Insights into Thymic Epithelial Tumors: Radiation Therapy

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OVERALL SURVIVAL FOR THYMIC NEOPLASMS
(Detterbeck, ANN THORAC SURG ‘04)

- **Inclusion criteria:** results of 100 pts by Masaoka stage
- **Thymic carcinoma excluded**
- **Both stage IVa & IVb**
- **9-yr Survival**
- **5 pts**
- **# in parentheses excluded**
- **R₀ = percent with complete resection**

<table>
<thead>
<tr>
<th>Study</th>
<th>n</th>
<th>% R₀</th>
<th>% 5-year Survival</th>
<th>% 10-year Survival</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>I</td>
<td>II</td>
</tr>
<tr>
<td>Kondo and Monden [39]</td>
<td>924</td>
<td>92</td>
<td>100</td>
<td>98</td>
</tr>
<tr>
<td>Regnard et al. [18]</td>
<td>307</td>
<td>85</td>
<td>89</td>
<td>87</td>
</tr>
<tr>
<td>Maggi et al. [19]</td>
<td>241</td>
<td>88</td>
<td>89</td>
<td>71</td>
</tr>
<tr>
<td>Verley and Hollmann [5]</td>
<td>200</td>
<td></td>
<td>85</td>
<td>60</td>
</tr>
<tr>
<td>Nakahara et al. [33]</td>
<td>141</td>
<td>80</td>
<td>100</td>
<td>92</td>
</tr>
<tr>
<td>Wilkins et al. [27]</td>
<td>136</td>
<td>68</td>
<td>84</td>
<td>66</td>
</tr>
<tr>
<td>Blumberg et al. [22]</td>
<td>118</td>
<td>73</td>
<td>95</td>
<td>70</td>
</tr>
<tr>
<td>Quintanilla-Martinez et al. [8]</td>
<td>116</td>
<td>94</td>
<td>100</td>
<td>100</td>
</tr>
<tr>
<td>Pan et al. [23]</td>
<td>112</td>
<td>80</td>
<td>94</td>
<td>85</td>
</tr>
<tr>
<td>Elert et al. [21]</td>
<td>102</td>
<td></td>
<td>83</td>
<td>90</td>
</tr>
<tr>
<td><strong>Average</strong></td>
<td>92</td>
<td></td>
<td>82</td>
<td>68</td>
</tr>
</tbody>
</table>
### Recurrence Rates for Thymic Neoplasms

**Inclusion criteria:** results of 100 pts, with results by Masaoka stage.

- Thymic carcinoma excluded
- IVa and Ivb
- 5 patients
- # in parentheses excluded

**Estimated, not specifically reported**

- Recurrences only in mediastinum excluded.
- 19% and 6% for IIa and IIb

**R** = complete resection

<table>
<thead>
<tr>
<th>Study</th>
<th>n</th>
<th>% Receiving</th>
<th>% With Recurrence</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>R0</td>
<td>Ch</td>
</tr>
<tr>
<td>Kondo and Monden [39]</td>
<td>862</td>
<td>100</td>
<td>12(^c)</td>
</tr>
<tr>
<td>Regnard et al. [18]</td>
<td>307</td>
<td>85</td>
<td>few</td>
</tr>
<tr>
<td>Maggi et al. [19]</td>
<td>241</td>
<td>88</td>
<td>7</td>
</tr>
<tr>
<td>Verley and Hollmann [5]</td>
<td>200</td>
<td>...</td>
<td>few</td>
</tr>
<tr>
<td>Cowen et al. [25]</td>
<td>149</td>
<td>42</td>
<td>100</td>
</tr>
<tr>
<td>Wilkins et al. [27]</td>
<td>136</td>
<td>68</td>
<td>7</td>
</tr>
<tr>
<td>Monden et al. [34]</td>
<td>127</td>
<td>80</td>
<td>...</td>
</tr>
<tr>
<td>Blumberg et al. [22]</td>
<td>118</td>
<td>73</td>
<td>32</td>
</tr>
<tr>
<td>Ruffini et al. [30]</td>
<td>114</td>
<td>100</td>
<td>...</td>
</tr>
<tr>
<td>Quintanilla-Martinez et al.</td>
<td>105</td>
<td>100</td>
<td>0</td>
</tr>
</tbody>
</table>

**Average**

|       | 4  | 14 | 26 | 46 |

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American Cancer Society, www.cancer.org

www.2007worldlungcancer.org
SURVIVAL S/P RESECTION FOR THYMIC NEOPLASMS

- Inclusion criteria: studies of >50 pts reporting outcomes s/p incomplete resection & biopsy.
- p value for R_{1,2} resection versus biopsy only.
- Only stage III and IV thymoma.
- Thymic carcinoma excluded.
- 5-yr Survival.
- Stage III pts only
- Bx = pts undergoing biopsy only;
- % 10-year Survival
- Excluding values in parentheses.
- NS = not significant;
- R_{1,2} = microscopically/grossly incomplete resection

<table>
<thead>
<tr>
<th>Study</th>
<th>n</th>
<th>R_0</th>
<th>R_{1,2}</th>
<th>Bx</th>
<th>R_0</th>
<th>R_{1,2}</th>
<th>Bx</th>
<th>p Value^b</th>
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</thead>
<tbody>
<tr>
<td>Kondo and Monden [39]</td>
<td>186</td>
<td>50</td>
<td>24</td>
<td>(93)^e</td>
<td>(64)^e</td>
<td>(36)^e</td>
<td></td>
<td>&lt;.003</td>
</tr>
<tr>
<td>Maggi et al. [19]</td>
<td>211</td>
<td>21</td>
<td>9</td>
<td>81</td>
<td>72f</td>
<td>27f</td>
<td></td>
<td>0.001</td>
</tr>
<tr>
<td>Nakahara et al. [33]^d</td>
<td>113</td>
<td>16</td>
<td>12</td>
<td>(94)^g</td>
<td>(68)^g</td>
<td>(0)^g</td>
<td></td>
<td>&lt; 0.01</td>
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<tr>
<td>Blumberg et al. [22]</td>
<td>86</td>
<td>18</td>
<td>14</td>
<td>70</td>
<td>28</td>
<td>24</td>
<td></td>
<td>NS</td>
</tr>
<tr>
<td>Mornex et al. [71]^d</td>
<td>4</td>
<td>31</td>
<td>55</td>
<td>...</td>
<td>43</td>
<td>31</td>
<td></td>
<td>&lt;0.02</td>
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<tr>
<td>Regnard et al. [18]^a</td>
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<td>12</td>
<td>75</td>
<td>29</td>
<td>35</td>
<td></td>
<td>NS</td>
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<tr>
<td>Gamondès et al. [3]^d</td>
<td>45</td>
<td>15</td>
<td>5</td>
<td>91</td>
<td>32</td>
<td>53</td>
<td></td>
<td>NS</td>
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<tr>
<td>Wang et al. [20]</td>
<td>34</td>
<td>9</td>
<td>18</td>
<td>48</td>
<td>20</td>
<td>20</td>
<td></td>
<td>NS</td>
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<tr>
<td>Kaiser and Martini [43]</td>
<td>39</td>
<td>13</td>
<td>7</td>
<td>82</td>
<td>48</td>
<td>44</td>
<td></td>
<td>...</td>
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</table>

**Average**^i

<p>| | | | | | | |</p>
<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
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</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>75</td>
<td>39</td>
<td>33</td>
<td></td>
<td></td>
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</tr>
</tbody>
</table>

American Cancer Society, www.cancer.org
www.2007worldlungcancer.org
THERAPEUTIC RATIO CHALLENGE

Tumor control vs. Complications

Radiation Dose

Tumor control: 100%
Complications
RECURRENCE RATE S/P RESECTION & ADJUVANT RADIOThERAPY
(Detterbeck, ANN THORAC SURG '04)

a Inclusion criteria: studies of > 50 pts by stage & completeness of resection.
b Thymic carcinoma excluded
c Stage II, III combined.
d <5 patients in this category
e Excluding values in parentheses.
NS = not significant
Obs = observation
RT = radiotherapy.
R₀ = complete resection

<table>
<thead>
<tr>
<th>Study</th>
<th>% R₀</th>
<th>% of Patients with Recurrence</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Obs</td>
<td>RT</td>
</tr>
<tr>
<td>Kondo and Monden [39]</td>
<td>100</td>
<td>...</td>
<td>...</td>
</tr>
<tr>
<td>Ruffini et al. [30]</td>
<td>100</td>
<td>5</td>
<td>0</td>
</tr>
<tr>
<td>Regnard et al. [18]</td>
<td>100</td>
<td>...</td>
<td>...</td>
</tr>
<tr>
<td>Haniuda et al. [59]²</td>
<td>100</td>
<td>0</td>
<td>(0)²</td>
</tr>
<tr>
<td>Monden et al. [34]²</td>
<td>100</td>
<td>8</td>
<td>0</td>
</tr>
<tr>
<td>Curran et al. [38]²</td>
<td>100</td>
<td>0</td>
<td>(0)²</td>
</tr>
<tr>
<td>Blumberg et al. [22]</td>
<td>100</td>
<td>...</td>
<td>...</td>
</tr>
<tr>
<td>Average²</td>
<td>3</td>
<td>0</td>
<td>15</td>
</tr>
</tbody>
</table>
SEER Analysis of Radiation Therapy in Thymoma (Houseman et al (Yale) ASTRO ’06)

• 671 cases of Thymoma from the Surveillance, Epidemiology, and End Results (SEER) dataset from (1988-2002)
• Is post-operative radiation (RT) associated with an overall survival benefit?
• The SEER data stratified by the best approximation of the Masaoka* staging system using groups defined by SEER extent of disease codes.
  • Group I and II were used for RT analysis.
  • Group III probably contained Masaoka III and IVa
Staging (Houseman et al (Yale) ASTRO ’06)

• Invasive carcinoma confined to gland of origin and localized disease not otherwise specified, were classified as group I, being most similar to Masaoka stage I.

• Invasion into adjacent connective tissue was classified as group II, being most similar to Masaoka stage II.

• Group III was defined as invasion into adjacent organs or structures. While group III likely includes most patients with Masaoka stage III thymomas, it probably also includes patients with pericardial or pleural dissemination (Masaoka stage IVa).

• Metastasis in the SEER system was classified as group IV, being most similar to Masaoka stage IVb, but may include some patients with IVa as well.
## Summary of Results  (Houseman et al (Yale) ASTRO ’06)

<table>
<thead>
<tr>
<th>Age</th>
<th>Median</th>
<th>Range</th>
<th>N</th>
<th>Male %</th>
<th>Female %</th>
</tr>
</thead>
<tbody>
<tr>
<td>55</td>
<td>8-91</td>
<td>599</td>
<td>54%</td>
<td>46%</td>
<td></td>
</tr>
</tbody>
</table>

| Follow up time | 3.9 | 0.4-14.8 |

<table>
<thead>
<tr>
<th>Group</th>
<th>10yr OS</th>
<th>N</th>
<th>Masaoka*</th>
<th>10yr OS</th>
<th>N</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>77%</td>
<td>143</td>
<td>I</td>
<td>80%</td>
<td>135</td>
</tr>
<tr>
<td>II</td>
<td>63%</td>
<td>90</td>
<td>II</td>
<td>78%</td>
<td>70</td>
</tr>
<tr>
<td>III</td>
<td>41%</td>
<td>234</td>
<td>III</td>
<td>47%</td>
<td>83</td>
</tr>
<tr>
<td>IV</td>
<td>29%</td>
<td>132</td>
<td>IV</td>
<td>30%</td>
<td>19</td>
</tr>
</tbody>
</table>
Favors use of RT

Against use of RT

Group I
N= 143
RT= 56%
HR= 1.95 (0.88-4.36)
P = 0.102

Group II
N= 90
RT= 74%
HR= 0.23 (0.08-0.68)
P = 0.008

Mortality HR of RT adjusted for age
Total Postop RT in 63%
Conclusions and Limitations

• The survival characteristics of the SEER groups are consistent with prior studies that have used Masaoka stages.

• According to the SEER data, RT appears to confer a survival advantage for group II, but not for group I patients. Suggesting the need for further analysis.

• Limitations:
  – Margin Status (sub-total vs total resection), Retrospective, Non-standardized criteria for who receives RT, no loco-regional recurrence data…
### MGH ADJUVANT RT EXPERIENCE
(Adapted from Wright et al ‘04, Ruffini et al ‘97)

<table>
<thead>
<tr>
<th>Stage</th>
<th>Recurrence with resection alone</th>
<th>Recurrence after resection and adjuvant radiation</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>7/145 (5%)</td>
<td>0/7 (0%)</td>
</tr>
<tr>
<td>II</td>
<td>2/45 (4%)</td>
<td>4/13 (31%)</td>
</tr>
<tr>
<td>III</td>
<td>6/36 (16%)</td>
<td>9/14 (64%)</td>
</tr>
<tr>
<td>IVa</td>
<td>1/4 (25%)</td>
<td>1/2 (50%)</td>
</tr>
<tr>
<td>All</td>
<td>9/85 (10%)</td>
<td>14/29 (48%)</td>
</tr>
<tr>
<td>Invasive</td>
<td></td>
<td>p=.0002</td>
</tr>
</tbody>
</table>

266 pts having a complete resection for thymoma, 30 patients developed a recurrence
### MGH ADJUVANT RT EXPERIENCE
(Adapted from Wright et al ‘04, Ruffini et al ‘97)

<table>
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<td>1/2 (50%)</td>
</tr>
<tr>
<td>All Invasive</td>
<td>9/85 (10%)</td>
<td>14/29 (48%)</td>
</tr>
</tbody>
</table>

266 pts having a complete resection for thymoma, 30 patients developed a recurrence

p=.0002
Overall surv. 95% at 5 yrs
(95% CI, 0.87–1.0) & 79% at 7 yrs (95% CI, 0.55–1.0)

PFSurvival time of 22 pts,
77% at 5 yrs
(95% CI, 0.58–1.0)
& 77% at 7 years
(95% CI, 0.58–1.0)
Development of Dichotomous Risk Classification
(Adapted from Wright, MGH data)
Influence of Risk (Stage and Histology) on Disease Specific Survival (Adapted from Wright)

Low risk
- 15y 98% (95% CI 92-100%)

High risk
- 53% (95% CI 44-64%)

\( p < .0001 \)
COMBINED-MODALITY APPROACH FOR CLINICALLY LOCALLY ADVANCED THYMIC NEOPLASMS
Induction Chemotherapy

22 patients completed
3 (14%) CRs
14 (63%) PRs
4 (18%) MRs
1 (5%) SD

Surgical Resection

22 tumors resectable
21 tumors resected

Radiation Therapy

16 (73%) patients received 60 Gy XRT
6 (27%) patients received 50 Gy XRT

Consolidation Chemotherapy

20 patients completed the planned multidisciplinary approach
1 patient died during radiation treatment
1 patient refused surgery and received only 54 Gy of radiation treatment
3D RECONSTRUCTION OF THYMOMA MASS & NORMAL OAR (Organs-at-Risk)---from Hung, Eng, Fuller, Scarbrough, & Thomas; 5th Ed Principles & Practice of Radiation Oncology, 2007 (in press)
DVH of IMRT plan, 66 Gy/33 fx. PTV = CTV + 7mm. Respiratory gating used---from Hung, Eng, Fuller, Scarbrough, & Thomas; 5th Ed Principles & Practice of Radiation Oncology, 2007 (in press)
Isodoses from an IMRT plan for treatment of a large thymoma ---from Hung, Eng, Fuller, Scarbrough, & Thomas; 5th Ed Principles & Practice of Radiation Oncology, 2007 (in press)
Multi-field arrangement in pt with thymoma
Multi-field arrangement in pt with thymoma
**Treatment Algorithm**

- Mediastinal mass on CXR
- History, Physical → CT scan
  - Is it resectable?
    - Yes
    - Final pathology
      - No invasion
        - Lifelong follow-up
      - Invasion present
        - ? Post-op radiotherapy (WHO B2-C)
    - Invasion present
      - Is tumor localized?
        - Yes
          - Preop ChemoRx or Chemoradiotherapy
            - then surgical resection (if sufficient cytoreduction)
        - No
          - ChemoRx alone
    - No invasion
    - Obtain tissue diagnosis with a core needle biopsy or open biopsy
MOLECULAR SIGNATURES MAY PREDICT THE NEED FOR RADIOTHERAPY (Caprioli, Cancer Res '05)

Cancer Research Reviews

Figure 1. Tissue/Serum Analysis by Mass Spectrometry
- Sample prep on target
- Acquire mass spectra
- Protein profiles
- Protein images

Aid to:
- Diagnosis
- Stage
- Risk
- Outcome
- Therapy

Protein Signature Discovery through Biocomputational Analysis
SUMMARY

1) Prospective clinical trials with risk-adaptive treatment strategies are needed to clarify the role of radiotherapy

Development of Dichotomous Risk Classification
(Adapted from Wright, MGH data)

Low Risk
n=88

High Risk
n=67

Stage
I
II-2
II-1
III
IV

Medullary
Cortical
WDTC
PDTC

Good

Bad

Low Risk
n=88

High Risk
n=67

Good

Bad
SUMMARY

1) Prospective clinical trials with risk-adaptive treatment strategies are needed to clarify the role of radiotherapy

2) External beam radiotherapy may be contribute to superior outcomes in select patients with invasive thymic neoplasms

3) Modern treatment planning & delivery may allow for safe administration of radiotherapy

ACKNOWLEDGMENTS

TY Eng
CD Fuller
D Houseman
PJ Loehrer
TJ Scarbrough
SJ Wang
Foundation for Thymic Cancer