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Medizinische Fakultät Mannheim
der Universität Heidelberg

Universitätsklinikum Mannheim

SPAEN Meeting: Desmoid Tumors

23rd of November 2012, Firenze, Italy

Update on systemic treatment options and clinical trials in desmoids

Bernd Kasper

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Background:

- Desmoid tumors describe a rare monoclonal, fibroblastic proliferation characterized by a variable and often unpredictable clinical course.
- The incidence is less than 3 % of soft tissue sarcomas and about 0.03 % of all malignancies.
- Therefore, desmoid tumors represent a rare disease with 3-4 cases/1.000.000 US citizens (**Germany:** ca. 200 new cases each year).
- Desmoids occur between the age of 15 and 60 years, but particularly during early adolescence and with a peak age of about 30 years.
- There is a correlation of desmoid tumors and the Familial Adenomatous Polyposis (FAP, Gardner Syndrome) with an incidence of 3.5-32 %.

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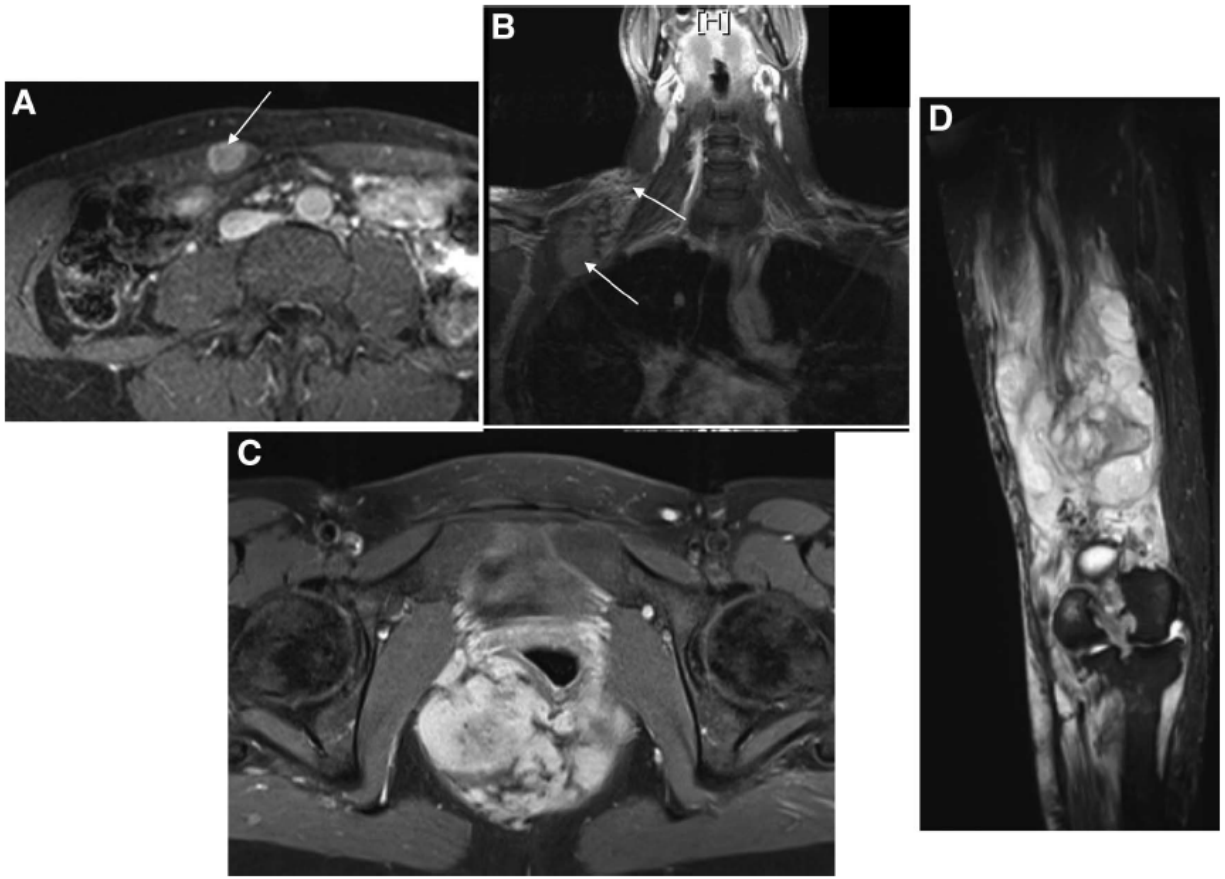
Examples: Typical localizations of desmoids including rectus abdominis muscle, head and neck, pelvis and extremities:



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Treatment Options:

- The first-line therapy for locally circumscribed, resectable desmoid tumors remains surgical resection.
- However, desmoids can often take a multiply relapsing, multifocal course and therefore not be amenable to curative surgical treatment.
- In many cases adjuvant radiotherapy or radiotherapy alone is performed. Cave: Radiation-related complications with doses above 56 Gy!!
- **Systemic treatment approaches comprise:**
  - **antihormonal therapy,**
  - **non-steroidal anti-inflammatory drugs,**
  - **chemotherapy or**
  - **tyrosine kinase inhibitors with highly variable results.**

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Antihormonal and anti-inflammatory Therapy:

- Response rates for antihormonal (e.g. tamoxifen) or anti-inflammatory drugs (e.g. sulindac, indomethacin) vary up to 50 %.
- However, there is only data from single-case reports or small series. Larger series of patients or data from clinical trials are not available.[1]
- **Indication:** Endocrine and/or NSAID therapy is often considered first-line medical treatment for unresectable, advanced disease without clinical symptoms.[2]

[1] Janinis J, Patriki M, Vini L, Aravantinos G, Whelan JS. The pharmacological treatment of aggressive fibromatosis: a systematic review. Ann Oncol 2003; 14: 181-190.

[2] Hansmann A, Adolph CV, Vogel T, Unger A, Moeslein G. High-dose tamoxifen and Sulindac as first-line treatment for desmoid tumors. Cancer 2004; 100: 612-620.

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Antihormonal and anti-inflammatory Therapy:

Table 1. Antiestrogen therapy in patients with aggressive fibromatosis: single-arm trials and case reports

Author	No. of patients	Sex	Age, range (median)	History of FAP	Primary or recurrent	Location	Hormonal agent	NSAID	Response	Response duration
Kinzbrunner et al. 1983 [26]	1	F	29	Yes	Recurrent	Multifocal	Tamoxifen 80 mg/day	No	PR	NR
Rock et al. 1984 [27]	5	NR	NR	NR	Recurrent	NR	Tamoxifen	No	2 SD, 3 PD	NR
Procter et al. 1987 [28]	1	F	26	No	Recurrent	Multifocal	Tamoxifen 40 mg/day	No	SD	14 months
Eagel et al. 1989 [29]	1	F	29	Yes	Recurrent	Mesentery	Tamoxifen 20 mg/day, megace 300 mg/day	No	SD	7 months
Sportiello and Hoogerland 1991 [30]	1	F	40	No	Recurrent	Pelvic	Tamoxifen 80 mg/day	No	CR	27 months
Thomas et al. 1990 [31]	1	F	30	No	Recurrent	Shoulder girdle	Tamoxifen 20 mg/day	No	CR	12 months
Wilcken and Tattersall 1991 [32]	2	F	40	No	Recurrent	Calf	Tamoxifen 20 mg/day	No	1 PR	8 years
		F	40	No	Primary	Mesentery	Megace 500 mg/day	No	1 PR	10 months
Brooks et al. 1992 [33]	20	15 F, 5 M	18–70 (29)	NR	12 Primary, 8 recurrent	14 Abdominal and pelvic	Toremifene 200 mg/day	No	1 CR, 10 PR, 6 SD	NR
Benson et al. 1994 [34]	1	F	17	NR	Primary	Retroperitoneum	Toremifene 200 mg/day	No	PR	9 months
Mukherjee et al. 1995 [35]	1	M	16	NR	Primary	Pelvis	Tamoxifen 20 mg/ day, prednisolone 60 mg/day	No	PR	2 years
Izes et al. 1996 [36]	1	M	54	NR	Primary	Pelvis	Tamoxifen 160 mg/day	Sulindac 300 mg/day	PR	54 months
Lackner et al. 1997 [37]	2	F	1	NR	Recurrent	Chest wall	Tamoxifen 2 mg/kg/day	Diclofenac 4 mg/kg/day	SD	4 years
		F	1.5	NR	Primary	Mandible	as above	as above	SD	1 year

55 %

CR, complete response; F, female; FAP, familial adenomatous polyposis; M, male; NR, not reported; NSAID, non-steroidal anti-inflammatory agent; PD, progressive disease; PR, partial response; SD, stable disease.

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Antihormonal and anti-inflammatory Therapy:

Review

Annals of Oncology 14: 181–190, 2003
DOI: 10.1093/annonc/mdg064

The pharmacological treatment of aggressive fibromatosis: a systematic review

J. Janinis[1]*, M. Patriki[1], L. Vini[2], G. Aravantinos[3] & J. S. Whelan[4]

[1]*Social Security Organization Oncology Center;* [2]*Athens Medical Center, Athens;* [3]*Saint Anargyri Cancer Center, Kifissia, Greece;* [4]*The London Bone and Soft Tissue Tumour Service, Meyerstein Institute of Oncology, Middlesex Hospital, London, UK*

Received 25 March 2002; revised 16 August 2002; accepted 16 September 2002

Table 3. Anti-inflammatory therapy in aggressive fibromatosis: case reports

Author	No. of patients	Sex	Age (median)	History of FAP	Primary or recurrent	Location	Anti-inflammatory treatment	Other	Response	Response duration
Tsukada et al. 1992 [48]	14	NR	29	Yes	Recurrent	Abdominal	Sulindac 300 mg/day	No	1 CR, 7 PR, 4 SD	NR
Klein et al. 1987 [23]	3	2 M, 1 F	NR	Yes	Recurrent	Abdominal wall, mesentery	Indomethacin 100 mg/day	No	2 PD, 1 SD	NR
Waddell and Kirsch 1991 [41]	8	4 F, 4 M	22–76 (39)	4 Yes, 4 No	NR	4 Mesentery	Sulindac 300–400 mg/day or indomethacin 75–300 mg/day	Warfarin	3 PR, 3 SD, 2 PD	NR
Belliveau and Graham 1984 [49]	1	M	36	Yes	Primary	Mesentery	Sulindac 200 mg/day	No	1 PR	
Dominguez-Malagon et al. 1992 [50]	3	F	30	No	Primary	Extra-abdominal	Colchicine 3 mg/day	No	PR	NR
		F	21	No	Primary	as above	as above	No	PR	NR
		M	47	No	Primary	as above	as above	No	PR	NR

CR, complete response; F, female; FAP, familial adenomatous polyposis; M, male; NR, not reported; PD, progressive disease; PR, partial response; SD, stable disease.

57 %

38 %

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Antihormonal and anti-inflammatory Therapy:

- Children's Oncology Group prospective phase II study: Evaluating high-dose **tamoxifen + sulindac** for desmoid-type aggressive fibromatosis in children[1]
- N = 61 (age < 19 years)
- Treatment schedule: tamoxifen + sulindac (each 3 mg/kg/dose daily PO BID) for 12 months, until disease progression or intolerable toxicity
- Response rate: 13 patients completed therapy without PD or withdrawal (including 4 PR and 1 CR = **8 % RR**)
- EFS at 1 year 44 %; OS at 2 years 96 %
- Safety: occasional grade 3 and three grade 4 toxicity (depression, hepatitis)
- **First prospective trial: Response rate and EFS were similar to prior results with vinblastine + methotrexate in pediatric patients.**

[1] Skapek SX, Anderson J, Raney RB et al. The safety and efficacy of high-dose tamoxifen and sulindac for desmoid-type aggressive fibromatosis in children: results of the Children's Oncology Group phase II study ARST0321. Presented at CTOS 2011, Oct. 26-28, Chicago, USA.

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Chemotherapy:

- **Indication:** Unresectable, rapidly growing and/or symptomatic and/or life threatening desmoid tumor.
- There are different chemotherapy regimens with highly variable results.
- Methotrexate / vinblastine has been evaluated in the pediatric patient population with reasonable activity and tolerable toxicity.
- However, the combination is toxic over time and adult patients generally cannot complete the recommended year of therapy.[1]
- Alternatively, the combination of methotrexate / vinorelbine can be administered and is likely much less toxic.[2]

[1] Skapek SX, Ferguson WS, Granowetter L et al. Vinblastine and methotrexate for desmoid fibromatosis in children; results of a Pediatric Oncology Group Phase II trial. J Clin Oncol 2007; 25: 501-506.

[2] Weiss AJ, Horowitz S, Lackman RD. Therapy of desmoid tumors and fibromatosis using vinorelbine. Am J Clin Oncol 1999;22:193-195.

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Chemotherapy:

- **Methotrexate/vinblastine** in a phase II trial of the Pediatric Oncology Group[1]
- N = 28 (27 eligible and 26 evaluable for response)
- Inclusion criteria: recurrent disease or not amenable to radiation or surgery
- CHT Schedule: MTX 30 mg/m²/weekly + Vbl 5 mg/m²/weekly for 26 weeks and every other week for an additional 26 weeks (1 year therapy!)
- Response rate: **5 (19 %) CR + PR** and 10 SD
- 18 pts. showed PD at a median time of 9.1 months
- Safety: neutropenia (22 pts.), anemia, nausea, vomiting
- **Combination of MTX / vinblastine can promote tumor regression or block tumor growth in most children.**

[1] Skapek SX, Ferguson WS, Granowetter L et al. Vinblastine and methotrexate for desmoid fibromatosis in children; results of a Pediatric Oncology Group Phase II trial. J Clin Oncol 2007; 25: 501-506.

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Chemotherapy:

- There is greater benefit from anthracycline based therapy regarding response rates (*compare Table*).
- In the series of de Camargo (n = 68) anthracyclines in combination with hormonal therapy demonstrated the greatest RECIST response rates.[1]
- Pegylated liposomal doxorubicin (50 mg/m²/every 4 weeks) has been reported to have significant activity with 4/11 objective responses **(RR = 36 %)** and seven stable diseases and therefore is considered treatment of choice by many investigators for refractory disease.[2]

[1] De Camargo VP, Keohan ML, D'Adamo DR, Antonescu CR, Brennan MF, Singer S, Ahn LS, Maki RG. Clinical outcomes of systemic therapy for patients with deep fibromatosis (desmoid tumor). Cancer 2010; 116: 2258-2265.

[2] Constantinidou A, Jones RL, Scurr M, Al-Muderis O, Judson I. Pegylated liposomal doxorubicin, an effective, well-tolerated treatment for refractory aggressive fibromatosis. Eur J Cancer 2009; 45: 2930-2934.

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Chemotherapy (selected regimens):

Reference	Chemotherapy regimen	Number of patients	Response	Follow-up [months]	
Patel	Doxorubicin 60-90 mg/m² + dacarbazine 750-1000 mg/m²	12	2 CR 4 PR 2 SD	28-235	50 %
Gega	Doxorubicin 20 mg/m² d1-4 + dacarbazine 150 mg d1-4, d28	7	3 CR 4 PR	33-108	100 %
Constantinidou	Pegylated liposomal doxorubicin 50 mg/m², d28	12	4 PR 7 SD	7-39	33 %
Wehl	Pegylated liposomal doxorubicin 50 mg/m², d28	4	4 PR	NR	100 %
Azzarelli	Vinblastine 6 mg/m² + methotrexate 30 mg/m², weekly	27	4 OR 19 SD	6-96	15 %
Weiss	Vinorelbine 20 mg/m² + methotrexate 50 mg/m², weekly	13	NR	< 12	
Skapek	Vinblastine 5 mg/m² + methotrexate 30 mg/m², weekly	27	8 PR 10 SD	5-37	30 %
Pilz	VAIA, VAC, cyclophosphamide + ifosfamide	19	4 CR 5 PR	NR	

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Chemotherapy:

- Chemotherapy in desmoid tumor patients: a study from the FSG[1]
- Retrospective analysis from desmoid tumor patients treated at FSG centers
- N = 62 (12 pts. with Gardner syndrome)
- Treatments: 37 pts. (55 %) received previously one or more lines of systemic treatment (44 % NSAID, 44 % antiestrogens, 31 % imatinib)
- CHT: 71 % combination CHT, 29 % single agent, 21 % anthracycline-based
- Response: 1 (2 %) CR, 12 (19 %) PR, 37 (60 %) SD and 12 (19 %) PD
- **Response rate was significantly higher for anthracycline-containing regimens: 54 % vs. 12 % (*p = 0.0011*)**
- Nonlimb location associated with improved PFS (*p = 0.03*)

[1] Garbay D, Le Cesne A, Penel N, et al. Chemotherapy in patients with desmoid tumors: a study from the French Sarcoma Group (FSG). Ann Oncol 2012; 23:182-186.

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Chemotherapy:

Protocol	Drugs
Mesna, adriamycin, ifosfamide, dacarbazine	Doxorubicin 20 mg/m^2 (day 1–day 3) Ifosfamide 2.5 g/m^2 (day 1–day 3) Dacarbazine 300 mg/m^2 (day 1–day 3) 21 days cycle
Adriamycin, dacarbazine	Doxorubicin 20 mg/m^2 (day 1–day 3) Dacarbazine 300 mg/m^2 (day 1–day 3) 21 days cycle
Metronomic etoposide	Oral etoposide 75 mg/day for 21 days of 28 days cycle
Metronomic cyclophospamide	Oral cyclophosphamide 50 mg/day for 21 days of 28 days cycle
Doxorubicin	Doxorubicin 60–75 mg/m^2 21 days cycle
Methotrexate–vinblastine	Vinblastine 6 mg/m^2 Methotrexate 30 mg/m^2 (J1, J8, 15, 21) 28 days cycle
Methotrexate	Methotrexate 30 mg/m2 (J1, J8, 15, 21) 28 days cycle
Vinorelbine	Vinorelbine 20 mg/m^2 (J1, J8) 21 days cycle

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Chemotherapy:

Table 1. Possible chemotherapy regimens for desmoid tumor patients with advanced disease

Study	Chemotherapy regimen	*n* of patients	Response	Follow-up (mos)
Patel et al. [41]	Doxorubicin, 60–90 mg/m², + dacarbazine, 750–1,000 mg/m²	12	2 CR, 4 PR, 2 SD	28–235
Gega et al. [42]	Doxorubicin, 20 mg/m², days 1–4, + dacarbazine, 150 mg, days 1–4, day 28	7	3 CR, 4 PR	33–108
Constantinidou et al. [44]	Pegylated liposomal doxorubicin, 50 mg/m², day 28	12	4 PR, 7 SD	7–39
Wehl et al. [58]	Pegylated liposomal doxorubicin, 50 mg/m², day 28	4	4 PR	NR
Azzarelli et al. [59]	Vinblastine, 6 mg/m², + methotrexate, 30 mg/m², weekly	27	4 OR, 19 SD	6–96
Weiss et al. [60]	Vinorelbine, 20 mg/m², + methotrexate, 50 mg/m², weekly	13	NR	<12
Skapek et al. [39]	Vinblastine, 5 mg/m², + methotrexate, 30 mg/m², weekly	27	8 PR, 10 SD	5–37
Pilz et al. [61]	VAIA, VAC, cyclophosphamide, + ifosfamide	19	4 CR, 5 PR	NR

Abbreviations: CR, complete response; NR, not reported; OR, objective response; PR, partial response; SD, stable disease; VAC, vincristine, actinomycin-D, and cyclophosphamide; VAIA, vincristine, doxorubicin, ifosfamide, and actinomycin-D.

No randomized trials!!

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Tyrosine kinase inhibitors - Imatinib:

- Initial data by *Mace et al. 2002*: Response in two patients with extra-abdominal aggressive fibromatosis treated with imatinib.
- In contrast to CML or GIST, in desmoids no genomic changes have been observed showing that the response to imatinib is not attributable to KIT expression.
- *Heinrich et al. JCO 2006* treated 19 patients with desmoids with 800 mg imatinib daily:
  - 3 PR and 4 SD **(RR = 16 %)**
  - No mutations of KIT, PDGFRA or PDGFRB were found
- *Penel et al. Ann Oncol 2010* presented the FNCLCC/French Sarcoma Group phase II study:
  - 3 % CR, 9 % PR and 83 % SD in 40 patients **(RR = 12 %)**
  - Non-progression rates at 3, 6, 12 months were 91, 80, 67 %
  - 2-years PFS and OS were 55 % and 95 %

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Tyrosine kinase inhibitors - Sorafenib:

- Preliminary data on the use of sorafenib have been published in 26 evaluable patients with desmoid tumors.
- The pilot non-randomized study demonstrated impressive response rates with 6/24 **(RR = 25 %)** partial responses and 17/24 (70 %) stable diseases and one patient with progressive disease and death.[1]
- Symptomatic improvement regarding pain and mobility was observed in 70 % of patients.

[1] Gounder MM, Lefkowitz RA, Keohan ML, et al. Activity of sorafenib against desmoid tumor/deep fibromatosis (DT/DF). Clin Cancer Res 2011, 17 (12): 4082-90.

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Treatment Strategies:

- However, it has not been possible to establish an optimal therapy protocol for this disease due to the lack of randomized data.
- Burning questions: - Which patients should be treated?
  - Which treatment should be selected?
  - When is the right time to start treatment?
- Obviously, multimodality treatment including surgery, radiotherapy and systemic treatment forms the basis of care for these patients.
- Considering the natural history of desmoids, a period of watchful waiting may be the most appropriate management in asymptomatic patients.
- Due to the heterogeneity of the biological behavior of desmoids, treatment should be individualized to reduce local tumor control failure with preservation of patients' quality of life.

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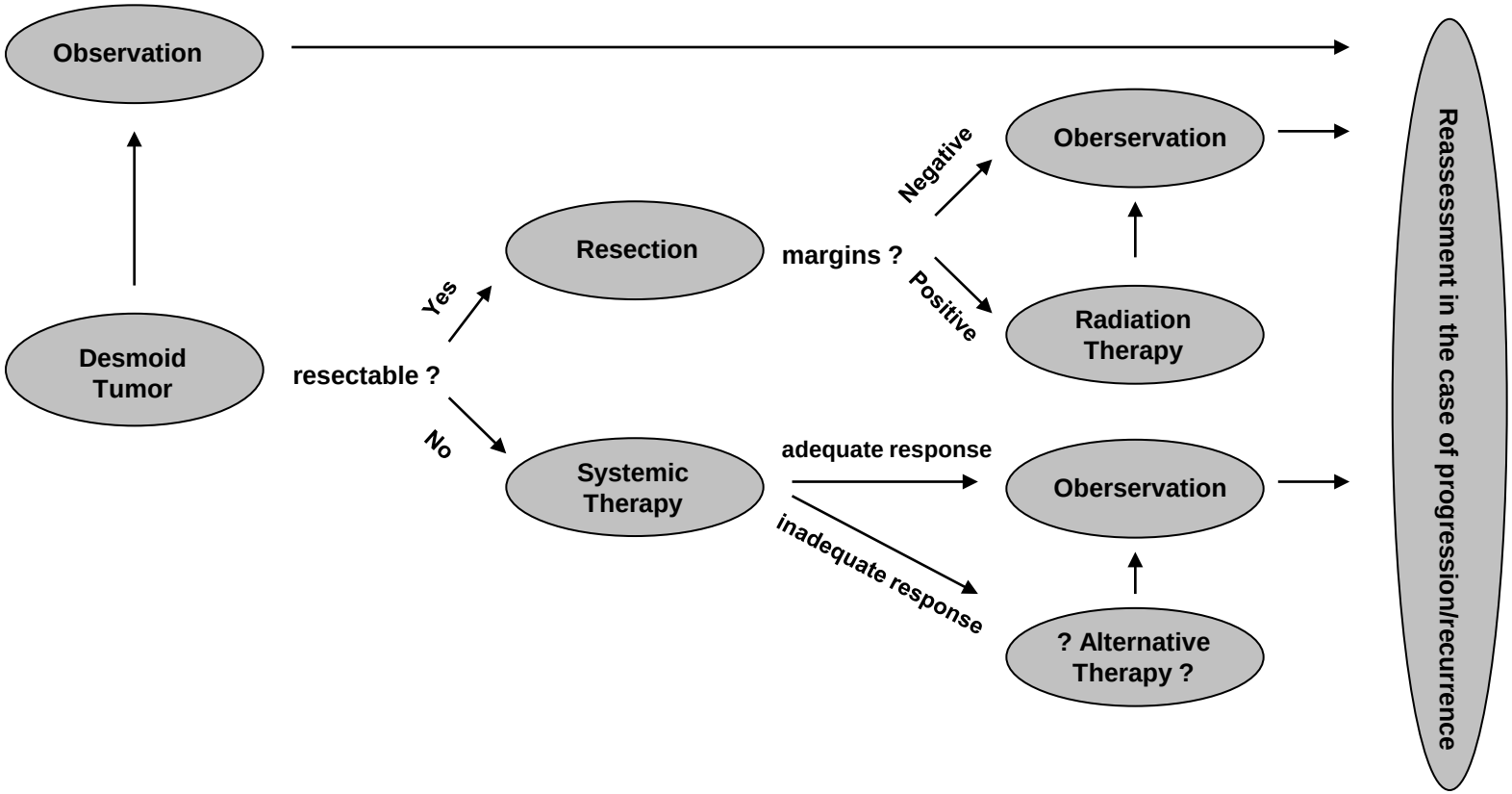
Treatment Strategies:



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Treatment Strategies:

Ann Surg Oncol (2009) 16:2587–2593
DOI 10.1245/s10434-009-0586-2

Annals of
SURGICAL ONCOLOGY
OFFICIAL JOURNAL OF THE SOCIETY OF SURGICAL ONCOLOGY

ORIGINAL ARTICLE – BONE AND SOFT TISSUE SARCOMAS

Desmoid-Type Fibromatosis: A Front-Line Conservative Approach to Select Patients for Surgical Treatment

Marco Fiore, MD[1], Françoise Rimareix, MD[2], Luigi Mariani, MD[3], Julien Domont, MD[4], Paola Collini, MD[5], Cecile Le Péchoux, MD[6], Paolo G. Casali, MD[7], Axel Le Cesne, MD[4], Alessandro Gronchi, MD[1], and Sylvie Bonvalot, MD, PhD[2]

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Lack of randomized trials and evidence-based data:

EUROPEAN JOURNAL OF CANCER 45 (2009) 2928–2929

available at www.sciencedirect.com

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journal homepage: www.ejconline.com

Editorial Comment

Management of aggressive fibromatosis: Can we unravel the maze of treatment options?

*Stefan Sleijfer**

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plored. Obviously, because of its rarity and heterogeneity, performing large studies in AF will be a major challenge. Nevertheless, it took the French Sarcoma Group one year to recruit 40 patients.[5] This clearly shows that by close collaboration in international networks it must be feasible to conduct large trials in AF. Only on the basis of such studies, it will be possible to make more evidence-based choices for AF patients.

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Phase II study to evaluate Glivec (imatinib mesylate) to induce progression arrest in aggressive fibromatosis / desmoid tumors not amenable to surgical resection with R0 intent or accompanied by unacceptable function loss (GISG-01)

Bernd Kasper
Mannheim University Medical Center
ITM - Interdisciplinary Tumor Center Mannheim
Sarcoma Unit
German Interdisciplinary Sarcoma Group (GISG)

Desmoid Study GISG-01

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Medication Intake:

- The target treatment consists of the oral intake of imatinib in a daily dose of **800 mg** (400 mg bid).
- To reach this dose level, it is permissible to initiate treatment with 400 mg imatinib daily, but the target dose of 800 mg should be reached within 4 weeks.
- For detailed information on the administration of imatinib please refer to the patient information leaflet of Novartis.

Desmoid Study GISG-01

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Amendment:

- Administration of **Nilotinib** 2 x 400 mg, if PD or intolerance under therapy with imatinib

Translational Research:

- Therapy monitoring using positron emission tomography (FDG PET) to determine early whether patients benefit from imatinib therapy or not
- Analysis of mutations in the beta-catenin gene *CTNNB1* and correlation with patients' survival (PFS)

Desmoid Study GISG-01

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Recrual Status:

- Cut-off-date 01.11.2012
- n = 25/39 in the following centers (since 07/2010):

  Mannheim n = 11
  Berlin n = 7
  Heidelberg n = 0
  Hannover n = 5
  Essen n = 2

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Currently recruiting clinical trials:

- A pilot study evaluating the use of mTOR inhibitor **Sirolimus** in children and young adults with desmoid-type fibromatosis: The purpose of the study is to explore whether mTOR inhibition may be beneficial for children and young adults with desmoid tumor (neoadjuvant Sirolimus for 28 days before surgery, n = 15, age < 30 years; Prof. Skapek, University of Chicago). ONGOING
- A phase II randomized study evaluating **Pazopanib versus Methotrexate / Vinblastine** in adult patients with desmoid tumors (DESMOPAZ): The purpose of this study is to evaluate the efficacy of pazopanib in comparison to chemotherapy with methotrexate and vinblastine in adult patients with desmoid tumors (phase II, n = …, age ≥ 18 years; Dr. Italiano, Institut Bergonié, Bordeaux). ONGOING

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Take-Home-Messages:

- Desmoid tumors represent an extremely heterogeneous disease with a natural biology varying between spontaneous regression and stabilization to rapid progression.
- The mutation status of the beta-catenin gene, *CTNNB1*, has prognostic significance and may be used to guide the therapeutic management.
- Medical treatment is indicated when local surgery is infeasible or associated with severe function loss or morbidity.
- A strategy of observation may be the most appropriate management for asymptomatic patients with a non progressive desmoid tumor.
- There is an unmet medical need for prospective and / or randomized clinical trials to gain more evidence-based data.
- There are only a few interesting clinical trials on the way, however, designing and funding studies in this rare disease remains extremely difficult.

ESMO Clinical Practice Guidelines 2012:

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desmoid-type fibromatosis

While principles for the diagnosis of STS apply also to desmoids, beta catenin mutational analysis may be useful when the pathological differential diagnosis is difficult.

Given the unpredictable natural history of the disease (with the possibility of long-lasting stable disease and even occasional spontaneous regressions, along with a lack of metastatic potential), and functional problems implied by some tumor anatomical locations, an initial watchful waiting policy can be proposed [27] [III, B], after a shared decision-making with the patient, with the exclusion of potentially life-threatening extra-abdominal locations (e.g. head and neck region), and intra-abdominal desmoids (mesenteric fibromatosis). Under such a policy, treatment is reserved for progressing cases. The preferred imaging modality is MRI, taking into consideration that the tumor signal is not meaningful with regard to the disease evolution.

For progressing cases, optimal treatment needs to be individualized on a multidisciplinary basis and it may consist of surgery (without any adjuvant therapy), radiation therapy, observation, isolated limb perfusion (if the lesion is confined to an extremity) or systemic therapy (see below) [28, 29] [V, B]. Systemic therapies include: hormonal therapies (tamoxifen, toremifene, Gn-RH analogues), nonsteroidal anti-inflammatory drugs; low-dose chemotherapy, such as methotrexate + vinblastine or methotrexate + vinorelbine; low-dose interferon; imatinib; sorafenib; full-dose chemotherapy (using regimens active in sarcomas, including liposomal doxorubicin). It is reasonable to employ the less toxic therapies before the more toxic ones in a stepwise fashion.

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More to read …

The Oncologist®
Sarcomas

Desmoid Tumors: Clinical Features and Treatment Options for Advanced Disease

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Key Words. Aggressive fibromatosis • Desmoid tumor • Advanced disease • β-catenin • Individualized treatment

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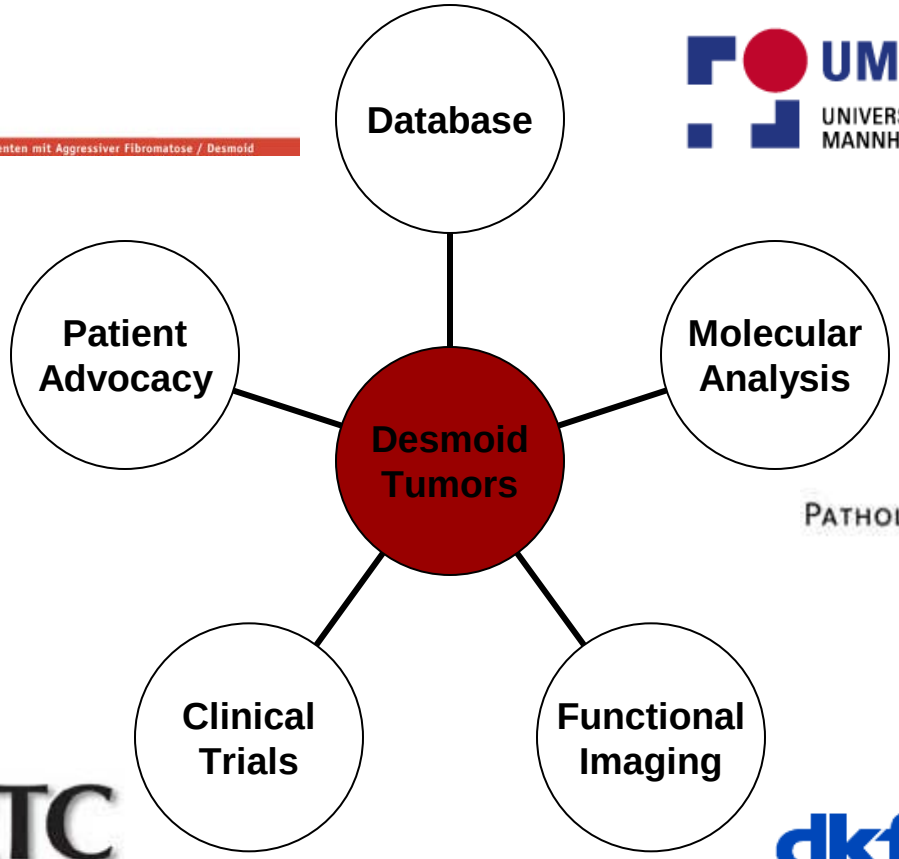

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Questions?