NSCLC: new developments in radiotherapy and combined modality therapies

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Medical University of Gdańsk, Poland

SAMO, Lucerne, February 1-2, 2013
Technical developments
Technical developments

- PET for staging and treatment (tx) planing
- 4DCT for image acquisition
- Image guided tx delivery
- Volumetric arc therapies

Higher precision:
- better outcomes
- less toxicity
4DCT: Respiration correlated imaging

- Chest belt + pressure sensor
- Infrared reflective markers + infrared camera
- Others: spirometer, thermistor

Slide courtesy: Prof. Dirk de Ruysscher
4DCT: Respiration correlated imaging

End-inspiration

Full respiratory cycle

4 sec

End-expiration

CT Image Sorting Program

Mid-exhale  "End-exhale"  "Mid-inhale"  End-inhale

PET: Interobserver variation in delineation

PET-CT: reduction in interobserver variation

Steenbakkers et al., IJROBP 2006

Slide courtesy: Prof. Dirk de Ruysscher
Size of FDG-based GTV is influenced by the contouring method

25 primary NSCLC, FDG based GTVs

Contouring methods:
- visually (GTV$_{vis}$)
- threshold = SUV 2.5 (GTV$_{2.5}$)
- 40% of maximum accumulation in lesion (GTV$_{40}$)
- contrast dependent algorithm (GTV$_{bg}$)

Significant differences correlating with
- SUV$_{max}$
- size of lesion
- inhomogeneity of accumulation

Stereotactic body radiotherapy (SBRT)
Stereotactic body radiation therapy

- Use of few large fractions with high precision to deliver biologically effective doses >100Gy to the target volume
- Adequate staging (PET, EBUS, EUS)
- Accounting for respiratory motion during tx planning
- Advanced (type B) dose calculation models
- Image guidance before treatment delivery
- Tracking of patient position during tx
SBRT for stage I NSCLC (N=676): Patterns of relapse

Senti et al., Lancet Oncol 2010
SBRT for stage I NSCLC (N=676):
Survival

Senti et al., Lancet Oncol 2010
SBRT for stage I NSCLC: Outcomes

N=257

Local Control Rate

Overall Survival

Onishi et al., J Thorac Oncol 2007
SBRT for stage I NSCLC: Outcomes
Population-based registry in Northern Holland

Patients age ≥ 75 years from North Holland diagnosed with stage I NSCLC between 1999 and 2007 with no prior history of lung cancer (N = 875)

Period A: 1999-2001
- Surgery (n = 99)
- Radiotherapy (n = 71)
- Neither (n = 104)
- Dead (n = 254)
- Alive (n = 20)

Period B: 2002-2004
- Surgery (n = 90)
- Radiotherapy (n = 82)
- Neither (n = 82)
- Dead (n = 219)
- Alive (n = 35)

Period C: 2005-2007
- Surgery (n = 110)
- Radiotherapy (n = 146)
- Neither (n = 91)
- Dead (n = 196)
- Alive (n = 151)

Palma et al., JCO 2010
SBRT for stage I NSCLC: Outcomes
Population-based registry in Northern Holland

Palma et al., JCO 2010
SBRT for stage I NSCLC: Outcomes
Population-based registry in Northern Holland

PATIENTS RECEIVING RADIOTHERAPY

Overall Survival (probability)


Palma et al., JCO 2010
SBRT for stage I NSCLC: Current challenges

- Centrally located tumors
- Large stage I-II tumors
- Use in selected operable stage I NSCLC
- Imaging follow-up for local relapse
- Use of systemic therapy to improve outcomes
SBRT for stage I NSCLC: Central location

- RTOG 0813: Dose escalation trial to establish safety of SBRT for centrally located tumors; starting dose 5 x 10Gy
- Amsterdam Free University experience: 8 x 7.5Gy
- EORTC multi-institutional phase II trial planned (PI: Dr. Ursula Nestle)

Lagerwaard et al., IJROBP 2008
SBRT for stage I NSCLC: Large tumors

- Limited experience
- Preliminary data on 18 patients with tumors >80cc show SBRT to be feasible, with relatively high risk of radiation pneumonitis best predicted by contralateral V_{5Gy}, and high mortality rate due to comorbidities

Ong et al., R&O 2010
SBRT for stage I NSCLC: Large tumors
Our largest in Gdansk: PTV=245cc
No evidence of progression > 2.5 years

Slide courtesy of Dr. K. Konopa
SBRT for stage I NSCLC: Operable disease

- Retrospective comparison of SBRT and wedge resections favors SBRT
- The Netherlands: ROSEL trial
  - randomized study with QoL end-point, failed due to poor recruitment
- United States: phase II RTOG 0618

Grills IS et al., JCO 2010
SBRT for stage I NSCLC: Imaging follow-up

- Local control is difficult to assess by conventional CT due to post-RT fibrotic changes that can mimic local relapse
- Role of PET-CT for assessing local relapse is under investigation
- Regional relapse is expected in ~10% - 15% of patients and distant relapse in ~20%
Definitive Chemoradiation
Stage III NSCLC
Chemoradiation in stage III NSCLC
RT alone vs. Sequential vs. Concurrent: Magnitude of Survival Benefit

Concurrent vs. Sequential Chemoradiation: Metaanalysis of Survival

<table>
<thead>
<tr>
<th>Trial</th>
<th>No. Deaths / No. Entered</th>
<th>O-E</th>
<th>Variance</th>
<th>Hazard Ratio</th>
<th>HR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CALGB 8831</td>
<td>45/46</td>
<td>39/45</td>
<td>2.4</td>
<td>20.9</td>
<td>1.12 (0.73 to 1.72)</td>
</tr>
<tr>
<td>WJLCG</td>
<td>131/156</td>
<td>142/158</td>
<td>-16.8</td>
<td>67.3</td>
<td>0.78 (0.61 to 0.99)</td>
</tr>
<tr>
<td>RTOG 9410</td>
<td>180/204</td>
<td>189/203</td>
<td>-20.5</td>
<td>91.1</td>
<td>0.80 (0.65 to 0.98)</td>
</tr>
<tr>
<td>GMMA Ankara 95</td>
<td>15/15</td>
<td>15/15</td>
<td>-1.0</td>
<td>7.0</td>
<td>0.87 (0.41 to 1.82)</td>
</tr>
<tr>
<td>GLOT-GFPC NPC</td>
<td>87/102</td>
<td>96/103</td>
<td>-9.9</td>
<td>45.0</td>
<td>0.80 (0.60 to 1.07)</td>
</tr>
<tr>
<td>EORTC 08972</td>
<td>63/80</td>
<td>66/78</td>
<td>-0.5</td>
<td>31.9</td>
<td>0.98 (0.69 to 1.39)</td>
</tr>
<tr>
<td>Total</td>
<td>521/603</td>
<td>547/602</td>
<td>-46.4</td>
<td>263.1</td>
<td>0.84 (0.74 to 0.95)</td>
</tr>
</tbody>
</table>

Test for heterogeneity: $\chi^2_g = 3.24, P = .66, I^2 = 0\%$

RT + Conc CT Better | RT + Seq CT Better

RT + conc CT effect: Log-rank test = 8.19, P = .004

Chemoradiation in stage III NSCLC
RT alone vs. Sequential vs. Concurrent: Toxicity

Acute ≥G3 Esophagitis:
- RT alone: 4%
- Sequential: 18%
- Concurrent: RR=4.9 (3.1-7.8)

≥G2 Pneumonitis:
- RT alone
- Sequential
- Concurrent: RR=0.69 (0.42-1.12)

Chemo-radiotherapy for stage III NSCLC: Optimal radiation dose and volume?
Chemo-radiotherapy for stage III NSCLC: Optimal radiation dose?

RTOG 0617 / U.S. Intergroup Trial

Chemo-radiotherapy for stage III NSCLC: Optimal radiation dose?

![Overall Survival Graph]

Overall Survival

- **60 Gy**: 58/213, **74 Gy**: 70/204

- **HR**: 0.45 (1.02, 2.05), **p** = 0.02

- **Patients at Risk**
  - 60 Gy: 213
  - 74 Gy: 204

- **Months since Randomization**
  - 0, 3, 6, 9, 12

- **One-sided p-value, left tail**

Bradley J. ASTRO 2011
Chemoradiation in stage III NSCLC: Unresolved issues

- Optimal drugs and schedules
- Use of consolidation therapy
- Combination with accelerated hyperfractionation
- Combination with accelerated hypofractionation
Chemoradiation in stage III NSCLC: Drugs and schedules

- Cisplatin - etoposide
- Cisplatin - vinorelbine
- Cisplatin - pemetrexed
- Carboplatin - paclitaxel (common in the US)
- Cisplatin daily (NKI)
Chemoradiation in stage III NSCLC: Pemetrexed phase II trials

<table>
<thead>
<tr>
<th>Reference</th>
<th>Chemotherapy</th>
<th>N</th>
<th>Median OS (months)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Govindan 2011</td>
<td>Carbo-PEM x 4 – PEM x 4 Carbo-PEM-Cetuximab x 4 PEM x 4</td>
<td>48 53</td>
<td>21.2 25.2</td>
</tr>
<tr>
<td>Gadgeel 2011</td>
<td>CIS-PEM x 3 – Docetaxel x 3</td>
<td>28</td>
<td>34</td>
</tr>
<tr>
<td>Xu 2011</td>
<td>Carbo-PEM x 5</td>
<td>21</td>
<td>NA</td>
</tr>
<tr>
<td>Brade 2010</td>
<td>CIS-PEM x 4</td>
<td>39</td>
<td>19.7</td>
</tr>
<tr>
<td>Choy 2010 (prelim)</td>
<td>Carbo-PEM x 3 – PEM x 3 CIS-PEM x 3 – PEM x 3</td>
<td>34 38</td>
<td>NA NA</td>
</tr>
</tbody>
</table>

Stinchcombe T, Bogart J. Oncologist 2012
Pemetrexed phase III trial – PROCLAIM
non-squamous histologies

Vokes E et al., Clin Lung Cancer 2009
Consolidation after chemoradiation
Phase III Hoosier Oncology Group Trial

Chemoradiation
Cisplatin 50 mg/m² d 1,8,29,36
Etoposide 50 mg/m² IV d 1-5 & 29-33
Concurrent RT 59.4 Gy (1.8 Gy/fr)

CR, PR, or SD; ECOG PS 0-2

R

Docetaxel 75 mg/m² q 3 wk × 3
Observation
Consolidation after chemoradiation
Phase III Hoosier Oncology Group Trial
2011 survival update

Median OS Observation = 26.1 months
95% CI (18.6 - 32.0)

Median OS for Docetaxel = 24.2 months
95% CI (18.6 - 34.8)

Log-rank p=0.7499

Jalal SI et al., Ann Oncol 2011
Induction chemotherapy followed by accelerated hyperfractionation:
ECOG HART Trial (N=112)

Survival Probability

Stratified Log Rank Test p=0.20

Daily RT HART

<table>
<thead>
<tr>
<th>Treatment Arm</th>
<th>TOTAL</th>
<th>DEAD</th>
<th>ALIVE</th>
<th>MEDIAN</th>
</tr>
</thead>
<tbody>
<tr>
<td>Arm 1</td>
<td>56</td>
<td>45</td>
<td>11</td>
<td>13.7m</td>
</tr>
<tr>
<td>Arm 2</td>
<td>56</td>
<td>40</td>
<td>16</td>
<td>20.3m</td>
</tr>
</tbody>
</table>

Belani C et al., JCO 2005
Induction chemotherapy followed by accelerated hyperfractionation: CHARTWEL experience

Baumann M et al., Radiother Oncol 2011

Phase III randomised trial
Final results of the randomized phase III CHARTWEL-trial (ARO 97-1) comparing hyperfractionated-accelerated versus conventionally fractionated radiotherapy in non-small cell lung cancer (NSCLC)

<table>
<thead>
<tr>
<th>Ctx</th>
<th>CF</th>
<th>CHARTWEL</th>
<th>HR</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>No</td>
<td>103/150</td>
<td>96/150</td>
<td>0.97</td>
<td>0.86</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>(0.69; 1.37)</td>
<td></td>
</tr>
<tr>
<td>yes</td>
<td>38/53</td>
<td>36/53</td>
<td>0.48</td>
<td>0.019</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>(0.26; 0.89)</td>
<td></td>
</tr>
</tbody>
</table>
## Chemotherapy and accelerated hypofractionation: SOCCAR (Stage III, N=130)

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Median OS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Definitive RT 55Gy/20fx concurrent with cisplatin – vinorelbine x 4</td>
<td>27.4 months</td>
</tr>
<tr>
<td>Definitive RT 55Gy/20fx sequential with cisplatin – vinorelbine x 4</td>
<td>18.6 months</td>
</tr>
</tbody>
</table>

Maguire JLM et al., J Clin Oncol 2011; 29: abstr. 7039 (PASCO)
Chemotherapy and accelerated hypofractionation: PET Boost trial (ongoing)

Concurrent chemo-radiotherapy

- T2-4N0-3M0
- Primary tumor diameter 4 cm or more
- MaxSUV>5
- Eligible for radical treatment

66Gy/24 fx + CISPLATIN DAILY

Dose calculation

- Dose escalation not possible
- Chemo-radiotherapy to tolerance
- Dose escalation possible

RANDOMIZE

- Homogeneous boost
- Inhomogeneous boost

Pis: De Ruysscher D, Belderbos J
Radiotherapy and targeted therapies
# Five reasons to combine drugs and RT

<table>
<thead>
<tr>
<th>Interaction mechanism</th>
<th>Basic idea</th>
<th>Primary endpoint</th>
<th>Example</th>
</tr>
</thead>
<tbody>
<tr>
<td>Spacial cooperation</td>
<td>RT → LR disease SYS → Distant mets</td>
<td>LRC &amp; distant progression, PFS</td>
<td>Adjuvant CT + RT for breast cancer</td>
</tr>
<tr>
<td>Cytotoxic enhancement</td>
<td>Enhancing radiation cell killing</td>
<td>LRC</td>
<td>Cisplatin + RT in NSCLC or cervical cancer</td>
</tr>
<tr>
<td>Biological cooperation</td>
<td>Different biological targets</td>
<td>LRC</td>
<td>Tirapazamine + RT</td>
</tr>
<tr>
<td>Temporal modulation</td>
<td>Modulating the 4Rs</td>
<td>LRC</td>
<td>Cetuximab + RT</td>
</tr>
<tr>
<td>Normal tissue protection</td>
<td>Reduce toxicity</td>
<td>Toxicity</td>
<td>KGF, amifostine</td>
</tr>
</tbody>
</table>

Temporal modulation

cetuximab in H&N cancer

Bonner JA et al., NEJM 2006
Radiotherapy and EGFR inhibitors: Rationale

Eicheler et al., Radiother Oncol 2005; Baumann M et al., Radiother Oncol 2007
Radio(chemo)therapy combined with EGFR inhibitors:

Lessons from lung cancer RT trials
### Definitive (Chemo)radiation + cetuximab: phase II data in lung cancer

<table>
<thead>
<tr>
<th>Reference</th>
<th>Chemotherapy</th>
<th>N</th>
<th>Median OS months (toxicity)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Jensen 2011 NEAR study</td>
<td>None (pts unfit for chemo)</td>
<td>30</td>
<td>19.5 (36.7% G3 tox)</td>
</tr>
<tr>
<td>Jatoi 2010</td>
<td>None (pts &gt;65 y.o. or PS=2)</td>
<td>57</td>
<td>15.1 (54% G3 tox)</td>
</tr>
<tr>
<td>Blumenschein 2011 RTOG 0324</td>
<td>Carbo-Paclitaxel weekly + cetuximab weekly – Carbo-Paclitaxel q 3weeks x 2 + weekly cetuximab x 6</td>
<td>87</td>
<td>22.7 (44% G3, 5% G5)</td>
</tr>
<tr>
<td>Govindan 2011 CALGB 30407</td>
<td>Carbo-PEM x 4 – PEM x 4 Carbo-PEM-Cetuximab x 4 - PEM x 4</td>
<td>48</td>
<td>21.2 (42% G3 tox)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>53</td>
<td>25.2 (38% G3 tox)</td>
</tr>
<tr>
<td>Beldebos/van den Heuvel RADITUX ESTRO/ASCO2012</td>
<td>DDP daily DDP daily + Cetuximab x 6</td>
<td>Total = 102</td>
<td>1-yr OS 72% (45% G3 tox) 1-yr OS 76% (69% G3 tox)</td>
</tr>
</tbody>
</table>
Raditux Phase II NKI Trial

XRT 66Gy/24fr. IMRT + CDDP 6mg/m² daily

Belderbos J/van den Heuvel M., ESTRO2012/ASCO 2012
## RADITUX: Acute Toxicity Grade ≥ 3 (CTCAE v 3.0)

<table>
<thead>
<tr>
<th>Non-hematological</th>
<th>CCRT(%)</th>
<th>CCRT+Cet(%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acne like rash</td>
<td>-</td>
<td>8</td>
</tr>
<tr>
<td>Anorexia</td>
<td>6</td>
<td>22</td>
</tr>
<tr>
<td>Dysphagia</td>
<td>14</td>
<td>22</td>
</tr>
<tr>
<td>Fatigue</td>
<td>16</td>
<td>18</td>
</tr>
<tr>
<td>Nausea</td>
<td>6</td>
<td>4</td>
</tr>
<tr>
<td>Vomiting</td>
<td>-</td>
<td>2</td>
</tr>
<tr>
<td>Pain</td>
<td>2</td>
<td>10</td>
</tr>
<tr>
<td>Cough</td>
<td>-</td>
<td>2</td>
</tr>
<tr>
<td>Pneumonia</td>
<td>-</td>
<td>10</td>
</tr>
<tr>
<td>Anemia</td>
<td>-</td>
<td>2</td>
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<tr>
<td>Hematological</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Leukopenia</td>
<td>10</td>
<td>8</td>
</tr>
<tr>
<td>Neutropenia</td>
<td>6</td>
<td>8</td>
</tr>
</tbody>
</table>

45% 69% (p=0.03)

Data presented at ESTRO 2012 Conference by Dr. J. Belderbos
Chemoradiation + cetuximab:
Phase III RTOG 0617/ U.S. Intergroup Trial
2 x 2 factorial design

RT 60Gy + Carboplatin/paclitaxel
RT 74Gy + Carboplatin/paclitaxel
RT 60Gy + Carboplatin/paclitaxel + Cetuximab
RT =74Gy + Carboplatin/paclitaxel + Cetuximab

Consolidation (2 cycles)

Possible clinically relevant interactions of EGFR inhibitors and radiochemotherapy

- Reduced DNA repair capacity in malignant cells
- Reduced DNA repair capacity in normal cells (increased toxicity)?
- G1 arrest in malignant cells – antagonism with chemotherapy?
SWOG 0023: Gefitinib maintenance after chemoradiation and docetaxel

Definitive RCT

Consolidation

Maintenance

CDDP/VP-16 XRT → Docetaxel → PLACEBO

CDDP/VP-16 XRT → Docetaxel → GEFITINIB

Kelly K et al. J Clin Oncol. 2008;26:2450-2456
SWOG 0023: OS with gefitinib maintenance after chemoradiation and docetaxel
Lung cancer radio(chemo)therapy and targeted therapies: Unresolved issues

- With modern radiotherapy, local control is getting better but systemic control remains the main issue. This argument favors sequential and not concomitant therapy.
- Effectiveness of chemotherapy + radiotherapy + targeted drug is difficult to predict in preclinical models and early phase trials.
- With recent failures in the field, there is much less interest from the industry in combined modality studies.
So how radiation oncologist can work with new targets in the genomic era?
1. Better understand radiation sensitivity *in vitro* and *in vivo* in subsets of patients with driving events

*EGFR* mutant cells are more sensitive to RT

Locoregional control for *EGFR* mut vs wt stage III NSCLC; retrospective

Das AK et al., Cancer Res 2007, Mak et al., Oncologist 2011
RADIOSCAPE: Virtual bank of stage III NSCLC tumor samples from patients treated with definitive radio(chemo)therapy with annotated clinical data

D. De Ruysscher, C. Faivre-Finn, C. Le Pechoux, R. Dziadziuszko, S. Peters and R. Stahel, on behalf of ETOP collaborators
2. Try to integrate targeted therapies into stage I – III radiotherapy-based protocols with a sequential approach

- RTOG 1210/Alliance 31101: Phase II proposal with sequential TKI followed by definitive chemoradiotherapy in stage III EGFR+ or ALK+ patients
- Trials with (chemo)radiotherapy followed by immunotherapy to exploit host immunization with tumor antigens during radiotherapy
Take-home messages

- Concept of concurrent radio(chemo)therapy and targeted drugs proved to be more difficult than previously thought

- Individualization of treatment according to molecular tumor characteristics in stage III NSCLC needs to be addressed soon!
Thank you for your attention!