Target Definition Based on Functional Imaging (aka Dose Painting)

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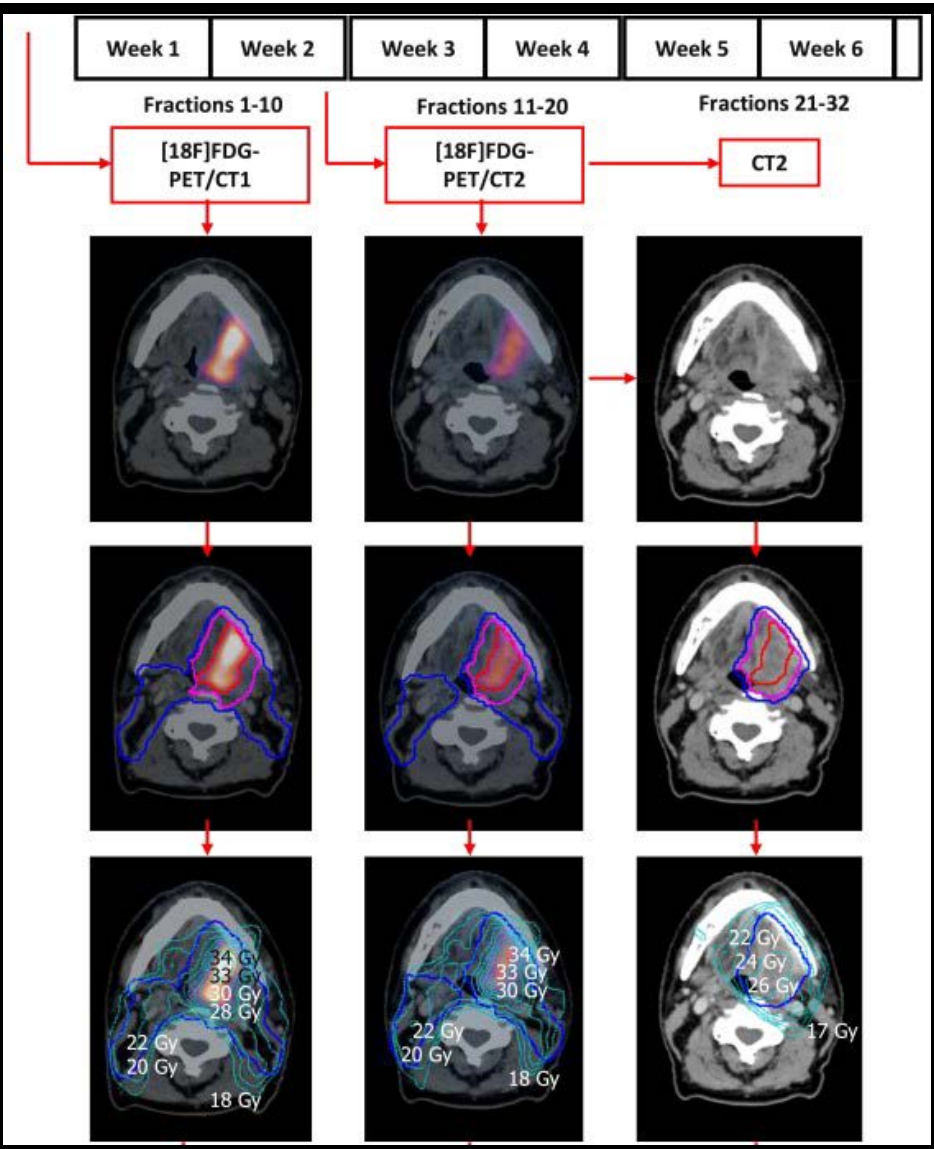
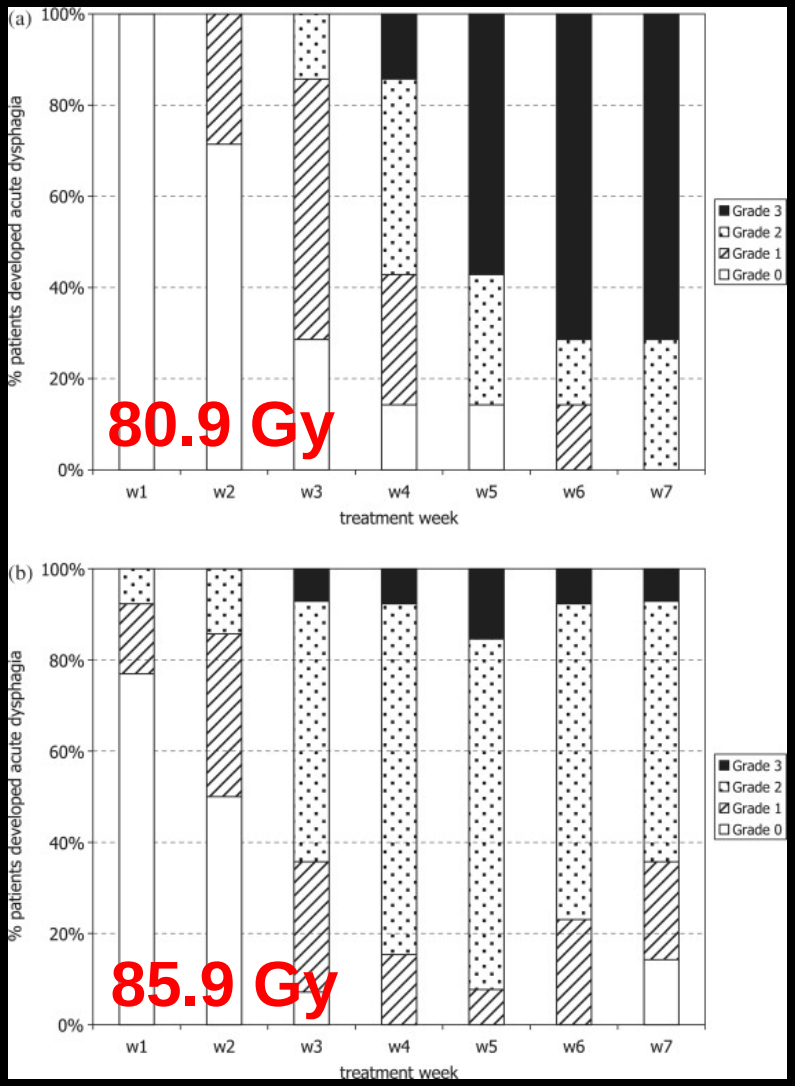
WHERE ARE WE TODAY?

HNSCC

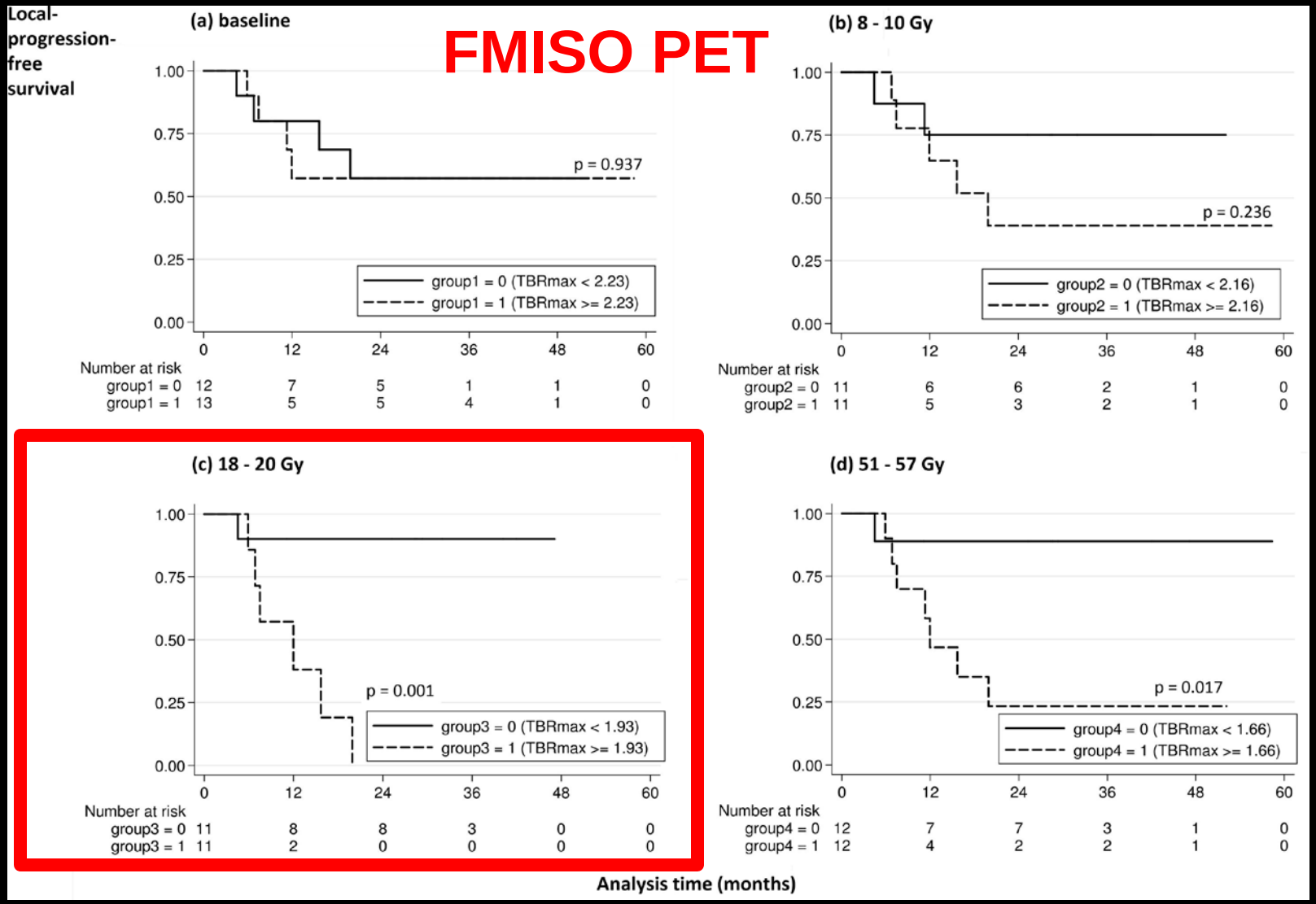
Dose boosting in HN





Duprez et al 2011, Int J Radiat Oncol Biol Phys, 80(4): 1045

What should be targeted?



FMISO PET

Zips et al 2012, Radiother Oncol 105: 21

Hypoxia image-guided RT (R01)

- Using **FMISO PET-based stratification**: patients with stage III-IVB HPV+ HNSCC *without evidence of baseline hypoxia* or *had resolving hypoxia one week into chemoradiation* are candidates for dose de-escalation

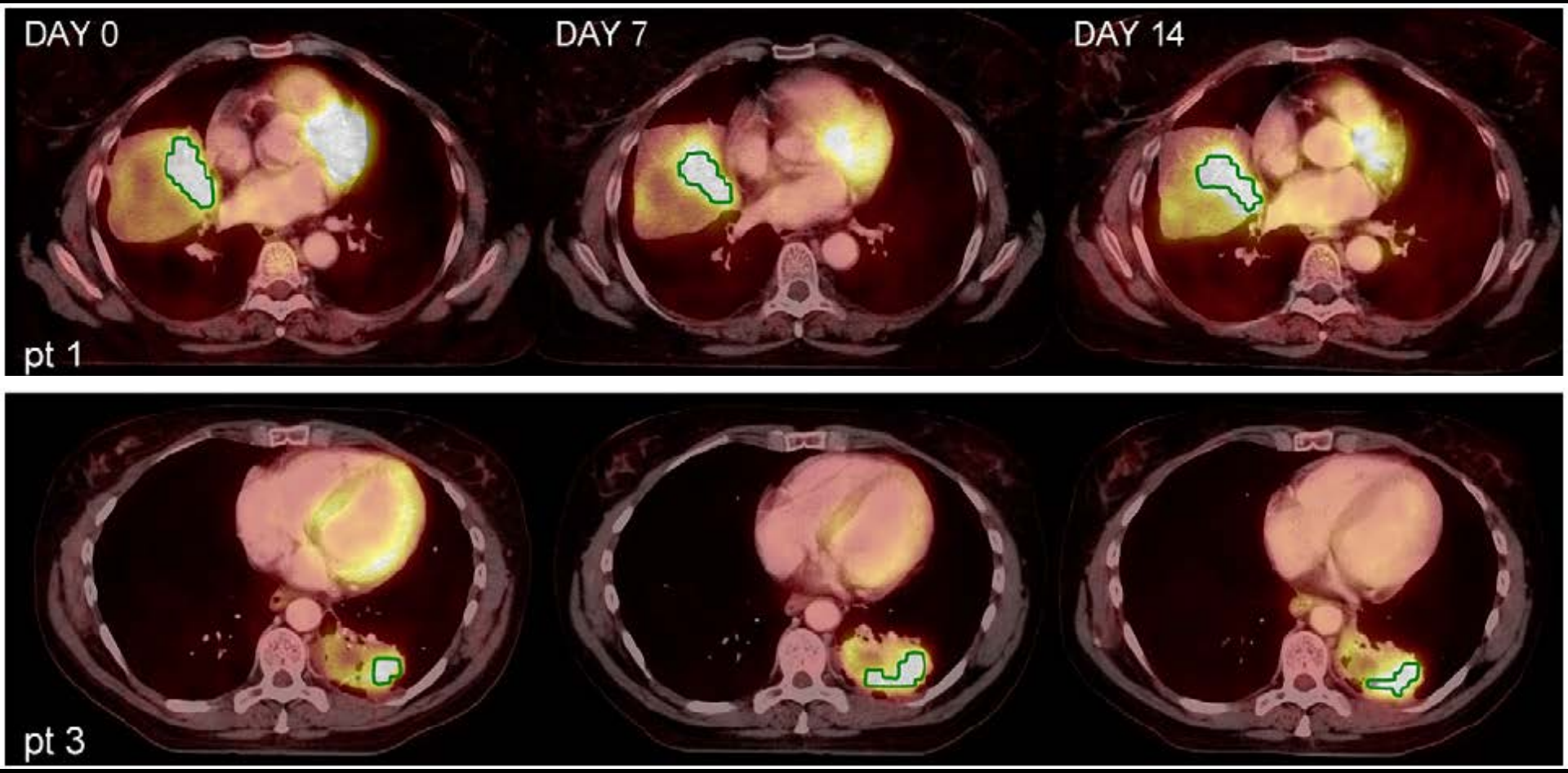
- To correlate the **quantitative metrics derived from hypoxia FMISO image** findings with treatment outcomes in HPV negative HNSCC

- To examine correlative **biological markers** (IHC staining of the following hypoxia biomarkers: HiF-1, LOX, Ki67) and clinical endpoints with FMISO imaging

Courtesy of Nancy Lee, MSKCC

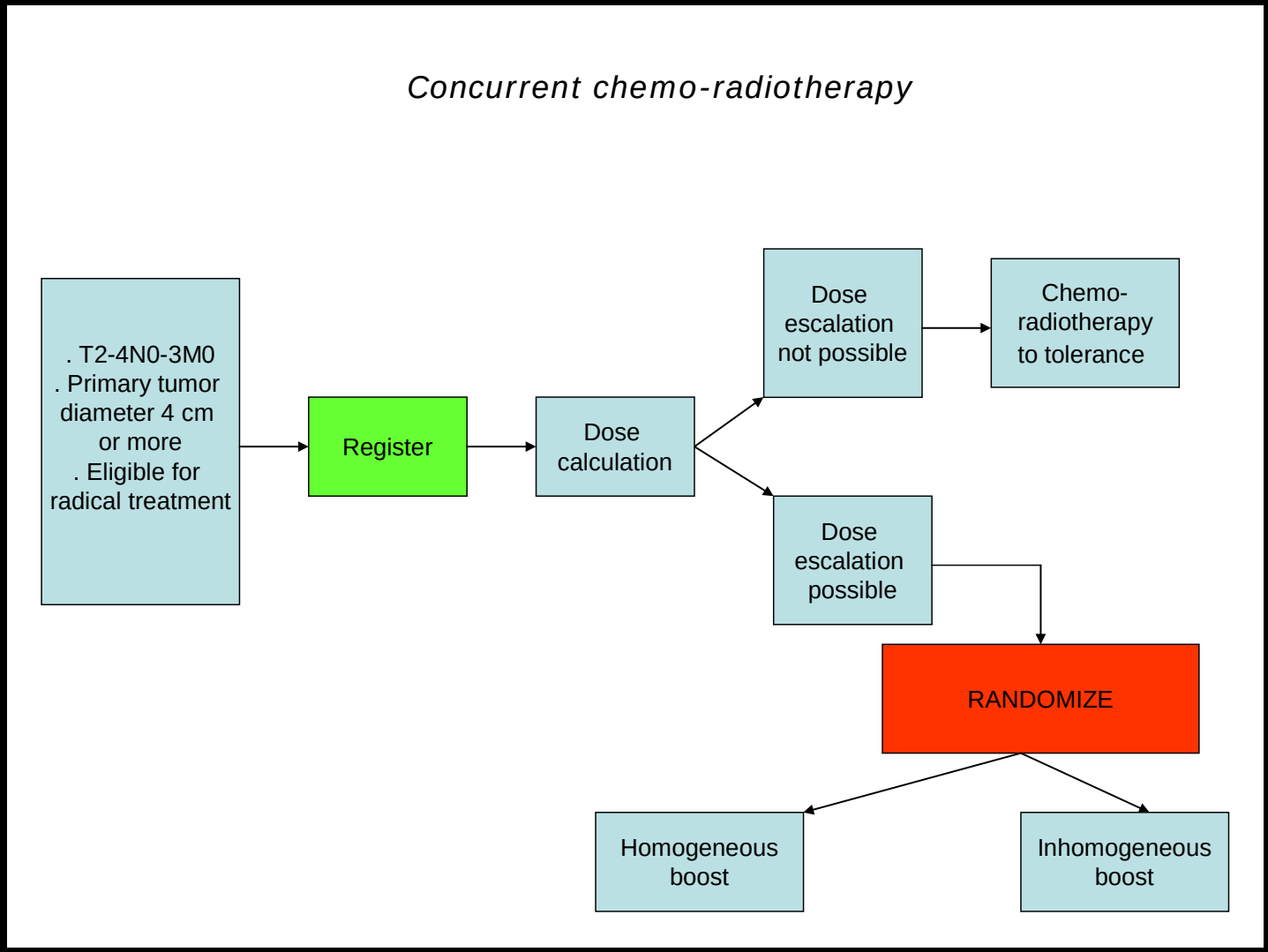
NSCLC

Stability of FDG uptake



Aerts et al 2008, Int J Radiat Oncol Biol Phys, 71(5): 1402

MAASTRO/NKI lung boost trial



Courtesy of Dirk De Ruysscher, UZ Leuven

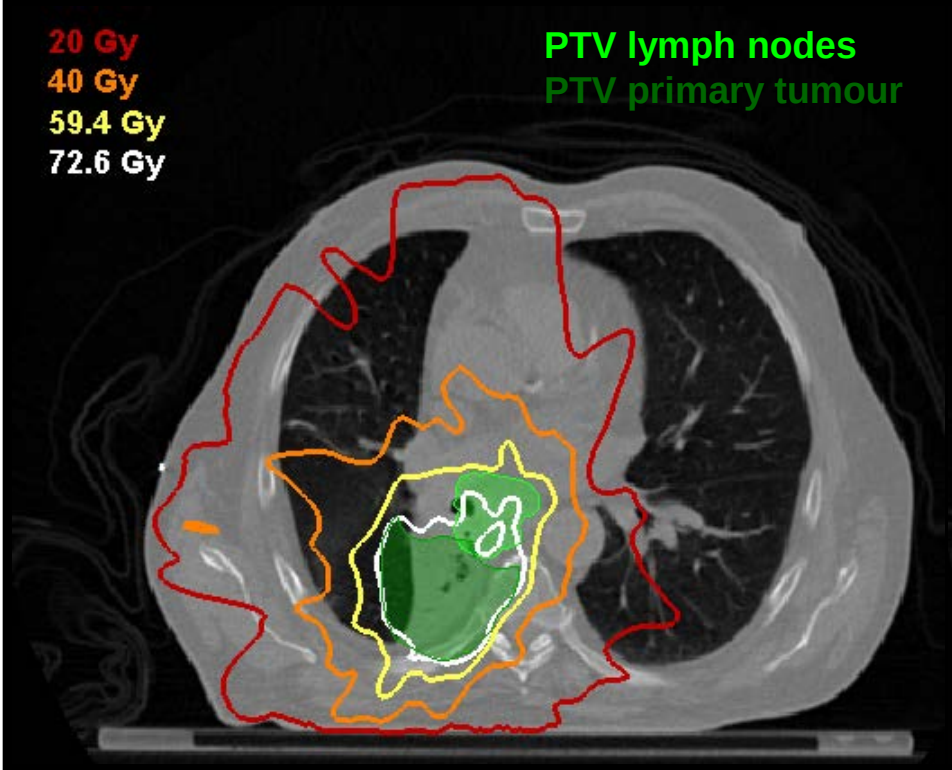
Dose specification

- Arm A
  - Primary tumour: integr. boost / 24 frac.
  - Nodes: 66 Gy / 24 frac.
  - Escalation up to normal tissue constraints
  - Homogeneity PTV primary tumour:
    90-115% of prescribed dose
  - Underdosage in 15% of PTV primary tumour is allowed if overlap with critical structures
- Arm B
  - Primary tumour: 66 Gy / 24 frac.
  - PTV high: integr. boost / 24 frac
  - Nodes: 66 Gy / 24 frac.
  - Escalation up to normal tissue constraints
  - Homogeneity PTV high:
    90-115% of prescribed dose
  - Underdosage in 15% of PTV primary tumour & PTV PET is allowed

Courtesy of Dirk De Ruysscher, UZ Leuven

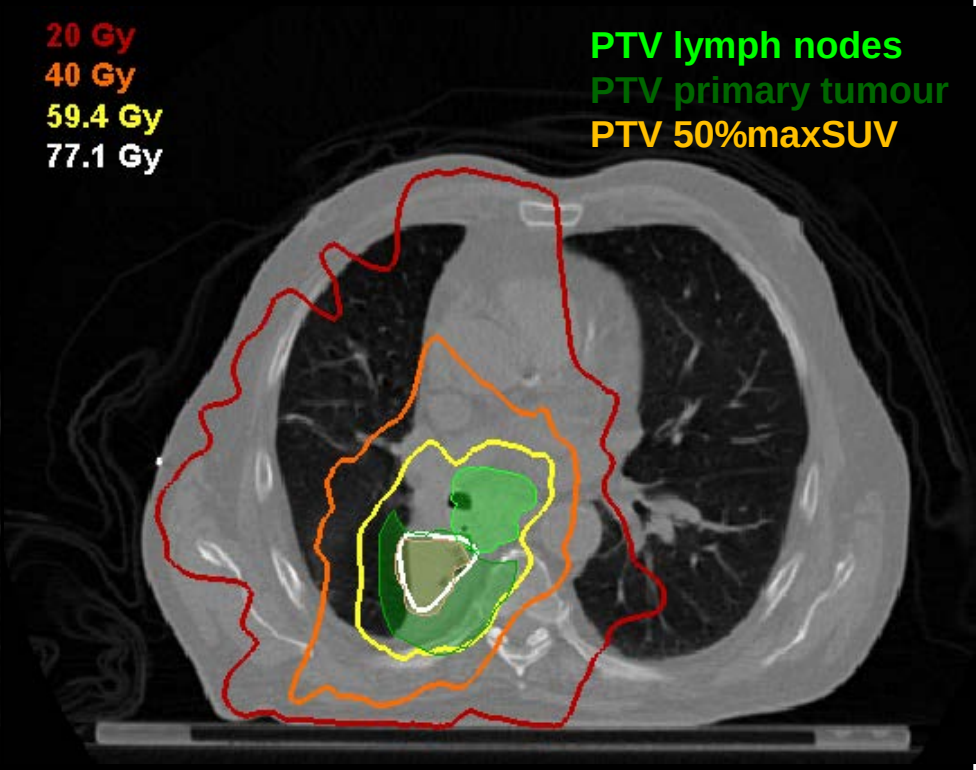
Dose distribution for two arms

Arm A
prescribed dose of 80.6 Gy



90% of 80.6 Gy = 72.6 Gy PTV primary tumour
90% of 66.0 Gy = 59.4 Gy PTV lymph nodes

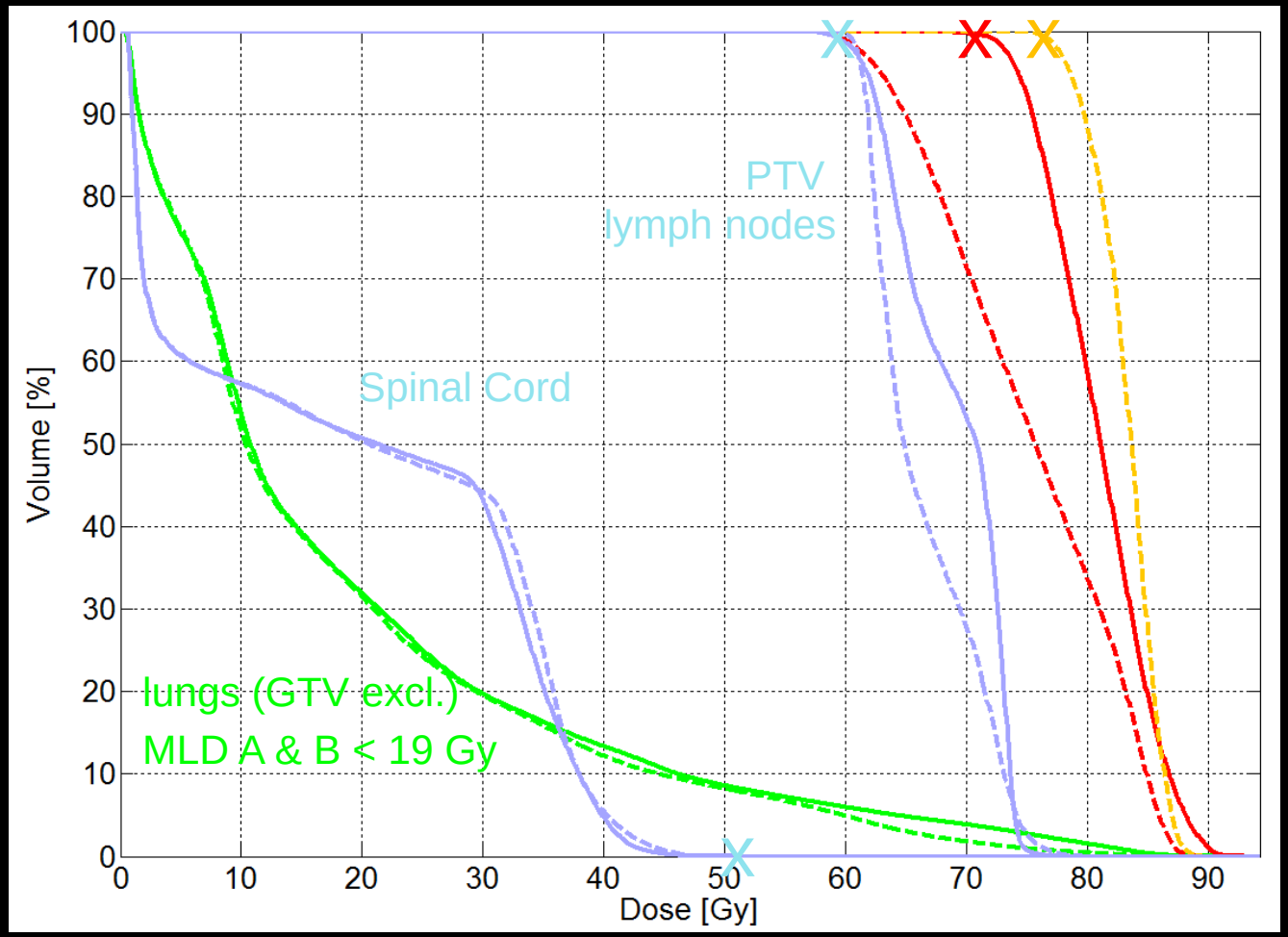
Arm B
Prescribed dose of 85.7 Gy



90% of 85.7
90% of 66.0 Gy = 59.4 Gy PTV lymph nodes

Courtesy of Dirk De Ruysscher, UZ Leuven

DVH: Arm 1 vs Arm 2



X = 90% 66.0 Gy

X = 90% 80.6 Gy

X = 90% 85.7 Gy

X = 51 Gy

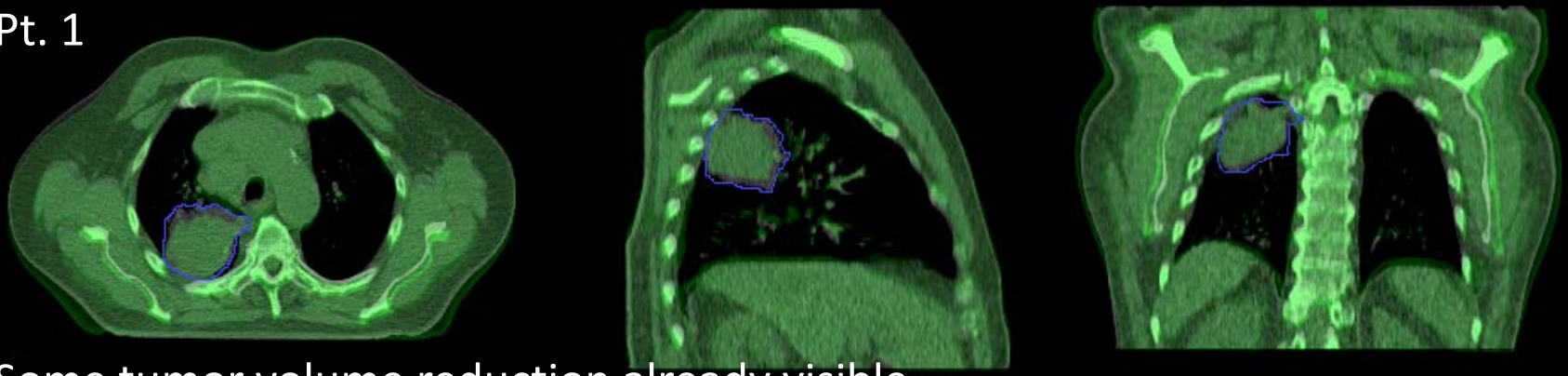
PTV 50% SUVmax

PTV primary tumour

Courtesy of Dirk De Ruysscher, UZ Leuven

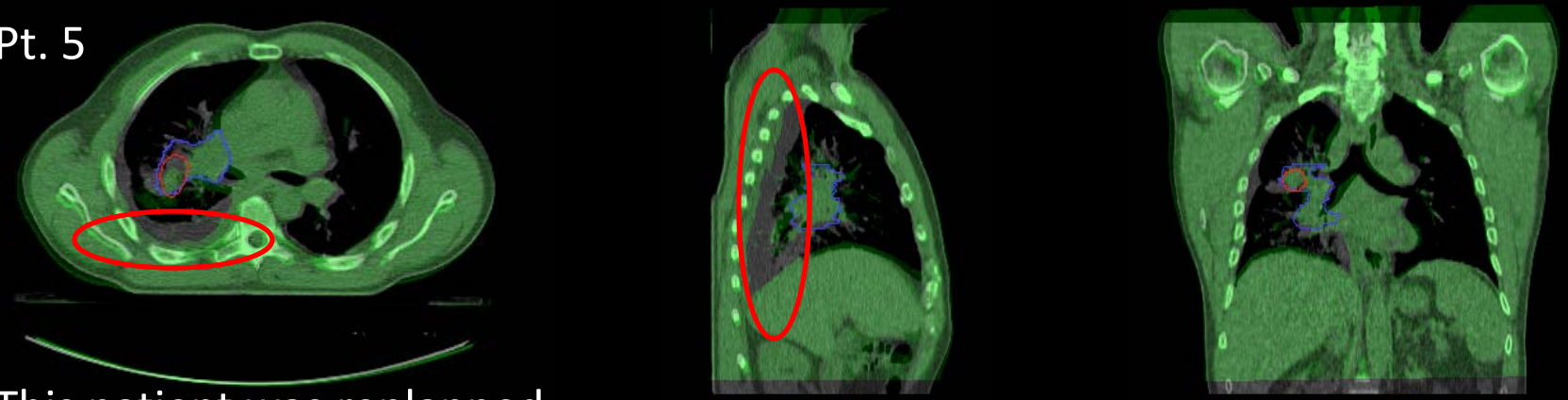
To Re-plan or Not To Re-plan?

Pt. 1



Some tumor volume reduction already visible.

Pt. 5

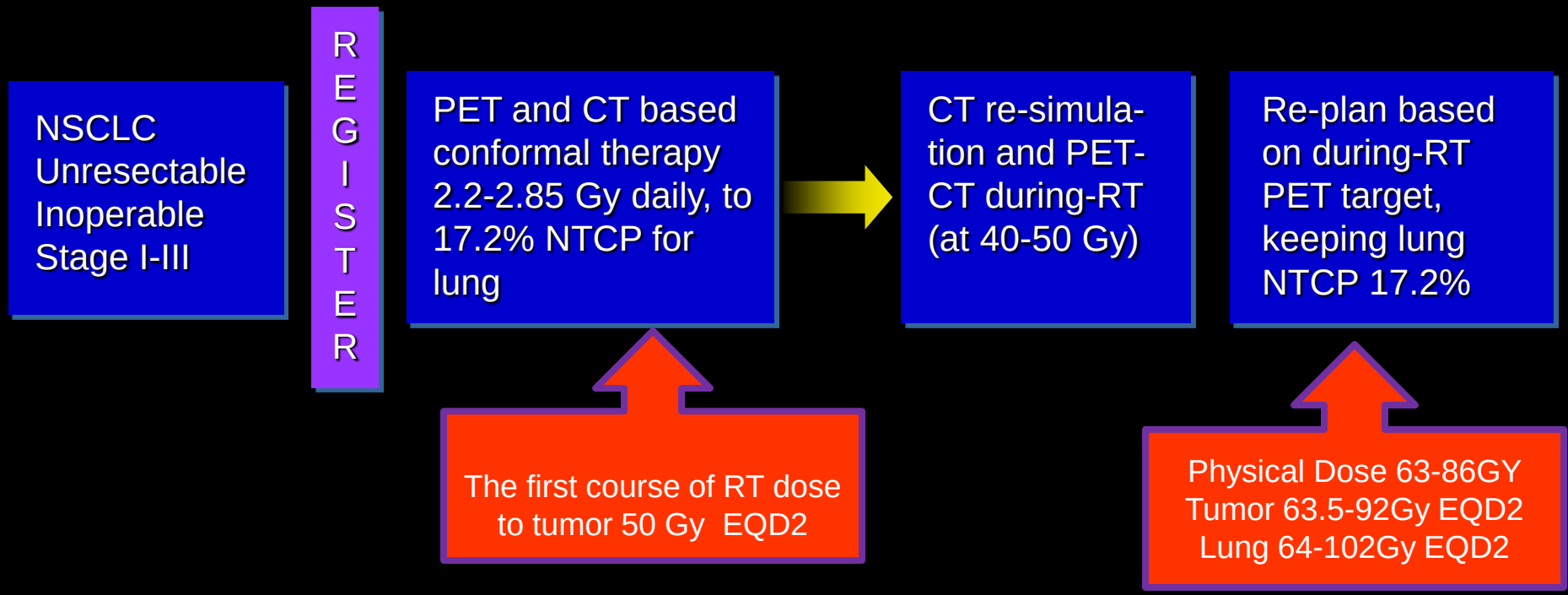


This patient was replanned.

Courtesy of Dirk De Ruysscher, UZ Leuven

Mid-treatment adaptive dose boost

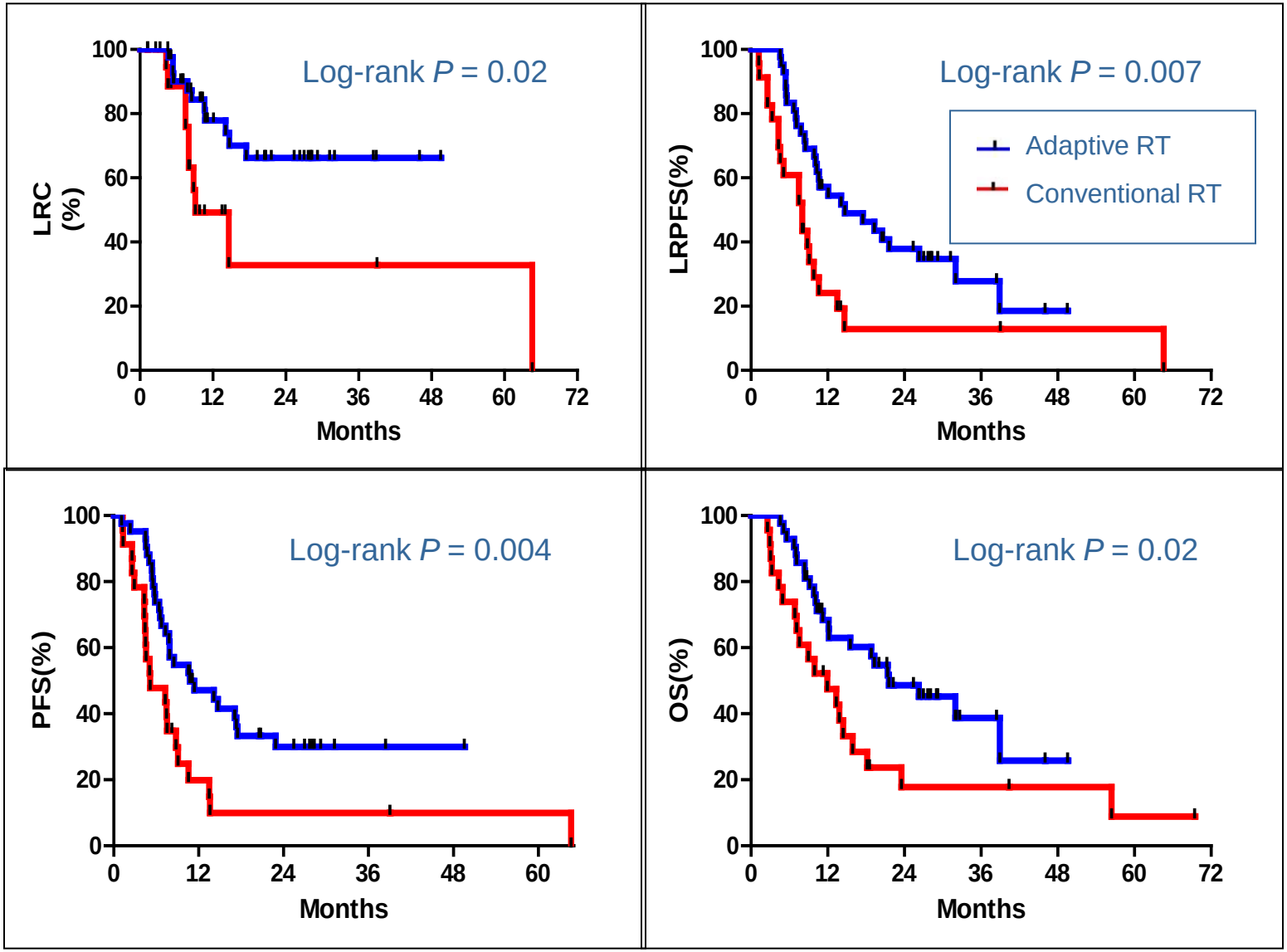
- RT: 30 daily fractions
- Chemo: concurrent weekly carboplatin / paclitaxel
  + consolidation carboplatin / paclitaxel x 3 cycles



Adaptive plan individualized to each tumor

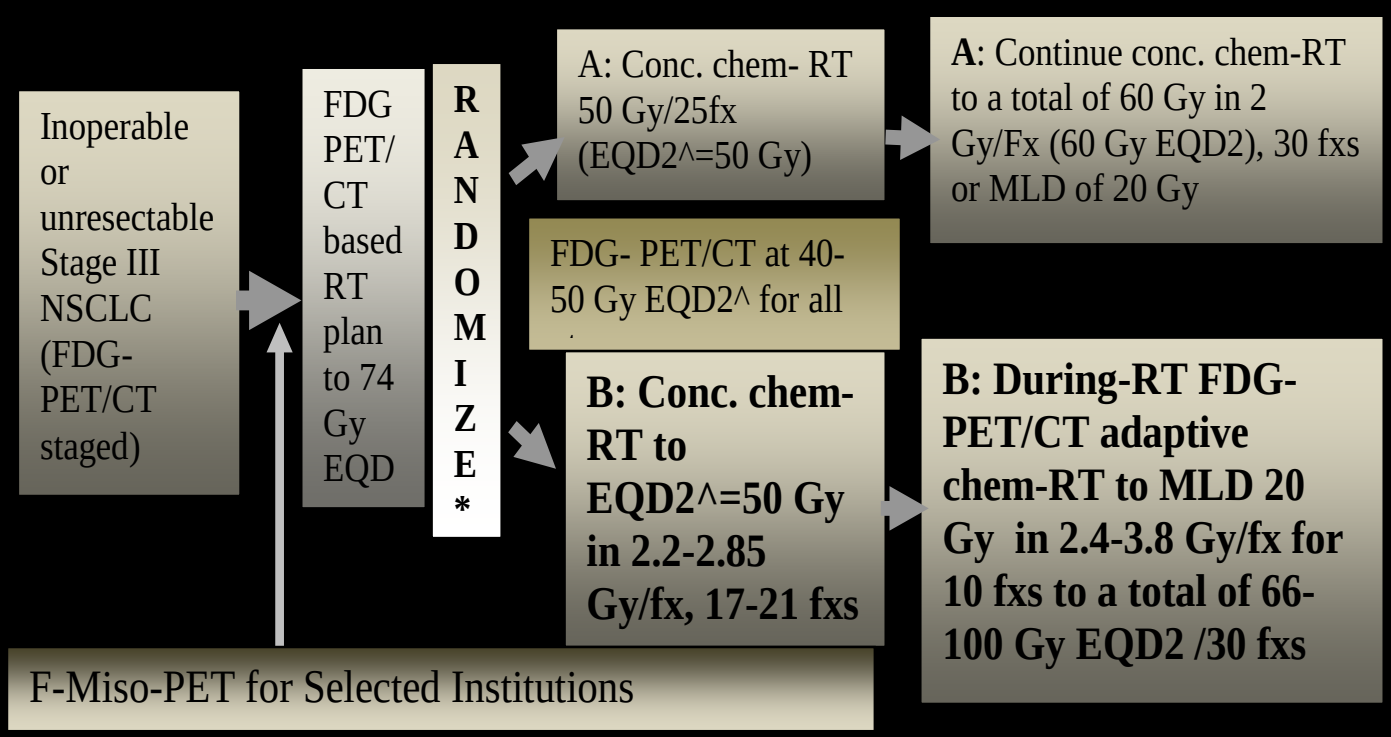
Courtesy of Spring Kong, GRU Cancer Center

Adaptation dose make a difference



Courtesy of Spring Kong, GRU Cancer Center

RTOG 1106/ACRIN 6697



Control arm: (RTOG 0617 arm) Uniform dose RT

Experimental arm: Individualized adaptive RT

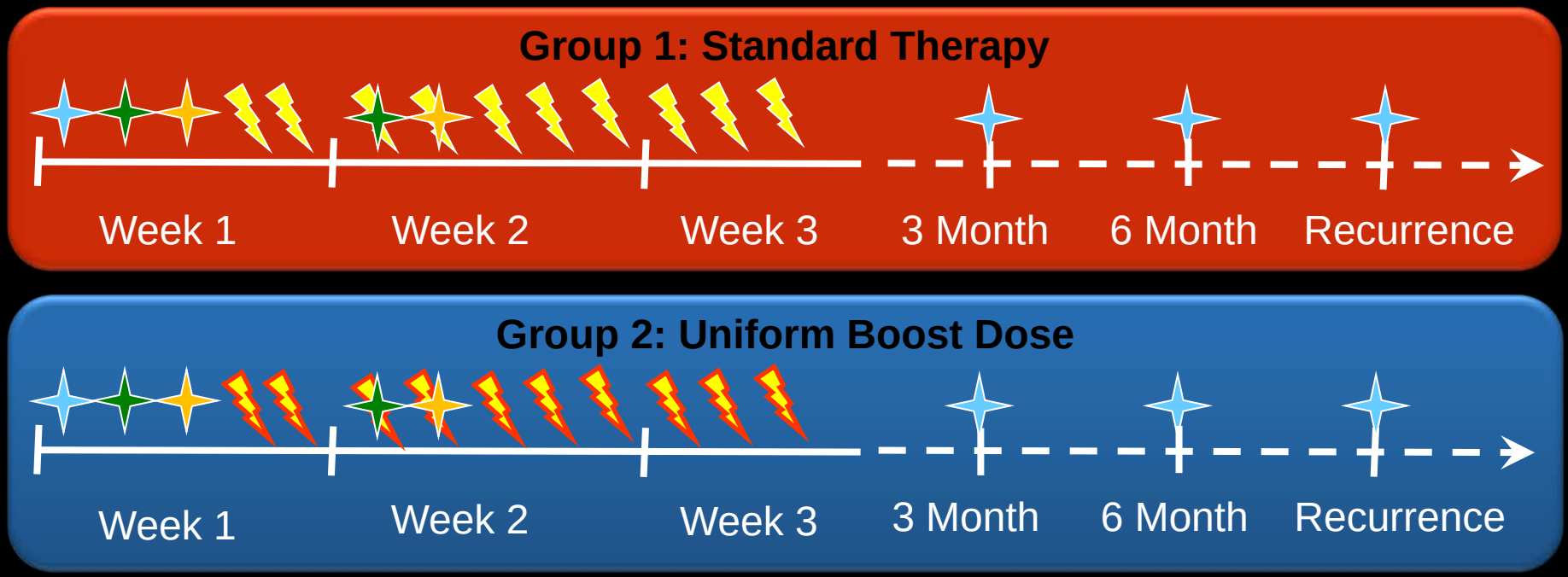
The Primary Endpoint: 2 year local-regional tumor control rate
*1:2 randomization, stratified by MLD > vs ≤14 Gy, GTV> vs ≤200cc, and squamous vs nonsquamous ca.

Courtesy of Spring Kong, GRU Cancer Center

WHAT DO WE DON'T KNOW YET? (IN HUMANS)

Best friends – also in research!

Canine dose painting clinical trial



= 42 Gy to PTV in 10 fx

= 42 Gy to PTV in 10 fx

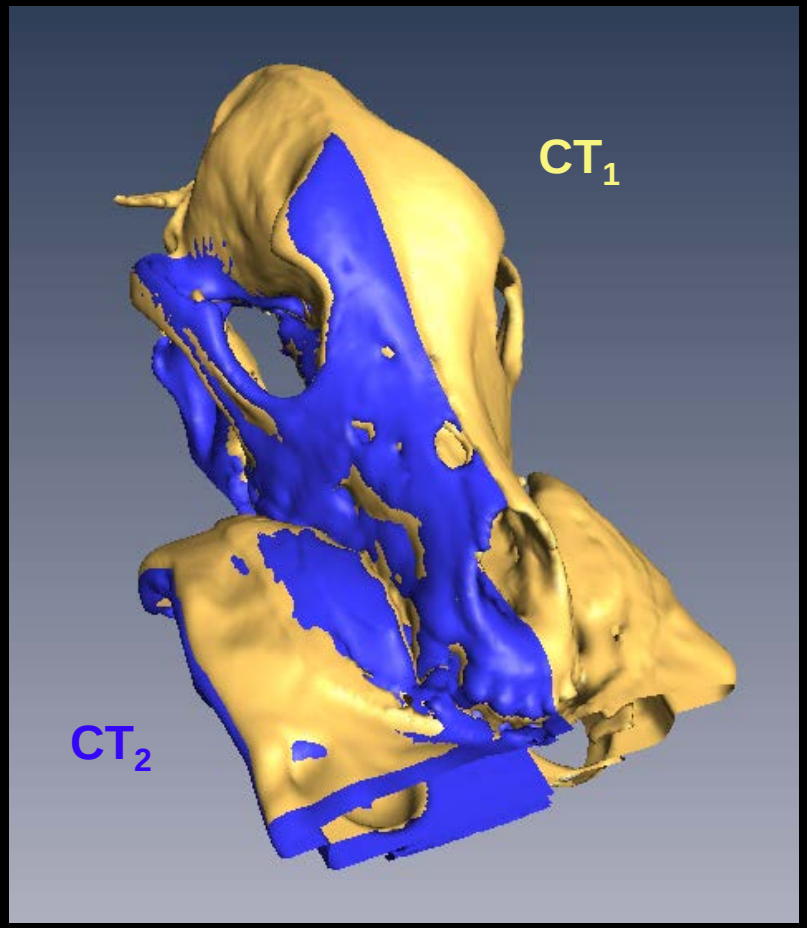
50 Gy to GTV in 10 fx

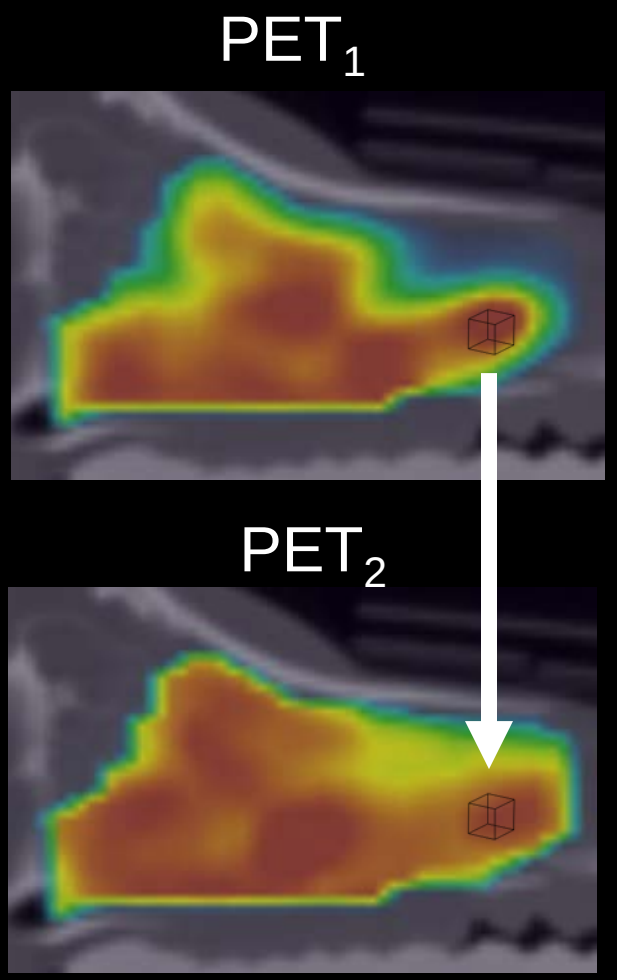
FDG PET + DCE CT

FLT PET + DCE CT

Cu-ATSM PET + DCE-CT

Sub-mm registration – HD biology!

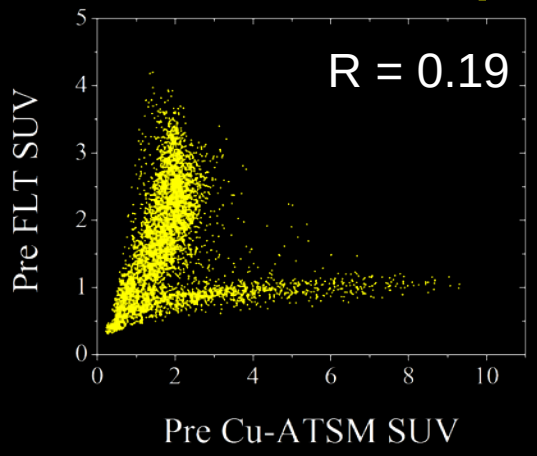




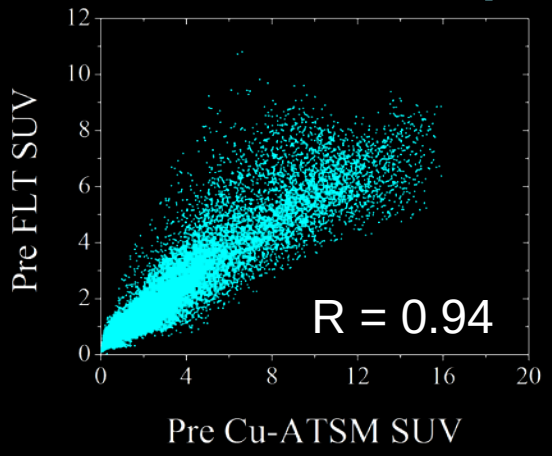
WHAT BIOLOGY TO TARGET?

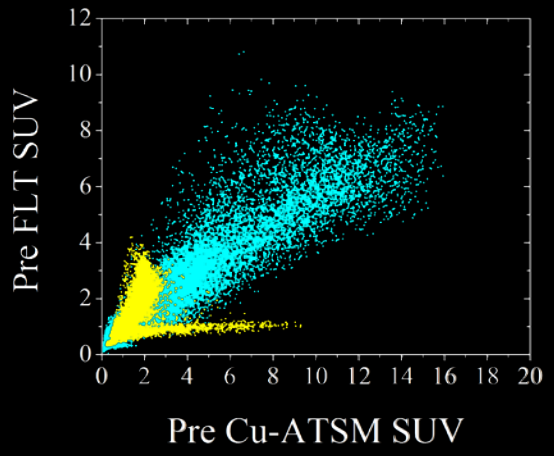
Phenotype correlations

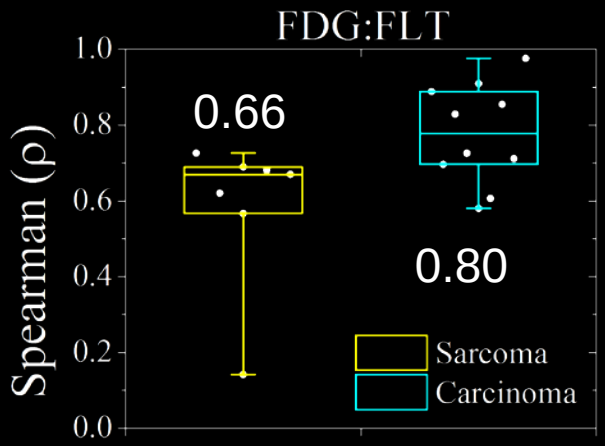
Sarcoma Example



Carcinoma Example







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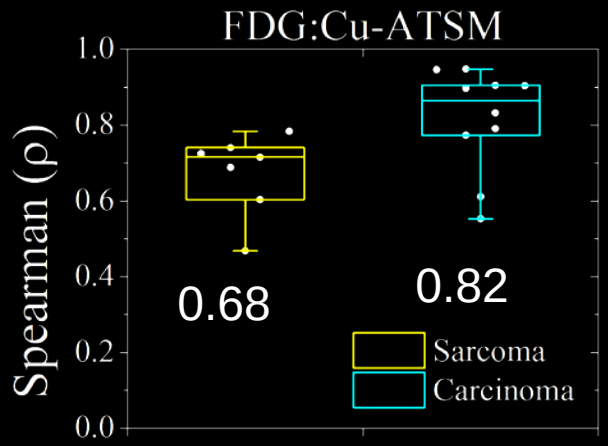

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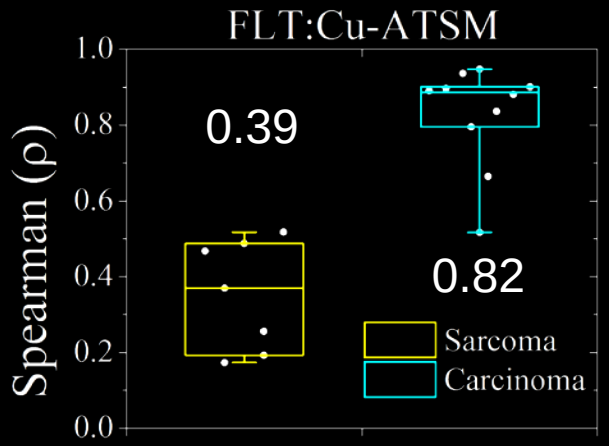
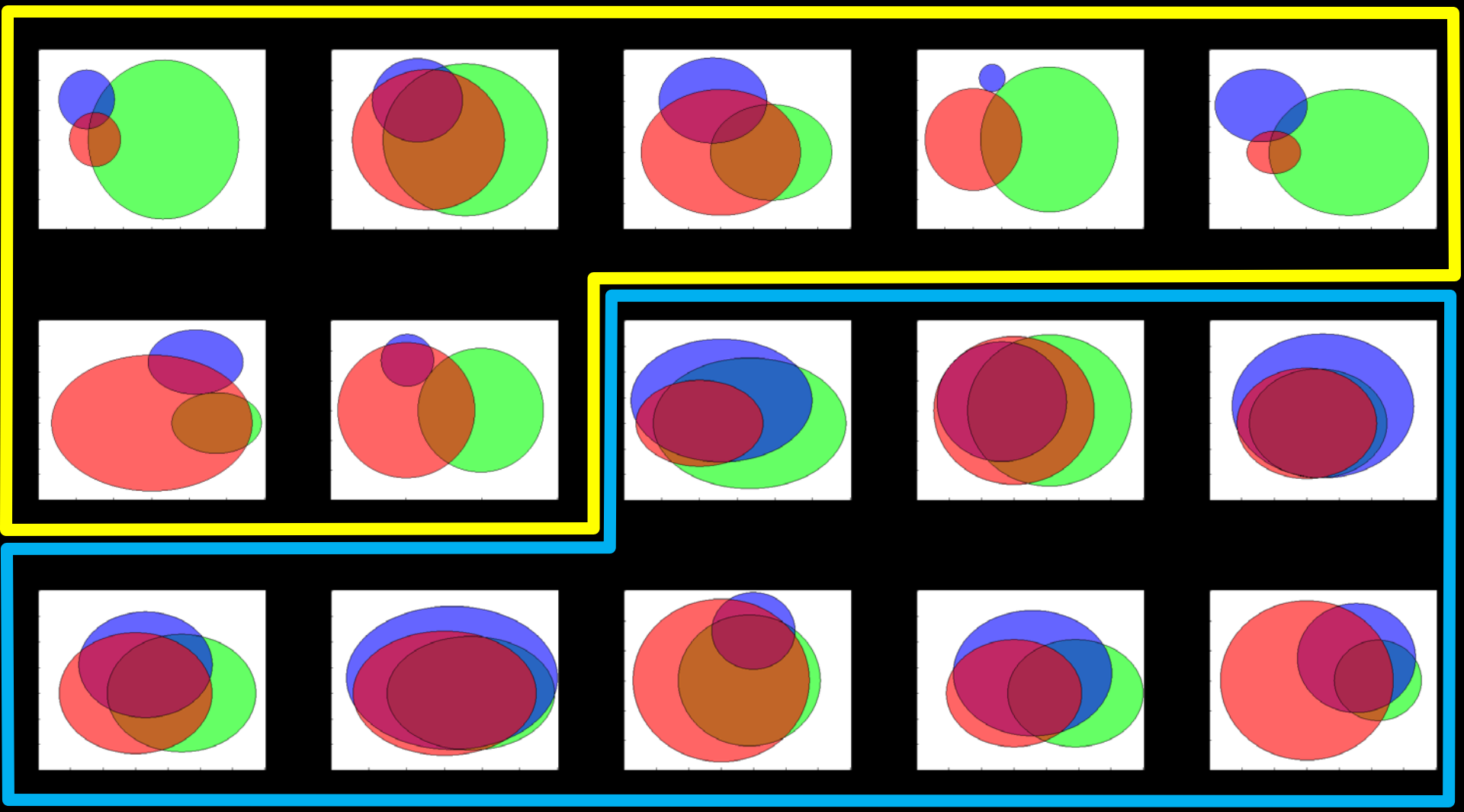


***p*=0.0001**

Bradshaw et al 2013, J Nucl Med 54(11):1931-7

Phenotype overlap

SARCOMA



CARCINOMA

Bradshaw et al 2013, J Nucl Med 54(11):1931-7

Different histologies – different targets?

Sarcomas

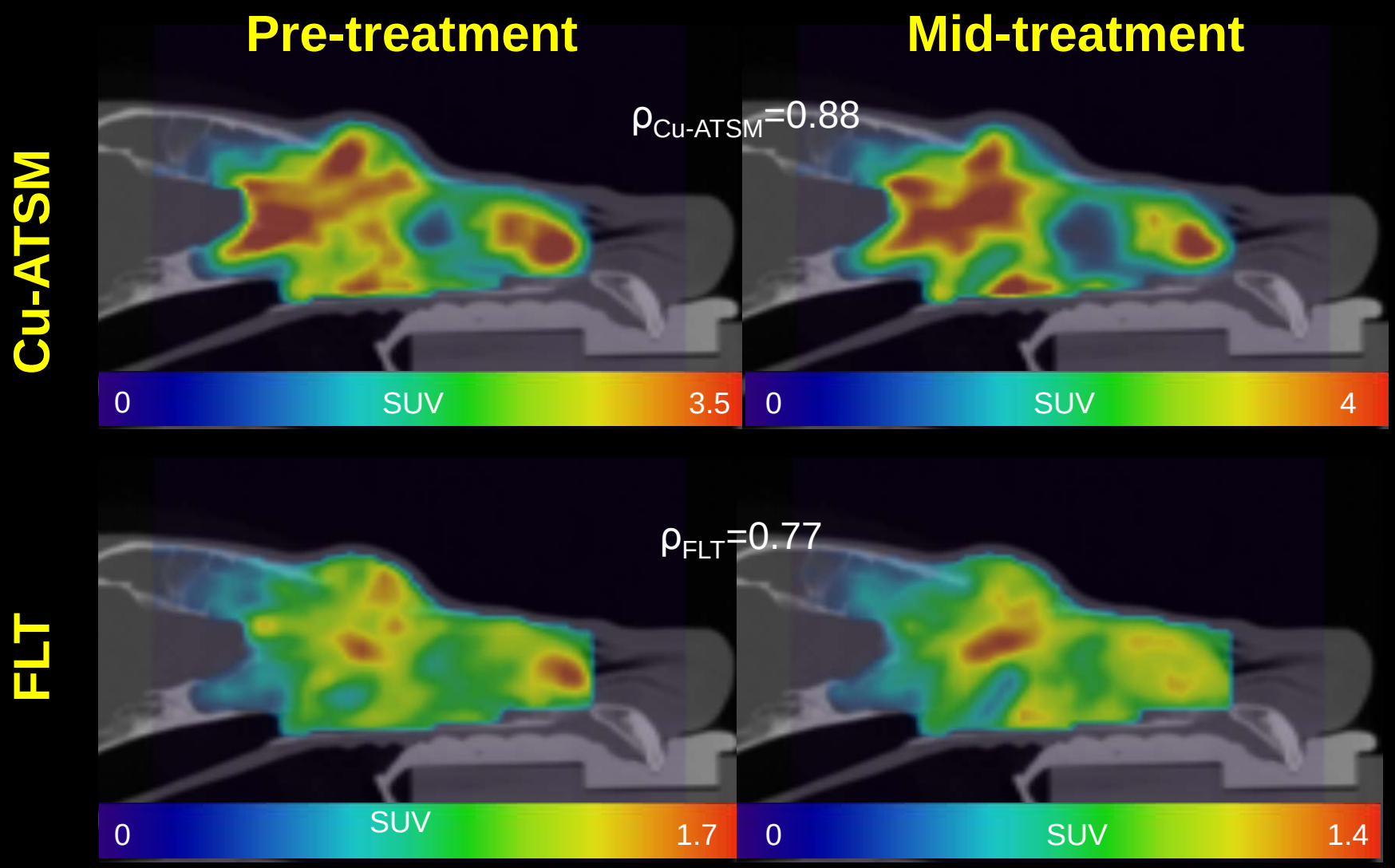
	3mo FDG Regression, N=7				
	β-FDGpre	β-FLTpre	β-CuPre	β-FLTmid	β-CuMid
mean	**0.42**	-0.23	0.03	0.21	0.25
P-val	**0.01**	**0.35**	**0.84**	**0.29**	**0.13**

Carcinomas

	3mo FDG Regression, N=11				
	β-FDGpre	β-FLTpre	β-CuPre	β-FLTmid	β-CuMid
mean	0.15	**-0.25**	-0.14	0.21	**0.47**
P-val	**0.11**	**0.01**	**0.24**	**0.45**	**0.001**

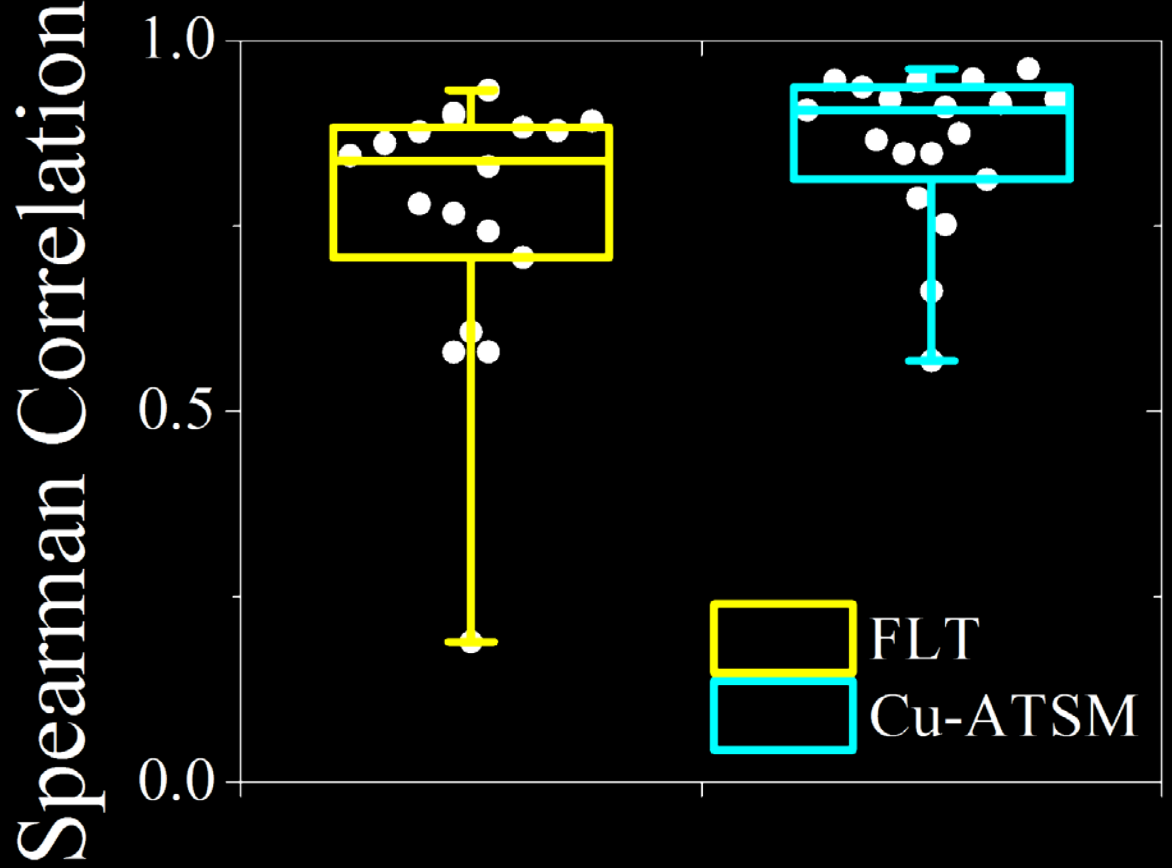
ARE THE TARGETS STABLE?

Cu-ATSM and FLT stability



Cu-ATSM and FLT stability

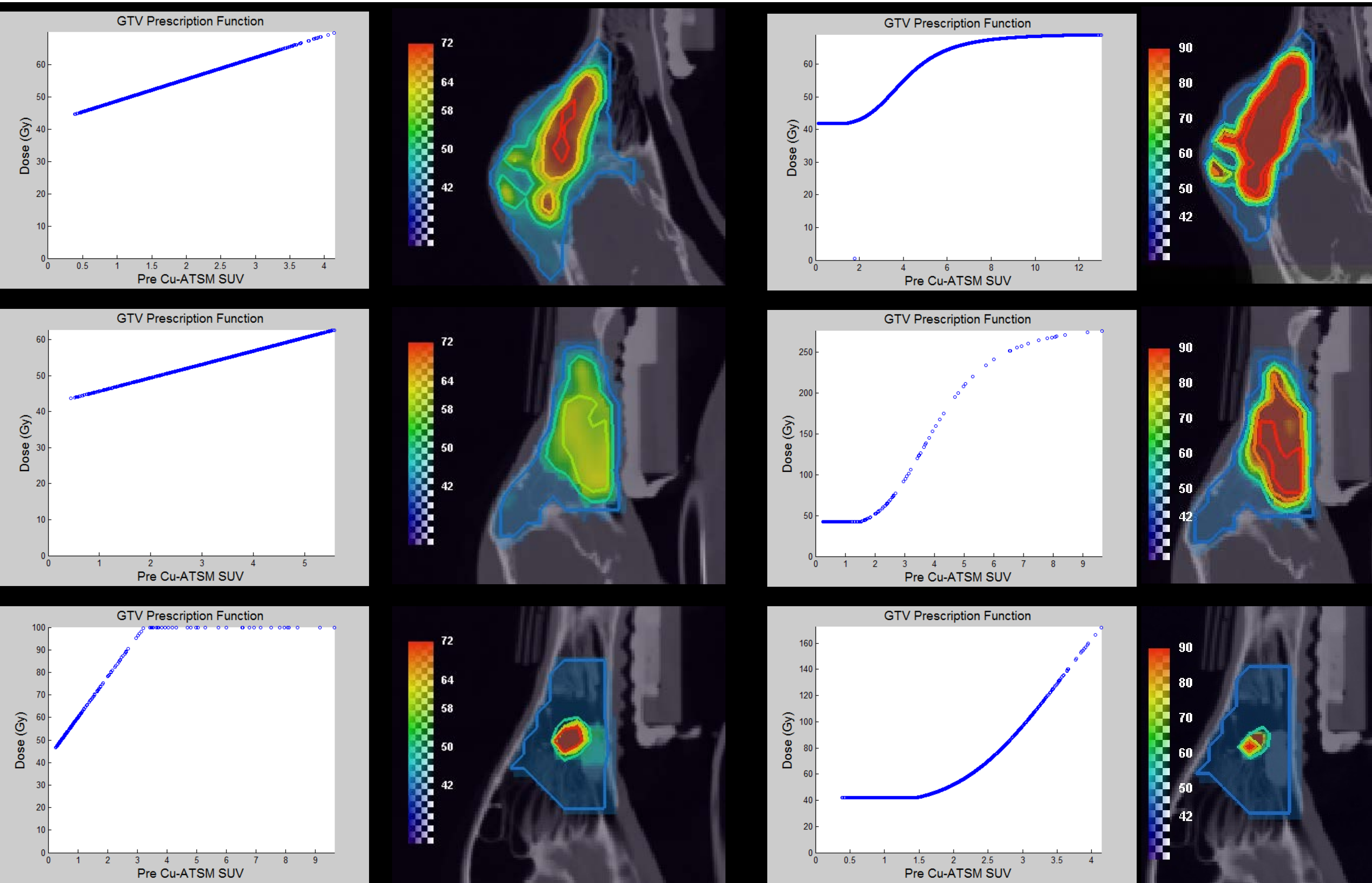
Extremely high correlations!



Bradshaw et al 2014, Int J Radiat Oncol Biol Phys (in press)

HOW TO PRESCRIBE THE DOSE?

Dose prescription function



HOW HIGH TO BOOST THE DOSE?

Dose volume analysis

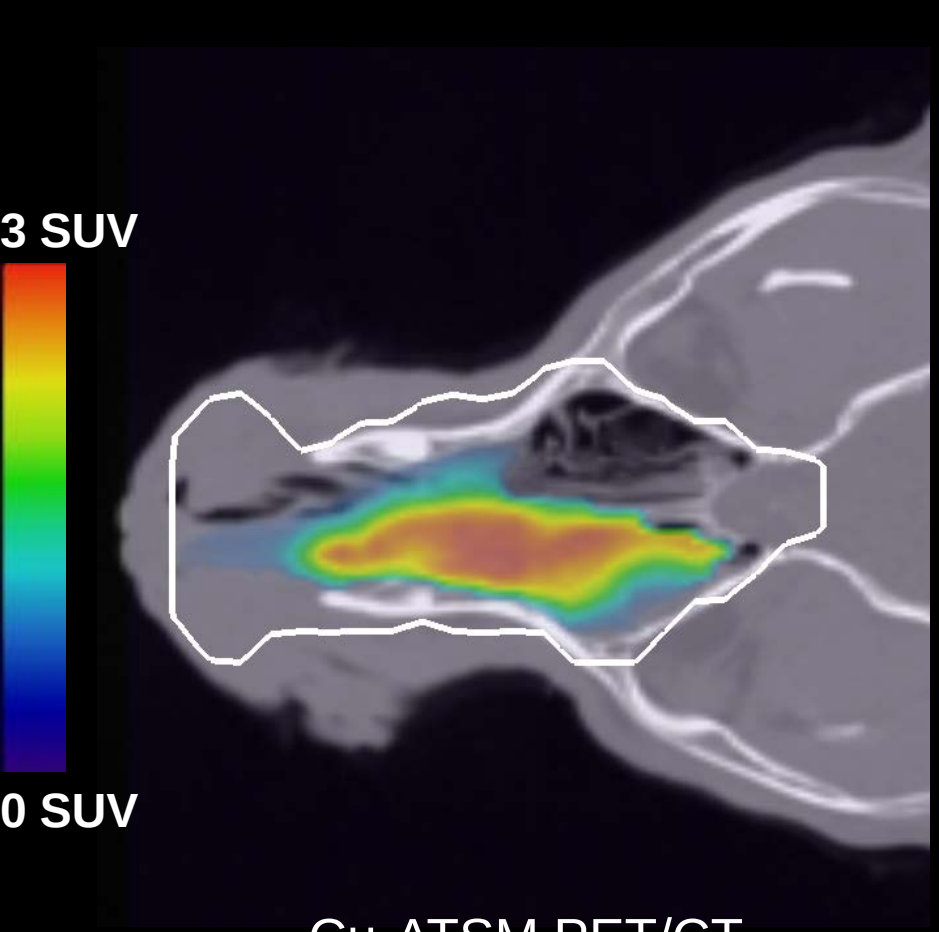
	%Vol of PTV **> 100%**	%Vol of PTV **> 150%**	%Vol of PTV **> 180%**	Max Dose
CARCINOMA				
CDP002	20.4	0.09	0	154 %
CDP005	22.2	0	0	144 %
CDP006	31.2	0.2	0	154 %
CDP007	23.9	0	0	140 %
CDP008	20.6	0	0	126 %
CDP009	3.2	0.84	0.56	200 %
CDP010	23.4	0	0	144 %
CDP011	11.9	1	0	156 %
CDP013	19.5	0.2	0	156 %
CDP018	15.9	4.9	1.6	200 %
CDP019	6.6	0.2	0	174 %
CDP020	18.9	0	0	138 %
CDP022	40.3	0	0	150 %
SARCOMA				
CDP001	19.4	0.3	0	168 %
CDP003	16.1	0.5	0.19	200 %
CDP012	26.3	0	0	142 %
CDP014	15.3	0.01	0	152 %
CDP015	30	2	0.13	199 %
CDP017	27	1.2	0.38	200 %
CDP023	19.6	3.3	1	200 %
AVERAGE	**20.6%**	**0.7%**	**0.2%**	**164 %**

Dose volume analysis (Max @ 200%)

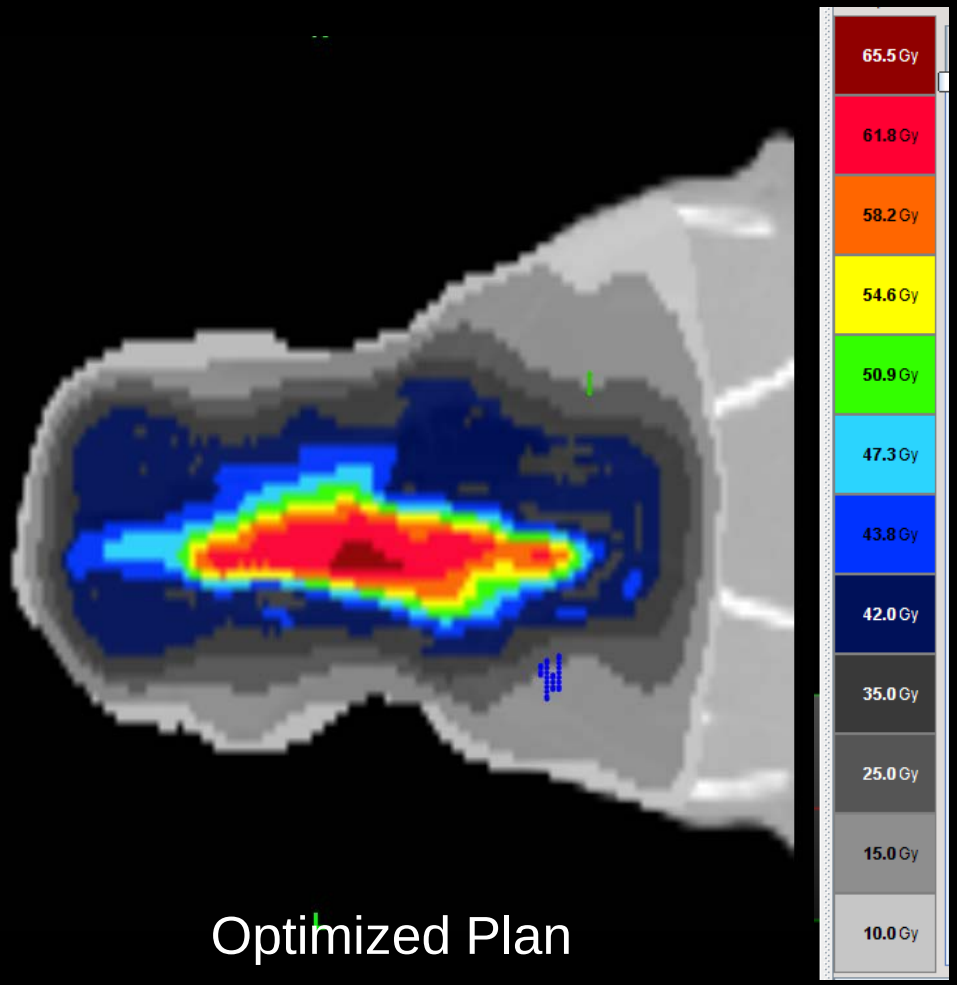
	%Vol of PTV > 100%	%Vol of PTV > 150 %	%Vol of PTV > 180 %	Max Dose
CDP009	3.2	0.84	0.56	200 %
CDP018	15.9	4.9	1.6	200 %
CDP003	16.1	0.5	0.19	200 %
CDP017	27	1.2	0.38	200 %
CDP023	19.6	3.3	1	200 %
AVERAGE	**16.3%**	**2.1%**	**0.7%**	**200 %**

HOW ACCURATELY CAN WE DELIVER HIGH GRADIENTS?

Example radiobiology targeted plan



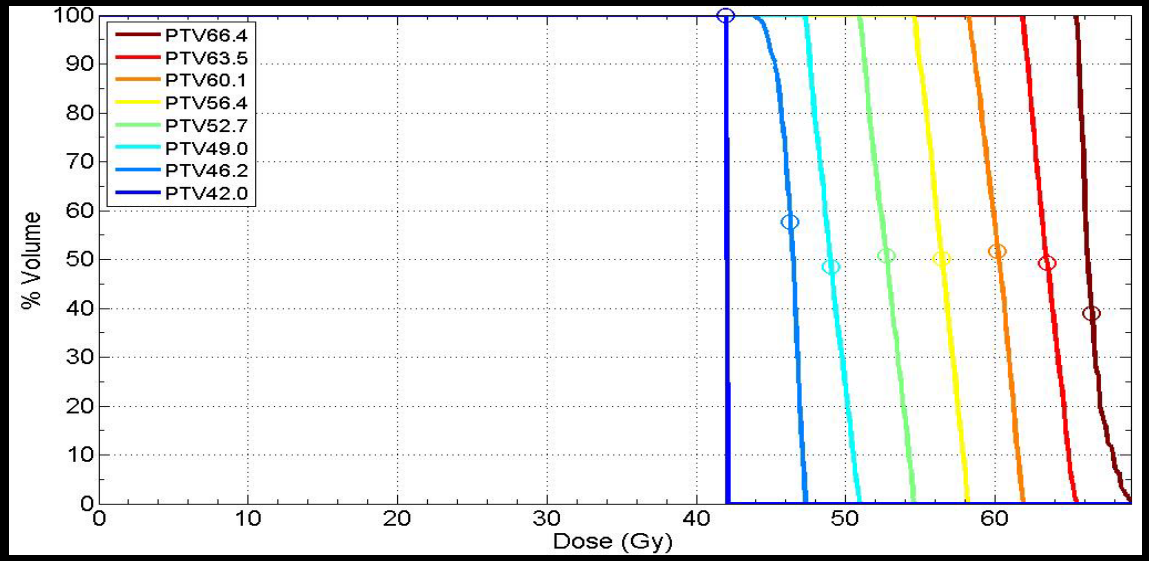
Cu-ATSM PET/CT



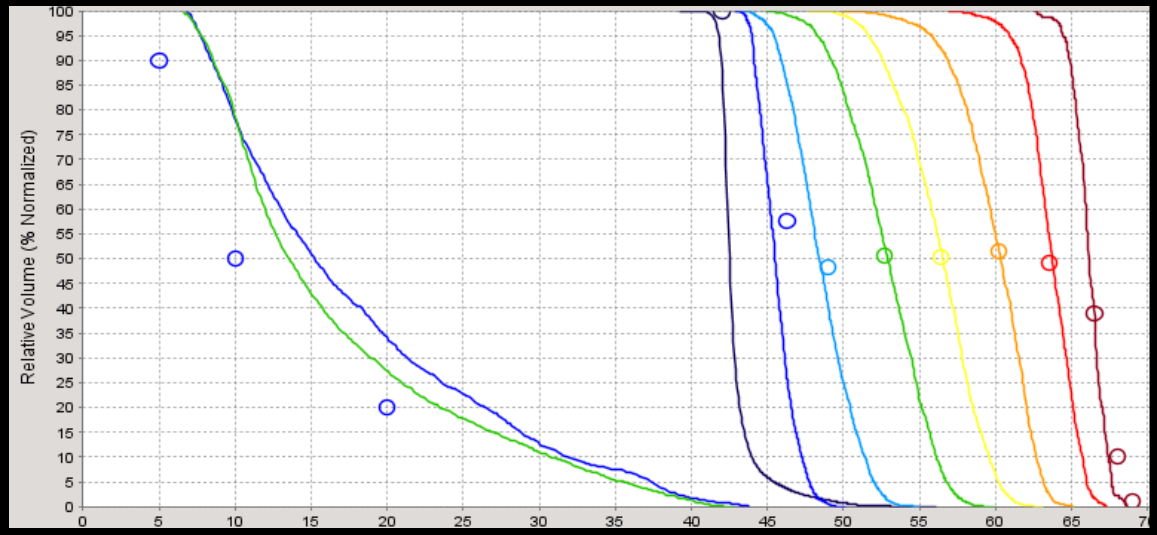
Optimized Plan

Planning and delivery

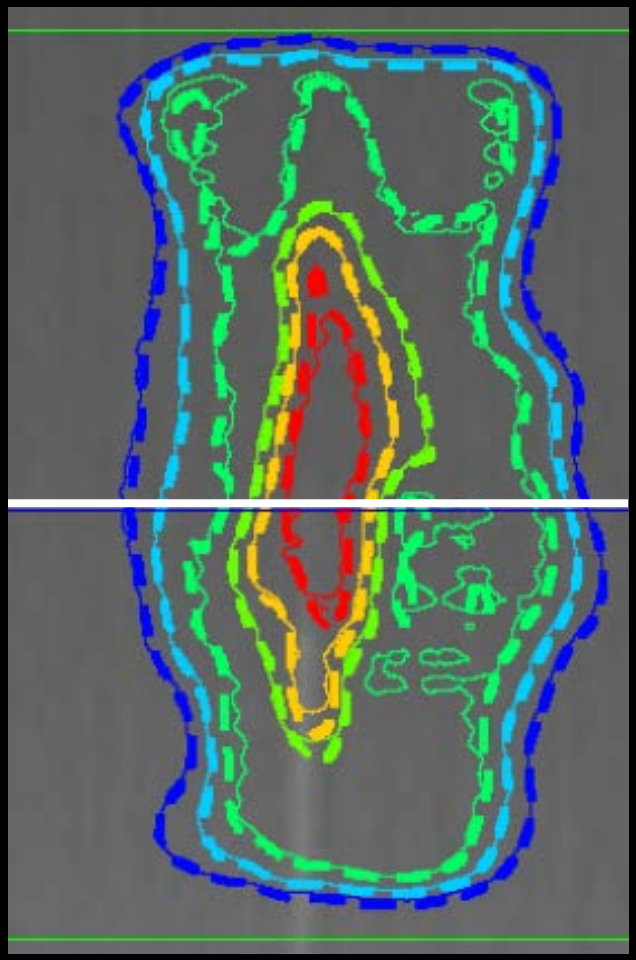
Treatment plan (by contours)

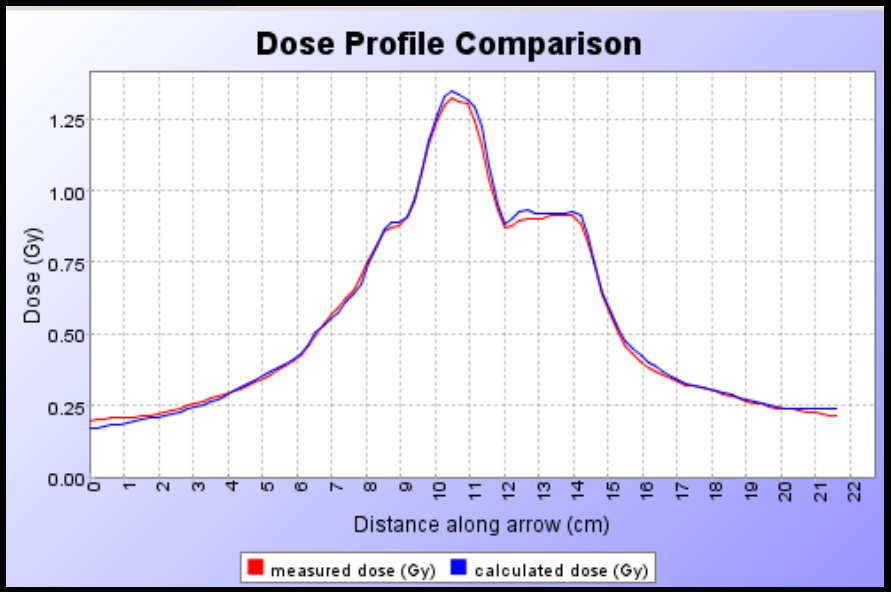


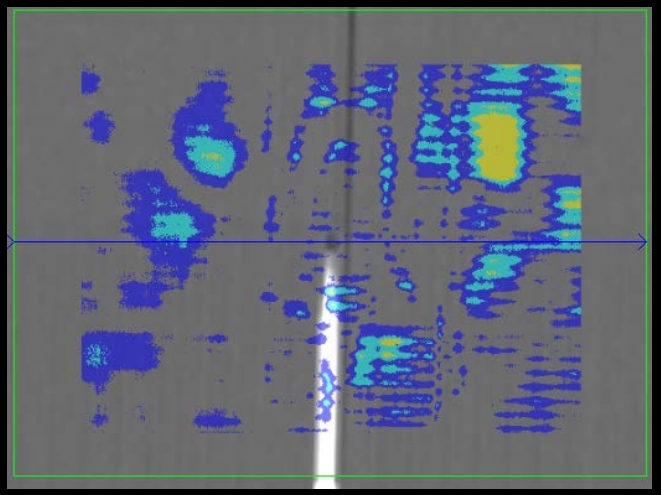
Dose Volume Hist. (by contours)



Dosimetry and QA

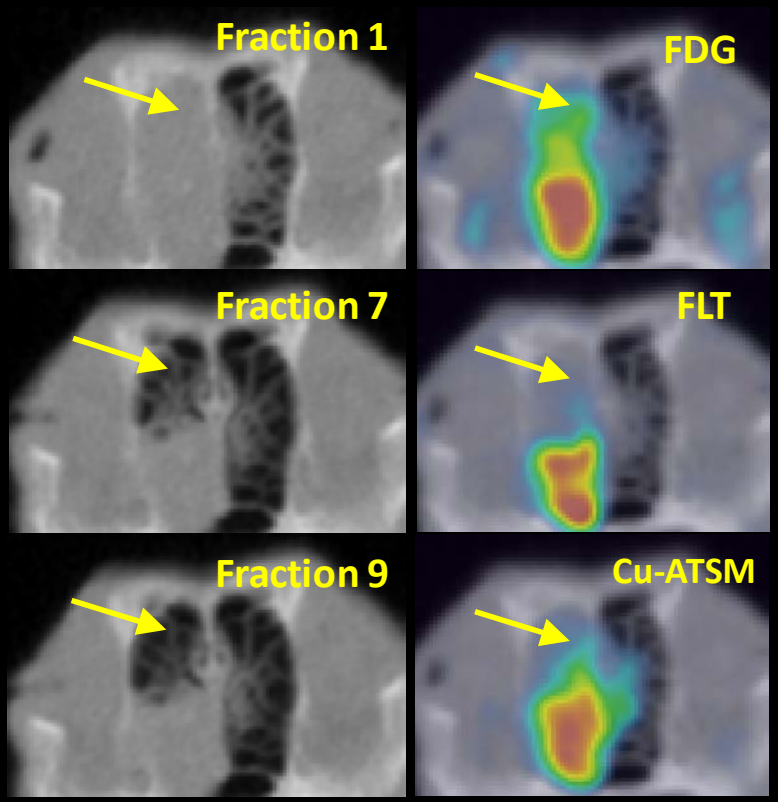




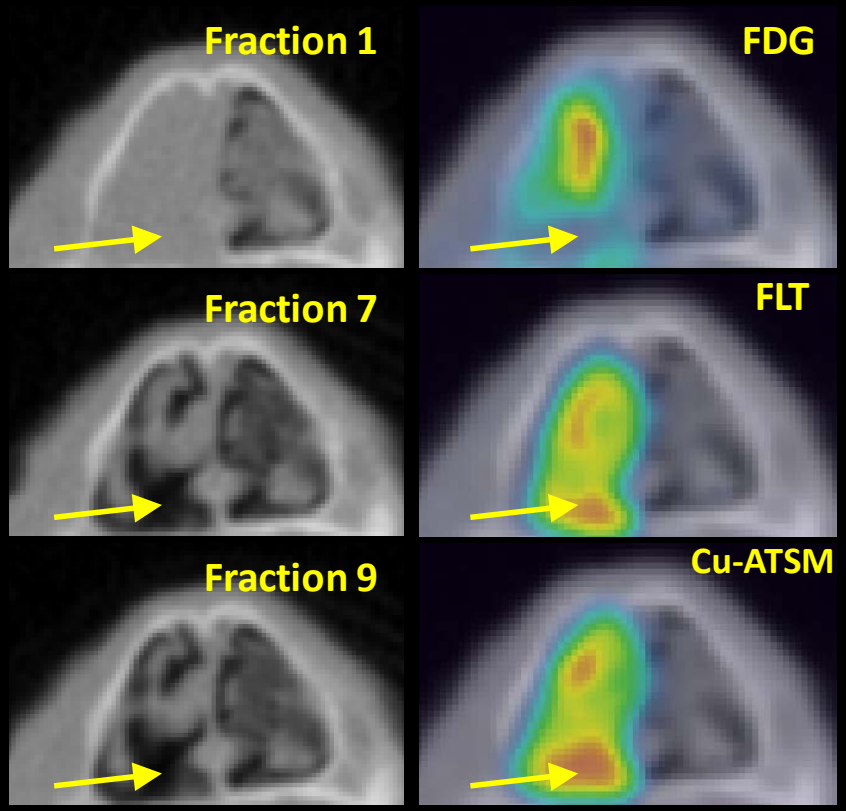


HOW TO DEAL WITH TUMOR SHRINKAGE?

Shrinkage through time (HypoFx)

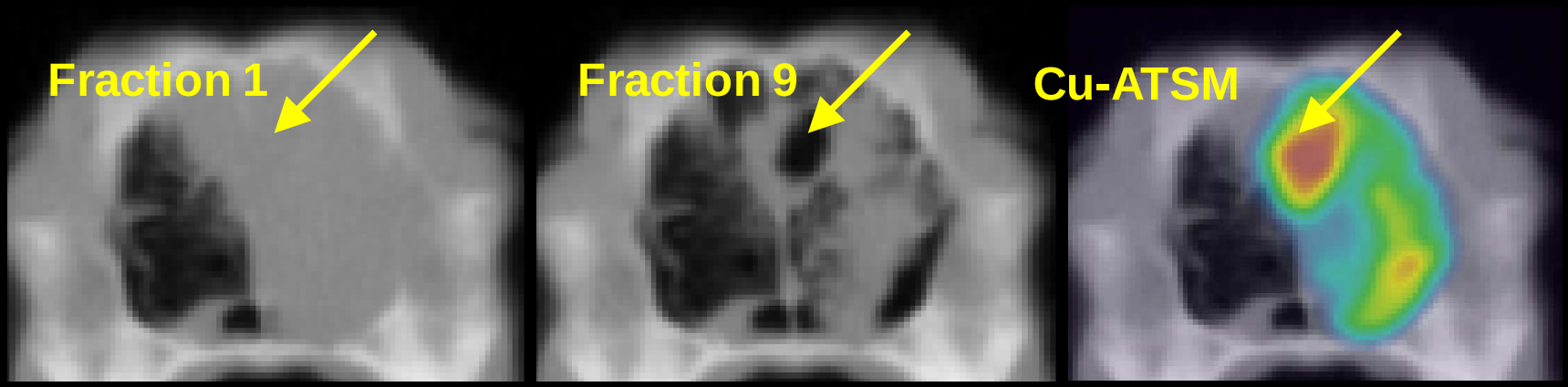


“Elastic” shrinkage



“Patchy” shrinkage

Need for adaptation



Conclusions

- **Dose painting is taking off:**
  - First clinical trial results arriving
  - Safety of PET-based dose escalation established (HNSCC, NSCLC)
  - Waiting for the outcome data

- **Still has many open questions:**
  - What biology to target?
  - How much to dose paint?
  - How to deal with motion, shrinkage?

Thanks to:

- **Image-guided therapy group**
  - Vikram Adhikarla
  - Tyler Bradshaw
  - Enrique Cuna
  - Ngoneh Jallow
  - Matt La Fontaine
  - Paulina Galavis
  - Stephanie Harmon
  - Tim Perk
  - Surendra Prajapati
  - Urban Simoncic
  - Peter Scully
  - Damijan Valentinuzzi
  - Natalie Weisse
  - Stephen Yip
  - Former students…
- **Funding**
  - NIH, PCF, UWCCC, Pfizer, AstraZeneca, Amgen, EntreMed
- **Human Oncology**
  - Søren Bentzen
  - Bert van der Kogel
  - Paul Harari
  - Mark Ritter
- **Veterinary School**
  - Lisa Forrest
  - David Vail
- **Medical Physics**
  - Rock Mackie
  - Jerry Nickles
  - Onofre DeJesus
- **Radiology**
  - Scott Perlman
  - Chris Jaskowiak
- **Medical Oncology/Hematology**
  - Glenn Liu
  - George Wilding
  - Mark Juckett
  - Brad Kahl
  - Anne Traynor
- **Phase I and GU Office**