ACPSEM
Australasian College of Physical Scientists & Engineers in Medicine

ACPSEM CPD Endorsed Activity

MIRSIG

ASMIRT APPROVED CPD PROGRAM
Appellation Code: SGHCCC-001544-2020

The ACPSEM Medical Image Registration Special Interest Group (MIRSIG) Online Webinars

The **current seminar** 1200, Tue 1st December 2020, will be chaired by Johnson Yuen

- Talk 1: **Adaptive Lung Radiotherapy**

Presented by Nicholas Hardcastle

Learning objectives for this talk:

- Understand the clinical evidence for adaptive radiotherapy in lung cancer
- Describe adaptive protocols in patients receiving radical radiotherapy for LA-NSCLC
- Understand the role and limitations of image registration tools in adaptive lung radiotherapy

Webinar activities!!

-Use the "Q&A" to ask questions!

Live Poll!

Poll information will be used to confirm CPD, so it is important to participate!

Post webinar survey!

Please answer survey when email is sent

Seminar material available online!

Please see https://www.acpsem.org.au/About-the-College/Special-Interest-Groups/MIRSIG

Be more involved!

1. MIRSIG welcomes professions from all disciplines, including radiation therapists and radiation oncologists
2. Sign up to the MIRSIG mailing list (https://www.acpsem.org.au/Home , click myACPSEM click speciality groups, tick MIRSIG)
3. Join MIRSIG as a member, email mirsig@acpsem.org.au

ADAPTIVE LUNG RADIOTHERAPY

Nick Hardcastle, PhD

Medical Physicist

Peter MacCallum Cancer Centre

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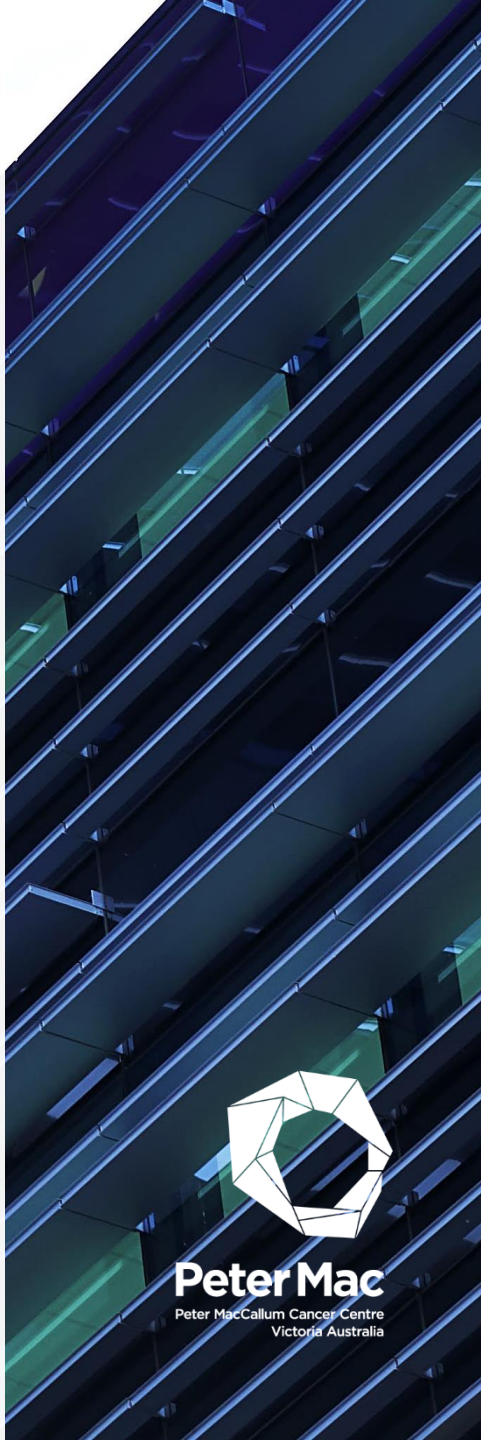
@HardcastleNick

LEARNING OBJECTIVES

- Understand the clinical evidence for adaptive radiotherapy in lung cancer
- Describe adaptive protocols in patients receiving radical radiotherapy for LA-NSCLC
- Understand the role and limitations of image registration tools in adaptive lung radiotherapy

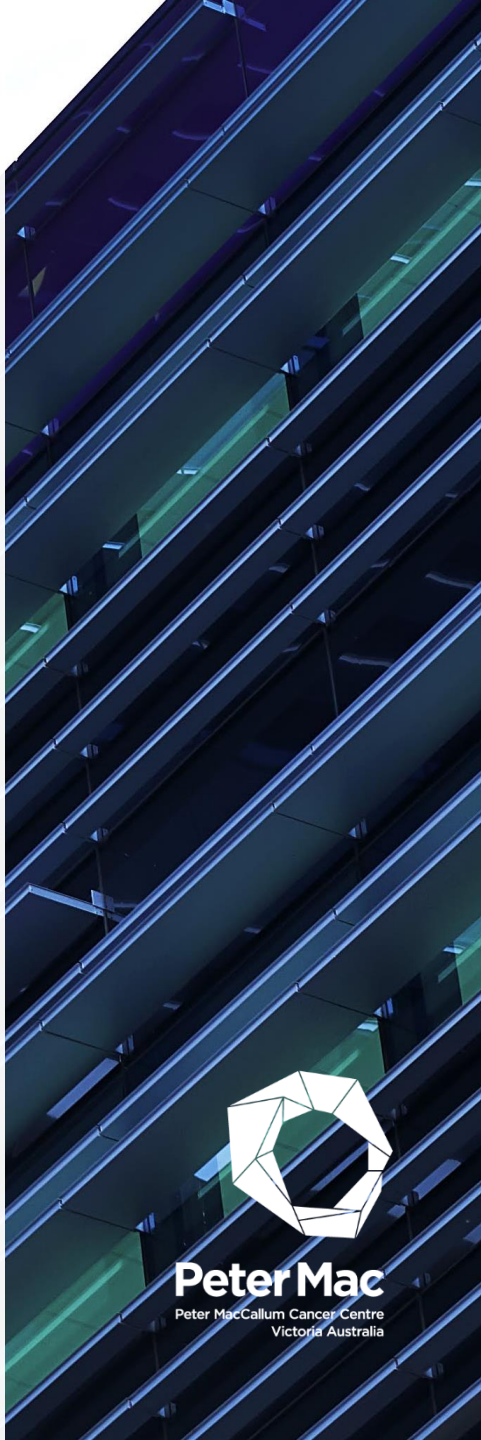


OUTLINE

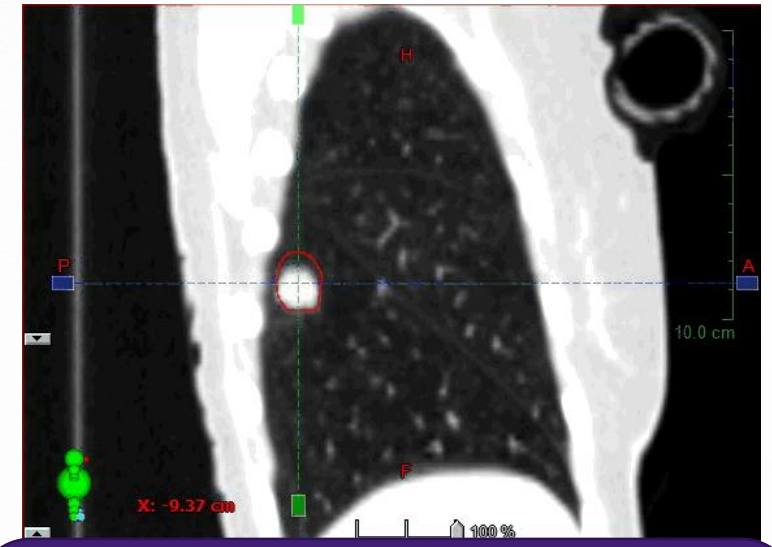
- What changes over the course of radiotherapy in LA-NSCLC?
- How can we adapt to changes, and what is the evidence for it?
- A case study using image registration in adaptive radiotherapy

- Focus on ‘adaptive radiotherapy’, defined as offline adaptation for anatomical or biological changes that occur over the course of treatment
- See special issue in SRO for wider discussion of adaptive radiotherapy

  Brock KK. Adaptive Radiotherapy: Moving Into the Future. Vol. 29, Seminars in Radiation Oncology. 2019. p. 181–4.

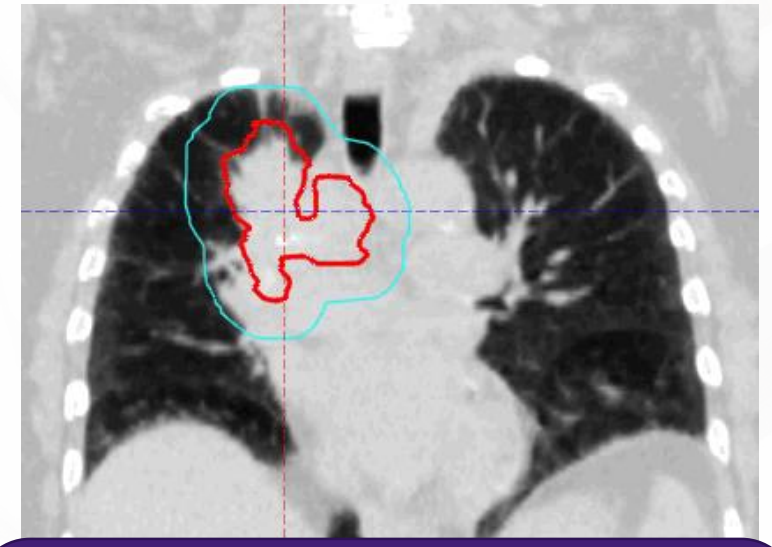


RADIOTHERAPY IN THE LUNG



Early stage lung cancer

Lung metastases



Primary lung cancer
NSCLC / SCLC

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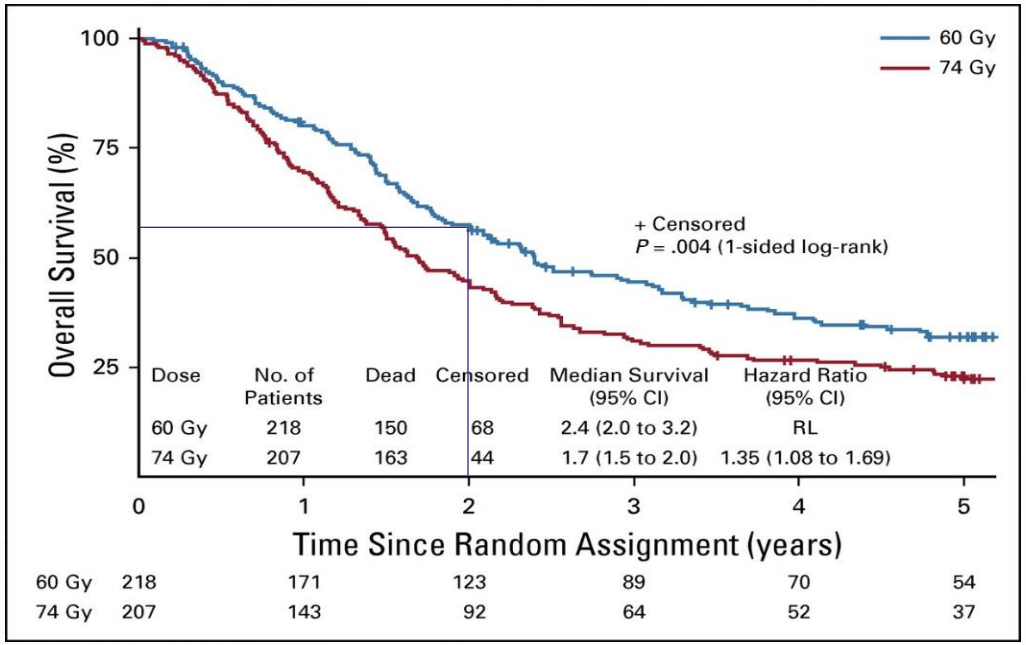
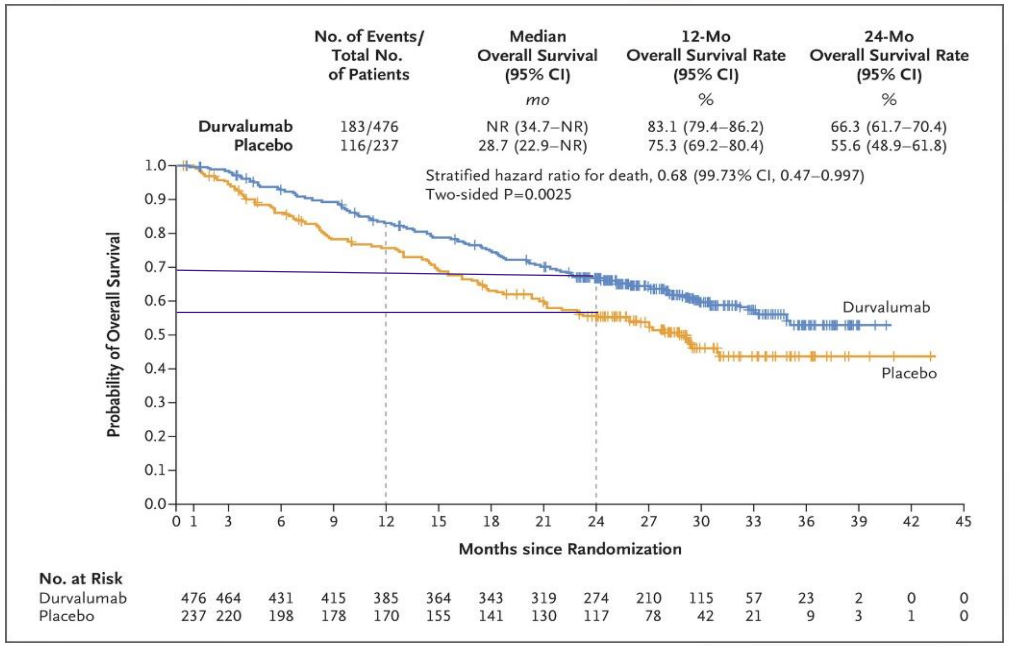
RADIOTHERAPY FOR LA-NSCLC

RTOG 0617: Uniform dose escalation is not safe



Bradley JD et. al. *J Clin Oncol*. 38(7) 2020

PACIFIC: immunotherapy after chemo-RT improves survival



Antonia SJ et. al. *N Engl J Med*. 377(20) 2017

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RADIOTHERAPY FOR LA-NSCLC

Local failure is a problem in LA-NSCLC:

TABLE 3. Patterns of Failure at 5 Years

	Standard Dose (60 Gy)		High Dose (74 Gy)		
Failure Pattern	**Failed, % (95% CI)**	**No. at Risk**	**Failed, % (95% CI)**	**No. at Risk**	***P***
Local	38.2 (31.7 to 44.8)	40	45.7 (38.7 to 52.4)	27	.07
Regional	35.7 (29.3 to 42.2)	37	38.4 (31.7 to 45.0)	27	.54
Locoregional	49.7 (42.8 to 56.3)	34	55.4 (48.3 to 61.9)	25	.17
Distant	52.3 (45.3 to 58.8)	36	57.6 (50.4 to 64.1)	24	.32

And there are significant side effects (RTOG 0617)

- Grade ≥ 3 Dysphagia/Oesophagitis (7.3% vs 20.8% SD vs HD)
- Grade ≥ 3 pulmonary toxicity ~ 20% in both arms
- Dose to the heart – link to survival and local control

Patients need to come out of (chemo)RT in good shape for IO therapy

Bradley JD et. al. *J Clin Oncol*. 38(7) 2020

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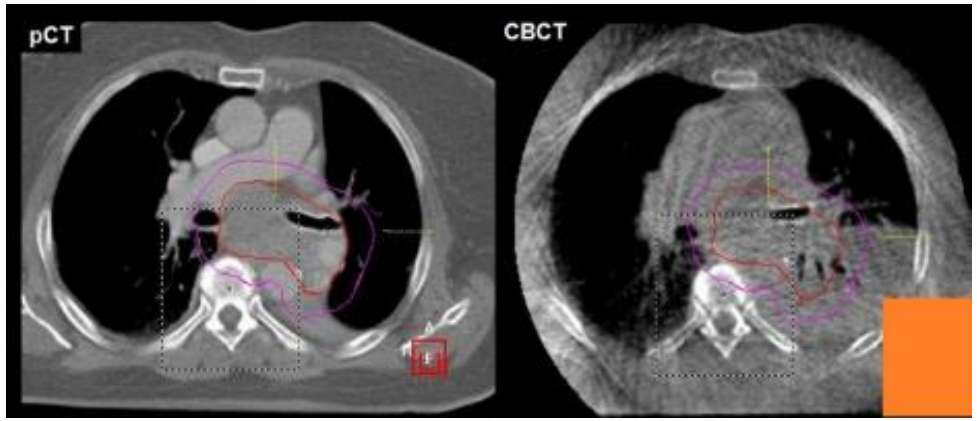
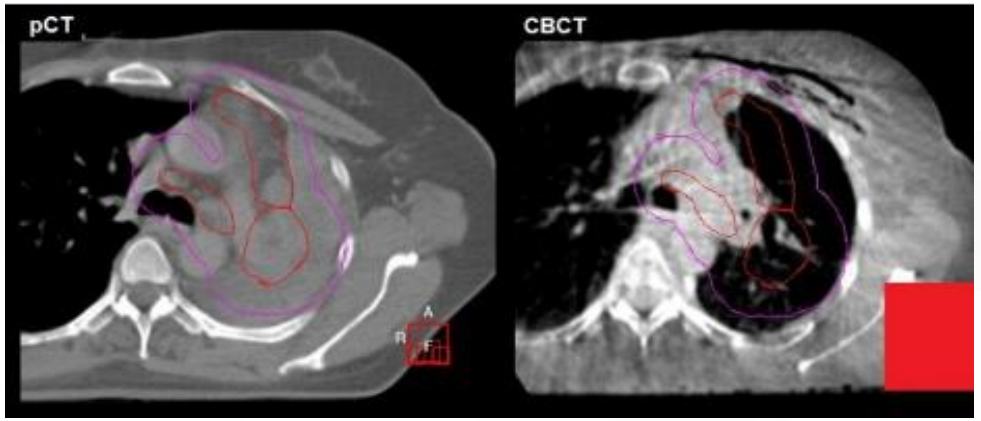
ANATOMICAL CHANGES

72% of LA-NSCLC patients have significant anatomical changes during the course of radiotherapy

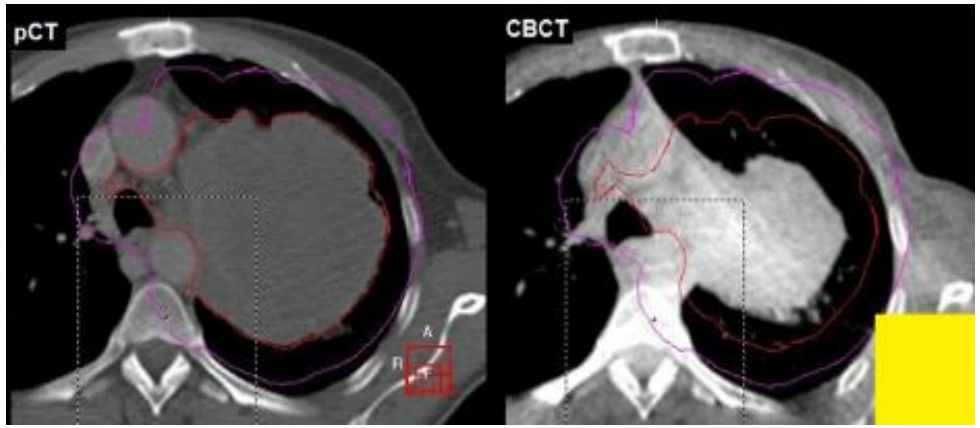
Atelectasis developing / Pleural effusion (19%)



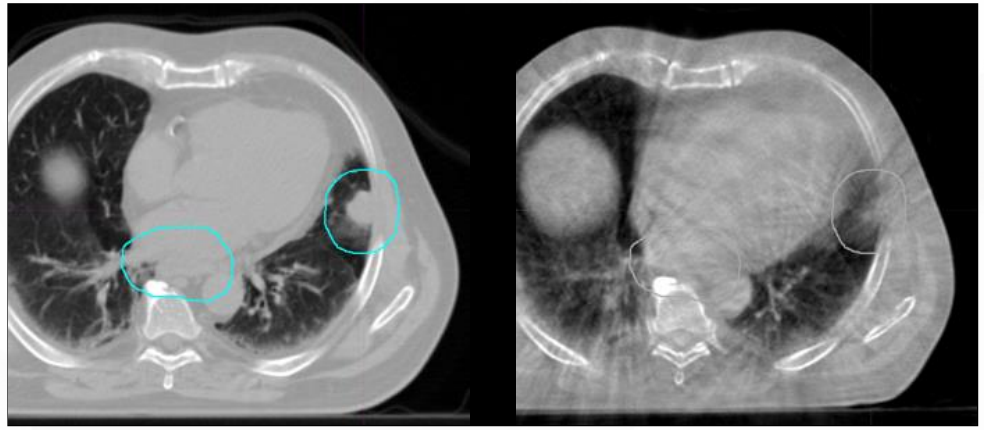
Atelectasis / pleural effusion resolving (6%)



Tumour regression / progression (45%)



Tumour position changes (27%)



Kwint M et. al. R & O 113 (2014)

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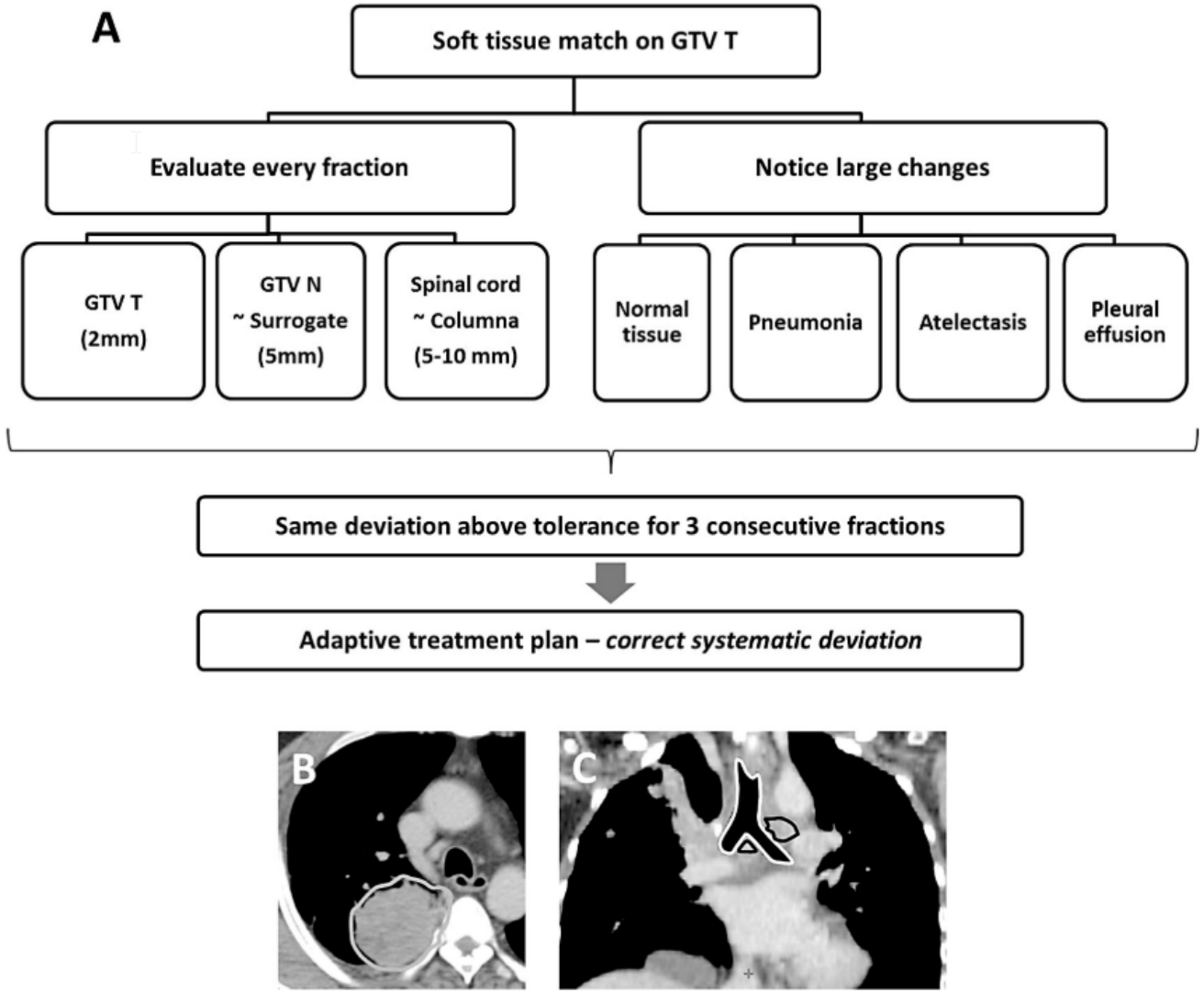
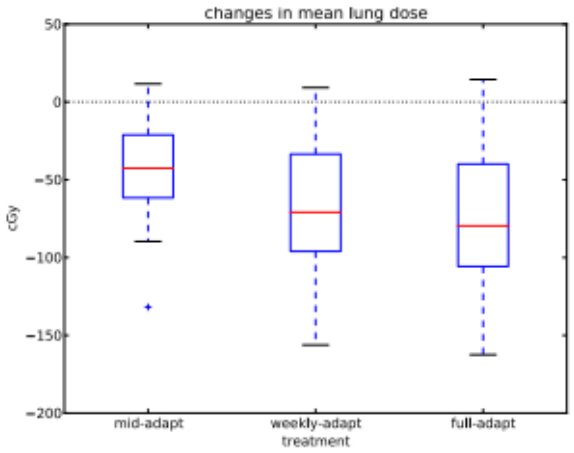
ANATOMICAL ADAPTATION

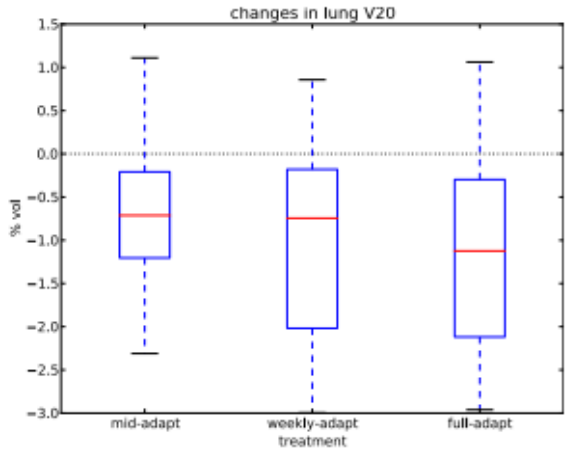


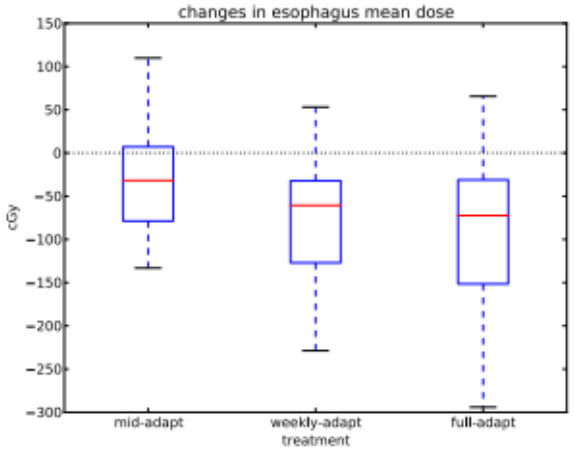
Møller DS et. al. *Radiother Oncol*. 121(1), 2016

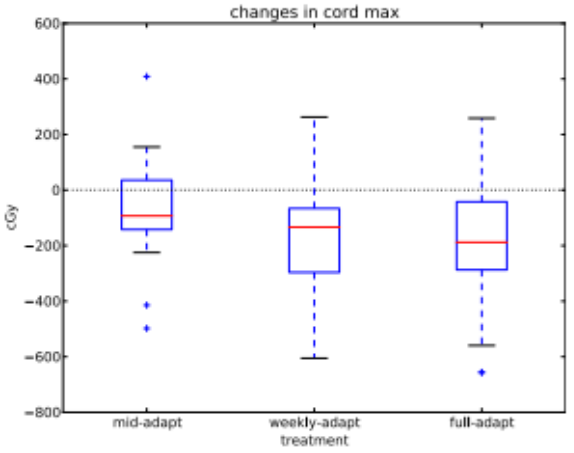
- 233 consecutive lung cancer patients
- 173 NSCLC / 60 SCLC
- Mostly Stage II-III
- Daily CBCT reviewed
- 63 patients re-planned
- The CTV was not adapted to shrinking tumours

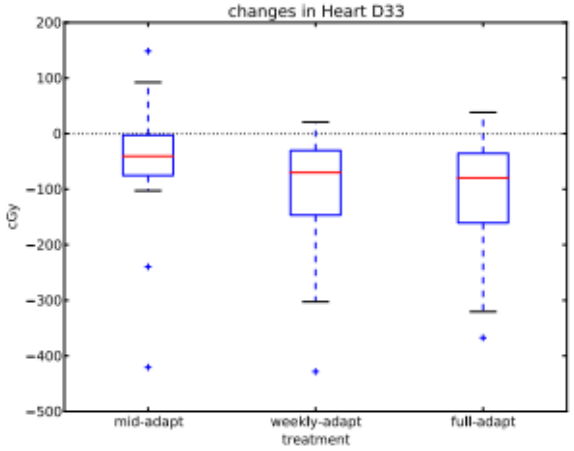
- 59 (75%) of adaptations were 'clinically beneficial' – maintain target coverage or reduce organ at risk dose

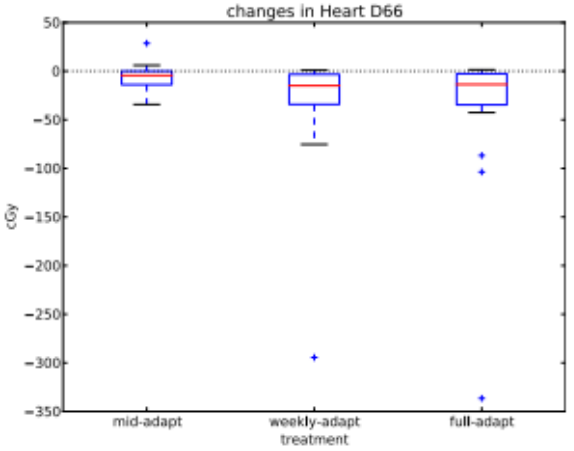












ANATOMICAL ADAPTATION

- Simulated adaptive strategy for 12 patients using synthetic dataset constructed from weekly CTs
- Tested single adaptation, weekly adaptation and daily adaptation
- Target volume was adapted on each image
- “On average, 65% of benefit was achieved with a single mid-treatment adaptation, and 85% was realized after weekly adaptation”

Dial C et. al. Med Phys. 2016;43(4)

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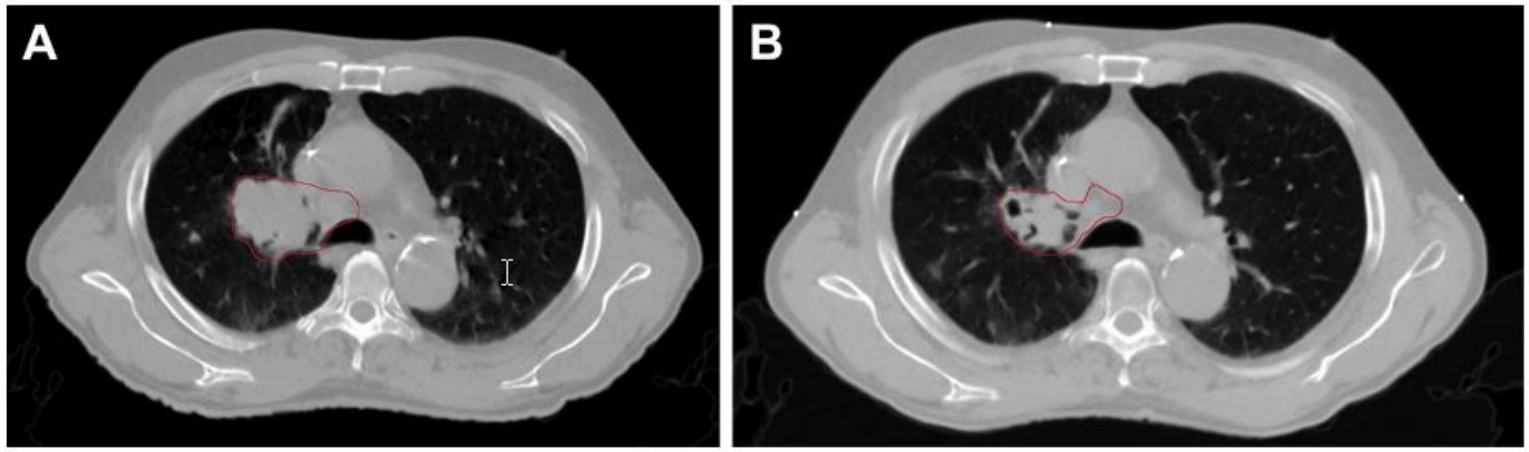
The LARTIA trial: Shrink CTVs?



- 217 LA-NSCLC patients over 3 years
- Weekly CTs -> if two ROs deemed tumour reduction present & clinically significant, replan contrast CT was acquired and adaptive plan performed
- Replanning (3DCRT) performed in 50/217 cases. Mean CTV 155 cc to 91 cc
- Powered to detect reduction in ≥ Grade 3 pulmonary toxicity: 4% (c.f. 15-20%)
- Local failures were infield (20%), marginal (6%), and out of field (4%)
  - Total local failure rate comparable to RTOG 0617 (31%)

Ramella S et. al. *J Thorac Oncol*. 12(7), 2017

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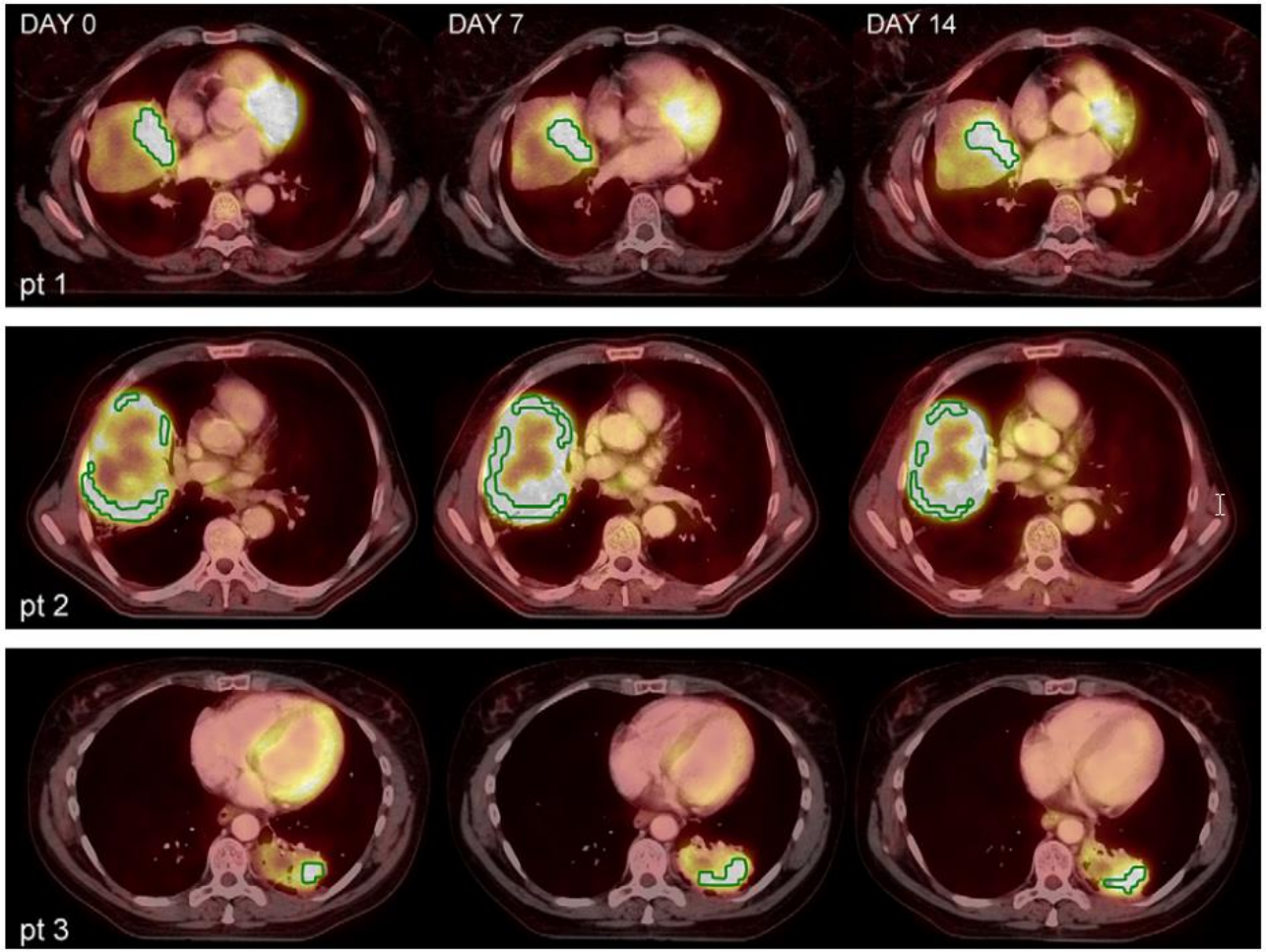
BIOLOGICAL CHANGES



- 23 patients with NSCLC had Day 0, 7 & 14 FDG PET
- Low and high FDG update areas within tumour remained stable during treatment
- Coupled with studies showing FDG avidity may be prognostic for local failure, potential for selective boosting to high FDG uptake areas

Aerts HJWL et. al. *Int J Radiat Oncol Biol Phys*. 2008;71(5)

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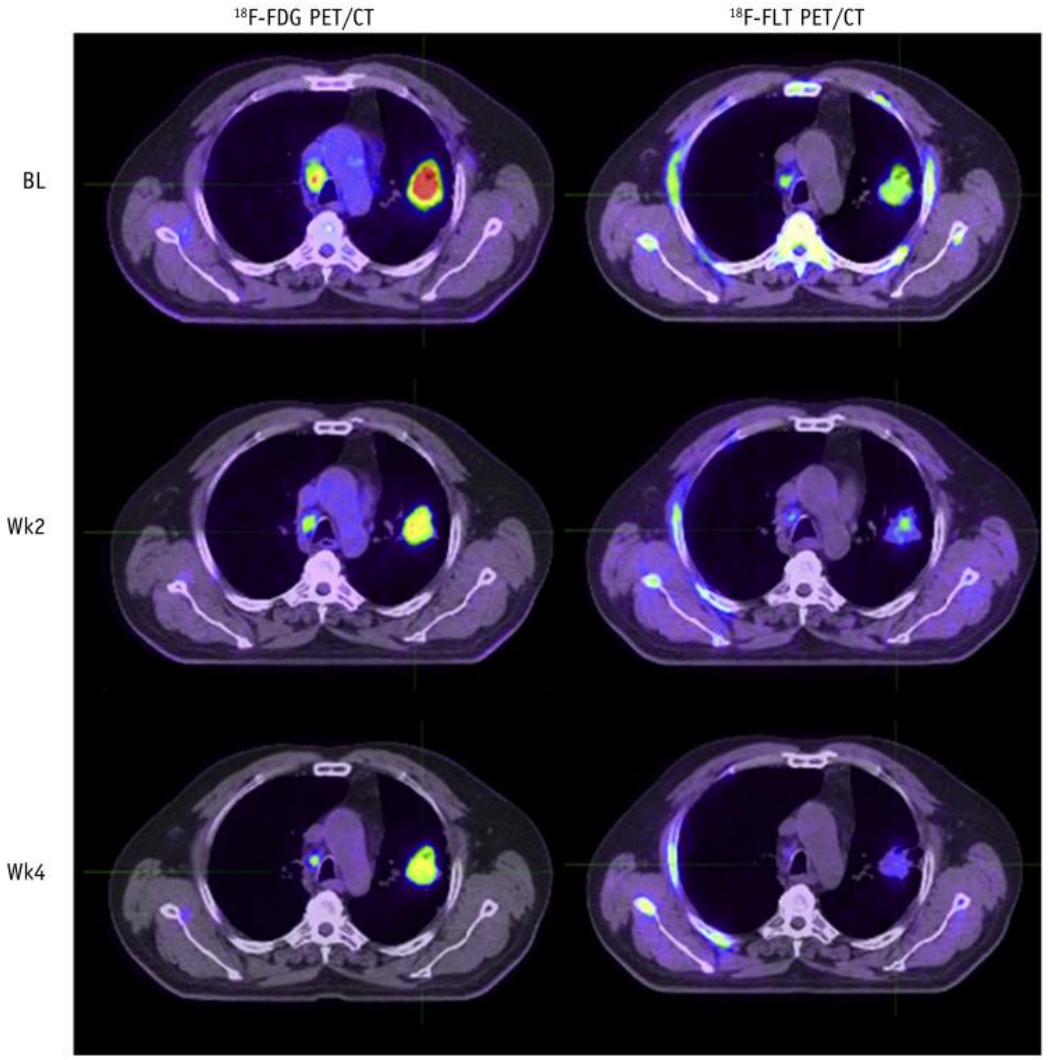
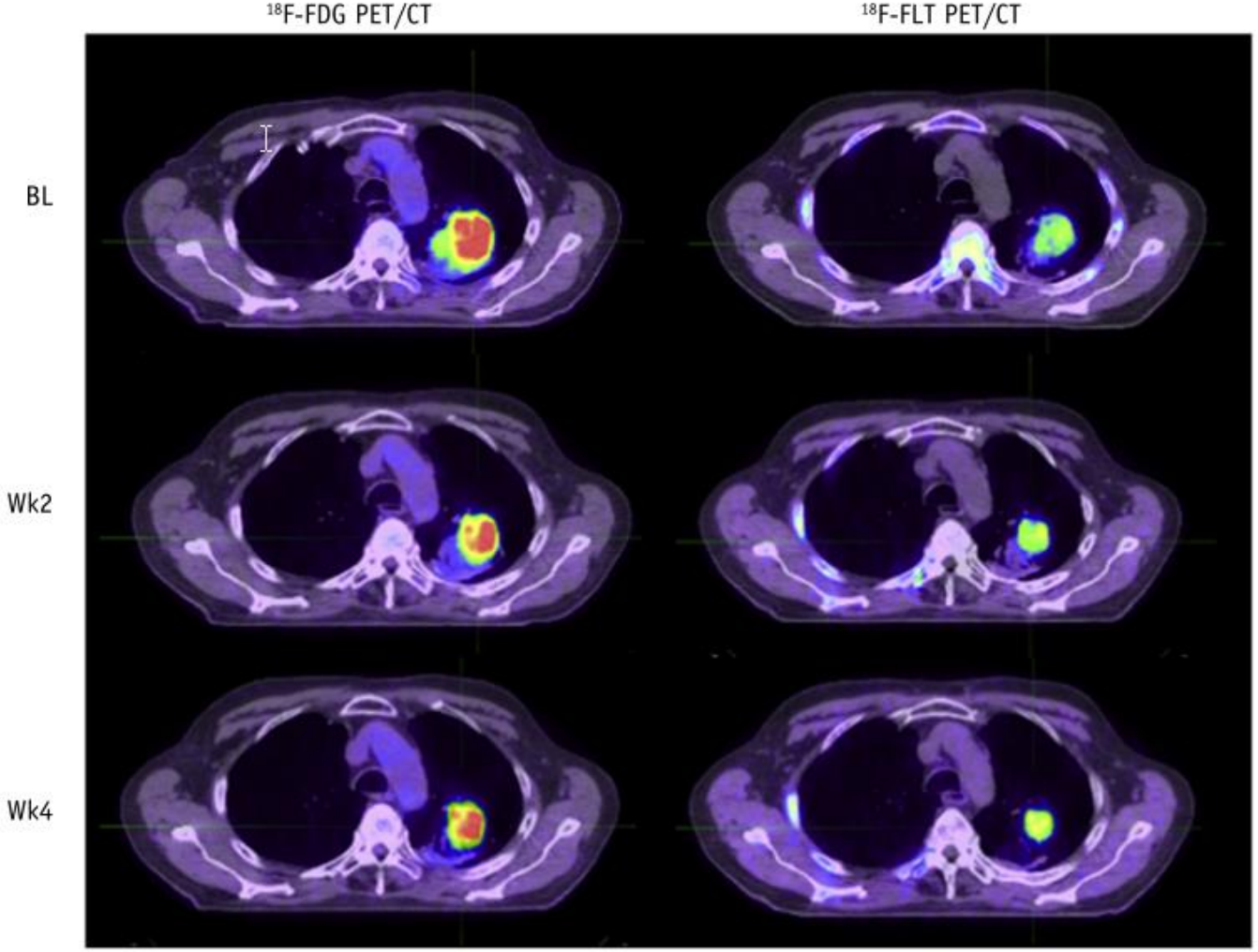
BIOLOGICAL CHANGES

Stable(ish) FDG uptake, FLT PET reduction



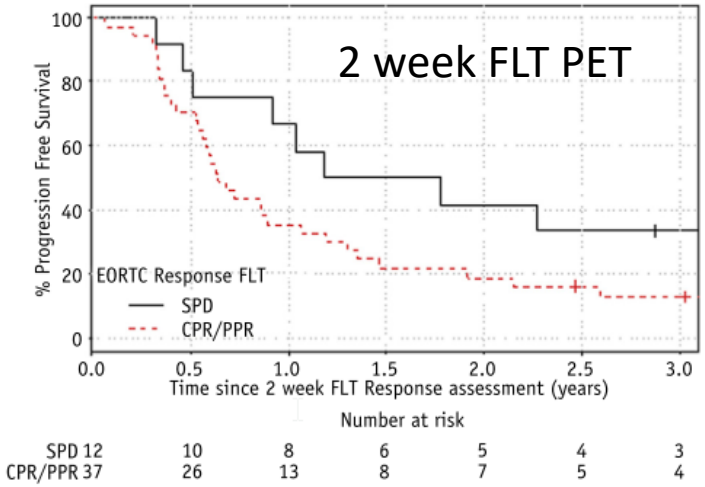
Stable FDG uptake, stable FLT uptake

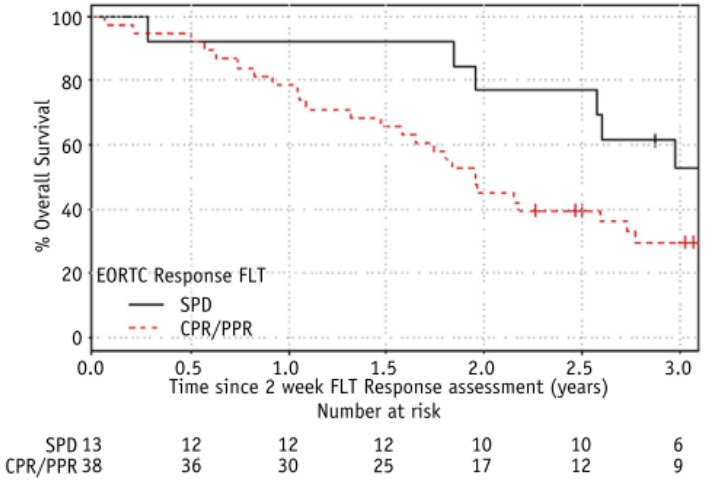


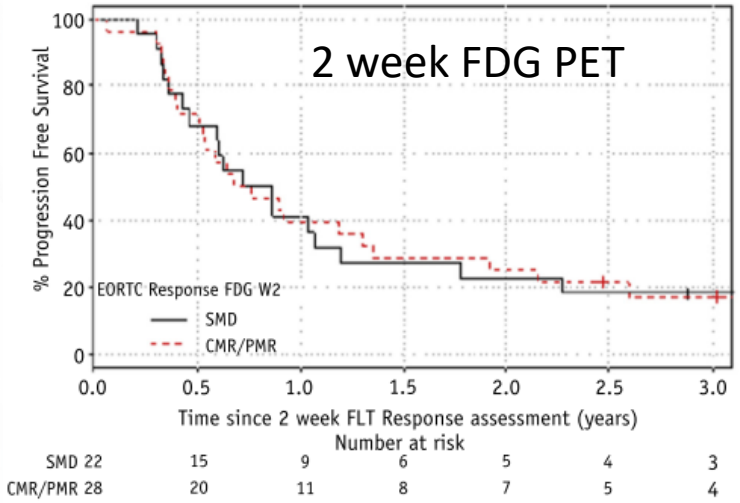
Everitt S et. al. *Int J Radiat Oncol Biol Phys*. 99(4), 2017

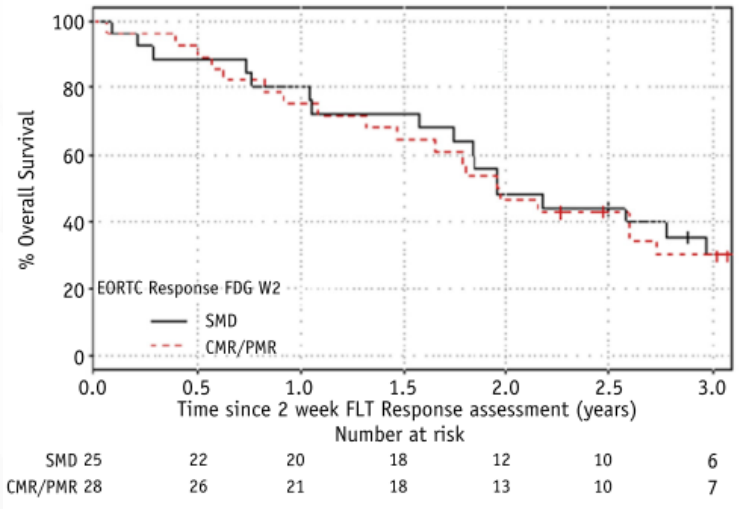
BIOLOGICAL CHANGES

If cell proliferation (FLT) signal decreases, patients do worse. FDG PET not able to discriminate









Everitt S et. al. *Int J Radiat Oncol Biol Phys*. 99(4), 2017

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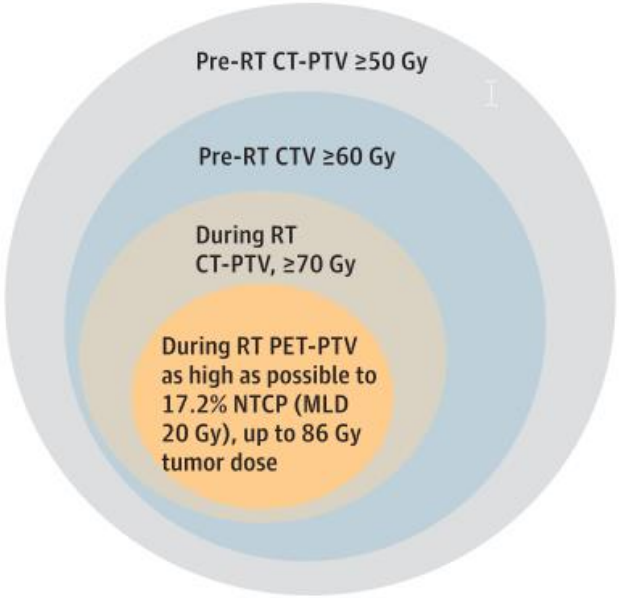
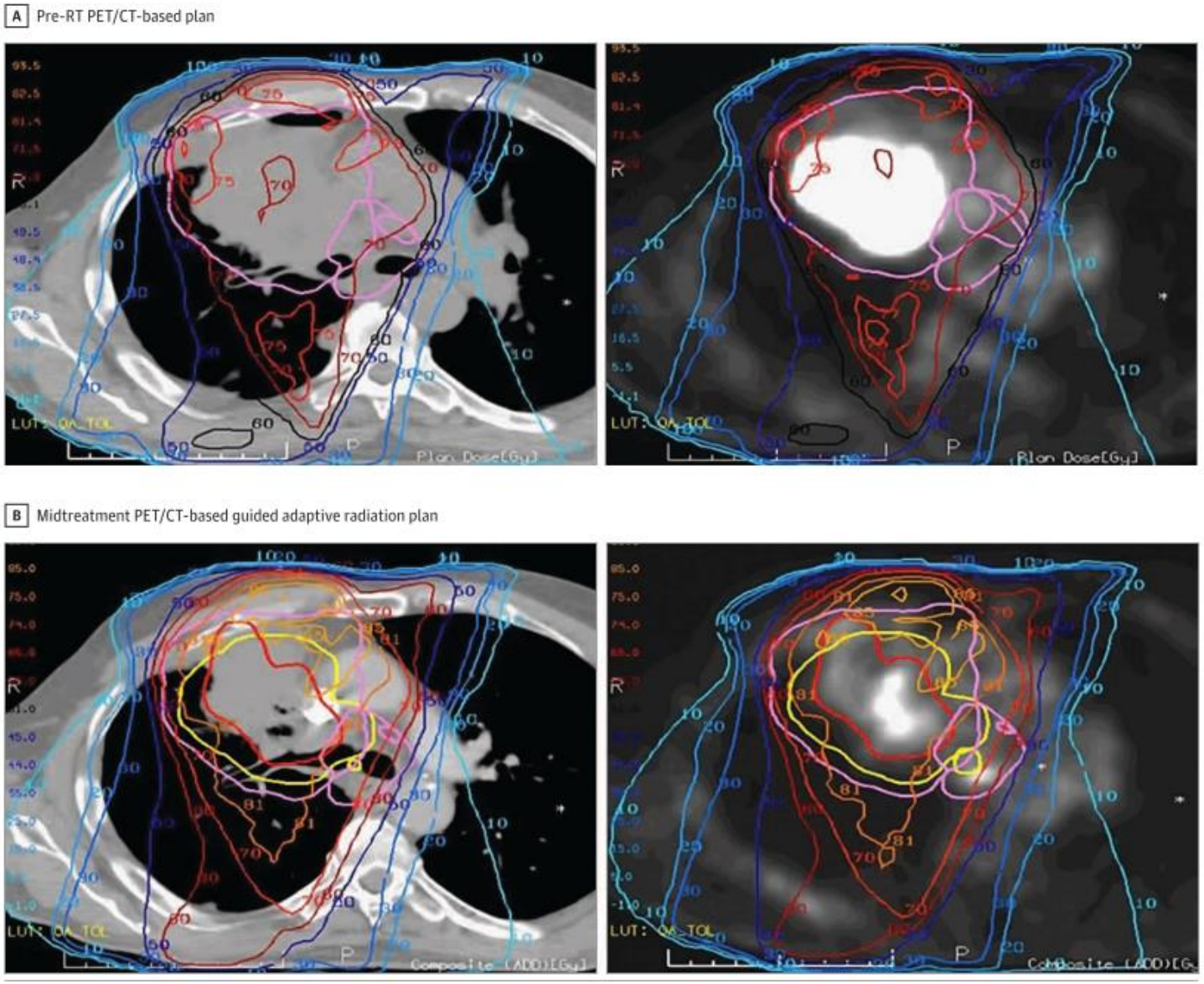
BIOLOGICAL ADAPTATION

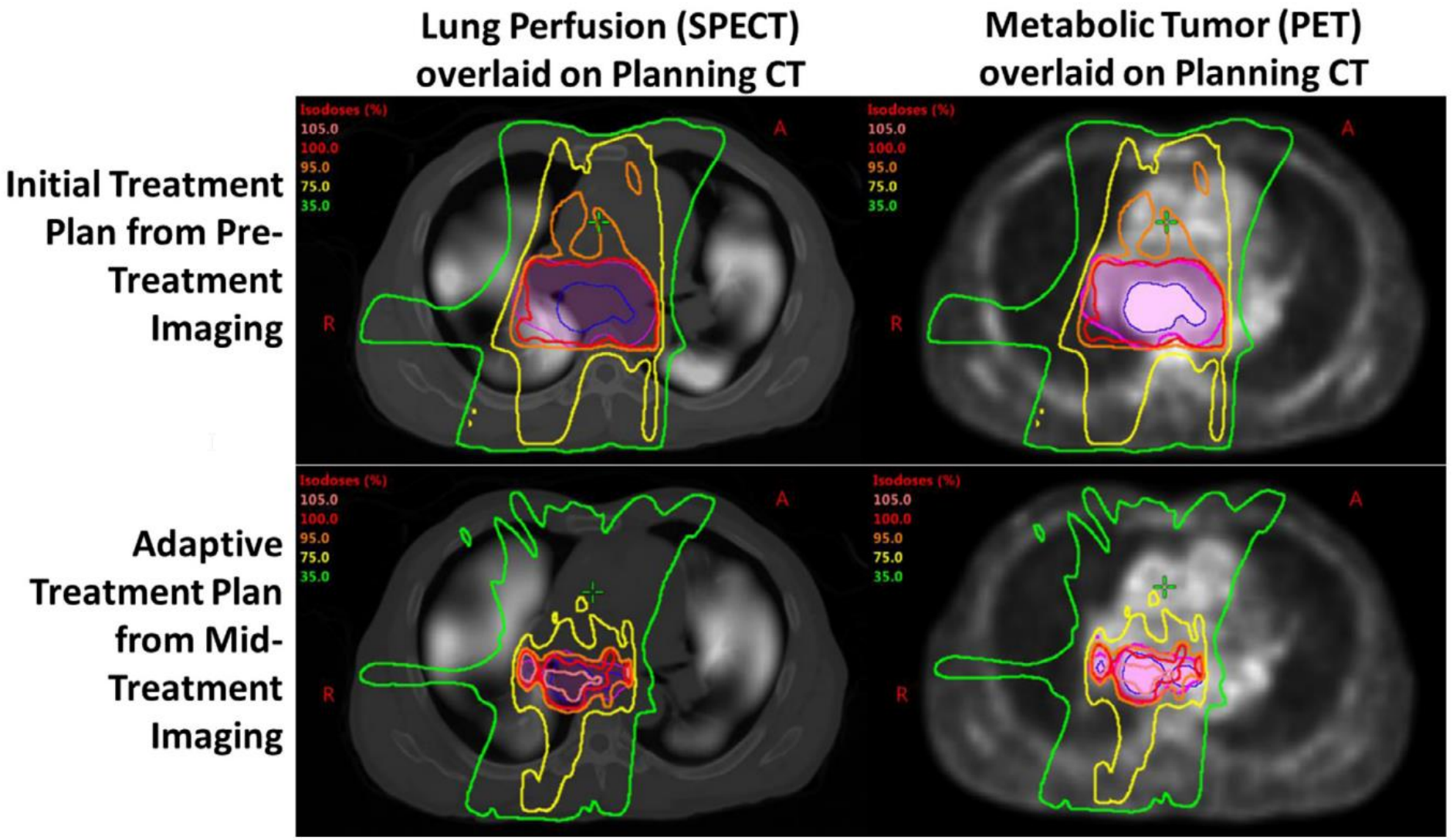


- Two centres, 42 patients
- FDG-PET acquired at 40-50 Gy
- Avid region boosted to 86 Gy, isotoxic approach
- Local control (primary endpoint) 82%
- Tested in phase III trial RTOG 1106, results pending…



Kong FM et. al. *JAMA Oncol*. 2017;3(10)

BIOLOGICAL ADAPTATION



Matuszak MM, *Semin Radiat Oncol*. 2019;29(3)

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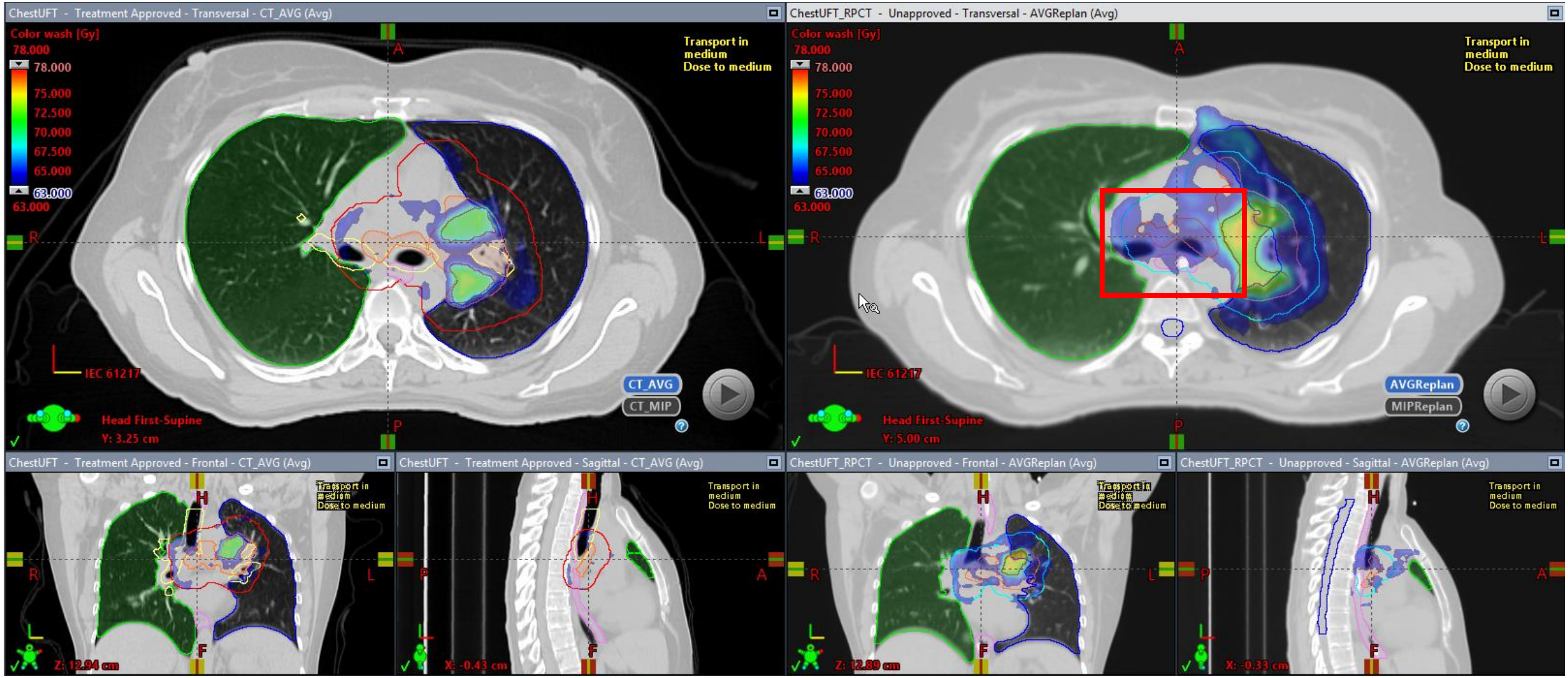
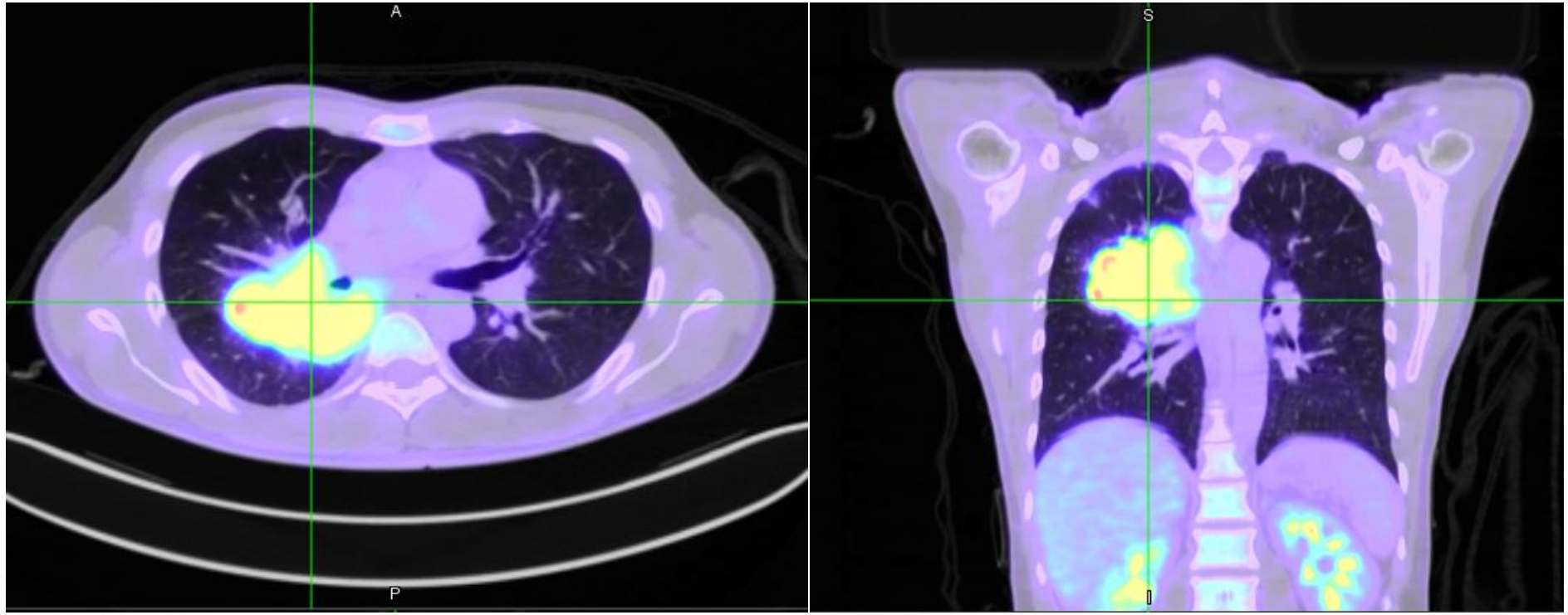
ADAPTIVE RT MAY BE MORE NECESSARY WHEN BOOSTING

Original plan (60 Gy to PTV, 69 Gy to FDG avid boost)

Original plan on repeat planning CT (fraction 20)



A CASE STUDY ON USE OF IMAGE REGISTRATION IN ADAPTIVE LUNG RT



60 Gy in 30 fractions prescribed to primary tumour + mediastinal nodes

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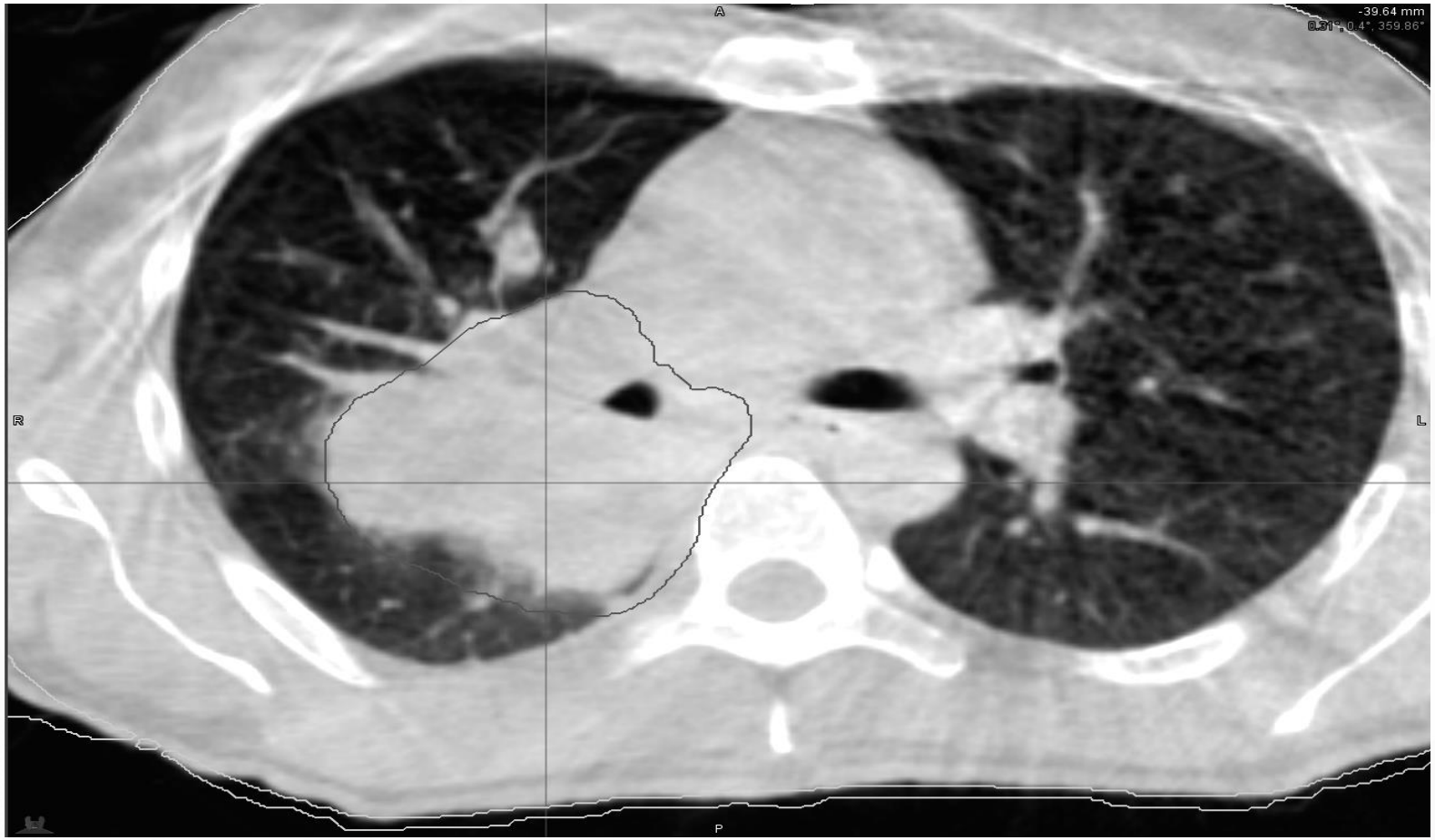
TUMOUR SHRINKAGE



CBCTs acquired from fraction 1 to 18 of a 60 Gy / 30 fraction treatment

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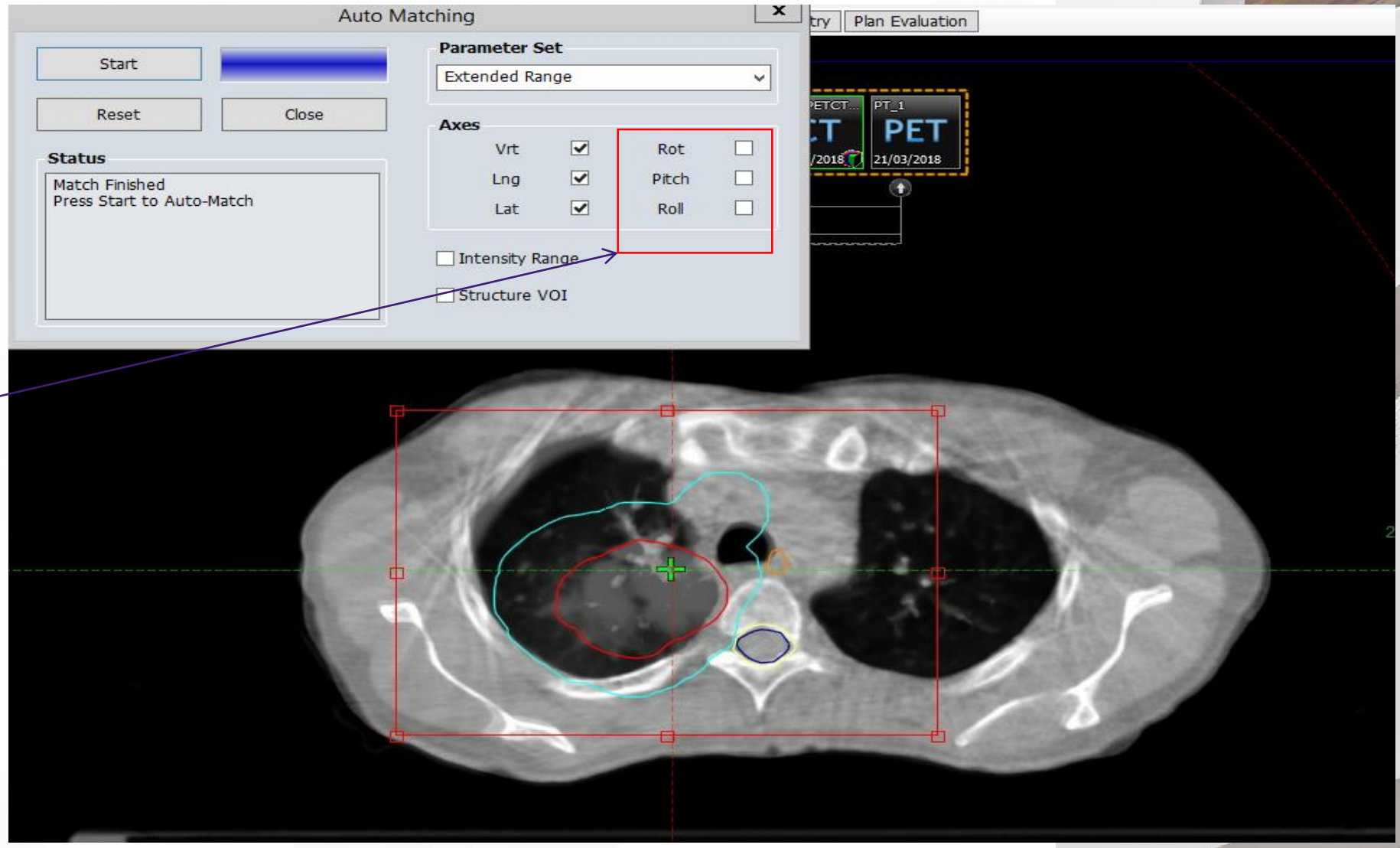
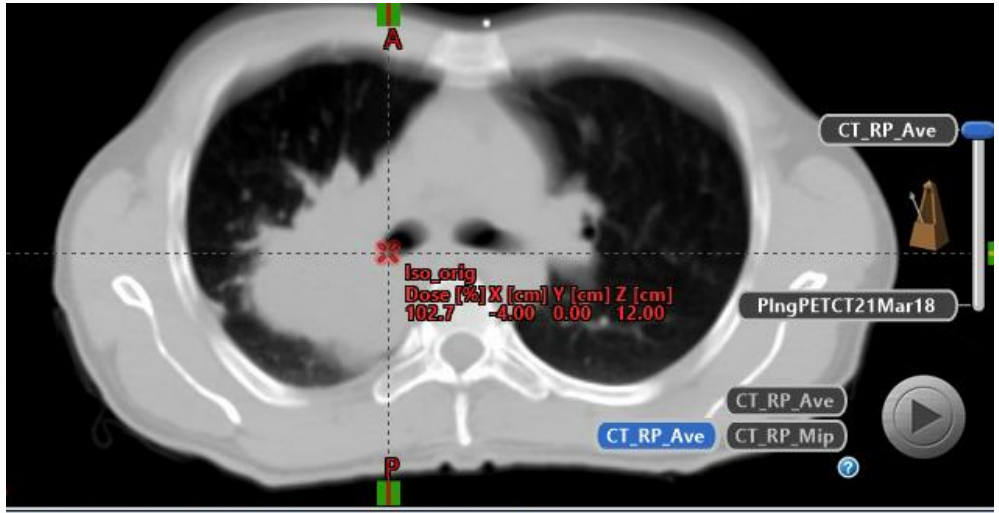
ASSESS ONLINE IMAGING WITH RESPECT TO PLAN

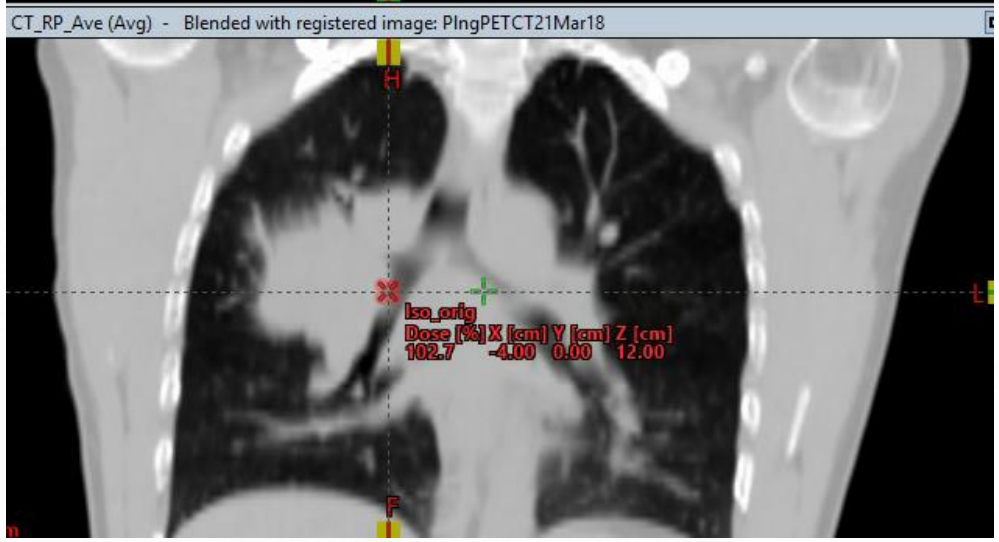
Perform rigid registration based on how you would be setting the patient up every day

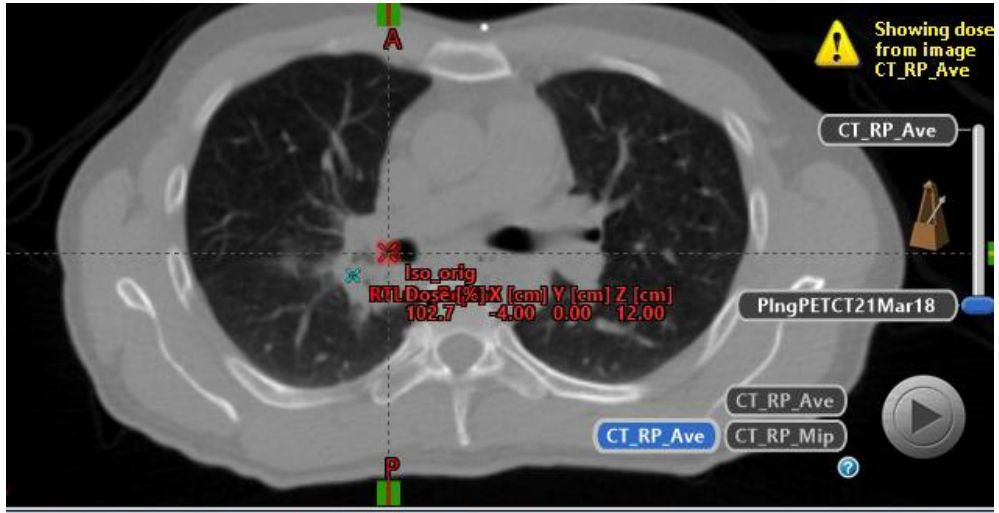


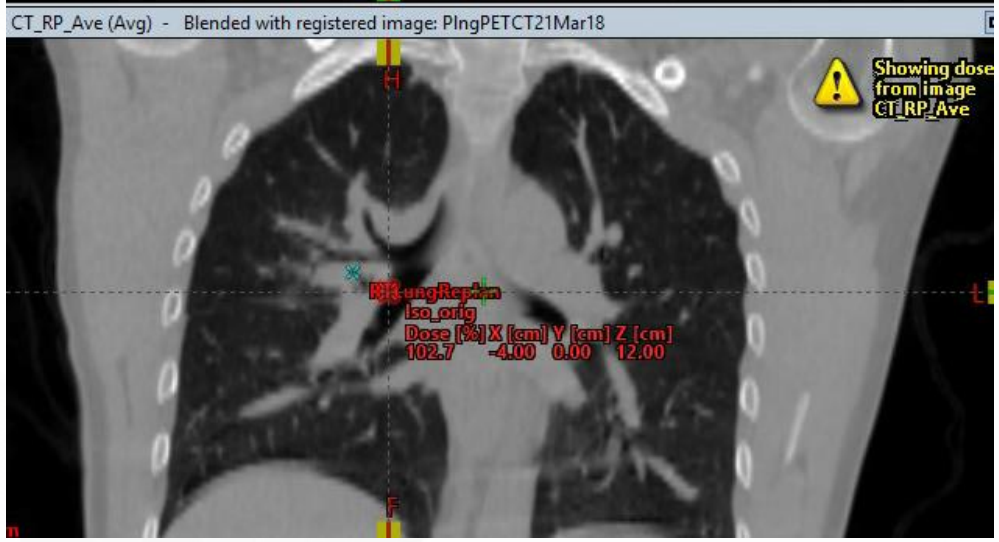
COPY PLAN TO NEW IMAGE

Make sure isocentre is where it would be at treatment delivery









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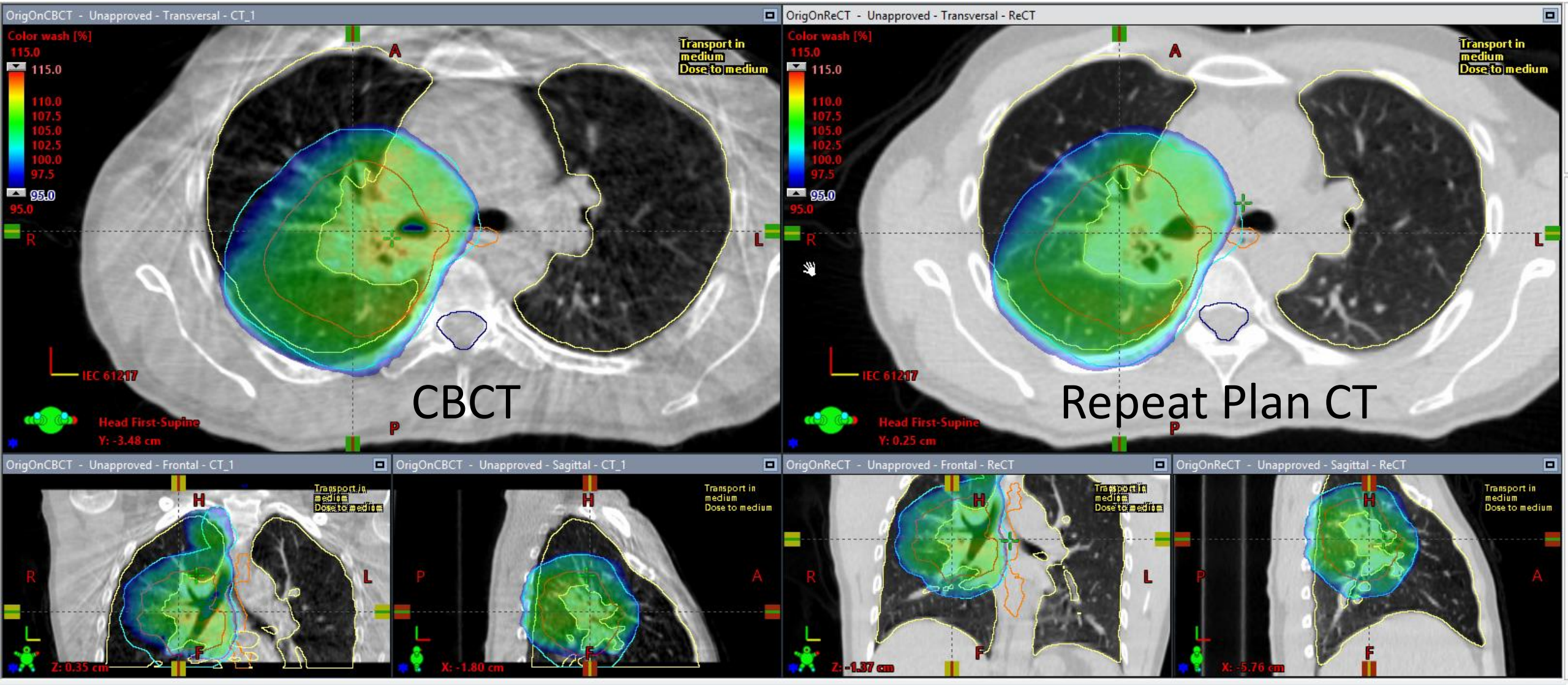
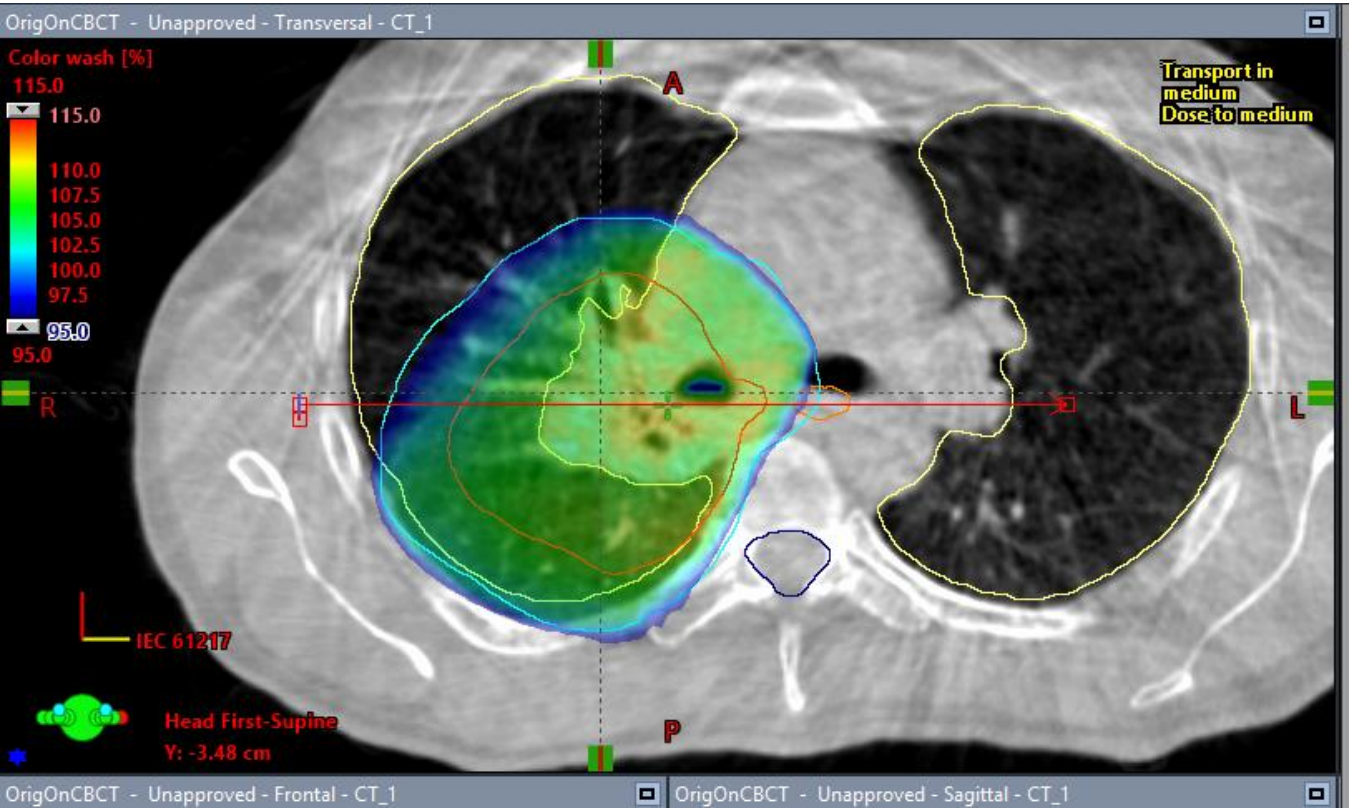
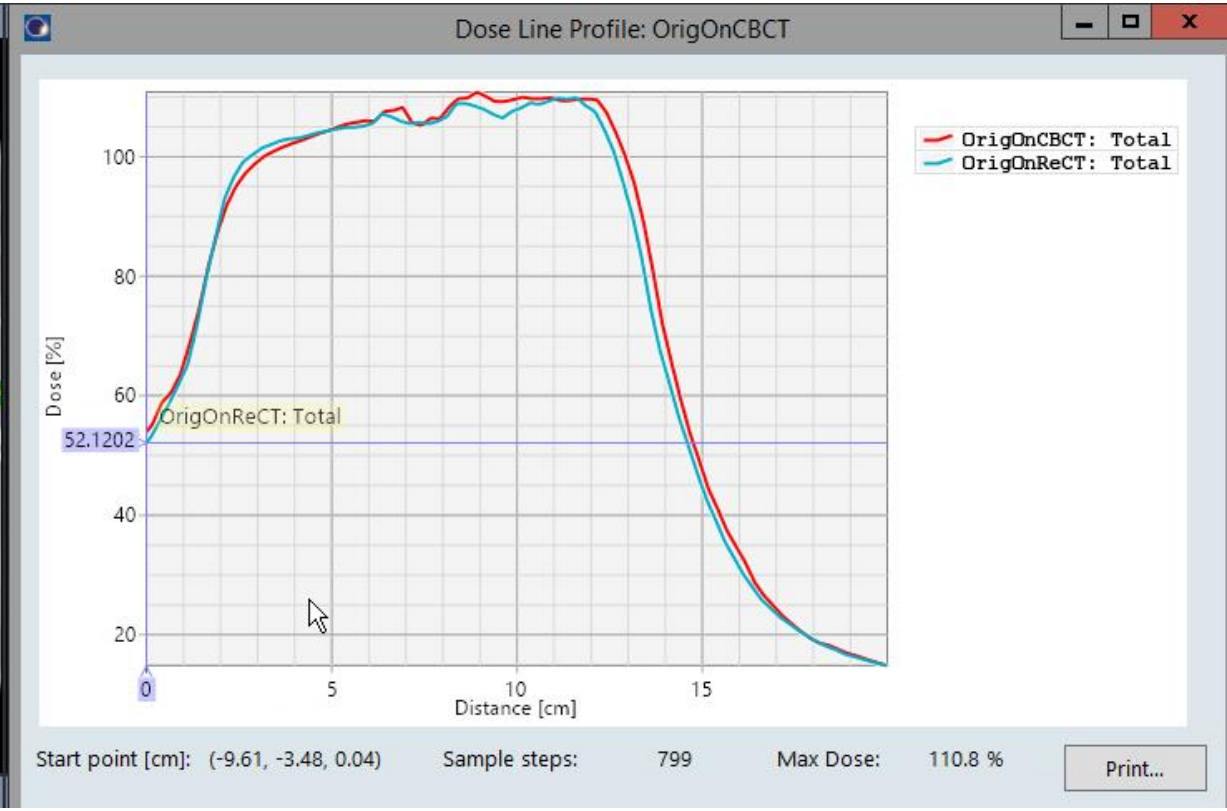
CALCULATE ON CBCT



CALCULATE ON CBCT

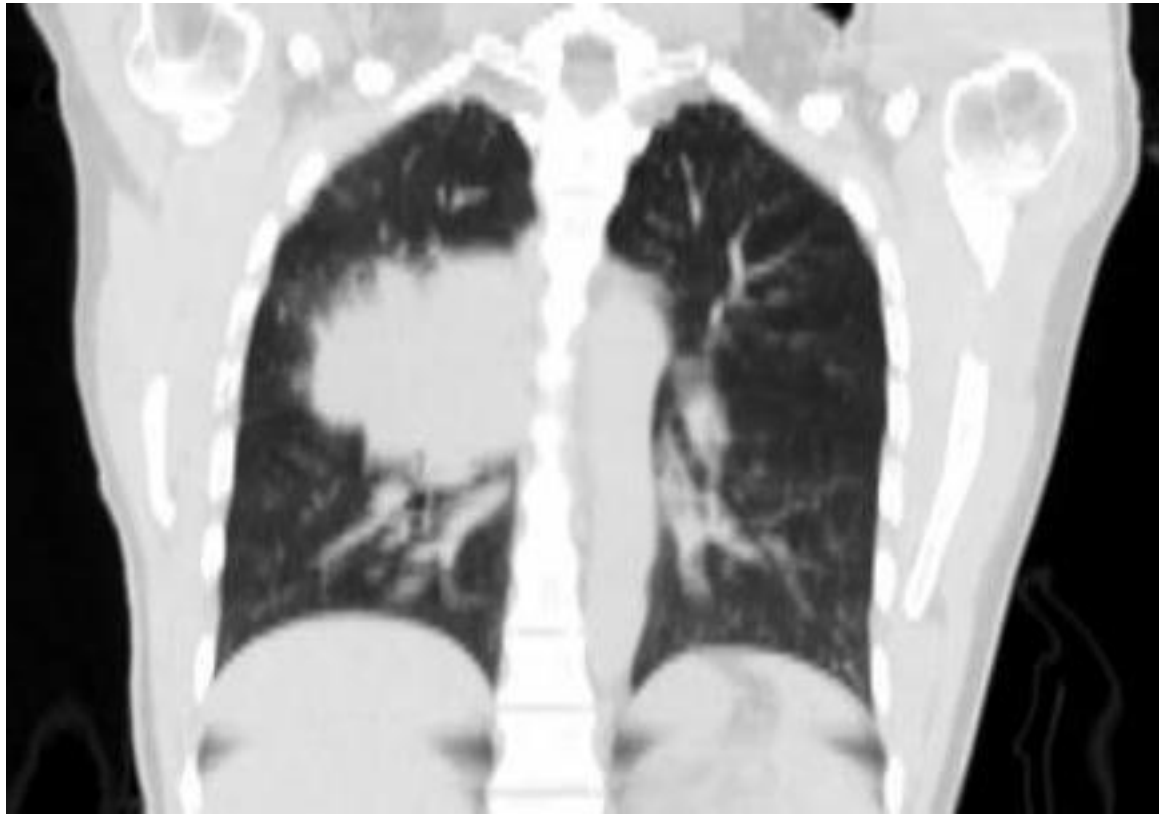




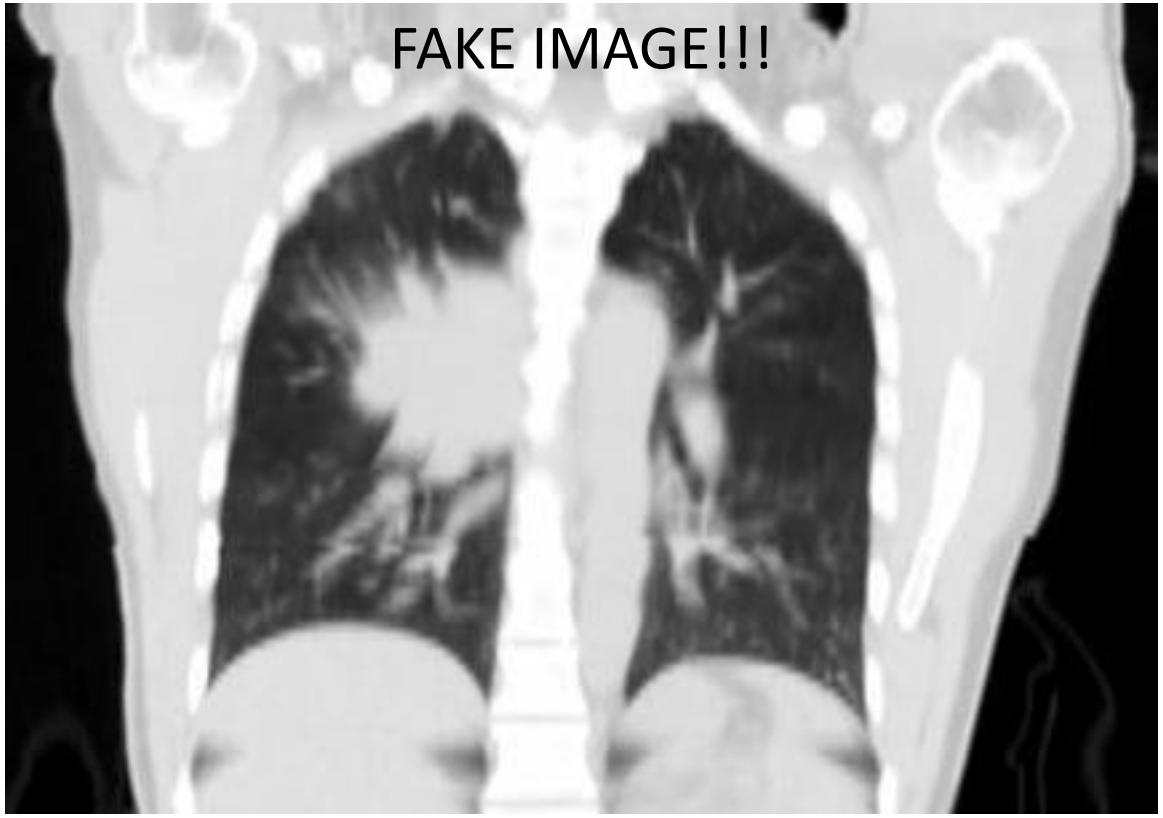
Probably a reasonable approximation, but beware of heterogeneities (esp. bone) and field of view limitations

SYNTHETIC CT

Deform planning CT to CBCT = Synthetic CT



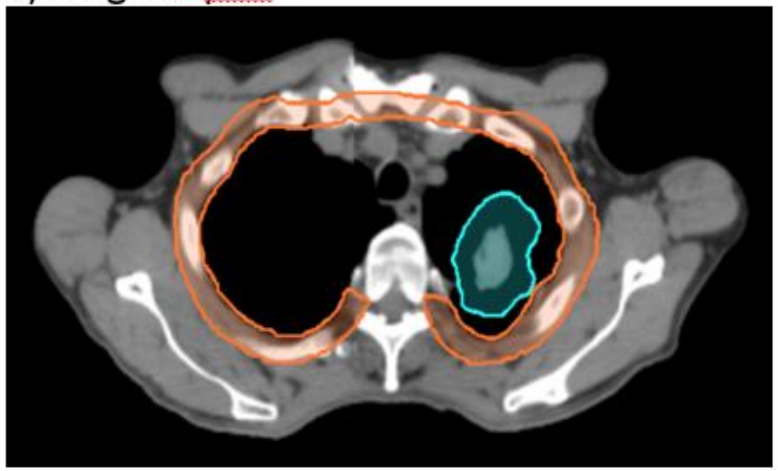
Planning CT fused with CBCT



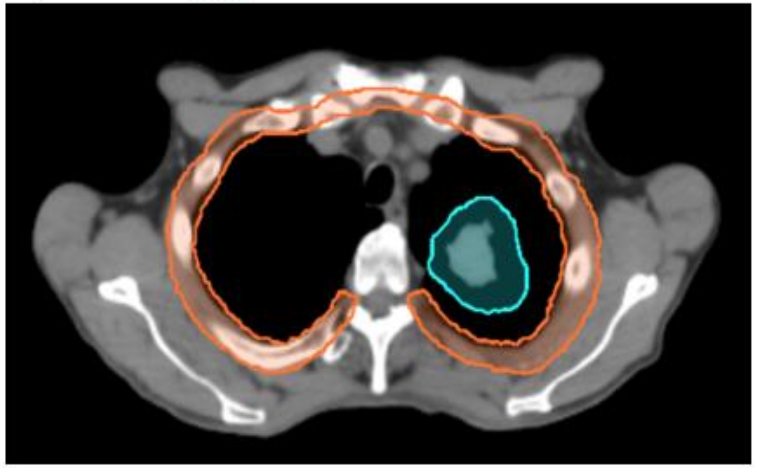
Planning CT warped to CBCT, with slices above and below CBCT range from planning CT

SYNTHETIC CT

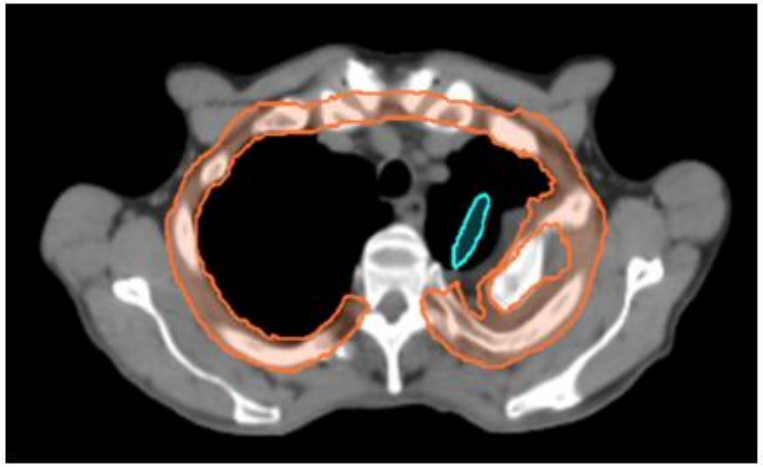
a) Original pCT



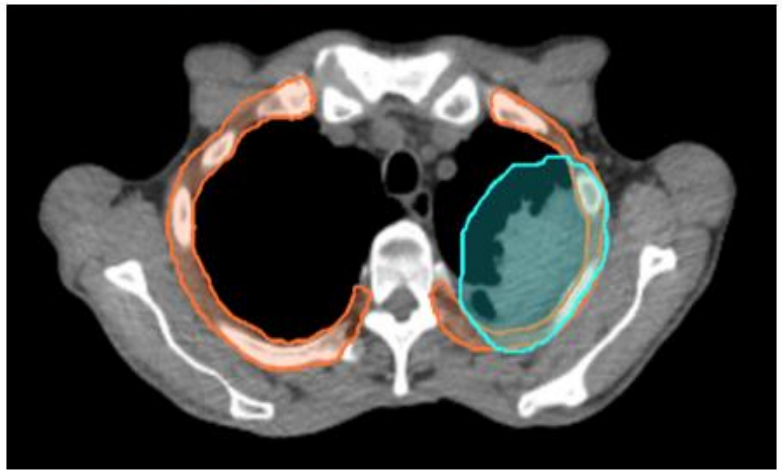
c) CDMP sCT



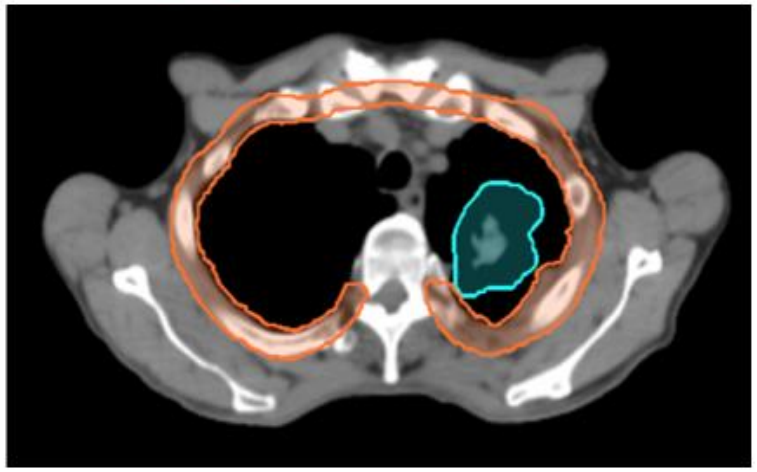
e) EDMP sCT



b) Replan pCT



d) DMP sCT



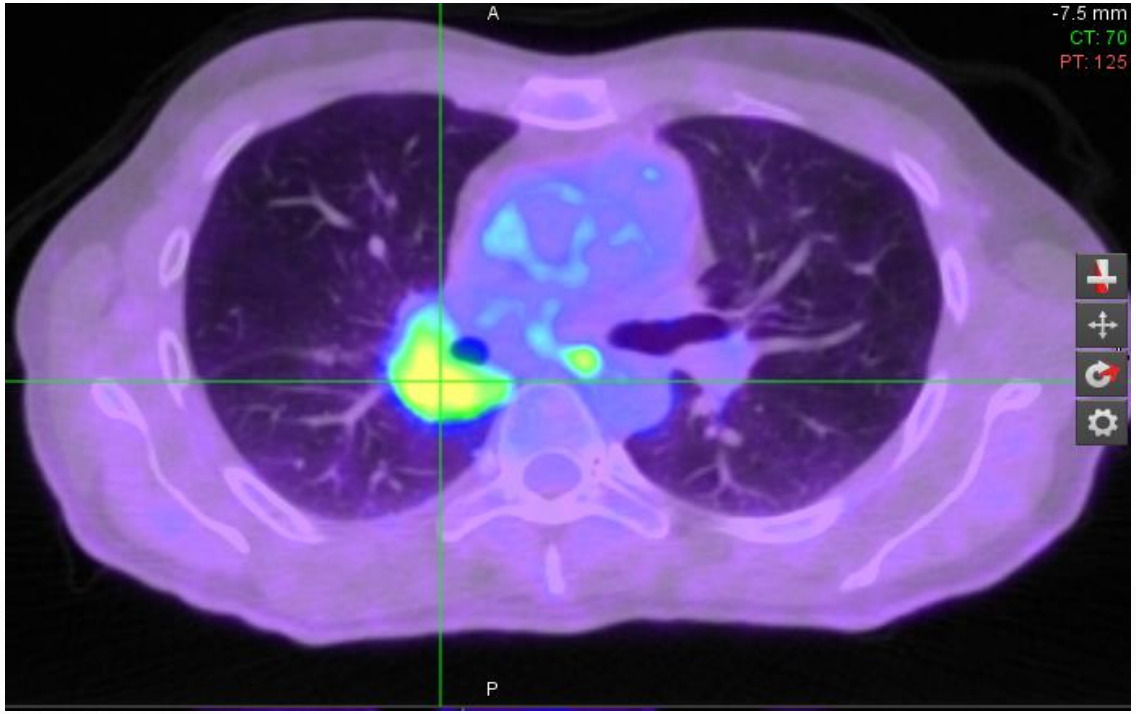
Courtesy of Caitlin Allen

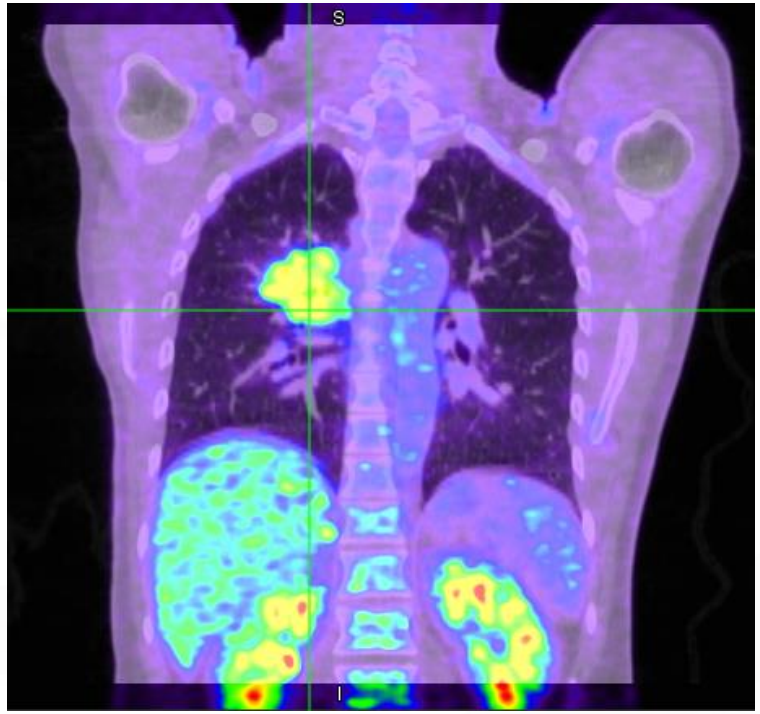
Synthetic CT may have significant anatomical inaccuracies

Should only be used for dose calculation, not contouring / visualisation of structures

NEW SIMULATION PET-CT

Repeat simulation PET/CT at fraction 18 showed metabolic tumour response





Decision was made to adapt plan, including the target volume

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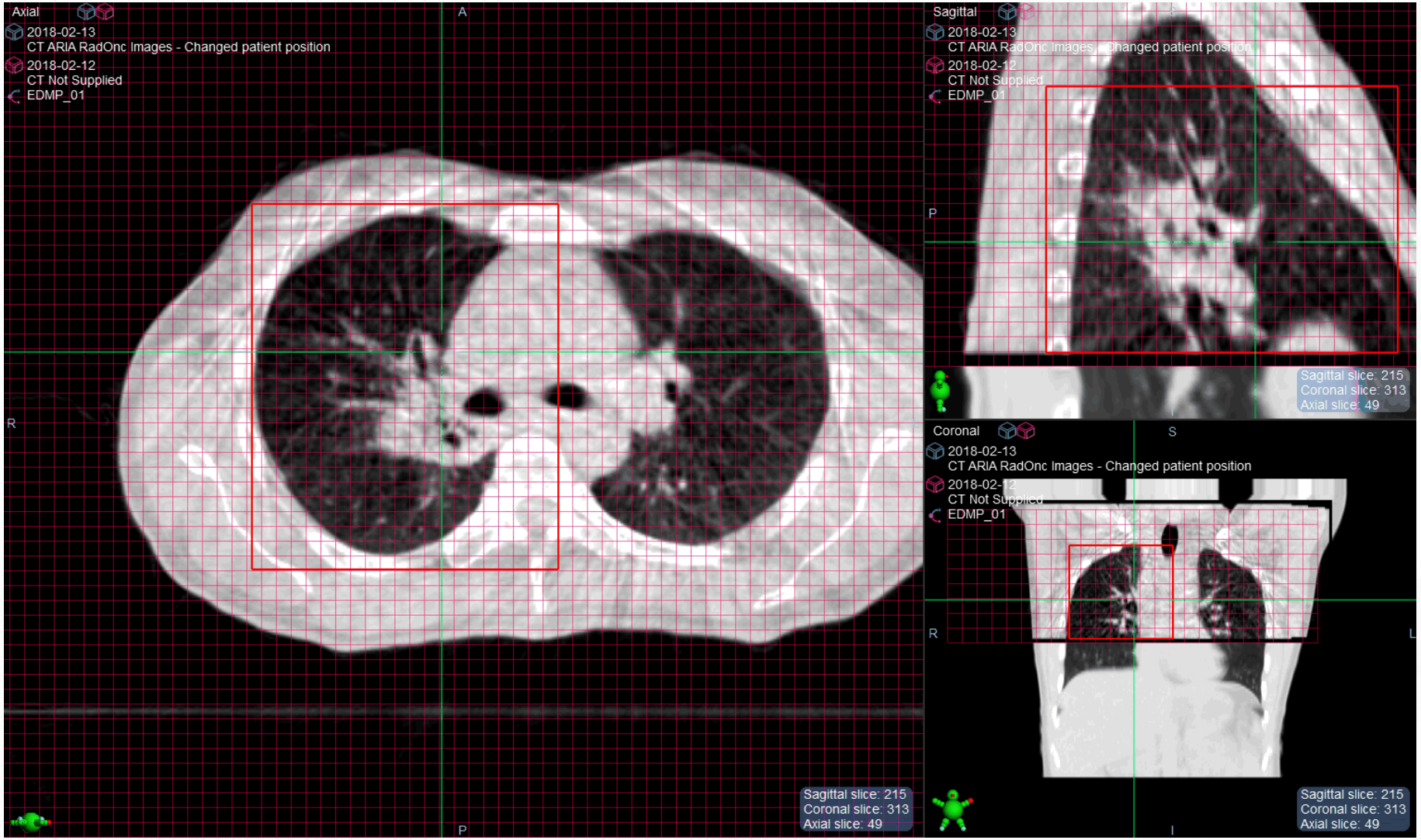
INITIAL DIR (B-SPLINES ALGORITHM))



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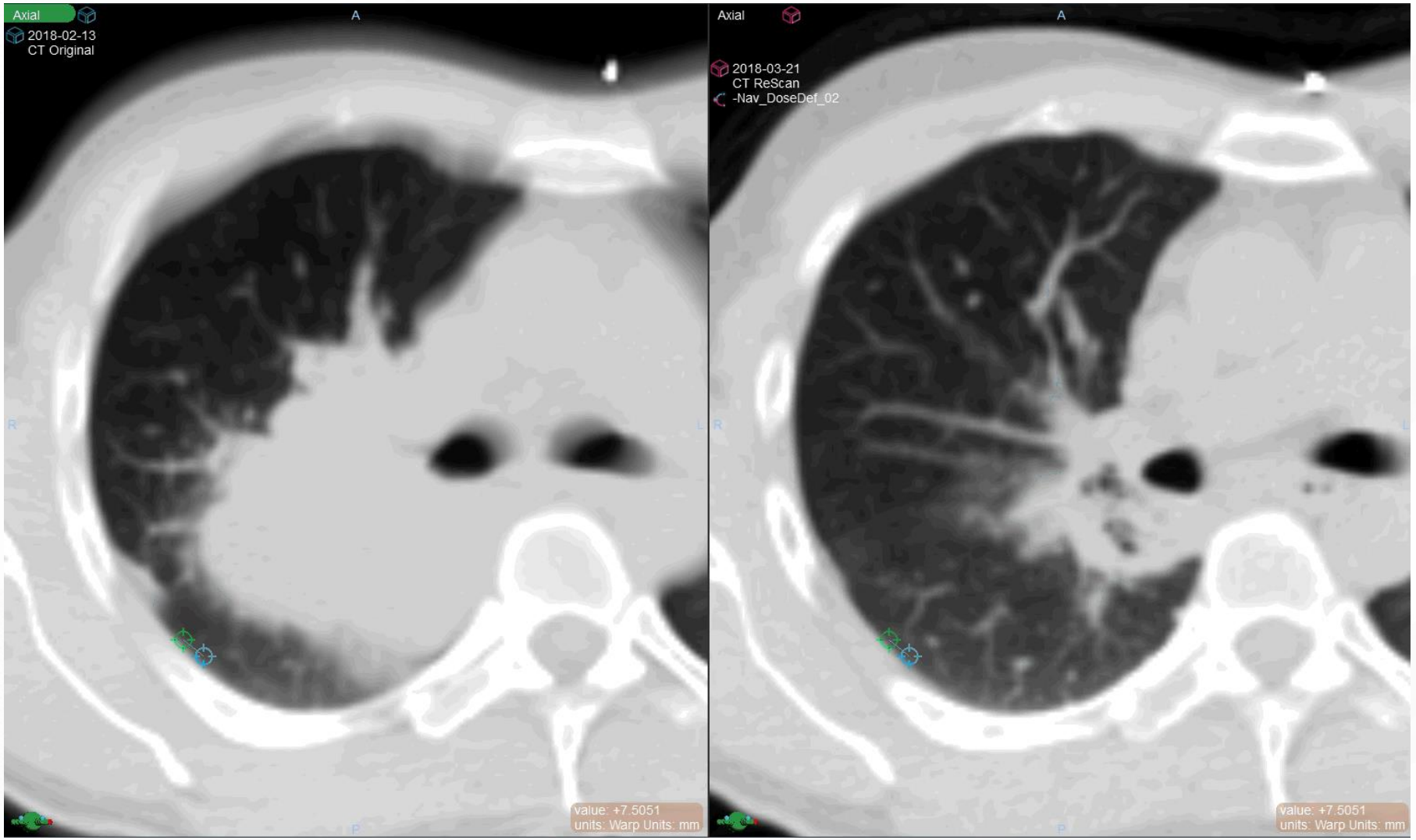
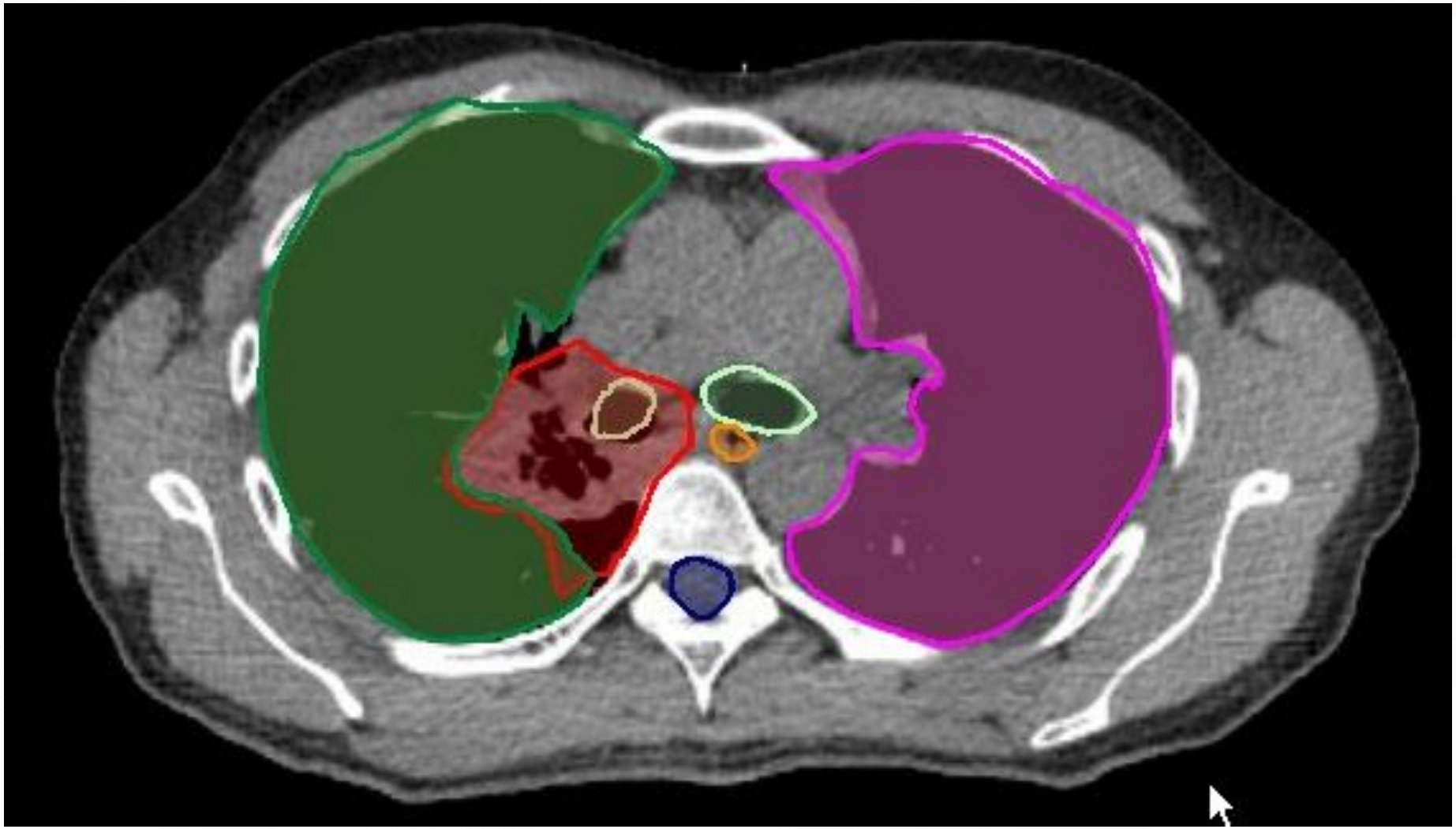
INITIAL DIR (B-SPLINES ALGORITHM))



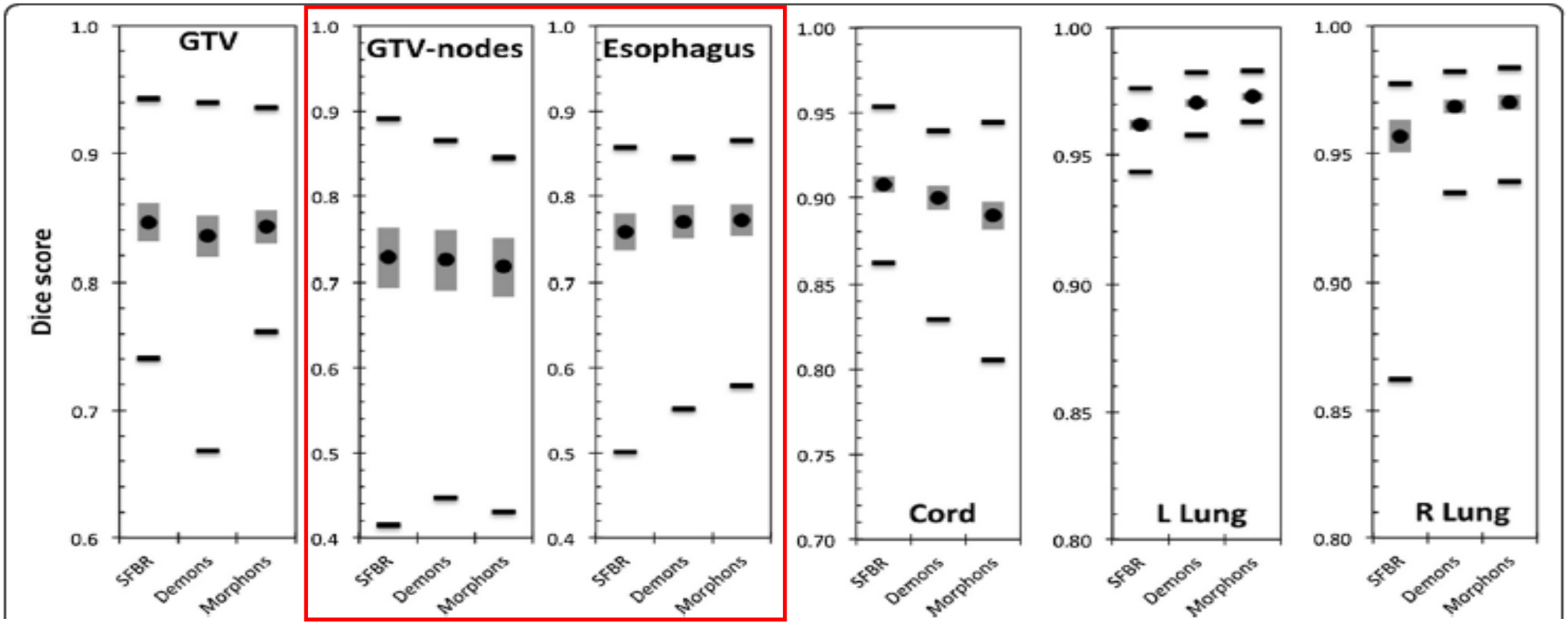
Green point (location in primary) | Blue point (where the green point maps to + out of plane)

CONTOUR PROPAGATION WITH DIR

Apply deformation map to initial planning contours to get them onto the new CT



ACCURACY OF DIR PROPAGATED CONTOURS IN LUNG



*note the different vertical scales

Poor scores where there is poor contrast

Hardcastle N et. al. Rad. Oncol. 2013 8:243

ACCURACY OF DIR PROPAGATED CONTOURS IN LUNG

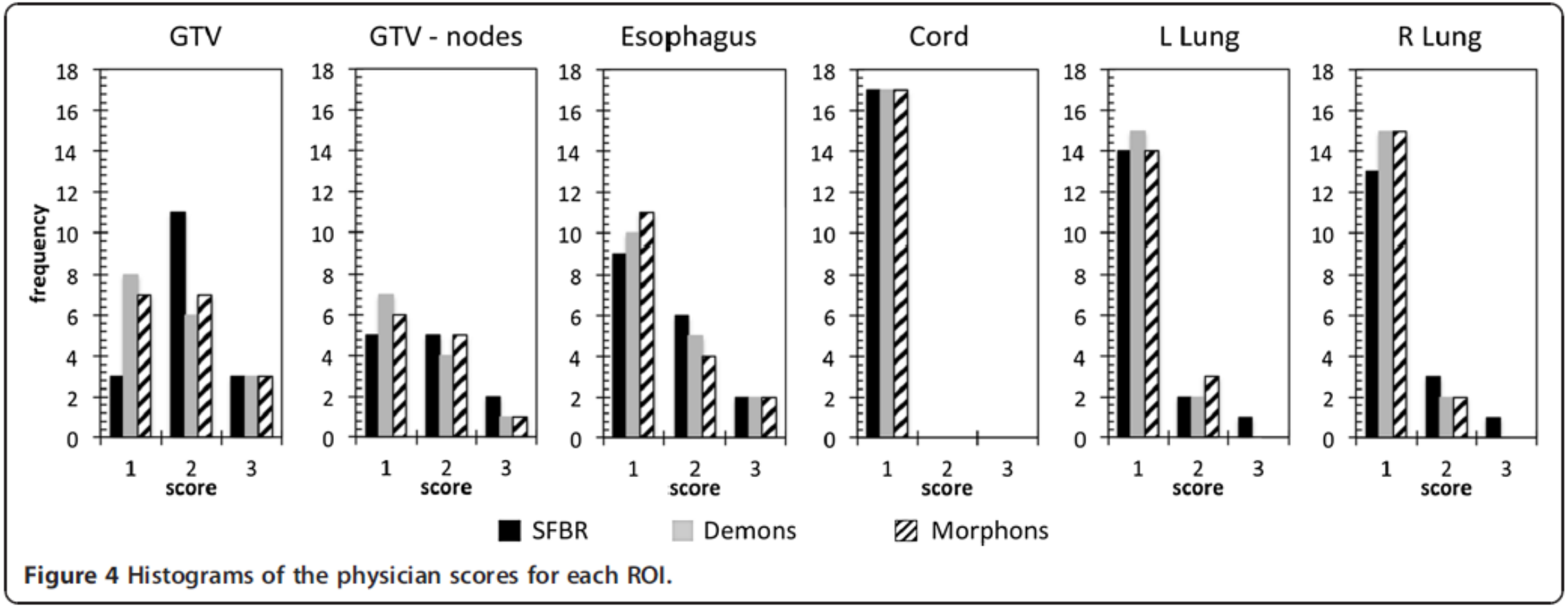


Figure 4 Histograms of the physician scores for each ROI.

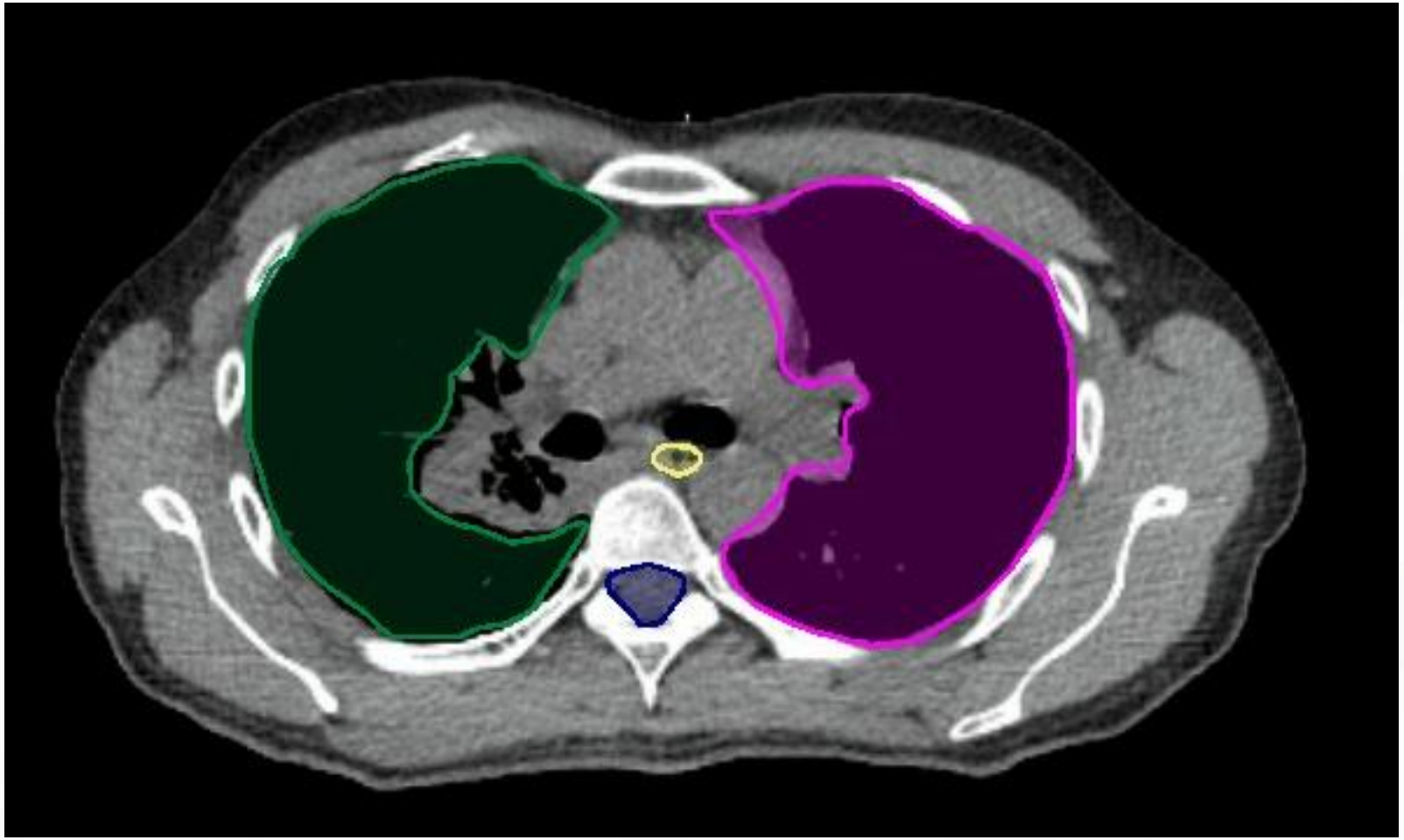
1 = clinically acceptable without modification

2 = clinically useful but required minor modification on several slices

3 = not clinically useful, more efficient to start the contouring from scratch.

CONTOUR PROPAGATION WITH DIR

Correct the deformed contours



CONTOUR PROPAGATION WITH DIR

Why do we spend time to correct the contours?

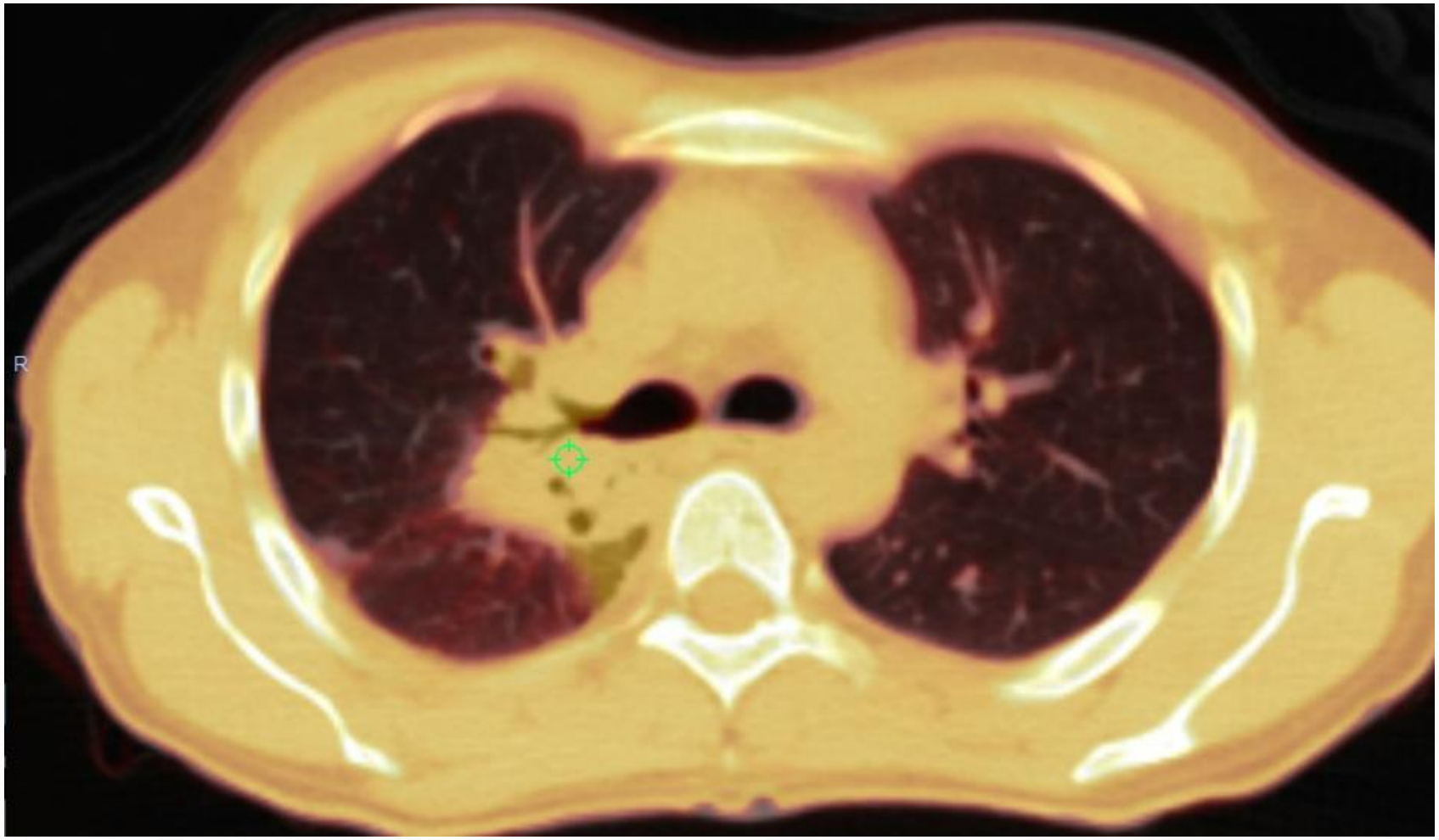
Make sure the contours were correct for treatment planning purposes

QA of the deformation (we may have future use for the deformation)

Provide a means to ‘update’ the deformation map, which again is useful for subsequent use of the deformation map

Alternative: AI segmentation

UPDATE THE DEFORMATION MAP



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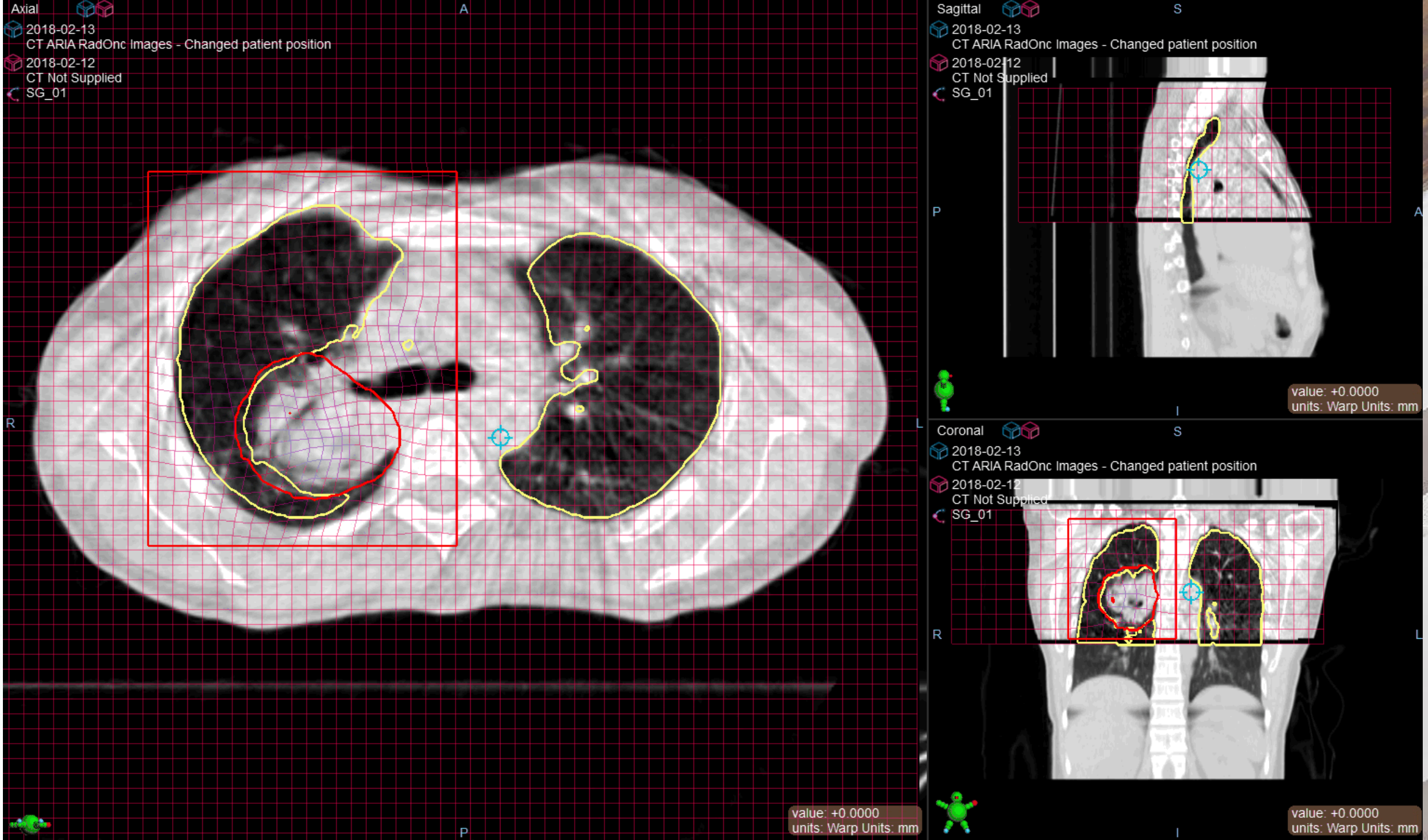
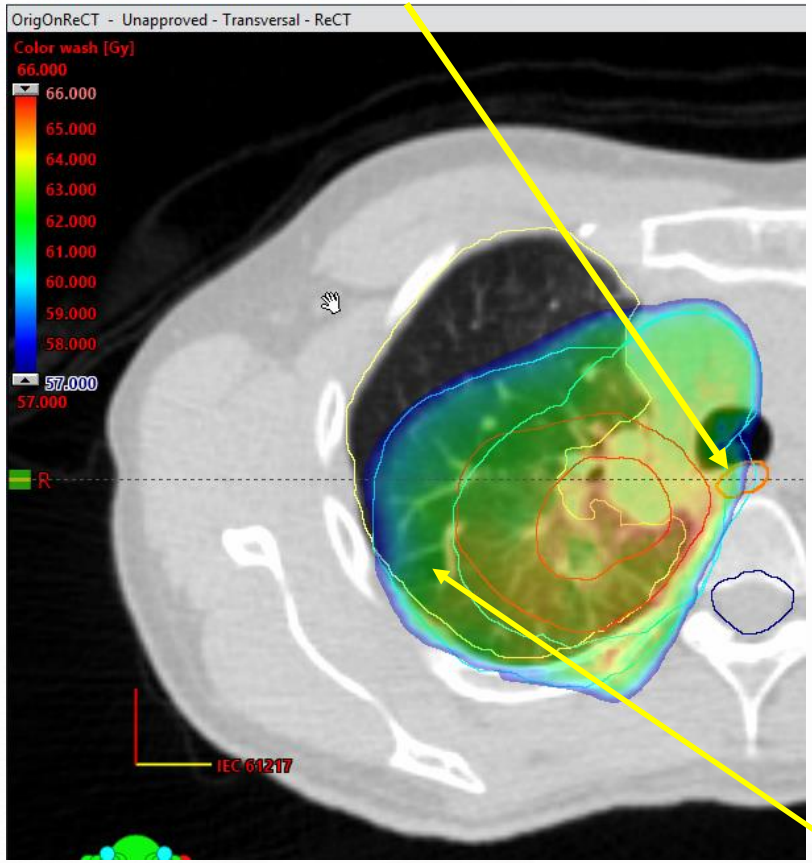
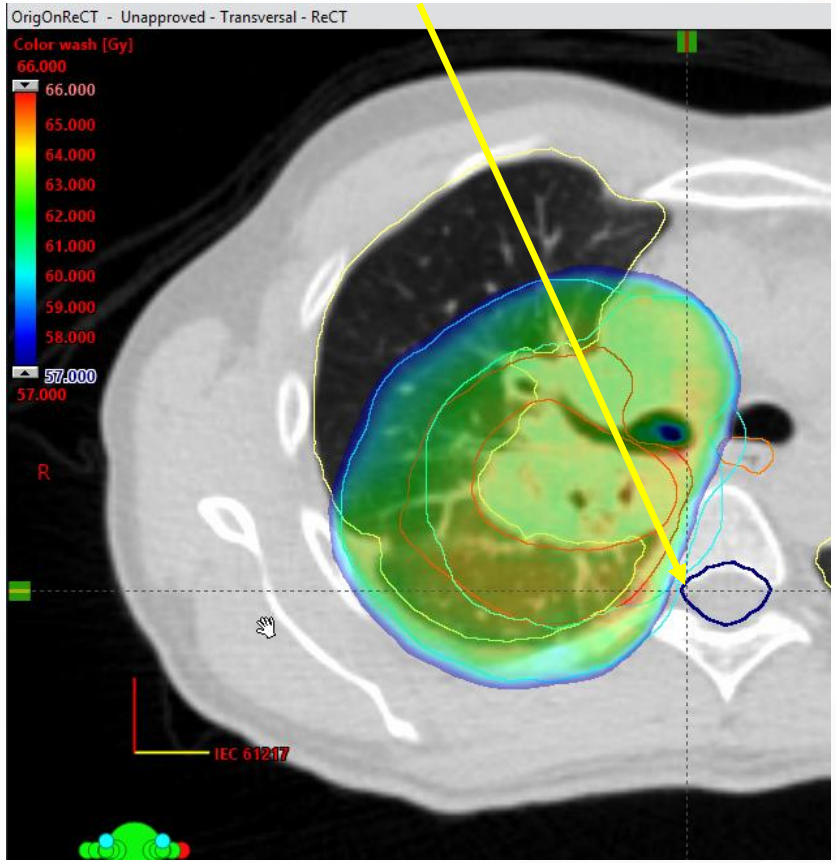

Axial
2018-02-13
CT ARIA RadOnc Images - Changed patient position
2018-02-12
CT Not Supplied
SG_01
A
R
L
P
value: +0.0000
units: Warp Units: mm
Sagittal
2018-02-13
CT ARIA RadOnc Images - Changed patient position
2018-02-12
CT Not Supplied
SG_01
S
P
A
I
value: +0.0000
units: Warp Units: mm
Coronal
2018-02-13
CT ARIA RadOnc Images - Changed patient position
2018-02-12
CT Not Supplied
SG_01
S
R
L
I
value: +0.0000
units: Warp Units: mm

CALCULATE ORIGINAL PLAN ON NEW IMAGE

Oesophagus near max exceeded



Spinal cord near max exceeded



Lung dose unnecessarily high (assuming this is lung and not tumour)

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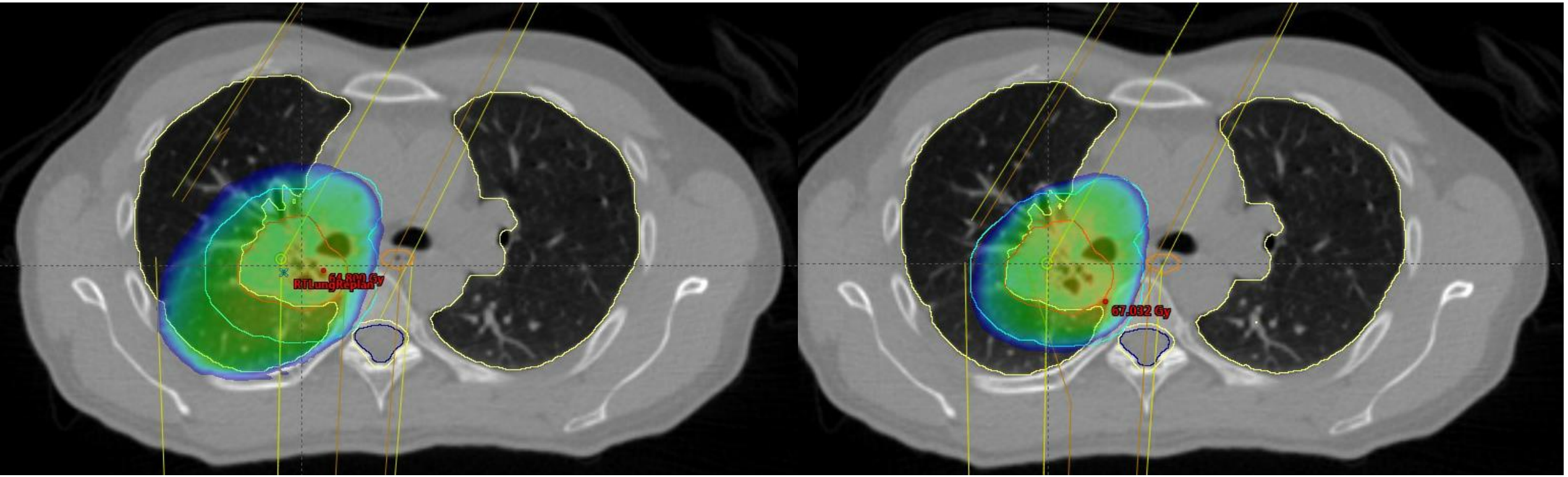
RE-PLAN/RE-OPTIMISE

Original plan on new anatomy → Re-optimised plan on new anatomy



New target volume covered, OAR doses reduced

DOSE WARPING – WHY?

We have dose calculated on the original planning image

We have dose calculated on the new planning image

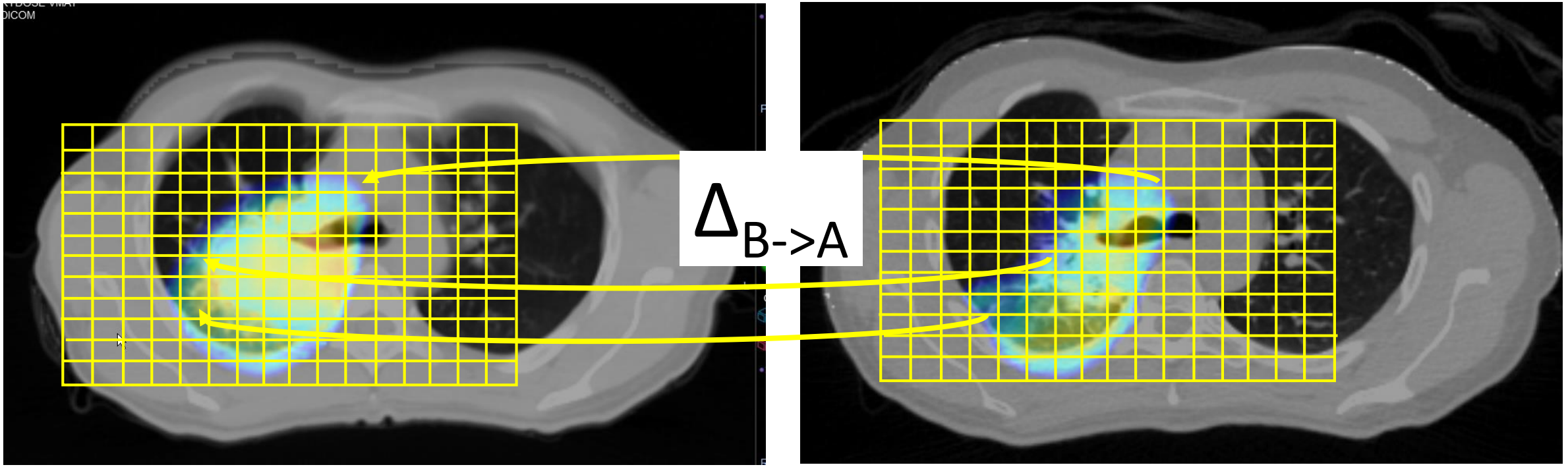
We want to estimate how much dose each OAR and the target gets

On the new planning image, we need to then sum the dose already delivered to each location in the image, with the dose that we plan on delivering from here on

DOSE WARPING WITH DIR

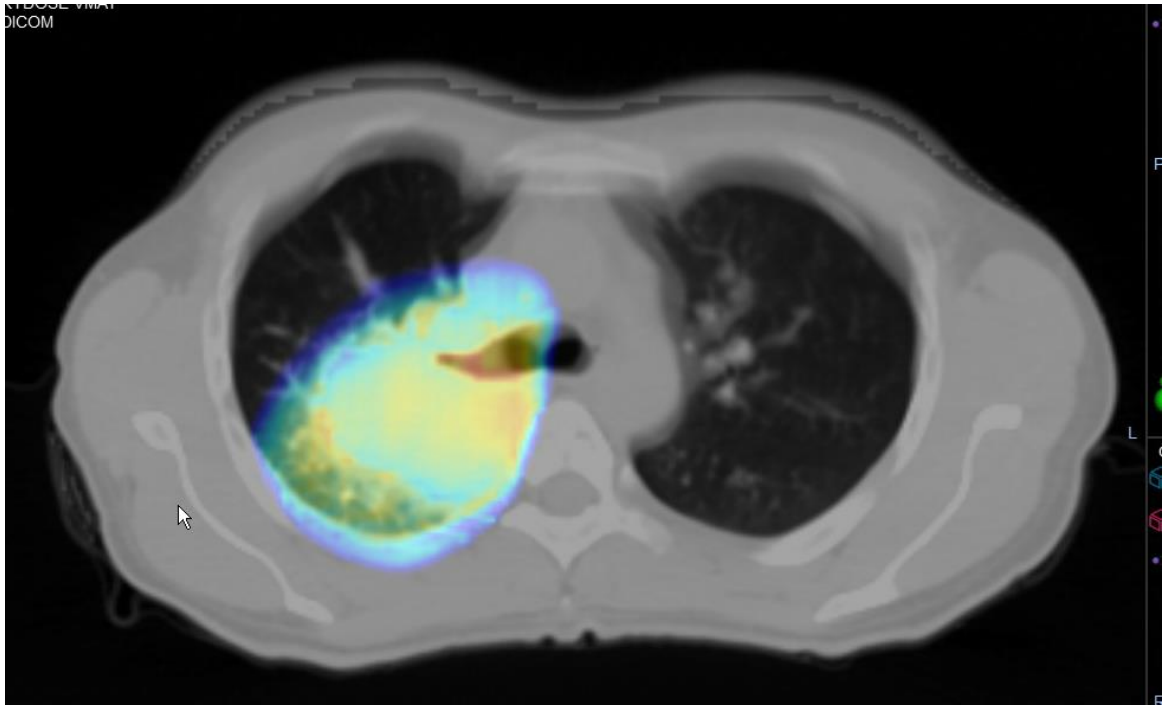
Original plan on original planning scan

Original dose warped to new planning scan

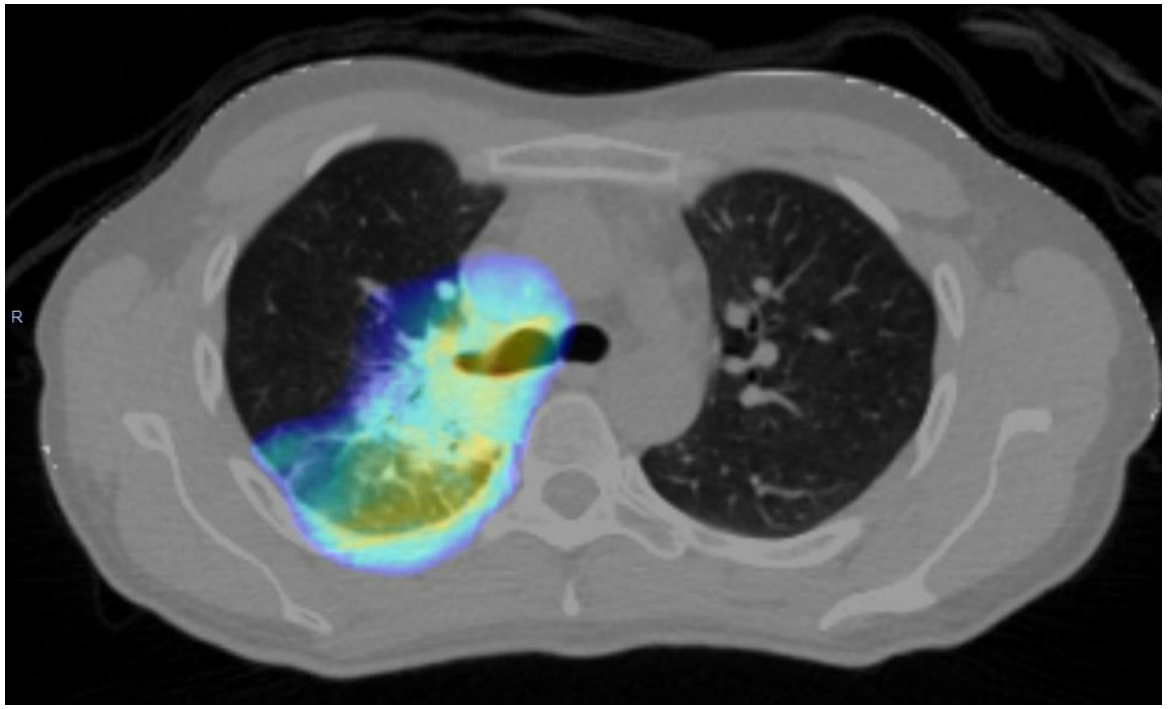


DOSE WARPING WITH DIR

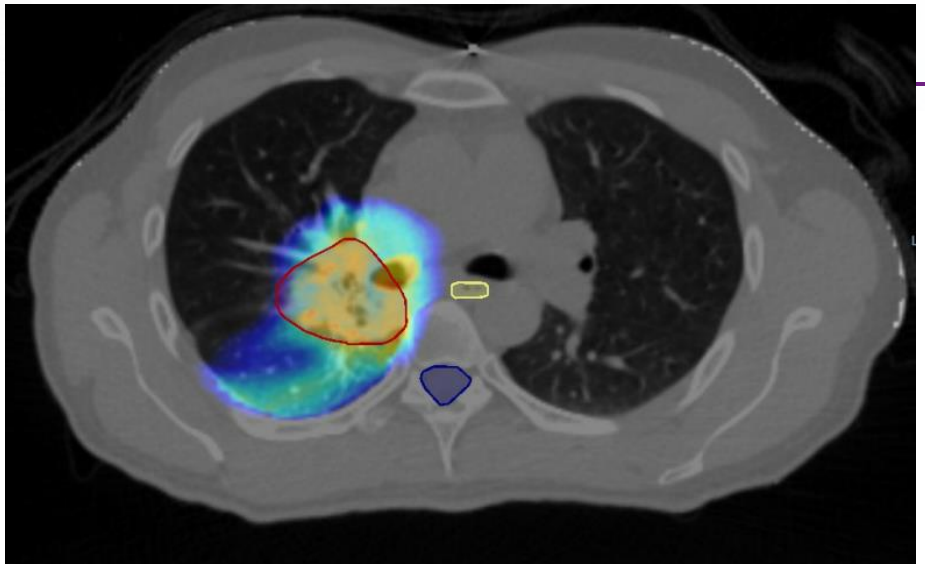
Original plan on original planning scan



Original dose warped to new planning scan



Original dose warped to new scan (this is what dose the current anatomy has already received)



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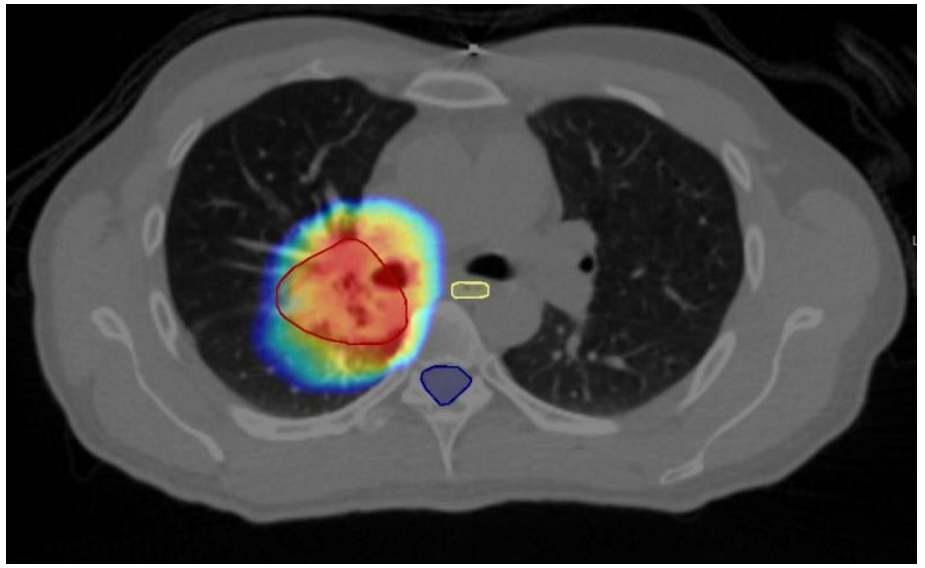
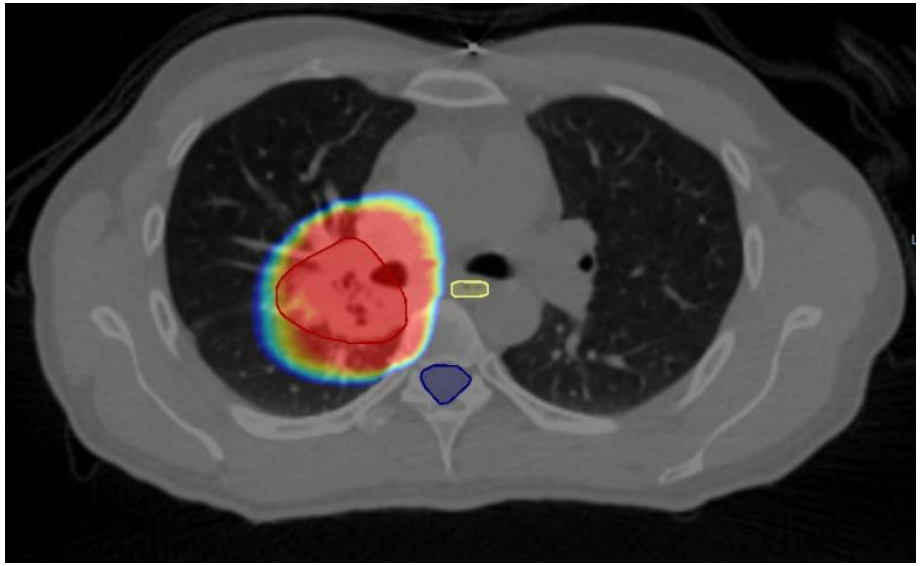
Accumulated dose on new scan



Re-plan dose on new scan (this is what dose the current anatomy will receive)



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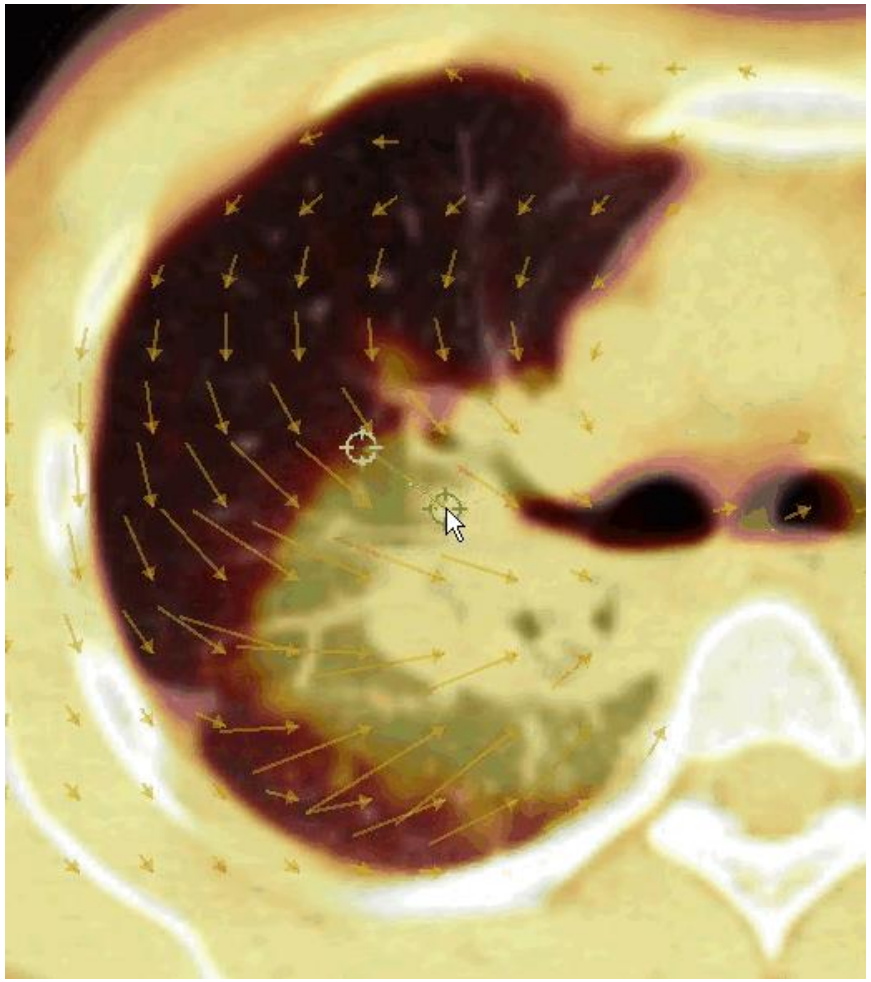
Approximations and assumptions!

VALIDATION

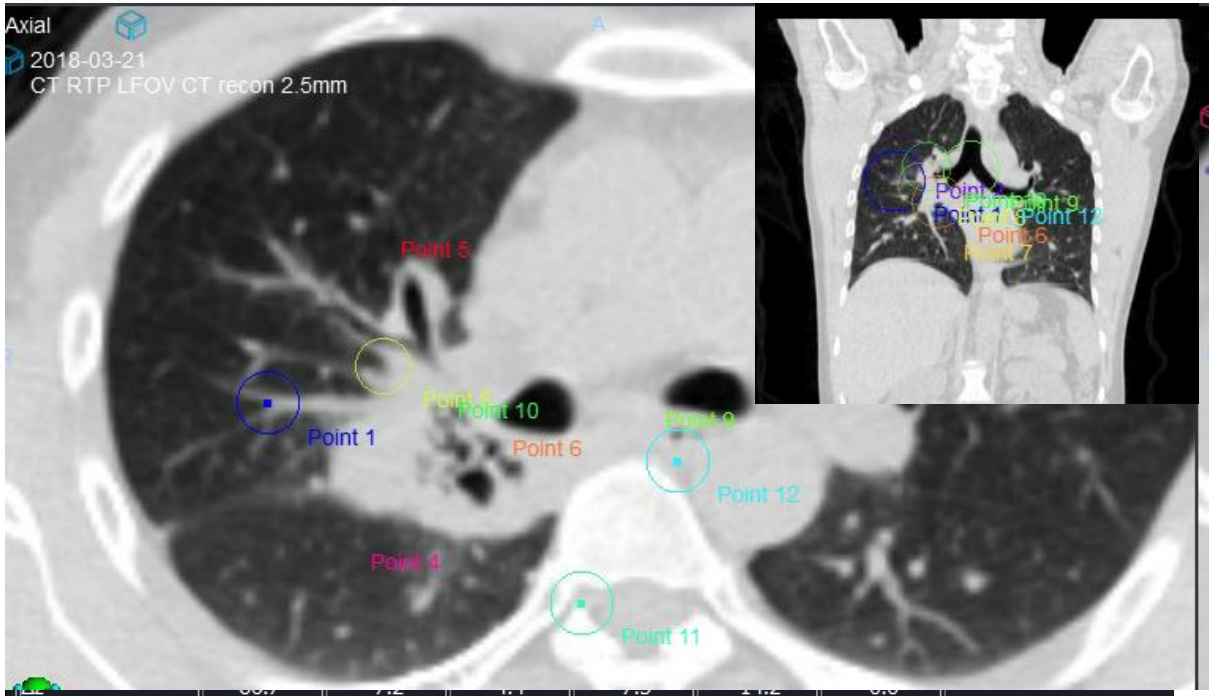
Three validation techniques are shown:

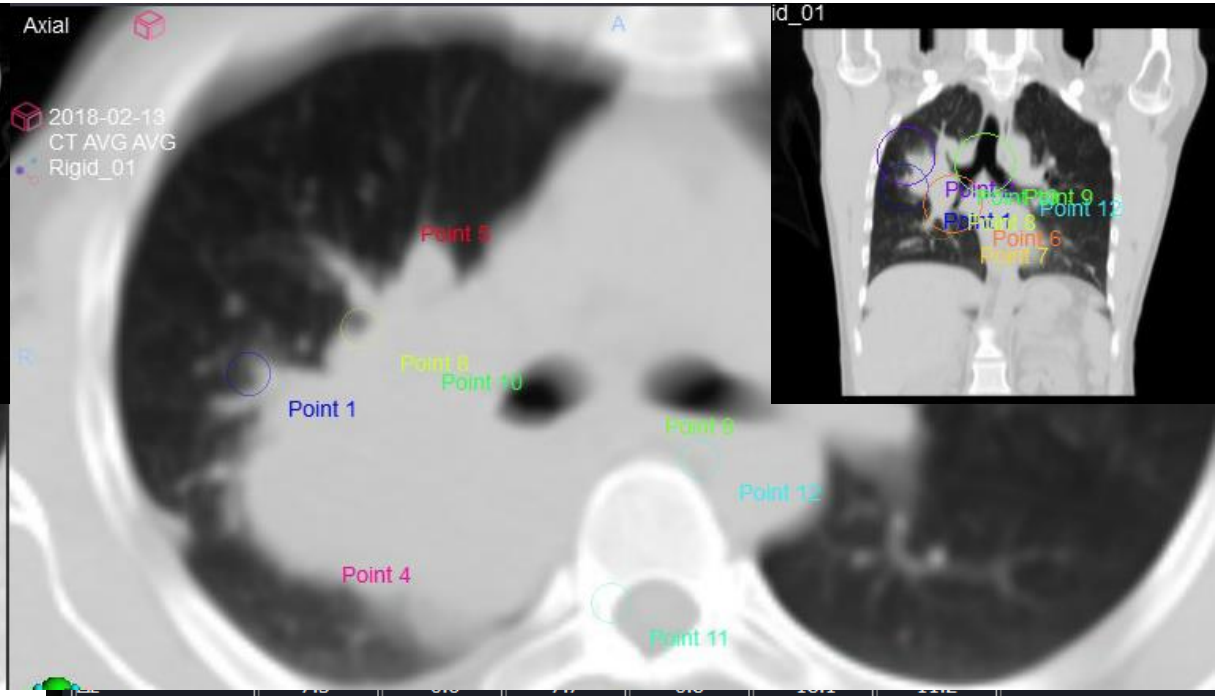
- Image fusion with different colour maps
- Vector maps
- Correlated pointer

The validation should be performed at the regions you are most interested/concerned with



VALIDATION: TARGET REGISTRATION ERROR (TRE)





Point Detailed Statistics

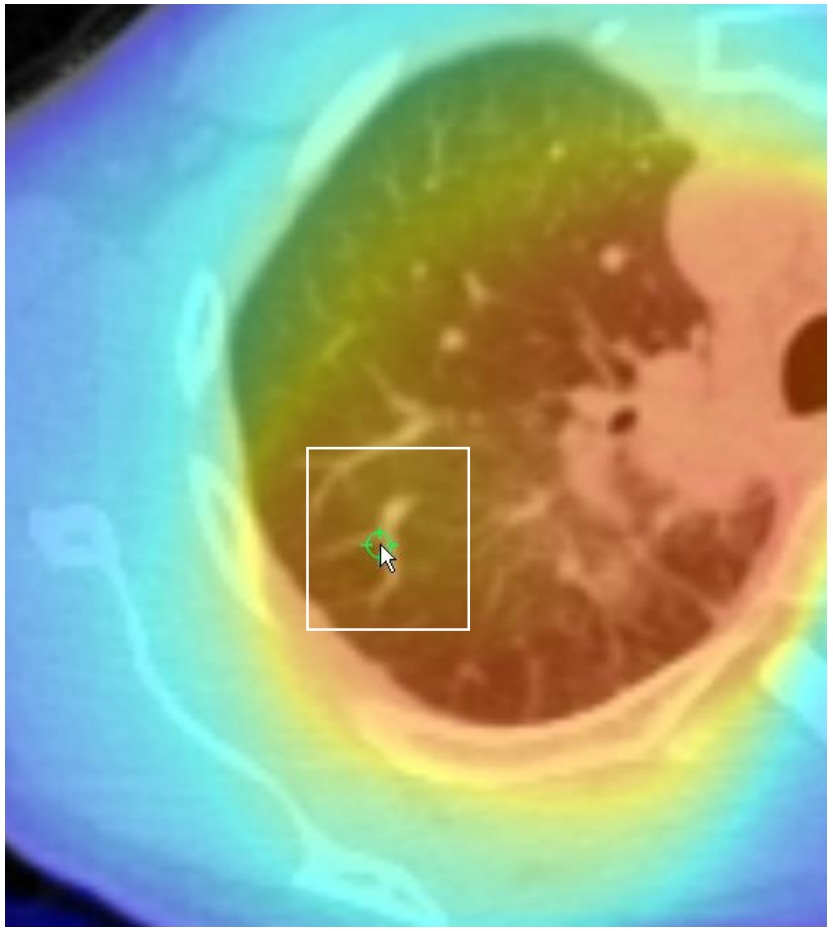
Point Name	Δx (mm)	Δy (mm)	Δz (mm)	|Δx| (mm)	|Δy| (mm)	|Δz| (mm)	(Δx)² (mm)	(Δy)² (mm)	(Δz)² (mm)	√(Δx²+Δy²+Δz²) (mm)
Point 1	8.4	-6.0	-14.2	8.4	6.0	14.2	70.0	36.3	202.9	17.6
Point 2	8.4	-4.7	-7.5	8.4	4.7	7.5	70.0	21.9	56.3	12.2
Point 3	9.0	-3.3	-7.5	9.0	3.3	7.5	81.6	11.2	56.3	12.2
Point 4	10.7	2.3	-7.5	10.7	2.3	7.5	114.6	5.5	56.3	13.3
Point 5	-0.3	-3.7	-10.0	0.3	3.7	10.0	0.1	13.5	100.0	10.7
Point 6	3.7	-2.0	-10.0	3.7	2.0	10.0	13.5	4.0	100.0	10.8
Point 7	1.7	-1.7	-10.0	1.7	1.7	10.0	2.8	2.8	100.0	10.3
Point 8	9.0	-8.0	-12.5	9.0	8.0	12.5	81.6	64.5	156.2	17.4
Point 9	4.3	1.3	-2.5	4.3	1.3	2.5	18.9	1.8	6.2	5.2
Point 10	7.7	-5.7	-5.0	7.7	5.7	5.0	59.2	32.3	25.0	10.8
Point 11	-2.0	0.0	-0.0	2.0	0.0	0.0	4.0	0.0	0.0	2.0
Point 12	-0.3	-0.3	-0.0	0.3	0.3	0.0	0.1	0.1	0.0	0.5

Point Detailed Statistics

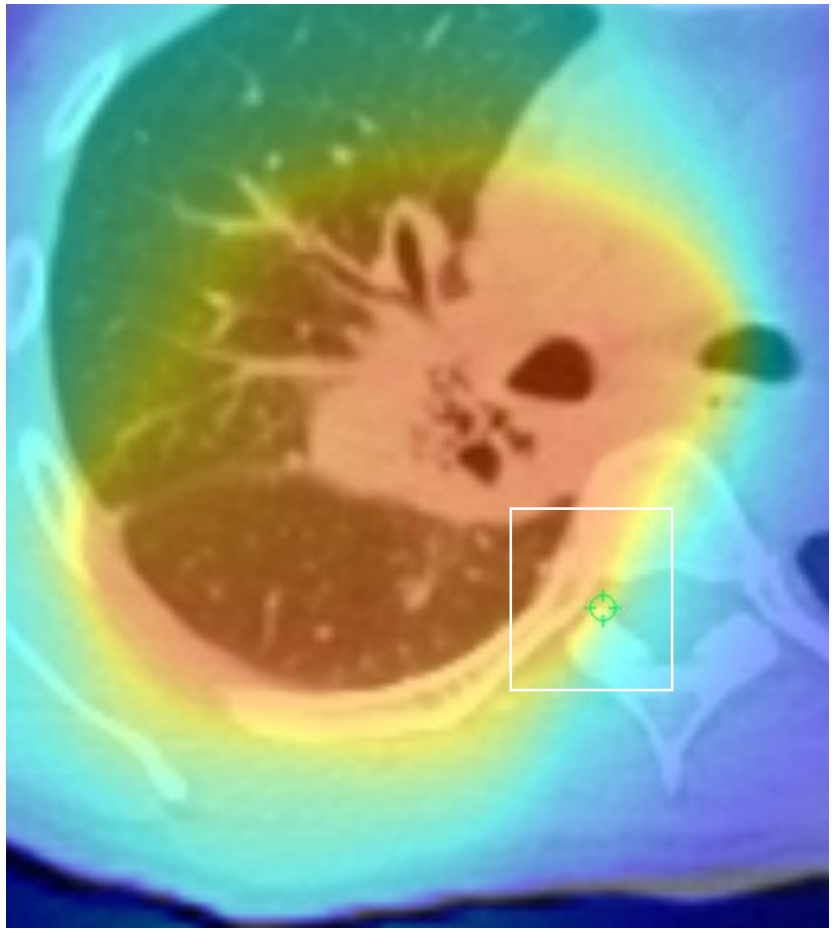
Point Name	Δx (mm)	Δy (mm)	Δz (mm)	|Δx| (mm)	|Δy| (mm)	|Δz| (mm)	(Δx)² (mm)	(Δy)² (mm)	(Δz)² (mm)	√(Δx²+Δy²+Δz²) (mm)
Point 1	-7.5	4.4	1.0	7.5	4.4	1.0	56.6	18.9	0.9	8.7
Point 2	-9.5	3.8	-13.1	9.5	3.8	13.1	90.4	14.7	171.9	16.6
Point 3	-6.6	1.1	-18.1	6.6	1.1	18.1	43.8	1.3	328.4	19.3
Point 4	-8.6	-3.7	11.2	8.6	3.7	11.2	73.8	13.8	126.0	14.6
Point 5	0.1	1.5	1.8	0.1	1.5	1.8	0.0	2.3	3.1	2.3
Point 6	-4.0	0.9	6.6	4.0	0.9	6.6	15.7	0.9	43.5	7.8
Point 7	3.6	0.3	5.0	3.6	0.3	5.0	13.3	0.1	25.1	6.2
Point 8	-1.2	0.1	0.2	1.2	0.1	0.2	1.3	0.0	0.0	1.2
Point 9	0.8	1.5	0.7	0.8	1.5	0.7	0.7	2.2	0.4	1.8
Point 10	-4.0	2.2	-2.5	4.0	2.2	2.5	15.8	4.9	6.3	5.2
Point 11	2.7	0.8	2.1	2.7	0.8	2.1	7.0	0.7	5.6	3.7
Point 12	-2.8	0.2	2.4	2.8	0.2	2.4	7.8	0.0	5.8	3.7

VALIDATION: DOSE AT EACH POINT

Point 3: Vessel



Bone



At a given anatomical location in the source image, record the dose and compare with the warped dose at the corresponding anatomical location in the fixed image

	Dose (Gy)		
Location	Source	Warped	% Diff
Point 1 Vessel	57.86	55.59	-3.9%
Point 2 Vessel	59.20	55.71	-5.9%
Point 3 Vessel	60.76	56.17	-7.6%
Carina	60.18	59.63	-0.9%
Bone	48.81	49.05	0.5%

SUMMARY

- There is room for improvement in radiotherapy in lung cancer
- We need to improve local control, and reduce side effects
- There are anatomical changes due to atelectasis, pleural effusion, tumour response and tumour movement
- Biological changes may also occur during treatment
- Adaptive radiotherapy strategies have been tested to account for anatomical and biological changes, with definitive results pending

- Image registration is a fundamental tool in assessment of the need for adaptive radiotherapy
- Image registration can be used to perform tasks in adapting a plan, including contour propagation, image warping and dose accumulation
- There are substantial limitations of many existing DIR algorithms when handling large anatomical changes

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The ACPSEM Medical Image Registration Special Interest Group (MIRSIG) Online Webinars

Questions and Answers from the December 2020 Webinar Chaired by Johnson Yuen (Talk 1 by Nicholas Hardcastle)

Question 1: When there are many consecutive CBCTs… have you performed DIR day by day to see if combination of this provides more reasonable results (than DIR of plan CT to each CBCT)

Answers:
We haven't done this as yet, mainly due to the amount of time required. I think this would be an appropriate approach for two reasons. The first is that gradual anatomical changes are more accurately handled by DIR algorithms, so this may improve the DIR accuracy compared with DIR for a large anatomical change. The second benefit is that we then fill in the blanks between different time-points, allowing more accurate assessment of delivered dose to date. More deformations does equal more QA though!

Question 2: I like the idea of using a 'behind the hood' registration for the most accurate dose calculation, but I'm curious about how you manage the workflow challenges- and avoid the risk of using this for contouring?

Answers:
This is a challenge – currently in our system the synthetic CT is the image on which the contours, plan and dose are applied. Therefore this is what is seen when reviewing the dose. The key is that the contours need to come from a 'true' image; in this case, dose metrics should be accurate as they are calculated from the structure set and dose distribution. The qualitative dose review however should be performed while overlaying the dose over the 'true' images, not the synthetic CTs. This is a challenge depending on the different software available. The current way we manage this is by having a small, well-trained team looking at this who are aware of the limitations with synthetic CT.

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Questions and Answers from the December 2020 Webinar Chaired by Johnson Yuen (Talk 1 by Nicholas Hardcastle)

Question 3: For those of us who don't have deformable registration tools

(i) do you think it sufficient to use the original planning scan (assuming set up and external anatomy are unchanged) together with the CBCT to modify the solid tumour and lung REDs in the area of change and recalculate the plan to assess impact of change.

(ii) (ii) Would you use this to adapt your plan or get a rescan.

Answers:

i) yes, this is perfectly reasonable and gets you pretty close to the true solution. There is more work required (contouring for density override), but it will be reasonable approximation.

ii) I wouldn't use this to adapt a plan, only to indicate that a rescan will be required. The field of view limitations are such that I don't think this method, or synthetic CT method are appropriate for dose calculation and treatment planning.

Question 4: What are the next biological target studies we need to do to have confidence in adapting to these images?

Answers:

This is really challenging. Some thoughts:

- Functional imaging (i.e. PET/CT) are limited due to insufficient signal from 'microscopic' disease that we still want to treat
- The required dose to control the microscopic disease is likely less than a solid tumour, however for a shrinking tumour this volume of tissue is actually shrunken tumour, not microscopic disease at the start, so is more likely at the tail of the cell survival curve
- Clinical trials where the target volume is adapted, and the local control is measured, are most useful. In particular if we can track the dose to different regions over the course of treatment, to figure out what dose has actually been delivered.
- Review of local failures in the context of volumetric imaging could also be of interest – try to quantify if there's a geometric reason for failure, or if the prescription dose was simply not enough for that patient's tumour.
- The shrinking volume thus likely depends on whether it's a capsule that's shrinking in, or if the tumour cells are eroding away. There has been some interesting work in H&N where fiducial markers were implanted at the border of oropharyngeal tumours, and the shrinkage was measured. Visible tumour edge was displaced more than the fiducials in a number of instances, suggesting the tumour was eroding away in these cases (which would be unsuitable for target volume adaptation) https://doi.org/10.1016/j.radonc.2016.10.012
- Similar approaches to measuring how tumours are shrinking I think are key

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Questions and Answers from the December 2020 Webinar Chaired by Johnson Yuen (Talk 1 by Nicholas Hardcastle)

Question 5: Using the simple rigid registration approach mentioned above, how do you suggest we report summed volumetric doses to OAR and targets?

Answers:
We probably can't do it accurately, but can do it consistently. Analogous to summation in brachytherapy + EBRT, we can sum maximum point doses for example. We could take this one step further and do a rigid registration at the location(s) of maximum doses. For more volumetric metrics e.g. mean dose metrics, this is more challenging and likely won't reflect the true values.

Question 6: What image registration software are you using and what software do you use for adaptive planning?

Answers:
We use Velocity v4.1 and Eclipse v15.6.