Challenges in Target delineation of Lung cancer

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Evolution of treatment of stage III NSCLC

• Only RT (1970-80)
• Sequential CT / RT (1990s)
• Concurrent CTRT (2000s)
• Consolidation Immunotherapy (current era)
Challenge with tumour motion
Challenges in Lung cancer

- Organ motion
- Tissue heterogeneity and dose calculation uncertainty
- Inter-fraction and intra-fraction changes
- Microscopic disease
## Motion Management Strategies

<table>
<thead>
<tr>
<th>Method</th>
<th>Technique</th>
</tr>
</thead>
<tbody>
<tr>
<td>Incorporate all movements</td>
<td>4DCT or Slow CT</td>
</tr>
<tr>
<td>Freeze movement</td>
<td>Breath hold</td>
</tr>
<tr>
<td>Intercept movement</td>
<td>Gated Radiotherapy</td>
</tr>
<tr>
<td>Track or Chase the tumor</td>
<td>Implanted markers and specialized treatment delivery</td>
</tr>
</tbody>
</table>
Immobilization

• Accurately re-position patient
• Reduce/Minimize patient voluntary and involuntary motion
• Reduce/Minimize organ/target motion
  • Abdominal compression
• Comfortable for long treatment
• Compatible with IGRT
• Not interfere with treatment beam

Body Pro-Lok TM frame
Body Fix
Abdominal Compression
Thermoplastic Long mask
Immobilization/Simulation

• Careful positioning in the immobilization device, supporting the hands and shoulders
  • premedication with analgesia (e.g., to prevent shoulder pain)
  • anxiolytic may be needed

• Scanning in TX Position
  • CT, MR, PET-CT

• CT scan with ≤ 3 mm slice thickness
• Contrast
CT Simulation

- Suppressed respiratory motion techniques
  - Compression Paddle, Pressure Belt
- Free Breathing (FB) & Slow CT-Scanners
- Free Breathing & Fast CT-Scanners
- Breath-Hold (BH) CT-Scans
- Respiratory Correlated CT (4D-CT)
Using 4DCT data to draw ITV
Conventional (3D) CT image

4DCT reconstruction showing all possible tumour positions
4DCT
Conventional (3D) CT image

4DCT reconstruction showing all possible tumour positions
Using 4DCT data to draw ITV

• ITV is an conservative estimate of the space that needs to be irradiated.

• Positive
  • Can provide quantitative extent of tumour motion
  • ITV structure accurately reflects tumour envelope that beams can encompass

• Negative
  • Requires multiple phase images and contouring of each phase
Using 4DCT data to draw ITV

• Contouring GTVs on all binned phase data sets (usually 10) and fuse.
• Contour on MIP image set.
• Contour GTV on select phases (end-inhale and end-exhale)
• MIP / AIP / Min IP / CIP generation
Using 4DCT data to draw ITV

- GTVs are contoured in each of the 10 phase bins of the 4DCT.
- ITV is defined as the volume encompassing all GTVs.
- Simpler approach - import only the two extreme phases of 4DCT:
  - the end-expiration and end-inspiration bins, generate an encompassing ITV
  - Hysteresis
4DCT

- Each voxel has a certain intensity (Hounsfield Unit)
- Intensity voxels in lung vary over respiratory cycle (10 bins)
- Reconstruction can be made from the 10 bins
  - Ave-IP calculates average intensity
  - Max-IP or MIP calculates maximum intensity
Maximal Intensity Projection (MIP)

• Automatically generated from the entire 4D-CT
• MIP scans reflect the highest data value encountered along the viewing ray for each pixel of volumetric data
  • full intensity display of the brightest object along each ray on the projection image.
• Lung tumor - high-density tumor voxels compared with lower density lung tissue voxels.
Maximal Intensity Projection (MIP)

5 different phases

MIP = [diagram]
ITV generation with MIP
## Quick comparison

<table>
<thead>
<tr>
<th>MOTION ENCOMPASSING TECHNIQUE</th>
<th>EASE OF DELINEATION</th>
<th>ADDITIONAL WORKLOAD</th>
<th>RELIABLE DOSE CALCULATION</th>
<th>ADDITIONAL COST</th>
</tr>
</thead>
<tbody>
<tr>
<td>Slow CT scan</td>
<td>-</td>
<td>-</td>
<td>+/-</td>
<td>-</td>
</tr>
<tr>
<td>Exhale-Inhale scan</td>
<td>+/-</td>
<td>+</td>
<td>+</td>
<td>-</td>
</tr>
<tr>
<td>ITV - MIP / AIP / CIP</td>
<td>+</td>
<td>++</td>
<td>-</td>
<td>++</td>
</tr>
<tr>
<td>Mid-ventilation CT</td>
<td>+</td>
<td>++</td>
<td>++</td>
<td>++</td>
</tr>
<tr>
<td>Mid-position CT</td>
<td>+</td>
<td>+++</td>
<td>++</td>
<td>+++</td>
</tr>
</tbody>
</table>
Using 4DCT data to draw ITV

- Contouring GTVs on all binned phase data sets (usually 10) and fuse.
- Contour on MIP image set.
- Contour GTV on select phases (end-inhale and end-exhale)
- MIP / AIP / Min IP / CIP generation
PET CT

• Advantages
  • Impact on staging
  • Nodal disease evaluation
  • Inter-observer variation

• Challenges
  • Limited spatial resolution
  • Acquisition position – challenges for registration
  • Time delay
  • Planning PETCT
PET CT

• Tumor is contiguous with a structure that has a similar density and boundary can be distinguished on CT – FDG avidity helps
PET CT

Area of atelectasis

Suggested PET based contour
PET CT
PET CT

• In areas with physiological uptake of FDG, GTV to be defined by CT images
PET based contouring

• No validated quantitative approaches for PET based ideal tumor delineation.

• SUV-based “magic line” where viable tumour burden ceases to exist and normal tissue begins - may be impossible
  • Visual inspection
  • SUV cut-off
  • SUV threshold
PET based contouring

- Use a simple linear grayscale (e.g., black to white) for reviewing the PET images alone.
- Use a linear scale to one or at most two colors (e.g., black to red to yellow).
  - Avoid polychromatic scales to avoid misleading color scaling contours.
PET based contouring

• SUV cut-off
  • 2.5

• SUV threshold
  • arbitrary value relative to the maximum intensity within the FDG-avid area,
    • e.g. 40%, 42%, or 50% of SUVmax.
Contouring GTV - Window effect

For Parenchymal disease: W=1600 L=-600
For Mediastinal disease: W=400 L=20

These correlate best with pathological tumor sizes
CTV / PTV

- iGTV
- CTV
  - 6-8mm from GTV
- CTV to PTV margin recipe
# PTV margins

<table>
<thead>
<tr>
<th>Motion management</th>
<th>Internal margin (cm)</th>
<th>Setup margin (cm, uniform)</th>
<th>Total PTV margin (cm)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Sup-Inf</td>
<td>Axial</td>
<td>Sup-inf</td>
</tr>
<tr>
<td>Free breathing</td>
<td>1</td>
<td>0.5</td>
<td>0.5</td>
</tr>
<tr>
<td>Breath hold or gating</td>
<td>0.5</td>
<td>0.3</td>
<td>0.5</td>
</tr>
<tr>
<td>Abdominal compression</td>
<td>0.8</td>
<td>0.5</td>
<td>0.5</td>
</tr>
<tr>
<td>4D CT</td>
<td>Union of CTVs</td>
<td>Union of CTVs</td>
<td>0.5</td>
</tr>
</tbody>
</table>

RTOG 1306
Inter-fraction changes

• Anatomical changes had larger impact on the target dose distribution than internal target motion.

<table>
<thead>
<tr>
<th></th>
<th>Mean (%)</th>
<th>Range (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anatomy (CT1, CT2)</td>
<td>1.28</td>
<td>0.1–4.0</td>
</tr>
<tr>
<td>Respiratory motion (CT1)</td>
<td>0.05</td>
<td>0–0.2</td>
</tr>
<tr>
<td>Interfraction baseline shifts (CT1)</td>
<td>0.20</td>
<td>0–0.8</td>
</tr>
<tr>
<td>Respiratory motion (CT2)</td>
<td>0.46</td>
<td>0.1–1.9</td>
</tr>
<tr>
<td>Interfraction baseline shifts (CT2)</td>
<td>0.65</td>
<td>0–2.1</td>
</tr>
</tbody>
</table>

CT1, planning 4DCT scan; CT2, mid-course 4DCT scan.
Process of ART

- Set criteria
- Monitor changes
- Adapt plan
Adaptive Radiotherapy

- Plan adaptation can be simple
  - acquire a new CT scan of the patient mid-way through treatment after a dramatic change is observed and
  - optimizing the treatment plan to accommodate the new anatomy.
- More complex adaptation strategies have also been investigated with varying re-planning frequencies.
Volume changes

• Positional shift
  • Resolution of atelectasis – re-aeration
  • Progression
    • Pleural effusion
    • New consolidation

• Tumour volume changes
  • Tumour progression
  • Tumour regression
  • Infiltrative change

INCREASE IN TARGET VOLUME

DECREASE IN TARGET VOLUME
Atelectasis

• Common with centrally located tumours.
• Central airways can become constricted or obstructed, inducing a collapse of the portion of the lung.
• Can range from complete collapse, affecting an entire lung, to partial collapse, affecting only a portion of a lobe.
• In CT images, appears as a smaller region of uniform, high intensity.
• Delineation difficulties – if located close to the collapsed lung
  • positron emission tomography (PET)
Atelectasis
Atelectasis
Pleural effusion
Tumour volume regression

- Tumour regression appears as a gradual, continuous change in tumour volume
  - ranging from 0.6% to 2.4% shrinkage per day
- Reported average tumour volume reductions
  - 24.7% halfway through treatment and
  - 44.3% by the end of treatment.
Tumour volume regression
Re-planning frequency

ART yields clinically relevant reductions in normal tissue doses for frequencies ranging from a single replan up to daily replanning.

Increased frequencies of adaptation result in additional benefit while magnitude of benefit decreases.

Fig. 3. Percent of potential benefit (i.e., allowable dose to target) as a function of replanning frequency. On average, 65% of benefit was achieved with a single midtreatment adaptation, and 85% was realized after weekly adaptation.
Shrinking volumes

• Extent of microscopic disease beyond gross tumour.
  • Does it change post NACT?

• Does areas of suspected microscopic disease become under-dosed?

• Unclear
Shrinking CTV

• Reviewing images important
• Microscopic disease shrinkage may not always be synchronous
• Watch for pattern
  • Expansive growth pattern of the GTV
  • Infiltrative growth pattern of the GTV
Nodal disease

- Enlarged Lymph nodes
  - PET+ 78%
  - PET- 13%
- Normal sized Lymph nodes
  - PET+ 70%
  - PET- 6%

Expected prevalence of cancer in the PET-group:
- 78%
- 13%
- 70%
- 6%

Expected prevalence of cancer in the EBUS-TBNA group:
- EBUS+ 100%
- EBUS- 16%
- EBUS+ 100%
- EBUS- 3%
- EBUS+ 100%
- EBUS- 14%
- EBUS+ 100%
- EBUS- 1%

Include lymph node in GTV:
- yes
- yes*
- yes
- no
- yes
- yes*
- yes
- no
Nodal disease

- GTVn should include all involved lymph nodes or lymph node stations based on pre-chemotherapy clinical, pathological and imaging information
  - even if a node has completely disappeared in imaging.

Nestle, RO, 2018
Nodal disease

2a: CTV including the affected lymph node station

2b: CTV including the nodal GTV plus 5-8 mm margin
Sequential vs concurrent

Auperin J Clin Oncol. 2010
Standard of care, but for who?

- Concurrent CTRT

- 60% patients were considered ineligible for CTRT.

- 80% patients did not receive standard treatment.
  - 35% discontinuation rate with CTRT

Figure 3. Percentage patients eligible for concurrent therapy.

De Ruysscher, Annals of Oncology, 2008
Van Der Meer, Anticancer res, 2016
NACT – for who?

- Advanced age
- PS>1
- Large volume
  - Dosimetric challenge
  - Poor pulmonary function
  - Consolidation

- Oligo-metastatic NSCLC
  - Consolidation RT after systemic therapy
How to contour post NACT?

• Patterns of failure studies
  • Failure at sites of gross disease
  • Lack of benefit from elective volume irradiation

• SCLC

• No Guidelines
Local Control and Toxicity of Adaptive Radiotherapy using Weekly CT Imaging: Results from the LARTIA Trial in Stage III NSCLC

- Local failures were in-field, marginal and out-of-field in 20%, 6% and 4% of cases, respectively.

Ramella, JTO 2017
Lessons from SCLC

Final Report of a Prospective Randomized Study on Thoracic Radiotherapy Target Volume for Limited-Stage Small Cell Lung Cancer With Radiation Dosimetric Analyses

TABLE 2. Patterns of First Treatment Failurea

<table>
<thead>
<tr>
<th>Failure Pattern</th>
<th>No. of Patients (%)</th>
<th>Study Arm</th>
<th>Control Arm</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Local/regional failure</td>
<td></td>
<td></td>
<td></td>
<td>.41</td>
</tr>
<tr>
<td>Isolated in-field</td>
<td>27 (7.8)</td>
<td>22 (14.9)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Isolated out-field</td>
<td>4 (2.6)</td>
<td>6 (4.1)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>In-field and out-field</td>
<td>2 (1.3)</td>
<td>1 (0.7)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Isolated marginal</td>
<td>1 (0.7)</td>
<td>1 (0.7)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Out-field and marginal</td>
<td>0 (0.0)</td>
<td>1 (0.7)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mixed failure</td>
<td></td>
<td></td>
<td></td>
<td>.79</td>
</tr>
<tr>
<td>In-field and distant</td>
<td>14 (9.2)</td>
<td>10 (6.8)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Out-field and distant</td>
<td>3 (1.9)</td>
<td>5 (3.4)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>In-field, out-field, and distant</td>
<td>1 (0.7)</td>
<td>1 (0.7)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Isolated distant</td>
<td>57 (35.8)</td>
<td>49 (32.7)</td>
<td></td>
<td>.50</td>
</tr>
</tbody>
</table>

No. of Patients (%)

<table>
<thead>
<tr>
<th>Toxic Effect/Grade</th>
<th>Study Arm</th>
<th>Control Arm</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acute toxic hematologic toxicity</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>grade ≥3a</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Leukopenia</td>
<td>69 (37.1)</td>
<td>56 (36.7)</td>
<td>.35</td>
</tr>
<tr>
<td>Grade 3</td>
<td>13 (8.2)</td>
<td>10 (6.7)</td>
<td></td>
</tr>
<tr>
<td>Grade 4</td>
<td>59 (37.1)</td>
<td>56 (37.3)</td>
<td></td>
</tr>
<tr>
<td>Neutropenia</td>
<td>41 (25.8)</td>
<td>34 (22.7)</td>
<td></td>
</tr>
<tr>
<td>Grade 3</td>
<td>32 (20.1)</td>
<td>19 (12.7)</td>
<td></td>
</tr>
<tr>
<td>Grade 4</td>
<td>16 (10.1)</td>
<td>12 (8.0)</td>
<td></td>
</tr>
<tr>
<td>Grade 5</td>
<td>1 (0.6)</td>
<td>0 (0.0)</td>
<td></td>
</tr>
<tr>
<td>Anemia</td>
<td>34 (21.4)</td>
<td>29 (19.3)</td>
<td>.59</td>
</tr>
<tr>
<td>Grade 3</td>
<td>15 (9.4)</td>
<td>8 (5.3)</td>
<td></td>
</tr>
<tr>
<td>Radiation-related toxicities b</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pneumonitis</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Grade 1-2</td>
<td>60 (39.4)</td>
<td>65 (43.9)</td>
<td>.40</td>
</tr>
<tr>
<td>Grade 3</td>
<td>2 (1.3)</td>
<td>1 (0.7)</td>
<td></td>
</tr>
<tr>
<td>Grade 4</td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
<td></td>
</tr>
<tr>
<td>Grade 5</td>
<td>2 (1.3)</td>
<td>0 (0.0)</td>
<td></td>
</tr>
<tr>
<td>Esophagitis</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Grade 1</td>
<td>87 (57.2)</td>
<td>63 (42.6)</td>
<td>.01</td>
</tr>
<tr>
<td>Grade 2</td>
<td>41 (27.0)</td>
<td>41 (27.7)</td>
<td></td>
</tr>
<tr>
<td>Grade 3</td>
<td>9 (5.9)</td>
<td>23 (15.5)</td>
<td></td>
</tr>
<tr>
<td>Weight loss</td>
<td></td>
<td></td>
<td>.16</td>
</tr>
<tr>
<td>Grade 1</td>
<td>30 (19.7)</td>
<td>43 (29.1)</td>
<td></td>
</tr>
<tr>
<td>Grade 2</td>
<td>12 (7.9)</td>
<td>9 (6.1)</td>
<td></td>
</tr>
</tbody>
</table>

This image is a page from a document discussing lessons from a study on thoracic radiotherapy in small cell lung cancer. The page includes a table summarizing patterns of first treatment failure and a section on acute toxic hematologic toxicity with specific grades. The study appears to be a randomized trial comparing different treatment arms. The data suggests a focus on the incidence of leukopenia and neutropenia, among other toxic effects, with statistical comparisons provided.
ESTRO ACROP guideline

ESTRO ACROP guidelines for target volume definition in the treatment of locally advanced non-small cell lung cancer

Ursula Nestle\textsuperscript{a,b,x}, Dirk De Ruysscher\textsuperscript{c,d}, Umberto Ricardi\textsuperscript{e}, Xavier Geets\textsuperscript{f}, Jose Belderbos\textsuperscript{g}, Christoph Pöttgen\textsuperscript{h}, Rafal Dziadyszko\textsuperscript{i}, Stephanie Peeters\textsuperscript{c}, Yolande Lievens\textsuperscript{j}, Coen Hurkmans\textsuperscript{k}, Ben Slotman\textsuperscript{l}, Sara Ramella\textsuperscript{m}, Corinne Faivre-Finn\textsuperscript{n}, Fiona McDonald\textsuperscript{o}, Farkhad Manapov\textsuperscript{b}, Paul Martin Putora\textsuperscript{q,r}, Cécile LePéchoux\textsuperscript{s}, Paul Van Houtte\textsuperscript{t}

• No specific recommendations for post NACT

• GTV of the primary tumour post induction chemotherapy should be based on current CT imaging
  • Pre-chemotherapy imaging (including PET-CT) should be considered
Summary - Practical considerations

• CTRT - standard

• Sequential treatment can be considered in patients unfit for CTRT.
  • Large volume
  • Poor PFT
  • Dosimetric challenge

• Post NACT
  • GTV – as visible on post NACT imaging
  • CTV – review pre NACT images, note pattern of spread