La Radioterapia nel trattamento integrato del carcinoma polmonare non microcitoma

La PET nella definizione del bersaglio

Umberto Ricardi
Università di Torino

Decrease in therapeutic nihilism about stage III NSCLC

Co-op Group Trial	MST (months)	3-yr SV
CALGB 8433 (RT)	9.6	10%
CALGB 8433 seq C-RT	13.7	24%
RTOG 9104 conc C-RT	19.6	40%
RTOG 9410 seq C-RT	14.6	31%
RTOG 9410 conc C-RT	17.1	37%
SWOG 9504	27.0	40%

We have made some progress!

Literature-based recommendations for treatment planning and execution for high-precision radiotherapy in lung cancer.

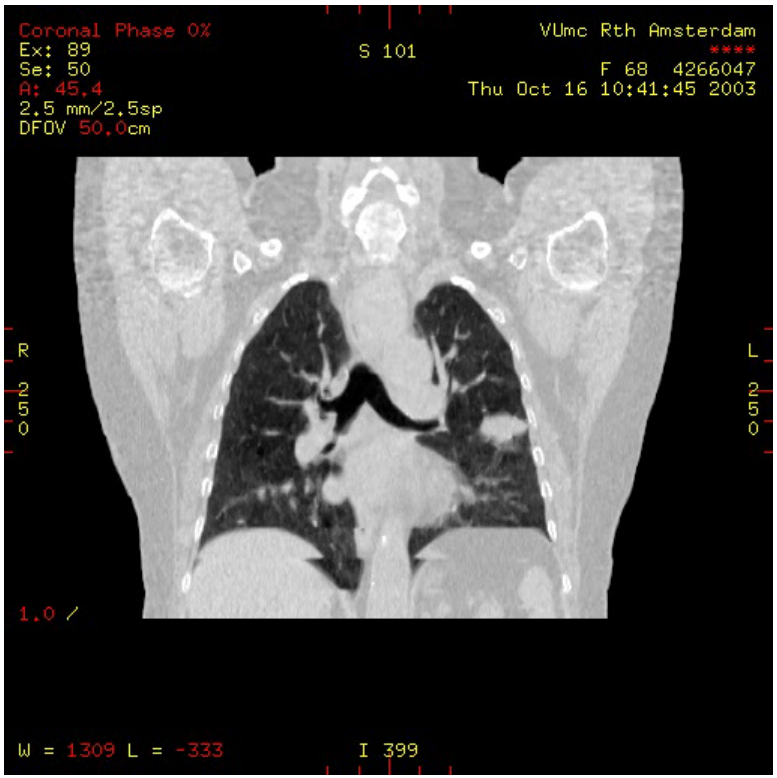
S. Senan, D. DeRuysscher et al., Radiother Oncol '04

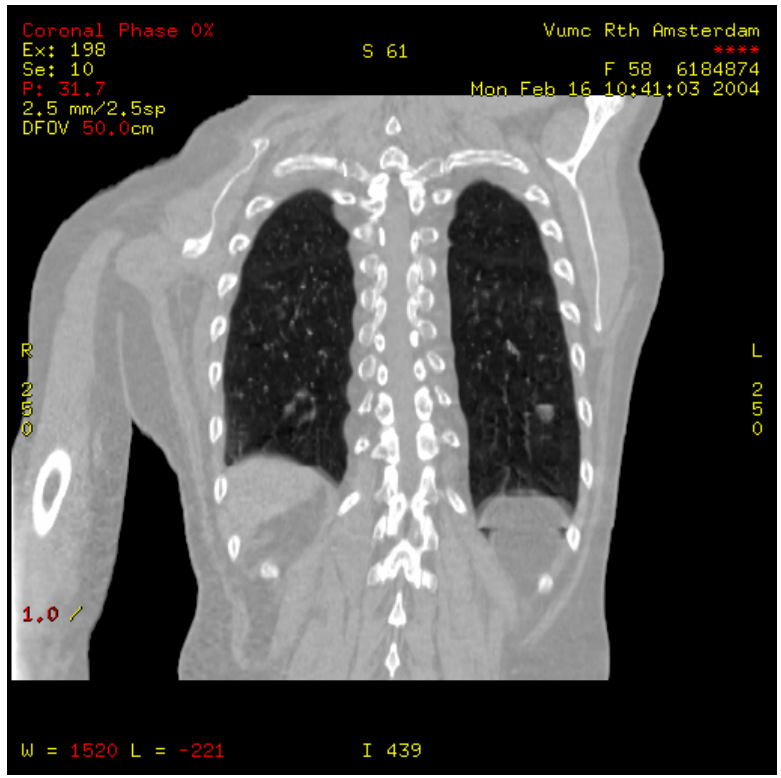
High-precision radiotherapy is a multi-step process, which is only as good as the weakest component

EORTC Recommendations Update 2005

- Spiral CT scans are superior to Single-slice CT scans
- I.V. contrast not mandatory for contouring mediastinal nodes but may improve contouring of central tumours.
- Treatment isocentre should be defined at the time of CT scan.
- Thin CT slices (2-3 mm) enable use of high-resolution DRR's, which removes the need for a separate simulation step.

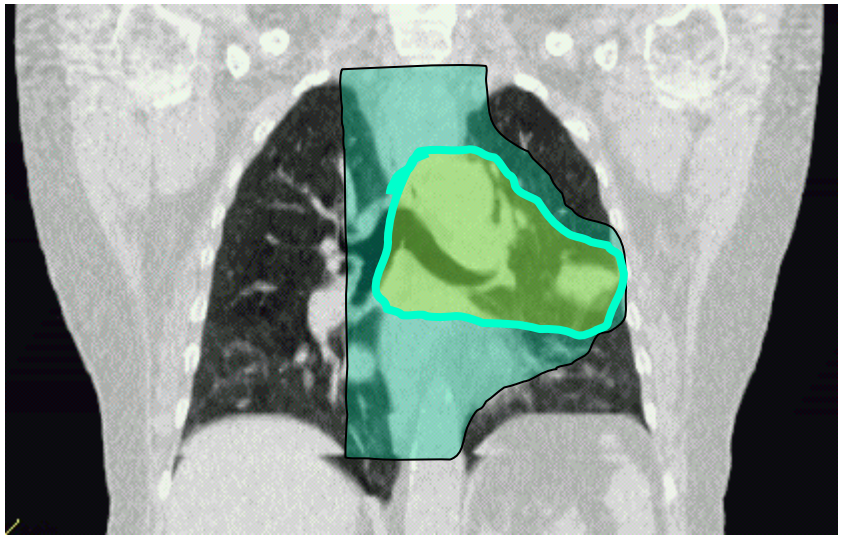
4D-CT = individualized treatment margins





Changes in radiotherapy fields

Elective nodal radiotherapy



Involved-field radiotherapy

CTV = GTV, but what is GTV?

Generating target volumes

- **Specify nodal stations using the Mountain/Dresler modifications from Naruke/ATS-LCSG map (1997).**
- **Include nodes with a short-axis diameter of ≥1cm in the GTV.**
- **FDG-PET scans superior to CT for mediastinal nodal metastases.**
- **Elective nodal irradiation not shown to confer a survival benefit in curative radiotherapy of NSCLC.**

ELSEVIER

l. Phys., Vol. 63, No. 1, pp. 170–178, 2005

0360-3016/05/$–see front matter

CLINICAL INVESTIGATIO **Lung**

CT-BASED DE STATIONS: AN AT AN

OLIVIER CHAPET . QUINT, M.D.,†
ANDREW C. CHANC M EISBRUCH, M.D.,*

Departments of *Radia ichigan, Ann Arbor, MI

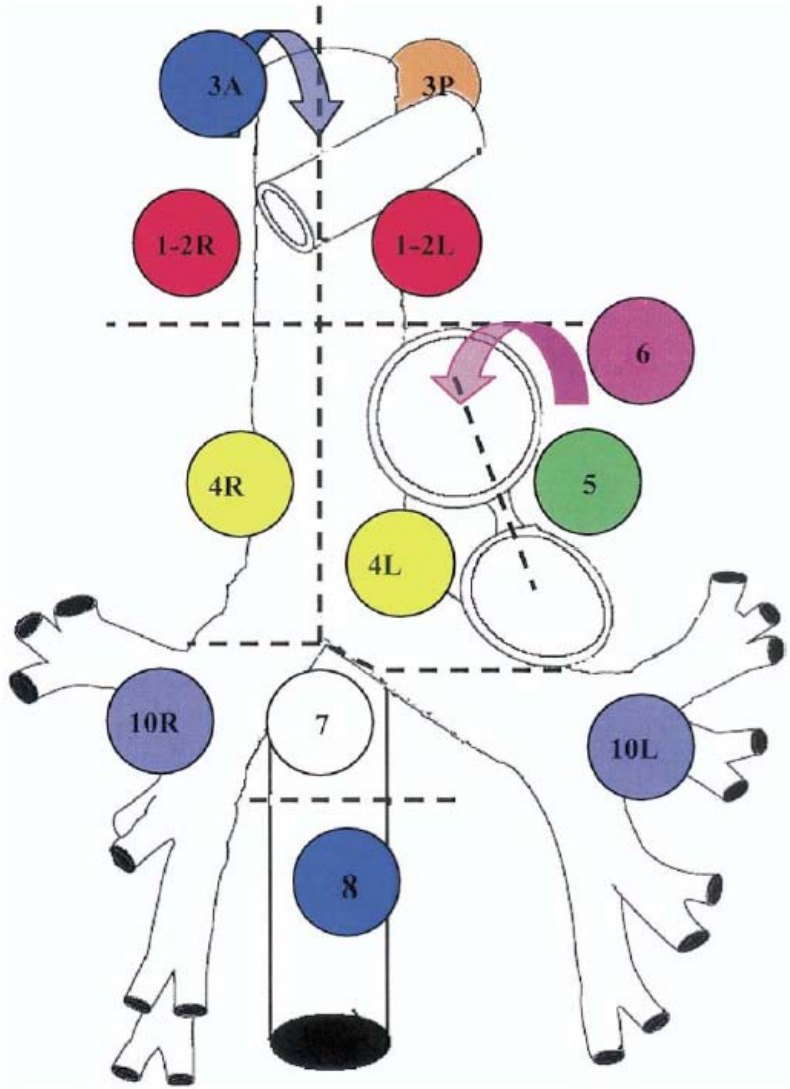


Fig. 1. Schema of Mountain and Dresler classification system, after Mountain and Dresler (1). Station 3A is anterior to Stations 1–2R and L and Stations 4R and L (blue arrow). Station 3P is posterior to trachea. Station 6 is anterior and lateral to aortic arch and ascending aorta (purple arrow).

Target Volume Definition For Stage III NSCLC:

Dummy Run Data from an International Clinical Trial

JR van Sörnsen de Koste, FJ Lagerwaard, RWM Underberg, SS Oei,
D Elshove, BJ Slotman and S Senan

INTRODUCTION

- A CD-ROM tool was developed to analyze target definition in involved-field chemo-radiotherapy for stage III NSCLC in an ongoing international study (PulmonART).

-4 academic centers performed a pilot study and generated 4 target volumes in a patient with stage III-N2 disease. Corresponding reference target volumes ('gold standard') were jointly generated by 3 clinicians at the VUmc.

- 17 PulmonART participants contoured the same target volumes as part of a mandatory quality control procedure.

Materials and Methods

- Clinicians received the CD-ROM with relevant clinical and radiological information. Contouring Window/Levels specified.

Patient Details

Diagnosis: NSCLC Stage IIIa (multiple N2)

Background: This patient will receive concurrent chemo-radiotherapy using only involved-fields. The primary tumour, involved mediastinal nodes and hilus will be contoured separately. The treatment protocol specifies that the adjacent hilus will be treated, even when radiological 'normal', when patients have mediastinal metastases.

Bronchoscopy: No abnormalities were seen. Bronchial lavage of the right upper lobe revealed the presence of cells consistent with an adenocarcinoma

FDG-PET scan (using an integrated CT-PET): Increased uptake seen in the following regions: right mid-lung, a mediastinal node in the right para-tracheal region (N4) and in a subcarinal node (N7).

CT scan (CD-ROM):

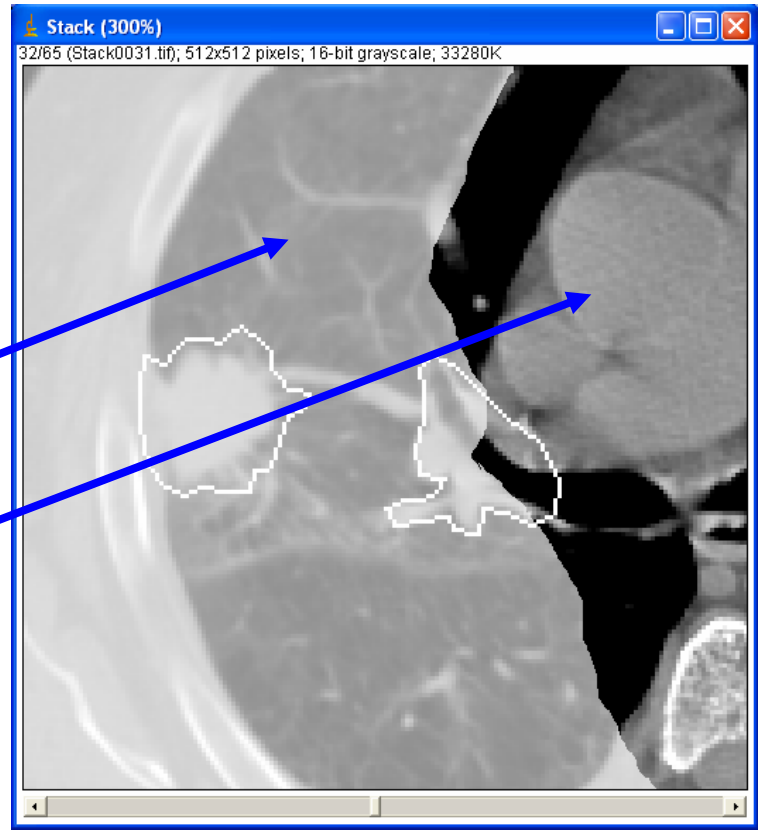
Lung setting *(click sequentially on 'Image, Adjust and Window/Level' and then 'AUTO'. The settings will be* ***L = 32552 and W= 3568)***

An irregular, spiculated tumour measuring approximately 3 cm is present in the right upper lobe (the lesion is clearly visible on image 30). The tumour extends to the pleural surface without invading the chest wall.

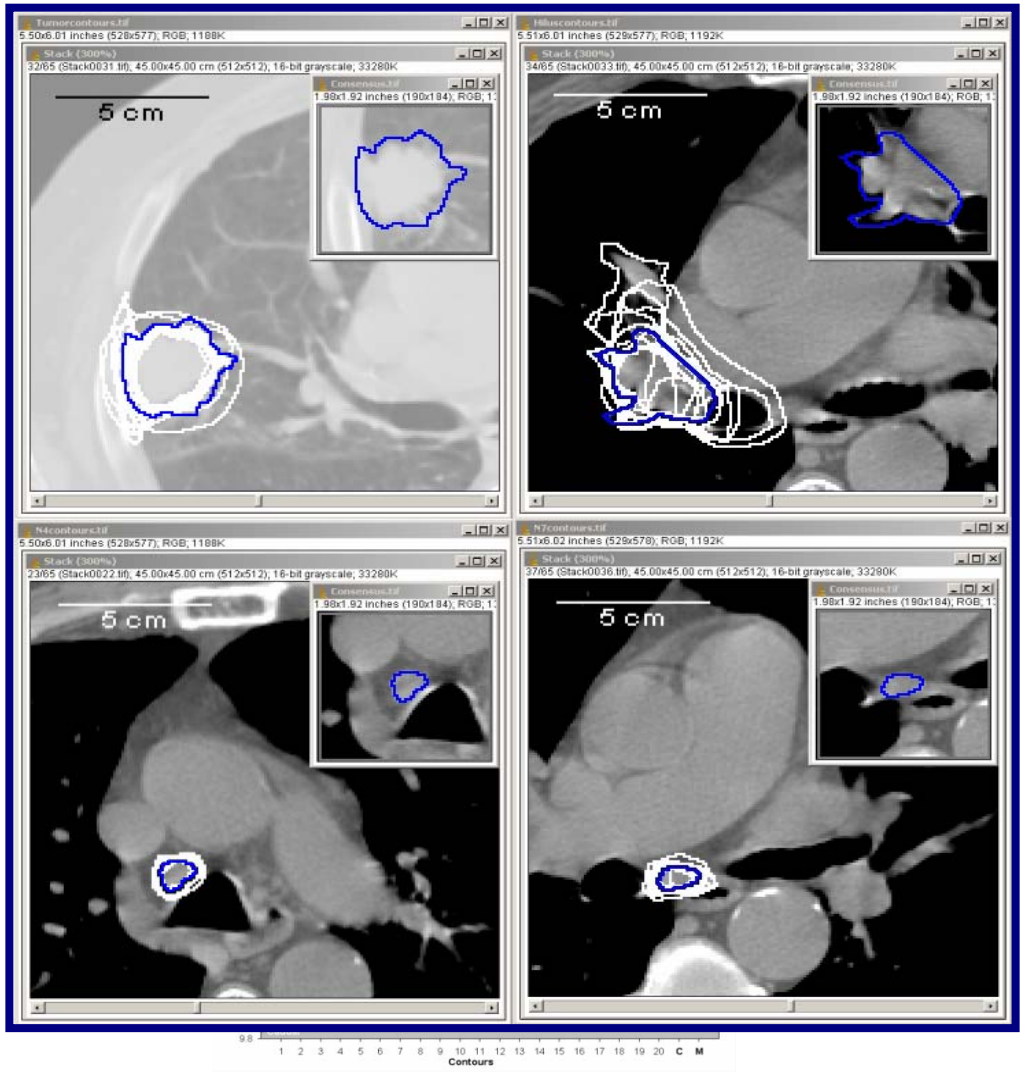
Mediastinal setting *(click sequentially on 'Image, Adjust and Window/Level' and then adjust the settings to* ***L = 33780 and W= 606)***

An enlarged pre-carinal node is present on the right side of the mediastinum (clearly visible on images 24-25).

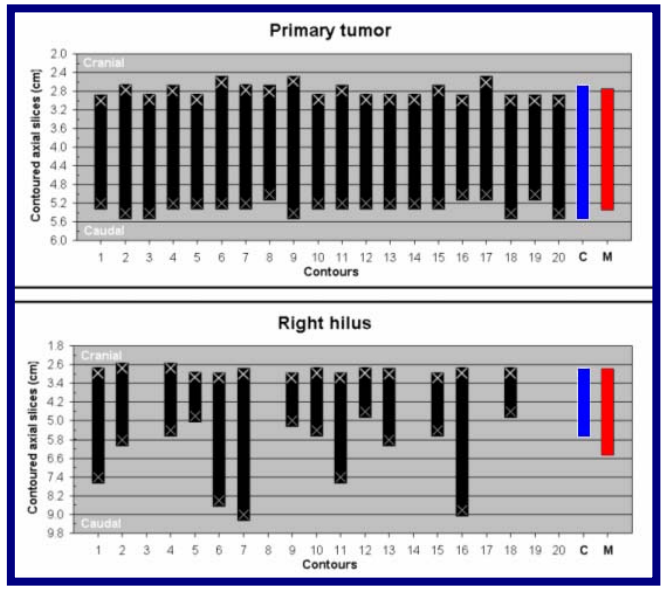
A subcarinal node, with a short-axis diameter of 1.3 cm, is present to the right of the esophagus (clearly visible on images 35).

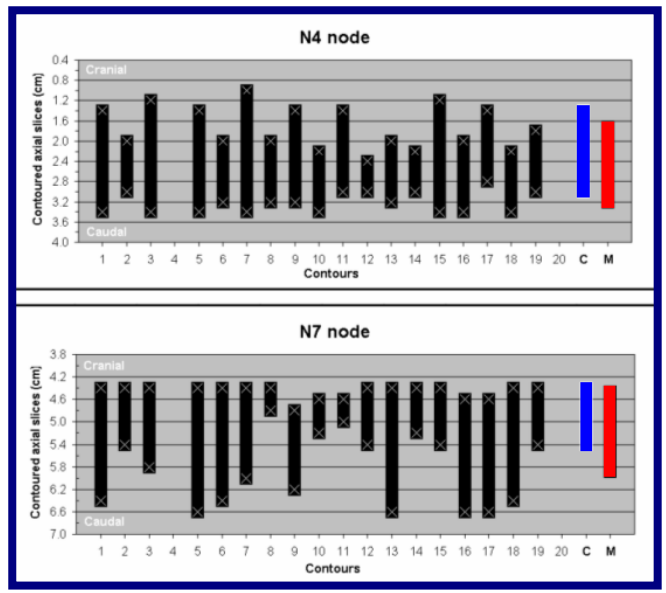


Results



Topographic inspection of targets

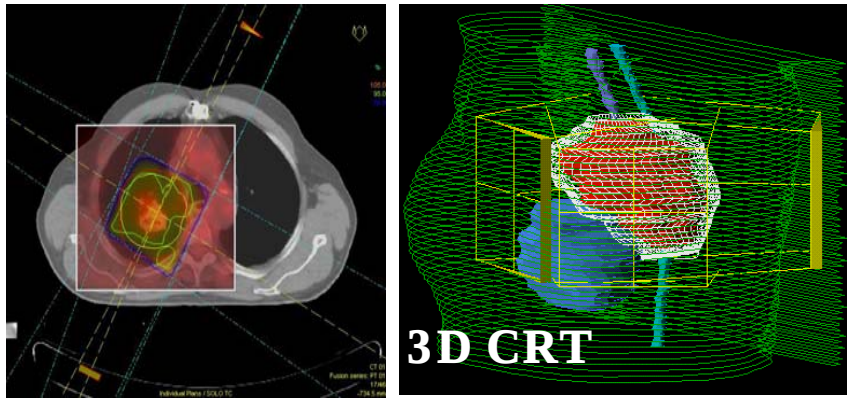




Advances to limit target definition variability and to improve tumor coverage

INT 0139 (Albain '05)

-Stage IIIA-N2 NSCLC –
Chemo-Radiotherapy followed by Surgery not superior to definitive Chemo-Radiotherapy

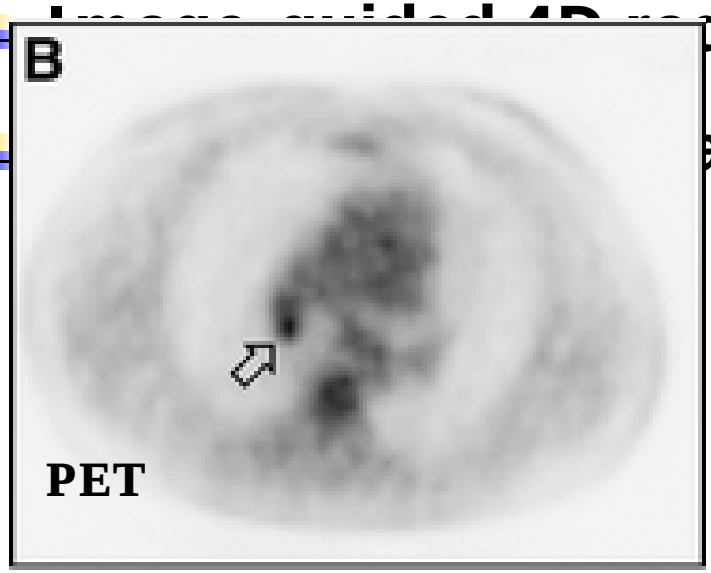


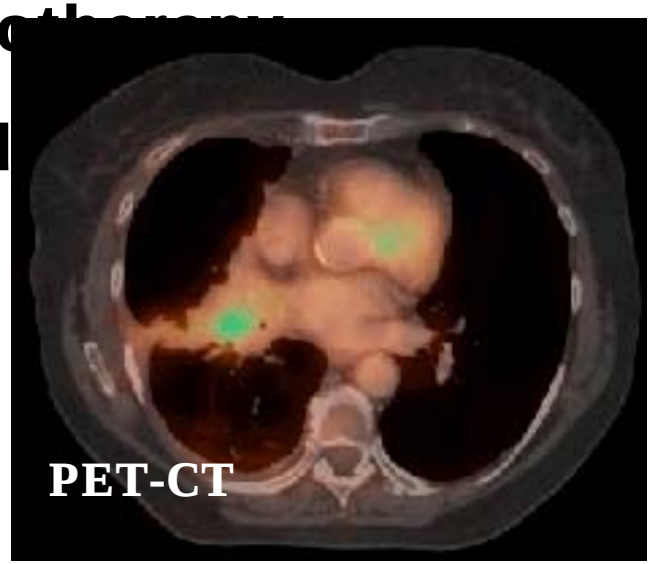
19% incidence of geographic miss of tumor

"In general, most tumors are radioresistent if they are not in the treatment beam"

Radiotherapy: new developments

- Integration of PET into radiotherapy planning
- Involved-field conformal radiotherapy
- Image-guided 4D radiotherapy
- Dose-escalated radiotherapy





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Radiotherapy and Oncology 55 (2000) 317–324

RADIOTHERAPY & ONCOLOGY

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The impact of ^{18}F-fluoro-2-deoxy-D-glucose positron emission tomography (FDG-PET) lymph node staging on the radiation treatment volumes in patients with non-small cell lung cancer

Luc J. Vanuytsel[a,*], Johan F. Vansteenkiste[b], Sigrid G. Stroobants[c], Paul R. De Leyn[d], Walter De Wever[e], Eric K. Verbeken[f], Giovanna G. Gatti[a], Dominique P. Huyskens[a], Gerald J. Kutcher[a]

[a]*Department of Oncology (Section Radiotherapy), University Hospital Gasthuisberg, Herestraat 49, B-3000 Leuven, Belgium*
[b]*Department of Pulmonology (Section Respiratory Oncology), University Hospital Gasthuisberg, Herestraat 49, B-3000 Leuven, Belgium*
[c]*Department of Nuclear Medicine, University Hospital Gasthuisberg, Herestraat 49, B-3000 Leuven, Belgium*
[d]*Department of Thoracic Surgery, University Hospital Gasthuisberg, Herestraat 49, B-3000 Leuven, Belgium*
[e]*Department of Radiology, University Hospital Gasthuisberg, Herestraat 49, B-3000 Leuven, Belgium*
[f]*Department of Pathology, University Hospital Gasthuisberg, Herestraat 49, B-3000 Leuven, Belgium*

Received 25 August 1999; received in revised form 8 December 1999; accepted 17 December 1999

- 105 NSCLC pts

Imaging studies including PET and CT scans, and a precise surgical mapping

- 73 pts with LN's thought to be positive on CT and/or PET, and for whom pathology data of all the suspected LN's were available, were used

- A total of 988 lymph node stations were available for review

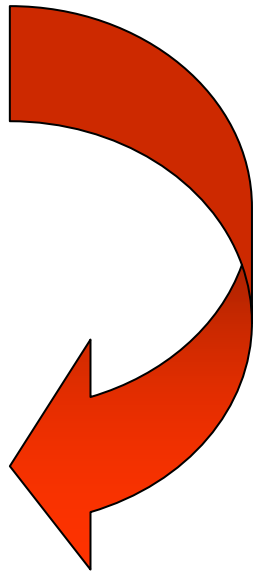
LN's were considered as positive for metastatic disease if they were equal to or larger than 1.5 cm at their maximal cross-sectional diameter

Vanuytsel, Rad.Oncol, 2000

	Node pathology	
	Benign (N^a)	Malignant (N^a)
Not enlarged on CT		
PET negative	839	20
PET positive	6	27
Enlarged on CT		
PET negative	40	5
PET positive	14	37
Totals	899	89

[a] *N*, number of lymph node stations.

Data of CT and PET in the assessment of 988 lymph node levels

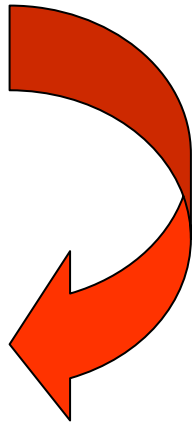


Overall accuracy for CT was 89% (887/988) vs. 95% (943/988) for PET (p<0.001)

Vanuytsel, Rad.Oncol, 2000

	CT		PET-CT	
	Included	Not included	Included	Not included
Group A (PET-CT < CT)	26	3	25	4
Group B (PET-CT > CT)	1	15	12	4
Group C (PET-CT = CT)	28	0	28	0
Totals	55	18	65	8

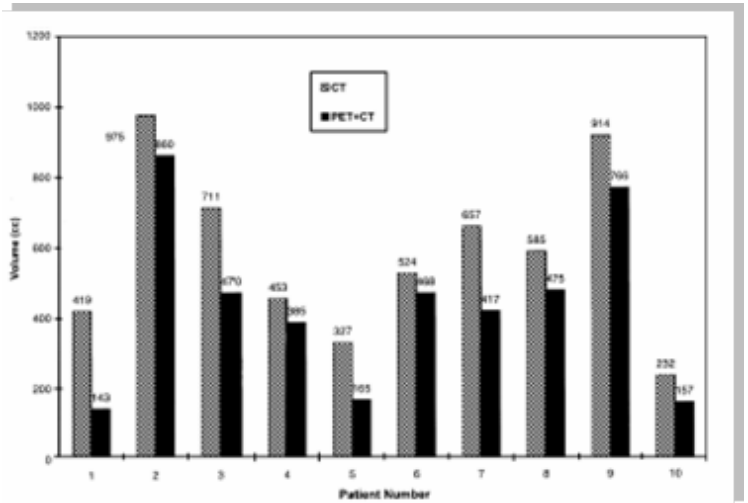
The number of patients in group A to C in whom all tumour would be included by the GTV according to the CT data or the PET-CT data



A GTV limited to LN's considered positive on CT alone, would include all pathological nodes in 55 out of 73 pts (75%).

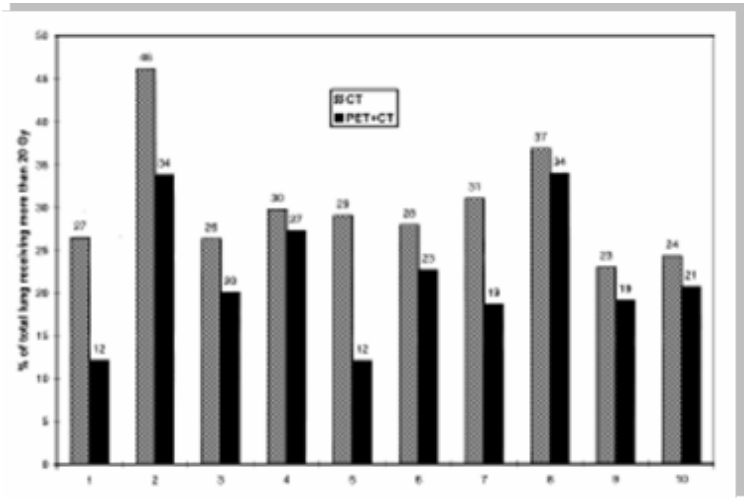
Using PET-CT data, inclusion of the pathological node would be obtained in a significantly larger number of pts, 65 out of 73 pts or 89% (p<0.005)

Vanuytsel, Rad.Oncol, 2000



PTV volume for all ten pts based on the CT and PET-CT data

- **The CT-PTV for the ten patients studied, ranged between 232 and 975 cc, the PET-CT-PTV between 143 and 860 cc.**
- **The target volume based on the PET-CT data was 29±18% (± 1 SD) smaller than the volume based on the CT data (p= 0.002).**



V20 Gy for the CT and PET-CT treatment plan for all ten pts

- **The percentage of V20 Gy was on an average reduced by 27±18% (±1SD) from 1107 to 787 cc (p< 0.001) with a minimum reduction of 8% and a maximum reduction of 59% from the CT treatment plan to the PET-CT treatment plan**

Vanuytsel, Rad.Oncol, 2000

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RADIOTHERAPY & ONCOLOGY

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The impact of ^{18}F-fluoro-2-deoxy-D-glucose positron emission tomography (FDG-PET) lymph node staging on the radiation treatment volumes in patients with non-small cell lung cancer

Luc J. Vanuytsel[a,*], Johan F. Vansteenkiste[b], Sigrid G. Stroobants[c], Paul R. De Leyn[d], Walter De Wever[e], Eric K. Verbeken[f], Giovanna G. Gatti[a], Dominique P. Huyskens[a], Gerald J. Kutcher[a]

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[f]*Department of Pathology, University Hospital Gasthuisberg, Herestraat 49, B-3000 Leuven, Belgium*

Received 25 August 1999; received in revised form 8 December 1999; accepted 17 December 1999

Conclusions

PET-CT improves the accuracy of the assessment of lymph node stations and can modify radiation treatment field in a substantial number of pts, minimizing the risk of geographical misses, while keeping the volume of normal tissues irradiated as low as possible

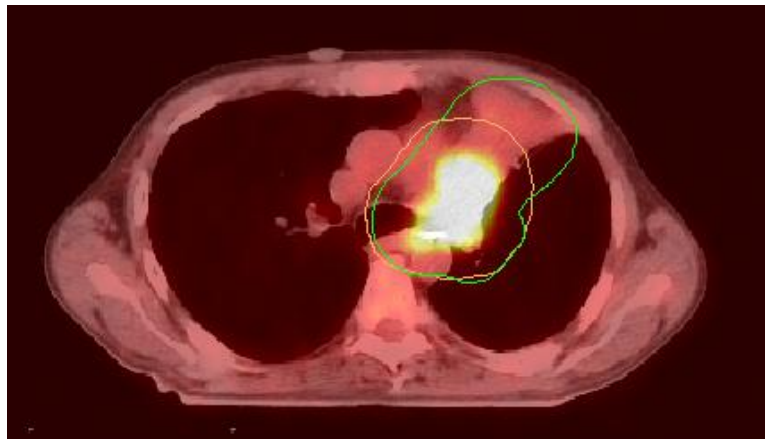
Vanuytsel, Rad.Oncol, 2000

CT

•The sensitivity of CT imaging is low for determining the extent of the nodal disease. Sensitivity and specificity for mediastinal staging is 57% and 84% respectively (Toloza et al.)

• CT assisted volume definition remains the gold standard for XRT

PET



• The sensitivity of PET imaging is high for determining the extent of the nodal disease. Sensitivity and specificity for mediastinal staging is 84% and 89% respectively (Toloza et al.)

• PET provides information on biologically active tumor tissue

Multidimensional conformal Radiation Therapy (BTV)

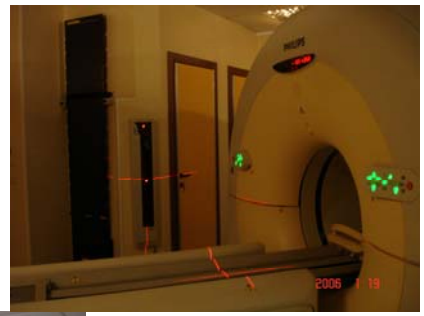
CT-PET based on-line Virtual Simulation Protocol

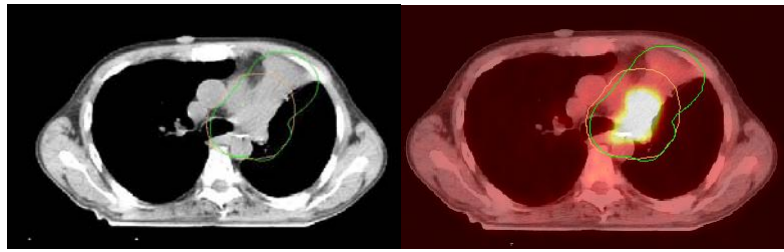
Immobilizzation system. Patients are placed on the PET/CT machine, which is customized with a flat-top taple

Three cross laser pointers integrated with the machine for simulation purpose

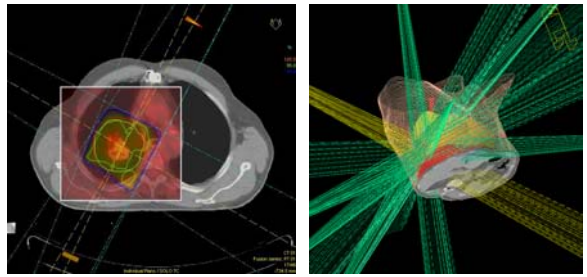
CT-PET scanning

Volumetric data

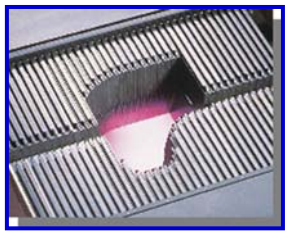




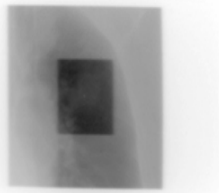
GTV/PTV/OAR
Beam arrangement



3D dose calculation/
evaluation/optimization
3D Beam arrangement



MLC - DRR
Plan documentation



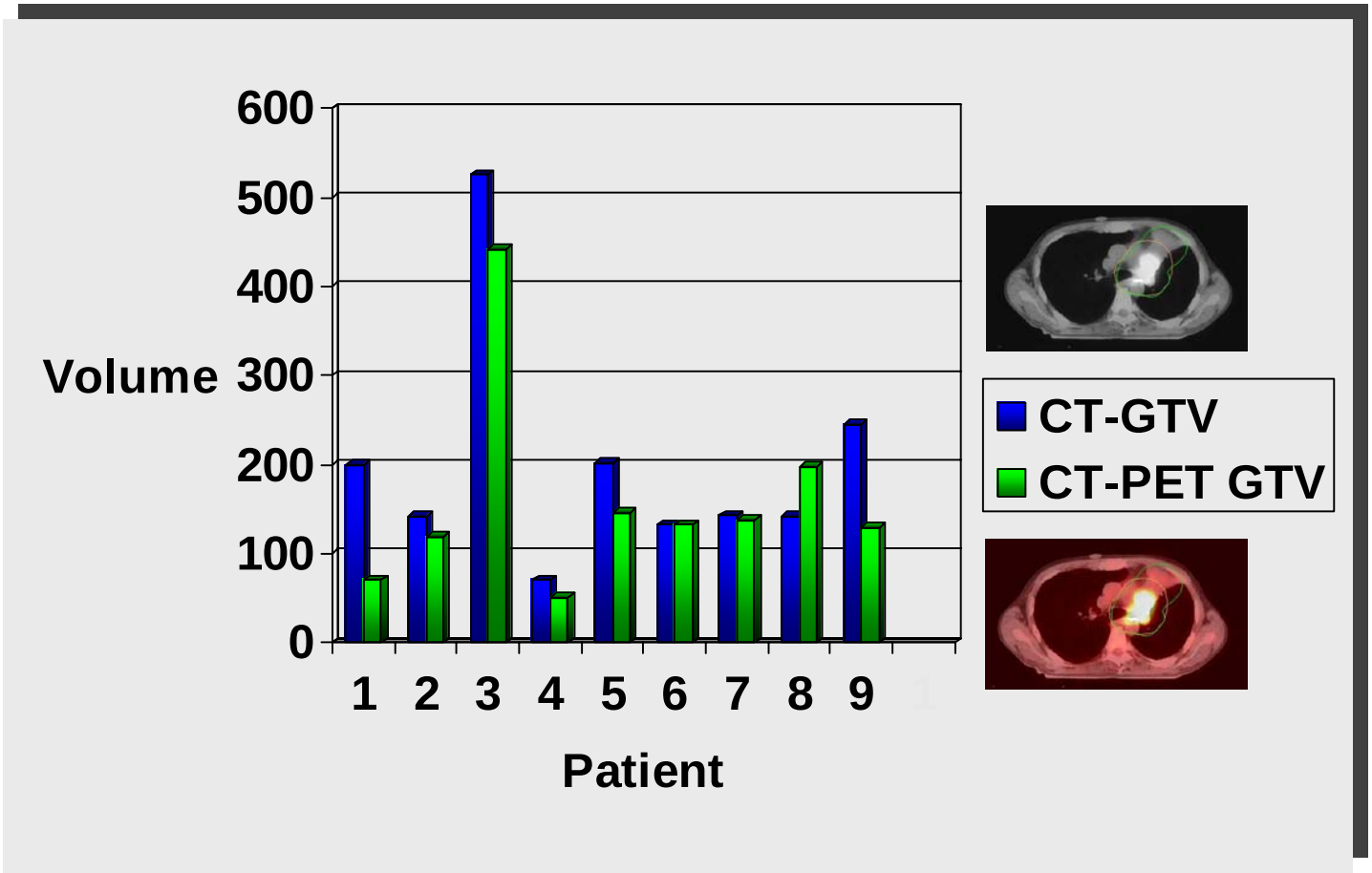
DRR | DPI

Radiograph verification

MU calculation
Treatment record/verify
On-line portal imaging

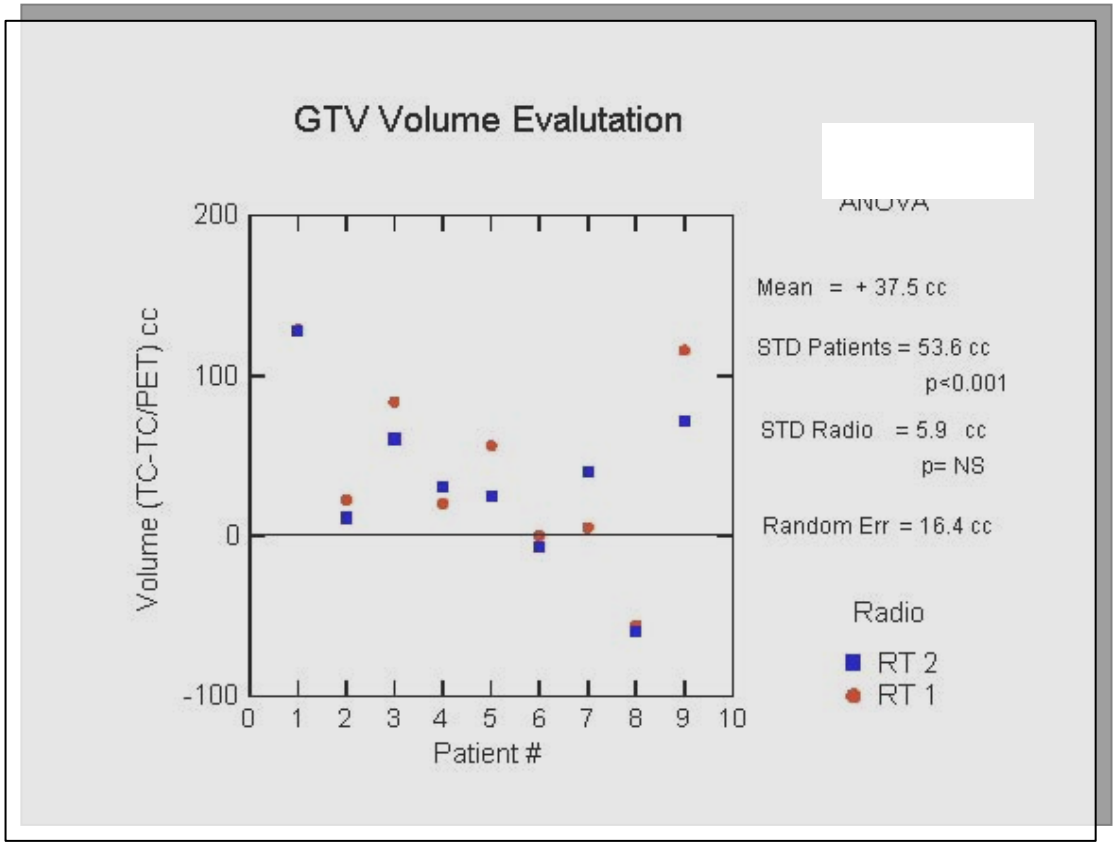
Patient characteristics

Patient	Age	Sex	Stage	Prior chemotherapy	Dose of radiation
1	63	M	cT2N2(IIIA)	yes	66 Gy
2	69	M	cT2N2(IIIA)	no	63 Gy
3	69	M	cT3N2(IIIA)	yes	66 Gy
4	69	M	cT2N2(IIIA)	yes	63 Gy
5	49	M	cT4N2(IIIB)	yes	66 Gy
6	69	M	cT2N2(IIIA)	yes	66 Gy
7	67	M	cT2N2(IIIA)	yes	64 Gy
8	62	M	cT4N2(IIIB)	yes	66 Gy
9	64	M	cT4N0(IIIB)	no	60 Gy
10	53	F	cT3N2(IIIA)	yes	Palliation

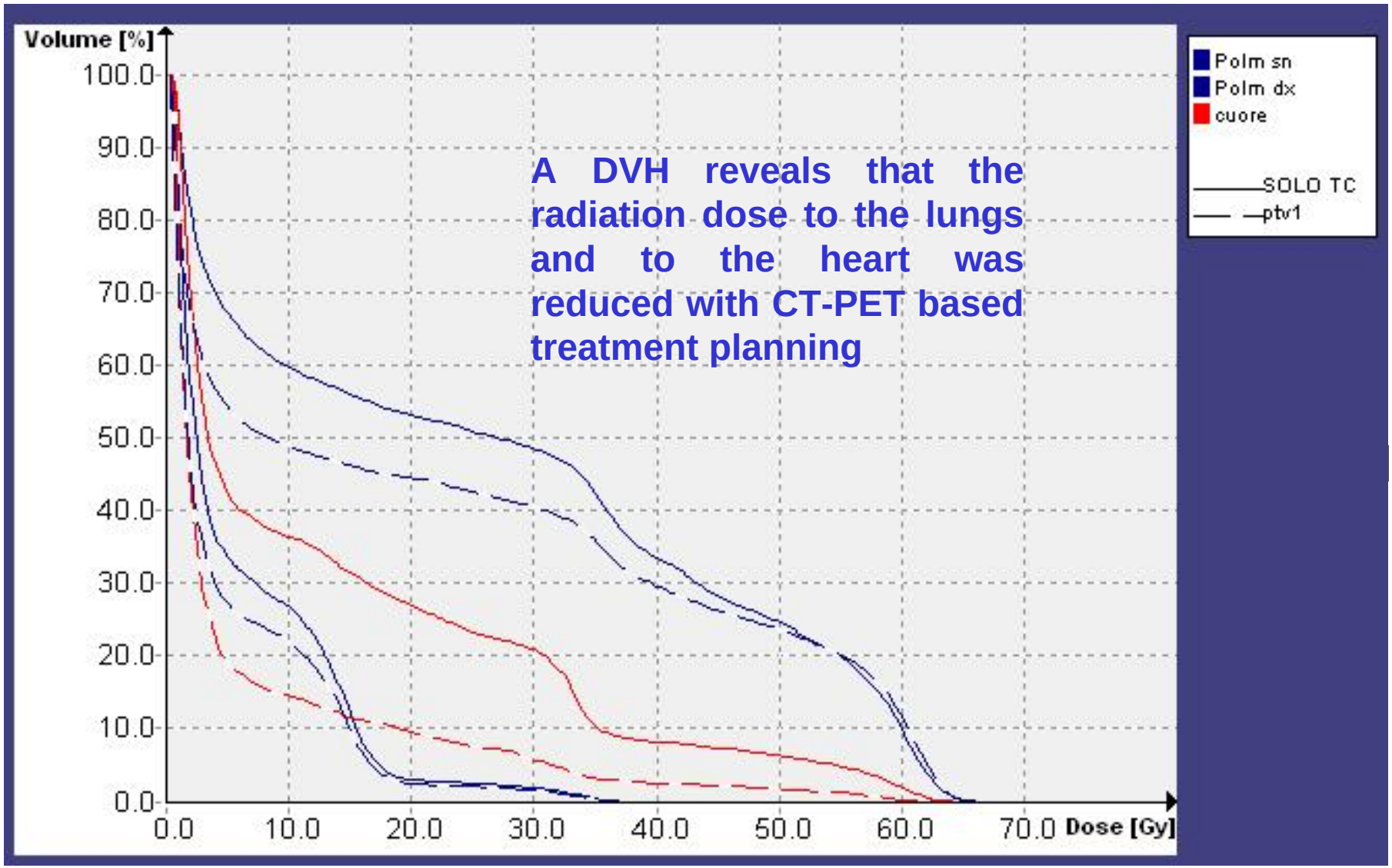


GTV volumes of the patients measured from CT and CT-PET data sets

Analysis of alterations in target volumes



Three-dimensional treatment planning of both datasets



^{18}FDG-PET in NSCLC RTP

- There are two possible consequnces of altered stage following PET for RT planning
- Upstaging due to previously undetected node involvement, which occurs in 10-25% of patients, translates into a larger GTV
- Smaller GTV due to exclusion of CT suspicious but PET negative nodes, noted in 15-35% of patients, may allow for dose escalation
- Vanuytsel study, as well as the more recent by De Ruysscher, reported a reduction in GTV as a consequnce of ecluding CT suspicious but PET negative nodes from GTV

^{18}FDG-PET in NSCLC RTP

- The question remains whether PET improves the accuracy in delineating the primary lung tumor
- According to the published studies reporting on delineation of primary tumor GTV, when information about node staging is excluded, **the PET derived primary tumor GTV was reported to be smaller in 13-17% of patients**
- This was largely accounted for by the ability of PET to distinguish tumour from uninvolved distant collapse/consolidation
- But, can FDG-PET help in the definition of primary lung tumor in patients without adjacent atelectasis?

Factors affecting Fdg-PET accuracy in delineation of primary lung tumour

- **Tumour edge definition**

No standard value applicable for all patients and techniques for individual thresholding

- **Spatial resolution**

The limited spatial resolution of PET significantly contributes to image blur and this is closely linked to the problem of tumor edge definition

- **Tumour motion**

Breath hold methods cannot be easily transferred to PET GTV acquisition. PET is a protracted procedure and multiple breath holds may not be tolerated by patients with NSCLC

CONTROVERSY SURROUNDING PET/CT PLANNING

Choosing the appropriate treatment planning volume to outline "BTV"

- The region encompassed by the 50% intensity level relative to the tumor maximum intensity

- The region encompassed by the 40% intensity level relative to the tumor maximum intensity

- The region including all areas with a standardized uptake value (SUV) $\geq$ 2.5

.....

CONTROVERSY SURROUNDING PET/CT PLANNING

How to contour treatment volumes on PET/CT images?

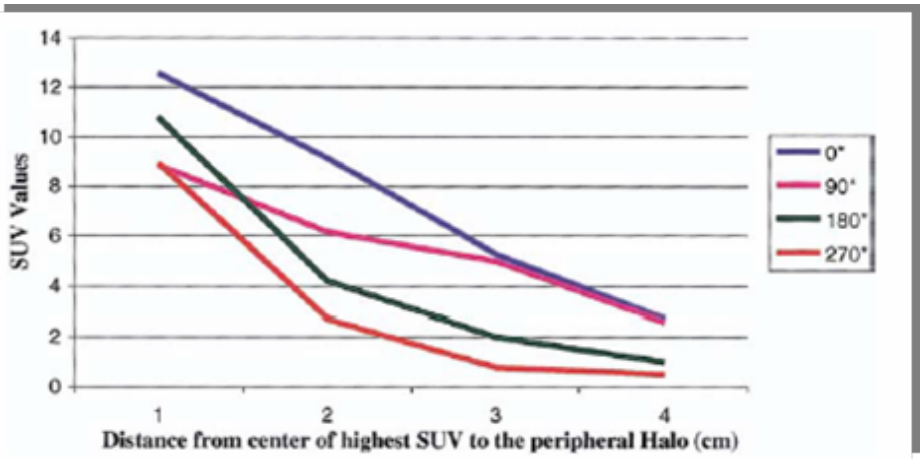
CONTROVERSY SURROUNDING PET/CT PLANNING

Author	# of pts.	Method of contouring	Interobserver variability	Comments
Black *et al.* (21)	Phantom	Regressive SUV function Threshold SUV = 0.307 × mean target SUV + 0.588	N/S	
Bradley *et al.* (14)	24	40% intensity level	N/S	
Mah *et al.* (11)	30	50% intensity level	N/S	Nonintegrated
Nestle *et al.* (7)	34	50% intensity level	N/S	Nonintegrated
Leong *et al.* (19)	15	PET avid disease	N/S	
Loo *et al.* (22)	10	Maximum local gradient magnitude or 50% intensity level	N/S	Gradient method produced closer estimate of gross tumor volume
Ciernik *et al.* (20)	39	Overlay positron emission tomography data on CT	25.7 cm^3 to 9.2 cm^3	
Black *et al.* (21)	Phantom	Regressive SUV function Threshold SUV = 0.307 × mean target SUV + 0.588	N/S	
Bradley *et al.* (14)	24	40% intensity level	N/S	
Ashamalla *et al.* (this article)	19	Halo phenomenon	28.3 cm^3 to 9.12 cm^3	Dose–volume histogram of non–halo PTV covered only 82% of halo PTV

...Choosing the appropriate treatment planning volume to outline...

- Halo phenomenon in different color maps -

A “halo” was identified by its distinct color at the periphery of the maximal areas of SUV uptake



Decline of SUV throughout the target in the 4 coordinates (90°,180°,270°,360°)

A steady decline of SUV was noted peripherally until SUV levels of 2 coinciding with the observed halo region.

Ashamalla, IJROBP, 2005

...Choosing the appropriate treatment planning volume to outline...

- Halo phenomenon in different color maps -

A “halo” was identified by its distinct color at the periphery of the maximal areas of SUV uptake

This halo was always included in the contoured GTV-Anatomic Biologic Contour

The use of 50% or 40% intensity levels may result in missing area at risk

Ashamalla, IJROBP, 2005

Positron Emission Tomography for target volume definition in the treatment of NSCLC

Take Home Messages

- **FDG-PET is useful in defining nodal extension for Radiotherapy in lung cancer**

- **In the absence of atelectasis adjacent to the primary tumour, there is no evidence to suggest that PET helps in the delineation of CT-defined primary lung tumour volume**

- **The impact of PET-based Radiation therapy planning will require evaluation in large-scale prospective studies**

torino 2006™