Management of desmoids

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Head of Visceral Surgery
Department of Surgery
Desmoid Tumors - overview

- Monoclonal proliferation of fibroblasts
- 3-4 cases / million persons / year
- Women > Men
- Risk factors
  - FAP / Gardner’s syndrome
  - Trauma
  - Pregnancy (Abdominal wall ++)
- Peak incidence 25 – 35 years of age
- ~ 85% CTNNB1 Mutations
AF: Clinical Properties

- Does not metastasize

- Does not de-differentiate to a high-grade malignancy in case of recurrence

- **No “grading”:** unpredictable clinical course with a same histologic morphology

- **Infiltrative growth:** the resection that is needed to achieve clear margins is often larger than for the same-sized sarcoma

- Desmoid = *cause of death 10% FAP*
1. Wait and see for recurrent but stable lesion
2. Wait and see for primary irresectable lesion
3. The effect of surgical margins is unclear. A conservative approach is preferable
4. Increased use of neo adjuvant treatments
5. Wait and see for selected primary resectable lesions
6. Option NCI, ESMO

54 years old female
Recurrent fibromatosis after surgery
Decision of wait and see
No change 6 years later

Treatment options

1. Observation
2. Medical treatment
3. ILP
4. Radiotherapy
5. Surgery
1) Observation
Primary AF: Disease-free survival according to surgery

- Recurrence (after surgery) and progression (after optimal non surgical treatment) appear in the same proportion
- The event (recurrence or progression) is probably a reflect of the tumor biology

Bonvalot et al. EJSO 2008
Observation

- 5-year PFS: 49.9% for the W&S group (these pts were over treated before)
- 5-year PFS: 58.6% for the medical therapy group
- 50 % pts with primary avoid any treatment
36-year-old woman
Primary fibromatosis (surgical biopsy)
No treatment
No change after 12 years

Exemple of « wait and see » policy on a resectable AF
Spontaneous Regression of Primary Abdominal Wall Desmoid Tumors: More Common than Previously Thought

Sylvie Bonvalot, MD, PhD1, Nils Ternès, MS2, Marco Fiore, MD3, Georgina Bitsakou, MD1, Chiara Colombo, MD3, Charles Honoré, MD1, Andrea Marrari, MD4, Axel Le Cesne, MD5, Federica Perrone, MD6, Ariane Dunant, MS2, and Alessandro Gronchi, MD3

FIG. 2 Cumulative incidence of overall strategy modification, switch to medical treatment with no further switch, and final switch to surgery

FIG. 3 Change in tumor size for patients with modification strategy (each point represents a patient)

FIG. 4 Change in tumor size for patients without modification strategy (each point represents a patient)
Evaluation of management of desmoid tumours associated with familial adenomatous polyposis in Dutch patients

<table>
<thead>
<tr>
<th>Time</th>
<th>0</th>
<th>12</th>
<th>60</th>
<th>120</th>
</tr>
</thead>
<tbody>
<tr>
<td>N patients surgery</td>
<td>36</td>
<td>23</td>
<td>14</td>
<td>7</td>
</tr>
<tr>
<td>N patients non-surgery</td>
<td>26</td>
<td>20</td>
<td>10</td>
<td>3</td>
</tr>
</tbody>
</table>
Evaluation of management of desmoid tumours associated with familial adenomatous polyposis in Dutch patients

MH Nieuwenhuis, EM Mathus-Vliegen, CG Baeten, FM Nagengast, J van der Bijl, AD van Dalsen, JH Kleibeuker, E Dekker, AM Langers, J Vecht, FT Peters, R van Dam, WG van Gemert, WN Stuifbergen, WR Schouten, H Gelderblom and HFA Vasen

BACKGROUND: The optimal treatment of desmoid tumours is controversial. We evaluated desmoid management in Dutch familial adenomatous polyposis (FAP) patients.

METHODS: Seventy-eight FAP patients with desmoids were identified from the Dutch Polyposis Registry. Data on desmoid morphology, management, and outcome were analysed retrospectively. Progression-free survival (PFS) rates and final outcome were compared for surgical vs non-surgical treatment, for intra-abdominal and extra-abdominal desmoids separately. Also, pharmacological treatment was evaluated for all desmoids.

RESULTS: Median follow-up was 8 years. For intra-abdominal desmoids (n = 62), PFS rates at 10 years of follow-up were comparable after surgical and non-surgical treatment (33% and 49%, respectively, \( P = 0.163 \)). None of these desmoids could be removed entirely. Eventually, one fifth died from desmoid disease. Most extra-abdominal and abdominal wall desmoids were treated surgically with a PFS rate of 63% and no deaths from desmoid disease. Comparison between NSAID and anti-estrogen treatment showed comparable outcomes. Four of the 10 patients who received chemotherapy had stabilisation of tumour growth, all after doxorubicin combination therapy.

CONCLUSION: For intra-abdominal desmoids, a conservative approach and surgery showed comparable outcomes. For extra-abdominal and abdominal wall desmoids, surgery seemed appropriate. Different pharmacological therapies showed comparable outcomes. If chemotherapy was given for progressively growing intra-abdominal desmoids, most favourable outcomes occurred after combinations including doxorubicin.
2) Medical treatment
Medical options

- Non-steroidal anti-inflammatory drugs (Sulindac, Meloxicam…)
  *COX-2 partially regulates proliferation because of beta-catenin stabilization in AF. COX-blocking agents results in reduced proliferation.*

- Hormone therapy (Tamoxifen, Toremifene, Gn-RH analogues)
  *Antiestrogen treatment could be mediated by estrogen receptor (ER) beta (Deyrup AT et al. Cancer. 2006)*

- Tyrosine kinase inhibitors

- Interferon

- Chemotherapy (single or multiple agents):
  - Vinca alkaloid (Vinblastine or Vinorelbine) + MTX
  - Anthracycline alone or in association (Doxo, liposomal Doxo, Doxo + Dacarbazine)

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Toxicity

No randomized trial
34 years old female: post partum
Percutaneous biopsy: Desmoid
Tamoxifen and agonist LHRH: 18 months

- The surgery would have been mutilating
- The radiation source of sequelae in this young patient
23-year-old man
Vinorelbine (12 months)
Glivec (8 months)

- Hormonal therapy: side effects/activity? on male
- Surgery: mutilating
- Radiation: source of sequelae (young patient)
Response to liposomal doxorubicin
CT scan before (A,C) and after (B,D) 9 cycles of liposomal doxorubicin
3) Isolated limb Perfusion
Isolated limb perfusion with tumor necrosis factor-alpha and melphalan has a possible role

<table>
<thead>
<tr>
<th>Study</th>
<th>N</th>
<th>CR</th>
<th>PR</th>
<th>Local progression</th>
</tr>
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<tbody>
<tr>
<td>Lev-chelouche (Surgery 1999)</td>
<td>6</td>
<td>2</td>
<td>3</td>
<td>2 (Follow up 45 months)</td>
</tr>
<tr>
<td>Bonvalot (Ann Surg Oncol 2010)</td>
<td>8</td>
<td>1</td>
<td>6</td>
<td>1 (Follow up 27 months)</td>
</tr>
<tr>
<td>Grunhagen (EJSO 2005)</td>
<td>12</td>
<td>3</td>
<td>9</td>
<td>?</td>
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</table>

20 years old Female Fibromatosis of the thigh
4) Radiotherapy
# Local Recurrence rates following RT alone

<table>
<thead>
<tr>
<th>Author</th>
<th>N pts</th>
<th>RT dose</th>
<th>Recurrence rate</th>
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<tbody>
<tr>
<td>Leibel 83</td>
<td>13</td>
<td>40-61 Gy</td>
<td>31%</td>
</tr>
<tr>
<td>Schmitt 92</td>
<td>21</td>
<td>30-64 Gy</td>
<td>24%</td>
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<tr>
<td>Acker 93</td>
<td>16</td>
<td>50-56 Gy</td>
<td>7%</td>
</tr>
<tr>
<td>Catton 95</td>
<td>8</td>
<td>50 Gy</td>
<td>25%</td>
</tr>
<tr>
<td>Kamath 96</td>
<td>24</td>
<td>33-70 Gy med 54</td>
<td>12%</td>
</tr>
<tr>
<td>Spear 98</td>
<td>15</td>
<td>10-70 Gy</td>
<td>7%</td>
</tr>
<tr>
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<td>23</td>
<td>&lt;50 Gy, &gt;50 Gy</td>
<td>60%</td>
</tr>
<tr>
<td>Nuyttens 00</td>
<td>102</td>
<td>10-74 Gy</td>
<td>22% (54% In-field failures)</td>
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<td>(Review of 22 studies)</td>
<td></td>
<td>Better results if Dose&gt;50 Gy</td>
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<td>50-75, &lt;56 Gy, &gt;56 Gy</td>
<td>32%</td>
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<td></td>
<td></td>
<td></td>
<td>10Yr LC:62%</td>
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<td>10yr LC:75%</td>
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**Recommended dose for desmoid tumors:** 50 to 56 Gy
## Local Recurrence rates following RT alone

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### Recurrence rate ≈ 20%

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**Recommended dose for desmoid tumors: 50 to 56 Gy**
Surgery versus radiation therapy for patients with aggressive fibromatosis or desmoid tumors
A comparative review of 22 articles

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<tr>
<th>1983</th>
<th>Surgery + RT</th>
<th>RT alone</th>
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<tr>
<td>1998</td>
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<td></td>
</tr>
<tr>
<td>Local Control rate</td>
<td>Margins</td>
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</tr>
<tr>
<td>-</td>
<td>94%</td>
<td>75%</td>
</tr>
<tr>
<td>+</td>
<td>75%</td>
<td>78%</td>
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<tr>
<td>overall</td>
<td>75%</td>
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- RT alone or S + RT results in significantly better local control than S alone
- When radiotherapy is expected feasible and necessary, why to operate the patient if RT alone seems equivalent to S+RT??

Nuyttens JJ et al  Cancer. 2000
Male 71 years old; Parkinson
Percutaneaous biopsy: desmoid
Pain ++
Exclusive RX 54 Gy
Female 59 years old
Surgical biopsy: desmoid
Initial wait and see
Progression
Exclusive radiotherapy 60 Gy
5) Surgery
**Surgery versus radiation therapy for patients with aggressive fibromatosis or desmoid tumors**

A comparative review of 22 articles

Nuyttens JJ et al  Cancer. 2000

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<tr>
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<td>+</td>
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|            | 72% | 41% | 61% |

Approximately 60% of the patients are controlled by surgery alone

Nuyttens JJ et al  Cancer. 2000
- 31 years old female
- AF (biopsy)
- Evolutive after 9 months including 6 mths TAM
- Parietectomy
A stepwise clinical approach to desmoids

How to make the difference between the 2 groups?
Size criteria is not sufficient...
Regression/Stabilisation in desmoids is likely to have been underestimated as it has been calculated in a group of patients with recurrences where surgical options have been exhausted...
Specific Mutations in the \textit{\textbeta-Catenin} Gene (CTNNB1) Correlate with Local Recurrence in Sporadic Desmoid Tumors

Alexander J.F. Lazar,† Daniel Tuvin,†§
Shohrae Hajibashi,†§ Sultan Habeeb,†§
Svetlana Bolshakov,†§ Empar Mayordomo-Aranda,†§
Carla L. Warneke,† Dolores Lopez-Terrada,†§
Raphael E. Pollock,†§ and Dina Lev†§

Copyright © American Society for Investigative Pathology
DOI: 10.2353/ajpath.2008.080475
Biopsy proven desmoid tumor

Rapidly enlarging or at anatomical sensitive sites (Head and neck, limb girdles)

Other tumors at less critical sites
Asymptomatic

Adopt wait and see
Stop of contraceptive
MRI @2 months

Significant progression (RECIST)

Stable disease: continue observation

Treatment

Toxicity

- +
Treatment

Female

Anti hormonal therapy
MRI@3 months
« Selected » significant progression

Stable disease:
At least 6 months treatment

Rapidly enlarging or at anatomical sensitive sites (Head and neck, limb girdles)

Toxicity

Vinca alkaloid
Doxorubicine/TKI
MRI@3 months

Male/
post menoposonal female

Significant progression
(RECIST)
Symptomatic

Further treatment

Significant progression

Stable disease:
At least 6 months treatment

Anti hormonal therapy
MRI@3 months

« Selected » significant progression

+
Rapidly enlarging or at anatomical sensitive sites (Head and neck, limb girdles)

**Female**
- Anti hormonal therapy
  - MRI@3 months
  - « Selected » significant progression
  - Stable disease: At least 6 months treatment

**Male/post menopausal female**
- Treatment
  - Male/ post menopausal female
  - Anti hormonal therapy
    - MRI@3 months
    - « Selected » significant progression
    - Significant progression
    - Further treatment

**Toxicity**
- Vinca alkaloid
  - Doxorubicine/TKI
  - MRI@3 months
    - « Selected » significant progression
    - Significant progression
    - Further treatment

**Symptomatic**
Significant progression
Further treatment

- Intra abdominal/thoracic and abdominal wall
- Extremities
- Head and neck, Limb girdles, Elderly patients

Surgery: only in those patients where resection is feasible without major sequelae

Radiotherapy

ILP
Significant progression
Further treatment

- Intra abdominal/thoracic and abdominal wall
- Extremities
- Head and neck
  Limb girdles
  Elderly patients

Toxicity

| Surgery | ILP | Radiotherapy |

Surgery: only in those patients where resection is feasible without major sequelae
Significant progression
Further treatment

Intra abdominal/thoracic and abdominal wall

Extremities

Head and neck
Limb girdles
Elderly patients

Surgery

ILP

Radiotherapy

Toxicity
Combination of treatments
### Desmoid and Pregnancy

**Total number**

<table>
<thead>
<tr>
<th></th>
<th>A</th>
<th>B</th>
<th>C</th>
<th>D</th>
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<tr>
<td></td>
<td>17</td>
<td>10</td>
<td>29</td>
<td>19</td>
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**DF progression during or after P**

<table>
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<th>C</th>
<th>D</th>
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<tr>
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<td>12 (70%)</td>
<td>-</td>
<td>16 (55%)</td>
<td>4 (21%)</td>
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**Treatment after progression**

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<th>D</th>
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<tbody>
<tr>
<td></td>
<td>9 (53%)</td>
<td>-</td>
<td>8 (28%)</td>
<td>3 (16%)</td>
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**Surgery**

<table>
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<th>C</th>
<th>D</th>
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**Medical therapy**

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<th>C</th>
<th>D</th>
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<td></td>
<td>4</td>
<td>-</td>
<td>2</td>
<td>1</td>
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**Spontaneous regression**

<table>
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<th>A</th>
<th>B</th>
<th>C</th>
<th>D</th>
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<tbody>
<tr>
<td></td>
<td>1 (5%)</td>
<td>1 (10%)</td>
<td>7 (24%)</td>
<td>1 (5%)</td>
</tr>
</tbody>
</table>

- 75 women
- Group A: DF diagnosed during P
- Group B: DF diagnosed within 6 months after P
- Group C: DF was *in situ* at the time of P
- Group D: DF was resected prior to P

- DF developing prior to or during P may progress during the course of P or after
- Spontaneous regression after P is observed.
- Wait & see is an option
- DF history is not an indication for therapeutic abortion nor a contraindication against subsequent pregnancy

**References**

- ASCO 2012
- Ann Surg 2013
- Istituto Nazionale dei Tumori, Milan, Italy
- Institute Gustave Roussy, Villejuif, France
- Brigham and Women's Hospital, Dana-Farber Cancer Institute
Conclusions

- Aggressive treatments that take their indications from retrospective studies should be re-evaluated in the light of new data.

- Observation alone could be considered for primary tumors.

- In cases of RECIST progression, treatment is tailored according to age, gender, location, symptoms...in specialized team.
Thanks for your support!!!