Individualised Radiotherapy: How biology, physics and genetics meet

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Taking advantage of heterogeneity

Lambin et al. Radiother Oncol 2010
Technological evolution is unprecedented and unpredictable ... for telephones ...
2014: Are mostly not used telephones anymore ...

Volumetric Arc Therapy (VMAT)
Successful radiotherapy

- Dose
- Time
- Volume

- Appropriate target volume definition
- Avoiding normal tissues
- Adequate delivery and QA
% Progression-free Survival of patients at 30 months (Martel et al. 1999)

\[ T_p = 3 \text{ days} \]
\[ T_k = 28 \text{ days} \]
\[ \gamma = 0.66 \text{ Gy/d} \]

NSCLC

If no prolif.

\[ \gamma_{50} = 1.94 \]

\[ \gamma_{50} = 1.5 \]

with proliferation, as published by Martel et al. 1999

Total dose in 2 Gy fractions (= NTD)

Optimising target volume definition with FDG-PET-CT scans
Non-Small Cell Lung Cancer

Theoretical radiation dose escalation with the *same toxicity* with FDG-PET-CT planning

van der Wel et al. Int J Radiat Oncol Biol Phys 2005
De Ruysscher et al. Radiother Oncol 2005
Non-Small Cell Lung Cancer

• median follow-up time post-radiotherapy 16 months (95 % CI 11-21)
• median actuarial overall survival: 21 months (95 % CI 14-28)
• median progression free survival: 18 months (95 % CI 12-24)

- 11/44 (25 %) local recurrence

- Only 1/44 isolated nodal failure
  (crude rate 2.3 %, upper bound 95 % CI 10.3 %)
  (CT and PET T2N0M0 left upper lobe SqCC 16 mo after RT in nodes 5 and 6)

*De Ruysscher et al. Int J Radiat Oncol Biol Phys 2005*
# Small Cell Lung Cancer

<table>
<thead>
<tr>
<th>Recurrences</th>
<th>No patients</th>
<th>%</th>
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<tbody>
<tr>
<td>None</td>
<td>21</td>
<td>35</td>
</tr>
<tr>
<td>Local (prim. tumor)</td>
<td>9</td>
<td>15</td>
</tr>
<tr>
<td>Exclusively in-field</td>
<td>3</td>
<td>5</td>
</tr>
<tr>
<td>Local and distant</td>
<td>7</td>
<td>11.7</td>
</tr>
<tr>
<td><strong>Isolated nodal</strong></td>
<td>2</td>
<td>3.3</td>
</tr>
<tr>
<td><strong>Nodal</strong></td>
<td>20</td>
<td>33.3</td>
</tr>
<tr>
<td>Exclusively in-field</td>
<td>8</td>
<td>13.3</td>
</tr>
<tr>
<td>Nodal and distant</td>
<td>18</td>
<td>30.0</td>
</tr>
<tr>
<td><strong>Distant</strong></td>
<td>34</td>
<td>56.7</td>
</tr>
<tr>
<td>Isolated distant</td>
<td>19</td>
<td>31.7</td>
</tr>
<tr>
<td>Distant and local/nodal</td>
<td>15</td>
<td>25.0</td>
</tr>
<tr>
<td>Isolated brain</td>
<td>9</td>
<td>15.0</td>
</tr>
</tbody>
</table>

van Loon et al Int J Radiat Oncol Biol Phys 2009
Optimising the overall treatment time
Hyperfractionated or Accelerated Radiotherapy in Lung Cancer: An Individual Patient Data Meta-Analysis

<table>
<thead>
<tr>
<th>Category</th>
<th>Exp. RT</th>
<th>Conv. RT</th>
<th>O-E</th>
<th>Variance</th>
<th>HR (95% CI)</th>
</tr>
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<tbody>
<tr>
<td>Very accelerated RT</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>PMCI 88C091</td>
<td>48/48</td>
<td>52/53</td>
<td>-0.8</td>
<td>24.3</td>
<td></td>
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<tr>
<td>PMCI 88C091 CT</td>
<td>51/51</td>
<td>56/56</td>
<td>-6.0</td>
<td>25.6</td>
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<tr>
<td>CHART</td>
<td>316/338</td>
<td>217/225</td>
<td>-29.4</td>
<td>120.7</td>
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<td>ECOG 2597</td>
<td>51/69</td>
<td>55/59</td>
<td>-7.4</td>
<td>25.8</td>
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<tr>
<td>CHARTWEL</td>
<td>132/150</td>
<td>132/150</td>
<td>0.0</td>
<td>65.8</td>
<td></td>
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<tr>
<td>CHARTWEL CT</td>
<td>40/53</td>
<td>47/53</td>
<td>-6.4</td>
<td>21.2</td>
<td></td>
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<tr>
<td>Subtotal</td>
<td>638/700</td>
<td>559/596</td>
<td>-37.8</td>
<td>283.4</td>
<td>0.88 (0.78 to 0.98)</td>
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<tr>
<td>Moderately accelerated RT</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Gliwice 2001</td>
<td>28/29</td>
<td>27/29</td>
<td>-1.4</td>
<td>13.2</td>
<td></td>
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<tr>
<td>Subtotal</td>
<td>28/29</td>
<td>27/29</td>
<td>-1.4</td>
<td>13.2</td>
<td>0.90 (0.52 to 1.54)</td>
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<td>Hyperfractionated RT—identical total dose</td>
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<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>NCCTG 902451</td>
<td>34/39</td>
<td>35/35</td>
<td>-7.0</td>
<td>15.7</td>
<td></td>
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<tr>
<td>NCCTG 942452</td>
<td>111/125</td>
<td>108/121</td>
<td>-2.6</td>
<td>54.6</td>
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<tr>
<td>Subtotal</td>
<td>145/164</td>
<td>143/156</td>
<td>-9.6</td>
<td>70.3</td>
<td>0.87 (0.69 to 1.10)</td>
</tr>
<tr>
<td>Hyperfractionated RT—increased total dose</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>RTOG 8808</td>
<td>155/163</td>
<td>156/163</td>
<td>-6.4</td>
<td>76.9</td>
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<tr>
<td>Subtotal</td>
<td>155/163</td>
<td>156/163</td>
<td>-6.4</td>
<td>76.9</td>
<td>0.92 (0.74 to 1.15)</td>
</tr>
<tr>
<td>Total</td>
<td>964/1,066</td>
<td>885/944</td>
<td>-55.2</td>
<td>443.7</td>
<td>0.88 (0.80 to 0.97), P = .009</td>
</tr>
</tbody>
</table>

Test for heterogeneity: $\chi^2 = 9.74$, P = .37, I ² = 8%
Test for interaction: $\chi^2 = 0.17$, P = .98
Small Cell Lung Cancer

De Ruysscher et al. J Clin Oncol 2006

Van Meerbeeck, Fenell, De Ruysscher. Lancet 2011
Individualisation based on optimal target volume definition short overall treatment time physical constraints
INDividualised Accelerated Radiotherapy (INDAR)

- Escalate the dose to the maximum tolerance
- Delivered in a short overall treatment time
- Directed to areas that are 18F-deoxyglucose (FDG) positive

Van der Wel et al. Int J Radiat Oncol Biol Phys 2005
De Ruysscher et al. Radiother Oncol 2005
De Ruysscher et al. Int J Radiat Oncol Biol Phys 2005
Survival by stage (large volume, multi-level N+, 25% WHO PS 2), sequential chemo-radiation

van Baardwijk et al. J Clin Oncol 2010
Dyspnea evolution after individualised radiotherapy:
10 % less patients with dyspnea

van Baardwijk et al. J Clin Oncol 2010
Early response: FDG changes during first week of chemo-RT and survival

- **FDG-PET:**
  - Cut-off: 15% (EORTC response)
  - Changes in maximum SUV and mean SUV significant predictive for 2-year overall survival
    - HR 1.26 (95% CI: 1.09 – 1.45) per 5% decrease of SUV
- **CT (volume)**
  - Tumour volume pre RT is predictive for survival
    - HR 1.040 (95% CI: 1.005 – 1.076) per 10 cm³ increase
  - Change in tumour volume (CT) is not correlated to survival

A Phase I Study of Concurrent Individualized, Isotoxic Accelerated Radiotherapy and Cisplatin–Vinorelbine–Cetuximab in Patients With Stage III Non–Small-Cell Lung Cancer

Anne-Marie C. Dingemans, MD, PhD,*, Gerben Bootsma, MD, PhD,† Angela van Baardwijk, MD, PhD,‡ Bart Reymen, MD,‡ Rinus Wanders, MD,‡ Boudewijn Brans, MD, PhD,§ Marco Das, MD, PhD,|| Monique Hochstenbag, MD, PhD,* Arne van Belle, MD,* Ruud Houben, MSc,‡ Philippe Lambin, MD, PhD,‡ and Dirk de Ruysscher, MD, PhD,§
Optimising by taking advantage of intra-tumour and intra-organ heterogeneity
Individual image-based tissue characterization: Possible prognostic and predictive use

- Tumor cells:
  - e.g., genetic instability, mutation status, resistance
- Microenvironment:
  - e.g., hypoxia
- Malignant potential:
  - e.g., undetermined pulmonary nodules
  - At screening or staging

Selection of systemic treatment
- Most appropriate drugs, dose, and sequence

Selection of local therapy
- Determination of best radiation dose: escalation or deescalation
- Selective avoidance of most susceptible parts of healthy organs

Tumor → Image analysis → Normal tissues (e.g., lungs, heart)

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CCR Translations

De Ruysscher D. Clin Cancer Res 2013
Heterogeneity in the tumour
Taking advantage of intra-tumour heterogeneity: PET-boost

Concurrent chemo-radiotherapy

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

Register

Dose calculation

Dose escalation not possible

Dose escalation possible

RANDOMIZE

Homogeneous boost

Inhomogeneous boost

Chemo-radiotherapy to tolerance
Upregulation of TAAs by radiation

- Caco-2, HCT116, WiDr, HT-29, LS 174T, SW1463, SW403, SW480, SW620, T84, LoVo, and COLO 205
- A549, SK-LU-1, SW900, HLF-a, NCI-H23, NCI-H647, Calu-1, H460, Calu1 and Calu3
- 22Rv1, DU 145, PC-3, PC3, DU145 and LNCaP
- MelJuSo, SK-MEL-37, CaSki and SiHa
- MDA-MB-469, MDA-MB-231 and MCF 7
- Saos, LM5, 143B, HOS, HU09, and M132

Dudek et al. Cyt Growth Fact Rev 2013
Phase II trial stage I-III small cell lung cancer

- PET-CT (mandatory)
- Contrast-enhanced CT Thorax and upper Abdomen (CT T/A)
- Brain MRI
- FFPE tissue and blood collection

**Chemotherapy:**
- 4 cycles of Cisplatin 25 mg/m² iv D1-3 or 75 mg/m² D1
- Etoposide 100 mg/m² iv D1-3 q21d.

**Thoracic Radiotherapy:**
- Accelerated twice-daily, administration of 1.5 Gy x 30 over three weeks (preferred)
- or once-daily radiotherapy, administration 1.8-2Gy per fraction up to 55-60Gy. Two options are allowed: start from D1 of cycle 1 or cycle 2.

**Prophylactic Cranial Irradiation (PCI):**
- 25 Gy in 10 fractions started between D8 and D15 of cycle 4 (to D22-29)

**Randomization:**
- should take place 5-6 weeks after Day 1 (between D35-42) of cycle 4

**Ipilimumab schedule:**
- Induction course of ipilimumab, at a dose of 10 mg/kg, once every 3 weeks x4, started 6-8 weeks after cycle 4 of chemotherapy (Day 42-56 of cycle 4)
- Maintenance: 10mg/kg, once every 12 weeks, for a maximum of 3 years after randomization

* CT at 8, 16 and 24 weeks and then every 3 months during 1st yr then every 6 months for 2 yrs until interim/safety analysis

**CT TA q3 mos for 12 months**
then q6 mos for 24 months from randomization
Stage IIIA / B NSCLC
Investigator’s choice

Screening, eligibility and enrolment
Stage IIIA / B NSCLC
Whole body FDG PET-CT

Standard treatment
chemo cycle 1
chemo cycle 2
chemo cycle 3
Radiotherapy 66Gy, 33 fractions
Radiotherapy 66Gy, 24 fractions

Trial treatment
Anti PD-1 consolidation: nivolumab 10mg/kg every 2 weeks

Chemotherapy: Cisplatin (or Carboplatin) doublet
CT after Radiotherapy
CT after Radiotherapy

Year 1: CT every 8 weeks
Year 2: CT every 12 weeks

Primary endpoint: Grade ≥3 pneumonitis (CTCAE V4.0) up to 6 months post-radiotherapy
Secondary endpoints: Time to first grade ≥3 pneumonitis; PFS, OS; objective response (RECIST 1.1); time to treatment failure; Adverse events by CTCAE 4.0
Heterogeneity between the tumour and metastases with
Heterogeneity in the lungs
FDG uptake in the lung before treatment correlates with subsequent radiopneumonitis

Changes in Hounsfield Units (HU) per Gy for each individual patient

$\Delta \text{HU/Gy}$ and dyspnoea $\geq G2$

$< \text{median}, 16/48 (33.3 \%)$  
$> \text{median}, 17/47 (36.1 \%)$  
$(p=0.77)$

De Ruysscher et al. Acta Oncol 2013
Step 1: Baseline HU of lung

- Saturation level of sigmoidal dose effect is a function of the background HU

\[ p = 0.04 \text{ in multivariate analysis} \]
Step 2: Heterogeneity within the lungs

- Concept
  - Denser region more sensitive
  - Limit radiation dose to denser regions
Step 2: Heterogeneity within the lungs

- Redistribution of radiation dose
Heterogeneity in the brain
Improvement of memory function after Prophylactic Cranial Irradiation (PCI) by avoidance of the hippocampus: A randomized phase III study in small cell lung cancer patients

Dirk De Ruysscher, MD, PhD, on behalf of the HA-PCI working group
**Inclusion criteria**
- Patients with either limited disease (LD) or extensive disease (ED) small cell lung cancer (SCLC) candidate for PCI after a partial or complete response to chemotherapy or chemoradiation
- WHO-performance status ≤ 2 (see Appendix IV)
- Sufficient proficiency in Dutch language
- No evidence of progressive extracranial metastatic disease

**Exclusion criteria**
- Prior radiotherapy to the brain
- Patients receiving any systemic anticancer treatment during PCI
- Pregnancy or lactation

**Randomization**
- The patient had chemoradiation or chemotherapy less than 6 weeks prior the randomization
- The patient will receive PCI within 2 weeks after randomization
- No signs of progressive disease after chemotherapy
- Signed informed consent
• **Primary Endpoint**
  
  • The total recall score of the Hopkins Verbal Learning Test–Revised (HVLT–R), assessed at 4 months after PCI. A decline in the total recall score of 5 points or greater compared with baseline will be considered a failure.

• **Secondary Endpoints**
  
  • Neurocognitive functioning and QoL, motor function
  • Assessment of structural and functional brain abnormalities
  • Incidence and location of brain metastases
  • Overall survival
  • Progression free survival
  • Bio-markers (neuro-inflammation)
Single task imaging

Red significance map: increased activity during the auditory relative to the visual task.
Green significance map: higher activity during the visual relative to the auditory task

Deprez S et al. Neuropsychologia 2013
Dual and multi-task imaging: Significance maps

Green: Higher activity during dual task compared to both single tasks
Red: Higher activation during multitask compared to both single tasks
Blue: Higher activation during multitask compared to dual-task

IPS: intra-parietal sulcus; PMC: premotor cortex; ACC: anterior cingulate cortex; OT: occipito-temporal; IFSa: activation in more anterior part of inferior frontal sulcus; IFSp: activation in more posterior part of inferior frontal

Deprez S et al. Neuropsychologia 2013
Functional connectivity maps

Deprez S et al. Neuropsychologia 2013
Applicable in proton therapy?
Applicable in proton therapy?
Applicable in proton therapy?
De Ruysscher D, Chang J. Sem Radiat Oncol 2013

\[ PD = 70 \text{ Gy} \]

<table>
<thead>
<tr>
<th>Organs at risk</th>
<th>3DCRT</th>
<th>IMRT</th>
<th>Protons PSPT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lung MLD</td>
<td>18.9 (7.3)(^a)</td>
<td>16.4 (5.5)(^a)</td>
<td>13.5 (6.2)</td>
</tr>
<tr>
<td>Esophagus D(_{\text{mean}})</td>
<td>28.3 (13.9)(^a)</td>
<td>26.0 (12.1)</td>
<td>24.4 (13.7)</td>
</tr>
<tr>
<td>Heart D(_{\text{mean}})</td>
<td>15.3 (11.6)(^a)</td>
<td>14.3 (10.3)(^a)</td>
<td>7.6 (7.2)</td>
</tr>
<tr>
<td>Patient ID</td>
<td>11.0 (5.4)(^a)</td>
<td>9.9 (4.4)(^a)</td>
<td>6.9 (3.9)</td>
</tr>
</tbody>
</table>

Roelofs E et al. J Thor Oncol 2012
Combining with genetics of the patient and of the tumour
Correlation with genetics?

Review

STROGAR – STrengthening the Reporting Of Genetic Association studies in Radiogenomics

Consor:um!
Clinical Biomarkers Data Models
Correlation of delta HU/ Gy (less multifactorial than dyspnoea) and genetics

rs2252070 (p=0.006, MMP13)
rs2230588 (p=0.009, JAK1)
rs12901071 (p=0.009, SMAD3)

MMP13 gene = matrix metalloproteinase 13, encoding for collagenase 6; implied in COPD (tissue destruction).

JAK1 gene = essential for signal transduction of many cytokines and cell adhesion; implied in COPD (increased inflammation).

SMAD3 gene = member of the TGF-β superfamily; multifunctional; implied in COPD (inflammation regulation).

De Ruyck, De Ruysscher et al. 2013, work in progress
RADIOSCAPE

A Project of the European Thoracic Oncology Platform (ETOP)

Dirk De Ruysscher, Suresh Senan, Rafal Dziadziszko, Cecile Le Pechoux, Corinne Faivre-Finn, Solange Peters, Rolf Stahel
on behalf of ETOP collaborators
Applicable in proton therapy?
Great future ...