Accelerated hemithoraciac radiation followed by extrapleural pneumonectomy for malignant pleural mesothelioma

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Role of surgery in mesothelioma

- The role of surgery in mesothelioma remains controversial

- The MARS trial demonstrated the lack of feasibility to randomize patients to extrapleural pneumonectomy (EPP) vs no surgery

- However, most investigators currently agree that macroscopic complete resection plays a vital role in the multimodality approach to mesothelioma

- The best multimodality strategy remains unknown

2. IMIG participants. *J Thorac Cardiovasc Surg* 2013;145:909-10
Induction IMRT followed by EPP

• We designed a new concept with induction accelerated hemithoracic radiation followed by EPP

• 25 to 30 Gy is delivered in 5 daily fractions over 1 week to the entire ipsilateral hemithorax by IMRT

• EPP is performed within two weeks after IMRT before the development of radiation pneumonitis

• Protocol started in 11/2008 with a phase I followed by a prospective single arm phase II study
The “SMART” approach

Algorithm:
Surgery for Mesothelioma
After Radiation Therapy

MPM cT1-3 cN0 M0
Histological confirmation
No prior therapy

Stage with CT and PET

Hemithoracic radiation IMRT
25Gy in 5 fractions over 1 week
5 Gy boost to area at risk based on PET and CT

Extrapleural pneumonectomy

ypN0-1
Observation

ypN2
Adjuvant chemotherapy
Rational

- Optimal delivery of radiation to the primary tumor based on PET and CT scan findings
- Sterilization of the edges of the tumor before surgery to decrease the risk of seeding
- Short treatment
- Potential immunogenic benefit
<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of patients</td>
<td>62</td>
</tr>
<tr>
<td>Age (years)</td>
<td>64 (41-75)</td>
</tr>
<tr>
<td>Gender</td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>52 (84%)</td>
</tr>
<tr>
<td>Female</td>
<td>10 (16%)</td>
</tr>
<tr>
<td>Histology</td>
<td></td>
</tr>
<tr>
<td>Epithelial</td>
<td>44 (71%)</td>
</tr>
<tr>
<td>Biphasic</td>
<td>18 (29%)</td>
</tr>
<tr>
<td>Side of tumor</td>
<td></td>
</tr>
<tr>
<td>Right</td>
<td>45 (73%)</td>
</tr>
<tr>
<td>Left</td>
<td>17 (27%)</td>
</tr>
<tr>
<td>Time between RT and EPP</td>
<td>6±2 days</td>
</tr>
</tbody>
</table>
Clinical stage

- T1N0 10 patients (16%)
- T2N0 35 patients (57%)
- T3N0 11 patients (18%)

Extension of indications

- Clinical T4N0 (chest wall) 2 patients (3%)
- Clinical N2 disease 2 patients (3%)
- Preo-op chemotherapy 2 patients (3%)
Extrapeural pneumonectomy

- Resection
  - Diaphragm (n=61)
  - Pericardium (n=58)
  - Chest wall (n=2)

- Bronchial stump coverage
  - Posterior pericardium (n=57)
  - Omental flap (n=3)
  - Thymic flap (n=2)
Postoperative grade 3+ complications (n=24)

- Atrial fibrillation
- Empyema
- Pulmonary emboli
- Pneumonia
- Chylothorax
- Hemothorax
- Wound problem
- Patch dehiscence
- Others

*6 patients had more than one grade 3+ complication*
Rate of grade 3+ complications decreased over time

Postoperative grade 3+ complications

First 20 patients

Last 42 patients

Percentage of grade 3+ complications

Other complications than atrial fibrillation

Atrial fibrillation alone

$p=0.02$
Total of 3 patients (4.8%)

- One patient died in hospital from pneumonia
  - Post-operative hospital mortality of 1.6%
- One patient died at home from unwitnessed cardiac arrest
- One patient died after discharged from hospital from empyema
Pathological stage

94% stage III and IV

52% N2+

Pathological stage

Number of patients

T1N0
T2N0
T3N0
T4N0
T4N2
T3N2
T2N2

I
II
III
IV
Overall survival

Intention-to-treat analysis (n=62)

Median survival 36 months

Percent survival

Months after start of treatment

Toronto General Hospital
University Health Network
Overall survival by histologic subtypes

cT1-3N0M0 treatment naive (n=56)

Median survival:
Epithelial  51 mo
Biphasic   10 mo

Overall survival (%)

Months after start of treatment
Disease free survival by histologic subtypes

cT1-3N0M0 treatment naive (n=56)

- Epithelial: 47 mo
- Biphasic: 8 mo

Median DFS:
- Epithelial 47 mo
- Biphasic 8 mo

p<0.0001

Disease free survival (%) vs. Months after start of treatment

52%
Disease free survival by nodal status in epithelial subtype

- **Epithelial ypT\text{x}N0**: 65%
- **Epithelial ypT\text{x}N+**: 43%

*p* = 0.02
First sites of recurrence

30 patients presented with recurrence*

- Contralateral chest: 17
- Abdomen: 16
- Ipsilateral chest: 8
- Nodes: 7
- Pericardium: 2

*11 patients had more than one recurrence
Conclusions

• Preoperative accelerated hemithoracic radiation is feasible and well tolerated

• Extrapleural pneumonectomy can be done safely, even after hemithoracic radiation therapy

• The mid-term results are encouraging for epithelial subtypes, but longer follow-up is required before definitive conclusions can be made

• This approach carries risk and should be done in centers with expertise in surgery and hemithoracic radiation for mesothelioma