Individualised Radiotherapy: How biology, physics and genetics meet

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Taking advantage of heterogeneity

Technological evolution is unprecedented and unpredictable ... for telephones ...

1890: First radiotherapy
1965: Mantle field radiotherapy
1985: Many phase III trials

2014: Are mostly not used telephones anymore ...

Successful radiotherapy

- Dose
- Time
- Volume

- Appropriate target volume definition
- Avoiding normal tissues
- Adequate delivery and QA

**Optimising target volume definition with FDG-PET-CT scans**

**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
(crust rate 2.3%, upper bound 95% CI 10.3%) (CT and PET T2N0M0 left upper lobe SqCC 16 mo after RT in nodules 5 and 6)

**Small Cell Lung Cancer**

<table>
<thead>
<tr>
<th>Recurrences</th>
<th>N' patients</th>
<th>%</th>
</tr>
</thead>
<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>Isolated nodal</td>
<td>2</td>
<td>3.3</td>
</tr>
<tr>
<td>Nodal</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>Isolated nodal and distant</td>
<td>19</td>
<td>31.7</td>
</tr>
<tr>
<td>Isolated brain</td>
<td>9</td>
<td>15.0</td>
</tr>
</tbody>
</table>

**Optimising the overall treatment time**

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

**INDividualisation based on optimal target volume definition short overall treatment time physical constraints**

![Graph showing survival by stage](image)

**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

![Graph showing survival by stage](image)

**Survival by stage (large volume, multi-level N+, 25% WHO PS 2), sequential chemo-radiation**

**54 Gy/30 F/3 wks**
- T3N0M0

**79.2 Gy/44 F/4.4 wks**
- pT4pN2M0

![CT scans showing tumor progression](image)
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-RRT and survival

- FDG-PET:
  - Cut-off: 15% (EORTC response)
  - Changes in maximum SUV and mean SUV significant predictor for 2-year overall survival
    - HR 2.26 (95% CI: 1.09 – 4.45) per 5% increase of SUV
- CT (volume):
  - Tumour volume pre RT is predictive for survival
    - HR 1.04 (95% CI: 1.005 – 1.076) per 10 cm³ increase
  - Change in tumour volume (CT) is not correlated to survival


Optimising by taking advantage of intratumour and intra-organ heterogeneity

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

J Thorac Oncol 2014

Heterogeneity in the tumour

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


Upregulation of TAAs by radiation

- Caco-2, HCT116, Wtvr, HT-29, LS 174T, SW1463, SW403, 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
- MiaPaCa, SK-MEL-37, CaSki and SiHa
- MDA-MB-469, MDA-MB-231 and MCF 7
- SAOS, S4488, HOS, HuGh09, and MI12

Dudek et al. Cyt Gloc Growth Factor Rev 2013

Concurrent chemo-radiotherapy

Phase II trial stage I-III small cell lung cancer

Heterogeneity between the tumour and metastases with

NICOLAS: Schema

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 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

Step 1: Baseline HU of lung
- Saturation level of sigmoidal dose effect is a function of the background HU

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
• 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)
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: intraparietal sulcus; PMC: premotor cortex; AIC: anterior cingulate cortex; ST: 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

Applicable in proton therapy?

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Roelofs E et al. J Thor Oncol 2012

Functional connectivity maps

Deprez S et al. Neuropsychologia 2013

Table:

<table>
<thead>
<tr>
<th>Parameter</th>
<th>PET</th>
<th>Diffusion</th>
</tr>
</thead>
<tbody>
<tr>
<td>Distance</td>
<td>89.53mm</td>
<td>51.57mm</td>
</tr>
<tr>
<td>SUVmax</td>
<td>32.75</td>
<td>181.25</td>
</tr>
<tr>
<td>SUVmean</td>
<td>18.75</td>
<td>112.50</td>
</tr>
<tr>
<td>SUVpeak</td>
<td>14.75</td>
<td>71.25</td>
</tr>
</tbody>
</table>

DeRuutter O. Cheg J. Sem Relaf Ostr 2013
Combining with genetics of the patient and of the tumour

Correlation with genetics?

Correlation of delta HU/ Gy (less multifactorial than dyspnoea) and genetics

r=2252070 (p=0.006, MMP13)
r=2230588 (p=0.009, JAK2)
r=12901071 (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

Applicable in proton therapy?
Great future ...