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
1. Theragnostic (treatment decision after diagnosis)
2. Gross Tumour Volume identification & contouring
3. Adaptive Radiotherapy
4. Metabolic response @ 3 months
5. $GTV_{LDU}$ ($LDU = Low\ drug\ uptake\ target$)
Personalized Medicine: Multifactorial Decision Support Systems

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

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)

Decision Support System of first generation: Nomogram Lung Cancer

Female NSCLC T4N1M0
Results: Risk groups

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

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

AAPM, 2013
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)

$^{18}$F-Fluoro-2-deoxy-D-glucose (FDG)
Multi Modal Imaging

CT

PET

Fusion

CT/PET
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

<table>
<thead>
<tr>
<th></th>
<th>CT</th>
<th>(CT-)PET</th>
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<tbody>
<tr>
<td>Sensitivity</td>
<td>33-83%</td>
<td>77-91%</td>
</tr>
<tr>
<td>Specificity</td>
<td>66-90%</td>
<td>67-92%</td>
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<tr>
<td>PPV</td>
<td>46-71%</td>
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<tr>
<td>NPV</td>
<td>68-86%</td>
<td>77-97%</td>
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<tr>
<td>Accuracy</td>
<td>65-80%</td>
<td>73-92%</td>
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</table>

*References:
- 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
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

$GTV_{40}$: 54 ml
$GTV_{bg}$: 95 ml
$GTV_{2.5}$: 165 ml
$GTV_{vis}$: 158 ml

$p=0.0004$

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
AAPM, 2013
Interobserver Variation in Delineation

PET-CT: reduction in interobserver variation
Interobserver Variation in Delineation

SBR-based delineation results in:

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

V55 (%)  MED (Gy)  Dmax (Gy)

van der Wel et al. Int J Radiat Oncol Biol Phys 2005
De Ruysscher et al. Radiother Oncol 2005
van der Wel et al. Int J Radiat Oncol Biol Phys 2005
De Ruysscher et al. Radiother Oncol 2005
Theoretical radiation dose escalation with PET-CT planning

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

Using wrong CT attenuation leads to large artefacts

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

<table>
<thead>
<tr>
<th>simulated lesion</th>
<th>gated PET gated atten.</th>
<th>gated PET avg. attn.</th>
<th>ungated PET gated atten.</th>
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<tbody>
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<td>125%</td>
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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

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
Pitfalls

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
1. Theragnostic (treatment decision)
2. Gross Tumour Volume identification & contouring
3. PET-guided Adaptive Radiotherapy
4. Metabolic response @ 3 months
5. $GTV_{LDU}$ ($LDU = \text{Low drug uptake target}$)
What is Adaptive RT?

“What 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 chosen 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 Elmp 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.
Example Lung cancer (NSCLC) of early (week 2) repeated imaging during RT


**van Elmp 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 Elmpet 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

Day 0  Day 8  Day 15  Day 90

Complete Response (Wait and See)

Partial Response (Surgery)

Van Stiphout et al. Radiother Oncol 2011
Hypoxia Imaging in Head & neck cancer

Local-progression-free survival

(a) baseline

- group1 = 0 (TBRmax < 2.23)
- group1 = 1 (TBRmax >= 2.23)

Number at risk
- group1 = 0: 12, 7, 5, 1, 1, 0
- group1 = 1: 13, 5, 5, 4, 1, 0

(b) 8 - 10 Gy

- group2 = 0 (TBRmax < 2.16)
- group2 = 1 (TBRmax >= 2.16)

Number at risk
- group2 = 0: 11, 6, 6, 2, 1, 0
- group2 = 1: 11, 5, 3, 2, 1, 0

(c) 18 - 20 Gy

- group3 = 0 (TBRmax < 1.93)
- group3 = 1 (TBRmax >= 1.93)

Number at risk
- group3 = 0: 11, 8, 8, 3, 0, 0
- group3 = 1: 11, 2, 0, 0, 0, 0

Analysis time (months)

(d) 51 - 57 Gy

- group4 = 0 (TBRmax < 1.66)
- group4 = 1 (TBRmax >= 1.66)

Number at risk
- group4 = 0: 12, 7, 7, 3, 1, 0
- group4 = 1: 12, 4, 2, 2, 1, 0

P-values:
- (a) p = 0.937
- (b) p = 0.236
- (c) p = 0.001
- (d) p = 0.017

Zips et al. Radiother Oncol 2012
AAPM, 2013
Biomarker: Hypoxia (F-MISO PET)

[18F]Misonidazol

[18F]FDG
Multimodal Imaging: Focus on Lung Cancer

1. Theragnostic (treatment decision)
2. Gross Tumour Volume identification & contouring
3. Adapative Radiotherapy
4. Metabolic response @ 3 months
5. $GTV_{LDU}$ ($LDU = \text{Low drug uptake target}$)
Follow-up: CTPET Evaluation at 3 months (Metabolic response + Met’s)

100 patients

PET-CT 3 months after treatment

24% relapses

Detected by CT only and/or non curative treatment

Detected by CTPET only + curative treatment: 3 patients

Van Loon et al. EJC 2008, 2010
Follow-up: Metabolic Response Evaluation at 3 months

Survival advantage

Costs

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

Functional imaging

Three months after treatment

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

Aerts et al. Radiother Oncol 2009; Lung Cancer 2012
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 = $F(\text{biomap})$
**Randomized Phase 2 trial MAASTRO-NKI**

remain in the study

- T2-4N0-3M0
- Primary tumor diameter 4 cm or more
- SUVmax>5
- Eligible for radical treatment

**Register**

- Dose calculation
  - Dose escalation not possible
    - Chemo-radiotherapy to tolerance
  - Dose escalation possible
    - Randomize
      - Chemo-radiotherapy to tolerance
        - Homogeneous boost
        - Inhomogeneous boost

**Dose**

- N: 66 Gy / 24 frac. of 2.75 Gy
  - + on 50% SUV max contour
  - 5.40 Gy * 24 fractions = 129.6 Gy (maximum)

**T: up to NT constraints**
Examples of treatment plans

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

Arm B: PET Boost
- Prescribed dose: 93.6 Gy
- MLD: 19.3 Gy
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)

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
An example: PET imaging of $^{89}$Zirconium–Cetuximab

FDG-PET-CT

89Zr-cetuximab-PET

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. Adaptive Radiotherapy
4. Biological target Volume Contouring

The Future:

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

“There are no radioresistant tumours. There are only radiosensitive tissues.”
Normal Lungs are also Heterogeneous

Lungs

Low perfused areas + bullae = NTPV

Zhang 2008, Perfusion scan

Petit et al. R&O 2010
Normal Lungs with high SUV uptake

= more radiosensitive

Petit et al. R&O 2010
Normal lungs with high SUV uptake = more radiosensitive

Normal lung + FDG uptake = NTAV

Petit et al. R&O 2010
The Ductus of the Parotid

NTAV

Van Luik et al. IJROBP 2009
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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