Multi Modal PET/CT Imaging: The *Clinical* Point of View – Focus on Non Small Cell Lung Cancer

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Learning Objectives: NSCLC

The Importance of CTPET

1. For prognosis and treatment decision (Theragnostic)
2. Gross Tumour Volume & Biological target Volume identification & contouring (4D-CTPET superior to 3D)
3. To adapt the treatment
4. *To use new Imaging Biomarkers (Hypoxia, Labeled drugs…)*
5. *To delineate new target volume: GTV $_{\text{Low drug uptake}}$, Normal Tissue Avoidance Volume & Normal tissue Preferential Volume*

Multimodal Imaging: Focus on Lung Cancer

1. Theragnostic (treatment decision after diagnosis)

2. Gross Tumour Volume identification & contouring

3. Adaptive Radiotherapy

4. Metabolic response @ 3 months

5. GTV_{LDU} (LDU = Low drug uptake target)

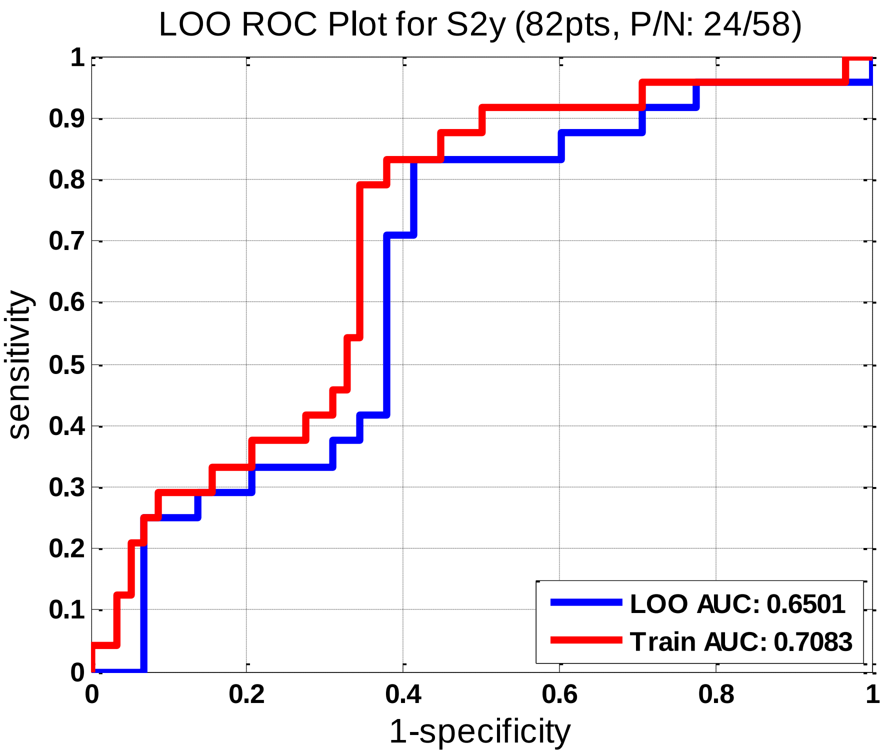
6. Normal Tissue Avoidance Volume & Normal tissue Preferential Target Volume

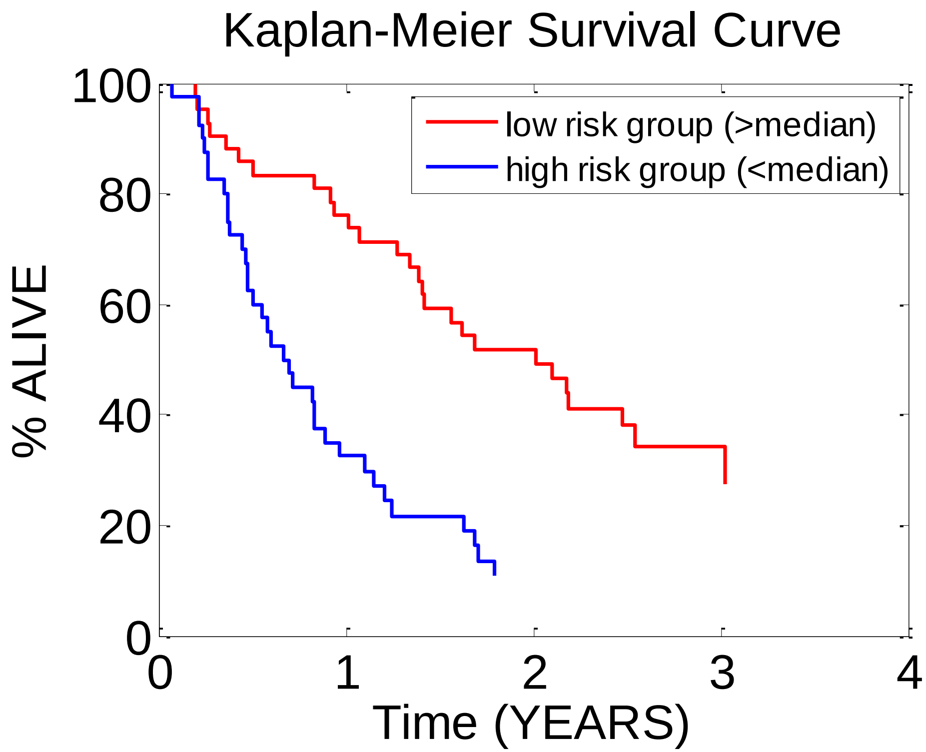
Personalized Medicine: Multifactorial Decision Support Systems

Lambin *et al.* Nature Rev. Clin. Oncol 2012; Lambin *et al.* Radiother Oncol 2013

Prediction of survival in Lung cancer: Clinical data only (TNM)

- Leave-one-out AUC: 0.65





Selected features: WHO-PS, clinical T stage, clinical N stage

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Lambin *et al.* Nature Rev. Clin. Oncol 2012, Dehing-Oberije *et al.*; Oberije *et al.*

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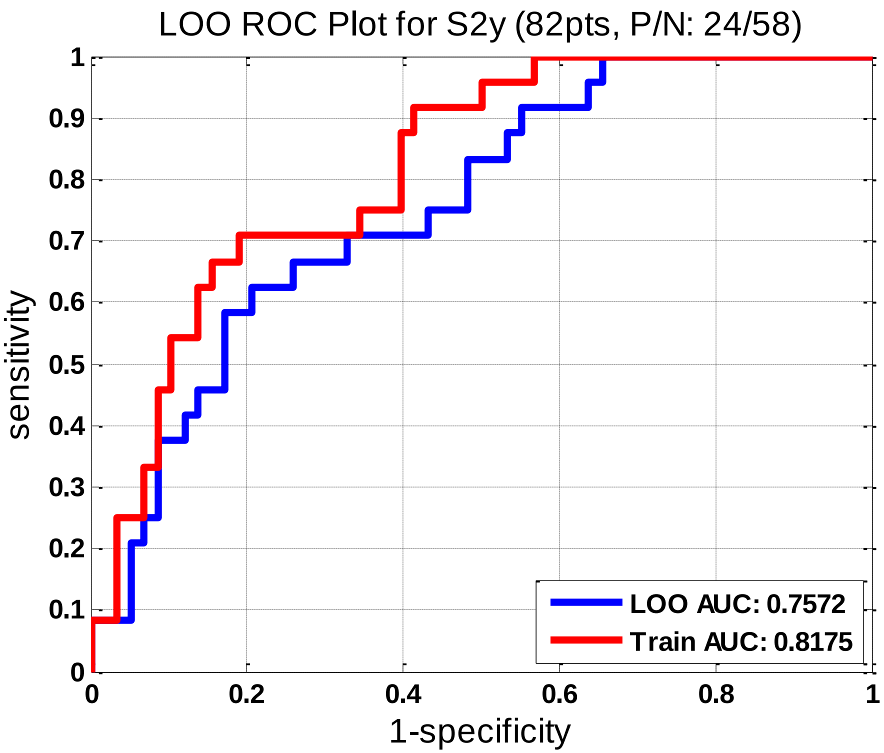
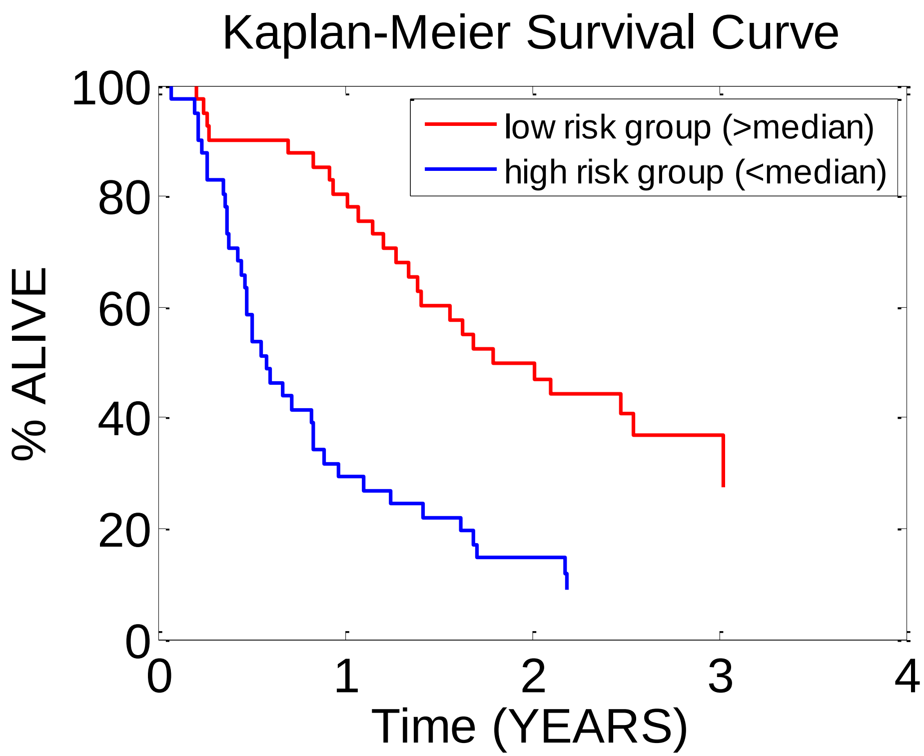
Prediction of survival in Lung cancer:
Clinical + Image data

- Leave-one-out AUC: 0.76





Selected features: WHO-PS, clinical T-stage,

number of positive lymph node stations (PET), gross tumor volume (CTPET)

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Lambin *et al.* Nature Rev. Clin. Oncol 2012, Dehing-Oberije *et al.;* Oberije *et al.*

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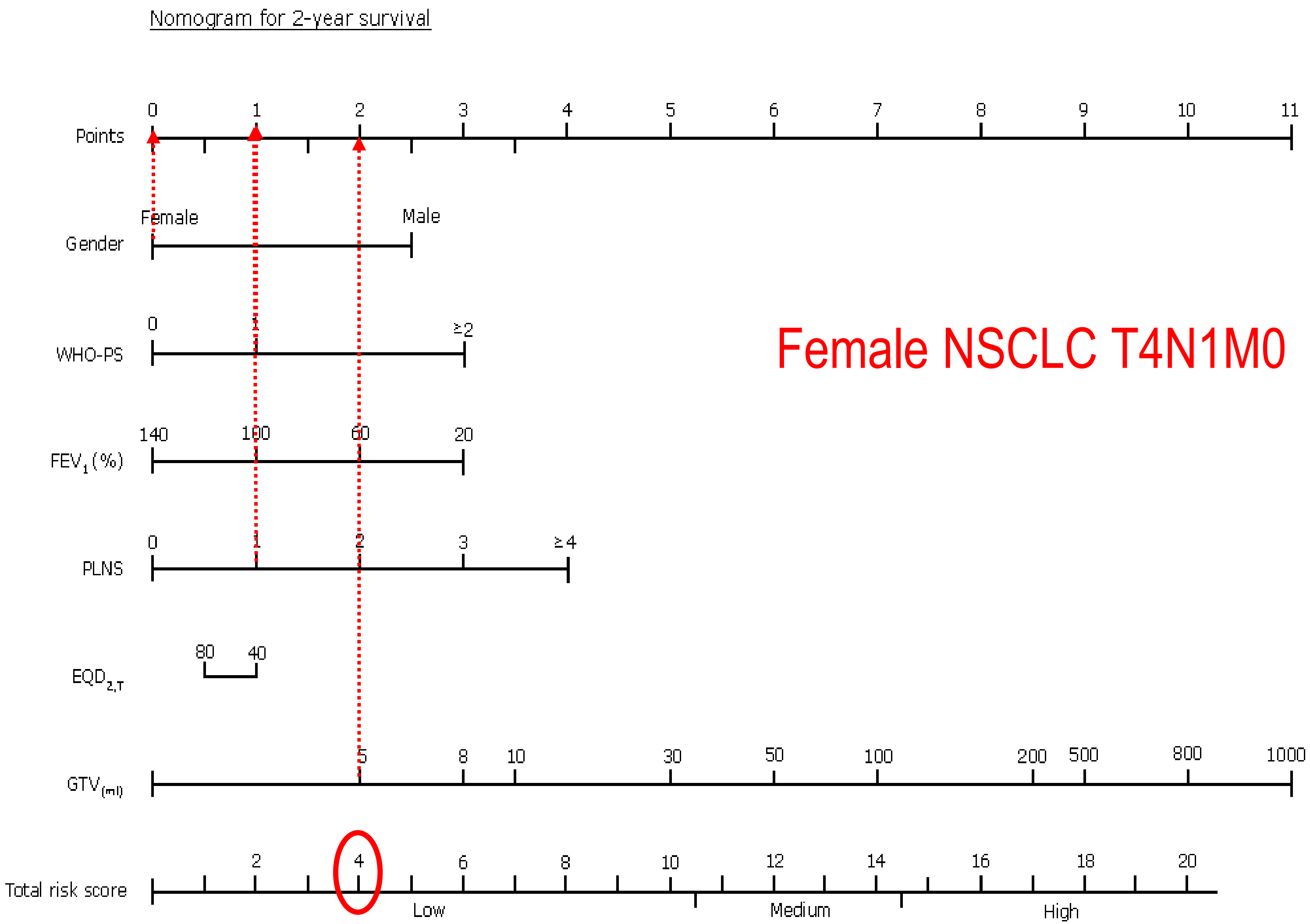
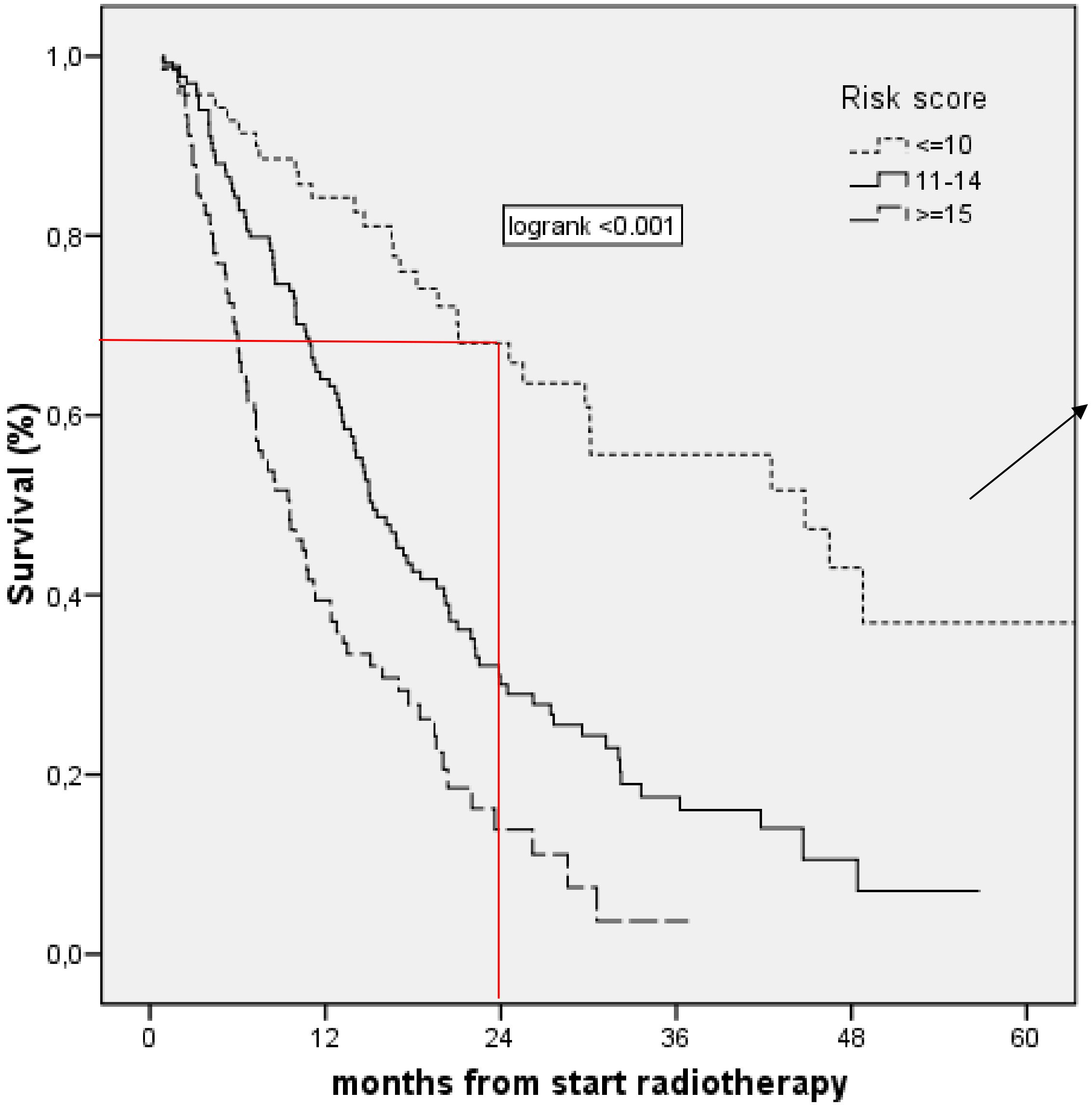
Decision Support System of first generation: Nomogram Lung Cancer

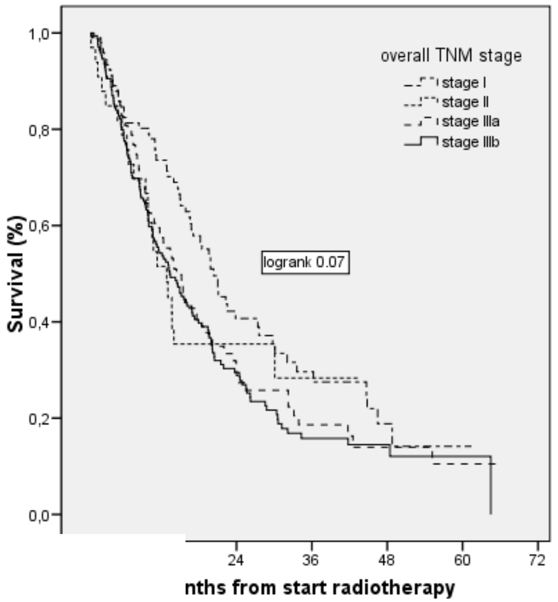


Dehing *et al*. IJROBP 09; www.predictcancer.info

Results: Risk groups



Stage IIIA 10 (14.3%)
Stage IIIB 13 (18.6%)
T4 12 (17.1%)



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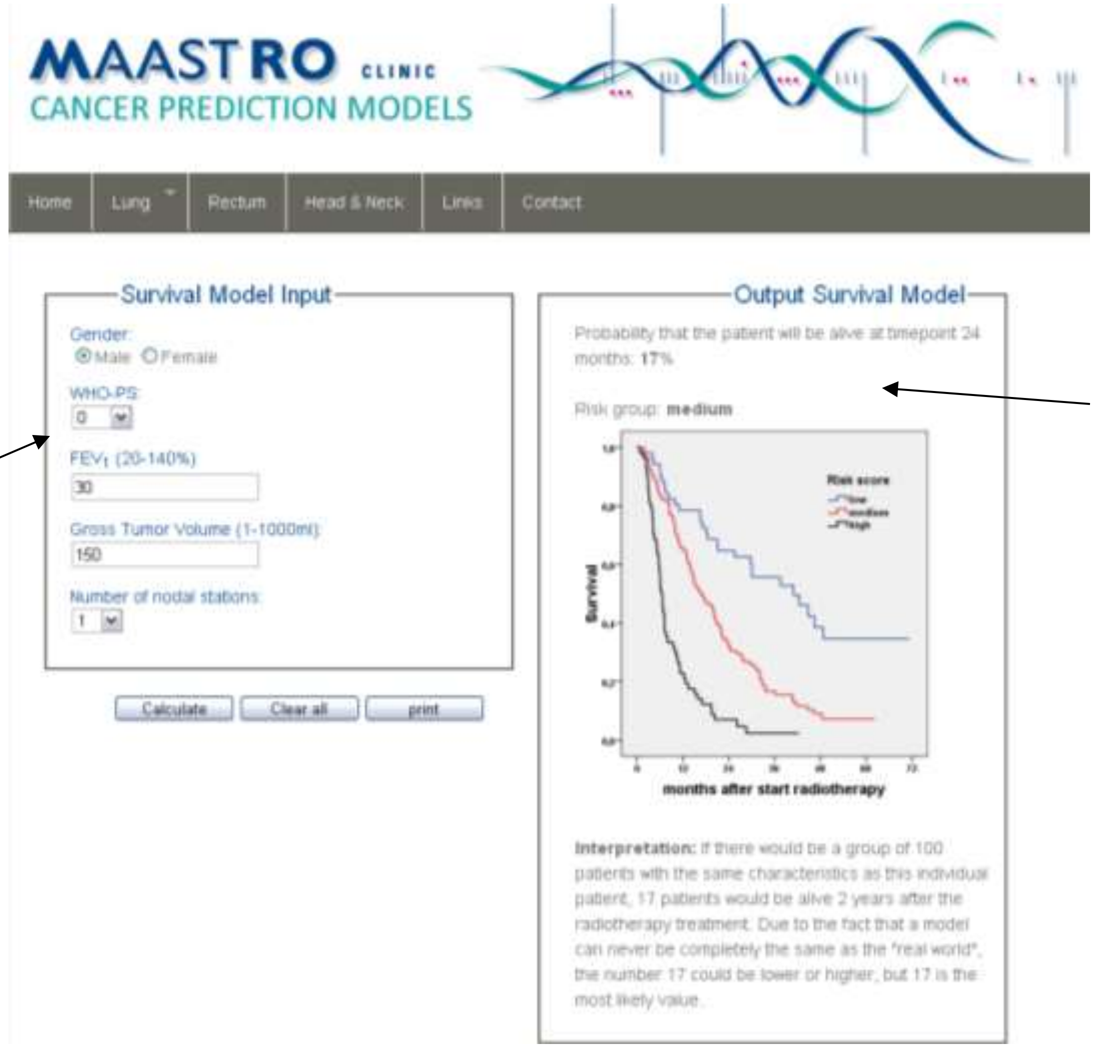
Dehing *et al*. IJROBP 09

www.predictcancer.org

Available:
All published MAASTRO models (Lung, rectum, H&N)

Online input of patient data



Online calculation of probability of outcome and risk group stratification

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Multimodal imaging: Focus on Lung Cancer

1. Theragnostic (treatment decision)

2. Gross Tumour Volume identification (GTV1-2) & contouring

3. Adaptive Radiotherapy

4. Metabolic response @ 3 months

5. GTV_{LDU} (LDU = Low drug uptake target)

6. Normal Tissue Avoidance Volume & Normal tissue Preferential Target Volume

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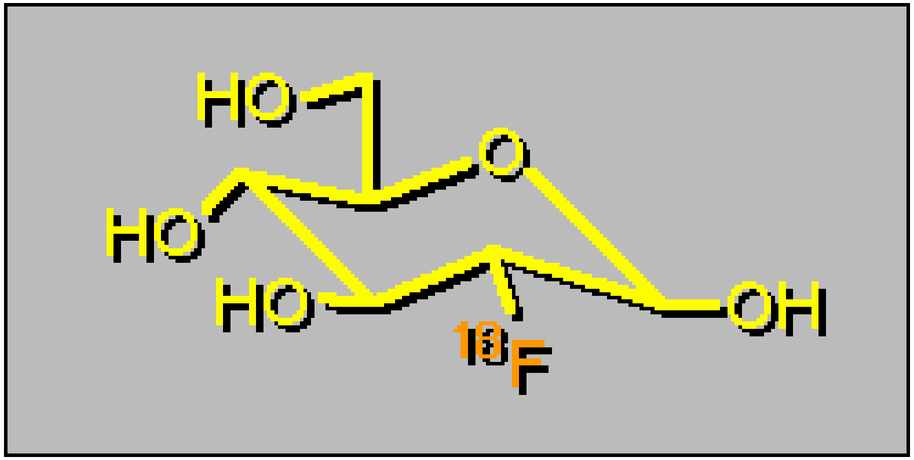
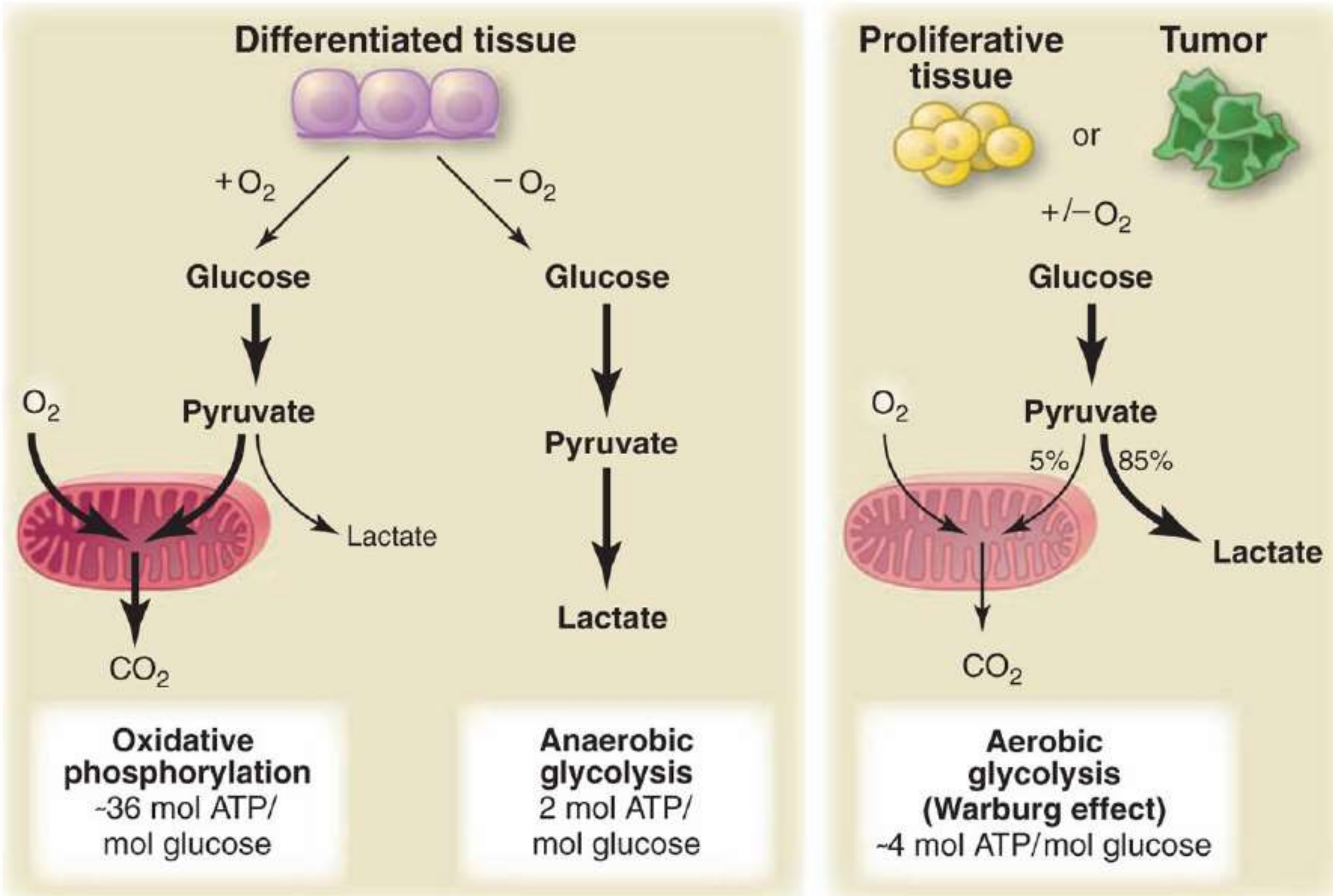
^{18}F-Fluoro-2-deoxy-D-glucose (FDG)





Vander Heiden M et al. Science 2009

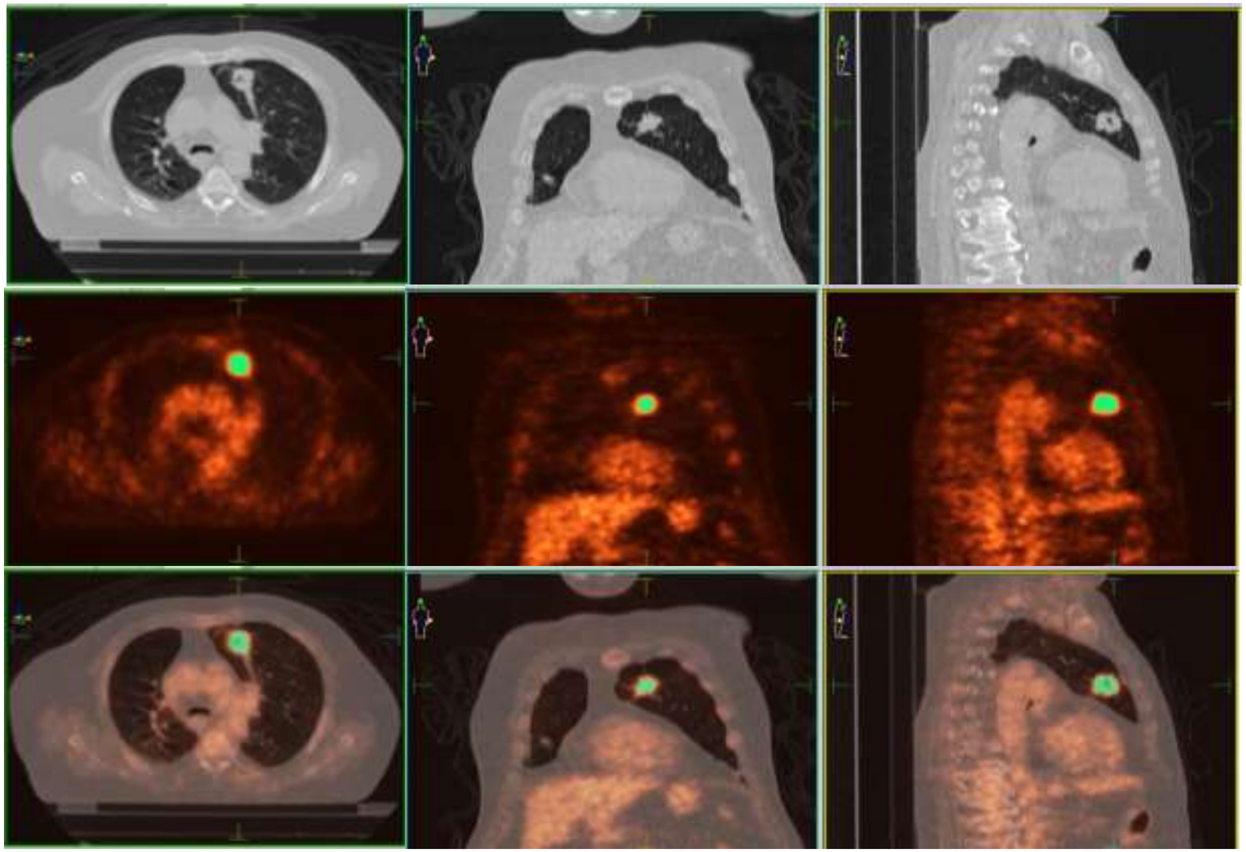
Multi Modal Imaging

CT

PET

Fusion

CT/PET



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PET-CT

Advantages:

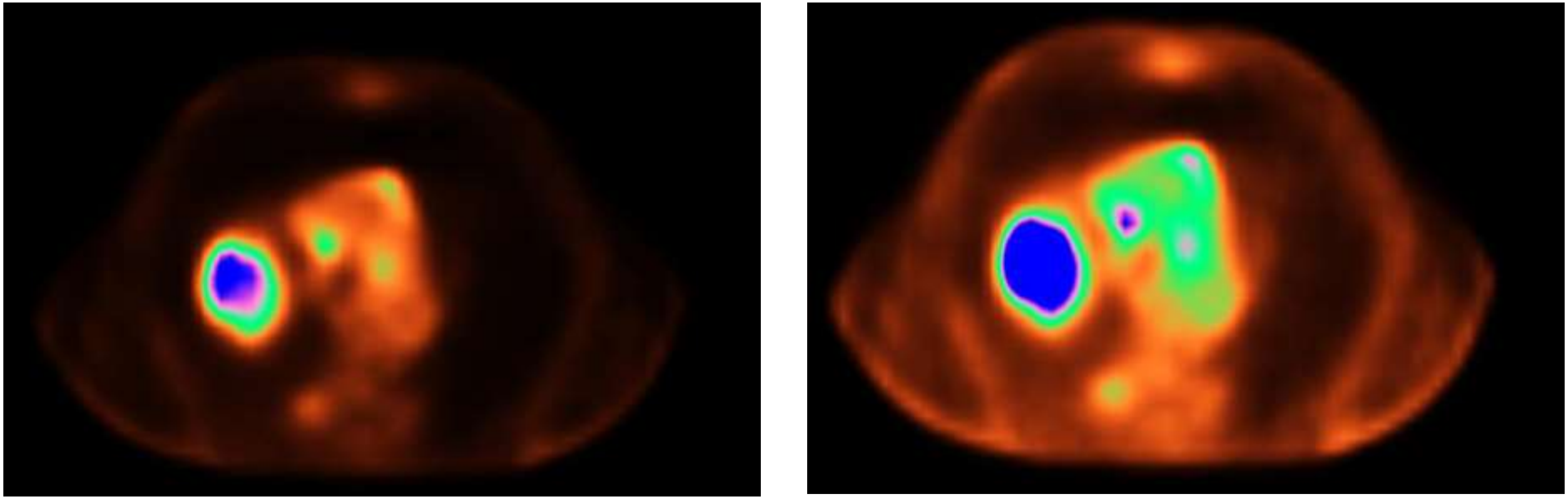
- Combination of anatomical and functional information
- Identical position of patient
- No time interval between PET and CT scan
- CT can be used for attenuation correction
- CT densities can be used for RT dose calculation

Planning PET-CT scan

- Images for simulation in treatment position
- Flat table + lasers
- Drawing of the lines on the patient
- Immobilisation system (mask, arm support…)
- Preference for 4D image acquisition

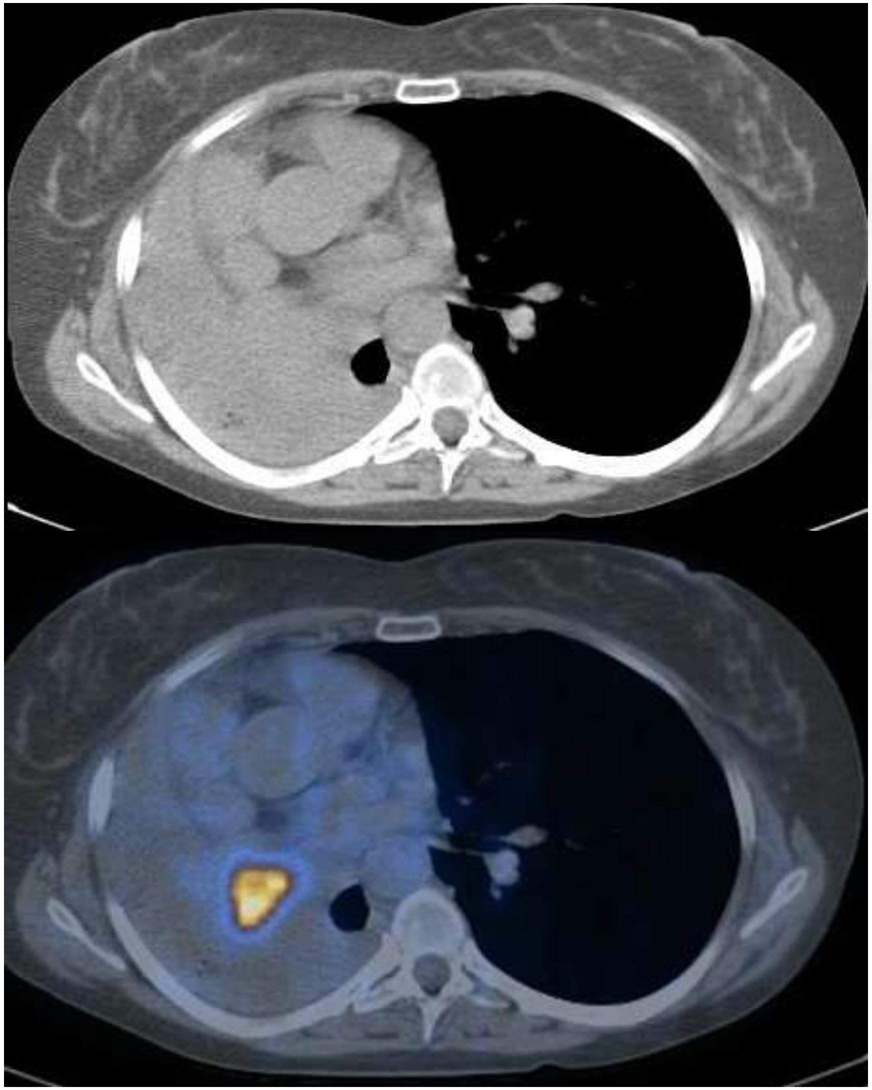
PET

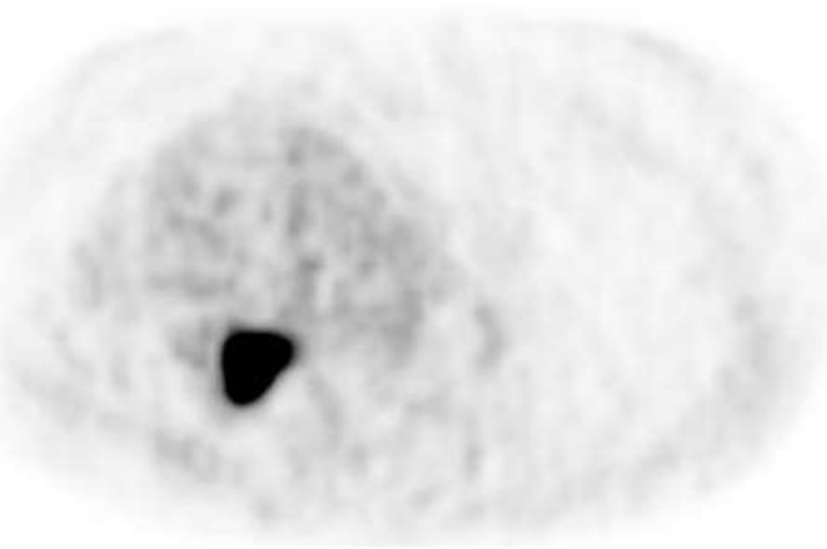
- Window-level setting:
  - standardized setting necessary **(! Also for CT)**
  - and other standardization… (*next speaker*)



Same tumor, different settings

Which volume to treat? GTV1





NSCLC with atelectasis

GTV2: N-staging in NSCLC

	CT	(CT-)PET
Sensitivity	33-83%	77-91%
Specifity	66-90%	67-92%
PPV	46-71%	67-90%
NPV	68-86%	77-97%
Accuracy	65-80%	73-92%

Dwamema et al., Radiology 1999

Fisher et al., Lancet Oncol 2001

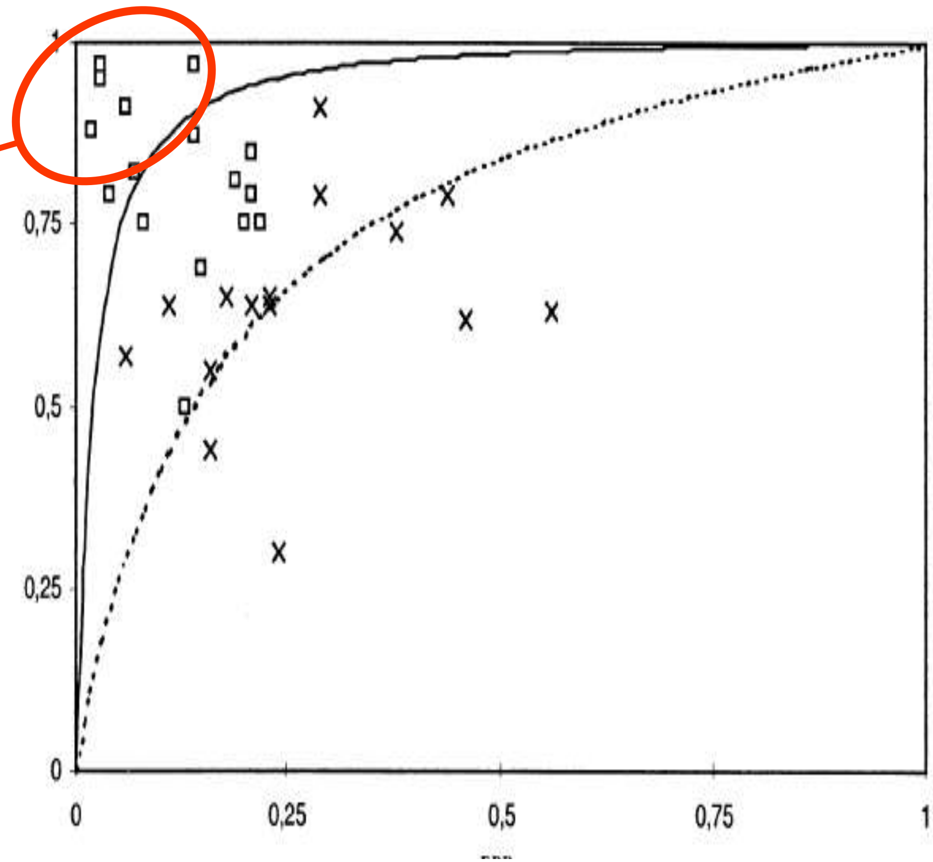
Gould et al., Ann Intern Med 2003

Kramer et al., Ann Surg 2003

And others

sROC-analysis FDG-PET vs. CT

Residual risk for undetected lymph node metastases in patients with NSCLC: ‹10%

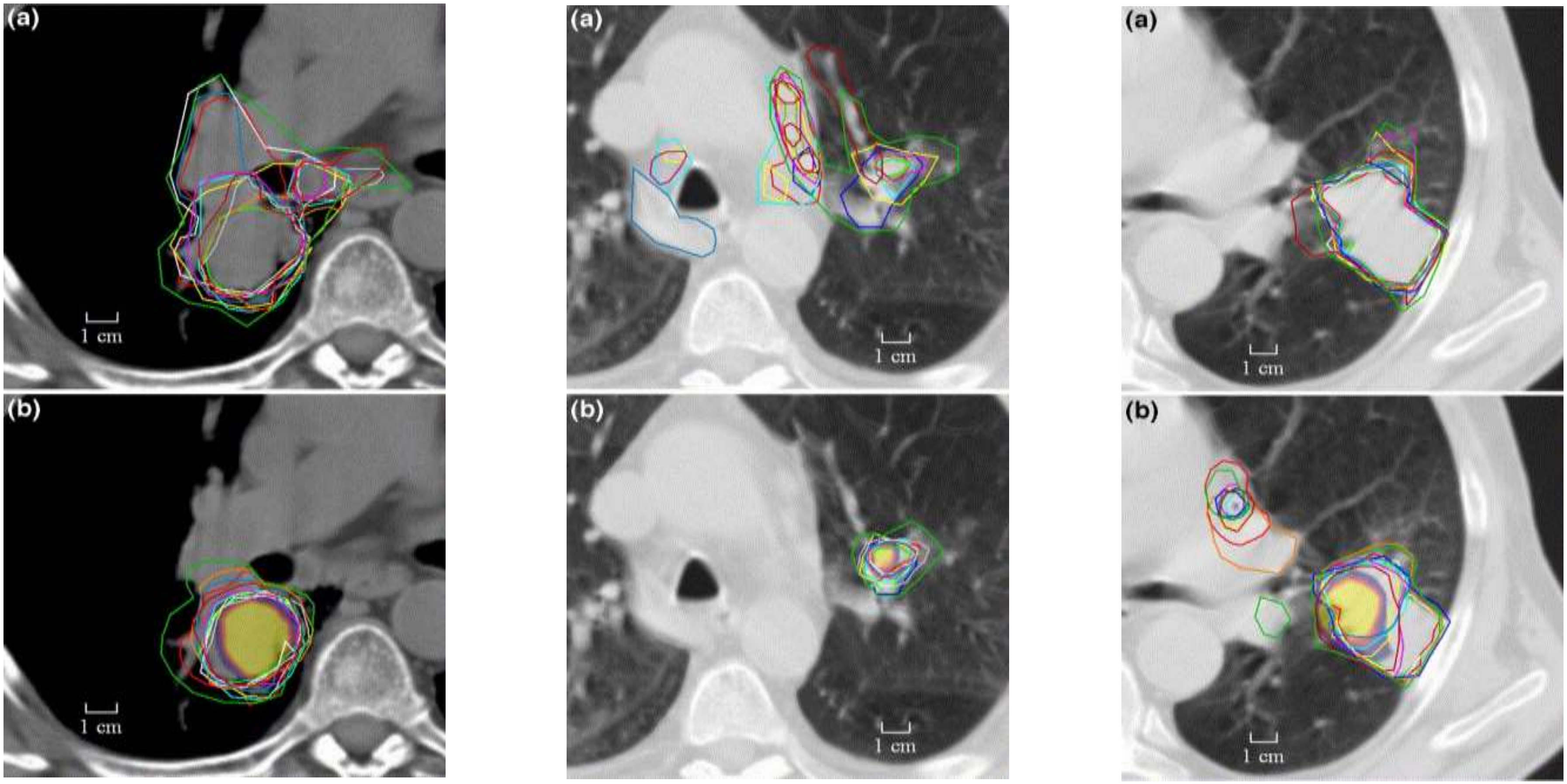


Without elective nodal irradiation < 5 % isolated nodal failures

CT: Senan et al. IJROBP 2002, Rozenzweig et al. JCO 2007

PET: De Ruysscher et al. IJROBP 2005; Belderbos et al. IJROBP 2006

Interobserver Variation in Delineation



CT: large interobserver variation

Steenbakkers et al., IJROBP 2006

PET Delineation

Methods

Manual:

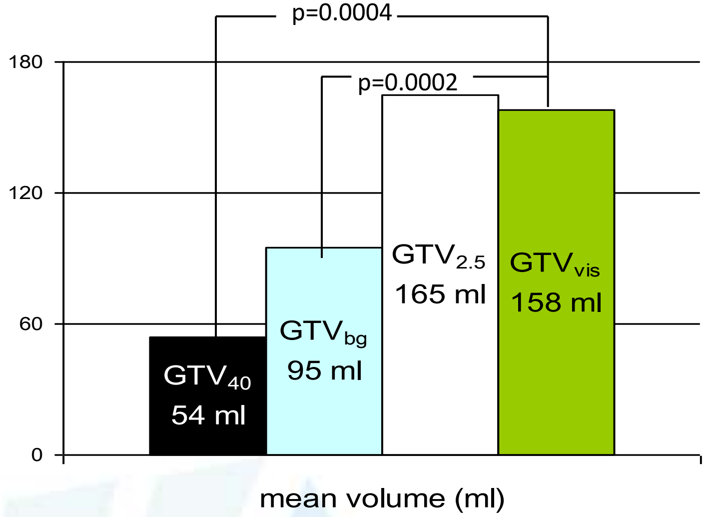
- Visual

Automated:

- SUV based
  - Fixed threshold (% of maximal SUV)
  - Fixed SUV value
- Source-to-background based methods (validated in H&N tumours)
- Watershed-clustering methods

Daisne, Radiology 2004; Hatt et al. Review

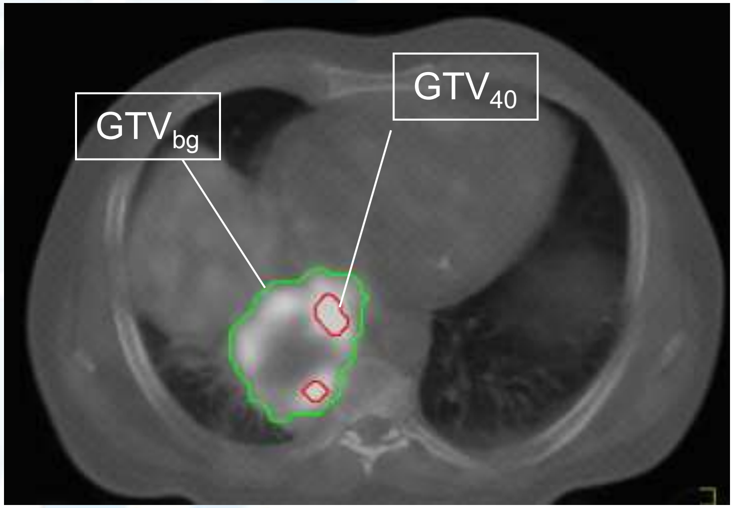
Size of FDG-based GTV is influenced by the contouring method



25 primary NSCLC, FDG based GTVs

Contouring methods:
- visually (GTV_{vis})
- threshold = SUV 2.5 ($GTV_{2.5}$)
- 40% of maximum accumulation in lesion (GTV_{40})
- contrast dependent algorithm (GTV_{bg})

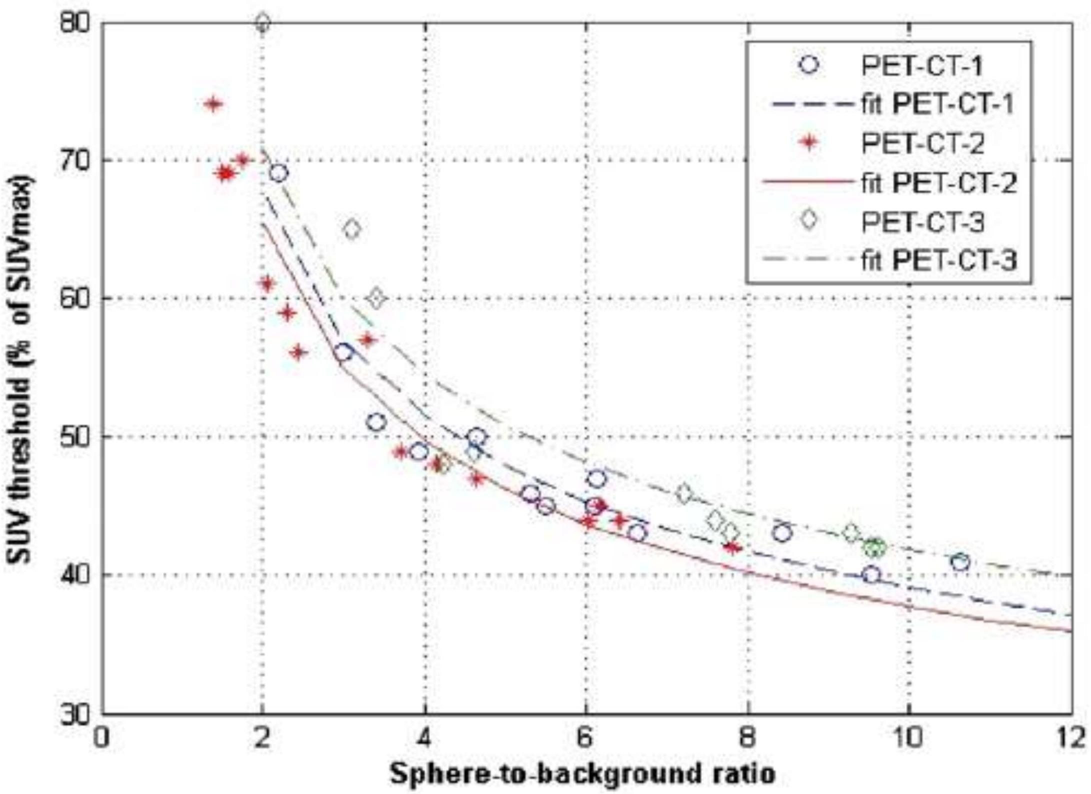
Significant differences correlating with
- SUV_{max}
- size of lesion
- inhomogeneity of accumulation



Nestle U et al. J Nucl Med 2005 46; 1342-1348

Delineation: SBR method

- SUV threshold dependent of source-to-background as measured in spheres
- Source: tumour
- Background: normal lung tissue or muscle

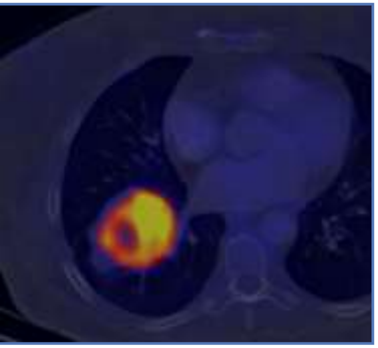


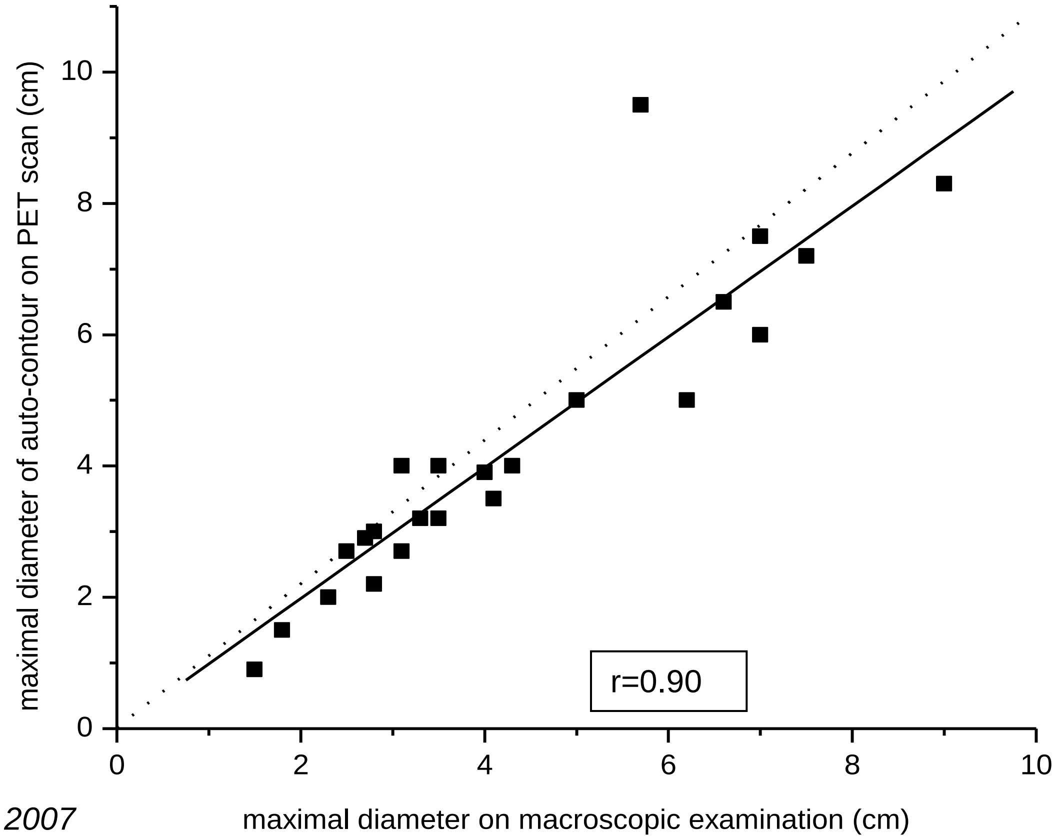
Multicentric calibration:

Öllers et al. Radioth Oncol 2008

Delineation: SBR method

- Validation of SBR based autocontouring in NSCLC
- Autocontouring as base for definitive target volume definition

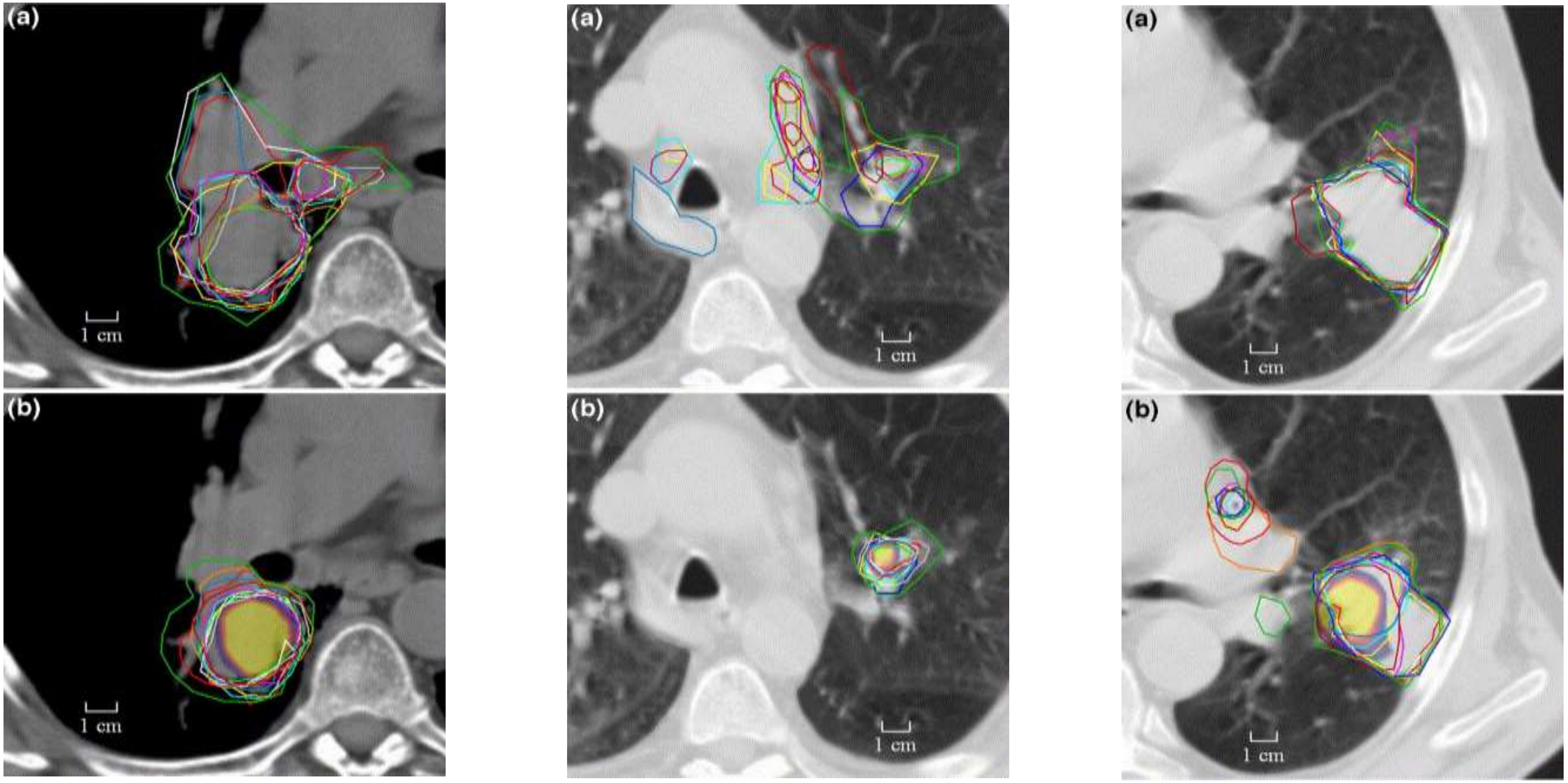




van Baardwijk et al.; IJROBP 2007

Other methods (FLAB): Hatt et al. J Nucl Med 2011

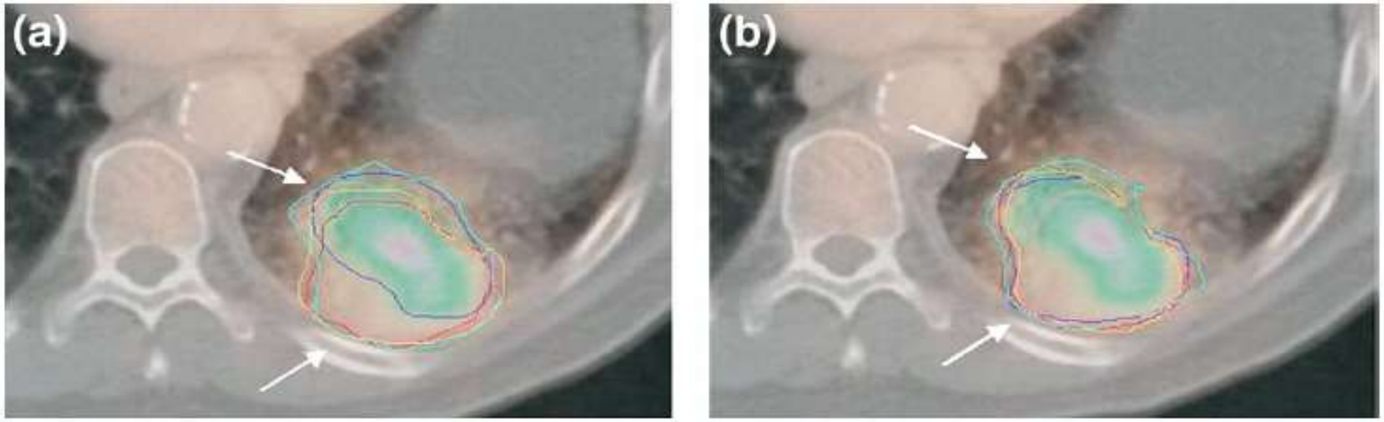
Interobserver Variation in Delineation



PET-CT: reduction in interobserver variation

Steenbakkers et al., IJROBP 2006

Interobserver Variation in Delineation



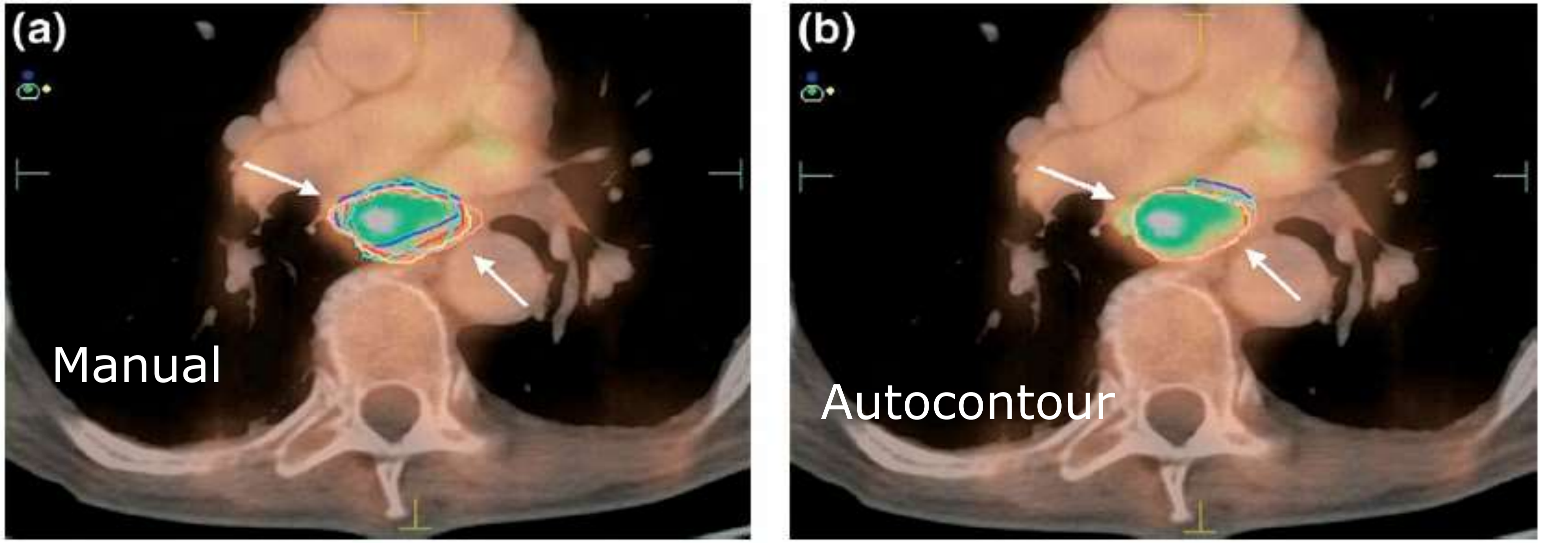
manual SBR-contour based

SBR-based delineation results in:

- a reduction in GTV volumes
- a reduction in interobserver variation

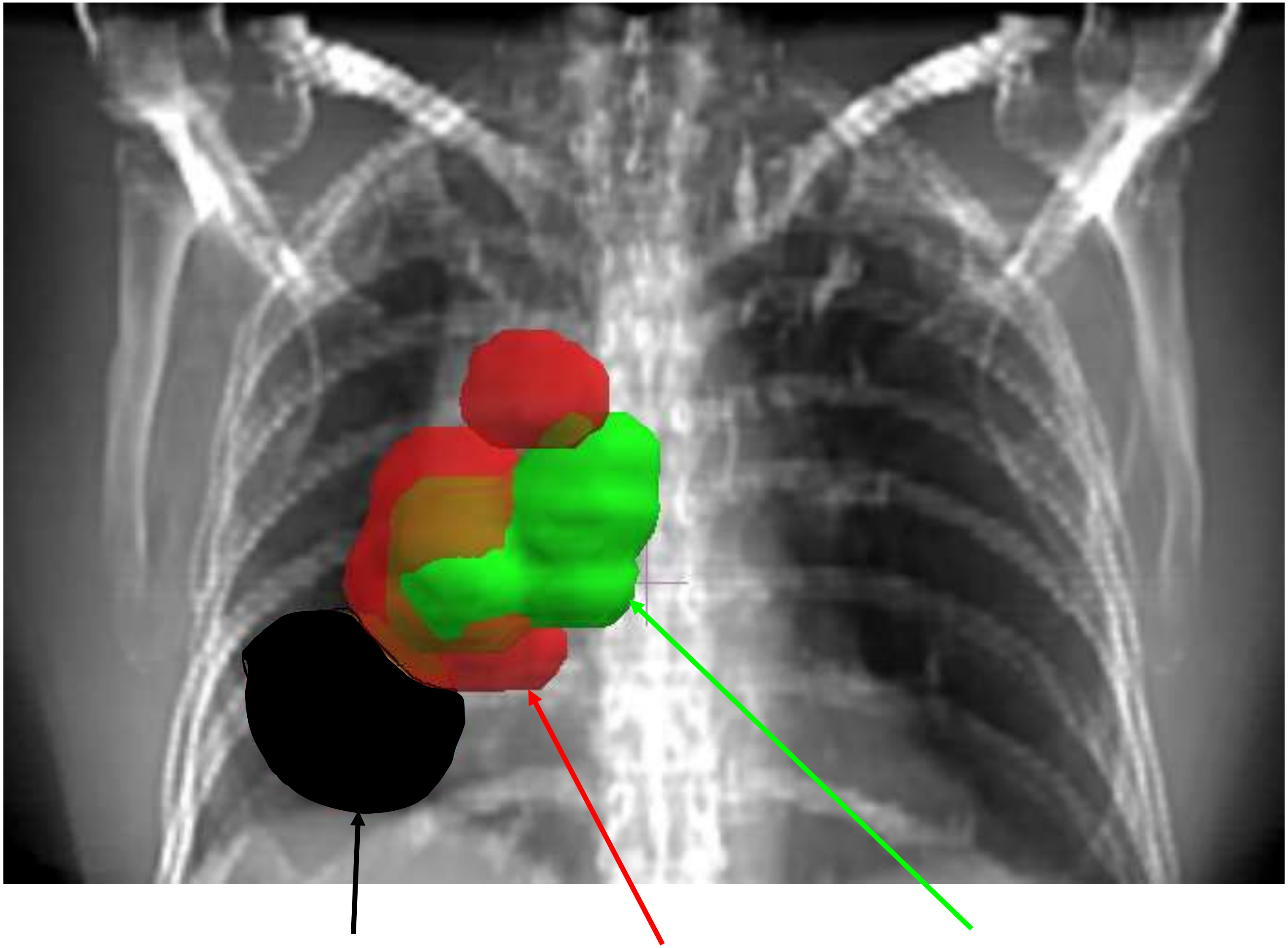
van Baardwijk et al.; IJROBP 2007

Auto-Contouring vs. Manual Contouring of Lymph Nodes

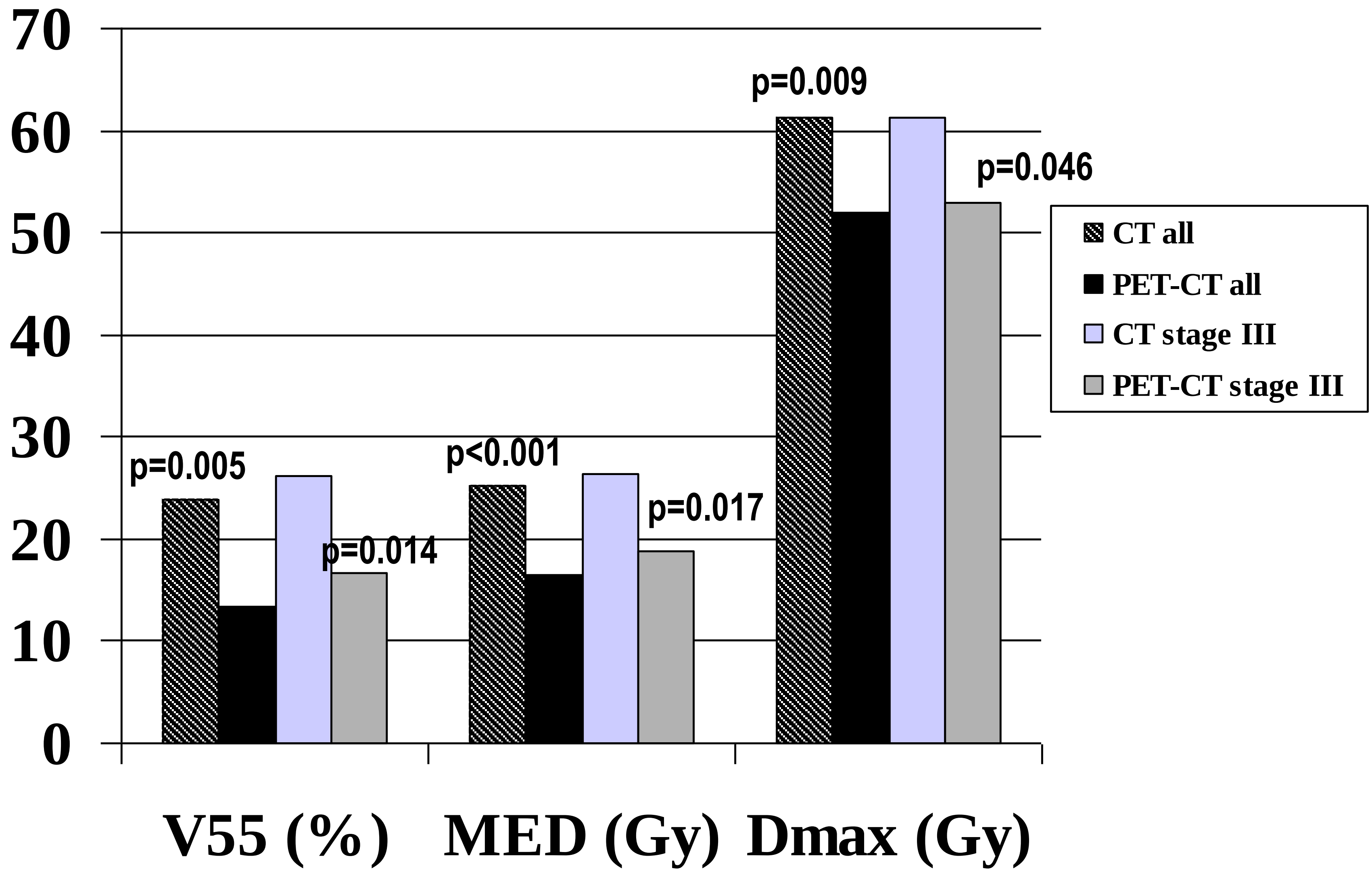


- Autocontouring is *more sensitive and specific* in detection lymph nodes
- Autodelineation significantly reduces lymph nodes volumes
- Reduces interobserver variability

van Baardwijk et al.; IJROBP 2007


PTV prim. tumour
PTV CT N+
PTV PET N+

Oesophagus



van der Wel et al. Int J Radiat Oncol Biol Phys 2005

De Ruysscher et al. Radiother Oncol 2005

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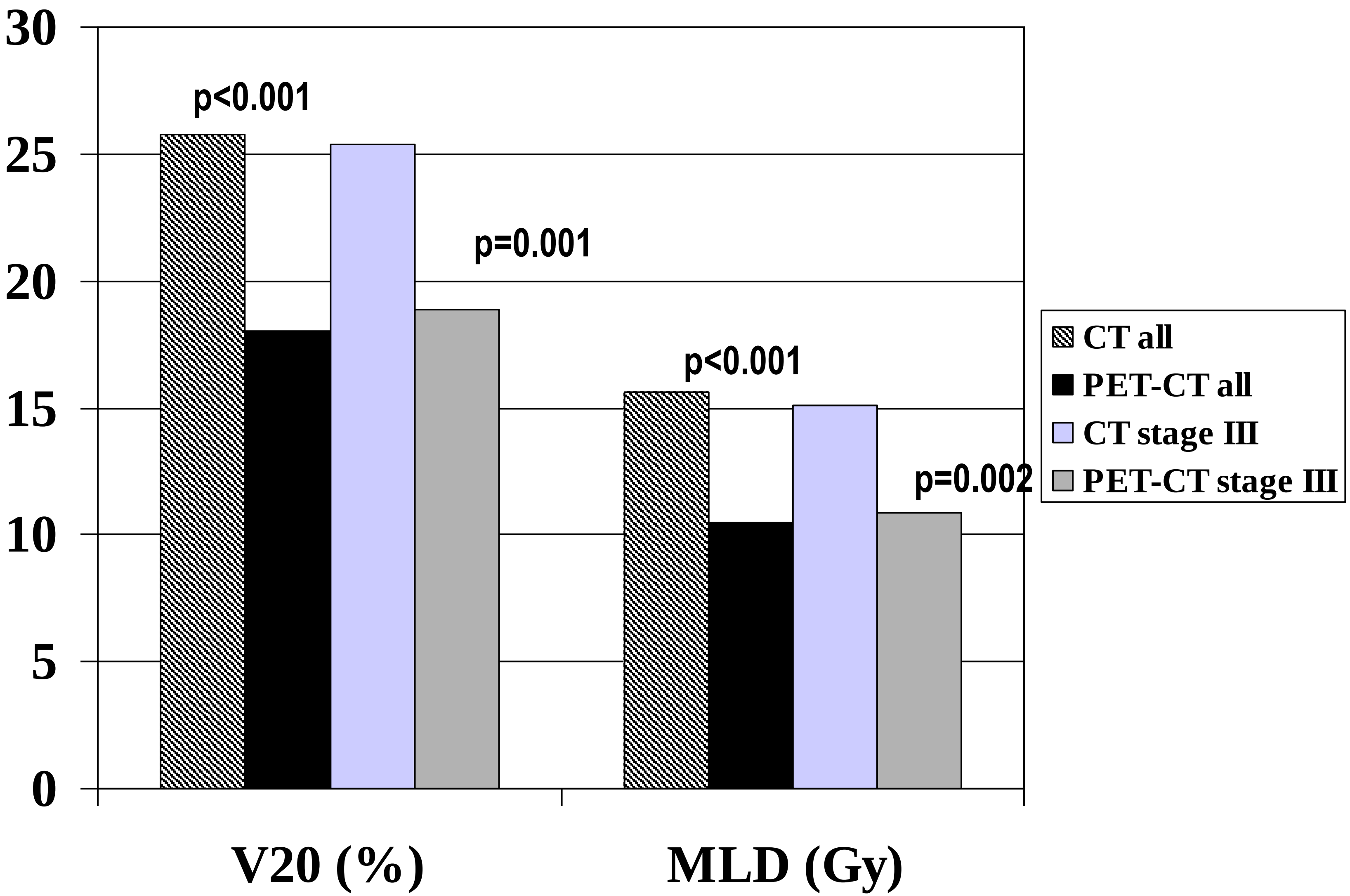
Lung



van der Wel et al. Int J Radiat Oncol Biol Phys 2005

De Ruysscher et al. Radiother Oncol 2005

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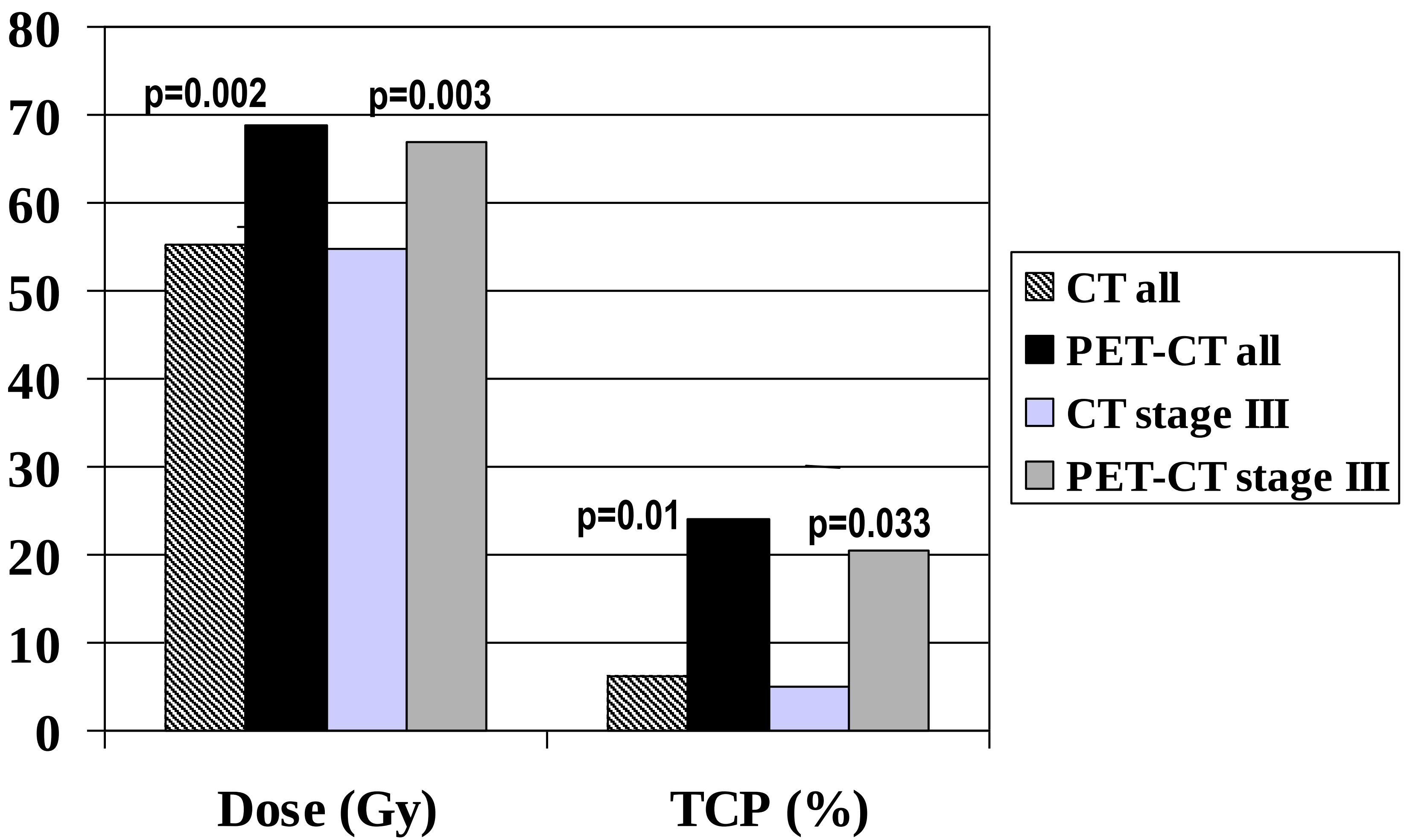
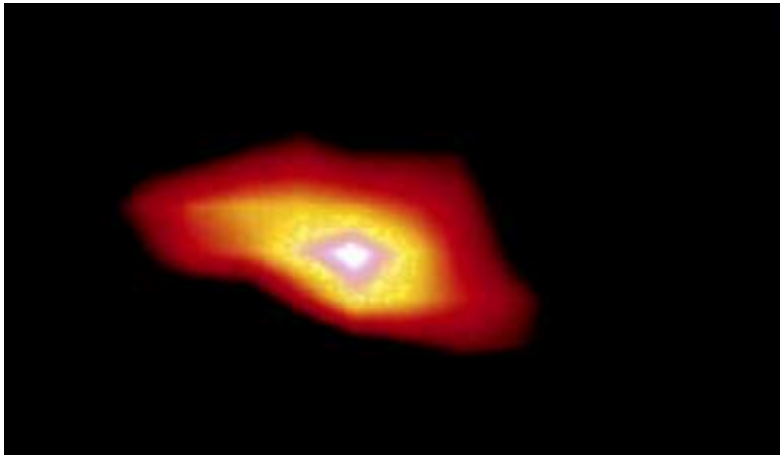
Theoretical radiation dose escalation with PET-CT planning



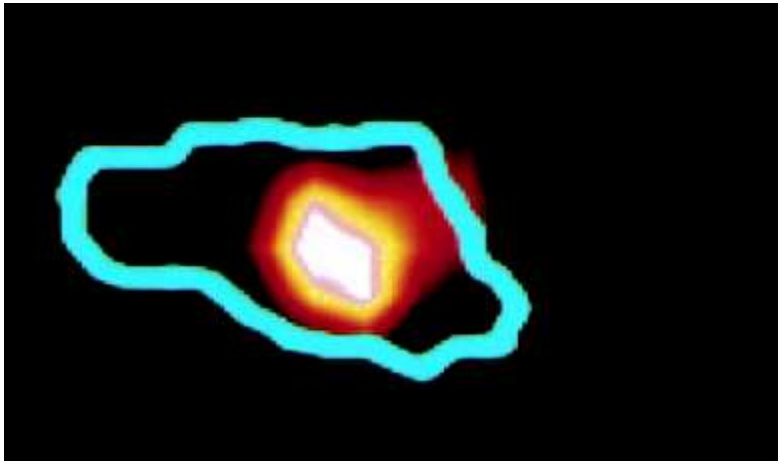
van der Wel et al. Int J Radiat Oncol Biol Phys 2005, De Ruysscher et al. Radiother Oncol 2005; van Baardwijk et al. J Clin Oncol 2010

4D imaging: Why?

- Improved tumor volume determination
- Improved SUV determination
- Improved (automatic tumor) contouring

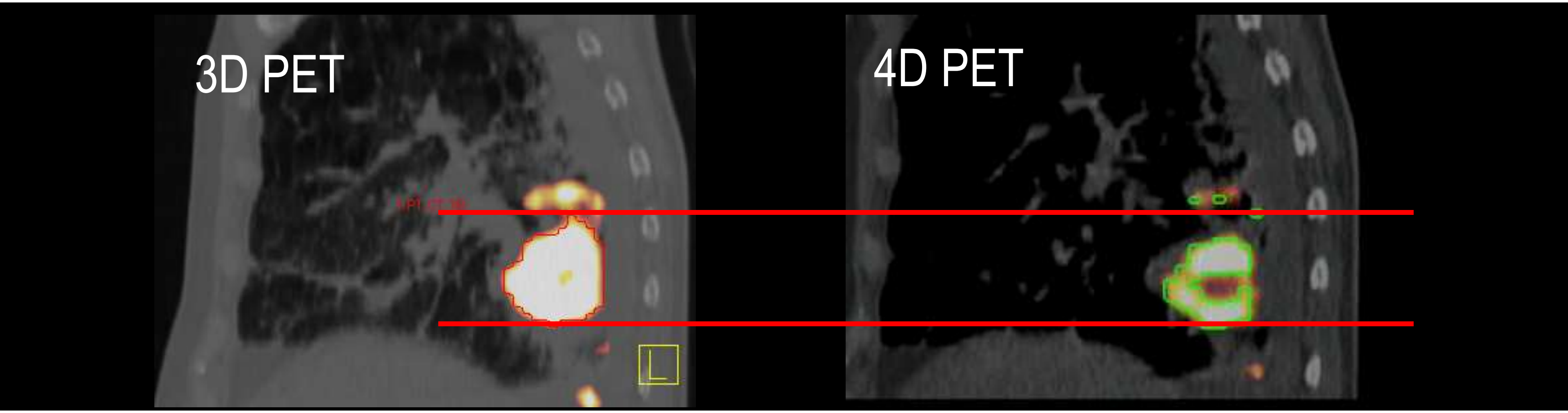


3D ‘normal’ PET



4D respiration correlated PET

Motion blurring of 3D PET

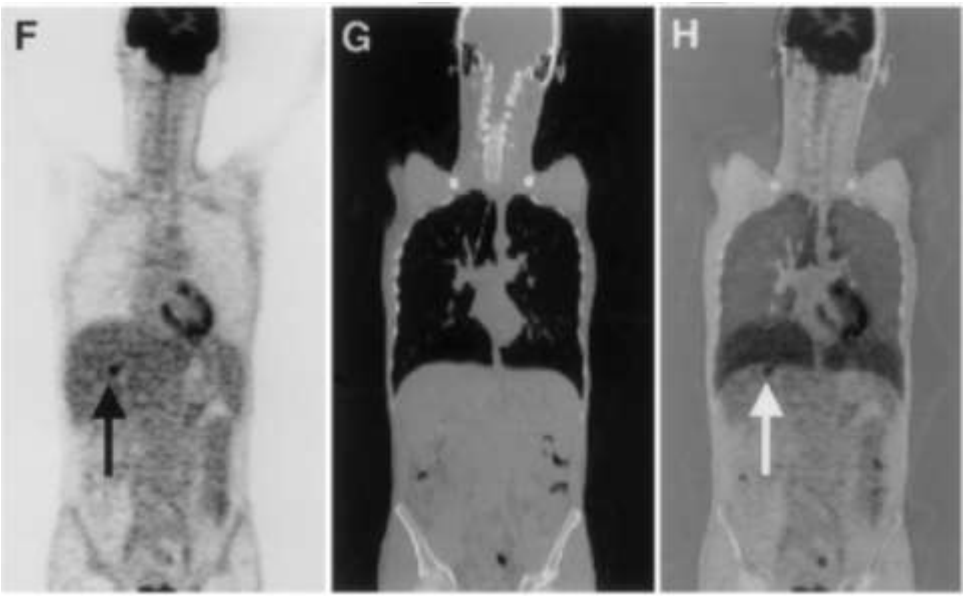


- Heterogeneous parts of the tumour might be completely missed
- High intensity regions are ‘averaged’; quantification of SUV is incorrect
- Gross tumour volume might be overestimated

Why 4D imaging?

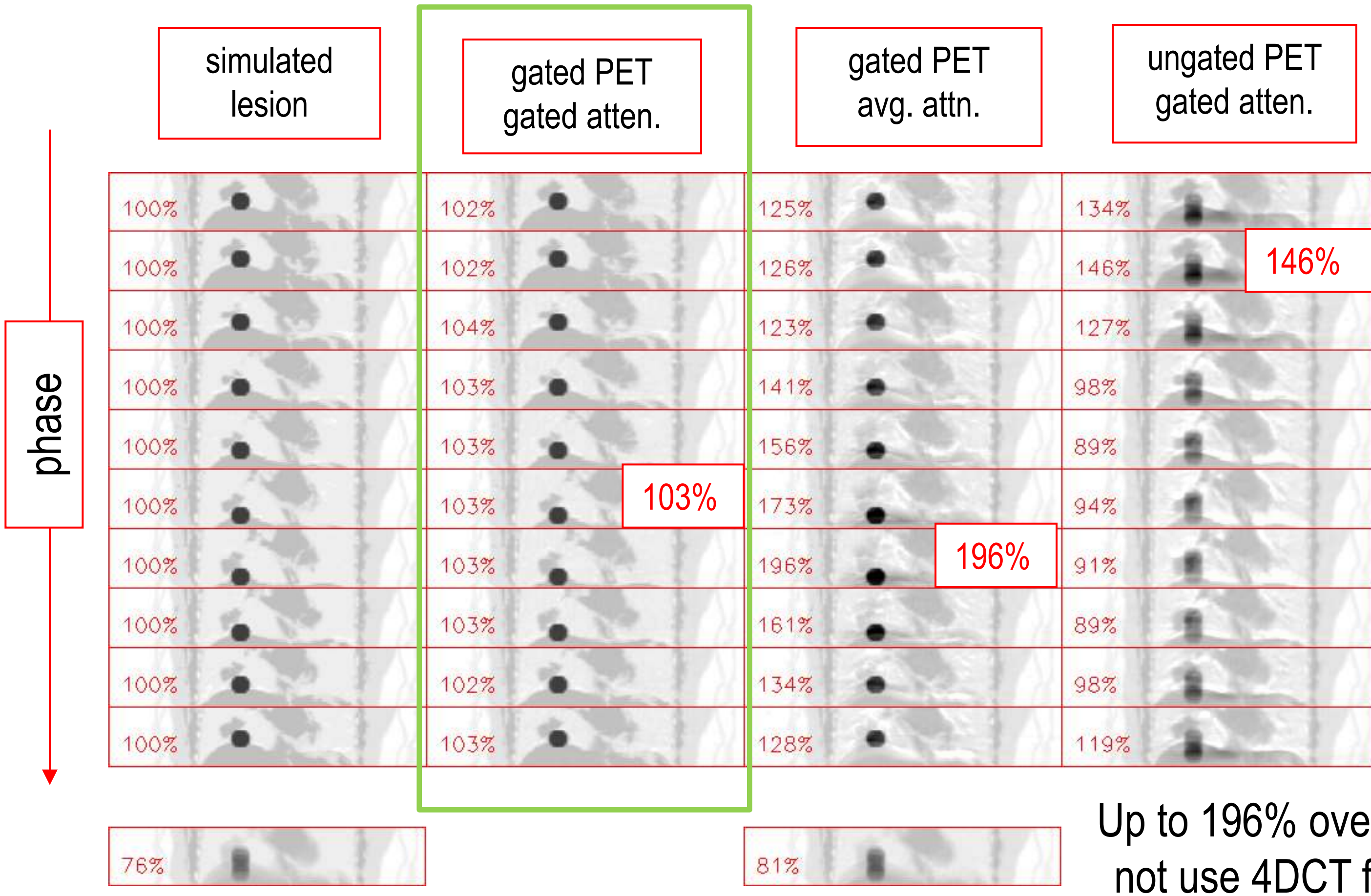
- 3D CT is used for attenuation correction of PET (in PET-CT scanners)
- This can lead to geographical errors and false positive lesions

Radiology 2003; 226: 906-910.



Using wrong CT attenuation leads to large artefacts

4DCT attenuation correction for 4DPET: small lesions near the diaphragm



Worst case scenario:
3 cm tumor at diaphragm

Other scenarios:
Small differences

Up to 196% overestimation SUV if you do not use 4DCT for attenuation correction

Hamill *et al*, *"Respiratory-gated CT as a tool for the simulation of breathing artifacts in PET and PET/CT,"* Med.Phys. 35(2):576-85 (2008).

Take Home Messages

- Use of window-level settings for both CT and PET

- Mediastinal node involvement:
  - PET: high sensitivity and specificity
  - CT: definition of nodal area border

- Target volume delineation:
  - PET: autocontouring (base for target volume delineation)
  - PET: reduction interobserver variation

- Be aware of pitfalls

Pittfalls

Be aware of:

• Adenocarcinoma in situ (BAC):	limited/no uptake of FDG
• Post-obstruction pneumonia:	increased uptake of FDG
• Inflammatory diseases:	increased uptake of FDG
• Heart:	or mediastinal involvement?
• Movement of tumor:	blurring of PET signal → 4D PET-CT

Multimodal Imaging: Focus on Lung Cancer

1. Theragnostic (treatment decision)

2. Gross Tumour Volume identification & contouring

3. PET-guided Adaptive Radiotherapy

4. Metabolic response @ 3 months

5. GTV_{LDU} (LDU = Low drug uptake target)

6. Normal Tissue Avoidance Volume & Normal tissue Preferential Target Volume

What is Adaptive RT?

"Adaptive radiotherapy is the optimization of the treatment plan based on information acquired during the course of treatment"

Examples:

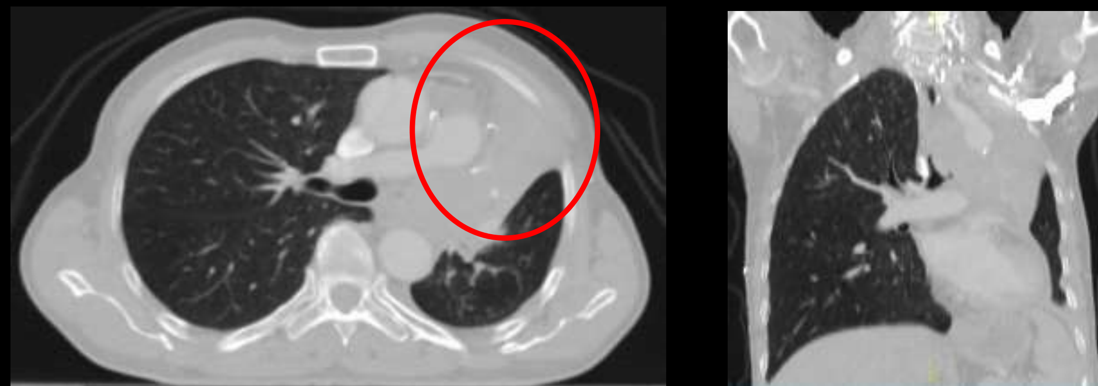
- Re-planning based on imaging (geometry) information
- Re-planning based on (early) response information / assessment (both for normal tissue toxicity or target volume)
- A plan choosen from a library of plans based on patient geometry during treatment

Not included in 'my' definition:

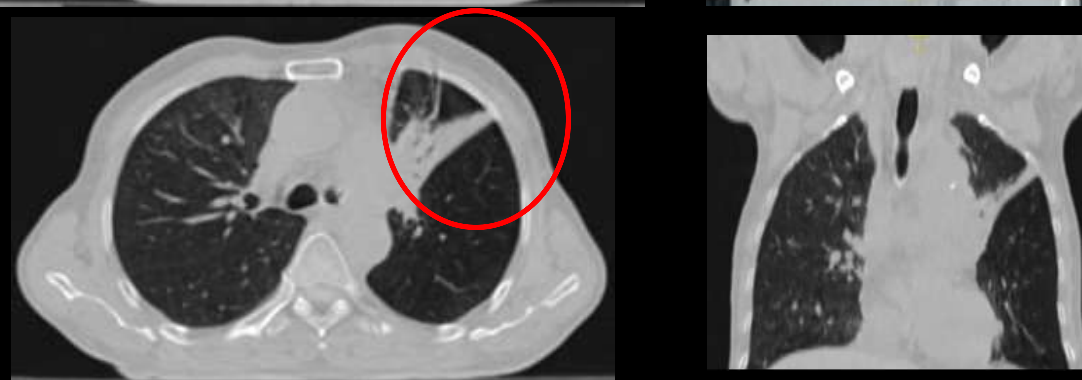
- IGRT is the optimization of the patient positioning during treatment

A lung cancer case

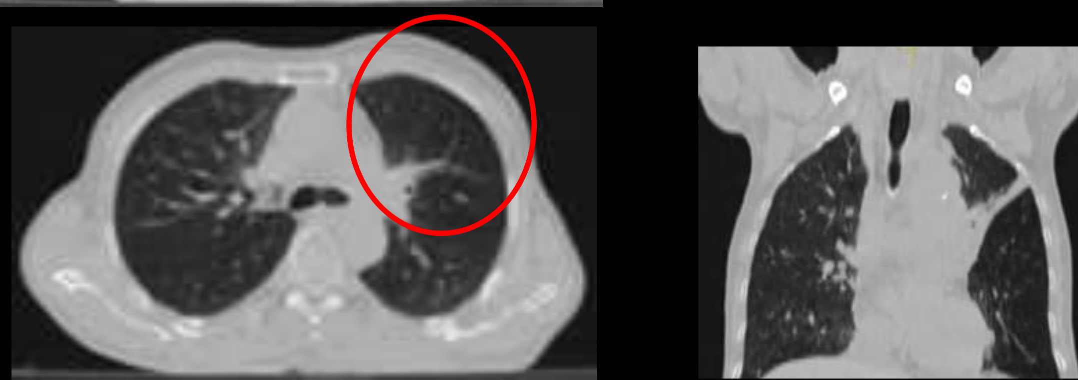
- First CT



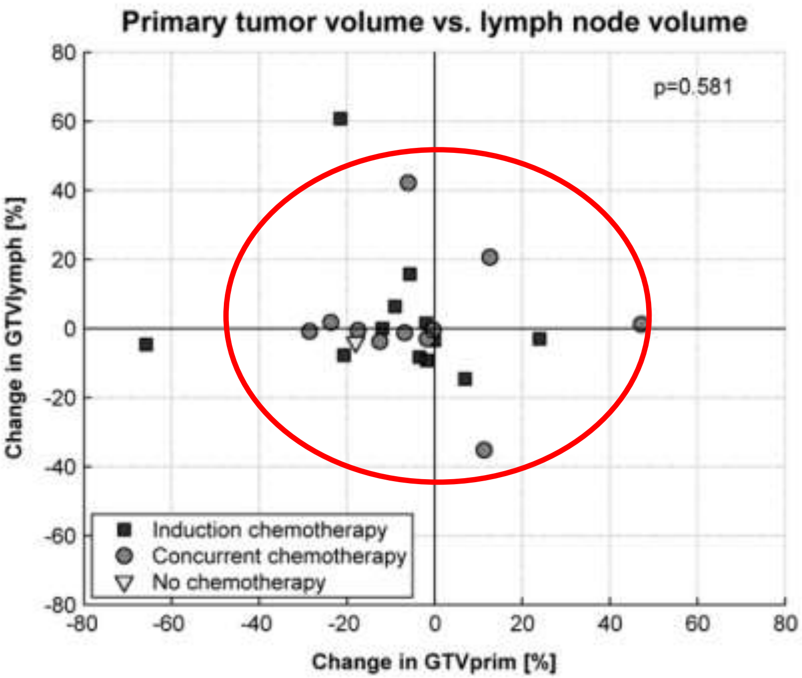
- Second CT
  after 3 fractions

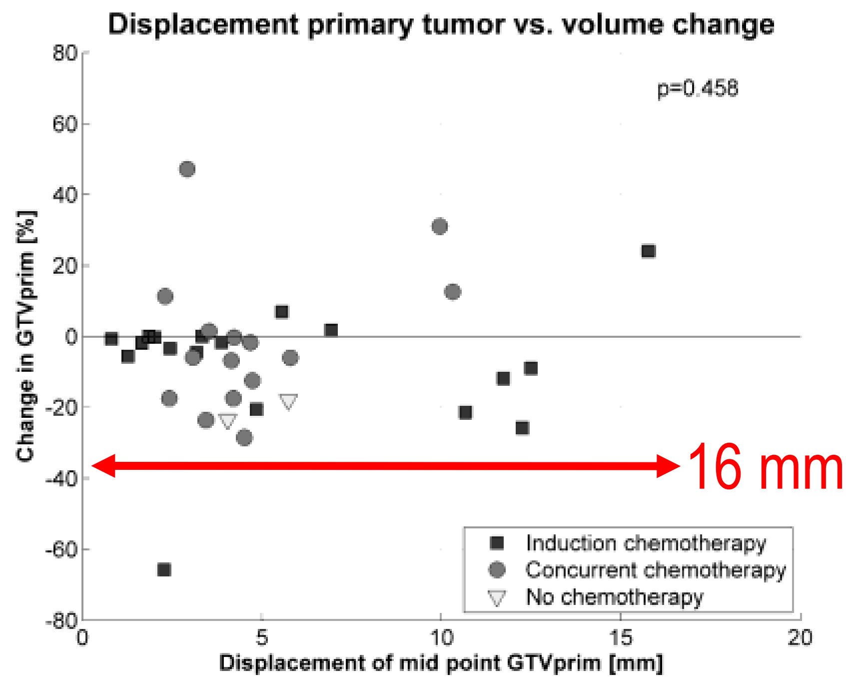


- Third CT
  after 17 fractions



Primary tumour volume vs. lymph node volume & displacement





No relation between change in lymph node volume and primary tumour volume!

A significant baseline shift of the primary tumour! (irrespective of volume change)

*van Elmpt et al; *"Volume or Position changes of primary lung tumor during (chemo-)radiotherapy cannot be used as a surrogate for mediastinal lymph node changes: The case for optimal mediastinal lymph node imaging during radiotherapy,"* IJROBP 79(1):89-95 (2011).

Repeated PET during treatment:

Hypothesis:

Early metabolic response assessment *during* treatment can ***better*** predict the outcome (overall survival & pathological complete response) of lung & rectum cancer patients.

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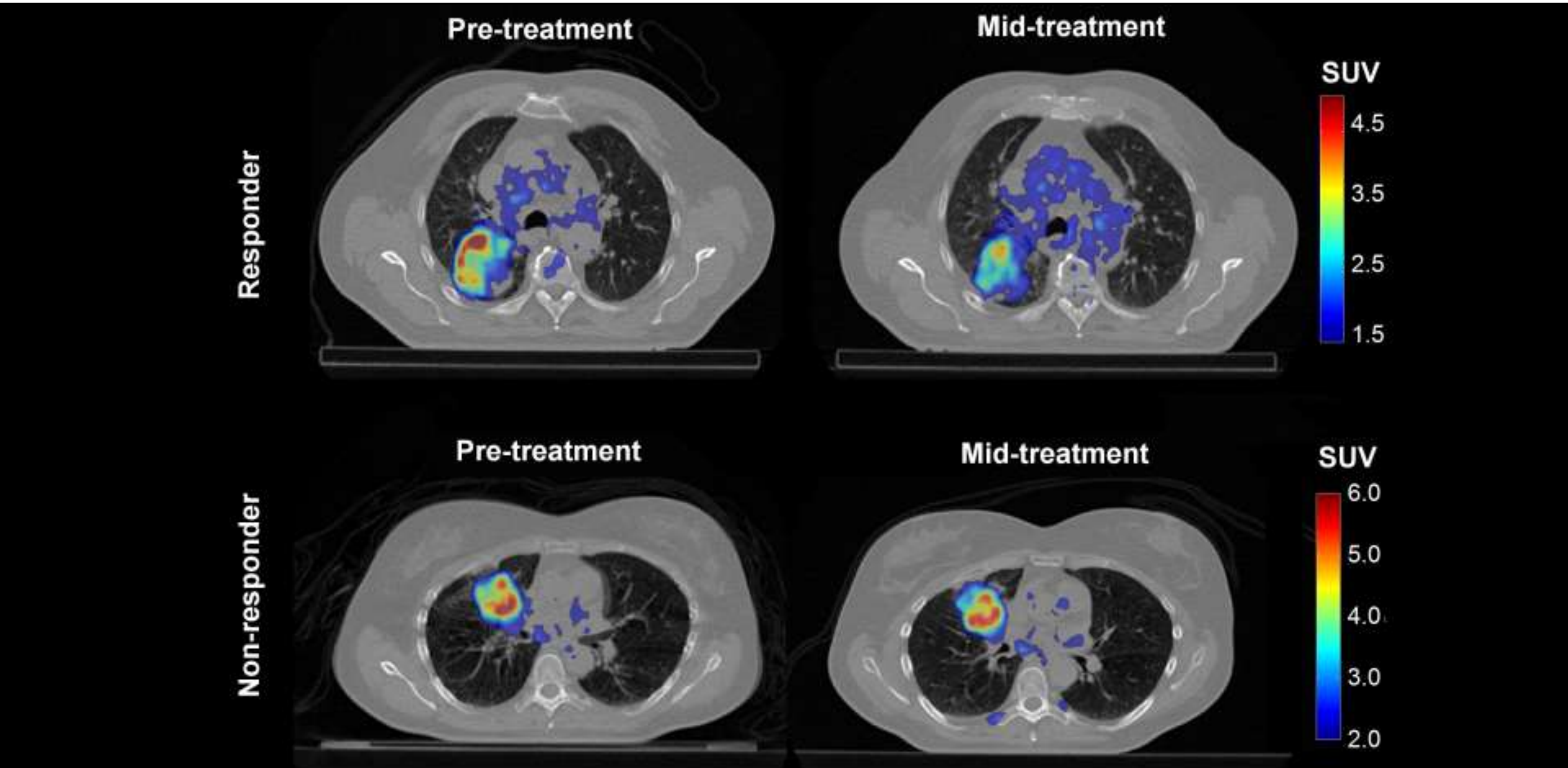
Example Lung cancer (NSCLC) of early (week 2) repeated imaging during RT



*van Elmpt et al, abstract World Conference on Lung Cancer, Amsterdam 2011.

**van Elmpt et al, "Response assessment using 18F-FDG PET early in the course of chemo-radiotherapy is correlated with survival in advanced stage non-small cell lung cancer " Revision for J Nucl Med 2012

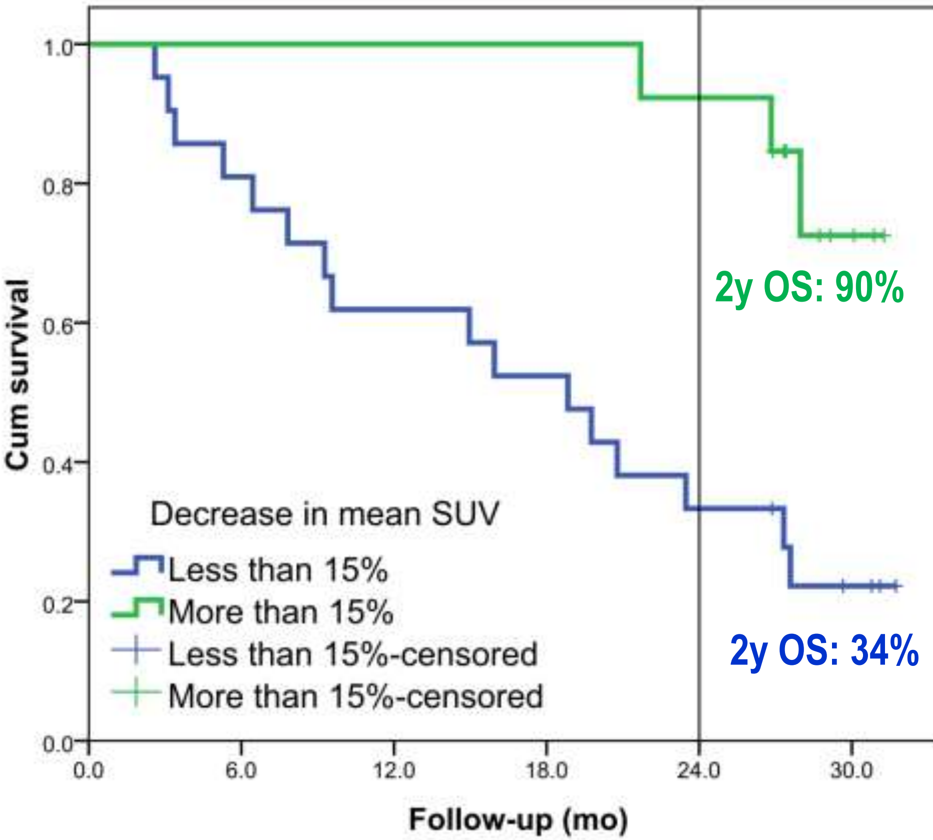
FDG-PET changes precede CT changes

FDG-PET:

- Cut-off: 15% (EORTC response)
- Changes in maximum SUV and mean SUV significant predictive for 2-year overall survival
    - HR 1.17 (95% CI: 1.05 – 1.30) per 5% decrease of SUV

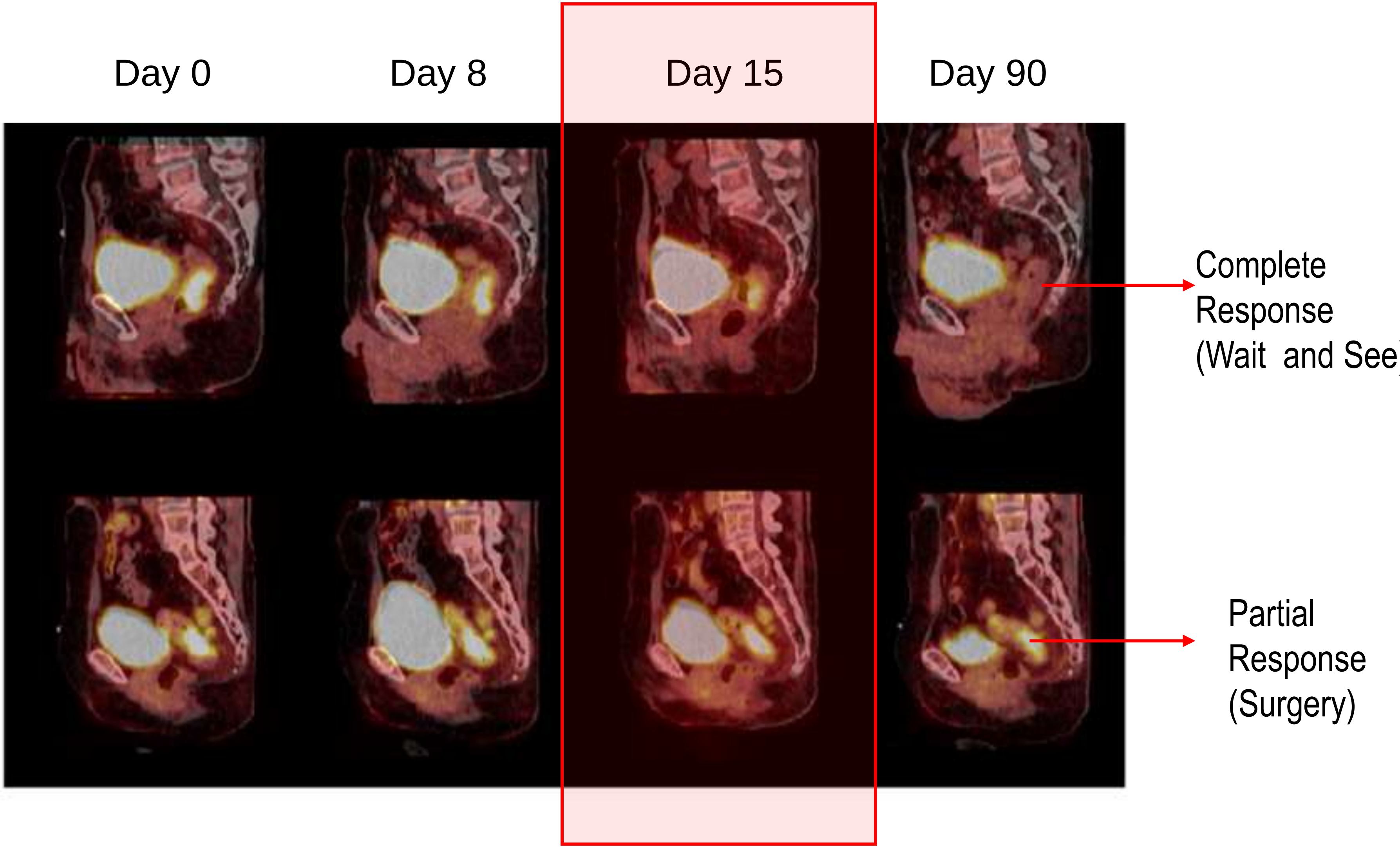
CT (volume)

- Tumour volume pre-treatment RT is predictive for survival (already known)
- Change in tumour volume (CT) is not correlated to survival!



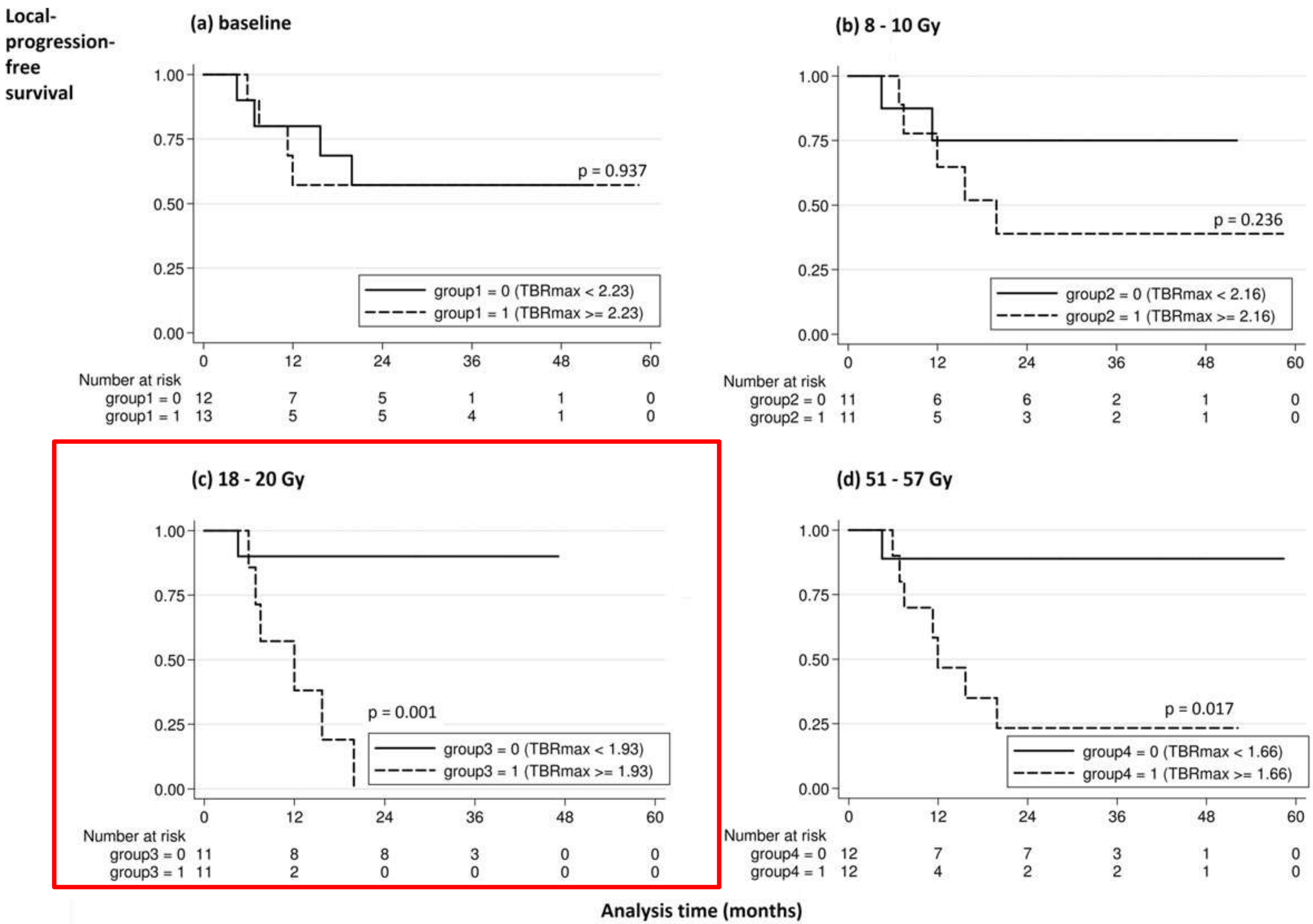
van Elmpt et al, “Response assessment using 18F-FDG PET early in the course of chemo-radiotherapy is correlated with survival in advanced stage non-small cell lung cancer ” J Nucl Med 2012

Repeated CTPET in Rectum cancer



Van Stiphout et al. Radiother Oncol 2011

Hypoxia Imaging in Head & neck cancer



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Zips et al. Radiother Oncol 2012

AAPM, 2013

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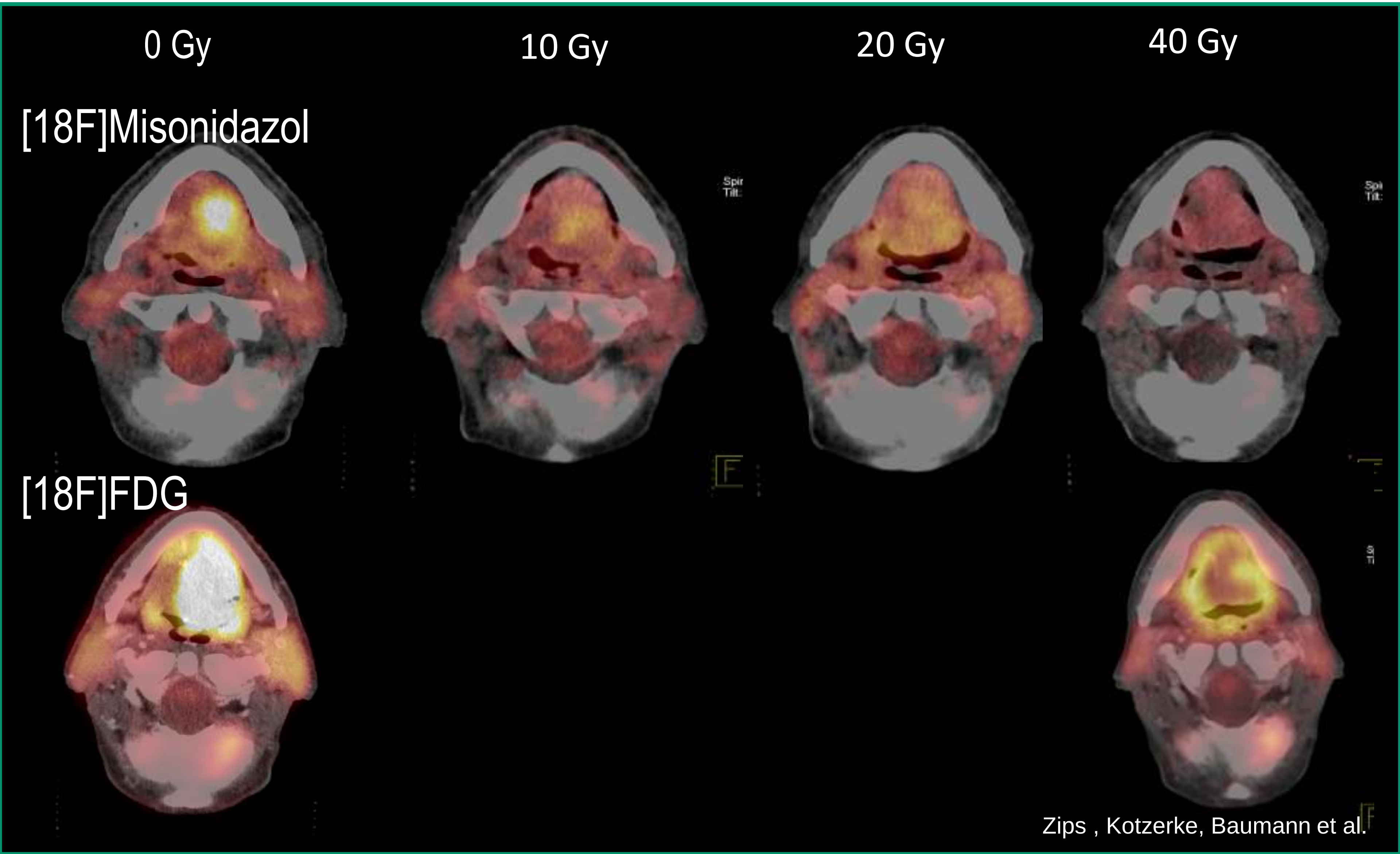
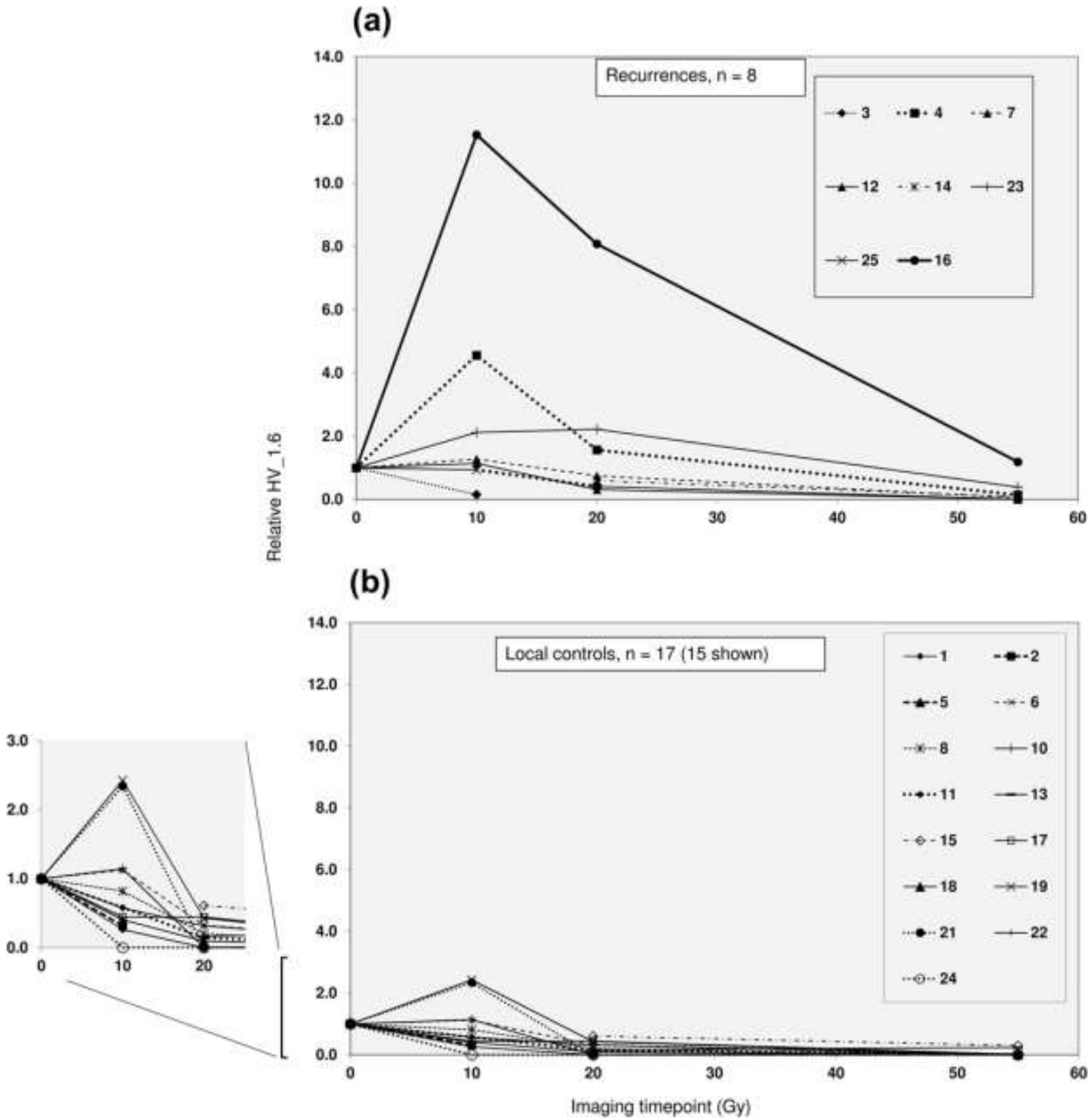
Biomarker: Hypoxia (F-MISO PET)





Zips et al. Radiother Oncol 2012

Multimodal Imaging: Focus on Lung Cancer

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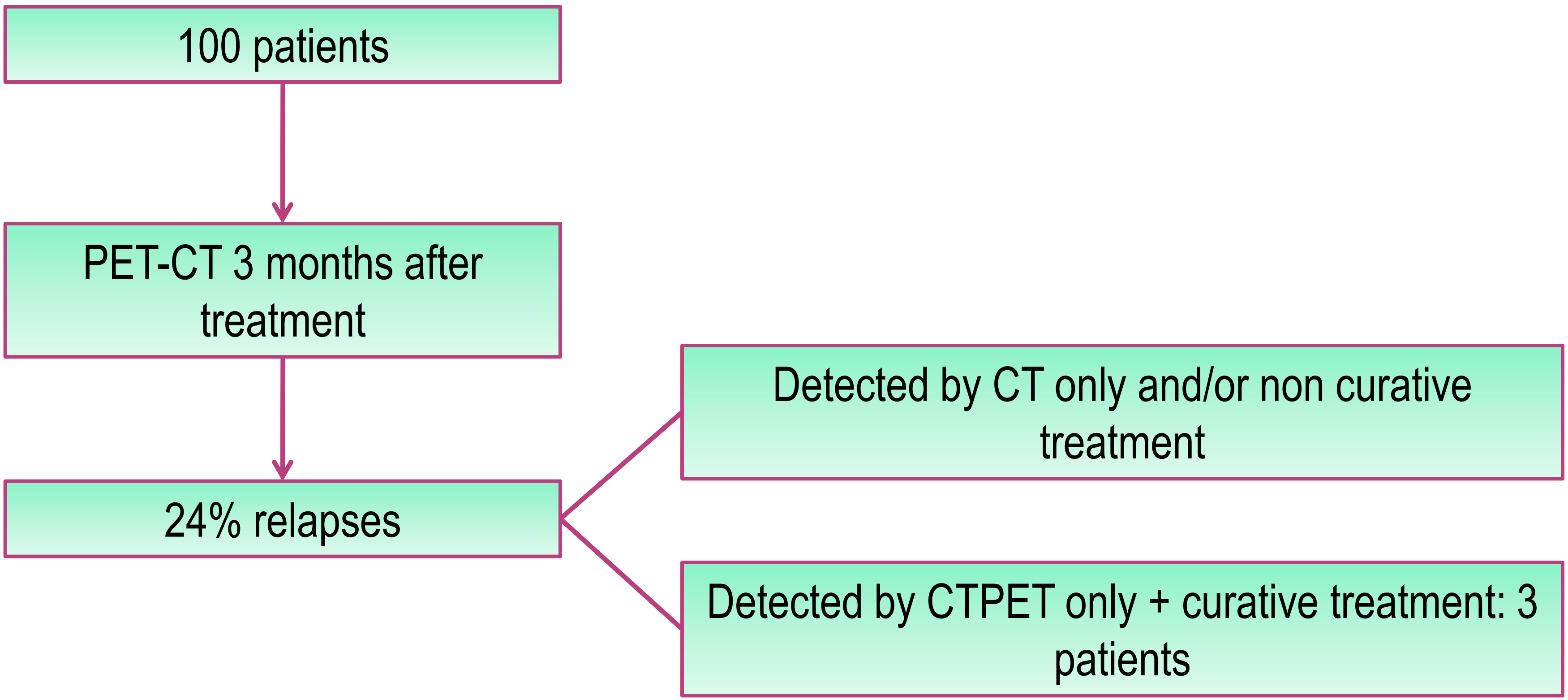
3. Adapative Radiotherapy

4. Metabolic response @ 3 months

5. GTV_{LDU} (LDU = Low drug uptake target)

6. Normal Tissue Avoidance Volume & Normal tissue Preferential Target Volume

Follow-up: CTPET Evaluation at 3 months (Metabolic response + Met's)



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Van Loon *et al.* EJC 2008, 2010

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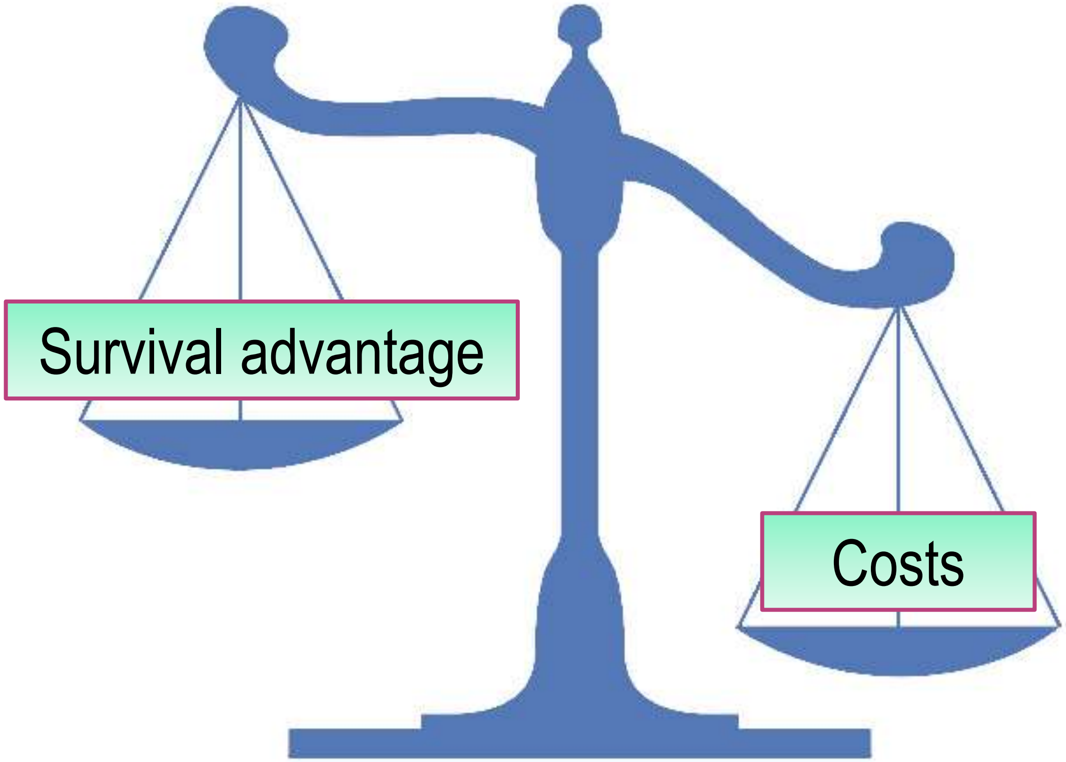
Follow-up: Metabolic Response Evaluation at 3 months



Van Loon *et al.* EJC 2008, 2010

Follow-up: Metabolic Response Evaluation at 3 months

- Costs per QALY (Quality-adjusted life year)
  - PET-CT: € 69.000
  - CT: € 264.000
- Is follow-up PET-CT cost-effective?
  - *More* cost effective than CT @ 3 months
  - Depending on varying societies acceptance to pay per QALY: The Netherlands example : max. € 80.000; UK: max. £ 30.000…

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Van Loon *et al.* EJC 2008, 2010

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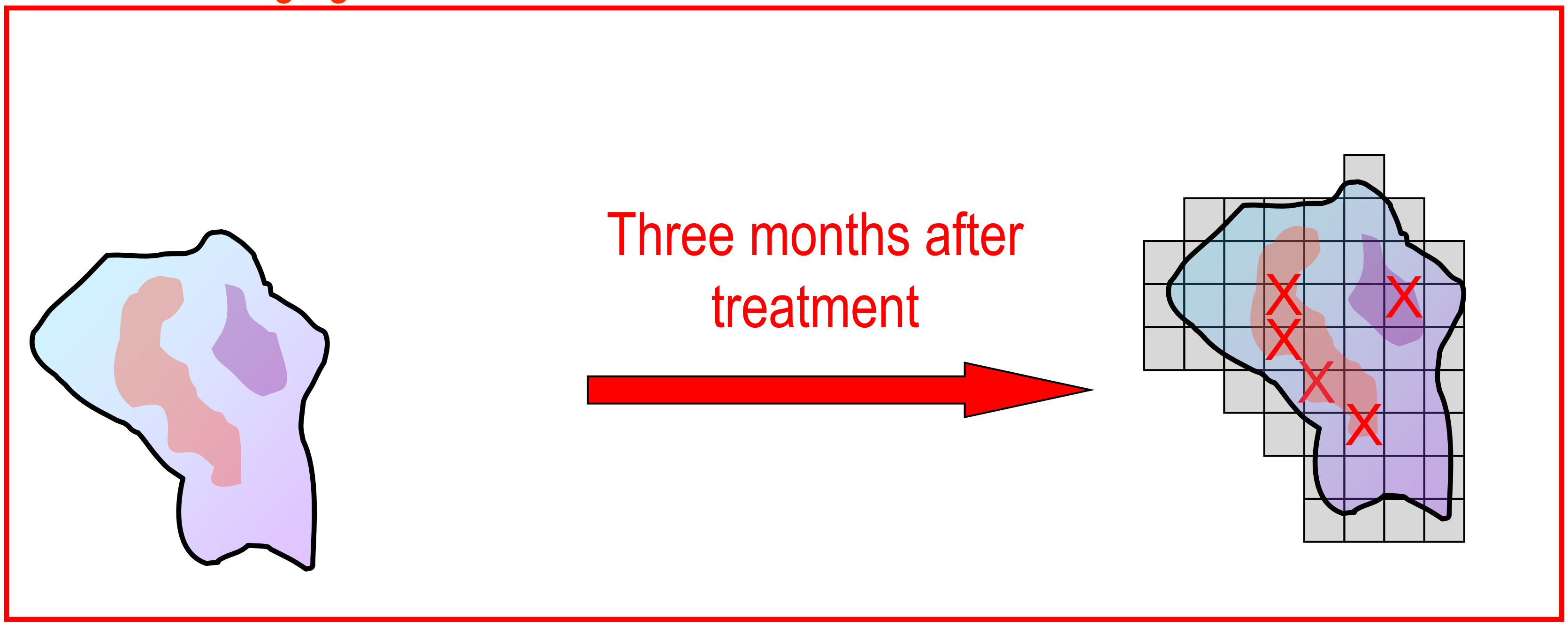
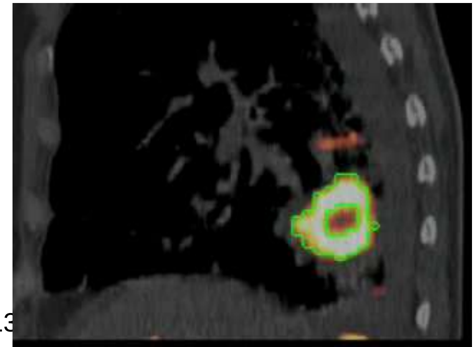
Voxel Control Probability (VCP) based on *Pattern of relapse studies*

Functional imaging



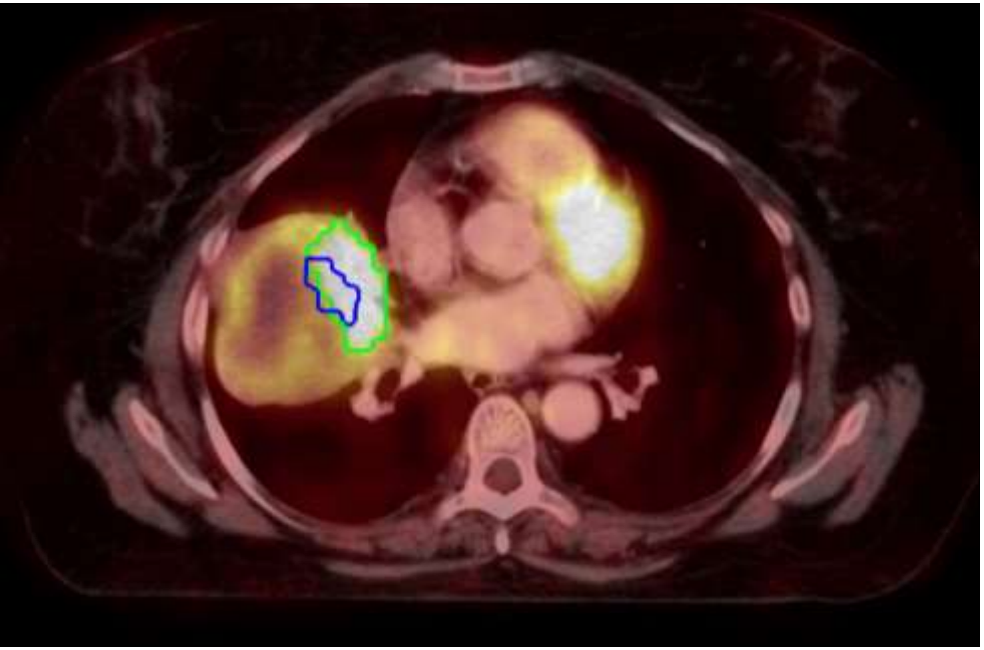
X= Intratumoral relapse (based on metabolic response)

Needed = 1. 4D CTPET
2. Validated automatic delineation software
3. Treatment position

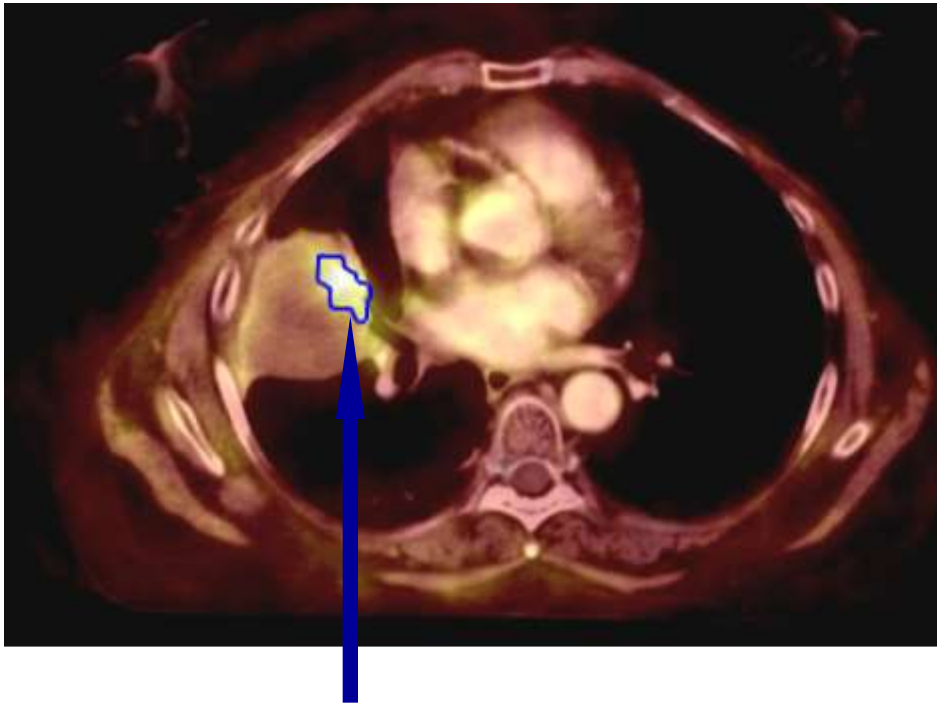


Identification of Radio Resistant Voxels in Lung Cancer

Status before treatment



Metabolic response
(3 months after treatment)



Intratumoral Relapse

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Aerts *et al.* Radiother Oncol 2009; Lung Cancer 2012

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Dose escalation strategies

Non specific dose escalation

- Max dose to target based on OAR constrains

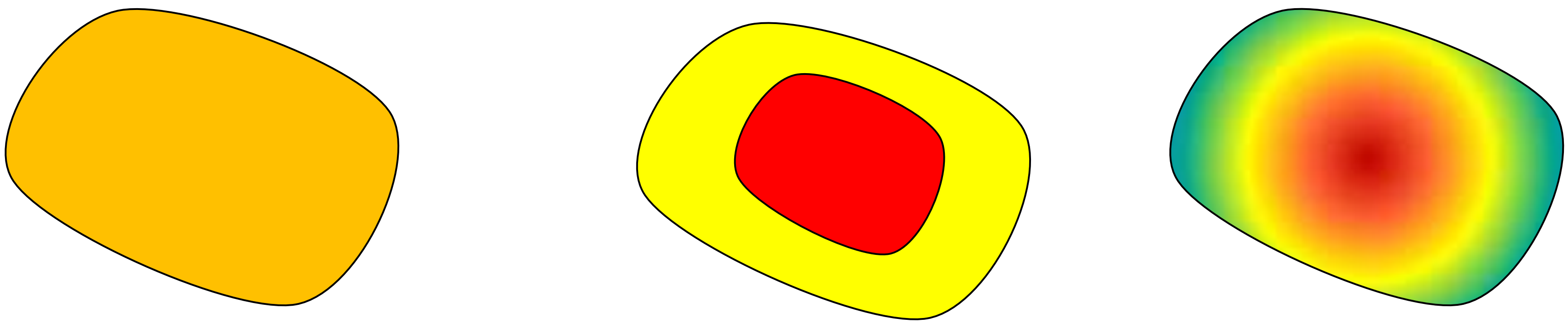
Dose painting (DP)

DP by contours

- Min. target dose
- Dose escalation to preselected region(s)

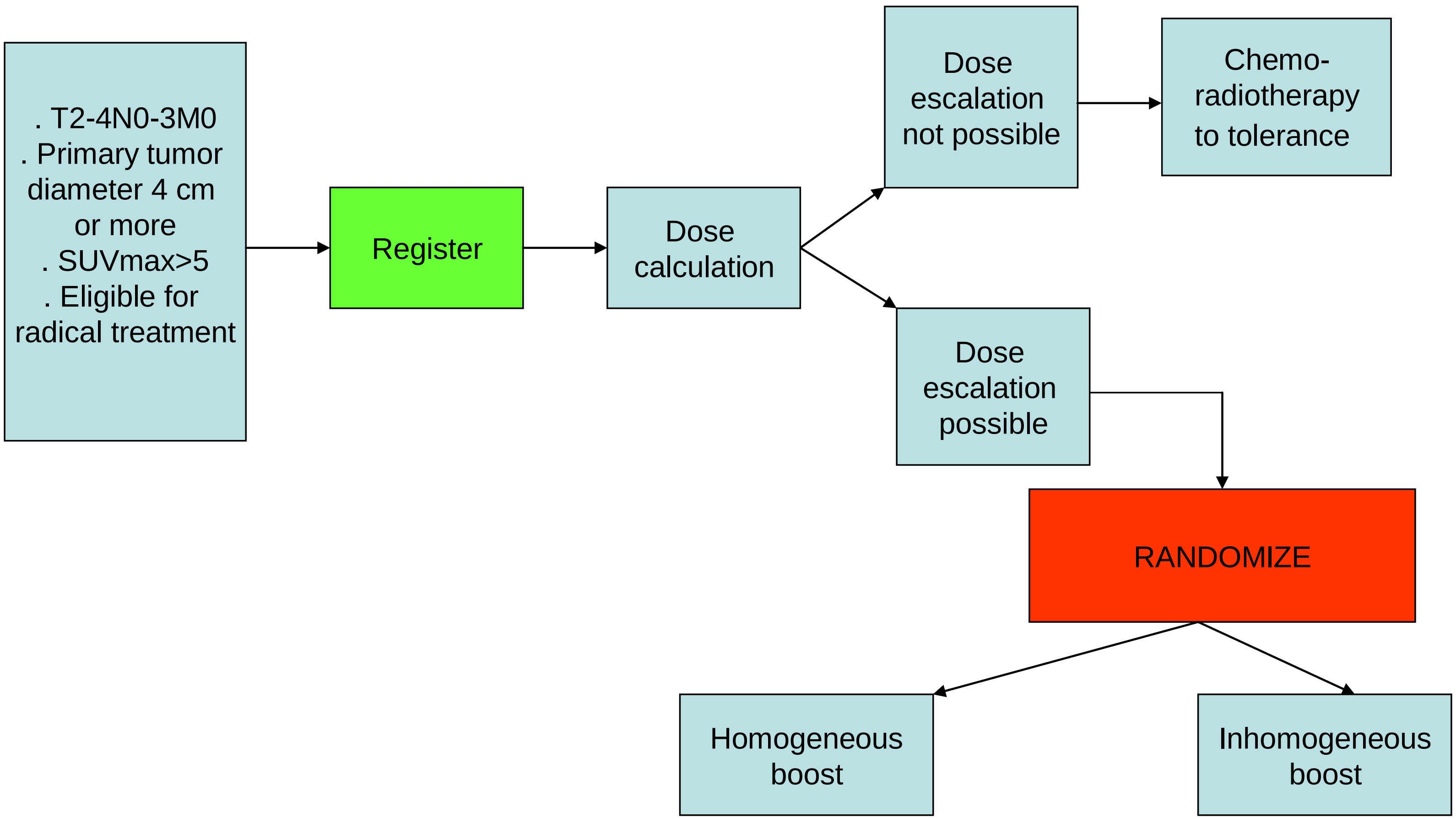
DP by numbers

- Min. target dose
- Dose = *F*(biomap)



Randomized Phase 2 trial MAASTRO-NKI

remain in the study



N: 66 Gy / 24 frac. of 2.75 Gy

T: up to NT constraints

66 Gy / 24 frac. of 2.75 Gy

+ on 50% SUV max contour

5.40 Gy * 24 fractions = **129.6 Gy** (maximum)

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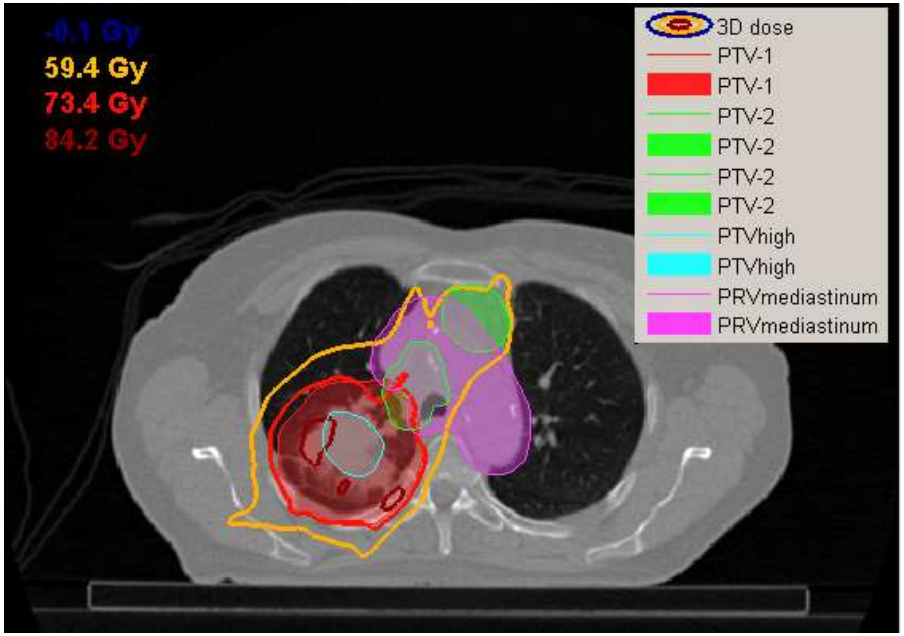
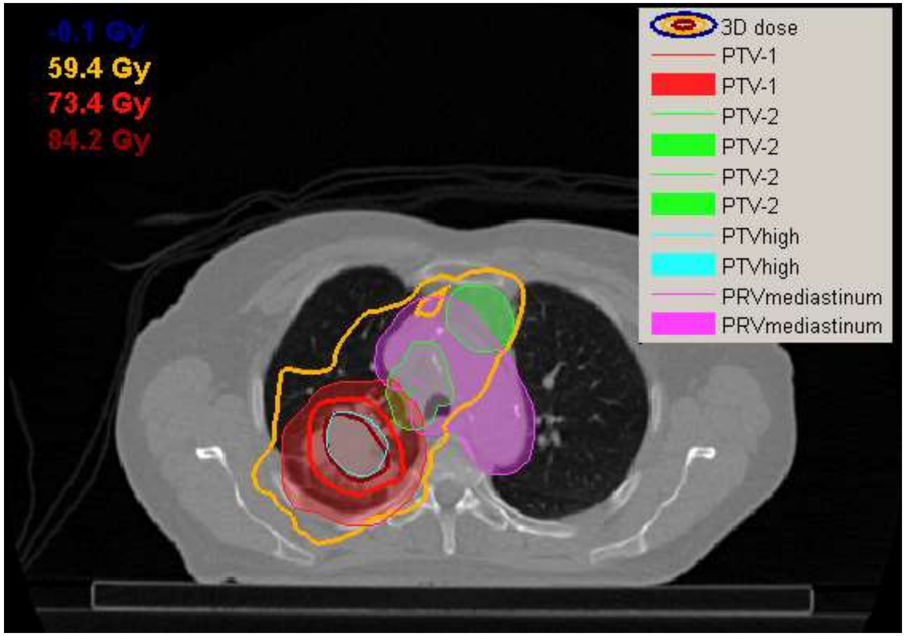
Examples of treatment plans

Arm A: Homogeneous boost



Arm A:
- Prescribed dose: 81.6 Gy
- MLD: 19.0 Gy

Arm B: PET Boost



Arm B:
- Prescribed dose: 93.6 Gy
- MLD: 19.3 Gy

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Multimodal Imaging: Focus on Lung Cancer

1. Theragnostic (treatment decision)

2. Gross Tumour Volume Contouring

3. Adapative Radiotherapy

4. Biological target Volume Contouring

The Future:

5. GTV_{LDU} (LDU = Low drug uptake)

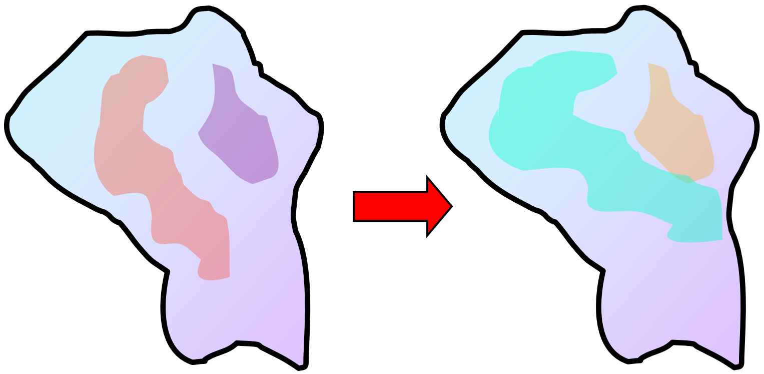
6. Normal Tissue Avoidance Volume & Normal tissue Preferential Target Volume

Voxel Control Probability (VCP)

Functional imaging

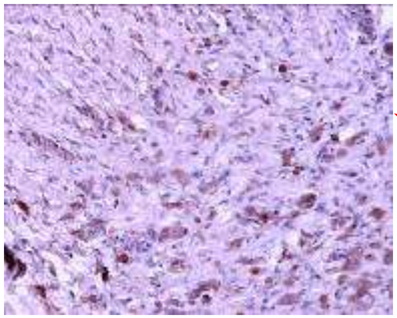
VCP Map $_{FI}$
functional imaging

VCP Map $_{LD}$
labeled drugs

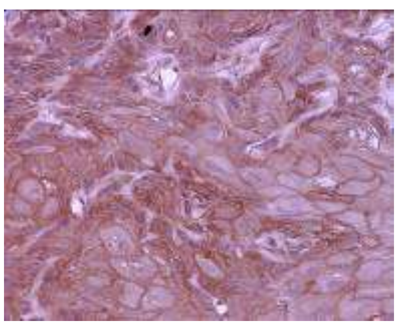


An example: PET Imaging of 89 Zirconium – Cetuximab

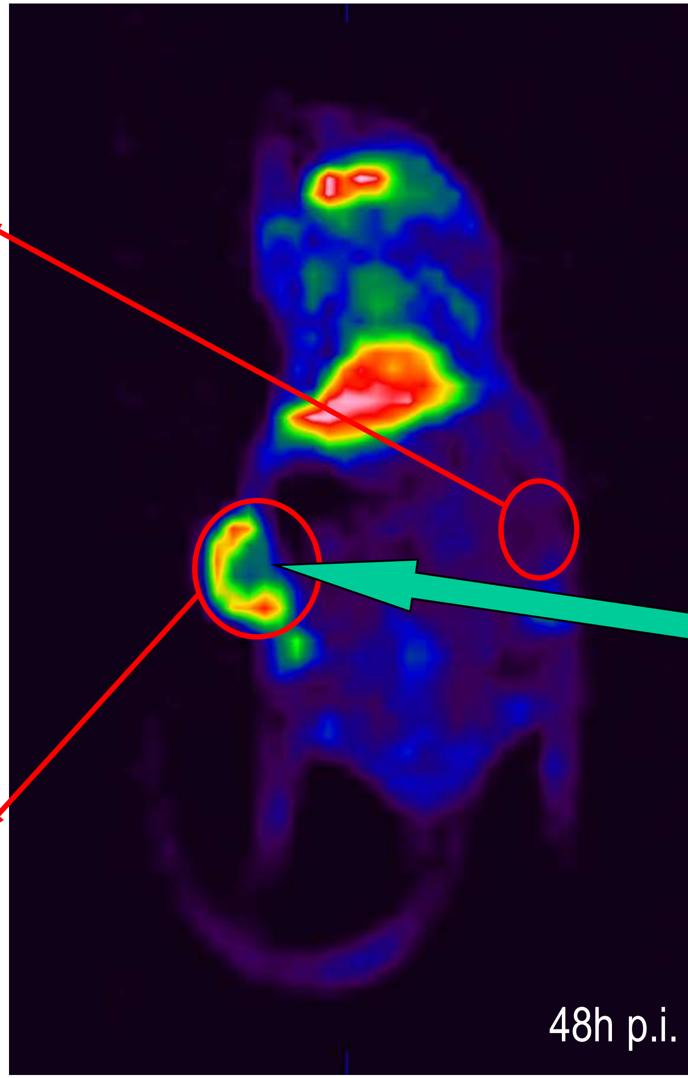
@EGFR (sc-03)

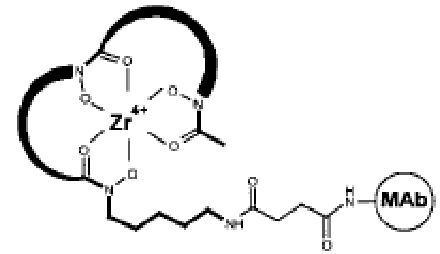


T47D



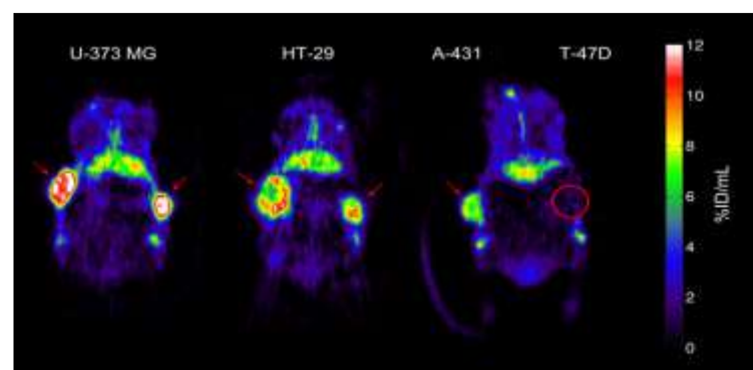
A431





MAb-*N*-succinyldesferal-^{89}Zr (MAb-*N*-sucDf-^{89}Zr) (*)

GTV_{LDU}



Aerts *et al*. JNM, 2009; Lambin *et al.* Radiother Oncol. 2010

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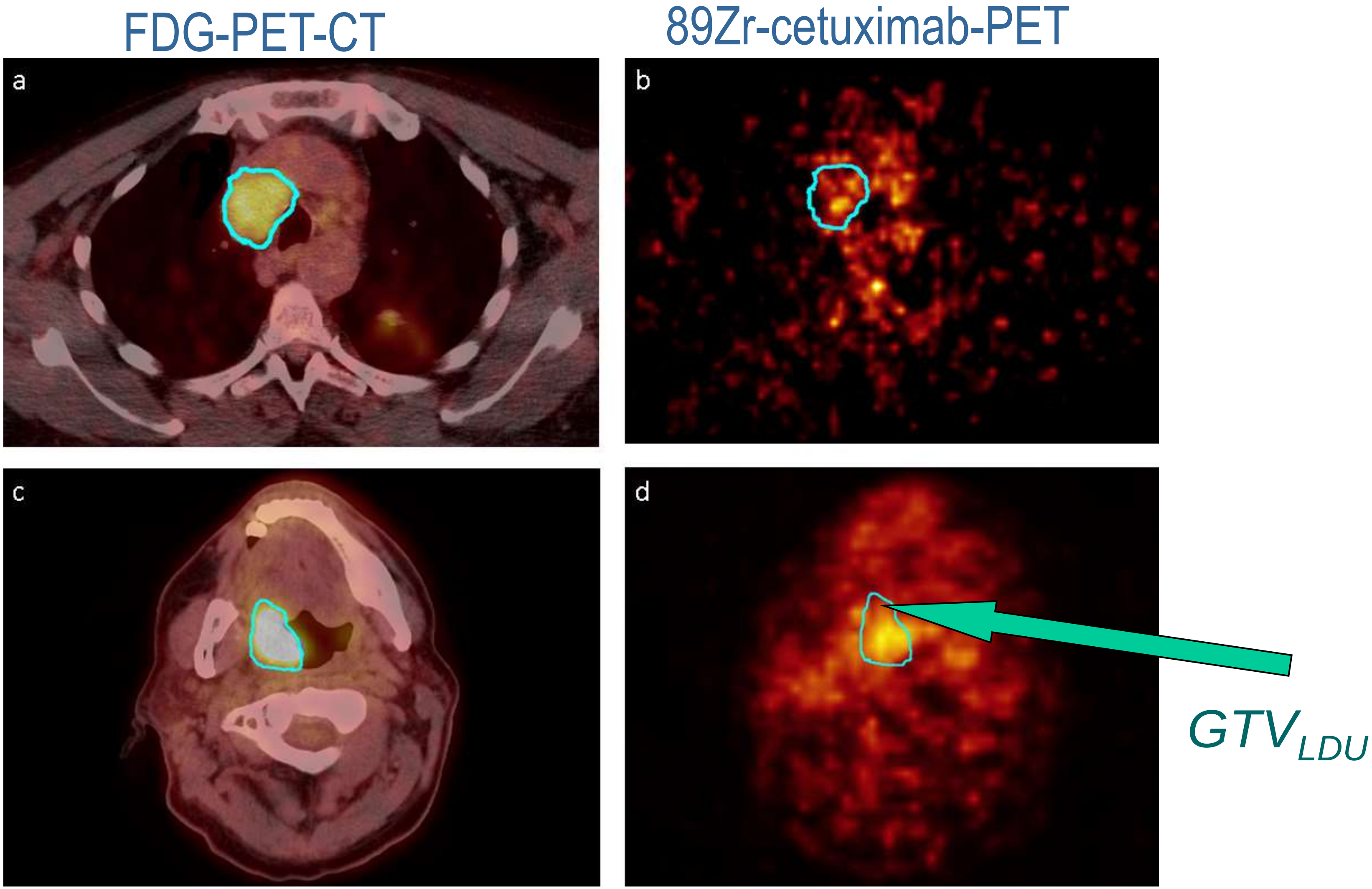
An example: PET imaging of 89Zirconium–Cetuximab



Aerts *et al*. JNM 2009; Lambin *et al.* Radiother Oncol. 2010

Van Loon *et al*. In preparation

Multimodal Imaging: Focus on Lung Cancer

1. Theragnostic (treatment decision)

2. Gross Tumour Volume Contouring

3. Adapative Radiotherapy

4. Biological target Volume Contouring

The Future:

5. GTV_{LDU} (LDU = Low drug uptake)

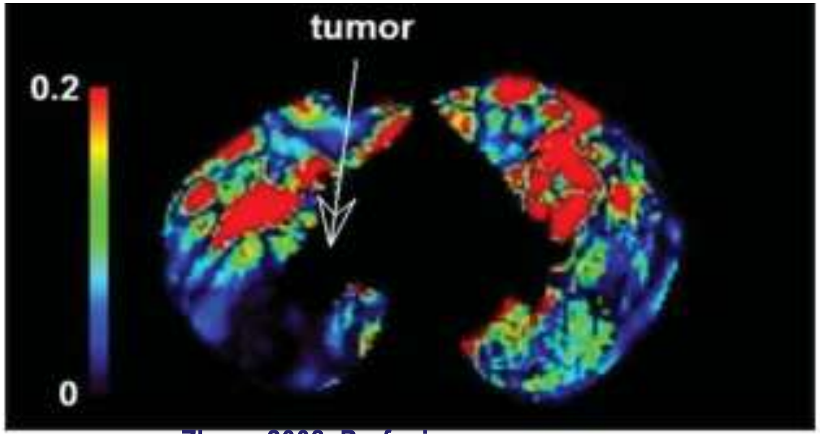
6. Normal Tissue Avoidance Volume & Normal tissue Preferential Target Volume

“There are no radioresitant tumours

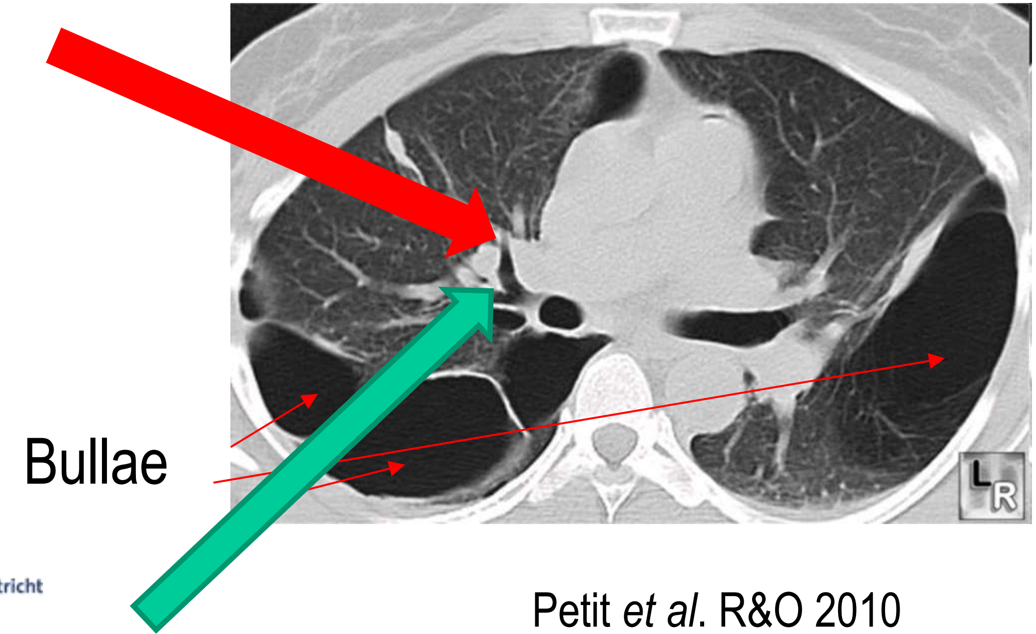
There are only radiosensitive tissues.”

Normal Lungs are also Heterogeneous

Lungs



Zhang 2008, Perfusion scan



Petit *et al*. R&O 2010

Low perfused areas + bullae = **NTPV**

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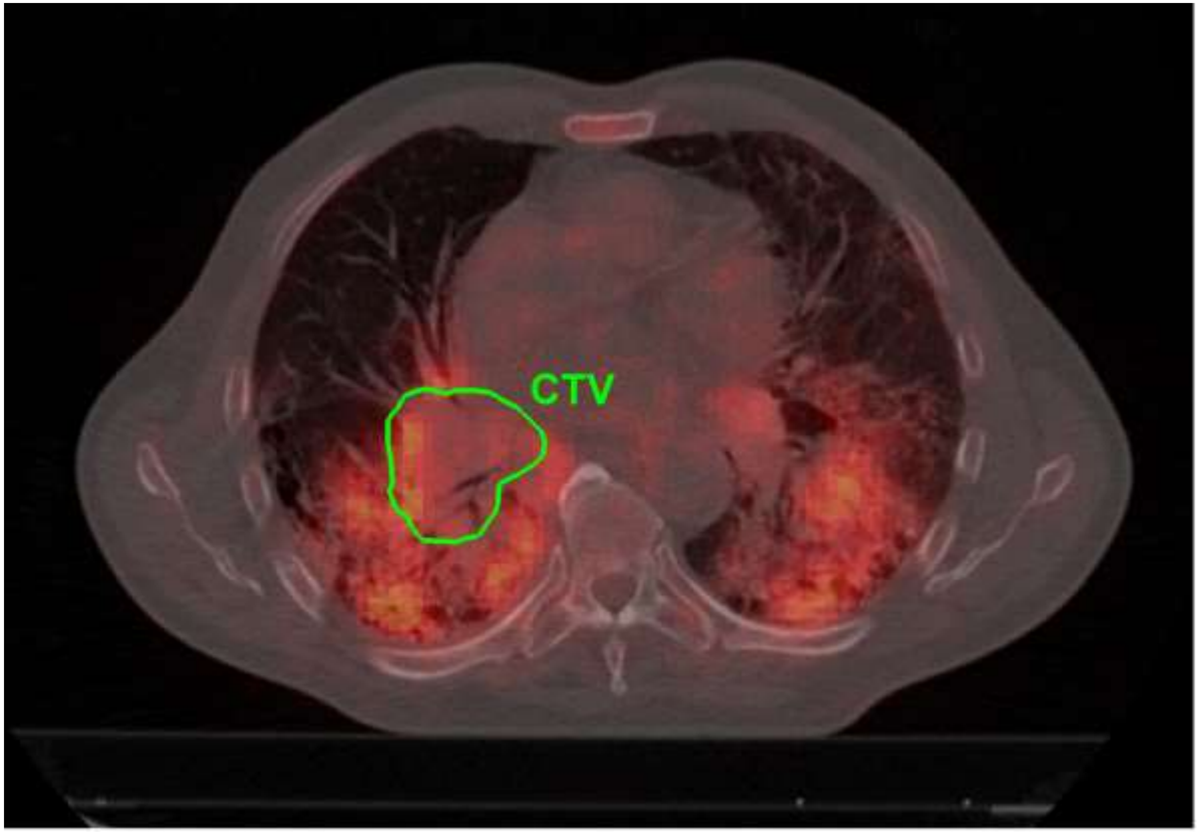
Normal Lungs with high SUV uptake

= more radiosensitive



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Petit *et al*. R&O 2010

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Normal lungs with high SUV uptake

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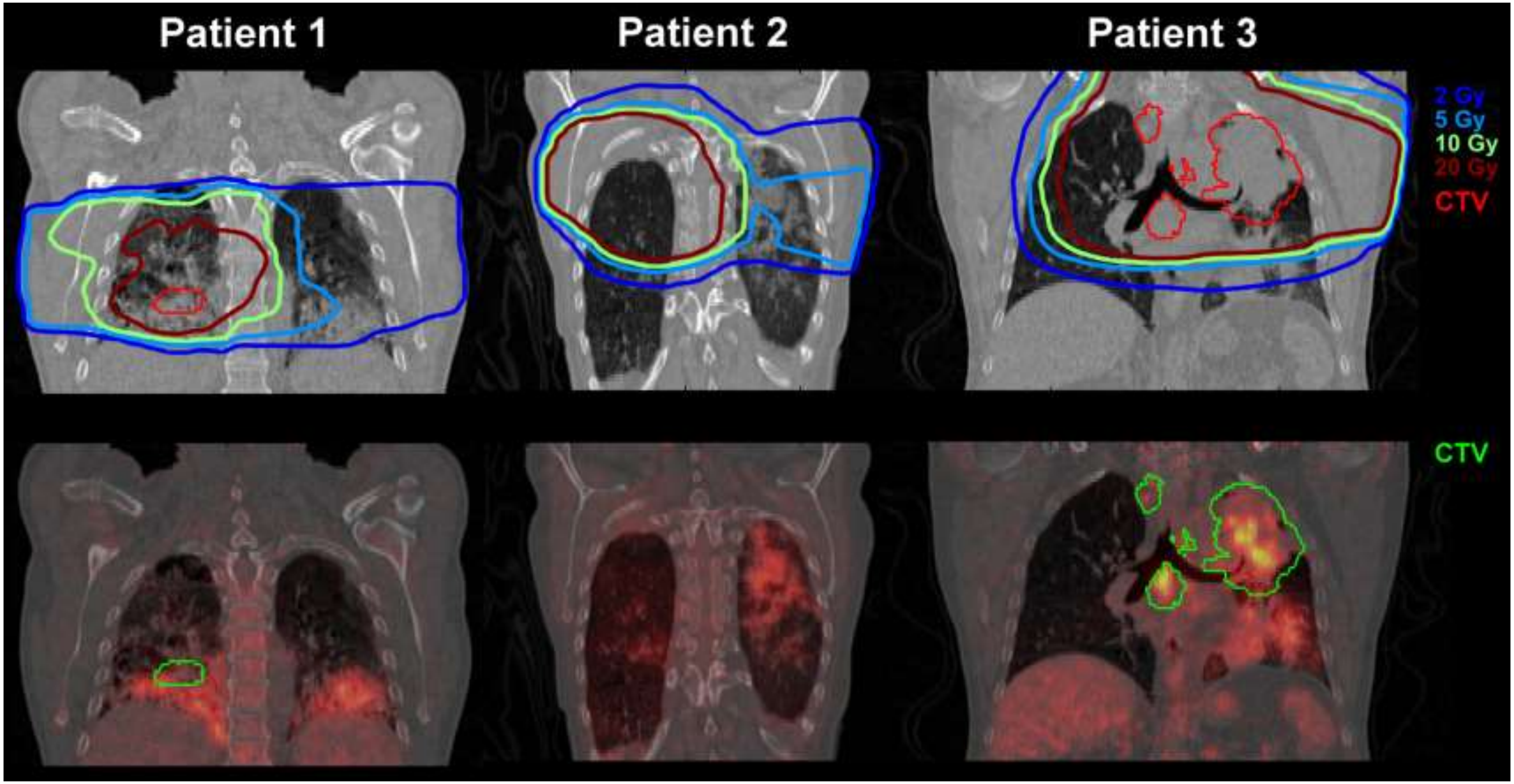

Normal lung + FDG uptake = **NTAV**

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Petit *et al*. R&O 2010

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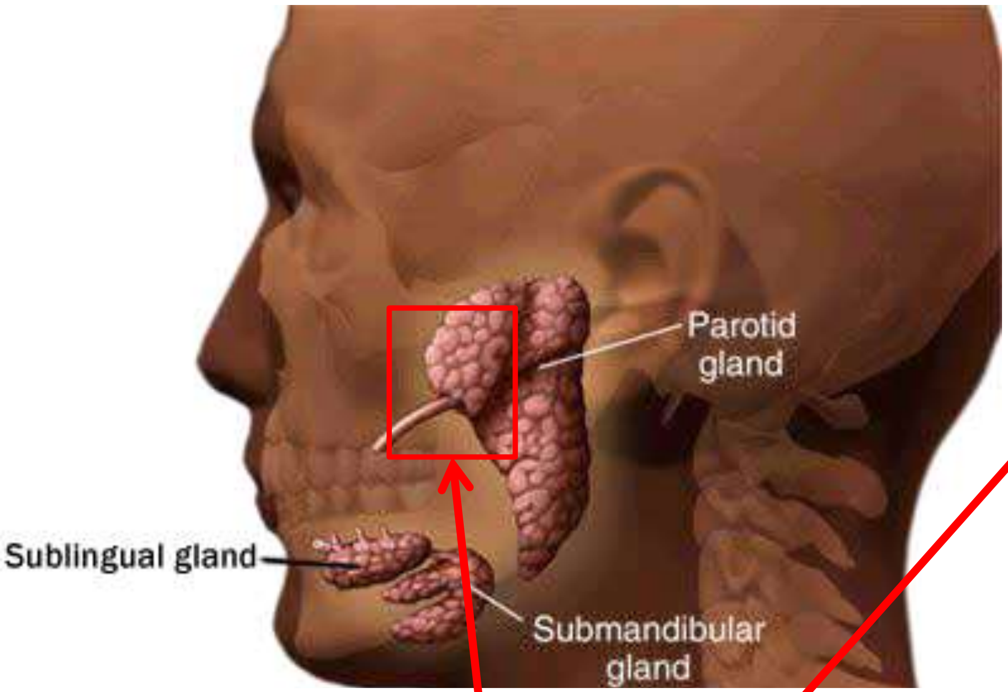
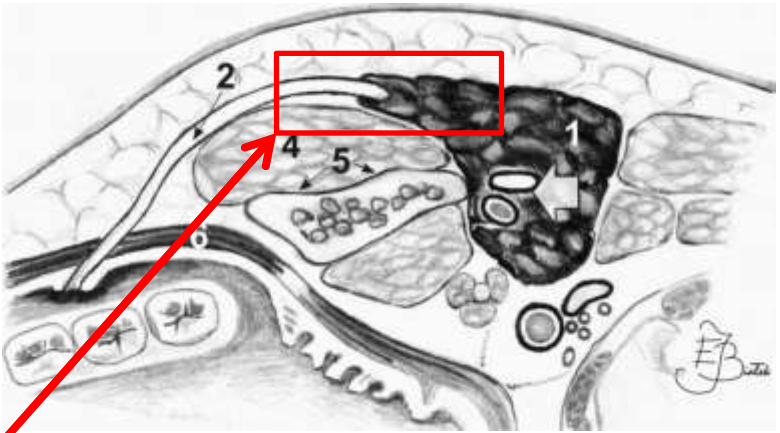
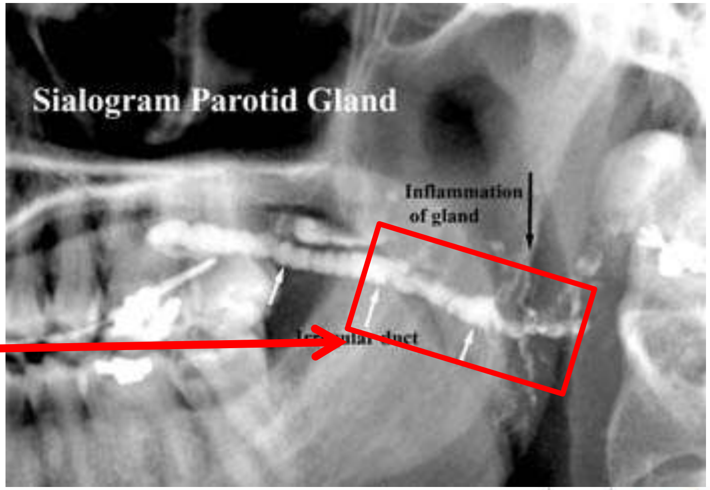
The Ductus of the Parotid







NTAV

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Van Luik *et al.* IJROBP 2009

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Conclusions

The importance of CTPET in Lung cancer

1. For prognosis and treatment decision (theragnostic)
2. For Gross Tumour Volume & Biological Target Volume contouring (GTV1-2; Dosimetric advantage, 4D-CTPET superior to 3D)
3. To adapt the treatment (repeated CTPET *during* treatment)
4. To use new Imaging Biomarkers (Hypoxia, Labeled drugs…) **= *Research***
5. To delineate new target volume: GTV Low drug uptake, Normal Tissue Avoidance Volume (NTAV) & Normal tissue Preferential Volume (NTPV) **= *Research***

Thank you for your attention

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www.maastro.nl, www.predictcancer.org, www.mistir.info, www.radiomics.info

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