Professor Suresh Senan
VU University Medical Center, Amsterdam
Tumor volume and survival

Radiation dose distribution and toxicity

Radiotherapy in mesothelioma

Isolated brain failures in LA-NSCLC

38PD: Dirk De Ruysscher (on behalf of Gilles Defraene)

156PD: Angela Botticella

82PD: Judi van Diessen
Tumor volume and survival in stage III NSCLC

- Radiotherapy plus low-dose cisplatin in 226 patients (2007-2011)
- Primary tumor and involved lymph nodes contoured
- Perf score, age, histology, gender, volume of primary tumor and SUVmax were tested as prognostic factors.
- Only significant factor for OS was the primary tumor volume (HR 1.002, p<0.001).

<table>
<thead>
<tr>
<th></th>
<th>Tumor volume &lt; 40 cc</th>
<th>Tumor volume ≥ 40 cc</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>LR (%)</td>
<td>1-year</td>
<td>6,5</td>
<td>20,4</td>
</tr>
<tr>
<td></td>
<td>2-year</td>
<td>17,8</td>
<td>33,5</td>
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<td>OS (%)</td>
<td>1-year</td>
<td>87,4</td>
<td>65,0</td>
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<td>2-year</td>
<td>68,5</td>
<td>48,1</td>
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82PD van Diessen J. ELCC 2015
Tumor size and survival (TROG 99.05)

- Prospective observational study in 509 patients
- 280 stage III patients (gross tumor volumes ≥ 270 cc in 8%)
- **Primary tumor** volume prognostic for **survival** only in 1st **18 months**, even after allowing for effects of T- and N- status.
- Similar proportion of long-term survivors in all quartiles.
Stage III NSCLC: Volume effect

- **Tumor volume** (PTV) and median overall survival (OS) after concurrent CT-RT

  - $< 350 \, \text{cm}^3$ (n = 17), OS 35.6 months
  - 350 – 700 $\, \text{cm}^3$ (n = 85), OS 24.2 months
  - 700 – 1050 $\, \text{cm}^3$ (n = 52), OS 15.7 months
  - $> 1050 \, \text{cm}^3$ (n = 36), OS 10.3 months

van Reij, Acta Oncol 2013
Concurrent CT-RT for large tumors

Single institution:
• 121 patients
• Planning Target Vol (PTV) >700cc (± N3) or PTV <700cc and N3

Toxicity: Gr ≥3 pneumonitis – 4%

Wiersma T, Lung Cancer 2013
Tumor volume and survival in stage III NSCLC

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- Investigate dose-painting (for dose redistribution) in a randomized phase II PET-boost trial in patients with a minimum primary tumor size of 4 cm (33 cc).

82PD van Diessen J. ELCC 2015

Surgery alone = 49%
Radiation alone = 24%
Surgery + radiation = 10%
No surgery or radiation = 15%

Larger primary tumor size associated with inferior survival in early stage NSCLC, in locally advanced disease, and in patients with extensive N disease

Zhang J, JTO 2015
Tumor volume and survival (SEER)

Zhang J, JTO 2015
• CT₀ characteristic, i.e. median density HU₀, appears to be a surrogate of radiosensitivity

• Denser subregions show a trend towards higher radiosensitivity (p=0.07)
Avoiding radiation-induced lung damage

• Methodology
  • 110 stage I-IV patients (30 from an external validation set)
  • Compare planning CT₀ and fup CT₃M : local **density changes (HU₃M-HU₀)**

• Results
  – **Sigmoidal dose response** relation: described by D₅₀ (position) and ΔHUₘₐₓ (saturation) for each patient

• Advantages over classical lung toxicity endpoints (e.g. QUANTEC)
  • Less multifactorial endpoint
  • Successful external validation (similar distributions of D₅₀ and ΔHUₘₐₓ)
  • Simple CT₀ characteristic, i.e. median density HU₀, is surrogate of radiosensitivity
    • Predicts for ΔHUₘₐₓ (p=0.003) between patients

38PD Defraene G, ELCC 2015
Randomised phase II trial

- Hypothesis: redistribution of radiation dose, sparing most sensitive lung regions, will reduce grade ≥2 radiation pneumonitis

Primary endpoint: incidence of grade 2-5 radiation pneumonitis (CTCAE 4.0) within 90 days after the end of radiotherapy.

Secondary endpoints: incidence of grade 2-4 cough (CTCAE 4.0), pulmonary function changes, overall survival, quality of life, identification of CT characteristics that improve the prediction model

38PD Defraene G, ELCC 2015
Hyperpolarised $^3$He MRI

STUDY PROTOCOL

Functional lung avoidance for individualized radiotherapy (FLAIR): study protocol for a randomized, double-blind clinical trial

Patients with Stage III NSCLC undergoing Concurrent Chemoradiotherapy

≥10 Pack-Year Smoking History

MRI with inhaled contrast

RANDOMIZATION

ARM 1

STANDARD RADIOThERAPY

FOLLOW-UP

QOL, Toxicity, Survival Outcomes

ARM 2

FUNCTIONAL LUNG AVOIDANCE RADIOThERAPY

FOLLOW-UP

QOL, Toxicity, Survival Outcomes

Figure 1 Study design: patients will be randomized in a 1:1 ratio between Arm 1 (standard radiotherapy) and Arm 2 (functional lung avoidance radiotherapy).

Hoover et al. BMC Cancer 2014, 14:934
4DCT-based fractional regional ventilation

Slide courtesy of Mistry N (see Mistry N, IJROBP 2013)
Fractional regional ventilation shown in axial slice for 3 different breathing maneuvers: (a) free breathing (FB), (b) audiovisual guidance (AV), and (c) active breathing control (ABC).

Mistry N, IJROBP 2013
Radiotherapy in mesothelioma.


• High-dose radiotherapy following extra-pleural pneumonectomy has been out of favour in Europe since results of MARS [Treasure T, Lancet Oncol 2011] and SAKK17/04 trial [Stahel R, ESMO 2014]

• Hemi-thorax radiotherapy after pleurectomy, or even in situ, is being explored
  – Why was RT ineffective? target coverage, toxicity
  – Role of newer techniques [VMAT, protons]
Table 2  Failure types and patterns

<table>
<thead>
<tr>
<th>Failure type</th>
<th>All patients (N=67)</th>
<th>Patients undergoing surgery (n=42)</th>
<th>Unresectable cases (n=25)</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>Number</td>
<td>%</td>
<td>Number</td>
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<tr>
<td>Locoregional failures</td>
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<tr>
<td>Total</td>
<td>44</td>
<td>66</td>
<td>25</td>
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<tr>
<td>In-field</td>
<td>43</td>
<td>64</td>
<td>24</td>
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<tr>
<td>Previous involved site</td>
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<td>48</td>
<td>14</td>
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<tr>
<td>New site</td>
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<td>16</td>
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<tr>
<td>Marginal</td>
<td>13</td>
<td>19</td>
<td>5</td>
</tr>
<tr>
<td>Out-of-field</td>
<td>25</td>
<td>37</td>
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<tr>
<td>Fissure</td>
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<td>16</td>
<td>6</td>
</tr>
<tr>
<td>Distant</td>
<td>32</td>
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<td>18</td>
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<td>Failure patterns</td>
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<tr>
<td>Local only</td>
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<td>13</td>
<td>6</td>
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<tr>
<td>Local and regional</td>
<td>8</td>
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</tr>
<tr>
<td>Local and distant</td>
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<td>15</td>
<td>6</td>
</tr>
<tr>
<td>Local, regional, and distant</td>
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<td>24</td>
<td>6</td>
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<tr>
<td>Regional only</td>
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<td>1</td>
<td>1</td>
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<tr>
<td>Regional and distant</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Distant only</td>
<td>6</td>
<td>9</td>
<td>6</td>
</tr>
</tbody>
</table>
Pattern-of-failure analysis in MPM

- 67 patients with malignant pleural mesothelioma (MPM)
- All were unresectable or underwent pleurectomy/decortication
- All received hemithoracic pleural IMRT (2004-2013)

- 64% in-field local failures (64%)

Rimner A, IJROBP 2014
• After P/D versus those who received a partial pleurectomy or were deemed unresectable, the median time to in-field local failure was 14 months versus 6 months, respectively,

• 1- and 2-year actuarial in-field local failure rates of 43% and 60% versus 66% and 83%, respectively (P=.03).

• 19% marginal failures (n=13), with 5 in costomediastinal recess.

• 37%) had out-of-field failures.

• 48% had distant failures

Rimner A, IJROBP 2014
Hemithoracic lung-sparing volumetric modulated arc therapy (VMAT) for malignant mesothelioma

AIM:
• To optimize target definition and treatment planning in lung-sparing VMAT for malignant mesothelioma

METHODS:
• 16 stage I-IV MPM patients included (retrospectively identified from an Institutional dataset)

➢ CONTOURING PHASE
1. Rigid co-registration between CT and 18FDG-PET/CT and CT and MRI (T1, T2)
2. 3 sets of gross tumour volumes (GTV) identified: GTV_{CT}, GTV_{CT+PET/CT}, and GTV_{CT+MRI}
3. “Qualitative” and “quantitative” evaluation of the GTVs performed

156PD: Angela Botticella ELCC 2015
Hemithoracic lung-sparing volumetric modulated arc therapy (VMAT) for malignant mesothelioma

- **PLANNING PHASE**

1. GTV with the highest rate of newly-identified tumour sites was chosen to generate the PTV
2. 12 patients - first 6 consecutive left-sided and right-sided
3. VMAT plans for all patients
4. Prescription dose: 50 Gy in 2-Gy fractions, and progressive dose-escalation steps with 4 Gy increment were attempted

156PD: Angela Botticella ELCC 2015
Hemithoracic lung-sparing volumetric modulated arc therapy (VMAT) for malignant mesothelioma

RESULTS - CONTOURING PHASE:
- MRI identified additional tumour sites in 15/16 patients compared to either CT or PET/CT
- PET/CT identified additional tumour sites in 12/16 patients
- Differences in mean volumes mild and not significant (range: 5-6%)

No significant volume increase + potentially lower risk of geographical miss = MRI-based volumes were selected for the planning phase

156PD: Angela Botticella ELCC 2015
Hemithoracic lung-sparing volumetric modulated arc therapy (VMAT) for malignant mesothelioma

RESULTS - PLANNING PHASE:

• For 10/12 patients, a 50 Gy VMAT plan was possible
• Max achievable dose:
  o 54 Gy → 7 patients
  o 58 Gy → 4 patients
  o 62 Gy → 1 patient
• Correlation at multivariate analysis between the ratio contralateral/ipsilateral lung volume and PTV/total lung volume (p=0.05)

MRI-based target definition in lung-sparing VMAT for pleural mesothelioma may improve the accuracy of GTV delineation

A higher ratio of contralateral/ipsilateral lung volume and lower ratio of PTV/total lung volume less likely to achieve therapeutic doses

156PD: Angela Botticella ELCC 2015
Hemithoracic lung-sparing volumetric modulated arc therapy (VMAT) for malignant mesothelioma

• First report showing that MRI-based target definition may improve the accuracy of GTV delineation and thus reduce the probability of geographical misses.