FDG PET for dose painting: a rationale choice

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The radiation dose is homogeneous, but what about the tumor?

Consequences of an homogeneous ( = “flat”) dose distribution

Flat dose
Heterogeneous tumor

Survival is not flat
- More tumor cell survival in resistant areas
- Overkill in sensitive zones: “waste” of dose

Exploiting patient heterogeneity for dose painting of radiation
Consequences of a homogeneous ( = “flat”) dose distribution

- Heterogeneous dose
- Heterogeneous tumor
- Survival is flat
- Re-distribution of dose: more to resistant areas, less to the susceptible
- Optimal tumor control with the same dose on normal tissues

Dose-escalation study

- Higher dose => higher tumor control probability (TCP)

- How to increase: up to normal tissue constraints
  - Uniform boosting
  - Selective boosting
    - Target dose to a specific feature
  - “Hypothesis based” e.g. hypoxia, Proliferation, cell density…
  - “Data based”: identification of the resistant voxels with “pattern of relapse studies”
  - Non-selective boosting
  - Non-uniform dose distribution to reach high EUD

Requirements for the “optimal” tracer

- Tracer should correlate consistently with survival and local tumour control
- Tracer should be widely available & imaging method should be standardized.
- Tracer should remain at the same location during treatment (“spatial reproducibility”)
- Tracer should be able to identify residual cancer within the tumour (“Pattern of relapse studies”).

Stability of FDG uptake during treatment


FDG
Can "radio-resistant" areas within the tumour be identified before the treatment?

Functional imaging

Three months after treatment

X= Intratumoral relapse

FDG PET scan: pre vs. post radiotherapy

1. Pre-treatment SUVmax prognostic factor for OS & LPFS
2. FDG uptake in post treatment scan is in the same region as high uptake prior to RT

Overlap fraction pre-RT and post-RT volumes

Overlap fraction = 70% of 50% SUVmax hotspot pre treatment with residual metabolic active areas after treatment

→ Confirmed at the Princess Margaret Hospital in Toronto and Radboud University Nijmegen

Registered pre and post RT scan

Petit S et al. Radiother Oncol 2009
Dose painting: Which dose?

Uniform boosting based on normal-tissue constraints

Although not the aim of this study, we observed a promising outcome, with a 1-year survival rate of 57% and an estimated 2-year survival rate of 47%. A median overall survival of almost 20 months is in line with other dose-escalation study results (2–4). However, we could achieve this with

![Diagram of dose painting: Which dose?](image1)

Randomized Phase 2 trial MAASTRO-NKI

- Arm A: Homogeneous boost
  - Prescribed dose: 81.6 Gy
  - MLD: 19.0 Gy
  - N: 116 Gy / 24 frac. of 2.75 Gy
  - T: up to NT constraints

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

Examples of treatment plans
What is next?

1. Better identification of therapy resistant areas
2. Taking drug uptake into account
3. Selective avoidance of sensitive parts of normal tissues

Imperfect overlap fractions ≠ Residue can be outside the pre-treatment thresholds

We need complementary "molecular" imaging to better predict therapy-resistant areas within the GTV

The two contours respectively represent the tumor contour based on FDG based SUV-thresholding (green) and the delineation of the HX4 – hypoxic positive regions within the tumor (pink).

What about overlap HX4 with radioresistant FDG hotspot?

Hypothesis 1: No overlap at all. *We stop studying HX4!*

Hypothesis 2: Major overlap (more then 70%). *We do not need HX4, just use FDG. Therefore we also stop studying HX4!*

Hypothesis 3: Significant overlap. *HX4 could help us to better define the radioresistant voxels. Therefore we continue studying HX4!*
Overlap of hypoxia (HX4) with the radioresistant FDG hotspots?

FDG-PET images of a lung cancer patient. In green the delineation of the FDG-hotspots within the tumor (75% SUV_{max}), in pink the contour of the HX-4 positive regions within the tumor delineated using gradient-based image analysis.

What is next?

1. Better identification of therapy resistant areas

2. Taking drug uptake into account

3. Selective avoidance of sensitive parts of normal tissues

Voxel Control Probability (VCP)

Functional imaging

VCP Map_{\text{in}}

VCP Map_{\text{out}}

VCP Map_{\text{out}}

An example: PET imaging of 89Zirconium–Cetuximab

@EGFR (sc-03)

T47D

A431

4th p.i.

Aerts et al. JNM, 2009
What is next?

1. Better identification of therapy resistant areas
2. Taking drug uptake into account
3. Selective avoidance of sensitive parts of normal tissues

Hypothesis: Normal lungs with high SUV uptake = more radiosensitive
FDG in the lungs

Hypothesis

Increase in FDG during RT → RILT

What about FDG pre-RT?

Hypothesis: Pre-treatment inflammation in the lung makes pulmonary tissue more susceptible to radiation damage.

YES! SUV95 and Overlap 5% hottest voxels with V2 and V5 (p=0.04)

FDG uptake in the lung before treatment correlates with subsequent radiopneumonitis

Patient with high FDG uptake in the lungs before radiotherapy. Only 5% of the voxels with the highest uptake are shown. A large overlap between these voxels and the 2 Gy iso-dose surface increased the risk on radiation induced lung toxicity (RILT).

By minimizing this overlap the risk on RILT may be decreased.

DATA FUSION: advantages: a) simpler & b) does not lose topographic information
In search for the Virtual Patient

We map (in a smart way) all patients onto a 2D map and choose as a virtual patient the patient that is situated in the middle. This VP patient has the property that is closest—in deformation terms—to all the rest of the patients. In other words, the deformation needed to go from the chosen VP to the rest of the patients is minimal.

Lung-Toxicity (RILT) study

CT and PET images were successfully deformed towards the reference “virtual patient” using the deformation fields resulting from registration. The mean SUV level for the lower lung lobes of the virtual patient was $0.90 \pm 0.06$, for the group whose RILT score increased, and $0.73 \pm 0.05$ for the no-increase-in-RILT group. Patients with higher FDG uptake in the lower lung lobes prior to radiation treatment were found to be more likely to develop RILT.

Conclusions:

1. We have to exploit intra tumour and organ differences to further optimize treatment using dose painting of radiation

2. The likely area not controlled with treatment can be identified using a pre-treatment CT-FDG PET scan (which has several advantages: wide availability, standardized protocols, stability of the uptake, correlation to several biological characteristics of the tumour, correlation to pneumonitis risk...).
Selected PhD students from MAASTRO

Ludwig Dubois (KU)
Wouter van Elmpt (3D QGRT)
Hugo Aerts (Pattern of Relapse; Cetuximab-Zo)
Steven Petit (Pattern of Relapse; VCP)

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Planning Arm A: Patient eligible for dose escalation?

All registered patients will have an initial treatment planning performed to a prescription dose of 66 Gy in 24 fractions (2.75 Gy per fraction) with an integrated boost to the primary tumor as a whole. If necessary, the boost dose can be increased up to 5.40 Gy per fraction to the whole tumor if the patient is eligible for the trial and will be randomized after contacting the NKI DATA centre.

• This ‘test planning’ is the treatment plan for Arm A in the study (boost entire primary tumor)

• Fractionation scheme: 24 fractions with integrated boost
  – 2.75 Gy * 24 fractions = 66 Gy
  – 5.40 Gy * 24 fractions = 129.6 Gy (maximum allowed dose)
### Constraints: Normal tissues

**Table A1: Conversion table between EQD2 and physical dose.**

For the calculation of the physical dose in 24 fractions, using the linear-quadratic model with an α/β ratio equal to 3 Gy, the resulting dose can be converted from the EQD2 value by using the full 3D physical dose distribution and recalculating the equivalent dose at each point.

<table>
<thead>
<tr>
<th>Structure of interest</th>
<th>Physical dose in 24 fractions</th>
<th>EQD2 (alpha/beta)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lungs: mean lung dose</td>
<td>Depends on distribution</td>
<td>&lt;20 Gy [alpha/beta = 3 Gy]</td>
</tr>
<tr>
<td>Brachial plexus: max. dose</td>
<td>59 Gy</td>
<td>66 Gy [alpha/beta = 2 Gy]</td>
</tr>
<tr>
<td>Whole heart: mean dose</td>
<td>46 Gy</td>
<td>46 Gy [alpha/beta = 3 Gy]</td>
</tr>
<tr>
<td>Mediastinal structures PRV: max. dose</td>
<td>76 Gy</td>
<td>94 Gy [alpha/beta = 3 Gy]</td>
</tr>
<tr>
<td>Esophagus: V50Gy</td>
<td>&lt; 80%</td>
<td>&lt; 80% [alpha/beta = 2 Gy]</td>
</tr>
<tr>
<td>Spinal cord: max. dose</td>
<td>51 Gy</td>
<td>52 Gy [alpha/beta = 2 Gy]</td>
</tr>
</tbody>
</table>

### Margins....

- **MAASTRO:**
  - GTV => CTV: standard 5 mm
  - (possibility to 'edit' at boundary of normal tissues)
  - CTV => PTV: individual margin based on amplitude tumor
    - How: Delimitate GTV on 50% Exhale CT (standard delineation CT scan)
    - 0% Inhale CT (delimitate only GTV prim. tumor)
    - 100% Inhale CT (delimitate only CTV prim. tumor)
    - Centre-of-mass from GTV 0% en 100% => amplitude in 3 directions => margin CTV to PTV
  - CTV => PTV for lymph nodes = 5 mm

- **NKI:** (does something different but similar)

### Study continued...

This group will stay in study, incl. follow-up etc.

### Dose specification

- **Arm A (uniform boost)**
  - Primary tumour: integrated boost / 24 fractions
  - (maximum dose: 129.6 Gy)

- **Arm B (selective boost)**
  - Primary tumour: 66 Gy / 24 fractions
  - PTV high: integrated boost / 24 fractions
    - Nodes: 66 Gy / 24 frac.
    - Underdosage in 15% of PTVs is allowed if overlap with critical structures
    - Dose-escalation up to normal tissue constraints
    - Prescribed dose: 1.1x dose level encompassing 99% of the PTV (95% isodose)
Some practical points…

- Study is designed as iso-toxic… MLD equal in both arms
  - Equal MLD should be iso-toxic for lung
  - Equal MLD results in equal ‘mean PTV dose’ (# photons)

- Implications:
  - To reach equal MLD in both arms of study; Arm A and Arm B need both to planned for every patient:
  - MLD A <> MLD B means rescaling of Arm A or Arm B

Examples of treatment plans

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

Arm B: PET Boost
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- MLD: 19.3 Gy

DVH comparison Arm A vs. Arm B

Randomized Phase 2 trial MAASTRO-NKI

remain in the study
Overlap fraction pre-RT and post-RT volumes

Overlap fraction = 70% of 50% Suvmax hotspot pre-treatment with residual metabolic active areas after treatment

→ Confirmed at the Princess Margaret Hospital in Toronto and Radboud University Nijmegen ("external validation studies")

... but we believe that this is enough to improve radiotherapy

Dose-escalation by boosting radiation dose within the primary tumor on the basis of a pre-treatment FDG-PET-CT scan in stage II and III NSCLC: A randomized phase II trial.

Principal Investigators (PI):
Dirk de Ruyscher: MAASTRO/ MUNIC / GROW
José Belderbos: NKI
Autoradiography quantification of $^{89}$Zr-Cetuximab

FDG in the lungs (FDG during RT and radiation induced lung toxicity (RILT))

FDG increase between day 0 and 14 ➔ risk RILT ↑

Intratumoral pretreatment SUV - Response Curves

One figure = One tumour – One patient

One circle = One voxel

De Ruysscher 2009, Radiother & Oncol

FDG during RT and radiation induced lung toxicity (RILT)