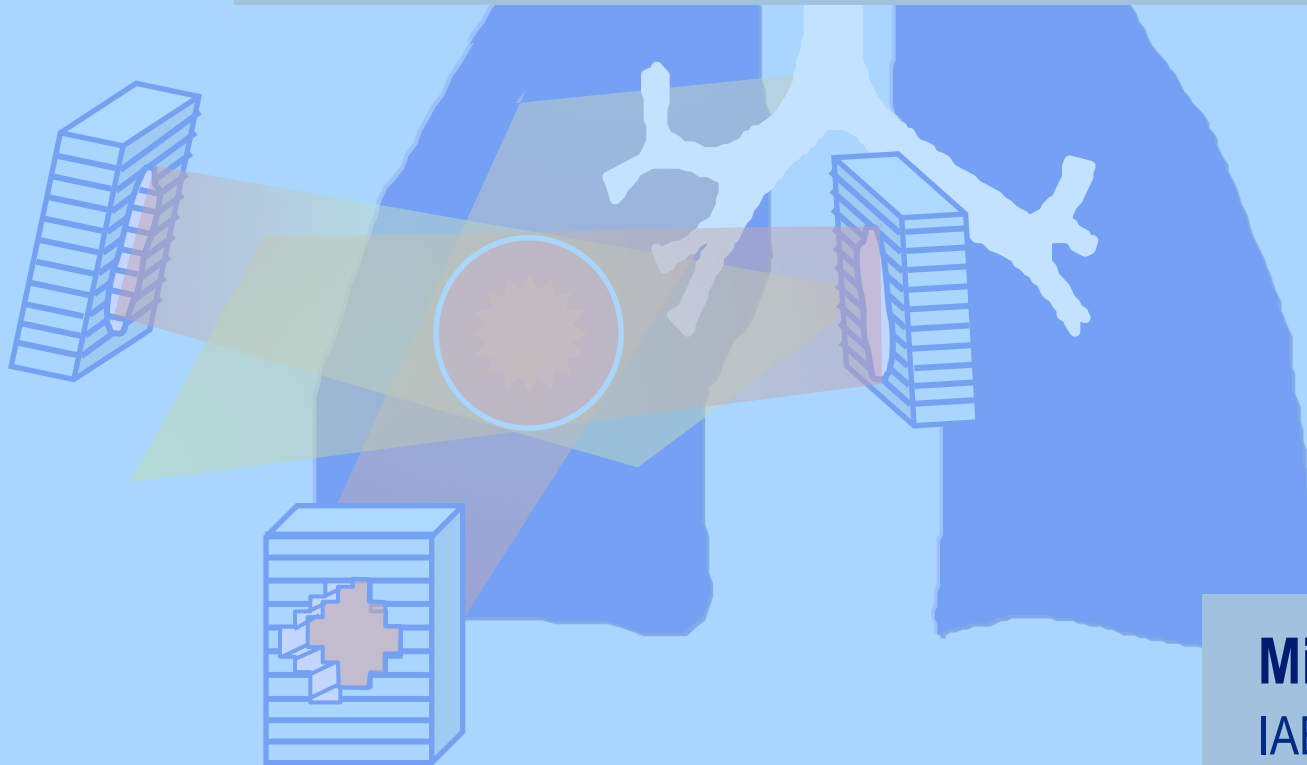


Radiotherapy in the management of non-small cell lung cancer (NSCLC)



Michael Brada

IAEA NTC Bratislava

19 March 2018

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Management options

Localized disease

operable

not fit for surgery

Locally advanced disease

suitable for radical radiotherapy

not suitable for radical radiotherapy

Disseminated disease

→ **Surgery**

Radical RT

**Palliative
Rx**

systemic therapy

Radiotherapy in non-small cell lung cancer (NSCLC)

Management options

Localized disease

operable

not fit for surgery

Locally advanced disease

suitable for radical radiotherapy

not suitable for radical radiotherapy

Disseminated disease

→ Surgery

Radical RT

Palliative
Rx

systemic therapy

Radiotherapy in non-small cell lung cancer (NSCLC)

63 year old man

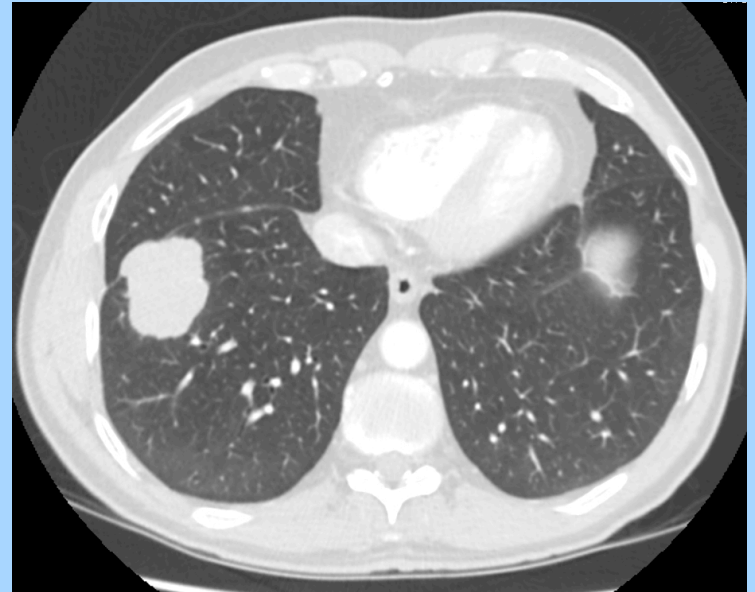
3 months history of cough & dyspnoea

past history

right deafness (injury in childhood)

Clinical case - presentation

T2N2M0

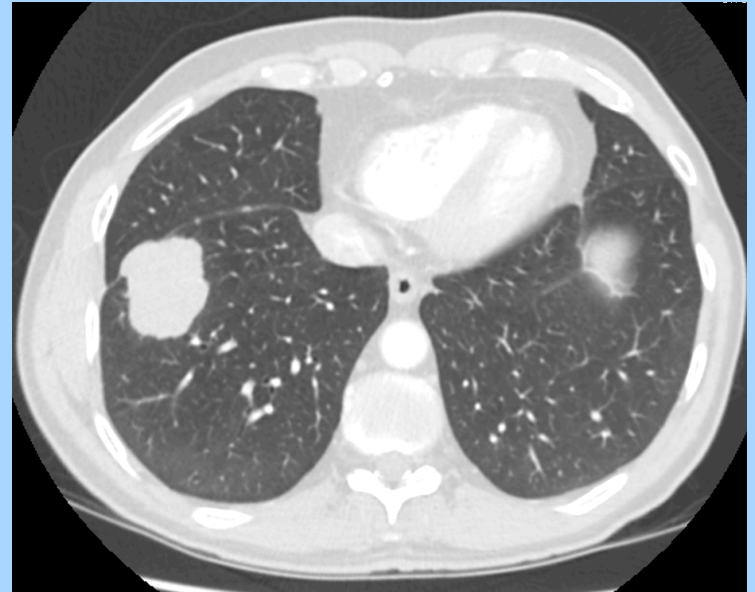


Clinical case – imaging & staging

T2N2M0



adenocarcinoma*



***EGFR – wild type
ALK - fusion**

Clinical case – imaging & staging

Best management option for ALK +ve stage IIIA (T2N2M0) adenocarcinoma treated with radical radiotherapy

radiotherapy alone

sequential chemo-radiotherapy

sequential chemo-radiotherapy followed
by surgery

concomitant chemo-radiotherapy

sequential targeted agents (TKI - crizotinib
or alectinib) followed by radiotherapy

sequential targeted agents (TKI) followed
by concomitant radiotherapy and TKI



The diagram shows a human silhouette with a lung cancer patient highlighted in blue. A white circle on the lung indicates the target area. Three colored beams (yellow, green, red) represent different radiation treatment plans. To the left, a 3D grid of blue and red cubes illustrates the spatial distribution of the radiation dose. Below the grid, a 3D grid of blue cubes shows a cross-section of the dose distribution, with a red cross-shaped area indicating the target volume.

current radiotherapy practice

localised disease

locally advanced disease

Radiotherapy in non-small cell lung cancer (NSCLC)



The diagram shows a human torso with a lung cancer patient. A radiation beam is shown entering the patient's chest area. The beam is represented by a series of colored rectangles (yellow, green, blue, red) that overlap. The text boxes are overlaid on the right side of the torso. The background is a solid light blue.

current radiotherapy practice

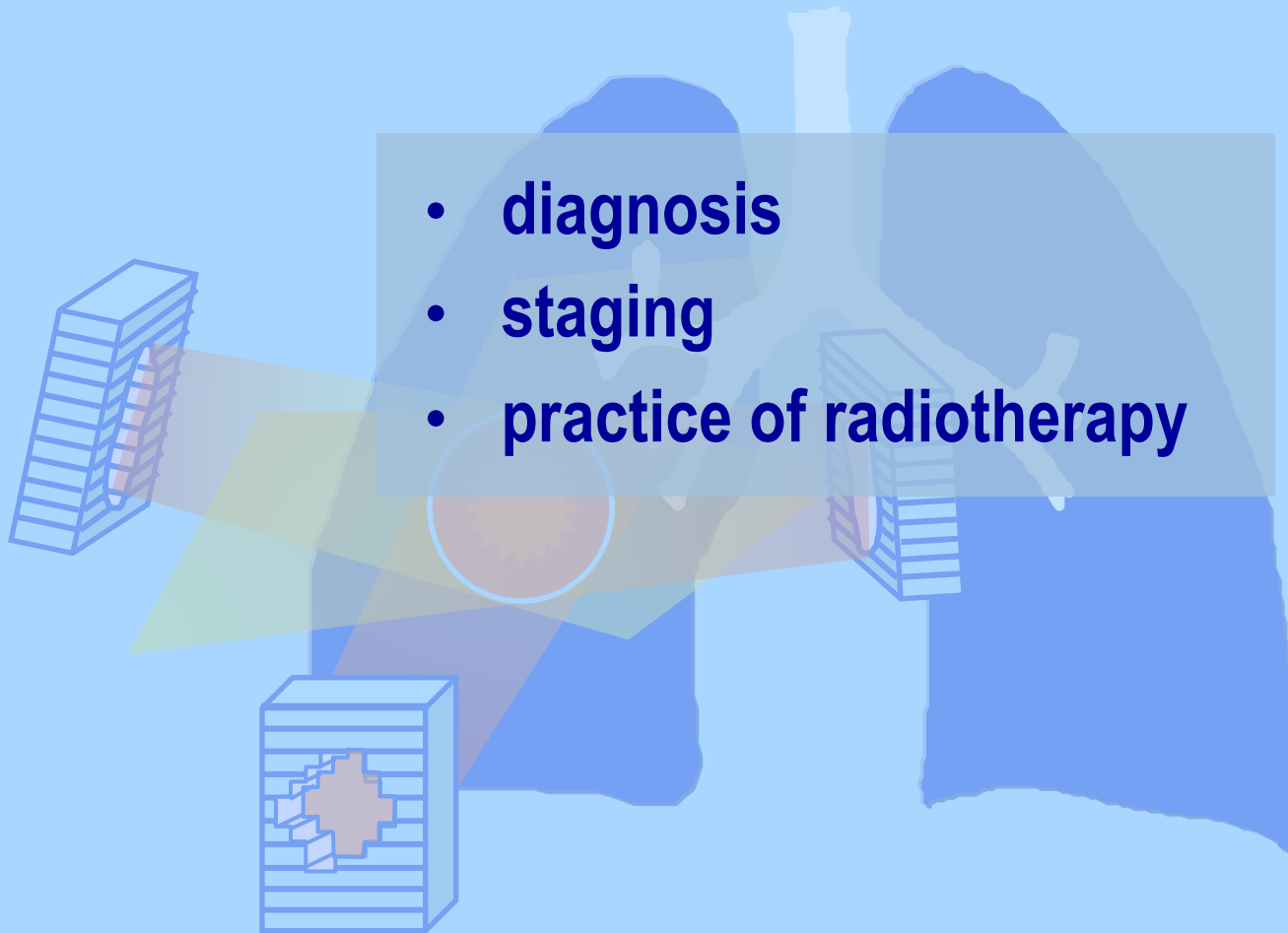
localised disease

locally advanced disease

Radiotherapy in non-small cell lung cancer (NSCLC)

Radical radiotherapy in NSCLC

- diagnosis
- staging
- practice of radiotherapy



Radiotherapy in non-small cell lung cancer (NSCLC)

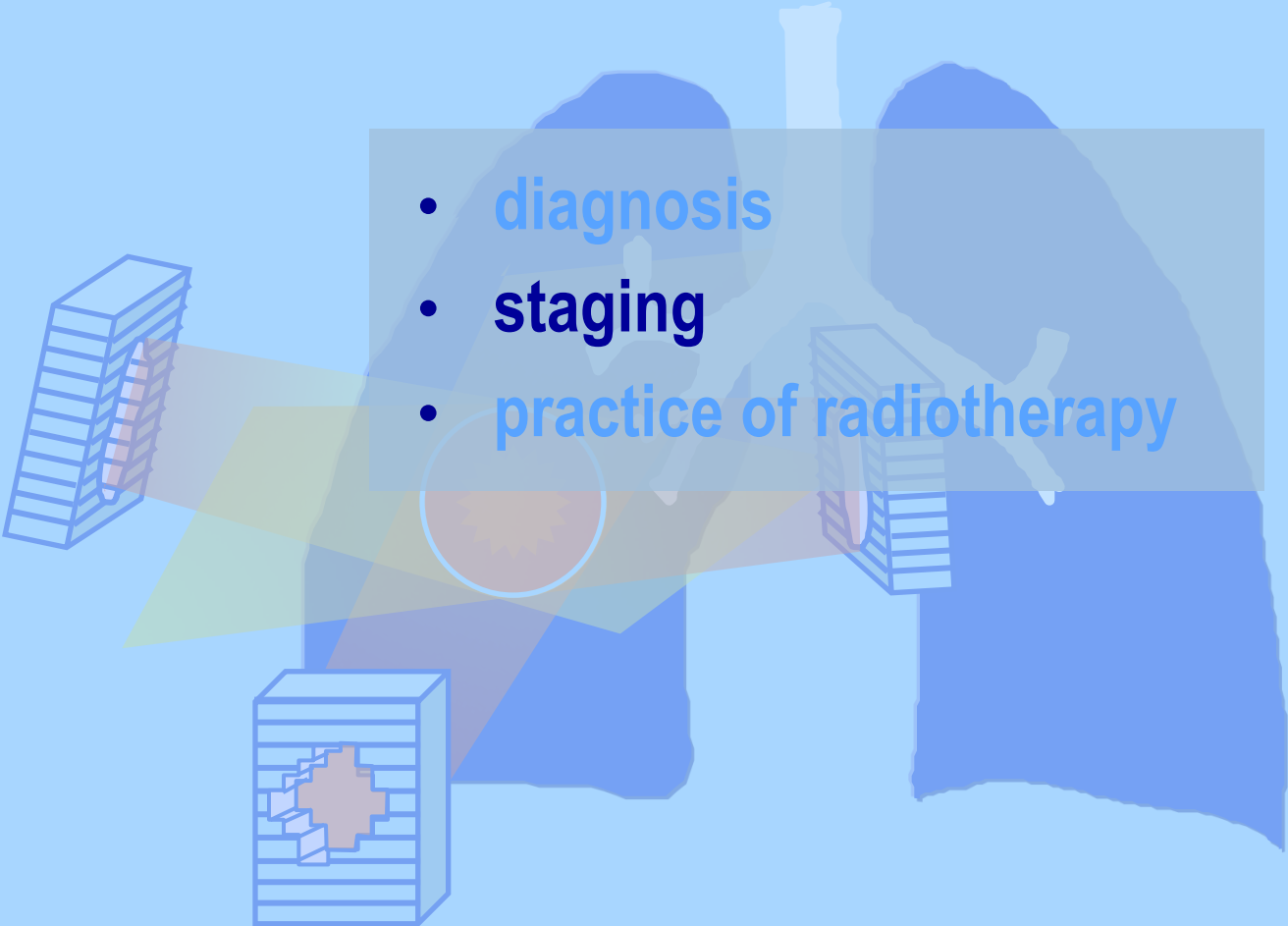
Radical radiotherapy in NSCLC

- 
- diagnosis
 - staging
 - practice of

histological subtype
mutational status
PD-1/PDL-1 status

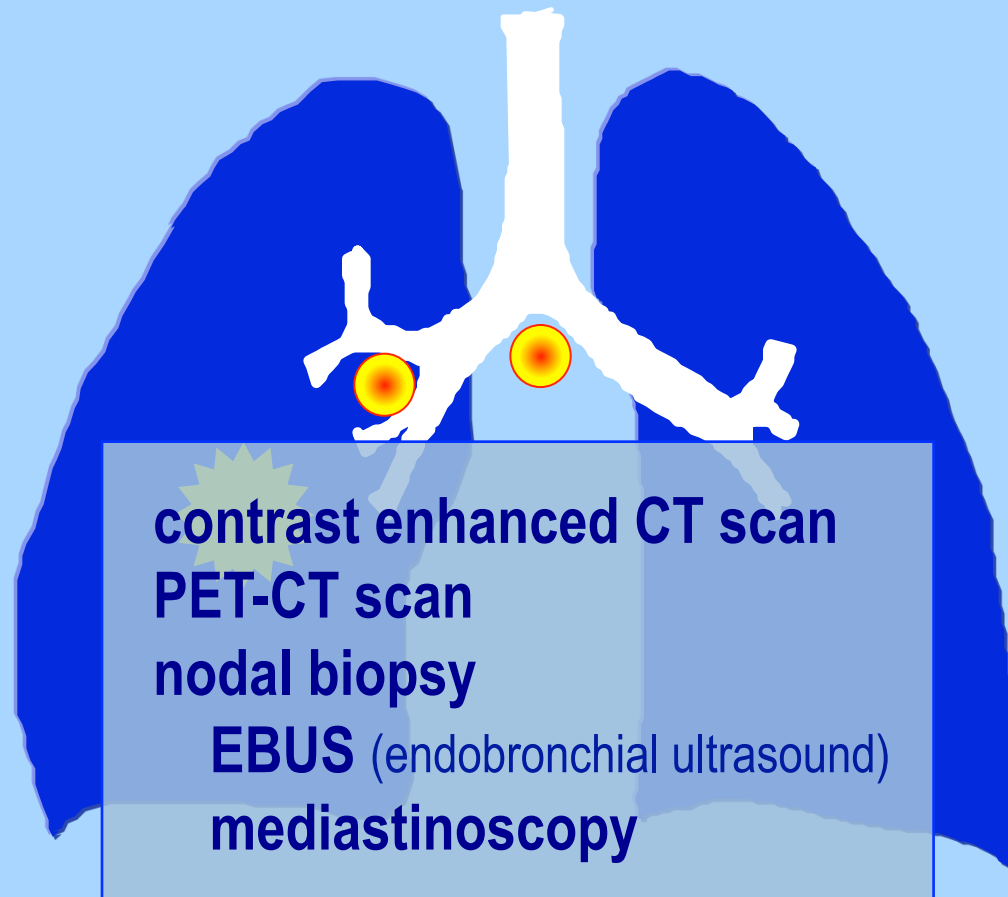
Radiotherapy in non-small cell lung cancer (NSCLC)

Radical radiotherapy in NSCLC

- 
- The diagram illustrates the application of radical radiotherapy in Non-Small Cell Lung Cancer (NSCLC). It features a central, semi-transparent blue silhouette of human lungs. Three rectangular blocks, representing radiotherapy treatment units, are positioned around the lungs: one on the left, one on the right, and one at the bottom center. Each block has a grid of horizontal lines and a central orange cross-like shape. Colored beams of light (yellow, green, and purple) emanate from these blocks and converge on a central point within the lung silhouette, where a small orange starburst indicates the target area. A semi-transparent grey rectangular box is overlaid on the central part of the lung silhouette, containing a bulleted list of three items: 'diagnosis', 'staging', and 'practice of radiotherapy'.
- diagnosis
 - staging
 - practice of radiotherapy

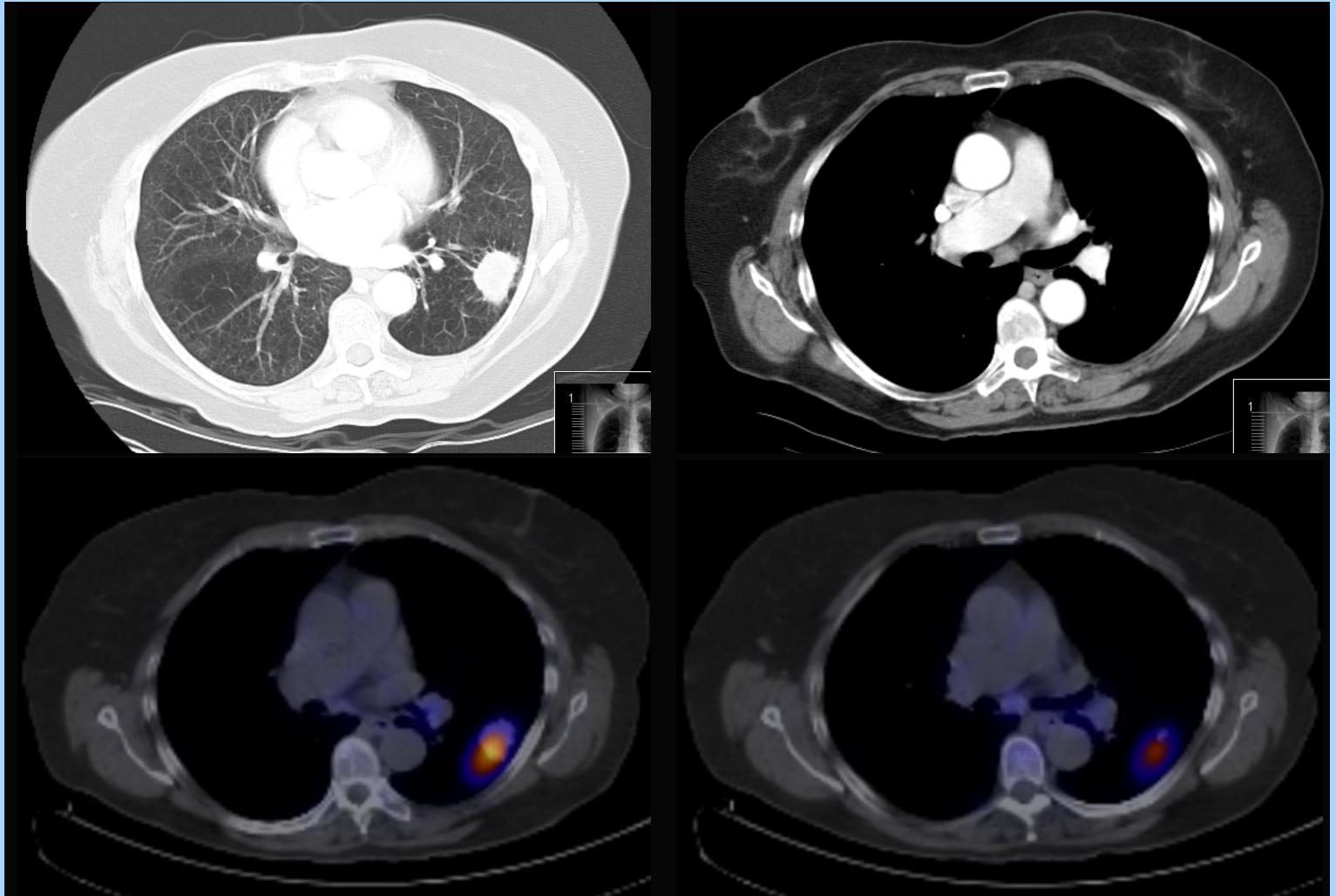
Radiotherapy in non-small cell lung cancer (NSCLC)

Lymph node staging




Staging of non-small cell lung cancer (NSCLC)

Lymph node staging



Staging of non-small cell lung cancer (NSCLC)

Radical radiotherapy in NSCLC

- 
- The diagram illustrates the application of radical radiotherapy in Non-Small Cell Lung Cancer (NSCLC). It features a central, semi-transparent illustration of human lungs. Overlaid on this are three 3D block-like structures representing radiation therapy beams: one on the left, one on the right, and one at the bottom. These beams converge towards a central point within the lung area, which is highlighted by a circular orange glow. A list of three items is positioned in the center of the image, overlaid on the lung illustration.
- diagnosis
 - staging
 - **practice of radiotherapy**

Radiotherapy in non-small cell lung cancer (NSCLC)

Preparation for treatment

immobilisation

imaging for planning

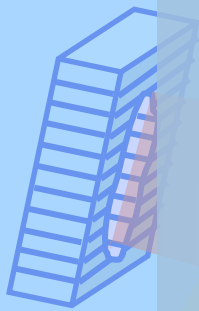
3D or 4D CT scan

PET-CT

target definition

margins

planning & dose constraints



Practical aspect of NSCLC radiotherapy

Preparation for treatment

immobilisation

imaging for planning

3D or 4D CT scan

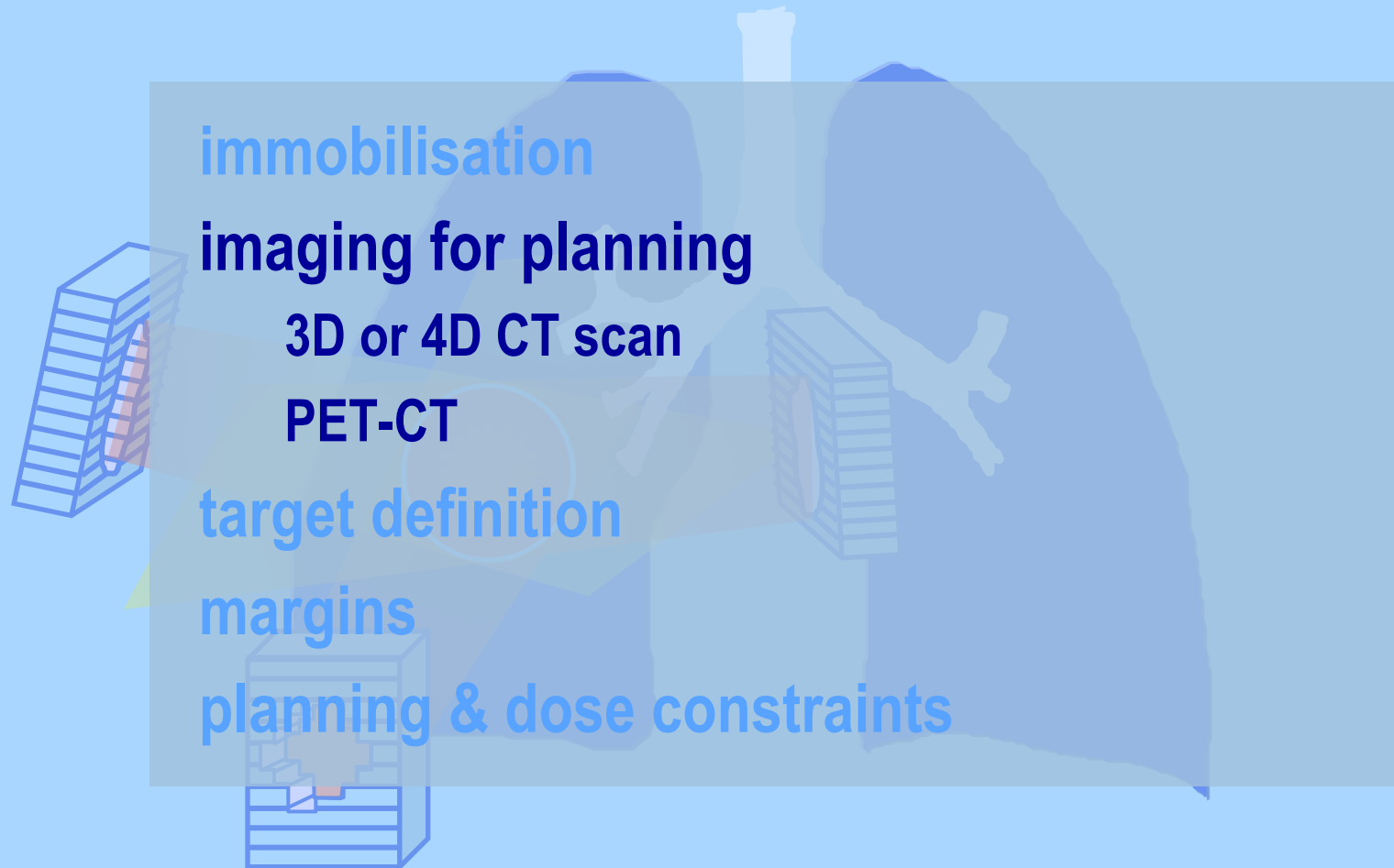
PET-CT

positioning constraints



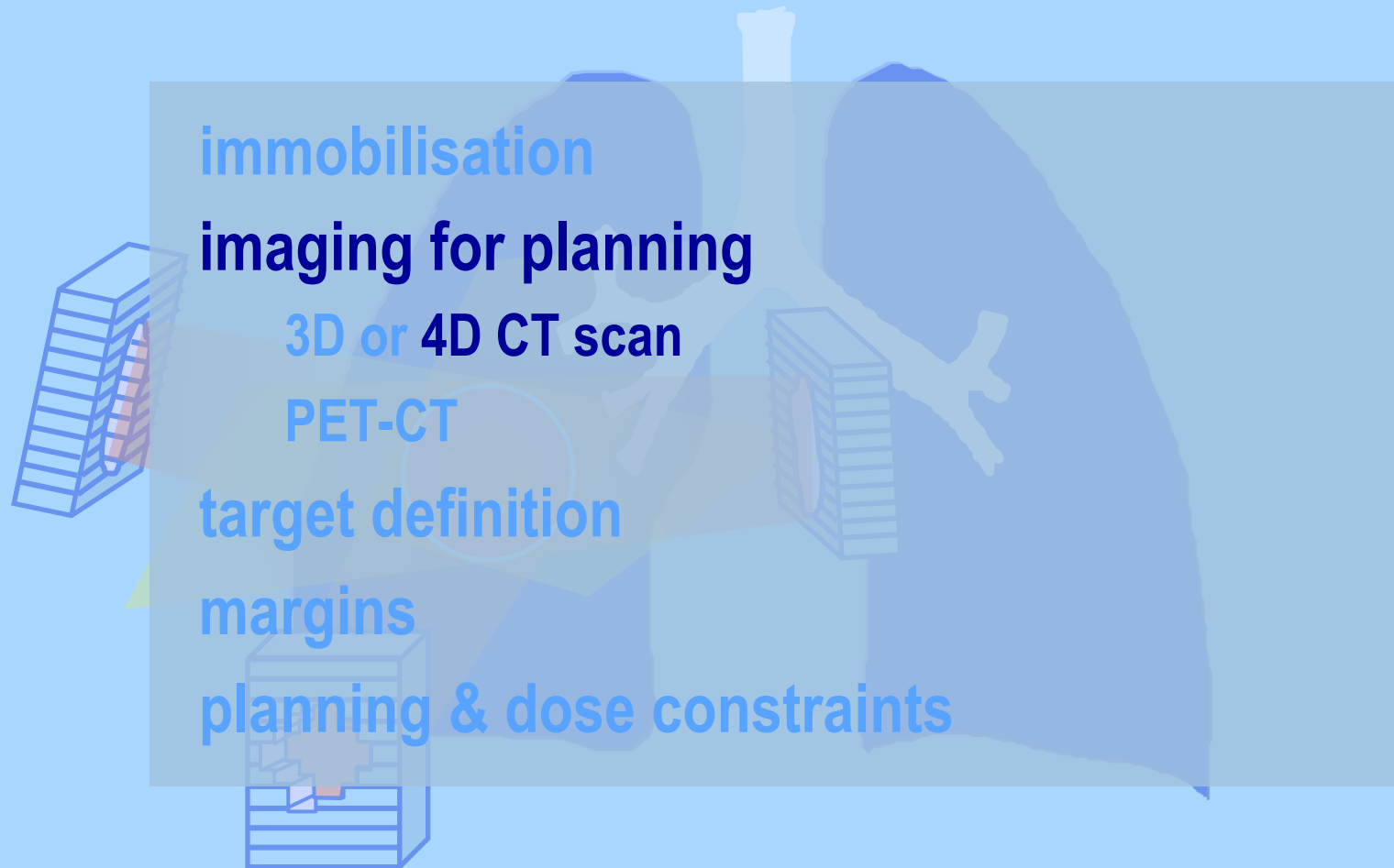
Practical aspect of NSCLC radiotherapy

Preparation for treatment



Practical aspect of NSCLC radiotherapy

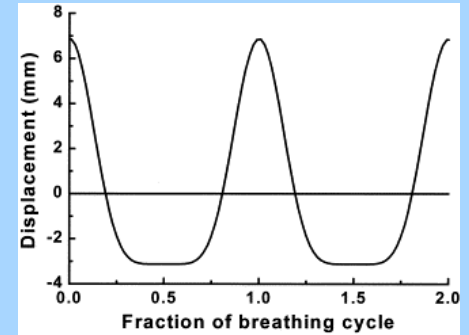
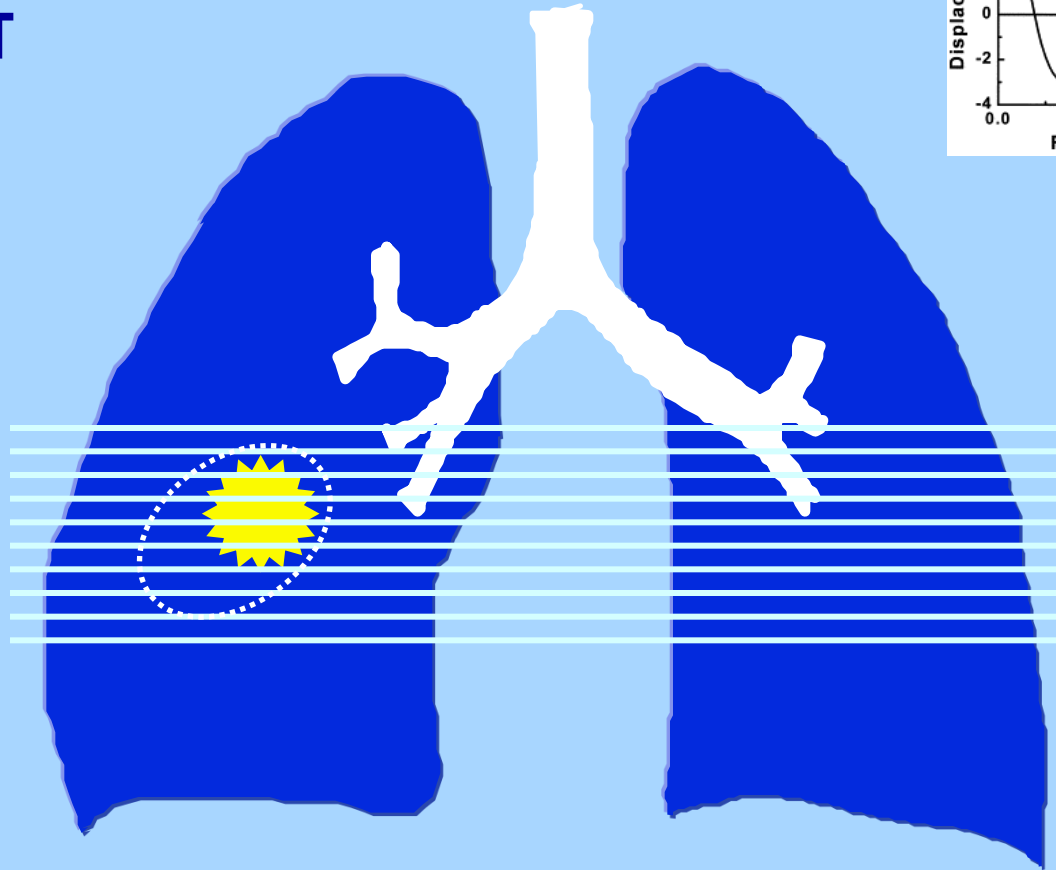
Preparation for treatment



Practical aspect of NSCLC radiotherapy

Imaging of a moving target

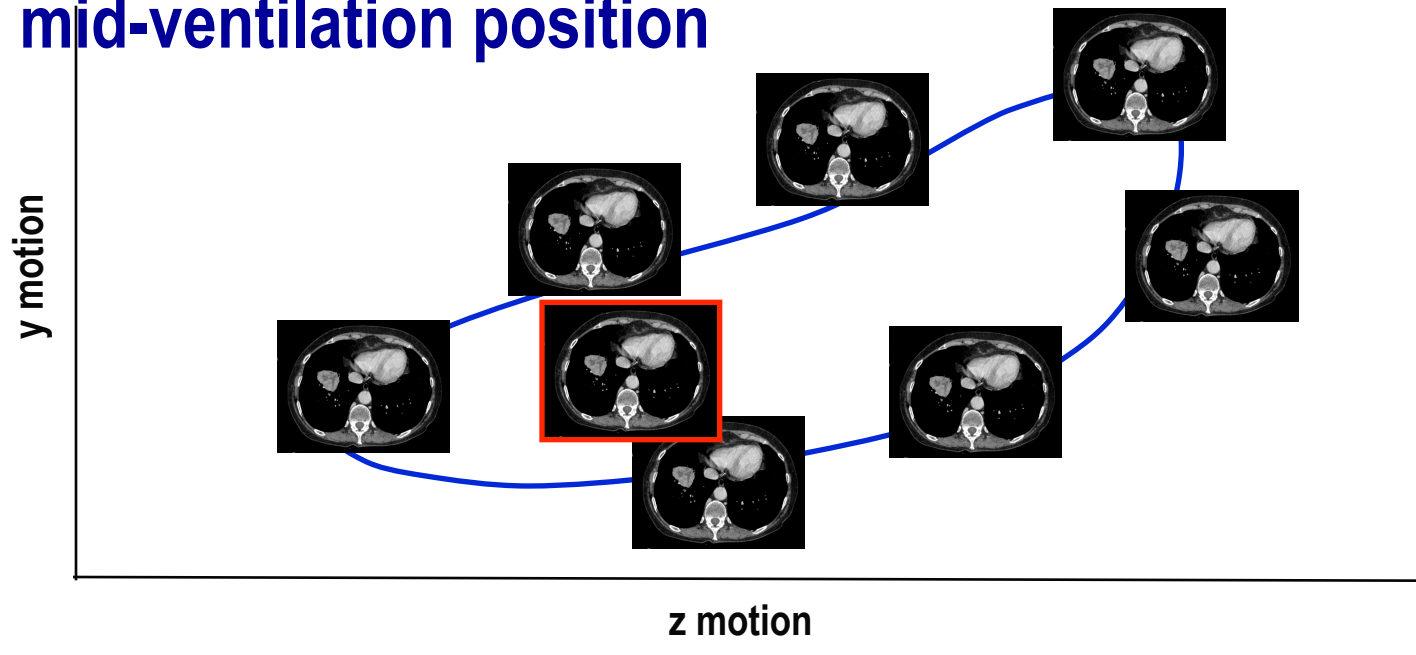
4D CT



CT for delineation of primary tumour

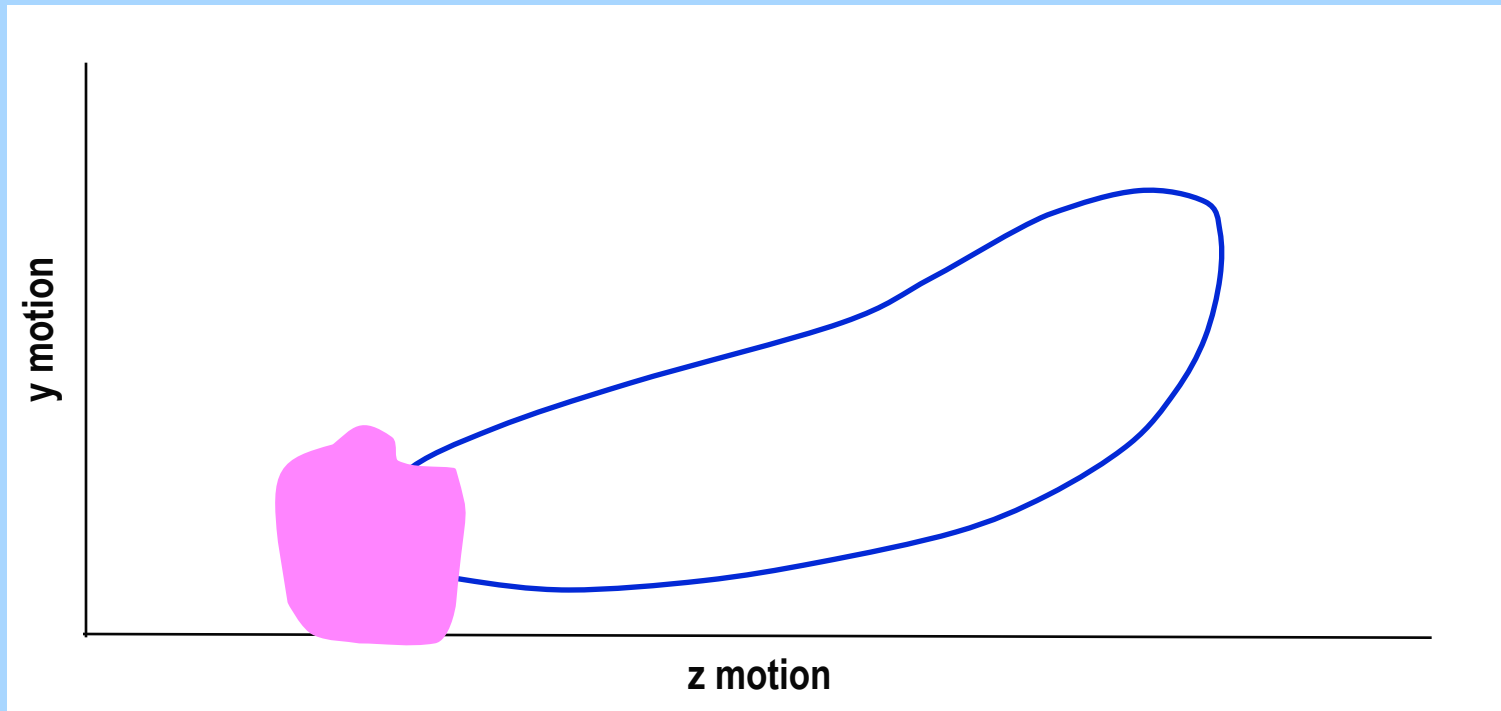
4D CT

mid-ventilation position



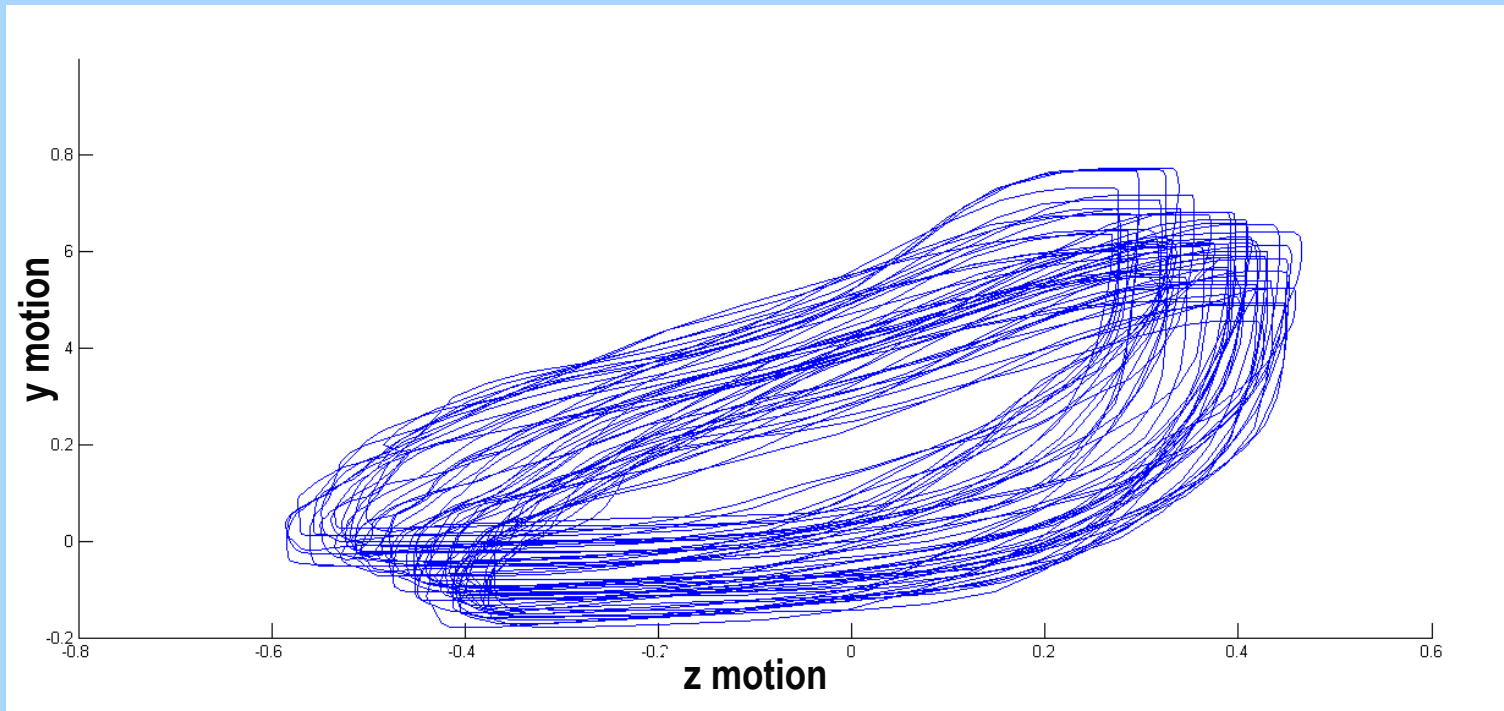
Defining the extent of movement

lung tumour hysteresis in 2 dimensions



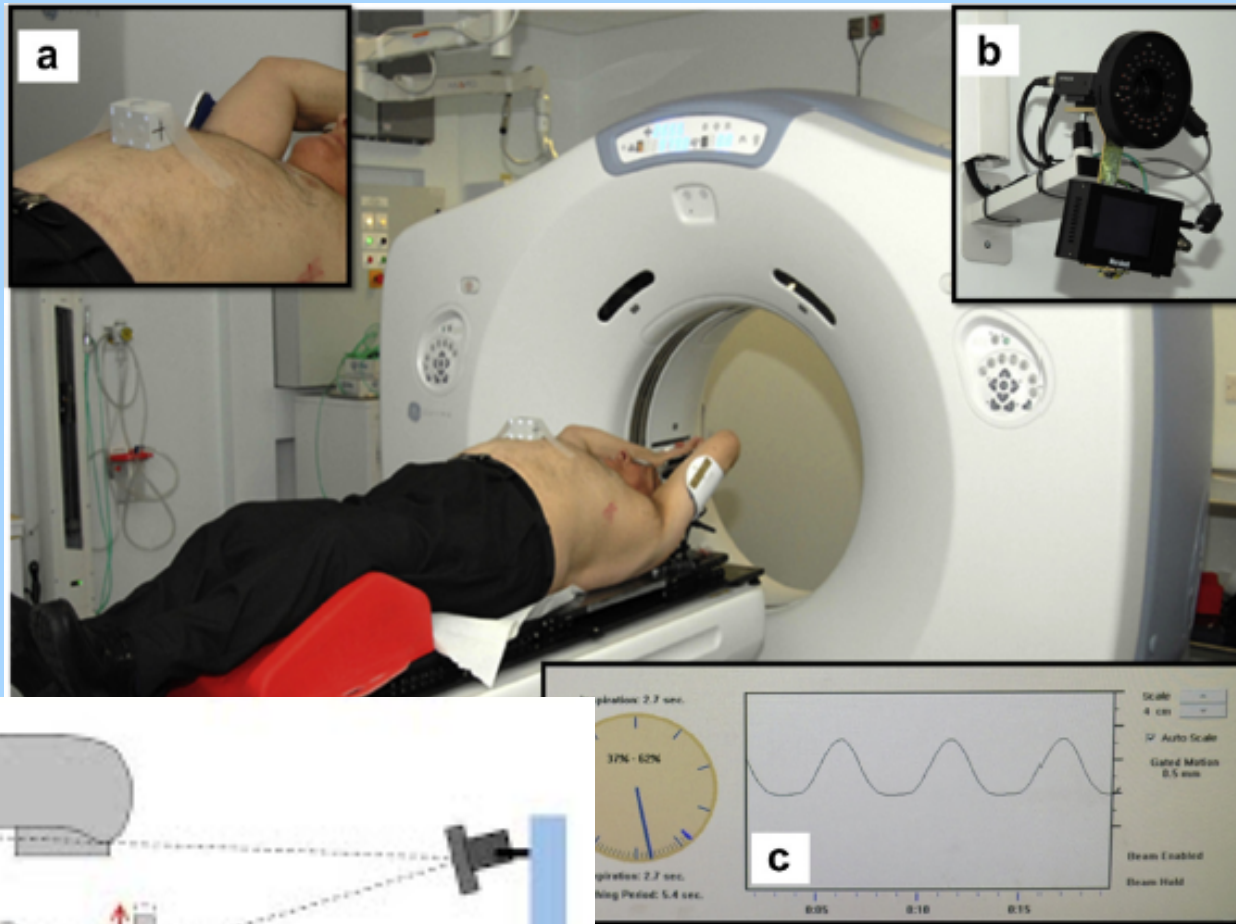
Respiratory induced tumour movement

realistic lung tumour hysteresis in 2 dimensions



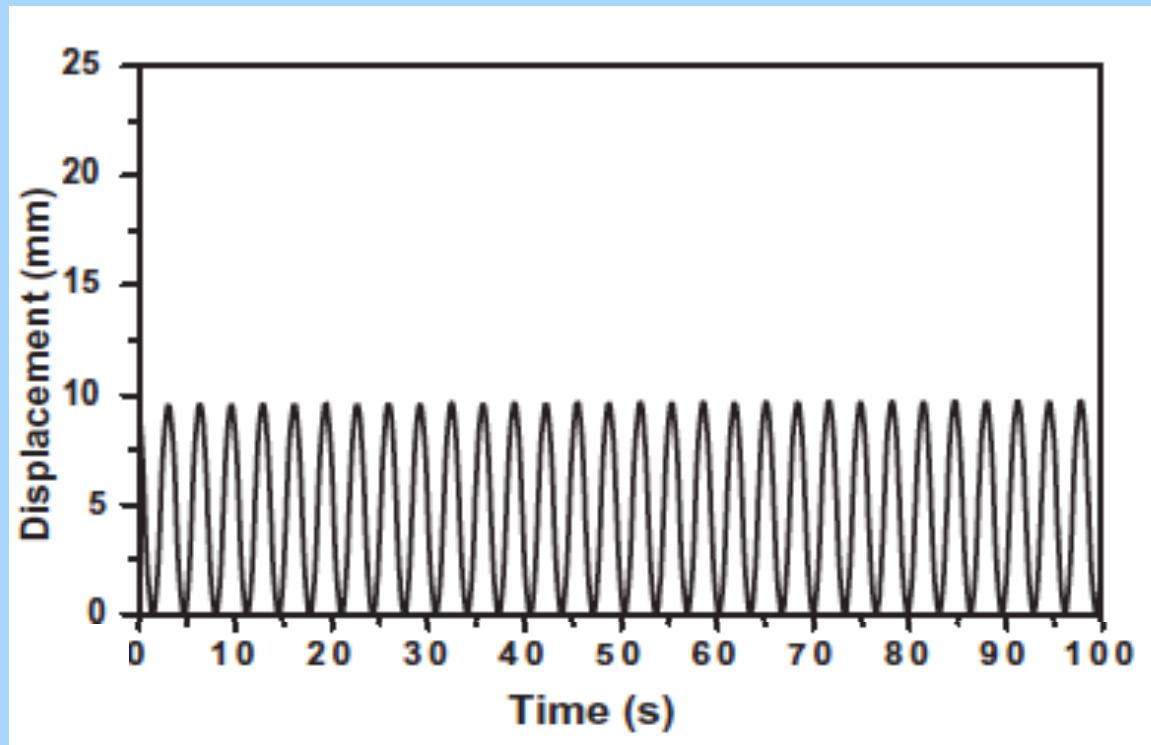
Respiratory induced tumour movement

Real-time Position Management (RPM) system



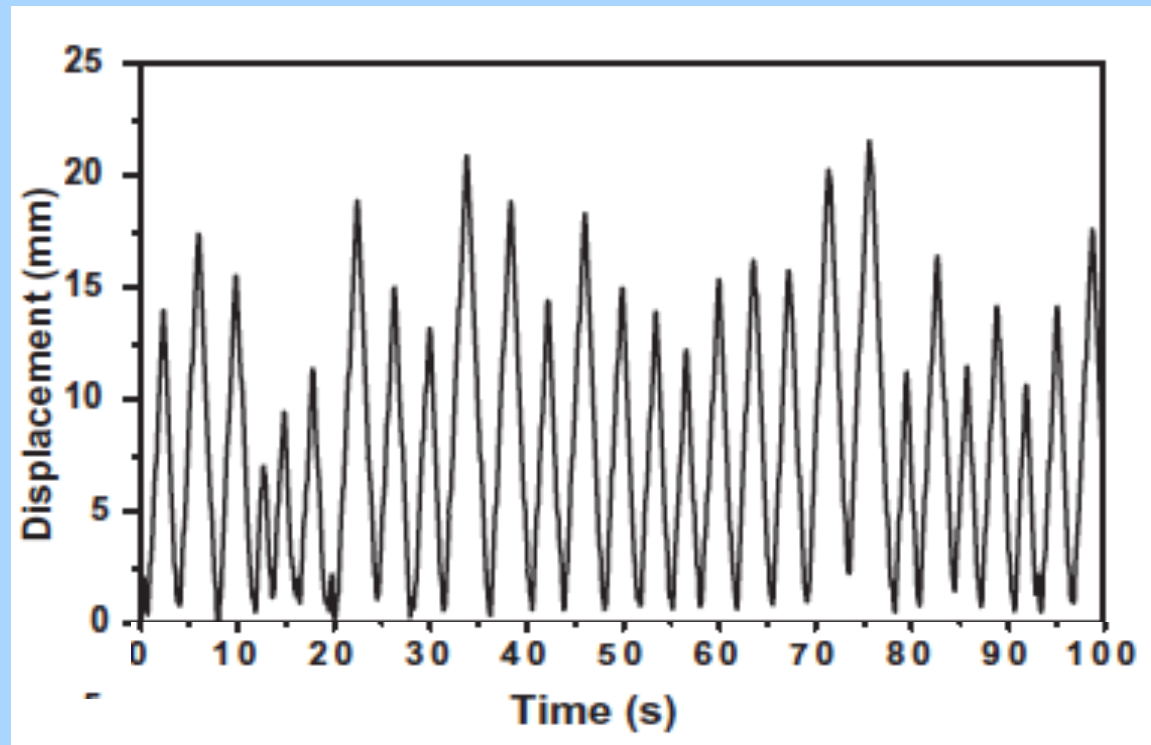
Capturing respiratory phase

Systems for assessing respiration (lung phantom simulating patient)



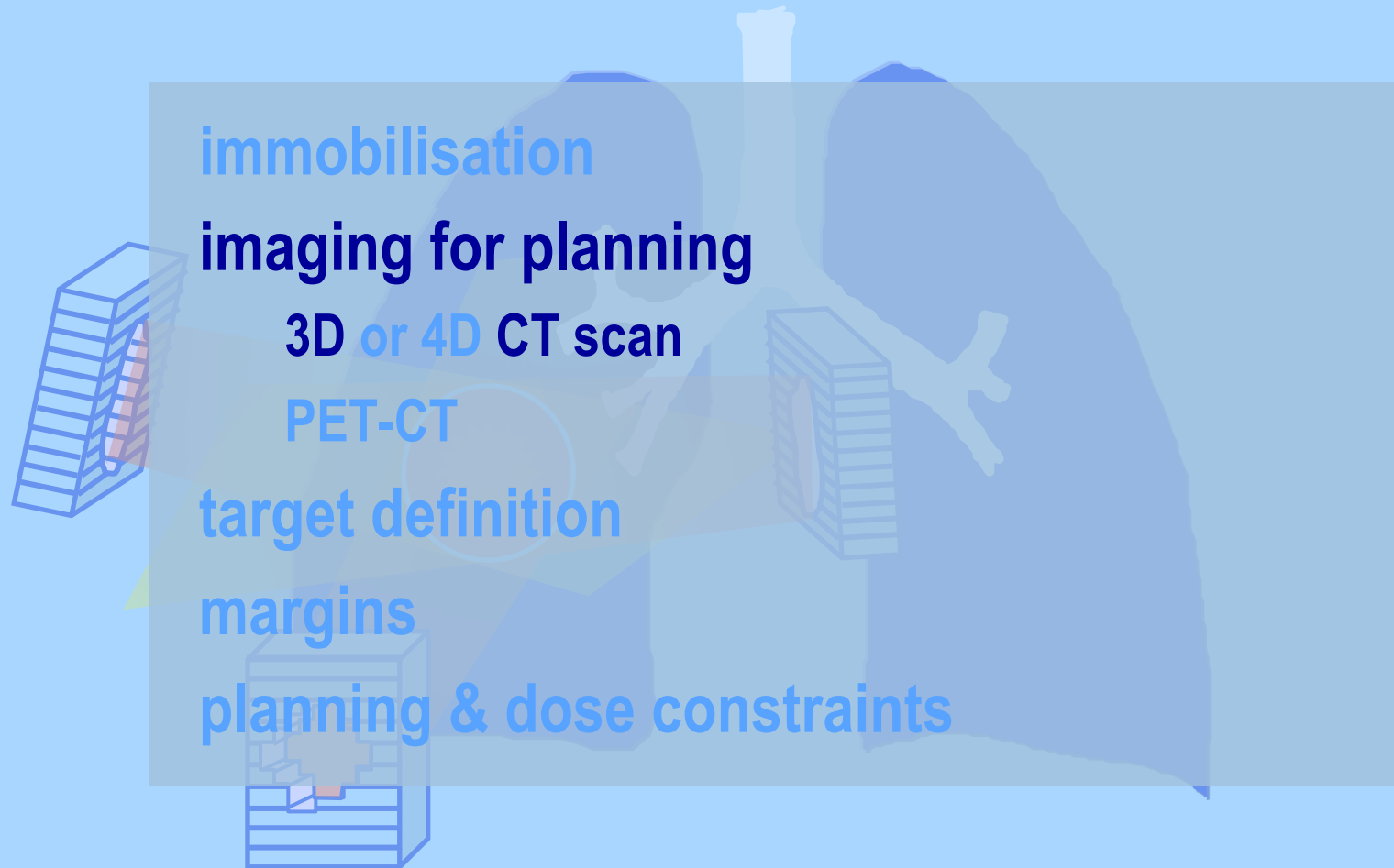
Capturing respiratory phase

Systems for assessing respiration (lung phantom simulating patient)



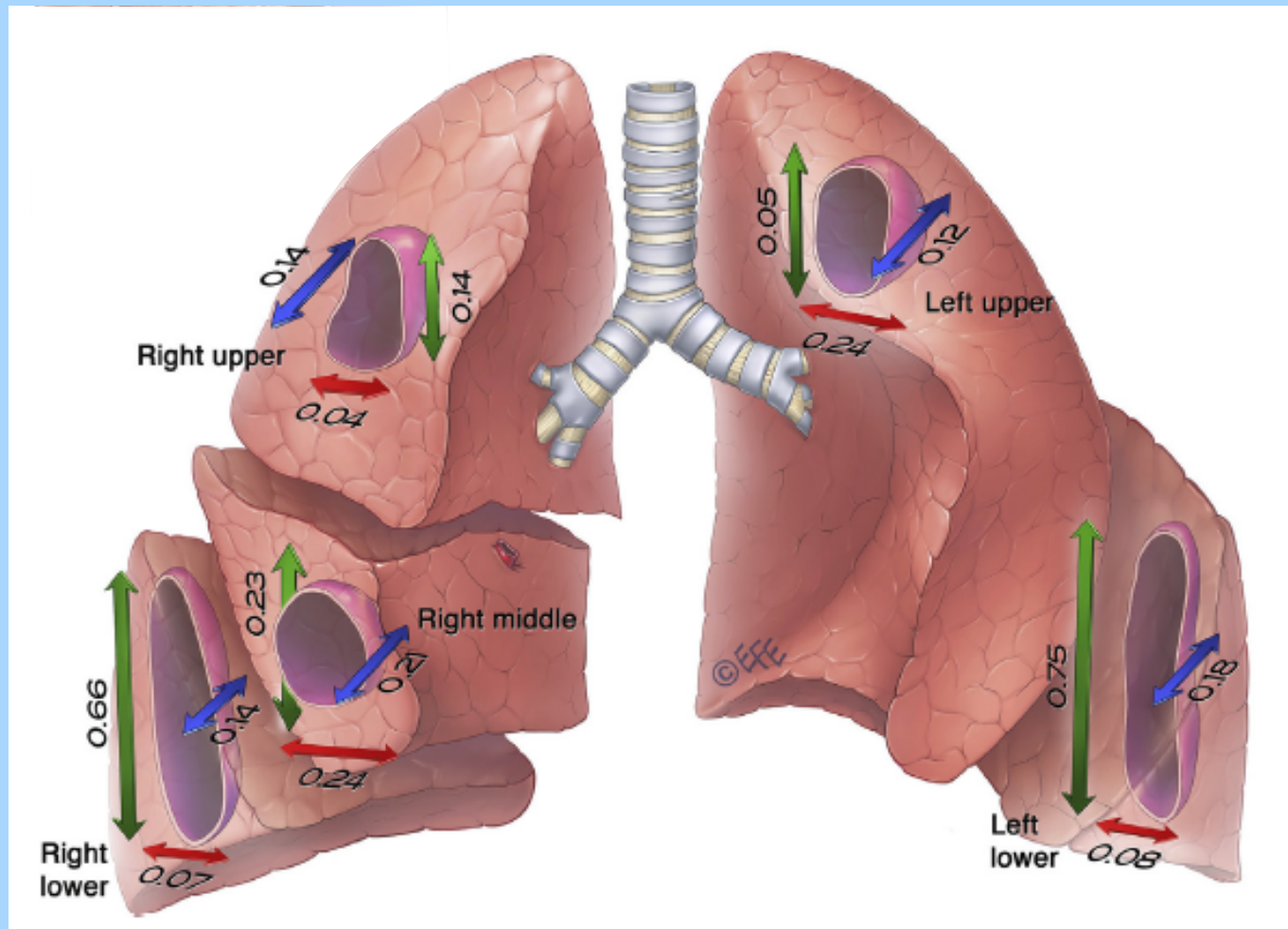
Capturing respiratory phase

Preparation for treatment



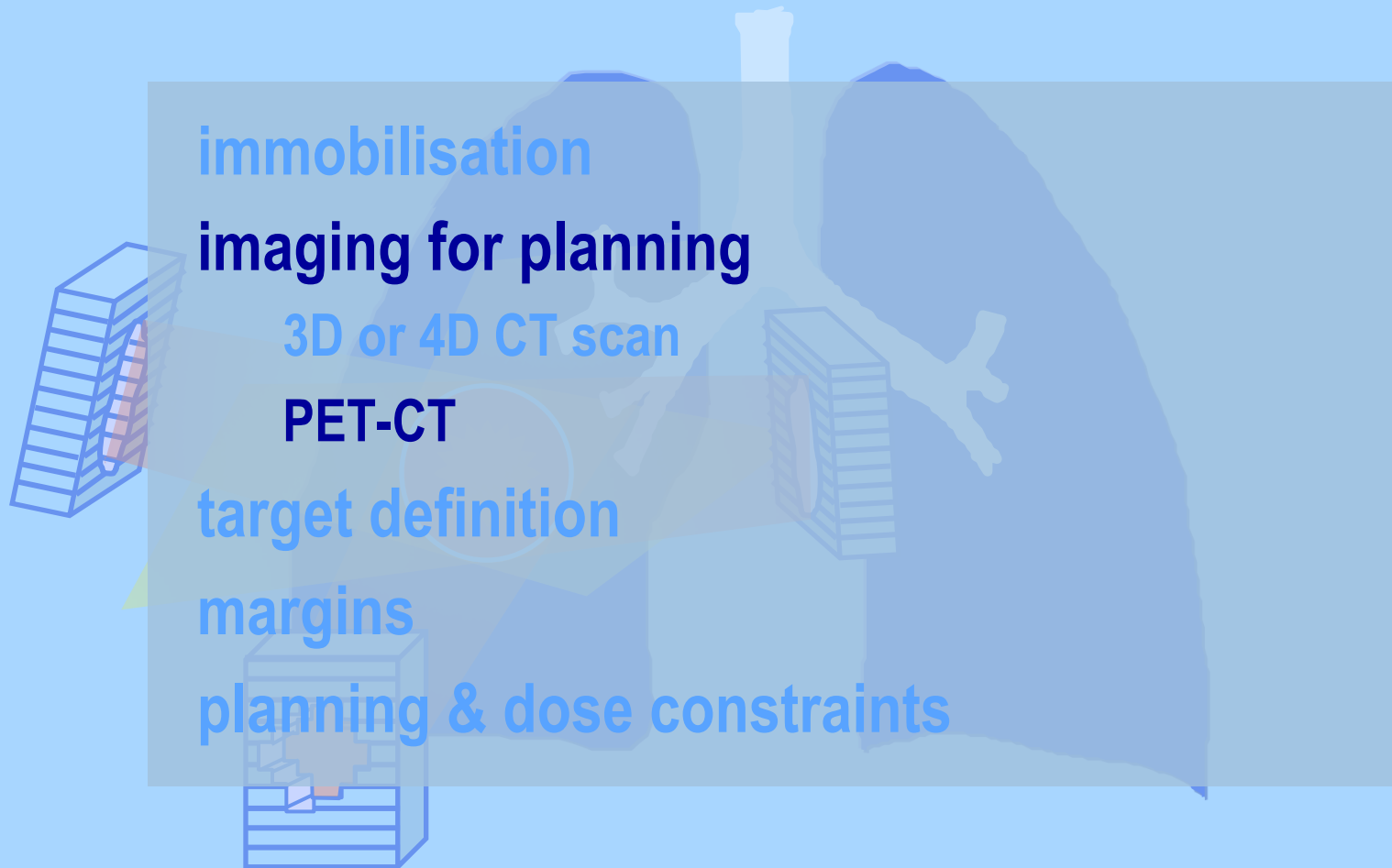
Practical aspect of NSCLC radiotherapy

Respiratory induced lung tumour motion

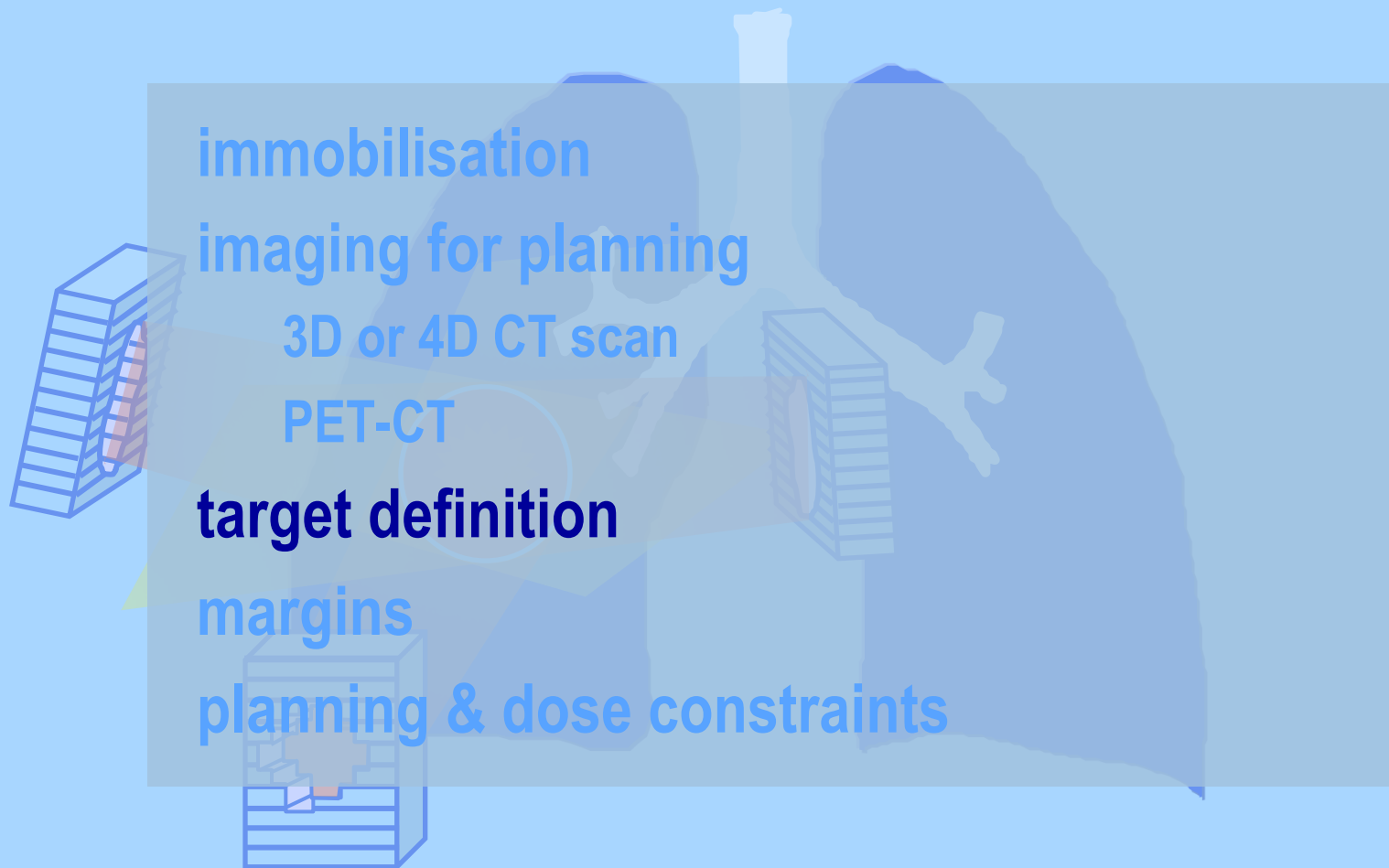


Measured tumour movement

Preparation for treatment

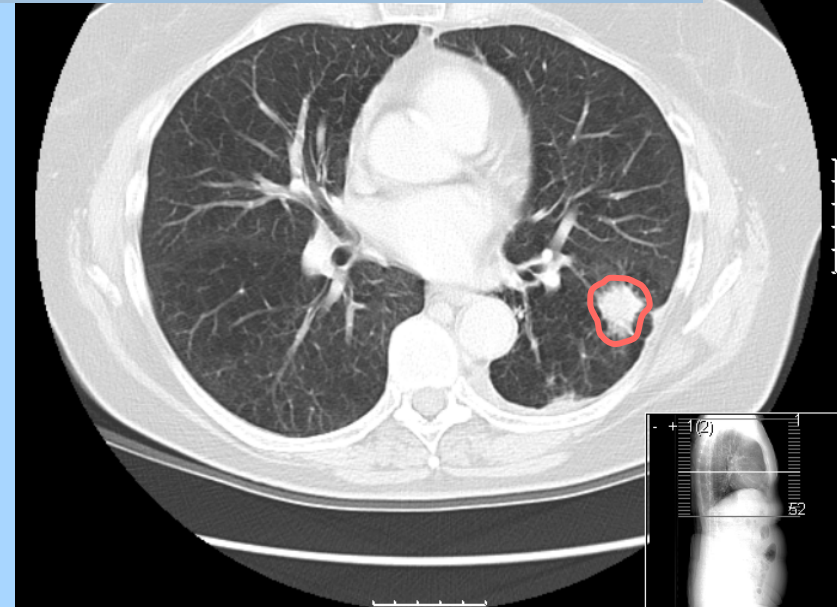
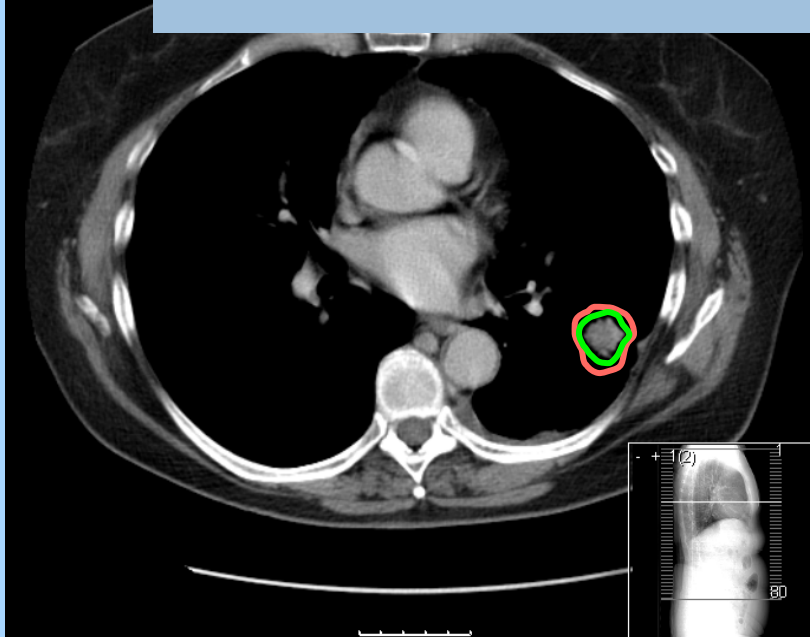


Practical aspect of NSCLC radiotherapy



Practical aspect of NSCLC radiotherapy

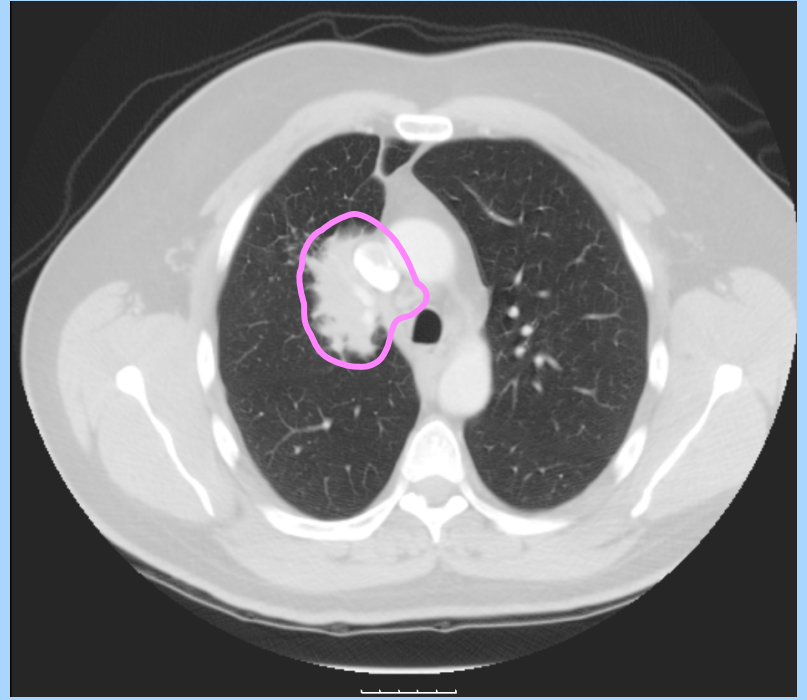
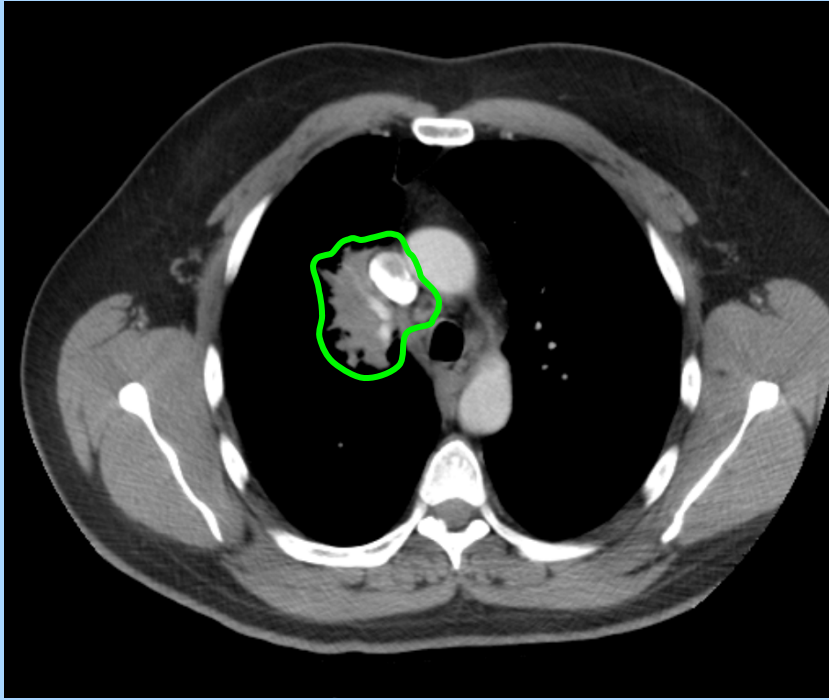
**pathological tumour size correlated better
with lung window tumour size**



**35 patients with T1N0 adenoca
wedge biopsy → lobectomy**

CT for delineation of primary tumour

Grills et al 2007

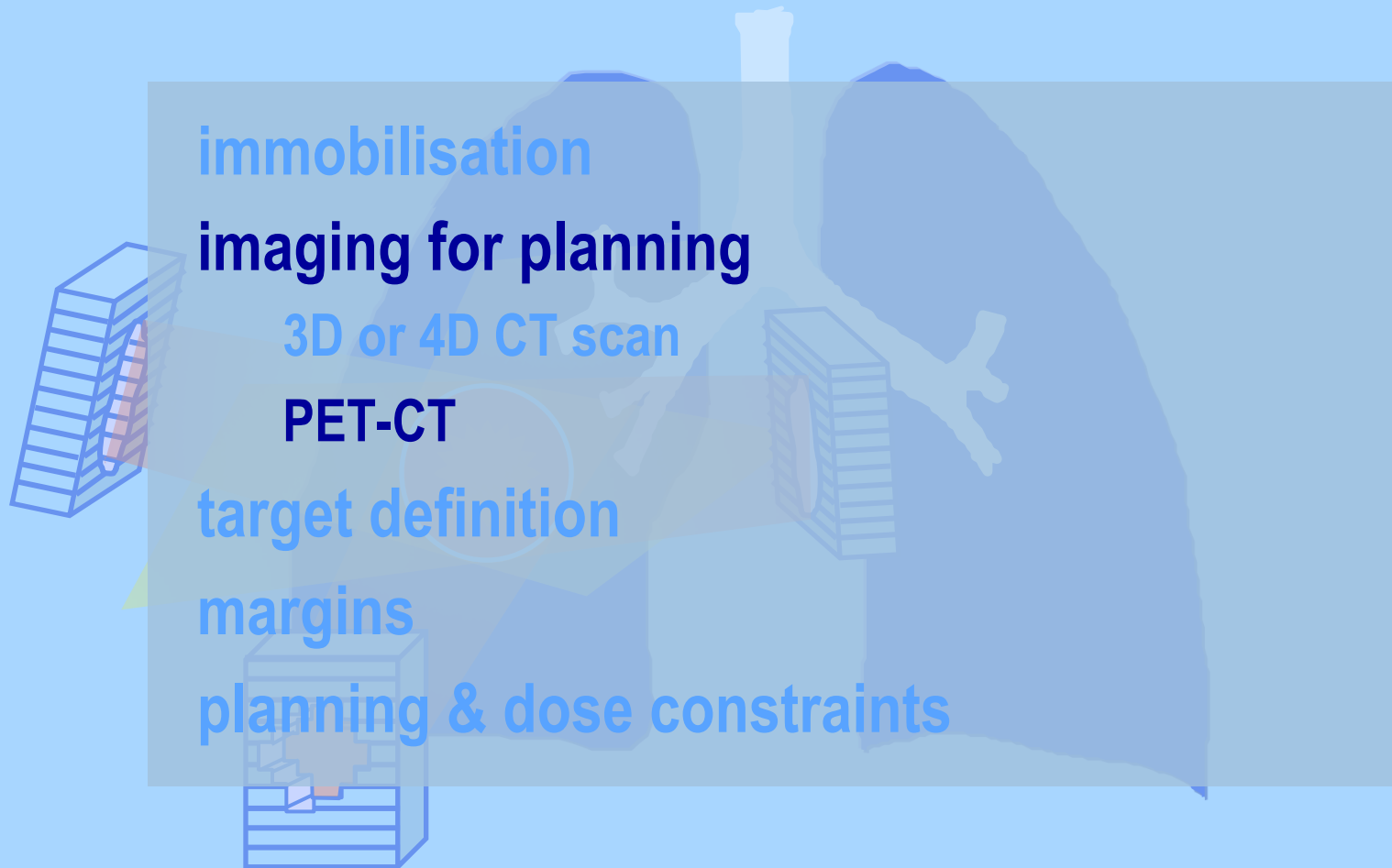


Delineation of primary tumour



Delineation of primary tumour

Preparation for treatment



Practical aspect of NSCLC radiotherapy

Which form of imaging used for outlining for radical RT has been shown to improve treatment outcome

3D CT

4D CT

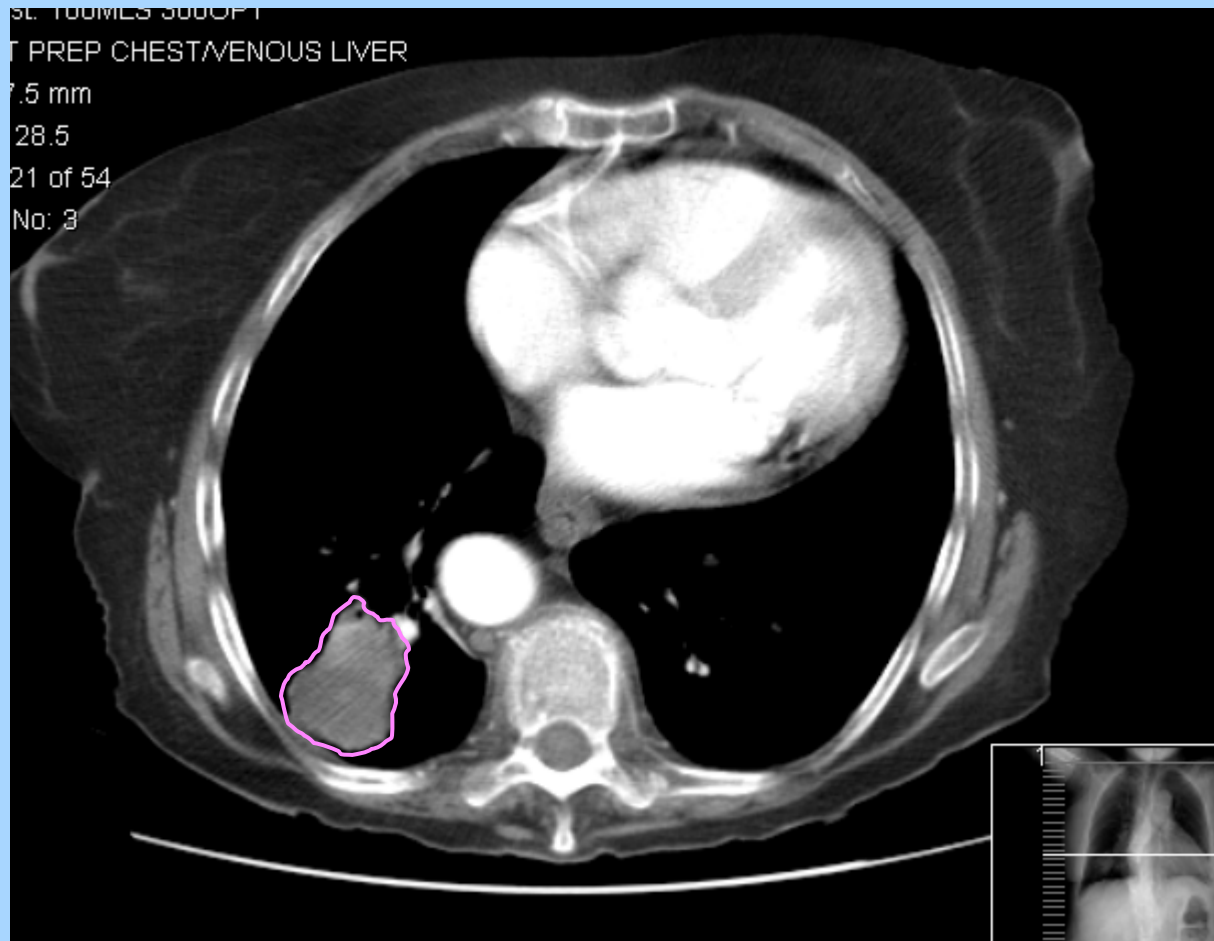
MRI

FDG-PET

FDG-PET fused with CT

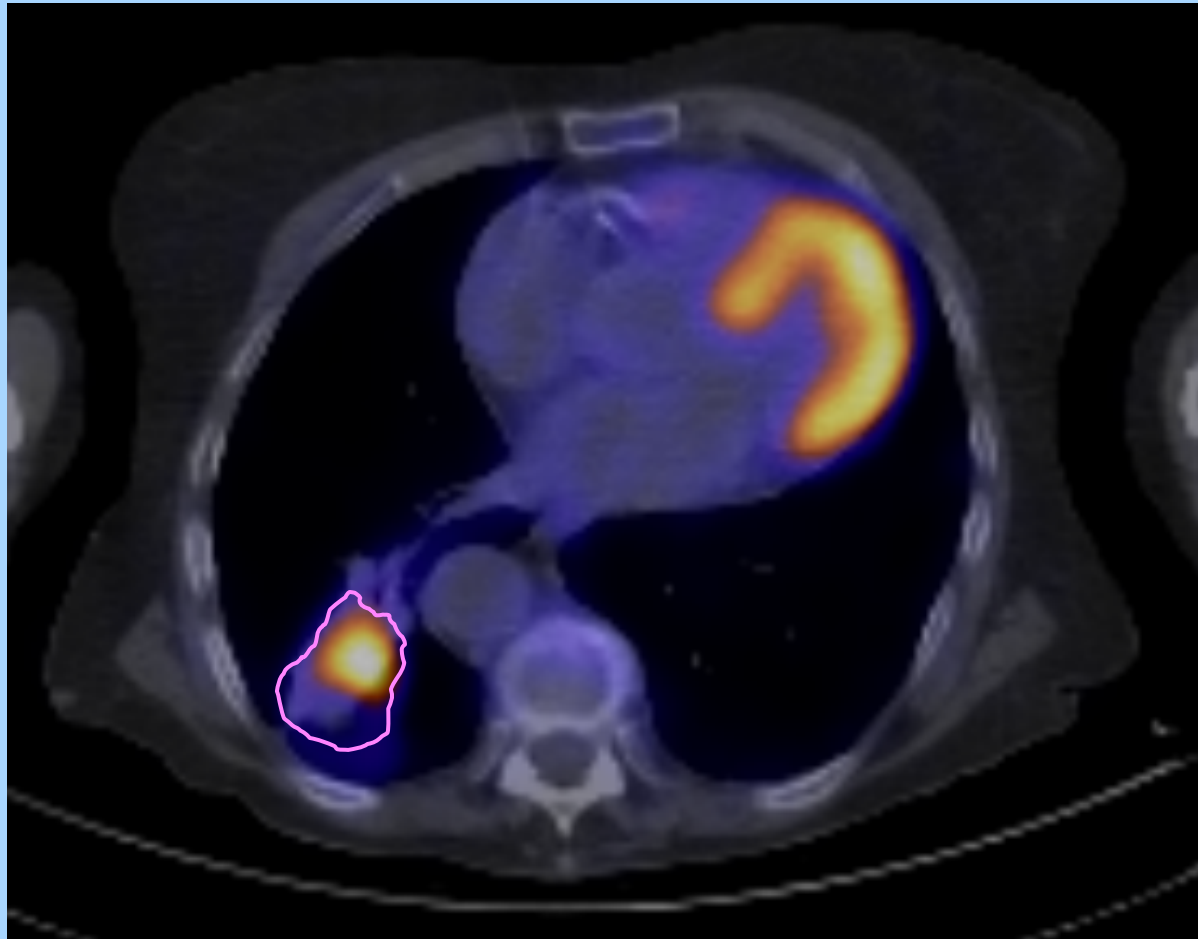
MRI

CT- PET



Delineation of primary tumour

CT- PET



Delineation of primary tumour

Preparation for treatment

immobilisation

imaging for planning

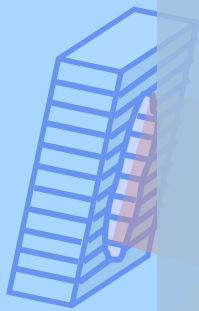
3D or 4D CT scan

PET-CT

target definition in 4D CT

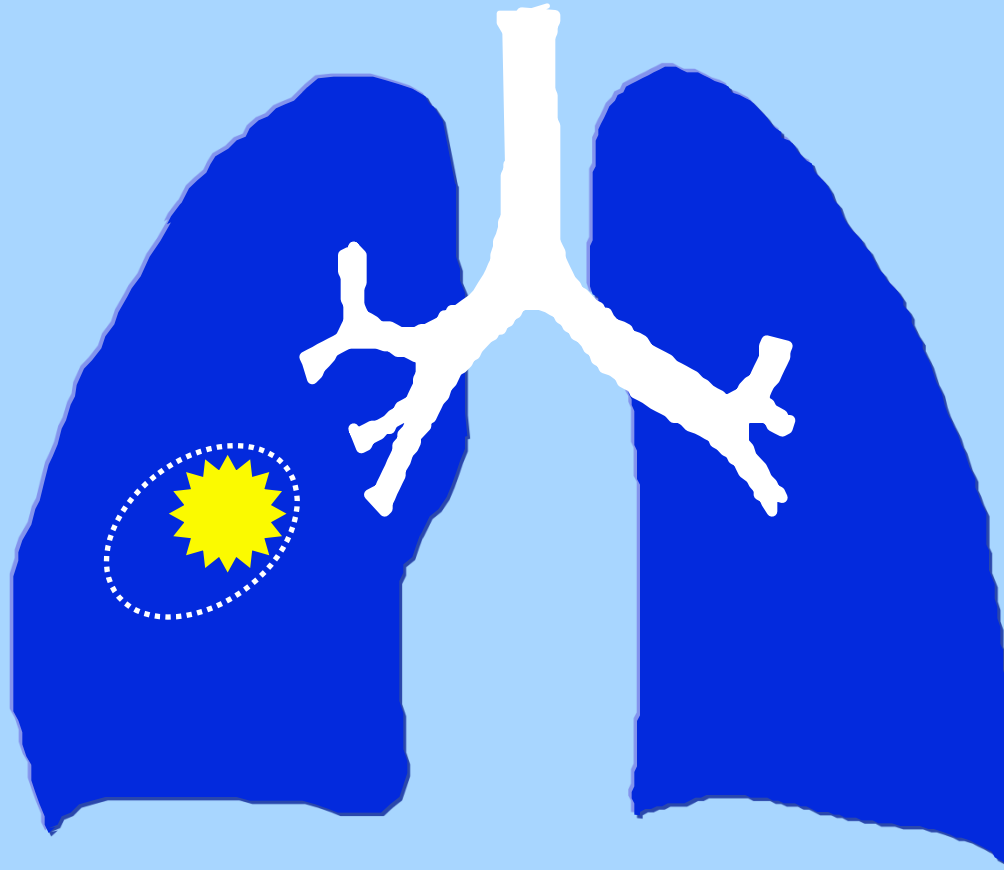
margins

planning & dose constraints



Practical aspect of NSCLC radiotherapy

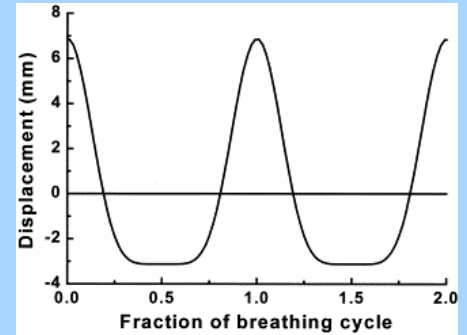
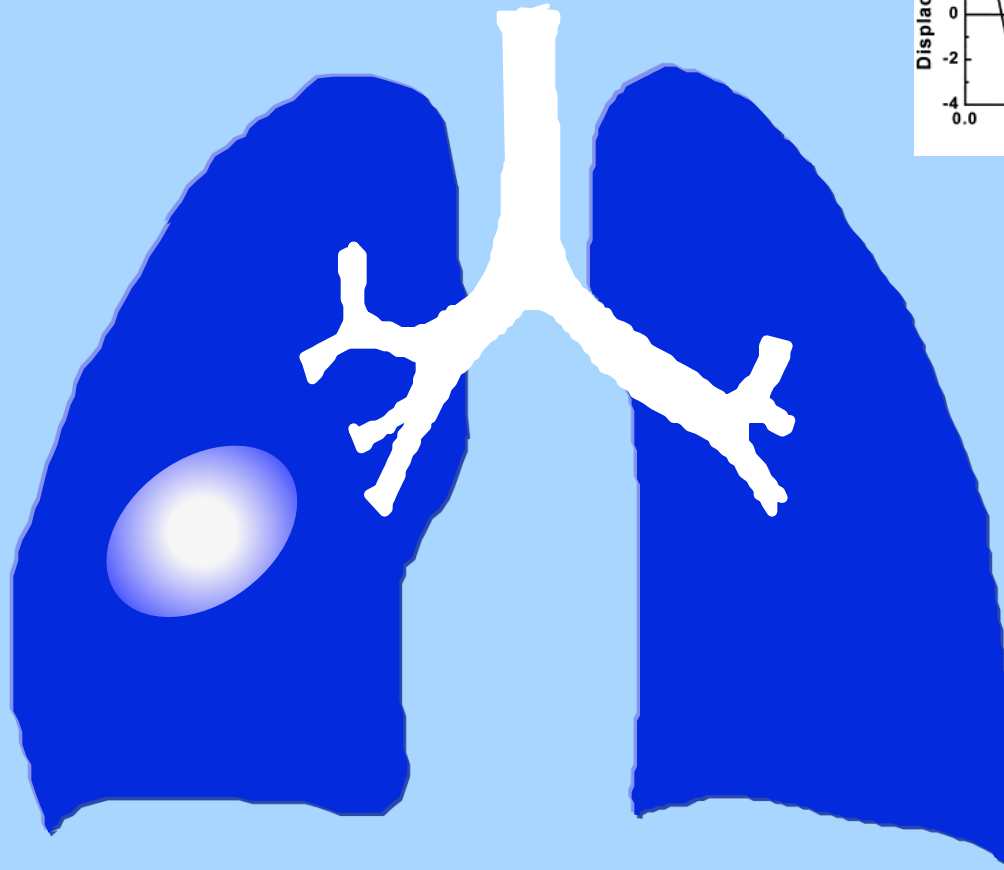
Imaging



CT for delineation of primary tumour

Imaging of a moving target

4D CT

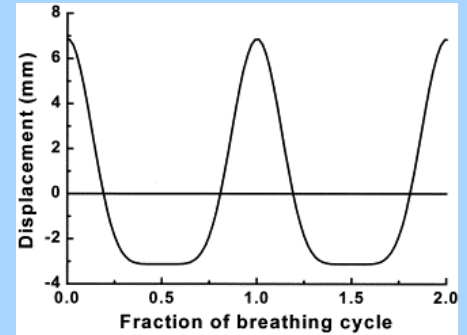
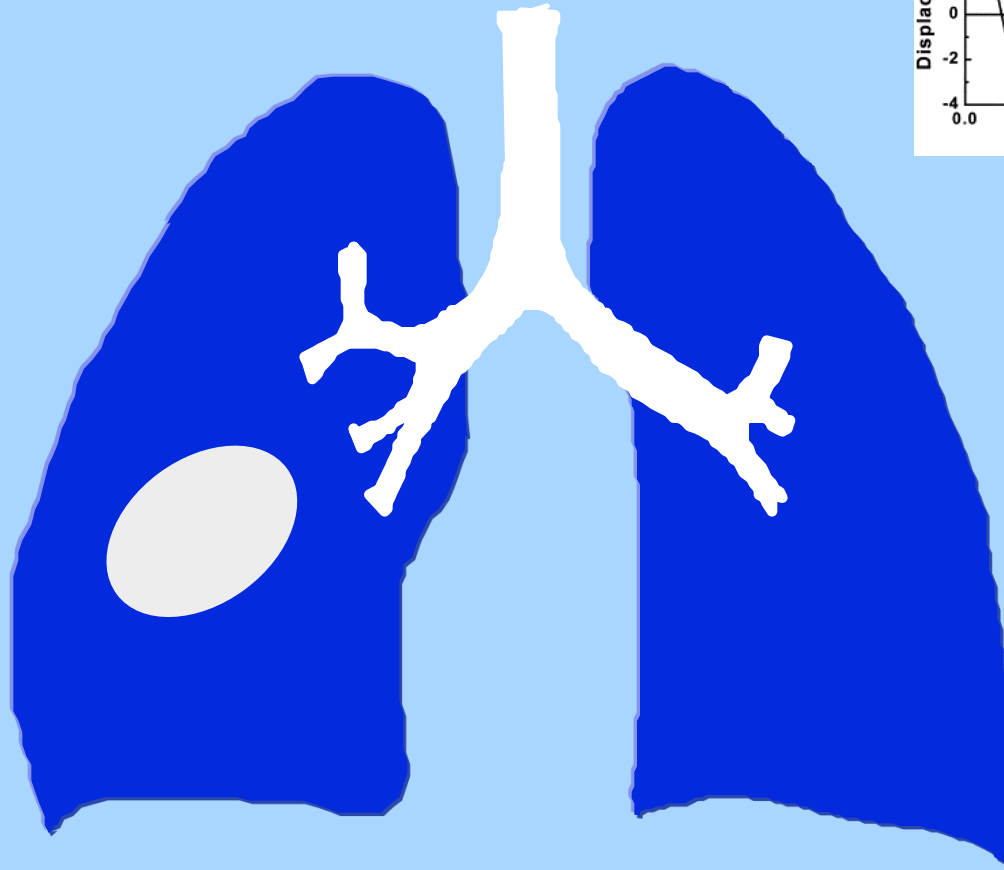


Average Intensity Projection - AIP

CT for delineation of primary tumour

Imaging of a moving target

4D CT

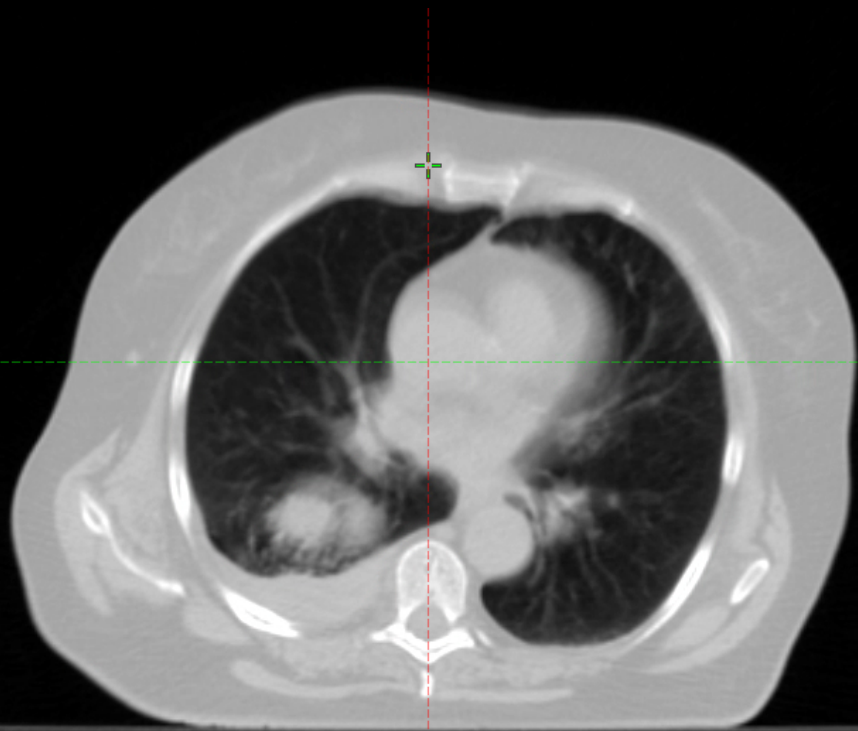


Maximum Intensity Projection - MIP

CT for delineation of primary tumour

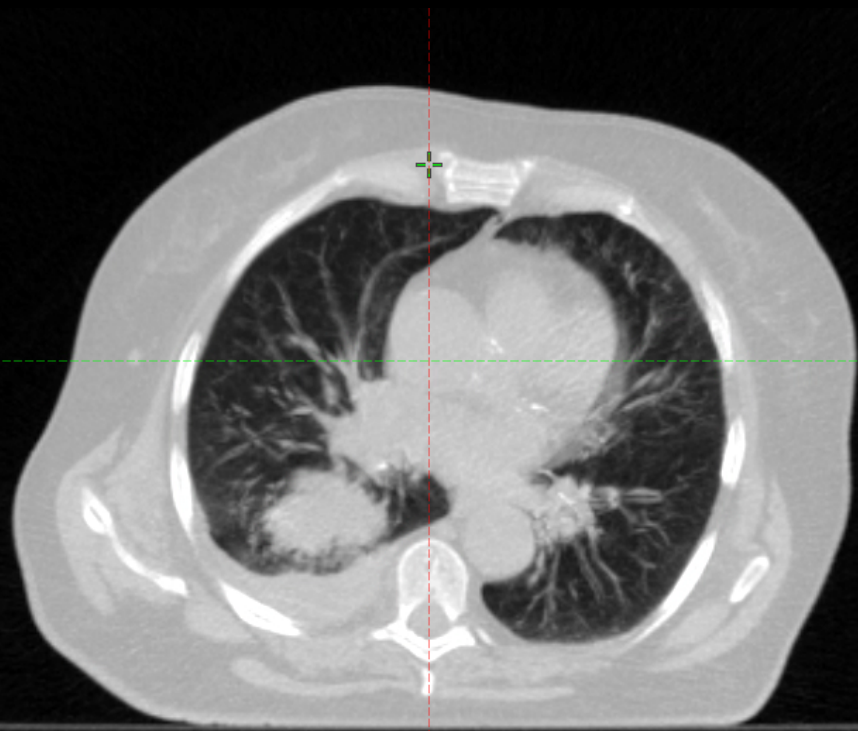
AIP

average intensity projection

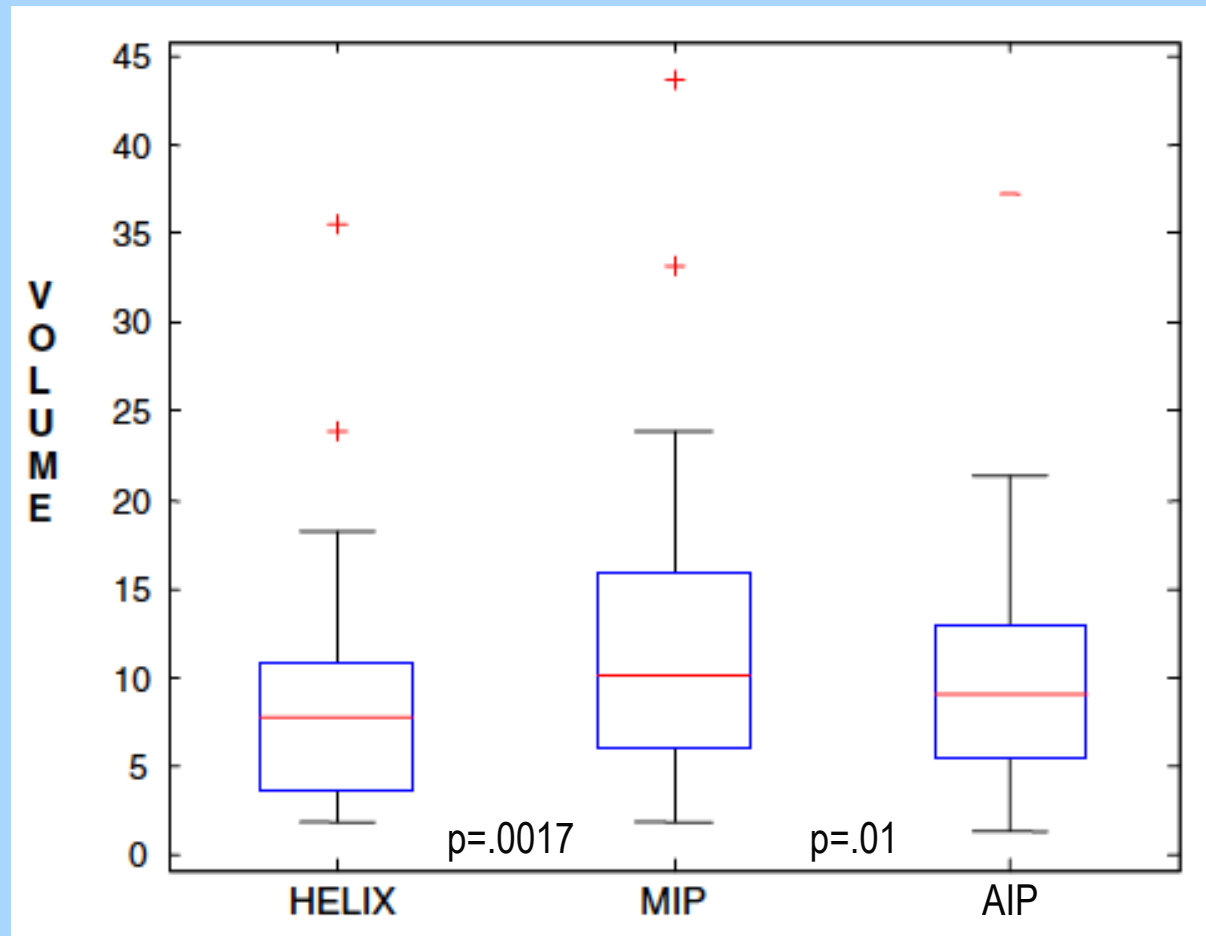


MIP

maximum intensity projection

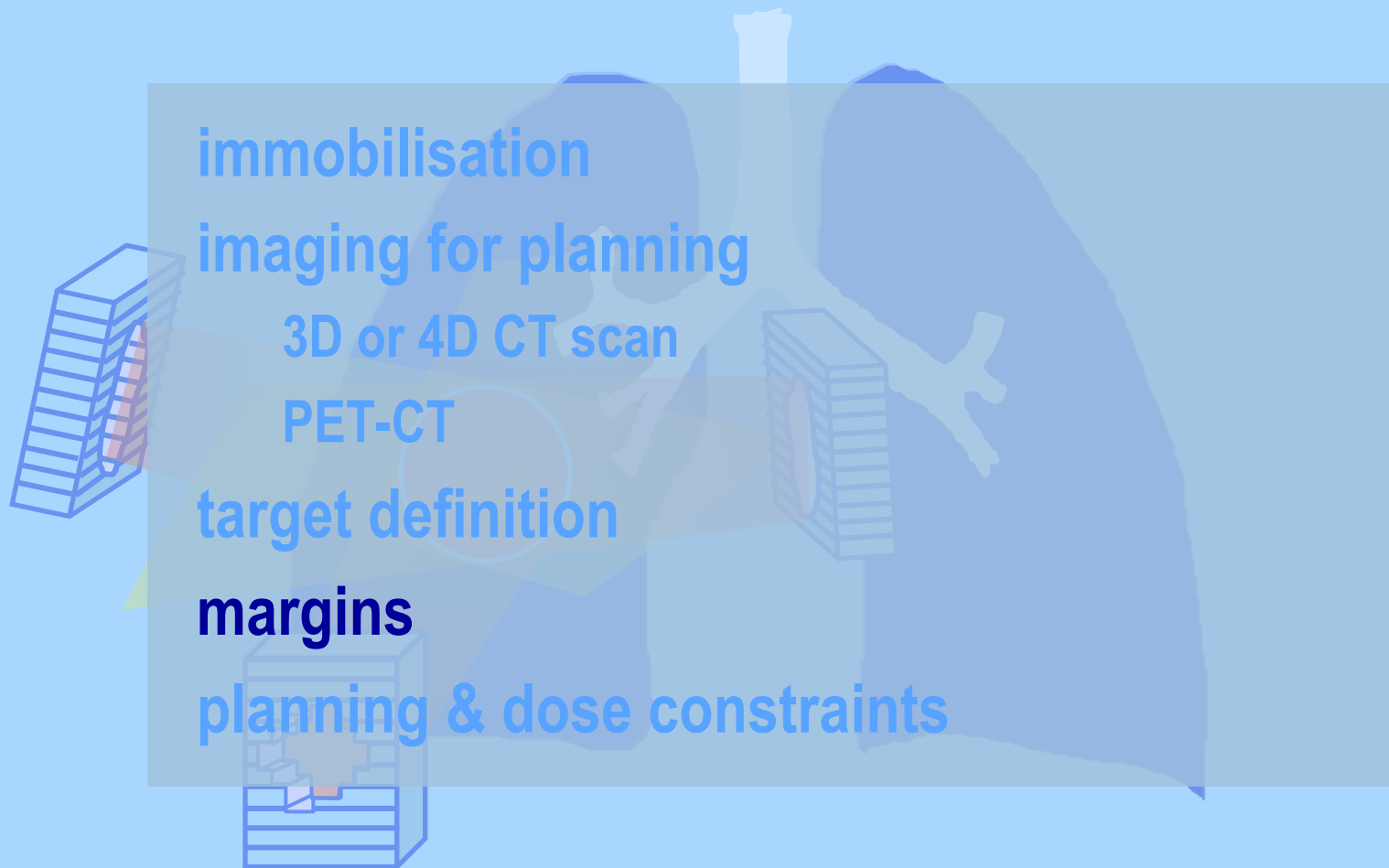


Comparison of internal target volumes (ITV)



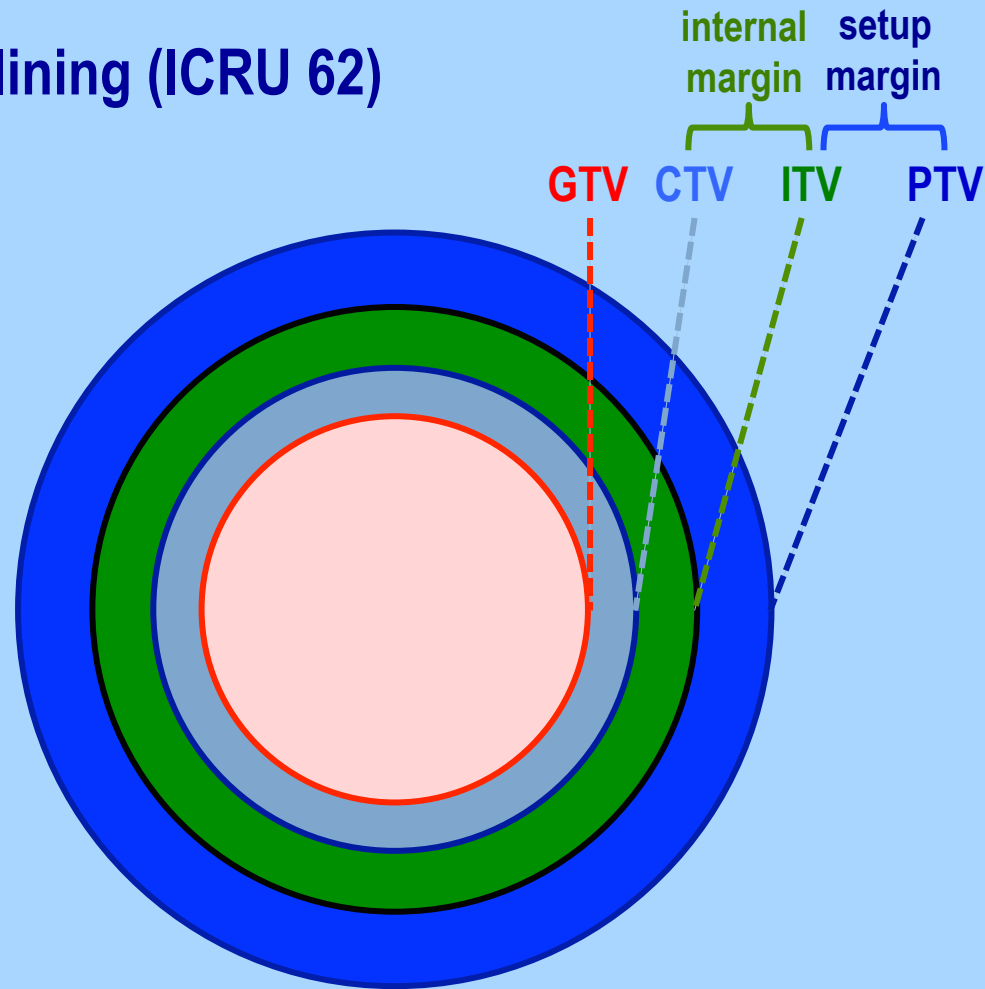
20 patients, stage I NSCLC

3D & 4DCT image acquisition



Practical aspect of NSCLC radiotherapy

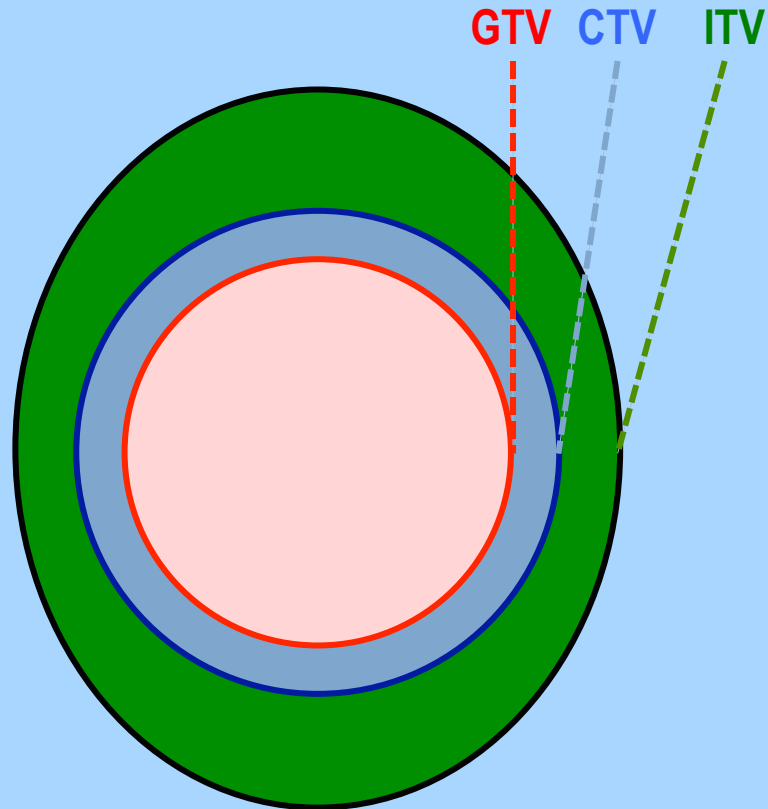
Theory of outlining (ICRU 62)



GTV gross tumour volume
CTV clinical target volume
ITV internal target volume
PTV planning target volume

Target volumes in 3D imaging

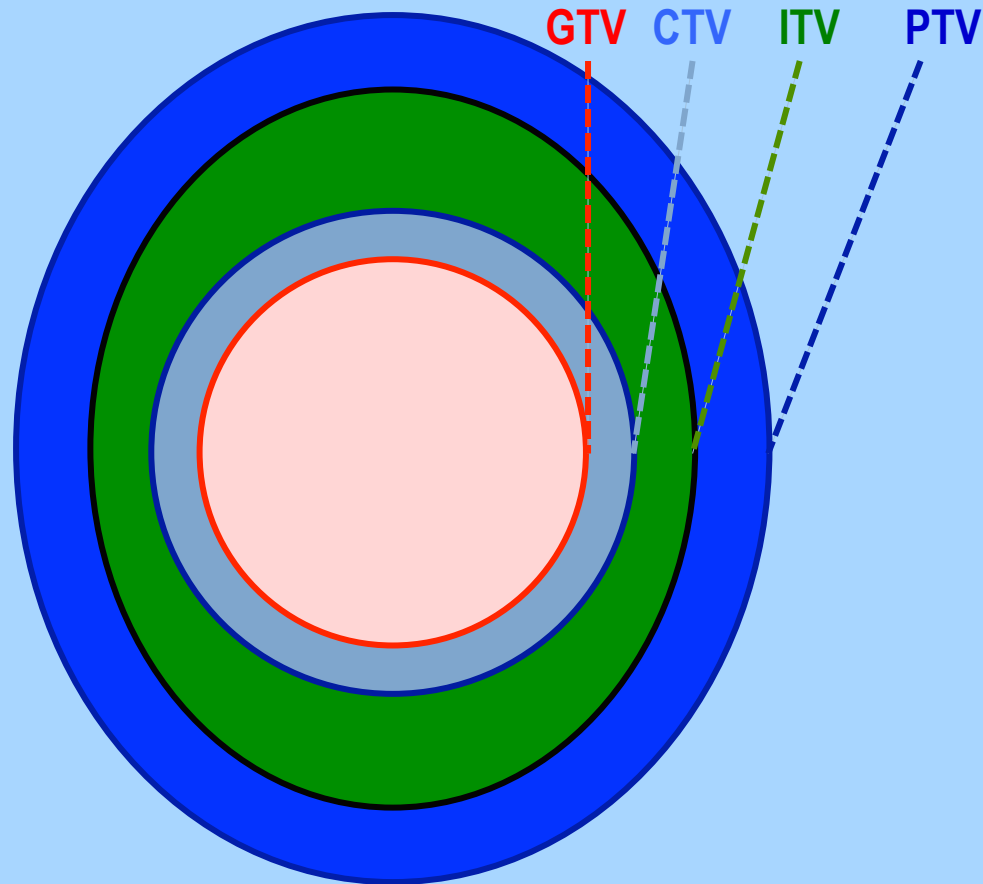
Theory of outlining



GTV gross tumour volume
CTV clinical target volume
ITV internal target volume
PTV planning target volume

Target volumes in 3D imaging

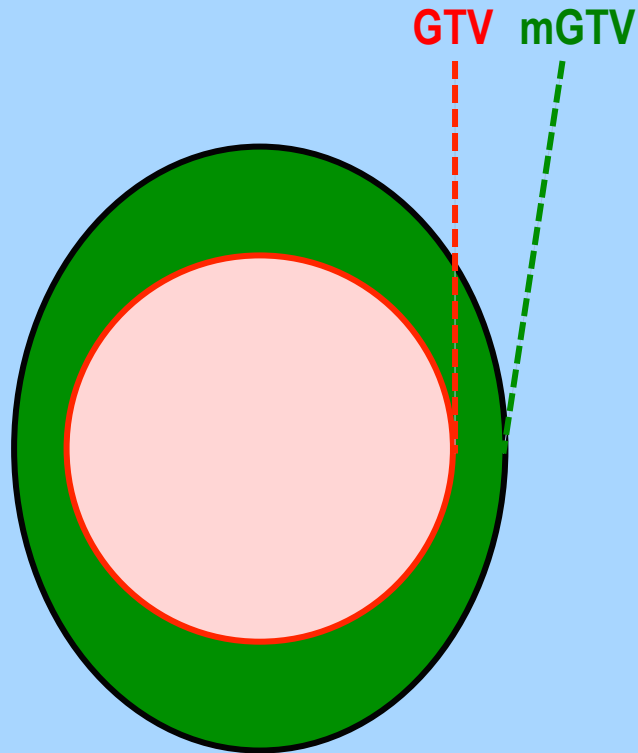
Theory of outlining



GTV gross tumour volume
CTV clinical target volume
ITV internal target volume
PTV planning target volume

Target volumes in 3D imaging

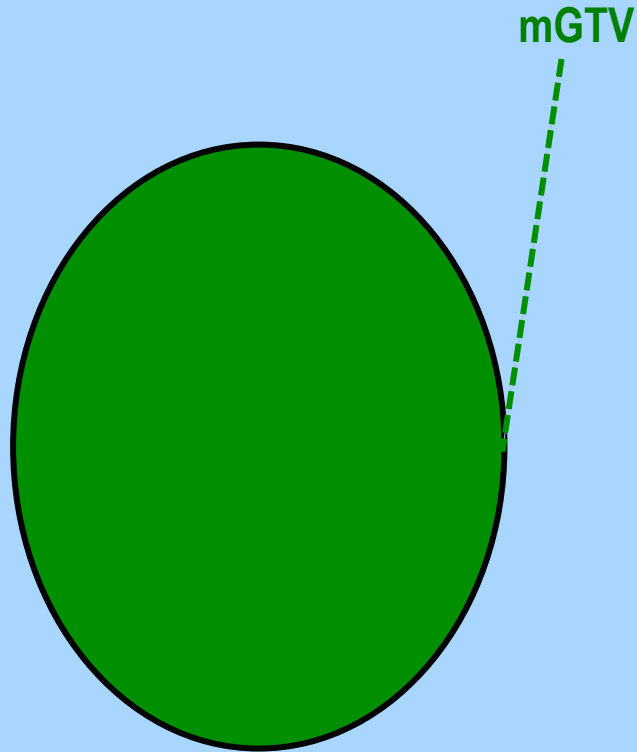
Practical outlining on 4DCT



GTV gross tumour volume
CTV clinical target volume
mGTV motion adapted GTV
PTV planning target volume

Target volumes in 3D imaging

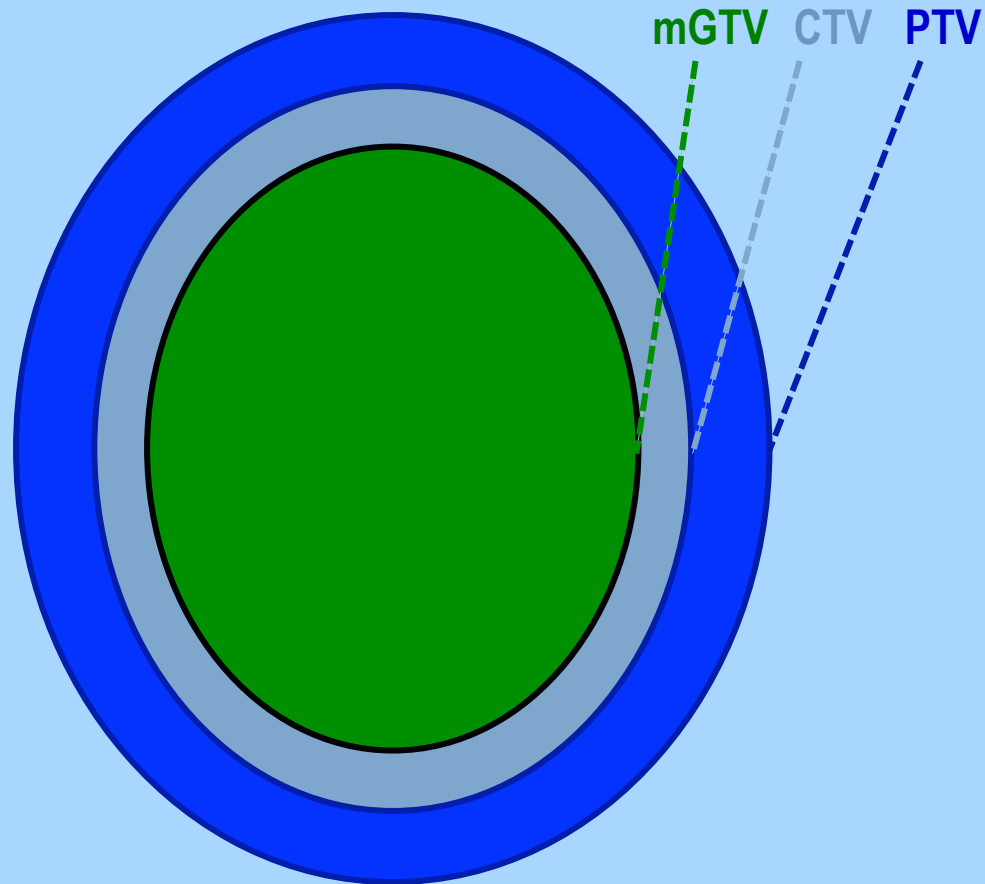
Practical outlining on 4DCT



mGTV motion adapted GTV
CTV clinical target volume
PTV planning target volume

Target volumes in 3D imaging

Practical outlining on 4DCT



mGTV motion adapted GTV
CTV clinical target volume
PTV planning target volume

Target volumes in 3D imaging

☐ MIP

☐ AIPCLINICIA...

☐ BODY

☐ BrachialPl...

☐ Bronchial...

☐ CouchIn...

☐ CouchSu...

☐ CTV_40/...

☐ Heart

☐ ITV

☐ Lung_L

☐ Lung_R

☐ Oesopha...

☐ PTV

☐ SpinalCanal

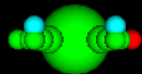
☐ SPR_ITV

☐ Trachea



R

L



Standard, HFS
Z: 15.00 cm

P

0 %

☐ MIP

☐ AIPCLINICIA...

- ☒ BODY
- ☒ BrachialPL...
- ☒ Bronchial...
- ☒ CouchIn...
- ☒ CouchSu...
- ☒ CTV_40/...
- ☒ Heart
- ☒ ITV
- ☒ Lung_L
- ☒ Lung_R
- ☒ Oesopha...
- ☒ PTV
- ☒ SpinalCanal
- ☒ SPR_ITV
- ☒ Trachea

R

L

Standard, HFS
Z: 15.00 cm

P

0 %

☐ MIP

☒ AIPCLINICIA...

☐ BODY

☐ BrachialPI...

☐ Bronchial...

☐ CouchIn...

☐ CouchSu...

☐ CTV_40/...

☐ Heart

☐ ITV

☐ Lung_L

☐ Lung_R

☐ Oesopha...

☐ PTV

☐ SpinalCanal

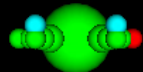
☒ SPR_ITV

☐ Trachea

GTV

R

L



Standard, HFS
Z: 15.00 cm

P

0 %

☐ MIP

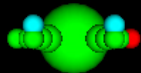
- ☒ AIPCLINICIA...
- ☒ BODY
- ☐ BrachialPL...
- ☐ Bronchial...
- ☐ CouchIn...
- ☐ CouchSu...
- ☒ CTV_40...
- ☐ Heart
- ☐ ITV
- ☐ Lung_L
- ☐ Lung_R
- ☐ Oesopha...
- ☐ PTV
- ☐ SpinalCanal
- ☒ SPR_ITV
- ☐ Trachea

GTV

mGTV

R

L



Standard, HFS
Z: 15.00 cm

P

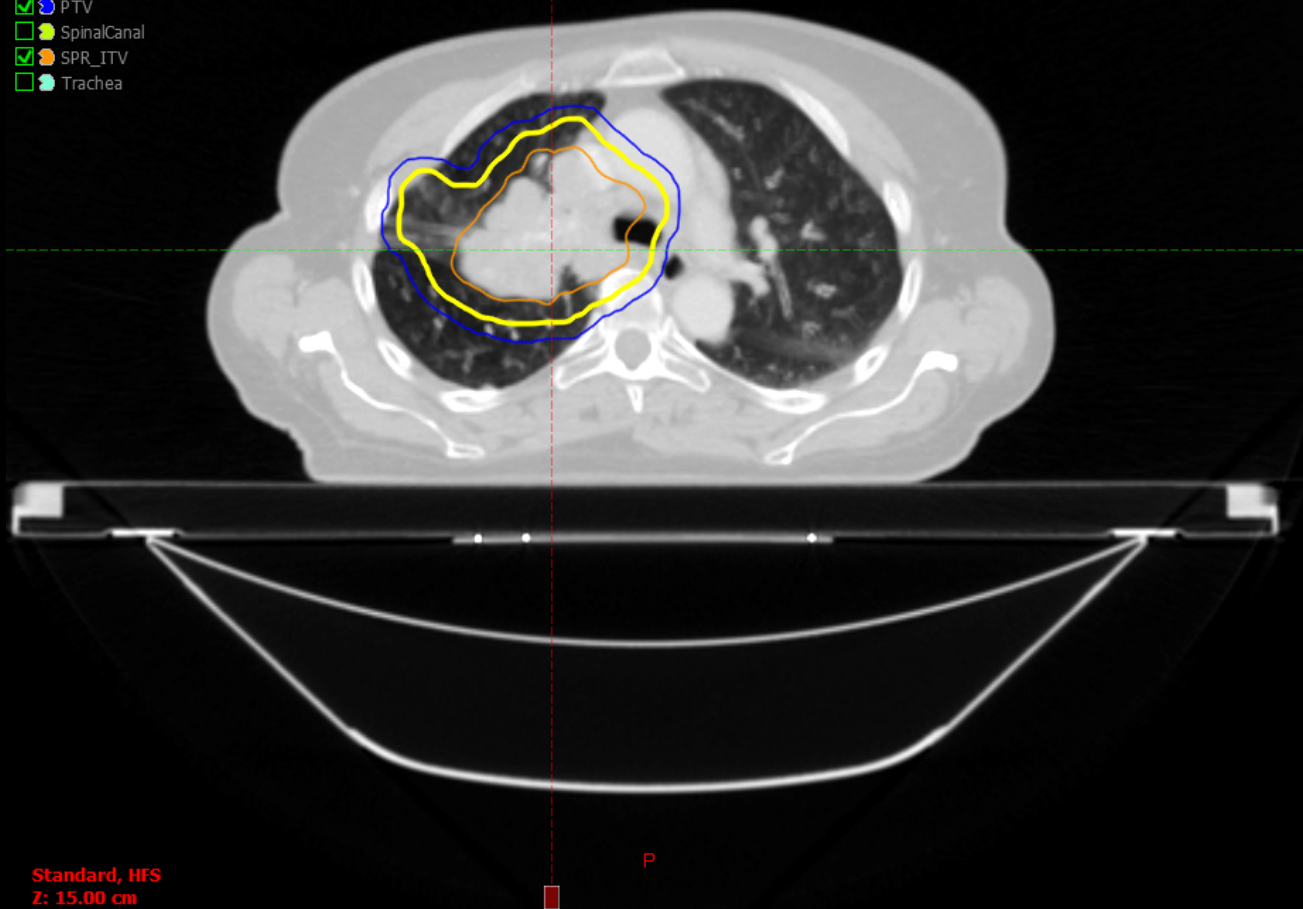
0 %

- ☒ AIPCLINICIA...
- ☐ BODY
- ☐ BrachialPL...
- ☐ Bronchial...
- ☐ CouchIn...
- ☐ CouchSu...
- ☒ CTV_40...
- ☐ Heart
- ☐ ITV
- ☐ Lung_L
- ☐ Lung_R
- ☐ Oesopha...
- ☒ PTV
- ☐ SpinalCanal
- ☒ SPR_ITV
- ☐ Trachea

GTV

mGTV

CTV



Standard, HFS
Z: 15.00 cm

MIP



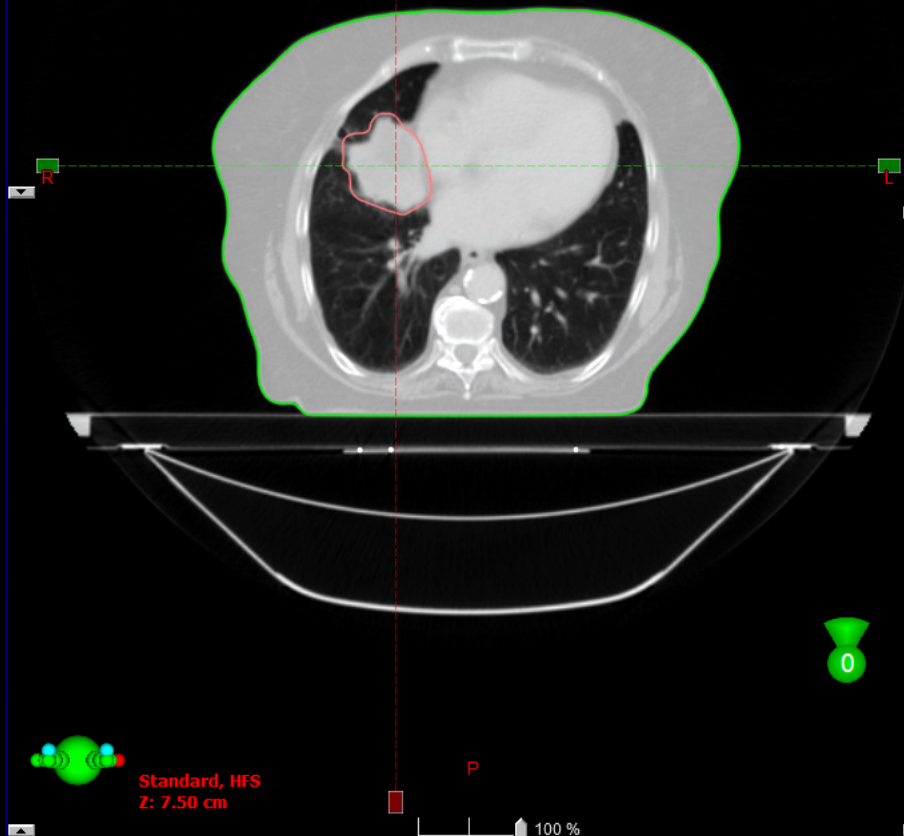
AIP



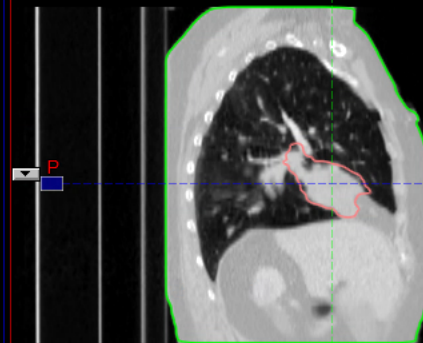
4D loop



- ☒ MIP
- ☒ BODY
- ☒ ITV
- ☒ CT0
- ☒ BODY

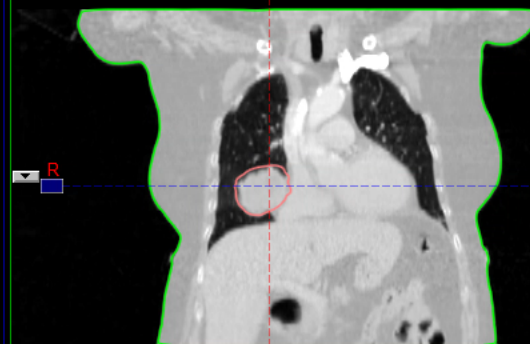


Standard, HFS
Z: 7.50 cm



X: -4.80 cm

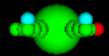
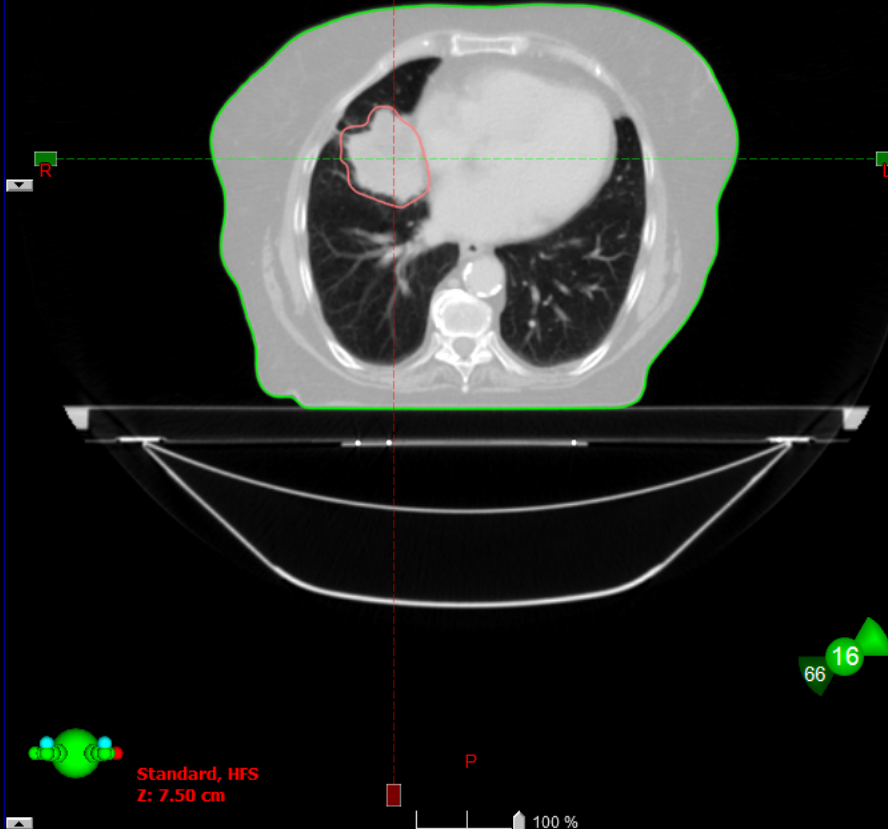
Frontal - MIP - CT0 - 25/05/2017 16:22



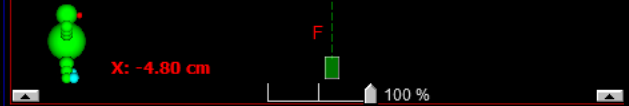
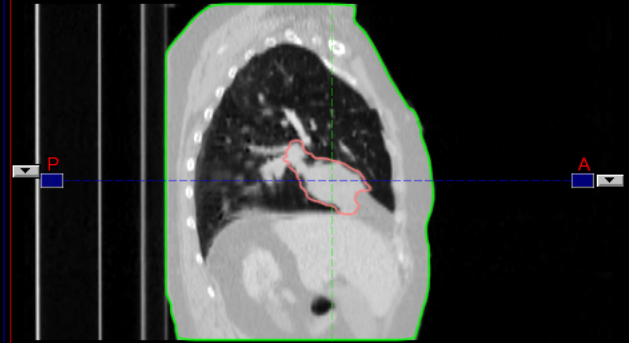
Y: 7.59 cm



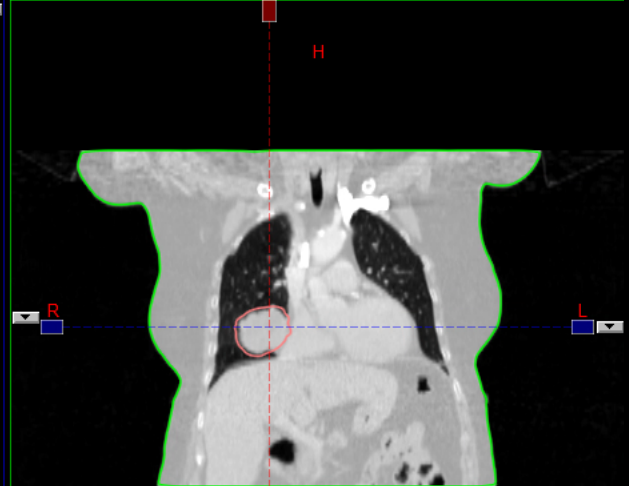
- ☒ MIP
- ☒ BODY
- ☒ ITV
- ☒ CT16
- ☒ BODY



Standard, HFS
Z: 7.50 cm



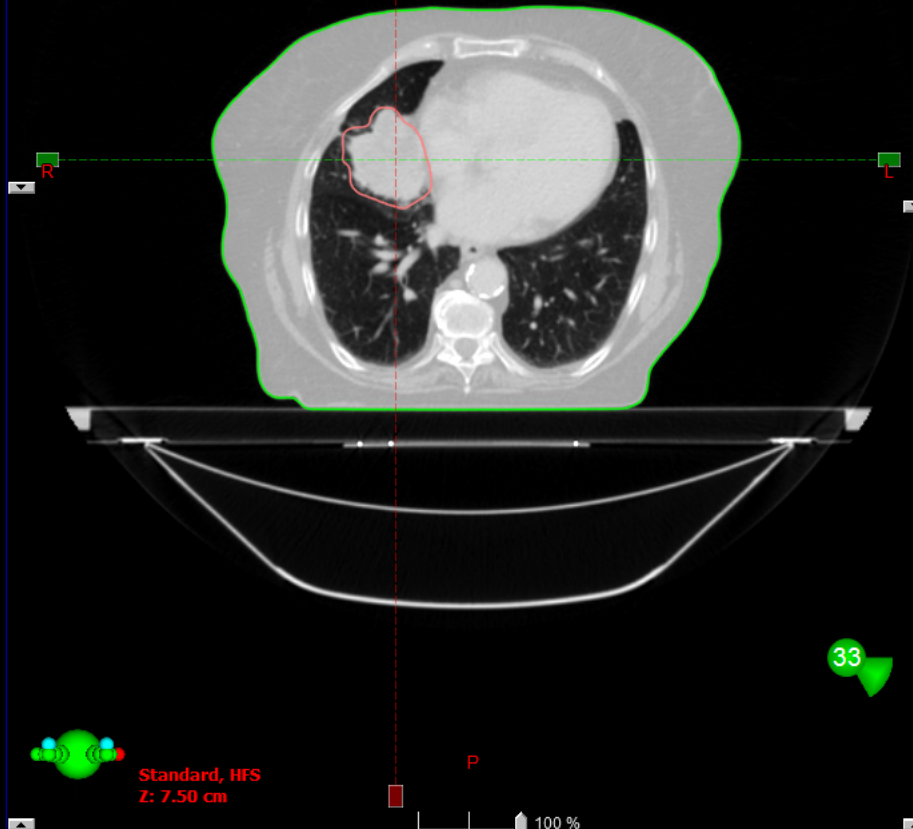
Frontal - MIP - CT16 - 25/05/2017 16:22



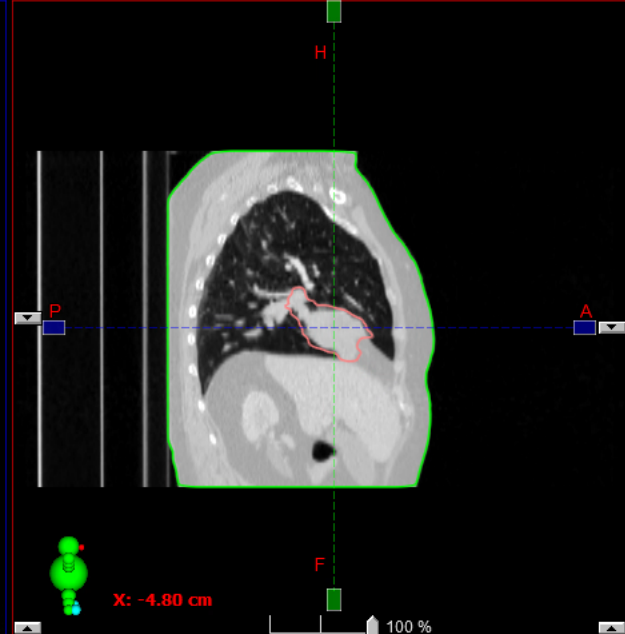
Y: 7.59 cm



- ☒ MIP
- ☒ BODY
- ☒ ITV
- ☒ CT33
- ☒ BODY

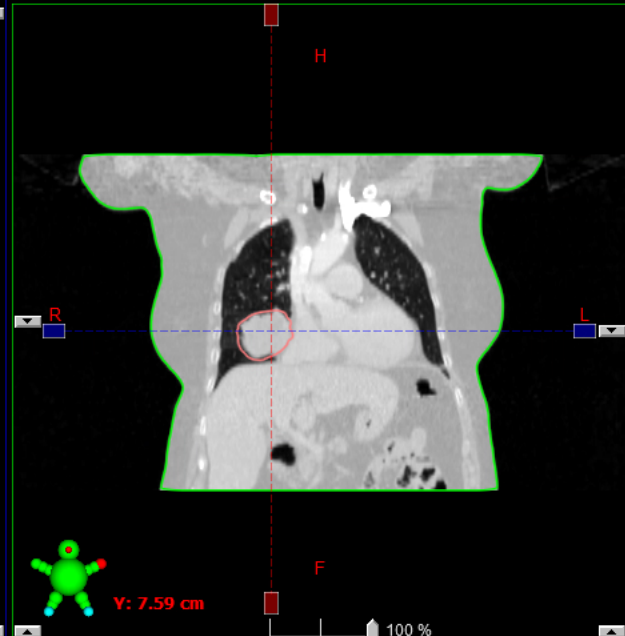


Standard, HFS
Z: 7.50 cm



X: -4.80 cm

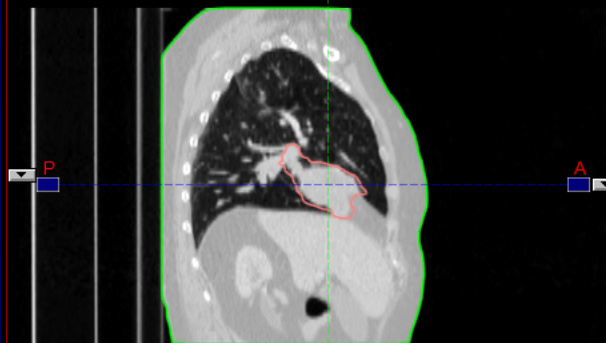
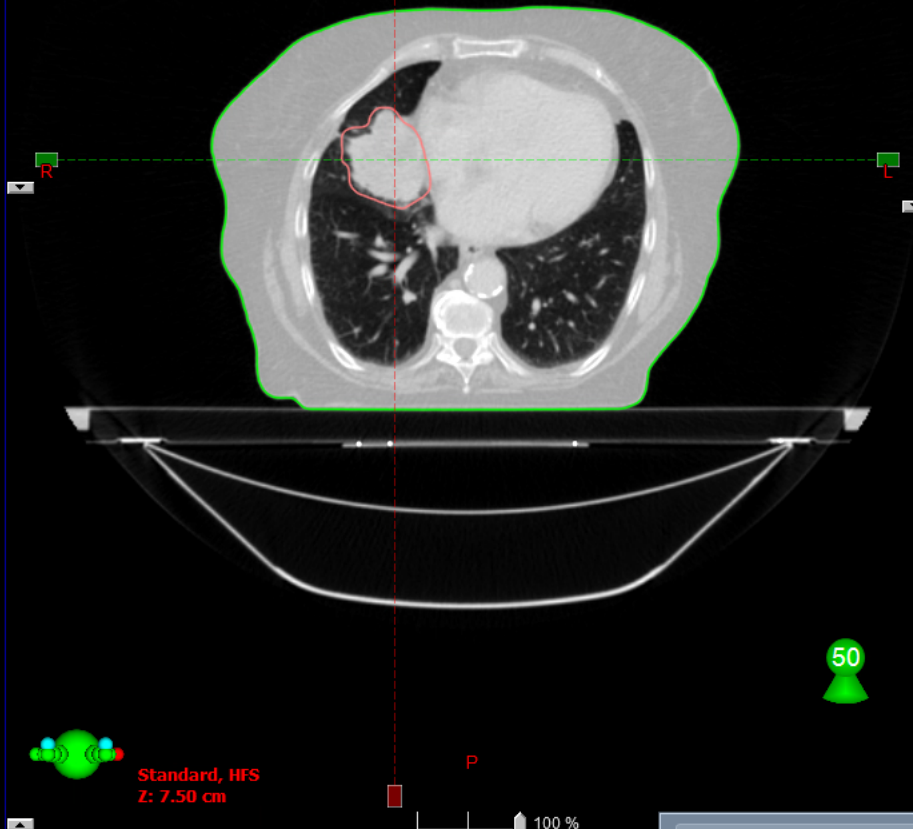
Frontal - MIP - CT33 - 25/05/2017 16:22



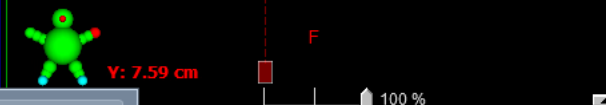
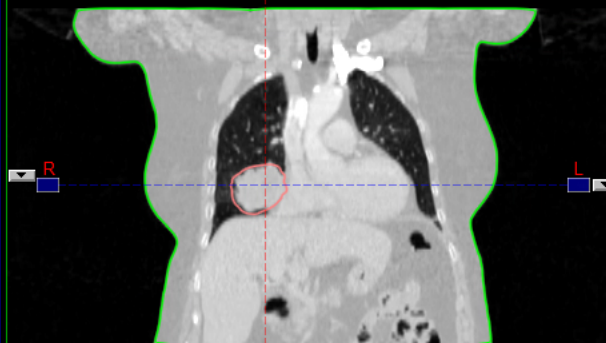
Y: 7.59 cm

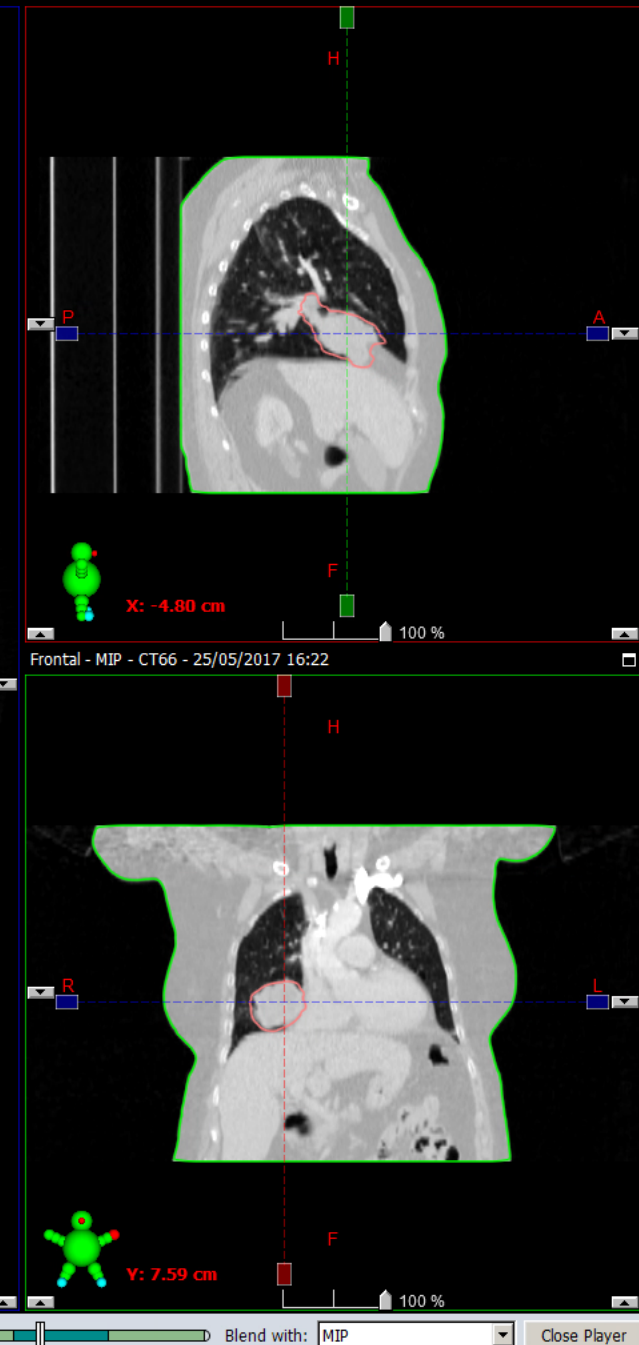
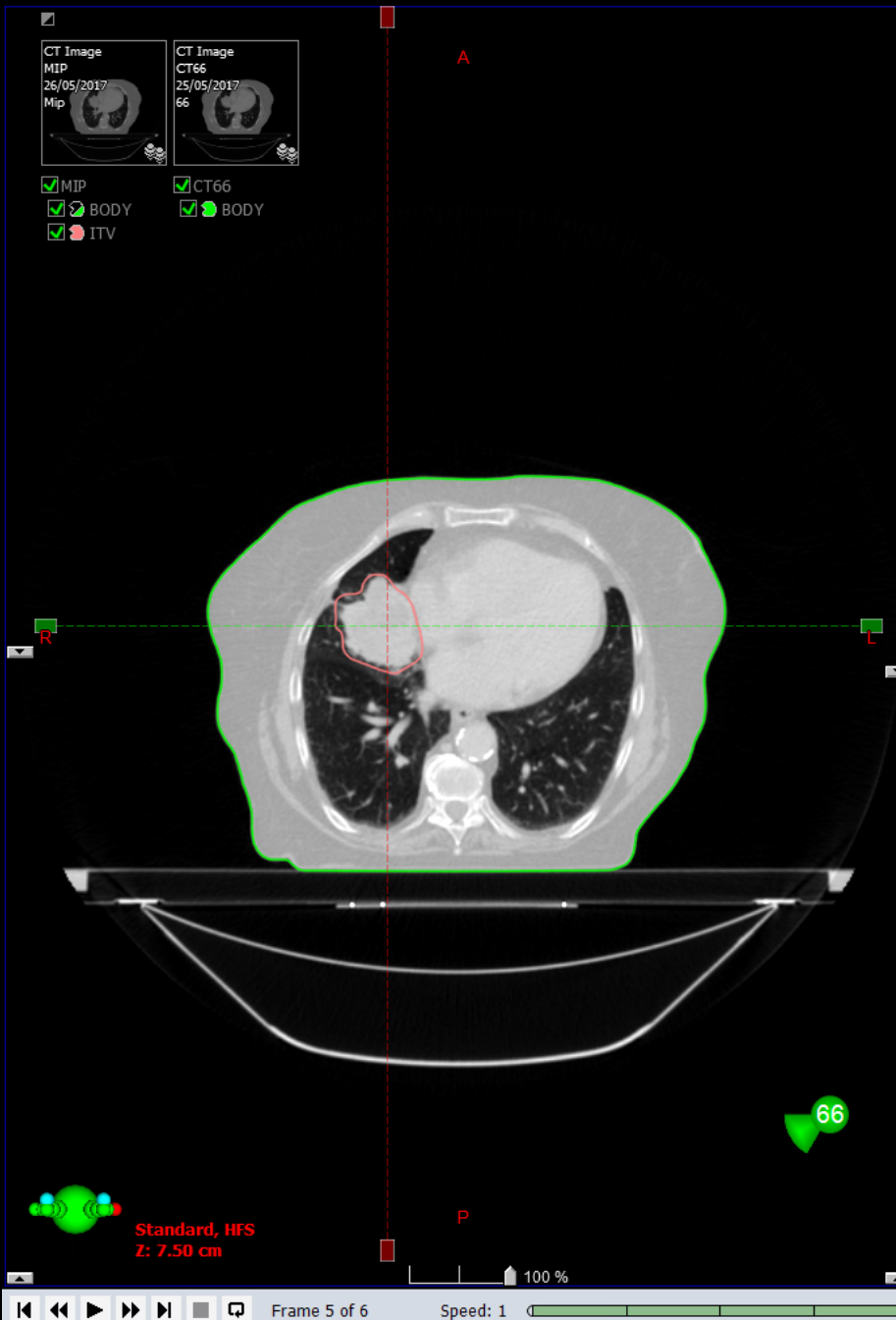


- ☒ MIP
- ☒ BODY
- ☒ ITV
- ☒ CT50
- ☒ BODY



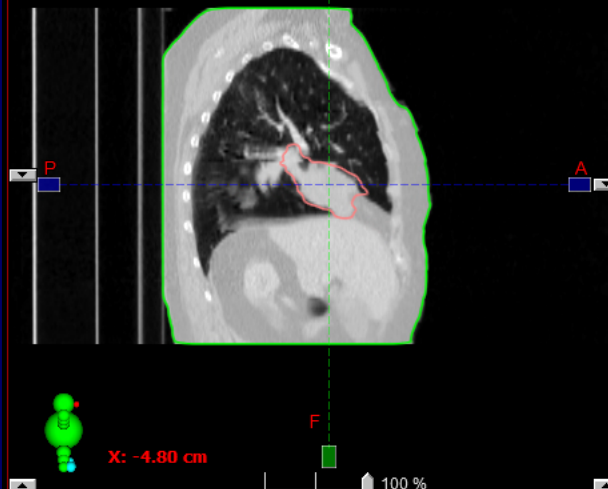
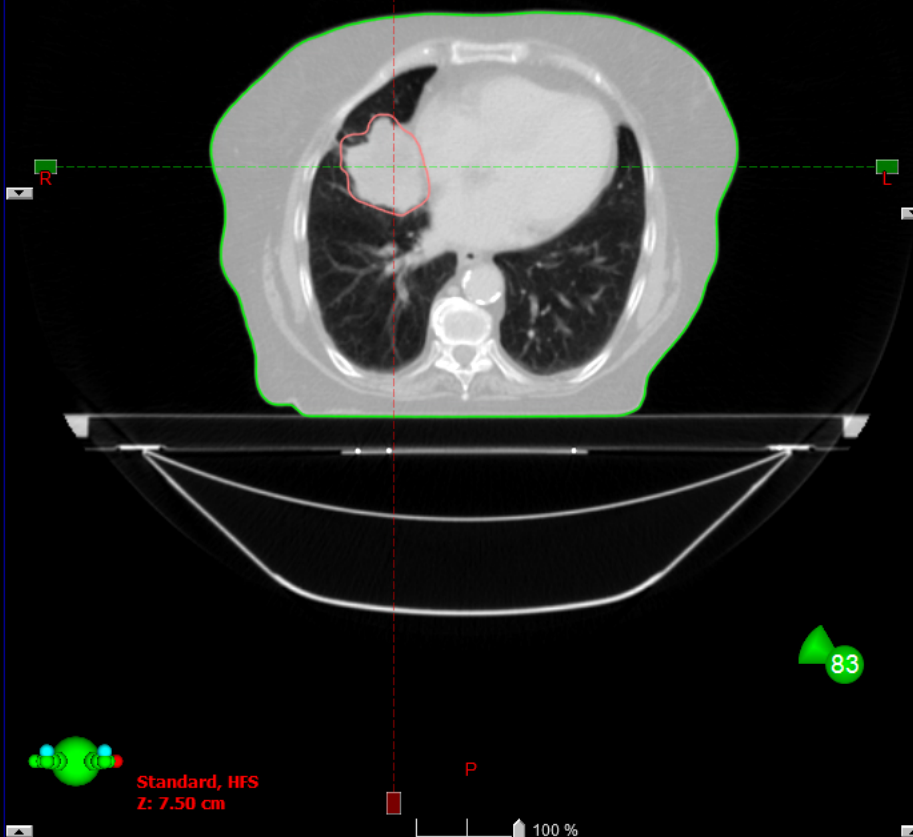
Frontal - MIP - CT50 - 25/05/2017 16:22



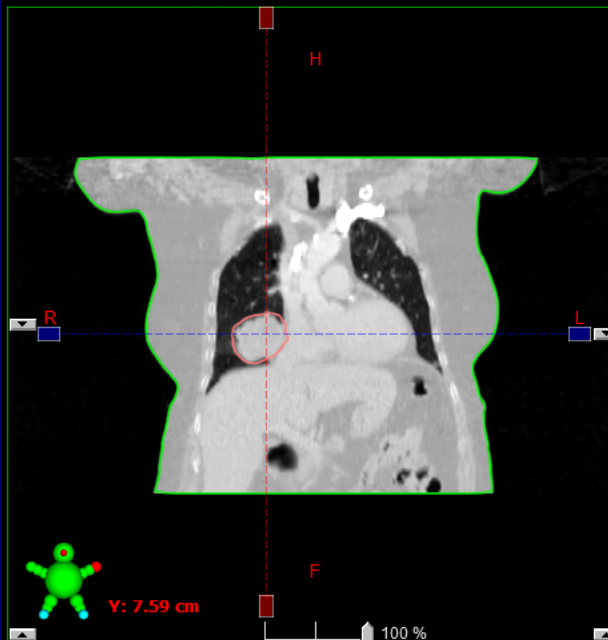




- ☒ MIP
- ☒ BODY
- ☒ ITV
- ☒ CT83
- ☒ BODY



Frontal - MIP - CT83 - 25/05/2017 16:22



Preparation for treatment

immobilisation

imaging for planning

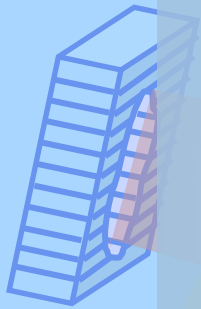
3D or 4D CT scan

PET-CT

normal tissue definition in 4D CT

margins

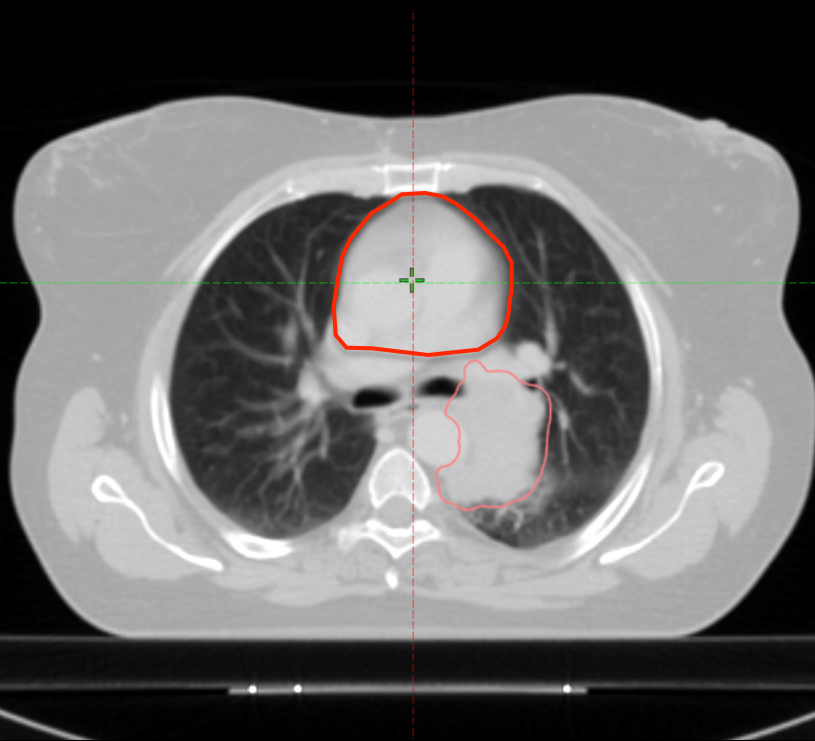
planning & dose constraints



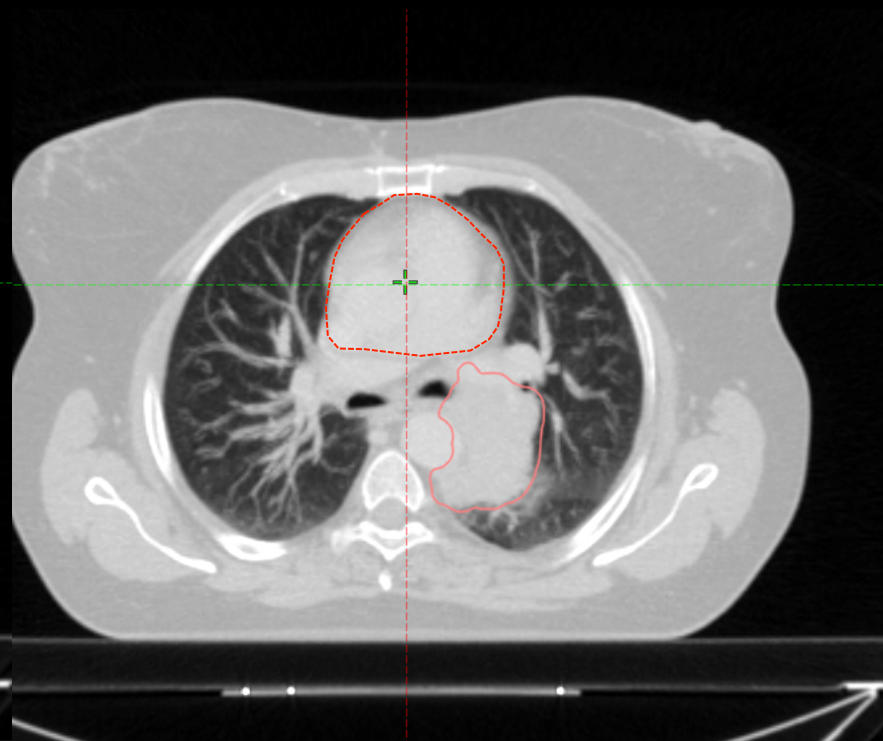
Practical aspect of NSCLC radiotherapy

organs at risk volume

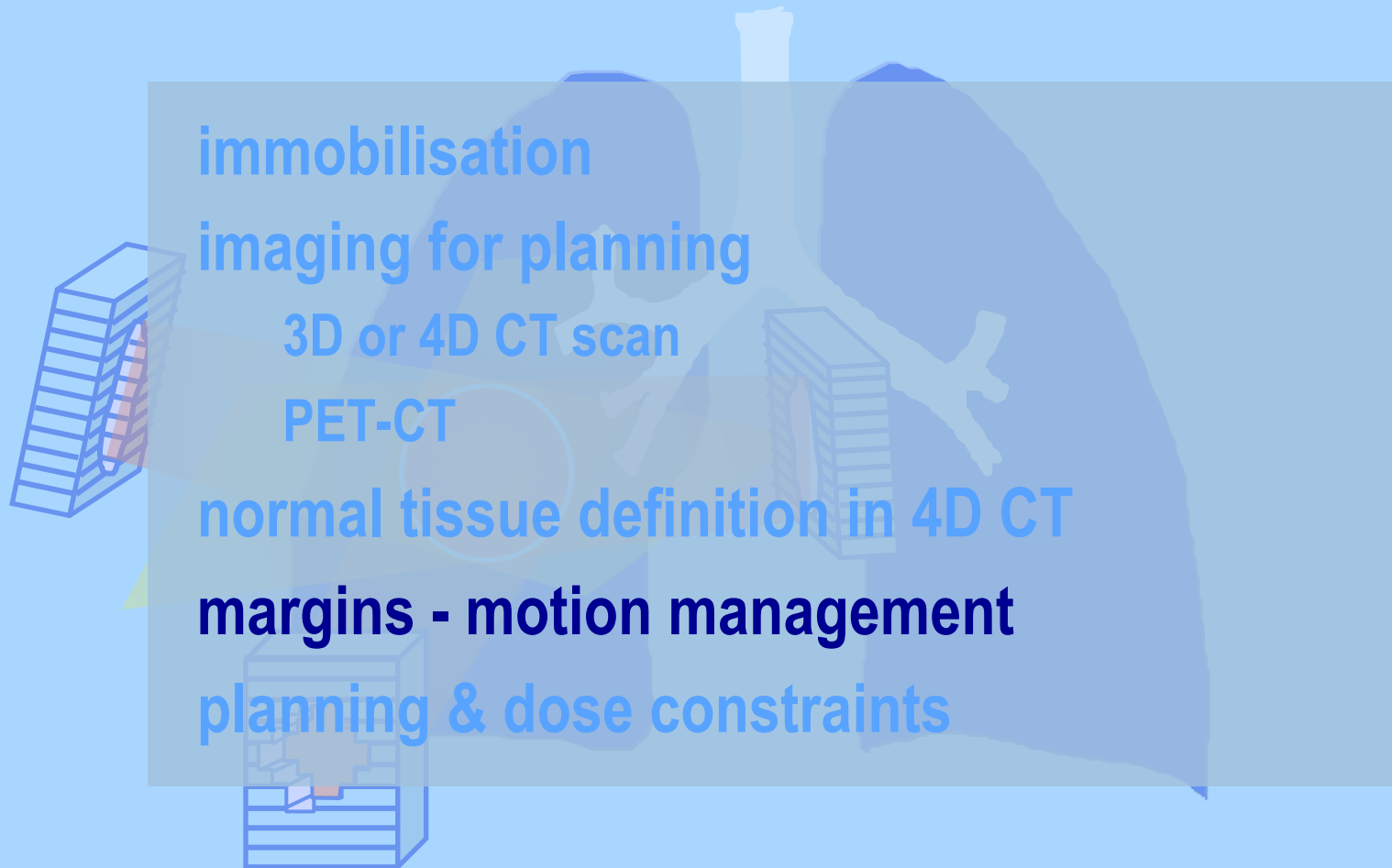
AIP



MIP

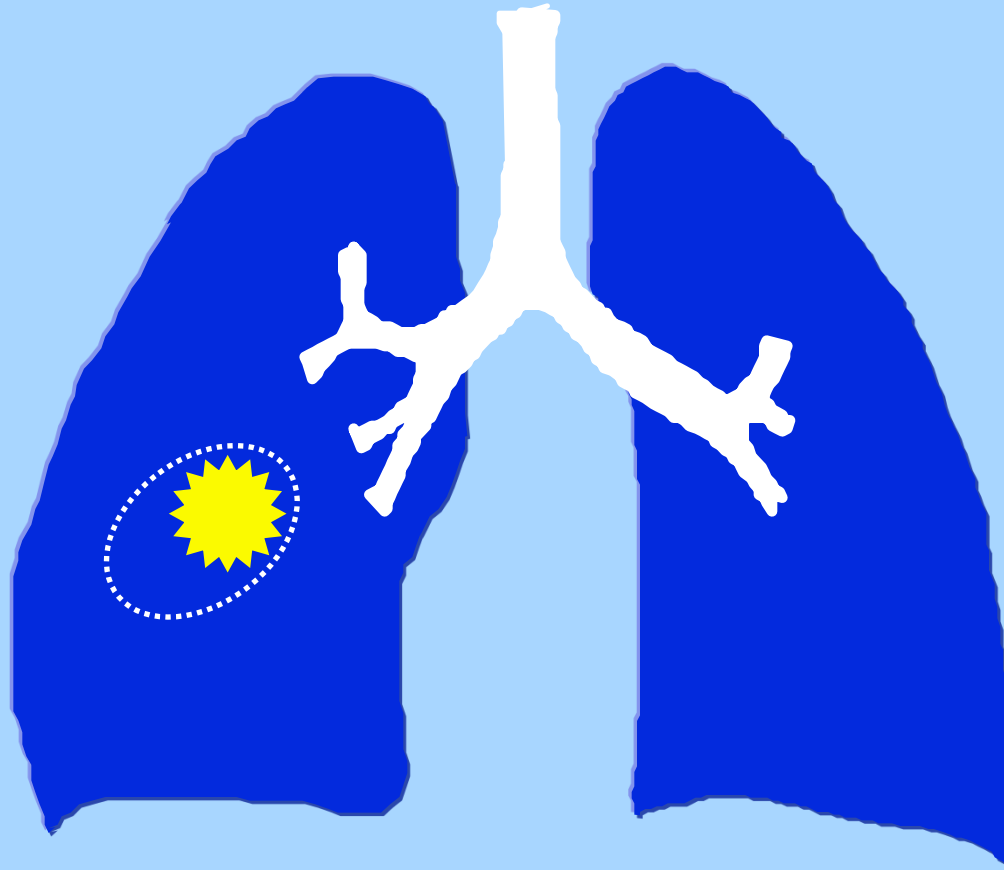


Preparation for treatment



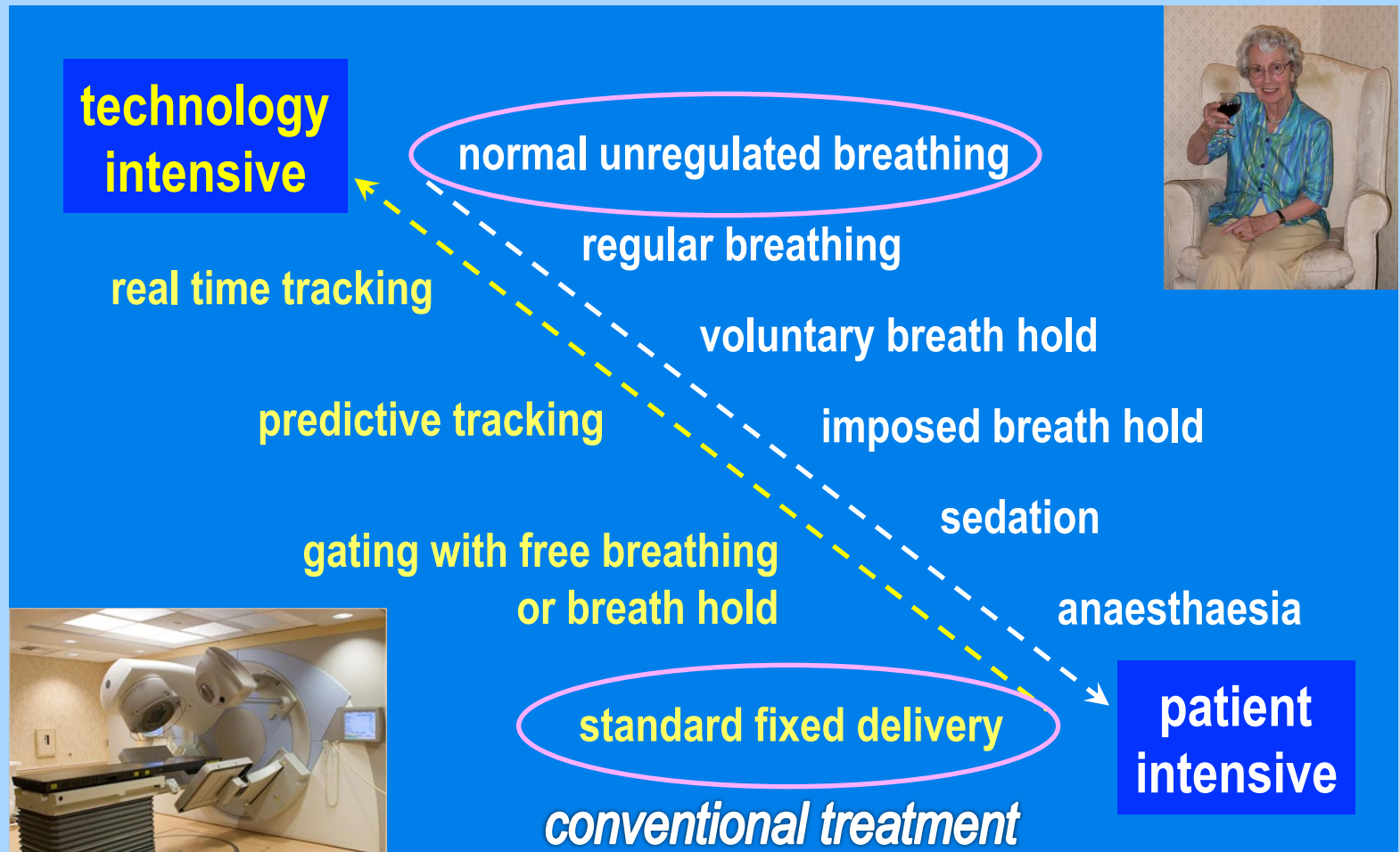
Practical aspect of NSCLC radiotherapy

motion management



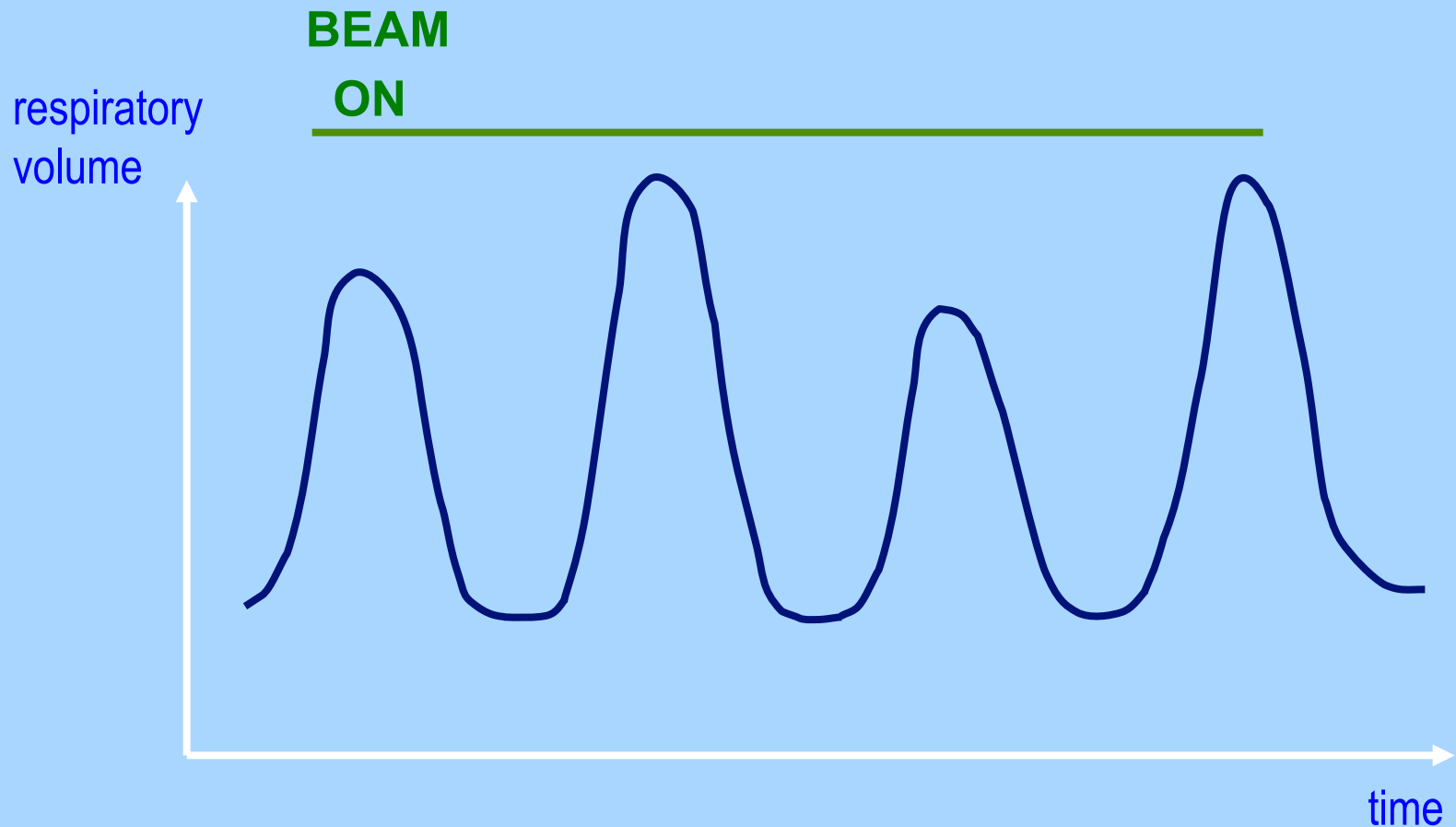
CT for delineation of primary tumour

Solutions to tumour motion



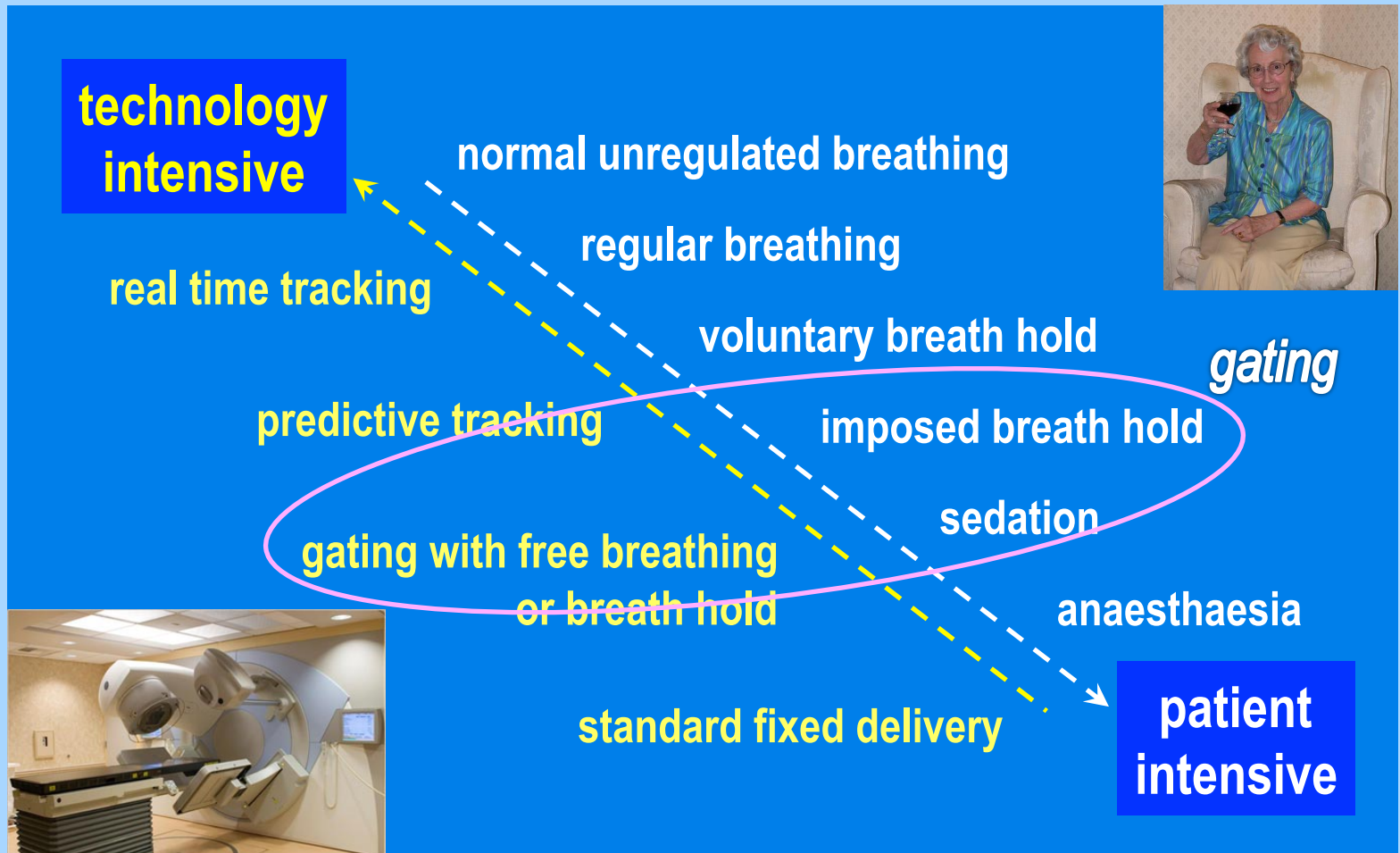
4D radiotherapy for non-small cell lung cancer

Radiotherapy to a moving target



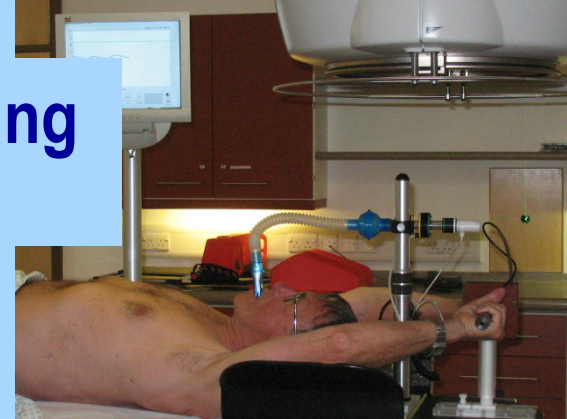
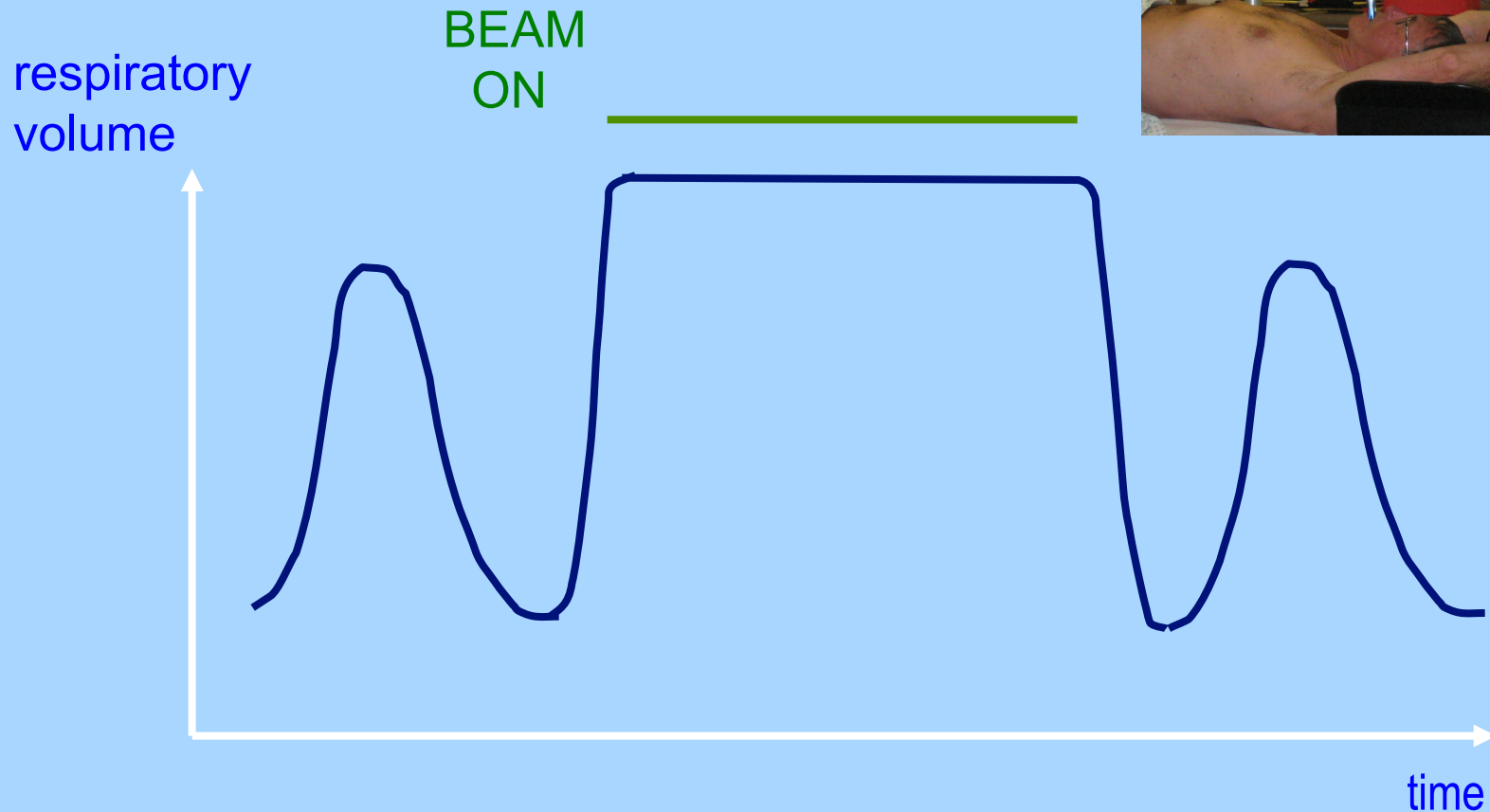
Conventional radiotherapy for non-small cell lung cancer

Solutions to tumour motion



4D radiotherapy for non-small cell lung cancer

Radiotherapy to a moving target - gating active breathing control (ABC)



4D gated radiotherapy with ABC for NSCLC

Radiotherapy with ABC cone beam verification

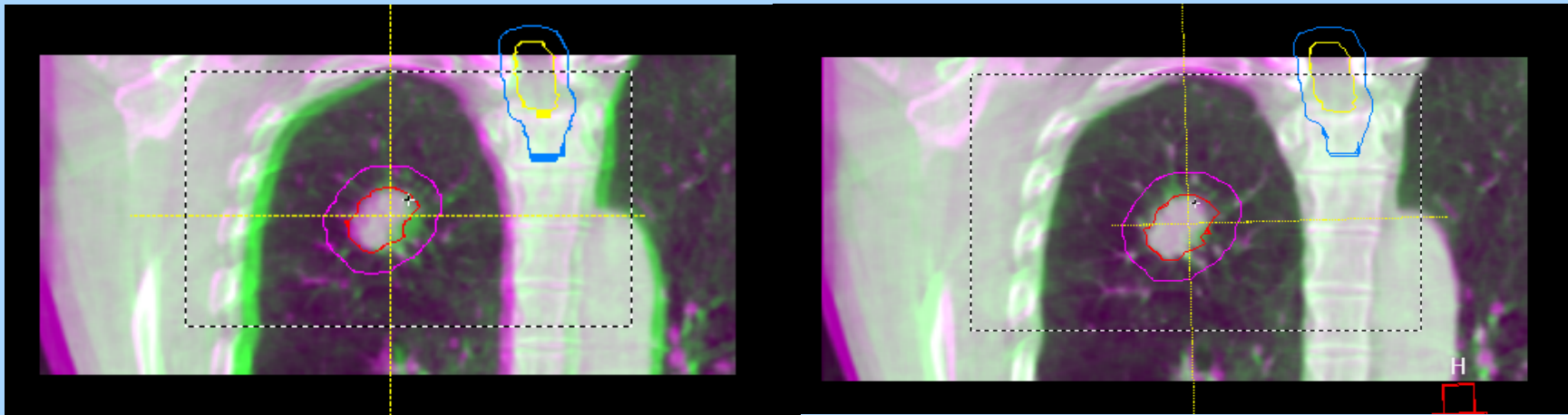
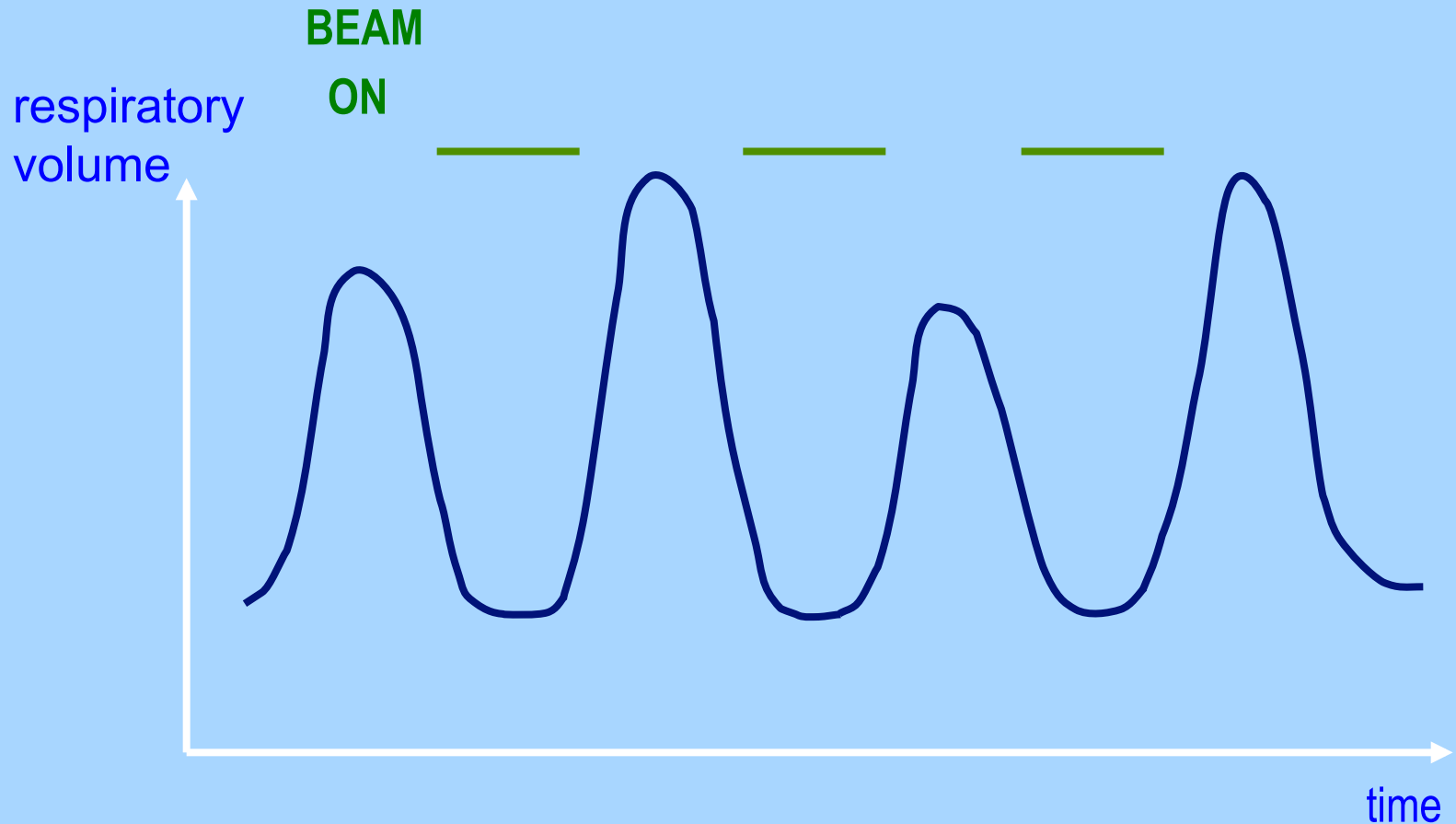


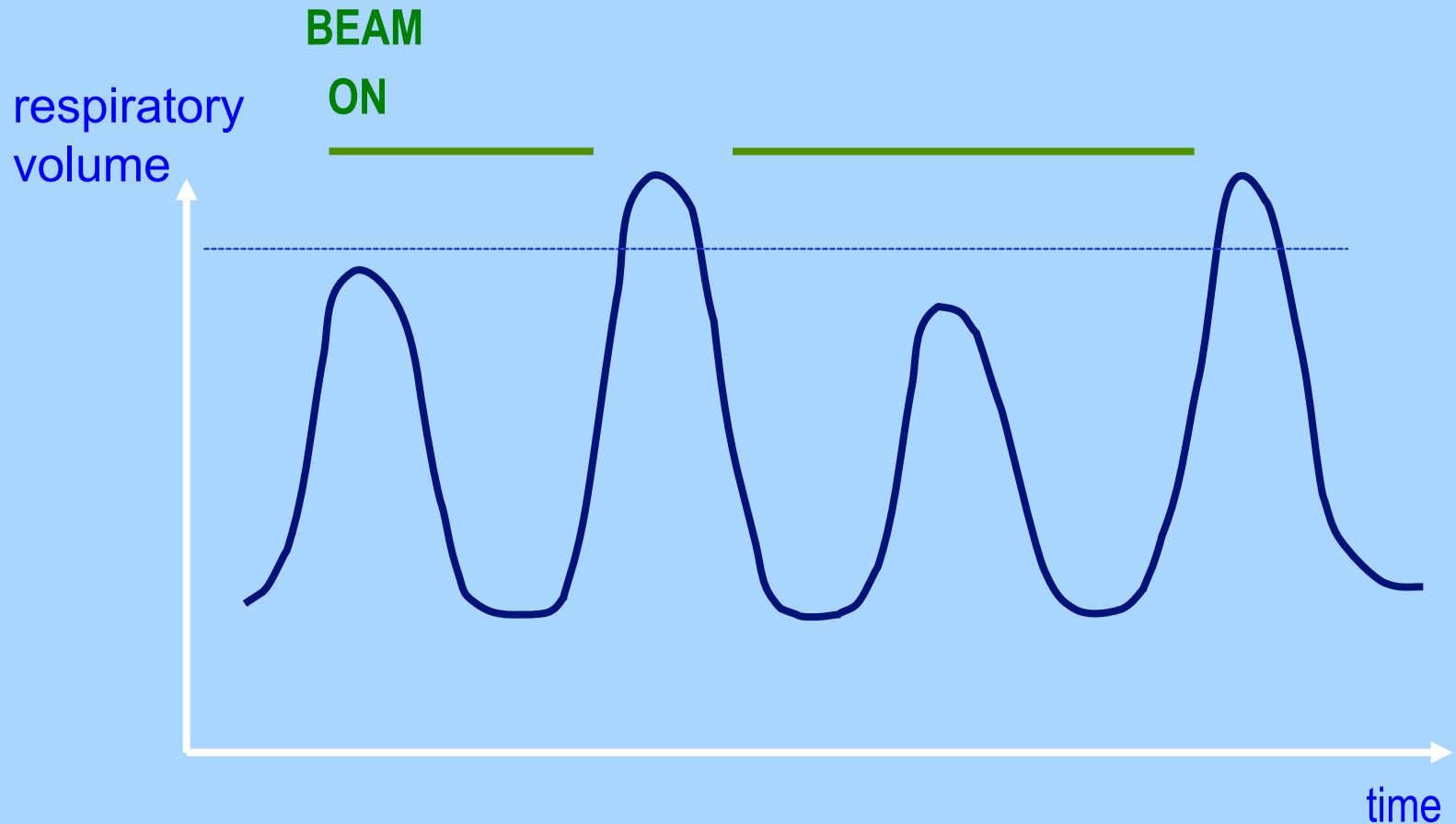
Image guided radiotherapy (IGRT)

Radiotherapy to a moving target - gating



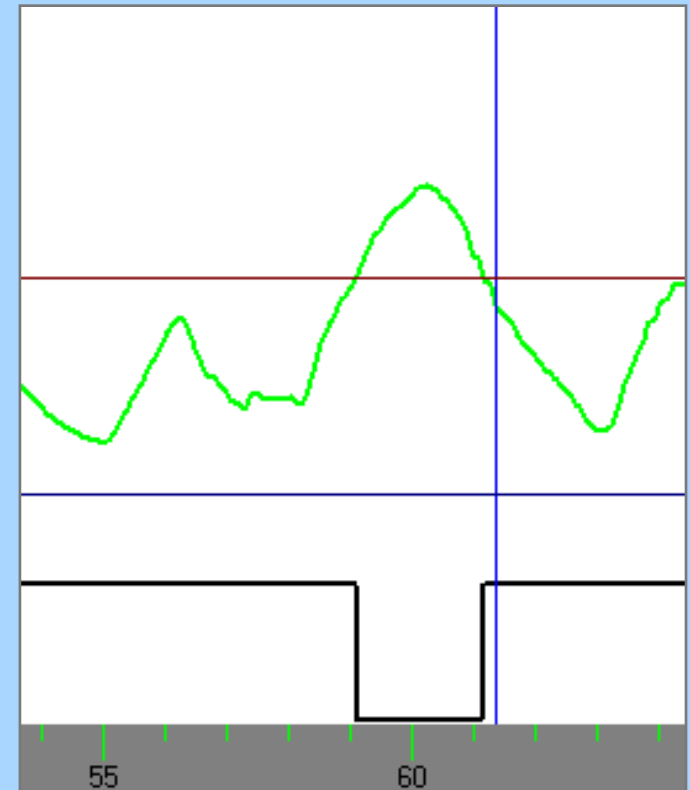
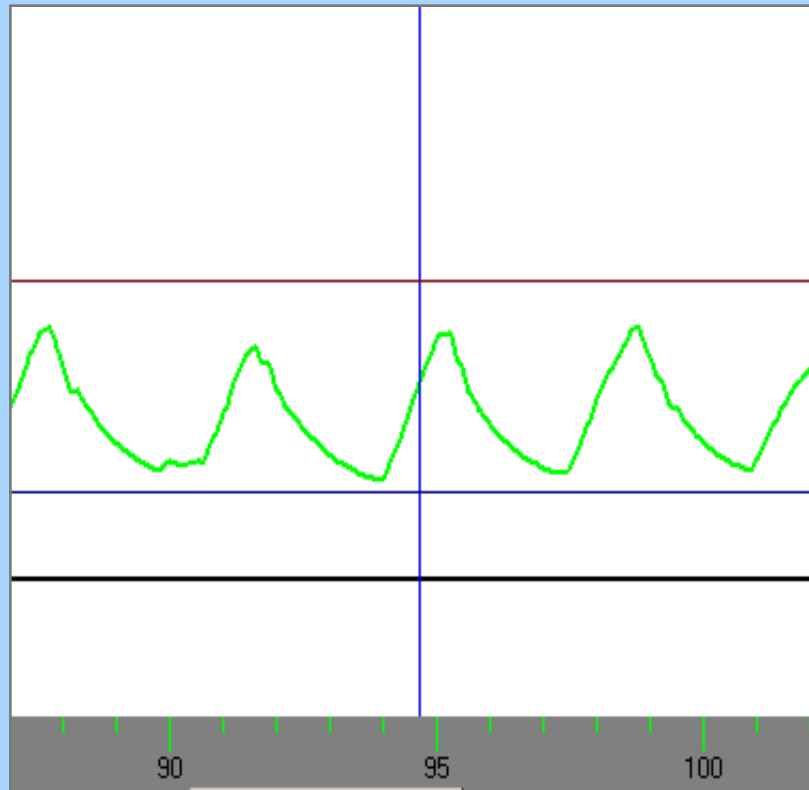
4D radiotherapy for non-small cell lung cancer

Radiotherapy to a moving target - gating



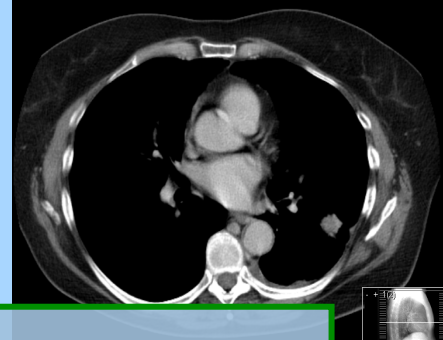
4D radiotherapy for non-small cell lung cancer

Radiotherapy to a moving target - gating example



4D radiotherapy for non-small cell lung cancer

Imaging for radiotherapy



Diagnosis
& staging

Planning

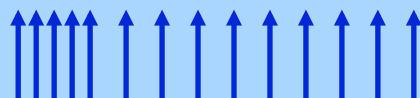
motion management
image interpretation

Diagnosis

Therapy

post treatment management

radiotherapy



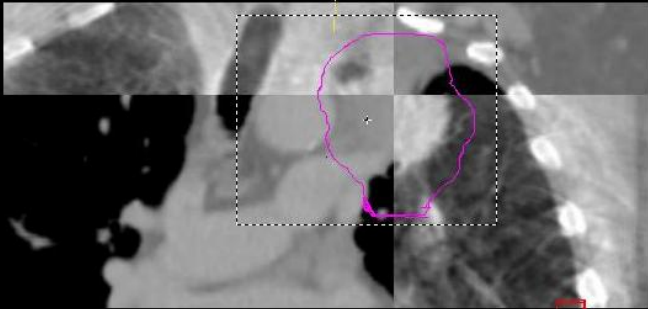
Verification

IGRT

Image guidance

visual assessment

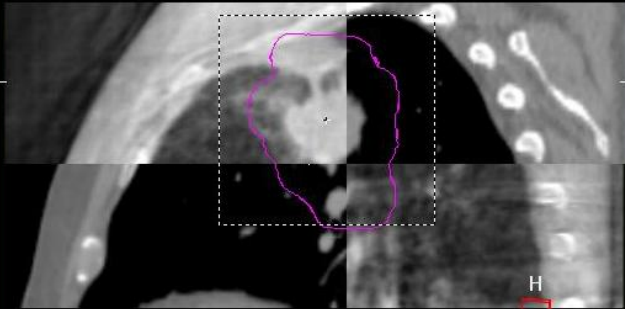
Coronal



Correction reference point = center of structure

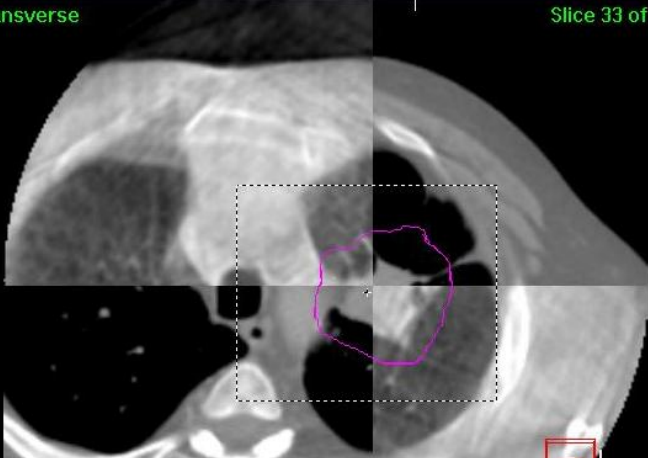
Slice 135 of 270

Sagittal



Slice 172 of 270

Transverse



Slice 33 of 128

Reference Preset

☒ Scan

☒ Alignment Clipbox

☒ Structures ..

Alignment

Position Error Translation (cm)

X	0.22
Y	-0.26
Z	0.29

Rotation (dg)

X	2.5
Y	0.8
Z	0.9

Table Correction

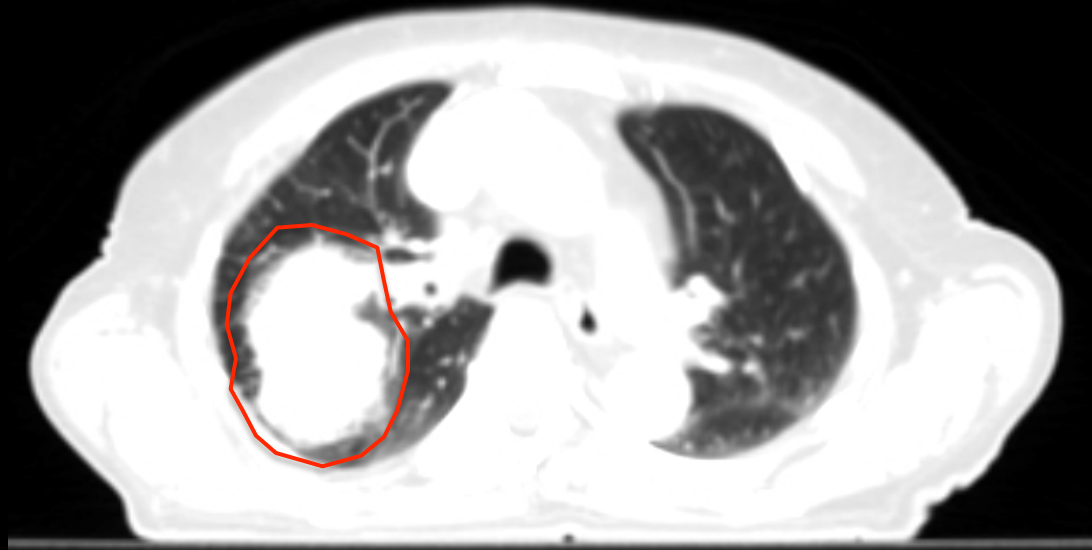
Lateral

Longitudinal

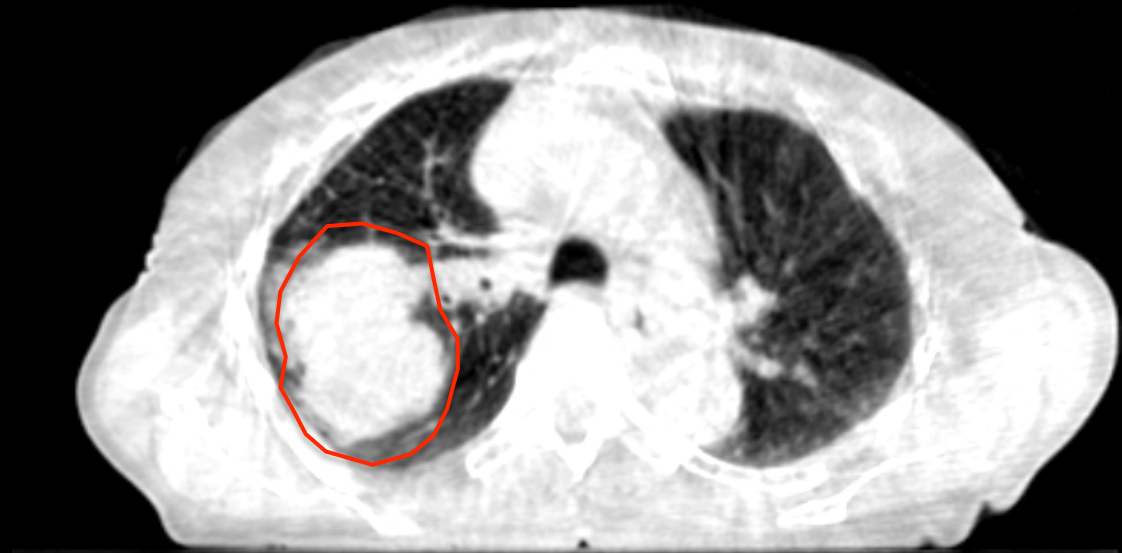
Vertical

Image guidance

Planning CT scan
13/08/2013



Cone beam CT scan
1#
02/09/2013



How would you adjust for the change seen on CBCT

Shift PTV

Enlarge PTV
and replan

No adjustment

Start antibiotics

Start
corticosteroids

Imaging for RT verification

Study

Evaluation of cone beam CT (CBCT) as a diagnostic CT scan

“correct image interpretation must precede RT verification”

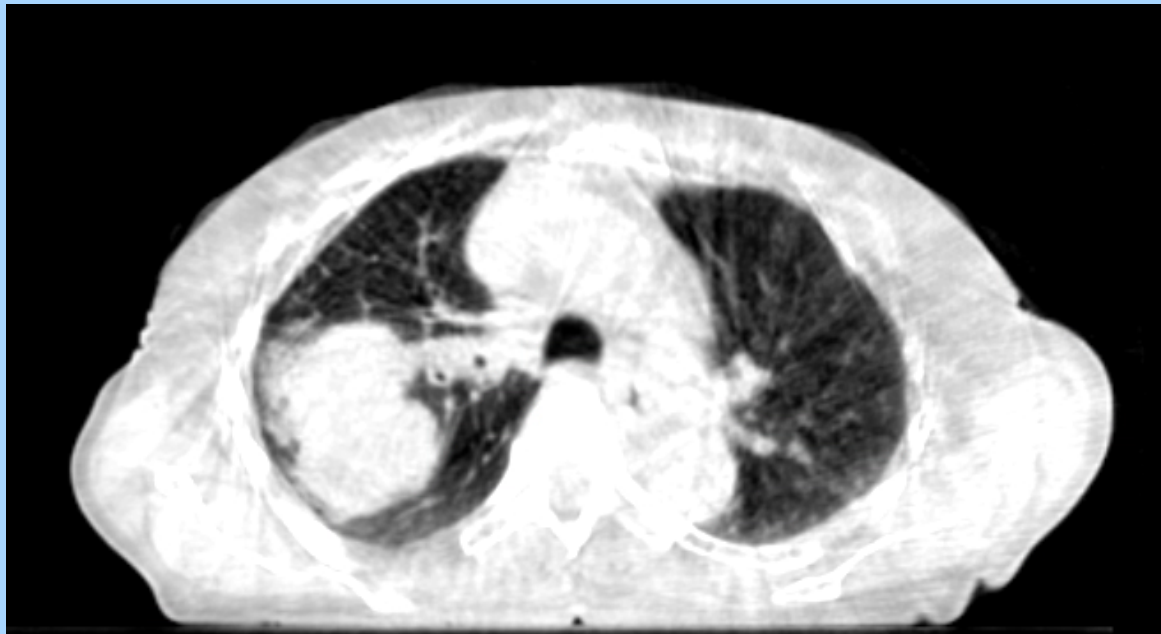


Image guidance during radiotherapy

Imaging for RT verification changes in tumour or adjacent to it (250 pts)

changes with potential need for volume adjustment

	apparent enlargement	<i>no. pts</i>	%
tumour	enlarging	41	
contiguous consolidation	new	14	} >1/2
	enlarging	30	
<i>total</i>		85	34%

CBCT as a diagnostic scan

Imaging for RT verification changes in tumour or adjacent to it (250 pts)

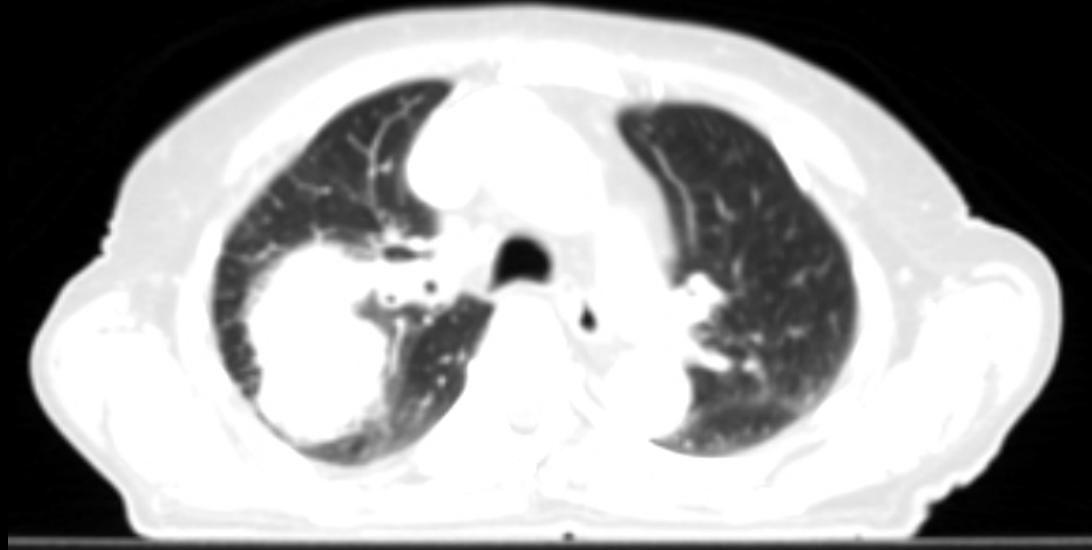
changes with potential need for volume adjustment

	apparent enlargement	<i>no. pts</i>	%
tumour	enlarging	41	
contiguous consolidation	new	14	
	enlarging	30	
atelectasis	new	6	
	enlarging	14	
<i>total</i>		105	42%

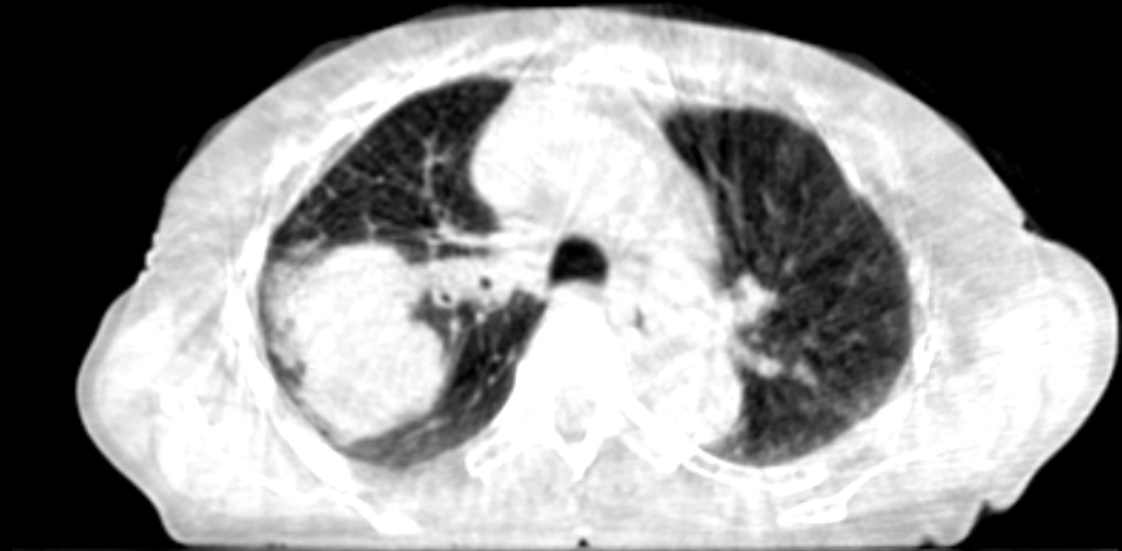
CBCT as a diagnostic scan

New contiguous consolidation

Planning CT scan
13/08/2013



Cone beam CT scan
1#
02/09/2013

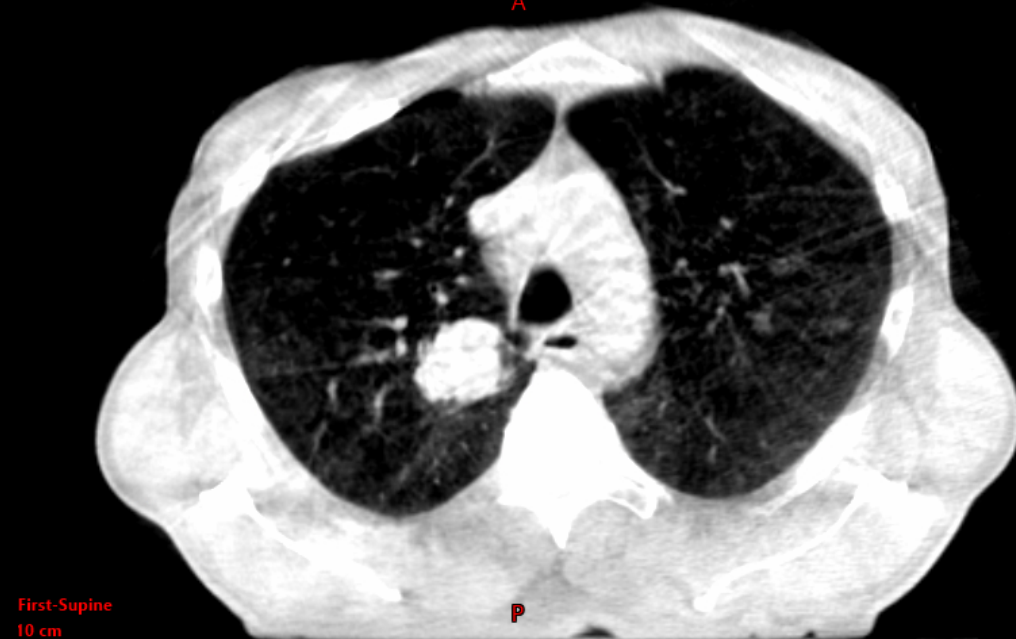


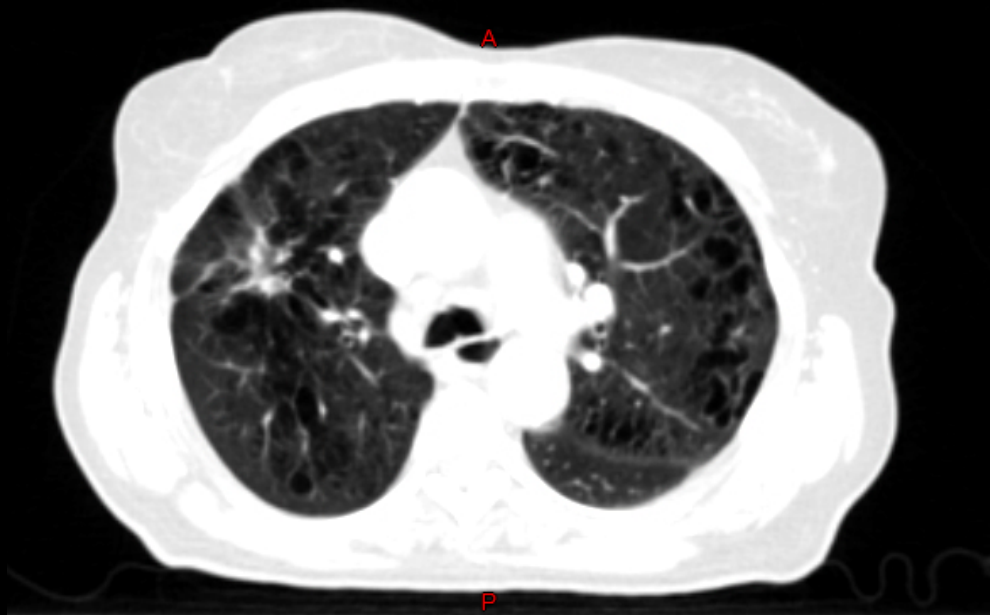
Tumour enlargement

Planning CT scan
27/10/2014



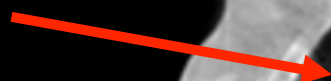
Cone beam CT scan
1#
10/11/2014





Planning CT scan
18/06/2014

Primary



Cone beam CT scan
4#
03/07/2014

IGRT

- quality assurance tool
- to reduce uncertainty of treatment delivery



The diagram features a central blue silhouette of a human torso. To the left, a stack of blue rectangular blocks is shown, with a red crosshair overlaid on one of the blocks. Below this stack is a blue rectangular block with a red crosshair. In the center, two overlapping gray rectangular boxes are positioned. The top box has a blue border and contains the text 'technical benefit'. The bottom box has a red border and contains the text 'clinical benefit'. The background is a light blue gradient.

technical benefit

clinical benefit

Image guided radiotherapy (IGRT)

IGRT

- quality assurance tool
- to reduce uncertainty of treatment delivery

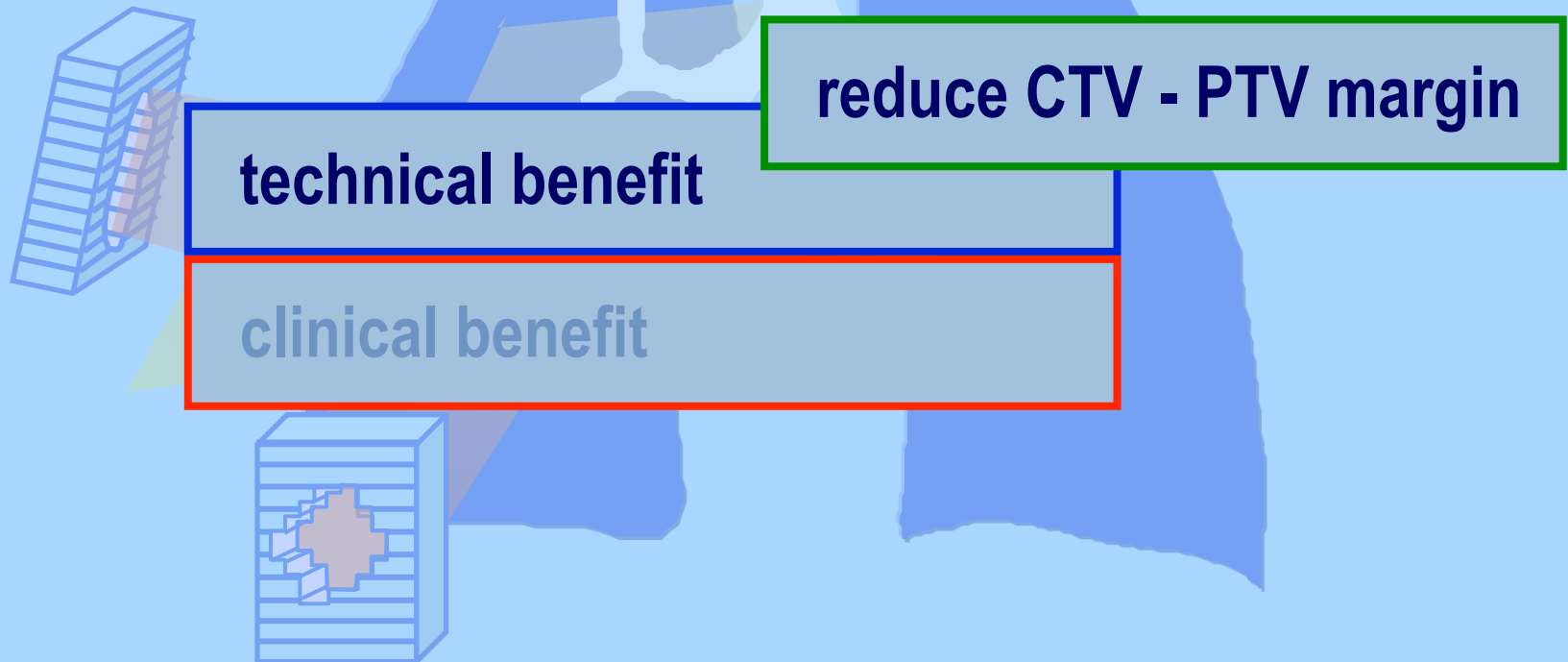


Image guided radiotherapy (IGRT)

CBCT frequency

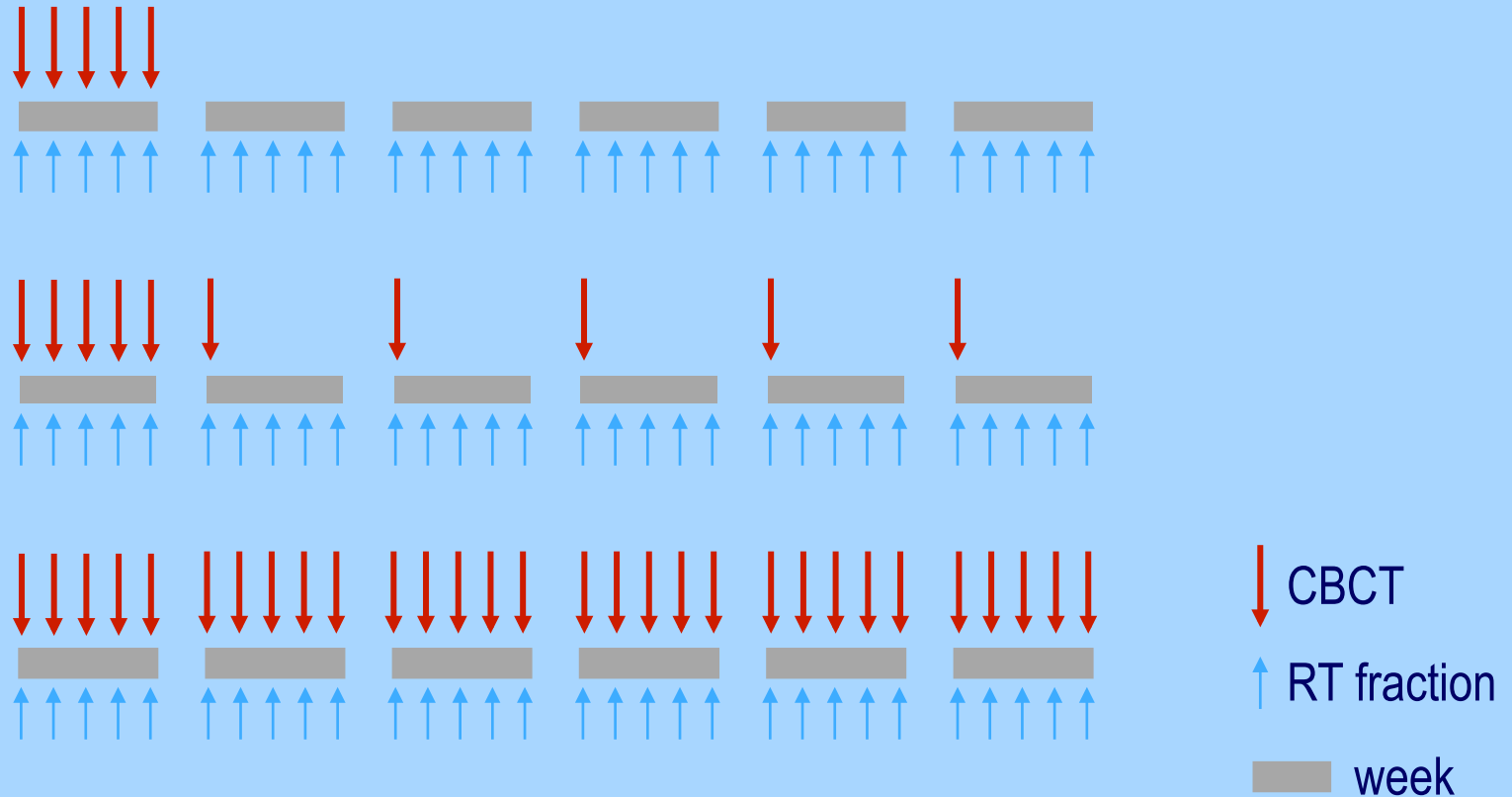
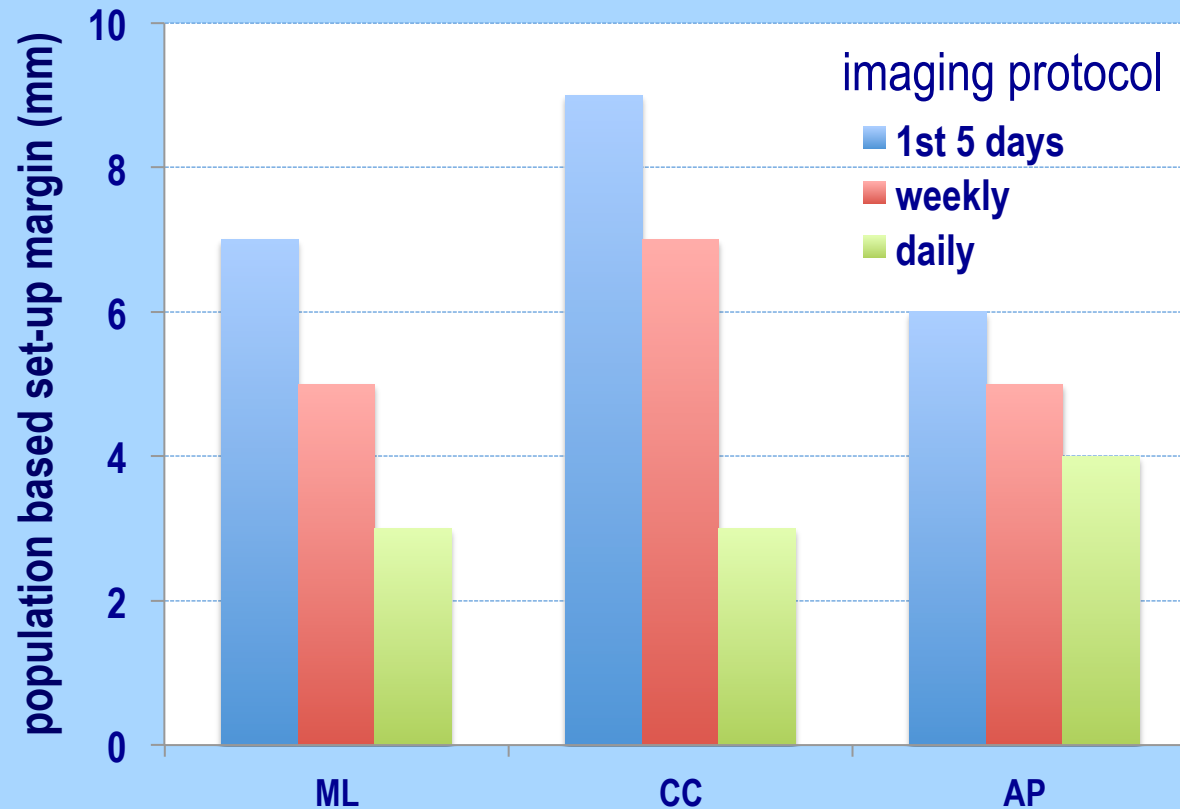


Image guidance in lung cancer radiotherapy

CBCT – cone beam CT

CBCT frequency and margin



CBCT - cone beam CT
ML - medio-lateral (L-R)
CC - cranio-caudal
AP - antero-posterior

Image guidance in lung cancer radiotherapy

IGRT

- quality assurance tool
- to reduce uncertainty of treatment delivery

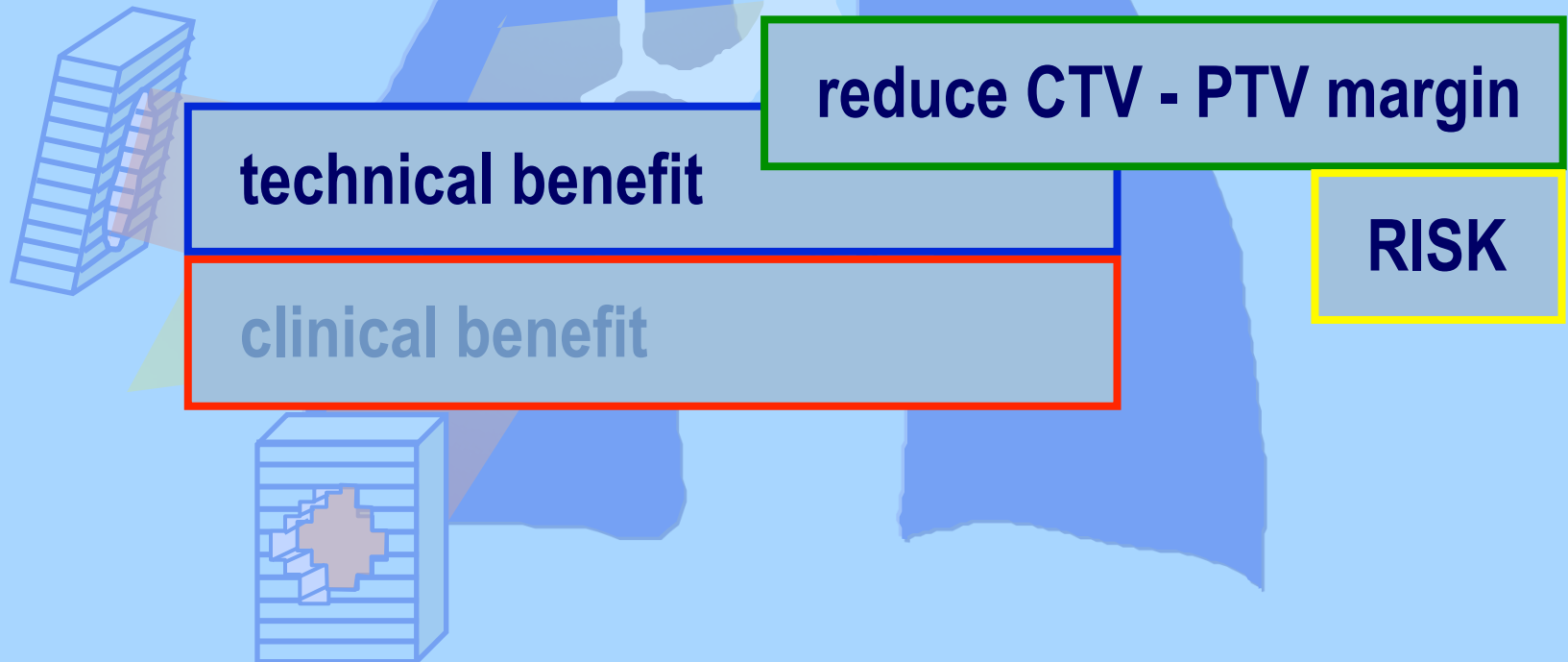


Image guided radiotherapy (IGRT)

IGRT

- quality assurance tool
- to reduce uncertainty of treatment delivery

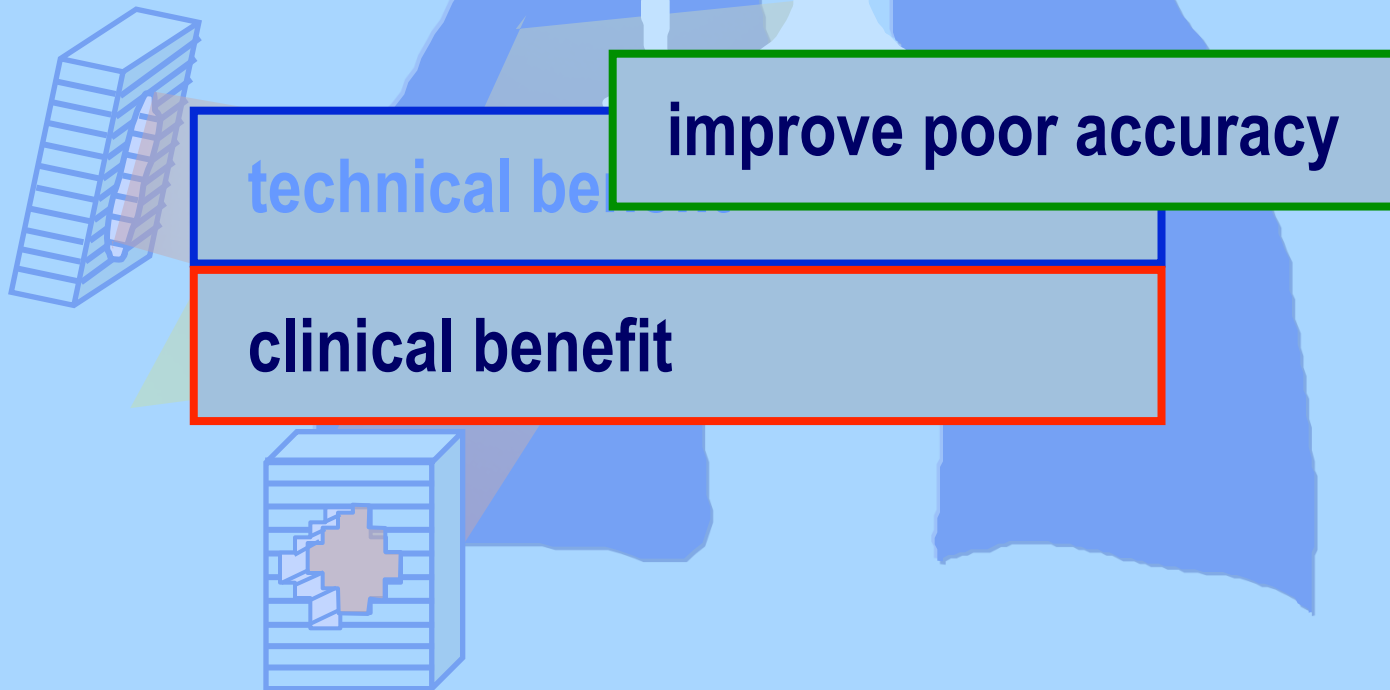
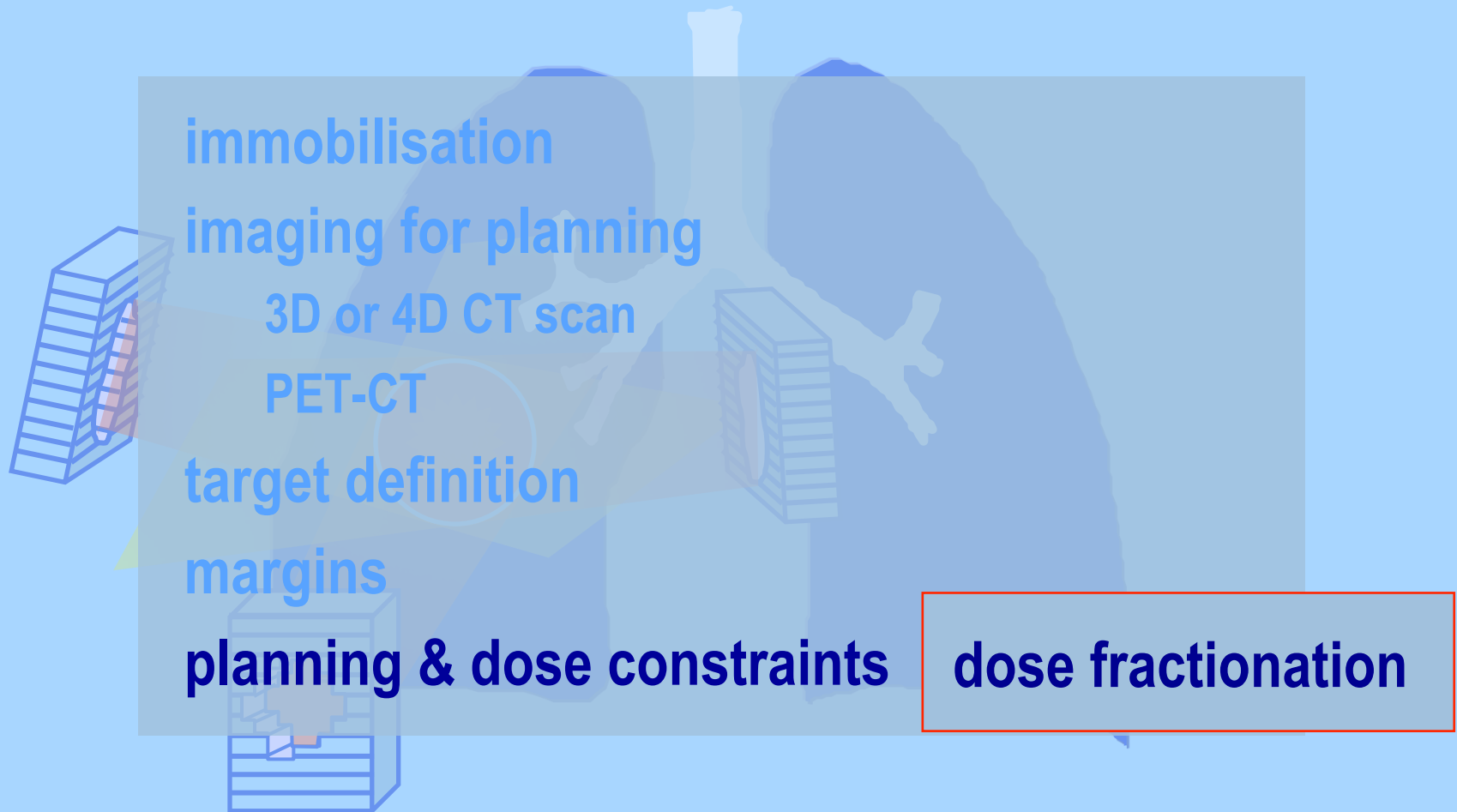


Image guided radiotherapy (IGRT)

Preparation for treatment



Practical aspect of NSCLC radiotherapy

Stage IIIA NSCLC treated with radical radiotherapy (+/- chemotherapy); which is the best RT regimen?

74Gy in 37 daily fractions
in 7+ weeks

66Gy in 33 daily fractions
in 6.5 weeks

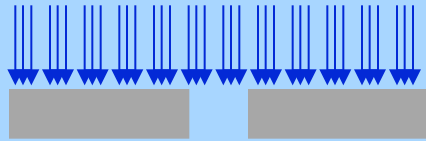
64Gy in 32 daily fractions
in 6+ weeks

60Gy in 30 daily fractions
in 6 weeks

55Gy in 20 daily fractions
in 4 weeks

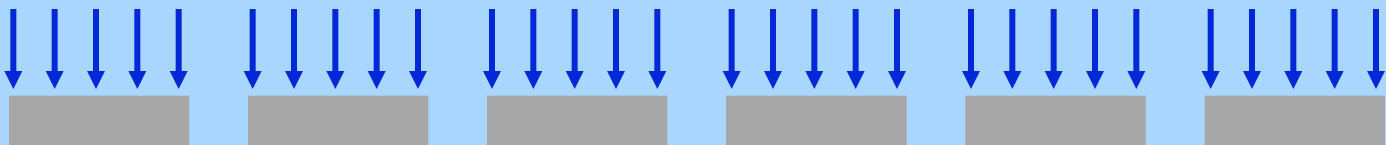
60Gy in 36 fractions
3x/day in 12 days (CHART)

Randomised trial of CHART



**Continuous Hyperfractionated Accelerated RadioTherapy
(CHART)**

54Gy 36 fract's in 12 days

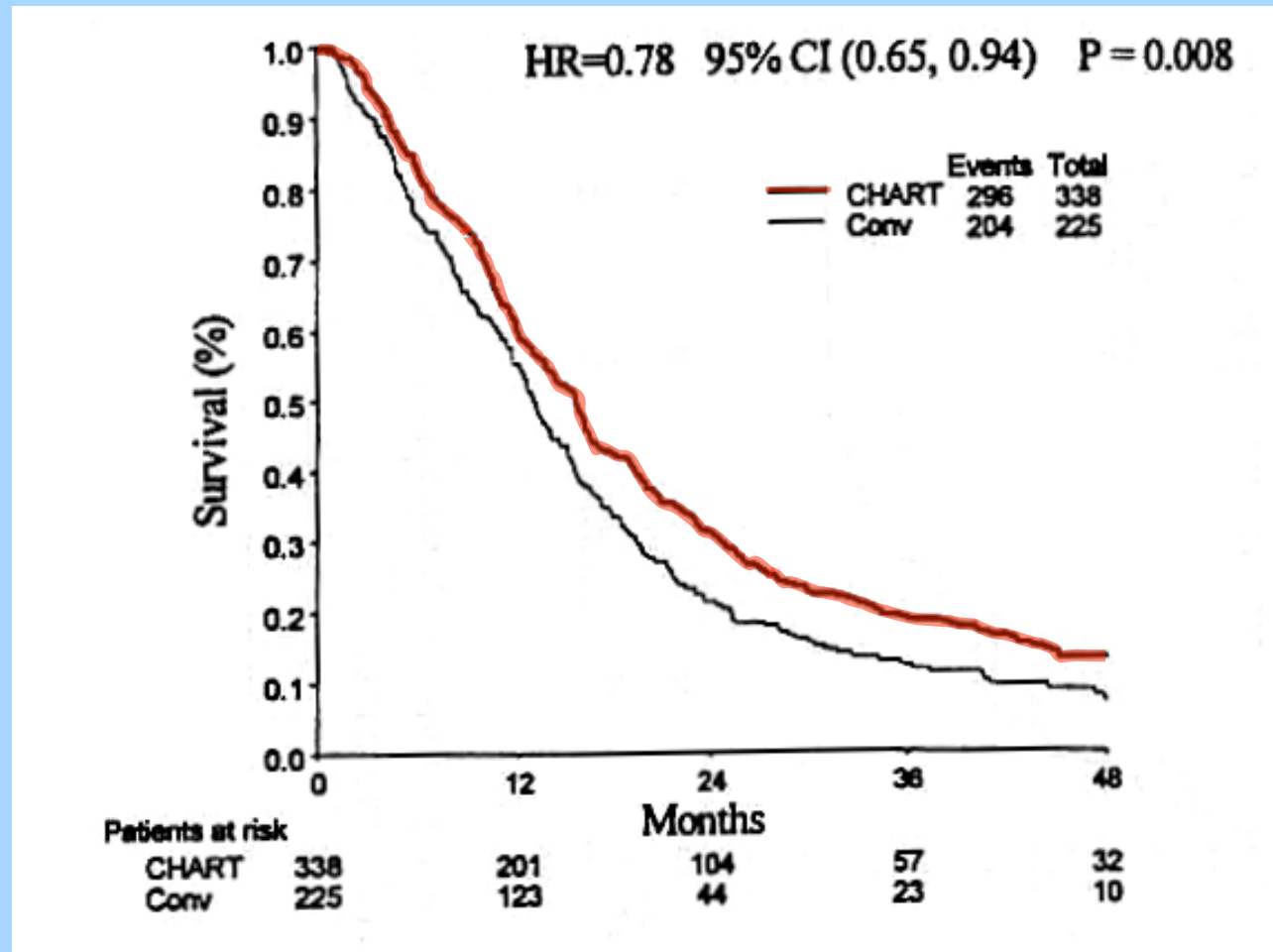


Conventional radiotherapy

60Gy 30 fract's in 6 weeks

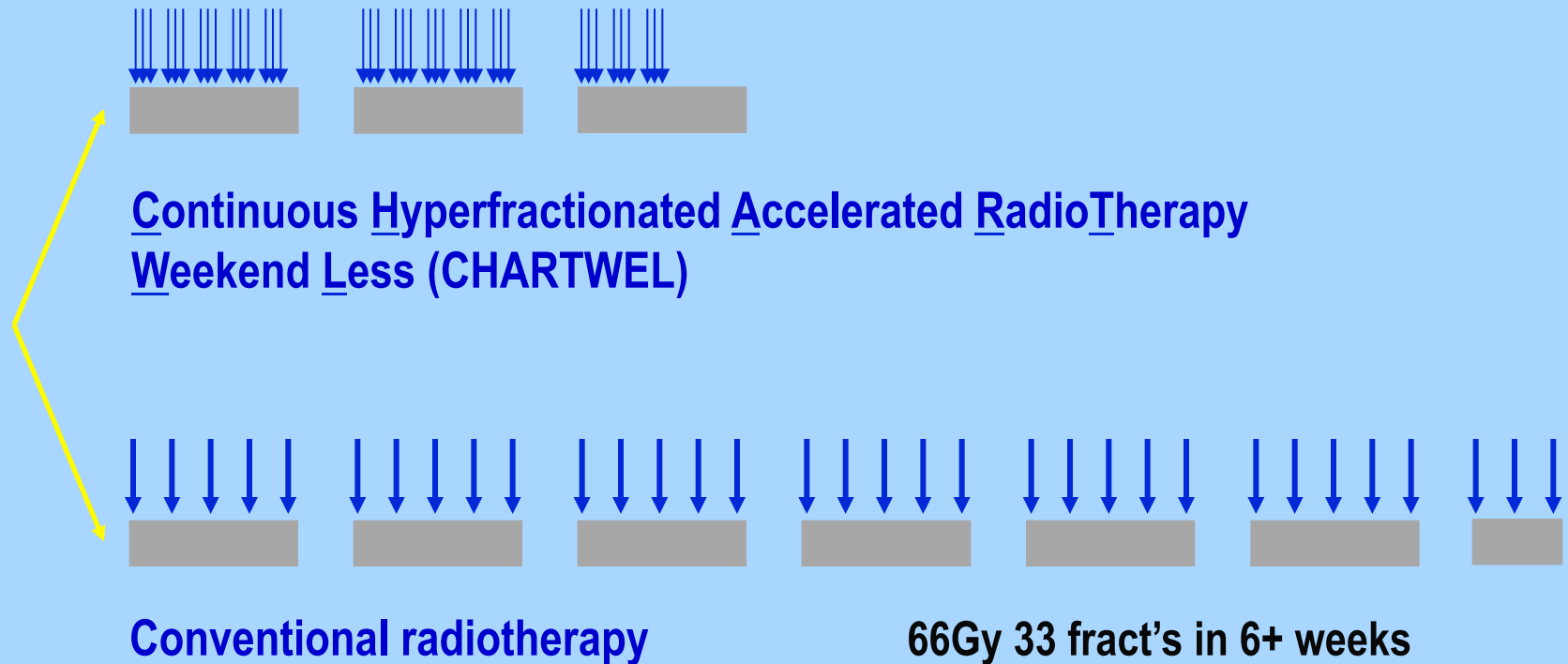
Dose escalation in radical RT of NSCLC

Randomised trial of CHART - survival



Dose escalation in radical RT of NSCLC

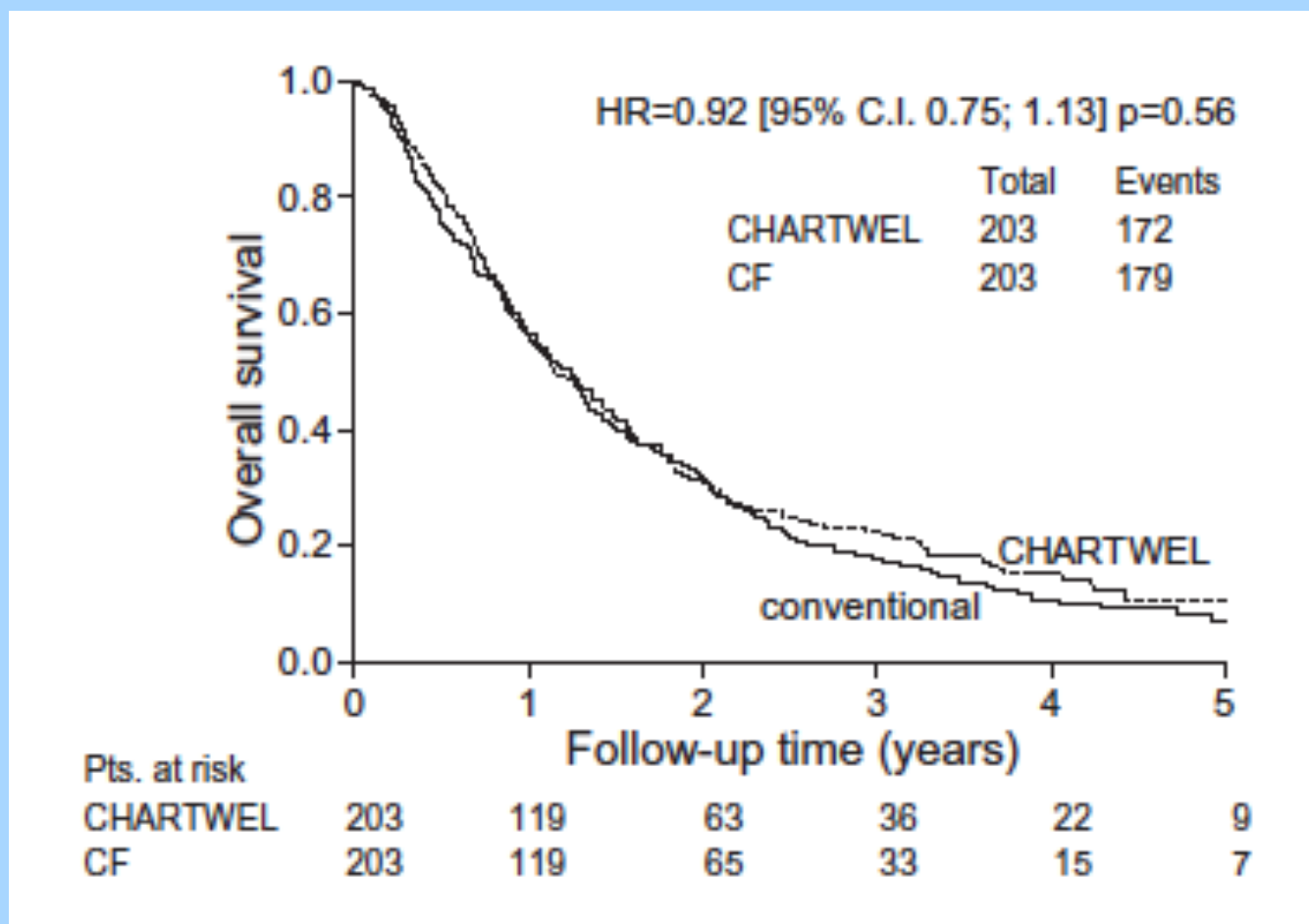
Randomised trial of CHARTWELL



Dose escalation in radical RT of NSCLC

Survival

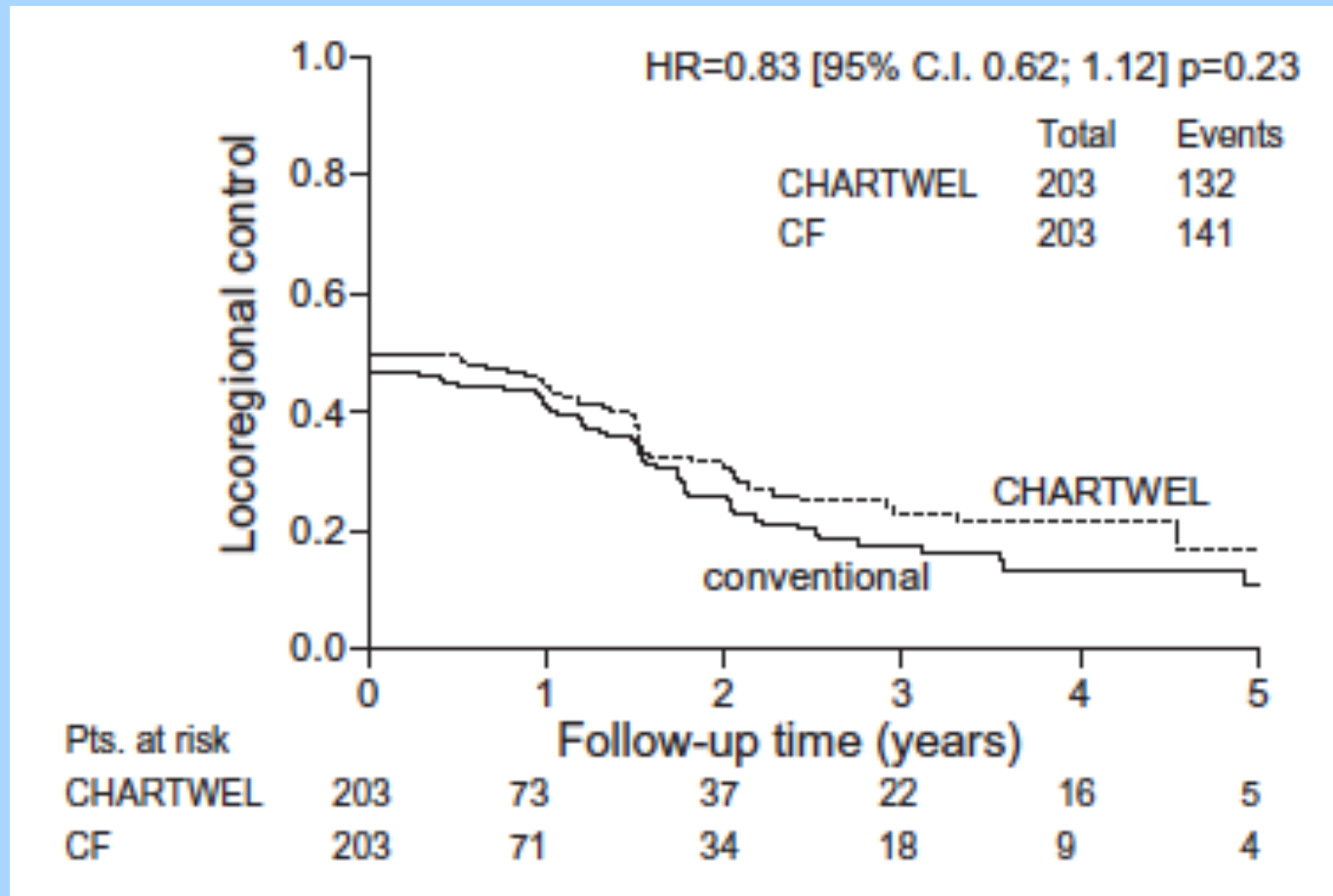
Randomised trial of CHARTWELL



Dose escalation in radical RT of NSCLC

Locoregional control

Randomised trial of CHARTWELL



Dose escalation in radical RT of NSCLC

Radical radiotherapy – dose escalation

Locally advanced
NSCLC



Phase I/II



increasing RT dose
(related to normal lung DVH)

Improving lung cancer radiotherapy



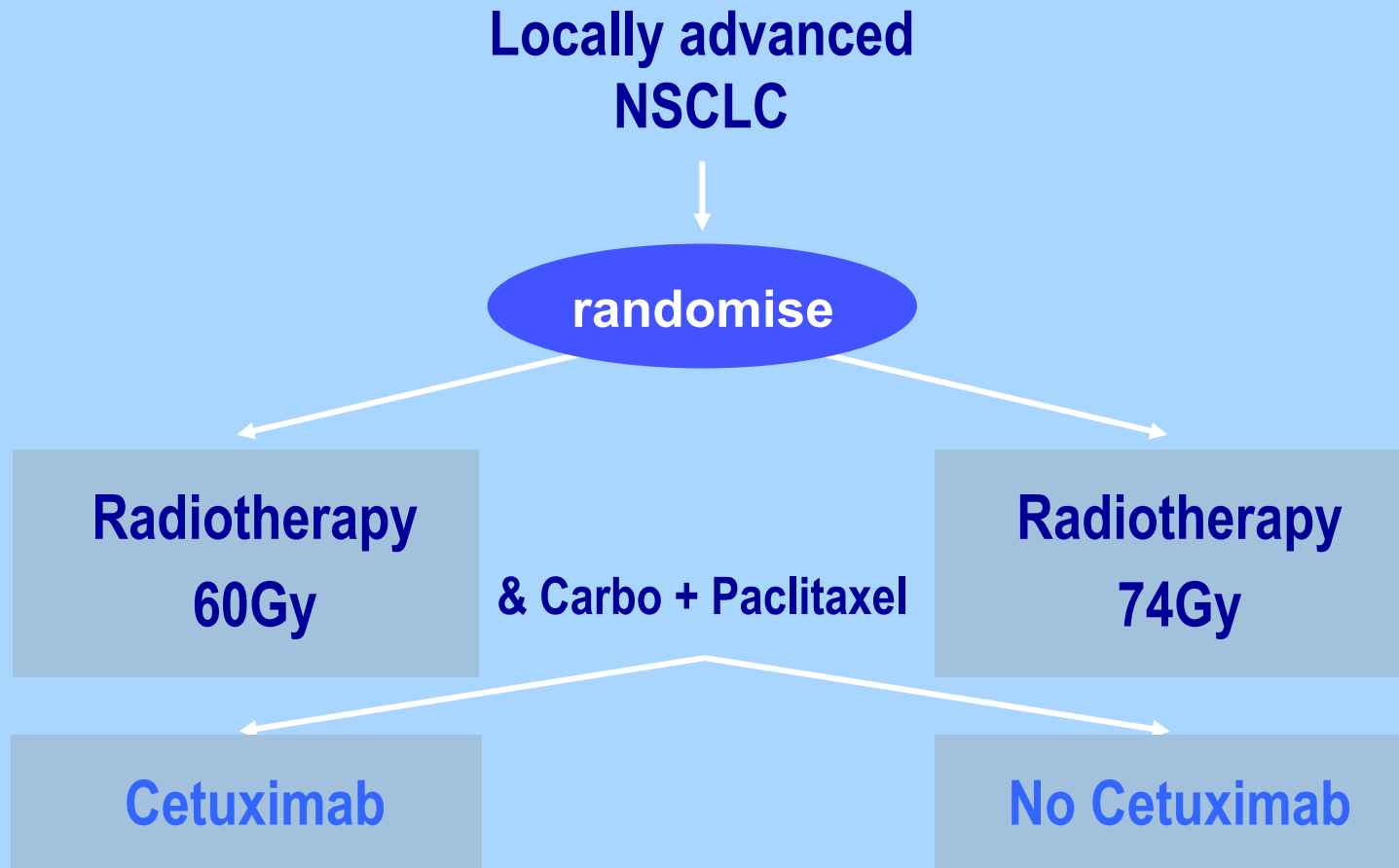
Radical radiotherapy dose fractionation

- stage IIIA NSCLC (without chemotherapy)

1. 74Gy in 37 daily fractions in 7+ weeks
2. 66Gy in 33 daily fractions in 6.5 weeks
3. 64Gy in 32 daily fractions in 6+ weeks
4. 60Gy in 30 daily fractions in 6 weeks
5. 55Gy in 20 daily fractions in 4 weeks
6. 60Gy in 36 fractions 3x/day in 12 days (CHART)

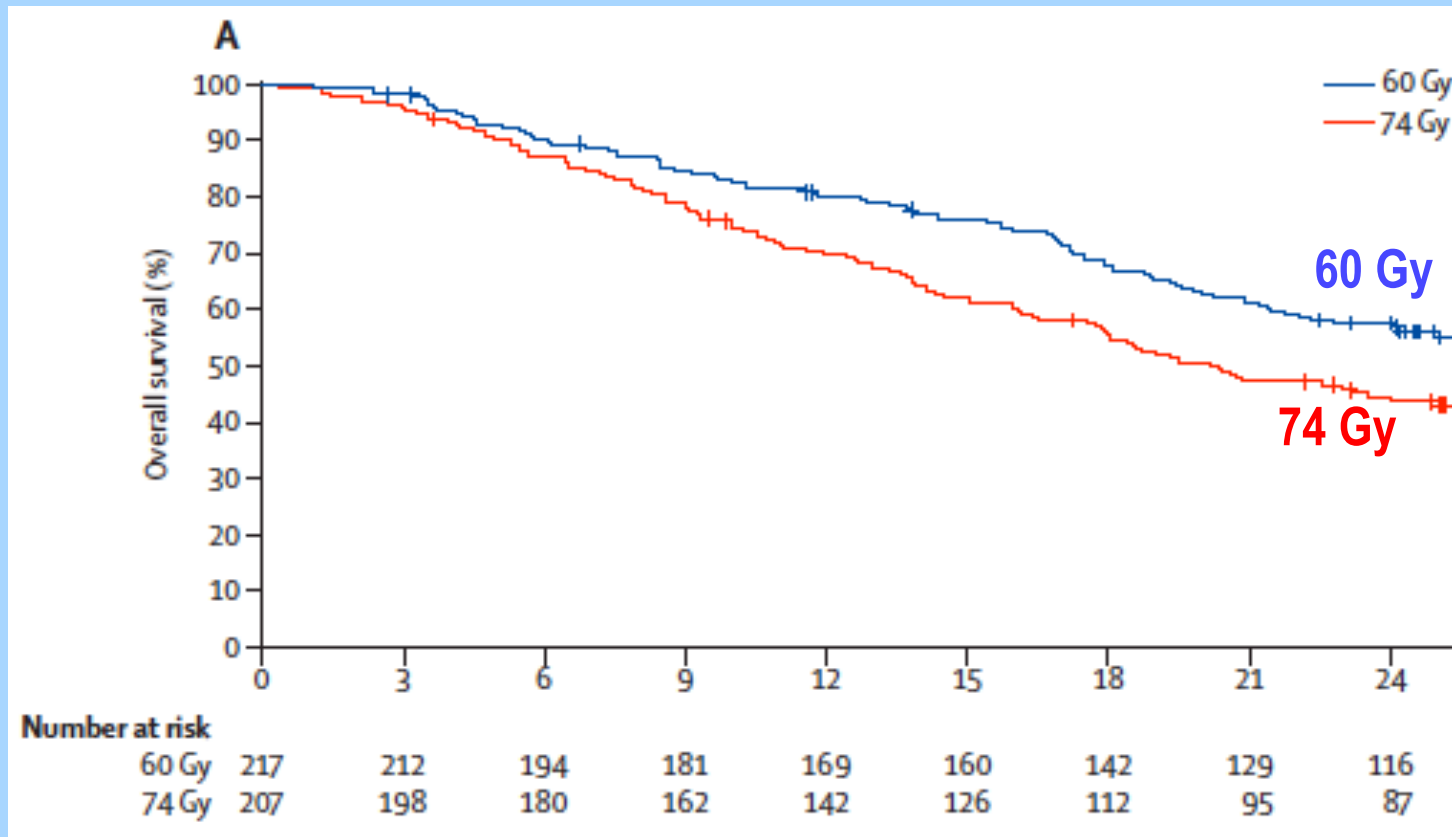
Stage IIIA (T2N2M0) NSCLC

Radical radiotherapy – dose escalation



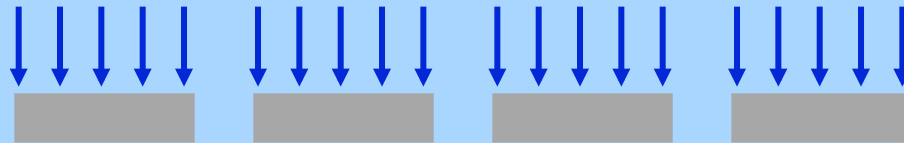
Dose response in non-small cell lung cancer (NSCLC)

Radical radiotherapy – dose escalation survival



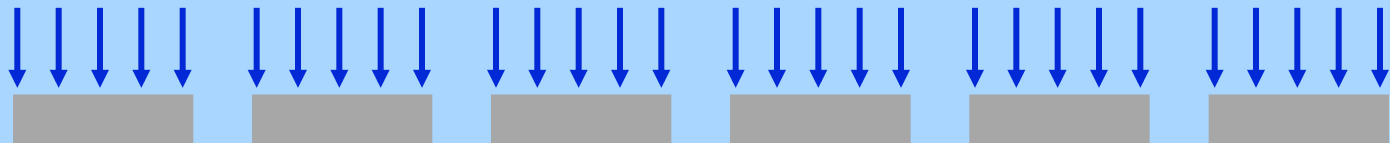
Dose escalation in locally advanced NSCLC

Hypofractionated radiotherapy



Accelerated hypofractionated

55Gy 20 fract's in 4 weeks

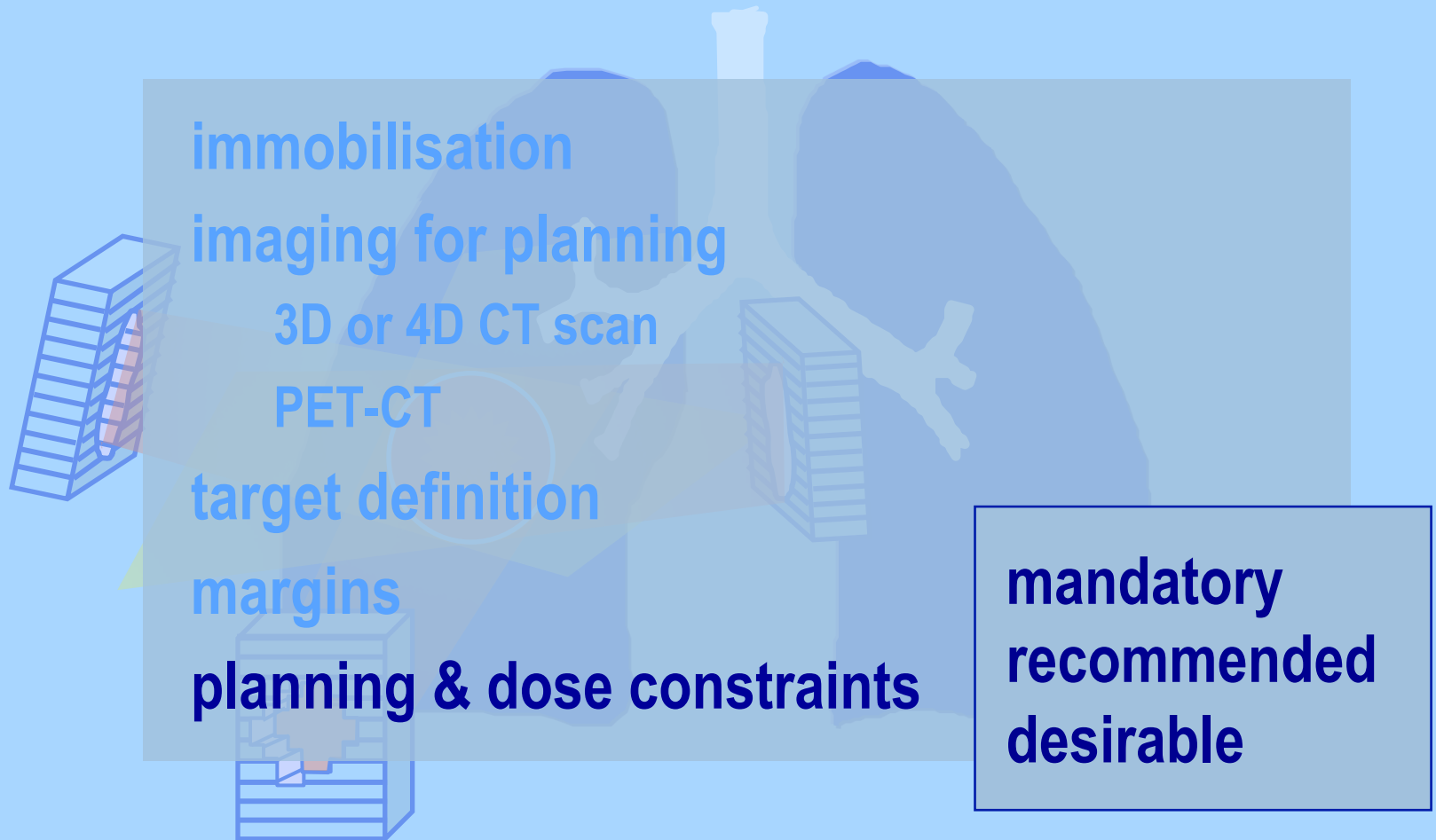


Conventional radiotherapy

60Gy 30 fract's in 6 weeks

Altered dose fractionation in radical RT of NSCLC

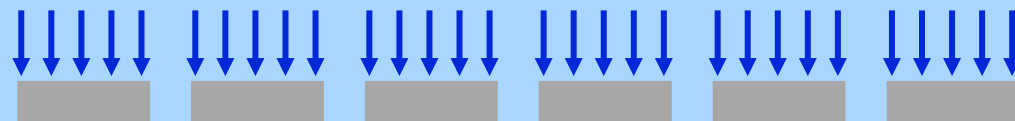
Preparation for treatment



Practical aspect of NSCLC radiotherapy

Mandatory dose constraints (for 2Gy/fraction)

<i>organ at risk</i>	<i>constraint</i>	<i>risk</i>
spinal cord	$D_{\max} \leq 50\text{Gy}$	$\leq 2\%$ myelopathy
brachial plexus	$D_{\max} \leq 60\text{Gy}$	$\leq 5\%$ nerve damage
lung (total - GTV)	$V_{20\text{ Gy}} \leq 35\%$	$\leq 20\%$ pneumonitis
oesophagus	$D_{1\text{cc}} \leq 60\text{ Gy}$	

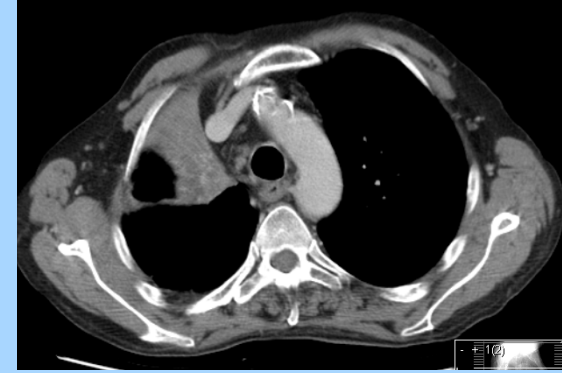


Conventional RT

60Gy 30 fract's in 6 weeks

OAR dose constraints for NSCLC radiotherapy

Locally advanced NSCLC



options

Radiotherapy

Radiotherapy

Systemic therapy

Radiotherapy
Systemic therapy

sequential

concomitant

Management options in locally advanced NSCLC

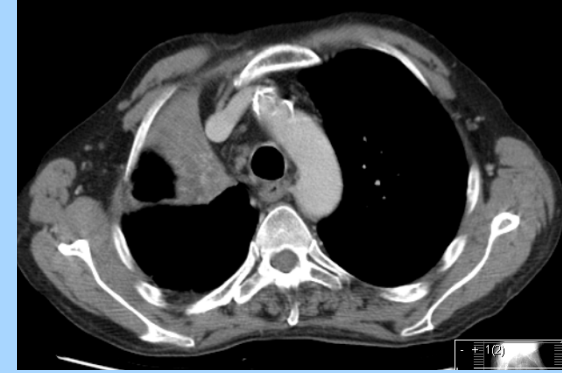
Radiotherapy in the management of non-small cell lung cancer (NSCLC)

Michael Brada BSc, MB ChB, FRCP, FRCR, DSc
Professor of Radiation Oncology
University of Liverpool

Department of Molecular and Clinical Cancer Medicine
& Department of Radiation Oncology
Clatterbridge Cancer Centre NHS Foundation Trust
Bebington, Wirral, CH63 4JY

michael.brada@liverpool.ac.uk

Locally advanced NSCLC



options

Radiotherapy

Radiotherapy

Systemic therapy

Radiotherapy
Systemic therapy

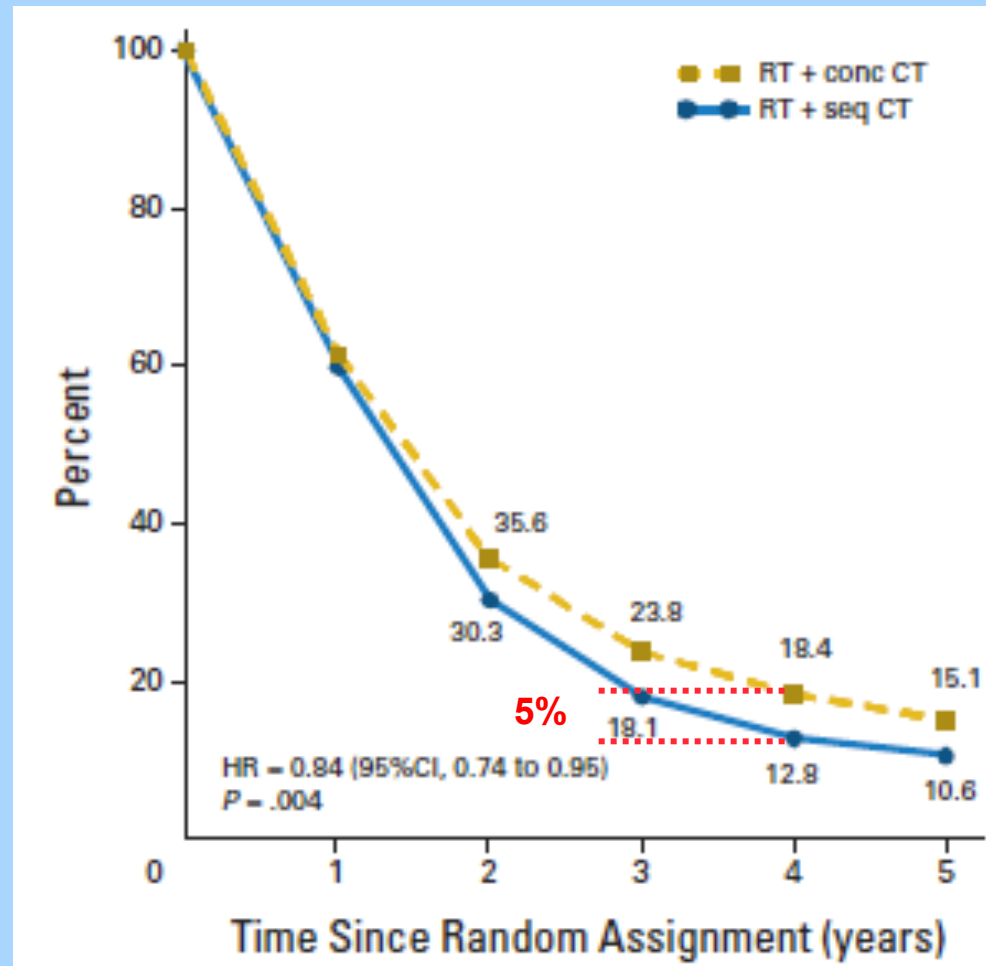
sequential

concomitant

Management options in locally advanced NSCLC

Concomitant vs sequential chemoradiotherapy - meta-analysis

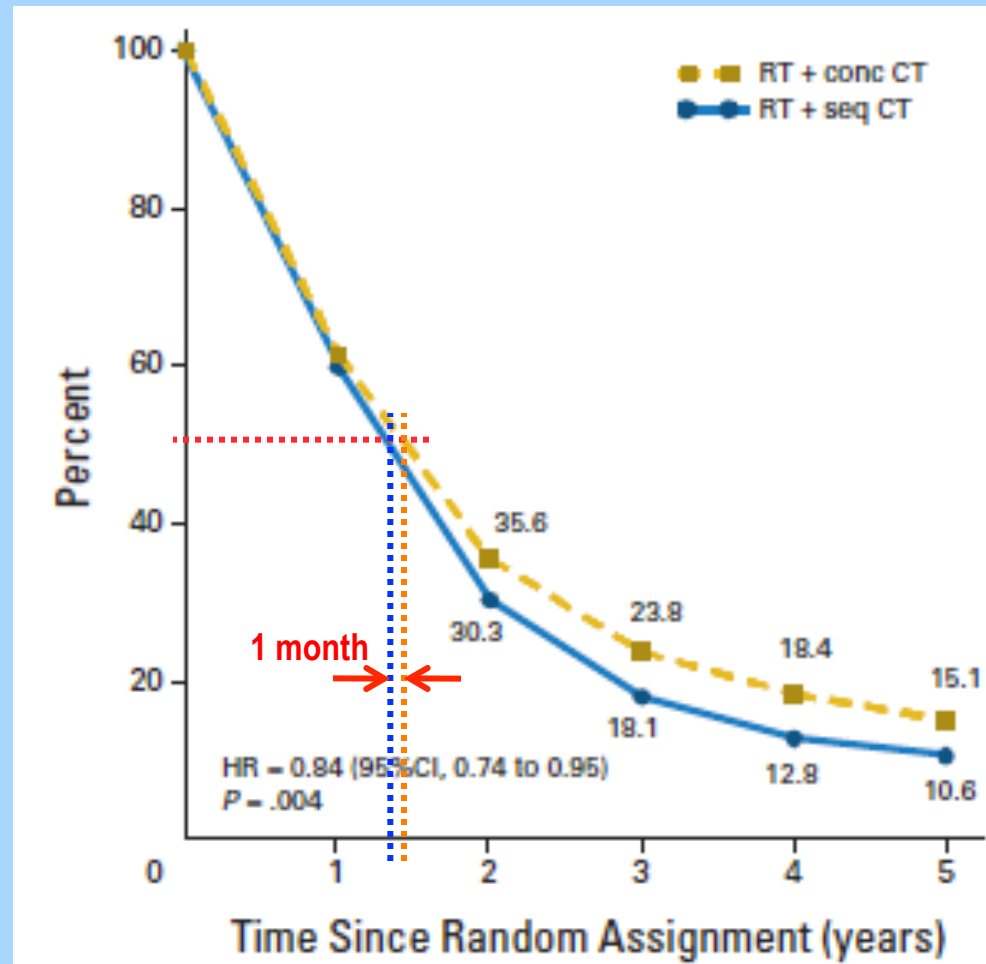
Survival



Chemoradiotherapy in locally advanced NSCLC

Concomitant vs sequential chemoradiotherapy - meta-analysis

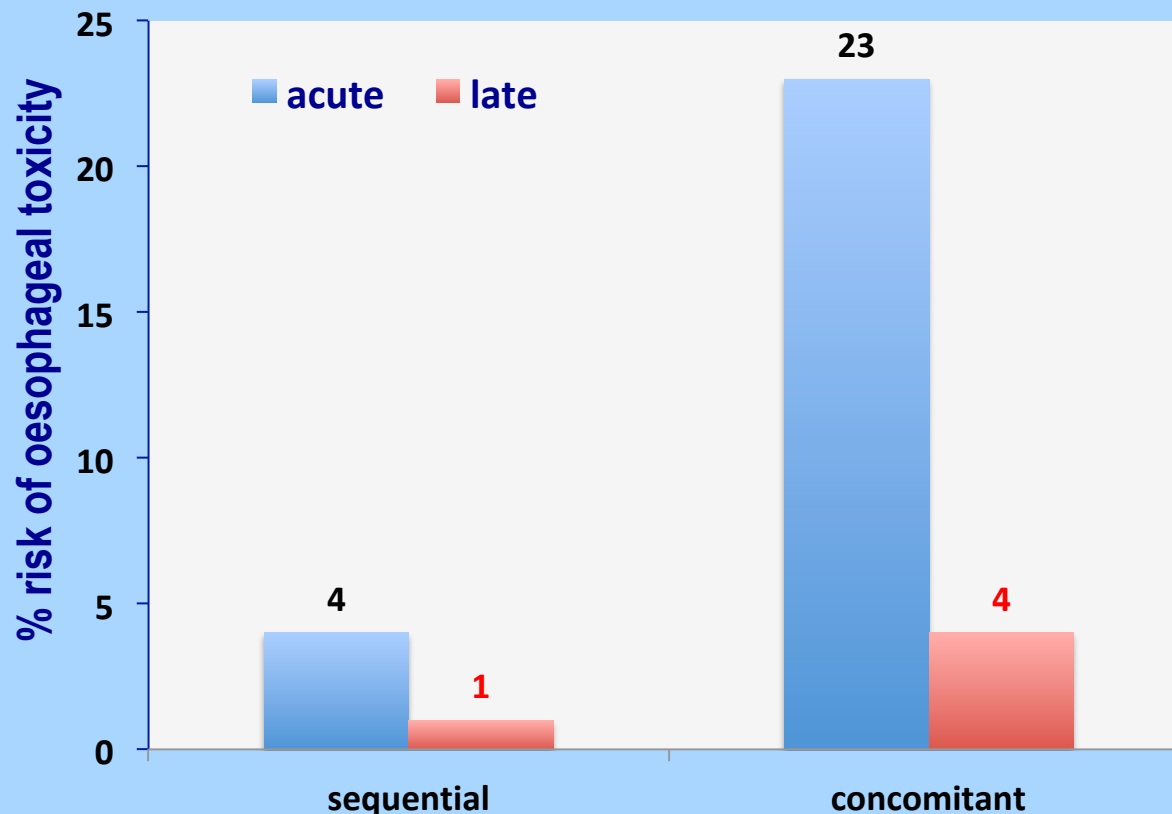
Survival



Chemoradiotherapy in locally advanced NSCLC

RTOG 9140 study - toxicity

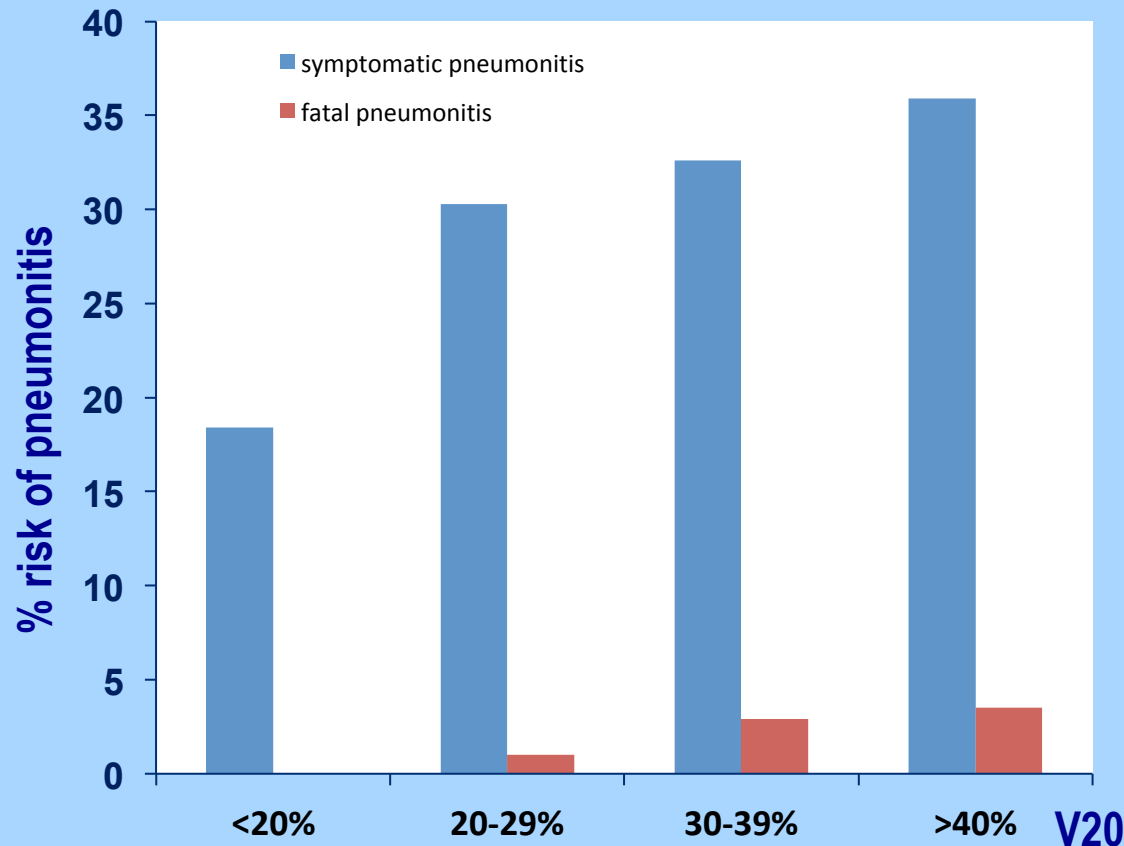
oesophageal toxicity (\geq grade 3)



Sequential vs concomitant chemotherapy in stage III NSCLC

Concomitant chemoradiotherapy and risk of pneumonitis

individual patient data meta-analysis (nonrandomised)



Combined modality therapy in locally advanced NSCLC