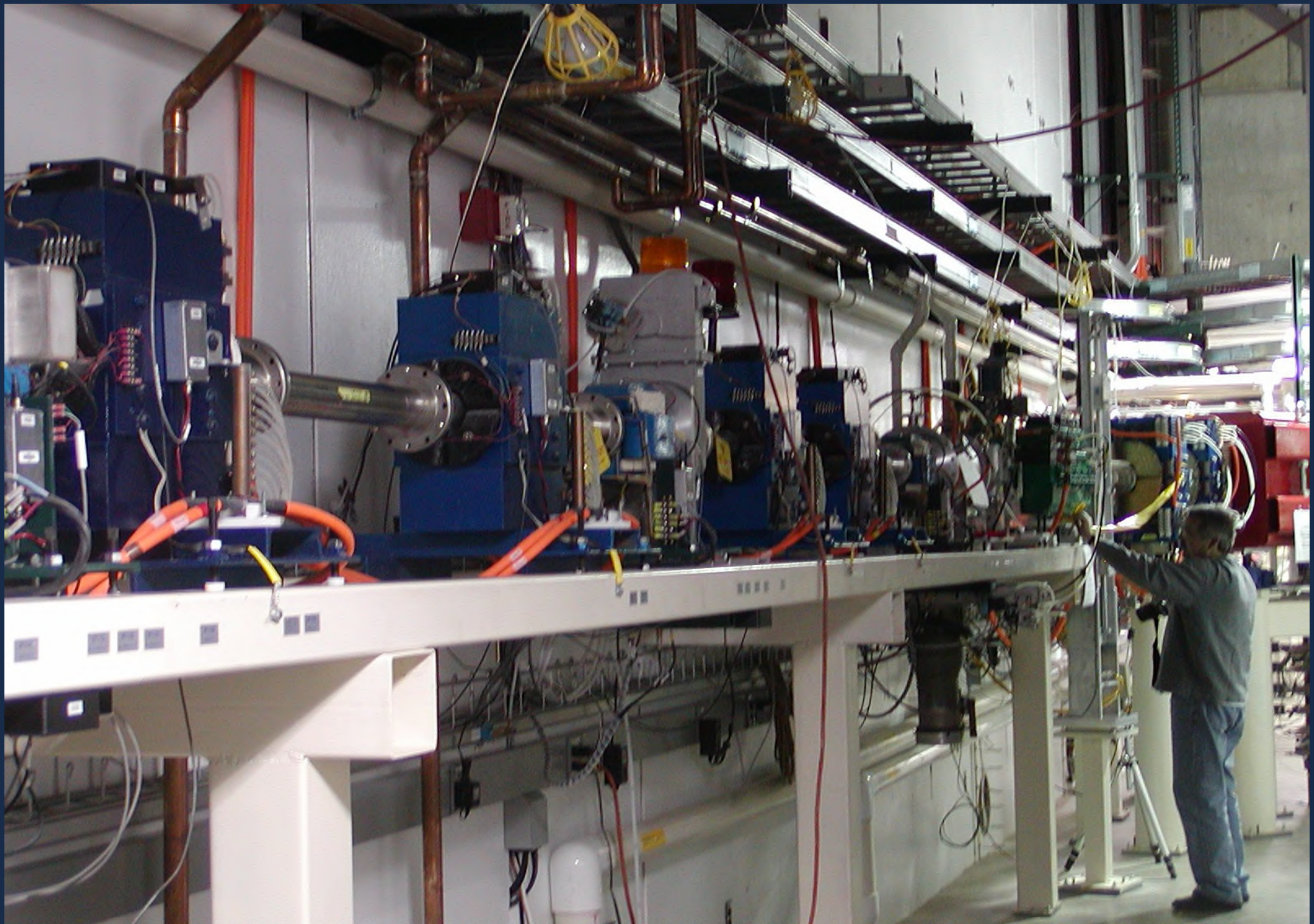
- Cooperative Groups
  - Alliance for Clinical Trials in Oncology
    - Rad Onc PI – AFT 16 and AFT 46

Proton Beam Techniques

- Passive Beam Scattering
  - Double Scattering System
    - Loma Linda University
    - Harvard MGH
    - MPRI Room 1
- Uniform Beam Scanning
  - “Wobbling beam”
    - Midwest Proton Radiotherapy Institute Rooms 2, 3
    - University of Florida
    - MD Anderson Cancer Center
- Active Beam Scanning
  - Spot Scanning
    - PSI
    - MD Anderson Cancer Center
    - Harvard

Cyclotron

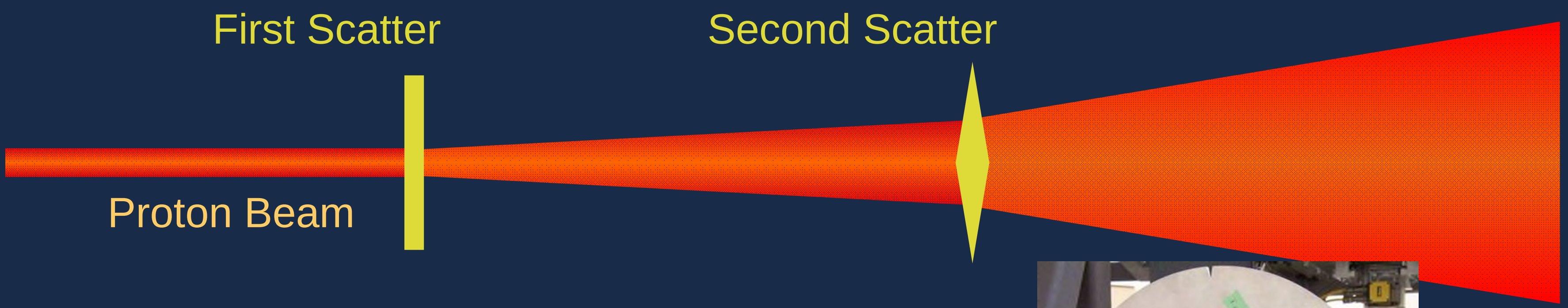
Proton Therapy Components: Beamline

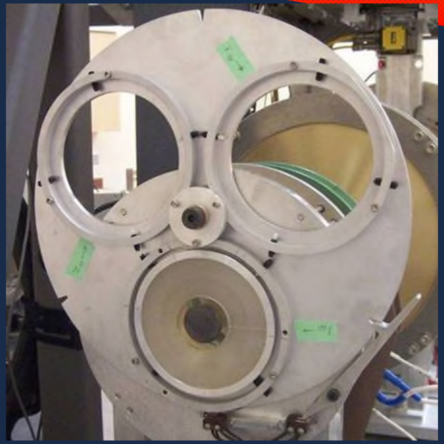


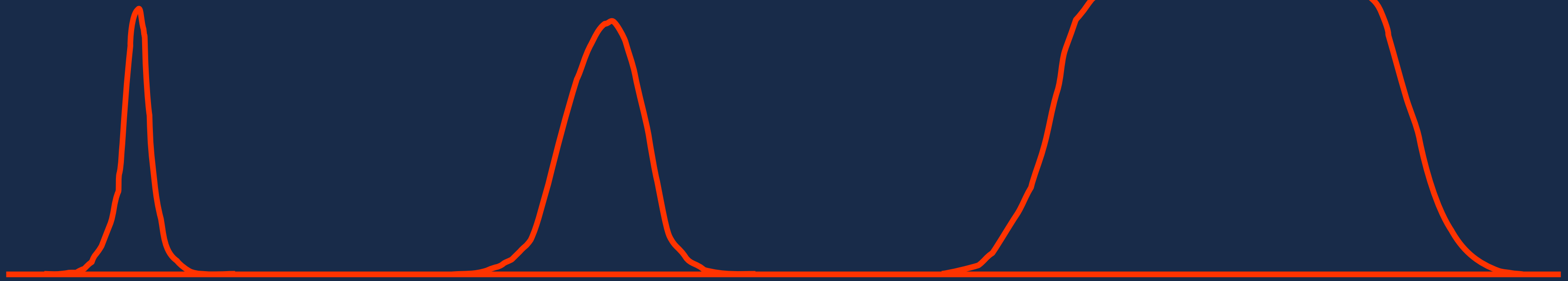
Passive Beam Scattering
Double Scattering System

Loma Linda University
Harvard MGH
MPRI Room 1 - Indiana University (Closed)

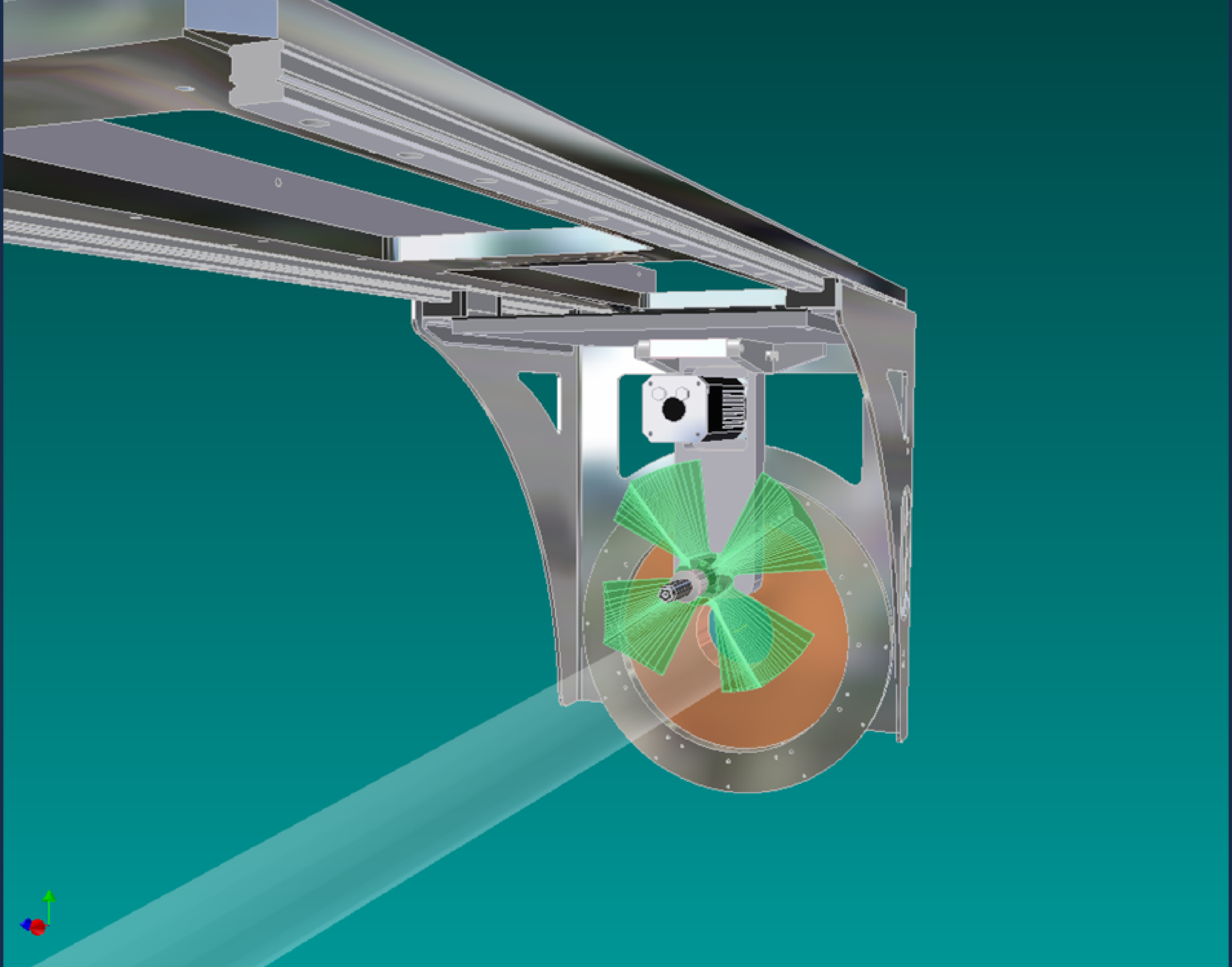
Passive Beam Lateral Scattering







After Koehler et al. HCL

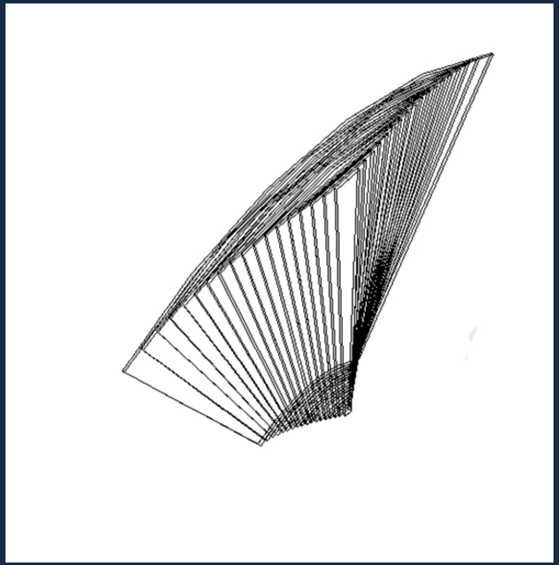


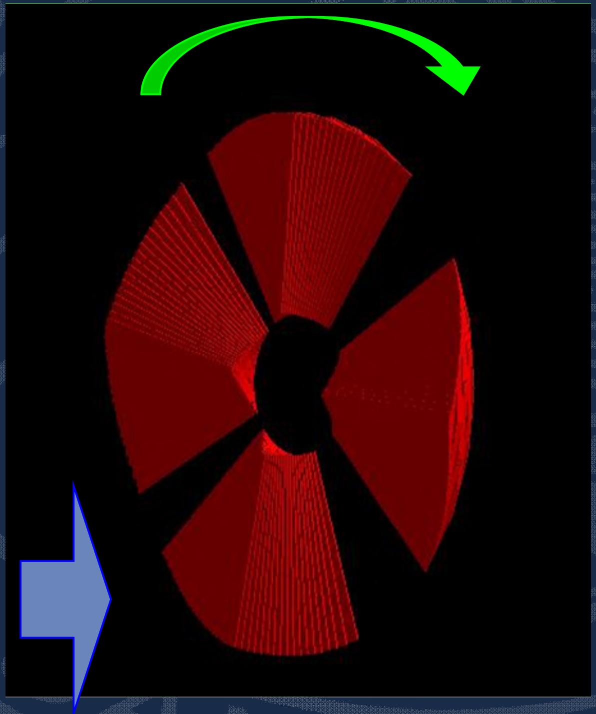
MODULATOR WHEEL

Pure Bragg Peak

Spread Out Bragg Peak (SOBP)

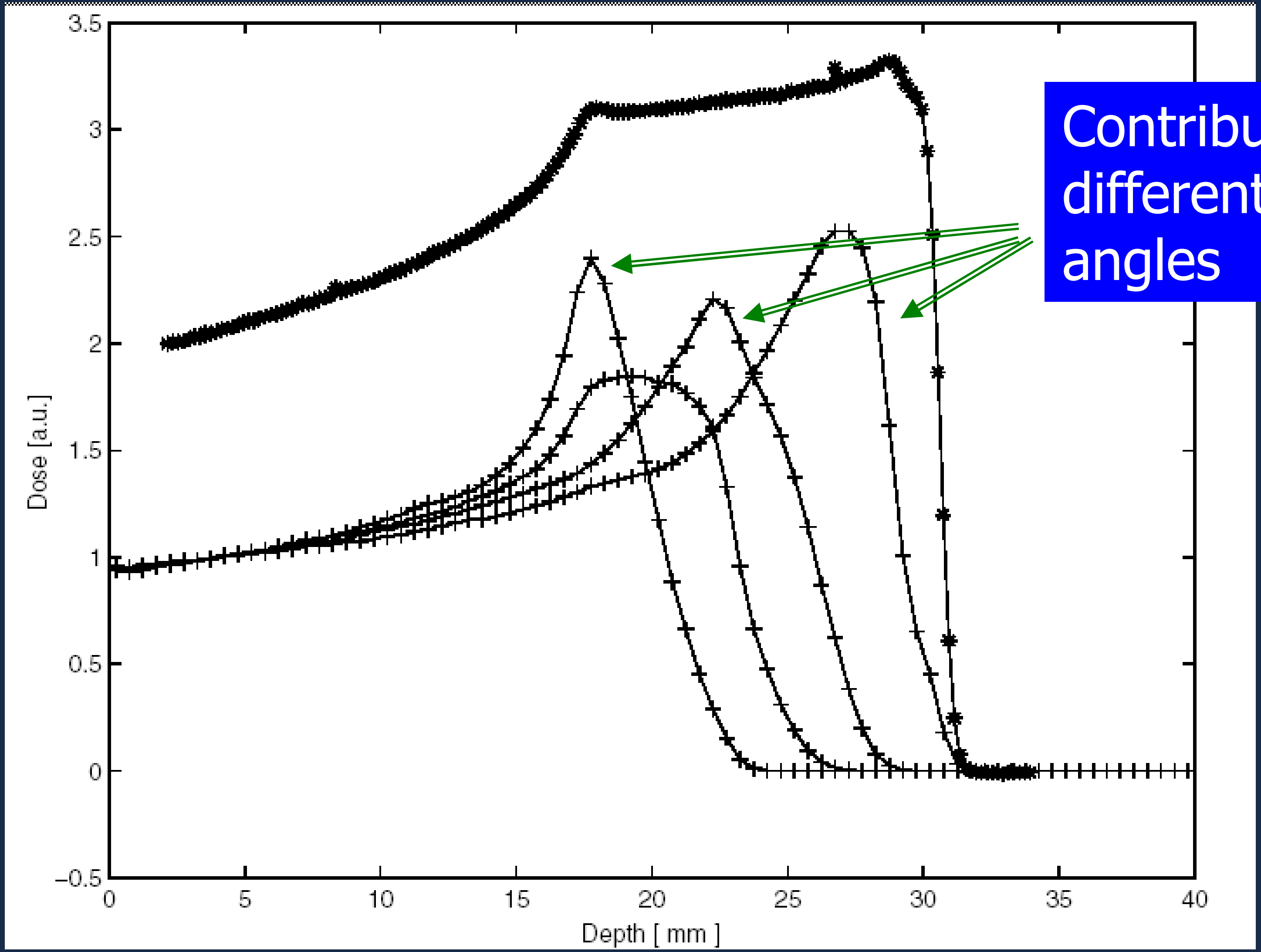
Modulator consists of multiple identical sectors





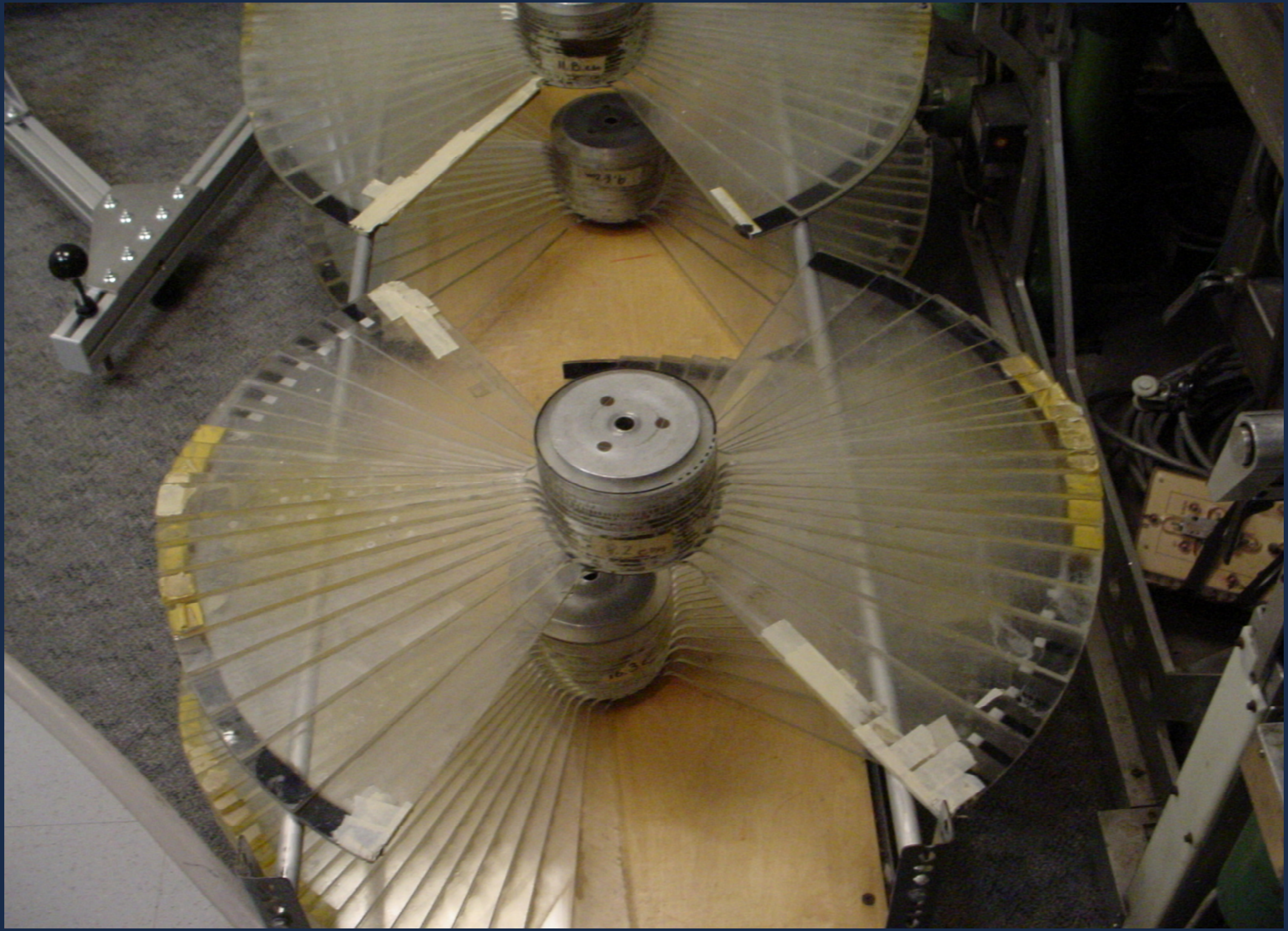
The modulator needs to be rotated around its axis parallel to the proton beam direction

The Spread Out Bragg Peak



Contribution from different modulator angles

Modulator Wheel (HCL)



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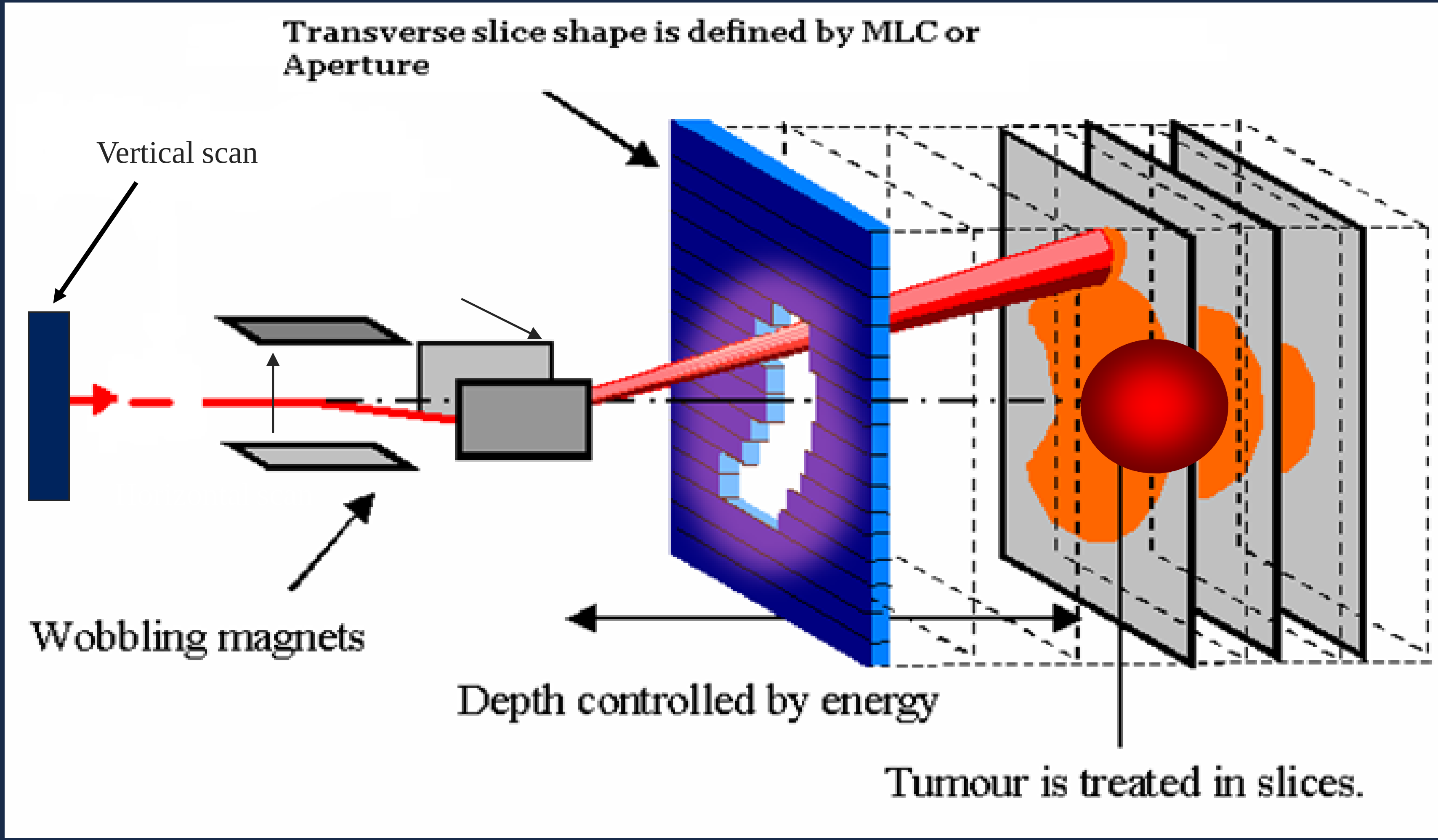
Uniform Beam Scanning
"Wobbling beam"

Midwest Proton Radiotherapy Institute Rooms 2, 3 – Indiana (Closed)
University of Florida
MD Anderson Cancer Center

UC San Diego
MOORES CANCER CENTER

Wobbling (Uniform Scanning) beam delivery system at MPRI in Gantries



Diego
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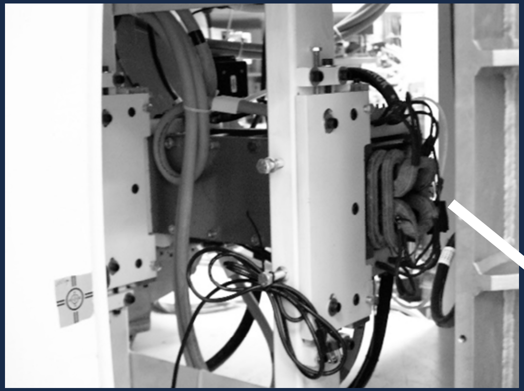
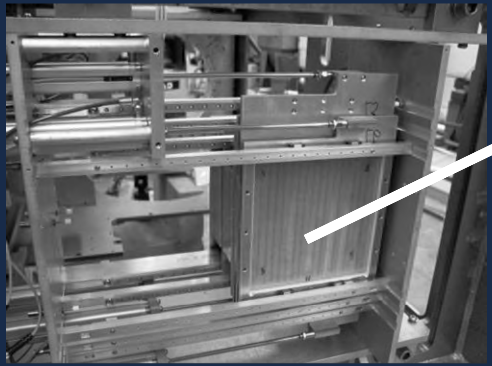
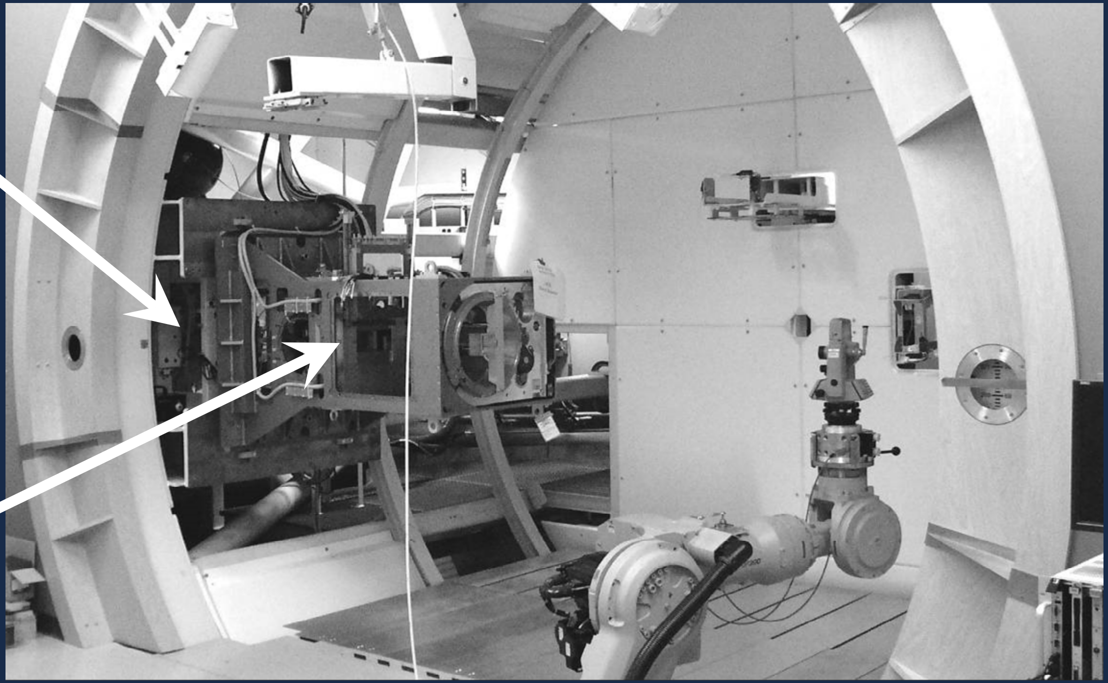
Proton Beam Wobbling

Beam Wobbler



Range Shifter





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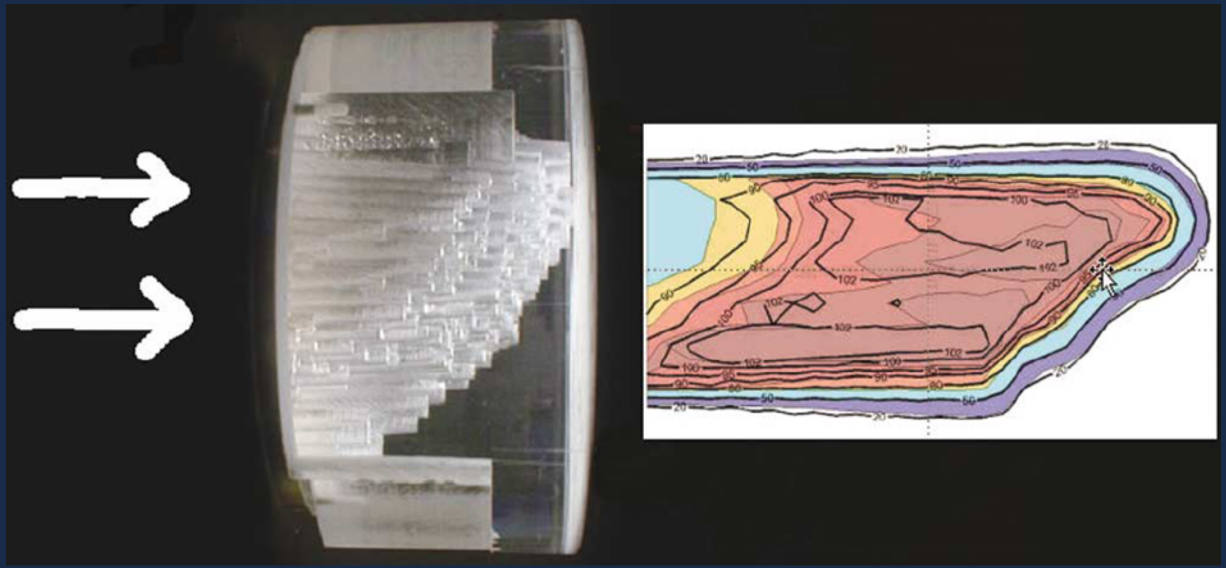
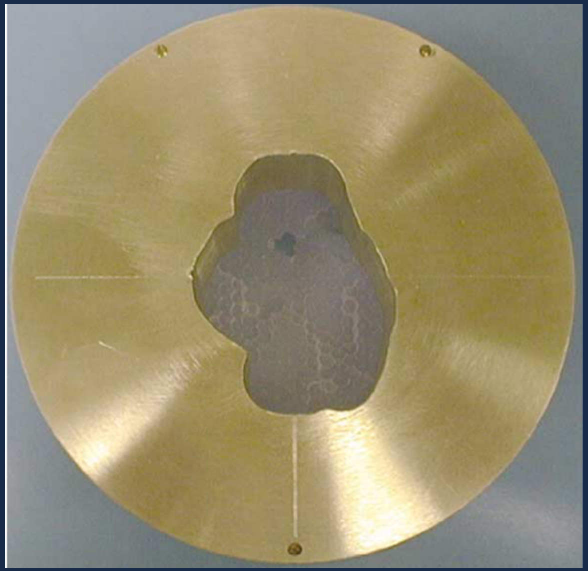


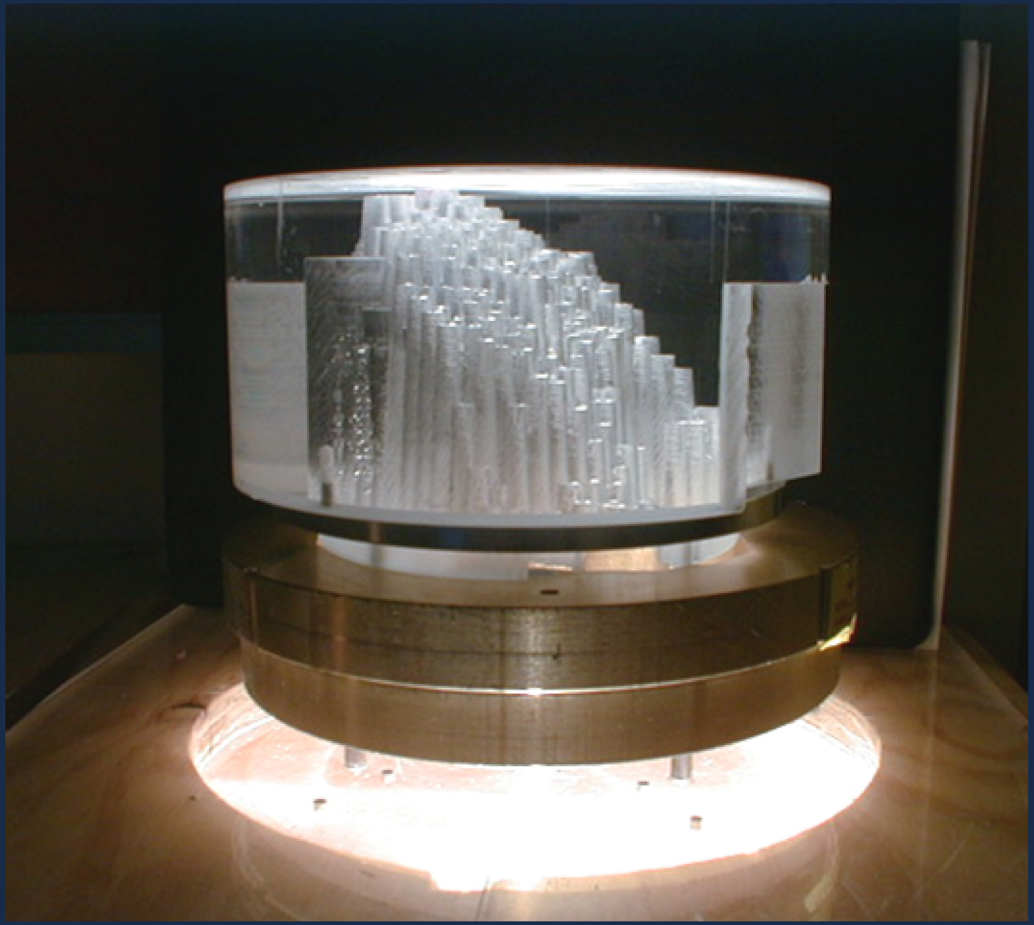
Lucite range compensator



aperture

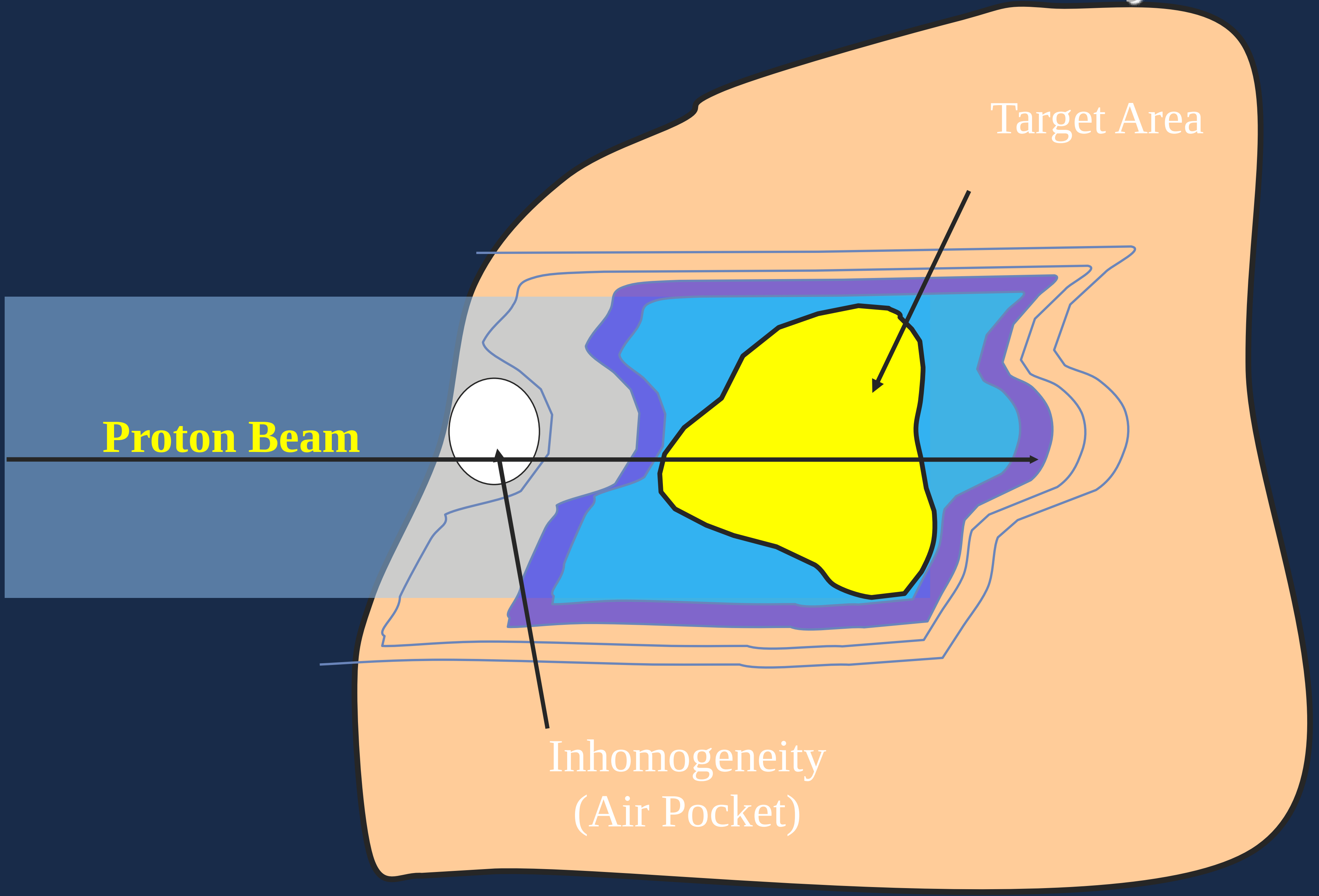
Bussiere and Adams 2003

Compensator 3D Distal Shaping

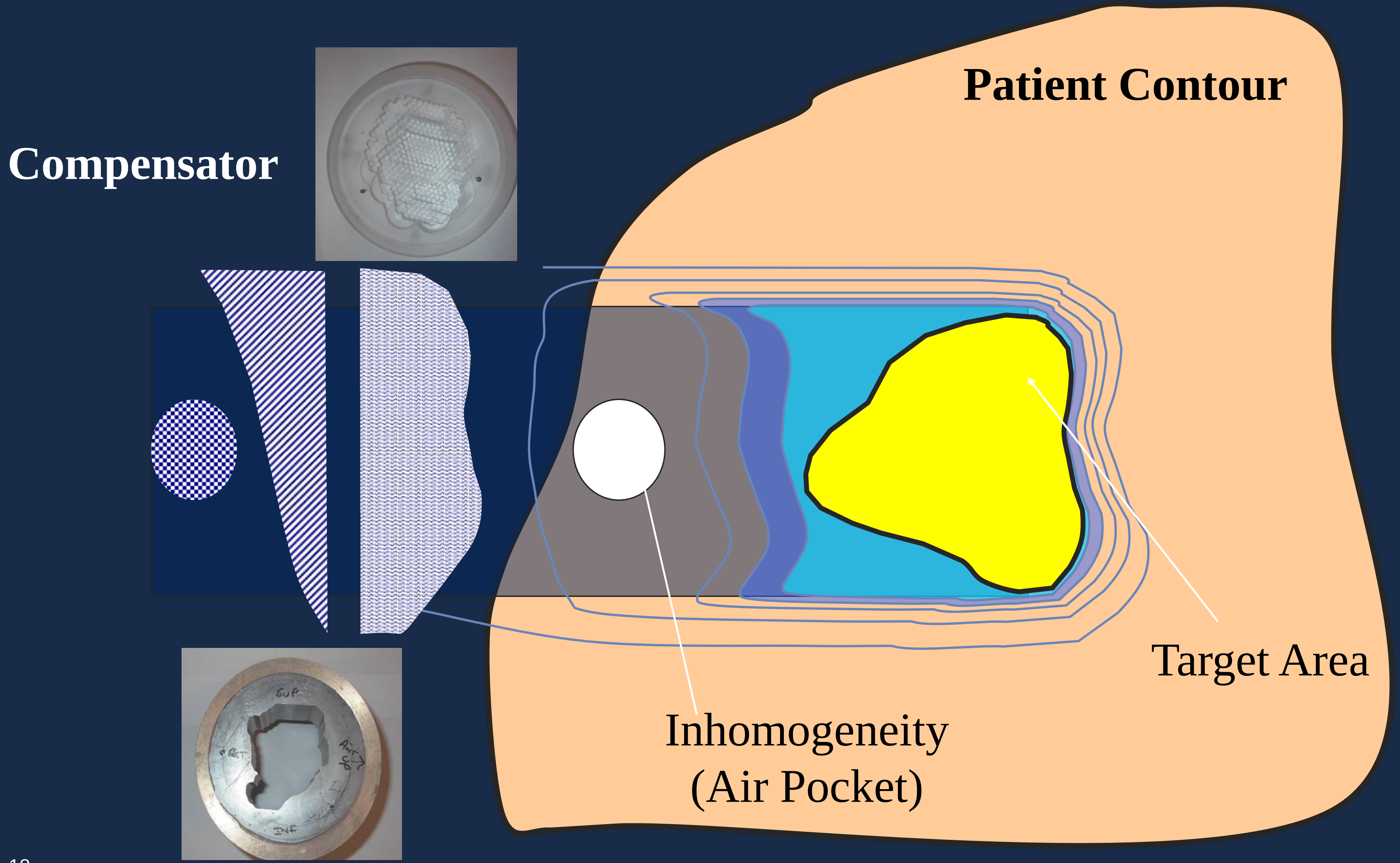


As well as spreading out the Bragg peak, the final range itself must be shaped to the distal surface of the target volume taking into account heterogeneities

Proton Passive Beam Delivery



Proton Beam with Beam Modification



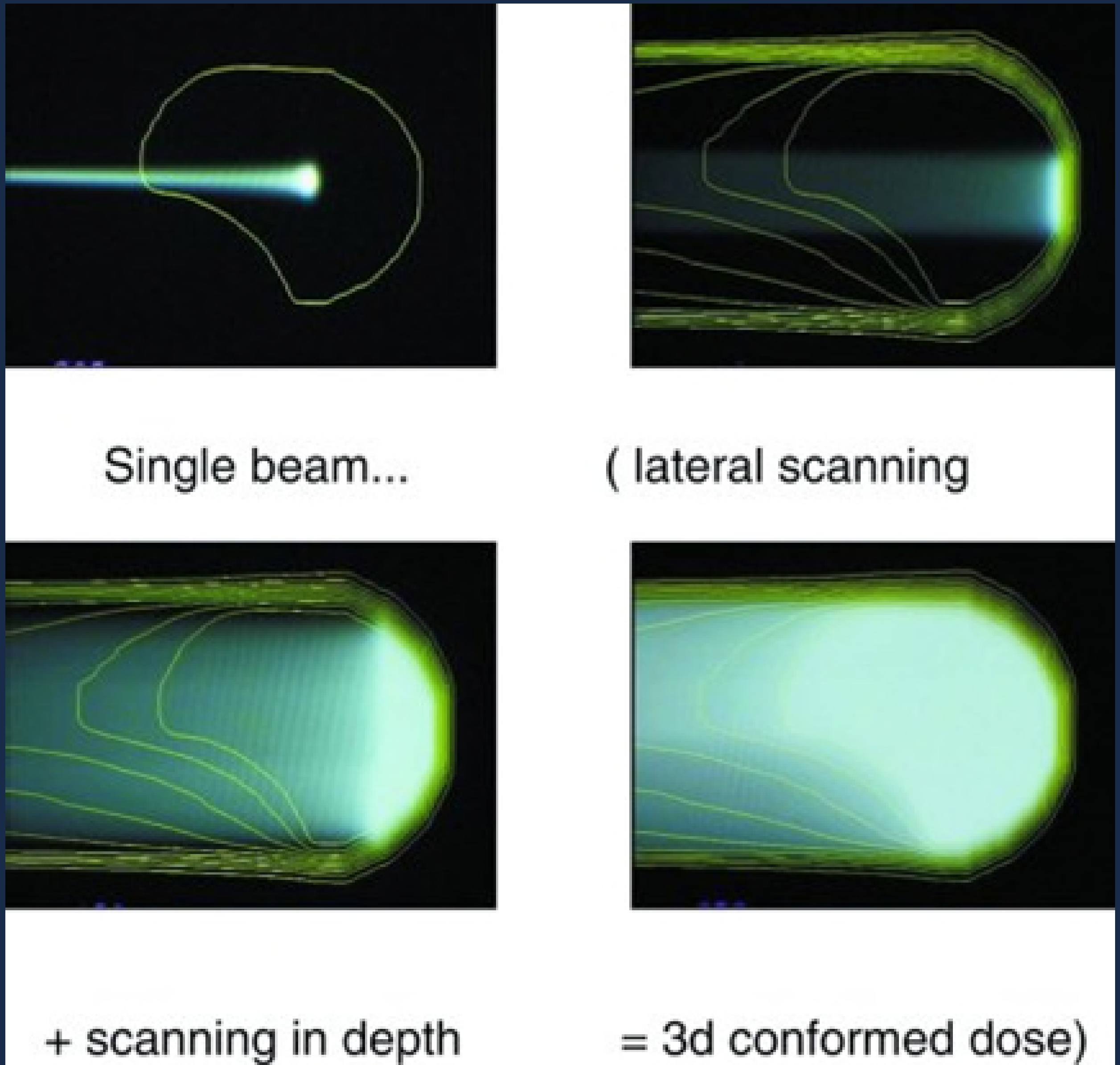
Active Beam Scanning
Spot Scanning

PSI
MD Anderson Cancer Center
Harvard

California Protons

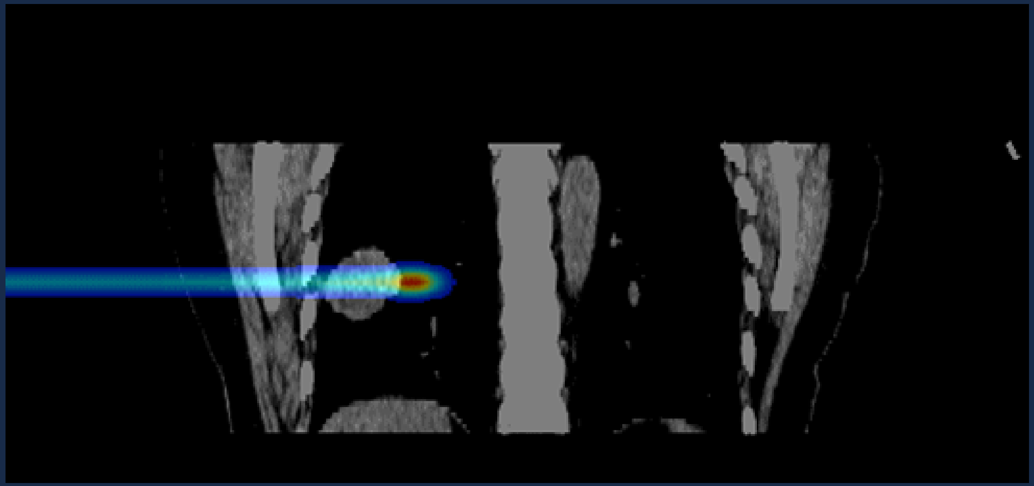
University of Maryland

Active Beam Spot Scanning
(Pencil Beam Scanning, “PBS”)

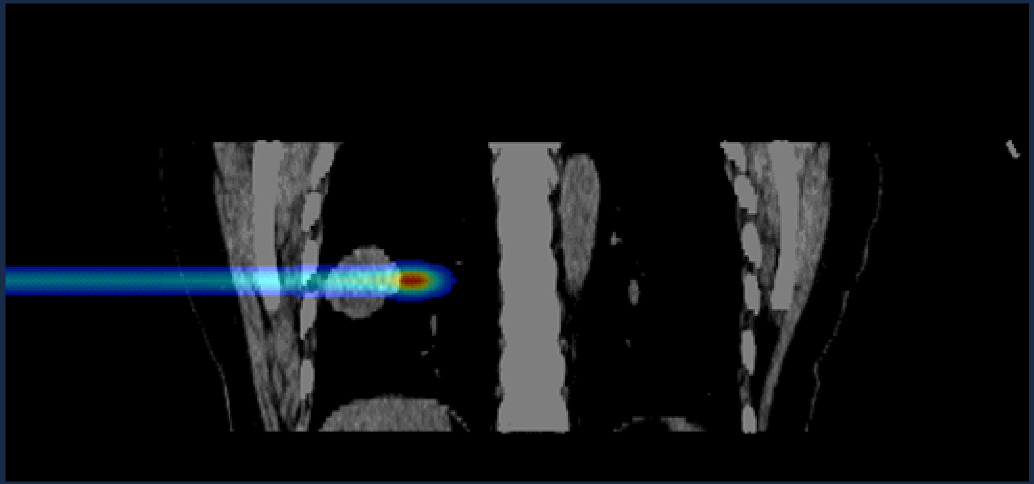


Courtesy
of PSI

Pencil Beam Scanning Technique to Delivery Highly Conformal Therapy



Scanning Beam



Cumulative Dose

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Dong/MDACC

Gantry Assembly

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Gantry Wheel

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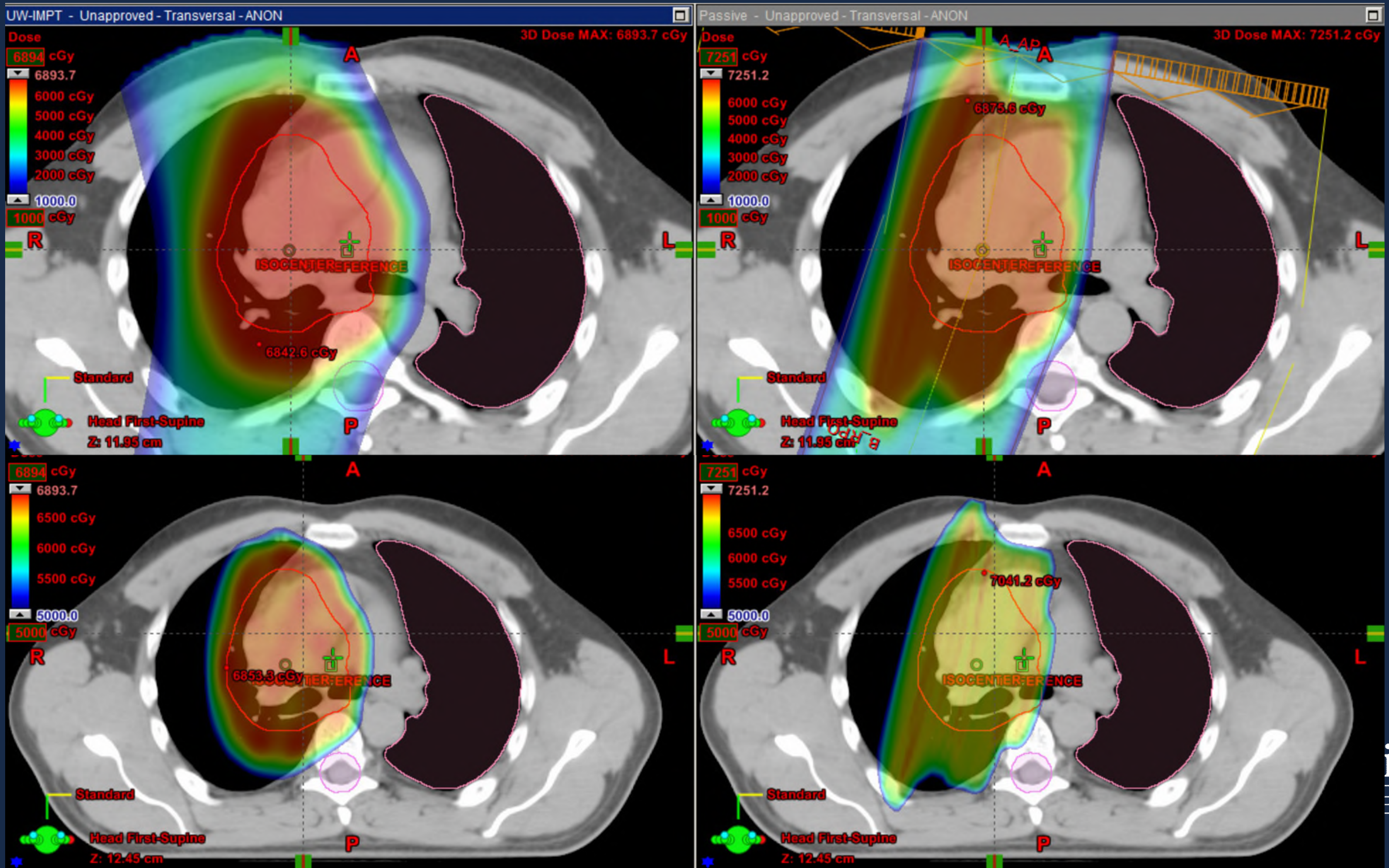
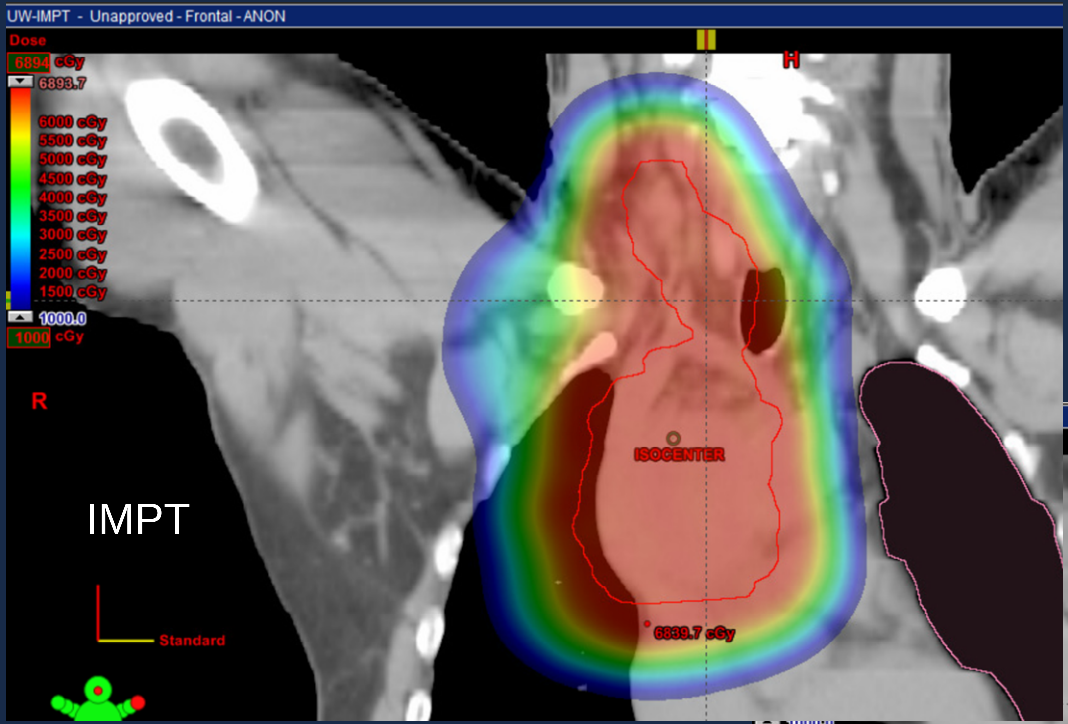
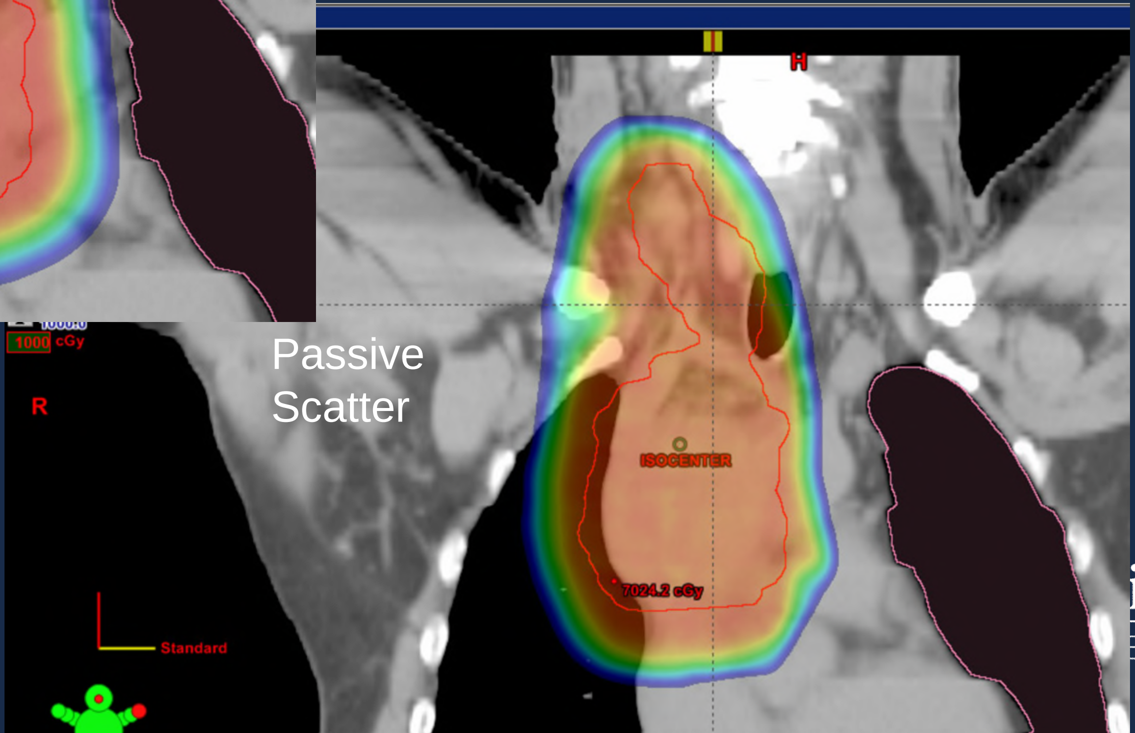
IMPT vs Passive Scatter

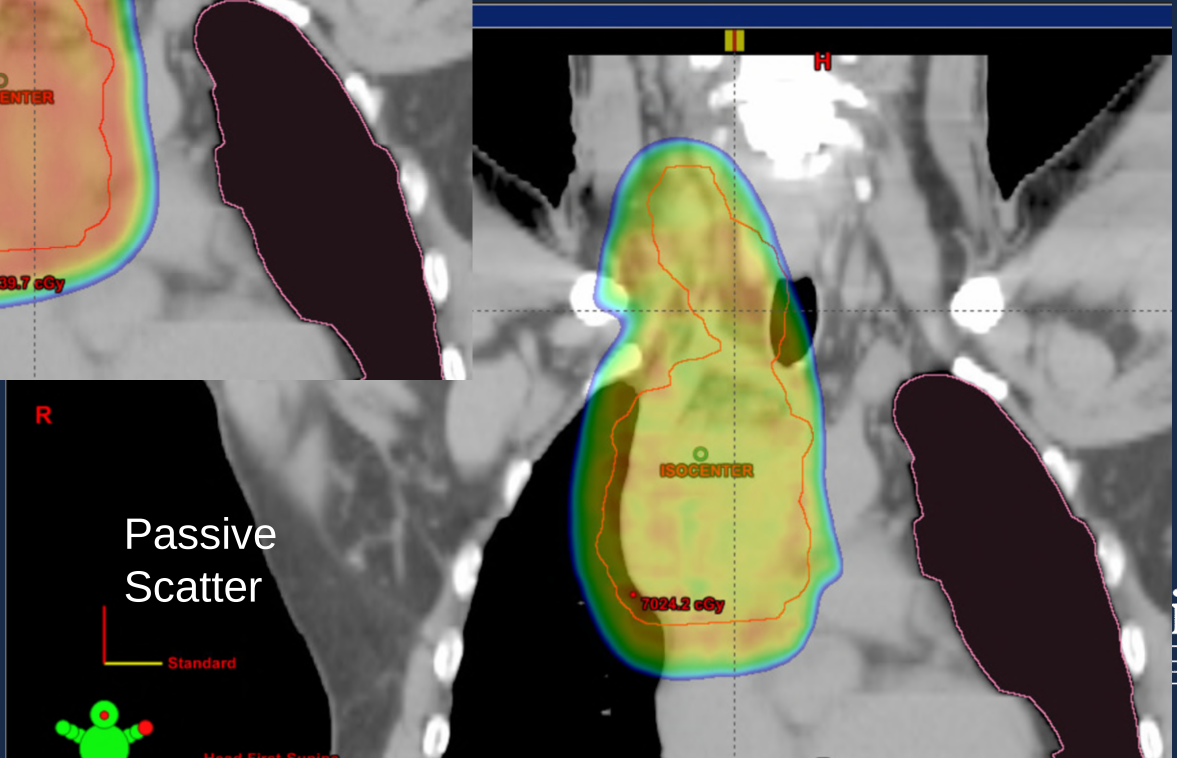


IMPT vs Passive Scatter coronal 10 Gy cloud

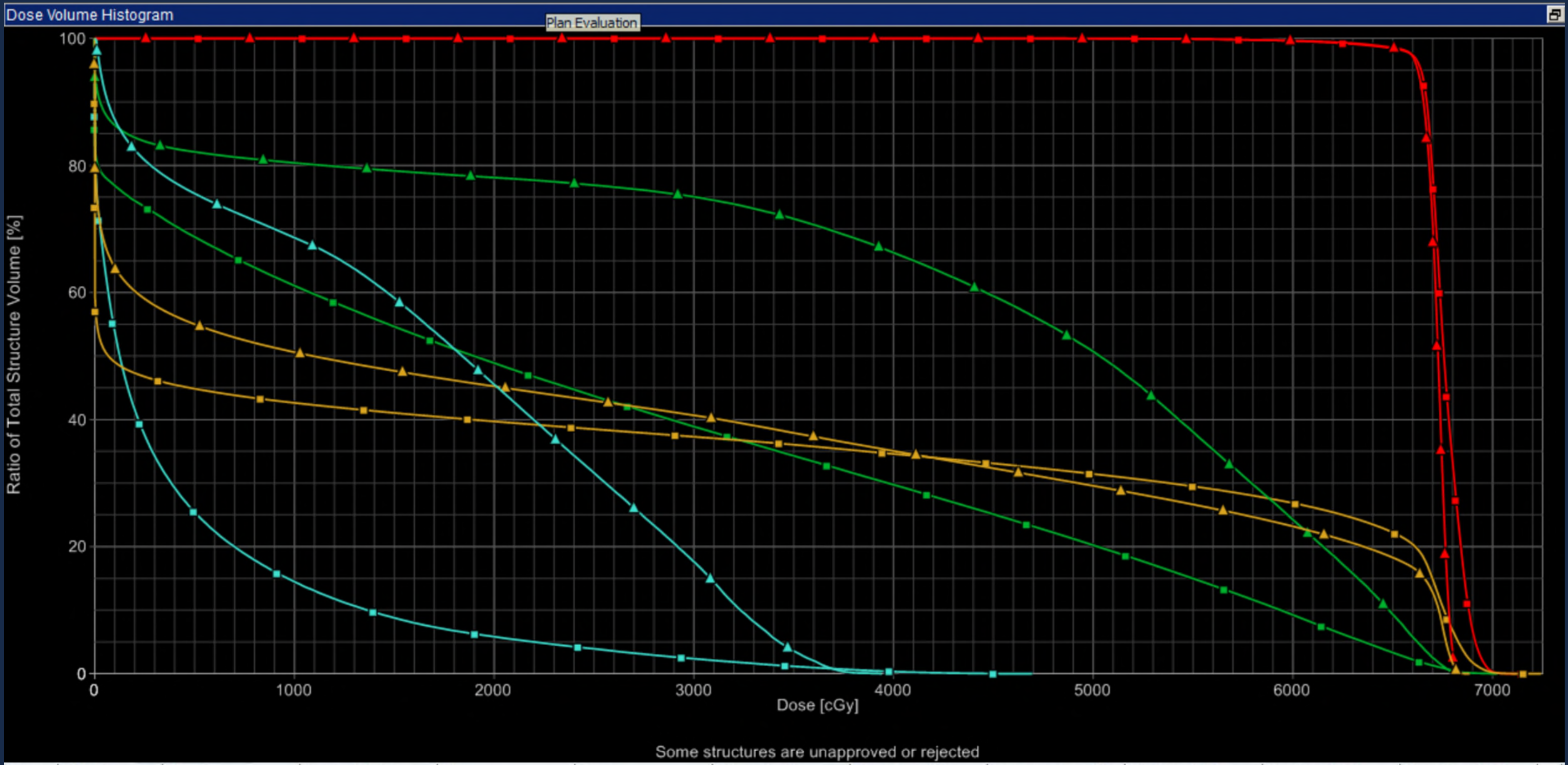




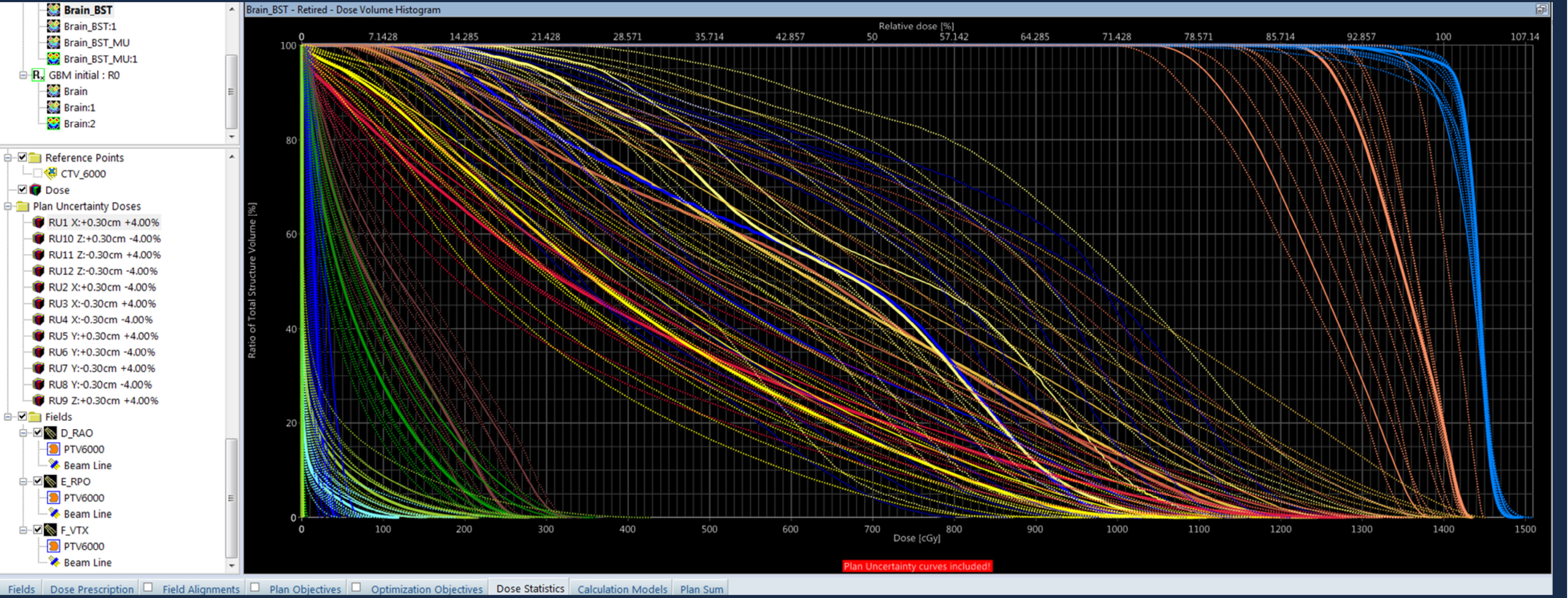
IMPT vs Passive Scatter 50 Gy Cloud



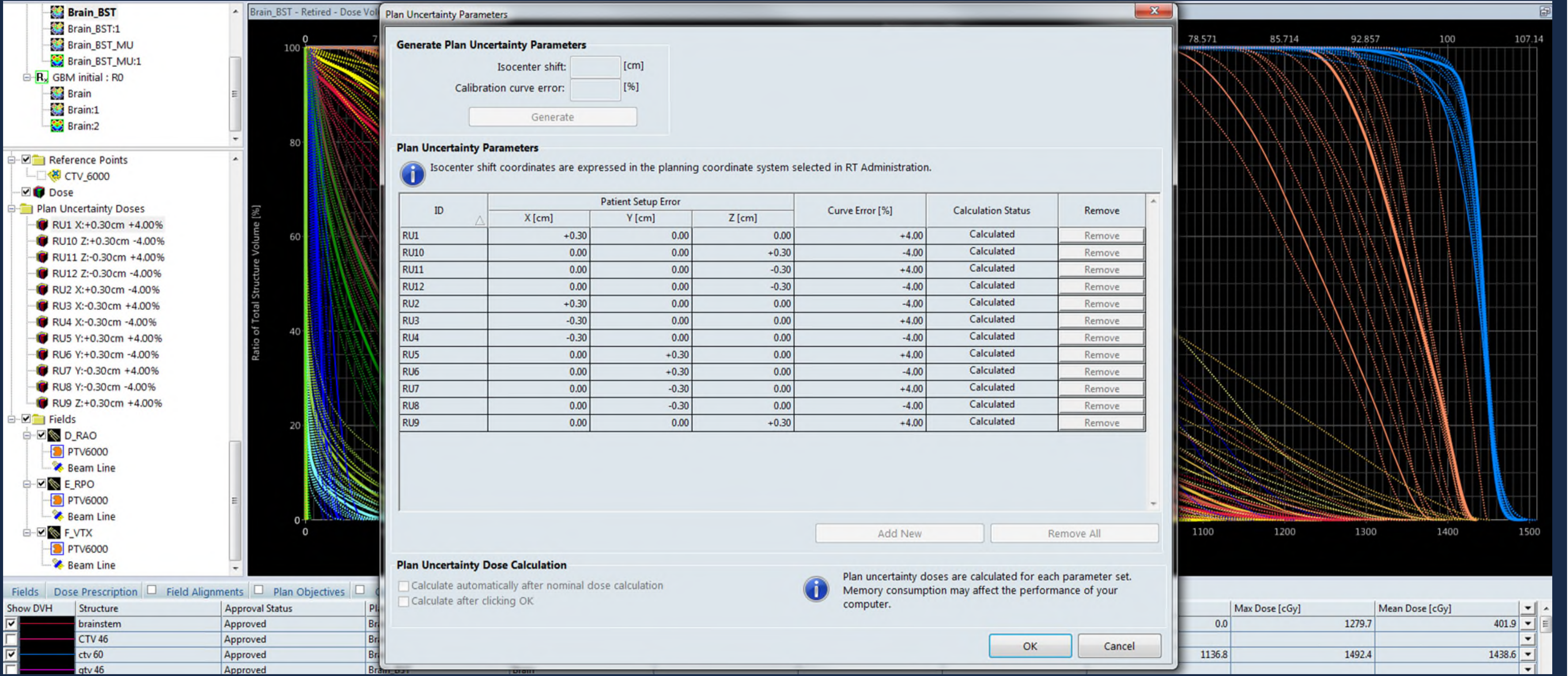
Passive scatter vs IMPT

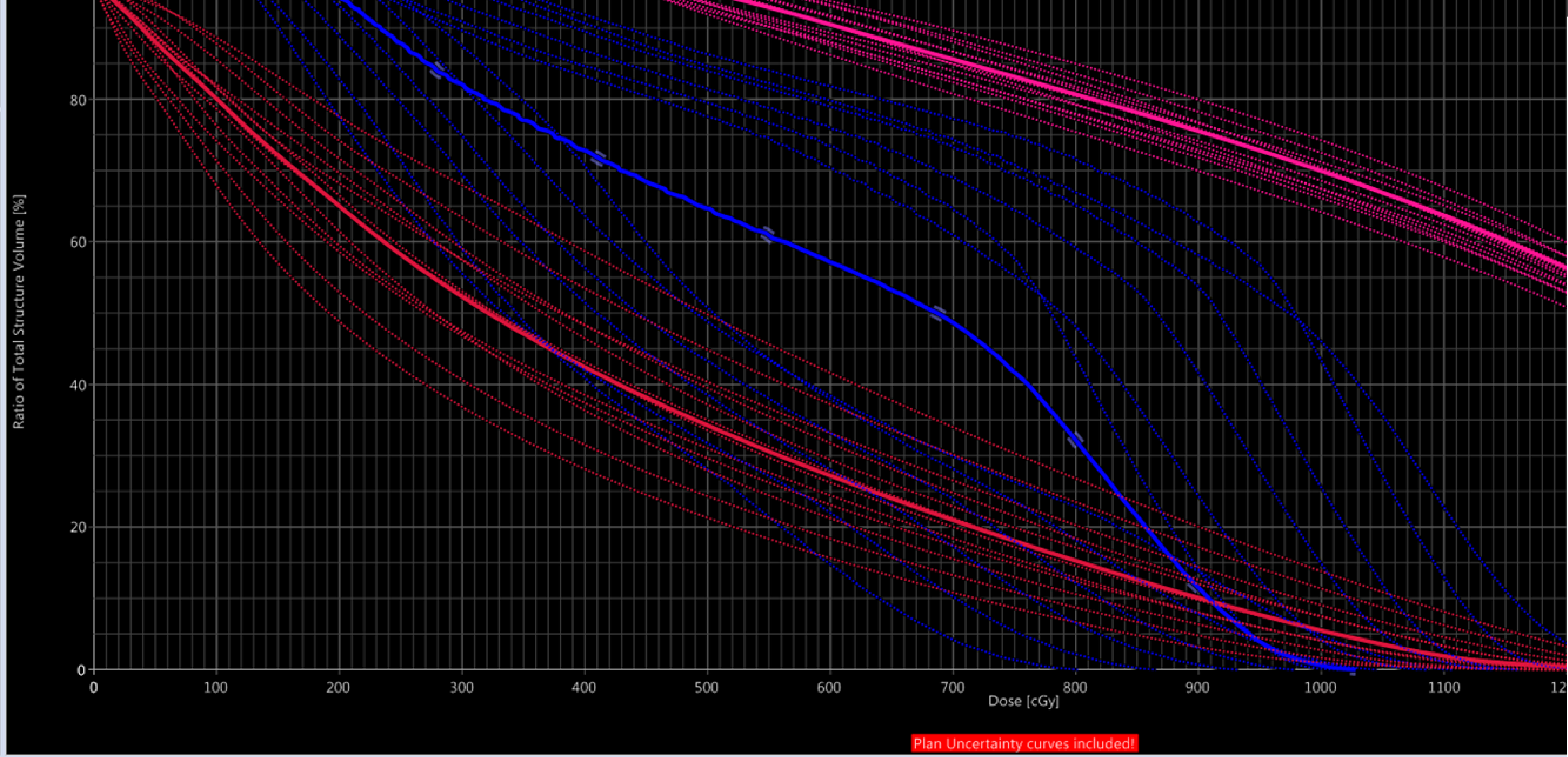


View	DVH Line	Structure	Approval Status	Plan	Course	Volume [cm³]	Dose Cover.[%]	Sampling Cover.[%]	Min Dose [cGy]	Max Dose [cGy]	Mean Dose [cGy]
☑		CTVTOTAL	Unapproved	Passive	Passive	636.5	100.0	100.0	4564.1	7157.7	6759.8
☑		Esophagus	Unapproved	Passive	Passive	43.4	100.0	100.2	0.0	7030.9	2458.0
☑		Lung_R	Unapproved	Passive	Passive	1529.9	100.0	100.0	0.0	7251.2	2415.9
☑		Cord	Unapproved	Passive	Passive	36.5	100.0	100.1	0.0	4703.0	449.8
☑		CTVTOTAL	Unapproved	UW-IMPT	IMPT	636.5	100.0	99.9	4443.6	6856.7	6714.9
☑		Esophagus	Unapproved	UW-IMPT	IMPT	43.4	100.0	99.4	0.0	6833.0	4171.5
☑		Lung_R	Unapproved	UW-IMPT	IMPT	1529.9	100.0	100.0	0.0	6890.4	2586.1
☑		Cord	Unapproved	UW-IMPT	IMPT	36.5	100.0	99.8	4.1	3947.5	1728.0



Brain_BST
Brain_BST:1
Brain_BST_MU
Brain_BST_MU:1
GBM initial : R0
Brain
Brain:1
Brain:2
Reference Points
CTV_6000
Dose
Plan Uncertainty Doses
RU1 X:+0.30cm +4.00%
RU10 Z:+0.30cm -4.00%
RU11 Z:-0.30cm +4.00%
RU12 Z:-0.30cm -4.00%
RU2 X:+0.30cm -4.00%
RU3 X:-0.30cm +4.00%
RU4 X:-0.30cm -4.00%
RU5 Y:+0.30cm +4.00%
RU6 Y:+0.30cm -4.00%
RU7 Y:-0.30cm +4.00%
RU8 Y:-0.30cm -4.00%
RU9 Z:+0.30cm +4.00%
Fields
D_RAO
PTV6000
Beam Line
E_RPO
PTV6000
Beam Line
F_VTX
PTV6000
Beam Line
Brain_BST - Retired - Dose Volume Histogram
Relative dose [%]
0 7.1428 14.285 21.428 28.571 35.714 42.857 50 57.142 64.285 71.428 78.571 85.714 92.857 100 107.14
Ratio of Total Structure Volume [%]
100 80 60 40 20 0
0 100 200 300 400 500 600 700 800 900 1000 1100 1200 1300 1400 1500
Dose [cGy]
Plan Uncertainty curves included!
Fields
Dose Prescription
Field Alignments
Plan Objectives
Optimization Objectives
Dose Statistics
Calculation Models
Plan Sum


Brain_BST
Brain_BST:1
Brain_BST_MU
Brain_BST_MU:1
GBM initial : R0
Brain
Brain:1
Brain:2
Reference Points
CTV_6000
Dose
Plan Uncertainty Doses
RU1 X:+0.30cm +4.00%
RU10 Z:+0.30cm -4.00%
RU11 Z:-0.30cm +4.00%
RU12 Z:-0.30cm -4.00%
RU2 X:+0.30cm -4.00%
RU3 X:-0.30cm +4.00%
RU4 X:-0.30cm -4.00%
RU5 Y:+0.30cm +4.00%
RU6 Y:+0.30cm -4.00%
RU7 Y:-0.30cm +4.00%
RU8 Y:-0.30cm -4.00%
RU9 Z:+0.30cm +4.00%
Fields
D_RAO
PTV6000
Beam Line
E_RPO
PTV6000
Beam Line
F_VTX
PTV6000
Beam Line
Brain_BST - Retired - Dose Vol
Ratio of Total Structure Volume [%]
Plan Uncertainty Parameters
Generate Plan Uncertainty Parameters
Isocenter shift: [cm]
Calibration curve error: [%]
Generate
Plan Uncertainty Parameters
Isocenter shift coordinates are expressed in the planning coordinate system selected in RT Administration.
ID | Patient Setup Error X [cm] | Y [cm] | Z [cm] | Curve Error [%] | Calculation Status | Remove
RU1 | +0.30 | 0.00 | 0.00 | +4.00 | Calculated | Remove
RU10 | 0.00 | 0.00 | +0.30 | -4.00 | Calculated | Remove
RU11 | 0.00 | 0.00 | -0.30 | +4.00 | Calculated | Remove
RU12 | 0.00 | 0.00 | -0.30 | -4.00 | Calculated | Remove
RU2 | +0.30 | 0.00 | 0.00 | -4.00 | Calculated | Remove
RU3 | -0.30 | 0.00 | 0.00 | +4.00 | Calculated | Remove
RU4 | -0.30 | 0.00 | 0.00 | -4.00 | Calculated | Remove
RU5 | 0.00 | +0.30 | 0.00 | +4.00 | Calculated | Remove
RU6 | 0.00 | +0.30 | 0.00 | -4.00 | Calculated | Remove
RU7 | 0.00 | -0.30 | 0.00 | +4.00 | Calculated | Remove
RU8 | 0.00 | -0.30 | 0.00 | -4.00 | Calculated | Remove
RU9 | 0.00 | 0.00 | +0.30 | +4.00 | Calculated | Remove
Add New
Remove All
Plan Uncertainty Dose Calculation
Calculate automatically after nominal dose calculation
Calculate after clicking OK
Plan uncertainty doses are calculated for each parameter set. Memory consumption may affect the performance of your computer.
OK
Cancel
Fields
Dose Prescription
Field Alignments
Plan Objectives
Show DVH | Structure | Approval Status
brainstem | Approved
CTV 46 | Approved
ctv 60 | Approved
gtv 46 | Approved
Max Dose [cGy]
Mean Dose [cGy]
1279.7
401.9
1136.8
1492.4
1438.6



Plan Objectives | Optimization Objectives | Dose Statistics | Calculation Models | Plan Sum

roval Status	Plan	Course	Volume [cm³]	Dose Cover.[%]	Sampling Cover.[%]	Min Dose [cGy]	Max Dose [
roved	Brain_BST	Brain					
roved	Brain_BST	Brain	0.2	100.0	100.0	4.8	
roved	Brain_BST	Brain	0.2	100.0	100.6	0.0	

BN001 – HGG
Hypofx RT vs Stnd Fx RT

STEP 2 REGISTRATION

STRATIFY
RPA Class: III, IV, or V
MGMT Status: Methylated, Unmethylated, or Indeterminate

RANDOMIZE**

Arm A2: Reference Arm
Photon irradiation using 3DCRT or IMRT:
46 Gy in 23 fractions followed by a sequential boost for an additional 7 fractions to 60 Gy
Plus
Concomitant temozolomide

4 weeks after completion of chemoradiation:
Adjuvant temozolomide x 6-12 cycles

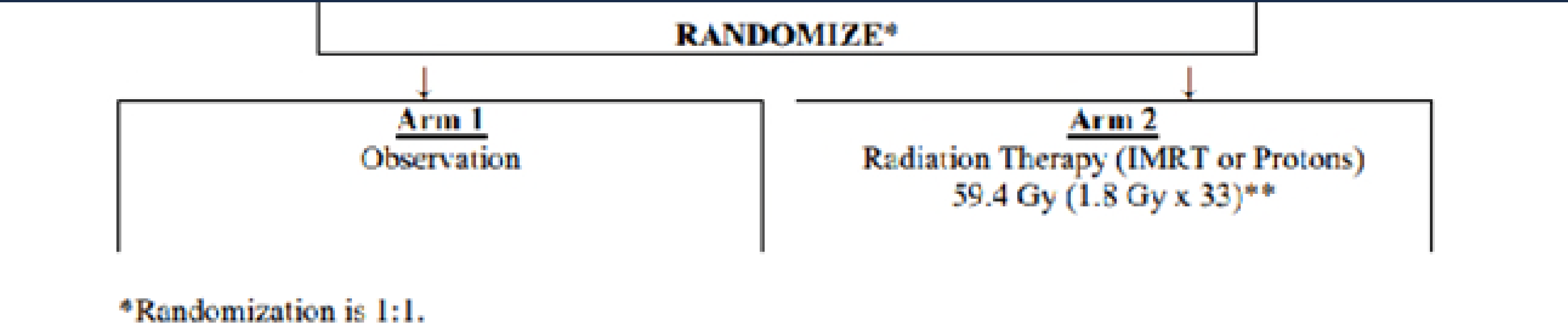
Arm C: Experimental Arm
Proton dose-intensified irradiation using passive scattered, uniform scanning beam, PBS or IMPT:
50 Gy(RBE) in 30 fractions with a simultaneous integrated boost to 75 Gy(RBE) in 30 fractions.
Plus
Concomitant temozolomide

4 weeks after completion of chemoradiation:

Adjuvant temozolomide x 6-12 cycles

*Randomization is 1:2 in favor of the experimental arm.

BN003 – Obs vs RT
GTR Grade II Meningioma



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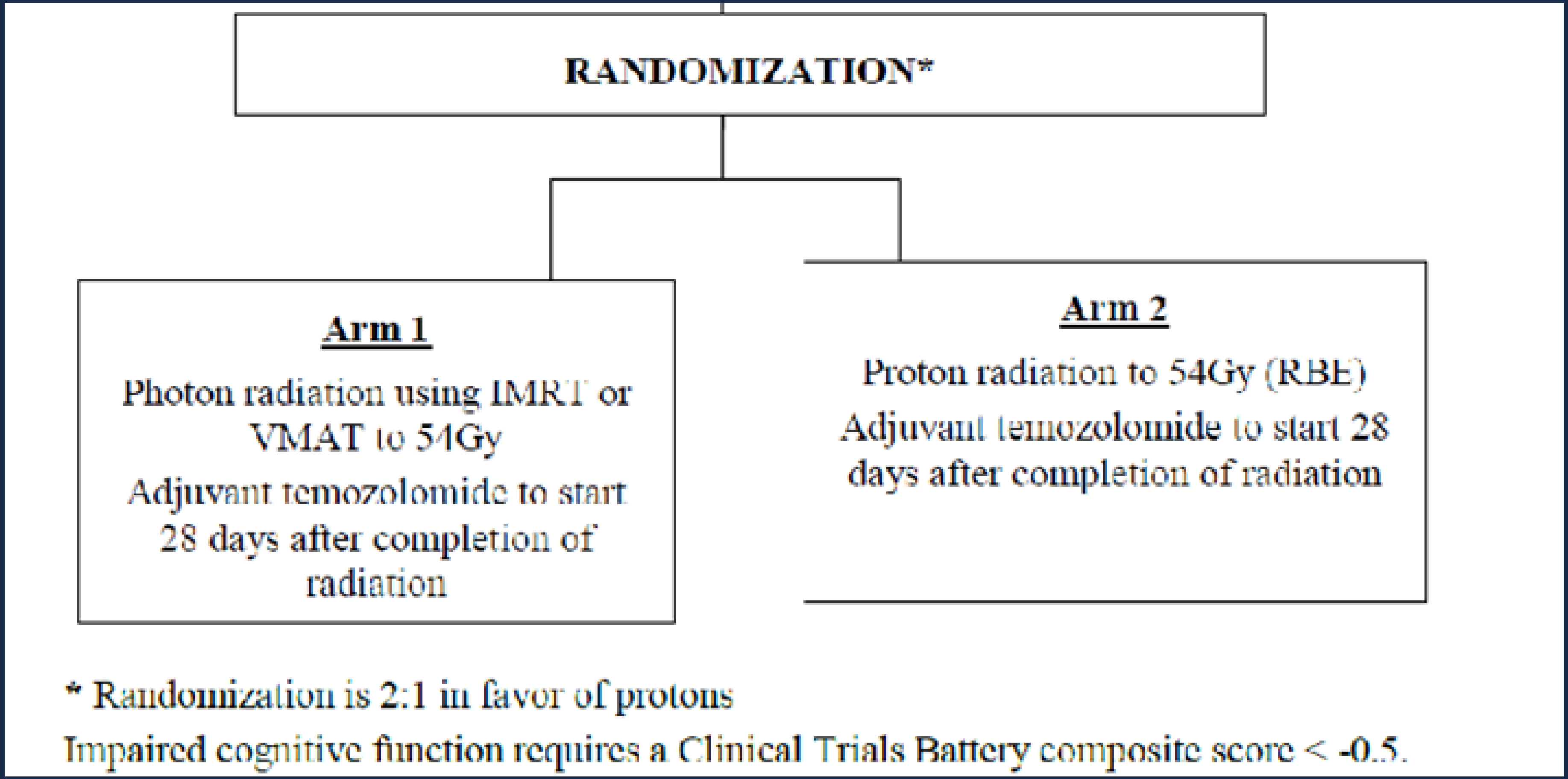
BN005 – Low Grade Glioma
IDH Mutant Low/Int Grade

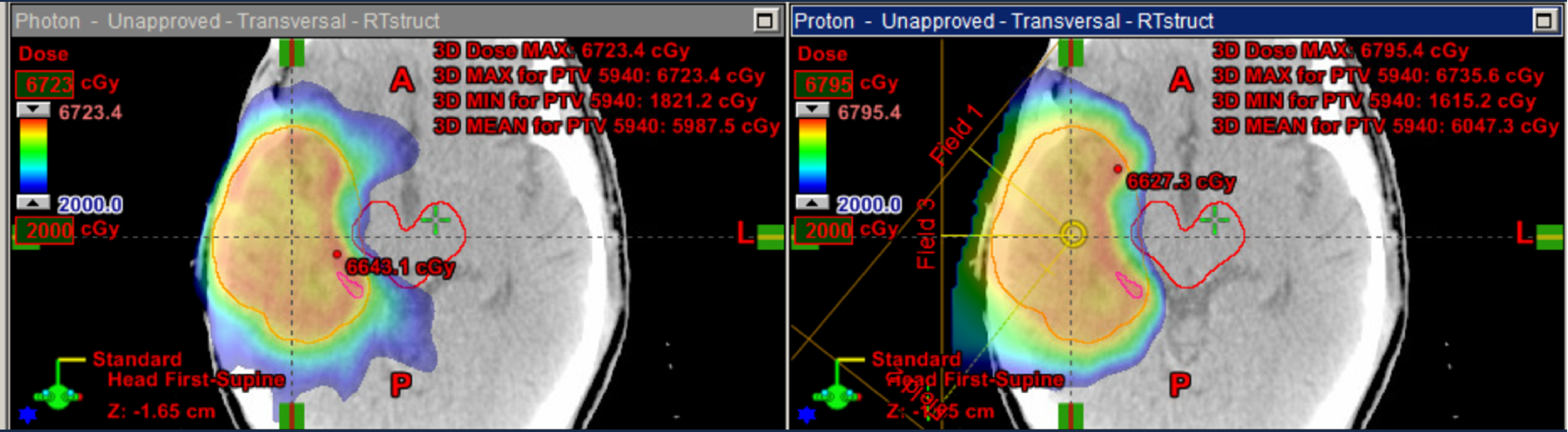


Strat Factors: 1p19q; GTR vs STR; baseline cognition

Objectives - LGG

1. Cognitive preservation
   - Secondary / Tertiary Endpoints
     - QOL
     - Safety
     - Outcomes

Photon vs Proton



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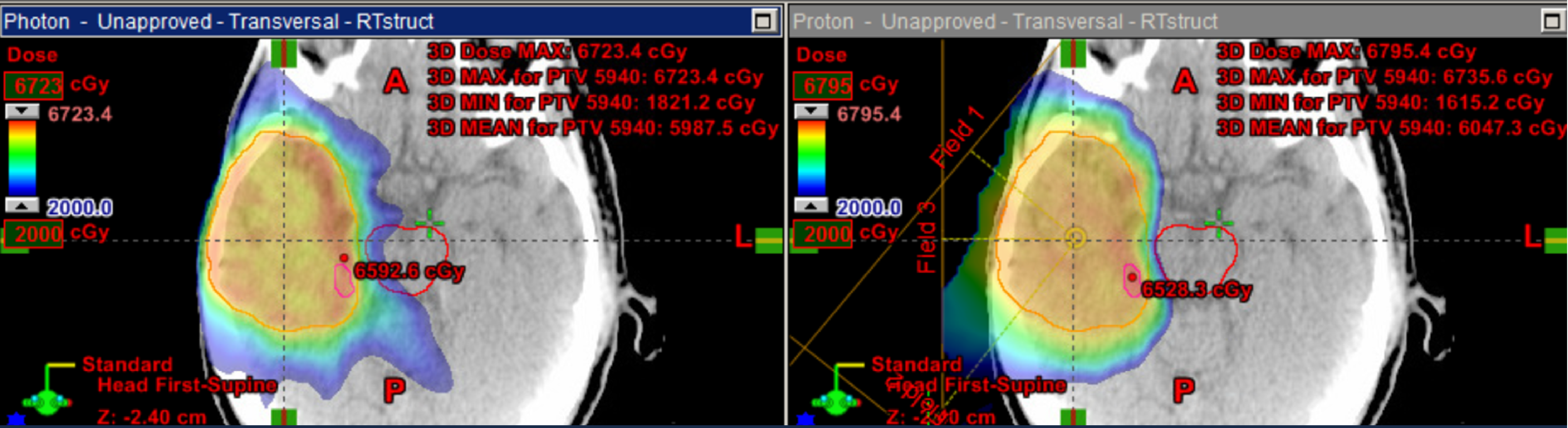
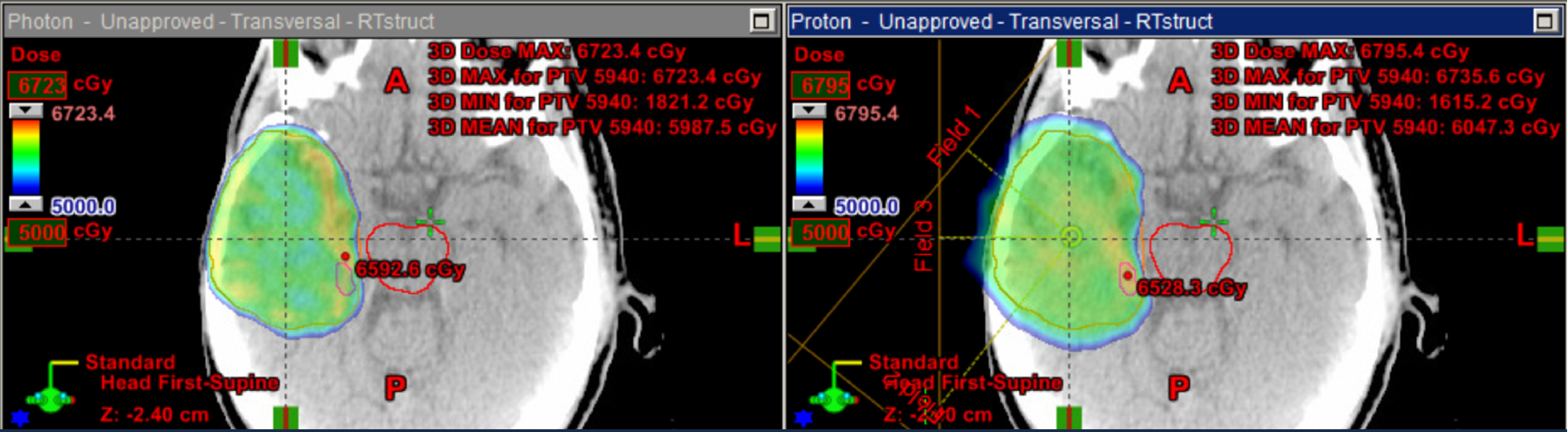
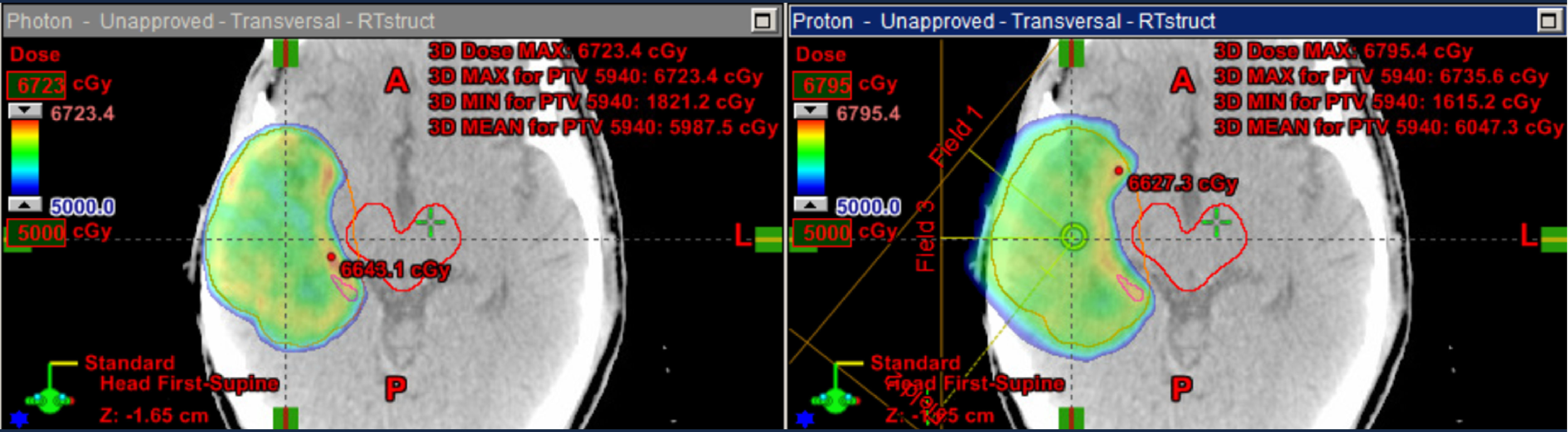

Photon - Unapproved - Transversal - RTstruct
Dose
6723 cGy
6723.4
2000.0
2000 cGy
3D Dose MAX: 6723.4 cGy
3D MAX for PTV 5940: 6723.4 cGy
3D MIN for PTV 5940: 1821.2 cGy
3D MEAN for PTV 5940: 5987.5 cGy
A
L
P
6592.6 cGy
Standard
Head First-Supine
Z: -2.40 cm
Proton - Unapproved - Transversal - RTstruct
Dose
6795 cGy
6795.4
2000.0
2000 cGy
3D Dose MAX: 6795.4 cGy
3D MAX for PTV 5940: 6735.6 cGy
3D MIN for PTV 5940: 1615.2 cGy
3D MEAN for PTV 5940: 6047.3 cGy
A
L
P
Field 1
Field 3
6528.3 cGy
Standard
Head First-Supine

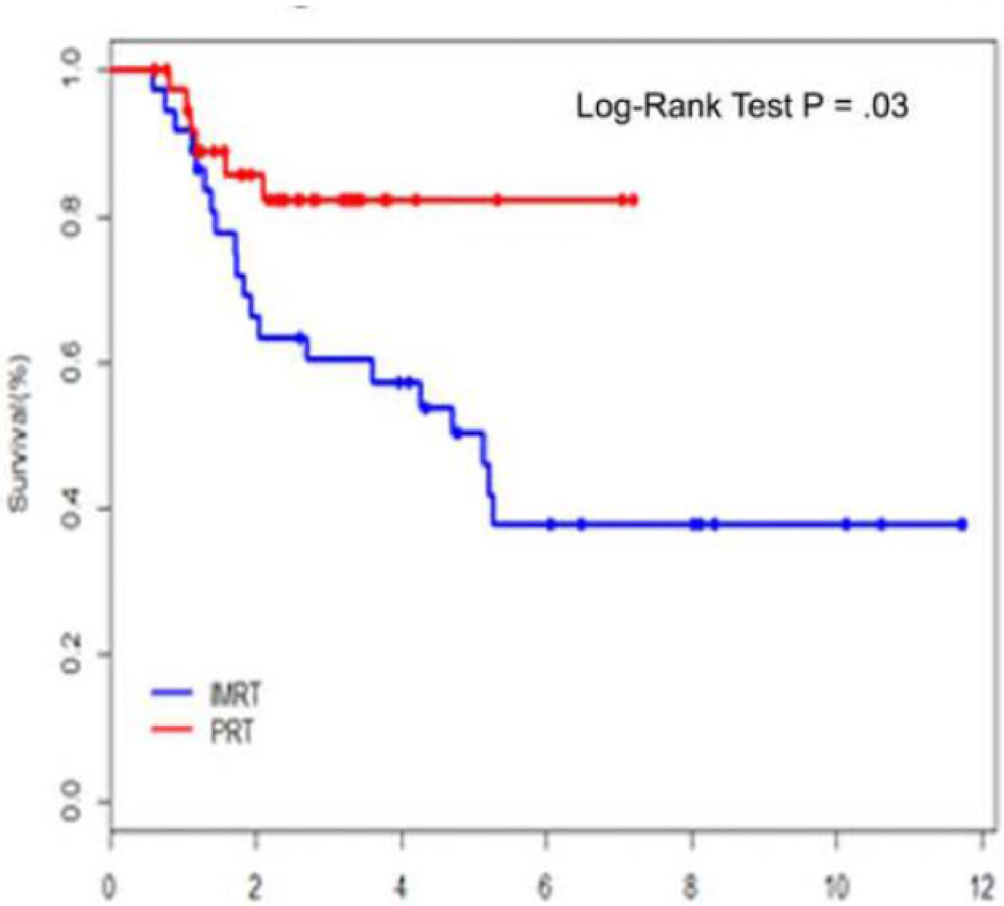

Photon - Unapproved - Transversal - RTstruct
Dose
6723 cGy
6723.4
5000.0
5000 cGy
3D Dose MAX: 6723.4 cGy
3D MAX for PTV 5940: 6723.4 cGy
3D MIN for PTV 5940: 1821.2 cGy
3D MEAN for PTV 5940: 5987.5 cGy
A
L
P
6592.6 cGy
Standard
Head First-Supine
Z: -2.40 cm
Proton - Unapproved - Transversal - RTstruct
Dose
6795 cGy
6795.4
5000.0
5000 cGy
3D Dose MAX: 6795.4 cGy
3D MAX for PTV 5940: 6735.6 cGy
3D MIN for PTV 5940: 1615.2 cGy
3D MEAN for PTV 5940: 6047.3 cGy
A
L
P
Field 1
Field 3
6528.3 cGy
Standard
Head First-Supine


Photon - Unapproved - Transversal - RTstruct
Dose
6723 cGy
6723.4
5000.0
5000 cGy
3D Dose MAX: 6723.4 cGy
3D MAX for PTV 5940: 6723.4 cGy
3D MIN for PTV 5940: 1821.2 cGy
3D MEAN for PTV 5940: 5987.5 cGy
A
L
P
6643.1 cGy
Standard
Head First-Supine
Z: -1.65 cm
Proton - Unapproved - Transversal - RTstruct
Dose
6795 cGy
6795.4
5000.0
5000 cGy
3D Dose MAX: 6795.4 cGy
3D MAX for PTV 5940: 6735.6 cGy
3D MIN for PTV 5940: 1615.2 cGy
3D MEAN for PTV 5940: 6047.3 cGy
A
L
P
Field 1
Field 3
6627.3 cGy
Standard
Head First-Supine

Meningioma case – skull base

Brain Necrosis

Progression-Free Survival of Children With Localized Ependymoma Treated With Intensity-Modulated Radiation Therapy or Proton-Beam Radiation Therapy

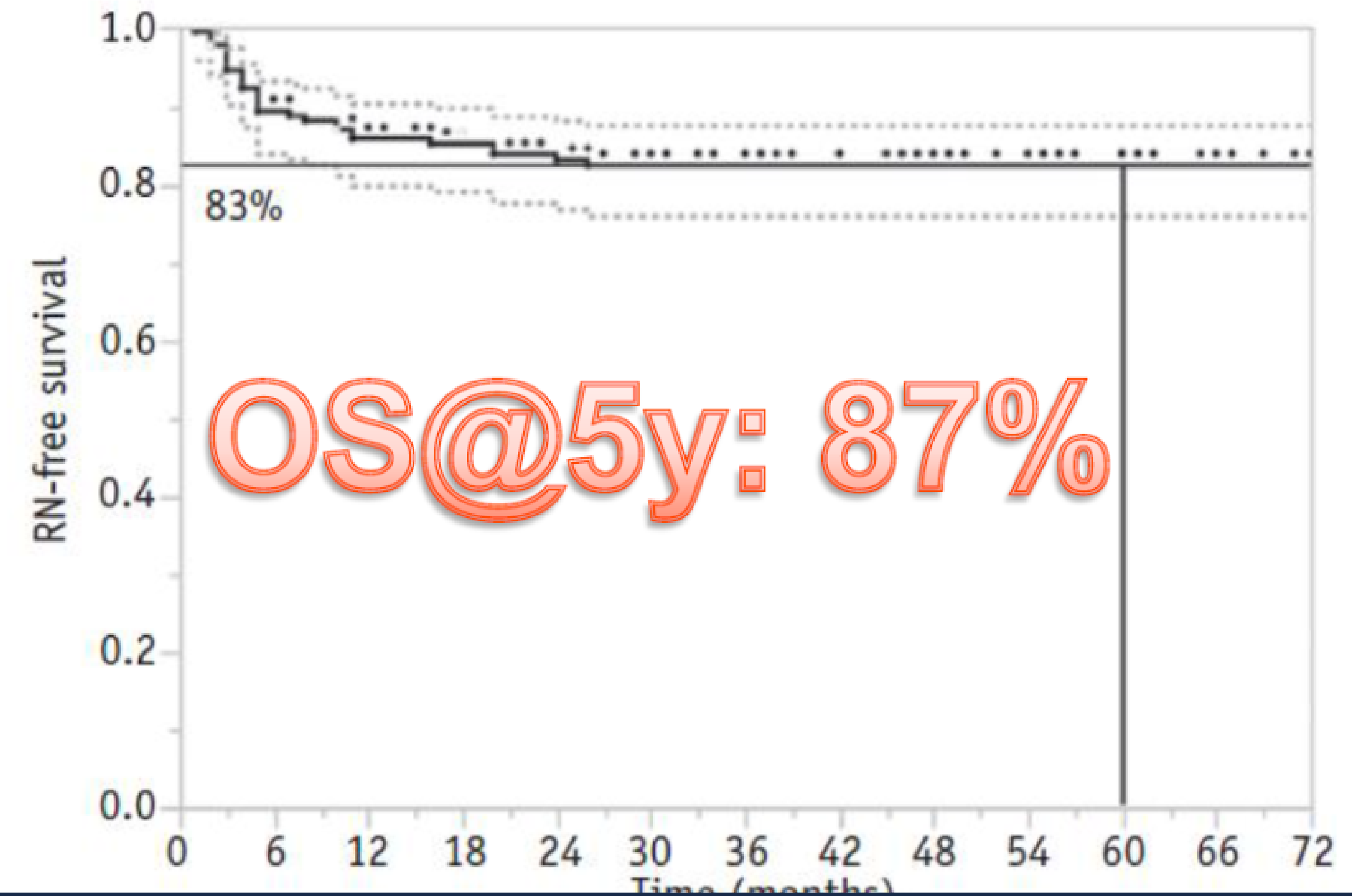


Type of RT	Brain necrosis 6/79 (8%)
PT	3(50%)
IMRT	3 (50%)

Cancer July 1, 2017

Sato

Radiation Necrosis and White Matter Lesions in Pediatric Patients With Brain Tumors Treated



Bojaxhiu IJROBP 2018
PSI Data

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RN Grade	N=	%
Grade 1	17	59
Grade 2	8	28
Grade 4	2	6.5
Grade 5	**2**	**6.5**
Total (median, 5 mo;1-26)	***29***	***17****

The characteristics of the 4 patients presenting with grade 4-5 toxicities were very young (median,2.9 years; range, 2.3-3.3 years), and half of them presented with ependymoma.

Of note, 50% of these challengingpatients had pre-PT pons infarction

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Int J Radiation Oncol Biol Phys, Vol. 100, No. 4, pp. 987–996, 2018

Brainstem Injury in Pediatric Patients With Posterior Fossa Tumors Treated With Proton Beam Therapy and Associated Dosimetric Factors

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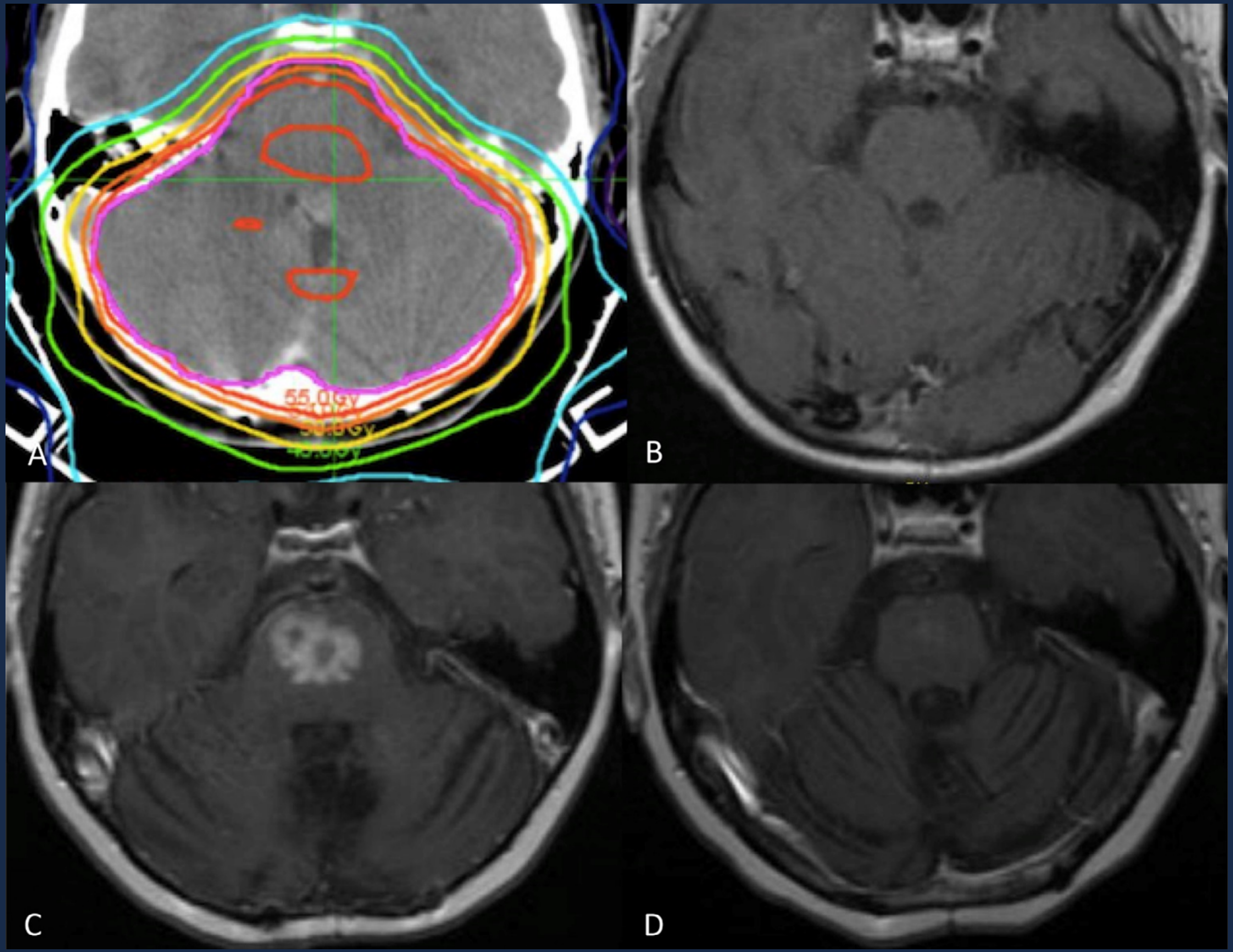
International Journal of Radiation Oncology • Biology • Physics
Volume 100, Issue 3, Pages 719-729 (March 2018)
DOI: 10.1016/j.ijrobp.2017.11.026

Fig. 1



International Journal of Radiation Oncology • Biology • Physics 2018 100, 719-729DOI: (10.1016/j.ijrobp.2017.11.026)

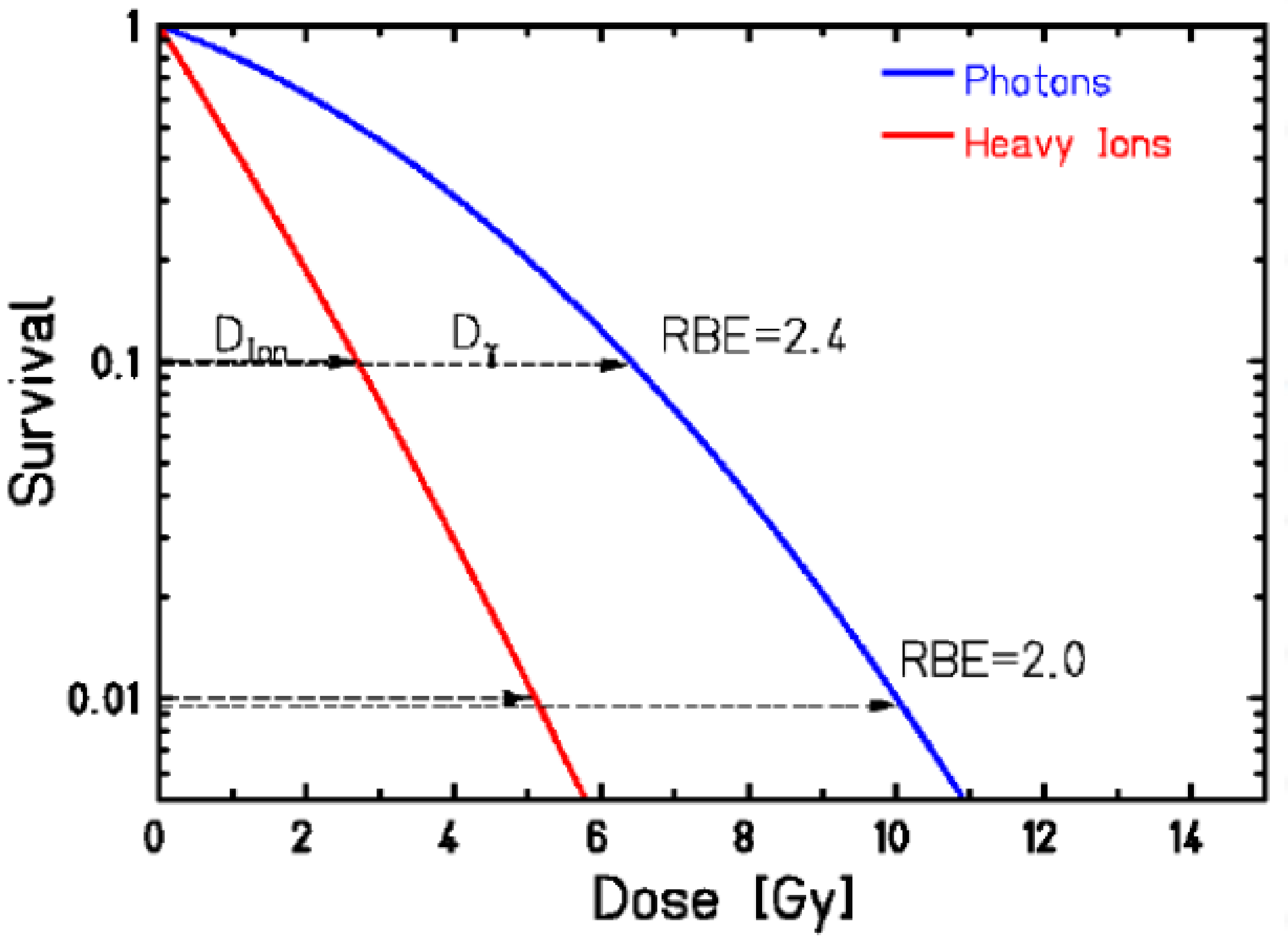
Table 3 Crude rate of brainstem injury in study patients with conventional high-risk factors

Factor	Total cohort (N=216), n (%)	Patients with brainstem injury, n (%)	*P* value
Young age (<5 y)	69 (31.9)	2 (2.9)	.67
No GTR	64 (29.6)	1 (1.6)	.74
Neurologic complications after surgery	121 (56.0)	5 (4.1)	.02
Tracheostomy	9 (4.2)	0 (0)	.98
PEG tube placement	35 (16.2)	0 (0)	.59
Posterior fossa syndrome	50 (23.1)	3 (6.0)	.02
High-dose chemotherapy with stem cell rescue	29 (13.4)	2 (6.9)	.04
Chemotherapy	180 (83.3)	4 (2.2)	.60

Abbreviations: GTR = gross total resection; PEG = percutaneous endoscopic gastrostomy.

In summary, our proton cohort data on pediatric patients with primary brain tumors of the posterior fossa demonstrate a low rate of brainstem injury with PRT (2% at 5 years), which is consistent with photon cohort data. Our dosimetric analysis further suggests this rate could be driven even lower if the D_{max} and V_{55} are kept <55.8 Gy RBE and ≤6.0%,

Definition of RBE

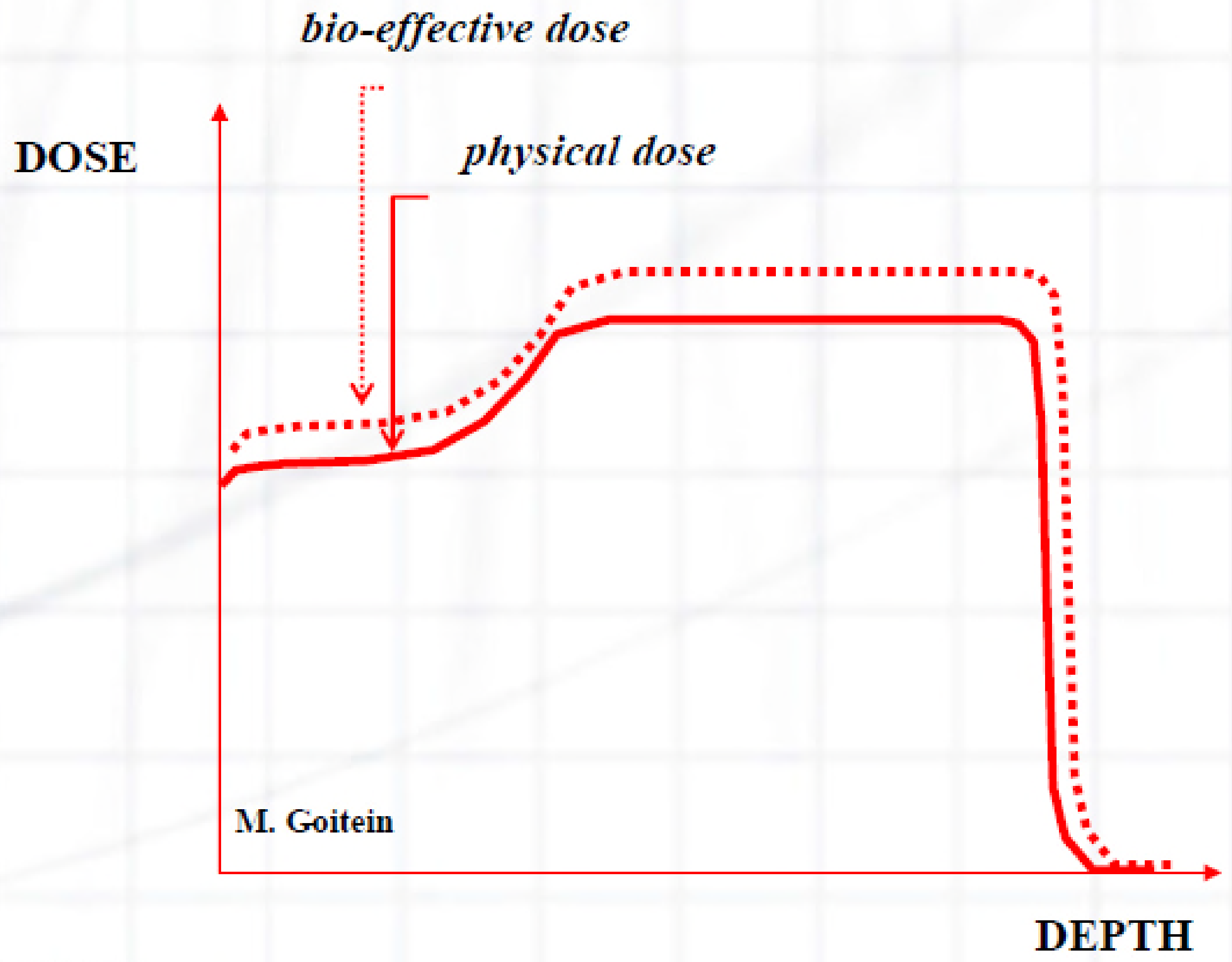


$$RBE = \frac{D_\gamma}{D_{ion}} \langle effect \rangle$$

M. Krämer, W. K. Weyrather, M. Scholz: Techn. Cancer Res. Treatm. 2, 427-436, 2003

Clinical RBE

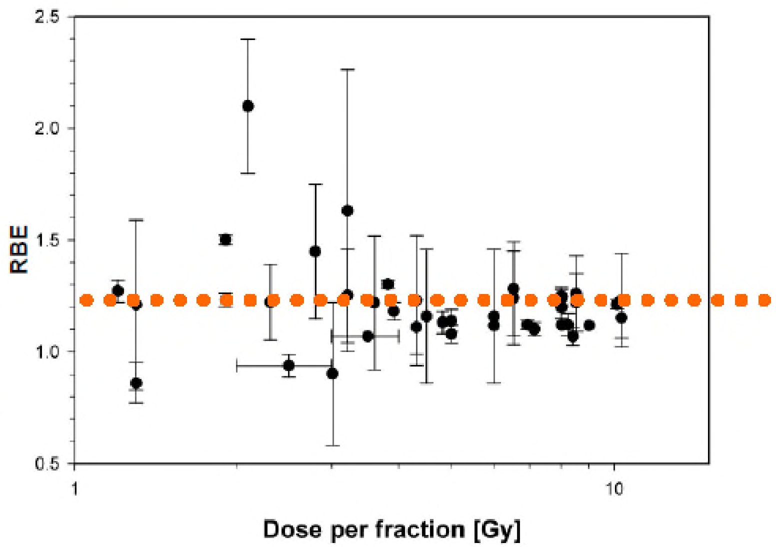
Proton therapy: RBE = 1.1



Clinical RBE

RBE from experimental data

RBE values *in vitro* (center of SOBP; relative to ^{60}Co)



1.21 ± 0.20

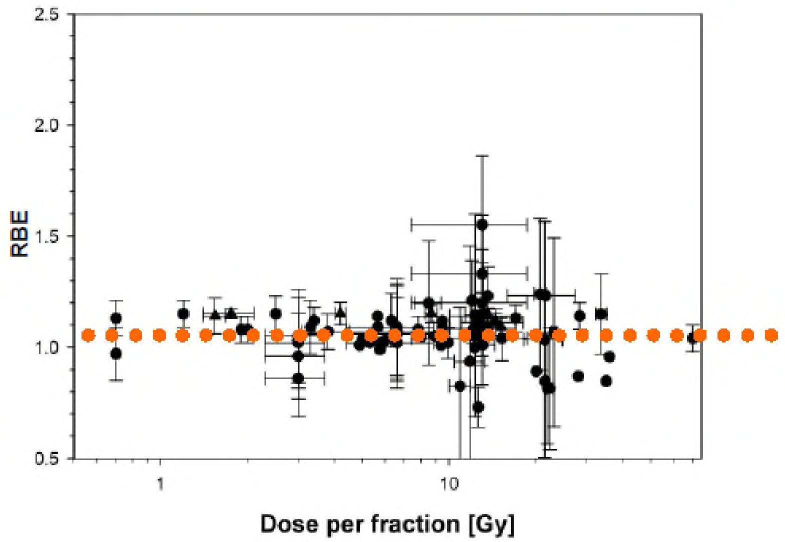
Endpoint: Cell Survival

Paganetti et al.: *Int. J. Radiat. Oncol. Biol. Phys.* 2002; 53, 407

Clinical RBE

RBE from experimental data

RBE values *in vivo* (center of SOBP; relative to ^{60}Co)



1.07 ± 0.12

Mice data: Lung tolerance, Crypt regeneration, Acute skin reactions, Fibrosarcoma NFSa

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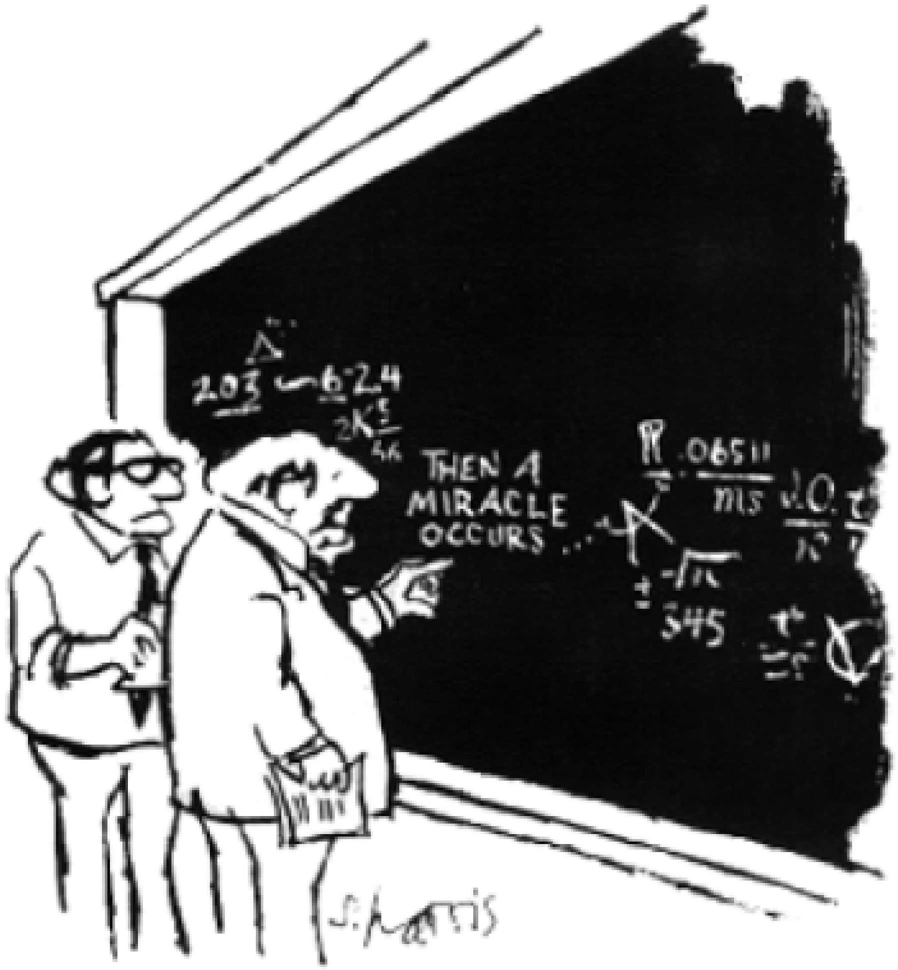
RBE depends on

- energy/LET
- dose
- tissue



"I think you should be more explicit here in step two."

LET

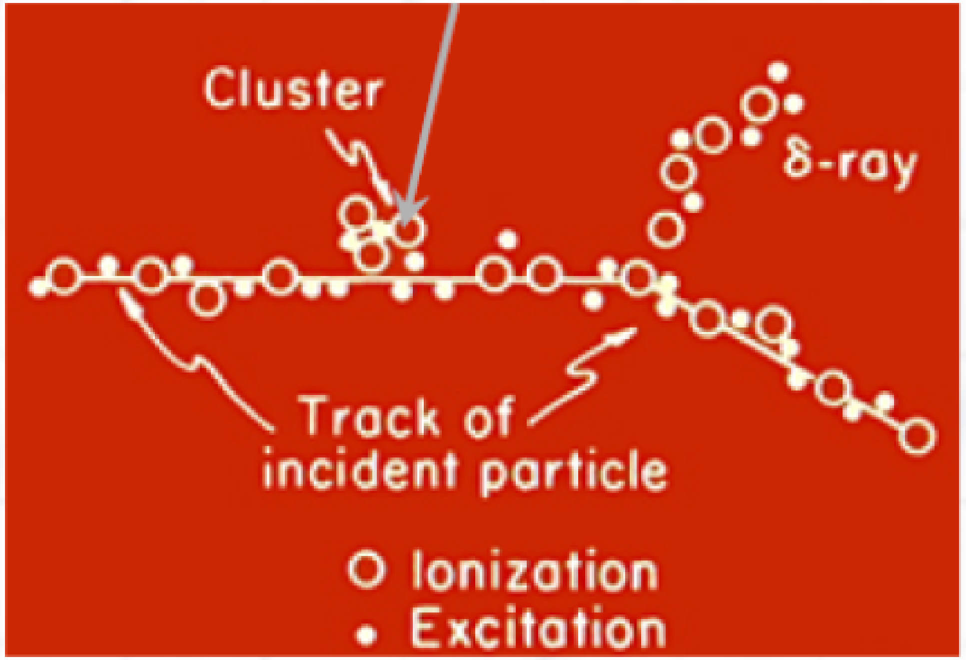
LET $\leftrightarrow$ Energy

Table 7.1. Linear Energy Transfer (LET) of Various Radiations

Radiation	LET (keV/μm)
Photons	
^{60}Co (~1.2 MeV)	0.3
200-keV X-ray	2.5
Electrons	
1 MeV	0.2
100 keV	0.5
10 keV	2
1 keV	10
Charged particles	
proton 2 MeV	17
alpha 5 MeV	90
carbon 100 MeV	160
Neutrons	
2.5 MeV	15–80
14.1 MeV	3–30

RBE as a function of particle energy / LET

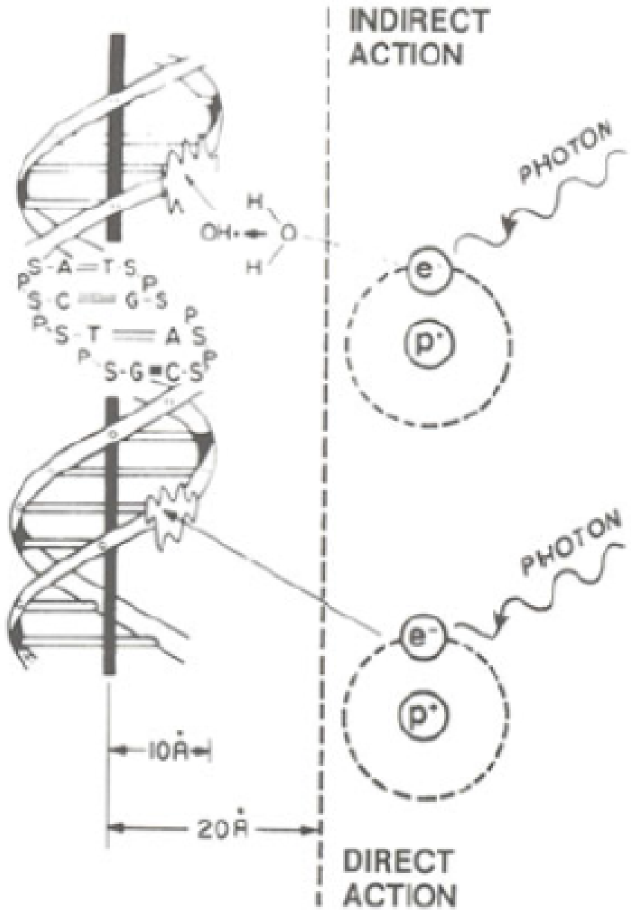
Lesion complexity



Lesions can be repairable or non-repairable

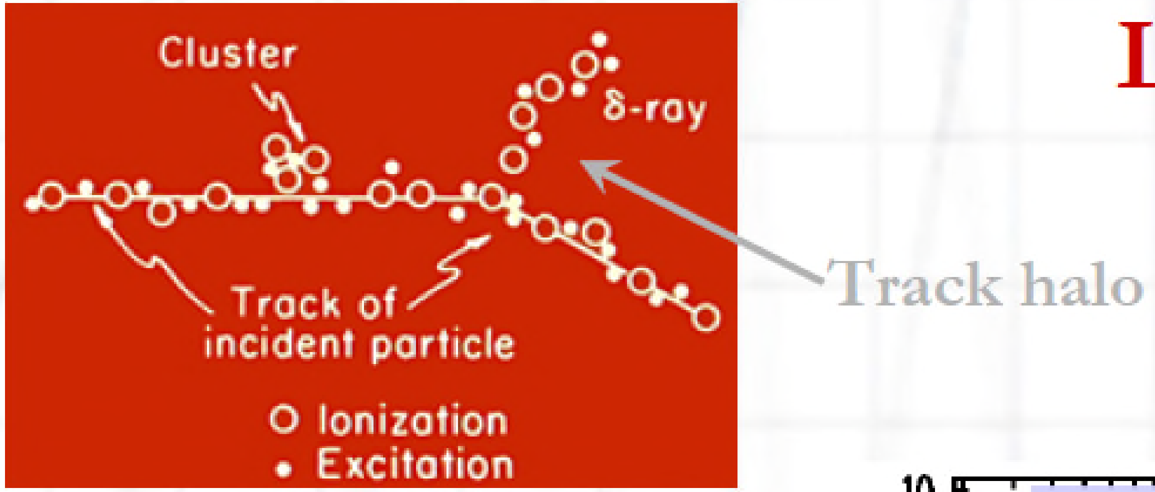
High-LET radiation produces more non-repairable lesions

Oxygen Enhancement Ratio



Hypoxic cells are more radio-resistant than well oxygenated cells for low-LET radiation

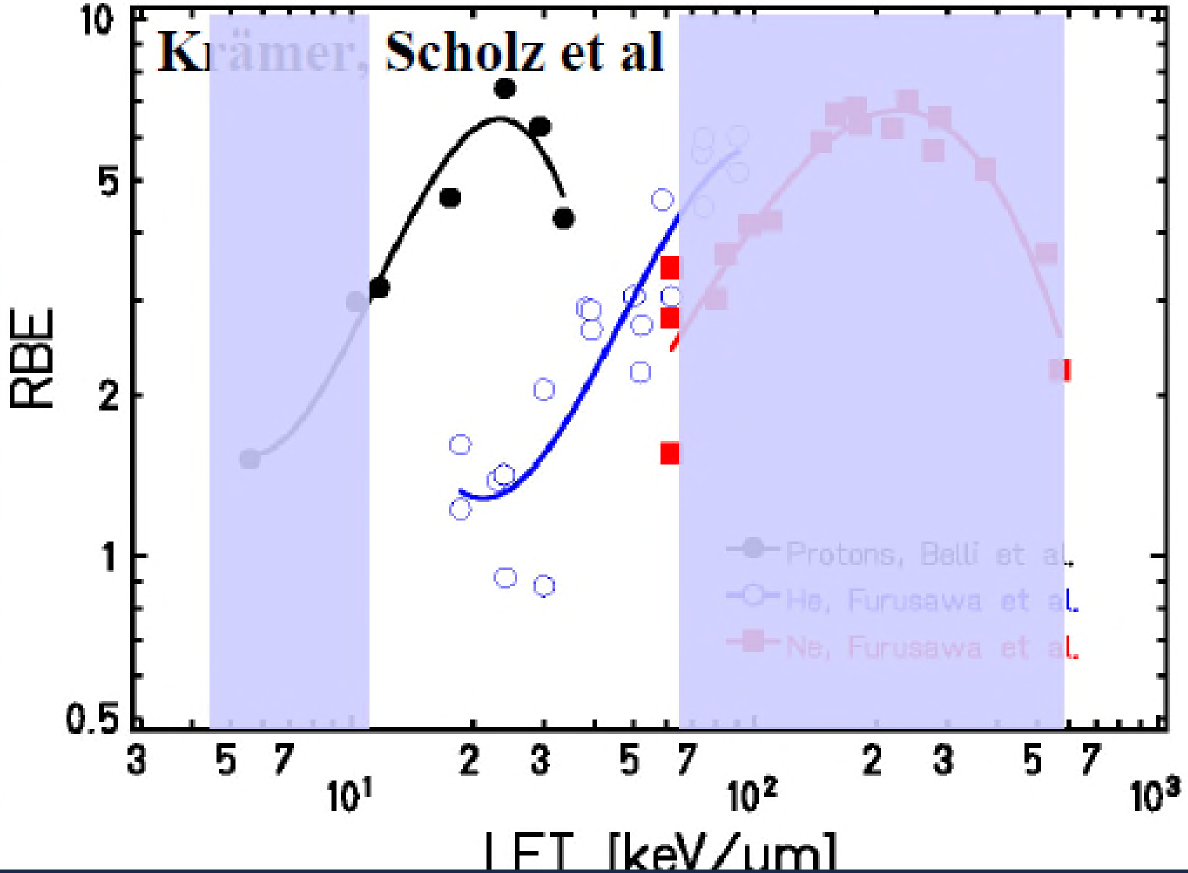
LET ↔ RBE



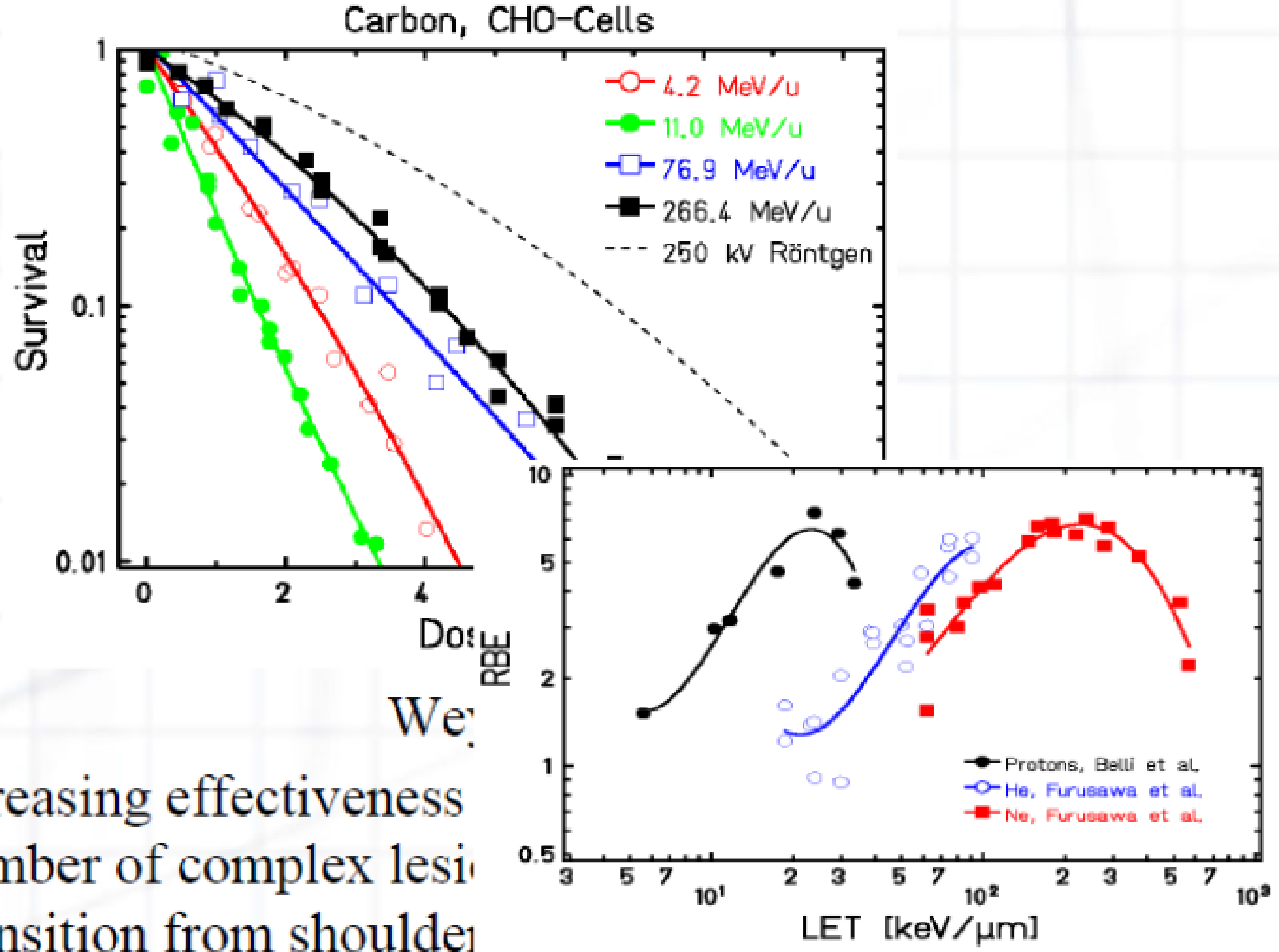
protons create lower energy δ-rays (smaller track halo) compared to heavy ions at a given LET

⇒ higher local dose

⇒ proton RBE > ion RBE at a given LET



RBE as a function of particle energy / LET



We

- Increasing effectiveness
- Number of complex lesi
- Transition from shoulde
- Saturation effects at very low energies

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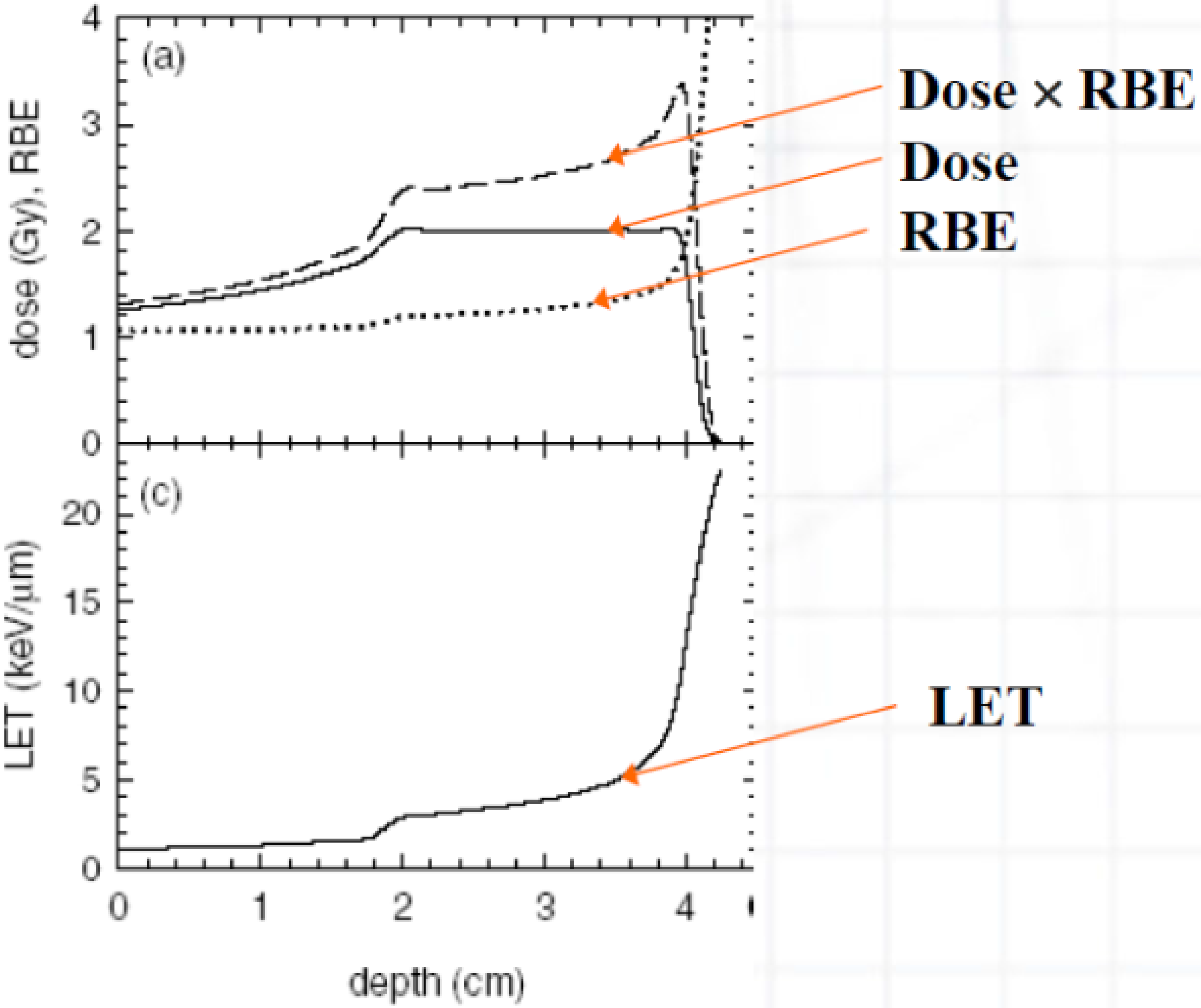
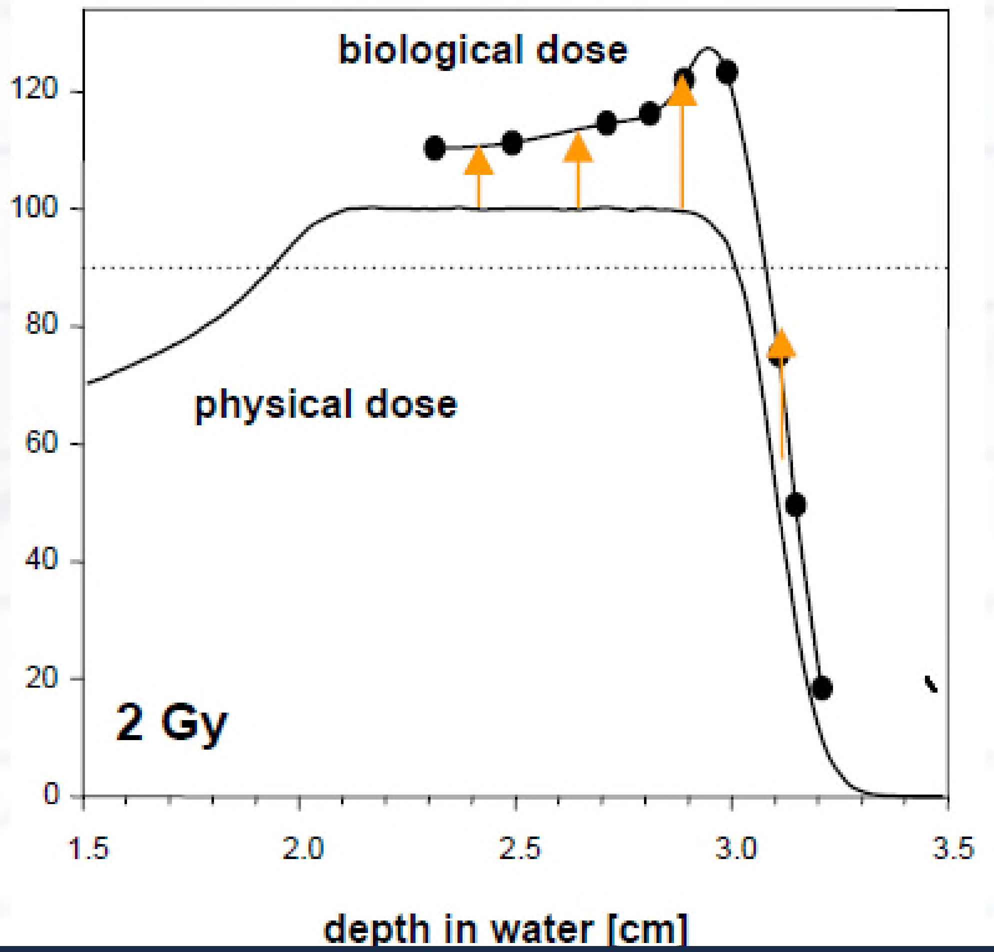
RBE as a function of particle energy / LET

Wilkens and Oelfke: *Phys Med Biol* 2004 49; 2811–2825



RBE as a function of particle energy / LET

An increasing RBE with depth cause an extended biologically effective range (1-2 mm)



Paganetti, Goitein: *Med. Phys.* 2000: 27, 1119-1126

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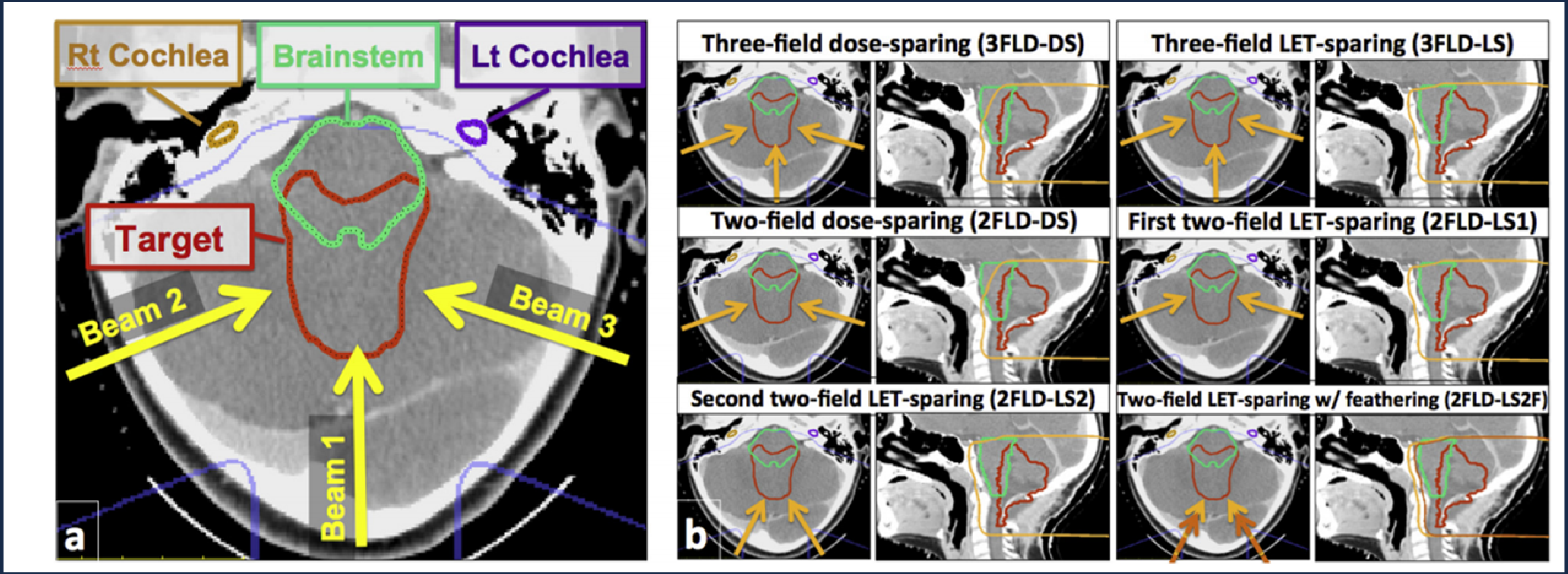
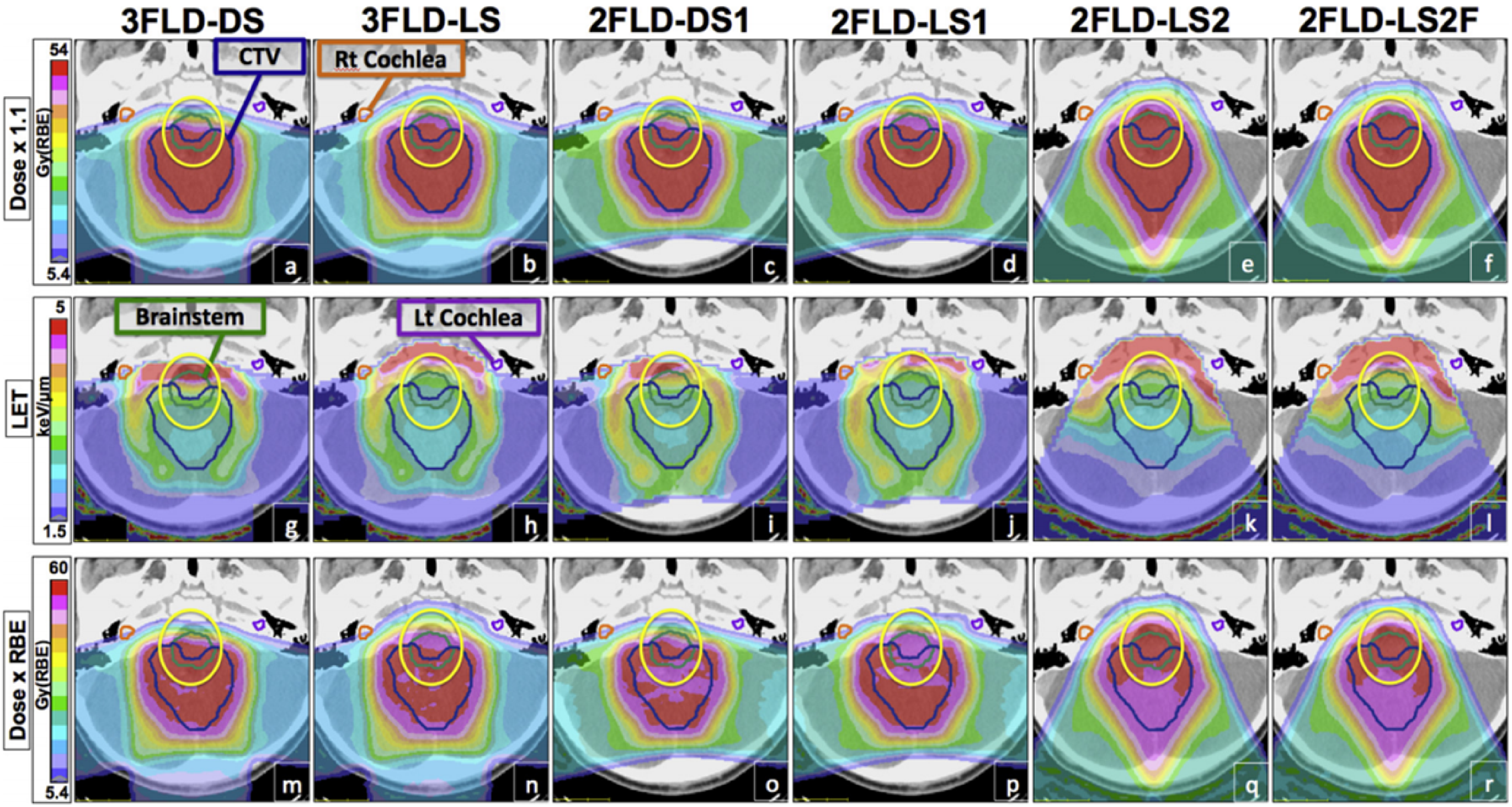
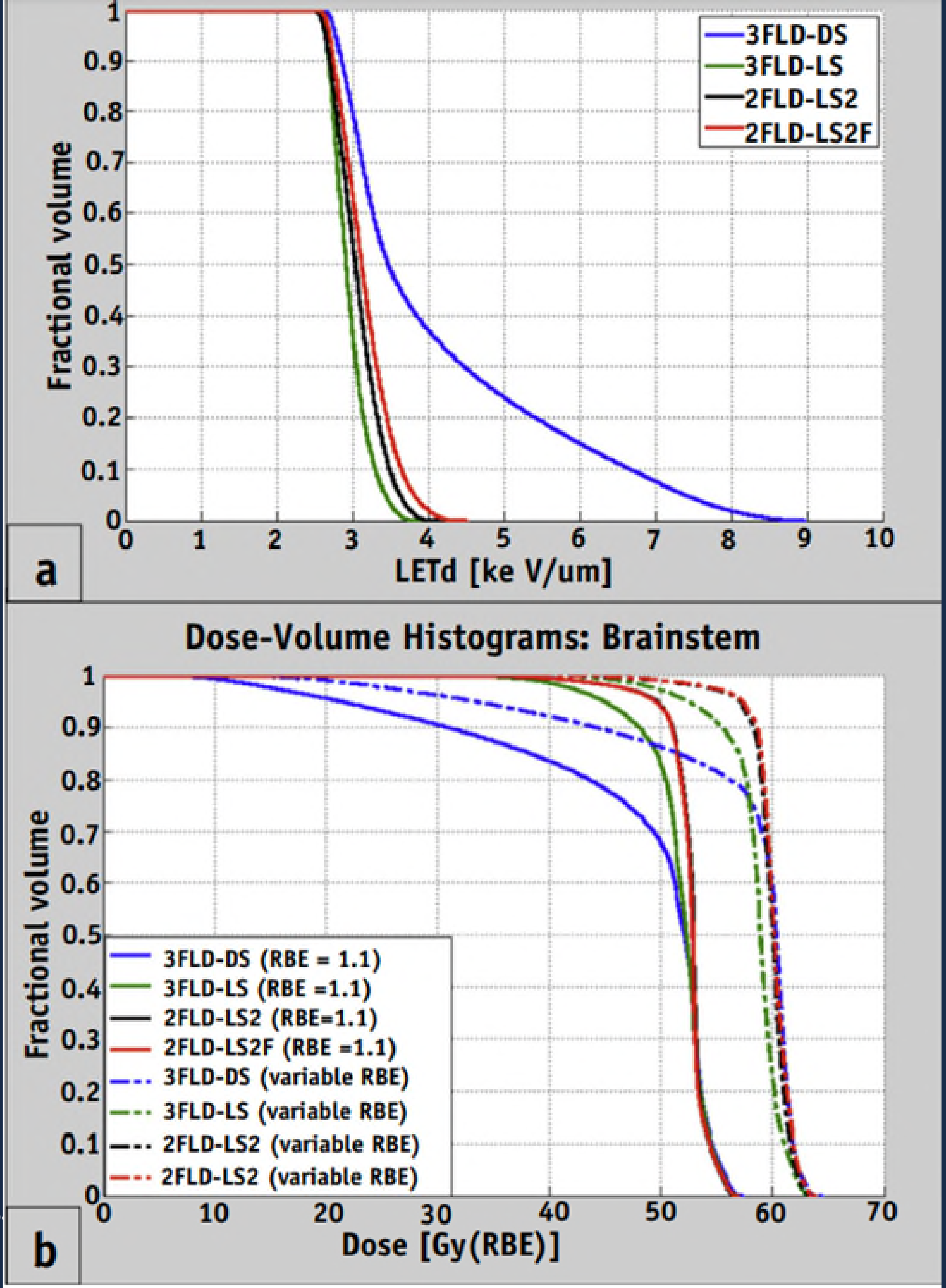
Passive Scatter Techniques



Giantsoudi IJROBP 2016



3FLD-DS
3FLD-LS
2FLD-DS1
2FLD-LS1
2FLD-LS2
2FLD-LS2F
Dose x 1.1
Gy(RBE)
54
5.4
CTV
Rt Cochlea
a
b
c
d
e
f
LET
keV/µm
5
1.5
Brainstem
Lt Cochlea
g
h
i
j
k
l
Dose x RBE
Gy(RBE)
60
5.4
m
n
o
p
q
r



Considering all these factors, we can conclude that if the objective is to minimize the volume of the brainstem being treated, then the dose-sparing approach should be preferred. The LET-sparing techniques may be beneficial if the maximum dose to the brainstem is the main concerning factor because they can achieve a lower maximum dose of approximately 2% compared with the dose-sparing techniques.

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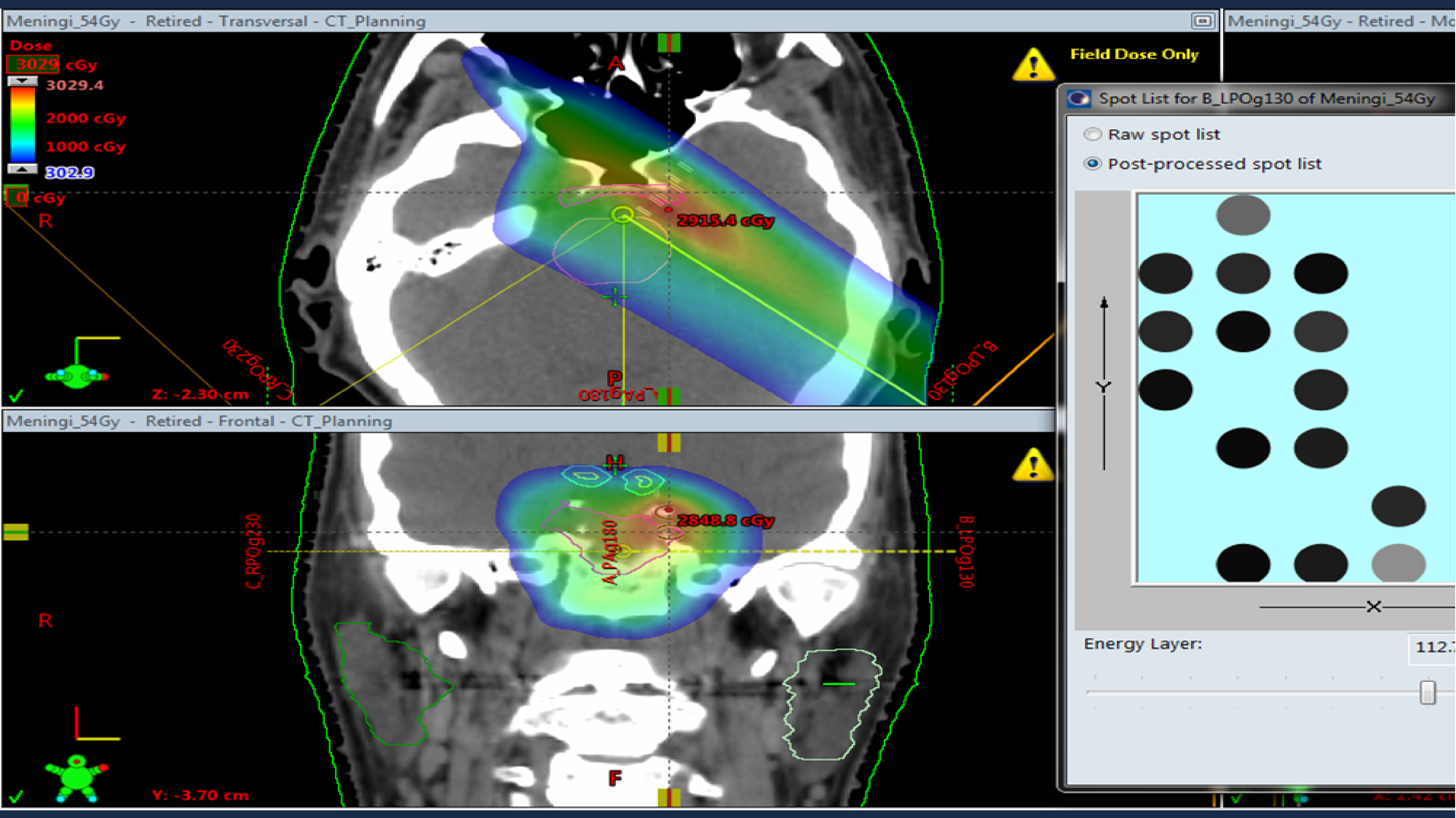
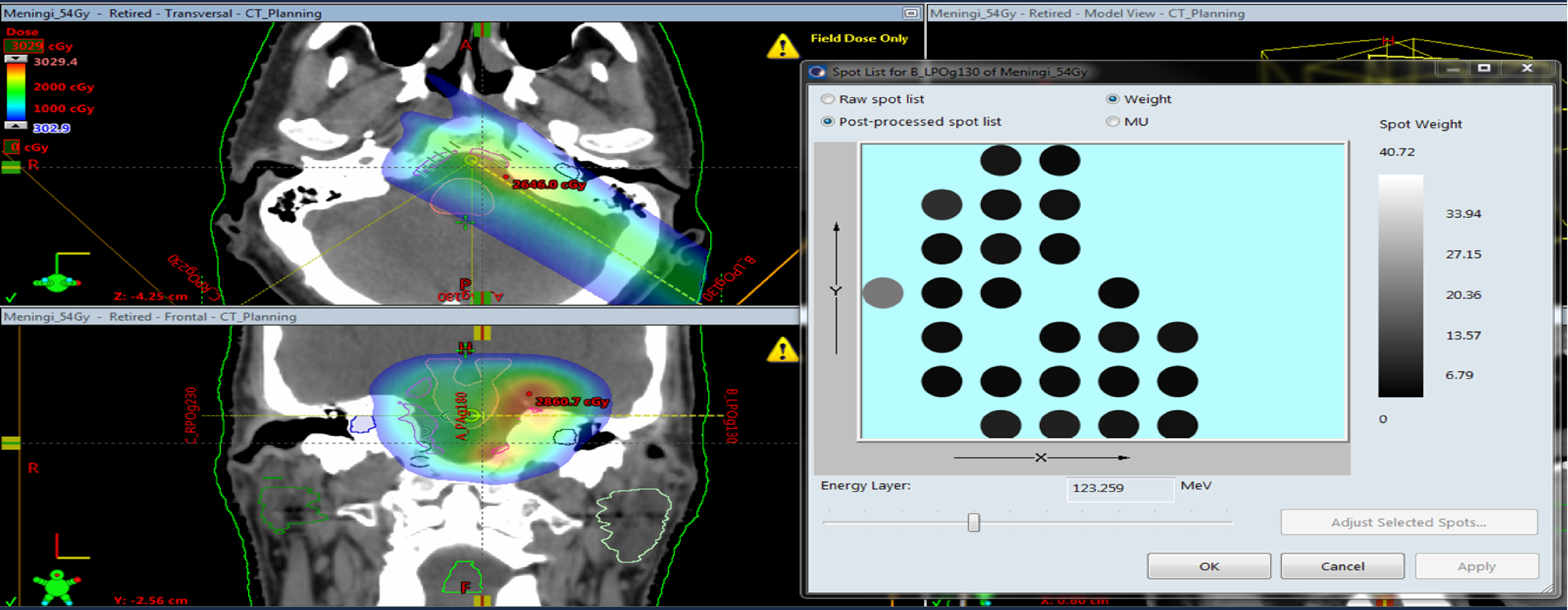
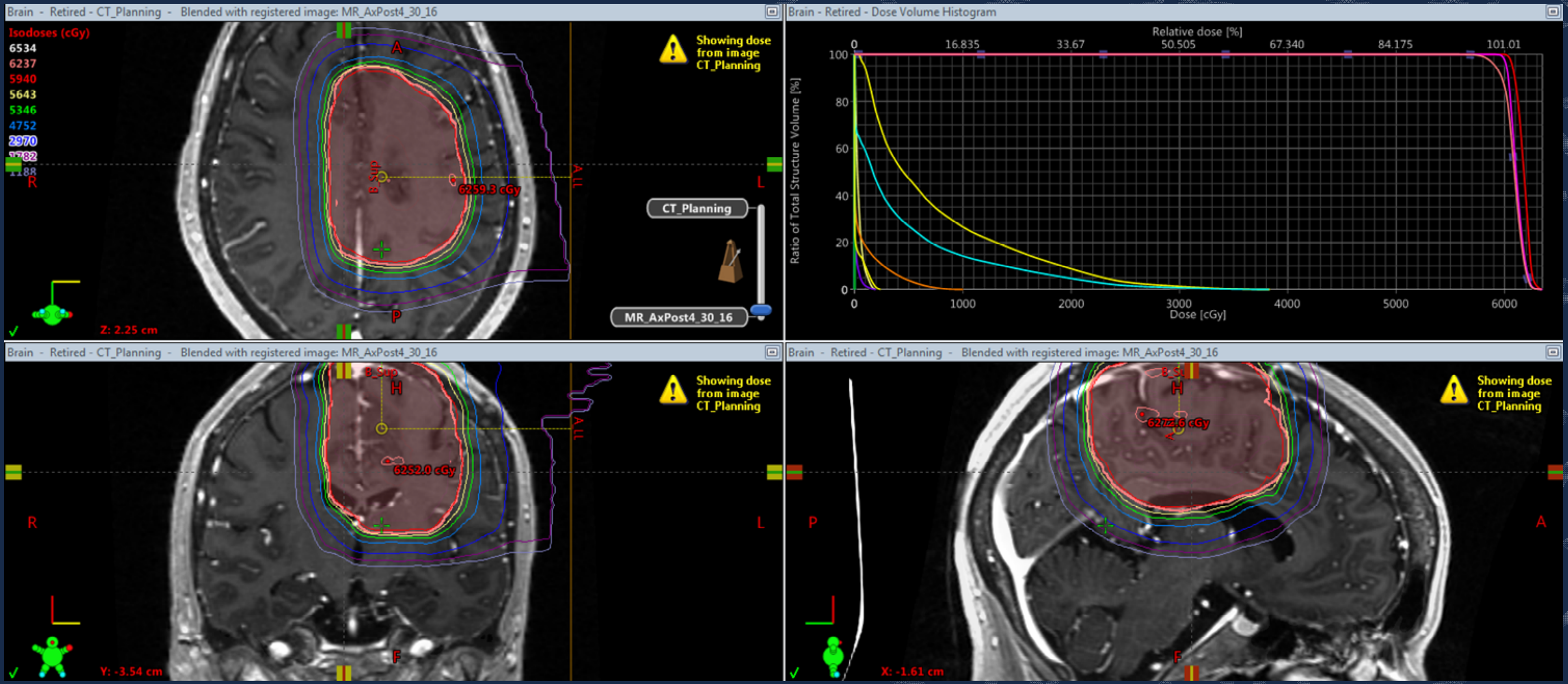


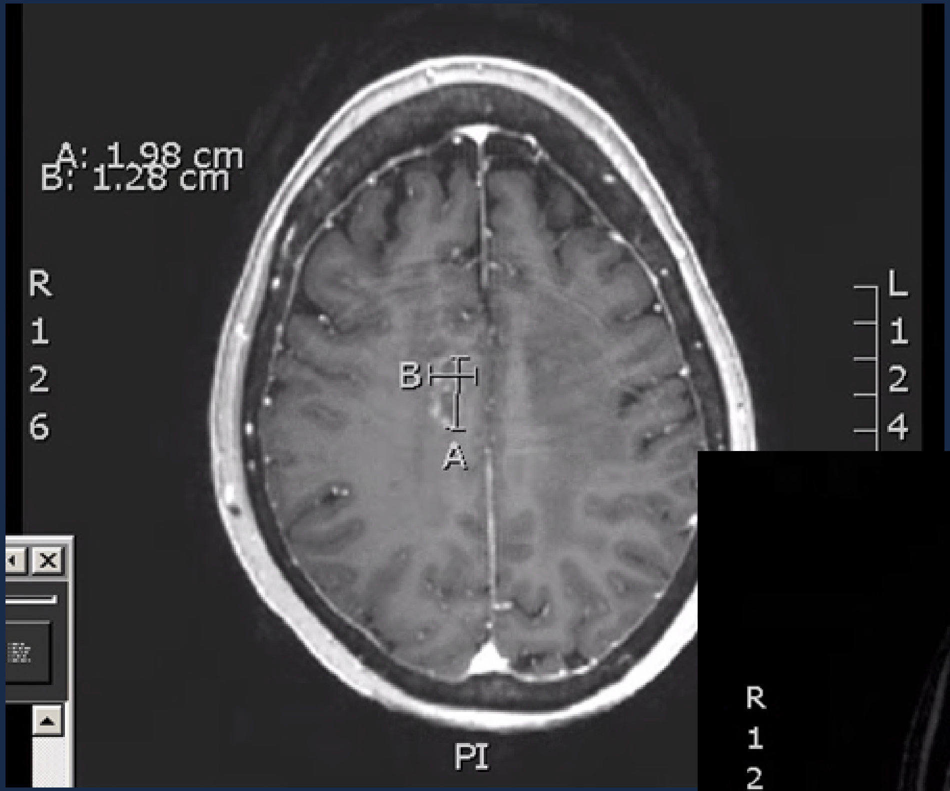
Meningi_54Gy - Retired - Transversal - CT_Planning
Dose
3029 cGy
3029.4
2000 cGy
1000 cGy
302.9
0 cGy
R
A
P
Field Dose Only
2915.4 cGy
Z: -2.30 cm
C_RPOg230
A_PAg180
B_LPOg130
Meningi_54Gy - Retired - Frontal - CT_Planning
H
F
2848.8 cGy
Y: -3.70 cm
Spot List for B_LPOg130 of Meningi_54Gy
Raw spot list
Post-processed spot list
Y
X
Energy Layer:

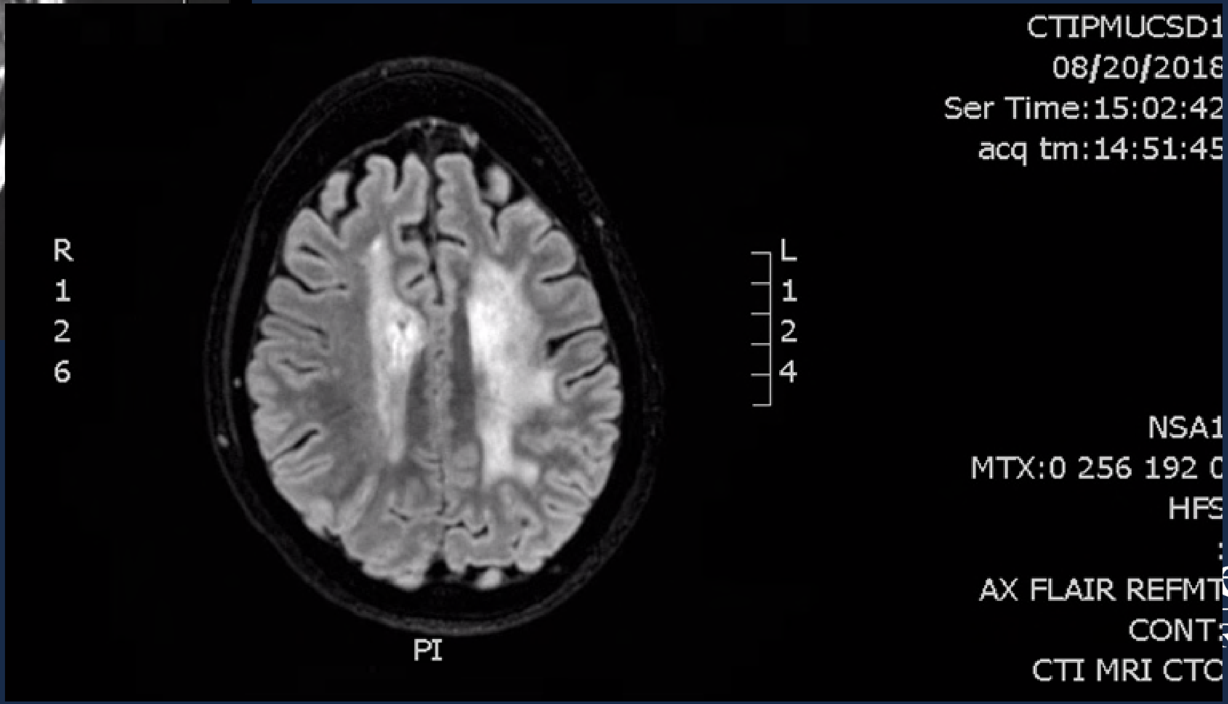


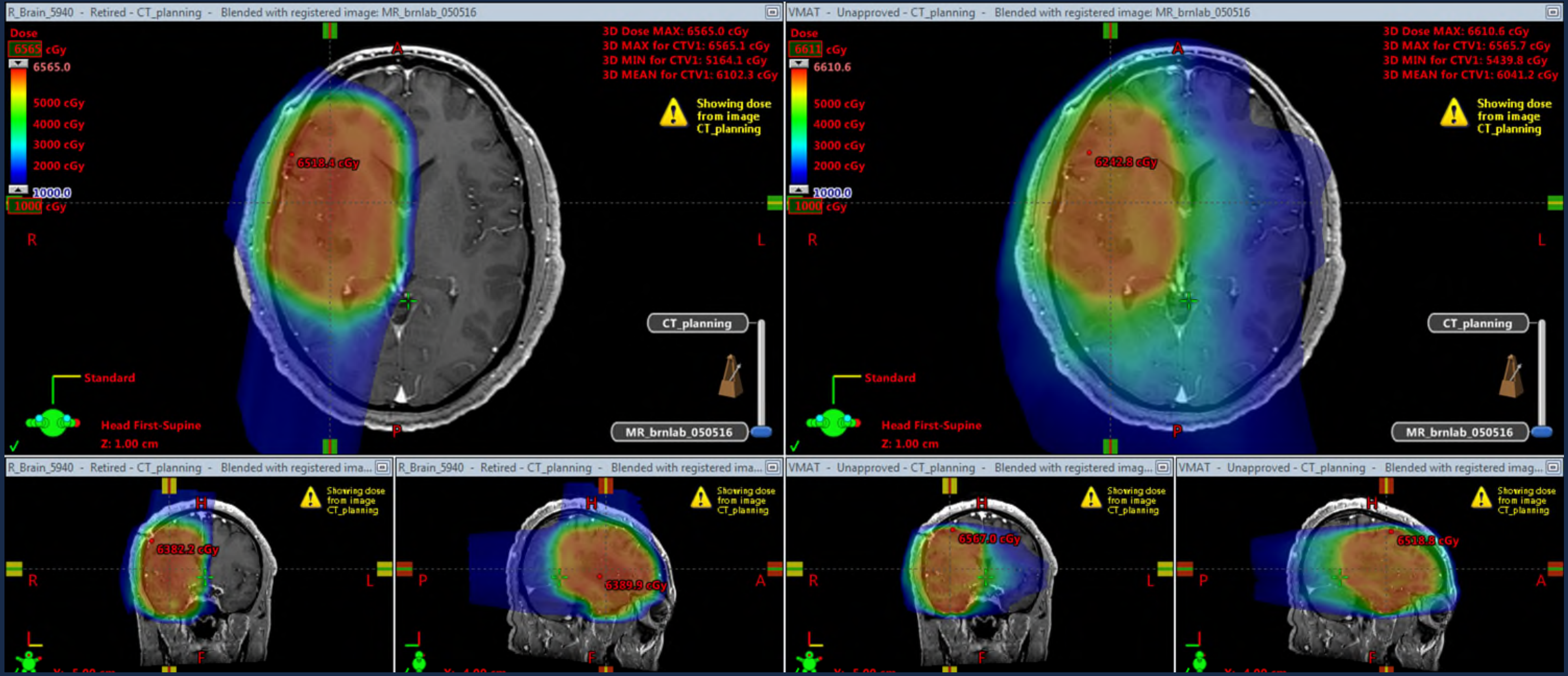
Meningi_54Gy - Retired - Transversal - CT_Planning
Dose
3029 cGy
3029.4
2000 cGy
1000 cGy
302.9
0 cGy
Field Dose Only
2646.0 cGy
Z: -4.25 cm
Meningi_54Gy - Retired - Frontal - CT_Planning
2860.7 cGy
Y: -2.56 cm
Meningi_54Gy - Retired - Model View - CT_Planning
Spot List for B_LPOg130 of Meningi_54Gy
Raw spot list
Post-processed spot list
Weight
MU
Spot Weight
40.72
33.94
27.15
20.36
13.57
6.79
0
Energy Layer:
123.259
MeV
Adjust Selected Spots...
OK
Cancel
Apply


Brain - Retired - CT_Planning - Blended with registered image: MR_AxPost4_30_16
Isodoses (cGy)
6534
6237
5940
5643
5346
4752
2970
1188
Showing dose from image CT_Planning
6259.3 cGy
CT_Planning
MR_AxPost4_30_16
Z: 2.25 cm
Brain - Retired - Dose Volume Histogram
Relative dose [%]
0
16.835
33.67
50.505
67.340
84.175
101.01
Ratio of Total Structure Volume [%]
100
80
60
40
20
0
1000
2000
3000
4000
5000
6000
Dose [cGy]
Brain - Retired - CT_Planning - Blended with registered image: MR_AxPost4_30_16
Showing dose from image CT_Planning
6252.0 cGy
Y: -3.54 cm
Brain - Retired - CT_Planning - Blended with registered image: MR_AxPost4_30_16
Showing dose from image CT_Planning
X: -1.61 cm

2+ year follow-up







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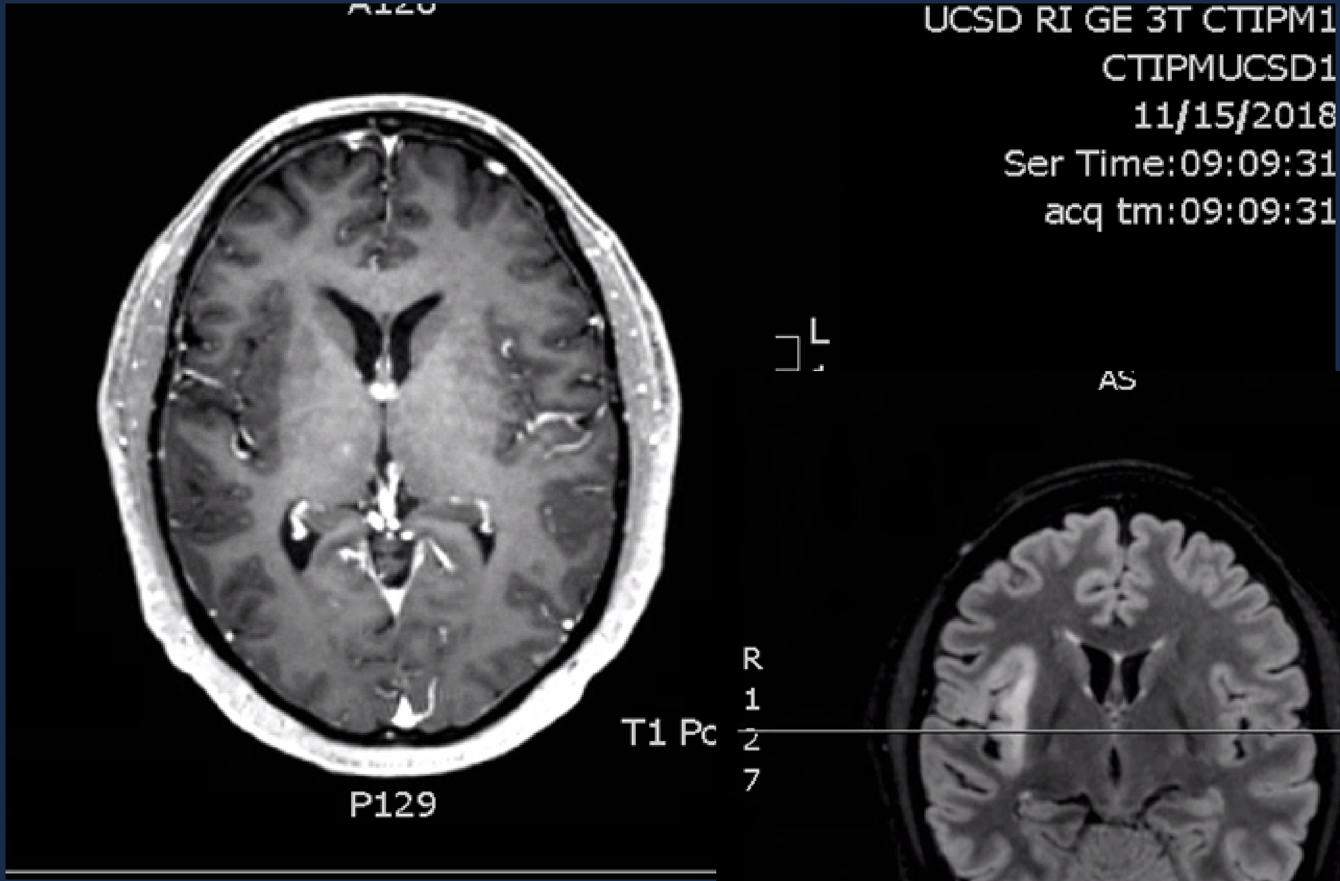
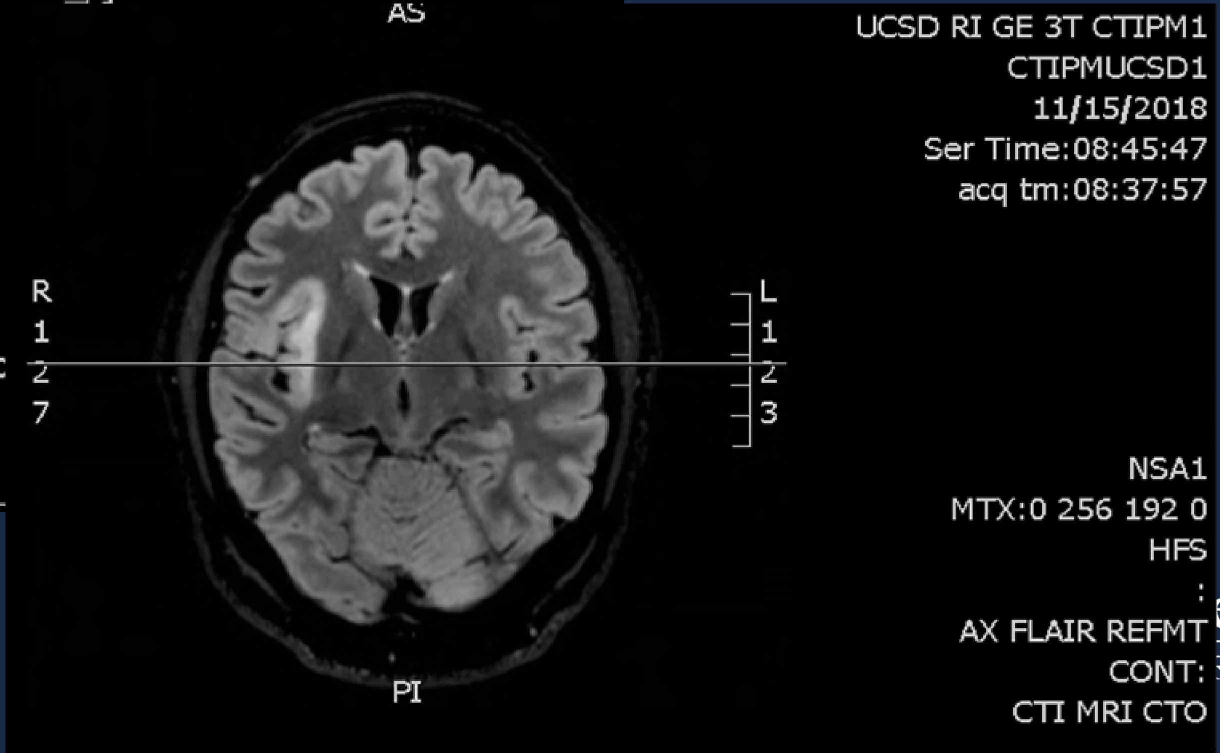
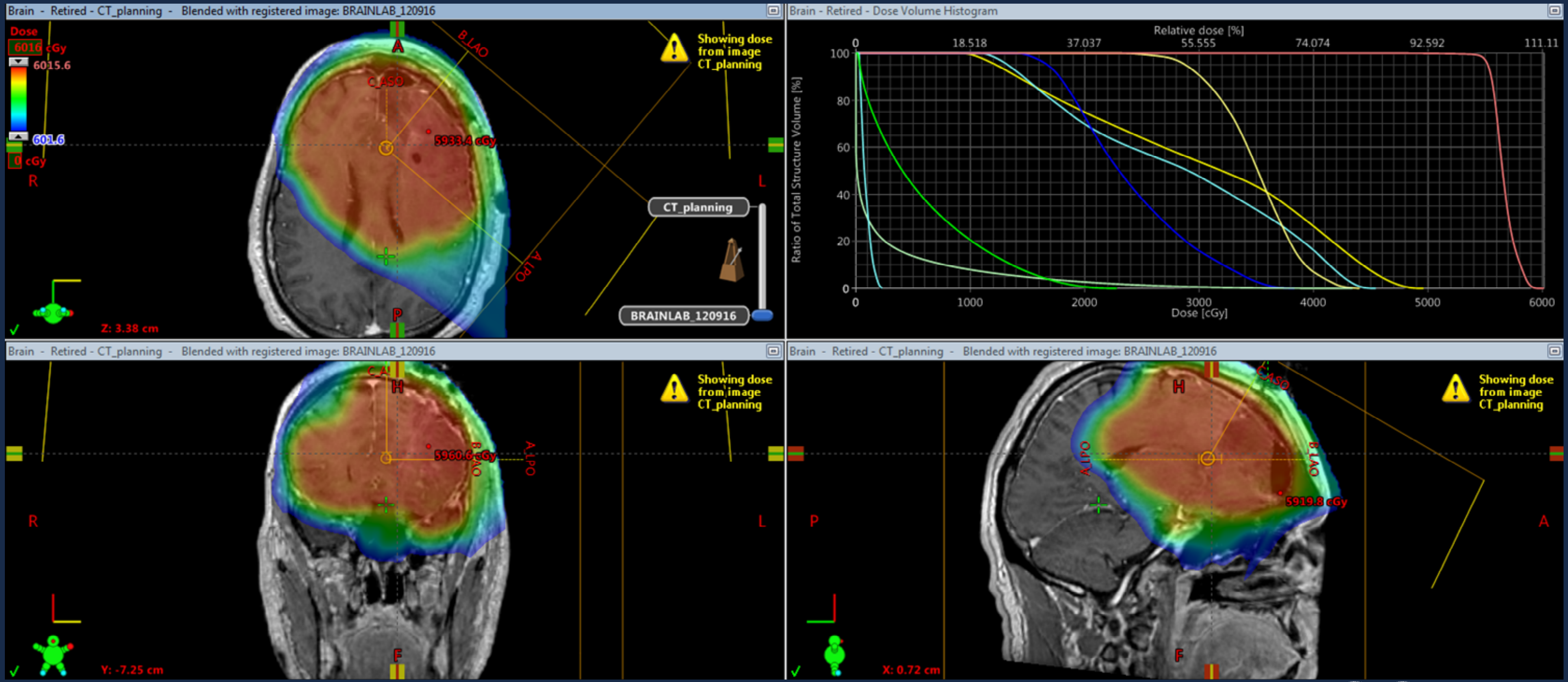
2+ year follow-up







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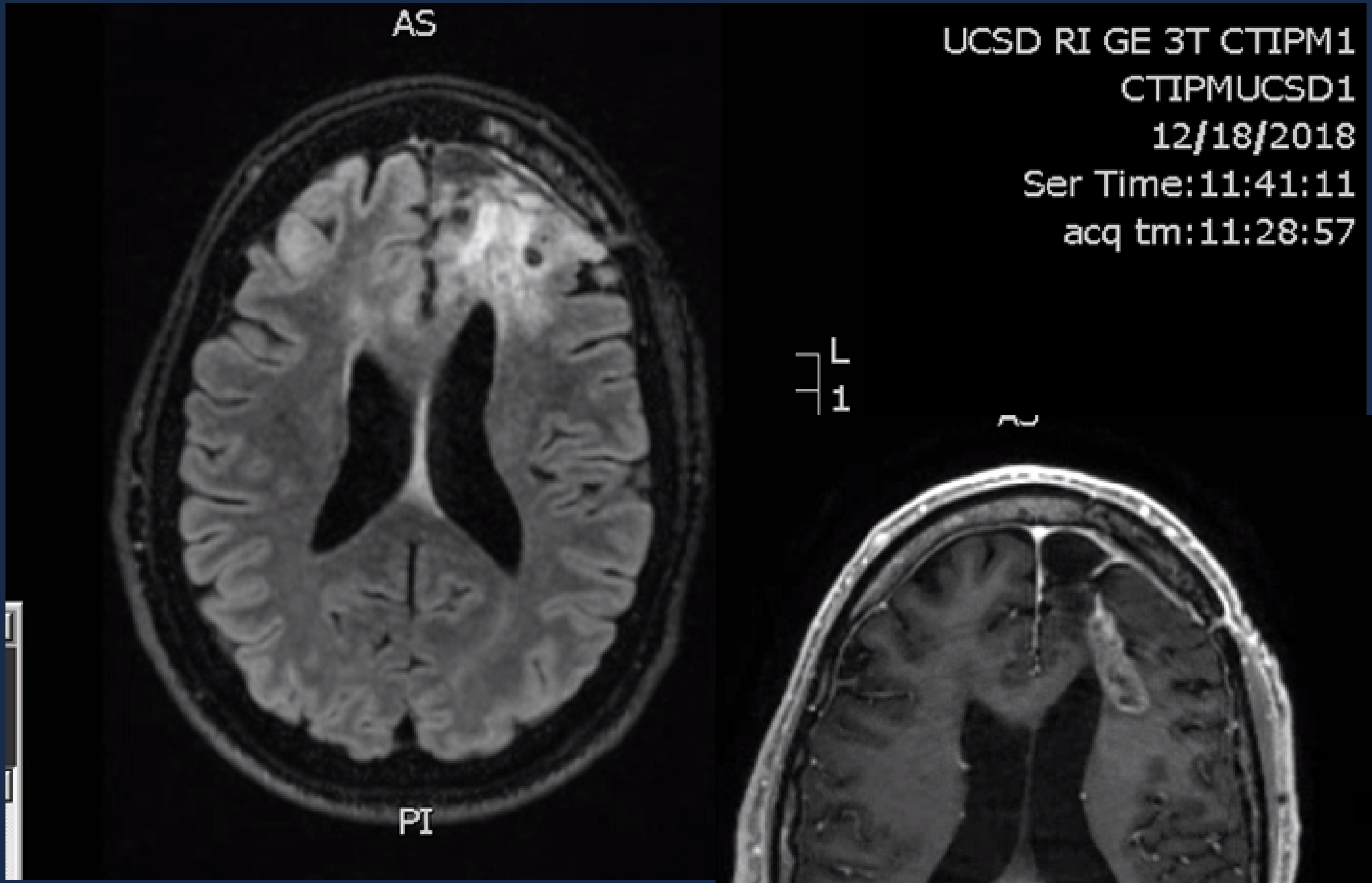
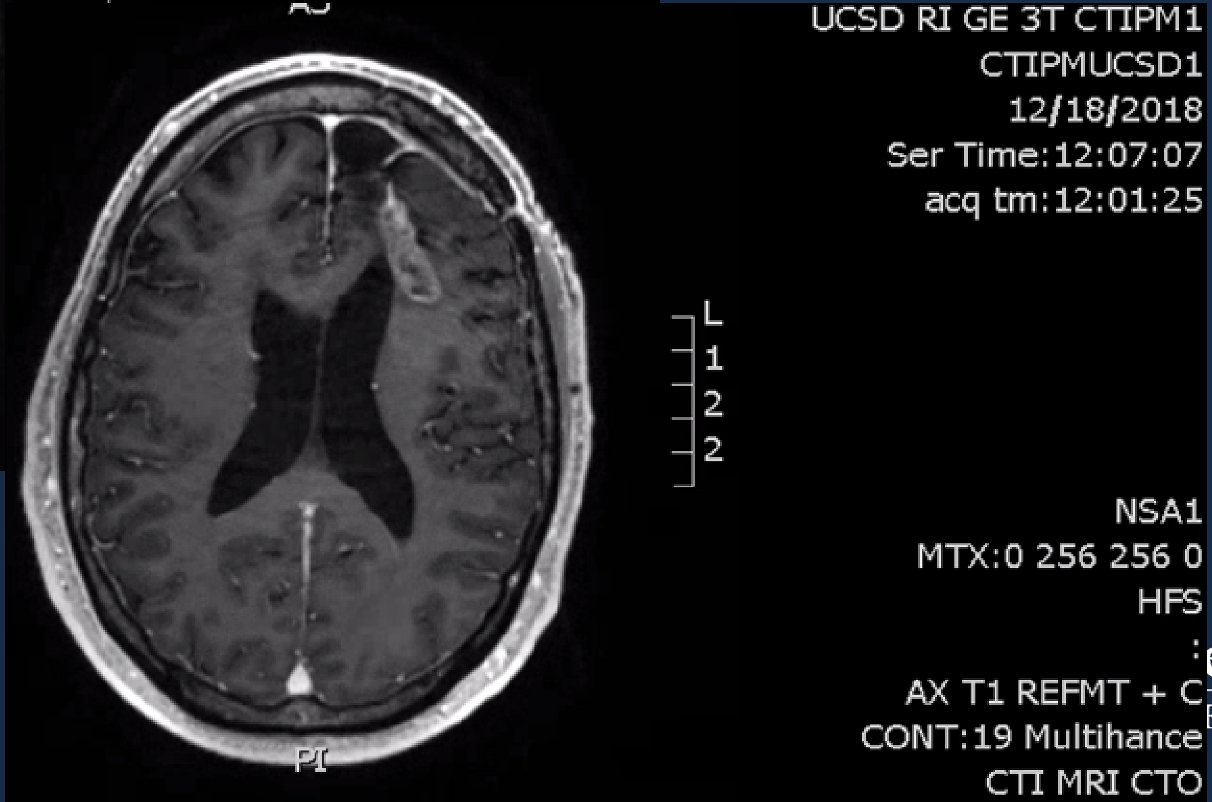
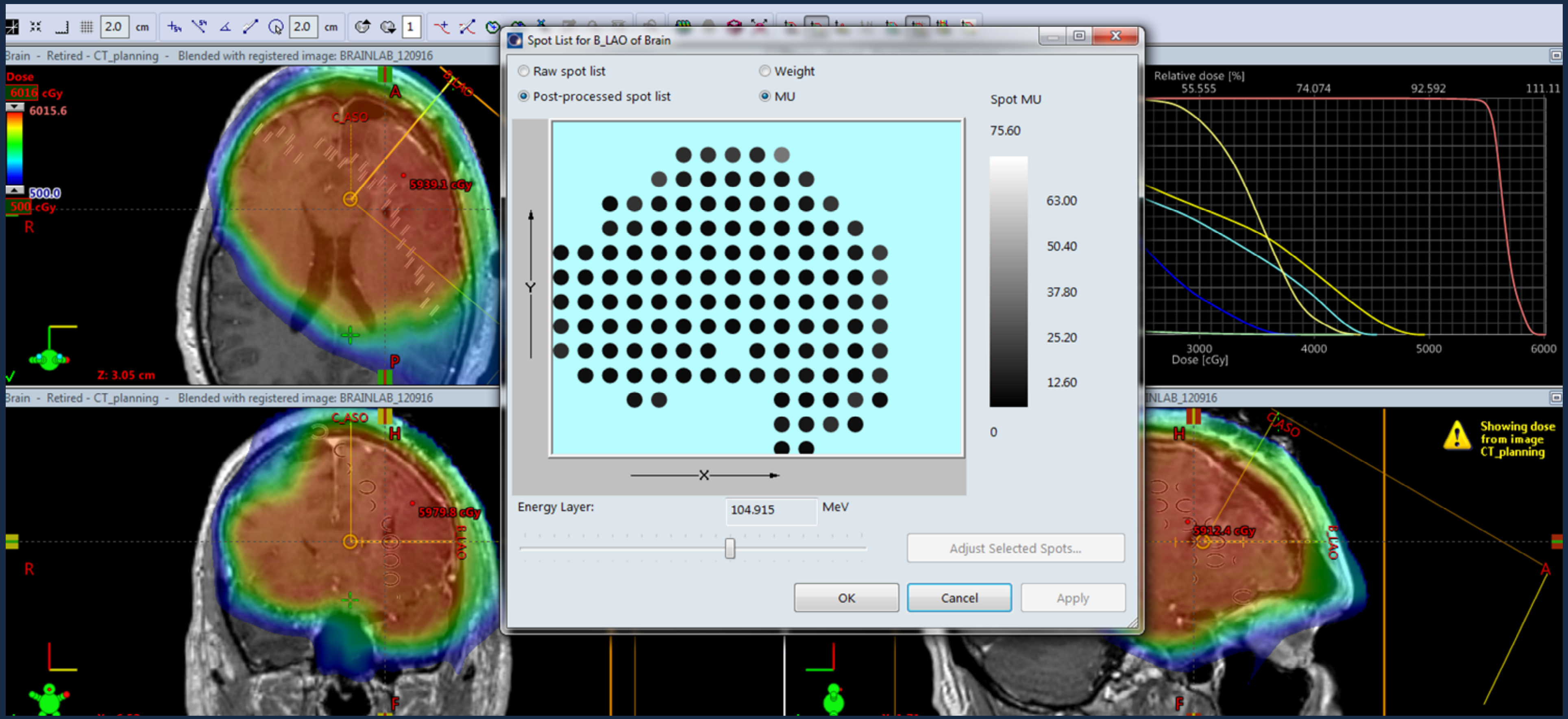
2 year follow-up







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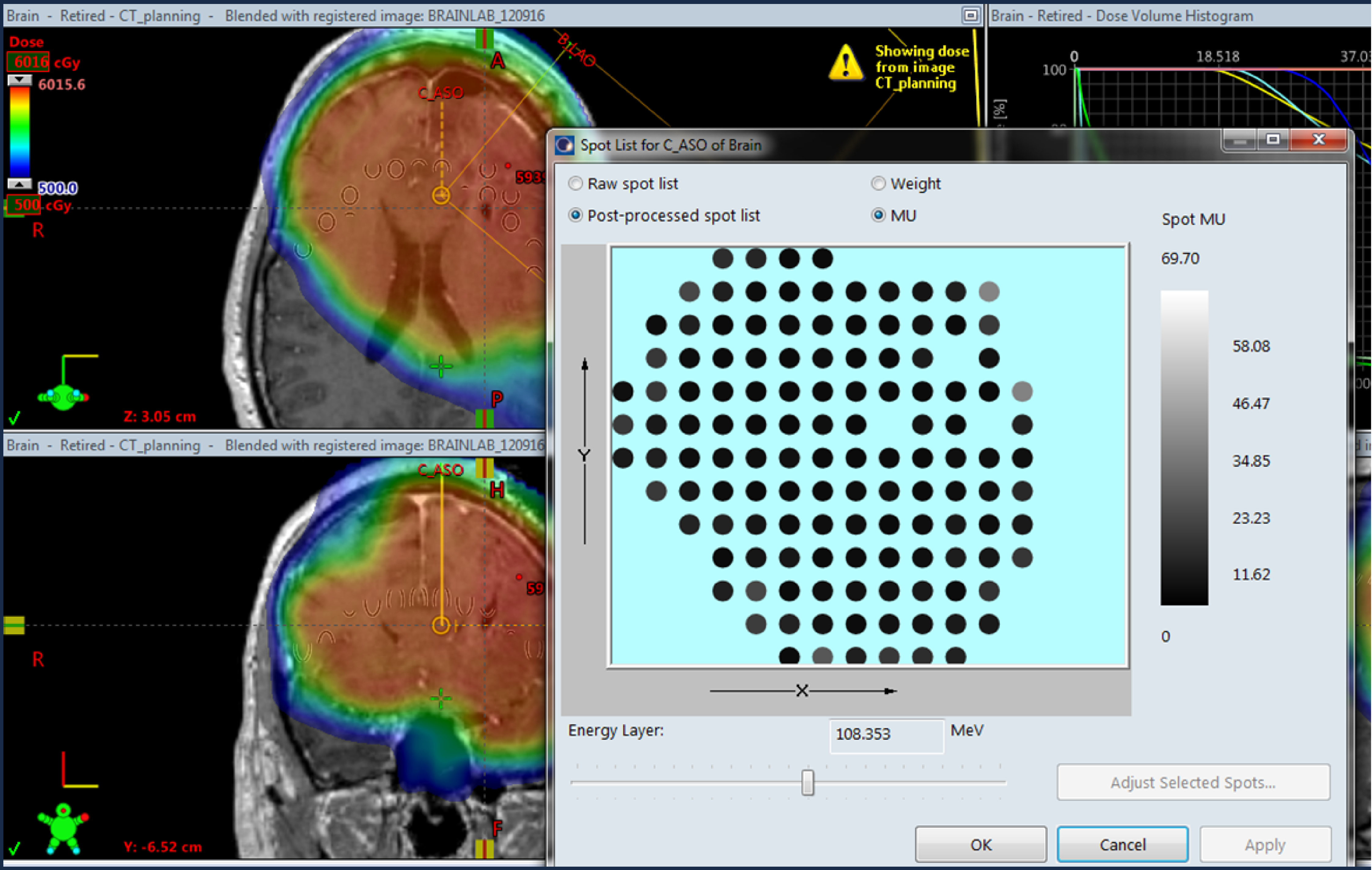
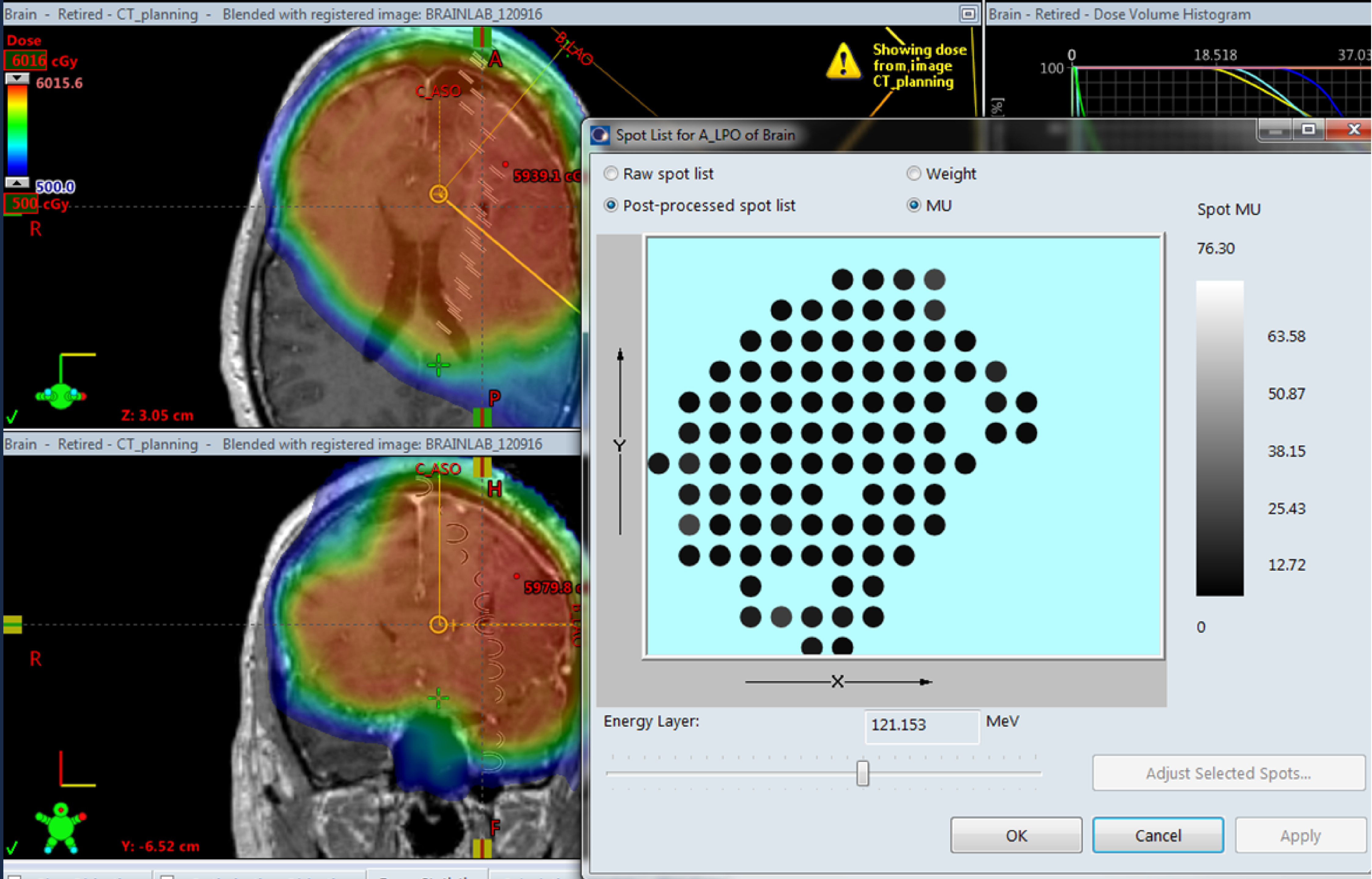
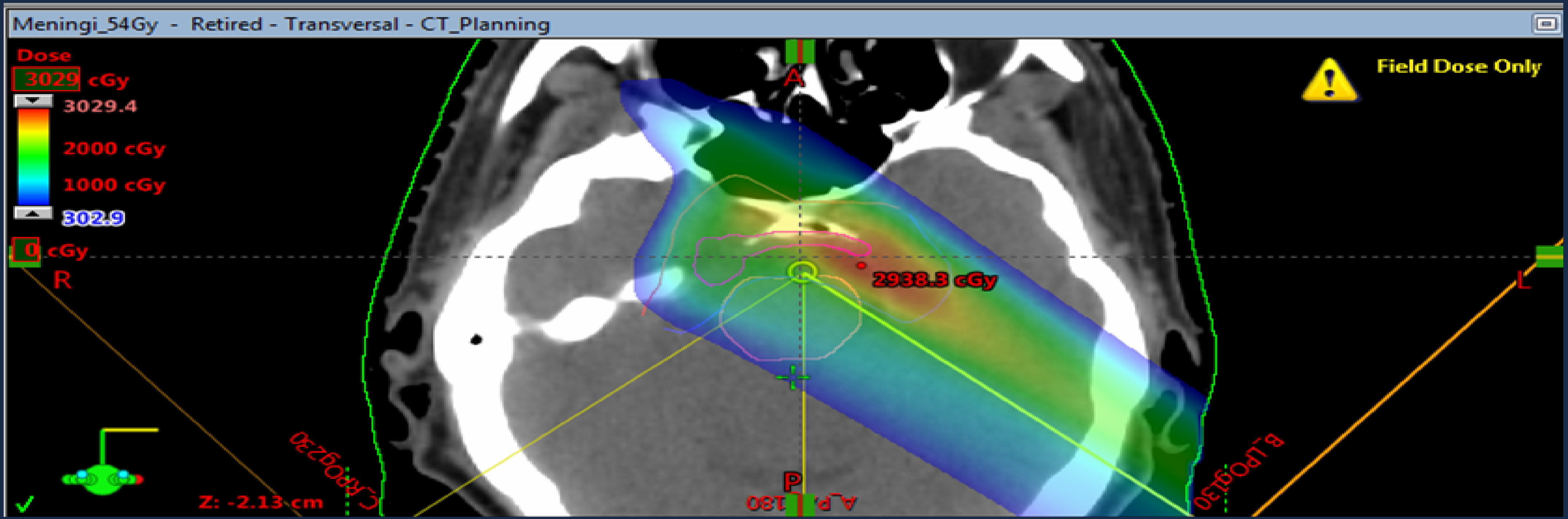

Brain - Retired - CT_planning - Blended with registered image: BRAINLAB_120916
Dose
6016 cGy
6015.6
500.0
500 cGy
R
A
P
C_ASO
Z: 3.05 cm
Showing dose from image CT_planning
Brain - Retired - Dose Volume Histogram
0
18.518
100
Spot List for C_ASO of Brain
Raw spot list
Post-processed spot list
Weight
MU
Spot MU
69.70
58.08
46.47
34.85
23.23
11.62
0
Y
X
Energy Layer:
108.353
MeV
Adjust Selected Spots...
OK
Cancel
Apply
Brain - Retired - CT_planning - Blended with registered image: BRAINLAB_120916
C_ASO
H
R
L
F
Y: -6.52 cm


Brain - Retired - CT_planning - Blended with registered image: BRAINLAB_120916
Dose
6016 cGy
6015.6
500.0
500 cGy
C_ASO
5939.1 cG
Z: 3.05 cm
Showing dose from image CT_planning
Brain - Retired - Dose Volume Histogram
Spot List for A_LPO of Brain
Raw spot list
Post-processed spot list
Weight
MU
Spot MU
76.30
63.58
50.87
38.15
25.43
12.72
0
Energy Layer:
121.153
MeV
Adjust Selected Spots...
OK
Cancel
Apply
5979.8
Y: -6.52 cm


Meningi_54Gy - Retired - Transversal - CT_Planning
Dose
3029 cGy
3029.4
2000 cGy
1000 cGy
302.9
0 cGy
A
R
L
P
Field Dose Only
2938.3 cGy
Z: -2.13 cm

Thank You

Time for Questions?

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