Challenges in thoracic imaging for image-guided radiotherapy

Professor Suresh Senan
Radiation oncologist

Disclosure

The VU University medical center has research agreements with Varian Medical Systems (Palo Alto, CA) and Velocity Medical Solutions (Atlanta, GA).

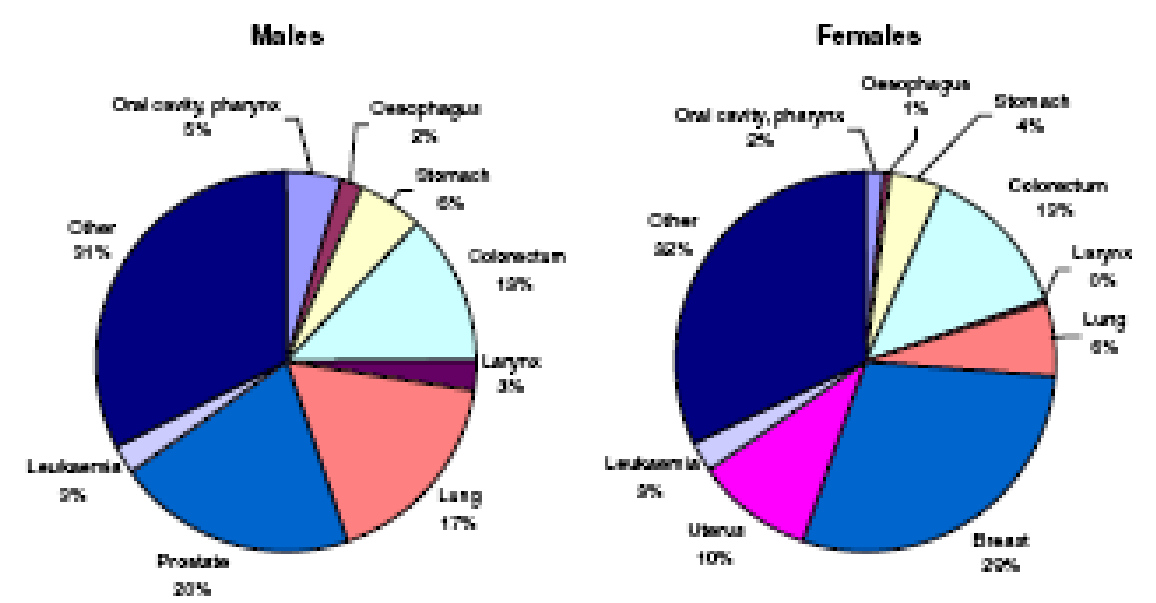
Overview

- *Definition of 4-D RT, IGRT*
- *Motion assessment: Fluoroscopy, slow CT, 4DCT, PET*
- *Motion of lymph nodes*
- *Use of FDG-PET scans for target definition*
- *Baseline shifts in tumor position*
- *Role of adaptive radiotherapy & replanning*

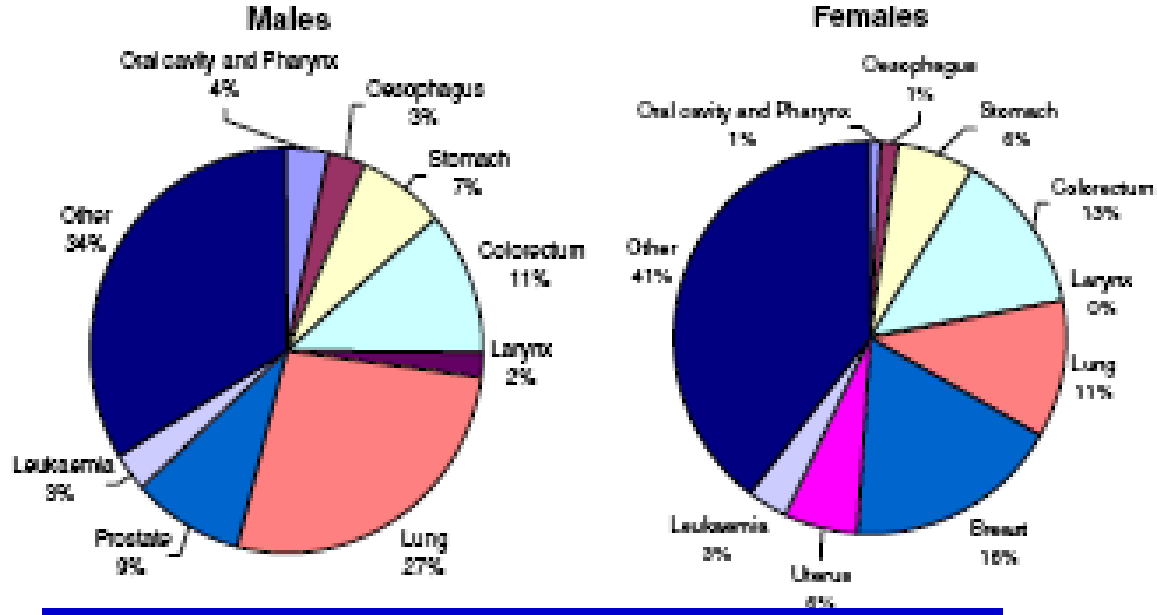
VUmc

Epidemiology of Cancer in Europe

Karim-Kos 2008

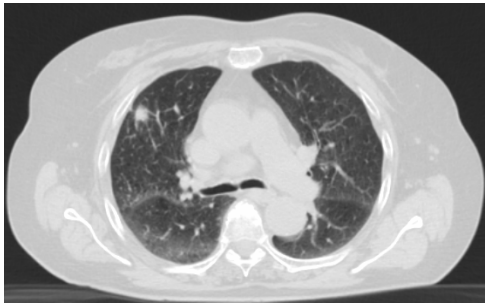


Distribution of new cancer **cases** in Europe 2006



Distribution of new cancer **deaths** in Europe 2006

Stage I NSCLC: local control



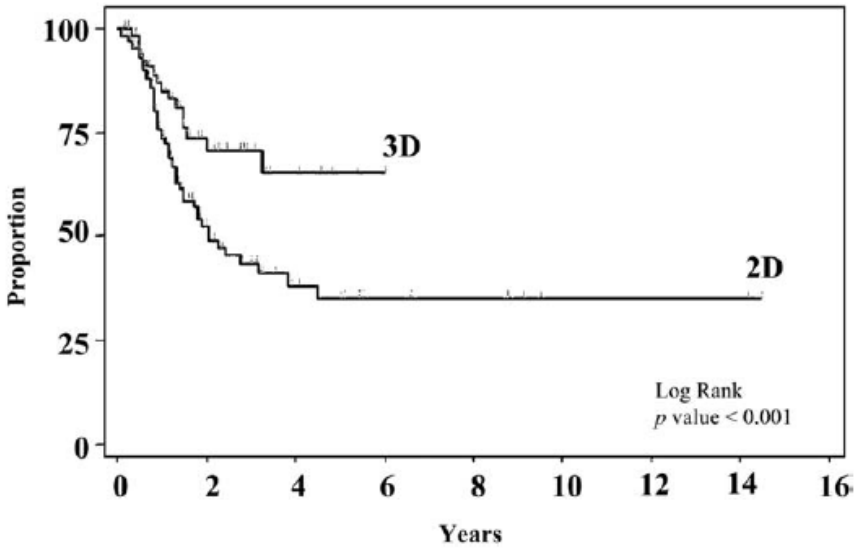


Fig. 4. Local-regional control for all patients.

Table 4. Pattern of failure

Site of failure	All pts., no. of patients (%)	2D, no. of patients (%)	3D, no. of patients (%)
Total failures	95/196 (48)	64/111 (58)	31/85 (36)
Local alone	26 (27)	18 (28)	8 (26)
Regional alone	6 (6)	5 (8)	1 (3)
Locoregional	4 (4)	2 (3)	2 (6)
DM only	23 (24)	10 (16)	13 (42)
DM + local	20 (21)	17 (27)	3 (10)
DM + regional	10 (11)	7 (10)	3 (10)
DM + locoregional	6 (6)	5 (8)	1 (3)

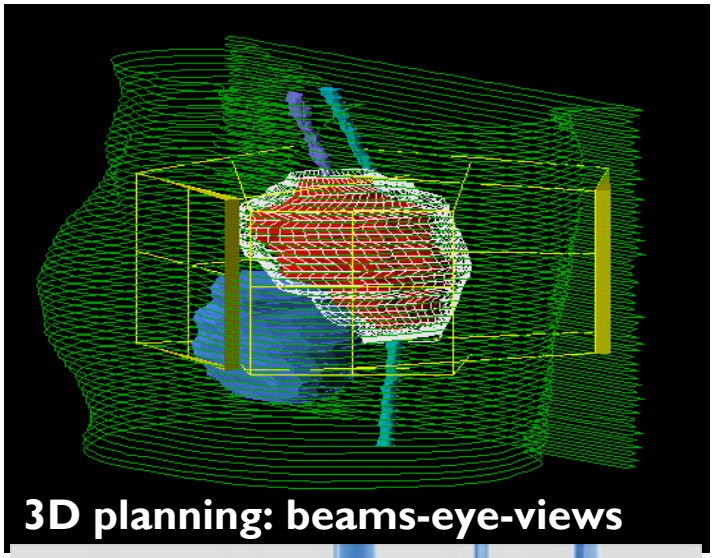
Abbreviation: DM = distant metastasis; other abbreviations as in Table 1.

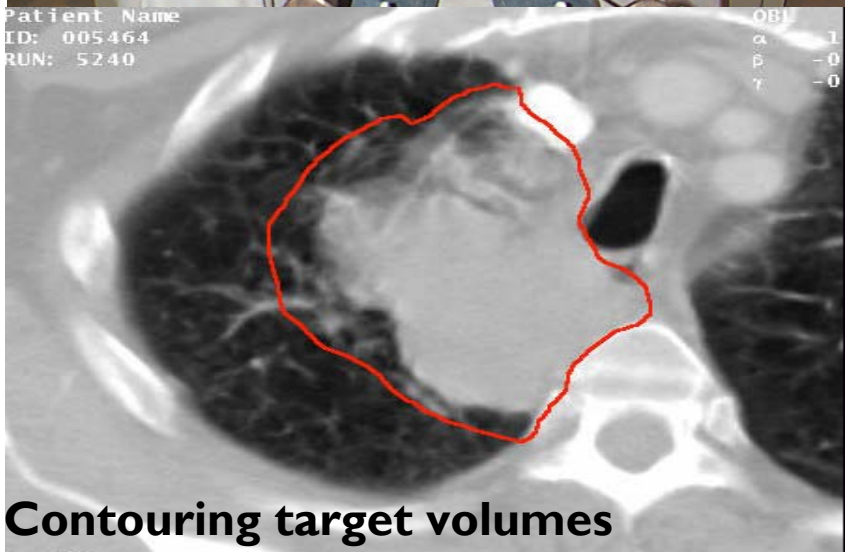
Fang LC, 2006

Is tumor motion an important cause of local failure?

3D Conformal radiotherapy

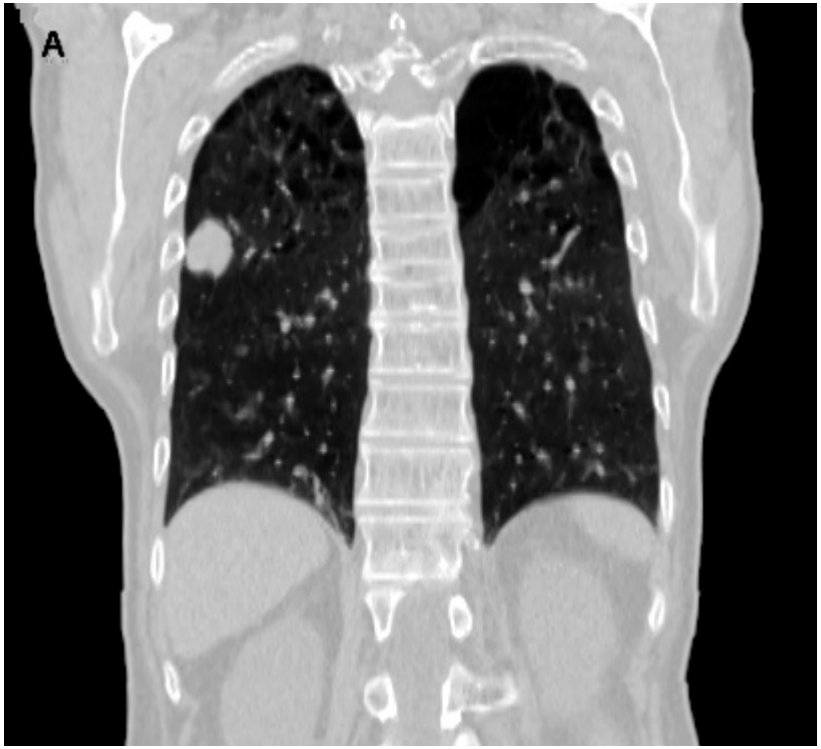
(*or how we used to work*)



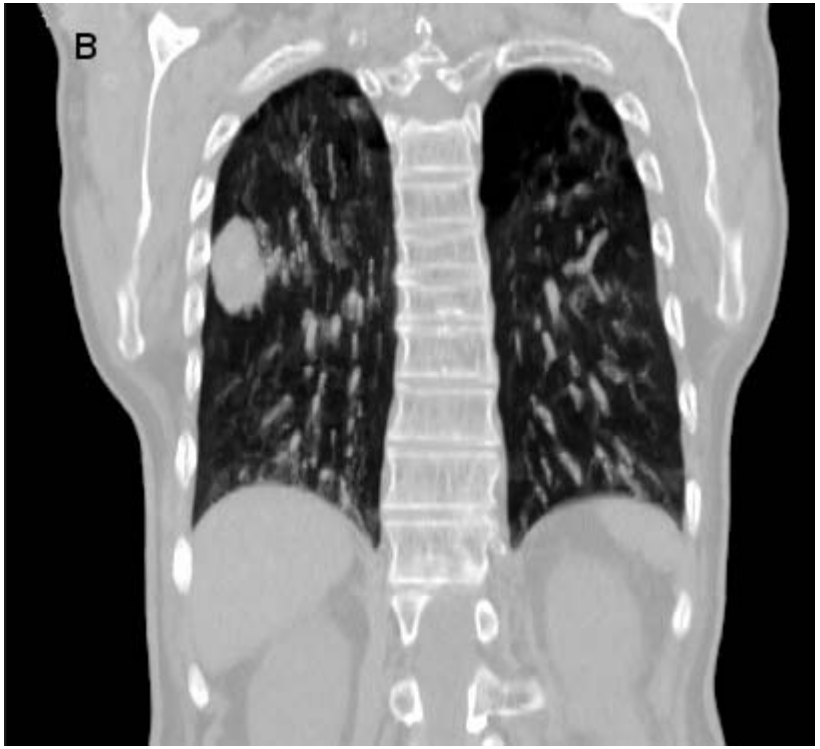


Planning CT for the thorax

Conventional (3D) CT image

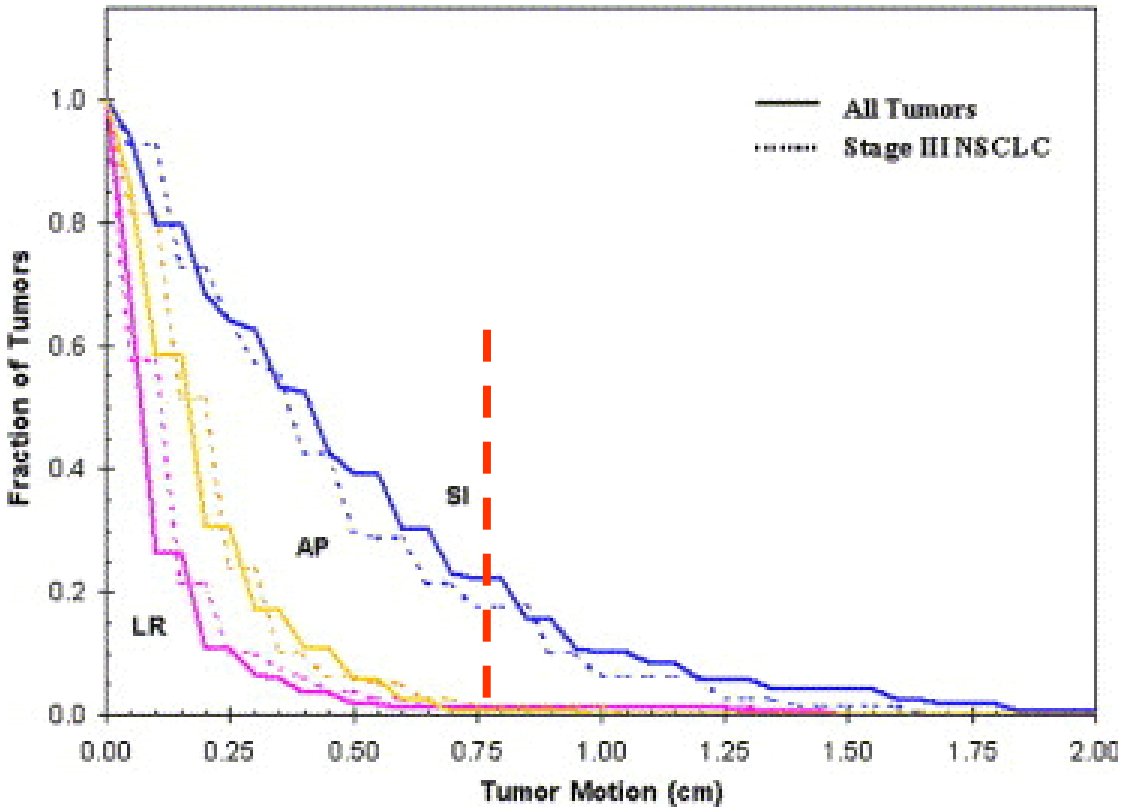


4DCT reconstruction showing all possible tumour positions



Motion of primary lung tumors

4DCT in 166 tumors



For **95% of the tumors**, motion in SI, lat and AP directions is **≤ 1.34 cm, 0.40 cm, and 0.59 cm**, respectively.

Liu 2007

VUmc

First routinely available 4D imaging technique for lung tumors

ELSEVIER

Int. J. Radiation Oncology Biol. Phys., Vol. 51, No. 4, pp. 932–937, 2001

0360-3016/01/$–see front matter

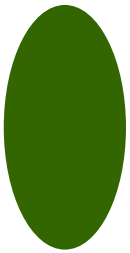
PII S0360-3016(01)01716-3

CLINICAL INVESTIGATION **Lung**

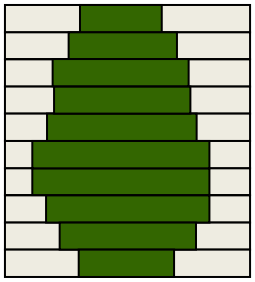
MULTIPLE "SLOW" CT SCANS FOR INCORPORATING LUNG TUMOR MOBILITY IN RADIOTHERAPY PLANNING

FRANK J. LAGERWAARD, M.D.,* JOHN R. VAN SORNSEN DE KOSTE,* MARGRIET R.J. NIJSSEN-VISSER,* REGINE H. SCHUCHHARD-SCHIPPER,* SWIE SWAT OEI, M.D.,* ARISTOTELES MUNNE,† AND SURESH SENAN, M.R.C.P., F.R.C.R., PH.D.*

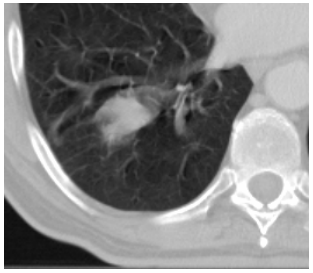
4D imaging using 'slow' CT scan



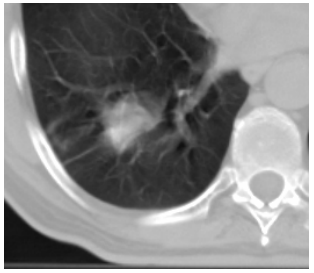
Actual tumor



'Slow' image



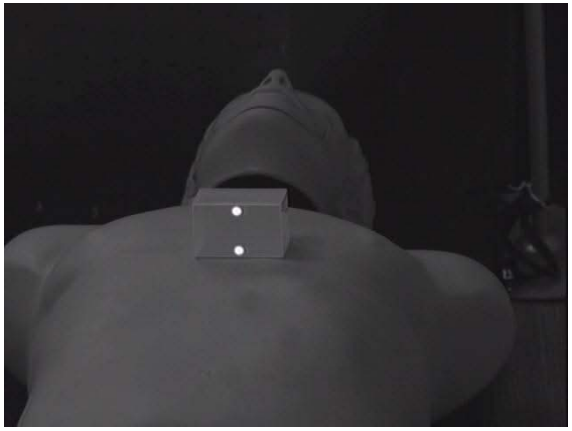
Fast CT



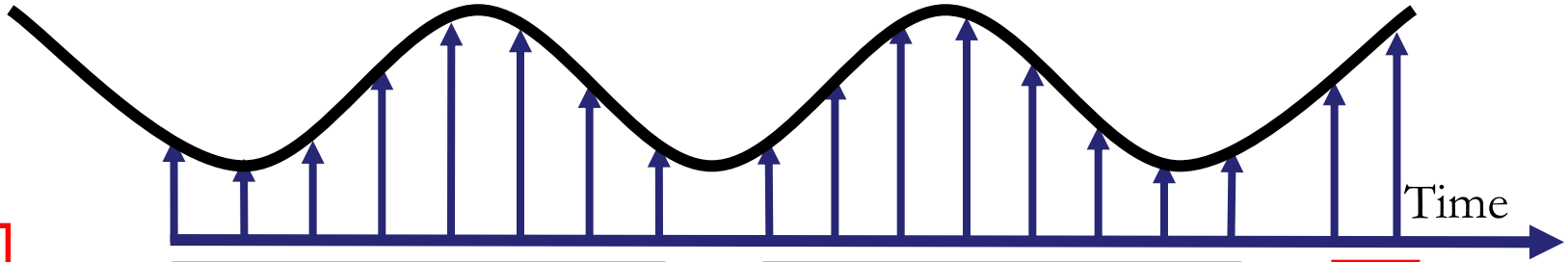
'Slow' CT

Lagerwaard 2001

4DCT, or respiration-correlated CT scan

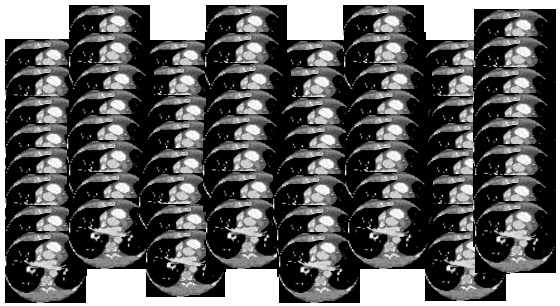


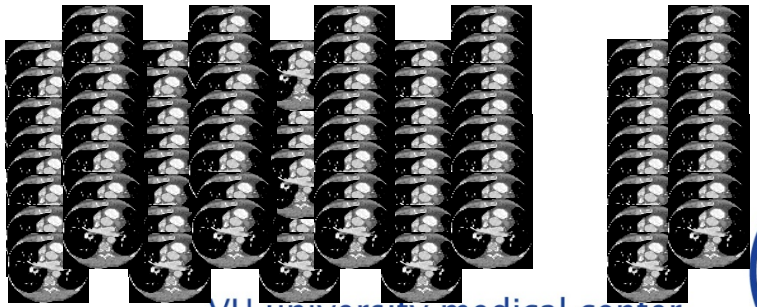
RPM Signal



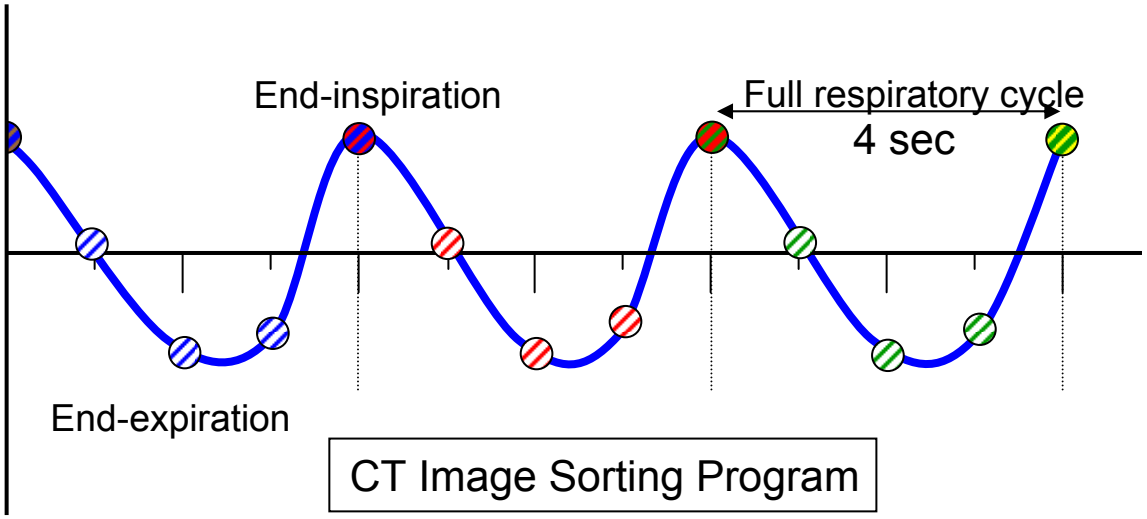
X-ray on

X-ray off

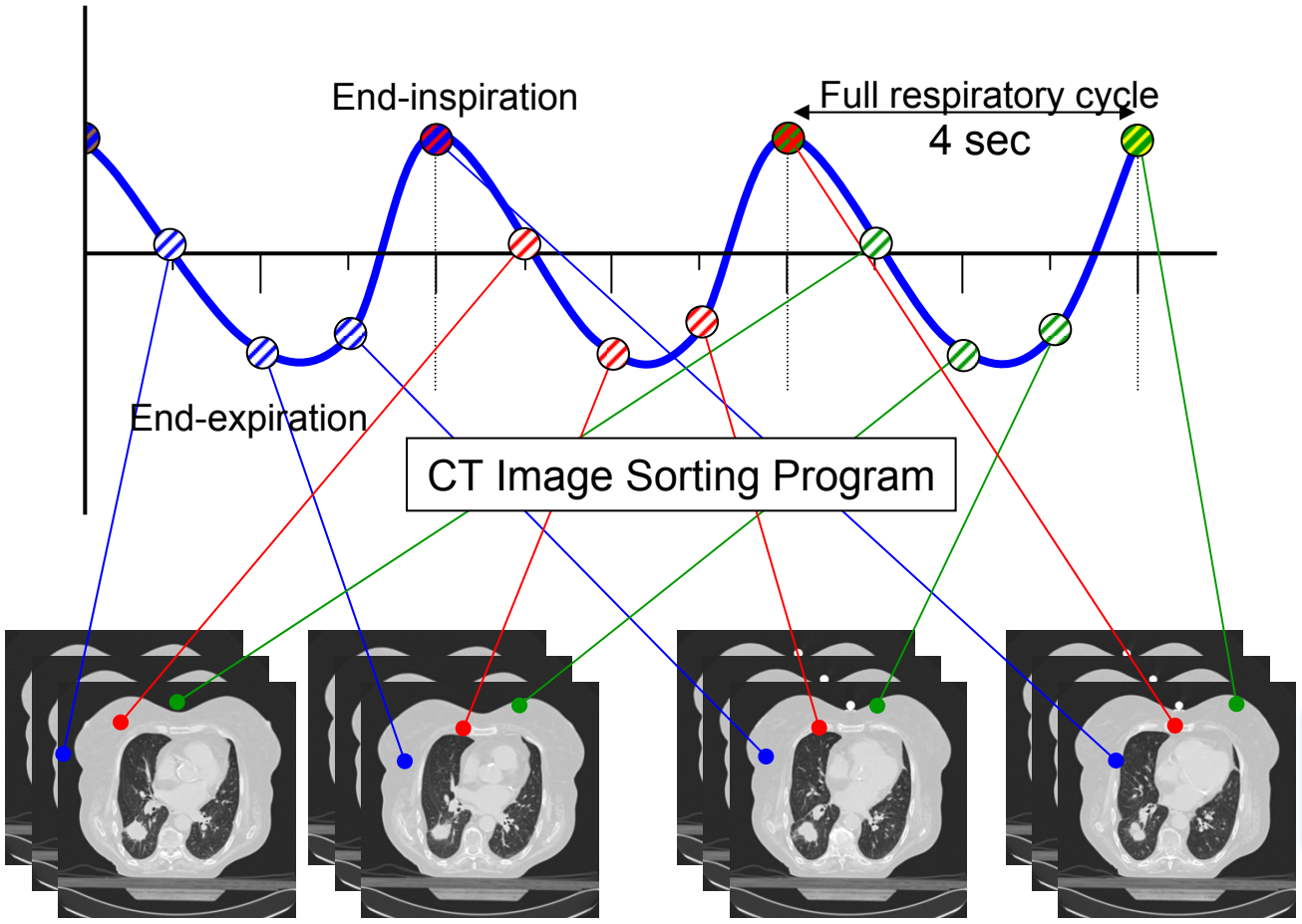




4D image sorting



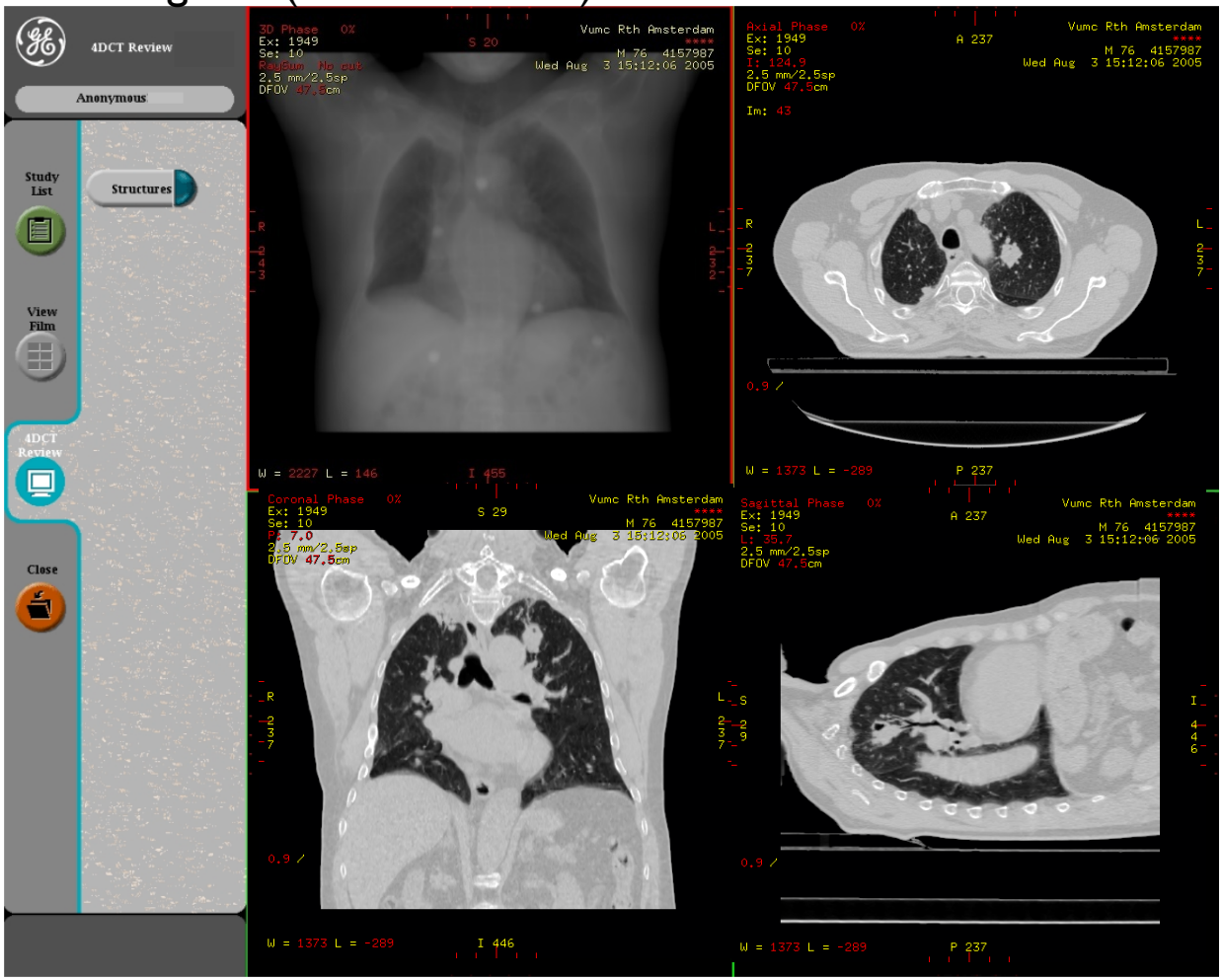
4D image sorting



10 respiratory 'bins' obtained

Screen-view of 4D viewer

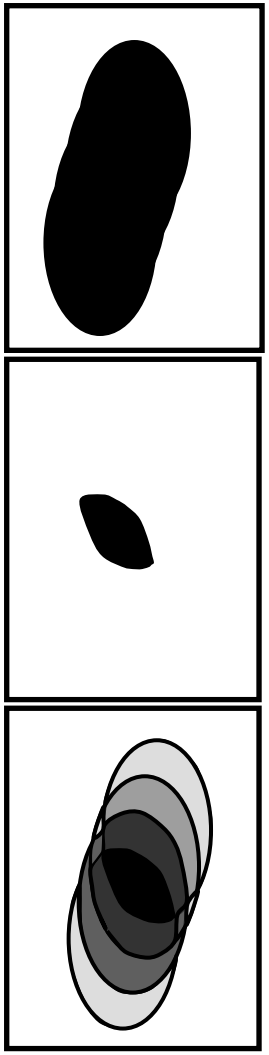
Advantage4D (GE Healthcare)



4DCT: Generating target volumes

Underberg R. IJROBP 2005

- **Max Intensity Projection (MIP):** maximum value of a pixel over all phases; indicates any location where tumor is present in any of the phases.
- **Min IP:** minimum value of each pixel over all phases; indicates only those locations where tumor is constantly present over all phases.
- **Mean IP:** mean value of each pixel over all phases; represents the time-weighted location of the tumor.

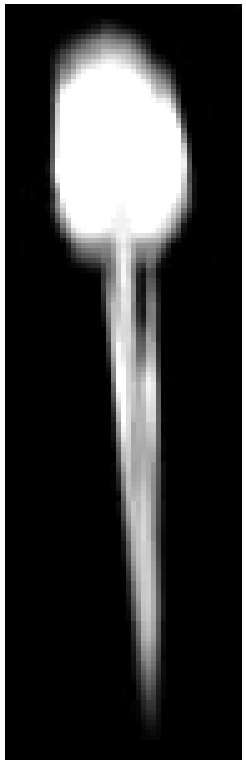


Slow CT versus MIP (4DCT)

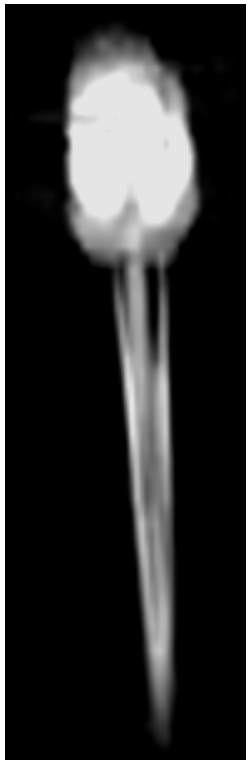
Underberg, 2005

Mean **single** phase volume = **16.3 cc +/- 0.6 cc**

4DCT MIP
21.9 cc



Slow CT
20.3 cc

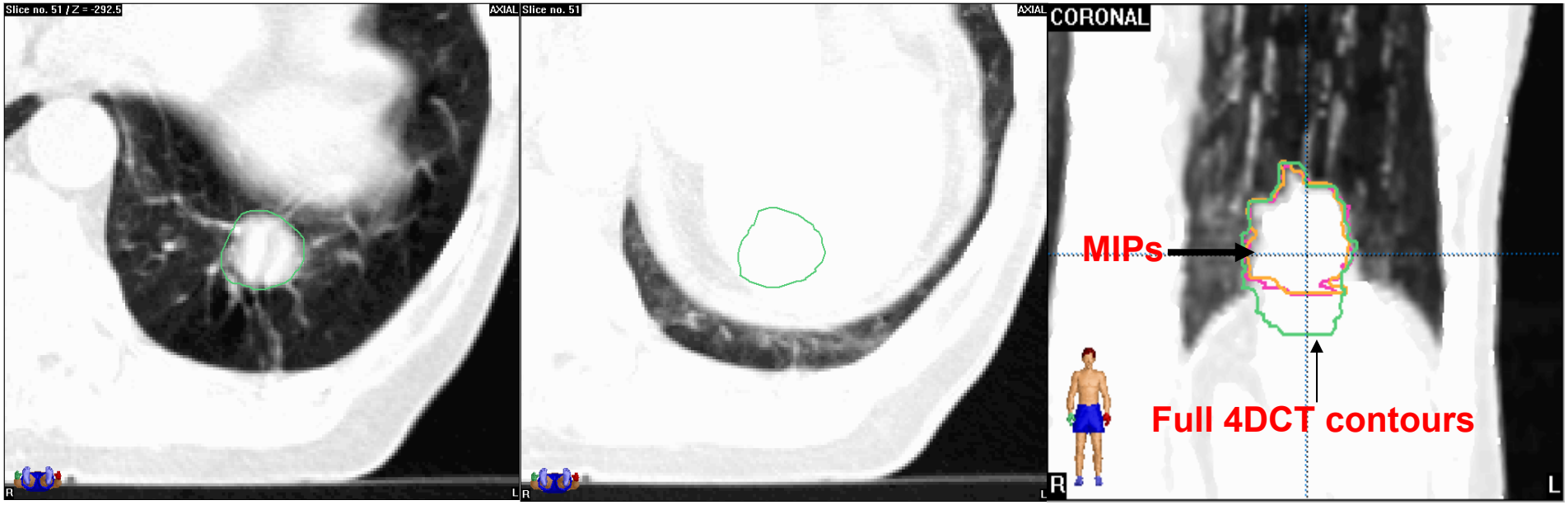


4DCT
Ave-IP

Limitations of using MIPs

MIP = Maximum Intensity Projections

- **Caution** with MIP's for tumors adjacent to mediastinum or diaphragm
- Review target volumes at extreme phases of a 4DCT scan



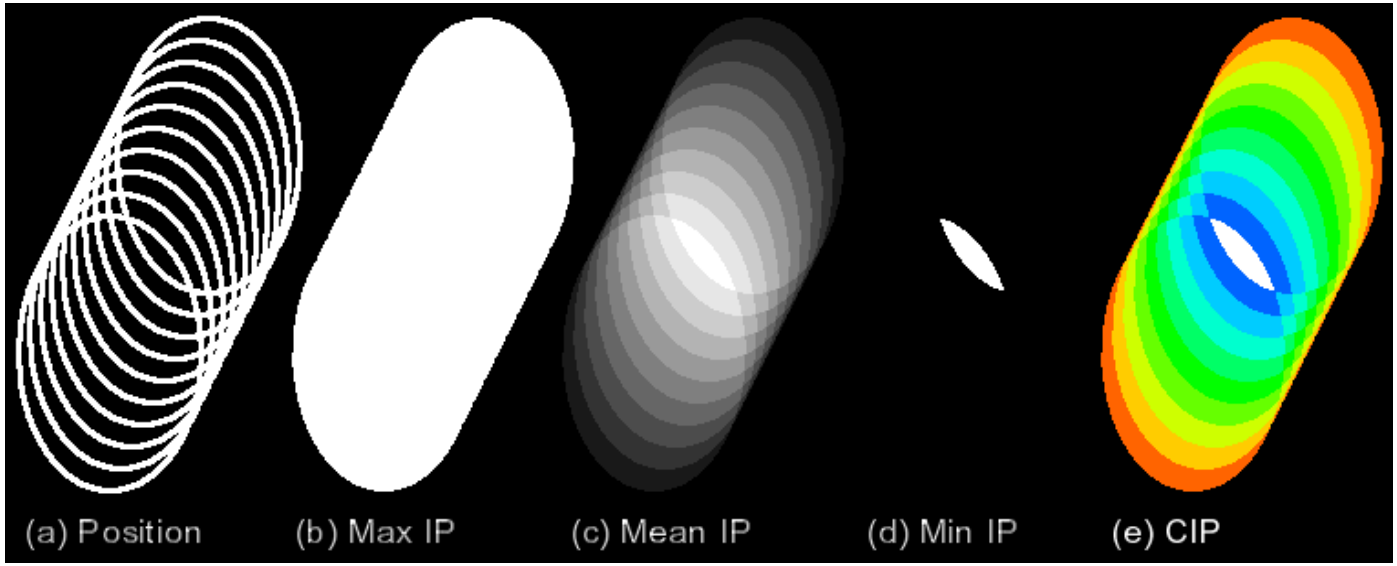
Underberg 2005

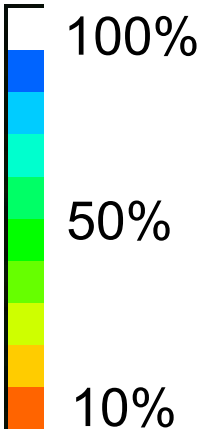
Limitations of using MIPs

Other developments to facilitate use of 4DCT data

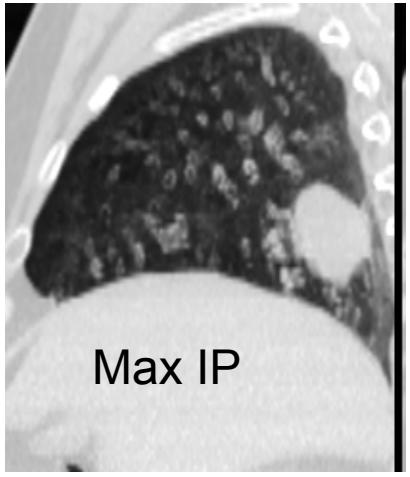
4DCT: Color intensity projections

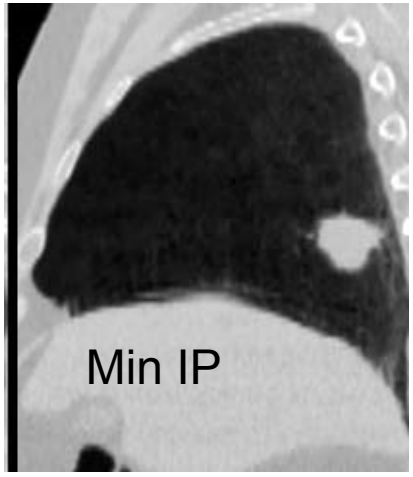
Cover, Lagerwaard, Senan. IJROBP 2006

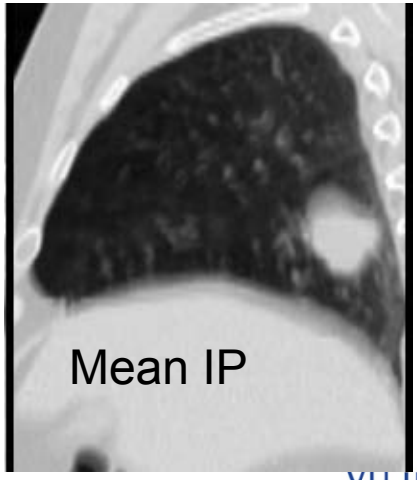


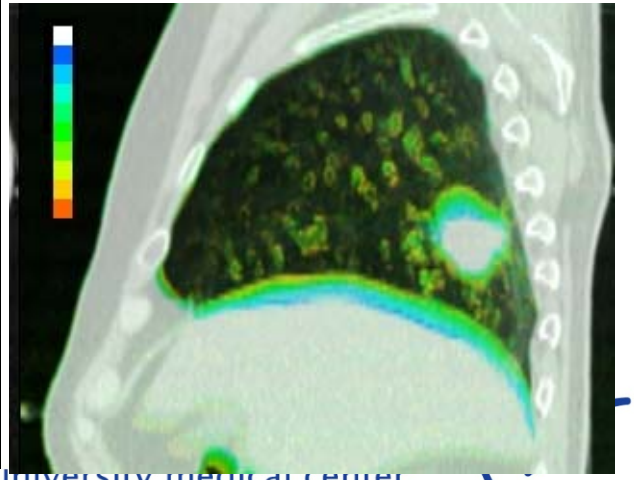


Color encoding of time period a structure is present at that location



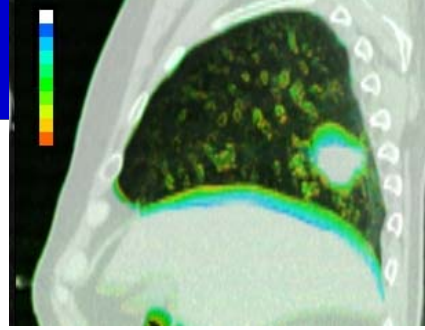






4DCT: Color intensity projections

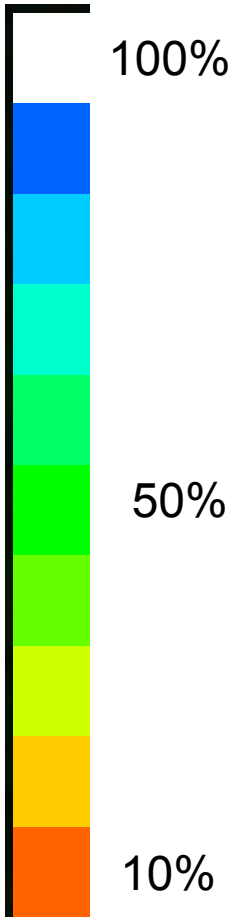
Cover, K 2006



- **Composite CIP images** calculated on a pixel-by-pixel basis;

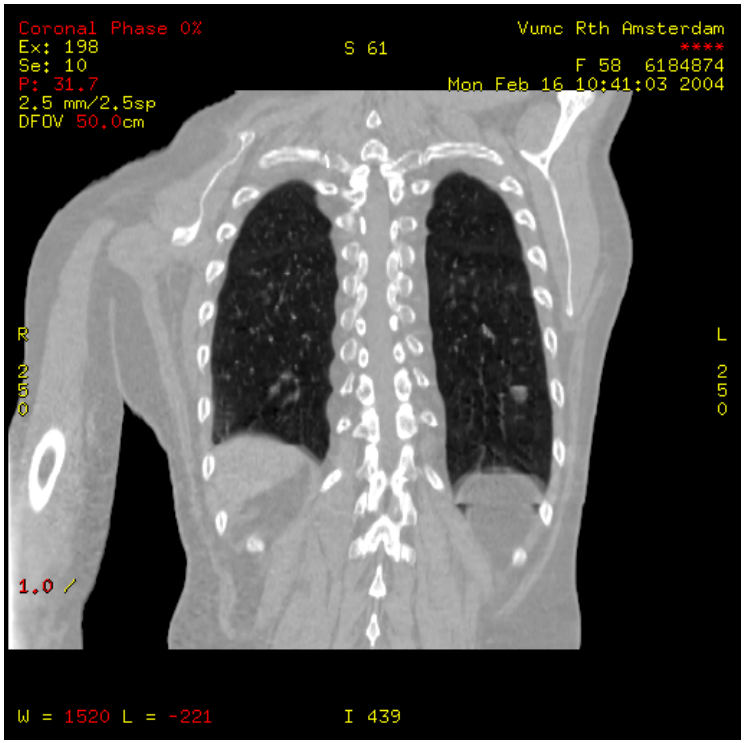
component phase images windowed and images scaled linearly. Max., mean, and min. intensity for each pixel over all phases calculated. Hue-saturation-brightness (HSB) for each pixel of CIP image calculated.

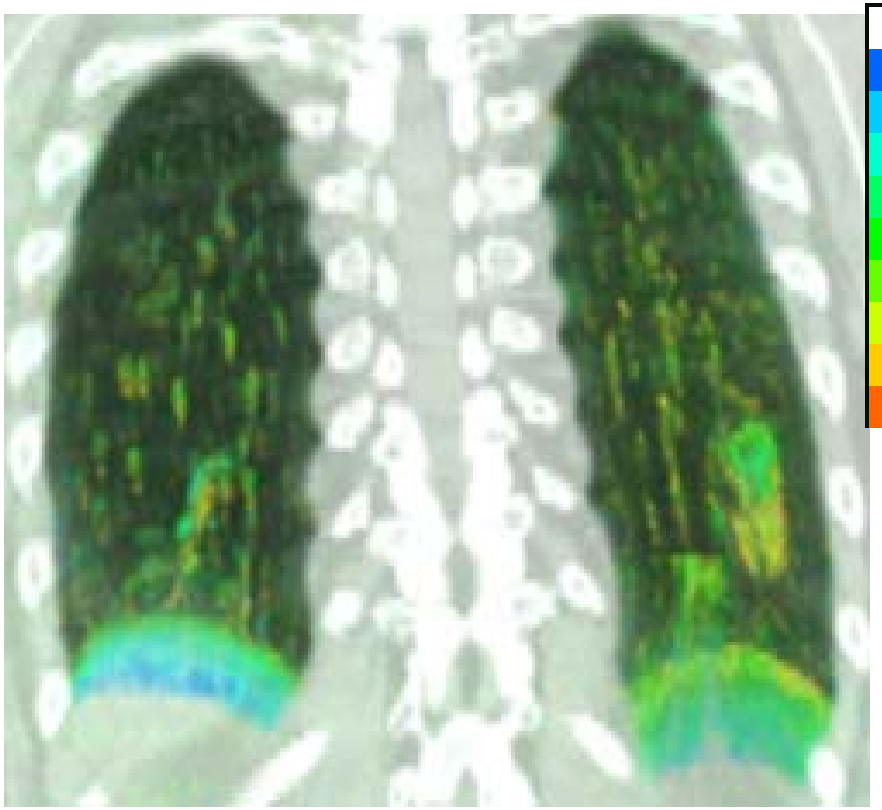
- Pixels **unchanged** in all bins appear **uncoloured**.
- Color encoding of period of **time** a **structure** present at location.
- **CIP** implemented as written plug-in to ImageJ (1.31v), a Java based image processing package (http://rsb.info.nih.gov/ij/)



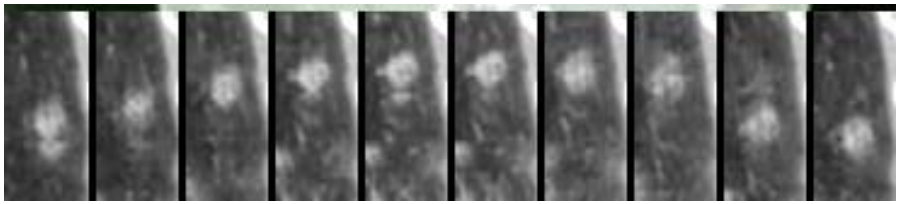
Color intensity projections

Cover K, 2006





Panel showing grayscale image at all phases



TARGET VOLUME DELINEATION IN STAGE I LUNG CANCER:

COMPARISON OF MAXIMAL INTENSITY PROJECTIONS (MIP) VS DEFORMABLE REGISTRATION TOOL FOR PROPAGATING GTV CONTOURS

J.R. van Sörnsen de Koste[1], I.E. van Dam[1], G.G. Hanna[2], R. Muirhead[3] , B.J. Slotman[1] and S. Senan[1]

[1] *Dept. of Radiation Oncology, VU University medical center, Amsterdam, The Netherlands*
[2] *Center for Cancer Research and Cell Biology, Queen's University Belfast, N. Ireland*
[3] *The Beatson, West of Scotland Cancer Center, Glasgow, United Kingdom*

10th Biennial ESTRO
MAASTRICHT
30 August • 3 September 2009

Study aim

- We assumed deformable image registration tool could avoid some drawbacks associated with contouring MIP.

- Our study compared target definition using MIP modified by 4DCT end-respiratory phases with contour propagation in all phases of 4DCT using a deformable registration tool.

Methods I

- 4DCT planning scans of 6 patients (varying tumor sizes, locations, radiological appearances and extent of tumor motion.

- 3 observers contoured visible tumor (GTV) on end-inspiration CT scan and again after two weeks; 2 observers contoured GTVs on all CT images of 4DCT and all MIPs.

- Contoured end-inspiration GTVs were propagated over 9 other 4DCT phases using a deformable registration tool (*Modified Bspline algorithm combined with Mattes formulation, Velocity Medical Systems*)

Methods II

- Intra- and inter observer variations in end-inspiration GTV determined for volumetric coverage and Dice volume similarity Coefficients (DC):

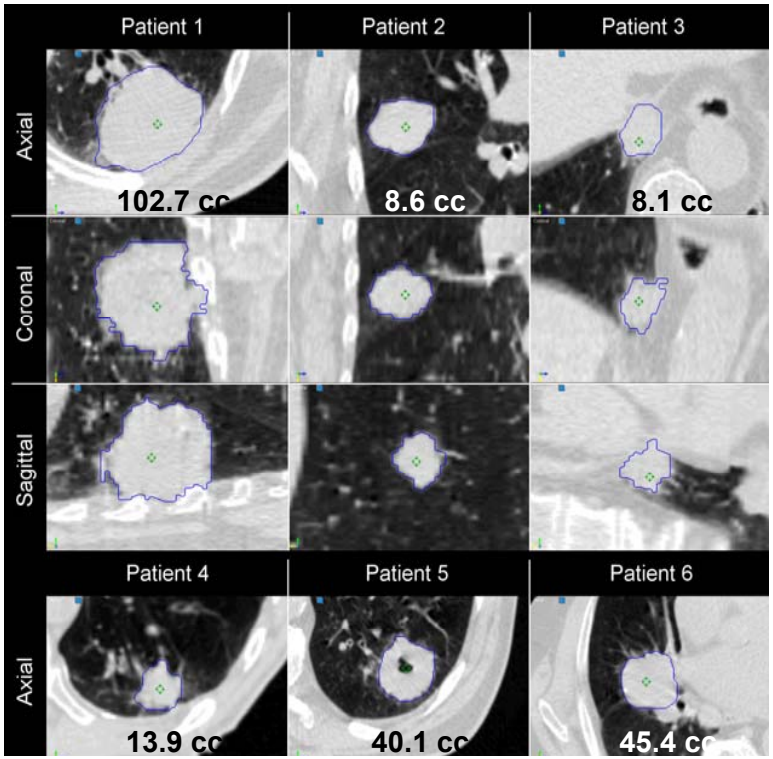
$$Dice's\ \ Coefficient = \frac{2(A \cap B)}{A + B}$$

- GTV motions and shapes were evaluated from contoured 4DCT scan (2 observers) and using deformable registration (1 observer).

- Routine MIP-based ITV definition compared to deformably reconstructed ITVs.

Results

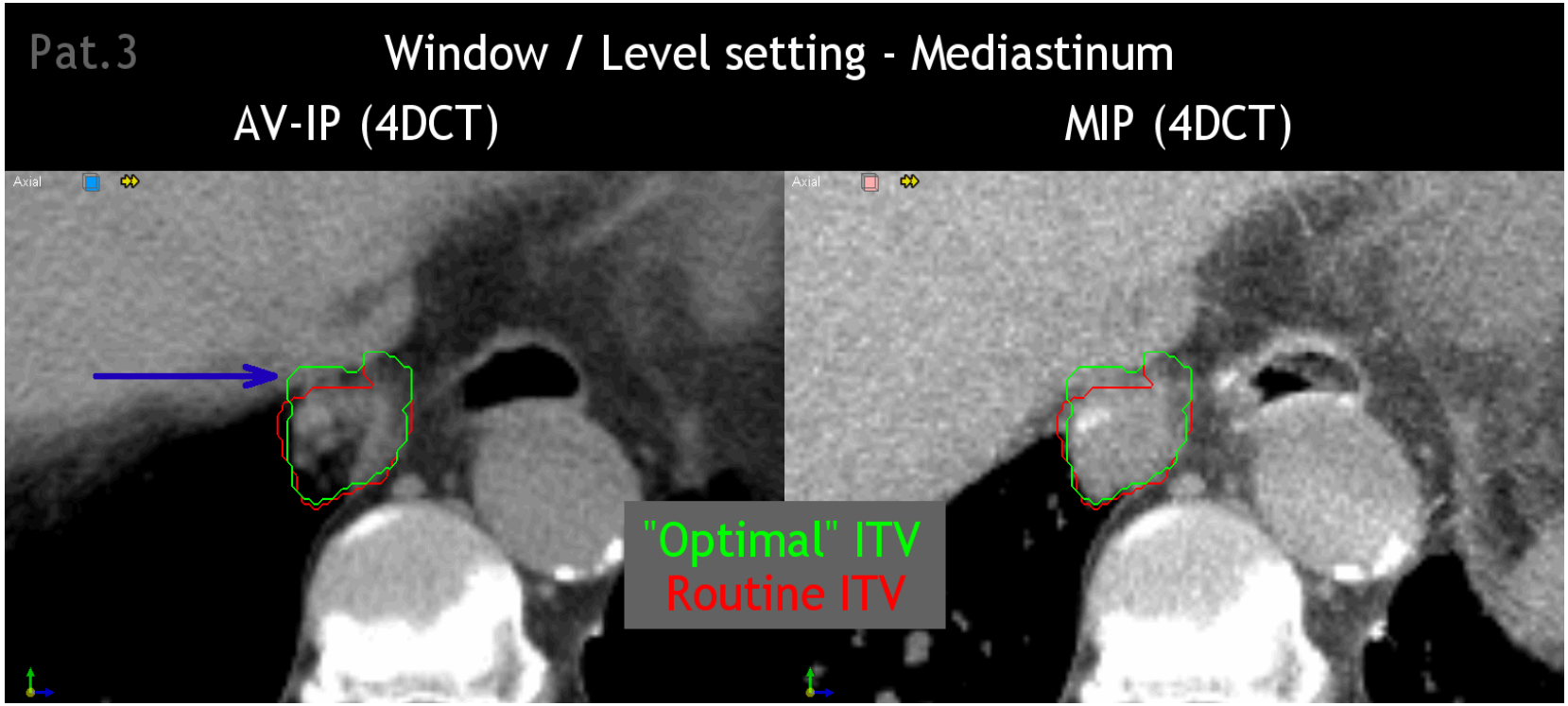
Contoured GTV in all patients



- Intra-clinician GTVs reproduced better than inter-clinician GTVs:
  92.9% (4.2%, 1SD) Vs. **86.0**% (10.6%, 1SD) [P< 0.02,T-test].
- Mean DC numbers indicate same trends: **0.93** vs. **0.89** [P<0.02].

Results

Deformable Vs. MIP-based ITV definition



Deformable registration - Summary

- Changes in tumor shape occur during respiration; deformable registration may better account for this without the confounding effects of intra-clinician variations in contouring.

- The 'optimal' ITV ($ITV_{10def\text{-}optimized}$) was smaller than our routine MIP-based ITV in 2 patients (2-10%) and was larger in 3 (5-10%).

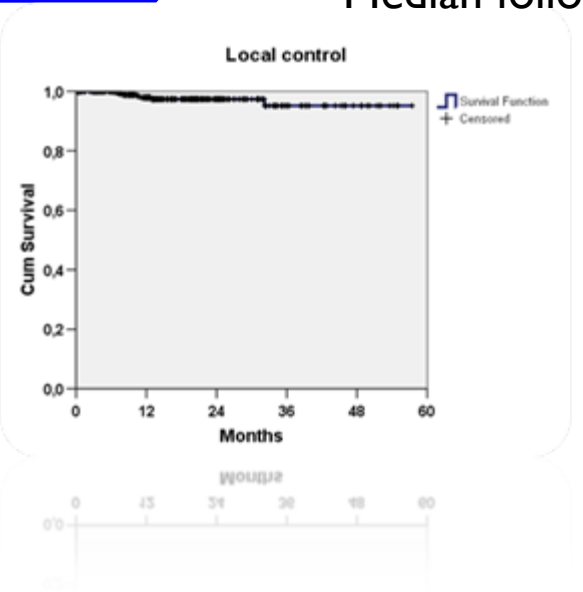
- Manual ITV from all 4DCT phases was larger than 'optimal' ITV in 5 of 6 patients (range 1-11%).

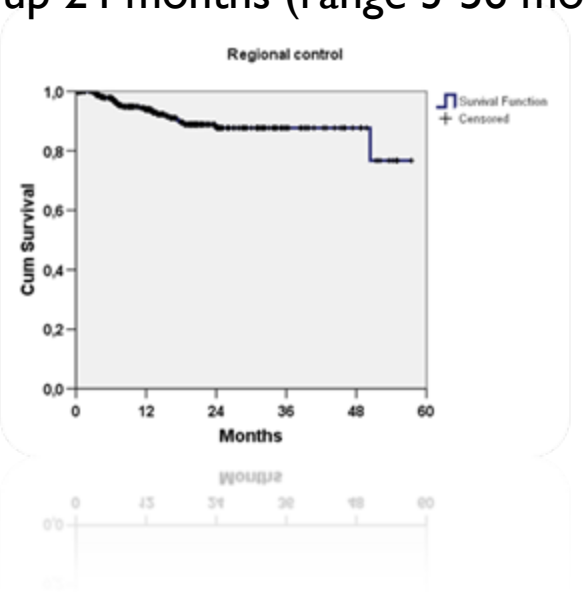
Conclusion

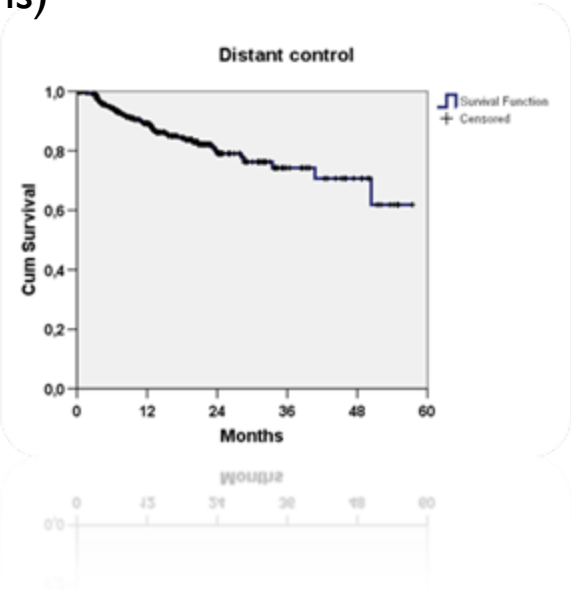
- **MIP-based ITV definition differ by up to 10% versus 'optimal' ITVs derived using deformable registration.**

Local-, regional- and distant failure

N= 402 patients with single T1-T2 tumor
Median follow-up 24 months (range 3-56 months)







Local Failure N=7 (1.7%)
Median time to LF 10 months

Actuarial local failure:
@1 year: 2.1%
@2 years: 2.7%
@3 years: 4.8%

Regional Failure N=26 (6.5%)
Median time to RF 8 months

Actuarial regional failure:
@1 year: 5.7%
@2 year: 12.0%
@3 year: 12.0%

Distant Failure N=52 (12.9%)
Median time to DF 8 months

Actuarial distant failure:
@1 year: 11.1%
@2 year: 21.2%
@3 year: 25.9%

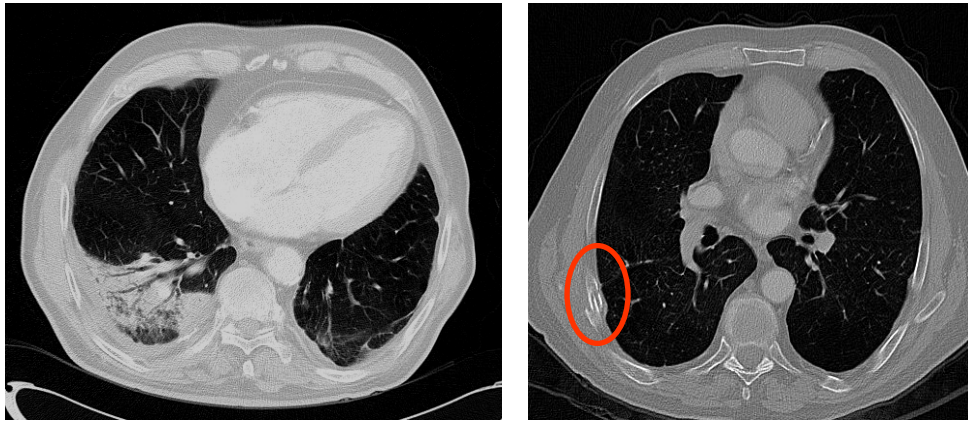
Lagerwaard F, Perspectives in Lung Cancer, Bruxelles, 2009

Stage I NSCLC: Toxicity of stereotactic RT

Lagerwaard, 2008

Acute and subacute

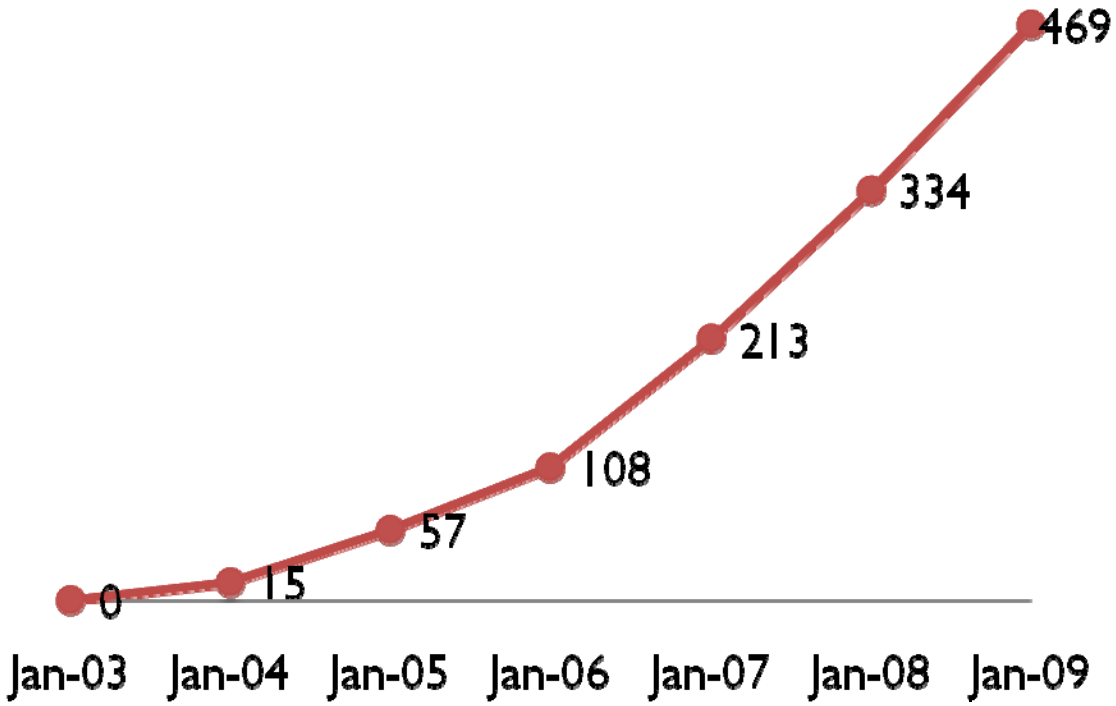
No toxicity	**51%**
Fatigue	**31%**
Chest pain	12%
Nausea	9%
Dyspnea	6%
Cough	6%
Erythema	2%
Hemoptysis	1%
Palpitations	1%



Late

Radiation pneumonitis	**9 (3%)**
Thoracic wall pain	6 (2%)
Rib fracture	4 (1%)
Pleural effusion	4 (1%)

Stage I NSCLC for SRT at VUmc



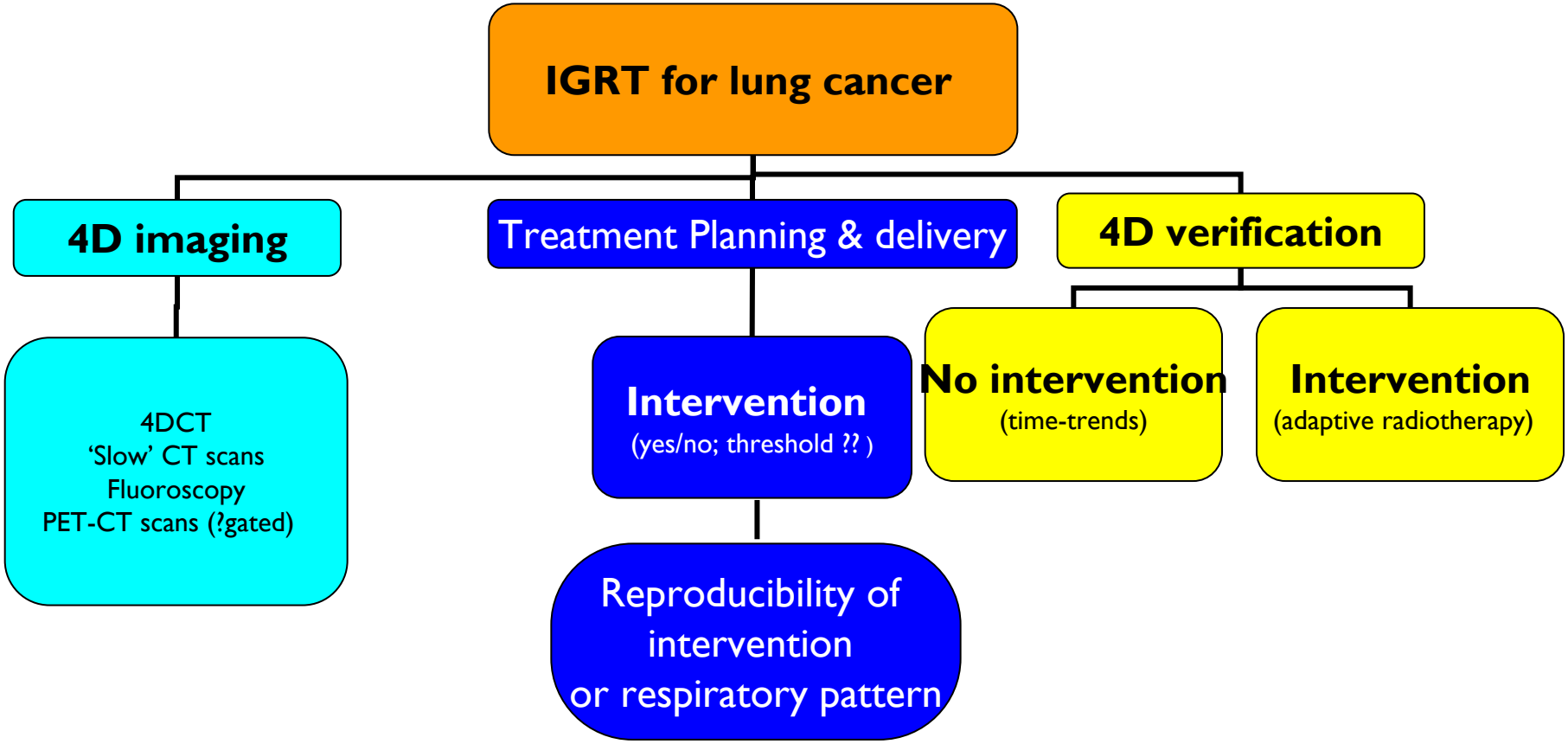
Number of Dutch centers performing lung SBRT	1	2	5	9

4-dimensional radiotherapy (4DRT)

- ***'explicit inclusion of the temporal changes in anatomy during the imaging, planning and delivery of radiotherapy'***
- In principle, 4D radiotherapy is intuitive and simple.
- In practice, 4D radiotherapy is a very difficult problem, with many levels of complexity.

Keall P, 2004

4D radiotherapy for lung cancer



Lagerwaard 2007

Image-guided radiotherapy

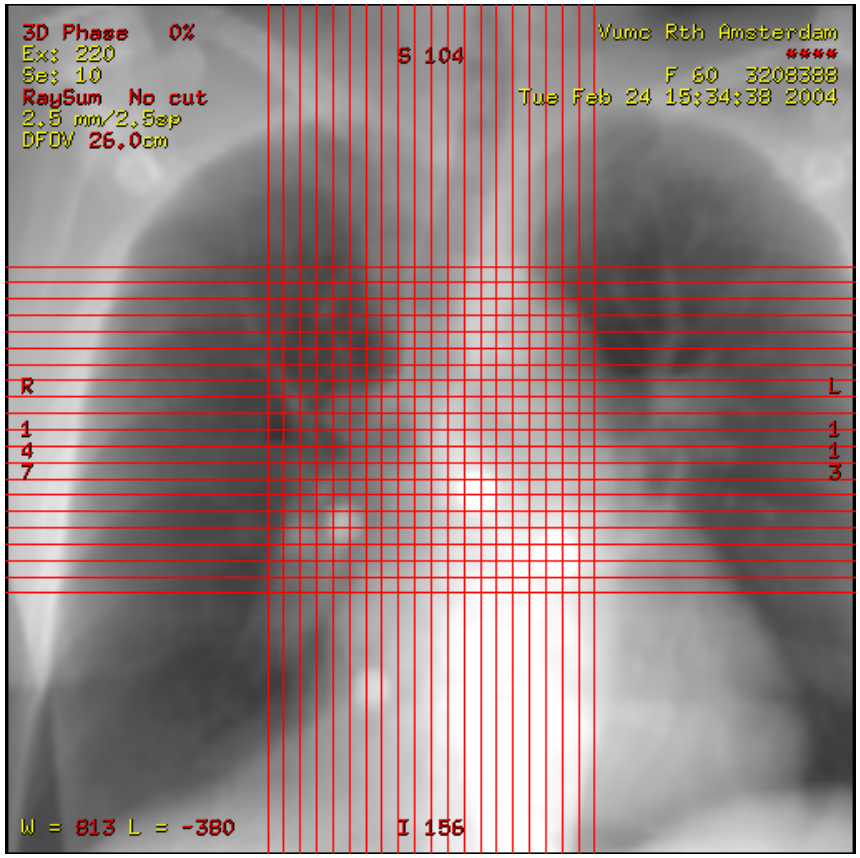
1. Frequent imaging during radiotherapy

2. Use of the images to improve precision and accuracy of radiation delivery (*reduced set-up errors = small radiation fields*)

Fluoroscopy to assess motion?

Van der Geld, 2006

- 29 peripheral lung tumors
- 4 clinicians scored mobility on fluoroscopy
- Contours in 4DCT used to measure mobility

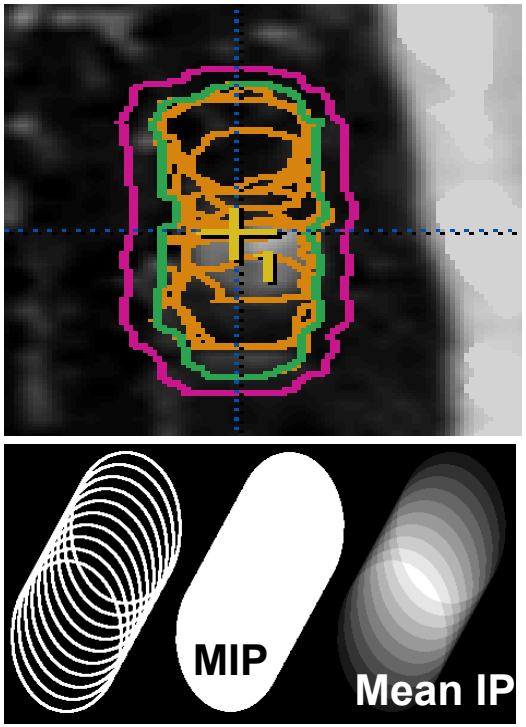


- Motion estimates not possible in 8 pts
- Mobility overestimated using fluoroscopy
- Mean ITVs derived with fluoroscopy are **52%**

larger than if 4DCT contours used

Use of ITV approach

- Mageras G, 2004 (MSKCC)
- Underberg R, 2004 (VUMC)
- Takayama K, 2005 (Kyoto U.)
- Hodge W, 2006 (Wisconsin U.)
- Bradley J, 2006 (Wash U.)
- Rietzel E, 2008 (MGH)
- Chang J, 2008 (MDAH)



Requires '10 mins'

Stage I NSCLC – contouring guidelines

Radiation Oncology

BioMed Central

Study protocol

Open Access

Recommendations for implementing stereotactic radiotherapy in peripheral stage IA non-small cell lung cancer: report from the Quality Assurance Working Party of the randomised phase III ROSEL study

Coen W Hurkmans*[1], Johan P Cuijpers[2], Frank J Lagerwaard[2], Joachim Widder[3], Uulke A van der Heide[4], Danny Schuring[1] and Suresh Senan[2]

Recommendations for ROSEL study

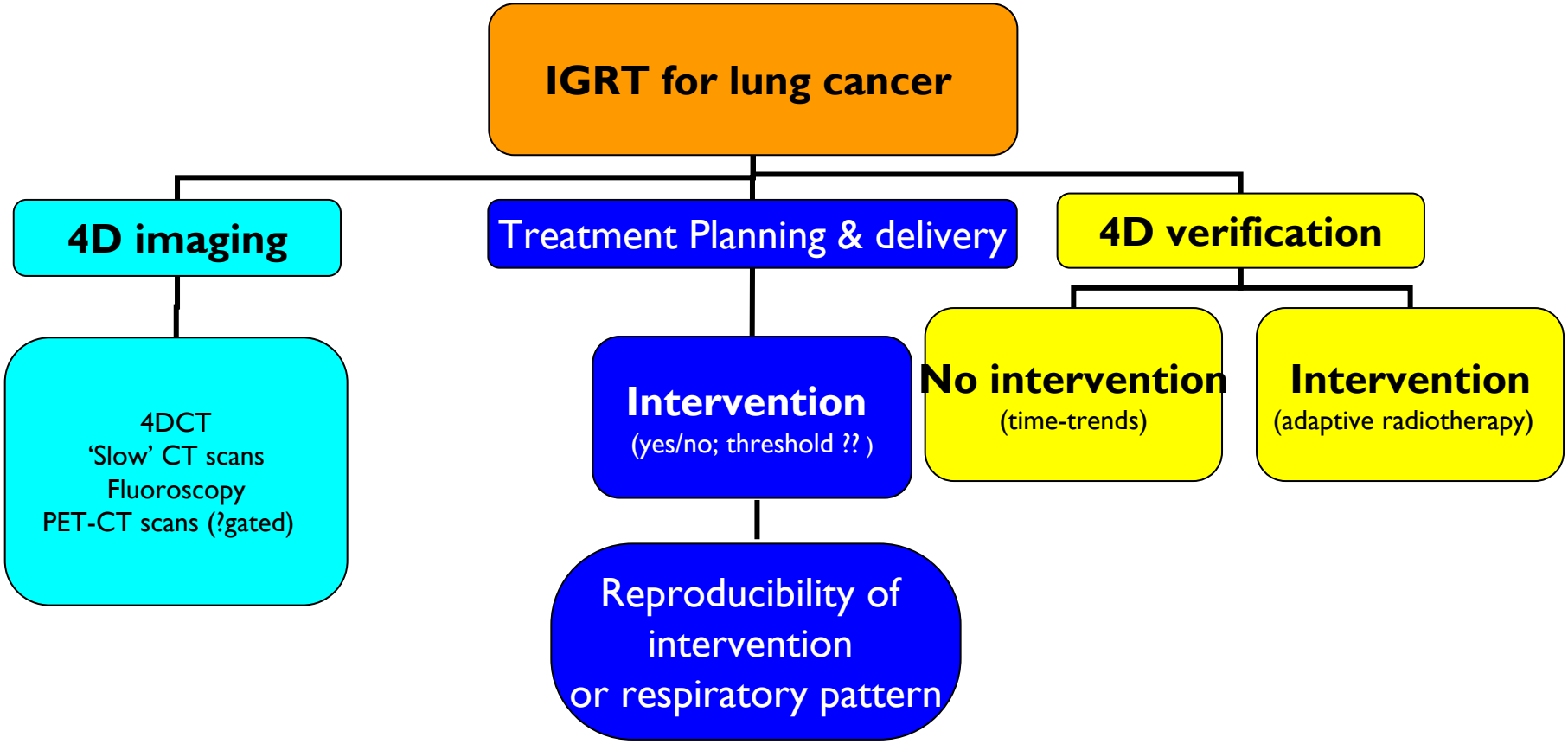
PTV based on the ITV concept

For 4D CT scans, the ITV can be derived from the union of GTV delineations on all breathing phases or alternatively, from contouring on a maximum intensity projection (MIP) CT-dataset [28,29]. The appropriateness of the MIP-delineation should at least be confirmed by a visual inspection of the projected ITV contours on the CT-data-sets of the end-inspiration and end-expiration phase bins using axial, sagittal and coronal views. In addition to the

PTV based on the mean tumour position

As an alternative to the ITV concept, planning and irradi-ation based on the time-averaged mean position of the tumour has been developed [32]. In contrast to the ITV to PTV margin discussed previously, the CTV to PTV margin needed here should take the tumour motion into account. However, similar to the reasoning given for the ITV to PTV margin, a minimum margin of 3 mm should be used for the incorporation of the other uncertainties.

4D radiotherapy for lung cancer



Lagerwaard 2007

Motion management strategies

Method	Technique	Comments
Incorporate all movements	4DCT or slow CT	May lead to increased risk of normal tissue toxicity
Freeze movement	Breath hold	Not feasible in all lung cancer patients
Intercept movement: *'gated'* radiotherapy	Respiratory cycle as surrogate of tumor position	(1) Treatment time increased (2) Difficulties in target verification
Track or chase tumor	Implanted markers and specialized treatment delivery	(1) Difficult endobronchial marker insertion (2) CT-guided insertion risks pneumothorax (3) Markers migrate after insertion (4) Difficult to predict normal tissues doses

Lagerwaard 2007

When to manage respiratory motion?

AAPM Task Group 76: respiratory management techniques should be considered if either of the following conditions occur:

- >**5 mm range of motion** is observed in any direction; or
- significant normal tissue sparing as determined by your clinic can be gained using a respiration management technique.

Keall 2006

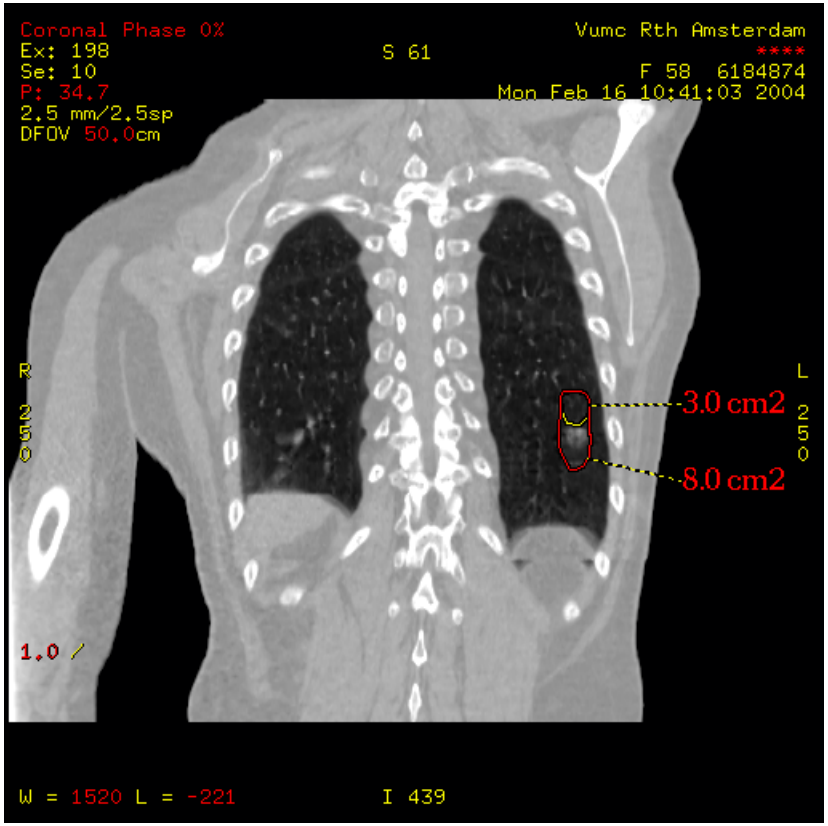
Motion intervention strategy?

Manage motion if in >5 mm [AAPM TG76],……. but what about r**eproducibility** of interventions?

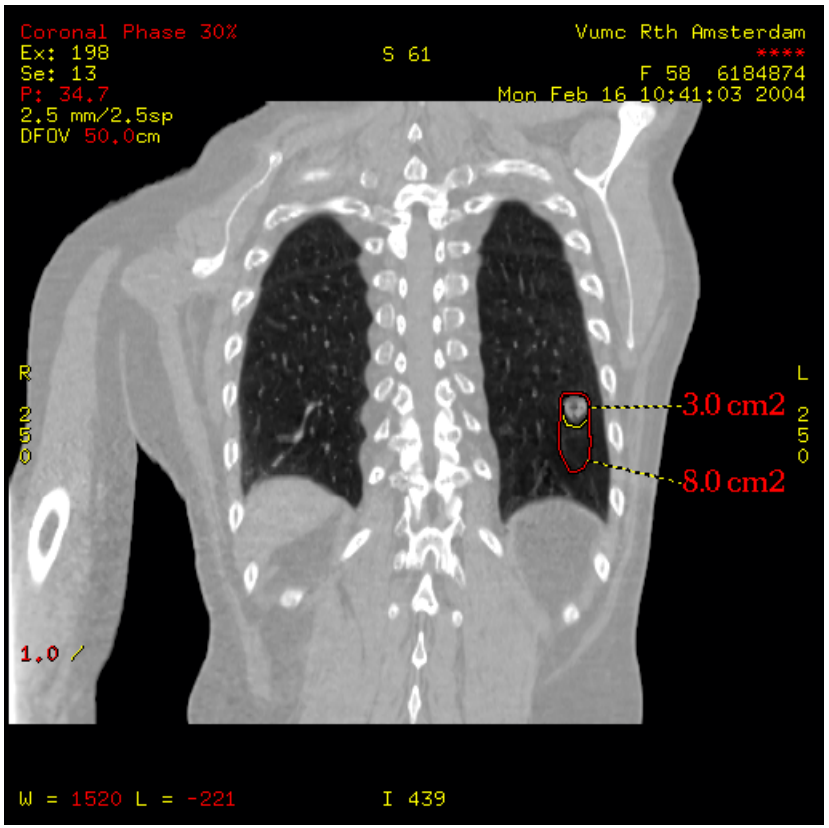
‘Motion may be less than the reproducibility of intervention to reduce motion’ [Dawson ’05]

4D respiratory-gating

Is gating needed in stage I NSCLC?



Conventional target volume

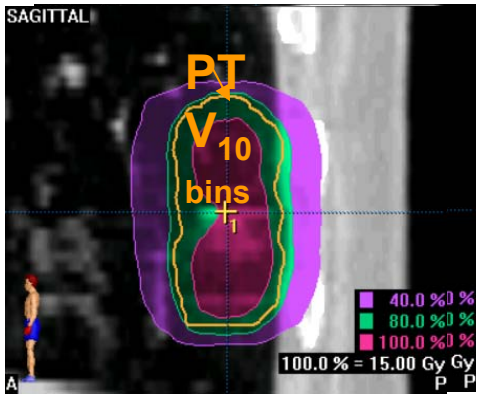


Gated target volume

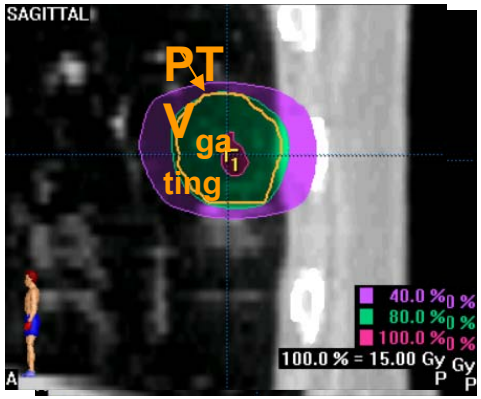
Is gated SRT necessary in stage I NSCLC ?

Underberg R, 2005

Non-gated PTV



Gated PTV



Analysis of 4DCT scans in 34 patients with stage I NSCLC

≥ 50% reduction in PTV achieved in **15 %** of tumors

≥ 30% reduction in PTV achieved in **38 %** of tumors

Respiratory gating: a warning!

- Respiratory gating… is better than not accounting for motion at all **only if it is carried out properly**.
- Tight margins increase the risk of geometric misses,.. require accurate treatment delivery.
- Such accurate delivery is **not trivial** because of inter- and intrafractional variations.

Li X, 2007

Can gating worsen outcomes?

Kato M, 2004

- Stage I NSCLC treated with carbon ion radiotherapy
- Total of 81 patients; 23.2% local recurrences

Details of local recurrence cases

Patient	Recurrence pattern (pattern)	Period (month)	Respiratory-gated irradiation	Provisional target (yes/no)	Fractionation	Total dose (GyE)	Number of irradiation portals	Type of tissue	Locus	Tumor size (mm)
1	1	11.6	Yes	No	18	79.2	2	Squamous	rt S^{8}	45
2	1	16.0	Yes	No	18	95.4	4	Adeno	lt S^{9}	20
3	1	6.8	Yes	No	9	72.0	4	Squamous	rt S^{6}	40
4	1	14.0	Yes	Yes	9	72.0	3	Squamous	lt S^{10}	60
5	2a	11.3	No	No	18	59.4	2	adeno	lt S^{10}	31
6	2a	6.2	Yes	No	18	59.4	2	Squamous	rt S^{2}	42
7	2a	13.2	No	No	18	64.8	2	adeno	lt S^{1+2}	18
8	2a	16.7	No	Yes	18	64.8	2	adeno	lt S^{9}	15
9	2a	27.2	Yes	No	18	64.8	2	Squamous	lt S^{6}	14
10	2a	12.7	No	Yes	18	72.0	2	Squamous	rt S^{6}	36
11	2a	6.6	Yes	Yes	18	72.0	2	Adeno	rt S^{2}	18
12	2a	13.6	Yes	No	18	72.0	2	Squamous	rt S^{5}	18
13	2a	11.7	Yes	No	18	72.0	2	Squamous	rt S^{9}	32
14	2a	14.5	Yes	No	18	79.2	2	Adeno	rt S^{2}	41
15	2a	13.6	Yes	Yes	18	79.2	4	Squamous	rt S^{6}	45
16	2a	18.3	Yes	No	18	86.4	2	Adeno	lt S^{4}	26
17	2a	9.3	Yes	Yes	9	72.0	4	Squamous	rt S^{4}	50
18	2b	7.9	No	No	18	59.4	2	Adeno	lt S^{5}	31
19	2b	17.0	No	No	18	72.0	2	Adeno	rt S^{1}	35

Improve quality of 4DCT using respiratory coaching ?

ELSEVIER

Int. J. Radiation Oncology Biol. Phys., Vol. 71, No. 4, pp. 1118–1123, 2008

0360-3016/08/$–see front matter

doi:10.1016/j.ijrobp.2007.11.061

CLINICAL INVESTIGATION **Lung**

IMPACT OF AUDIO-COACHING ON THE POSITION OF LUNG TUMORS

CORNELIS J. A. HAASBEEK, M.D., FEMKE O. B. SPOELSTRA, M.D., FRANK J. LAGERWAARD, M.D., PH.D., JOHN R. VAN SÖRNSEN DE KOSTE, PH.D., JOHAN P. CUIJPERS, PH.D., BEN J. SLOTMAN, M.D., PH.D., AND SURESH SENAN, M.R.C.P., F.R.C.R., PH.D.

Int. J. Radiation Oncology Biol. Phys., Vol. 71, No. 4, pp. 1118–1123, 2008

0360-3016/08/$–see front matter

ELSEVIER

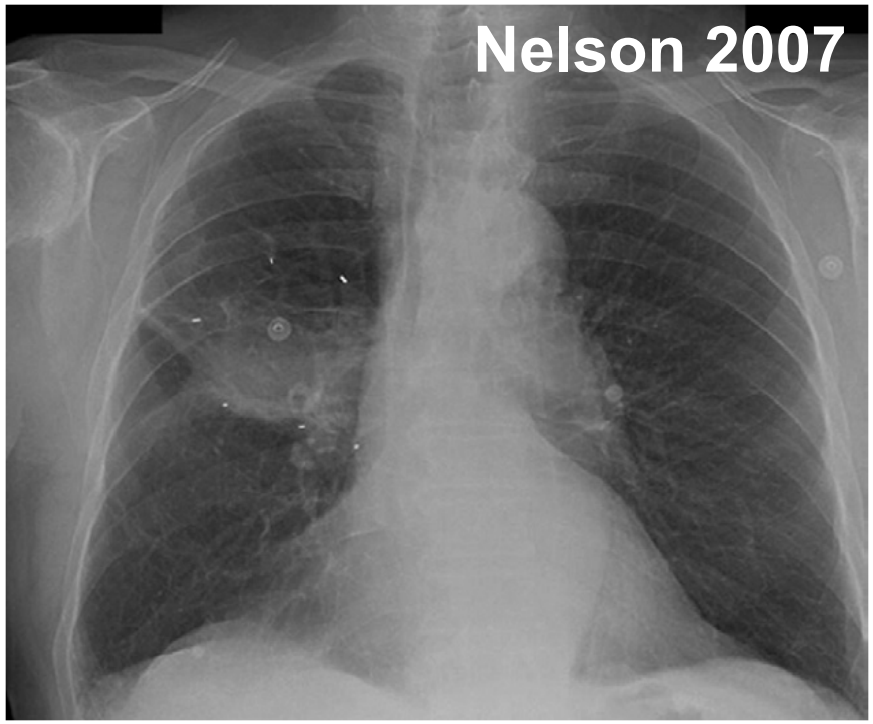
doi:10.1016/j.ijrobp.2007.11.061

CLINICAL INVESTIGATION **Lung**

IMPACT OF AUDIO-COACHING ON THE POSITION OF LUNG TUMORS

- Starting audio coaching led to displacements in ITV position of ≥5mm in up to 56% of mobile tumors.
- Respiratory gating at end-inspiration and end-expiration were equally susceptible to displacements.
- Underscores importance of ensuring similar respiratory patterns during imaging and delivery of gated radiotherapy.

Fiducial markers

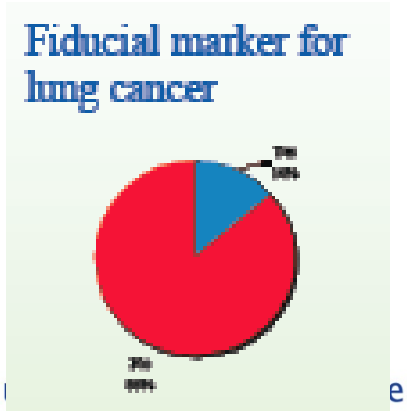


- Difficult endobronchial marker insertion
- CT-guided insertion risks pneumothorax
- Markers migrate after insertion
- Difficult to predict normal tissues doses with tracking

Fiducial markers

- **Imura 2005**: Markers in bronchial tree allow for setup accuracy of ± 2 mm during a 1–2-week treatment period.
- Relationship between markers and tumor can change significantly after 2 weeks.

- **Nagata 2005**: Only 14% of Japanese centers use fiducial markers



Pneumothorax rates

- Choi CM, 2004: **22%** of 458 pts; but was delayed in **3.3%** (pneumothorax not developing later than 3h was defined as a delayed pneumothorax).

- Geraghty PR, 2003: **38%** of 324 patients after use of 18-gauge needles and **23%** of 522 after use of 19-gauge needles.

Is a single 4D imaging scan sufficient?

'Baseline shifts' in tumor position?

Reproducibility of 4DCT

Haasbeek CJA, 2007

- 60 tumors (59 patients) using 4DCT scans repeated after 2 or more fractions of stereotactic radiotherapy.
- Repeat scans performed at a mean of 6.6 days (range 2–12 days) after the first fraction
- Original SRT plan applied to PTV_{4DCT2}, and coverage by the 80% prescription isodose determined

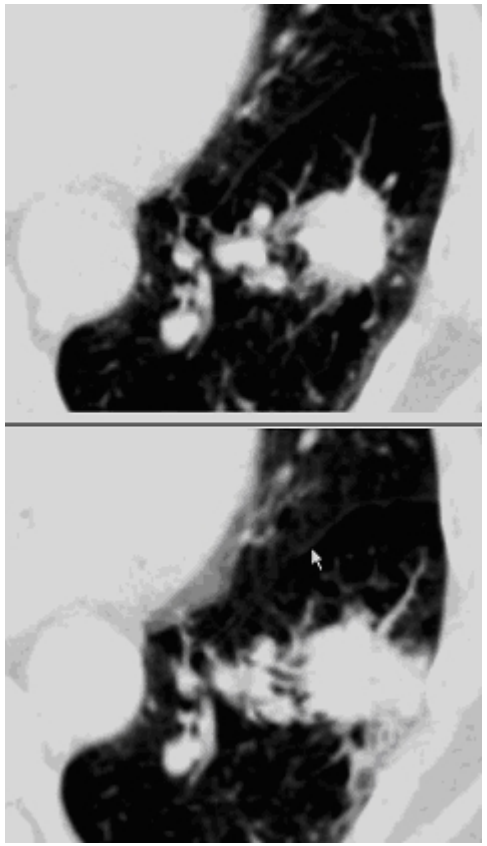
Reproducibility of 4DCT

Haasbeek CJA, 2007

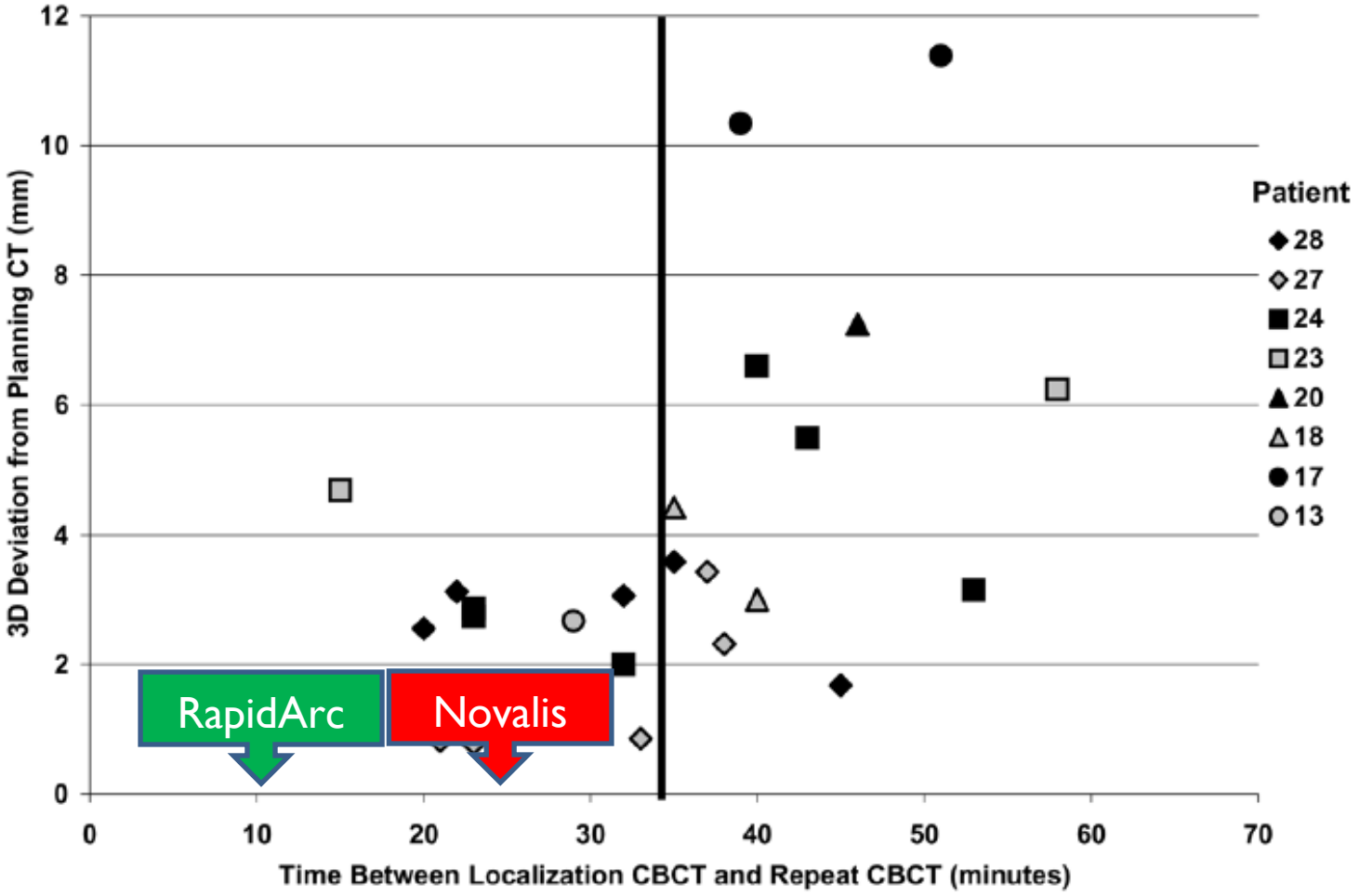
- Mean 3D displacement between center of mass of both PTVs was 2.0 mm.
- Initial 80% prescription isodose ensured a mean coverage of 98% for repeat PTVs

- 80% isodose encompassed repeat ITV in all but 1 tumor**.

***"Inadequate" coverage caused by new area of atelectasis adjacent to tumor on the repeat 4DCT.*



Reproducibility in target position using repeat CBCT imaging (n= 8 patients)



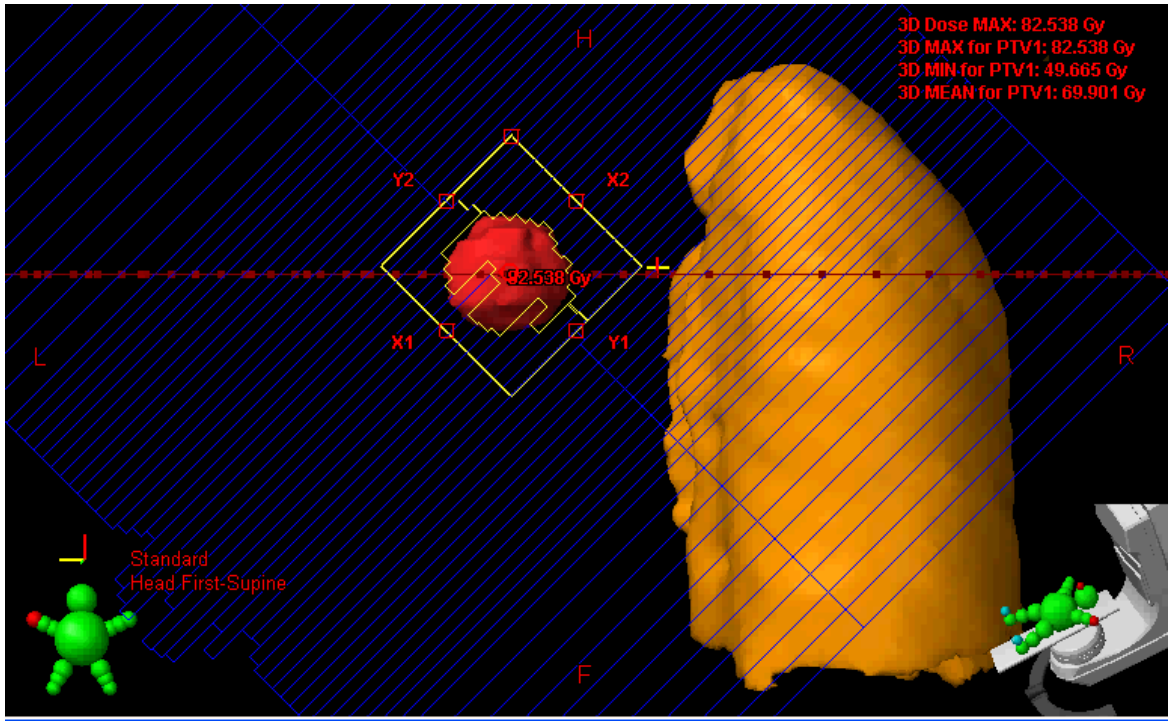
Purdie TG 2007

New Eclipse optimisation algorithm that **simultaneously changes 3 parameters** during treatment

- shape of treatment aperture
- delivered dose intensity
- speed of gantry rotation

Volumetric modulated arc therapy

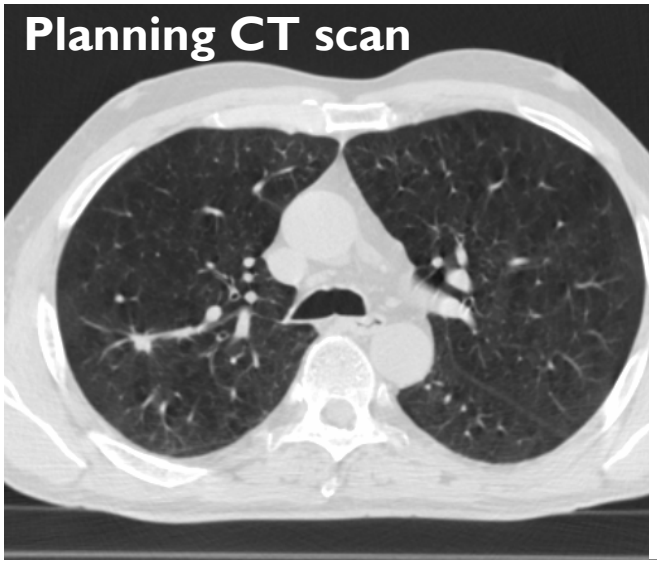
Rapidly changing dose rate throughout a continuous range alows greater variation in intensity levels at different gantry angles.



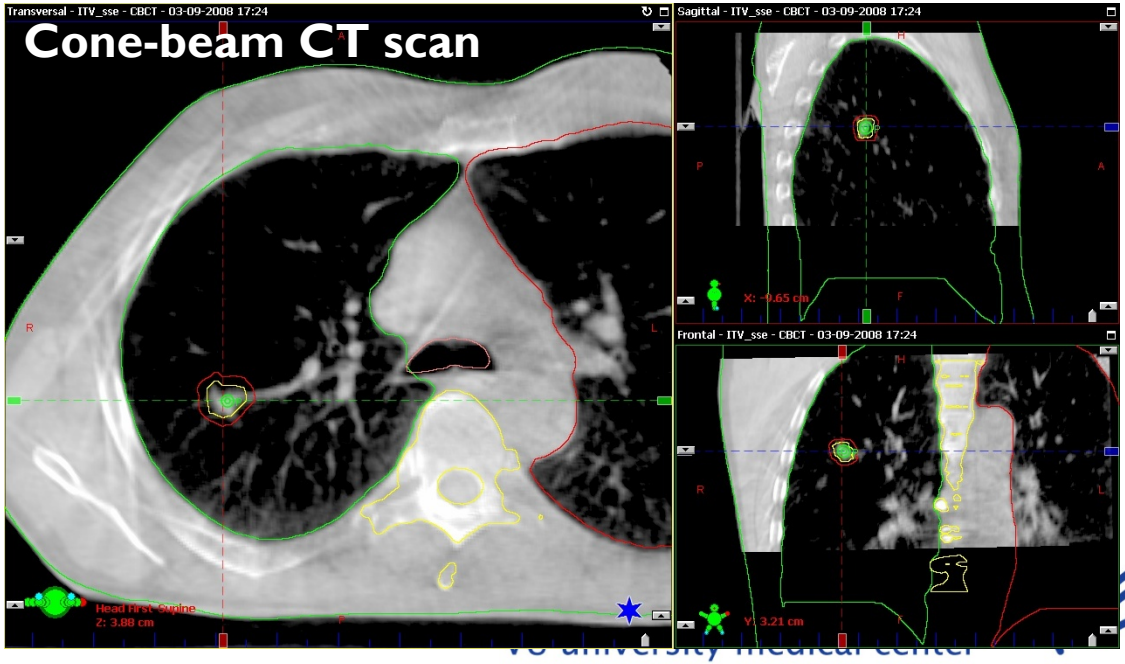
Example of critical structure avoided by traversing leaf pairs across it while dose rate is reduced to nearly zero.

Recent advances in lung SBRT

Daily setup based on tumor position



SBRT delivery in <12 mins using RapidArc [Verbakel W, 2009]



Role of FDG-PET for target definition

- Established role for in PET staging
- PET for defining target volumes ?
- PET for 'adaptive radiotherapy' ?

PHYSICS CONTRIBUTION

CAN PET PROVIDE THE 3D EXTENT OF TUMOR MOTION FOR INDIVIDUALIZED INTERNAL TARGET VOLUMES? A PHANTOM STUDY OF THE LIMITATIONS OF CT AND THE PROMISE OF PET

Curtis B. Caldwell, Ph.D.,*† Katherine Mah, M.Sc.,‡§ Matthew Skinner, M.Sc.,‡ and Cyril E. Danjoux, M.D.‡§

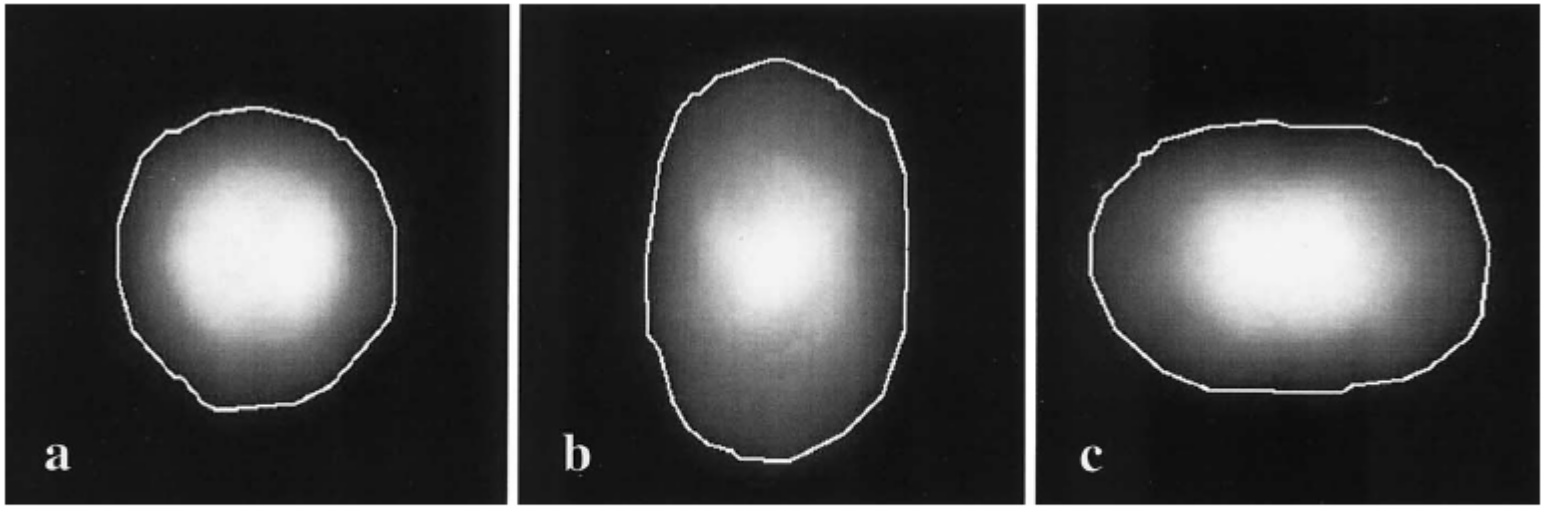


Fig. 4. AP maximum pixel ray trace ^{22}Na-PET images of the same sphere while (a) stationary and moving 25 mm in the (b) longitudinal and (c) transaxial directions. The period was 4 s, and the images were acquired over 20 min. The graphical overlay represents the region localized using a threshold defined by 15% of the maximum voxel value. These images illustrate that the time-averaged, capsule-shaped geometry that the moving sphere traces is better represented by PET compared with spiral CT.

Microscopic tumor extensions

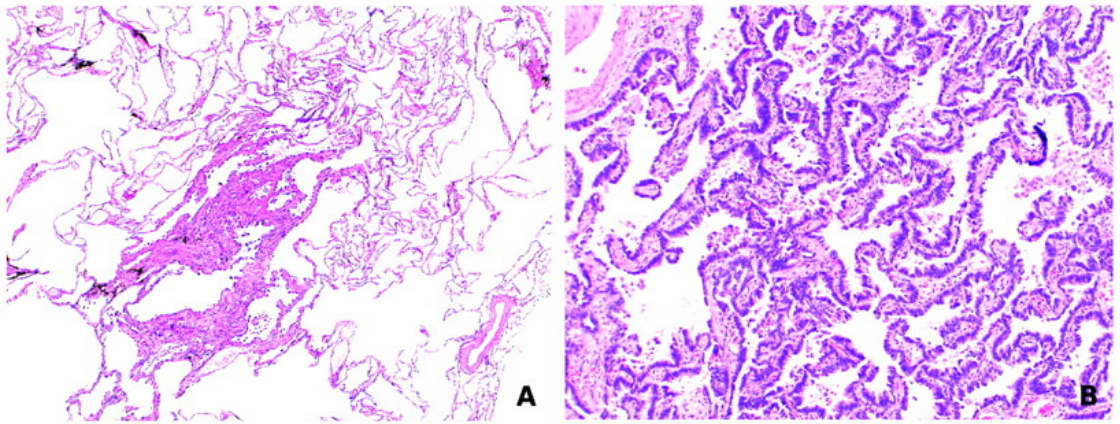
- 70 surgical specimens; mean microscopic tumour extension of 2.69 mm (adenocarcinomas) and 1.48 mm (squamous cell)

- To account for **95% of all microscopic extension**, use of margins of 8 mm (adenoca.) and 6 mm (squamous)

Giraud 2000

Bronchoalveolar carcinoma

AAH: atypical adenomatous hyperplasias



AAH with surrounding normal lung

Pure BAC

Mixed BAC and adenocarcinoma

Raz, D. J. et al. Clin Cancer Res 2006;12:3698-3704

PET for target definition

Number of cancer cells needed for detection?

3 human cancer cell lines [glioblastoma and 2 subtypes of SCLC] in concentrations 10^4 -10^7 were seeded on 6-well plates or plastic tubes and treated with FDG-glucose in vitro.

FDG retention measured in a PET/CT scanner and in a calibrated well counter. Clinical situation simulated using a cylinder phantom with a background concentration of FDG.

Theoretical detection limit was around **10^5 malignant cells.** In a **cylinder phantom** the detection limit was **increased** by a factor of 10. FDG retention measured by PET and a gamma counter was closely correlated to the number of cells and a linear relationship was found.

Detection limit of PET is in magnitude of 10^5 to 10^6 malignant cells.

Fischer BM. 2006

Optimal Distance of Malignant Negative Margin in Excision of Nonsmall Cell Lung Cancer: A Multicenter Prospective Study

Sawabata 2004, N = 118 cases of NSCLC

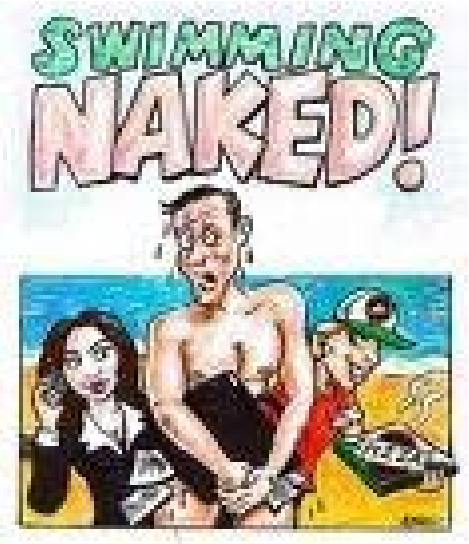
Conclusions. Malignant positive margins were not found when the margin distance was greater than the maximum tumor diameter, which was considered to be the optimal margin distance for prevention against margin relapse.

(Ann Thorac Surg 2004;77:415–20)

Belief in PET-based target volumes?

"When the tide goes out, we find out who's been swimming without a bathing suit."

Warren Buffett, 2007



Stereotactic RT (SRT): PET-only target definition

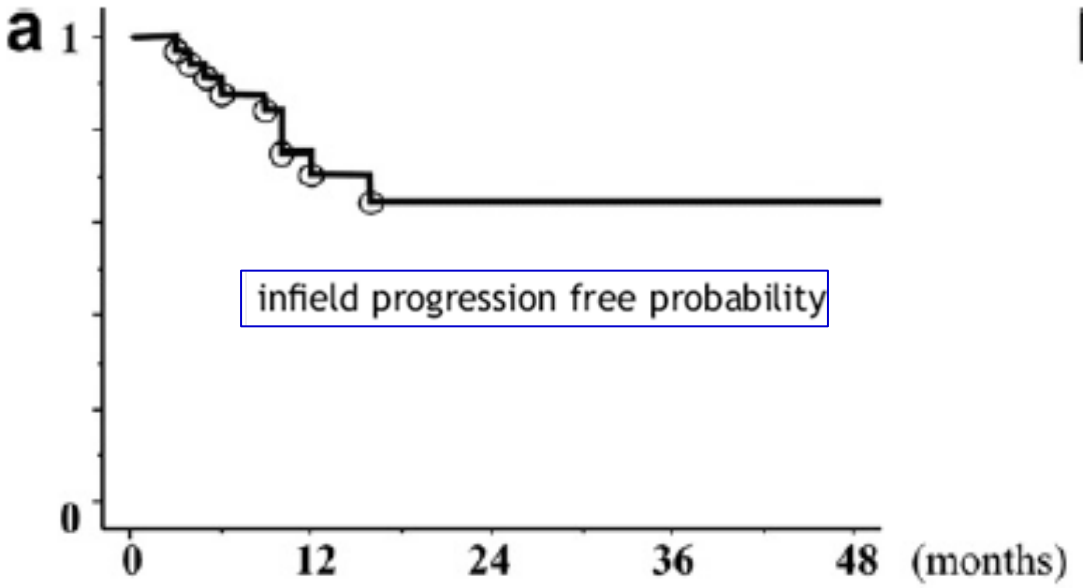
- SRT planning performed using BrainSCAN 5.31 to total dose of 60Gy (8×7.5Gy / isocenter)
- Planning spiral CT performed in shallow tidal breathing.
- FDG-PET scan in treatment position and images co-registered with CT
- Delineated tumor volume based on CT and FDG-PET information to compensate for internal motion

Bral S, 2007

Stereotactic RT (SRT): **PET-only** target definition

In-field tumor progression-free probability

at 2 years was only 64.7%



Bral S, 2007

PET heterogeneity versus pathology

N=5 patients

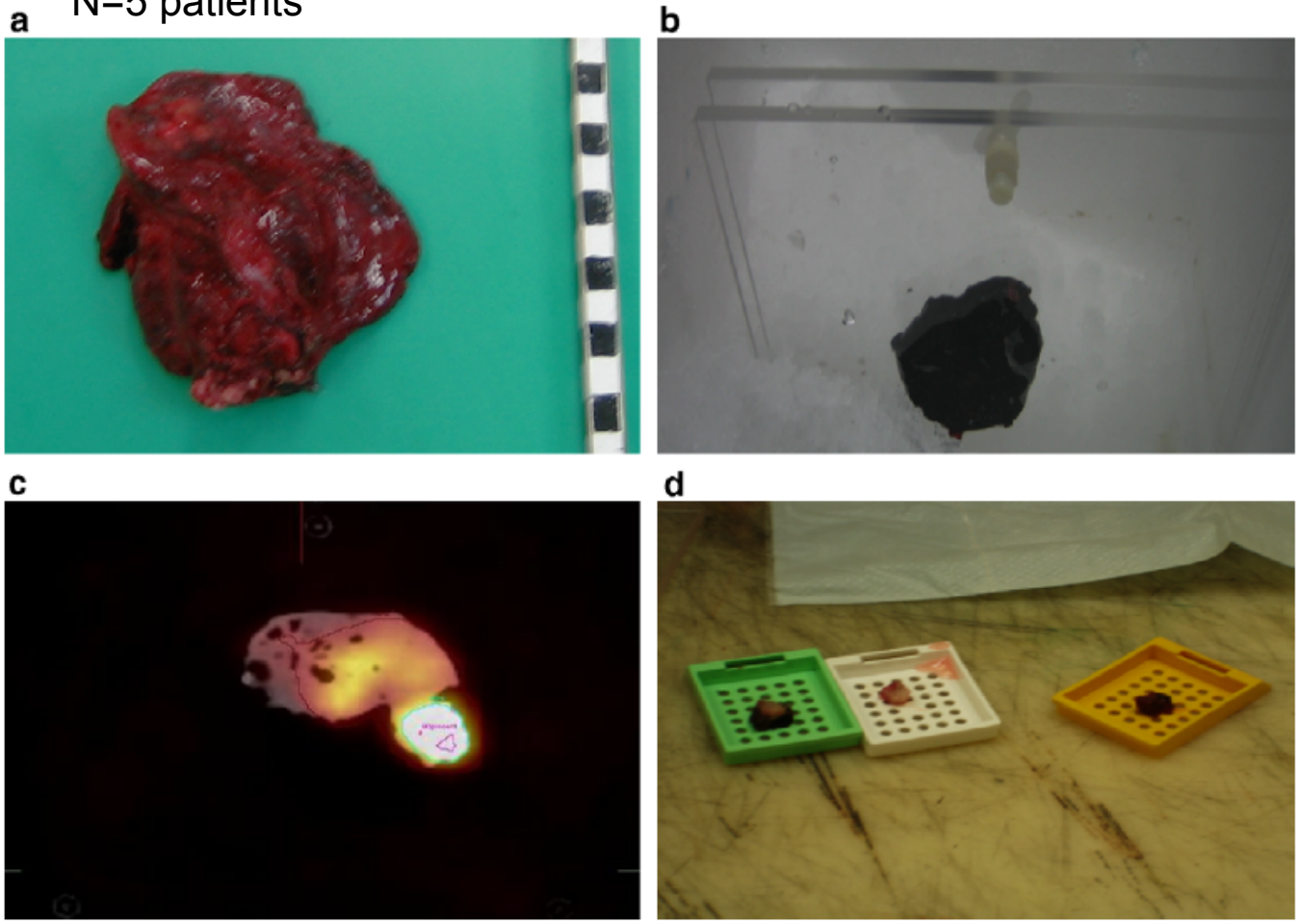


Fig. 1. Visualization of the total procedure: Total surgical specimen (a), specimen sectioned in parallel slices of 1 cm thickness ready to be scanned (b), delineation of tumour heterogeneity in E-soft with regions with 80% (pink line), 50% (green line) and 20% (red line) of maximal uptake of FDG (c) and biopsies from the different regions (d).

van Baardwijk 2008

PET heterogeneity versus pathology

Distributions of microscopic evaluation for the different biopsies out of regions with a low, median or high uptake of FDG

	Low uptake	Median uptake	High uptake
Mainly vital tumour (>75%)	2	1	2
Mainly fibrosis (>75%)	3*	1	0
Combination of vital tumour, fibrosis and/or inflammation or necrosis	2	7	5

No significant differences in distribution patterns were observed ($p = 0.16$).

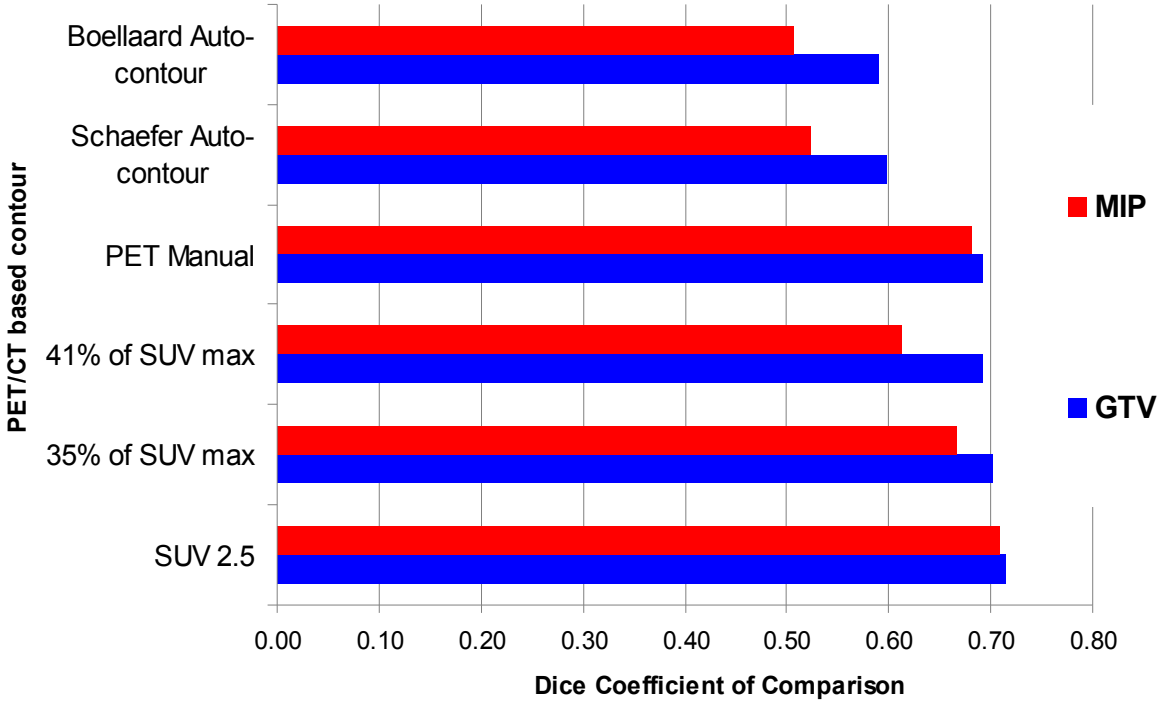
* Two samples showed no vital tumour cells.

Van Baardwijk 2008 (N= 5 patients)

Use of FDG-PET to define target volumes?

- **Methods**: SRT target volumes (TV) using 4DCT were compared to 6 different approaches for PET TV's in 7 patients with stage I NSCLC.
- Dice similarity coefficient used to assess volume, shape and positional change in PET-generated TVs versus 4DCT TVs.
- **Conclusion**: Conventional PET-TVs do not correspond to MIP-based TVs commonly used for SRT, and all were significantly smaller

Conformality (Dice coeff) of PET outlining techniques with MIP-modified volumes in **7 patients**



Hanna GG, *submitted*

PET for target definition

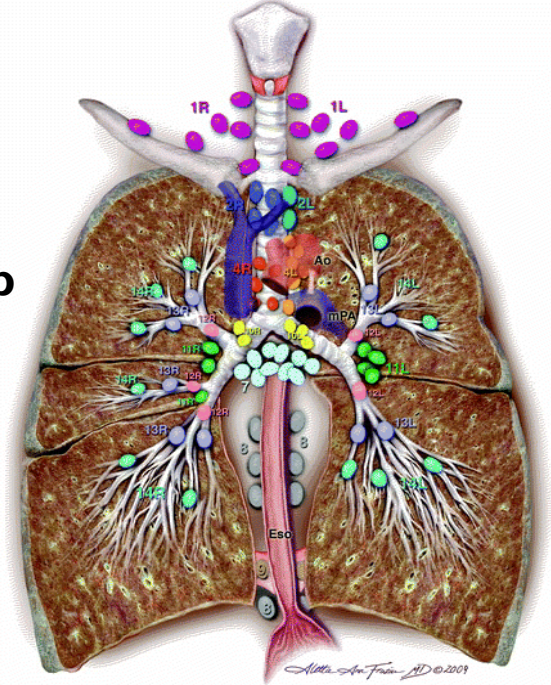
Stereotactic RT aims to **cure** stage I disease.

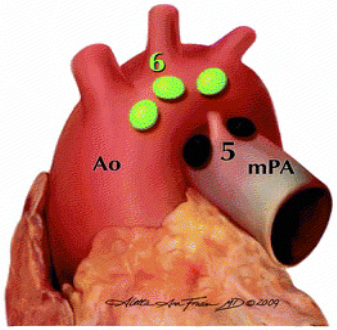
Focus on FDG-PET as a means of reducing inter-clinician variability may have reduced cure rates at some institutes.

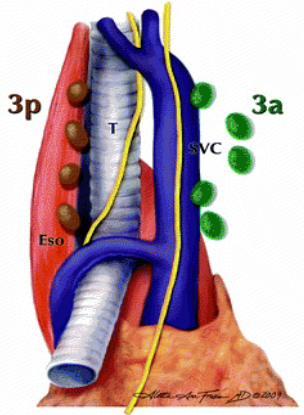
VUmc

New International Lymph Node Map

IASLC Lung staging project
[Rusch V, 2009]







Supraclavicular zone
- 1 Low cervical, supraclavicular, and sternal notch nodes

SUPERIOR MEDIASTINAL NODES

Upper zone
- 2R Upper Paratracheal (right)
- 2L Upper Paratracheal (left)
- 3a Prevascular
- 3p Retrotracheal
- 4R Lower Paratracheal (right)
- 4L Lower Paratracheal (left)

AORTIC NODES

AP zone
- 5 Subaortic
- 6 Para-aortic (ascending aorta or phrenic)

INFERIOR MEDIASTINAL NODES

Subcarinal zone
- 7 Subcarinal

Lower zone
- 8 Paraesophageal (below carina)
- 9 Pulmonary ligament

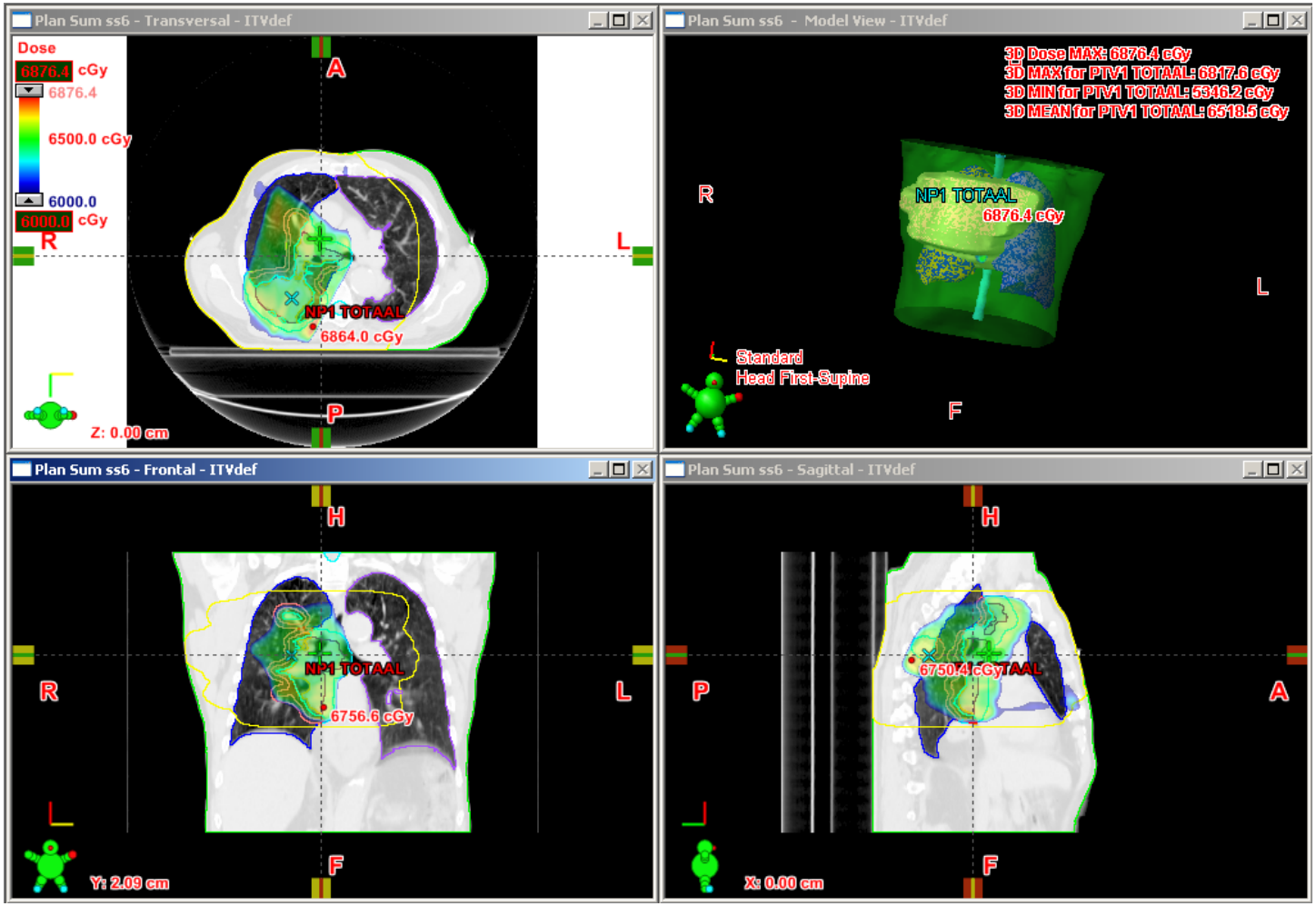
N1 NODES

Hilar/Interlobar zone
- 10 Hilar
- 11 Interlobar

Peripheral zone
- 12 Lobar
- 13 Segmental
- 14 Subsegmental

Stage III nsclc – Delivery of higher doses

IMRT-based approaches allowing delivery of 66 Gy
Availability of better dose constraints for standard CT-RT



Defining nodal GTVs

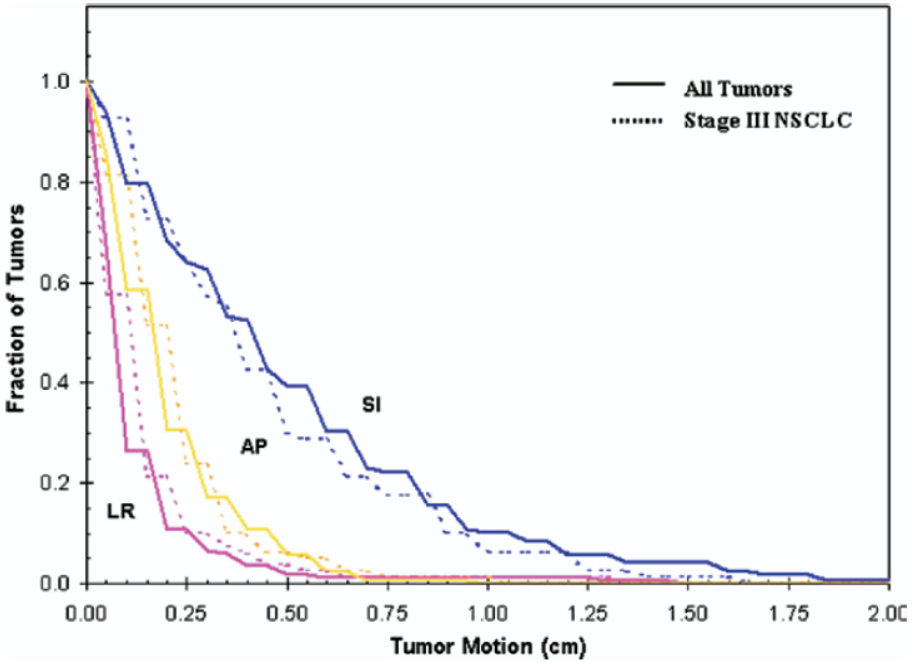
Nodal Diameter (short-axis)	Approach	Comment
< 1 cm & PET +ve	Include in GTV	High positive predictive value of PET scan
< 1 cm & PET –ve	Exclude from GTV	Only if dedicated PET scan was used
> 1 cm & PET +ve	Include in GTV unless representative cytology from the node is negative	EUS-guided aspiration cytology has sensitivity of 88% & accuracy of 91%
1-1.5 cm & PET -ve and if no cytology available	If primary PET+ve, exclude node from GTV unless cytologically +ve	
≥ 1.5 cm & PET –ve and if no cytology available		**21%** probability of **N2** disease [meta-analysis, de Langen 2006]

VUmc scheme [Modified from Senan 2004]

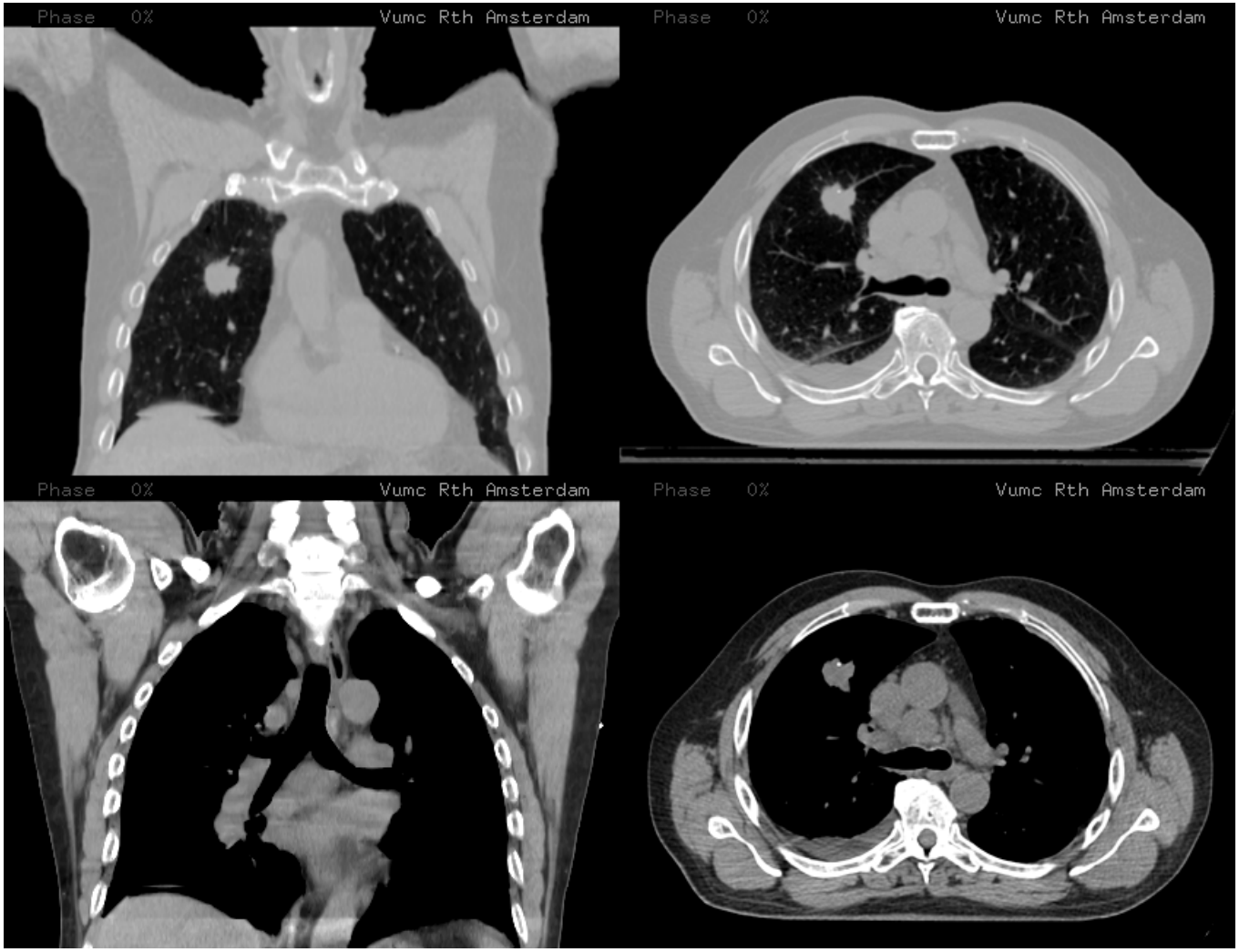
Tumor and nodal motion

Liu et al, IJROBP 2007
166 lung tumors, 48% Stage III

Proportion of primary tumors with motion > 0.5 cm during normal breathing:
SI axis: 39.2%
ML axis: 1.8%
AP axis: **5.4%**

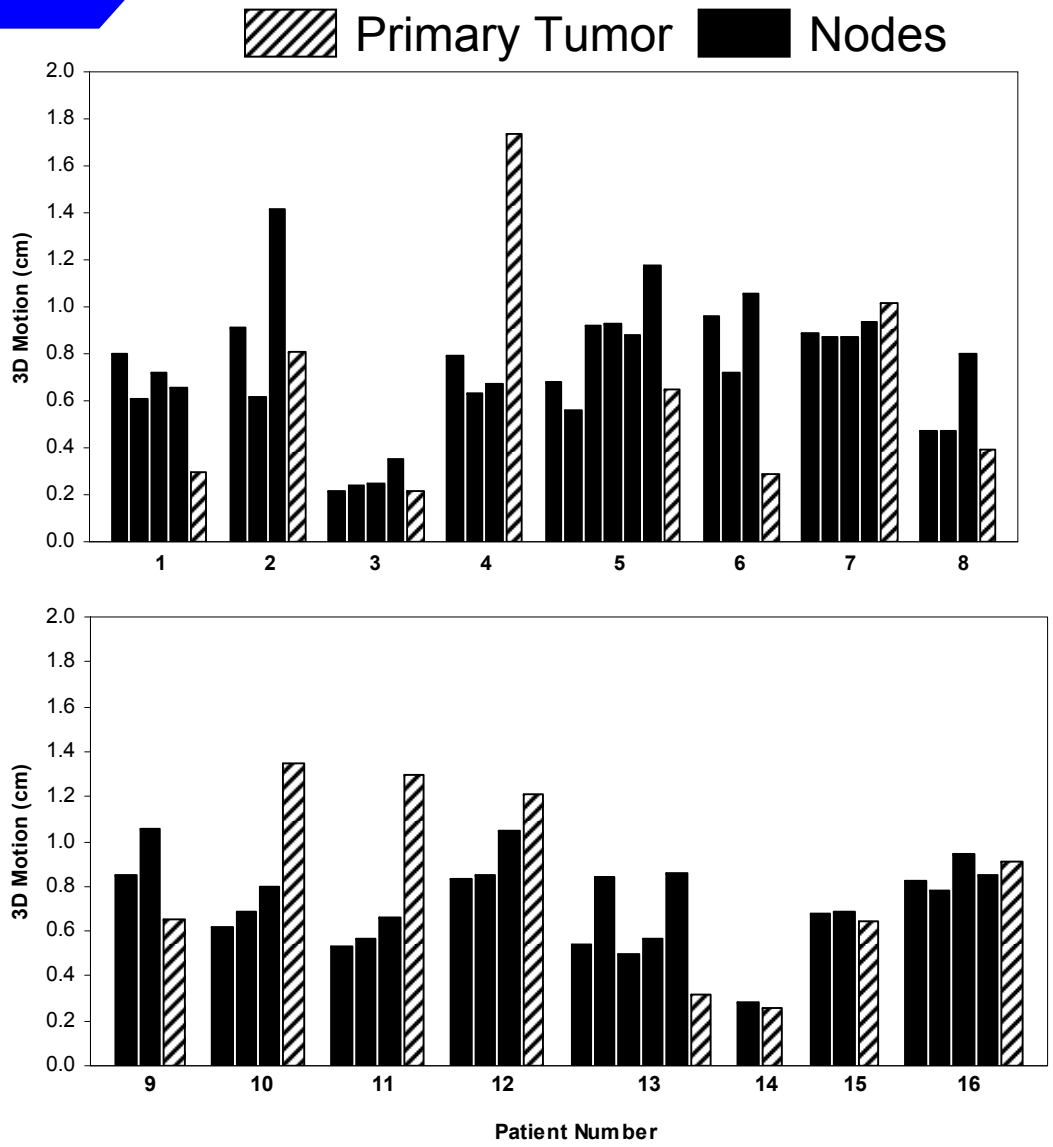


Differential motion of primary and nodes



No involved-field radiotherapy without 4DCT

Motion of primary and nodes in same patients



In 11 of 16 patients, ≥1 malignant node moved more than primary tumor.

In 6 patients with "immobile" lung tumors, 4 had nodes with motion > 0.5 cm.

No correlation between 3D motion of primary tumor and nodal motion

Pantarotto J, *in press*

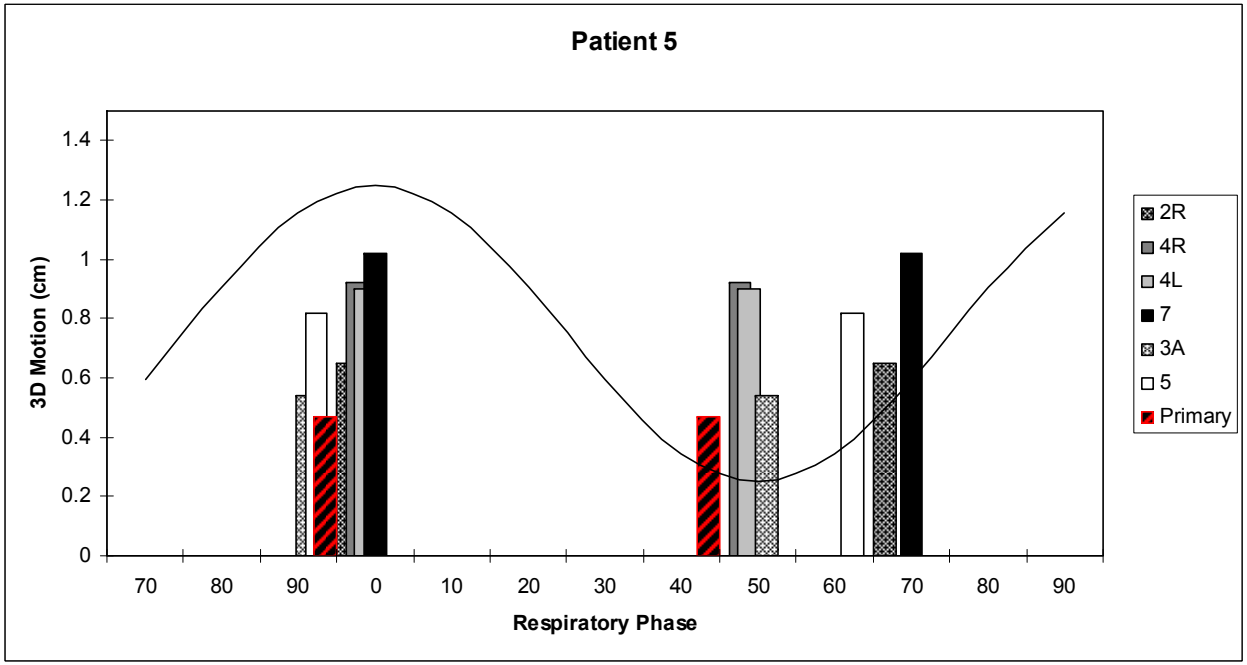
Adaptive radiotherapy ?

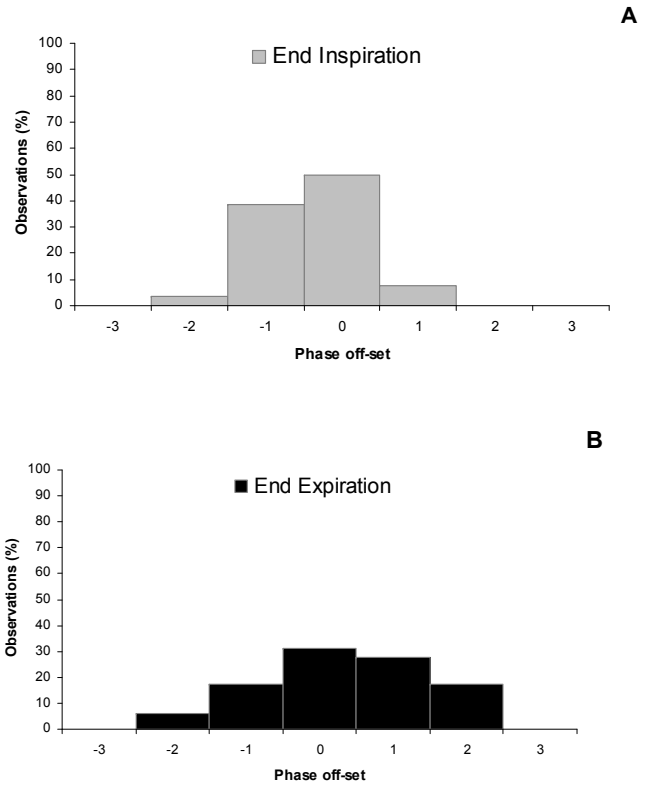
- “Use of new image-guidance technologies to visualize changes in tumour size, shape and position
- Allow for planning adjustments to be made during a course of radiotherapy in order to improve both target coverage and normal tissue avoidance”

Verellen 2007

Phase discrepancy in motion

Primary tumor and nodes may not move in phase.



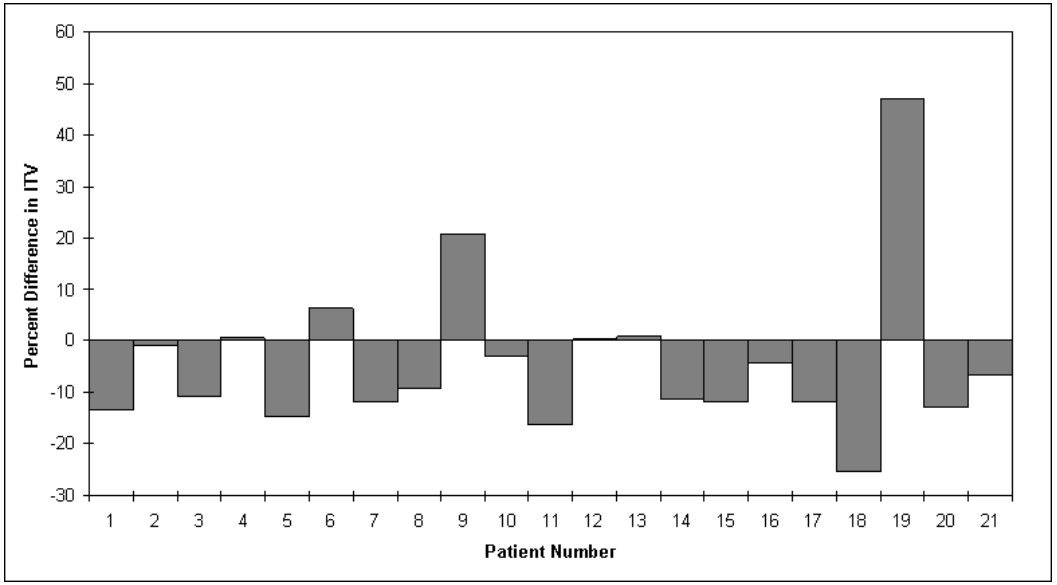


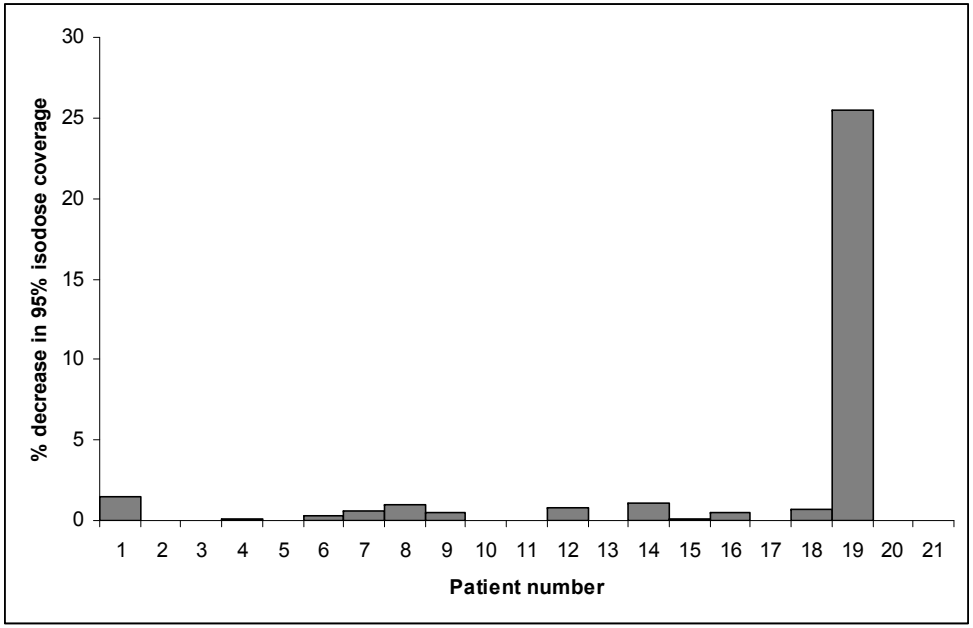
Pantarotto J, 2008

Prospective data with full-dose CT-RT

Spoelstra F, 2008

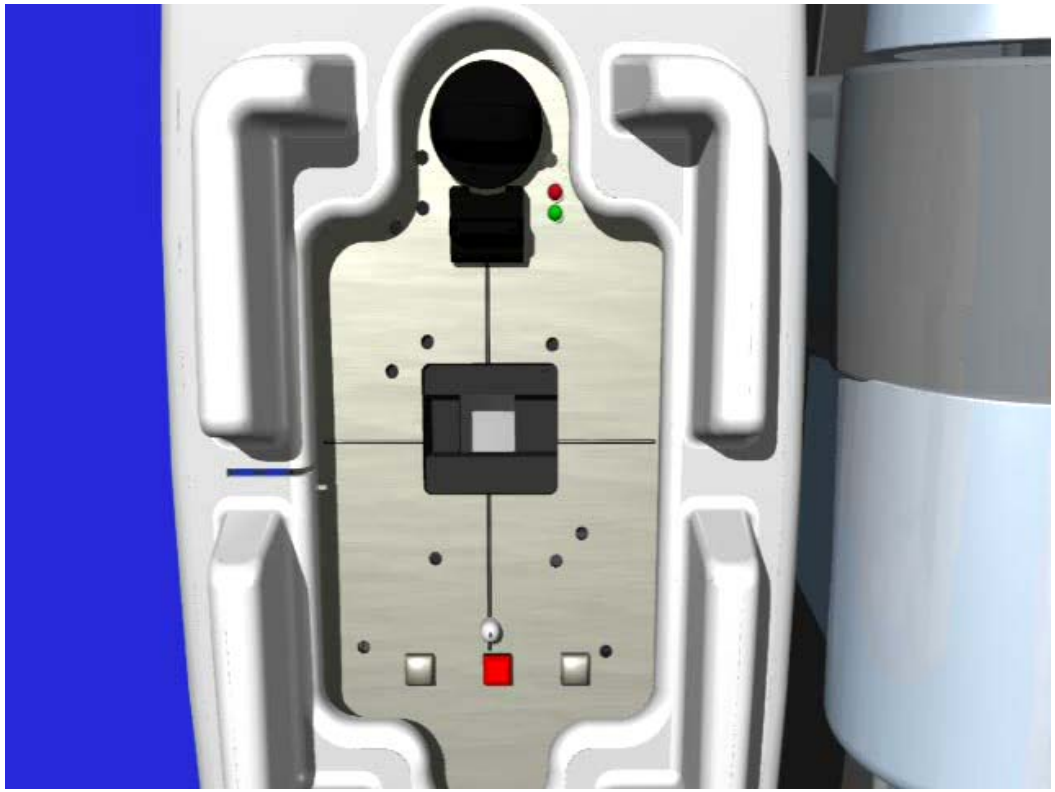
Change in internal target volumes for 21 patients between time of simulation and at 30 Gy full-dose CT-RT

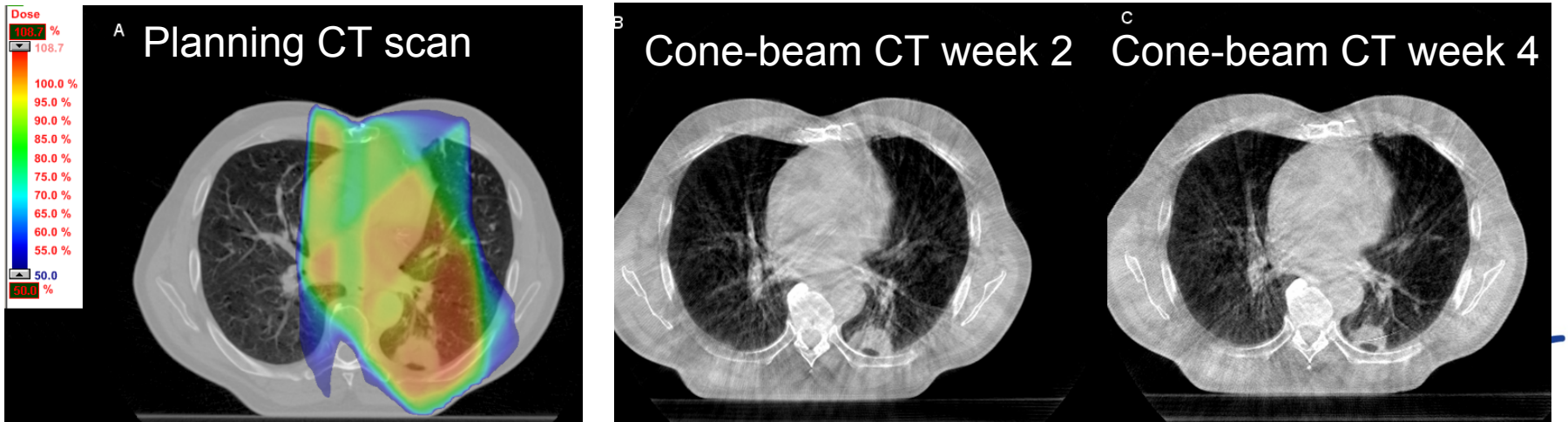




Degree of dosimetric miss for 21 patient PTVs observed at 30 Gy CT-RT.

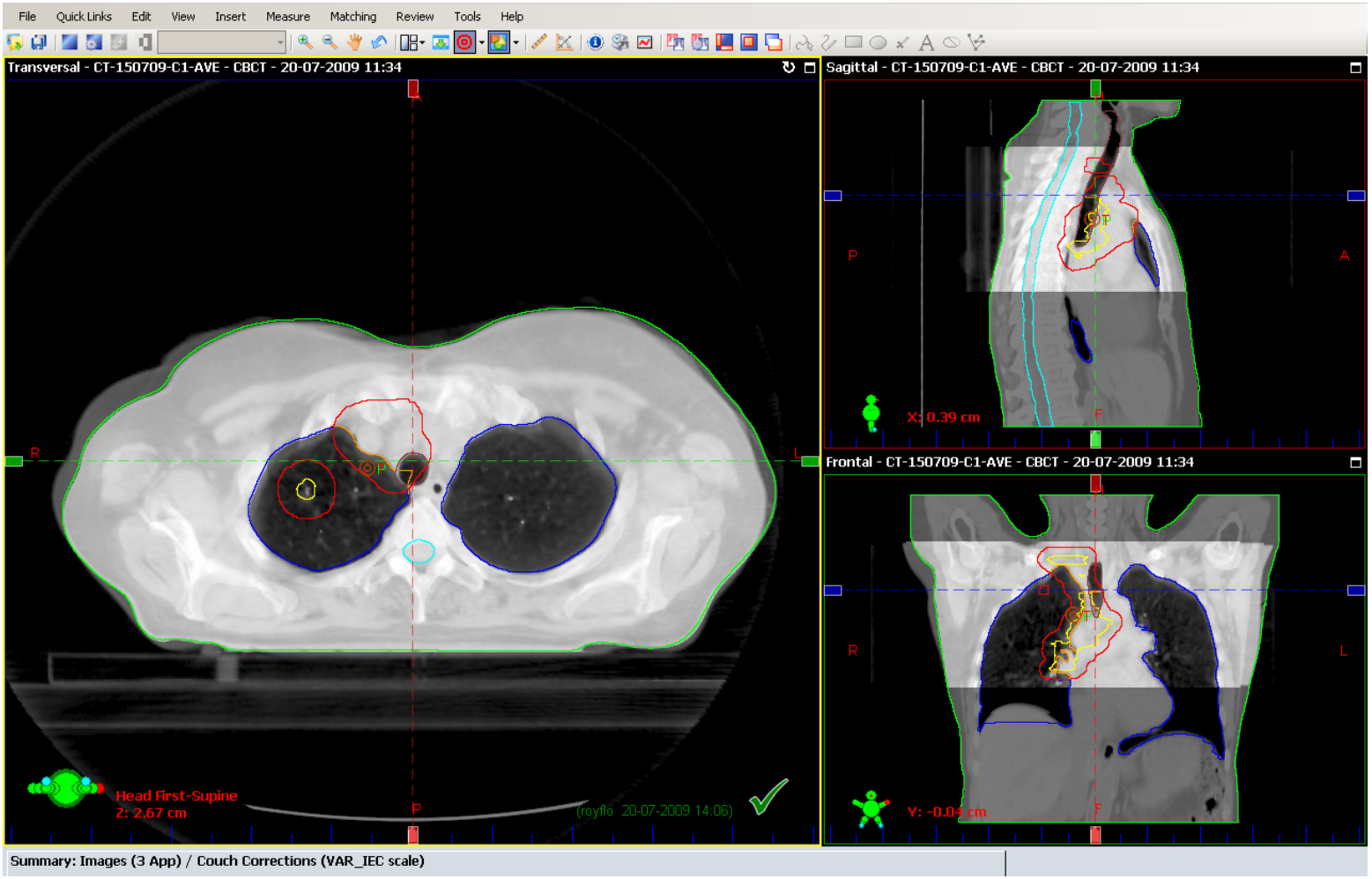
Cone-beam CT scan on Linear accelerator





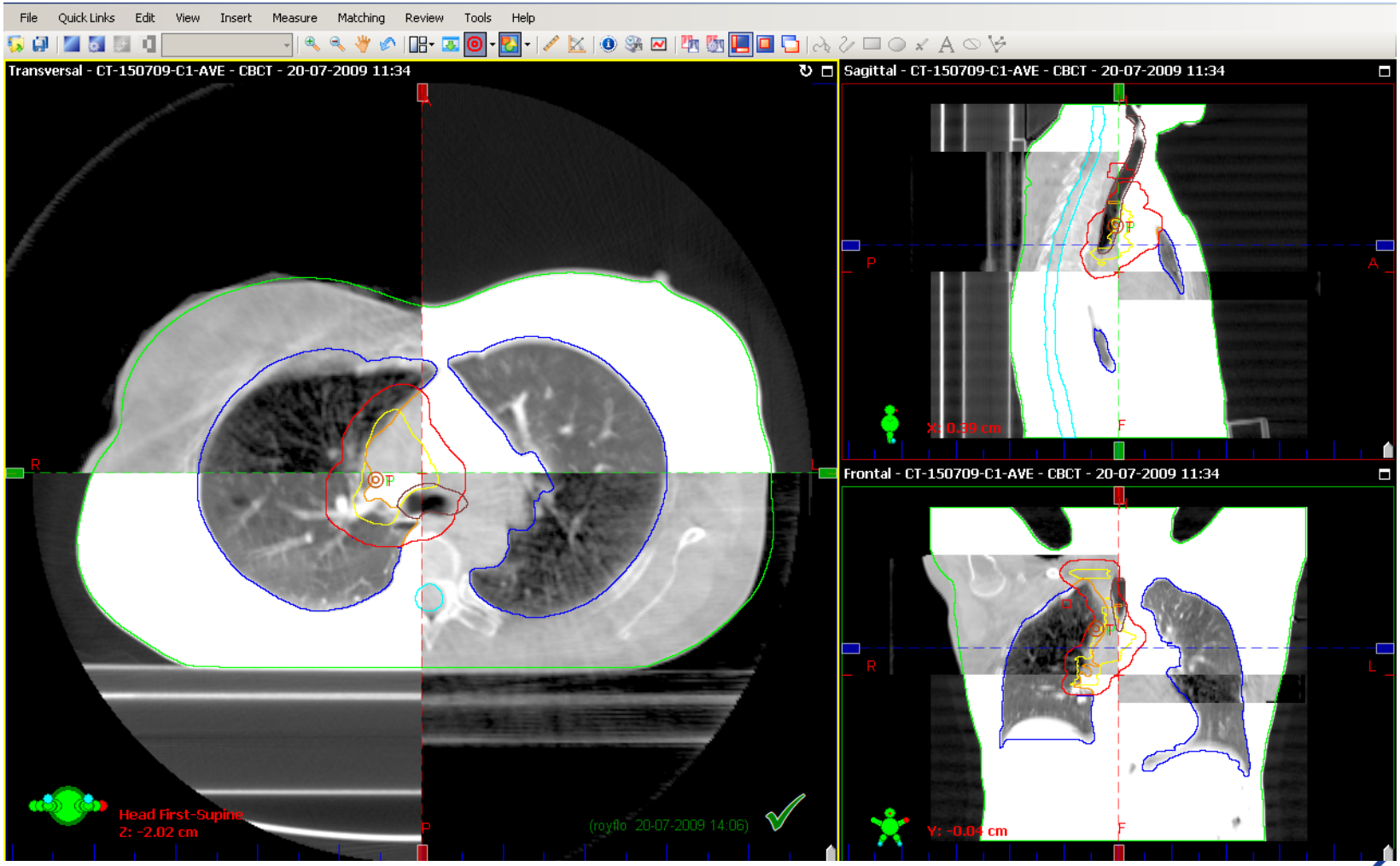
Daily patient set-up & verification of delivery

Cone-beam CT images



Daily patient set-up & verification of delivery

Cone -beam CT images



Cone-beam CT for adaptive RT?

CLINICAL INVESTIGATION

COMPARISON OF SPINE, CARINA AND TUMOR AS REGISTRATION LANDMARKS FOR VOLUMETRIC IMAGE-GUIDED LUNG RADIOTHERAPY

JANE HIGGINS, B.SC.,*† ANDREA BEZJAK, M.D.,*† KEVIN FRANKS, M.D.,‡ LISA W. LE, M.SC.,†§
B. C. CHO, M.D, PH.D.,*† DAVID PAYNE, M.D.,*† AND JEAN-PIERRE BISSONNETTE, PH.D.*†

*Radiation Medicine Program and §Department of Biostatistics, Princess Margaret Hospital, Toronto, ON, Canada; †University of Toronto, Toronto, ON, Canada; and ‡St. James Institute of Oncology, Leeds Teaching Hospitals, National Health Service Trust, Leeds, England

Purpose: To assess the feasibility, reproducibility, and accuracy of volumetric lung image guidance using different thoracic landmarks for image registration.

Methods and Materials: In 30 lung patients, four independent observers conducted automated and manual image registrations on Day 1 cone-beam computed tomography data sets using the spine, carina, and tumor (720 image registrations). The image registration was timed, and the couch displacements were recorded. The intraclass correlation was used to assess reproducibility, and the Bland-Altman analysis was used to compare the automatic and manual matching methods. Tumor coverage (accuracy) was assessed through grading the tumor position after image matching against the internal target volume and planning target volume.

Results: The image-guided process took an average of 1 min for all techniques, with the exception of manual tumor matching, which took 4 min. Reproducibility was greatest for automatic carina matching (intraclass correlation, 0.90–0.93) and lowest for manual tumor matching (intraclass correlation, 0.07–0.43) in the left-right, superoinferior, and anteroposterior directions, respectively. The Bland-Altman analysis showed no significant difference be-

Conclusion: For advanced lung cancer, the spine or carina can be used equally for cone-beam computed tomography image registration without compromising target coverage. The carina was more reproducible than the spine, but additional analysis is required to confirm its validation as a tumor surrogate. Soft-tissue registration is unsuitable at present, given the limitations in contrast resolution and the high interobserver variability.

Acta Oncologica, 2008; 47: 1186–1187

EDITORIAL

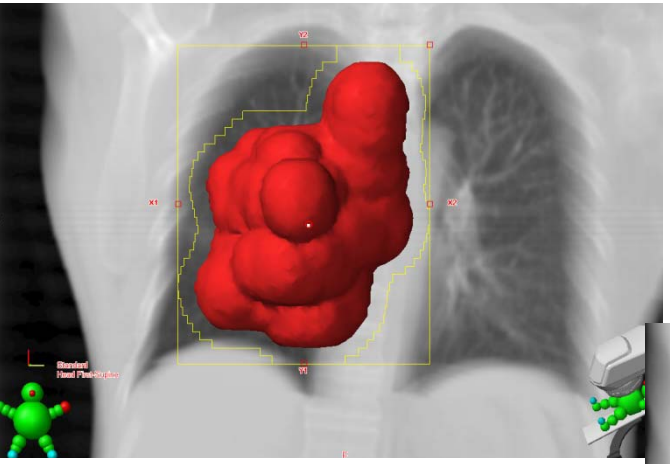
Will IGRT live up to its promise?

MARCEL VAN HERK

Finally, the increased complexity of IMRT and IGRT therapy makes it more error-prone, while anatomical guidance fails to validate the complex beam delivery. I therefore think we should rethink verification, and build in independent verification of the entire chain, otherwise big errors that occur in a small fraction of patients may go unnoticed. For that reason, we have implemented a portal dosimetry program that validates the treatment of each curative patient efficiently (*in vivo*) [3].

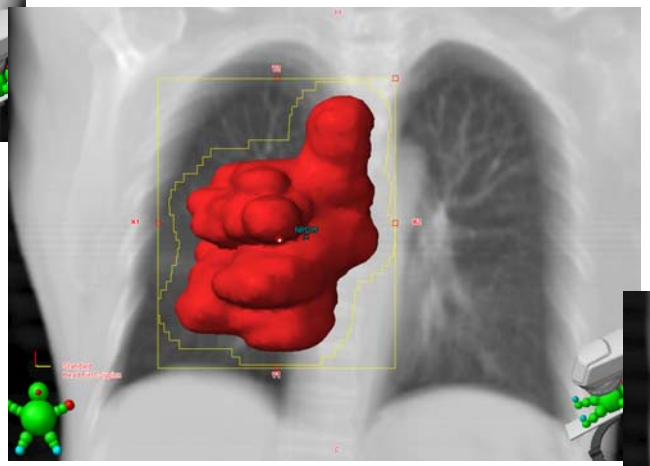
Smaller PTVs using 4D techniques

Beams-eye-views

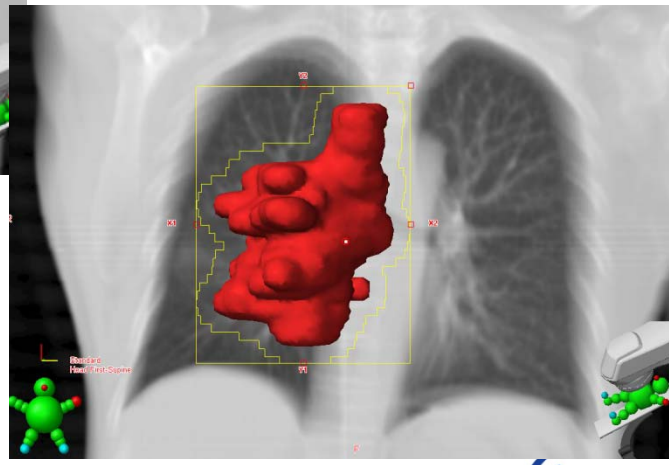


Use of ‘standard’ margins

Individualized (4DCT-based)



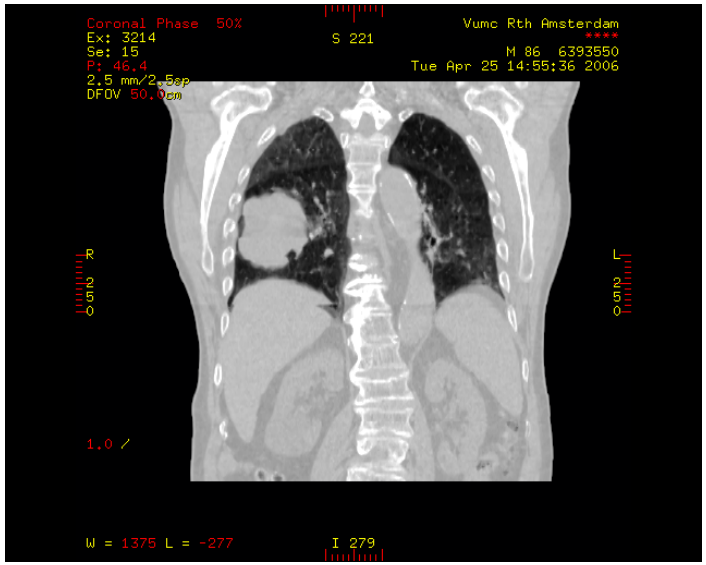
4DCT-based ‘gated’ delivery



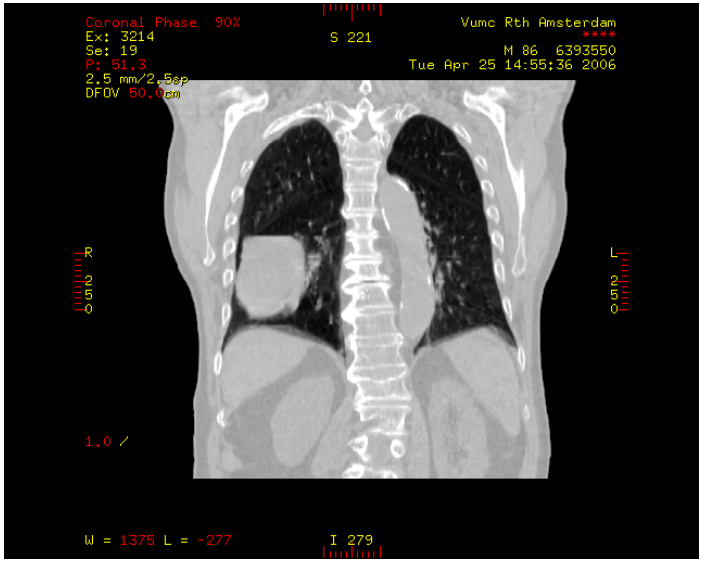
Pantarotto & Senan, *in press*

Audio-coached gated radiotherapy

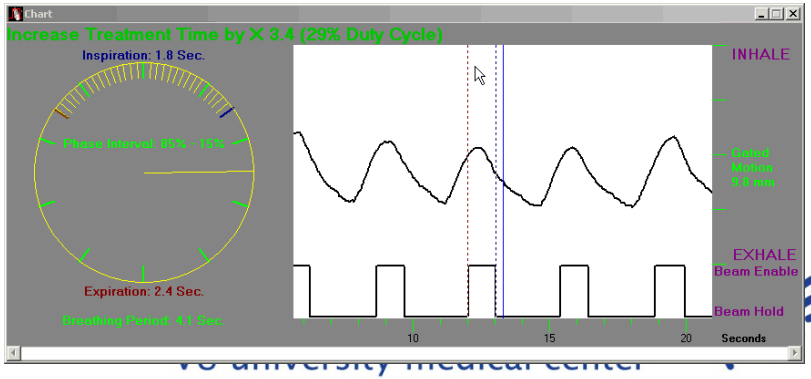
Motion (all phases of respiration)



Residual motion in 3 phases



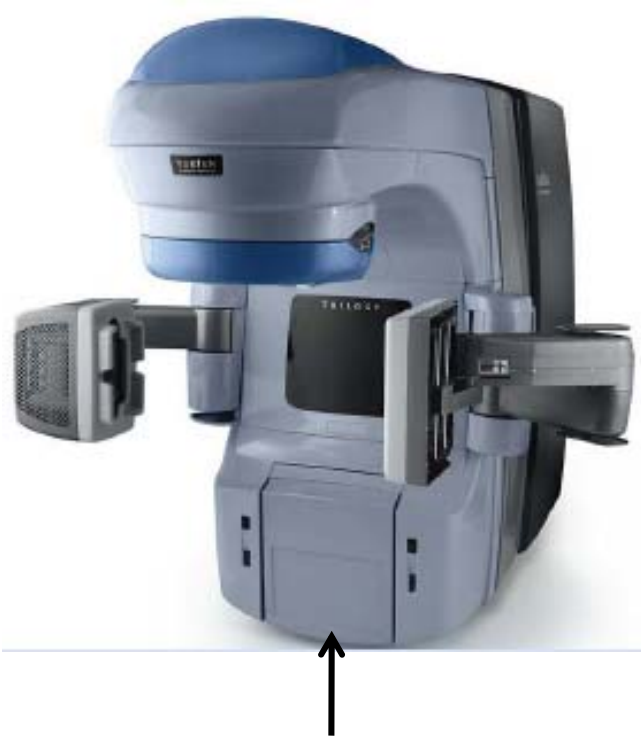
RPM waveform during gating →



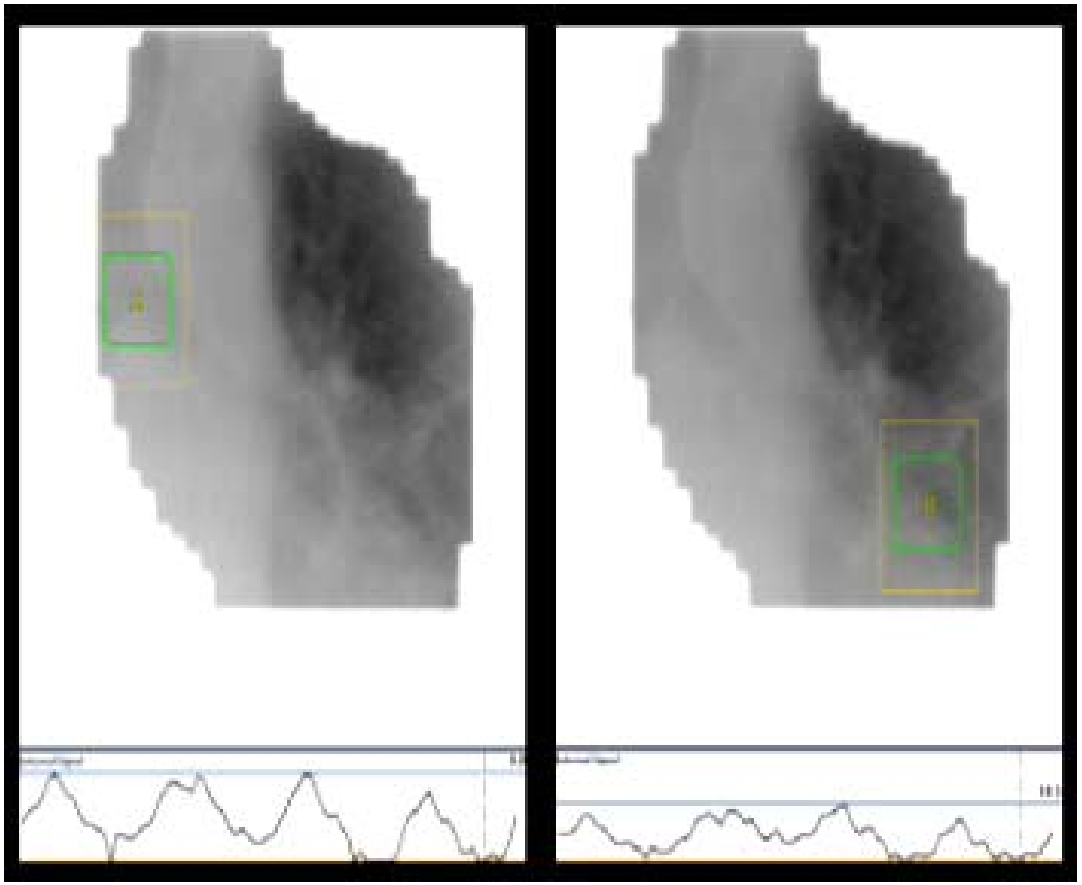
Spoelstra F, 2008

Intra-fraction motion assessment

MV cinē images & marker-less tracking

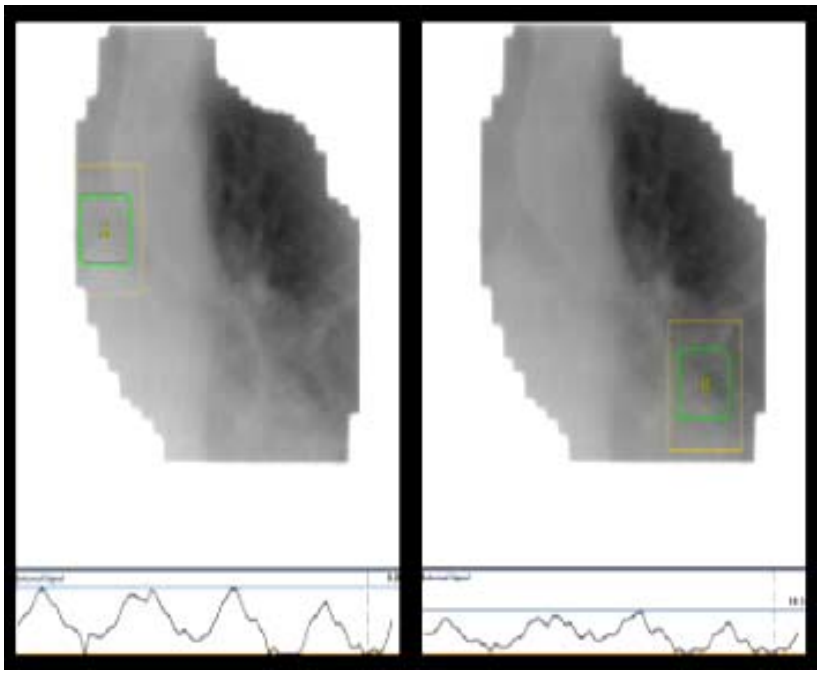


PORTALVISION MV imaging system



Muirhead R, submitted

MV cinē images & marker-less tracking



Carina visible in 81% of cine-images; tumor mass in 77%; hilar lesion in 15%

In 7% of internal structures, observed motion exceeded that seen at 4DCT.

Impaired ability to identify structures include treatment bed bar, use of wedge angles >60°, fields < 6cm in size, and delivery of <50 monitor units.

Muirhead R, submitted

Overview

- *Definition of 4-D RT, IGRT*
- *Motion assessment: Fluoroscopy, slow CT, 4DCT, PET*
- *Motion of lymph nodes*
- *Use of FDG-PET scans for target definition*
- *Baseline shifts in tumor position*
- *Role of adaptive radiotherapy & replanning*