Progress in Mesothelioma

Princess Margaret Hospital

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Mesothelioma Research Program

• Early Detection Study
  – LDCT scan, questionnaire, biomarkers, spirometry

• Treatment Protocols
  – Trimodality therapy
  – Neo-adjuvant IMRT
  – Advanced disease chemo studies

• Basic Research Studies
  – Genetic profiling of tumours
  – Immunomodulation in mesothelioma
  – Screening new therapies

• Epidemiology Studies
  – Asbestos related lung disease

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# Mesothelioma Research Program

<table>
<thead>
<tr>
<th>Name</th>
<th>Role</th>
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</thead>
<tbody>
<tr>
<td>Michael R. Johnston, MD</td>
<td>Thoracic Surgeon</td>
</tr>
<tr>
<td>Heidi Roberts, MD</td>
<td>Radiologist</td>
</tr>
<tr>
<td>Marc de Perrot, MD</td>
<td>Thoracic Surgeon</td>
</tr>
<tr>
<td>Ming Tsao, MD</td>
<td>Pathologist</td>
</tr>
<tr>
<td>Ron Feld, MD</td>
<td>Medical Oncologist</td>
</tr>
<tr>
<td>Brenda O’Sullivan</td>
<td>Coordinator</td>
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<tr>
<td>Li Zhang, PhD</td>
<td>Immunologist</td>
</tr>
<tr>
<td>Masaki Anraku, MD</td>
<td>Thoracic Oncology Fellow</td>
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<tr>
<td>John Cho, MD</td>
<td>Radiation Oncologist</td>
</tr>
<tr>
<td>Geofrey Liu, MD, PhD</td>
<td>Molecular Epidemiologist</td>
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<tr>
<td>Martin Tammamagi, PhD</td>
<td>Epidemiologist</td>
</tr>
<tr>
<td>Demetris Patsios, MD</td>
<td>Radiologist</td>
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<tr>
<td>Gregory Pond</td>
<td>Statistician</td>
</tr>
<tr>
<td>Albert Ebidia</td>
<td>Database support</td>
</tr>
</tbody>
</table>

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Survival by Stage in Adjuvant Trials

Brigham (Sugarbaker)  
EPP+chemo+rads+chemo

Memorial (Rusch)  
EPP+rads

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“Early” Mesothelioma

21 year old student

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## First Sites of Relapse after EPP and 54 Gy Rad Tx

<table>
<thead>
<tr>
<th>Site</th>
<th>Count</th>
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<tr>
<td>Locoregional only</td>
<td>2</td>
</tr>
<tr>
<td>Distant only</td>
<td>30</td>
</tr>
<tr>
<td>Locoregional and distant</td>
<td>5</td>
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<tr>
<td>Locoregional</td>
<td>7</td>
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<tr>
<td>Pleural</td>
<td>3</td>
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<tr>
<td>Nodal</td>
<td>4</td>
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<td>Distant</td>
<td>30</td>
</tr>
<tr>
<td>Peritoneal</td>
<td>17</td>
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<tr>
<td>Intralateral visceral</td>
<td>5</td>
</tr>
<tr>
<td>Contralateral pleural</td>
<td>13</td>
</tr>
<tr>
<td>Contralateral lung</td>
<td>8</td>
</tr>
<tr>
<td>Bone</td>
<td>7</td>
</tr>
<tr>
<td>Central nervous system</td>
<td>0</td>
</tr>
<tr>
<td>Other</td>
<td>5</td>
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</tbody>
</table>

Some patients had more than one site of recurrent disease at relapse.

Treatment Protocol

Malignant pleural Mesothelioma

- pathology review
- pleurodesis

- staging
- Cisplatin based chemotherapy
- re-stage
- Extrapleural pneumonectomy
- Hemithoracic radiation
Chemotherapy Toxicities (N=19)

- No compl.: 14 patients
- Nausea: 2 patients
- Paresth.: 2 patients
- Fever: 2 patients
- PE: 2 patients

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Extrapleural Pneumonectomy

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Major Post-operative Complications

57 consecutive patients undergoing EPP

- Deaths
- Technical*
- Esophageal perf
- BPF/Empyema
- ARDS/pneumonia
- Pulm emboli
- Cardiac arrest
- Atrial Fib

Total Complications

% of patients
### Risk Factors for Major Complications

<table>
<thead>
<tr>
<th>Risk Factor</th>
<th>Univariate</th>
<th>Multivariate</th>
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<tbody>
<tr>
<td>Right sided EPP</td>
<td>0.01</td>
<td>0.02</td>
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<tr>
<td>RBC transf &gt;4 units</td>
<td>0.03</td>
<td>0.03</td>
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<tr>
<td>Age (≥ 60 yo)</td>
<td>0.06</td>
<td>0.1</td>
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<tr>
<td>Induction chemo</td>
<td>0.5</td>
<td>0.5</td>
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</table>

* p-value

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Impact of Induction Chemotherapy

- Preop Hb (g/l)
- Blood transf. (units)
- Hosp stay (days)

Legend:
- No induction therapy
- Induction chemotherapy

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Hemi-thoracic Radiation

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Hemithoracic Radiation (N=12)

Grade 1: Skin erythema, Nausea, Esophagitis
Grade 2: Fatigue, Nausea
Grade 3: Vertigo

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Toronto Trimodality Therapy Update

- 2001 - December, 2007: 60 patients
  - Induction chemotherapy: 50
    - Cisplatin + vinorelbine 26; pemetrexed 24; other 10
  - No resection: 15
    - Progressive disease: 4
    - Unresectable: 6
    - Positive mediastinoscopy: 5
  - EPP: 45
    - Operative mortality: 3 (7%)
  - Adjuvant hemi-thoracic radiation: 30
    - 3-D conformal (54 Gy in 30 fractions)
    - IMRT (50 Gy in 25 fractions)

dePerrot, JCO; in press

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## Complications of Trimodality Therapy

Table 2. Severe adverse events recorded during the tri-modality therapy*

<table>
<thead>
<tr>
<th>Complications</th>
<th>Chemotherapy</th>
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<th>Surgery</th>
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<th>Radiation</th>
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<tr>
<td></td>
<td>Grade 3</td>
<td>Grade 4</td>
<td>Grade 5</td>
<td>Grade 3</td>
<td>Grade 4</td>
<td>Grade 5</td>
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<tr>
<td>Pulmonary emboli</td>
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<td>Leukopenia</td>
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<tr>
<td>Cardiac herniation</td>
<td>10</td>
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<tr>
<td>Cardiac arrhythmia</td>
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<tr>
<td>Bronchopleural fistula</td>
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<td>Esophageal perforation</td>
<td>1</td>
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<tr>
<td>Gastric herniation</td>
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<td>Chyllothorax</td>
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<tr>
<td>Fatigue</td>
<td>1</td>
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<td></td>
<td>5</td>
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<tr>
<td>Nausea</td>
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</tbody>
</table>

* Severe adverse events defined by grade 3 to 5 toxicity according to the NCI CTCAE version 3.0 guidelines.
Overall Survival

60 patients; median survival 14 months

dePerrot, JCO; in press
Survival According to Nodal Status and Therapy

dePerrot, JCO; in press
Disease-free Survival in Patients Who Completed Trimodality Therapy

N = 30
Toronto Trimodality Therapy

• Median survival
  – Epithelial vs biphasic: 18 vs. 12 mo (p=0.002)
  – N 0 disease
    • Completed trimodality therapy vs incomplete
    • 59 vs. 8 mo (p=0.0001)
  – Chemo regimen: ns

• 5 year disease-free survival
  – 53% in all N0 patients
    • 75% in T1-2
    • 45% in T3-4
Recurrance Following Trimodality Therapy

• Recurrences
  – 16/30 patients
    • Ipsilateral chest: 4 \textit{local}
    • Pericardium: 1
    • Peritoneum: 5 \textit{surgical seeding}
    • Contralateral chest: 4 \textit{vs distant mets?}
    • Chest and peritoneum: 2
Tumour Seeding
Neo-adjuvant IMRT for Mesothelioma

Cho, dePerrot, Feld

• Phase 2 study in 25 patients with cT1-2 N0
  – Resectable patients only
• 25 Gy in 5 fractions over 1 week
  – 5 Gy boost to gross disease
• EPP 1 week following XRT
• Pathologic node negative > no treatment
• Pathologic node positive > adjuvant chemo

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Low-dose Computed Tomography For The Early Diagnosis Of Mesothelioma And Lung Cancer In Prior Asbestos Workers: Preliminary Results

Michael R. Johnston, MD, FRCSC
Heidi Roberts, MD

University of Toronto University Health Network
Toronto, Ontario, Canada
Methods

• Early detection study in a population at risk for pleural mesothelioma
  – Prevalence and incidence

• Inclusion criteria
  – History of asbestos exposure at least 20 years ago
  – Asbestos exposure with pleural plaques on chest x-ray
Methods: follow up flow chart

Baseline low-dose CT

- No or inconspicuous plaques or no or non-specific nodules
  - Annual repeat
  - No change
    - Bi-annual repeat
  - Growth
    - Annual repeat
    - Biopsy etc.
  - Resolved (mucous)
    - Annual repeat
    - Bronchoscopy

- Indeterminate nodules (≥5 mm solid or ≥8 mm non-solid)
  - 6 months f/u
  - No change
    - Annual repeat
- Suspicious plaques or nodules
  - 3 months f/u
  - No change
    - Annual repeat
  - Growth
    - Biopsy etc.
  - Stable
    - Annual repeat

- Endobronchial nodules
  - Immediate biopsy
    - Lobulated, asymmetric, effusion
    - Mass-like plaques with effusion

- Suspicious nodules (≥15 mm)
  - Immediate biopsy
Update on Early Detection Study (9/08)

- 751 participants (98% male; average age 61)
  - 84% with lung nodule (20% > 4mm; 1% GGO)
  - 62% with pleural plaques
  - 2% with pleural effusion
- 14 cancers found
  - 6 meso (3 pleural, 3 peritoneal)
  - 8 lung cancers
- Mesothelin and osteopontin assays are in progress
- Expanding endpoints to include asbestos related lung disease

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Plasma markers in patients with MPM

Prospective evaluation in patients with MPM (38) and asbestos exposed matched controls (64)

Anraku, IMIG; 2008