Clinical and genomic characterization of desmoid fibromatosis

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Desmoid Tumor Research Foundation
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Desmoid fibromatosis

- Locally aggressive tumor without metastatic potential.
- Associated in 85% of patients with mutation in *CTNNB1* gene, rarely in context of Gardner’s syndrome.
- Historically treated with surgery though high rates of local recurrence were reported (25-50%).
- Radiation has been considered in the adjuvant setting, but rarely used now.
- Now have options of:
  - Chemotherapeutics like sorafenib or Doxil
  - Observation
Clinical questions in management of desmoid fibromatosis

• How do we counsel patients?
  – Who is most likely to progress during an initial period of observation?
  – Who are best candidates for surgical versus medical management?

• Are clinical and pathologic factors sufficient to predict outcomes or can molecular characteristics improve models?
Who are best candidates for surgical versus medical management?
Outcomes after desmoid resection

- 495 patients underwent surgical resection of a desmoid tumor.
- Between 1982 and 2011.
- Median follow-up 60 months.
- Longest follow-up 327 months.
Post-operative outcomes

90% underwent complete gross resection

More likely to have R2 resection if:
• >10cm
• Abdominal tumor
• FAP

Five year RFS 71%

Recurrence free survival R0/R1

- 71% of recurrence by two years
- 94% of patients by five years

Very few patients died after desmoid resection

<table>
<thead>
<tr>
<th>Age</th>
<th>Gender</th>
<th>Year of surgery</th>
<th>Site</th>
<th>Margin</th>
<th>Cause of Death</th>
</tr>
</thead>
<tbody>
<tr>
<td>16y.o.</td>
<td>M</td>
<td>2001</td>
<td>Intraabdominal</td>
<td>R2</td>
<td>Gardner’s disease, died 5 yrs. s/p intestinal transplant</td>
</tr>
<tr>
<td>45y.o.</td>
<td>M</td>
<td>1983</td>
<td>Intraabdominal</td>
<td>R2</td>
<td>Intraabdominal treated with surgery and RT, details of death unclear</td>
</tr>
<tr>
<td>43y.o.</td>
<td>M</td>
<td>1974</td>
<td>Intraabdominal</td>
<td>R2</td>
<td>H/o metastatic testicular cancer treated with surgery and chemo complicated by cardiac failure, subsequent intraabdominal desmoid.</td>
</tr>
<tr>
<td>29y.o.</td>
<td>M</td>
<td>2007</td>
<td>Intraabdominal</td>
<td>R2</td>
<td>Died in hospice after attempt at small bowel transplant</td>
</tr>
<tr>
<td>21y.o.</td>
<td>F</td>
<td>1996</td>
<td>Paraspinal</td>
<td>R2</td>
<td>Gardner’s syndrome, rapid increase in tumor size with high narcotic requirement</td>
</tr>
<tr>
<td>62y.o.</td>
<td>F</td>
<td>2001</td>
<td>Base of skull</td>
<td>R2</td>
<td>Progression on chemotherapy</td>
</tr>
<tr>
<td>43y.o.</td>
<td>M</td>
<td>1974</td>
<td>Mediastinum</td>
<td>R2</td>
<td>Died of pneumonia in context of progressive, chemo-resistant disease</td>
</tr>
</tbody>
</table>
Clinical characteristics and outcome in primary desmoids

Age and recurrence

- >65 y.o.
- 46-65 y.o.
- 26-45 y.o.
- 15-25 y.o.

Site and recurrence

- Abdominal wall
- Other
- Chest wall
- Intraabdominal
- Extremity

P-values:
- Age and recurrence: p=0.015
- Site and recurrence: p<0.001

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Clinical characteristics and outcome in primary desmoids

Size and recurrence

Margin and recurrence

No affect seen when stratified by:
• Gender
• Presentation status (primary vs. recurrent)
## Clinical characteristics and outcome – multivariate analysis

<table>
<thead>
<tr>
<th>Factor</th>
<th>Hazard ratio (95% confidence interval)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Margin status (R1 vs. R0)</td>
<td>1.01 (0.66, 1.56)</td>
<td>0.96</td>
</tr>
<tr>
<td>Presentation status (recurrent vs. primary)</td>
<td>1.15 (0.70, 1.89)</td>
<td>0.59</td>
</tr>
<tr>
<td>Depth (deep vs. superficial)</td>
<td>1.44 (0.56, 3.67)</td>
<td>0.45</td>
</tr>
<tr>
<td>Gender (female vs. male)</td>
<td>1.30 (0.82, 2.09)</td>
<td>0.26</td>
</tr>
<tr>
<td><strong>Primary site (vs. abdominal wall)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Extremity</td>
<td>5.09 (2.17, 11.9)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Chest wall</td>
<td>3.13 (1.18, 8.32)</td>
<td>0.022</td>
</tr>
<tr>
<td>Intraabdominal</td>
<td>2.72 (0.98, 7.56)</td>
<td>0.054</td>
</tr>
<tr>
<td>Other</td>
<td>1.50 (0.30, 7.49)</td>
<td>0.62</td>
</tr>
<tr>
<td><strong>Primary size (vs. &lt;5cm)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>5-10cm</td>
<td>0.82 (0.46, 1.46)</td>
<td>0.50</td>
</tr>
<tr>
<td>&gt;10cm</td>
<td>1.69 (0.93, 3.07)</td>
<td>0.086</td>
</tr>
<tr>
<td><strong>Age (vs. &lt;25y.o.)</strong></td>
<td>1.00</td>
<td></td>
</tr>
<tr>
<td>25-65y.o.</td>
<td>0.57 (0.37, 0.89)</td>
<td>0.013</td>
</tr>
<tr>
<td>&gt;65y.o.</td>
<td>0.29 (0.099, 0.83)</td>
<td>0.021</td>
</tr>
</tbody>
</table>
Prognosis in abdominal wall desmoids –
A nomogram to predict post-operative recurrence

* A 35 y.o. woman with a small, rectus sheath desmoid has <10% chance of recurring after surgery based on the nomogram
Prognosis in extremity desmoids

* Risk is much higher for a young patient with a large, extremity lesion

External validation of desmoid nomogram

Outcomes of 426 patients in European database analyzed by Salas et al.

Risk factors for progression and recurrence:
• Size
• Patient age
• Tumor location

Created a three point risk stratification schema.

External validation of the nomogram performed on subset of these patients having undergone R0 or R1 resection of a desmoid.

Comparison of nomogram & three point system – relative concordance indices

<table>
<thead>
<tr>
<th></th>
<th>MSKCC</th>
<th>French data</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nomogram</td>
<td>0.703</td>
<td>0.659</td>
</tr>
<tr>
<td>Three point system</td>
<td>0.532</td>
<td>0.570</td>
</tr>
</tbody>
</table>

Conclusions

- Clinical risk factors can predict recurrence after surgical resection.
- A nomogram which calculates risk of local recurrence following surgical resection of desmoids can assist clinicians in counseling patients.
- Patients with large, extremity tumors have a high risk of local recurrence and may benefit from systemic treatments as first line therapy as compared to those with abdominal wall tumors who are almost always cured with surgery.
- Future studies will examine the role of genetic markers in improving our ability to predict risk of post-operative recurrence.
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