



Value of FDG-PET-CT in Lung Cancer

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Outline

- Diagnosis (characterization of nodules)
- Initial Staging
 - Tumor
 - Nodes
 - Metastasis
- Restaging after neoadjuvant treatment
- PET in radiation treatment planning

PET in Lung Cancer - Diagnosis

- FDG-PET useful to distinguish benign vs malignant nodules
 - many well documented prospective series
 - Meta-analysis Gould et al; JAMA, 2001
 - sensitivity 96% - specificity 78% - **accuracy 91%**
- Limits
 - sensitivity: subcentimetric nodules – carcinoids- BAC- GGO
Nomori et al; Lung Cancer 2004
 - 136 non-calcified nodules <3cm
 - 20 nodules **<1 cm**: 0/8 cancers true +
 - 101 **solid** nodules 1-3 cm: 57/63 cancers true +
 - 15 **GGO** nodules 1-3 cm: 1/10 cancers true +
 - specificity: inflammatory/granulomatous lesions
 - Use of threshold values (e.g. SUV >2.5) not superior
 - Dual time point imaging

Fluoro-deoxy-glucose positron emission tomography for evaluation of indeterminate lung nodules: assigning a probability of malignancy may be preferable to binary readings

Suk C. Kim Ann Nucl Med (2008) 22:165–170

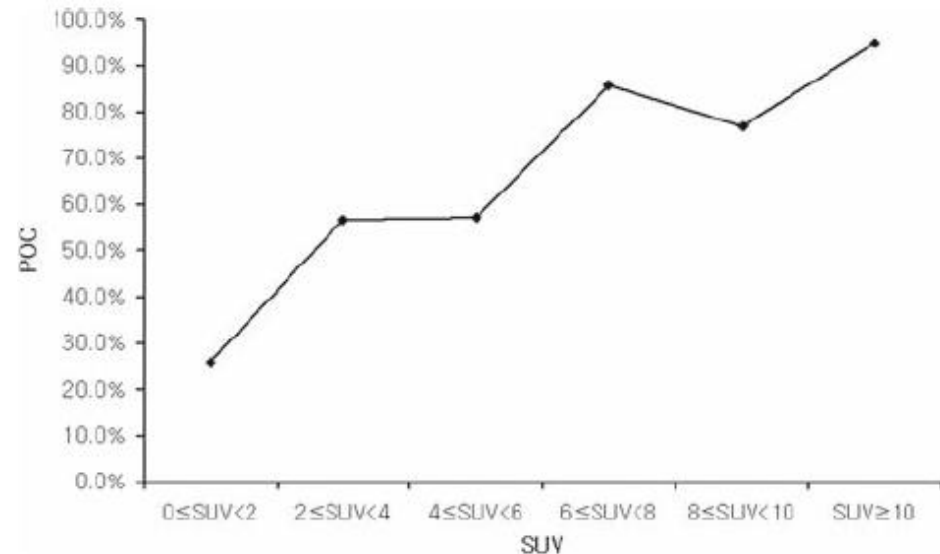
Table 1 Final tissue diagnosis for benign lesions and malignant lesions

Diagnosis	n (%)
Benign (n = 55)	
Inflammation/infection	17 (30.9)
Granuloma	17 (30.9)
Focal fibrosis	3 (5.6)
Hamartoma	3 (5.6)
Unspecified	15 (27.2)
Malignant (n = 103)	
Small cell carcinoma	9 (8.7)
Non-small-cell carcinoma (NSCLC) (n = 83)	
Squamous cell carcinoma	21 (20.4)
Adenocarcinoma	39 (37.9)
Bronchioloalveolar adenocarcinoma	9 (8.7)
Large cell carcinoma	2 (1.9)
Unspecified or mixed NSCLC ^a	12 (11.7)
Metastases	
Carcinoid	3 (2.9)
Lymphoma	1 (1)

^aUnspecified, poorly differentiated non-small-cell carcinoma, or adeno-squamous cell carcinoma

Table 2 The sensitivity and specificity of fluorine-18 fluoro-2-deoxy-D-glucose positron emission tomography (FDG-PET) with the cutoff SUV_{raw} of 2.5 for differentiating benign from malignant pulmonary nodules less than 2 cm and 2 cm or greater in diameter

	Lesion < 2 cm (n = 42)	Lesion ≥ 2 cm (n = 89)	All (n = 131)
Sensitivity (%)	75.0	91.9	89.3
Specificity (%)	72.2	40.7	50.9
Accuracy (%)	73.8	76.4	75.9



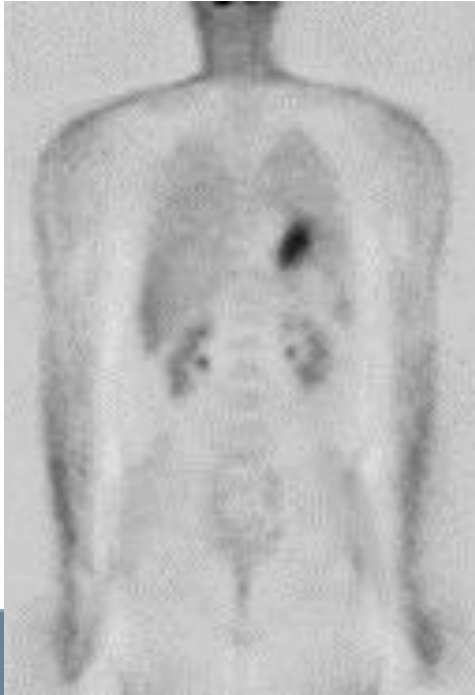
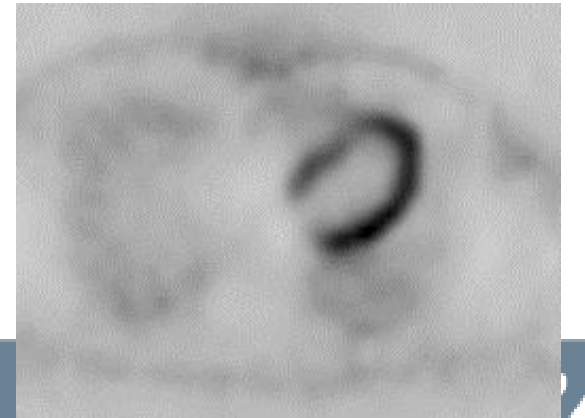
Characterization of SPN

Accidental finding of a SPN in RLL adjacent to the oesophagus.
Bronchoscopy normal; Sputum cytology normal

EUS +FNAC fibroblasts, epithelial cells, benign aspect

PET

Thoracotomie: Hamartoma



PET in Lung Cancer - Diagnosis

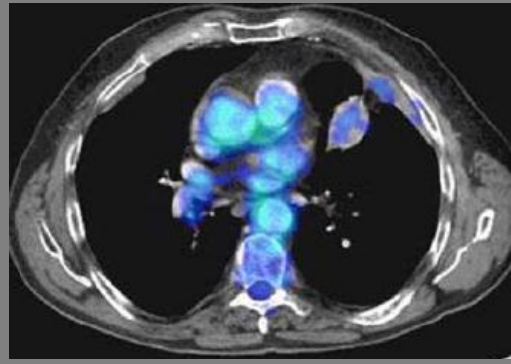
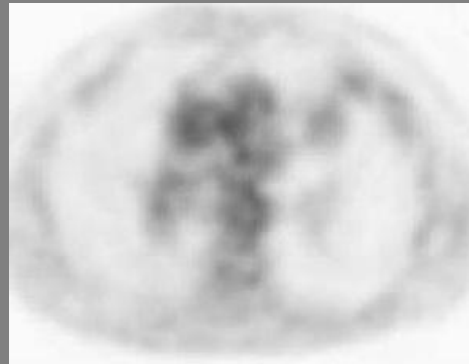
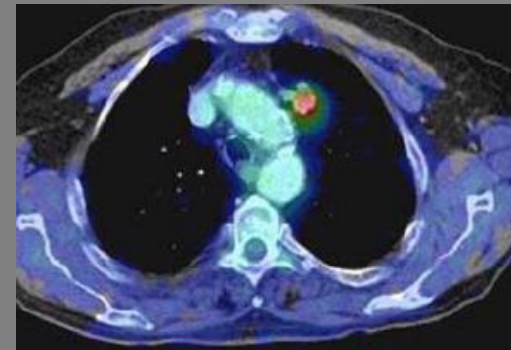
- For lesions > 1 cm without GGO aspect
 - overall good NPV: correct exclusion of malignancy in the vast majority of nodules seen in daily practice
 - surgical procedure can be avoided, repeat XR or CT after 3, 6, 12 and 24 months to confirm absence of growth
- For lesions < 1 cm
 - Negative PET does not exclude malignancy
 - high PPV
- PPV can be disappointing in region with endemic granulomatous disease

Outline

- Diagnosis (characterization of nodules)
- **Initial Staging**
 - Tumor
 - Nodes
 - Metastasis
- Restaging after neoadjuvant treatment
- PET in radiation treatment planning

PET for T- staging

- T-stage depending on size and local extension
 - Limited value of PET due to poor anatomical resolution
 - DD T4 in Lung Ca based on 2 lesions or atelectasis

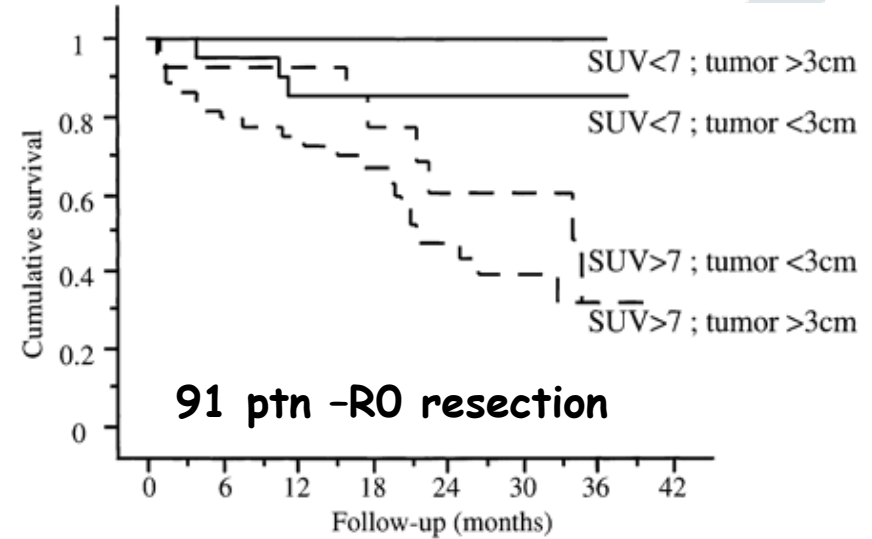
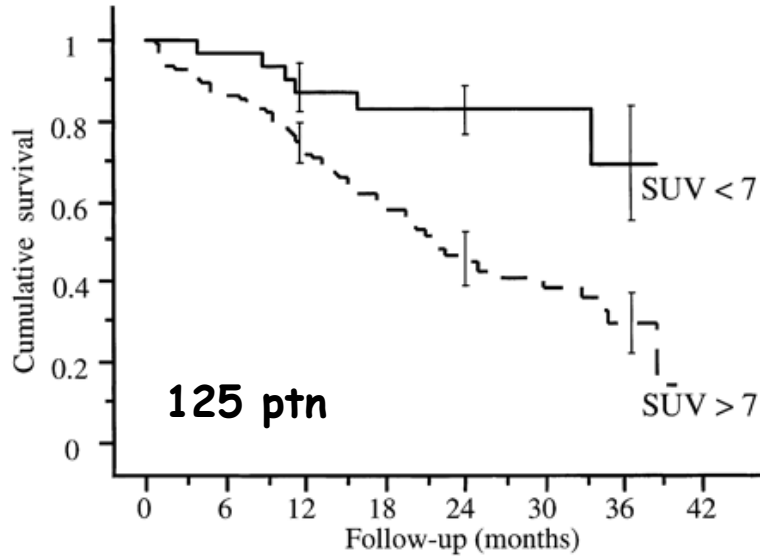


T4 (2 lesions)

T1 + fibrotic mass

FDG uptake as prognostic marker

J Vansteenkiste et JCO 1999; 17: 3201-3206



Can PET guide adjuvant therapy?

- Prospective studies needed

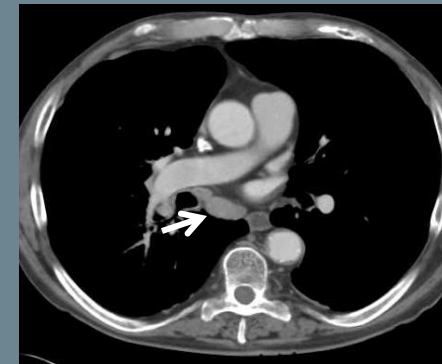
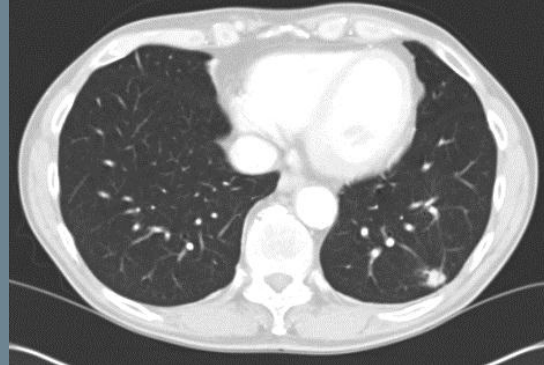
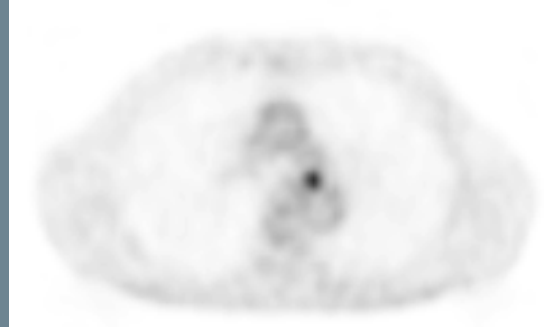
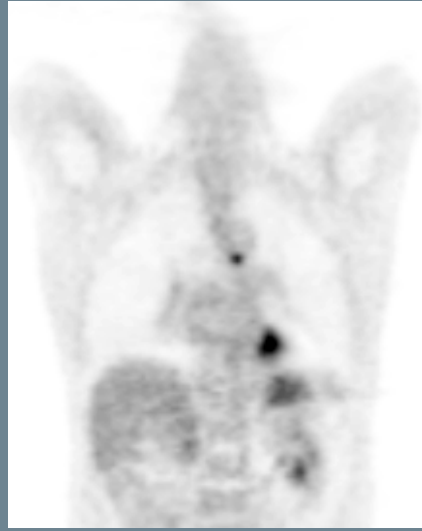
Threshold = center dependent

- Standardization and cross calibration

PET for N-staging

- Diagnosis of metastatic involvement based on increased metabolism
 - Detection of M+ in small LN
 - Exclusion of M+ in inflammatory enlarged LN

PET for N-staging



P

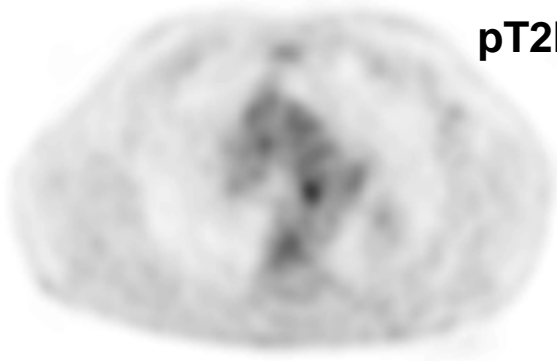
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pT1N2

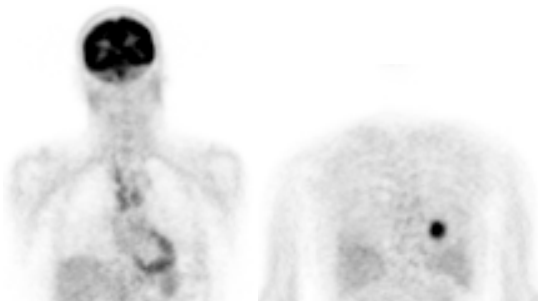
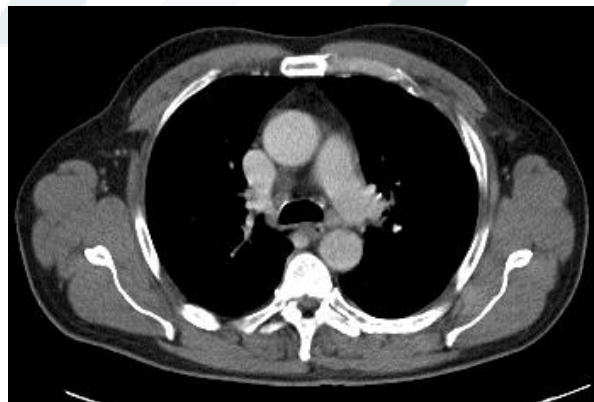
pT1N0

IVE

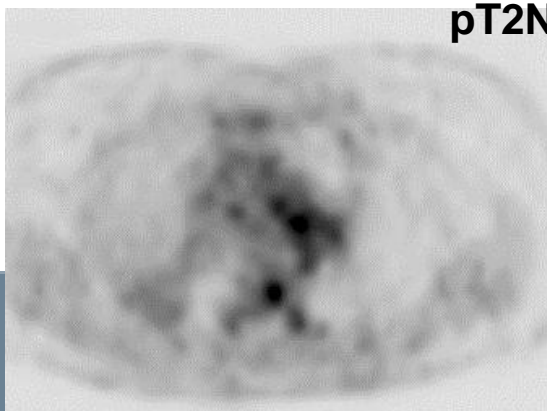
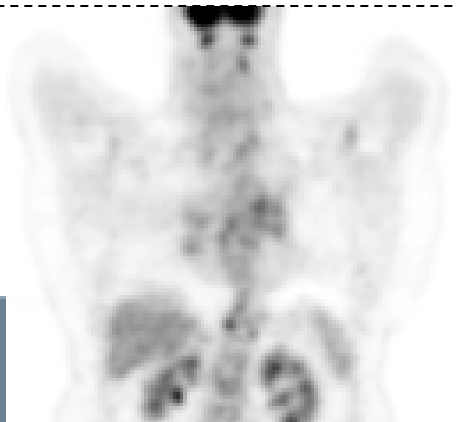
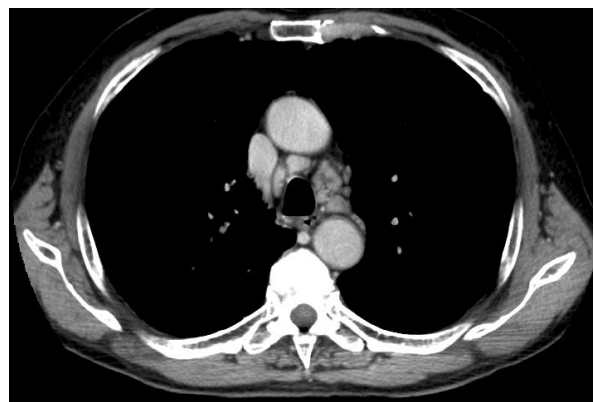
DD malignant vs benign LN



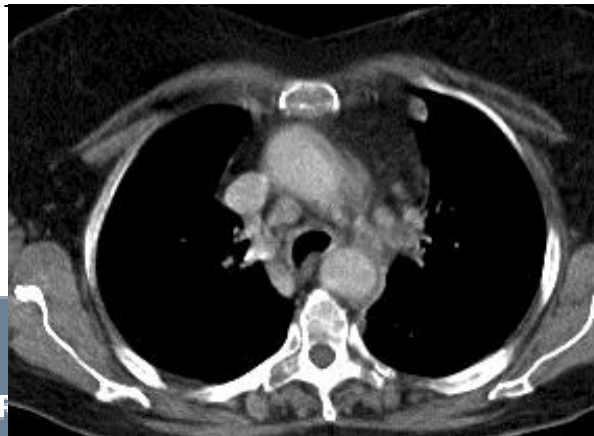
pT2N0



pT1N0



pT2N3



PET for N-staging

- Pitfalls

- Minimal disease → false negative
- Inflammatory disease → false positives
- Limited spatial resolution → N1 vs N2, central T

Impact of size of metastatic foci

Nomori et al, J. Thorac cardiovasc Surg 2004

TABLE 5. Diagnostic results of PET and CT scanning

Variable	PET	CT	Difference
Sensitivity	0.78	0.53	$P = .026$
Specificity	0.98	0.98	0.63
Accuracy	0.97	0.96	0.28
Positive predictive value	0.74	0.70	0.77
Negative predictive value	0.98	0.97	0.08

PET, Positron emission tomography; *CT*, computed tomography.

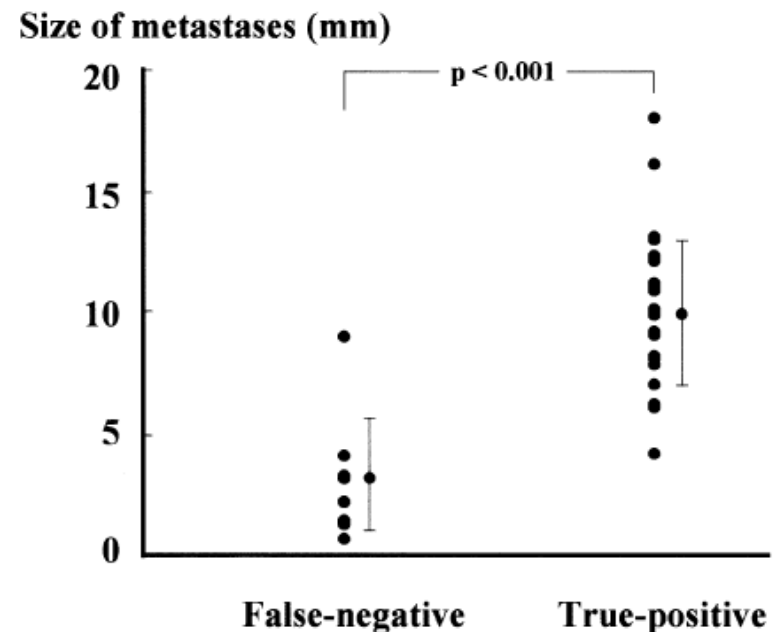


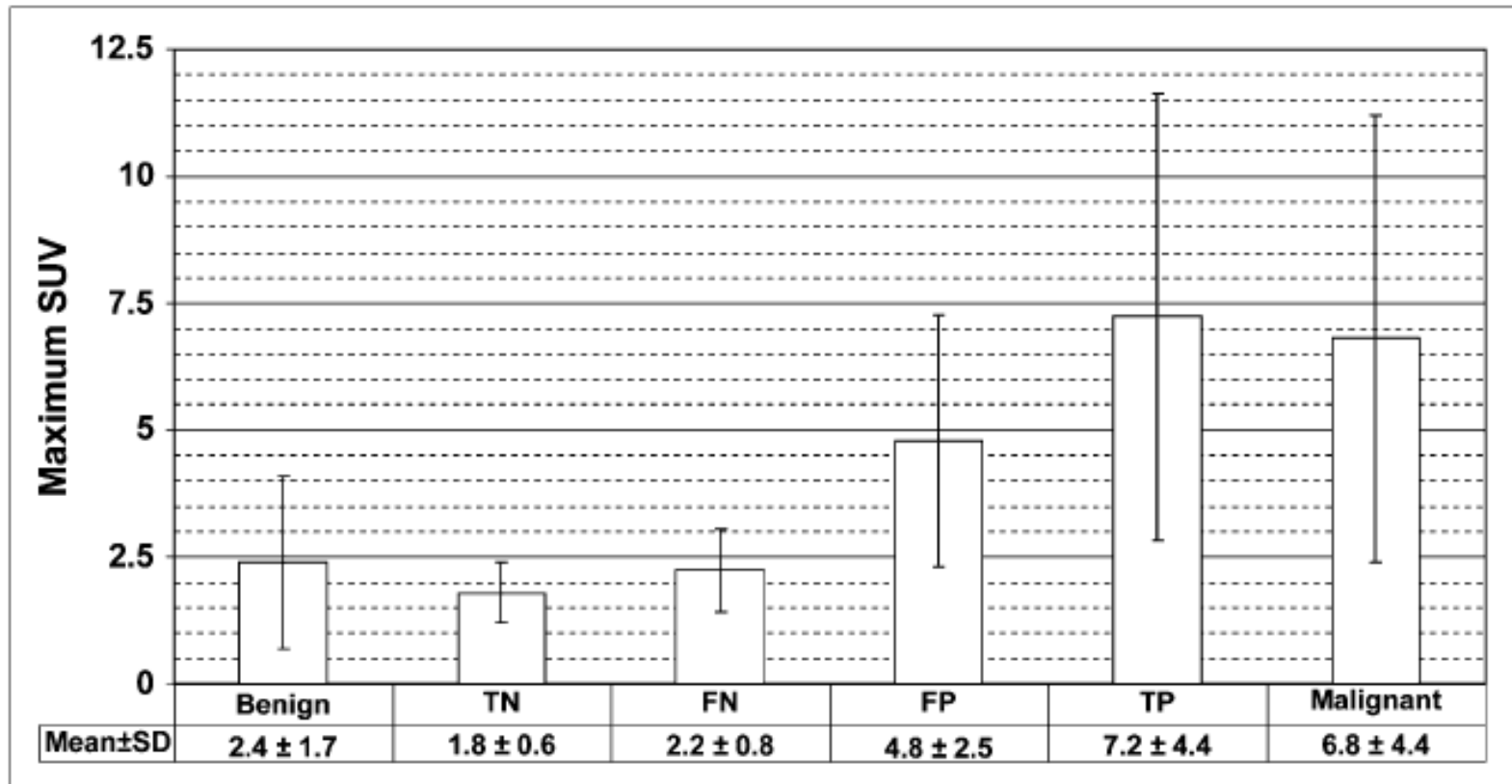
Figure 2. The distribution of sizes of metastatic foci in false-negative and true-positive lymph nodes with PET scan.

Definition of PET+LN

Hellwig et al, JNM 2007

Retrospective analysis of 95 patients with suspected NSCLC and underwent mediastinoscopy and had PET prior to surgery

Comparison of visual analysis (> mediastinal BG) and SUV max LN

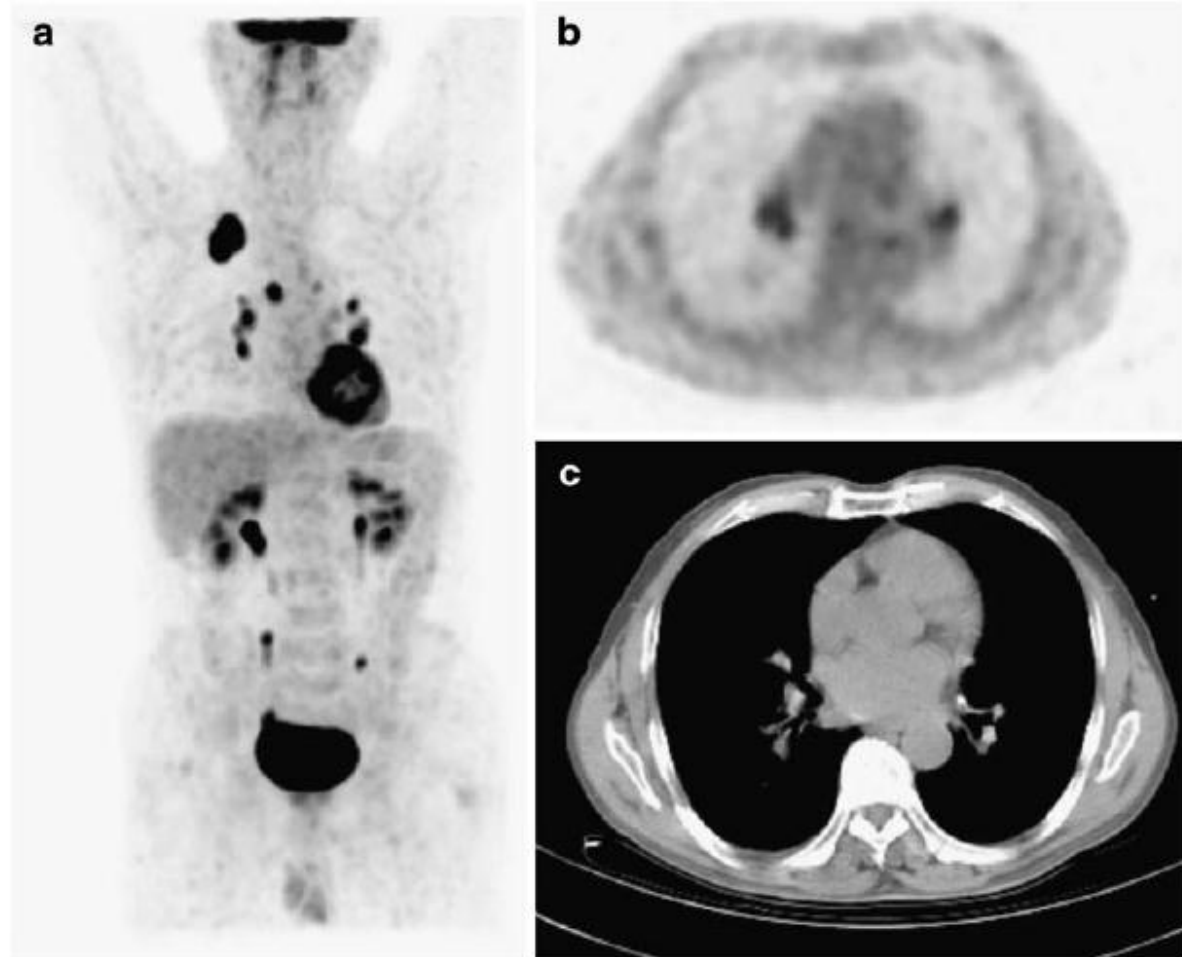


Include “pattern” and CT features in LN characterisation

1800 Lee et al (Korea), PET/CT in TB endemic region

Eur J Nucl Med Mol Imaging (2009) 36:1794–1802

Fig. 4 Typical benign lymph node distribution pattern in a 65-year-old man with right upper lobe squamous cell cancer. **a** Projection image shows multiple bilateral hilar and interlobar lymph nodes with increased FDG uptake. Pathology showed reactive hyperplasia in every lymph node selected. **b** Axial PET image shows bilateral hilar hypermetabolism. **c** Noncontrast CT image shows calcification of bilateral lymph nodes



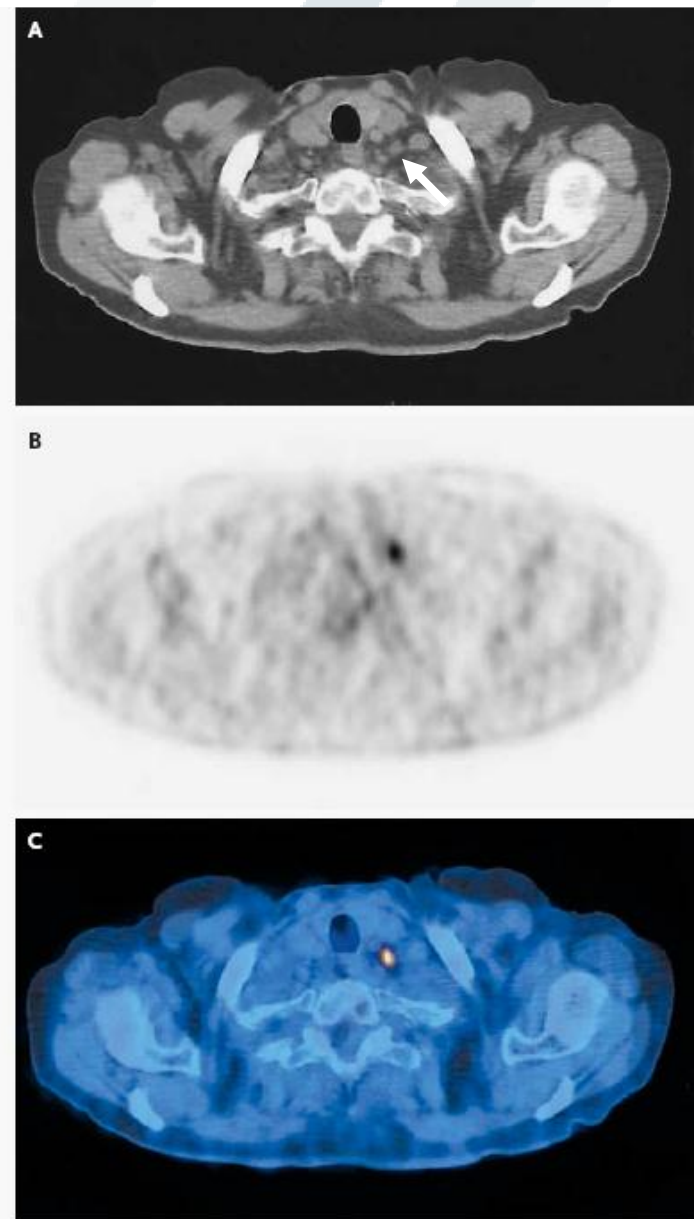
ORIGINAL ARTICLE

Staging of Non–Small-Cell Lung Cancer with Integrated Positron-Emission Tomography and Computed Tomography

Didier Lardinois, M.D., Walter Weder, M.D., Thomas F. Hany, M.D., Ehab M. Kamel, M.D., Stephan Korom, M.D., Burkhardt Seifert, Ph.D., Gustav K. von Schulthess, M.D., Ph.D., and Hans C. Steinert, M.D.

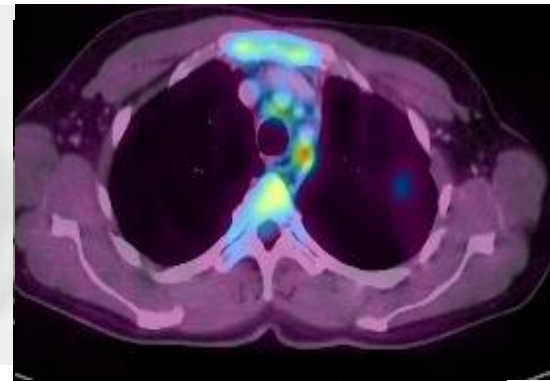
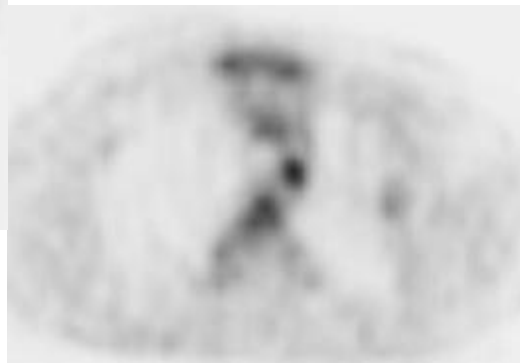
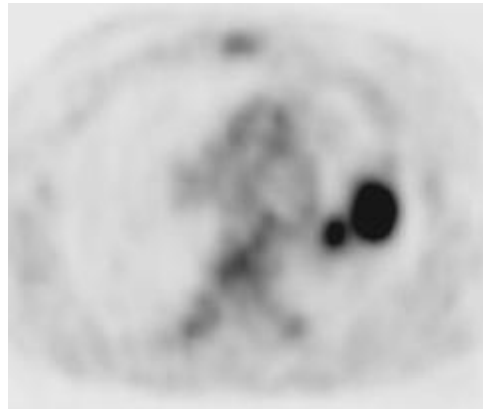
Table 3. Diagnostic Accuracy of the Imaging Methods with Respect to Node Stage in 37 Patients.

Imaging Method	Classification Correct (Score of 3)	Classification Correct	Classification Incorrect
		but Equivocal (Score of 2)	(Score of 0 or 1)
<i>no. of patients (%)</i>			
CT alone	22 (59)	2 (5)	13 (35)
PET alone	18 (49)	14 (38)	5 (14)
Visual correlation of PET and CT	22 (59)	4 (11)	11 (30)
Integrated PET–CT	30 (81)	1 (3)	6 (16)



PET for N-staging

Impact of integrated PET-CT



pT2N1

PET for N-staging

Impact of integrated PET-CT

Lee et al. (Journal of Thoracic and cardioovascular surgery 2007)

Comparison of PET (n=210) and intergrated PET-CT (n=126) with ISS
Definition of PET+ = visual (> mediastinal BG)

TABLE 4. Efficacy of mediastinal staging by PET versus PET/CT

	Standard PET (n = 210)	Integrated PET/CT (n = 126)	P value*
Sensitivity (% , 95% CI)	61.1 (43.5-76.9)	85.7 (67.3-96.0)	.0299
Specificity (% , 95% CI)	94.3 (89.7-97.2)	80.6 (71.4-87.9)	.0005
Positive predictive value (% , 95% CI)	68.8 (50.0-83.9)	55.8 (39.9-70.9)	.2552
Negative predictive value (% , 95% CI)	92.1 (87.2-95.6)	95.2 (88.1-98.7)	.3658
Accuracy (% , 95% CI)	88.6 (87.2-95.6)	81.7 (88.1-98.7)	.0808

PET, Positron emission tomography; CT, computed tomography. CI, confidence interval. *P value for χ^2 test.

TABLE 5. Analysis of operations performed

	Standard PET (n = 210)	Integrated PET/CT (n = 126)
Mediastinoscopy or mediastinotomy (No., %)	33 (16)	25 (20)
Mediastinoscopy followed by thoracotomy (No. %)	51 (24)	44 (35)
Thoracotomy (No. %)	126 (60)	57 (45)

PET, Positron emission tomography; CT, computed tomography. P value for χ^2 test = .029.

PET for N-Staging

Langen et al, Eur J Cardio Thor Surgery 2006

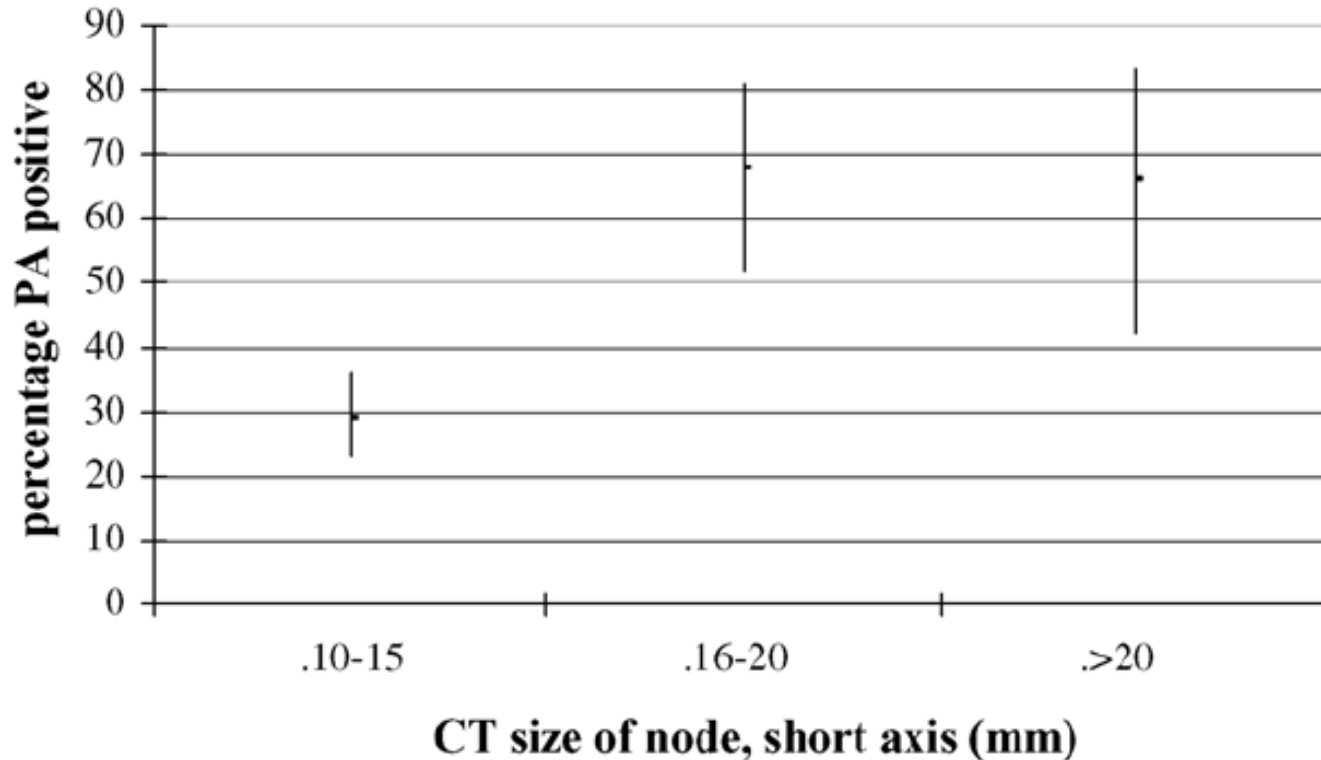


Fig. 2. Pooled values of metastatic involvement of CT-based lymph node size categories (error bars represent 95% CIs).

PET for N-staging

Langen et al, Eur J Cardio Thor Surgery 2006

Table 2

Predicted positive and negative values of FDG-PET in patients with enlarged lymph nodes of different size categories, assuming FDG-PET sensitivity of 91% and specificity of 78% for enlarged nodes [4]

Lymph node size category	NPV (%)	PPV (%)
CT 10–15 mm	95	62
CT 16–20 mm	81	90
CT >20 mm, with outlier	82	90
CT >20 mm, without outlier	80	90

NPV: negative predictive value; PPV: positive predictive value.

PET for N-staging

Predictors of false negative PET

Al-Sarraf et al. (Eur J of cardiothoracic Surgery, 2008)

Retrospective analysis in patients who underwent direct thoracotomy after a negative mediastinal PET-CT and were found to have occult N2 disease

PET+ if SUV max >2.5

N= 153; occult N2 in 25 (16%) especially ATS 7 and 4R

Univariate analyse

Central tumour p=0.049

RUL p=0.040

Enlarged LN on CT p=0.048

PET N1 p=0.006

Histology, T stage, differentiation, SUV max primary p=NS

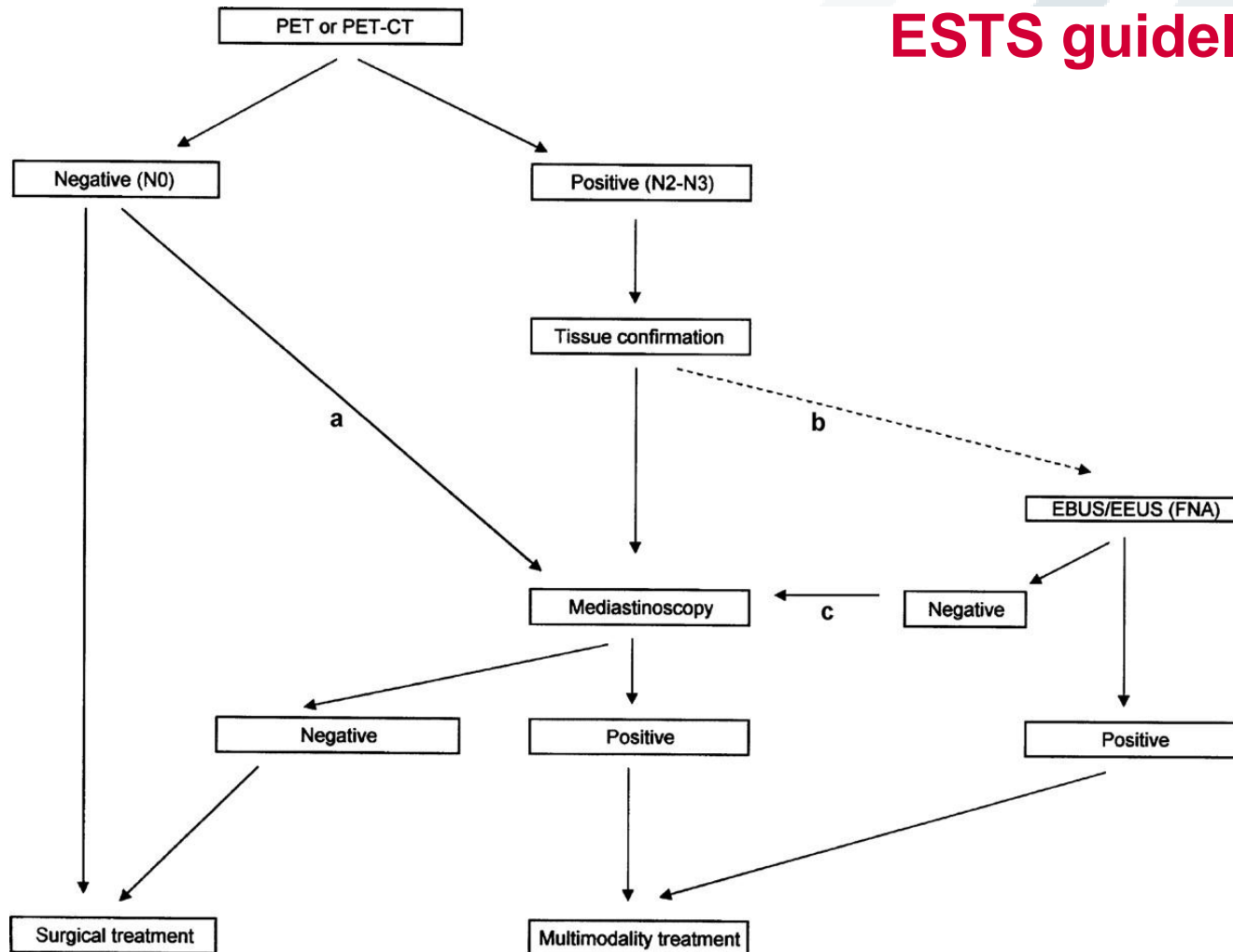
Multivariate analysis

Central T, RUL and PET N1

PET for N- staging

Conclusions

- High NPV of PET-CT in LN staging
 - > omit invasive tests
- BUT “side conditions”
 - adequate FDG-uptake of primary tumour
 - caution with central tumours and hilar N1 disease
 - Large nodes on CT
- Always confirm PET+ nodes histologically
 - PET and EBUS/EUS are complementary



a : In central tumors, tumors with low FDG uptake, tumors with LNs $\geq 1,6$ cm and/or PET N1 disease
invasive staging remains indicated

b : Endoscopic techniques are minimally invasive and can be the first choice

c : Due to its higher NPV mediastinoscopy remains indicated

EUS : endoscopic esophageal ultrasound

EBUS : endobronchial ultrasound

NPV : negative predictive value

N0 : LN < 1 cm

PET for M-Staging

- PET improves conventional staging (CS) ¹
 - detection of lesions missed on CS (5 - 20%)
 - differentiation of lesions equivocal on CS (7 – 19%)
 - caution if lesion < 1 cm !
 - change in overall stage in 27 - 62% (up > down)
- PET impacts on choice of treatment in 25-41% ²
- Never alter treatment based on PET+ only
 - Up to 50% of single lesions are not M+!!! ³

¹ Pieterman et al, N Engl J Med 343:254-261, 2000

² Hicks et al, J Nucl Med 42:1605-1613, 2001

³ Lardinois et al, J Clin Oncol. 23:6846-6853, 2005

PET for M-Staging

Mac Manus et al. Int J. Rad Oncol Biol Phys. 2002

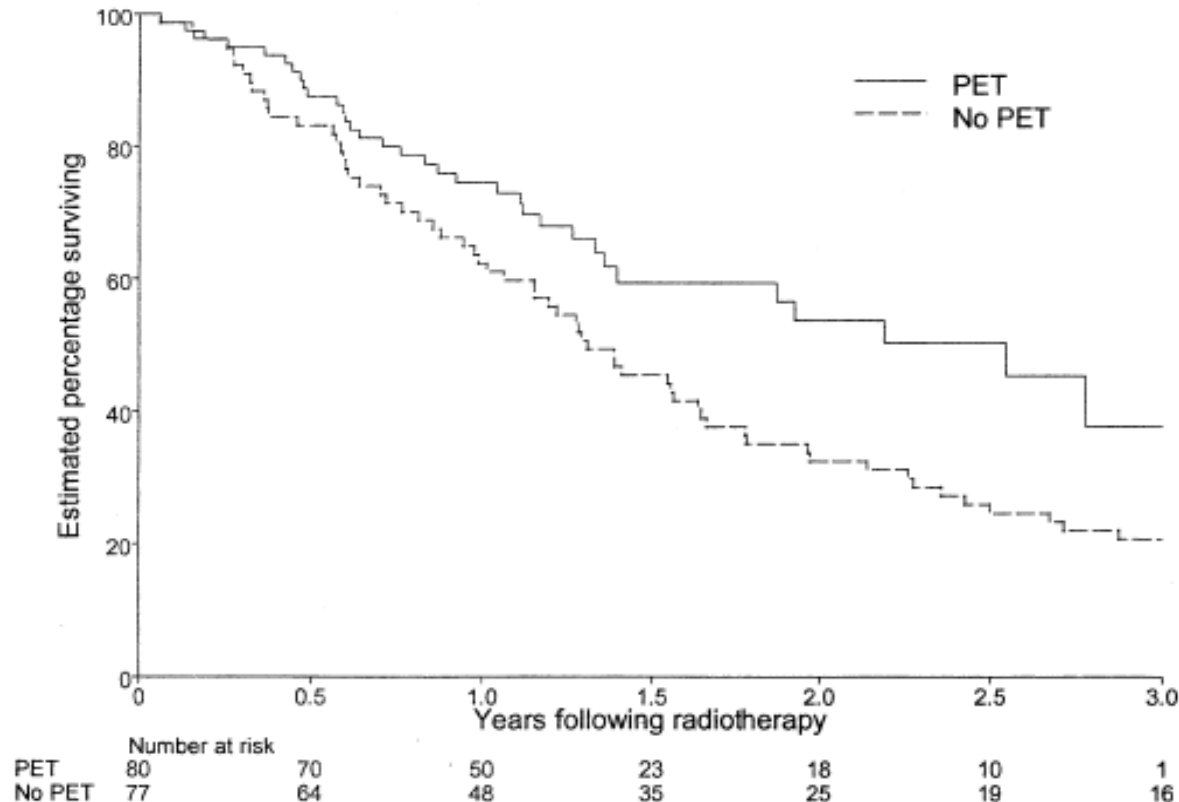
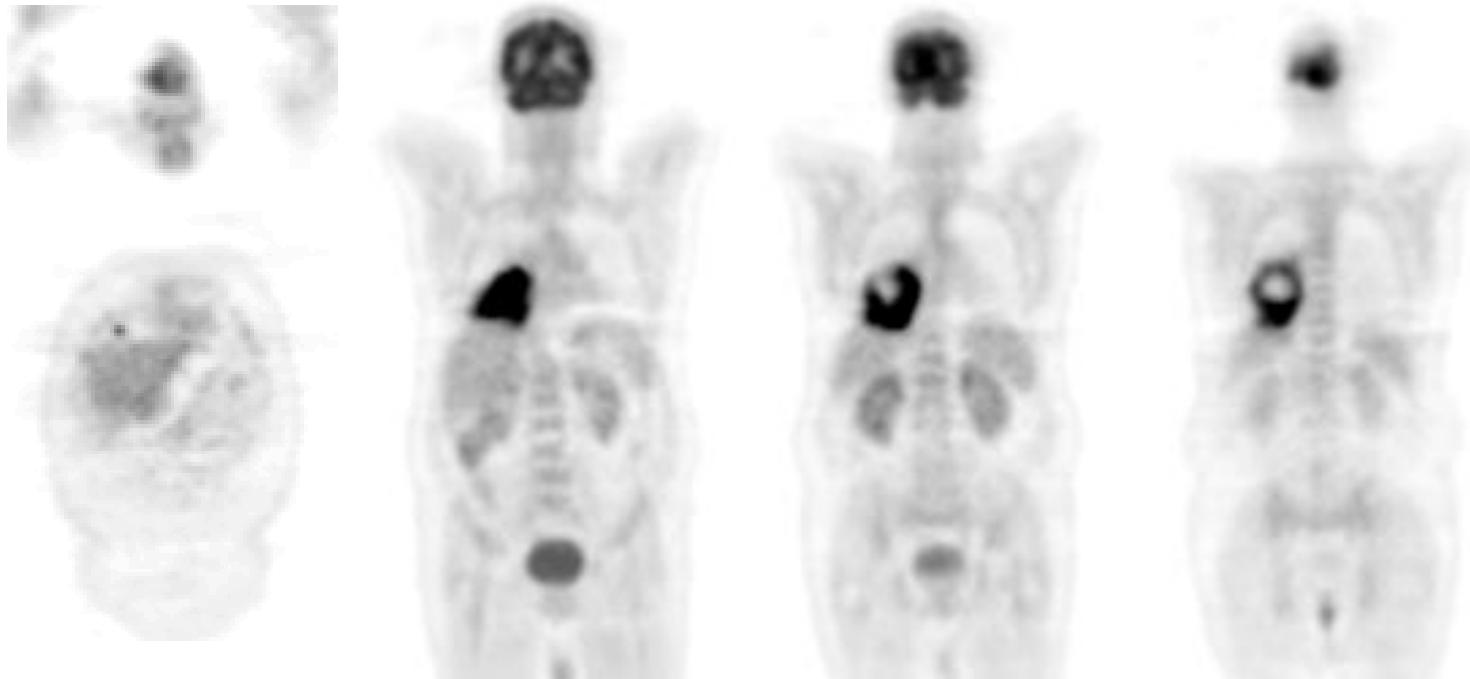
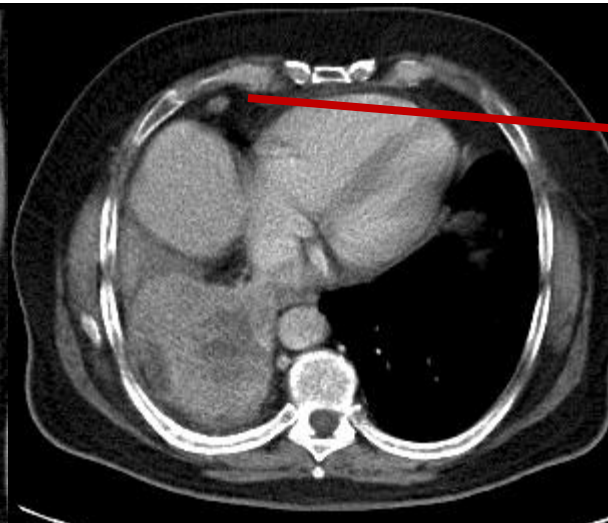
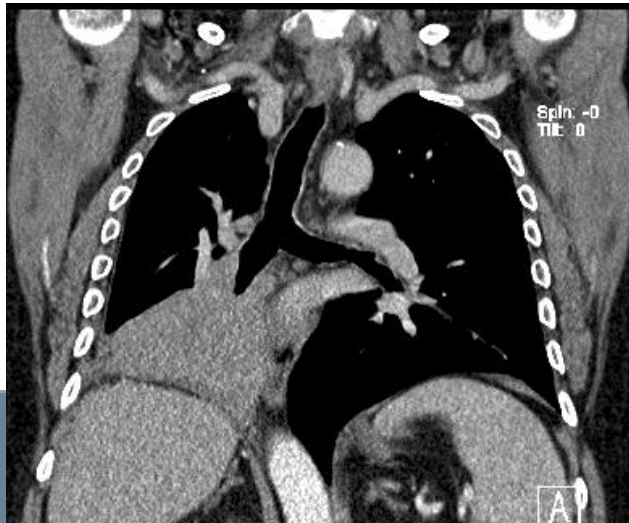


Fig. 2. Comparison of overall survival.

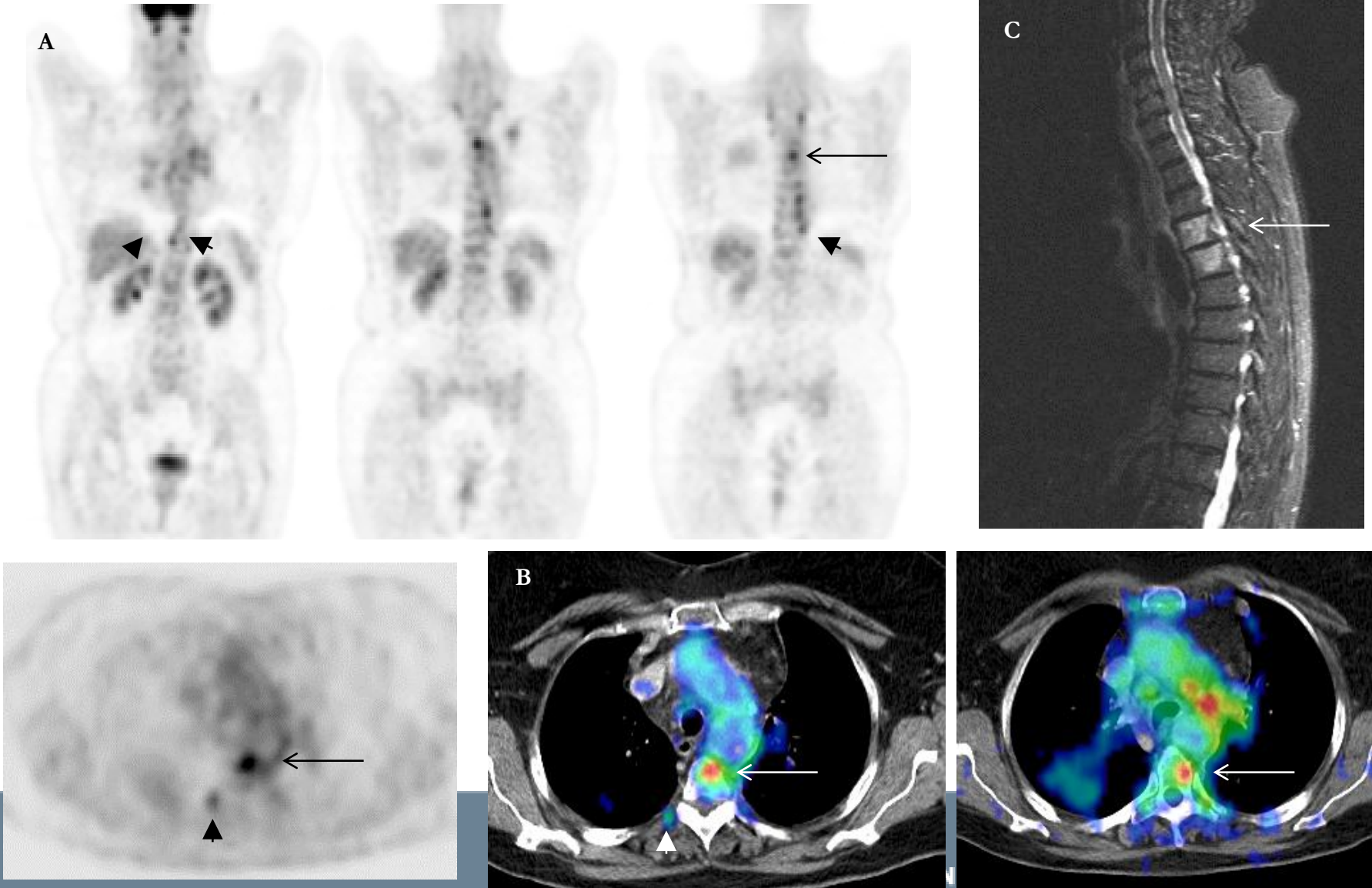
PET for M-Staging



pTx N2 M1



PET for M-Staging



ORIGINAL ARTICLE

Preoperative Staging of Lung Cancer with Combined PET-CT

Barbara Fischer, Ph.D., Ulrik Lassen, Ph.D., Jann Mortens

1. Reduction number of thoracotomies
20/91 (22%) → 38/98 (39%)

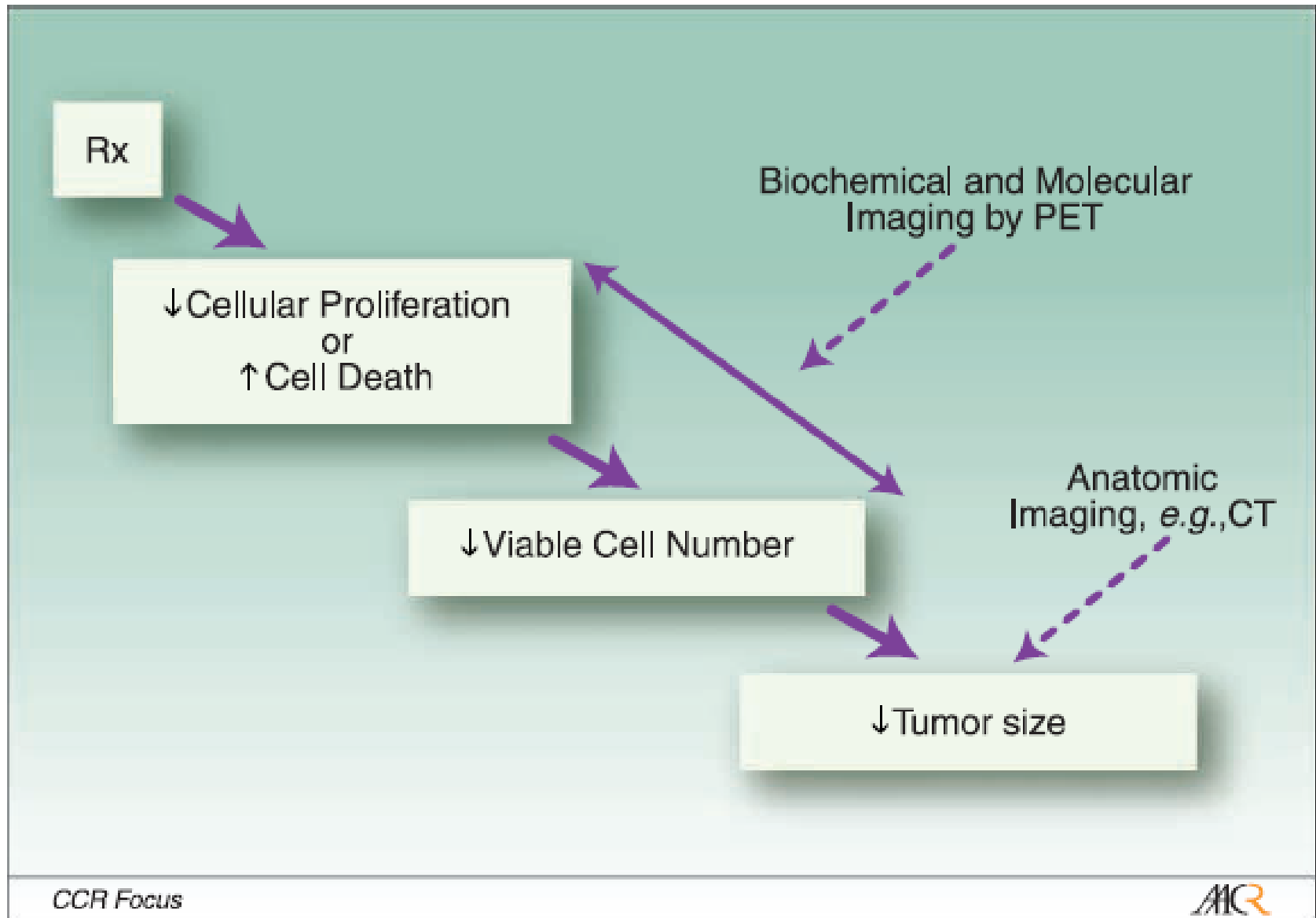
2. Reduction number of futile thoracotomies
21/60 (35%) → 38/73 (52%)

Table 3. Distribution of Futile Thoracotomies.*

Characteristic	PET-CT	Conventional Staging	Total
<i>number (percent)</i>			
Futile thoracotomy			
No	39 (65)	35 (48)	74 (56)
Yes†	21 (35)	38 (52)	59 (44)
Total	60 (100)	73 (100)	133 (100)
Reason that thoracotomy was considered futile			
Exploratory thoracotomy	5 (24)	4 (11)	9 (15)
Benign lung lesion	0	3 (8)	3 (5)
Stage IV disease	3 (14)	0	3 (5)
Stage IIIB disease	4 (19)	8 (21)	12 (20)
Stage IIIA (N2) disease	5 (24)	6 (16)	11 (19)
Recurrence within 12 mo	3 (14)	13 (34)	16 (27)
Death within 12 mo	1 (5)	4 (11)	5 (8)
Total	21 (100)	38 (100)	59 (100)

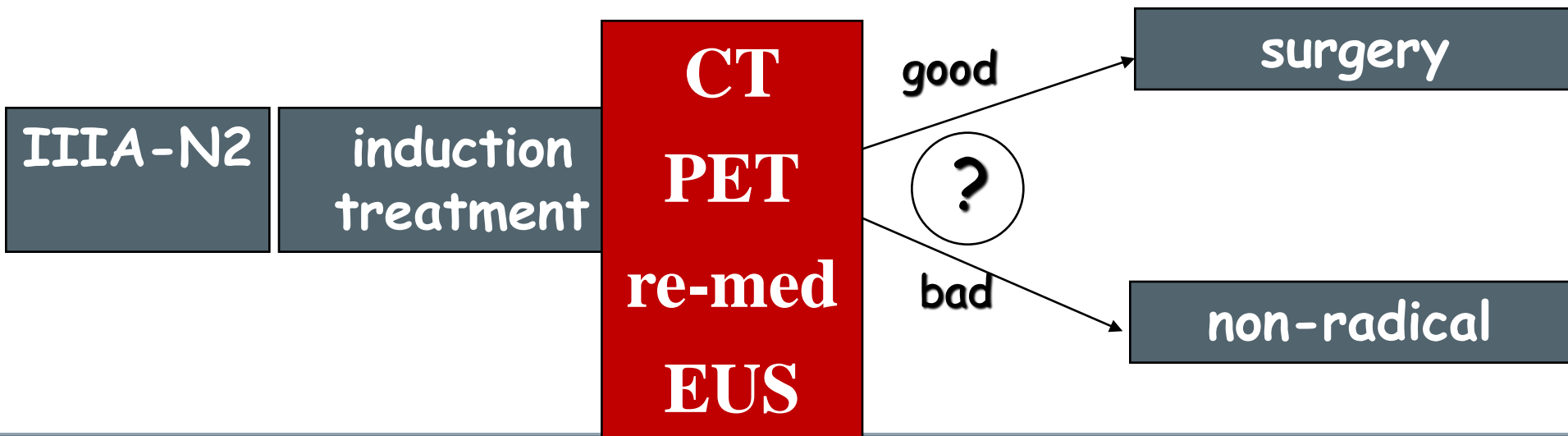
Outline

- Diagnosis (characterization of nodules)
- Initial Staging
 - Tumor
 - Nodes
 - Metastasis
- **Restaging after neoadjuvant treatment**
- PET in radiation treatment planning



Stage III-N2 NSCLC

- Important prognostic factors
 - tumour clearance of mediastinal LNs (so-called *LN downstaging*)
 - pathologic response of *primary tumour*
- These factors can only be assessed **post-surgery**



PET after IC Residual N2 disease

Corneline Hoekstra et al, Journal of Clinical Oncology 2005

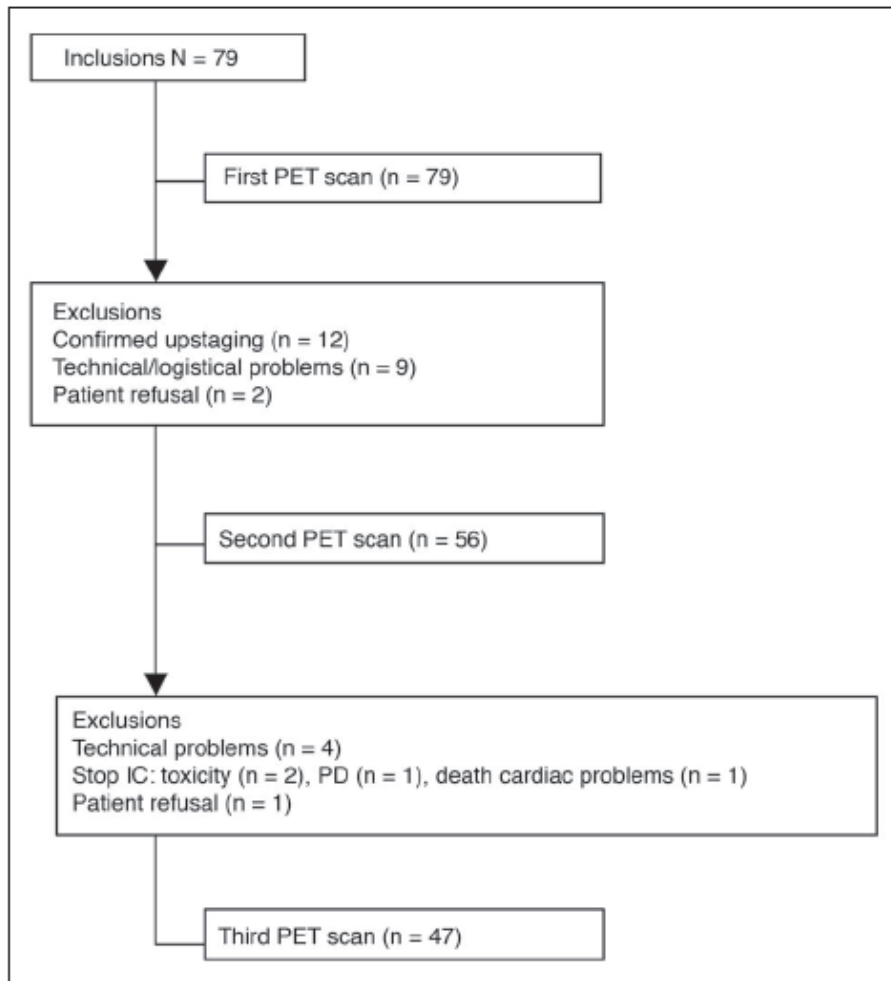
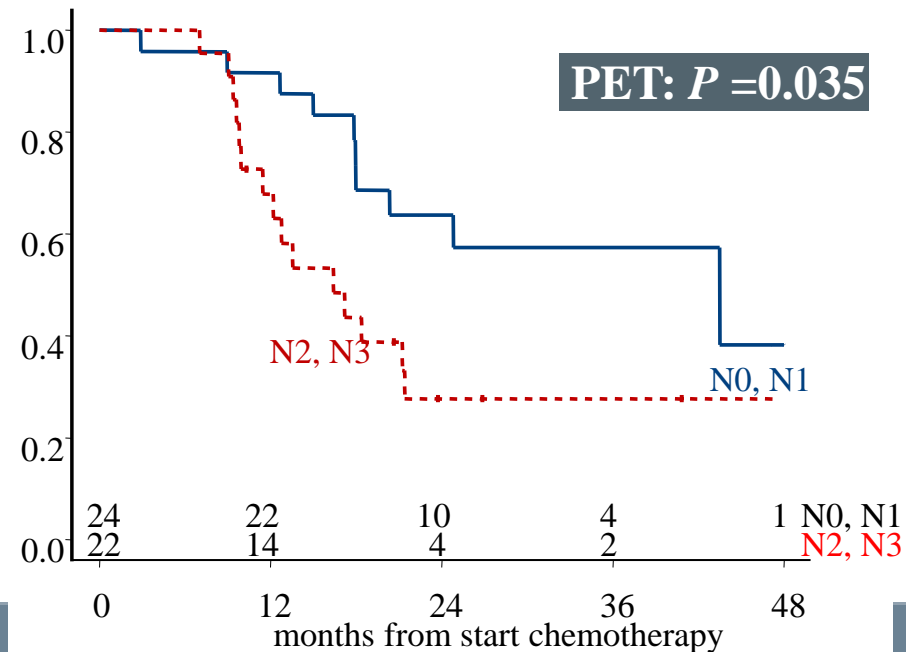


Fig 2. Flow chart exclusions. PET, positron emission tomography; IC, induction chemotherapy; PD, progressive disease.

Pathology in 25 patients

Sensitivity	50%
Specificity	71%
PPV	66%
NPV	67%



PET for N-restaging

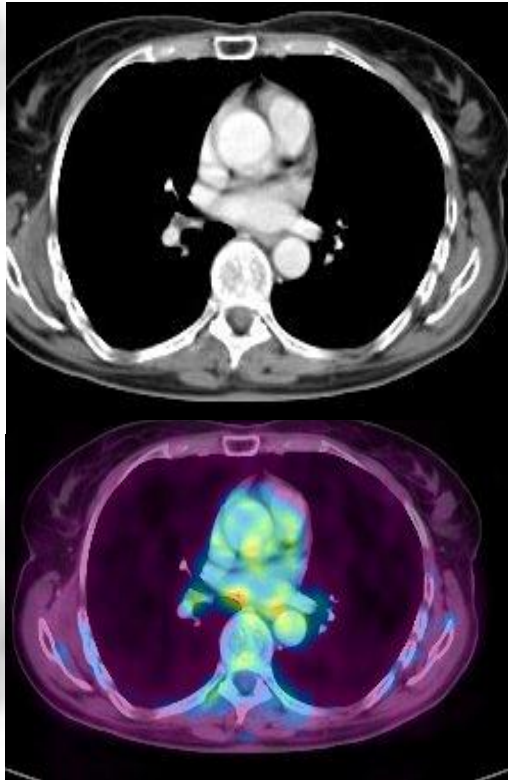
Study	Year	N	Stage	CTRTR	Imaging	Sensitivity	Specificity
Vansteenkiste et al.	2001	31	IIIA-N2	0%	PET + CT (visual corr.)	71%	88%
Akhurst et al.	2002	56	I-III	29%	PET + CT (visual corr.)	67%	61%
Ryu et al.	2002	26	III	100%	PET + CT (visual corr.)	58%	93%
Cerfolio et al.	2003	34	IB-IIIA	21%	PET + CT (visual corr.)	50%	99%
Hellwig et al.	2004	37	III	70%	PET + CT (visual corr.)	50%	88%
Port et al.	2004	25	I-IIIA	0%	PET + CT (visual corr.)	20%	71%
Hoekstra et al.	2005	25	IIIA-N2	0%	PET + CT (visual corr.)	50%	71%
Cerfolio et al.	2006	93	IIIA-N2	100%	Integrated PET-CT	62%	88%
Pottgen et al.	2006	37	IIIA/B	100%	Integrated PET-CT	73%	89%
De Leyn et al.	2006	30	IIIA-N2	0%	Integrated PET-CT	77%	92%

Mediastinal downstaging after IC

- De Leyn et al, JCO 2006
 - Prospective study
 - 30 patients stage IIIA-N2 NSCLC
 - Cisplatinium based IC
 - PET-CT after IC prior to surgery
 - Re – mediastinoscopy
 - Lymphadenectomy at surgery

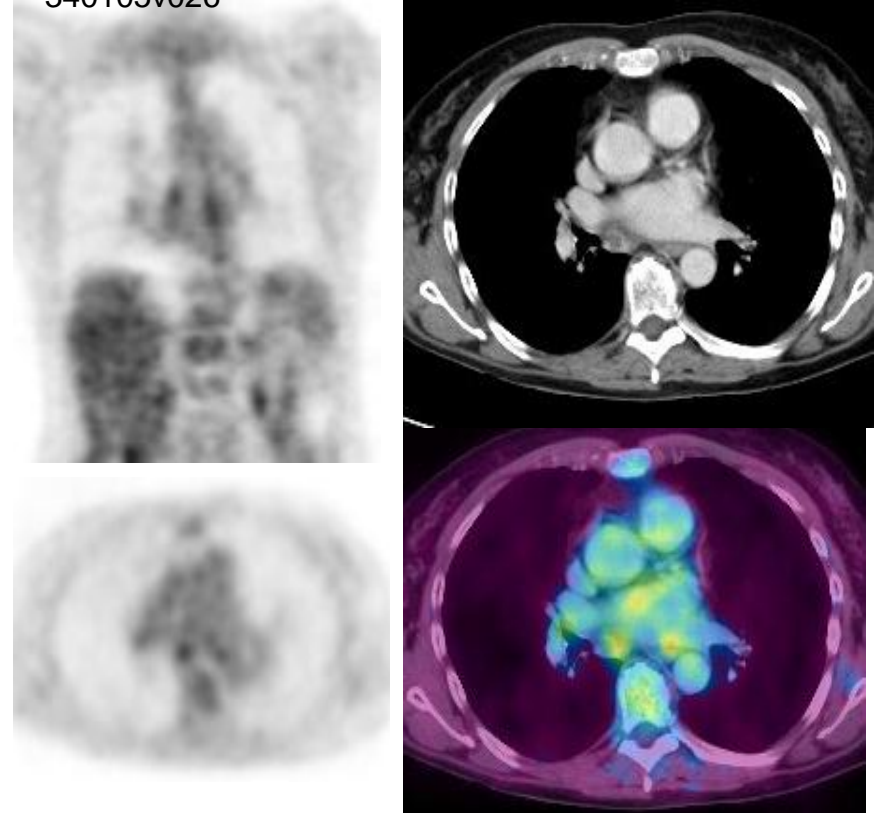
Example PET-CT after IC

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PET-N2 → PET-CT N0

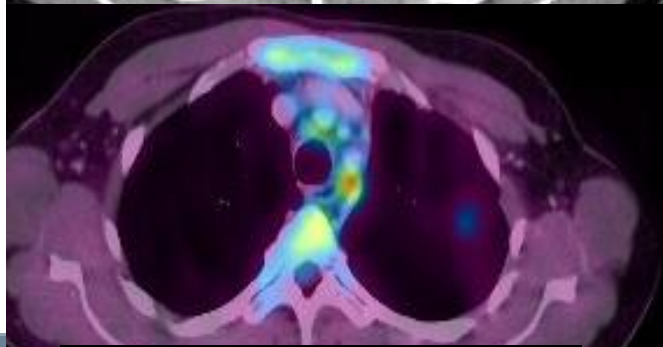
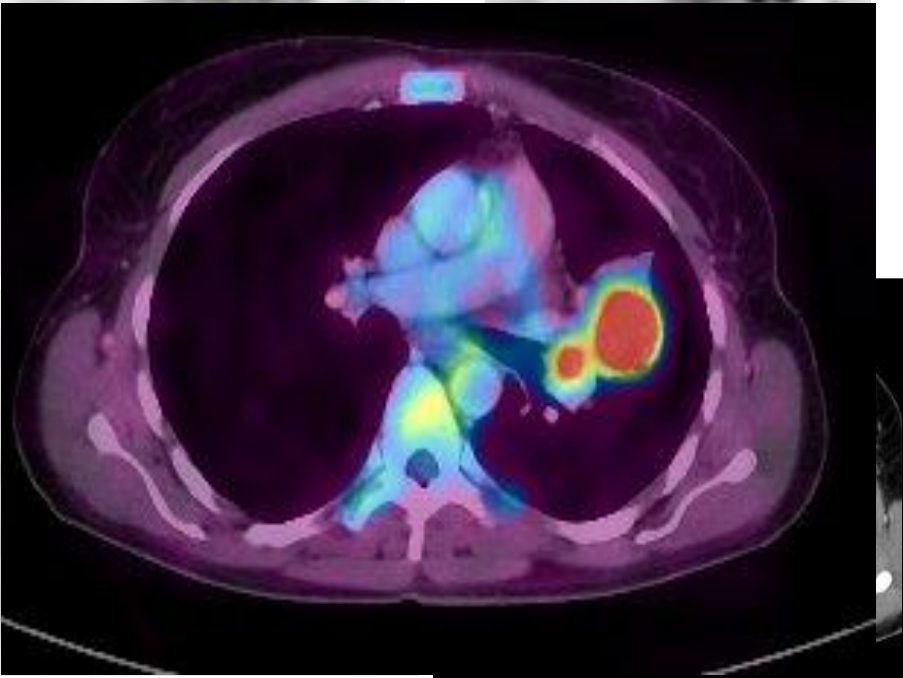
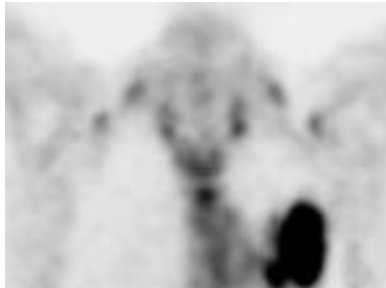
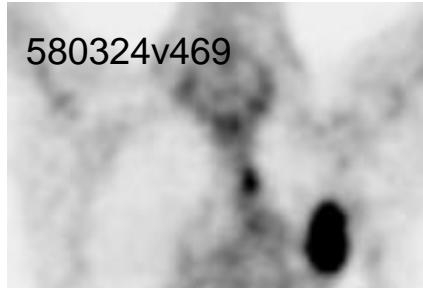
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PET-N2 = PET-CT N2

Example PET-CT after IC

580324v469



PET-N2 → PET-CT N1

Prospective Comparative Study of Integrated Positron Emission Tomography-Computed Tomography Scan Compared With Remediastinoscopy in the Assessment of Residual Mediastinal Lymph Node Disease After Induction Chemotherapy for Mediastinoscopy-Proven Stage IIIA-N2 Non-Small-Cell Lung Cancer: A Leuven Lung Cancer Group Study

Paul De Leyn, Sigrid Stroobants, Walter De Wever, Toni Lerut, Willy Coosemans, Georges Decker, Philippe Nafteux, Dirk Van Raemdonck, Luc Mortelmans, Kristiaan Nackaerts, and Johan Vansteenkiste

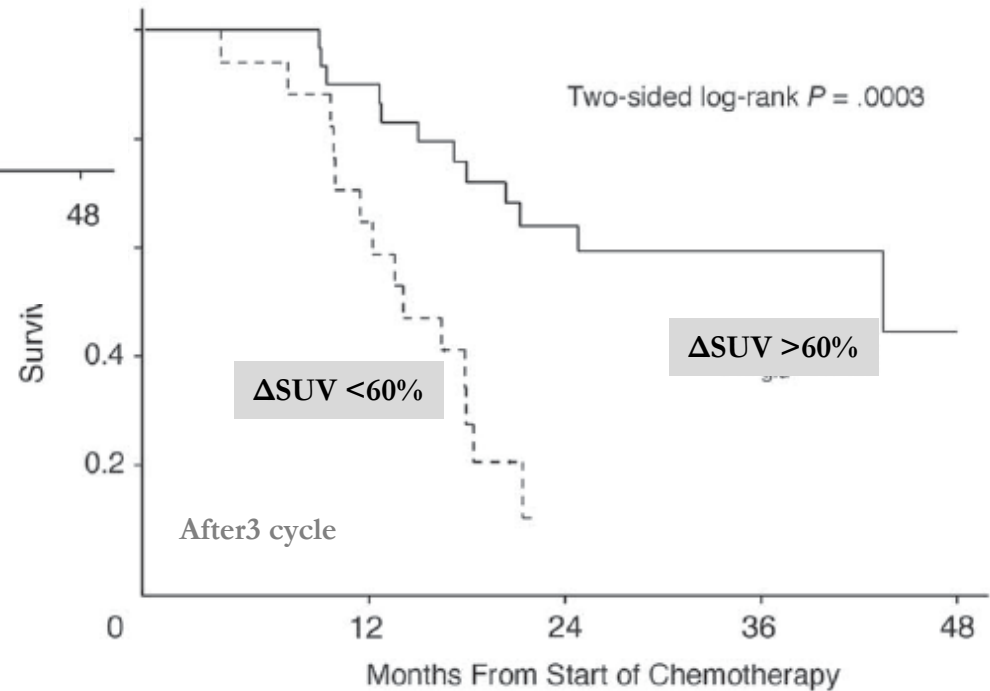
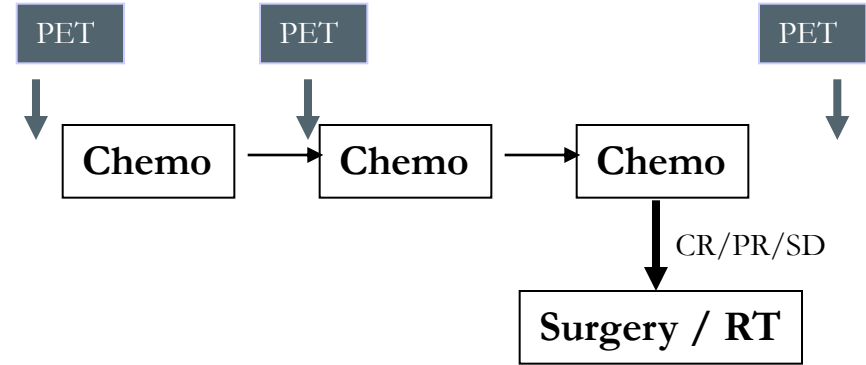
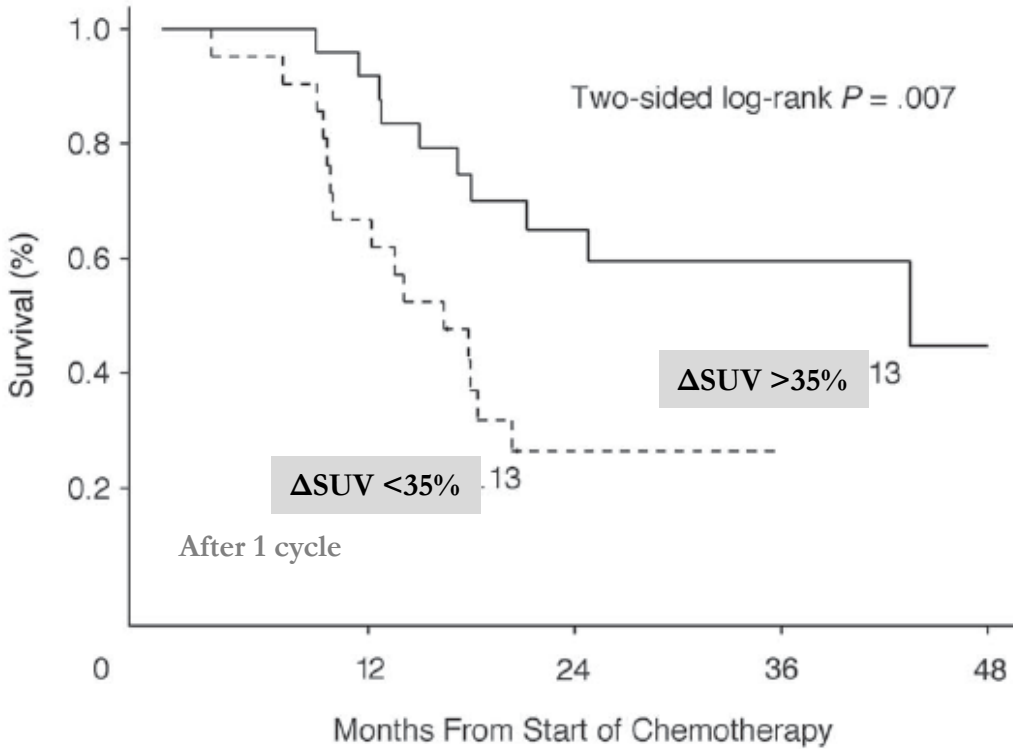
Table 2. Comparison of CT Alone, PET Alone, and PET-CT for Detection of Residual Mediastinal Nodal Disease After Induction Chemotherapy

Test	CT Alone (%)	PET Alone (%)	PET-CT (%)
Sensitivity	59	71	77
Specificity	62	69	92
Accuracy	60	70	83
PPV	66	75	93
NPV	53	64	75

Abbreviations: CT, computed tomography; PET, positron emission tomography; PPV, positive predictive value; NPV, negative predictive value.

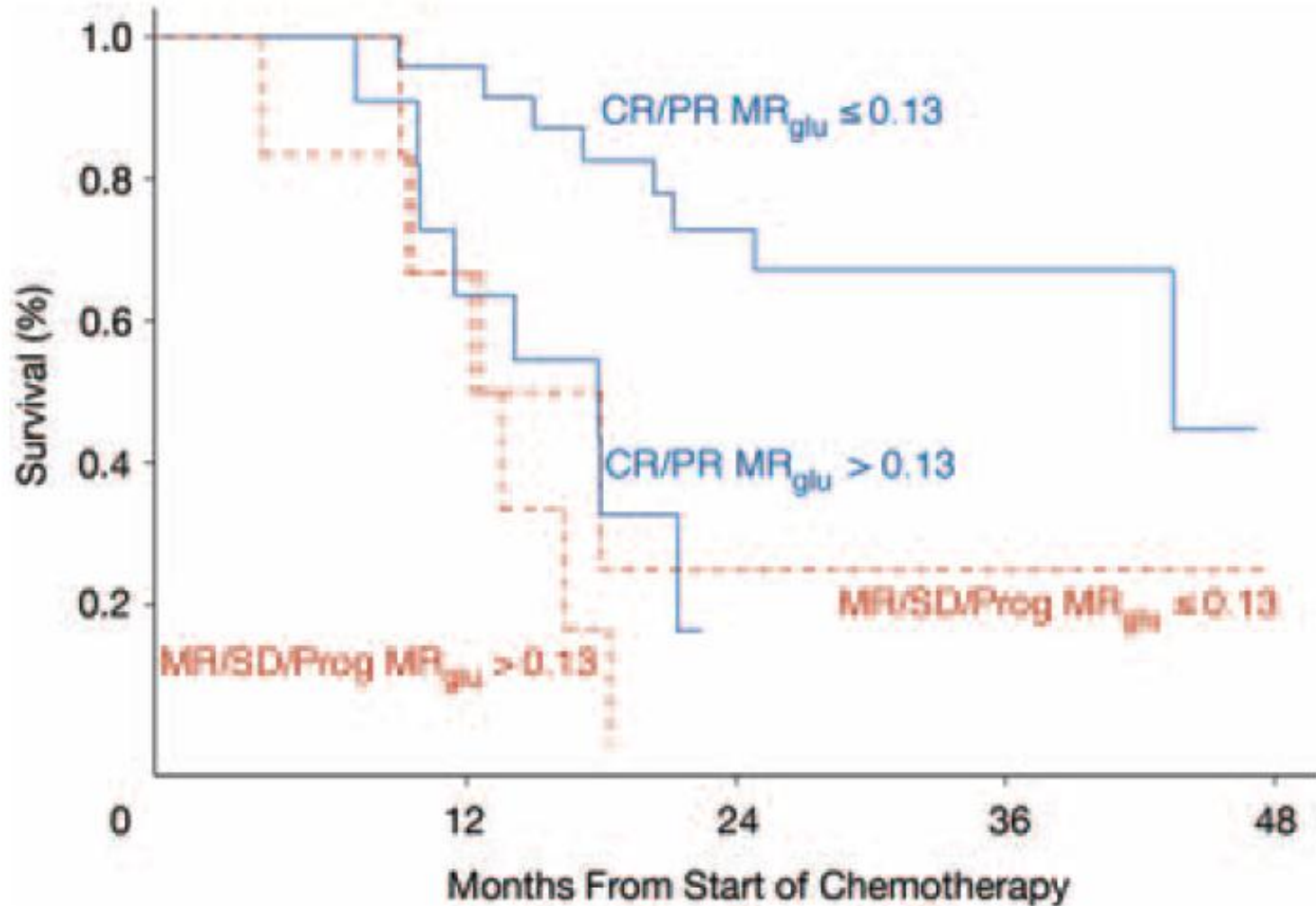
PET as a surrogate marker of OUTCOME

Hoekstra et al, Journal of Clinical Oncology 2005



PET and Response after IC

Corneline Hoekstra et al, Journal of Clinical Oncology 2005



PET for Restaging in NSCLC

- Lower accuracy for detection of mediastinal involvement compared to chemonaive patients
 - Use of other modalities
 - eg. PET-CT + EBUS/EUS upfront, re-mediastino after
- Promising results as an early prognostic marker
 - Validation in a multicenter setting

Outline

- Diagnosis (characterization of nodules)
- Initial Staging
 - Tumor
 - Nodes
 - Metastasis
- Restaging after neoadjuvant treatment
- **PET in radiation treatment planning**

Use of FDG-PET in RTP

- Patient selection
 - Detection of “unknown” M+ in 10-20% of patients
- Follow-up during/after radiotherapy
 - Better discrimination between viable tissue vs necrosis/fibrosis/scar
 - But also uptake in inflammatory tissue!
- Target volume delineation

PET in Radiotherapy planning

Target volume delineation

- New RT techniques are able to accurately conform the dose to PTV
 - Steep dose gradients
 - ➔ reduced dose to normal tissue
 - allows dose escalation in some patients
 - Accurate delineation of gross tumor volume (GTV) is crucial
- Drawbacks of CT-based GTV
 - High inter-observer variability
 - Relatively low accuracy for nodal staging

Is PET-CT better?

Observer variation in target volume delineation of lung cancer related to radiation oncologist-computer interaction: A 'Big Brother' evaluation

Roel J.H.M. Steenbakkera^a, Joop C. Duppen^a, Isabelle Fitton^a, Kirsten E.I. Deurloo^a, Lambert Zijp^a, Apollonia L.J. Uitterhoeve^b, Patrick T.R. Rodrigus^c, Gijsbert W.P. Kramer^d, Johan Bussink^e, Katrien De Jaeger^a, José S.A. Belderbos^a, Augustinus A.M. Hart^a, Peter J.C.M. Nowak^f, Marcel van Herk^a, Coen R.N. Rasch^{a,*}

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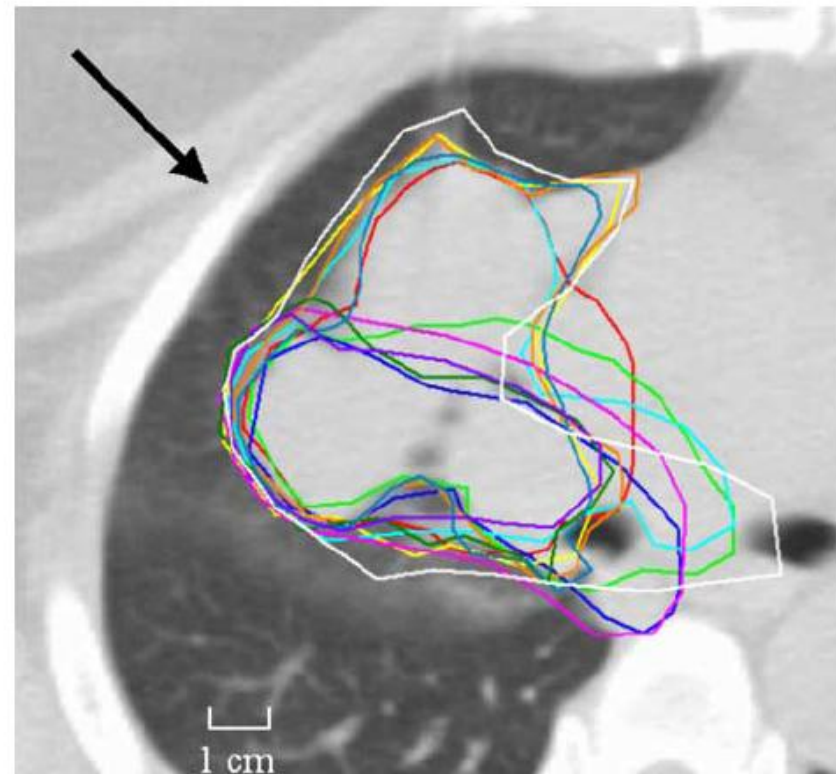
Radiotherapy and Oncology 77 (2005) 182-190

11 RO delineate 22 NSCLC pts

mean GTV 36cm³ - 129 cm³

Difficulties

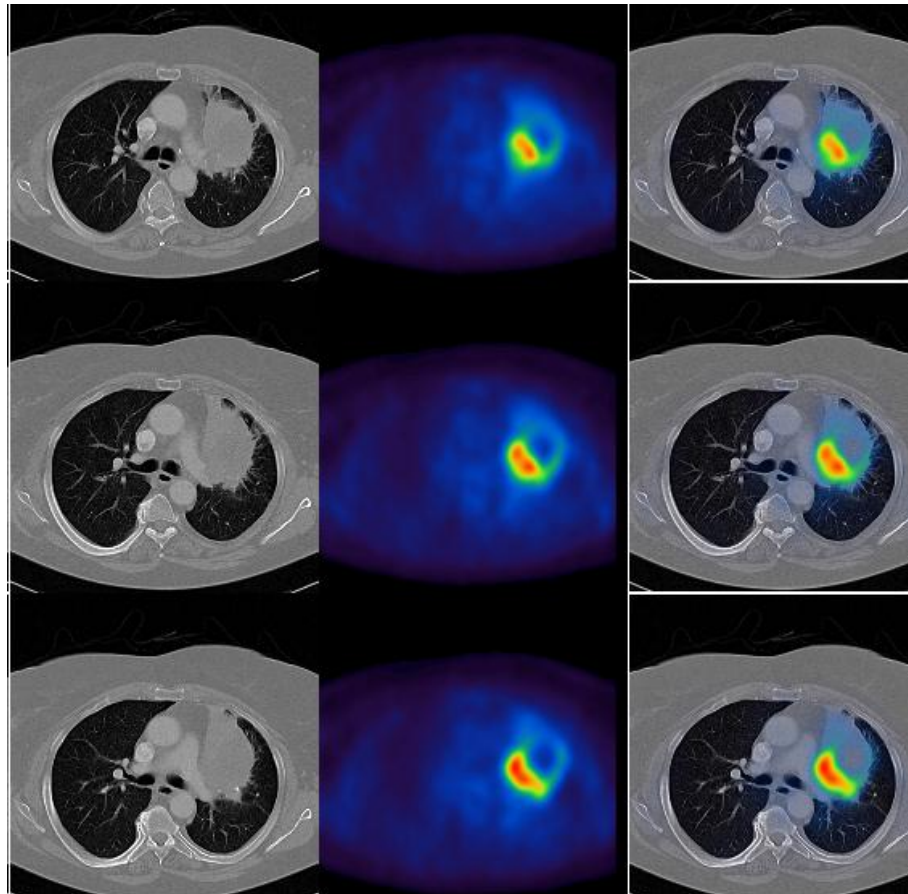
DD Tumor/atelectasis/inflamm
identification of involved LN



PET in Radiotherapy planning

Target volume delineation

→ No FDG uptake in atelectasis



Courtesy of Prof Baum, Bad Berka, Germany

PET in Radiotherapy planning

Target volume delineation

Van Baardwijk et al, Cancer treatment reviews, 2006

Table 3 Impact of PET on target volume in radiation treatment planning

Tumour site (author, year of publication)	No. of patients	Conventional imaging based target volume	Influence of PET on target volume	Conclusions
<i>Lung</i> Vanuytsel 2000 ¹¹¹		PTV _{CT} 579 ml	PTV _{PET} 402 ml	$p = 0.002$ PTV _{PET} was significant smaller than PTV based on CT
Ciernik 2003 ³⁵	6	GTV _{CT} 36.1 ml PTV _{CT} 444.4 ml	GTV _{PET} 27.8 ml PTV _{PET} 399.7 ml	Mean change in PTV of 26%
Bradley 2004 ¹⁰⁶	24	GTV _{CT} 111.3 ml	GTV _{PET} 99.8 ml	$p = ns$ No difference in GTV _{ct} and GTV _{PET} in the total group
Van der Wel 2005 ¹¹⁹	21	<i>Lymph nodes</i> GTV _{CT} 13.7 ml	GTV _{CT-PET} 9.9 ml	$p = 0.011$ Adding PET data decreased GTV in mediastinal nodes

- Alterations in GTV by adding PET data in 25-50% of patients
 - Decrease in GTV (atelectasis, PET- enlarged LN);
 - sometimes increase in GTV (PET+ non-enlarged LN)
- Reduced inter-observer variability



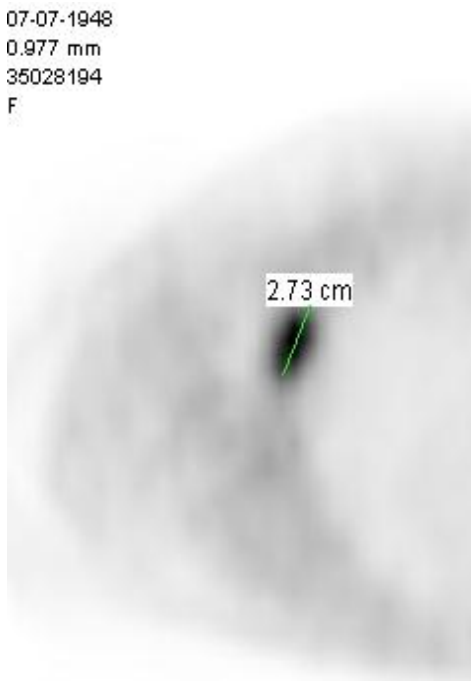
What are the pitfalls?

PET in Radiotherapy planning

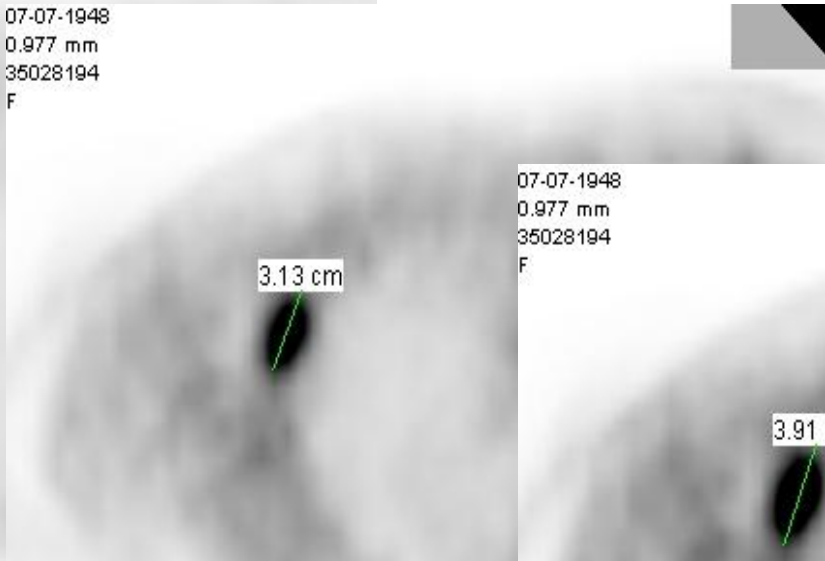
Target volume delineation

Display window setting affects lesion size

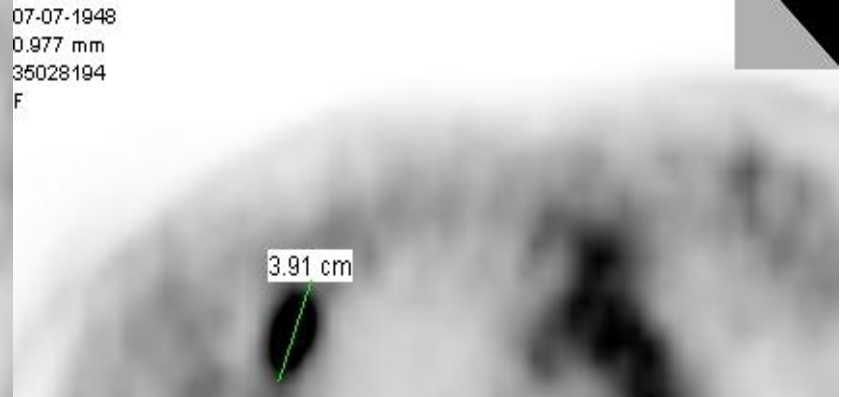
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0.977 mm
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07-07-1948
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F



PET in Radiotherapy planning Target volume delineation

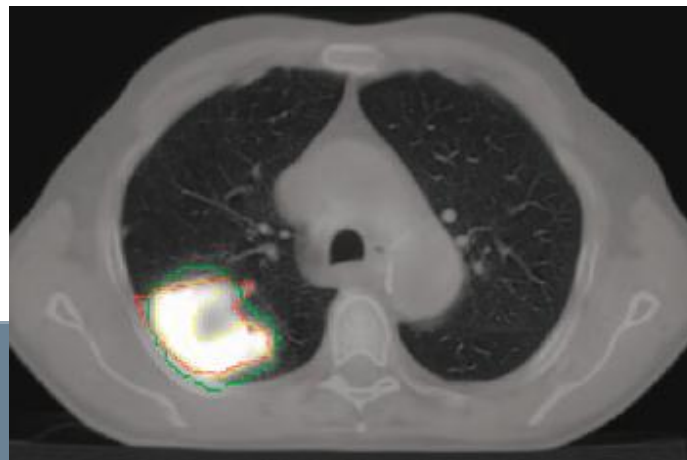
Nestle et al JNM 2005

TABLE 1

Results of GTV Delineation Following Different Philosophies for Contour Definition: All Patients

<i>n</i>	SUV_{max}	GTV_{vis}		$GTV_{2.5}$		GTV_{40}		GTV_{bg}	
	25	25		24		25		22	
		Volume (mL)	Radius* (cm)	Volume (mL)	Radius* (cm)	Volume (mL)	Radius* (cm)	Volume (mL)	Radius* (cm)
Mean	17.1	157.7	3.03	164.6	3.05	53.6	2.18	94.7	2.52
Median	17.2	107.8	2.95	108.3	2.96	41.4	2.15	62.2	2.45
Maximum	38.8	666.2	5.42	655.7	5.39	168.3	3.42	318.0	4.23
Minimum	1.7	9.3	1.30	8.1	1.24	5.7	1.11	3.7	0.96

— GTV_{CT}
— $GTV_{PET\ bg}$
— $GTV_{PET\ 40}$



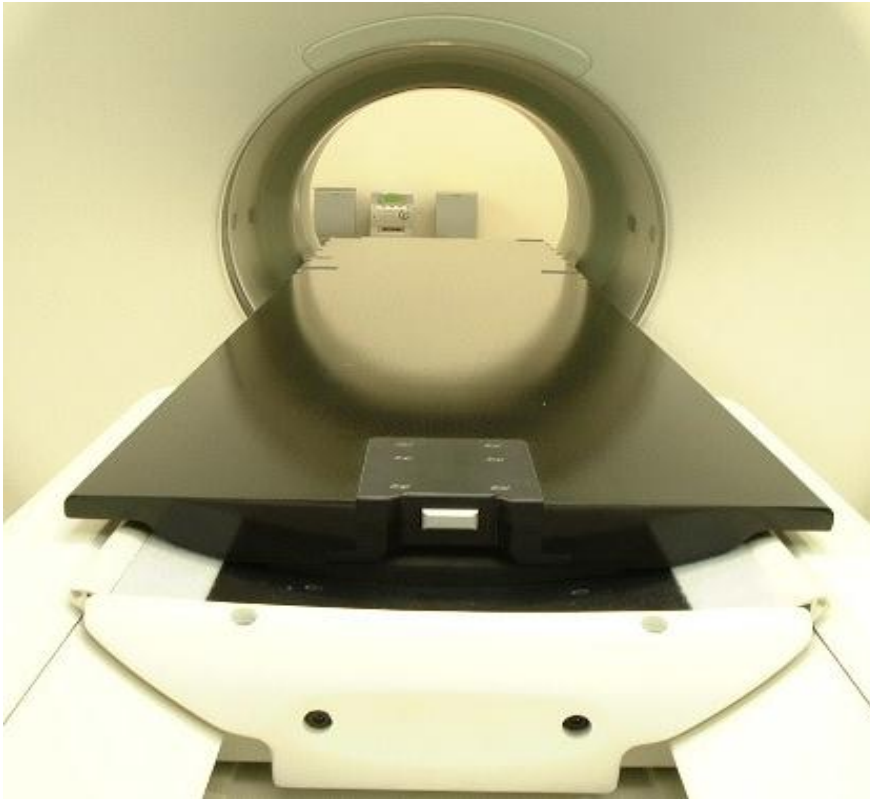
PET in Radiotherapy planning

Target volume delineation

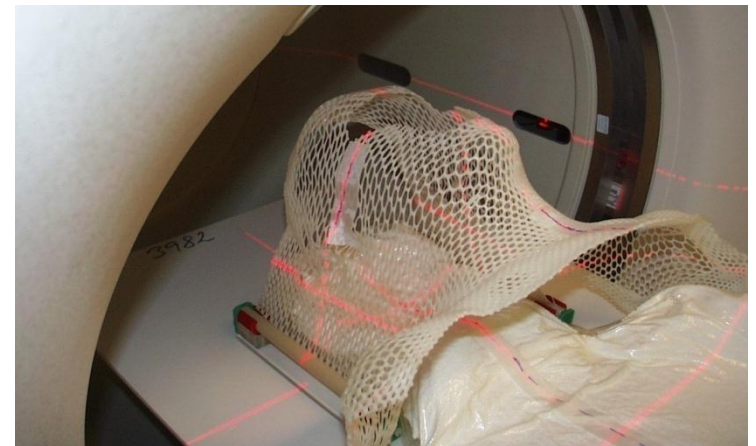
- What is the best method?
 - lack of “gold” standard (pathology)
 - comparison with phantom data/CT volumes
 - Best results currently SBR
Center dependent!!!!!!
- Control of patient set up and organ motion
 - hybrid PET-CT in treatment position
 - respiratory gating

PET in Radiotherapy planning

Target volume delineation



**Klinisk Fysiologisch og
Nuklearmedicinsk Klinik**



PET in NSCLC

- **T staging**
 - Limited additional value
 - SUV max as prognostic factor?
- **N-staging**
 - Important additional value for INITIAL staging
 - High NPV omit invasive procedures
 - Cave! Central tumors, large LN
 - Always confirm PET+ nodes
 - Restaging and use of RTP still experimental
- **M-staging**
 - Most important additional value
 - Confirm PET + lesions alter treatment