# Mediastinale (her)stadiering dmv beeldvorming

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# Imaging for mediastinal staging

- **Computer tomography**
  - Based on size criteria (> 10 mm short axis)

- **FDG-PET**
  - Based on increased glycolysis of cancer cells

- **Magnetic Resonance Imaging**
  - Size (T1)
  - Morphology (T2)(cortical thickening, obliteration of fatty hilum)
  - USPIO
  - Diffusion

# PET for N-staging

**Meta analysis Gould et al. Annals of Internal Medicine 2003**

*Table.* Summary of Meta-Analysis Results*

| Variable | Median Sensitivity (IQR) | Median Specificity (IQR) | Maximum Joint Sensitivity and Specificity (95% CI)† | Sensitivity at Point on Summary ROC Curve Corresponding to Median Specificity (95% CI) | Specificity at Point on Summary ROC Curve Corresponding to Median Sensitivity (95% CI) | Likelihood Ratio for Positive Test‡ | Likelihood Ratio for Negative Test‡ |
|---|---|---|---|---|---|---|---|
| | ← | | | % | | → | |
| **CT** | | | | | | | |
| All studies (1119 patients in 23 studies) | 61 (50–71) | 79 (66–89) | 70 (67–73) | 59 (52–66) | 78 (72–83) | 2.8 | 0.5 |
| **PET** | | | | | | | |
| All studies (1959 patients in 32 studies) | 85 (67–91) | 90 (82–96) | 86 (84–88) | 81 (74–86) | 86 (81–90) | 8.1 | 0.2 |
| Patients with enlarged lymph nodes on CT (214 patients in 12 studies) | 100 (90–100) | 78 (68–100) | 85 (79–90) | 91 (79–96) | NC | 4.1 | 0.1 |
| Patients without enlarged lymph nodes on CT (479 patients in 14 studies) | 82 (65–100) | 93 (92–100) | 87 (84–89) | 75 (59–87) | 90 (82–95) | 10.7 | 0.3 |

\* CT = computed tomography; IQR = interquartile range; NC = not able to calculate; PET = positron emission tomography; ROC = receiver-operating characteristic.
† The maximum joint sensitivity and specificity is the point on the summary ROC curve at which sensitivity and specificity are equal; it is a global measure of test performance, similar to the area under the curve, and does not necessarily represent the optimal operating point or the one applied in everyday clinical practice.
‡ To calculate likelihood ratios, we used the point on the summary ROC curve that corresponded to the median specificity.
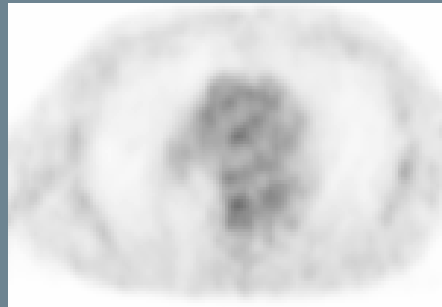
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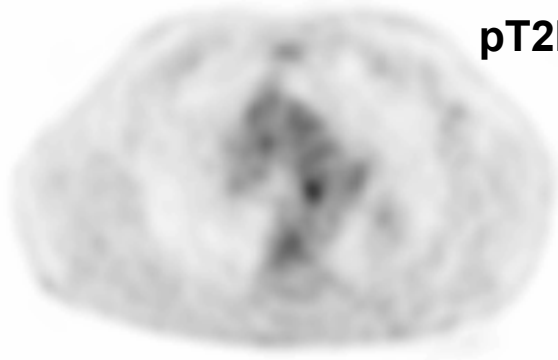UNIVERSITAIR ZIEKENHUIS ANTWERPEN
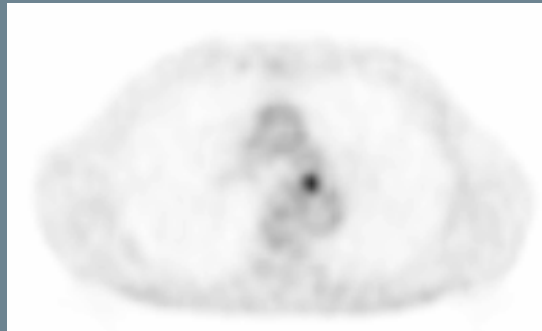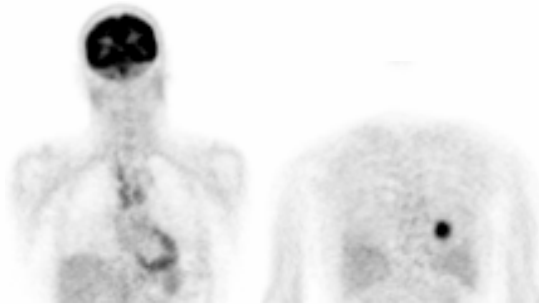
# PET for N-staging
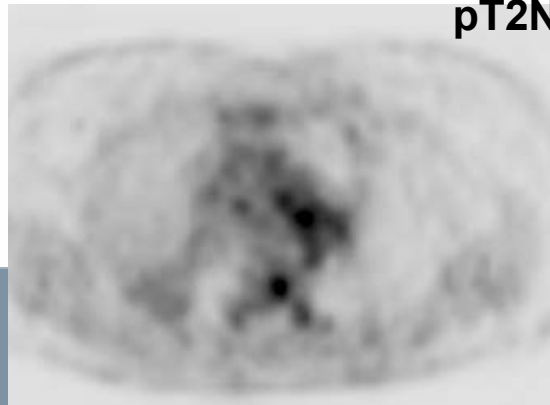


pT1N2
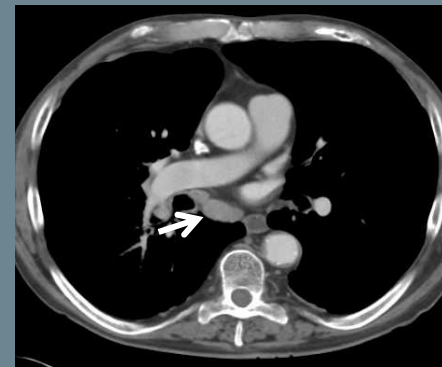
pT1N0
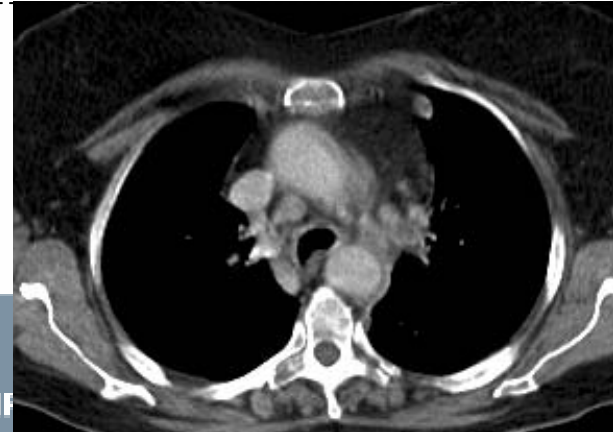
# DD malignant vs benign LN



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.
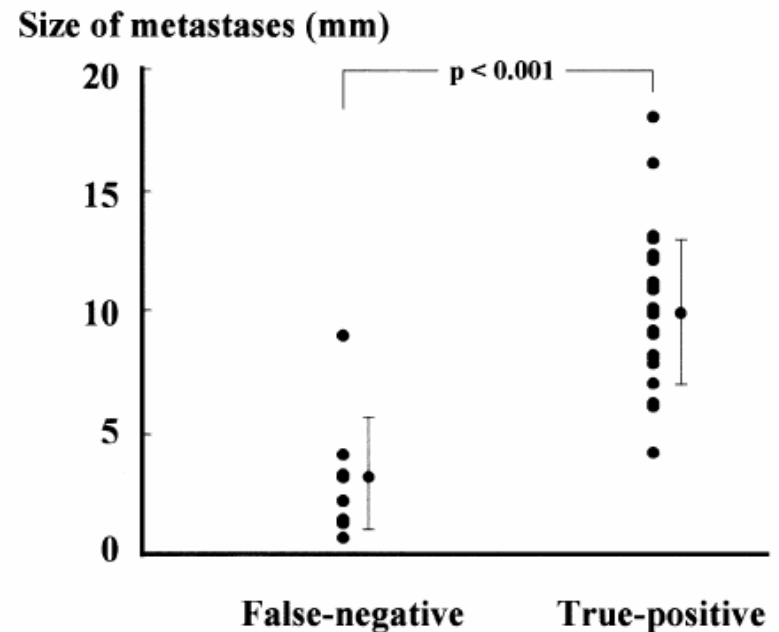
Size of metastases (mm)

$p < 0.001$

False-negative    True-positive

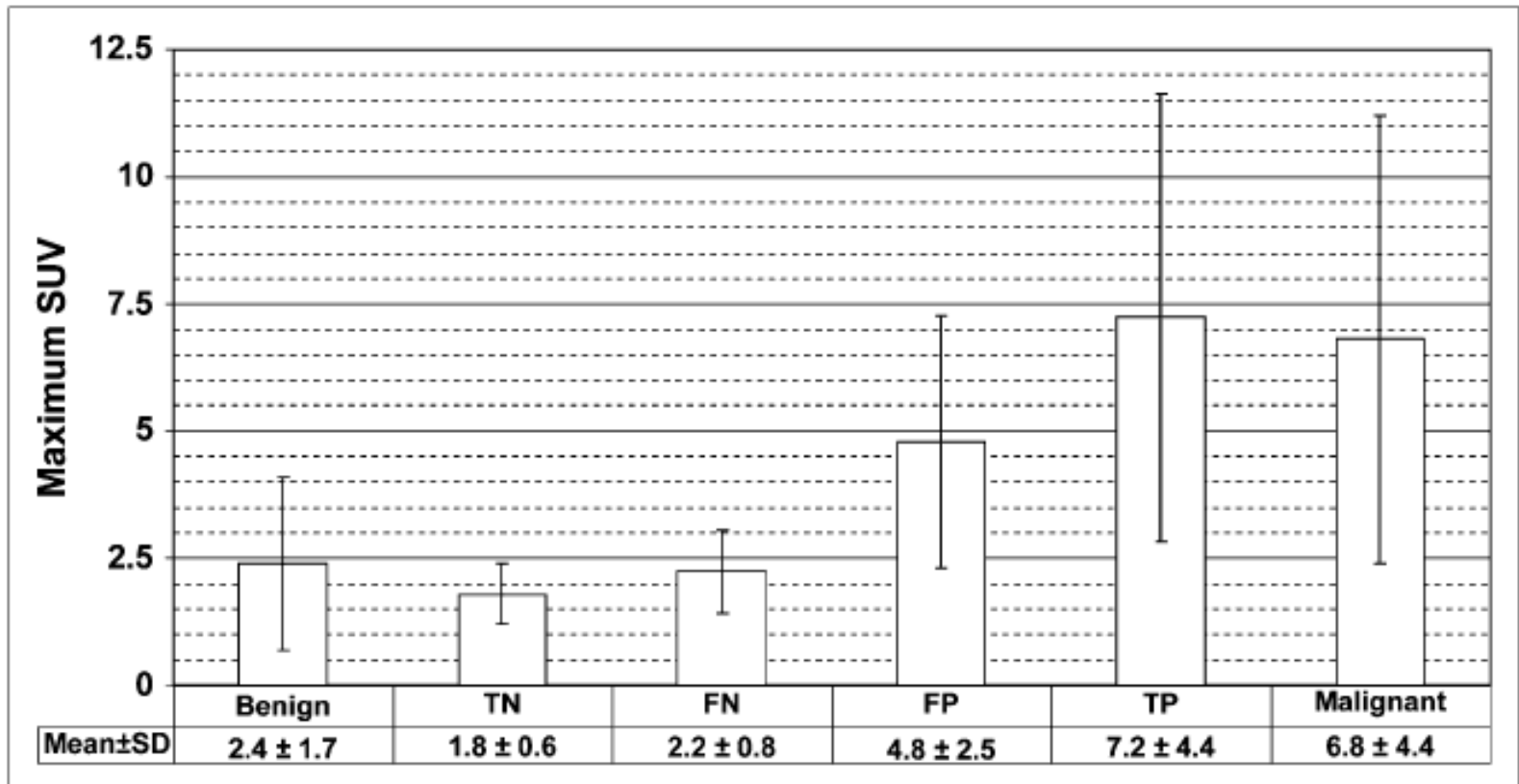Figure 2. The distribution of sizes of metastatic foci in false-negative and true-positive lymph nodes with PET scan.

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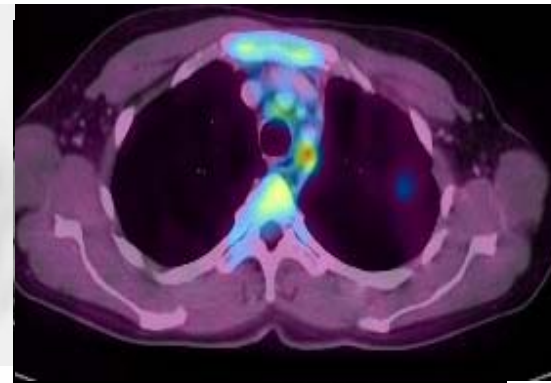
# Definition of PET+LN

Hellwig et al, JNM 2007
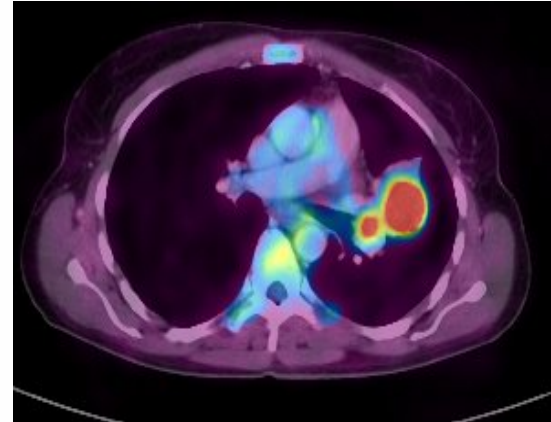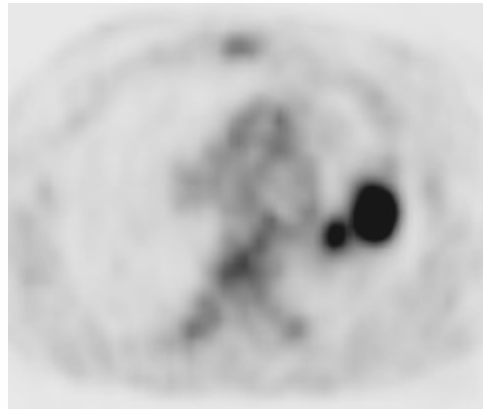Retrospective analysis of 95 patients with suspected NSCLC and underwent mediastinoscopy and had PET prior to surgery
Comparison of visual analysis (> mediastinal BG) and SUV max LN



| | Benign | TN | FN | FP | TP | Malignant |
|---|---|---|---|---|---|---|
| Mean±SD | 2.4 ± 1.7 | 1.8 ± 0.6 | 2.2 ± 0.8 | 4.8 ± 2.5 | 7.2 ± 4.4 | 6.8 ± 4.4 |

# PET for  N-staging
# Impact of integrated PET-CT



**pT2N1**

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 but Equivocal (Score of 2) | Classification Incorrect (Score of 0 or 1) |
|---|---|---|---|
| | no. of patients (%) | | |
| CT alone | 22 (59) | 2 (5) | 13 (35) |
| PET alone | 18 (49) | 14 (38) | 5 (14) |
| Visual cor-relation of PET and CT | 22 (59) | 4 (11) | 11 (30) |
| Integrated PET–CT | 30 (81) | 1 (3) | 6 (16) |

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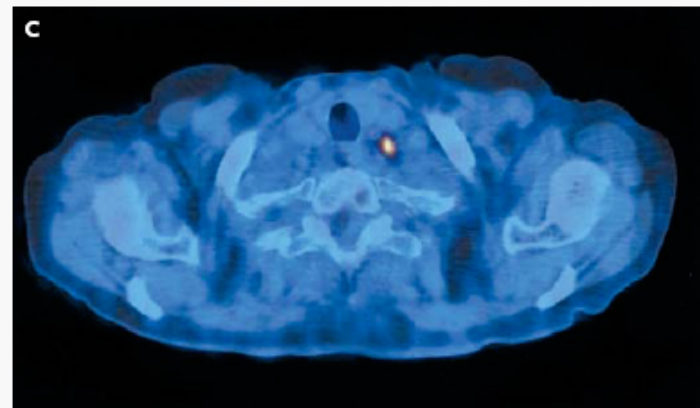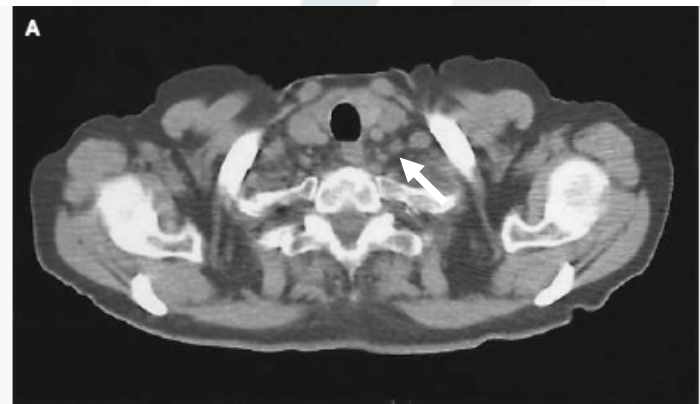
ORIGINAL ARTICLE

# 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 |
|---|---|---|---|
| | | number (percent) | |
| 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) |

# 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 $\chi^2$ 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 $\chi^2$ test = .029.

# PET for N-Staging

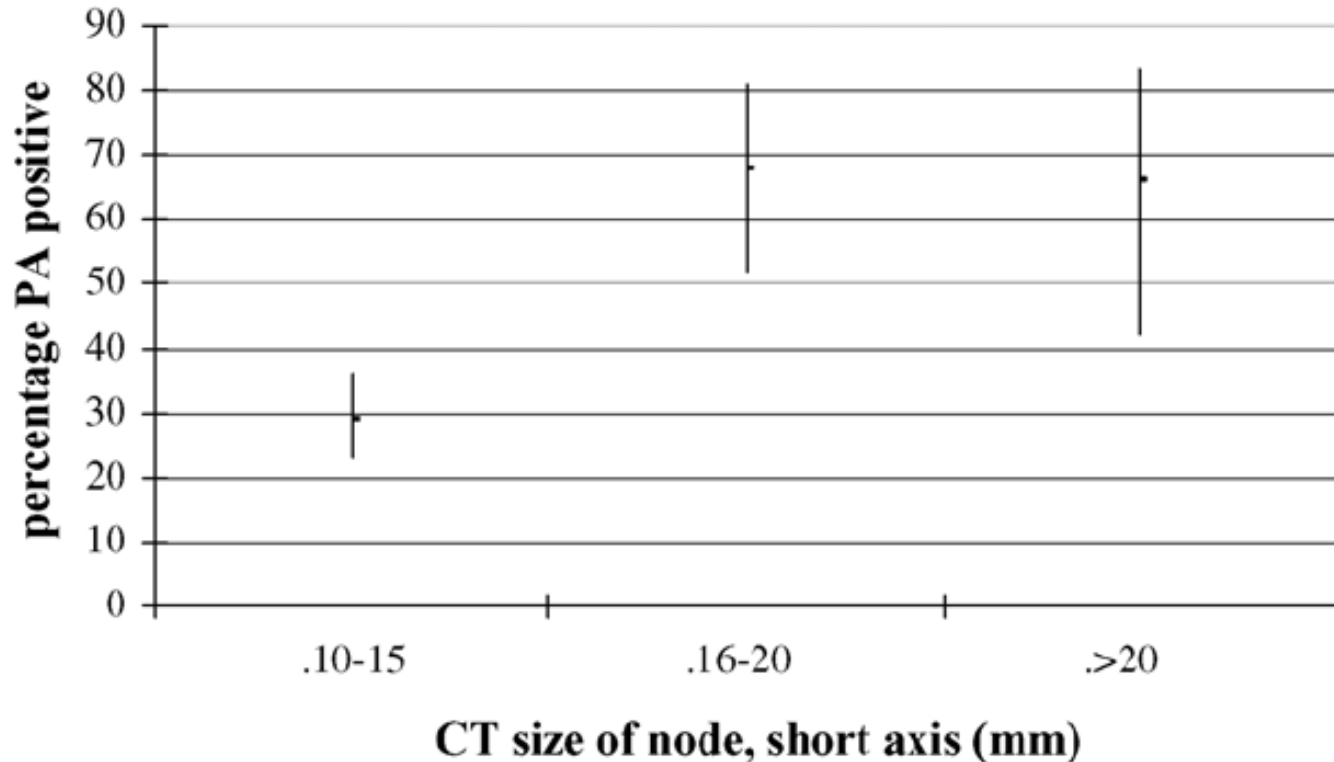Langen et al, Eur J Cardio Thor Surgery 2006



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
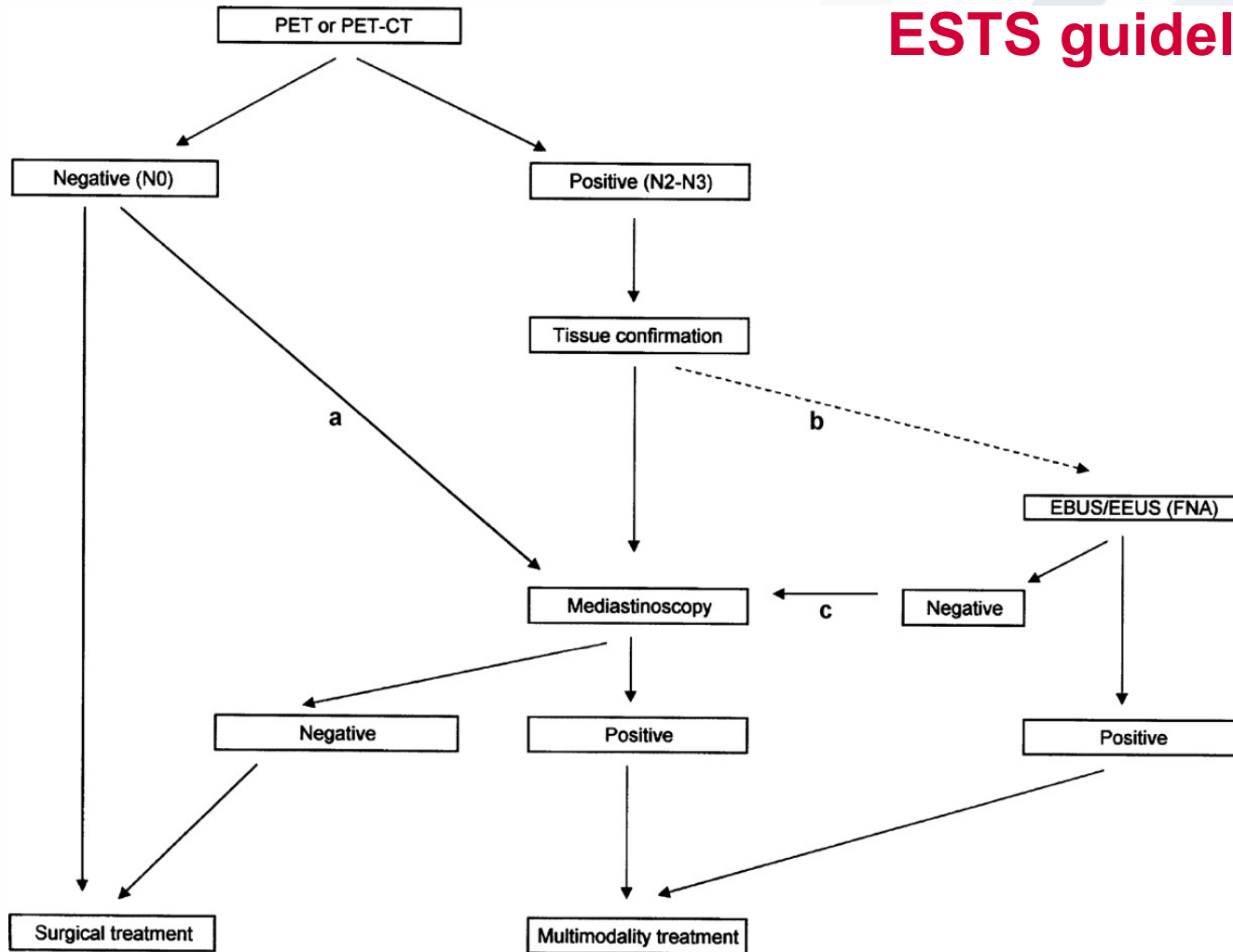
a : In central tumors, tumors with low FDG uptake, tumors with  LNs ≥ 1,6 cm and/or PET N1 disease
    invasive staging remains indicated
b : Endoscopic techniques are minimally invasive and can be the first choice
c : Due to its higher NPV mediastinoscopy remains indicated

EUS : endoscopic esophageal ultrasound
EBUS : endobronchial ultrasound
NPV : negative predictive value
N0 : LN < 1 cm

# PET for mediastinal restaging

# PET after IC Residual N2 disease

Corneline Hoekstra et al, Journal of Clinical Oncology 2005
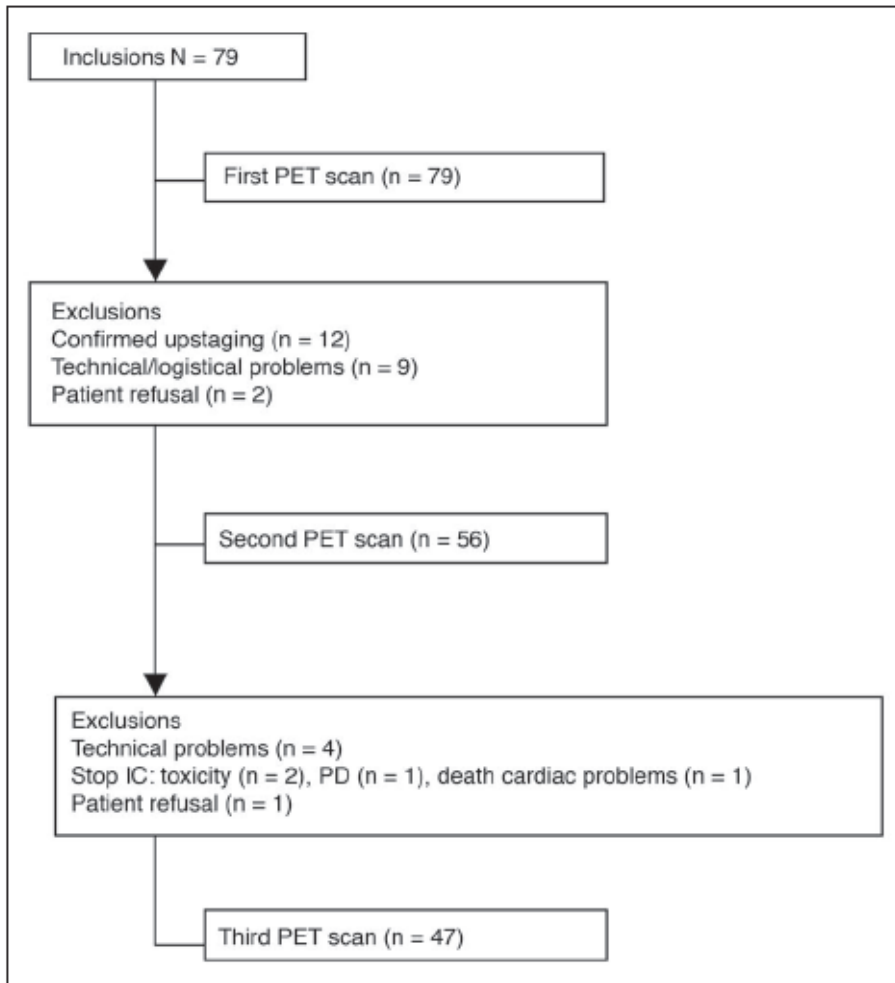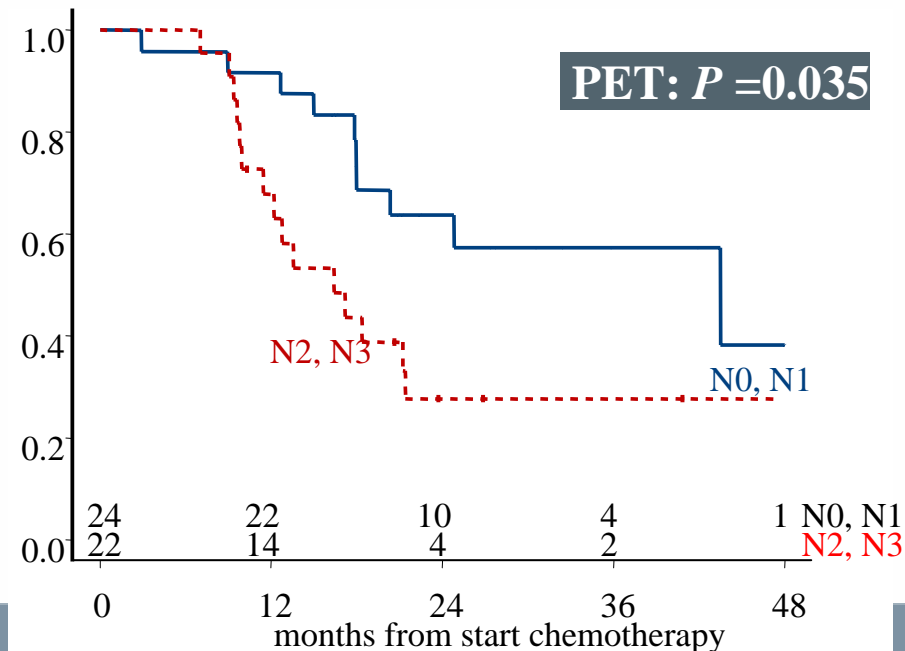


Fig 2. Flow chart exclusions. PET, positron emission tomography; IC, induction chemotherapy; PD, progressive disease.

Pathology in 25 patients

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

PET: $P = 0.035$

# PET for N-restaging

| Study | Year | N | Stage | CTRT | 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
  - Cisplatinum based IC
  - PET-CT after IC prior to surgery
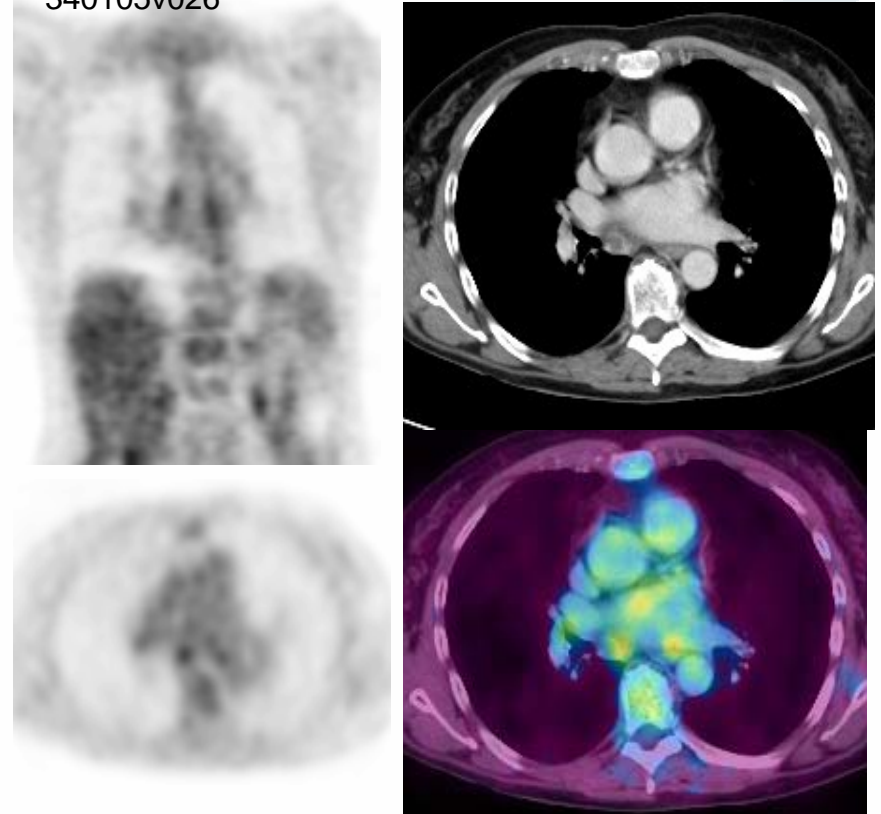  - Re – mediastinoscopy
  - Lymphadenectomy at surgery

# Example PET-CT after IC



480419v054
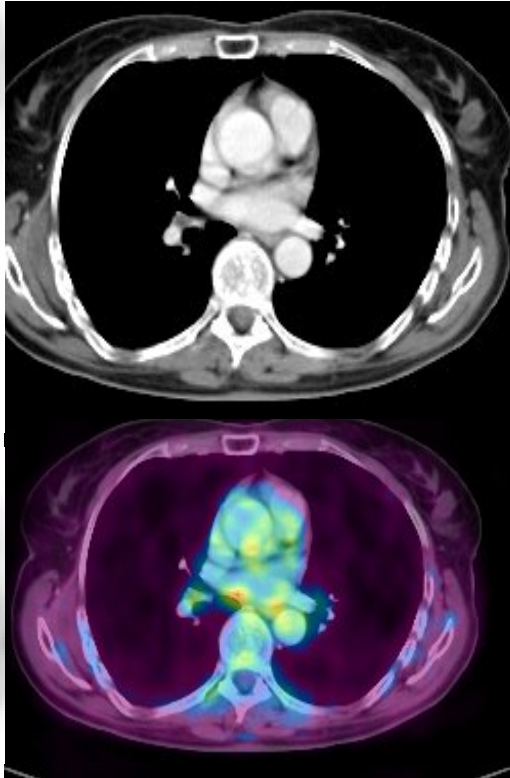
340105v026

PET-N2 → PET-CT N0

PET-N2 = PET-CT N2

# 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

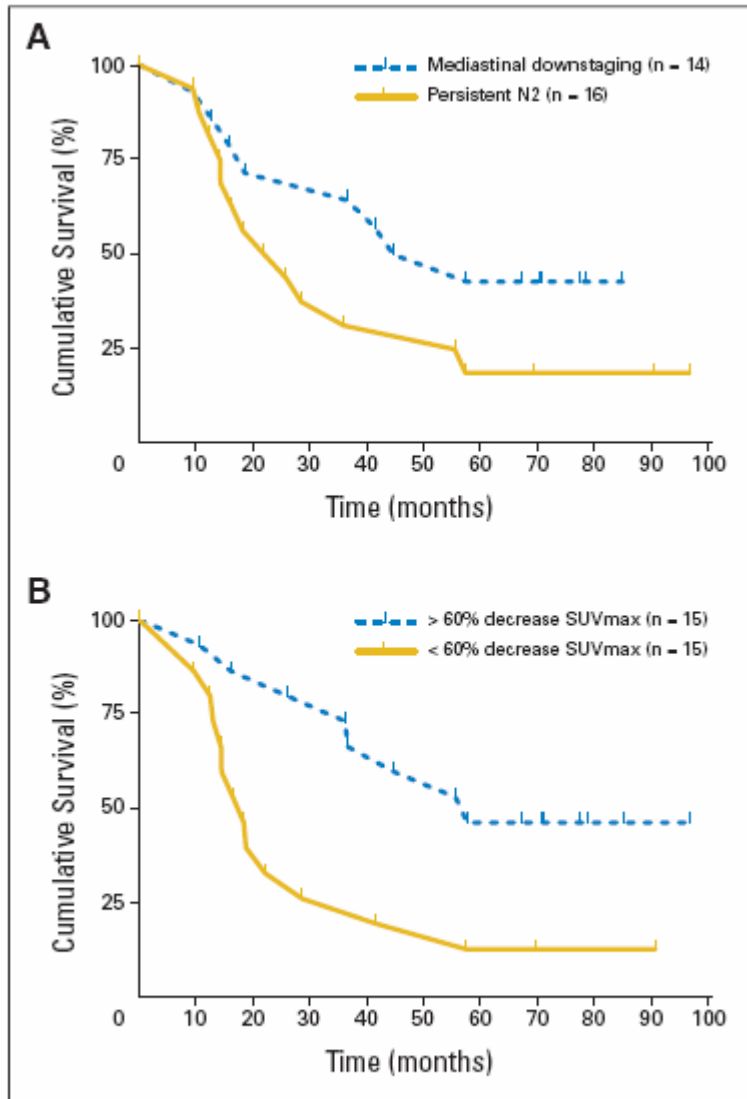| Test | CT Alone (%) | PET Alone (%) | PET-CT (%) |
|------|--------------|---------------|------------|
| Sensitivity | 59 | 71 | 77 |
| Specificity | 62 | 69 | 92 |
| Accuracy | 60 | 70 | 83 |
| PPV | 66 | 75 | 93 |
| NPV | 53 | 64 | 75 |

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
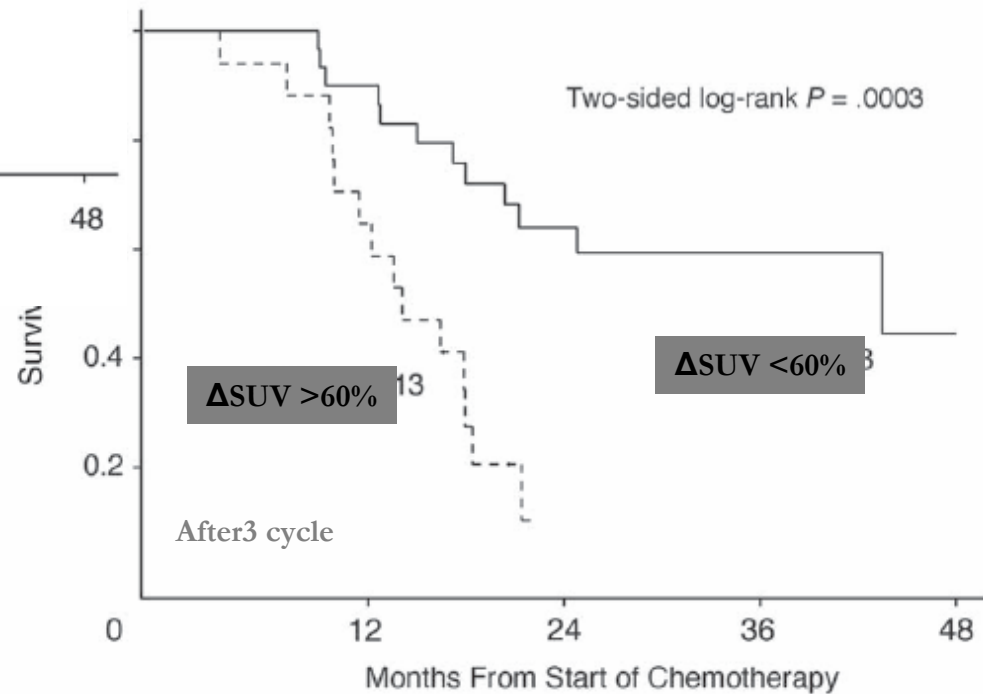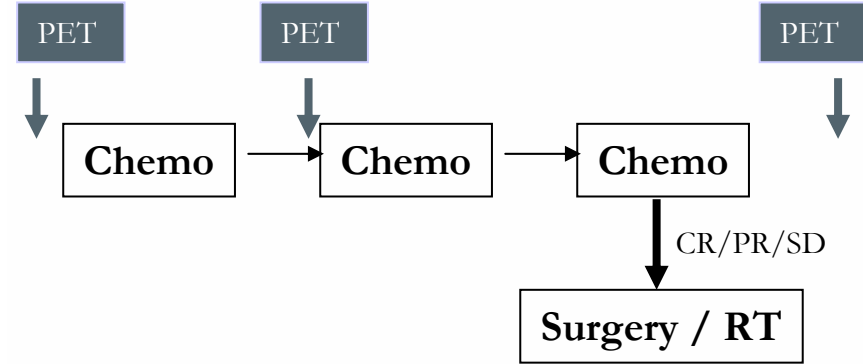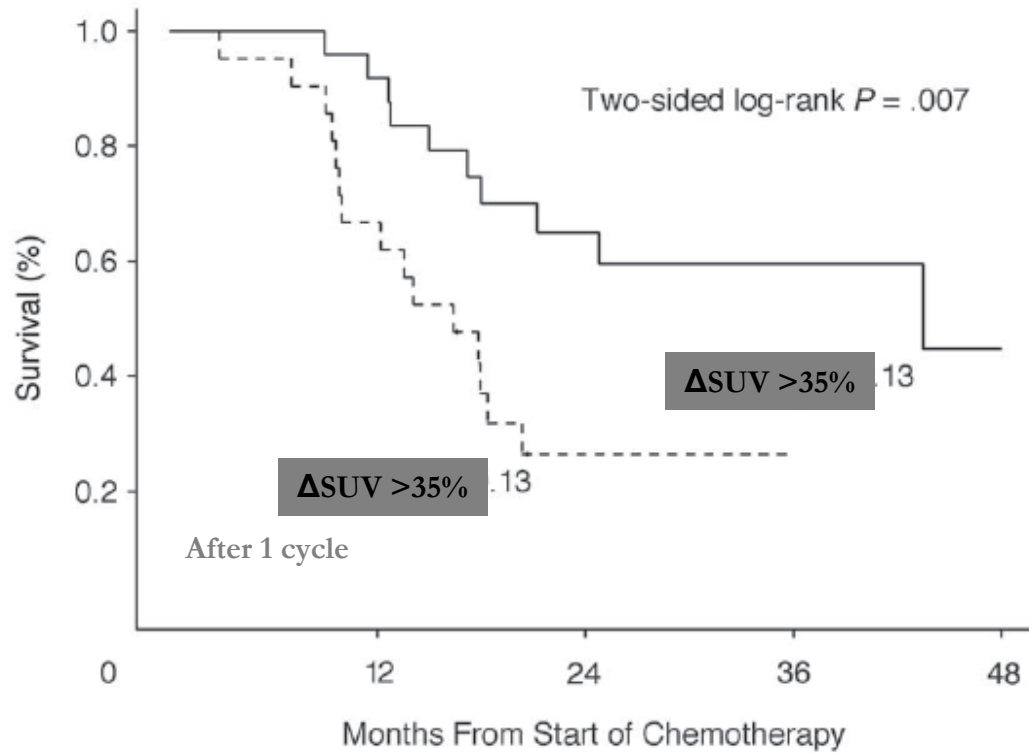
# Optimal patient selection



Fig 1. Kaplan-Meier survival curve of single-item prognostic factors according to (A) pathologic mediastinal N stage, and (B) percentage decrease in maximum standardized uptake value (SUVmax) on primary tumor.

➡ Combination of a different parameters

Dooms et al, JCO 2008
30 pts with NSCLC stage IIIA-N2
3 cycles IC + surgery
PET before and after IC
Histopathology of LN

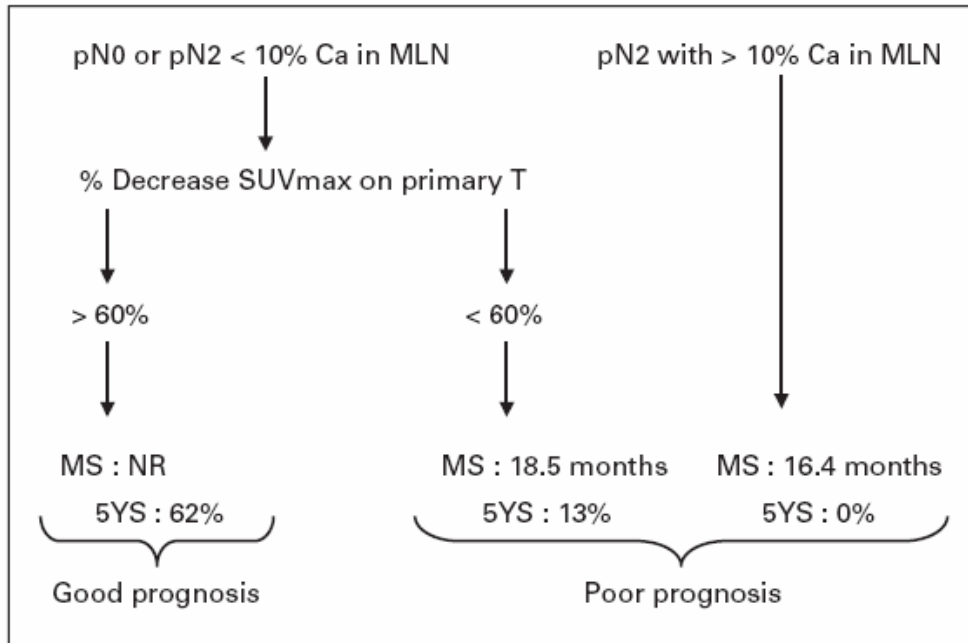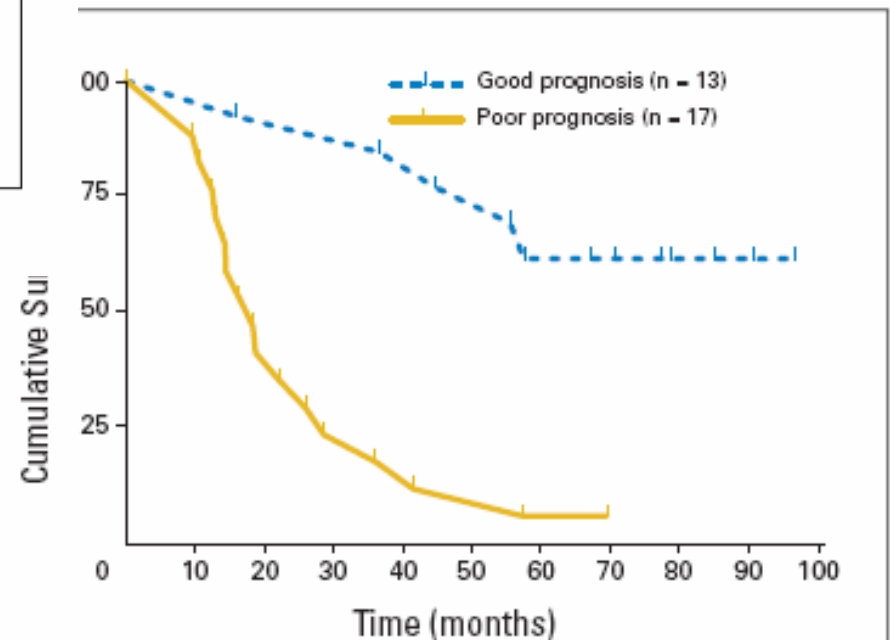# Optimal Prognostic Model
## Dooms et al, JCO 2008



Fig 4. Decision flow chart after induction chemotherapy.

# 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 prognostic marker
  - Validation in a multicenter setting