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FUNCTIONAL ANALYSIS OF YOUNG PATIENTS WITH DESMOID-TYPE FIBROMATOSIS: INITIAL SURVEILLANCE DOES NOT JEOPARDIZE LONG TERM QUALITY OF LIFE

Running title: Functional sequelae in desmoid-type tumor

Authors: G. Duhil de Bénazé^{1,19}, M. Vigan², N.Corradini³, V.Minard-Colin⁴, A. Marie-Cardine⁵, C.Verite⁶, AS. Defachelles⁷, E.Thebaud⁸, MP.Castex⁹, N.Sirvent¹⁰, D.Bodet¹¹, L.Mansuy¹², A.Rome¹³, A.Petit¹⁴, D.Plantaz¹⁵, A.Jourdain¹⁶, P. Mary¹⁷, M. Carton², D Orbach¹⁸.

Affiliations:

¹University Hospital of Nice- Archet 2, Department of Pediatric Hematology-Oncology, Nice, France. ²Institut Curie- PSL Research University, Biometry Unit-, Paris, France. ³IHOPE, Centre régional de lutte contre le cancer- Centre Léon Bérard, Lyon, France. ⁴Gustave Roussy Cancer Campus, Department of Children and Adolescents Oncology, Villejuif, France. ⁵Rouen University Hospital, Department of Pediatric Hematology-Oncology, Rouen, France. ⁶Bordeaux University Hospital, Pediatric Hematology Department, Bordeaux, France. ⁷Centre Oscar Lambret, Service d'Oncologie Pédiatrique, Lille, France. ⁸University Hospital Nantes, Pediatric Oncology Department, Nantes, France. ⁹Children's Hospital of Toulouse- CHU Toulouse, Pediatric Hemato-oncology Department, Toulouse, France. ¹⁰University Hospital of Montpellier, Department of Pediatric Onco-Hematology, Montpellier, France. ¹¹Caen University Hospital, Department of Pediatric Hematology and Oncology, Caen, France. ¹²Children's University Hospital, Department of Pediatric Hematology and Oncology, Nancy, France. ¹³Centre Hospitalier Universitaire, Department of Pediatric Oncology, Marseille, France. ¹⁴Assistance Publique-Hôpitaux de Paris AP-HP- GH HUEP- Armand Trousseau Hospital, Department of Pediatric Hematology and Oncology, Paris, France. ¹⁵University Hospital Centre of Grenoble, Department of Pediatric Hematology-Oncology, Grenoble, France. ¹⁶CHU Tours, Department of Pediatric Oncology and Hematology, Tours, France. ¹⁷Pediatric Orthopedics Department, Armand Trousseau Hospital, Paris, France. ¹⁸Institut Curie, SIREDO Oncology Center Care- Innovation and research for children and AYA with cancer- PSL Research University, Paris, France.

Corresponding author: G. Duhil de Bénazé, University Hospital of Nice-Archet 2, Department of
Pediatric Hematology-Oncology, Nice, France. Phone: 04 92 03 67 02; Fax: 04 92 03 65 78. Mail:
duhildebenaze.g@chu-nice.fr

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Abstract

Background: With recent conservative strategies, prognosis of patients with desmoid-type fibromatosis (DTF) is about function preservation. We analyzed the long-term quality of life (QoL) of pediatric patients with DTF.

Methods: All French young patients (<21years) treated between 2005-2016 for a DTF in the EpSSG NRSTS-05 study were analyzed. A first wait-and-see strategy was recommended. Patients' QoL was analyzed with the internationally validated Child Health Questionnaire (CHQ). We focused on the relevant subscales scores: physical functioning (PF), role social limitations physical (RP), bodily pain (BP), general health perception (GH) and physical (PhS) and psychosocial (PsS) summary measures.

Results: Among the 81 patients, 52 families answered the CHQ (median delay since diagnosis=6.2years; min2.2-max13.3years). Median age at diagnosis was 11.5years. Primary site: limbs (52%), head/neck (27%), or trunk (21%). Five year-Progression Free Survival was 39.1% (95%CI: 27.7-50.5%). As initial management for these 52 patients, 30 patients were first observed (57%), 13 had surgery (25%) and 9 received chemotherapy (18%). Total burden of therapy was exclusive surgery (9pts/18%), exclusive chemotherapy (18pts/35%), surgery+chemotherapy (13pts/25%), chemotherapy+radiotherapy (1pt), surgery+chemotherapy+radiotherapy (1pt), wait and see (10pt). Regarding the parent forms, patients have significant lower PF (86.0vs.96.1; $p=0.03$), RP (82.0vs.93.6; $p=0.04$), GH (60vs.73; $p<0.005$) and PhS (46.2 vs.53; $p=0.02$) scores compared to healthy population. Comparison of QoL subscales scores according to initial strategy (wait-and-see vs.surgery/chemotherapy) did not reveal any difference (PF=87.3vs.84.9; $p=0.80$ /RP=83.4vs.78.7; $p=0.72$ /BP=78.9vs.78.2; $p=0.95$ /GH=59.7vs.60; $p=0.97$). Similar results were found using the children or adult forms.

69 **Conclusions:** Initial wait-and-see strategy does not affect long term functional impairment.

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71 **Key words:** desmoid-type tumor; children; conservative strategy; quality of life; Child Health
72 questionnaire.

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75 Number counts: Table=4, supplemental Table=1; Figure=2, abstract word=246, total words=2355

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Introduction

Desmoid-type fibromatosis (DTF) are rare benign tumors of soft tissues, they can be locally invasive, but without any metastatic potential. The incidence of desmoid tumors in general population is low. It usually affects children (6-15years) and women (puberty-40years) (1–4). Because DTF are often large and infiltrative, complete resection is rarely feasible (6-25% in children) (1,5). DTF can spontaneously stabilize or resolve after diagnosis, but relapses are common (until 60%) (6–8). Surgery has been hypothesized to stimulate the onset and growth of DTF (9–11). This hypothesis and the observation of relapses after surgery lead to a conservative approach in the EpSSG (12–14). Between 2005 and 2016, European children and adolescents (age at diagnosis ≤ 21 years) with proven diagnosis of DTF were prospectively registered in the EpSSG Non-Rhabdomyosarcoma Soft Tissue Sarcoma study (NRSTS). Results of this protocol regarding DTF have been recently published (4). The EpSSG NRSTS Committee recommended a minimally aggressive strategy and considered as first approach the wait-and-see strategy. A treatment should be considered in case of rapid tumor growth, uncontrollable symptoms or tumor located in a threatening site. Primary resection should be considered for small tumors if it appears to be complete without mutilation. In large extensive tumors, when a medical therapy was indicated, chemotherapy (methotrexate-vinblastine) was recommended. Radiotherapy was discouraged. This group suggests initial wait-and-see strategy (4), which did not compromise outcomes. But “*outcome could be better assessed by a combination of progression-free survival and functional sequelae.*”(4). This study aims to assess the long term quality of life (QoL) of children and adolescents affected by DTF and analyze functional consequences according to initial therapeutic strategy.

Material and methods

Study design and Population

We conducted a retrospective, multicenter cohort study in which we selected all French patients with DTF included in the NRSTS protocol treated in 19 different oncology centers. Parental/guardians written consent was collected at the inclusion in the study.

Methods

All clinical and outcome data were prospectively registered in the EpSSG NRSTS 2005 databases and updated for this analyze. Patients were classified by tumor site and clinical staging was defined using the TNM system (15). Study (IRS) grouping system was used (16).

Patients' quality of life was analyzed by the internationally quality of life (QoL) questionnaire: Child Health questionnaire (CHQ) (17–20). We picked the 50 items parents form (CHQ-PF50), and the 87 items for children ≥ 10 years old (CHQ-CF87). For young patients that become adults during the follow-up, this questionnaire has been adapted to age (professional activity and family life). After agreement of their reference center, the questionnaire was sent to families.

Long term adverse events were reported accorded to the Common Terminology Criteria for adverse Events (CTCAE) (21) by sending a case report form to all the clinicians. Data was updated at the time point of 1st September 2018.

Statistical analysis methods

We compared clinical data for patients/families who answered to CHQ and the ones who did not with Chi-2 or Fisher test. We separated answers depending if it were parents; patients still remaining children, or patients who had become adults. The CHQ was scored using the customary algorithm, which calculates subscale scores ranging from 0 to 100, with higher scores indicating better health status (22). Comparison of scores with general US population was

available for CHQ-PF50 and CHQ-CF87. The link between variables of the treatment and QoL was tested with Wilcoxon test. Other variables (radiotherapy, number of surgeries, localization of the tumor, mutilating surgery, 2 or more lines of chemotherapy, chemotherapy during more than 2years) were described but not tested because of insufficient number of patients. We focused the analysis on the most relevant subscale scores: physical functioning (PF, presence and extent of physical limitations), role social limitations physical (RP, extent of limitations in school-related activities and activities with friends), bodily pain (BP, intensity and frequency of general pain), and general health perception (GH, subjective assessment of overall health and illness). We also used the physical (phS) and psychosocial (psS) summary measures which aggregate CHQ-PF50 items and scales (parent form). Subscale scores are presented as mean (standard deviation). All tests were bilateral (cut-off 5%) and R software version 3.4.4 (<http://www.R-project.org>) was used for the statistical analyses. PFS was estimated using the Kaplan–Meier method, and median follow-up duration using the reverse Kaplan–Meier method.

Results

Overall, 81 patients with DTF at a median age at diagnosis of 11.6 years (1month- 18.3years) were included in the EpSSG NRSTS 2005 study in France. Patients' characteristics of the whole cohort are described in **Table 1**. Sex ratio was 1:1. Palpation of a pain-free mass was the only symptom leading to the diagnosis in 49 (60.5%) patients. The majority of DTF primaries were on extremities (47%). The tumor size was mainly large with 63% larger than 5 cm at diagnosis. Overall, 82% of patients had first a biopsy to reach diagnosis; the other ones had a tumor resection.

After a median follow-up of 5.5 years (range 0.8-13), 49 tumor events occurred in 81 patients (all progressive disease) and one accidental death occurred in a patient leading to a 5y-PFS of 39.1 % (95%CI: 27.7%-50.5%; [figure 1](#)).

CHQ questionnaires were sent between February and April 2018 to all parents and/or alive patients (n=80), except one patient with a complex social situation. Overall, 29 parents answered the questionnaire, of which 22 children completed the CHQ-CF87 form. In addition, 23 patients who reached adult age answered the questionnaire, giving a total of 52/80 participations (65%). Median delay between diagnosis and answer to the questionnaire was 6.2years (2.2-13.3). Overall characteristics of the subgroup with QoL analysis available were quite similar to the entire cohort ([supplemental Table 1](#)). Median follow-up for this population was 5.4years (0.8-13).

Among these 52 patients, 30 were first observed (group A; 58%), 13 underwent immediate surgery (group B; 25%), and 9 received immediate chemotherapy (group C; 17%). Treatment according to tumor evolution and overall tolerance are detailed in [Table 2](#). In group A, only 10/30 patients did not receive any treatment after biopsy (except non-steroid anti-inflammatory drugs, n=4) and are still currently monitored, the other ones required chemotherapy (n=13), surgery (n=3), chemotherapy and surgery (n=4). In group B, 7/13 patients were operated on more than one time. Among these 13 patients, 7 received chemotherapy and one required radiotherapy (50.4Gy). All 9 patients in group C received methotrexate and vinblastine for a median duration of 11.9 months (range=1.5-29.1). Among them, 7 started chemotherapy due to the threat to an adjacent organ, and two because of refractory pain. Chemotherapy was prematurely stopped in 5 patients (tumor progression n=2; persistence of pain n=1, partial response after 8 months n=1, stable disease after 11 months n=1). Two patients of the group C received a second line of chemotherapy for non-improvement of pain or tumor progression. Overall 2 patients received

radiotherapy; one (50.4Gy) for tumor progression (DTF of the arm) despite 4 surgeries and two lines of chemotherapy, and another one (DTF of the knee) after one line of chemotherapy because of severe uncontrolled pain (21Gy). No mutilating surgery was performed.

CHQ global scale and subscales scores results for the 52 patients with DTF are detailed in **Table 3**. Comparison between our subjects and the normative sample of healthy children shows that they have significant lower PF and RP scores according to both parents and child forms, and lower MH, GH, PE and PhS scores according to the parent's forms (**Figure 2**). Comparisons of QoL subscales scores (PF, RP, BP, GH) between patients first observed (30 cases), and the ones who received immediate first-line treatment (surgery n=13, or chemotherapy n=9) do not reveal any significant difference (**Table 4**).

Between patients who received at least one line of chemotherapy (n=33) and those who did not (n=19), we were able to show a trend via the CHQ-PF50: patients who did not receive chemotherapy tend to present a better PF and PsS scores, however not significant (p=0.09 and 0.16). It was also the case for PF scores evaluated by children (CHQ-CF87): 93.7 vs 77.8 (p=0.13). RP score analyzed by patients who had become adults was better if they did not receive chemotherapy (73.6 vs 100, p=0.028). Among 3 patients who received 3 or more lines of chemotherapy (1 adult, 2 children), only one children had a low RP score (RP=44) compared to US healthy population (mean score 93.7), while PF/BP/GH scores were globally satisfactory (100/85/70, 80/90/100, 70/82/61).

When comparing QoL subscales scores between 23 patients who underwent at least one surgery and 29 never operated patients, no significant difference was found (CHQ-PF50: PF score 85.7vs86.9, p=0.89; RP score 81.9vs81.4, p=0.97; BP score 80.8vs77.1, p=0.72; GH score 57.5vs61.4, p=0.57; PsS score 44.1vs50.2, p=0.24; PhS score 46.1vs46.4, p=0.96). Notably, two

patients who underwent 3 surgeries and one patient who underwent 4 surgeries answered the questionnaire. We can notice that these three patients have poorest BP (40, 70, and 40) and GH (88, 43, and 59) scores compared to mean scores in healthy population (BP 81.7; GH 73).

Two patients received RT, associated to 2 lines of chemotherapy for both and 4 surgeries for one of them. These two patients had decreased GH scores (43 and 59). RP and BP scores were low for one of them (respectively 44 and 40) while the PF score was correct (100 and 89).

Finally, we compared QoL scores between non-treated patients (n=10), and those who received treatment (chemotherapy, surgery or radiotherapy), and no significant difference was found (CHQ-PF50: PF score 83.4vs98.2, p=0.15; RP score 78.3vs94.5, p=0.28; BP score 78.3vs80, p=0.91; GH score 58.1vs66.4, p=0.21).

We obtained additional information from clinicians for 42/52 patients. Overall, 3 had at worse a grade 1 long term adverse event (AE) (pain or musculoskeletal deformity or paresthesia), 15 patients had a grade 2 (pain n=2 and/or musculoskeletal deformity n=6 and/or asthenia n=1 and/or unequal limb length n=2 and/or muscle weakness n=4) and 3 a grade 3 (pain n=2, musculoskeletal deformity n=1). These 18 patients with grade 2 or 3 sequelae had lower mean scores compared to general population: PF score (67.6 vs 96.1), RP score (67.0 vs 93.6), BP score (58.3 vs 81.7), and GH score (51.5 vs 73.0).

Discussion

DTF should be considered a chronic disease, but not a life-threatening one. The important outcome remains morbidity. This is the first study which describes and analyses QoL with a well validated tool in children. Recently, a study reported interviews of 27 adults suffering from DTF (23); it reports difficulties such as long delayed diagnosis, treatment uncertainty, treatment-

related side-effects, debilitating symptoms, limitations in physical and psychosocial functioning affecting daily activities. This study showed how much QoL can be affected by a chronic disease. But a non-validated QoL questionnaire was used, and no children were included. Management of this tumor has changed over the last years. In the past, it was first recommended surgery, leaving chemotherapy and/or radiotherapy for recurrent disease or inoperable tumors. But complete resection is often quite impossible, and local recurrences after surgery are common (5–7,24,25). Moreover, it has been suggested that surgery may activate tumor progression. Furthermore, DTF can spontaneously stabilize or regress (9,26). This finding has been confirmed in a study including patients with refractory DTF in a randomized trial comparing sorafenib vs. placebo. An objective tumor regression was observed in 20% in the placebo group (95% CI, 8–38%)(27). Initial wait-and-see strategy seems to be now the recommended first line attitude in children and adults (28). To avoid any unnecessary surgery, chemotherapy is recommended in cases of progression or unacceptable symptoms. Orbach *et al.* recently showed that this wait-and-see strategy doesn't affect outcomes in terms of OS and PFS in children (4). The overall characteristics of our cohort were in accordance to literature data (1,4,29,30), except that there were less patients with IRS stage I tumors than expected. Patients who responded to the questionnaire were nevertheless representative of the whole population. Not surprisingly in a chronic disease, our long-term analysis demonstrated that children with DTF have significant lower scores in QoL than the general population. Analyzing QoL of patients after initial wait-and-see strategy, we did not find any difference in comparison to patients who underwent more aggressive initial therapies (surgery or chemotherapy), showing that this conservative strategy does not jeopardize the long-term outcome of children with DTF. Overall, the type of initial strategy does not seem to strongly influence long-term outcome. Nevertheless, patients who

underwent several surgeries or several lines of chemotherapy seem to have lower QoL global scores. These patients are probably more severe at diagnosis, and that could induce a bias.

We recognize that this present study has some limitations. The total number of patients included remains low to draw definitive conclusions, that's why our results must be confirmed in a largest European population. That can be partly explained by the rarity of this disease in the children. Moreover, we have only included French patients from the EpSSG group, and QoL may be differently perceived in different European countries. A large part (64%) of families included in the original study answered but not all of them. This may give a potential bias, even if analysis showed that our population was clinically representative of the whole cohort.. Some patients in our cohort were adults at the time of analysis and no specific validated QoL questionnaire exist for both adults and children. Due to the limited number of patients, we have not been able to study the association between QoL and some clinical factors. International prospective studies with a larger number of patients and systematic QoL analyze are needed to validate these results. In summary, our study showed that an initial wait-and-see strategy does not affect outcomes in term of functional impairment, pain or social behavior. These results encourage to first observe children with DTF like it was suggested by Orbach and all (4). Medical management of adults' patients affected by DTF is currently changing. Tyrosine kinase inhibitors drugs are currently tested and appear to be really effective (27,31–36). These drugs seem to be well tolerated and could change the tolerance of treatment. Nevertheless, long-term effects of these drugs in children are not well known and should be strongly considered in the overall strategy deciding to treat patients.

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Table 1. Patients and DFT characteristics

Abbreviations: QoL=quality of life. Actual age is the age at the time of QoL analyses.

	National cohort (n=81)	QoL analyzis (n=52)
Sex:		
Male	41 (51%)	24 (46%)
Female	40 (49%)	28 (54%)
Actual age:		
<18 years	42 (52%)	28 (54%)
≥18 years	39 (48%)	24 (46%)
Familial history of desmoid-type fibromatosis	1 (1%)	1 (2%)
Germline APC mutation	5 (6%)	4 (8%)
Tumour size> 5cm	51 (63%)	32 (62%)
Presence of pain	17 (21%)	11 (21%)
Tumour stage:		
T1	56 (69%)	33 (63%)
T2	25 (31%)	19 (37%)
IRSG stage:		
I	5 (6%)	1 (2%)
II	9 (11%)	7 (13%)
III	67 (83%)	44 (85%)
Primary site:		
Head and neck	22 (27%)	14 (27%)
Limbs	38 (47%)	27 (52%)
Trunk	21 (26%)	11 (21%)
Mutifocal sites	5 (6%)	5 (10%)
At least one surgery	34 (42%)	23 (44%)
At least one line of chemotherapy	54 (67%)	33 (63%)

Supplemental Table 1. Comparison between initial patients and tumor characteristics according the response or not to the CHQ.

	Answers available to CHQ (n=52)	No answer (n=29)	p value
Sex: Male Female	24 (46%) 28 (54%)	17 (59%) 12 (41%)	0.3
Actual age: <18 years ≥18 years	28 (54%) 24 (46%)	14 (48%) 15 (52%)	0.6
Familial history of desmoid-type fibromatosis	1 (2%)	0	1
Germline APC mutation	4 (8%)	1 (3%)	0.7
Tumour size> 5cm	32 (62%)	19 (66%)	0.8
Pain	11 (21%)	6 (21%)	1
Tumour stage: T1 T2	33 (63%) 19 (37%)	23 (79%) 6 (21%)	0.2
IRSG stage: I II III	1 (2%) 7 (13%) 44 (85%)	4 (14%) 2 (7%) 23 (79%)	0.09
Primary site: Head and neck Limbs Trunk	14 (27%) 27 (52%) 11 (21%)	8 (28%) 11 (38%) 10 (34%)	0.6
Multifocal site	5 (10%)	0	0.1
At least one surgery	23 (44%)	11 (38%)	0.6
At least one line of chemotherapy	33 (63%)	21 (72%)	0.5

Table 2. Treatments delivered for patients with DTF who answered to the CHQ according to initial strategy adopted.

	Initial therapeutic strategy			Total
Treatment delivered	Wait-and-see strategy Group A n=30	Immediate surgery Group B n=13	Immediate chemotherapy Group C n=9	Entire Cohort n=52
Medical therapies:				
1 st line chemotherapy <i>Median duration</i>	17 (57%) <i>12.3 months</i>	7 (54%) <i>8 months (one still ongoing)</i>	9 (100%) <i>11.9 months</i>	33 (63%)
2nd line chemotherapy <i>Median duration</i>	10 (33%) <i>14.8 months</i>	3 (23%) <i>13.6 months</i>	2 (22%) <i>9.4 months</i>	15 (29%)
3rd line chemotherapy <i>Median duration</i>	2 (7%) <i>8.4 months</i>	1 <i>8.1 months</i>	0	3 (6%)
4th line chemotherapy <i>Median duration</i>	1 (3%) <i>Unknown</i>	1 <i>0.9 month</i>	0	2 (4%)
Non steroid anti-inflammatory drugs	14 (47%)	1	1	16(31%)
Tumor resection:				
Delayed surgery n°1	7 (23%)	13 (100%)	3 (33%)	23 (44%)
Surgery n°2	2 (7%)	4 (31%)	0	6 (12%)
Surgery n°3	1 (3%)	2 (15%)	0	3 (6%)
Surgery n°4	0	1 (8%)	0	1 (2%)
Radiotherapy:	0	1 (8%)	1 (11%)	2 (4%)
Total burden of therapy:				
Wait-and-see, no further treatment	10 (33%)	0	0	10 (19%)
Exclusive chemotherapy	13 (43%)	0	5 (56%)	18 (35%)
Exclusive surgery	3 (10%)	6 (46%)	0	9 (17%)
Surgery + chemotherapy	4 (13%)	6 (46%)	3 (33%)	13 (25%)
Radiotherapy + Chemotherapy	0	0	1 (11%)	1 (2%)
Surgery + chemotherapy + radiotherapy	0	1 (8%)	0	1 (2%)
Long term effects:				
Grade 1 or 2 sequelae	12 (40%)	3 (23%)	3 (33%)	18(35%)
Grade 3 sequelae	1 (3%)	1 (8%)	1 (11%)	3 (6%)

Table 3. CHQ global scale and subscales scores for 52 patients treated for DFT during childhood : mean, SD, and p compared to healthy population.

Abbreviations: GGH = General Health perceptions ; PF = physical Functioning ; REB = Role/social limitation emotional behavior ; RE = Role/social Emotional ; RB = Role/social Behavior ; RP = Role/Social limitations physical ; BP = Bodily pain ; BE= General behavior ; GBE = Global behavior item ; MH = Mental health ; SE= Self Esteem ; GH = General health ; PE = Parental impact-emotional ; PT = Parental impact-time ; FA = Family – limitation in activity ; FC = Family cohesion ; PhS = Physical summary score ; PsS = Psychosocial summary score

	General US population Mean	Parents form n=29			Child form n=22			Adult form n=23	
		Mean	SD	p value	Mean	SD	p value	Mean	SD
GGH	-	76,9	23.1	-	76	23.8	-	73	23.4
PF	96.1	86	23.2	0.03	83	23.3	0.02	78	25.5
REB	92.5	82	30.4	0.07	-	-	-	-	-
RE	-	-	-	-	87	19.6	-	83	20.8
RB	-	-	-	-	83	22.7	-	83	23.7
RP	93.6	82	30.7	0.04	88	17	0.04	81	27
BP	81.7	78,6	26.6	0.5	73	27.1	0.08	67	31.7
BE	75.6	75	14.8	0.8	80	9.5	0.9	83	11.5
GBE	-	80	16.6	-	72	15	-	77	15.2
MH	78.5	72	16.3	0.05	78	11.1	0.7	65	20.1
SE	79.8	74	19.5	0.1	71	14.8	0.01	66	16.1
GH	73.0	60	17.8	0.0004	67	22.3	0.1	62	22
PE	80.3	68	27,6	0.03	-	-	-	-	-
PT	87.8	79	27	0.1	-	-	-	-	-
FA	89.7	85	23	0.3	89	16.7	0.2	92	14.4
FC	72.3	71	21.6	0.8	75	23.2	1	77	29.3
PhS	53.0	46.2	14.5	0.02	-	-	-	-	-
PsS	51.2	47.6	10.7	0.09	-	-	-	-	-

Table 4. Quality of life scores according to the initial strategy adopted : Wait-and-see strategy (n=30) vs. surgery or chemotherapy (n=22)
Abbreviations: WS= wait-and-see strategy; PF = physical Functioning; RP = Role/Social limitations physical; BP = Bodily pain; GH = general health

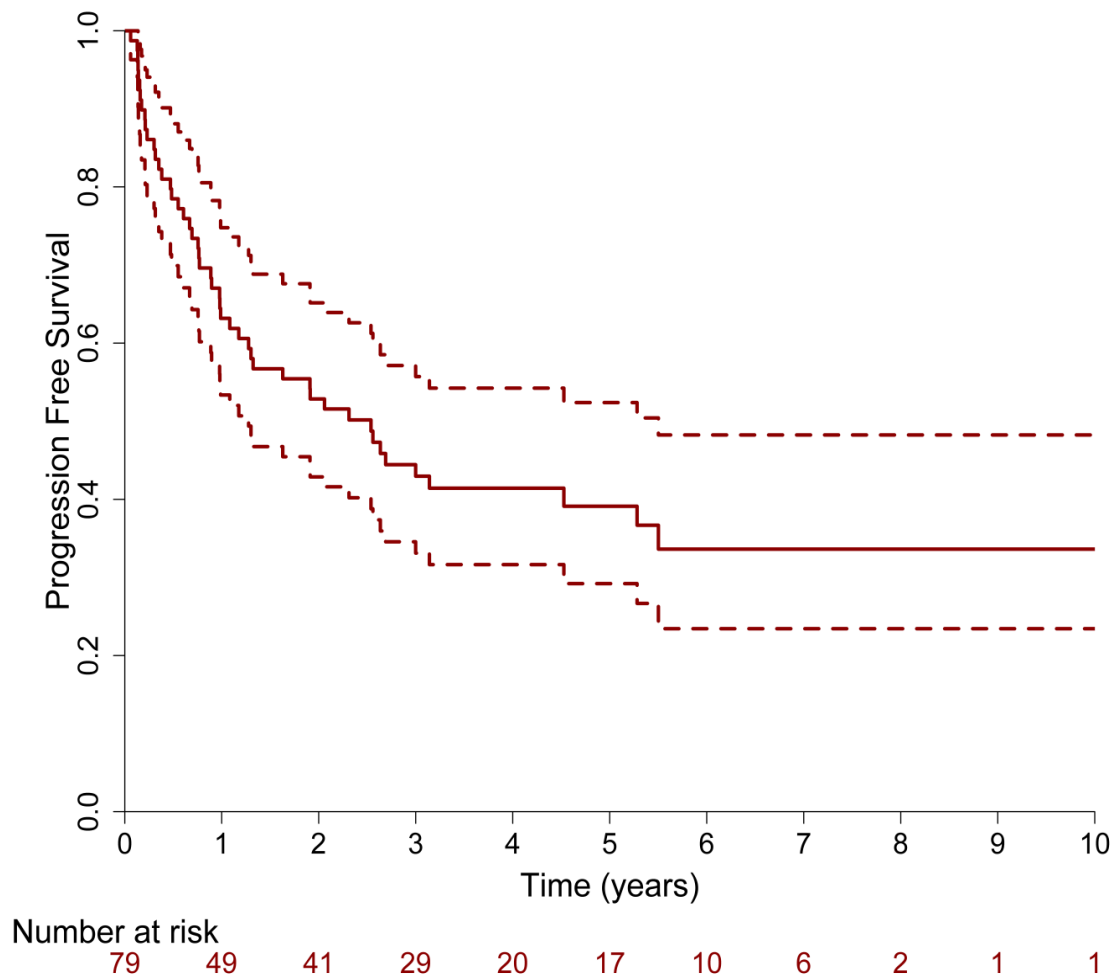
		Parents form (n=29)					Children form (n=22)					Adults form (n=23)				
	First line of treatment	Min	Median	Max	Mean	p-value	Min	Median	Max	Mean	p-value	Min	Median	Max	Mean	p-value
PF	WS	22	100	100	87.3	0.80	70.4	88.9	100	88.7	0.48	37	88.9	100	82.6	0.46
	Surgery or chemotherapy	17	100	100	84.9		0	81.5	100	70.4		7.4	77.8	100	74.1	
RP	WS	0	100	100	83.4	0.72	44.4	100	100	85.2	0.15	22.2	100	100	82.4	0.77
	Surgery or chemotherapy	0	100	100	78.7		66.7	100	100	95.2		33.3	88.9	100	78.9	
BP	WS	20	90	100	78.9	0.95	20	80	100	76	0.49	20	80	100	68.5	0.69
	Surgery or chemotherapy	0	90	100	78.2		0	70	100	65.7		10	65	100	63	
GH	WS	30.8	64.2	80.8	59.7	0.97	34.2	69.6	100	67.2	0.96	10.8	55.6	91.7	56.4	0.19
	Surgery or chemotherapy	26.7	60	89.2	60		25	82.1	93.8	67.7		44.6	70.6	97.9	68.5	

Figures legends

Figure 1: Progression-free survival (PFS) for the whole cohort (solid line) and 95% confidence interval (dotted line).

Figure 2: Mean (+SD) of CHQ global scale and subscales scores for 52 patients treated for DTF during childhood for parent form (Top) and child form (Bottom) in black for cohort study and grey for US healthy population. Numbers are p-values of Wilcoxon tests of comparison between the 2 groups.

Figure 1. Progression-free survival (PFS) of the entire cohort (n=81)



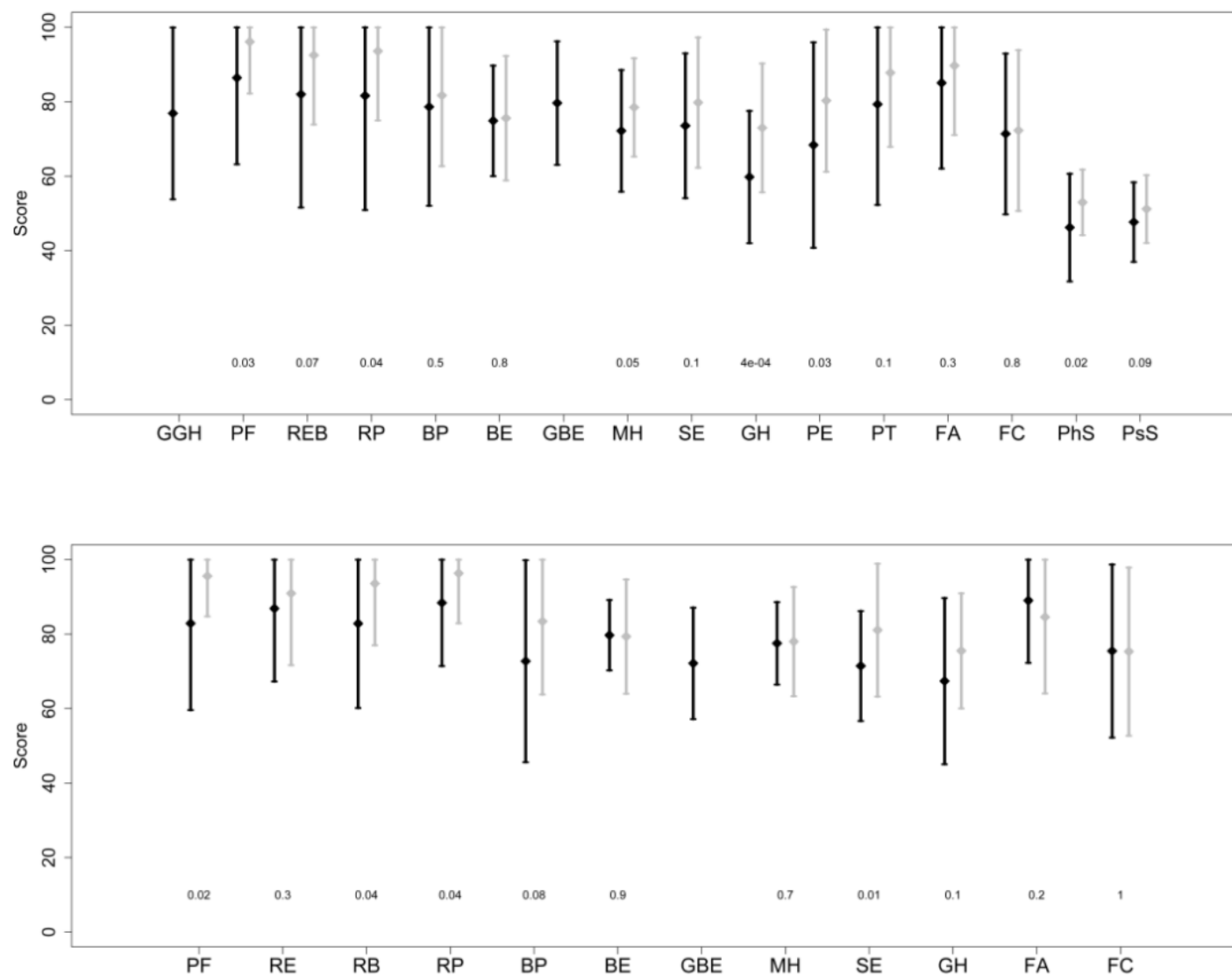


Figure 2. Mean (+SD) of CHQ global scale and subscales scores for 52 patients treated for DTF during childhood for parent form (Top) and child form (Bottom) in black for cohort study and grey for US healthy population. Numbers are p-values of Wilcoxon tests of comparison between the 2 groups.

Abbreviations: GGH = General Health perceptions; PF = physical Functioning; REB = Role/social limitation emotional behavior; RE = Role/social Emotional; RB = Role/social Behaviour; RP = Role/Social limitations physical ; BP = Bodily pain; BE= General behaviour; GBE = Global behaviour item; MH = Mental health; SE= Self Esteem ; GH = General health; PE = Parental impact-emotional; PT = Parental impact-time; FA = Family – limitation in activity FC = Family cohesion; PhS = Physical summary score; PsS = Psychosocial summary score; SD= standard deviations.