Challenges in Target delineation of Lung cancer

Naveen Mummudi,

Associate Professor,

Department of Radiation oncology,

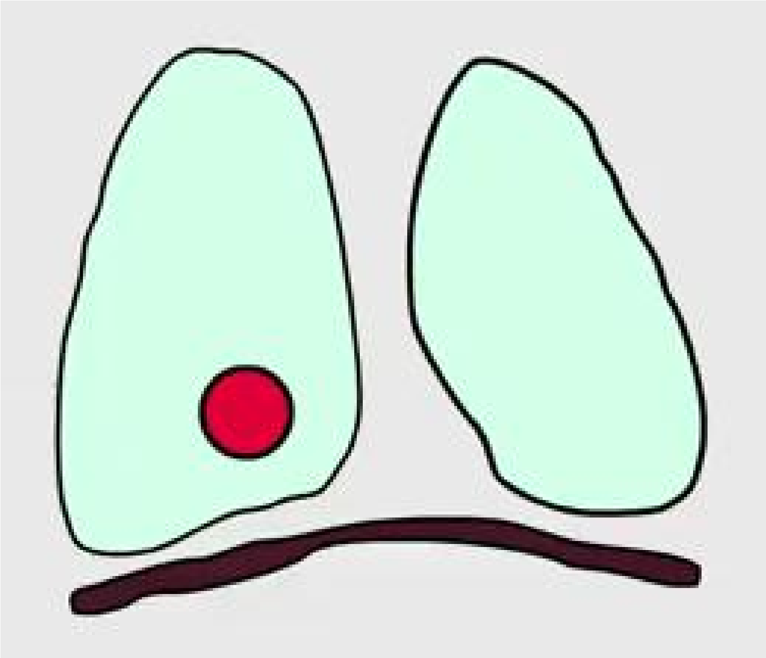
Tata Memorial Centre,

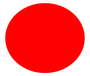
Homi Bhabha National Institute, Mumbai

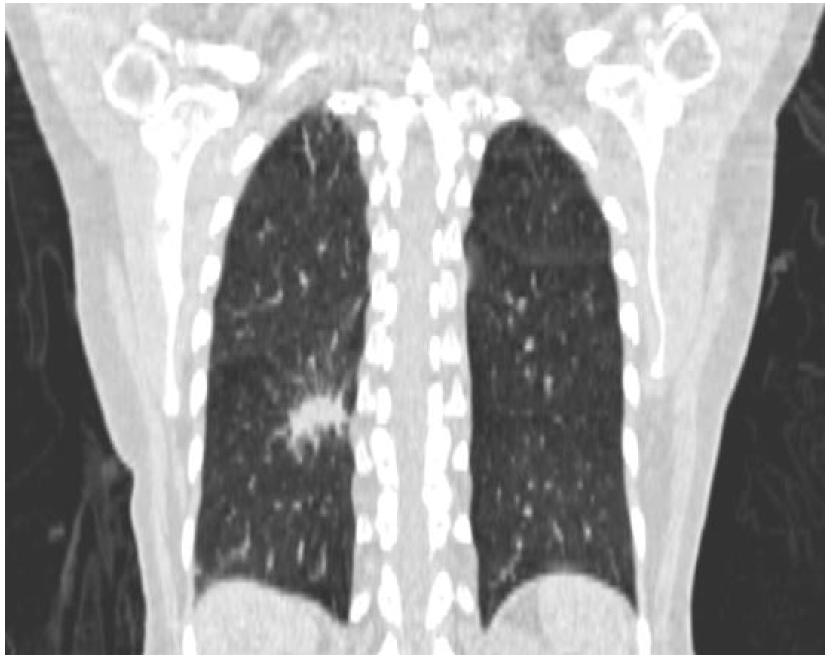
Evolution of treatment of stage III NSCLC

- Only RT (1970-80)
- Sequential CT / RT (1990s)
- Concurrent CTRT (2000s)
- Consolidation Immunotherapy (current era)

Challenge with tumour motion

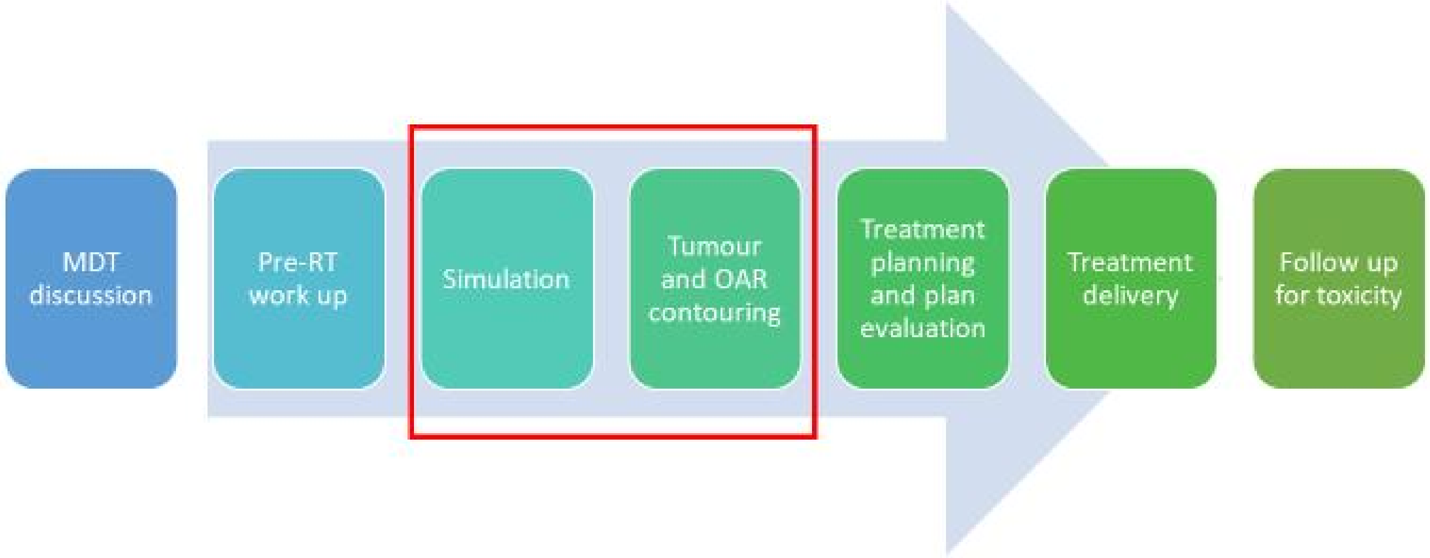






Challenges in Lung cancer

- Organ motion
- Tissue heterogeneity and dose calculation uncertainty
- Inter-fraction and intra-fraction changes
- Microscopic disease



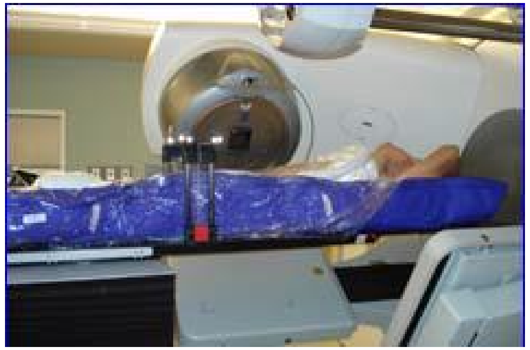
Motion Management Strategies

Method	Technique
Incorporate all movements	4DCT or Slow CT
Freeze movement	Breath hold
Intercept movement	Gated Radiotherapy
Track or Chase the tumor	Implanted markers and specialized treatment delivery

Immobilization

- Accurately re-position patient
- Reduce/Minimize patient voluntary and involuntary motion
- Reduce/Minimize organ/target motion
  - Abdominal compression
- Comfortable for long treatment
- Compatible with IGRT
- Not interfere with treatment beam

Thermoplastic Long mask



Body Pro-Lok TM frame

Body Fix

Abdominal Compression

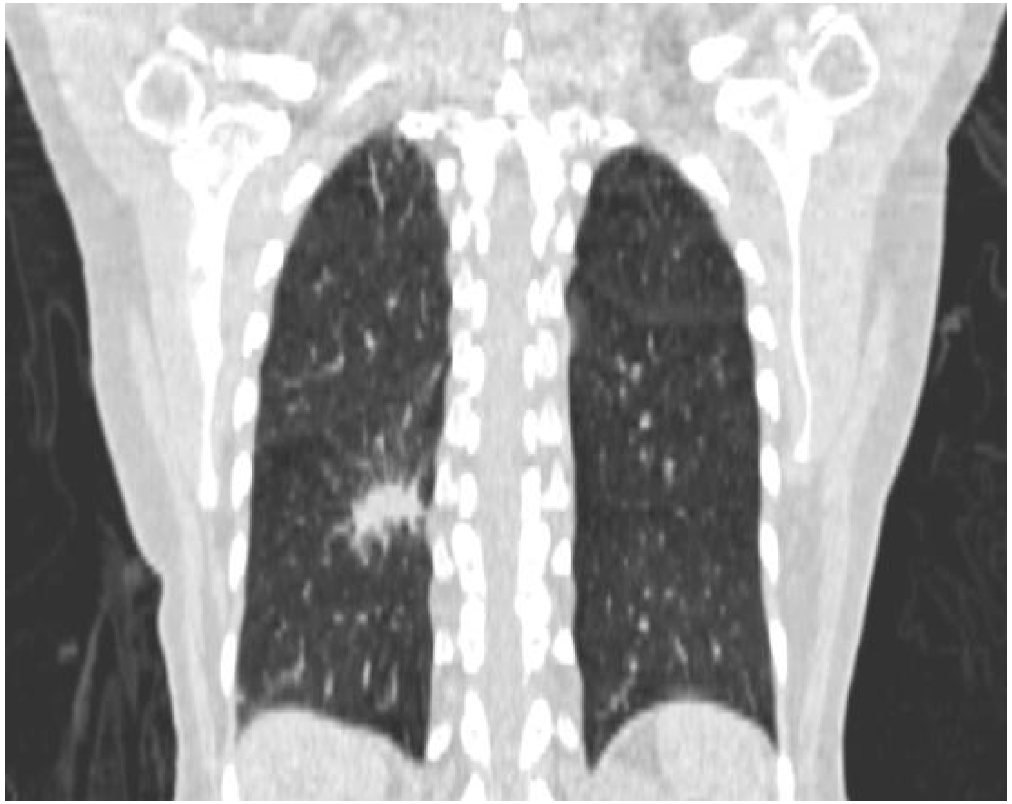
Immobilization/Simulation

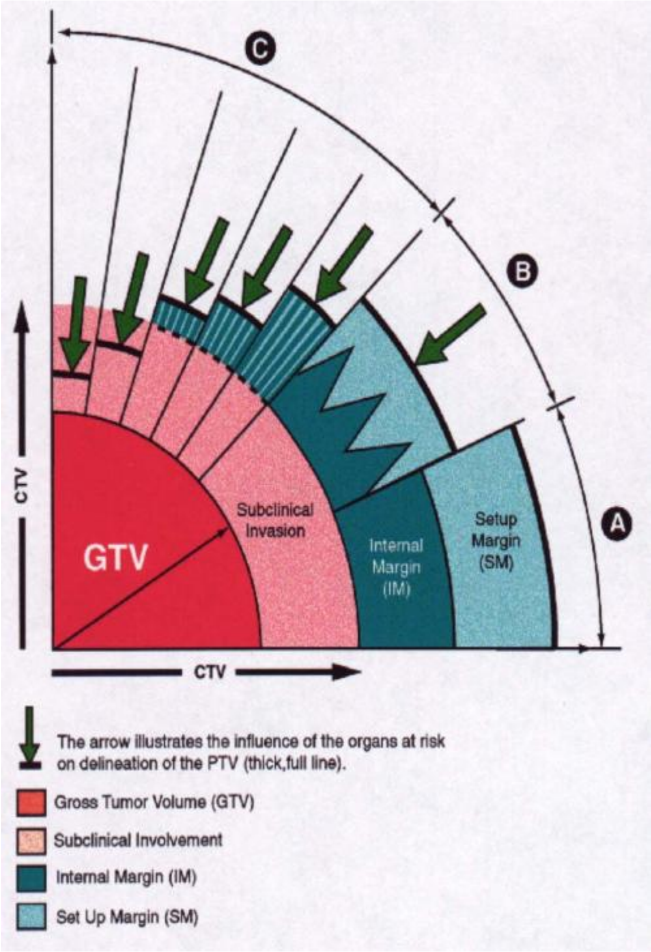
- Careful positioning in the immobilization device, supporting the hands and shoulders
  - premedication with analgesia (e.g., to prevent shoulder pain)
  - anxiolytic may be needed
- Scanning in TX Position
  - CT, MR, PET-CT
- CT scan with $\leq$ 3 mm slice thickness
- Contrast

CT Simulation

- Suppressed respiratory motion techniques
  - Compression Paddle, Pressure Belt
- Free Breathing (FB) & Slow CT-Scanners
- Free Breathing & Fast CT-Scanners
- Breath-Hold (BH) CT-Scans
- Respiratory Correlated CT (4D-CT)

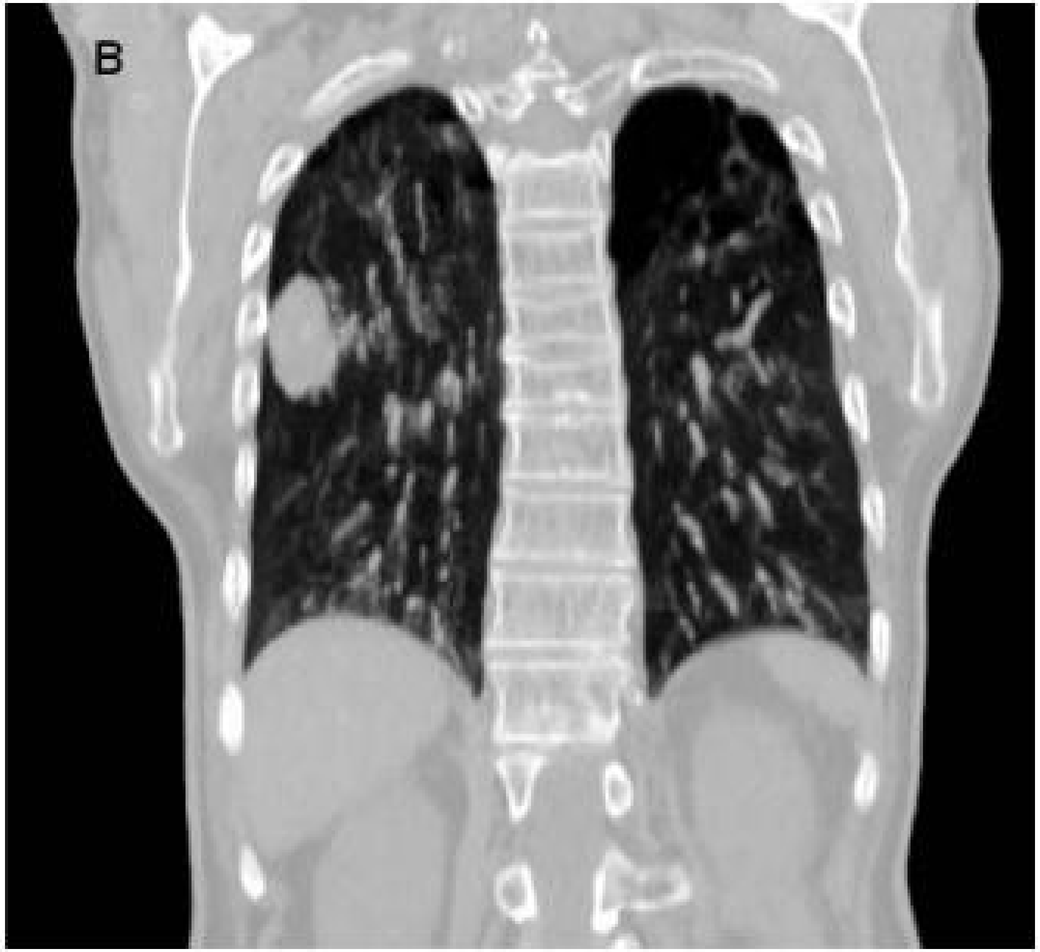
Using 4DCT data to draw ITV



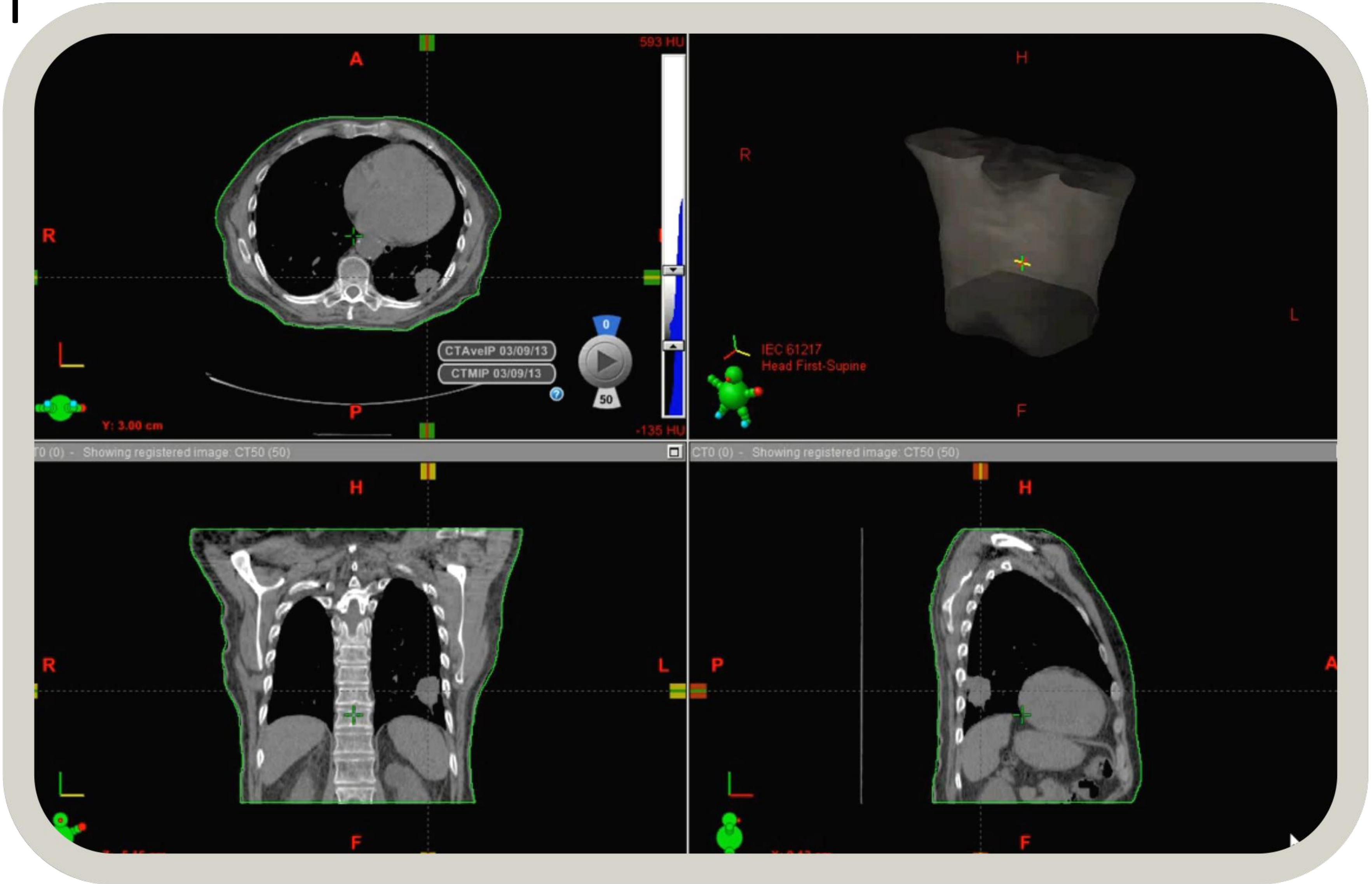


Conventional (3D) CT image

4DCT reconstruction showing all possible tumour positions



4DCT


A
R
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CTAveIP 03/09/13
CTMIP 03/09/13
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Y: 3.00 cm
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IEC 61217
Head First-Supine
T0 (0) - Showing registered image: CT50 (50)
CT0 (0) - Showing registered image: CT50 (50)
H
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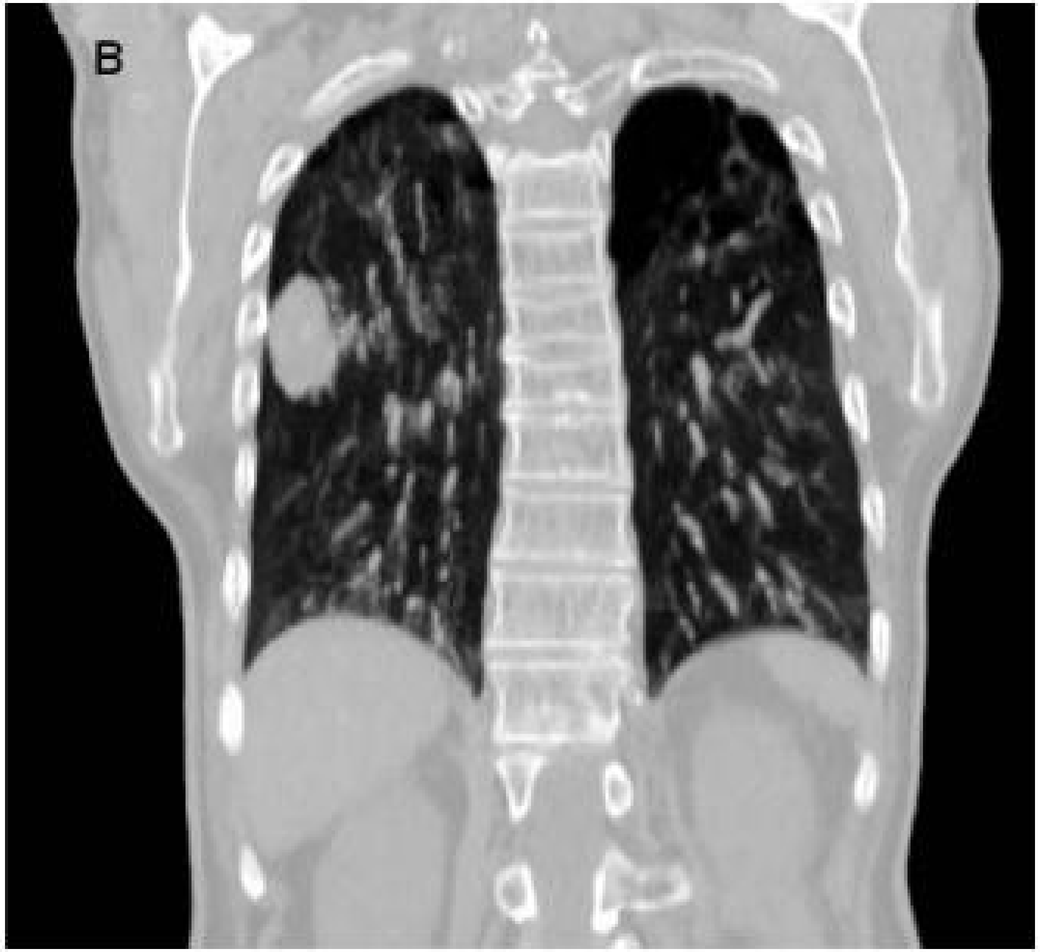
H
P
A
F

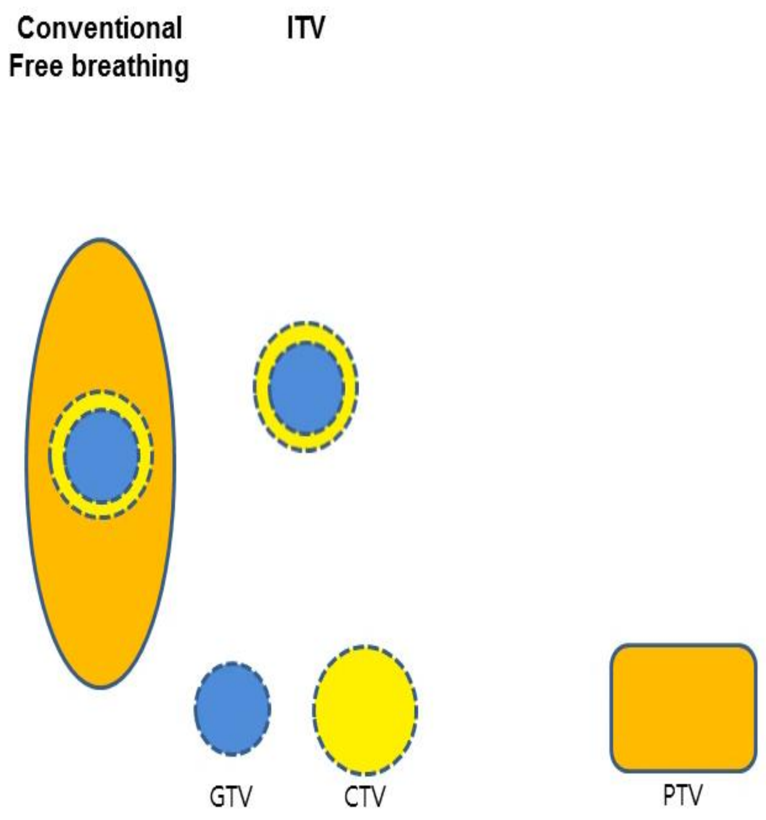
Conventional (3D) CT image

4DCT reconstruction showing all possible tumour positions



Using 4DCT data to draw ITV

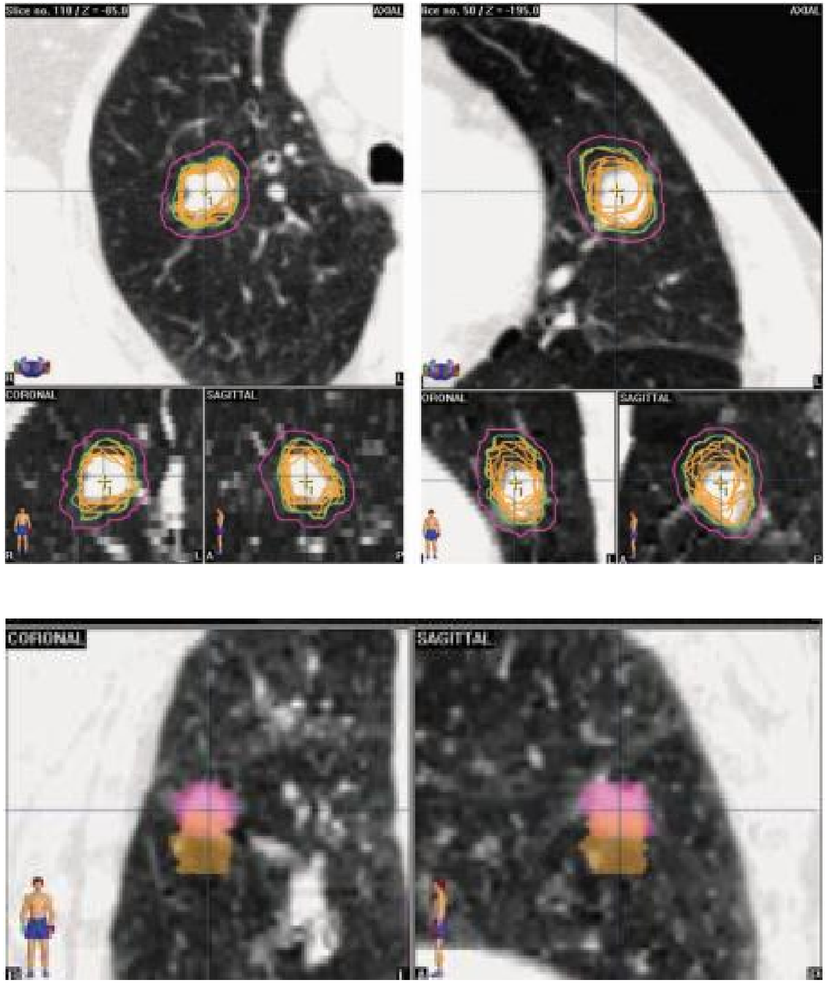
- ITV is an conservative estimate of the space that needs to be irradiated.
- Positive
  - Can provide quantitative extent of tumour motion
  - ITV structure accurately reflects tumour envelope that beams can encompass
- Negative
  - Requires multiple phase images and contouring of each phase



Using 4DCT data to draw ITV

- Contouring GTVs on all binned phase data sets (usually 10) and fuse.
- Contour on MIP image set.
- Contour GTV on select phases (end-inhale and end-exhale)
- MIP / AIP / Min IP / CIP generation

Using 4DCT data to draw ITV



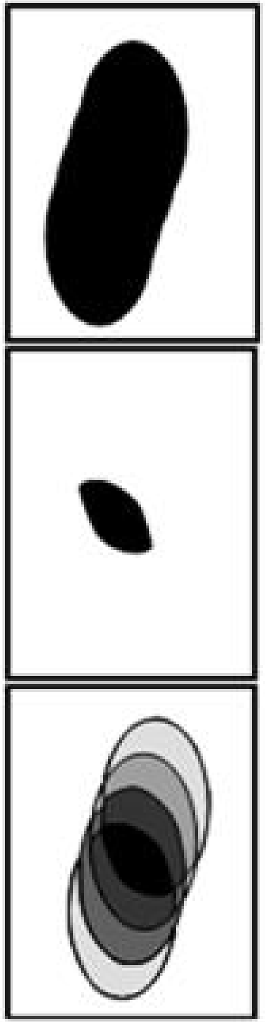
- GTVs are contoured in each of the 10 phase bins of the 4DCT.
- ITV is defined as the volume encompassing all GTVs
- Simpler approach - import only the two extreme phases of 4DCT
  - the end-expiration and end-inspiration bins, generate an encompassing ITV
  - Hysteresis

4DCT

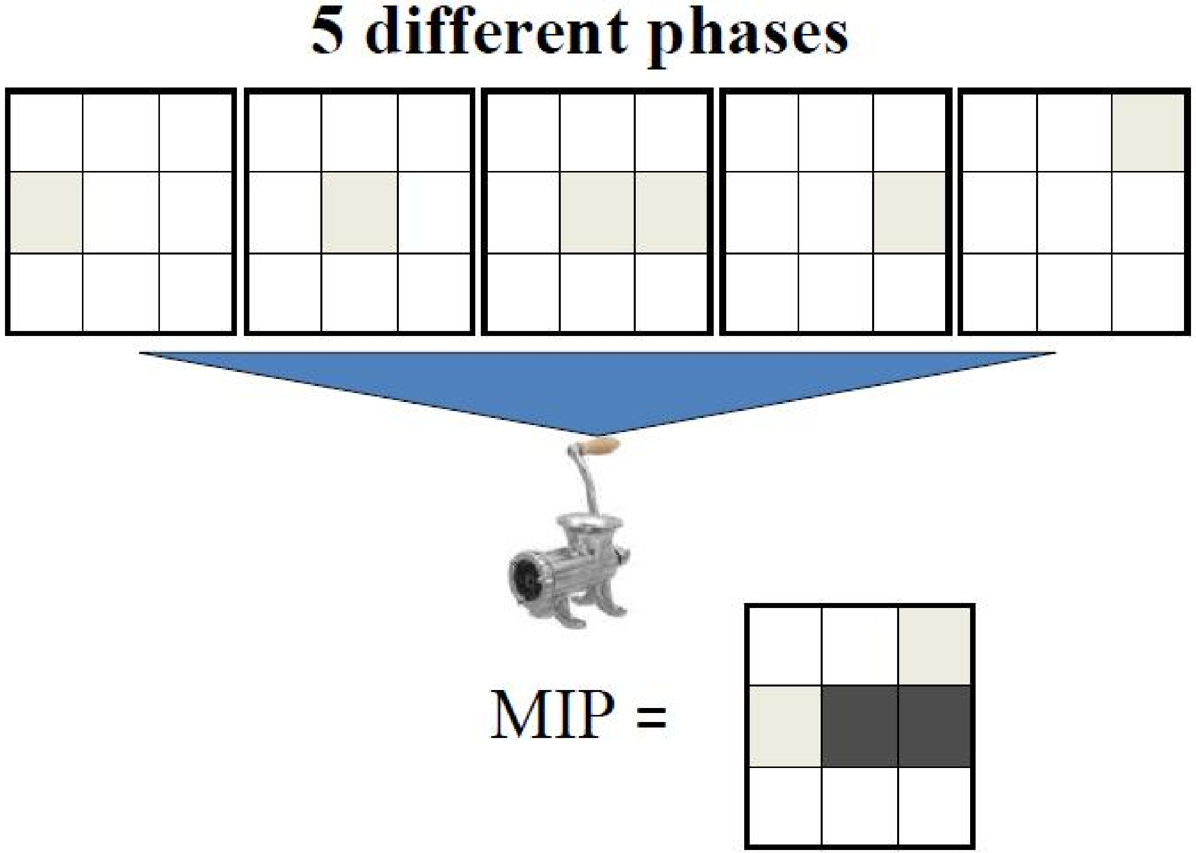
- Each voxel has a certain intensity (Hounsfield Unit)
- Intensity voxels in lung vary over respiratory cycle (10 bins)
- Reconstruction can be made from the 10 bins
  - Ave-IP calculates average intensity
  - Max-IP or MIP calculates maximum intensity

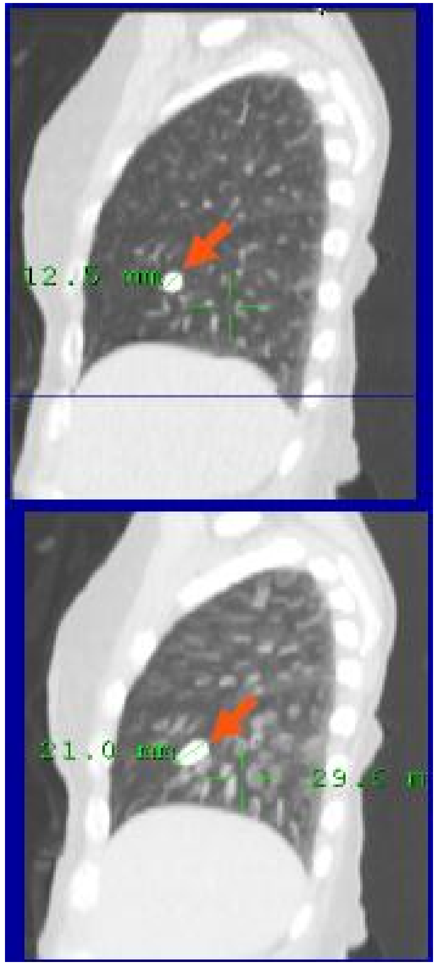
Maximal Intensity Projection (MIP)

- Automatically generated from the entire 4D-CT
- MIP scans reflect the highest data value encountered along the viewing ray for each pixel of volumetric data
  - full intensity display of the brightest object along each ray on the projection image.
- Lung tumor - high-density tumor voxels compared with lower density lung tissue voxels.

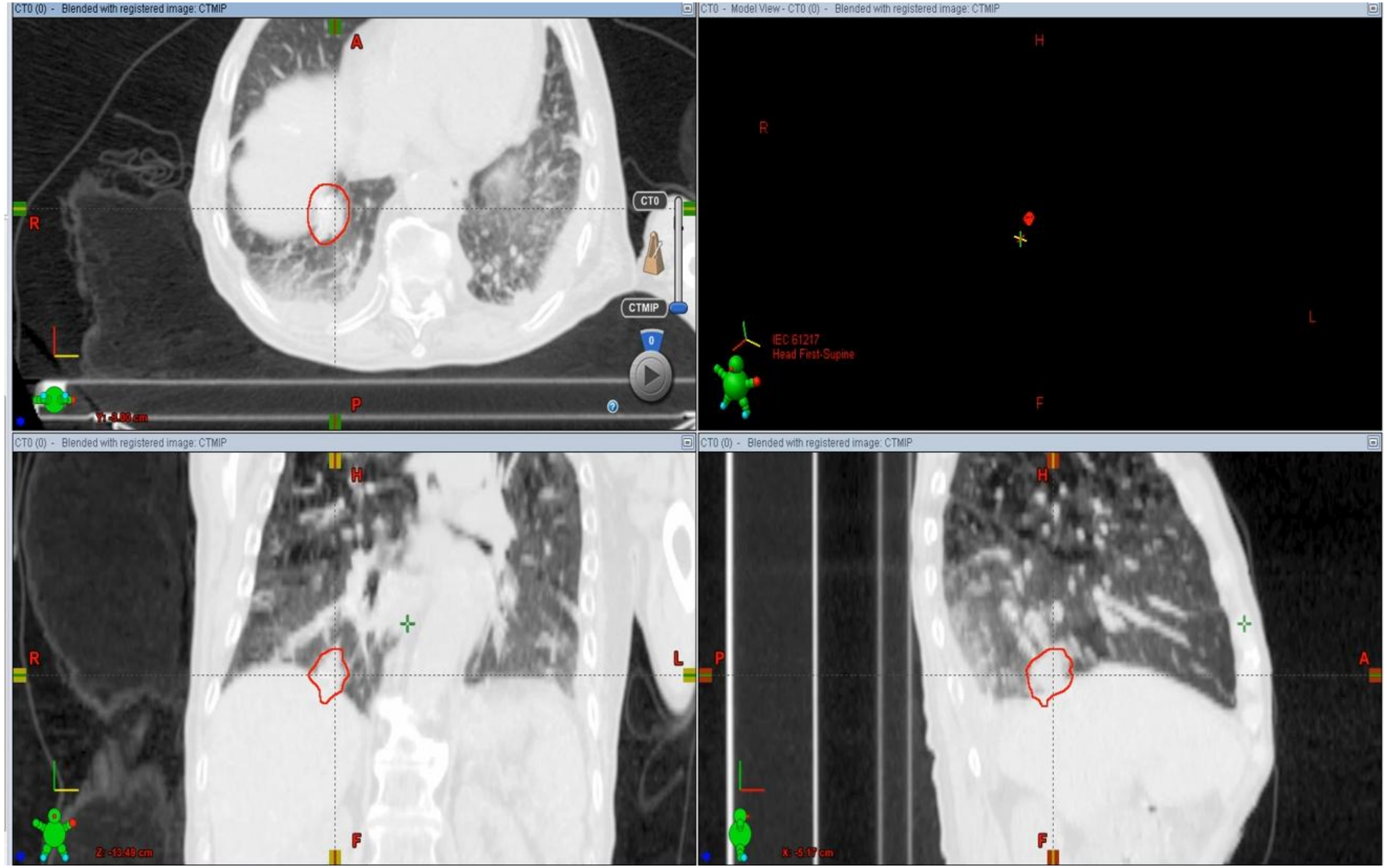


Maximal Intensity Projection (MIP)





ITV generation with MIP



Quick comparison

MOTION ENCOMPASSING TECHNIQUE	EASE OF DELINEATION	ADDITIONAL WORKLOAD	RELIABLE DOSE CALCULATION	ADDITIONAL COST
Slow CT scan	-	-	+/-	-
Exhale-Inhale scan	+/-	+	+	-
ITV - MIP / AIP / CIP	+	++	-	++
Mid-ventilation CT	+	++	++	++
Mid-position CT	+	+++	++	+++

Using 4DCT data to draw ITV

- Contouring GTVs on all binned phase data sets (usually 10) and fuse.
- Contour on MIP image set.
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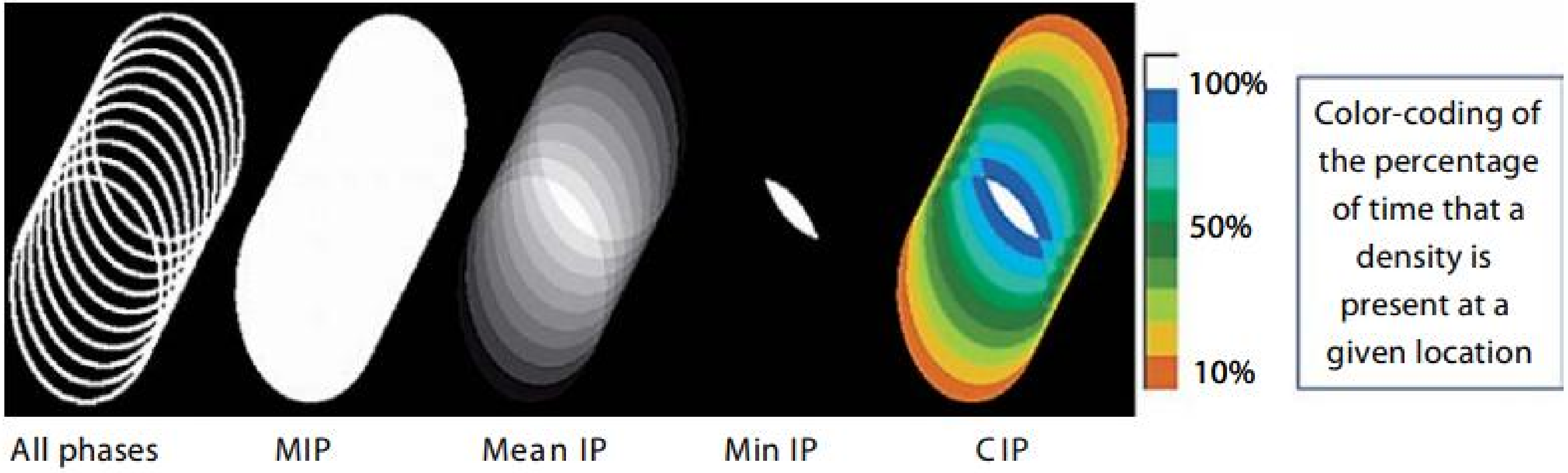


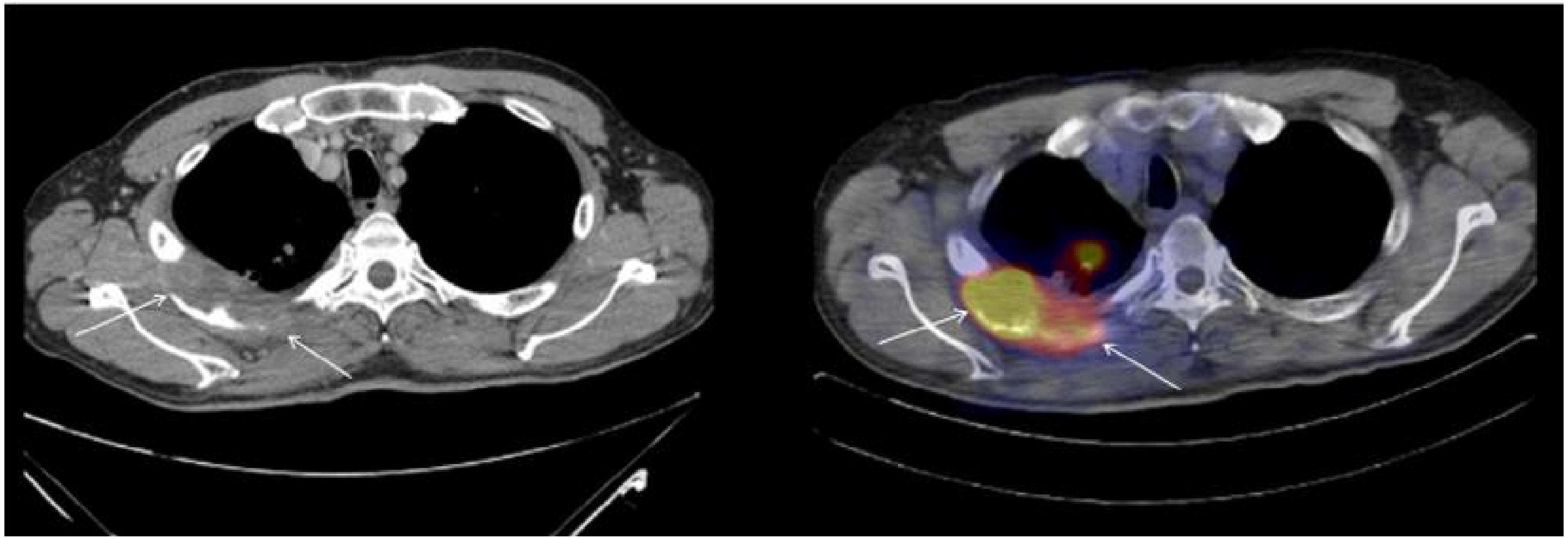
PET CT

- Advantages
  - Impact on staging
  - Nodal disease evaluation
  - Inter-observer variation

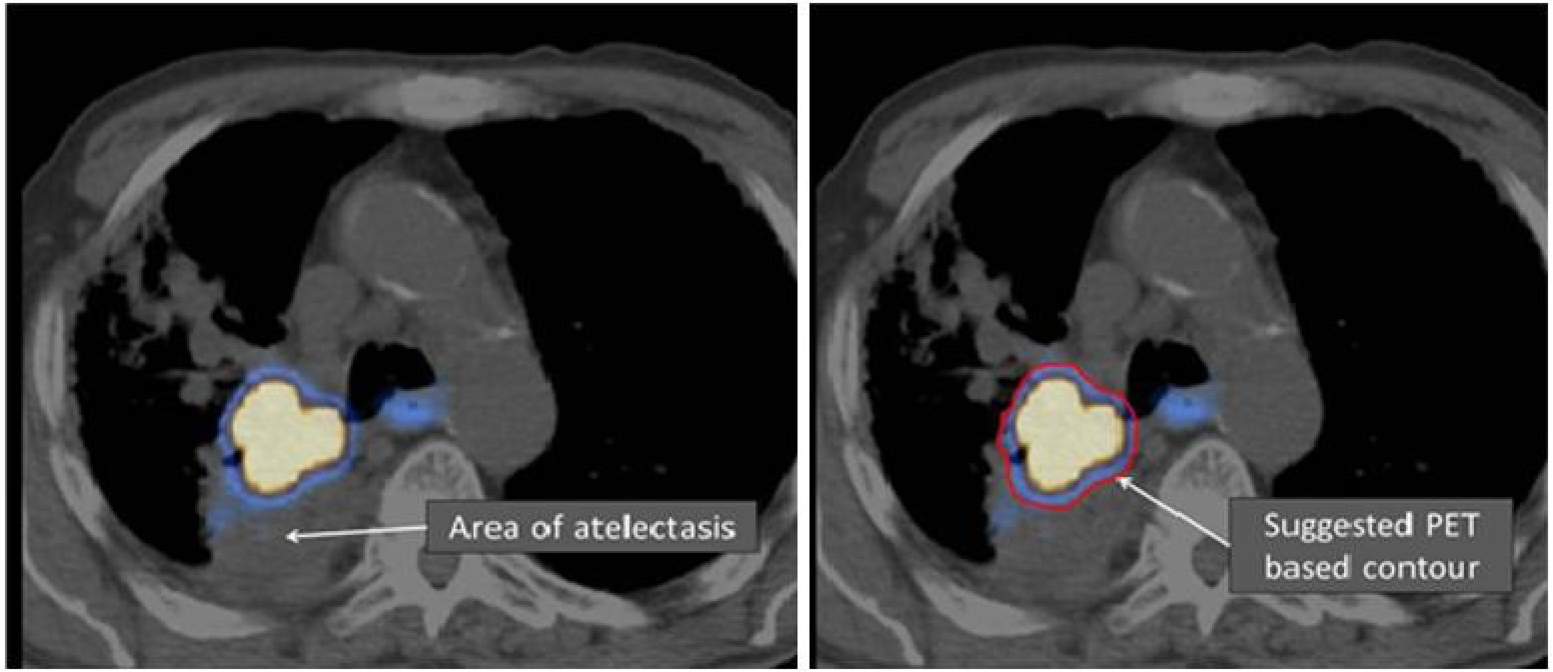
- Challenges
  - Limited spatial resolution
  - Acquisition position – challenges for registration
  - Time delay
  - Planning PETCT

PET CT

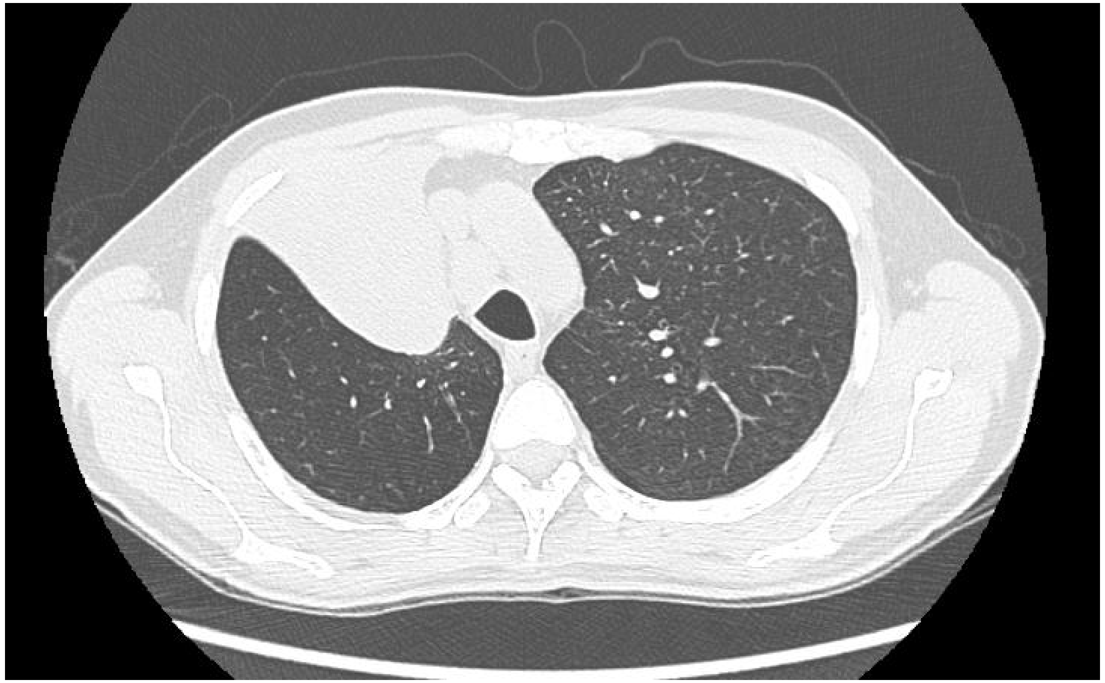
- Tumor is contiguous with a structure that has a similar density and boundary can be distinguished on CT – FDG avidity helps

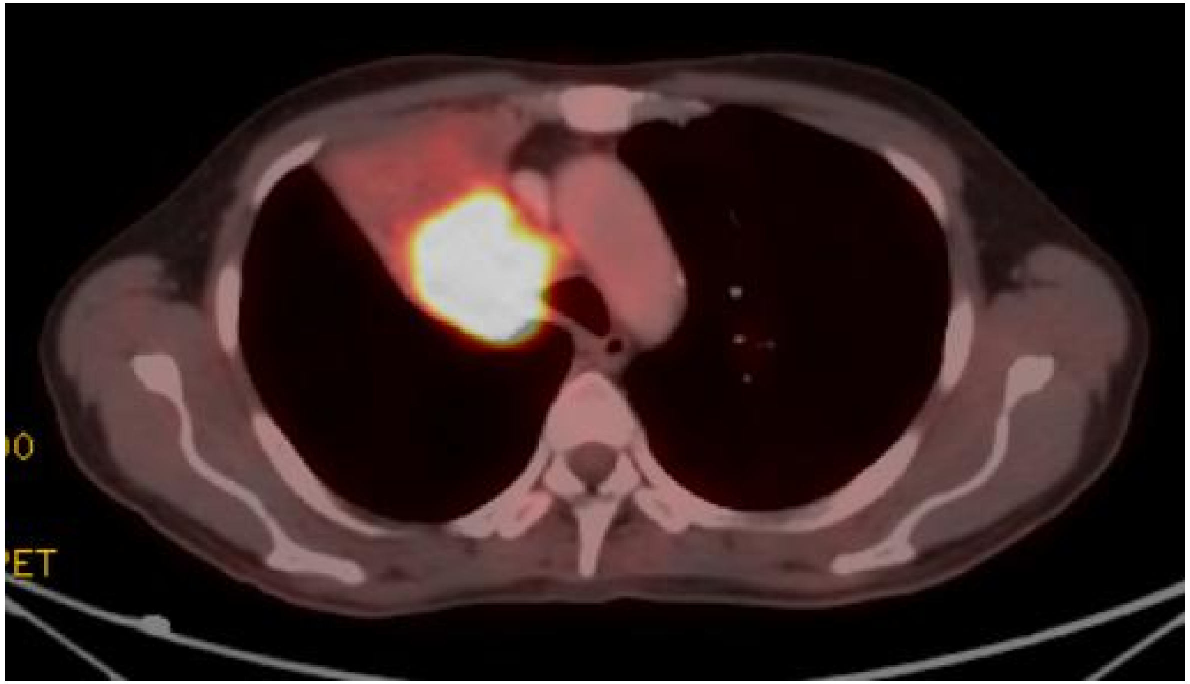


PET CT



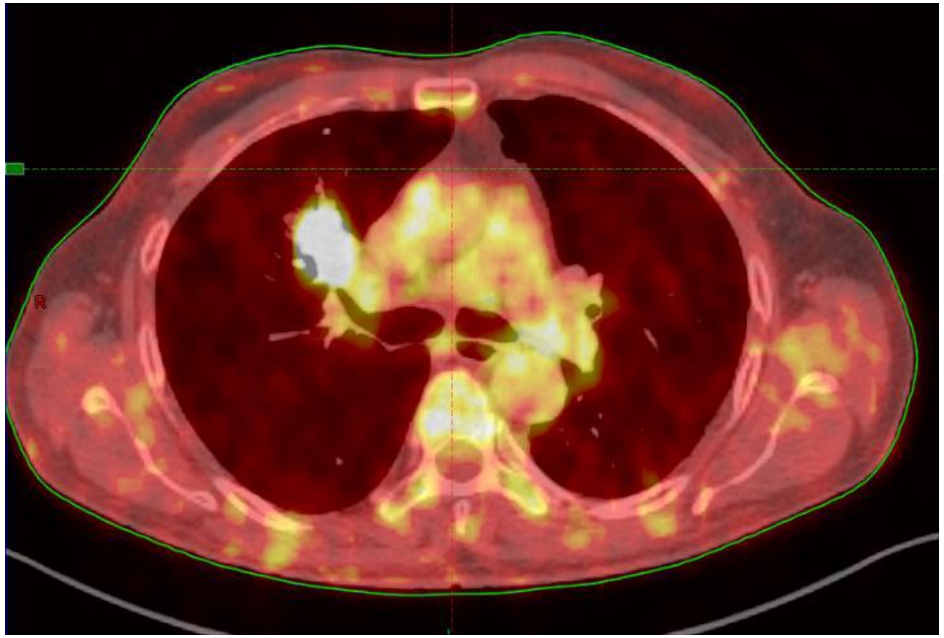
PET CT

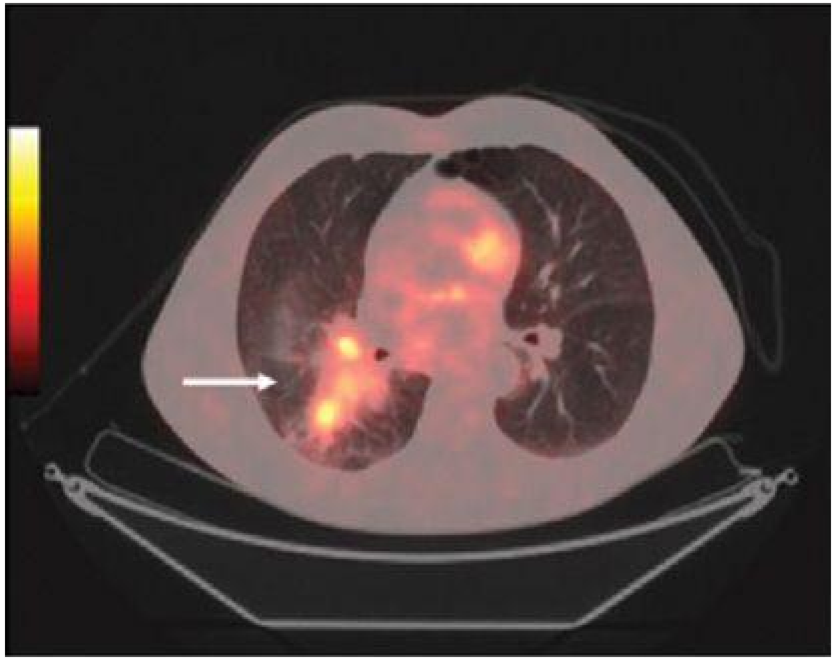




PET CT

- In areas with physiological uptake of FDG, GTV to be defined by CT images

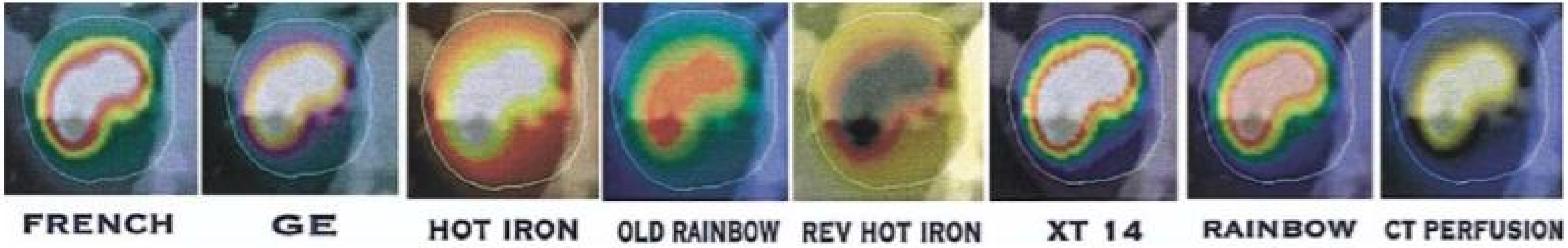




PET based contouring

- No validated quantitative approaches for PET based ideal tumor delineation.
- SUV-based ‘‘magic line’’ where viable tumour burden ceases to exist and normal tissue begins - may be impossible
  - Visual inspection
  - SUV cut-off
  - SUV threshold

PET based contouring



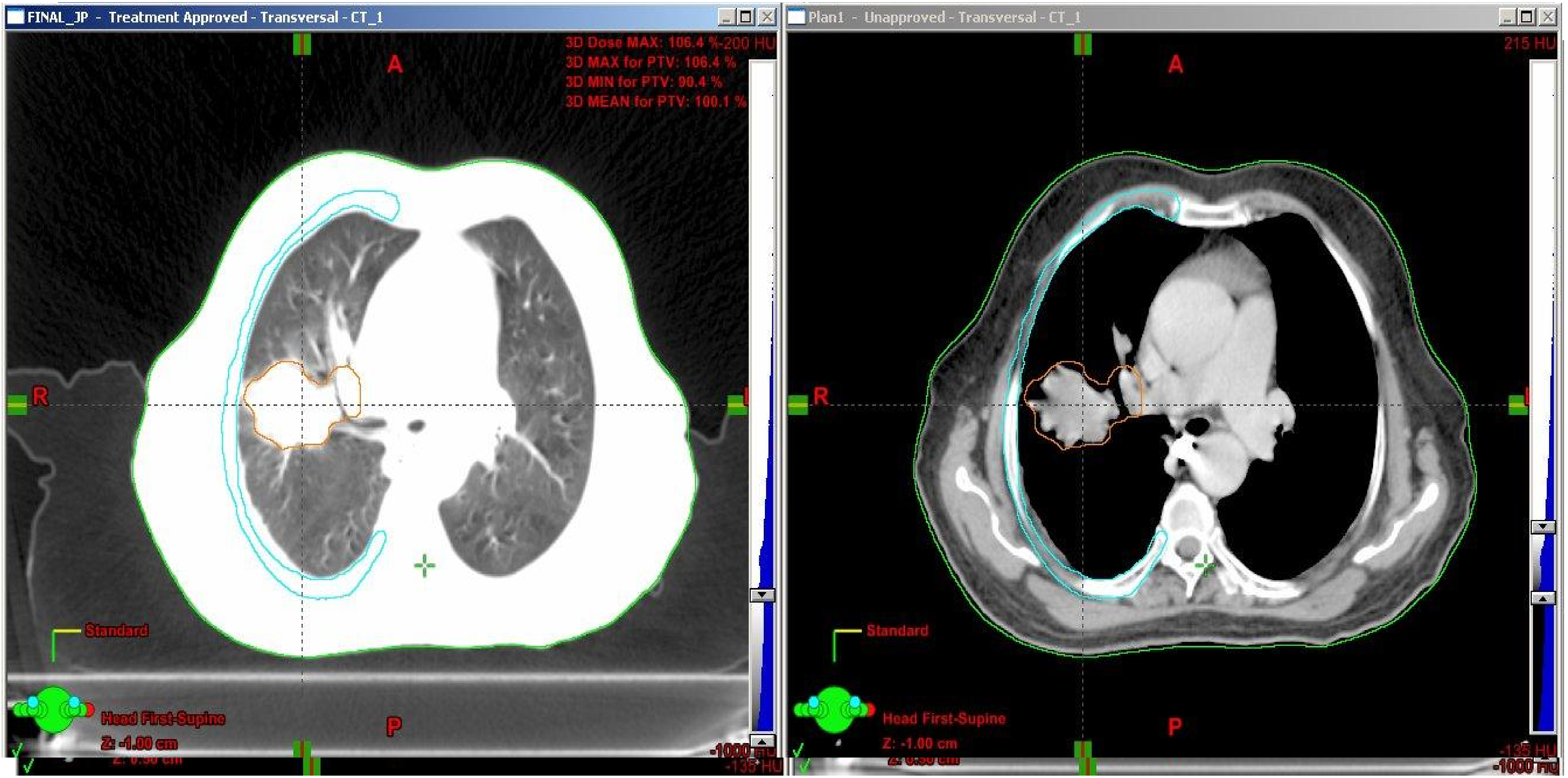
- Use a simple linear grayscale (e.g., black to white) for reviewing the PET images alone.
- Use a linear scale to one or at most two colors (e.g., black to red to yellow).
  - Avoid polychromatic scales to avoid misleading color scaling contours

PET based contouring

- SUV cut-off
    - 2.5

- SUV threshold
    - arbitrary value relative to the maximum intensity within the FDG-avid area,
        - e.g. 40%, 42%, or 50% of SUVmax.

Contouring GTV - Window effect



For Parenchymal disease: W=1600 L= -600

For Mediastinal disease: W=400 L=20

These correlate best with pathological tumor sizes

CTV / PTV

- iGTV
- CTV
  - 6-8mm from GTV
- CTV to PTV margin recipe

PTV margins

Motion management	Internal margin (cm)		Setup margin (cm, uniform)	Total PTV margin (cm)	
	Sup-Inf	Axial		Sup-inf	Axial
Free breathing	1	0.5	0.5	1.5	1
Breath hold or gating	0.5	0.3	0.5	1	0.8
Abdominal compression	0.8	0.5	0.5	1.3	1
4D CT	Union of CTVs	Union of CTVs	0.5	Union of CTVs + 0.5 cm	Union of CTVs + 0.5 cm

RTOG 1306

Inter-fraction changes

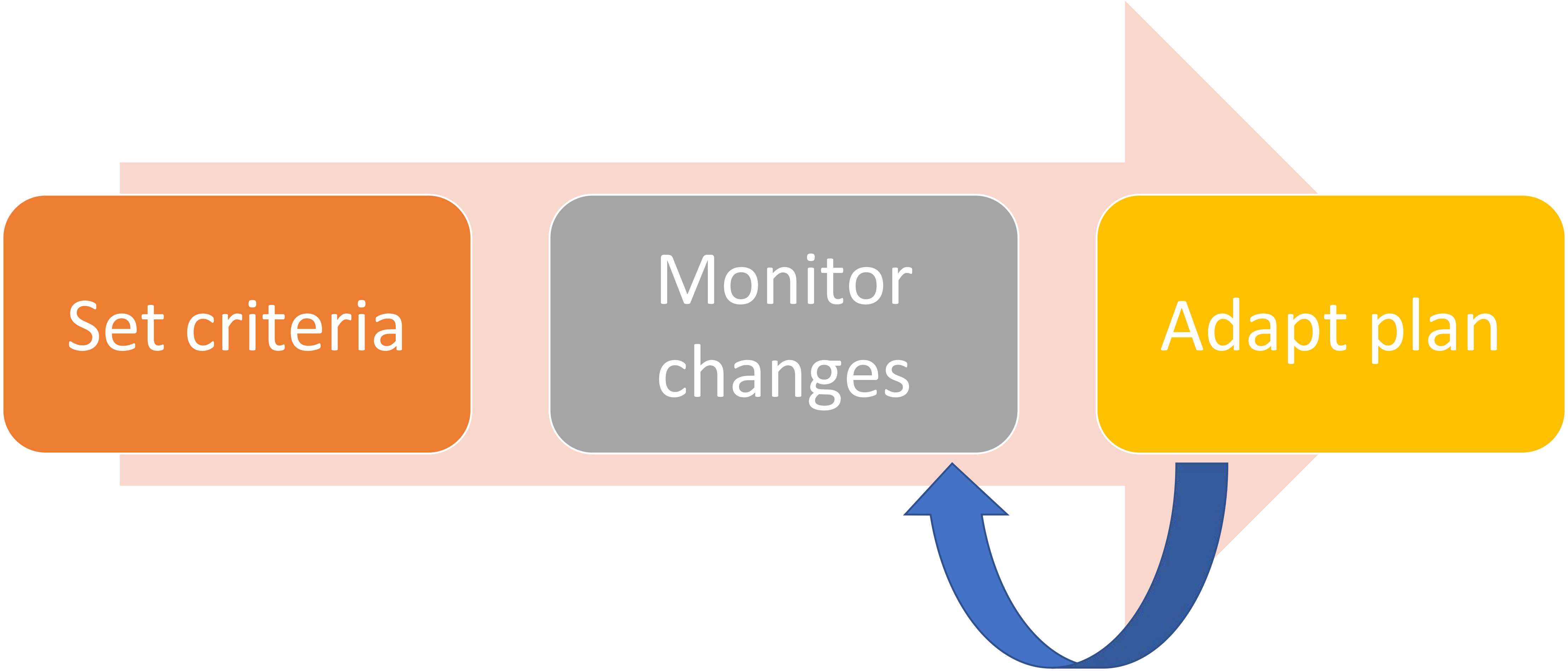
- Anatomical changes had larger impact on the target dose distribution than internal target motion.

	Mean (%)	Range (%)
Anatomy (CT1, CT2)	1.28	0.1–4.0
Respiratory motion (CT1)	0.05	0–0.2
Interfraction baseline shifts (CT1)	0.20	0–0.8
Respiratory motion (CT2)	0.46	0.1–1.9
Interfraction baseline shifts (CT2)	0.65	0–2.1

CT1, planning 4DCT scan; CT2, mid-course 4DCT scan.

Schmidt et al, Acta Oncologica 2013

Process of ART

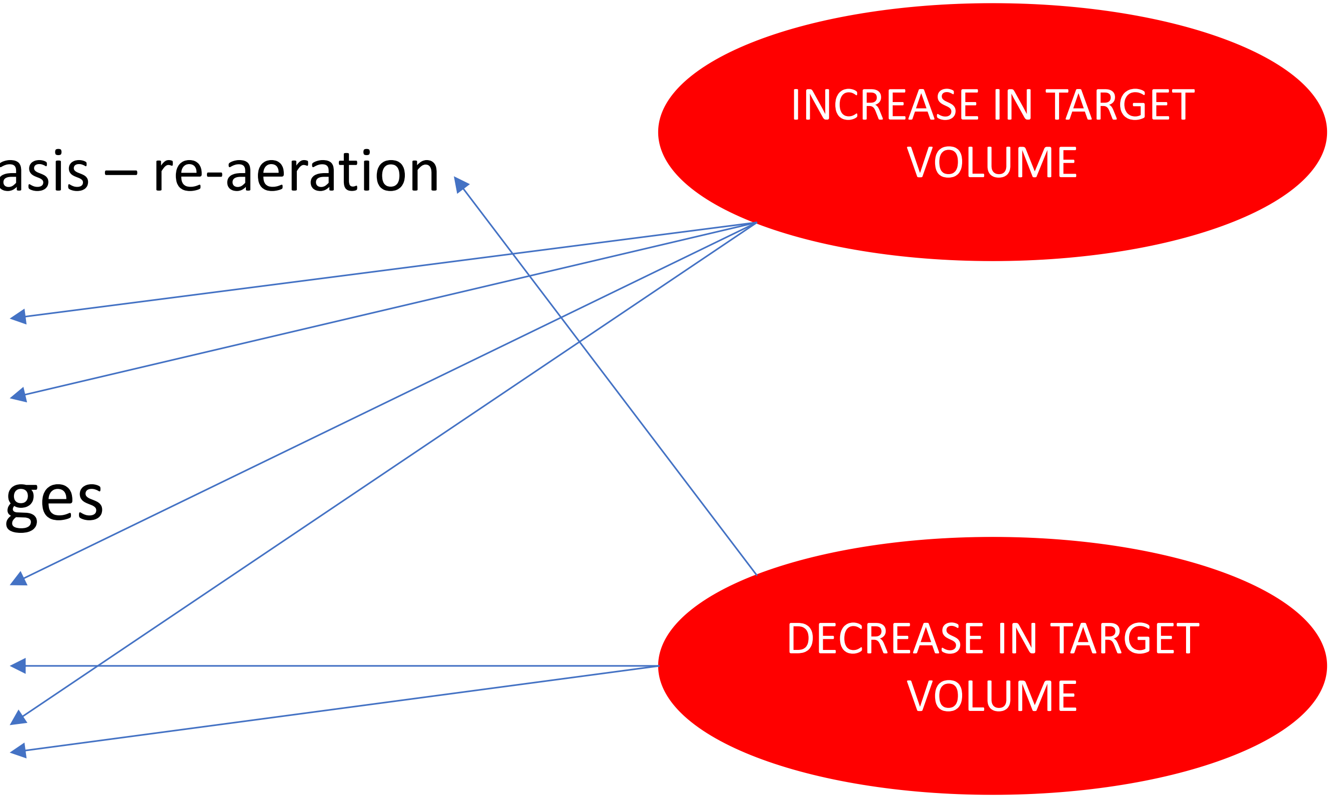


Adaptive Radiotherapy

- Plan adaptation can be simple
  - acquire a new CT scan of the patient mid-way through treatment after a dramatic change is observed and
  - optimizing the treatment plan to accommodate the new anatomy.
- More complex adaptation strategies have also been investigated with varying re-planning frequencies.

Volume changes

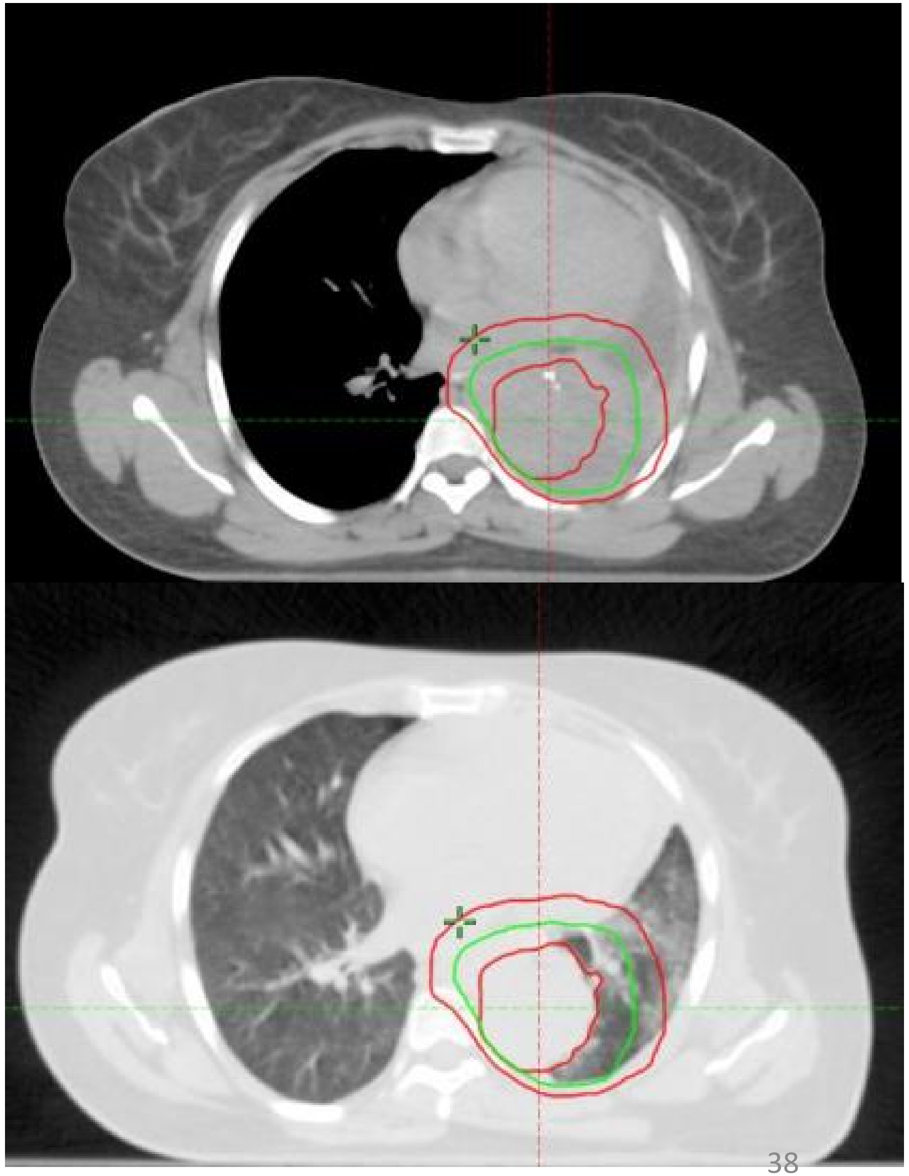
- Positional shift
  - Resolution of atelectasis – re-aeration
  - Progression
    - Pleural effusion
    - New consolidation
- Tumour volume changes
  - Tumour progression
  - Tumour regression
  - Infiltrative change



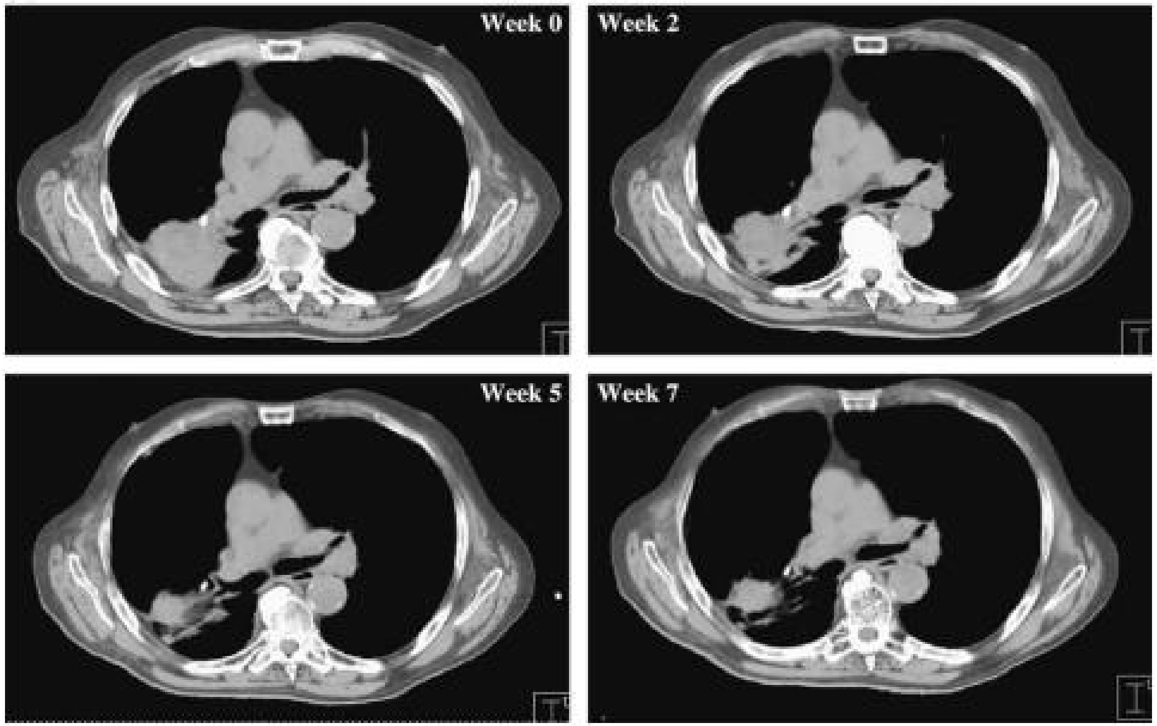
Atelectasis

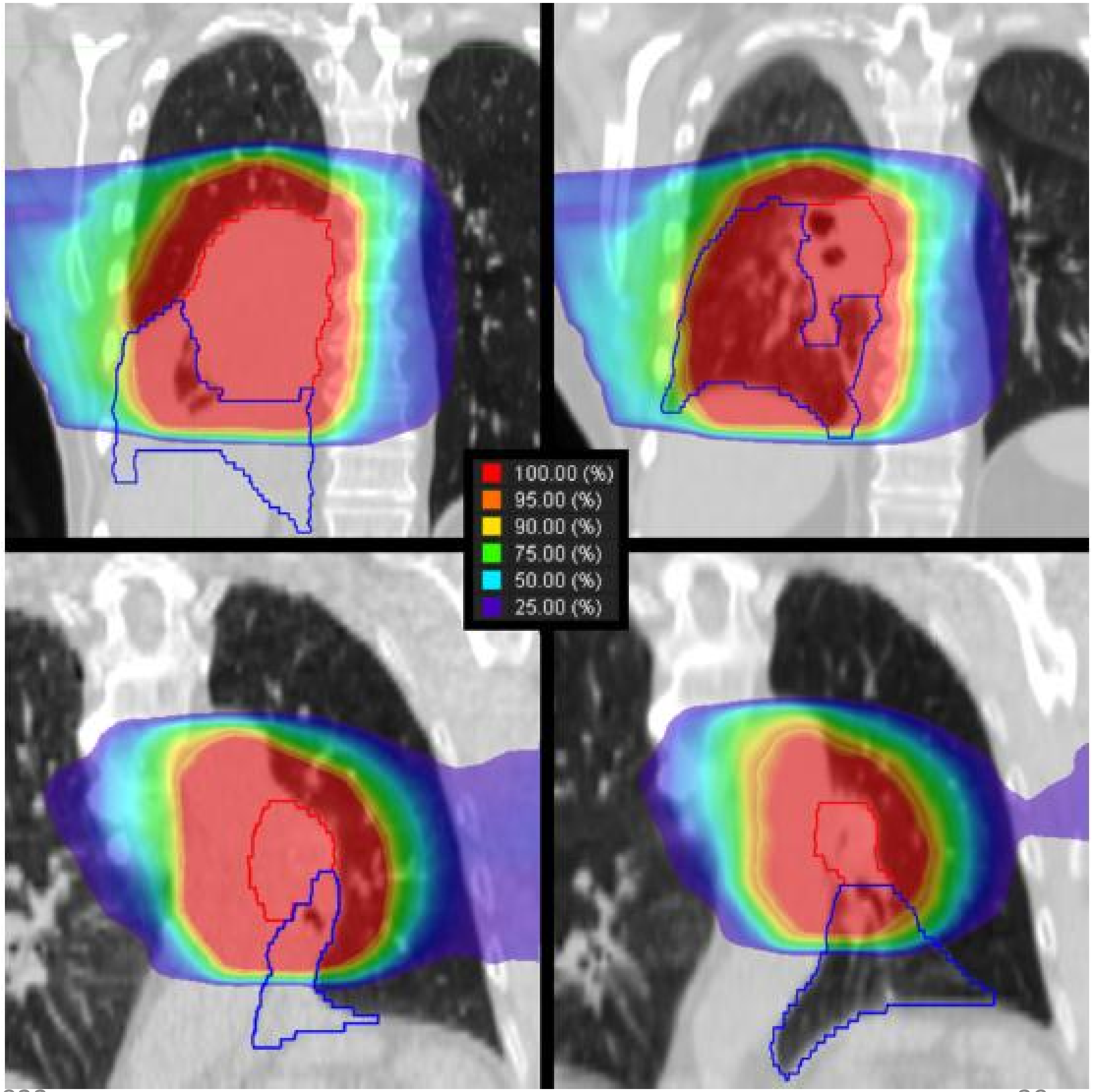
- Common with centrally located tumours.
- Central airways can become constricted or obstructed, inducing a collapse of the portion of the lung.
- Can range from complete collapse, affecting an entire lung, to partial collapse, affecting only a portion of a lobe.
- In CT images, appears as a smaller region of uniform, high intensity.
- Delineation difficulties – if located close to the collapsed lung
    - positron emission tomography (PET)

Atelectasis

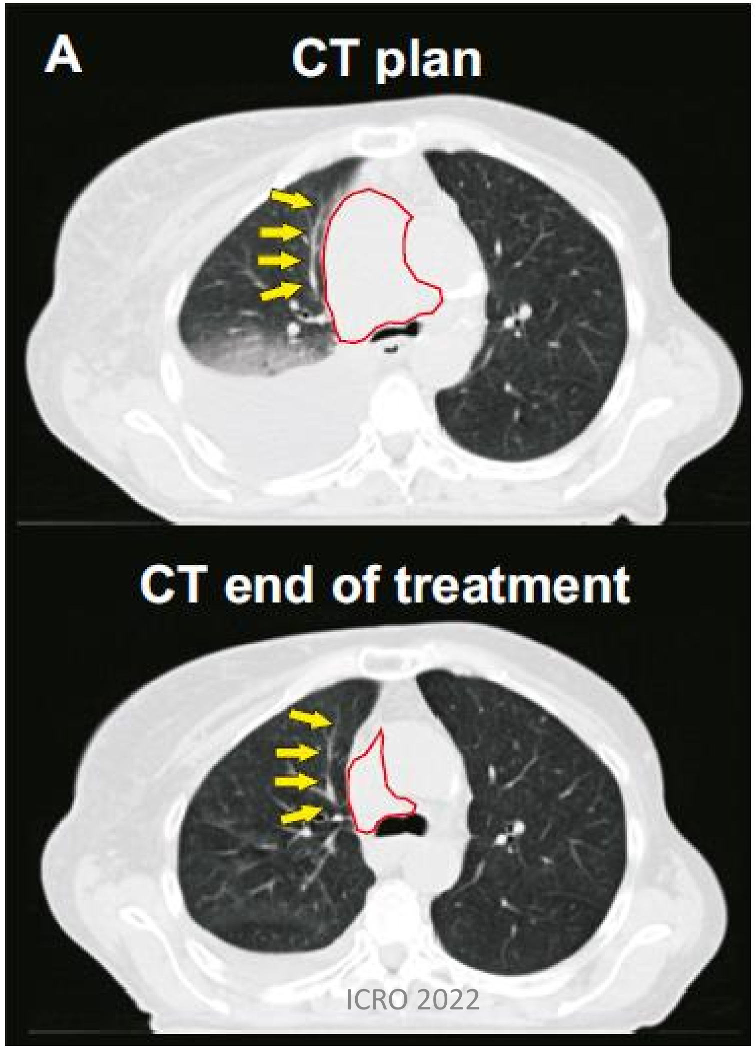


Atelectasis





Pleural effusion

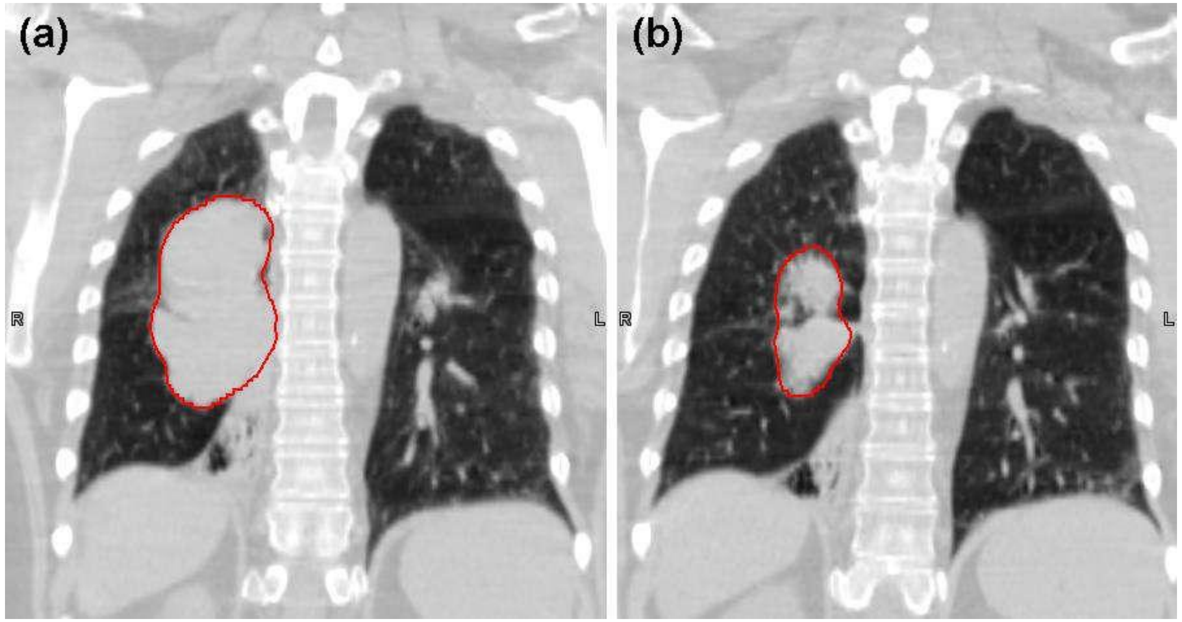


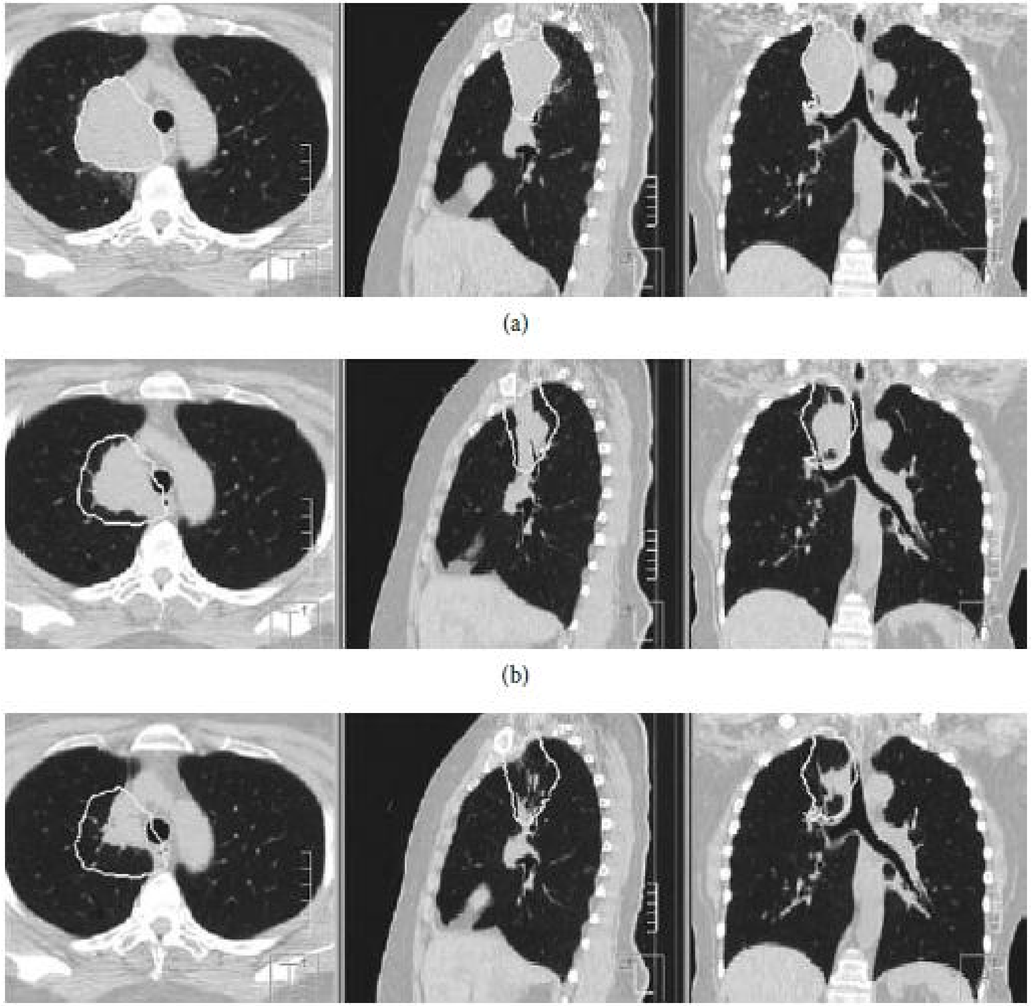
Tumour volume regression

- Tumour regression appears as a gradual, continuous change in tumour volume
  - ranging from 0.6% to 2.4% shrinkage per day
- Reported average tumour volume reductions
  - 24.7% halfway through treatment and
  - 44.3% by the end of treatment.

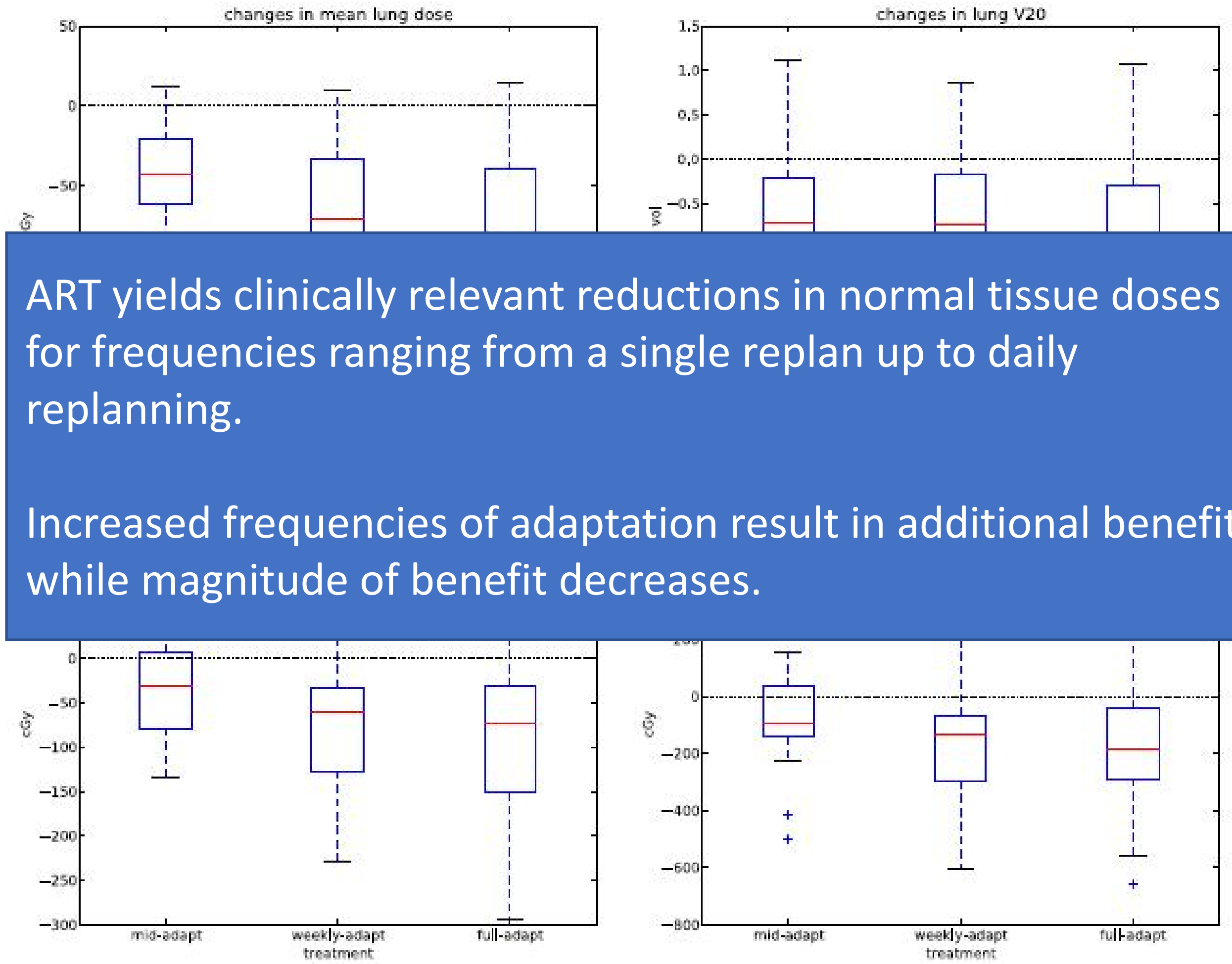
	No. Patients	Modality	Regression Rate (%/d)
Erridge 2003 Edinburgh–NKI/AvL	25	EPID	−0.9
Kupelian 2005 M.D. Anderson	10	In room MV-CT	−1.2
Siker 2006 Wisconsin	25	MVCT	−2.4
Bosmans 2008 Maastro	23	FDG-PET/CT	−0.39
McDermott 2006 NKI/AvL	1	EPID	−1.5
Underberg 2006 VUMC	40	4D-CT and conventional CT	−1.4
Britton 2007 M.D. Anderson	8	In room KV-CT	−1.3
Woodford 2007 Ontario	17	In room MV-CT	−0.79
Fox 2009 Johns Hopkins	22	MVCT	−1.2
Feng 2009 Michigan	14	Mid-RT FDG-PET/CT	−1.4
Van Zwienen 2008 NKI/AvL	114	In room kV-CBCT	−0.6

Tumour volume regression





Re-planning frequency



ART yields clinically relevant reductions in normal tissue doses for frequencies ranging from a single replan up to daily replanning.

Increased frequencies of adaptation result in additional benefit while magnitude of benefit decreases.

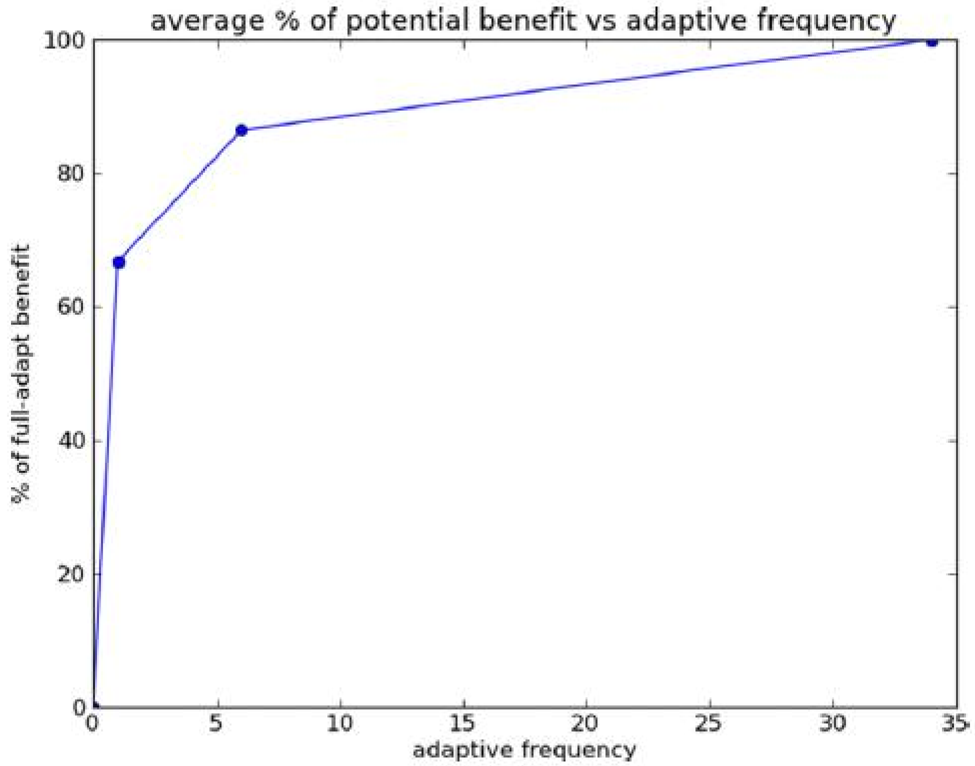


Fig. 3. Percent of potential benefit (i.e., allowable dose to target) as a function of replanning frequency. On average, 65% of benefit was achieved with a single midtreatment adaptation, and 85% was realized after weekly adaptation.

Dial, Med Phy 2016

Shrinking volumes

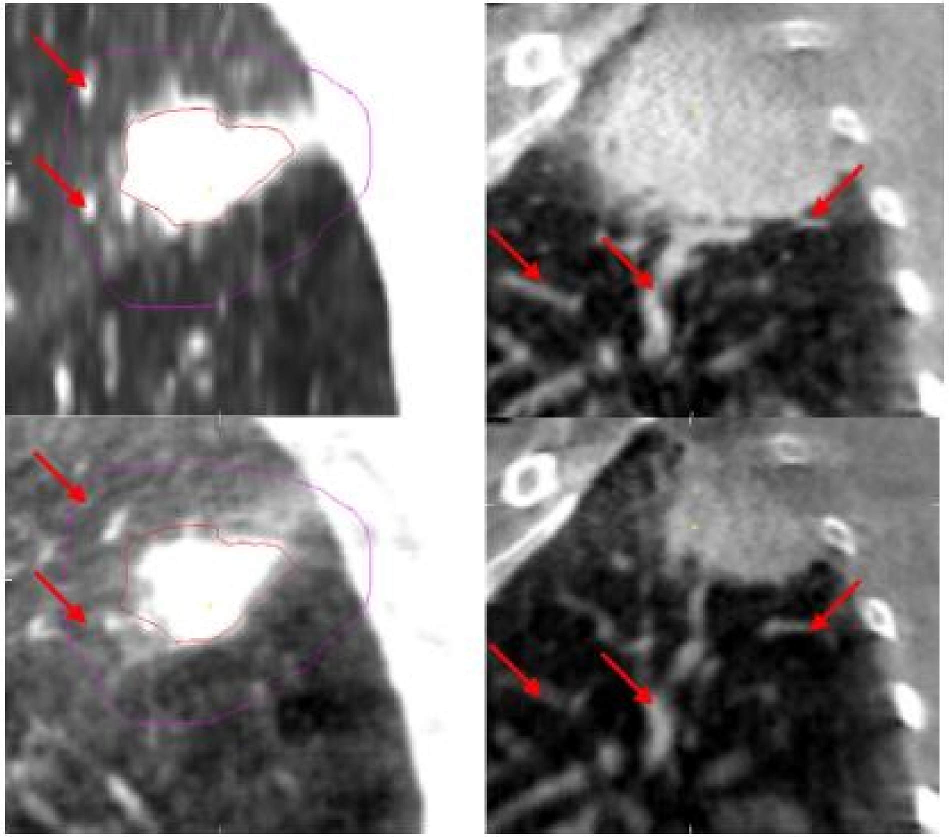
- Extent of microscopic disease beyond gross tumour.
  - Does it change post NACT?
- Does areas of suspected microscopic disease become under-dosed?

- Unclear

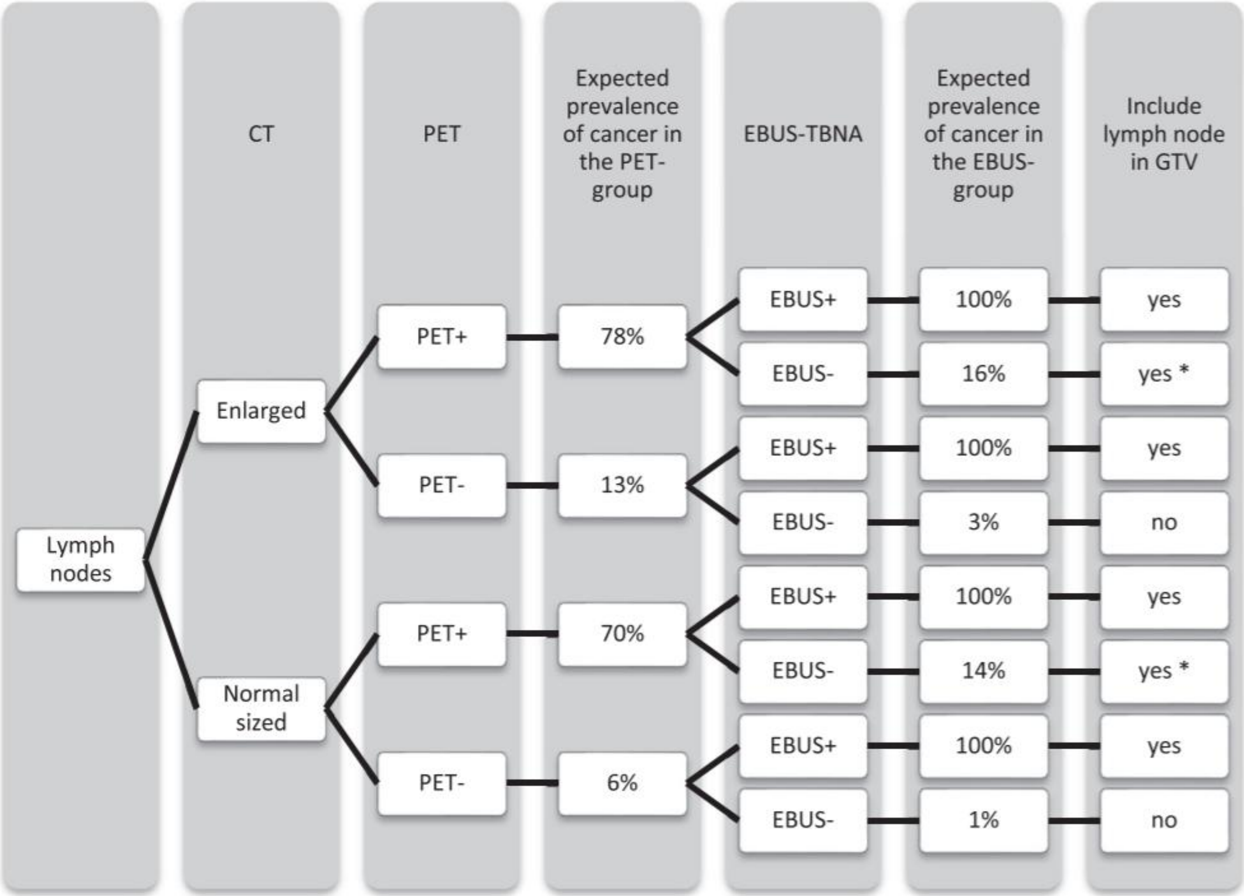
Guckenberger, IJROBP 2011

Shrinking CTV

- Reviewing images important
- Microscopic disease shrinkage may not always be synchronous
- Watch for pattern
  - Expansive growth pattern of the GTV
  - Infiltrative growth pattern of the GTV



Nodal disease



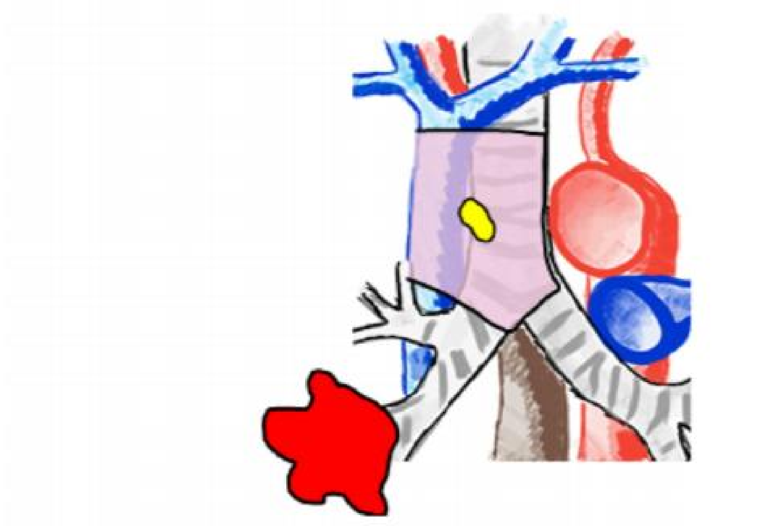
Nodal disease

- GTVn should include all involved lymph nodes or lymph node stations based on pre-chemotherapy clinical, pathological and imaging information
  - even if a node has completely disappeared in imaging.

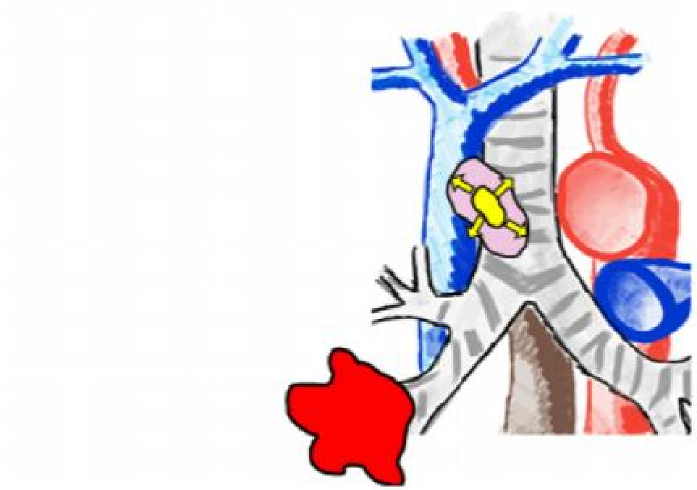
Nestle, RO, 2018

Nodal disease

2a: CTV including the affected lymph node station

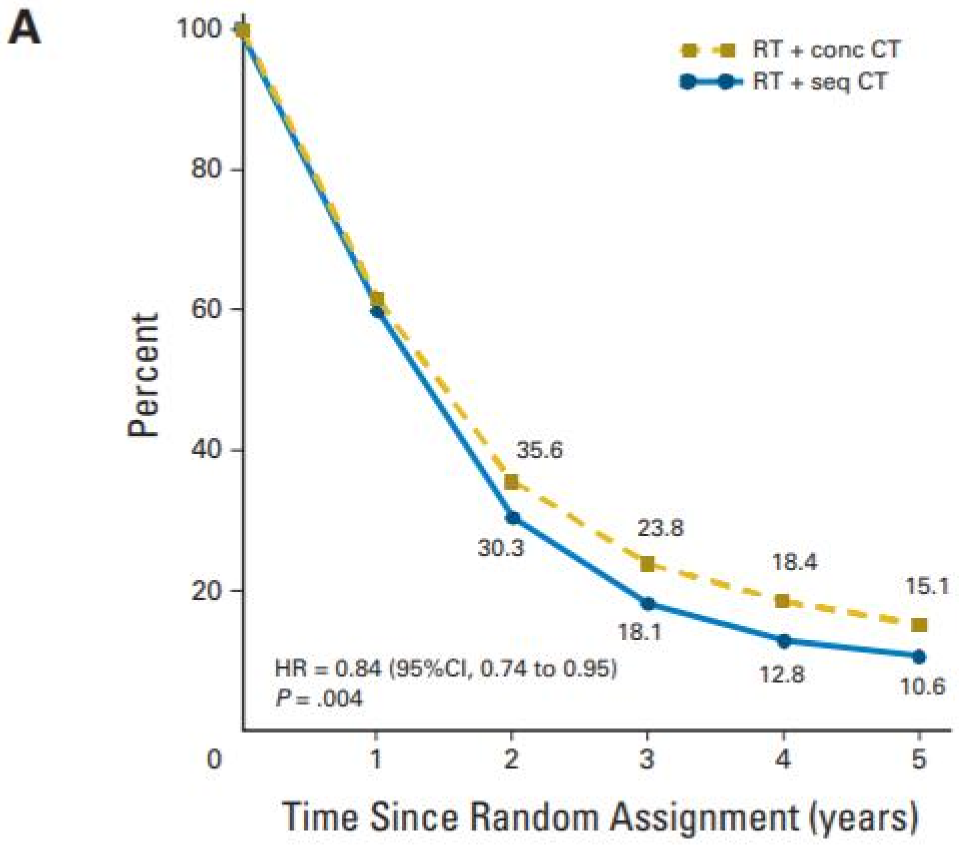


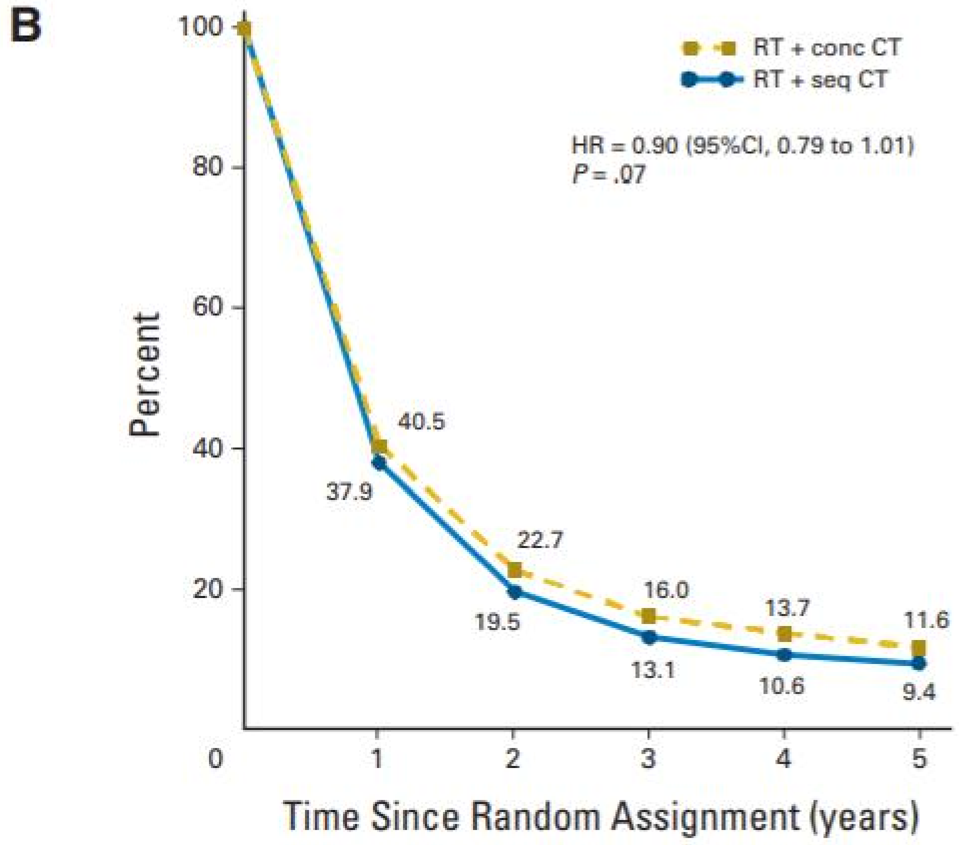
2b: CTV including the nodal GTV plus 5-8 mm margin



Nestle, RO, 2018

Sequential vs concurrent





	Deaths/Person-Years by Period				
	0y–1y	1y–2y	2y–3y	3y–4y	> 4y
RT+ conc CT (n = 595)	365/408	98/170	36/104	12/80	21/134
RT+ seq CT (n = 589)	391/399	90/133	33/80	13/58	12/100

Auperin J Clin Oncol. 2010

Standard of care, but for who?

- Concurrent CTRT

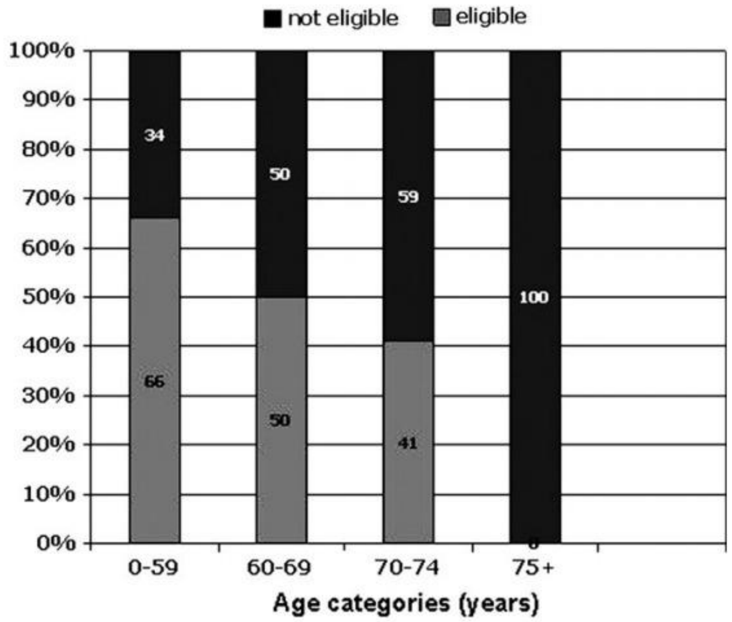


Figure 3. Percentage patients eligible for concurrent therapy.

- 60% patients were considered ineligible for CTRT.
- 80% patients did not receive standard treatment.
  - 35% discontinuation rate with CTRT

De Ruysscher, Annals of Oncology, 2008
Van Der Meer, Anticancer res, 2016

NACT – for who?

- Advanced age
- PS>1
- Large volume
  - Dosimetric challenge
  - Poor pulmonary function
  - Consolidation

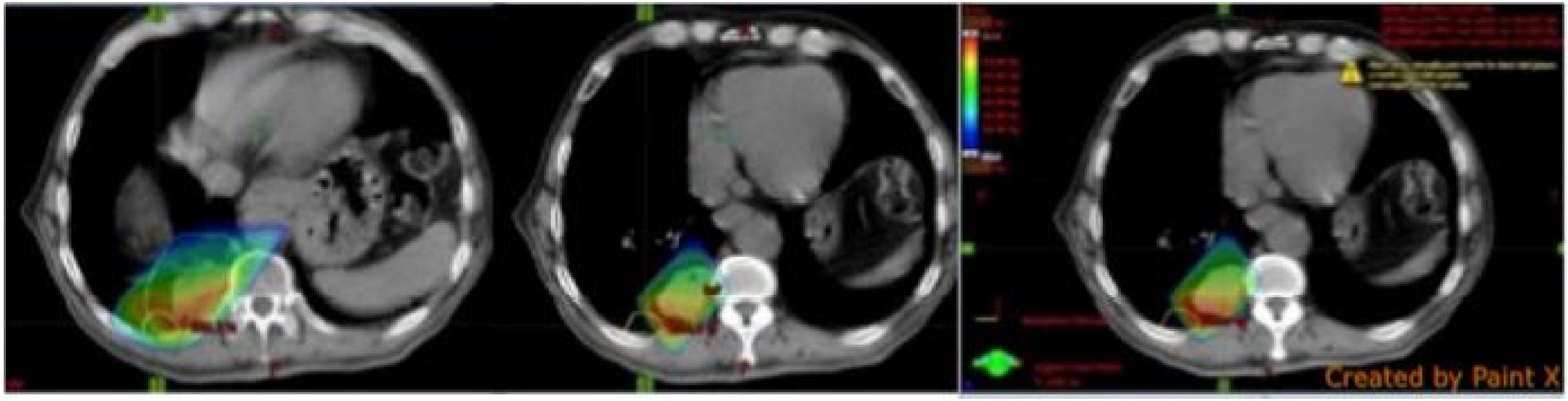
- Oligo-metastatic NSCLC
  - Consolidation RT after systemic therapy

How to contour post NACT?

- Patterns of failure studies
  - Failure at sites of gross disease
  - Lack of benefit from elective volume irradiation
- SCLC
- No Guidelines

Local Control and Toxicity of Adaptive Radiotherapy using Weekly CT Imaging: Results from the LARTIA Trial in Stage III NSCLC

- Local failures were in-field, marginal and out-of-field in 20%, 6% and 4% of cases, respectively.



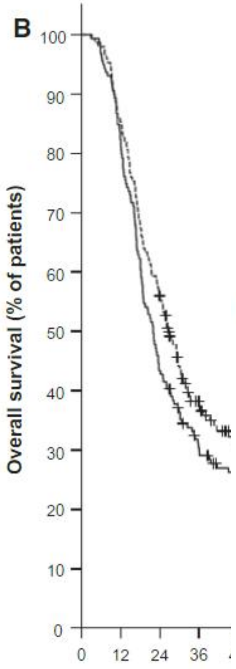
Ramella, JTO 2017

Lessons from SCLC

Final Report of a Prospective Randomized Study on Thoracic Radiotherapy Target Volume for Limited-Stage Small Cell Lung Cancer With Radiation Dosimetric Analyses

TABLE 2. Patterns of First Treatment Failure[a]

Failure Pattern	No. of Patients (%) Study Arm	Control Arm	P
Local/regional failure			.41
Isolated in-field	27 (7.8)	22 (14.9)	
Isolated out-field	4 (2.6)	6 (4.1)	
In-field and out-field	2 (1.3)	1 (0.7)	
Isolated marginal	1 (0.7)	1 (0.7)	
Out-field and marginal	0 (0.0)	1 (0.7)	
Mixed failure			.79
In-field and distant	14 (9.2)	10 (6.8)	
Out-field and distant	3 (1.9)	5 (3.4)	
In-field, out-field, and distant	1 (0.7)	1 (0.7)	
Isolated distant	57 (35.8)	49 (32.7)	.50



Toxic Effect/Grade	No. of Patients (%) Study Arm	Control Arm	P
Acute toxic hematologic toxicity grade ≥3[b]			
Leucopenia			
Grade 3	59 (37.1)	55 (36.7)	.35
Grade 4	13 (8.2)	10 (6.7)	
Neutropenia			
Grade 3	59 (37.1)	56 (37.3)	.72
Grade 4	41 (25.8)	34 (22.7)	
Thrombocytopenia			
Grade 3	32 (20.1)	19 (12.7)	.34
Grade 4	16 (10.1)	12 (8.0)	
Grade 5	1 (0.6)	0 (0.0)	
Anemia			
Grade 3	34 (21.4)	29 (19.3)	.59
Grade 4	15 (9.4)	8 (5.3)	
Radiotherapy-related toxicities[c]			
Pneumonitis			
Grade 1-2	60 (39.4)	65 (43.9)	.40
Grade 3	2 (1.3)	1 (0.7)	
Grade 4	0 (0.0)	0 (0.0)	
Grade 5	2 (1.3)	0 (0.0)	
Esophagitis			
Grade 1	87 (57.2)	63 (42.6)	.01
Grade 2	41 (27.0)	41 (27.7)	
Grade 3	9 (5.9)	23 (15.5)	
Weight loss			
Grade 1	30 (19.7)	43 (29.1)	.16
Grade 2	12 (7.9)	9 (6.1)	

Hu, Cancer 2020

ESTRO ACROP guideline

ESTRO ACROP guidelines for target volume definition in the treatment of locally advanced non-small cell lung cancer

Ursula Nestle [a,b,*], Dirk De Ruysscher [c,d], Umberto Ricardi [e], Xavier Geets [f], Jose Belderbos [g], Christoph Pöttgen [h], Rafal Dziadiuszko [i], Stephanie Peeters [c], Yolande Lievens [j], Coen Hurkmans [k], Ben Slotman [l], Sara Ramella [m], Corinne Faivre-Finn [n], Fiona McDonald [o], Farkhad Manapov [p], Paul Martin Putora [q,r], Cécile LePéchoux [s], Paul Van Houtte [t]

- No specific recommendations for post NACT
- GTV of the primary tumour post induction chemotherapy should be based on current CT imaging
  - Pre-chemotherapy imaging (including PET-CT) should be considered

Nestle, RO, 2018

Summary - Practical considerations

- CTRT - standard
- Sequential treatment can be considered in patients unfit for CTRT.
  - Large volume
  - Poor PFT
  - Dosimetric challenge
- Post NACT
  - GTV – as visible on post NACT imaging
  - CTV – review pre NACT images, note pattern of spread