New clinical indications for BNCT?  
The point of view  
of the radiation oncologist

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In-hospital neutron source: PHoNeS Photoconverter

- Recently INFN research groups and University of Trieste Physics Dept. Lab. designed and manufactured a special photoconverter to apply to the Linac head to produce thermal/epithermal neutrons.

- Neutrons are generated by Giant Dipole Resonance (g,n) reactions on high Z target from high energy photons produced in Linac’s (18-25 MV) used in radiotherapy department for cancer treatment.
### The PhoNeS Project
**an innovative approach**

<table>
<thead>
<tr>
<th>Neutron source</th>
<th>High Energy Linac + PhoNeS photoconverter</th>
</tr>
</thead>
<tbody>
<tr>
<td>BPA uptake Method</td>
<td>Ex-vivo perfusion of human lung lobe</td>
</tr>
<tr>
<td>Tumours studied</td>
<td>Non small cell lung cancer and malignant pleural mesothelioma</td>
</tr>
<tr>
<td>$^{10}$B concentration</td>
<td>Cr-39 track detectors</td>
</tr>
</tbody>
</table>

**A procedure for BNCT research on biological trials ENTIRELY applied in hospital departments**
Non small cell lung cancer and pleural mesothelioma

New clinical targets for BNCT?
## Multidisciplinary management of NSCLC

<table>
<thead>
<tr>
<th>Stage</th>
<th>%</th>
<th>Terapeutical Strategy</th>
<th>5y-S %</th>
</tr>
</thead>
<tbody>
<tr>
<td>I A</td>
<td></td>
<td>Surgery</td>
<td>55-70</td>
</tr>
<tr>
<td>I B</td>
<td>20-25</td>
<td>Surgery ± Adjuvant Treatment</td>
<td>25-40</td>
</tr>
<tr>
<td>II</td>
<td></td>
<td>Surgery ± Adjuvant Treatment</td>
<td></td>
</tr>
<tr>
<td>III A</td>
<td>30-35</td>
<td>Neoadjuvant Treatment + Surgery ± Adjuvant Treatment</td>
<td>10-25</td>
</tr>
<tr>
<td>III A N2</td>
<td>30-35</td>
<td>Chemotherapy + Radiotherapy</td>
<td>10-20</td>
</tr>
<tr>
<td>III B</td>
<td>50-40</td>
<td>Chemotherapy±Biologics + BSC</td>
<td>1-3</td>
</tr>
<tr>
<td>IV</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
TWO COMPARTMENT MODEL OF COMBINED MODALITY THERAPY FOR LOCALLY ADVANCED NSCLC

Radiotherapy

Local-Regional Disease

Brain Sanctuary

Distant Micrometastases

Chemotherapy

D Gandara, JCO 2003
### POTENTIAL OPTIONS FOR CHEMORADIATION THERAPY IN NSCLC

1. **Sequential Chemoradiation**
2. **Concurrent Chemoradiation**
3. **Induction → Concurrent**
4. **Concurrent → Consolidation**
**UNRESECTABLE RA-NSCLC Concomitant CT/RT Patients' Selection**

- Performance status 0 -1 (2 ?)
- Absence of weight loss > 5–10%
- FEV-1 > 1L
- Small volume
- Absence of pleural and/or pericardial effusion
- Absence of SC LN
- Absence of comorbidity
UNRESECTABLE REGIONAL ADVANCED-NSCLC
New Radiotherapy Role

- 3D-conformal radiotherapy
- Intensity modulated RT (IMRT)

- High doses in tumor region
- Spare normal tissue
DVH - Toxicity

- Pneumonitis

\[ V_{20} = \% \text{ lung volume receiving a dose } > 20 \text{ Gy} \]
**DVH – Toxicity**

**V_{20} \rightarrow PNEUMONITIS \geq GRADE 2**

<table>
<thead>
<tr>
<th>V_{20}</th>
<th>Risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;22%</td>
<td>0</td>
</tr>
<tr>
<td>22-31%</td>
<td>7%</td>
</tr>
<tr>
<td>32-40%</td>
<td>13%</td>
</tr>
<tr>
<td>&gt;40%</td>
<td>36%</td>
</tr>
</tbody>
</table>

*Not modified by CT*

Graham IJROBP 1999
DVH - Toxicity

- Esophagitis

Acute esophagitis rates by volume $\geq 60$ Gy

Bradley, Deasy, Bentzen IJROBP 2004

Modified by CT
CT/RT IN STAGE III NSCLC
Survival Comparison (Choy H, 2007)
### REGIONAL ADVANCED-NSCLC TREATMENT
Current Status of Chemoradiotherapy

<table>
<thead>
<tr>
<th>Regimen</th>
<th>MST mos</th>
<th>1 YS %</th>
<th>2 YS %</th>
<th>TOX TRT G 3-4 %</th>
</tr>
</thead>
<tbody>
<tr>
<td>RT</td>
<td>10</td>
<td>40</td>
<td>15</td>
<td>10</td>
</tr>
<tr>
<td>CT → RT</td>
<td>14</td>
<td>55</td>
<td>30</td>
<td>25</td>
</tr>
<tr>
<td>CT+RT</td>
<td>17</td>
<td>65</td>
<td>35</td>
<td>50</td>
</tr>
<tr>
<td>CT → CT/RT</td>
<td>16</td>
<td>60</td>
<td>40</td>
<td>35</td>
</tr>
<tr>
<td>CT/RT → CT</td>
<td>26</td>
<td>78</td>
<td>54</td>
<td>&lt; 20</td>
</tr>
</tbody>
</table>
How to improve survival in lung cancer?

- Stop smoking
- CT/PET Screening
- Serum markers
- New chemotherapeutic agents
- Targeted therapies
- Vaccines

Patients selection

Biologic characterization
Targeted therapy
Biologic characterization of pulmonary cancers

Recognized predictive factor (FDA & EMEA)

Predictive factor

EGFR mutations

Thymidylate Synthase

ERCC1
RRM1
BRCA
KRAS
HER2
VEGF
PDGFR
LKB-1
Histotype

Promising predictive factor

c-met
Molecular EGFR pathways amenable to targeting with novel agents in combination with radiotherapy

Anti-EGFR mAb:
- Cetuximab

EGFR TKI:
- Erlotinib, Gefitinib

Nyati et al, Nature 2006;6:876-885
Identification of the target population

• **Predicting response to EGFR TKIs:**
  - patient ethnicity and gender
  - tumour histology
  - molecular characteristics: EGFR mutations, amplification and gene copy number

• **Predicting response to anti-EGFR Monoclonal Antibodies:**
  - tumour specimens positive for EGFR by IHC

• **Rash:**
  - it appears to correlate with disease response and survival
Vascular-Targeting Agents and Radiation Therapy in Lung Cancer: Where Do We Stand in 2005?

David Raben, Anderson Ryan

**TABLE 4.** Ongoing Trials with Novel Agents in Combination with Chemoradiation in Stage III Non-small Cell Lung Cancer.

<table>
<thead>
<tr>
<th>Study/Organization</th>
<th>Population</th>
<th>Novel Agent</th>
<th>Regimen</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ongoing SWOG 0533&lt;sup&gt;53&lt;/sup&gt; Phase I/II</td>
<td>Unresectable stage III A2 or B</td>
<td>Bevacizumab (Avastin; Genentech, South San Francisco, CA, USA) Anti-VEGF monoclonal antibody</td>
<td>Bevacizumab introduced either with (1) docetaxel consolidation, (2) day 8 of PE/RT, or (3) day 1 of PE/RT</td>
</tr>
<tr>
<td>SWOG 0429&lt;sup&gt;54&lt;/sup&gt; Phase I</td>
<td>Poor-risk stage IIIA or IIIB</td>
<td>Cetuximab (erbitux; ImClone Systems, New York, NY, USA and Bristol-Myers Squibb, New York, NY, USA)</td>
<td>Cetuximab with concurrent RT with or without concurrent docetaxel</td>
</tr>
<tr>
<td>CALGB 30407&lt;sup&gt;55&lt;/sup&gt;</td>
<td>Unresectable stage IIIA or B</td>
<td>Anti-EGFR monoclonal antibody</td>
<td>Pemetrexed, carboplatin, and RT with or without cetuximab</td>
</tr>
<tr>
<td>Dartmouth – DMS0410&lt;sup&gt;56&lt;/sup&gt;</td>
<td>Unresectable stage IIIA or B stratified by stage, PS, and weight loss</td>
<td>Erlotinib (Tarceva; Genentech, South San Francisco, CA, USA) EGFR TKI</td>
<td>Concurrent radiotherapy with docetaxel and carboplatin followed by erlotinib or placebo</td>
</tr>
</tbody>
</table>

ChemoRT, chemoradiotherapy; EGFR, epidermal growth factor receptor; PE, cisplatin, etoposide; PS, performance status; RT, radiotherapy; TKI, tyrosine kinase inhibitor; VEGF(R), vascular endothelial growth factor (receptor).
Current treatment paradigms for locally advanced NSCLC

- EGFR inhibitors have markedly changed the management of advanced NSCLC individualized therapy

- Treatment selection may reflect patient ethnicity and gender, as well as tumour histology and molecular characteristics

- Yet despite these apparent advances, for most patients with NSCLC, EGFR inhibitors have not dramatically changed clinical outcomes

- The molecular complexity of lung cancer underlies these disappointments
Malignant pleural mesothelioma

- It is a rare malignancy
- European incidence: 1.1-1.25 cases/10^5 people/year
- Worldwide incidence is expected to increase over the next decade
- More than 80% of MPM cases have been attributed to asbestos exposure
- Median survival time (MST): 9-17 months, regardless of disease stage at diagnosis
Malignant pleural mesothelioma
The role of Surgery

- Pleurectomy/decortication (P/D)
- Extrapleural pneumonectomy (EPP)

- In either case, residual disease is typically left behind
- Various strategies have been investigated to improve LC: intrapleural CT, photodynamic therapy, brachytherapy, ERT ± systemic CT
PET/CT images of a patient with malignant pleural mesothelioma

Before EPP

After EPP
Malignant pleural mesothelioma
The role of Radiotherapy

- RT as a prophylactic therapy: 21 Gy/3 fr. with Electrons (12-15 MeV) 10-15 days after pleural incision
- RT as a definitive therapy after P/D or EPP: intraoperative BT, adjuvant hemithoracic 3D-CRT or IMRT
- RT as a palliative therapy: ≥40 Gy in 10 to 15 fractions
Malignant pleural mesothelioma
RT as a definitive therapy

- **Total dose:** 54 Gy/30 fr.
- **Superior border:** top of T1 - **inferior border:** bottom of L2
- **Organs at risk:** contralateral lung, liver, kidneys, heart, stomach, homerus
- After 41,40 Gy the spinal cord is blocked from the treated field
- After 19,80 Gy the heart is blocked from the treated field, when the left hemithorax is treated
Simulation film of right hemithorax

Simulation film of left hemithorax
IMRT treatment plan for a patient with right-sided mesothelioma after EPP
### IMRT optimization parameters

<table>
<thead>
<tr>
<th>Normal tissue</th>
<th>Dose-volume constraints</th>
</tr>
</thead>
<tbody>
<tr>
<td>Contralateral lung</td>
<td>V20 &lt; 20% and MLD &lt; 15 Gy</td>
</tr>
<tr>
<td>Contralateral kidney</td>
<td>V15 &lt; 20%</td>
</tr>
<tr>
<td>Liver</td>
<td>V30 &lt; 33% and liver MD &lt; 31 Gy</td>
</tr>
<tr>
<td>Heart</td>
<td>V45 &lt; 30%</td>
</tr>
<tr>
<td></td>
<td>V50 &lt; 20%</td>
</tr>
<tr>
<td></td>
<td>no portion &gt; 60 Gy</td>
</tr>
<tr>
<td>Spinal cord</td>
<td>90% ≤ 45 Gy</td>
</tr>
<tr>
<td></td>
<td>no portion &gt; 50 Gy</td>
</tr>
</tbody>
</table>

- **13 patients** (December 2004 - September 2005)
  - Median age: 66 years - Range: 39-68 - M/F: 11/2

- **IMRT** total dose: 54 Gy - 1.8 Gy/fr.

- **Chemotherapy:**
  - Neoadjuvant (2 pts) with intravenous cisplatin/pemetrexed
  - Adjuvant (10 pts) intraoperative with heated cisplatin (12 pts)

- **Fatal pneumonitis:** 6/13 pts.
  - Median time: 30 days - Range: 5-57 days

- **Nausea and vomiting Grade 3:** 4/13 pts.

- **Thrombocytopenia Grade 3:** 1/13 pts.
Comparison of dosimetric values of patients with and without fatal pneumonitis


<table>
<thead>
<tr>
<th></th>
<th>All patients</th>
<th>Patients with pneumonitis</th>
<th>Patients without pneumonitis</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>V20</td>
<td>15.7% (3-24%)</td>
<td>17.6% (15.3-22.3%)</td>
<td>10.9% (5.5%-24.7%)</td>
<td>0.08</td>
</tr>
<tr>
<td>MLD</td>
<td>13.8 (7.3-17) Gy</td>
<td>15.2 (13.3-17) Gy</td>
<td>12.9 (8.7-16.9) Gy</td>
<td>0.07</td>
</tr>
<tr>
<td>V5</td>
<td>92.4% (66-100%)</td>
<td>98.6% (81-100%)</td>
<td>90% (66-98.3%)</td>
<td>0.20</td>
</tr>
</tbody>
</table>
## Trimodality Treatment for Pleural Mesothelioma


<table>
<thead>
<tr>
<th>Study (first author)</th>
<th>N</th>
<th>Stage III/IV (%)</th>
<th>Trimodality Regimen</th>
<th>Operative/30-Day Mortality</th>
<th>Median OS Months</th>
</tr>
</thead>
<tbody>
<tr>
<td>Weder</td>
<td>45</td>
<td>23 (37.7)</td>
<td>Chemo / EP / ±radiation</td>
<td>2.2</td>
<td>23</td>
</tr>
<tr>
<td>Maggi</td>
<td>32</td>
<td>23 (71.8)</td>
<td>Pleurectomy, decortication or EPP / Chemo, radiation</td>
<td>6.25</td>
<td>NR</td>
</tr>
<tr>
<td>Flores</td>
<td>8</td>
<td>8 (100)</td>
<td>Chemo / EPP / radiation</td>
<td>0</td>
<td>33.5</td>
</tr>
<tr>
<td>Opitz</td>
<td>63</td>
<td>39 (62)</td>
<td>Chemo / EPP / ±radiation</td>
<td>3.2</td>
<td>NR</td>
</tr>
<tr>
<td>Pagan</td>
<td>44</td>
<td>33 (75)</td>
<td>EPP / chemo / radiation</td>
<td>4.5</td>
<td>20</td>
</tr>
<tr>
<td>Rea</td>
<td>17</td>
<td>16 (76.2)</td>
<td>Chemo / EPP / radiation</td>
<td>0</td>
<td>25.5</td>
</tr>
<tr>
<td>Batirel</td>
<td>20</td>
<td>8 (47)</td>
<td>EPP / chemo / radiation</td>
<td>5</td>
<td>17</td>
</tr>
<tr>
<td>Sugarbaker</td>
<td>183</td>
<td>142 (78)</td>
<td>EPP / chemo / radiation</td>
<td>3.8</td>
<td>19</td>
</tr>
<tr>
<td>Present study</td>
<td>46</td>
<td>33 (71.7)</td>
<td>Chemo / EPP / radiation</td>
<td>4.3</td>
<td>25</td>
</tr>
</tbody>
</table>
How to improve survival in malignant pleural mesothelioma?

- A small number of patients can withstand aggressive surgery
- For these patients trimodality therapy has been proposed as a curative treatment, but survival is still limited
- No curative treatment has been proposed for the MPM patients who cannot tolerate aggressive surgery, because of age, medical illness, and advanced MPM stage

...Why don’t consider BNCT?
Feasibility of BNCT for MPM from a viewpoint of dose distribution analysis

### DVH data for the lung

<table>
<thead>
<tr>
<th></th>
<th>$D_{95}$ (Gy-Eq)</th>
<th>Mean dose (Gy-Eq)</th>
<th>$D_{05}$ (Gy-Eq)</th>
<th>$D_{05}/D_{95}$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Case 1</td>
<td>3.6</td>
<td>4.2</td>
<td>5.0</td>
<td>1.4</td>
</tr>
<tr>
<td>Case 2</td>
<td>3.5</td>
<td>4.1</td>
<td>5.0</td>
<td>1.4</td>
</tr>
<tr>
<td>Case 3</td>
<td>2.2</td>
<td>3.5</td>
<td>5.0</td>
<td>2.3</td>
</tr>
</tbody>
</table>

### DVH data for the tumour

<table>
<thead>
<tr>
<th></th>
<th>$D_{95}$ (Gy-Eq)</th>
<th>Mean dose (Gy-Eq)</th>
<th>$D_{05}$ (Gy-Eq)</th>
<th>$D_{05}/D_{95}$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Case 1</td>
<td>14.3</td>
<td>22.4</td>
<td>31.5</td>
<td>2.2</td>
</tr>
<tr>
<td>Case 2</td>
<td>9.6</td>
<td>24.9</td>
<td>34.8</td>
<td>3.6</td>
</tr>
<tr>
<td>Case 3</td>
<td>15.0</td>
<td>27.2</td>
<td>39.5</td>
<td>2.6</td>
</tr>
</tbody>
</table>
Feasibility of BNCT for MPM from a viewpoint of dose distribution analysis


DVH for the tumour and normal lung in 3 cases
Conclusions

• BNCT can deliver a mean dose of 22.4-27.2 Gy-Eq to MPM by irradiating normal lung at a mean dose of 3.5-4.2 Gy-Eq.
• Assuming an $\alpha/\beta$ coefficient of 3 for normal lung tissues, according to the LQM:
  $3 \text{ fr.} \times 3.5 - 4.2 \text{ Gy-Eq} = 13.7 - 18.1 \text{ Gy in 2 Gy/fr.}$
• Because the mean lung dose of 15-20 Gy is reported to be an acceptable limit for the treatment of NSCLC, a three-fractionated BNCT might be considered for the treatment of locally advanced NSCLC and MPM
Conclusions

• BNCT might have the possibility to deliver a curative dose to tumours spreading in radiosensitive organs, such as locally advanced NSCLC and MPM, without causing fatal adverse effects.

• A fractionated regimen could be easier and safer performed in a Radiotherapy Department for cancer treatment, with LINAC and PhoNeS photoconverter facility.

• A combination of BNCT and external RT might be exploited, as it has been experimentally studied in brain tumours models (Barth RF, et al IJROBP 2004).