# Staging of oligometastatic lung cancer

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Padua, 31 March 2017

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- Definition of oligometastatic disease
- The role of PET/CT in lung cancer
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- PET/CT and the site of oligo-metastases
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# Definition of oligometastatic disease

- Approximately 7% of patients with metastatic disease from an NSCLC will have a solitary metastasis after full evaluation[1,2]
- These solitary metastases include:
  - Synchronous (≤ 6 months after surgery)
  - Metachronous (>6 months after surgery)
- Isolated distant metastases=restricted tumor load=oligometastatic disease (OMD)[3]
- OMD is often defined as maximum 5 metastatic lesions[4]
- OMD can be divided in two categories[5]:
  - With controlled primary site (oligorecurrence)
  - With uncontrolled primary

[1]Luketich JD, et al. Ann Thorac Surg 1995; 60(6): 1609-11
[2]Albain KS, et al. JCO 1991; 9(9):1618-26
[3]Hellman S, et al. JCO 1995; 13(1): 8-10
[4]Liao S, et al. Academic Radiology 2012; 19(1): 69-77
[5]Niibe Y, et al. Pulmonary Medicine Book

# Prerequisites for OMD and PET/CT

Multiple steps of metastasis[1*]:

1) Aggressive phenotype
2) Invasiveness
3) Angiogenesis and inflammation factors
4) Intravasation
5) Vascular adhesion and platelet association
6) Favorable distant environment
7) Homing in the metastatic site
8) Vascular remodeling and extravasation
9) Survival in distant site
10) Colonization in the distant site

*Hellman and Weichselbaum

How does PET/CT help?

1) FDG PET/CT
2) FDG PET/CT
3) 64Cu-ATSM/18F-FAZA and FDG PET/CT
4) None
5) None
6) None
7) FDG PET/CT
8) None
9) FDG PET/CT
10) FDG and FLT PET/CT

[1]Gupta GP, et al. Cell 2006; 119(5):1998-2004

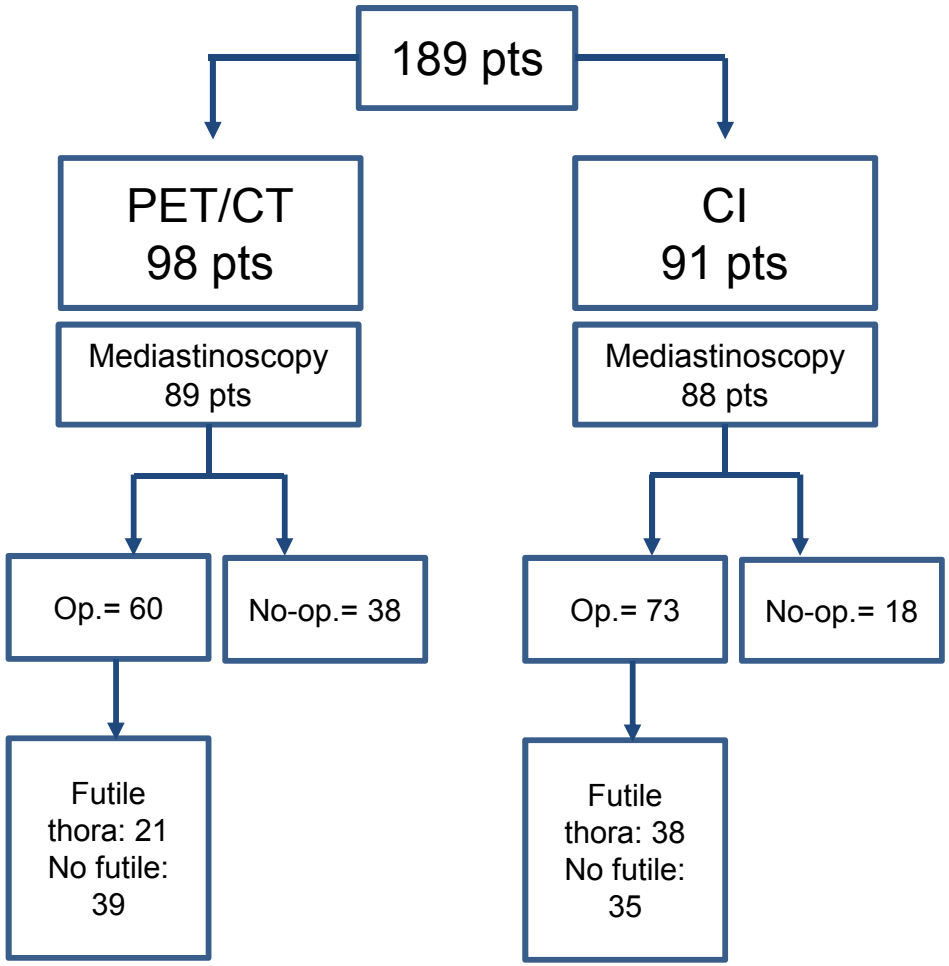
# PET/CT in the lung cancer

- Initial staging
- Evaluation of recurrence
- Evaluation of response to treatment
  - Neoadjuvant
  - Adjuvant
  - others

# PET/CT for the local staging (N)*

## Studio randomizzato

Fisher B, et al. NEJM 2009; 361(2):32-39




*nodal disease burden can greatly influence the potential success of the OMD

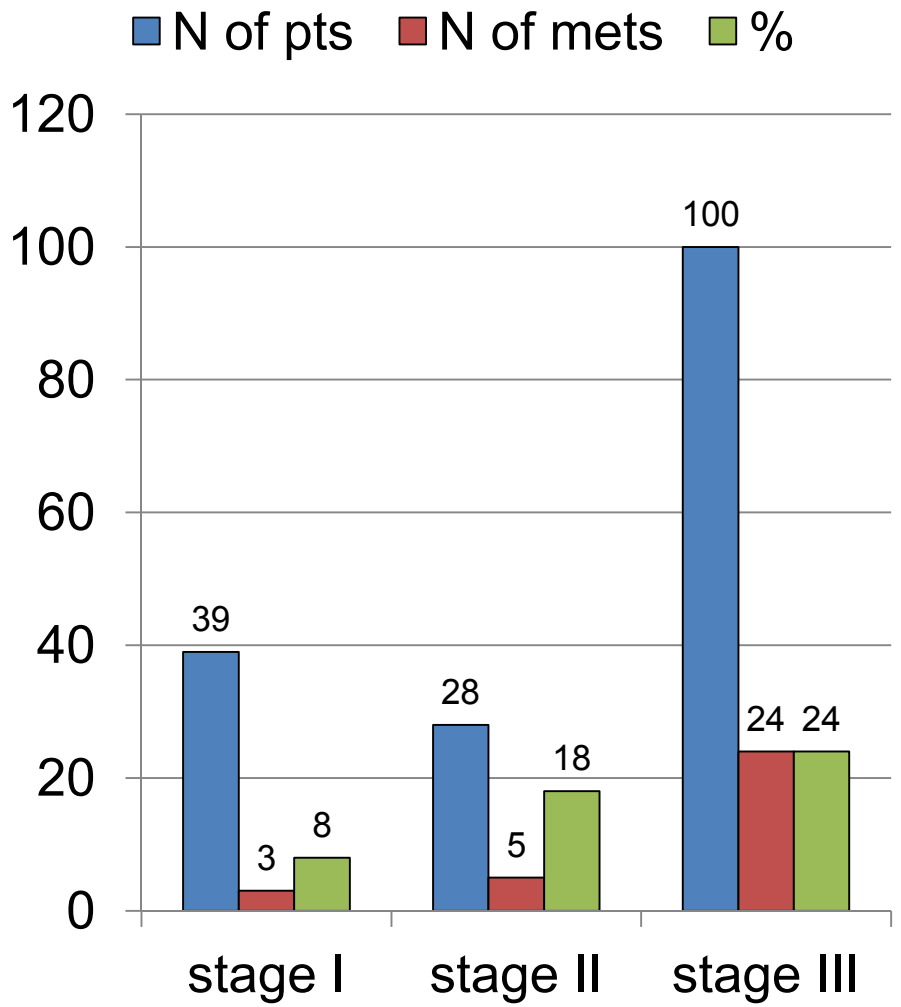
| Author, year (ref) | Sensitivity % | Specificity % |
|---|---|---|
| Gould 2003 (1) | 85 (67-91) | 90 (82-96) |
| Toloza 2003 (2) | 84 (78-89) | 89 (83-93) |
| Birim 2003 (3) | 83 (77-87) | 92 (89-95) |
| Hellwig 2006 (4) | 83 (65-89) | 89 (81-95) |
| Silvestri 2007 (5) | 74 (69-79) | 85 (84-88) |


(1) Gould MK, et al. Ann Intern Med 2003; 139 :879-92
(2) Toloza EM, et al. Chest 2003; 123:132S-146S
(3) Birim O, et al. Ann Thorac Surg 2005; 79:375-82
(4) Hellwig D. Universitat des Saanlandes 2006; 62-80
(5) Silvestri GA, et al. Chest 2007; 132:178S-201S

# PET/CT for the distant staging (M)

According to NICE (National Institute for Clinical Excellence):

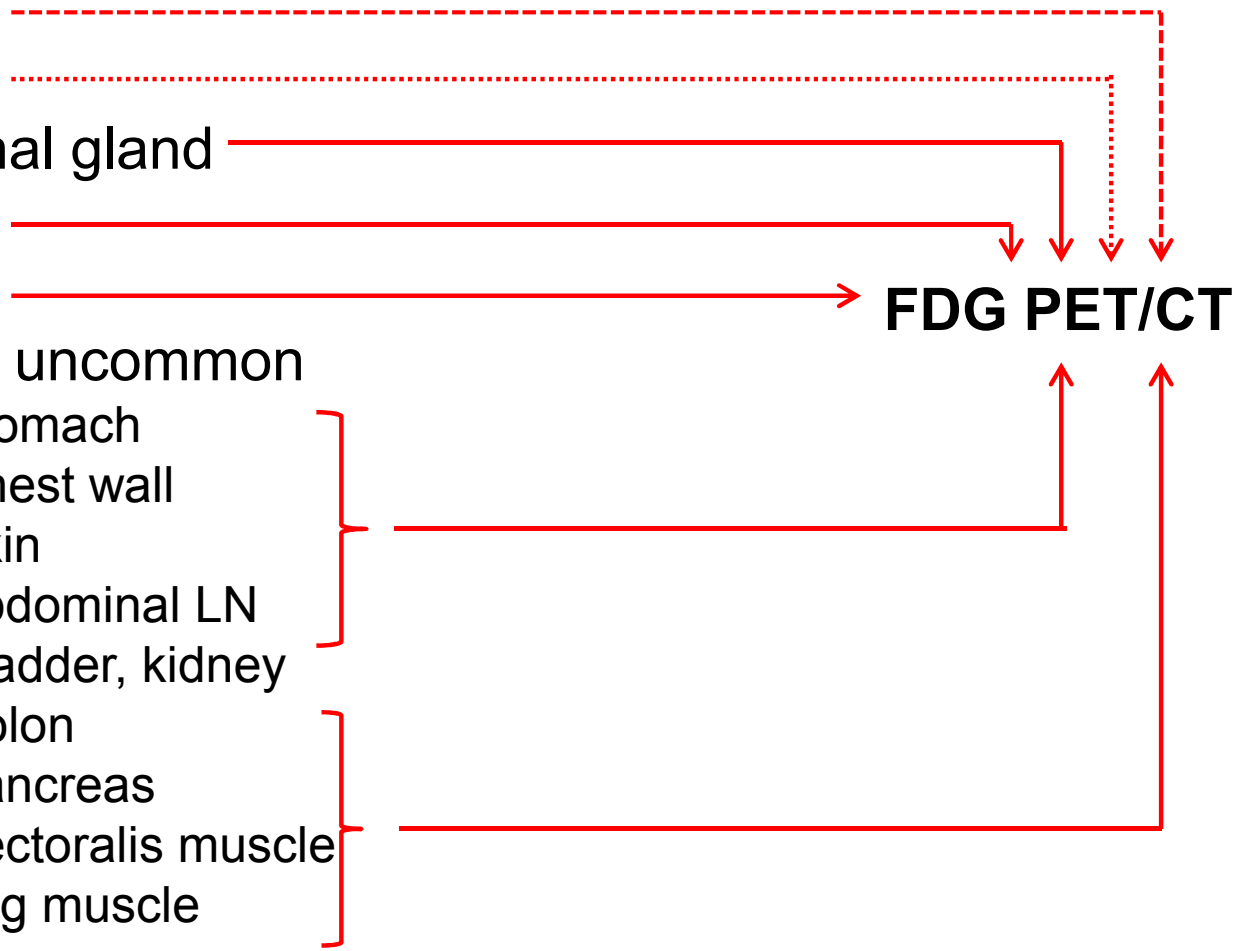
- Sensitivity: 93%
- Specificity: 96%
- Moreover, an average of 15% of pts had unexpected distant metastases detected by PET (otherwise missing by CI)




Mac Manus MP, et al. Int Rad Oncol Biol Phy 2001;50(2):287-93

# PET/CT for the staging of OMD in lung cancer

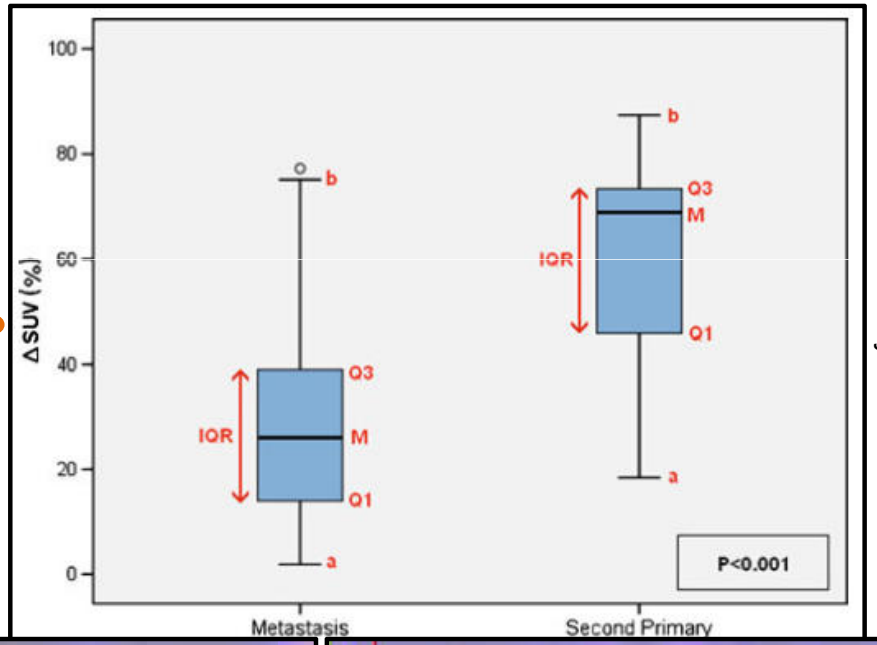
- The site of OMD in lung cancer are:
  - Lung
  - *30-55% Brain
  - **10% Adrenal gland
  - Bone
  - Liver
  - Other uncommon
    - Stomach
    - Chest wall
    - Skin
    - Abdominal LN
    - Bladder, kidney
    - Colon
    - Pancreas
    - Pectoralis muscle
    - Leg muscle



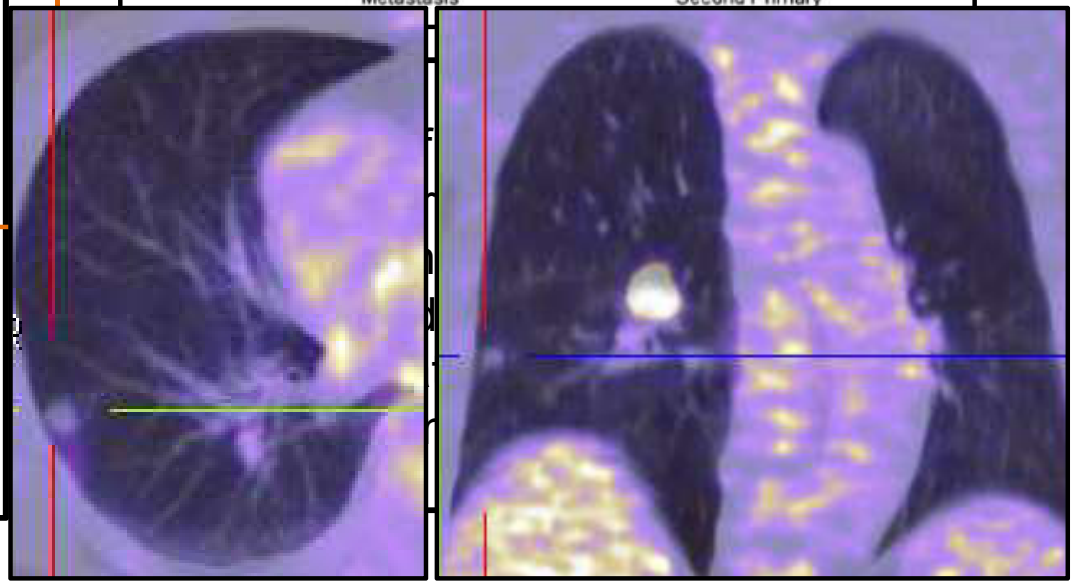

*Rodrigus P, Lung Cancer 2001; 32:129-36
**Allard P, Cancer 1990; 66:457-62

# PET/CT and lung metastases

- Discriminating metastastic disease from secondary primary lung cancer
- Tumor histology may be different, but they can share the same characteristics
- SUVs may be related the histology and staging (therefore SUV is similar for metastasis and different in case of diverse tumors)

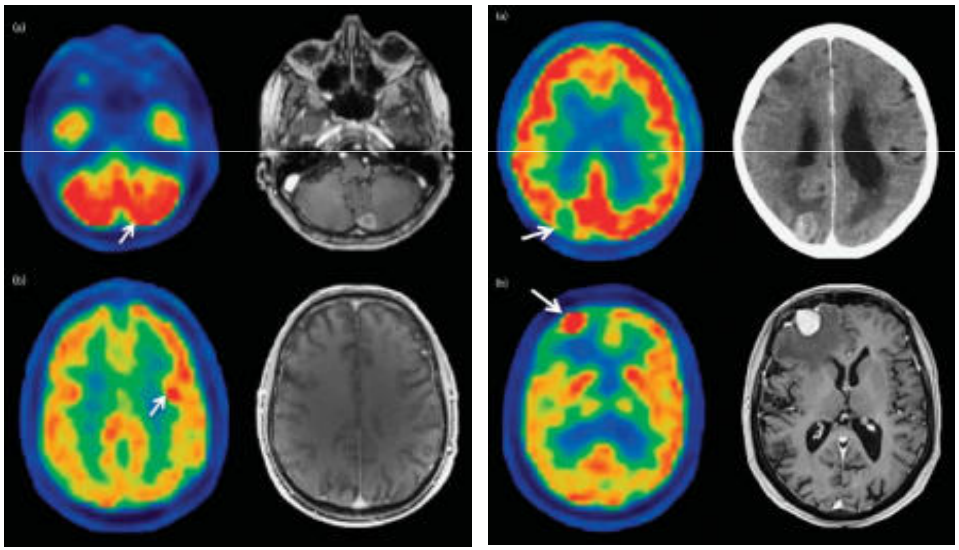



ΔSUV was related to the difference between the SUVmax of primary and secondary lesion



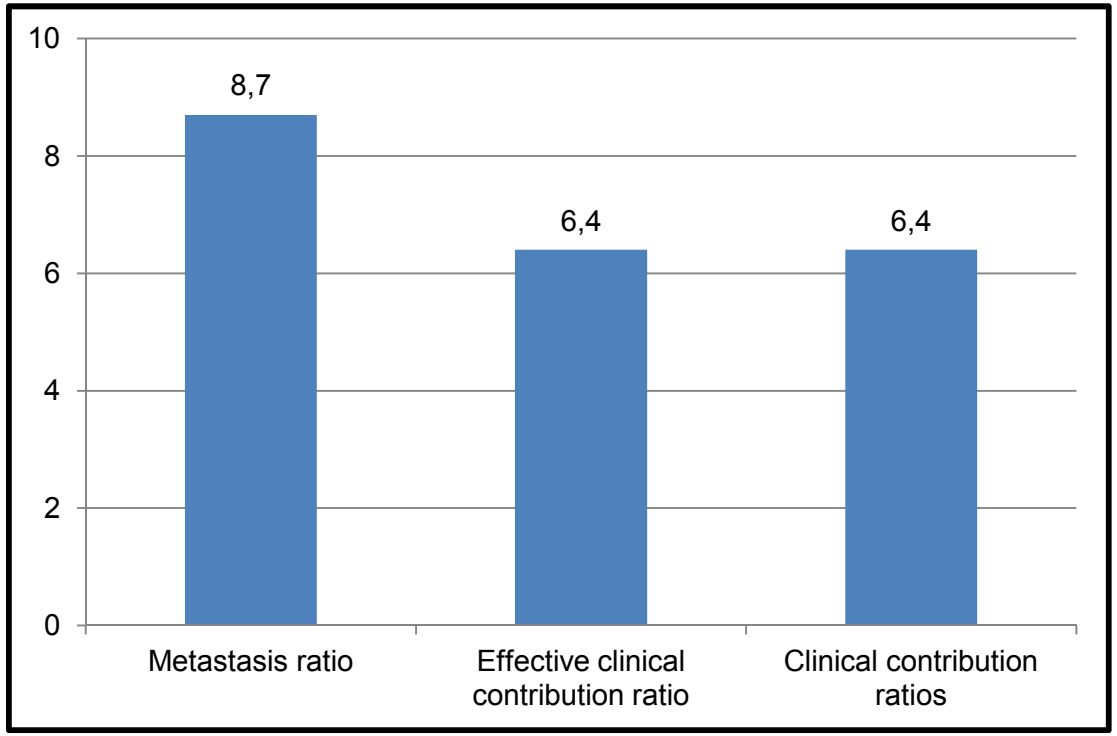
Dijkman BG, EJNMMI 2010; 37:2037-47

# PET/CT and brain metastases



| Authors, year | Sensitivity | Specificity |
|---|---|---|
| Lee HY[1], 2009 | 24% | 100% |
| Kruger[2], 2011 | 27.3% | 97.6% |
| Hjothaug[3], 2015 | 72% | 100% |

A negative 18F-FDG PET/CT does not exclude brain metastases and therefore a MRI is warranted




[4]Metastasis ratio: number of mets/total of mets
Effective clinical contribution ratio: number of bed/change of management
Clinical contribution ratio: change of management based on the site of mets


[1]Lee HY, ANM2008; 22:281-6
[2]Krüger S, Nuklearmedizin. 2011;50:101-6
[3]Hjorthaug K, Nucl Med Comm 2015; 36:1084-90
[4]Tasdemir B, Radiol med 2016; 121:218-24

# PET/CT, brain lesions and prognosis

- In a case series[1-9] of surgically resected solitary brain lesions from NSCLC, the 5-year survival rates for patients were
  - Pre-PET-era prior 2000: ~ 13%
  - Post-PET-era after 2000: ~ 19%
- The trend in improved survival in the PET-era is likely a reflection of improved staging due to higher sensitivity of PET for site of metastatic disease
- That is, patients in the PET-era are more appropriately selected for definitive oligometastatic therapy (*).

[1]Furak J, Ann Thor surg 2005; 79:241-7; [2]Getman V, EJCS 2004; 25:1107-13; [3]Billing PS, J Thor Card Surg 2001; 122:548-53; [4]Bonnette P, Chest 2001; 119:1469-75; [5]Saitoh Y, Lung cancer 1999;24:99-106; [6]Mussi A, JTCS 1996; 112:146-53; [7]Burt M, JTCS 1992; 103:399-410; [8]Rossi NPZD, Respiration 1987; 51:170-8; [9]Magilligan DJ Jr, ATS 1986; 42:360-4

# (*) M1b and M1c descriptors from the proposed TNM 8 classification of lung cancer

| TNM 7 descriptor | Proposed TNM 8 descriptor |
|---|---|
| **M0** no distant mets | **M0** no change to TNM 7 |
| **M1** distant mets | **M1** no change to TNM7 |
| **M1a** separate tumor nodule in a contralateral lobe; tumor with pleural or pericardial effusion | **M1a** no change to TNM7 |
| **M1b** distant (extrathoracic) metastasis | **M1b** single extrathoracic metastasis*, ** **M1c** multiple extrathoracic metastass in one or more organs |

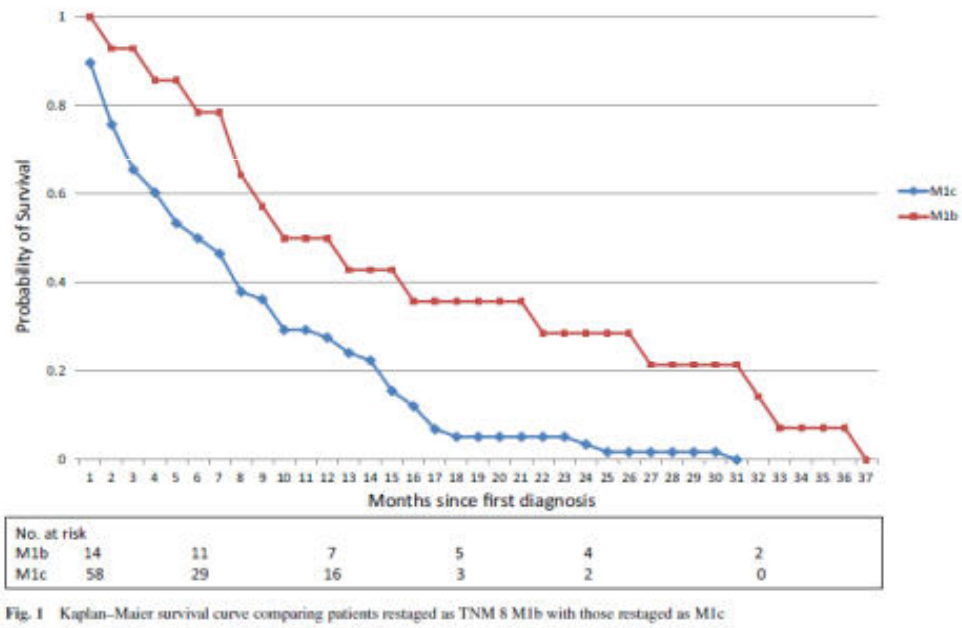


Fig. 1 Kaplan–Maier survival curve comparing patients restaged as TNM 8 M1b with those restaged as M1c

*OS M1b disease staged with PET/CT = 21.4 mo.
*vs.*
*OS M1b staging without PET/CT = 7.0 mo.
*(p= 0.0296)*

**this includes involvement of a single distant (nonregional) lymph node

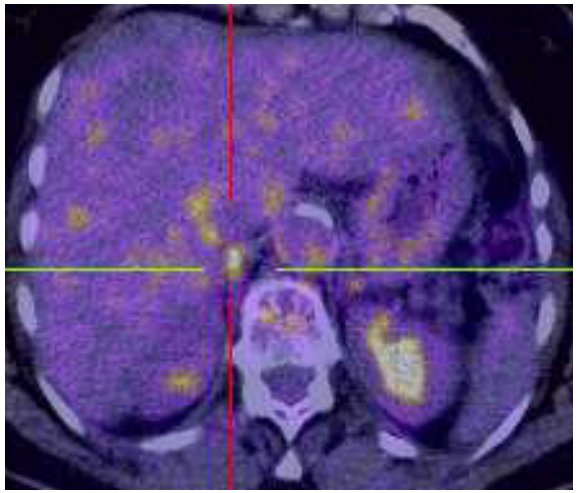
Tufman A, Stahlenther Onkol; published online 28/02/2017

# FDG PET/CT and adrenal gland metastases-1

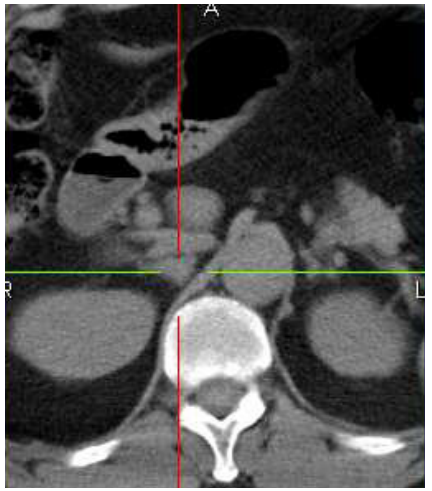
| Subjects | SUVmax right | SUVmax left |
|---|---|---|
| Healthy | 1.13-2.31 | 1.20-2.70 |
| Lung cancer | 1.02-2.71 | 0.95-3.29 |

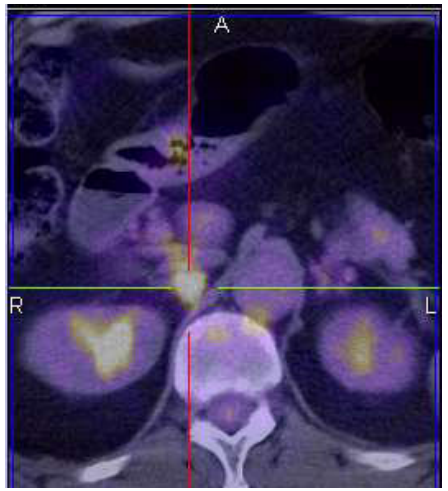
| | SUVmax | | AL ratio | |
|---|---|---|---|---|
| | Right | Left | Right | Left |
| Healthy | 2.08 | 2.46 | 0.81 | 0.92 |
| Lung cancer | 2.39 | 2.64 | 1.03 | 1.13 |

Benign



Malignant





Kim BS, ANM 2015; 29: 276-83

# FDG PET/CT and adrenal gland metastases-2

| Optimal cut-off | Sensitivity | Specificity | Accuracy |
|---|---|---|---|
| SUVmax > 2,7 | 88.9% | 87.5% | 88.5% |
| SUV ratio* > 1,3 | 84.4% | 100% | 88.5% |
| HU > 18 | 86.7% | 81.2% | 85.2% |
| Size > 20 mm | 53.3% | 87.5% | 62.3% |
| SUV ratio > 1,3 and HU > 18 | 97.7% | 81.2% | 93.4% |

*SUV ratio: SUVmax adrenal/liver

The criteria of SUV ratio > 1,3 and HU > 18 can improve the accuracy of differentiating benign and metastatic adrenal lesions in lung cancer patients

Cho AR, NMMI 2011; 45:42-58

# FDG PET/CT and bone metastases-1

| | Bone scan | | FDG PET/CT | |
|---|---|---|---|---|
| **Author, year** | **Sensitivity** | **Specificity** | **Sensitivity** | **Specificity** |
| Fisher[1], 2007 | 22% | 84% | 78% | 100% |
| Lee[2], 2012 | 37% | 92% | 100% | 100% |
| Rodrigues[3], 2016 | 87.8% | 97.5% | 97.7% | 100% |

**Bone scan[4]:**

1) Able to identify more lesions in the skull.
2) Less expensive
3) Only bone information
4) Less sensitive and specific as compared PET/CT

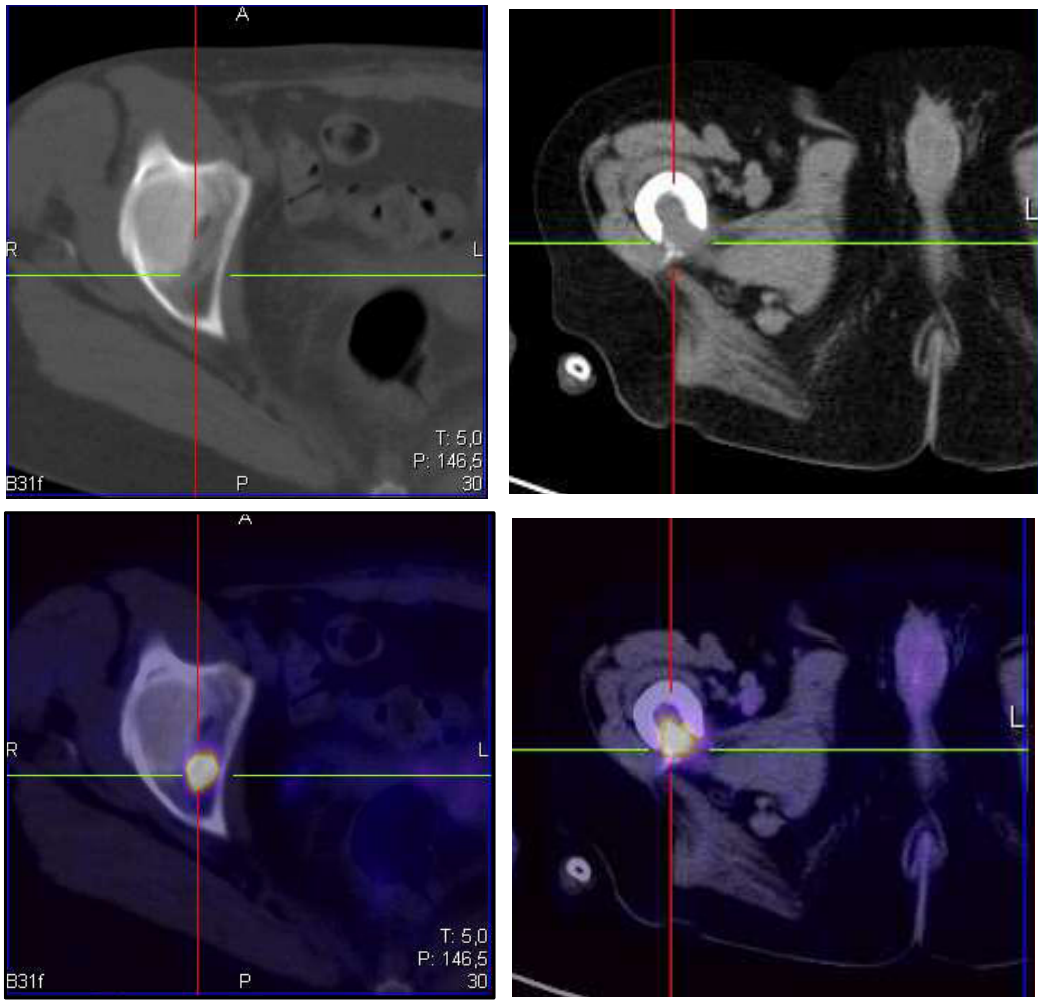
**FDG PET/CT[4]:**

1) Can replace BS in the staging procedure of lung cancer
2) Not reliable for detecting metastases in the brain or in the skull
3) In the spine and in the pelvis detects more lesion than BS
4) CT component can help in detecting sclerotic lesions

[1]Fisher BM, Ann Oncol 2007; 18:338-45; [2]Lee JW, ANM 2012; 31:124-9; [3]Rodrigues M, QJNMMI 2016; 60:62-8;
[4]Mitchell MD, Acad Radiol 2016; 23:1047-1056

# FDG PET/CT and bone metastases-2

Osteomedullar lesion

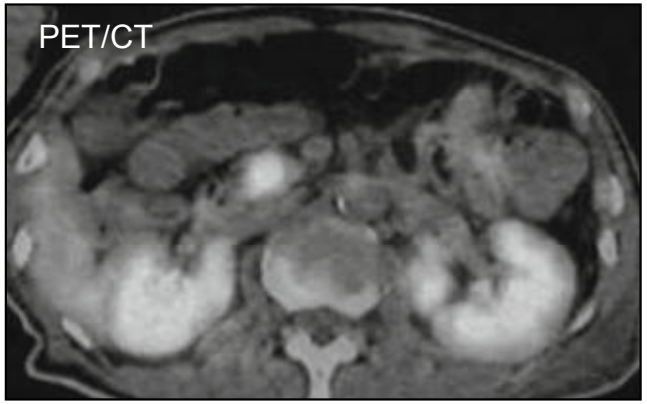



Osteolytic lesion

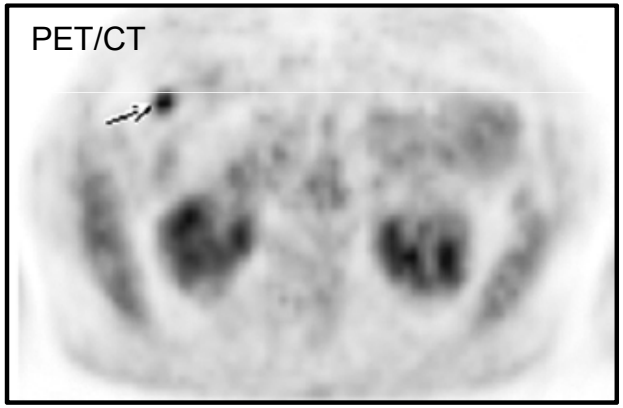
- Osteomedullary lesions can be detected only by FDG PET/CT and MRI
- Osteolytic lesions are visible on CT and PET/CT
- Osteoblastic lesions can be missed by PET/CT, but CT component can be useful.

# PET/CT and the other site of metastases

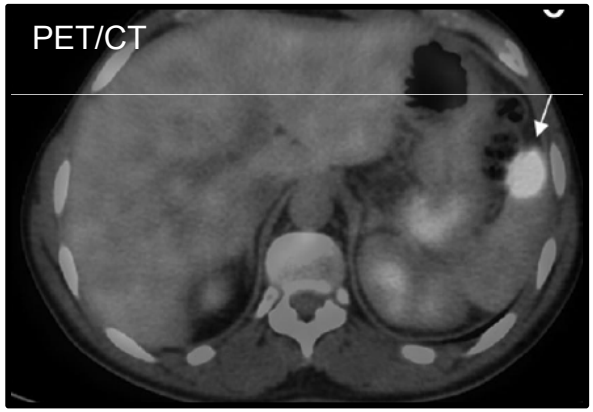
Pancreas metastasis




Sato M, Ann Nucl Med 2009; 23:49–57

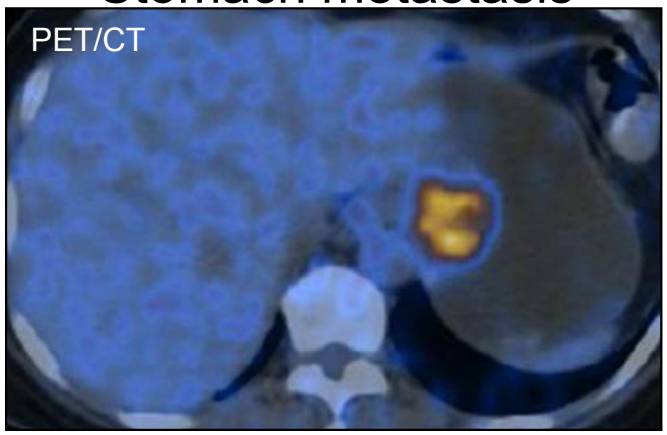



Abdominal lymph node metastasis

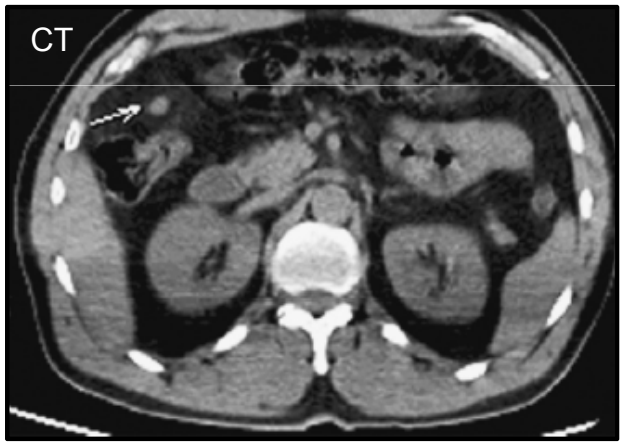



Spleen metastasis

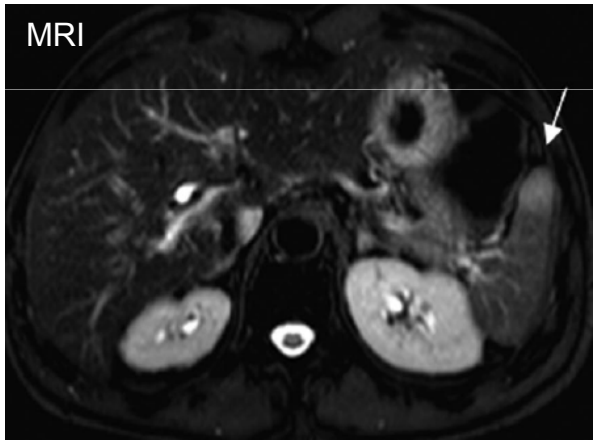
Stomach metastasis




Ding L, Oncotarget, 2016; 7:87479-84




Clin Nucl Med 2013; 38: 691-4




Clin Nucl Med 2011; 36: 707-9

# PET/CT as a guide for the treatment of OMD

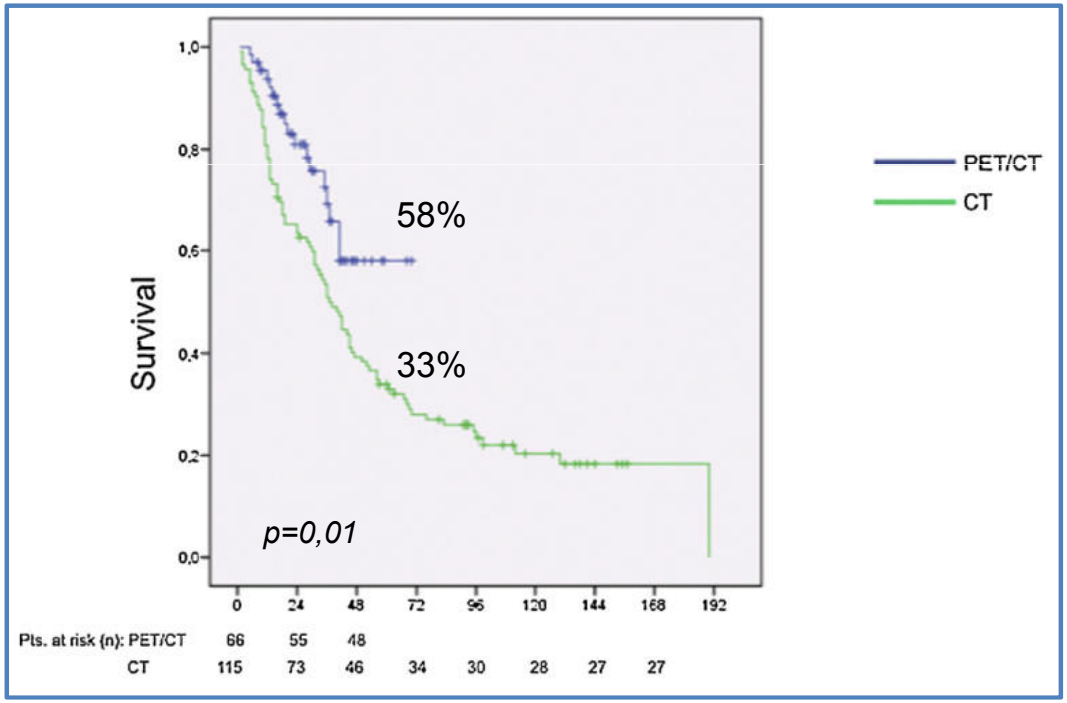
181 pts
Lung cancer
Initial staging

66 pts
PET/CT

115 pts
CT

181 pts with OMD in:
Lung, brain, adrenal, bone and other

Lobectomy (n=7)
Pneumectomy (n=10)
Segment – and wedge resection (n=98)
Resections for extrapulmonary metastases (n=66)




Results of multivariate analysis for factors affecting overall survival.

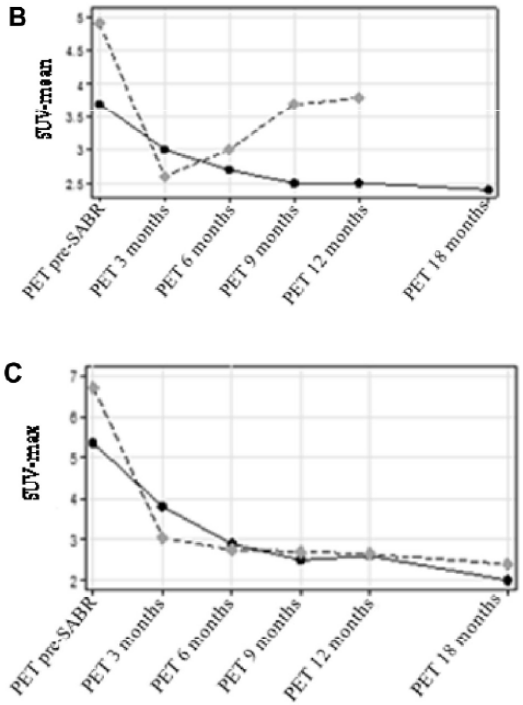
| | Patients (*n*) | Hazard ratio | 95% CI | *P*-value |
|---|---|---|---|---|
| PET/CT | | | | |
| PET/CT vs. | 66 | 0.508 | 0.299–0.861 | 0.012 |
| CT | 110 | 1.970 | 1.161–3.342 | |
| Lymph node involvement | | | | |
| N0 vs. | 101 | 0.643 | 0.433–0.955 | 0.029 |
| N1/2/3 | 75 | 1.554 | 1.047–2.308 | |
| Metastatic site | | | | |
| Pulmonary vs. | 113 | 0.539 | 0.355–0.819 | 0.004 |
| Extrapulmonary | 63 | 1.855 | 1.221–2.819 | |

Tonnies S, Lung Cancer 2016; 93:28–34

# PET/CT and the evaluation of response to therapies

SABR: stereotactic Ablative Radiation Therapy

| | No. lesions | Median SUVmax (range) | Median SUVmean (range) | Median MTV (range) |
|---|---|---|---|---|
| **Baseline** | 70 | 6.5 (4-17) | 3.7 (2.5-6.5) | 2.3 (0.2-31) |
| **FUP 3 mo.** | 70 | 3.8 (1.9-14) | 3 (1.9-6.5) | 3.9 (0.25-50) |
| **FUP 6 mo.** | 51 | 2.8 (2-20) | 2.7 (1-5) | 5 (1-18) |
| **FUP 9 mo.** | 24 | 2.5 (2-11) | 2.5 (2-4) | 7 (0.05-10) |
| **FUP 12 mo.** | 18 | 2.6 (1.7-11.5) | 2.5 (2-4) | 7.8 (0.05-10) |
| **FUP 18 mo.** | 6 | 2.4 (2-3.7) | 2.4 (2-2.7) | NA |




B=local failure (dashed line); no local failure (solid line)
C= SUVmax in patients with mets after SABR (dashed line); no mets after SABR (solid line)

- Post-SABR radiological changes are frequently detected on diagnostic CT scan imaging
- In case of mass-like patterns on CT scans after SABR, it is difficult to differentiate between radiation fibrosis and recurrence
- FDG PET/CT may assess the response to therapy in OMD lung patients by using metabolic parameters.

Mazzola R, J Thorac Oncol 2016; 12: 547-55

# Take home messages

In OMD lung cancer patients

- Semiquantitative metabolic PET parameters are useful to:
  - Differentiate second lung cancer from metastatic lung cancer
  - Evaluate the presence of adrenal metastasis
  - Define the response to local treatments (i.e SABR)
- PET/CT is able to guide to surgical treatment, with a significant impact on the prognosis
- PET/CT has a low sensitivity for brain metastases.

# Thanks!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