THELANCETCHILDADOL-D-17-00119R2
S2352-4642(17)30045-7
Embargo: September 7, 2017—23:30 (BST)
Doctopic: Primary Research

The EpSSG NRSTS 2005 treatment protocol for desmoid-type fibromatosis in children: an international prospective case series

Daniel Orbach, Bernadette Brennan, Gianni Bisogno, Max Van Noesel, Véronique Minard-Colin, Julia Daragjati, Michela Casanova, Nadege Corradini, Ilaria Zanetti, Gian Luca De Salvo, Anne Sophie Defachelles, Anna Kelsey, Myriam Ben Arush, Nadine Francotte, Andrea Ferrari

Summary

Background In 2005, the European Pediatric Soft Tissue Sarcoma Study Group (EpSSG) proposed a conservative treatment algorithm—consisting of an initial wait-and-see strategy, non-mutilating surgery, and minimal-morbidity chemotherapy (in the case of tumour progression)—for paediatric patients with desmoid-type fibromatosis. We aimed to investigate the outcomes of this algorithm.

Methods In this case series, patients (<25 years) with desmoid-type fibromatosis from 57 centres in eight countries were prospectively registered through a web-based system. Diagnosis was based on histological analysis of the tumour specimen after biopsy or surgery, and we classified patients by tumour site, clinical stage (TNM system), and post-surgical stage (Intergroup Rhabdomyosarcoma Study system). Progression-free survival was defined as the time from diagnosis until disease progression (clinical or radiological progressive disease, relapse, or death from any cause).

Findings From Oct 1, 2005, to July 31, 2016, 173 patients (median age 11·4 years [IQR 4·0–14·1], 88 [51%] male patients) were registered. After excluding patients with missing data, 54 (35%) patients had no immediate therapy (wait-and-see strategy), 47 (31%) had immediate surgery, and 53 (34%) had immediate chemotherapy after diagnosis. 5-year progression-free survival was 36·5% (95% CI 27·8–45·2) overall, 26·7% (14·2–41·0) in the wait-and-see group, 41·2% (25·8–55·9) in the surgery group, and 42·8% (27·2–57·6) in the chemotherapy group (overall log-rank p=0·17; wait-and-see *vs* surgery p=0·12; wait-and-see *vs* chemotherapy p=0·13). In multivariable analysis, large tumour size (>5 cm) was associated with worse progression-free survival (hazard ratio 2·25, 95% CI 1·34–3·76; p=0·0021). Apart from one patient in the chemotherapy group who died from a secondary tumour (head and neck anaplastic embryonal rhabdomyosarcoma), all patients were alive at the time of analysis. 13 (8%) patients had biopsy only (no further treatment), 65 (42%) had chemotherapy only, 31 (20%) had surgery only, 36 (23%) had both chemotherapy and surgery, and nine (6%) had radiotherapy in addition to other therapies.

Interpretation In paediatric patients with desmoid-type fibromatosis, the EpSSG conservative strategy did not compromise outcomes and could be adopted to reduce treatment burden.

Funding S Wisnia and la Città della Speranza Foundation.

Introduction

Desmoid-type fibromatosis is a rare, monoclonal, proliferative, soft tissue lesion that arises from the deep fascia or soft tissues derived from mesenchymal stem cells, and has an incidence of 0·2–0·4 per 100 000 people per year in the USA. This tumour is classified in the group of "fibroblastic/myofibroblastic tumours with intermediate malignancy, locally aggressive"; it has a tendency to recur locally after therapy but distant metastases are rare.[1] This tumour is usually solitary, but in 3% of cases it can be multifocal.[2] The cause is unknown, but desmoid-type fibromatosis might be associated with trauma and familial adenomatous polyposis coli (APC).[1,3,4] Sporadic disease is mainly due to a pathogenic somatic mutation in *CTNNB1*, which encodes β-catenin. As desmoid-type fibromatosis is frequently locally invasive, complete initial resections are successful in only 6–25% of children,[2,5,6] and local relapse is common (21–64%).[2,5–8] Despite its locally aggressive behaviour, prolonged stabilisation and regression without therapy have been reported.[9] Surgery has been hypothesised to stimulate the onset and growth of desmoid-type fibromatosis, possibly because growth factors released during the initial phase of wound healing might promote β-catenin activation to genetically altered cells during soft tissue repair mechanisms.[10–13] Results from a retrospective study[10] in adults showed that some patients can be managed with a non-aggressive surgical approach and a watch-and-wait strategy at diagnosis, and that in selected cases therapy might be considered only at the time of tumour progression. In children, the availability of relatively effective drugs is shifting the treatment focus from aggressive surgery to a multidisciplinary approach that takes the functional and cosmetic outcomes into account.[11,14]

In 2005, the European Pediatric Soft Tissue Sarcoma Study Group (EpSSG) developed treatment algorithms for desmoid-type fibromatosis within the protocol dedicated to non-rhabdomyosarcoma soft tissue

Lancet Child Adolesc Health 2017
Published Online
September 7, 2017
http://dx.doi.org/10.1016/S2352-4642(17)30045-7
See Online/Comment
http://dx.doi.org/10.1016/PII

SIREDO Oncology Center (Care, Innovation and Research for Children, Adolescents and Young Adults with Cancer), Institut Curie, Paris, France (D Orbach MD); **Department of Paediatric Oncology** (B Brennan MD) **and Department of Diagnostic Paediatric Histopathology** (A Kelsey MD), **Royal Manchester Children's Hospital, Manchester, UK; Pediatric Hematology and Oncology Division, Padova University, Padova, Italy** (Prof G Bisogno PhD); **Princess Maxima Center for Pediatric Oncology, Utrecht, Netherlands** (M Van Noesel MD); **Department of Paediatric and Adolescent Oncology, Gustave-Roussy, Villejuif, France** (V Minard-Colin PhD); **Clinical Trials and Biostatistics Unit, IRCCS Istituto Oncologico Veneto, Padova, Italy** (J Daragjati PhD, I Zanetti MSc, G L De Salvo MD); **Pediatric Oncology Unit, Fondazione IRCCS Istituto Nazionale Tumori, Milano, Italy** (M Casanova MD, A Ferrari MD); **Institut d'Hematologie et d'Oncologie Pediatrique, Centre Leon Berard, Lyon, France** (N Corradini MD); **Pediatric Oncology Department, Centre Oscar Lambret, 59020 Lille, France** (A S Defachelles MD); **Pediatric Department, Rambam Health Care Campus Haifa, Israel** (Prof M Ben Arush PhD); **and Department of Pediatrics, CHC-Clinique Esperance, Montegnee, Belgium** (N Francotte MD)

Correspondence to:
Dr Daniel Orbach, SIREDO Oncology Center (Care, Innovation and Research for Children, Adolescents and Young Adults with Cancer), Institut Curie, 75005 Paris, France
daniel.orbach@curie.fr

Research in context

Evidence before this study

Desmoid-type fibromatosis is a rare, monoclonal, proliferative, soft tissue lesion. It is usually locally invasive, complete initial resections are rarely possible, and local relapses are frequent. This type of tumour is frequently solitary but sometimes might be multifocal. Although surgical resection has been the main standard of care, it has been suggested to stimulate the growth and onset of desmoid tumours, possibly because growth factors released during the initial phase of wound healing might transmit signals that promote β-catenin activation to genetically altered cells during soft tissue repair mechanisms. In 2005, the European Paediatric Soft Tissue Sarcoma Study Group (EpSSG) developed a conservative treatment algorithm based on non-mutilating surgery and a wait-and-see strategy, and minimal-morbidity systemic chemotherapy in the case of progression, for paediatric patients (≤25 years) with desmoid-type fibromatosis.

Added value of this study

This study represents the first large, prospective, international study for paediatric patients with desmoid-type fibromatosis and shows that large collaborative studies of rare tumours in paediatric patients are feasible. We showed that an initial wait-and-see strategy did not compromise outcomes when compared with a more aggressive surgical approach. Notably, with this conservative strategy more than half of the patients avoided surgery (and its sequelae) and radiotherapy. Of the systemic treatments used, best responses were seen with methotrexate and vinblastine or methotrexate and vinorelbine.

Implications of all the available evidence

A conservative strategy is preferable in paediatric desmoid-type fibromatosis. Surgery should be avoided as much as possible and medical therapies should be used in cases of tumour progression after an observation period.

For more on **EpSSG** see http://www.epssgassociation.it

sarcomas (EpSSG NRSTS 2005) for paediatric patients (aged ≤25 years). The aim was to recommend a uniform treatment with a conservative approach—ie, non-mutilating surgery or a wait-and-see strategy—for patients with desmoid-type fibromatosis, and minimal-morbidity systemic chemotherapy in the case of progression. In this study, we aimed to investigate the outcomes of this treatment approach.

Methods

Study design and participants

Patients with desmoid-type fibromatosis aged 25 years or younger from 57 centres in eight countries (France, Italy, UK and Ireland, The Netherlands, Israel, Belgium, Spain, and Czech Republic) were prospectively registered in the EpSSG Remote Data Entry database (CINECA, Casalecchio sul Reno, Bologna, Italy) through a web-based system. This arbitrary cutoff age was uniform in all the EpSSG non-rhabdomyosarcoma soft tissue sarcoma protocols.[15] Data included in the electronic case report forms were checked by a local oncologist and validated by the national coordinator of each country. The EpSSG study board prepared and reviewed these electronic case report forms every 6 months, and the International Data Center requested data amendment from individual study centres in case of inconsistent data (appendix). We used a web system for all aspects of data management, and the International Data Center (Istituto Oncologico Veneto IRCCS, Padua, Italy) managed system access in collaboration with the national data centres of each participating country. Each national coordinator, in collaboration with their national data centre, was responsible for the data validation process for their country. The complete protocol (available upon request) and more details of the study are available on the EpSSG website and the appendix.

For more on the **rules established by the European Parliament** see https://ec.europa.eu/health/sites/health/files/files/eudralex/vol-1/dir_2001_20/dir_2001_20_en.pdf

See **Online** for appendix

We classified patients by tumour site[16] and defined clinical staging using the TNM system: T1 or T2 according to the invasion of contiguous organs and N0 or N1 according to the presence of lymph node. We assessed lymph node involvement clinically or by MRI or CT. We defined postsurgical staging according to the Intergroup Rhabdomyosarcoma Study (IRS) grouping system:[17] group I was initial complete resection, with free histological margins (corresponding to the so-called R0 resection); group II was microscopic residual disease (R1 resection); and group III was macroscopic residual disease after surgery (R2 resection) or biopsy (unresected disease).

Diagnosis was based on histological analysis of the tumour specimen after biopsy or surgery.1 In difficult cases, tumours were prospectively reviewed in real time at diagnosis by a national or international panel of at least four members from the EpSSG Pathology Committee. Molecular analysis to identify the presence of CTNNB1 somatic mutation was recommended, and if this mutation was absent, constitutional analysis of the APC gene was suggested.18,19 Institutional ethics board approval was obtained for all participating centres according to the rules established by the European Parliament. Written consent for treatment and use of data was obtained from parents or guardians according to local research ethics requirements.

Procedures

After diagnosis, if the primary tumour was in a non-threatening site, then the first approach was to consider a wait-and-see strategy to understand tumour growth (figure 1). Even when the lesion appeared to be operable with no risk to vital structures, surveillance was recommended after biopsy. In this case, we recommended

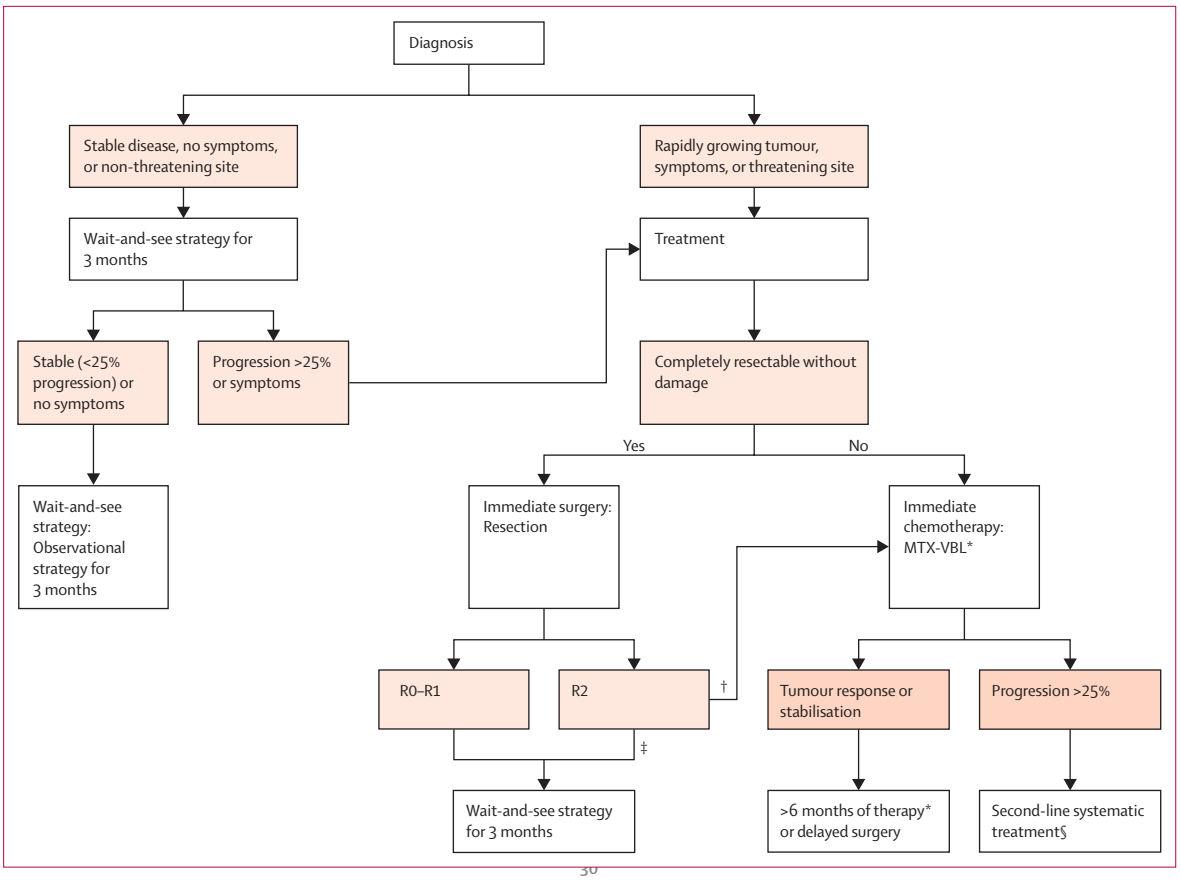


Figure 1: **EpSSG treatment algorithm for paediatric patients with desmoid-type fibromatosis**
EpSSG=European Pediatric Soft Tissue Sarcoma Study Group. MTX-VBL=methotrexate and vinblastine. R0=complete resection. R1=microscopic residue. R2=biopsy or macroscopic residue. *6 months of chemotherapy with full doses, followed by 6 months of spacing the administration to every 2 weeks. †In case of progressive residue. ‡In the absence of disease progression. §See table 1.

clinical and radiological assessments with local MRI every 3–4 months for the first 2 years, then less frequently (every 4 months for 1 year, then every 6 months for 2 years). However, front-line treatment (methotrexate and vinblastine [MTX-VBL]; table 1)[2,5,14,20] was proposed in life-threatening cases or organ function-threatening situations, for severe symptoms associated with tumour growth, or for rapid and clinically significant tumour progression (>25–30% increase in volume). Tumour resection was considered only in the case of expected R0 resection without mutilation.

We proposed chemotherapy for 6 months with full doses, followed by 6 months of spacing the administration to every 2 weeks. The aim was either tumour shrinkage to allow subsequent resection or prolonged tumour stabilisation without any further local therapy. In patients receiving chemotherapy, we proposed two further options after tumour control: delayed resection (when complete and non-mutilating surgery was considered feasible) after chemotherapy response or stop therapy after 12 months followed by a new wait-and-see strategy.

No adjuvant systemic therapy was recommended after complete or microscopically incomplete resection at first approach or after delayed surgery; it was only considered after macroscopically incomplete resection. Consequently, we proposed careful surveillance, with chemotherapy only in the case of marked progression of the residual tumour.

In the case of further local recurrence after first-line therapy, we considered various second-line systemic therapies (table 1). Additional surgery was considered acceptable if it was likely to be complete and non-mutilating; radiotherapy was discouraged and considered only after failure to respond to several lines of chemotherapy and in the case of progression despite multiple surgeries to avoid further surgery that might cause mutilation. Recommended radiotherapy doses (total 50 Gy for microscopically complete resection and 55 Gy for macroscopic residual disease) were based on previous reports for the treatment of paediatric and adult patients.[21,22]

Outcome assessment

In patients with measurable disease, we assessed response to chemotherapy every 3–4 months on the basis of radiologically identified tumour volume reduction: complete response (ie, complete disappearance of the visible tumour with no residual disease), major partial

	Doses	Route	Schedule
Methotrexate and vinblastine (MTX-VBL)	Methotrexate 30 mg/m² and vinblastine 6 mg/m² (maximum 10 mg) on day 1	Intravenous	Once a week
Methotrexate and vinorelbine (MTX-VNR)	Methotrexate 30 mg/m² and vinorelbine 20 mg/m² on day 1	Intravenous	Once a week
Ifosfamide, vincristine and dactinomycin (IVA)	Ifosfamide 3 g/m² per day on days 1–2; vincristine 1·5 mg/m² (maximum 2 mg) and dactinomycin 1·5 mg/m² (maximum 2 mg) on day 1	Intravenous	Every 3 weeks
Vincristine, dactinomycin and cyclophosphamide (VAC)	Vincristine 1·5 mg/m² (maximum 2 mg) on days 1, 8, and 15; dactinomycin 1·5 mg/m² (maximum 2 mg) and cyclophosphamide 1·2 g/m² on day 1	Intravenous	Every 3 weeks
Vincristine and dactinomycin (VA)	Vincristine 1·5 mg/m² (maximum 2 mg) on days 1, 8, and 15; dactinomycin 1·5 mg/m² (maximum 2 mg) on day 1	Intravenous	Every 3 weeks
Tamoxifen	5 mg twice a day if younger than 10 years, or 10 mg twice a day if 10 years or older	Oral	Daily
Non-steroidal anti-inflammatory drugs			
Sulindac	4 mg/kg twice a day (maximum dose 100–200 mg twice daily)	Oral	Daily
Celecoxib	4 mg/kg twice a day (maximum dose 100 mg twice daily)	Oral	Daily
Hydroxyurea	20 mg/kg per day to start, then after 2 weeks increase to 30 mg/kg per day	Oral	Daily

Table 1: **Chemotherapy regimens**

response (reduction by 66–99%), minor partial response (reduction by 34–65%), stable disease (reduction by <33% or progression by <33%), and progressive disease (>33% increase in tumour volume).[23] We analysed the proportion of patients who achieved an objective response to specific regimens of chemotherapy (ie, complete response, major partial response, and minor partial response). Only tumour progression of more than 33% was considered as treatment failure and second-line treatment was suggested.

For desmoid-type fibromatosis, treatment failure might occur without clear evidence of tumour progression or relapse, and symptom control could also inform the need to consider alternative treatments. Therefore, we considered both event-free survival (time from diagnosis to an event, [defined as clinical or radiological progressive disease, relapse, death from any cause], or any event [eg, pain, threatening site, or physician's choice] that caused a change of the therapeutic strategy) and progression-free survival (time from diagnosis to disease progression, defined as clinical or radiological progressive disease, relapse, or death from any cause). Patients who had not had an event or a progression by the end of the study were censored at the date of last observation. Local control was defined as disappearance of all radiological signs of disease at the primary tumour site or stable residual radiographic images for at least 6 months after completion of treatment.

Statistical analysis

Data from the Remote Data Entry system were analysed at the International Data Center. We constructed survival curves by the Kaplan-Meier method and used survival multivariable analysis with the Cox proportional hazard regression method to investigate the effect of sex, age (≤10 years or >10 years), *CNTTB1* mutation (absent or present), IRS group (I, II, or III), and tumour size (≤5 cm *vs* >5 cm) on progression-free survival. A stepwise variable selection procedure was applied to the covariates with a p value of at least 0·25 in the univariate analysis. We calculated hazard ratios (HRs) with 95% CIs according to the Wald method. We did all data analyses with the SAS statistical package (version 9.4).

Role of the funding source

The funder of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Results

From Oct 1, 2005, to July 31, 2016, 173 patients with desmoid-type fibromatosis (median age at diagnosis 11·4 years, IQR 4·0–14·1, range 0·1–24·2; figure 2) were registered. Two patients had a familial history of desmoid-type fibromatosis and ten patients had a familial history of early colonic cancers (table 2). Previous local trauma preceded desmoid-type fibromatosis in 12 patients (7%; table 2). The most common primary tumour site was the limbs (78 [45%] patients); tumours were multifocal in ten patients (6%) and were larger than 5 cm in 106 (65%) of 164 patients (data missing from nine patients; table 2). At the time of diagnosis, pain in the tumour was reported in 42 (27%) of 155 patients (table 2).

Details of the first therapy received were not specified for 19 patients; therefore, they were not considered further in the outcome analysis. Of the 154 patients with outcome data, somatic *CTNNB1* exon 3 mutation was analysed in 51 patients and was present in 37 (73%; table 3). Germline *APC* mutation was only analysed in 17 patients and was present in four (24%) patients (table 2). Three of these four patients were also analysed for somatic *CTNNB1* exon 3 mutation, of whom one had the somatic mutation. Of the ten patients (six girls and four boys) presenting with multifocal synchronous

tumours at diagnosis (IRS stage IIIa), two had previous trauma. One of these patients had a family history of desmoid-type fibromatosis, and the father of the other patient had early colonic cancer. Of the four patients with a germline *APC* mutation, two had fathers who also had a germline *APC* mutation (screening only done in three families). Family history was not available for all patients, especially for patients registered at the beginning of the study, and it was not compulsory to add them to the Remote Data Entry system.

Of 154 patients included in the analysis, a wait-and-see approach was chosen for 54 patients (table 2). Among them, 13 patients did not receive any treatment and no tumour events occurred after a median follow-up of 21·4 months (IQR 11·3–45·1); nine of these patients had tumour stabilisation and four had spontaneous regression. In 41 patients, after a median observation period of 6·1 months (3·7–11·0), treatment was started because of tumour progression (n=32; 19 with radiological progressive disease, 11 with clinical progressive disease, and two with both) or because of increasing symptoms or functional impairment (n=9). Systemic first-line treatments given were MTX-VBL (n=24), methotrexate and vinorelbine (MTX-VNR; n=5), non-steroidal anti-inflammatory drugs (NSAIDs; n=7), or vincristine and dactinomycin (VA; n=1). Four patients had surgery only. The median duration of first-line therapy was 11·9 months (IQR 6·4–15·2). After chemotherapy, two patients had delayed surgery and two had radiotherapy. Overall, five patients needed more than one line of therapy. Among the 41 patients who had treatment, after a median follow-up of 57·8 months (IQR 38·9–76·7) 20 patients had a stable residual tumour mass, nine patients had complete response and were off therapy, seven patients were still having therapy at the time of the analysis, four patients had progressive disease, and one patient was lost to follow-up and still had desmoid-type fibromatosis residue at last contact. At 5 years, event-free survival was 16·5% (95% CI 6·8–29·8) and progression-free survival was 26·7% (95% CI 14·2–41·0; figure 3), and all patients were alive. The total burden of therapy for this group was biopsy only (13 [24%] patients), chemotherapy only (32 [59%]), surgery only (three [6%]), chemotherapy with surgery (four [7%]), and radiotherapy with or without other therapies (two [4%]).

47 (31%) patients had immediate surgery after diagnosis (table 2). 20 of them had complete resection and 27 had microscopic residue. 37 patients had tumorectomy, seven had wide tumour resection, and three had other types of resection (limited diaphragm excision, limited abdominal wall excision, or extensive chest wall extension). Overall, local relapse occurred in 25 patients. 21 patients received no further therapy and were still in observation at the time of analysis (including one patient with local relapse). 26 patients received additional therapies (24 because of local relapse and two because of physician decisions), which included systemic therapy (15 patients after a median delay of 11·4 months [IQR 7·8–16·8]), another surgery (three patients after a median delay of 23 months [9·3–25·2]), or both (six patients). Two patients additionally received radiotherapy after surgeries with or

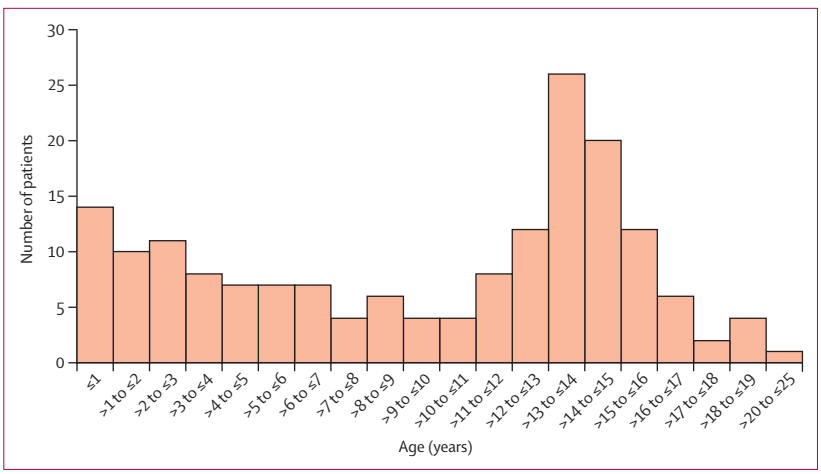


Figure 2: **Age distribution of patients**

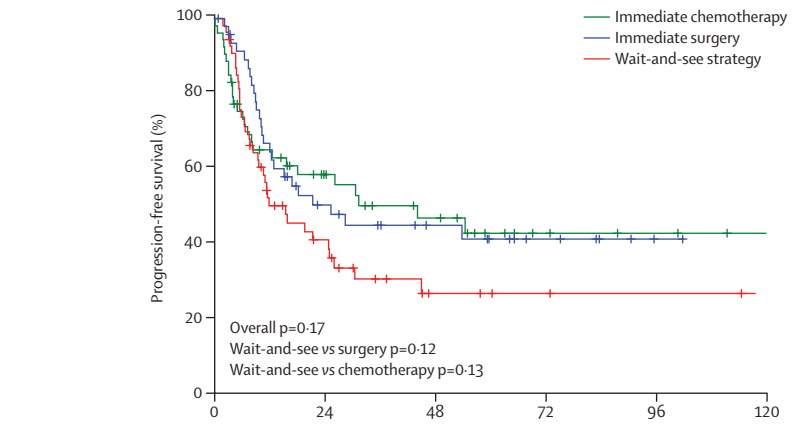
	Patients with outcome data (n=154)*			Entire cohort (n=173)
	Wait-and-see strategy (n=54)	Immediate surgery (n=47)	Immediate chemotherapy (n=53)	
Sex				
Male	28/54 (52%)	21/47 (45%)	29/53 (55%)	88/173 (51%)
Female	26/54 (48%)	26/47 (55%)	24/53 (45%)	85/173 (49%)
Familial history of desmoid-type fibromatosis	1/49 (2%)	0	1/46 (2%)	2/150(1%)
History of early colonic cancers	3/47 (6%)	6/45 (13%)	1/40 (3%)	10/140 (7%)
Germline APC mutation (presence/analyses done)	1/9	1/3	2/5	4/19 (21%)
Previous trauma	5/50 (10%)	0	5/49 (10%)	12/173 (7%)
Tumour size larger than 5 cm	35/54 (65%)	22/42 (52%)	37/51 (72%)	106/164 (65%)
Pain	14/49 (29%)	11/44 (22%)	15/51 (29%)	42/155 (27%)
Tumour stage				
T1	31/51 (61%)	33/46 (72%)	29/53 (55%)	105/168 (63%)
T2	20/51 (39%)	13/46 (27%)	24/53 (45%)	63/168 (38%)
Primary site				
Limbs	23/54 (43%)	22/47 (47%)	27/53 (51%)	78/173 (45%)
Other (trunk)	18/54 (33%)	12/47 (26%)	10/53 (19%)	49/173 (28%)
Head and neck	13/54 (24%)	13/47 (28%)	16/53 (30%)	45/173 (26%)
Not specified	0	0	0	1/173 (1%)
Multifocal	3/54 (6%)	1/47 (2%)	5/53 (9%)	10/173 (6%)
IRS stage				
Stage I	0	20/47 (43%)	0	24/173 (14%)
Stage II	0	27/47 (57%)	0	27/173 (16%)
Stage III	54/54 (100%)	0	53/53 (100%)	122/173 (71%)

Data are n/N (%), unless otherwise stated. IRS=Intergroup Rhabdomyosarcoma Study. *19 patients did not have outcome data and were excluded from the outcome analysis.

Table 2: **Patient characteristics, by first treatment received**

	n (%)
Nuclear β-catenin immunostaining (n=98)	
Positive	68 (69%)
Negative	25 (26%)
Uncertain	5 (5%)
Cytoplasmic β-catenin immunostaining (n=81)	
Positive	58 (72%)
Negative	20 (25%)
Uncertain	3 (4%)
***CTNNB1* exon 3 mutation (n=51)**	
Presence	37 (73%)
Absence	14 (27%)

Table 3: **β-catenin immunostaining and CTNNB1 exon 3 mutations in patients with complete data (n=154)**



Number at risk (number censored)						
Immediate chemotherapy	53 (0)	22 (10)	14 (14)	5 (22)	3 (24)	1 (26)
Immediate surgery	47 (0)	19 (6)	12 (11)	6 (16)	1 (21)	0 (22)
Wait-and-see strategy	54 (0)	17 (7)	5 (14)	3 (16)	2 (17)	0 (18)

Figure 3: **Progression-free survival**
The p values are the log-rank test values.

without chemotherapy. Overall, 21 patients received chemotherapy (15 received MTX-VBL, two received MTX-VNR, two received NSAIDs, one received VA, and one received VNR plus oral cyclophosphamide). The median duration of first-line chemotherapy was 11·9 months (6·9–13·2, range 2·7–31·6 months) for 19 patients. For two patients, chemotherapy treatment was still ongoing at the time of the last analysis. The median follow-up duration was 58·3 months (35·8–86·7), and all patients were alive at the time of the last analysis. At 5 years, event-free survival was 36·8% (95% CI 22·1–51·6) and progression-free survival was 41·2% (95% CI 25·8–55·9; figure 3). The total burden of therapy for this group was initial surgery only (21 [45%] patients), multiple surgeries (three [6%]), initial surgery plus chemotherapy (15 [32%]), initial surgery plus chemotherapy and additional surgeries (six [13%]), and initial surgery plus radiotherapy with or without other therapies (two [4%]).

After diagnosis, 53 patients (34%) received immediate chemotherapy (table 2). Therapeutic decisions were mainly based on having a tumour in a threatening site (n=23), rapid tumour progression (n=18), isolated pain (n=8), or other reasons (n=4). The first-line regimens administered were MTX-VBL (n=32), MTX-VNR (n=11), NSAIDs (n=4), tamoxifen (n=1), tamoxifen-diclofenac (n=2), VA (n=2), and vinblastine (n=1). The median duration of first-line chemotherapy was 10·8 months (IQR 5·5–12·4) for 51 patients; two patients were still on therapy at the time of the last analysis. 11 patients had local progression after the end of the initial therapy and started various second-line treatments. 52 of 53 patients were alive at the time of the last analysis: 13 had complete response and were off therapy, eight were still on therapy, five had progressive disease or relapse, and 25 had residual mass under surveillance, and one was lost to follow-up and had complete response at last contact. One patient developed a head and neck anaplastic embryonal rhabdomyosarcoma as a secondary tumour after receiving therapy for parameningeal desmoid-type fibromatosis and this death was related to secondary malignancy; both tumours were reviewed and confirmed by the international panel. The median follow-up duration was 44·5 months (23·8–71·7). At 5 years, event-free survival and progression-free survival were both 42·8% (95% CI 27·2–57·6; figure 3). The total burden of therapy for this group was exclusive chemotherapy (32 [60%] patients), initial chemotherapy with additional surgery (16 [30%]), and chemotherapy plus radiotherapy with or without other therapies (5 [10%]).

For the whole population, 5-year event-free survival was 31·8% (95% CI 23·6–40·3) and 5-year progression-free survival was 36·5% (95% CI 27·8–45·2). In the univariate analysis, sex (p=0·59), *CTNNB1* mutation (p=0·86), and IRS group (p=0·24) did not affect progression-free survival (appendix). 5-year progression-free survival was higher in children younger than 10 years (43·9 [95% CI 30·8–56·3] *vs* 30·3 [19·5–41·8] in those >10 years; p=0·043) and those with small tumours (59·6% [43·1–72·7] for ≤5 cm *vs* 25·6% (16·1–36·1) for >5 cm; p=0·0016; appendix). In the multivariable analysis, only large tumour size (>5 cm) had a significant association with worse progression-free survival (HR 2·25, 95% CI 1·34–3·76; p=0·0021; appendix). Overall, 65 (42%) of 154 patients with desmoid-type fibromatosis were treated with chemotherapy only, 31 (20%) patients with surgery only, 36 (23%) with both chemotherapy and surgery, and nine (6%) with radiotherapy in addition to other therapies. 13 (8%) patients had a biopsy without any further therapy.

Response to chemotherapy was assessable for 109 patients (38 patients after initial wait-and-see strategy, 20 after initial surgery, and 51 in the first chemotherapy group; table 4). Two (2%) patients had complete response, ten (9%) had major partial response, 26 (24%) had minor partial response, 49 (45%) had stable disease, and 22 (20%) had progressive disease. Overall,

38 (35%) patients responded to chemotherapy, and 49 (45%) achieved tumour stabilisation after systemic treatment. The proportion of patients who achieved a major or minor partial response to MTX-VBL or MTX-VNR after the initial wait-and-see strategy was 17 (57%) of 30 patients in total and after initial chemotherapy was 14 (33%) of 42 patients (table 4).

	Complete response	Major partial response	Minor partial response	Stable disease	Progressive disease
MTX-VBL					
Wait-and-see strategy	..	5	9	8	2
Initial surgery	..	1	3	9	1
Initial chemotherapy	..	1	8	14	8
Specific response	..	7/69 (10%)	20/69 (29%)	31/69 (45%)	11/69 (16%)
MTX-VNR					
Wait-and-see strategy	..	1	2	2*	1
Initial surgery	..	1	..	1	..
Initial chemotherapy	..	1	4	4	2
Specific response	..	3/19 (16%)	6/19 (32%)	7/19 (37%)	3/19 (16%)
Non-steroidal anti-inflammatory drugs with or without tamoxifen					
Wait-and-see strategy	..	..	..	4	2
Initial surgery	..	..	..	1	1
Initial chemotherapy	..	..	..	2	4
Specific response	..	..	..	7/14 (50%)	7/14 (50%)
VA					
Wait-and-see strategy	..	..	..	1	..
Initial surgery	1	..	..	..	..
Initial chemotherapy	..	..	..	2	..
Specific response	1/4 (25%)	..	..	3/4 (75%)	..
Other drugs†					
Wait-and-see strategy	..	..	..	1	..
Initial surgery	..	..	..	..	1
Initial chemotherapy	1	..	..	..	..
Specific response	1/3 (33%)	..	..	1/3 (33%)	1/3 (33%)
Overall response	2 (2%)	10 (9%)	26 (24%)	49 (45%)	22 (20%)

Initial therapeutic strategy was determined at diagnosis or after tumour progression. Data are n or n/N (%). MTX-VBL=methotrexate and vinblastine. MTX-VNR=methotrexate and vinorelbine. VA=vincristine and dactinomycin. *One patient had concomitant non-steroidal anti-inflammatory drugs given at the same time as MTX-VNR or as second-line treatment. †Other drugs included vinorelbine and cyclophosphamide, vinblastine alone, and tamoxifen alone (one case each).

Table 4: **Evaluable tumour response to specific chemotherapy regimens, by initial therapeutic strategy**

Discussion

We described results of the conservative therapeutic approach in the EpSSG NRSTS 2005 protocol for paediatric patients with desmoid-type fibromatosis. To our knowledge, this study represents the first large, prospective, international study for paediatric patients with this tumour type. Our experience shows that large, prospective, collaborative studies in paediatric patients with rare tumours can be undertaken at the European level. The overall compliance of participating centres was high (eg, systematic resection at diagnosis was avoided in more than two-thirds of the patients and minimal-morbidity chemotherapy was chosen as first therapy in many cases). We showed that a wait-and-see strategy had similar outcomes for patients with desmoid-type fibromatosis compared with a more aggressive surgical approach. Previous studies[7,22,24] recommended immediate initial tumour resection in all cases after diagnosis and indicated chemotherapy or radiotherapy only in case of recurrence or inoperable tumours. By contrast, we showed that initial observation of the tumour might be a good way to select patients who need therapy; therefore, we propose to deliver therapies only in case of rapidly progressive tumours. Although the three therapeutic groups (initial surgery, initial wait-and-see strategy, and initial chemotherapy) were not comparable in terms of tumour characteristics and therapy received, the outcome was similar. Only a prospective randomised study, which would have treatment groups with comparable tumour and other characteristics at baseline, would fully answer this question. A non-inferiority trial would be the ideal design to inform a definitive consensus regarding the best choices for intervention in each clinical scenario. However, once the intervention guidelines are established, undertaking such a trial is unlikely to be feasible and would not be ethically appropriate. Because of the rarity of this tumour, no prospective comparative trials exist in children or adults. However, the conservative strategy used in our study meant that more than half of the patients avoided surgery (and its sequelae) and radiotherapy.

An additional finding was that small tumour size correlated with improved outcomes. Surgical margins (ie, IRS groups) did not affect outcomes. Because initial complete resection was rarely feasible, as documented in previous paediatric studies (appendix),[2,5,7,8,24] and surgical trauma might stimulate desmoid-type fibromatosis growth,[3,10,12] surgery should be avoided when possible. Hence, a wait-and-see strategy using minimal systemic therapy in cases of rapid tumour progression or progression at a threatening site is recommended.[11,13] Notable responses to chemotherapy have been reported in patients with desmoid-type fibromatosis, with the proportion of patients who achieved an objective response ranging from 15% to 54% depending on the type of chemotherapy used.[2,3,5,25] In retrospective studies[26,27] of adult patients with desmoid tumours, objective response was higher in patients who received anthracycline-based regimens (58%) than in those who received other types of regimens (12%), but MTX and vinca alkaloids have been shown to be active and effective. In children, MTX-VBL is associated with an overall tumour response of 31–51%.[2,3,5,14,25] In our case series, initial observation after diagnosis did not reduce the chance of achieving disease control with chemotherapy following tumour progression. Overall response to all medical therapy was 35% in terms of tumour reduction, but 80% if we considered also tumour stabilisation. Consistent with published work,[14,20] NSAIDs with or without tamoxifen could lead to tumour stabilisation at best, and best

responses were seen after MTX-VBL or MTX-VNR, which should be proposed as first-line regimens after tumour progression. Notably, around a quarter of patients in the wait-and-see group did not receive any therapy after biopsy and had spontaneous tumour stabilisation or regression. Taken together, we are in favour of proposing an initial wait-and-see strategy for all tumours located in non-threatening sites and associated with few symptoms. This proposal might lead to improved definition of spontaneous tumour evolution and the possibility of observing spontaneous regression and selecting patients who need therapy when tumour progression occurs.

Desmoid-type fibromatosis can be distinguished histologically from other fibromatous tumours (eg, lipofibromatosis, myofibromatosis, palmar-plantar infantile fibromatosis, and infantile digital fibromatosis),[1,28] and the presence of the somatic *CTNNB1* mutation helps to confirm the diagnosis in case of histological doubt. β-catenin immunostaining is sometimes used to help with diagnosis, but the value of intranuclear staining remains debatable.[29] In our case series, β-catenin staining was frequently present in both nuclei and cytoplasm (around 70% each) in patients analysed and therefore was not helpful in the discrimination of patients who had sporadic desmoid-type fibromatosis from those with inherited disease. Moreover, in our experience, the presence of a somatic *CTNBB1* mutation does not affect outcome.

In our case series, less than 5% of desmoid-type fibromatosis occurred in an obvious context of *APC* familial predisposition. However, only 19 patients were tested for germline *APC* mutation and some patients with the mutation might have been missed. Because *CTNNB1* and *APC* mutations seem to be mutually exclusive, the somatic analysis of *CTNNB1* could help to guide genetic counselling.[4,30] However, among the four patients with germline *APC* mutation, one had a concomitant somatic *CTNNB1* mutation. In our study, just over a quarter of tested tumours had no somatic *CTNNB1* exon 3 mutation; these patients and their families should have been offered genetic counselling and *APC* gene constitutional analysis to investigate whether the desmoid-type fibromatosis co-occurred with Gardner syndrome, which will require specific colonic surveillance for patients from the age of 10 years. Notably, two of three patients with multifocal synchronous tumours had germline *APC* mutations that might indicate a need for a genetic test.

The strategy of offering the least aggressive care possible was drawn from experience in adult patients with desmoid-type fibromatosis and was first introduced in the paediatric setting in 2005, when the study started. Our case series included children with unselected desmoid-type fibromatosis, and occurrence in the head and neck region was more frequent than that reported in adults (26% *vs* 7%).[10] The sex ratio in our study (male:female 1·04) is consistent with that in previous paediatric studies (0·88–1·56),[2,5,24] whereas in adults the tumour is more common in women than in men (0·23–0·53).[9,10,31] Desmoid-type fibromatosis could be stimulated by oestrogen secretion in women, mainly during pregnancy. Our study had a wide age range of patients, and although the occurrence seemed to peak after puberty onset (median age 11·4 years), the proportion of girls and boys were similar. Therefore, we were unable to analyse the specific role of puberty in tumourigenesis. Furthermore, in a single-centre retrospective study[11] of 93 paediatric patients with desmoid-type fibromatosis, 17 (18%) had a history of antecedent trauma. In adult studies,[10,11] among 112 patients treated in a single institution between 1988 and 2003, 17 (15%) had desmoid-type fibromatosis after trauma. The prevalence of previous trauma is slightly lower (7%) in our study, and the exact cause of this discrepancy is unclear.

Because of the length of this study and its international nature, recruitment bias was possible. However, the clinical behaviour of the tumour seemed similar to that observed in adults (5-year progression-free survival 49·9% [SE 7·7] for the wait-and-see approach and 58·6% [7·3] for patients who had immediate treatment).[3] In the absence of clear prognostic factors to inform decision, the identification of molecular variables is warranted to better define patients who can benefit from a wait-and-see approach or those who need immediate therapy after diagnosis.

Our results confirmed that desmoid-type fibromatosis is a complex disease and the best outcome for patients is difficult to measure. In the three therapeutic categories, 5-year progression-free survival ranged between 26·7% and 42·8%, but tumour progression or relapse did not affect survival or even the response to further therapy. This finding suggests that event-free survival or progression-free survival might not be the best outcome measures in view of the benign and chronic behaviour of desmoid-type fibromatosis. Outcome could be better assessed by a combination of progression-free survival and functional sequelae, and the therapeutic decisions should consider tumour evolution, in addition to the patient's age, location of the disease, and especially the risk of functional or life-threatening consequences correlated with both the tumour and the therapies. In this regard, a major limitation of our study is the absence of data on functional sequelae, which were not collected as part of the protocol. To overcome this, we are planning to follow up on the existing cohort to determine the long-term prognosis for each of the intervention groups.

Prospective studies are needed to test new targeted drugs, such as sorafenib or sunitinib, and to understand the biological pathway in paediatric desmoid-type fibromatosis,[32,33] which might also allow target discovery and hence new therapeutic interventions. Tyrosine kinase inhibitors have been shown to be effective in adults.[34] Therefore, the clinical behaviour and biology of paediatric desmoid-type fibromatosis need to be compared with that in adults to determine whether new treatments developed for adults could be extended to the paediatric population.

In conclusion, the outcomes in our study and the feasibility of a wait-and-see strategy after diagnosis will help to reassure patients and parents to accept a conservative strategy in which medical therapy is given only when the tumour progresses. Better outcome measures (eg, functional sequelae) to assess interventions in paediatric desmoid-type fibromatosis are needed, which will be the aim of the next EpSSG study.

Contributors

DO, BB, GB, and AF did the study design, data collection, data interpretation, writing, and had final approval. MVN, VM-C, NC, and ASD did the data collection, reviewed the paper, and had final approval. JD did the data analysis, data interpretation, reviewed the paper, and had final approval. MC and NF did the study design, data collection, reviewed the paper, and had final approval. IZ did the data analysis, data interpretation, writing, reviewed the paper, and had final approval. GLDS did the study design, data analysis, data interpretation, reviewed the paper, and had final approval. AK did the study design, writing, reviewed the paper, and had final approval. MBA did the data collection, reviewed the paper, and had final approval.

Declaration of interests

GB reports personal fees from Medik, Loxo Oncology, and Merck, and grants from Indena outside the submitted work. All other authors declare no competing interests.

Acknowledgments

The EpSSG is supported by La Città della Speranza Foundation and S Wisnia, who provided financial support for the creation of a specific section in the Remote Data Entry system and a part-time dedicated data manager.

References

1 Fletcher C, Bridge J, Hogendoorn PC, Mertens AC. Desmoid-type fibromatosis. In: Fletcher CDM, Unni KK, Mertens F, eds. WHO classification of tumours of soft tissue and bone. Lyon: International Agency for Research on Cancer; **2013:** 72–74.

2 Oudot C, Orbach D, Minard-Colin V, et al. Desmoid fibromatosis in pediatric patients: management based on a retrospective analysis of 59 patients and a review of the literature. *Sarcoma* 2012; **2012:** 475202.

3 Fiore M, Rimareix F, Mariani L, et al. Desmoid-type fibromatosis: a front-line conservative approach to select patients for surgical treatment. *Ann Surg Oncol* 2009; **16:** 2587–93.

4 Penel N, Coindre JM, Bonvalot S, et al. Management of desmoid tumours: a nationwide survey of labelled reference centre networks in France. *Eur J Cancer* 2016; **58:** 90–96.

5 Meazza C, Bisogno G, Gronchi A, et al. Aggressive fibromatosis in children and adolescents: the Italian experience. *Cancer* 2010; **116:** 233–40.

6 Woltsche N, Gilg MM, Fraissler L, et al. Is wide resection obsolete for desmoid tumors in children and adolescents? Evaluation of histological margins, immunohistochemical markers, and review of literature. *Pediatr Hematol Oncol* 2014; **32:** 60–69.

7 Rutenberg MS, Indelicato DJ, Knapik JA, et al. External-beam radiotherapy for pediatric and young adult desmoid tumors. *Pediatr Blood Cancer* 2011; **57:** 435–42.

8 Buitendijk S, van de Ven CP, Dumans TG, et al. Pediatric aggressive fibromatosis: a retrospective analysis of 13 patients and review of literature. *Cancer* 2005; **104:** 1090–99.

9 Salas S, Dufresne A, Bui B, et al. Prognostic factors influencing progression-free survival determined from a series of sporadic desmoid tumors: a wait-and-see policy according to tumor presentation. *J Clin Oncol* 2011; **29:** 3553–58.

10 Bonvalot S, Eldweny H, Haddad V, et al. Extra-abdominal primary fibromatosis: aggressive management could be avoided in a subgroup of patients. *Eur J Surg Oncol* 2008; **34:** 462–68.

11 Honeyman JN, Theilen TM, Knowles MA, et al. Desmoid fibromatosis in children and adolescents: a conservative approach to management. *J Pediatr Surg* 2013; **48:** 62–66.

12 Colombo C, Miceli R, Le Pechoux C, et al. Sporadic extra abdominal wall desmoid-type fibromatosis: surgical resection can be safely limited to a minority of patients. *Eur J Cancer* 2015; **51:** 186–92.

13 Holme H, Westbury CB, Morgenstern D, et al. An important role for initial observation in the management of paediatric desmoid fibromatosis. *Clin Oncol (R Coll Radiol)* 2013; **25:** e16.

14 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:** 501–06.

15 Ferrari A, Trama A, De Paoli A, et al, RARECAREnet Working Group. Access to clinical trials for adolescents with soft tissue sarcomas: Enrollment in European pediatric Soft tissue sarcoma Study Group (EpSSG) protocols. *Pediatr Blood Cancer* 2016; published online Nov 24. DOI:10.1002/pbc.26348.

16 Donaldson SS, Draper GJ, Flamant F, et al. Topography of childhood tumors: pediatric coding system. *Pediatr Hematol Oncol* 1986; **3:** 249–58.

17 Maurer HM, Beltangady M, Gehan EA, et al. The Intergroup Rhabdomyosarcoma Study-I. A final report. *Cancer* 1988; **61:** 209–20.

18 Le Guellec S, Soubeyran I, Rochaix P, et al. CTNNB1 mutation analysis is a useful tool for the diagnosis of desmoid tumors: a study of 260 desmoid tumors and 191 potential morphologic mimics. *Mod Pathol* 2012; **25:** 1551–58.

19 Enzo MV, Rastrelli M, Rossi CR, Hladnik U, Segat D. The Wnt/beta-catenin pathway in human fibrotic-like diseases and its eligibility as a therapeutic target. *Mol Cell Ther* 2015; **3:** 1.

20 Skapek SX, Anderson JR, Hill DA, et al. Safety and efficacy of high-dose tamoxifen and sulindac for desmoid tumor in children: results of a Children's Oncology Group (COG) phase II study. *Pediatr Blood Cancer* 2013; **60:** 1108–12.

21 Nuyttens JJ, Rust PF, Thomas CR Jr, Turrisi AT 3rd. Surgery versus radiation therapy for patients with aggressive fibromatosis or desmoid tumors: a comparative review of 22 articles. *Cancer* 2000; **88:** 1517–23.

22 Jabbari S, Andolino D, Weinberg V, et al. Successful treatment of high risk and recurrent pediatric desmoids using radiation as a component of multimodality therapy. *Int J Radiat Oncol Biol Phys* 2009; **75:** 177–82.

23 Miller AB, Hoogstraten B, Staquet M, Winkler A. Reporting results of cancer treatment. *Cancer* 1981; **47:** 207–14.

24 Soto-Miranda MA, Sandoval JA, Rao B, et al. Surgical treatment of pediatric desmoid tumors. A 12-year, single-center experience. *Ann Surg Oncol* 2013; **20:** 3384–90.

25 Faulkner LB, Hajdu SI, Kher U, et al. Pediatric desmoid tumor: retrospective analysis of 63 cases. *J Clin Oncol* 1995; **13:** 2813–18.

26 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:** 182–86.

27 Palassini E, Frezza AM, Mariani L, et al. Long-term efficacy of methotrexate plus vinblastine/vinorelbine in a large series of patients affected by desmoid-type fibromatosis. *Cancer J* 2017; **23:** 86–91.

28 Wu C, Amini-Nik S, Nadesan P, Stanford WL, Alman BA. Aggressive fibromatosis (desmoid tumor) is derived from mesenchymal progenitor cells. *Cancer Res* 2010; **70:** 7690–98.

29 Lazar AJ, Tuvin D, Hajibashi S, et al. Specific mutations in the beta-catenin gene (CTNNB1) correlate with local recurrence in sporadic desmoid tumors. *Am J Pathol* 2008; **173:** 1518–27.

30 Meazza C, Belfiore A, Busico A, et al. AKT1 and BRAF mutations in pediatric aggressive fibromatosis. *Cancer Med* 2016; **5:** 1204–13.

31 El-Haddad M, El-Sebaie M, Ahmad R, et al. Treatment of aggressive fibromatosis: the experience of a single institution. *Clin Oncol (R Coll Radiol)* 2009; **21:** 775–80.

32 Gounder MM, Lefkowitz RA, Keohan ML, et al. Activity of sorafenib against desmoid tumor/deep fibromatosis. *Clin Cancer Res* 2011; **17:** 4082–90.

33 Skubitz KM. Biology and treatment of aggressive fibromatosis or desmoid tumor. *Mayo Clin Proc* 2017; **92:** 947–64.

34 Szucs Z, Messiou C, Wong HH, et al. Pazopanib, a promising option for the treatment of aggressive fibromatosis. *Anticancer Drugs* 2017; **28:** 421–26.