Desmoid Tumors

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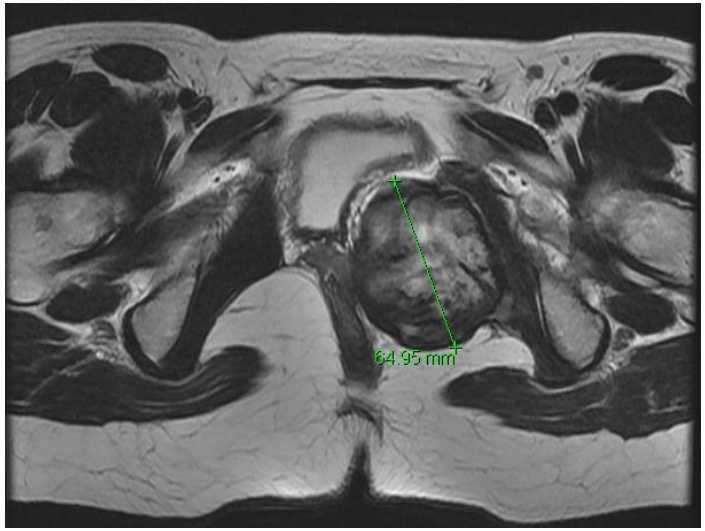
Position Paper

Management of sporadic desmoid-type fibromatosis: A European consensus approach based on patients' and professionals' expertise – A Sarcoma Patients EuroNet and European Organisation for Research and Treatment of Cancer/Soft Tissue and Bone Sarcoma Group initiative

B. Kasper [a,*], C. Baumgarten [b], S. Bonvalot [c], R. Haas [d], F. Haller [e], P. Hohenberger [a], G. Moreau [f], W.T.A. van der Graaf [g], A. Gronchi [h], on behalf of the Desmoid Working Group [1]

DIAGNOSIS



2.1. Biopsy

A biopsy confirming DF diagnosis is mandatory and a definitive histology should be awaited before undertaking any further treatment steps. In most cases, diagnosis of DF can be made on core needle biopsies using 14G or 16G systems; an excisional biopsy is not needed. Given the rarity of this disease, a diagnosis of DF has to be confirmed by an expert soft tissue pathologist.

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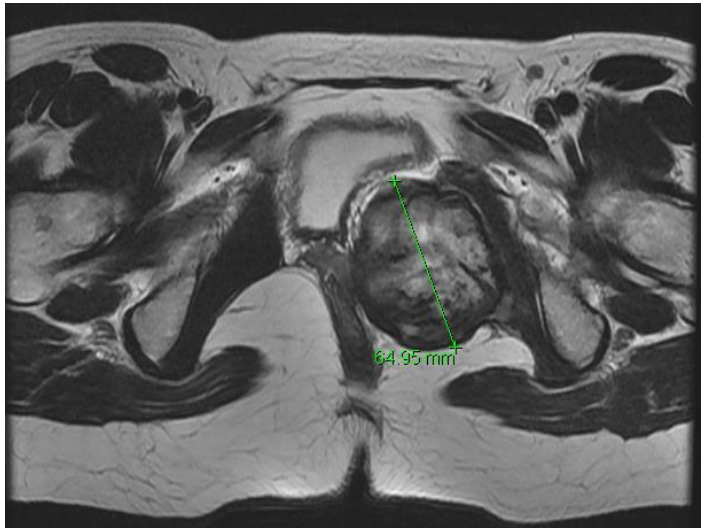

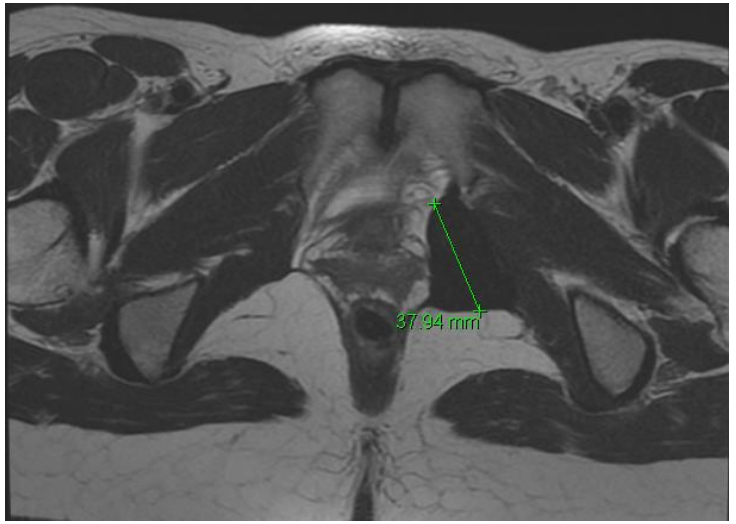

Management of desmoid tumors: A nationwide survey of labeled reference center networks in France

- From 2010 to 2013, the expert pathologists of FSG confirmed the diagnosis of DT in 861 pts
- 445 pts initially diagnosed outside the referral centers, were reviewed
- Prior to the review, DT was diagnosed in 389/545 cases (71·3%)
- 156/545 cases (28·7%) had another diagnosis
- The most common misdiagnoses were:

- sarcoma in 35/156 cases (22·4%)
- GIST in 26/156 cases (16·6%)
- nodular fasciitis 20/156 cases (12·8%)
- leiomyoma 6/156 cases (3·8%)

Penel et al ESMO 2015 *(EJC 2016 in press)*

Ann Surg Oncol (2012) 19:4028–4035
DOI 10.1245/s10434-012-2638-2

Annals of
SURGICAL ONCOLOGY
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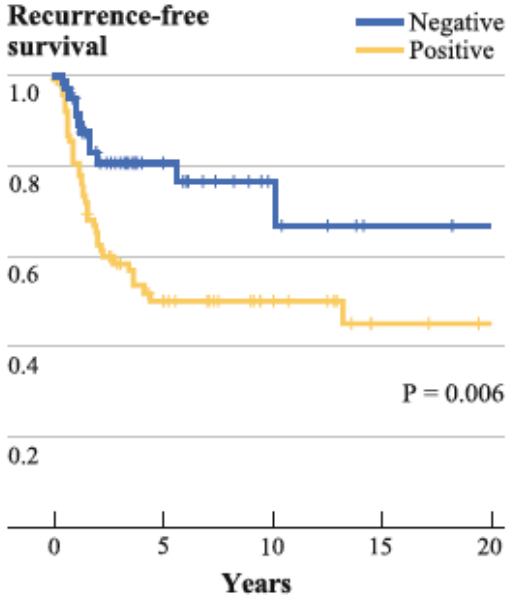
ORIGINAL ARTICLE – BONE AND SOFT TISSUE SARCOMAS

Desmoid Tumor: Analysis of Prognostic Factors and Outcomes in a Surgical Series

John T. Mullen, MD[1], Thomas F. DeLaney, MD[2], Wendy K. Kobayashi, BA[2], Jackie Szymonifka, BA[3], Beow Y. Yeap, ScD[3], Yen-Lin Chen, MD[2], Andrew E. Rosenberg, MD[4], David C. Harmon, MD[5], Edwin Choy, MD, PhD[5], Sam S. Yoon, MD[1], Kevin A. Raskin, MD[6], G. Petur Nielsen, MD[4], and Francis J. Hornicek, MD, PhD[6]



Ann Surg Oncol (2012) 19:4036–4042
DOI 10.1245/s10434-012-2634-6

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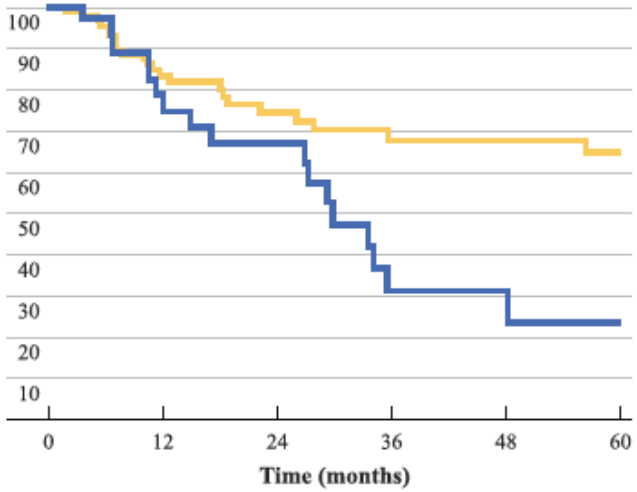
ORIGINAL ARTICLE – BONE AND SOFT TISSUE SARCOMAS

Management and Recurrence Patterns of Desmoids Tumors: A Multi-institutional Analysis of 211 Patients

Peter D. Peng, MD[1], Omar Hyder, MD[1], Michael N. Mavros, MD[1], Ryan Turley, MD[2], Ryan Groeschl, MD[3], Amin Firoozmand, MD[1], Michael Lidsky, MD[2], Joseph M. Herman, MD, MSc[1], Michael Choti, MD[1], Nita Ahuja, MD[1], Robert Anders, MD, PhD[1], Daniel G. Blazer III , MD[2], T. Clark Gamblin, MD[3], and Timothy M. Pawlik, MD, MPH, PhD[1]



Ann Surg. 2013 August ; 258(2): 347–353. doi:10.1097/SLA.0b013e31828c8a30.

A prognostic nomogram for prediction of recurrence in desmoid fibromatosis

Aimeé M. Crago, M.D., Ph.D.[1], **Brian Denton, M.S.**[2], **Sébastien Salas, M.D., Ph.D.**[3], **Armelle Dufresne, M.D.**[4], **James J. Mezhir, M.D.**[1], **Meera Hameed, M.D.**[5], **Mithat Gonen, Ph.D.**[2], **Samuel Singer, M.D., FACS**[1], and **Murray F. Brennan, M.D., FACS**[1]

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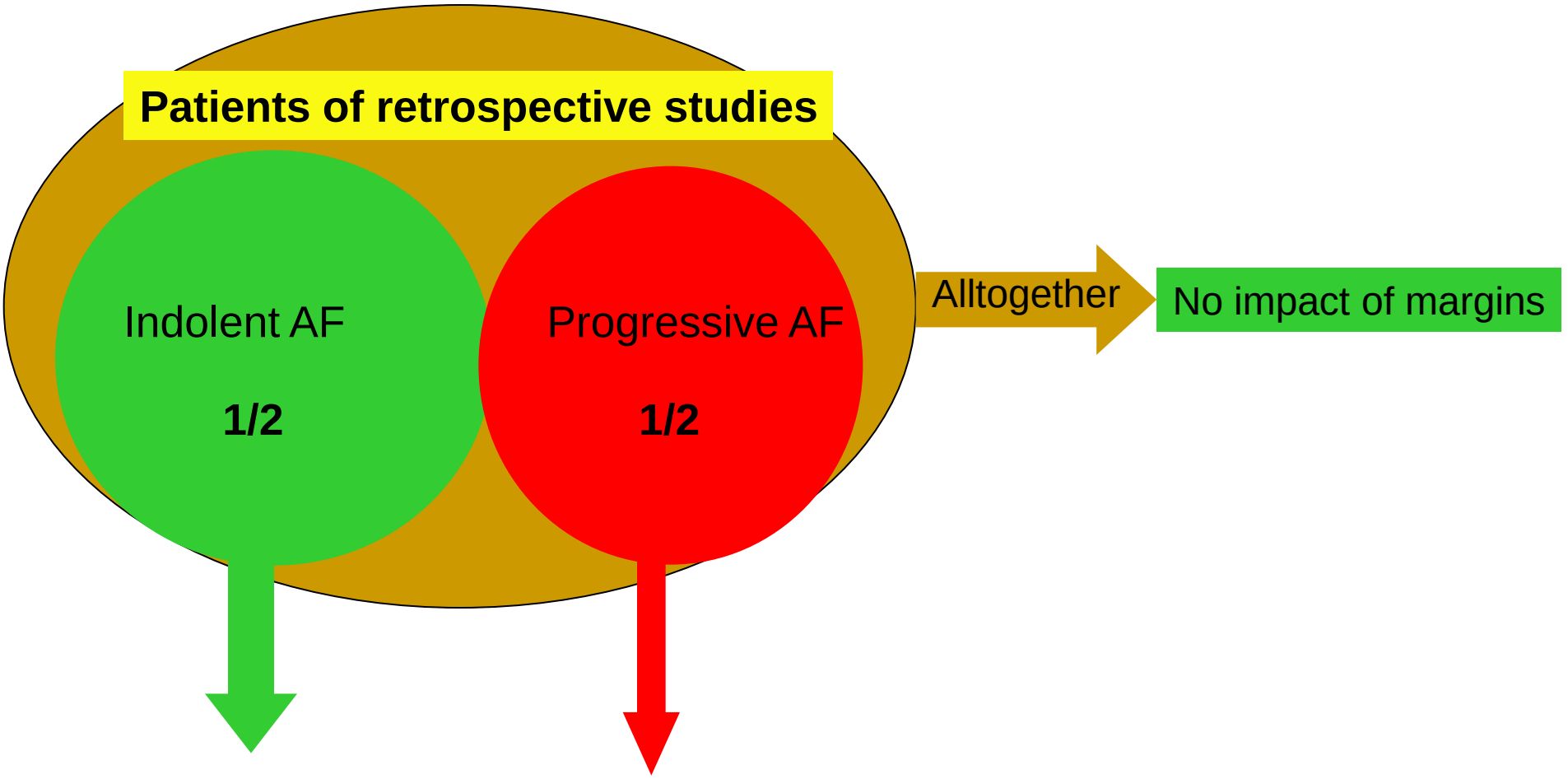
Analysis of factors predicting local recurrence after desmoid resection

	Univariate		Multivariate	
Factor	**Hazard ratio (95% CI)**	**p-value**	**Hazard ratio (95% CI)**	**p-value**
Margin status (R1 vs. R0)	1.18 (0.78, 1.80)	0.42	0.99 (0.65, 1.52)	0.97
Presentation status (recurrent vs. primary)	1.32 (0.82, 2.14)	0.28	1.16 (0.70, 1.90)	0.57
Depth (deep vs. superficial)	1.56 (0.63, 3.84)	0.34	1.37 (0.54, 3.45)	0.51
Gender (female vs. male)	1.17 (0.75, 1.84)	0.49	1.32 (0.82, 2.10)	0.25
Location (vs. abdominal wall)				
Extremity	5.21 (2.25, 12.1)	<0.001	5.02 (2.14, 8.42)	<0.001
Chest wall	3.31 (1.27, 8.62)	0.014	3.12 (1.20, 8.42)	0.02
Intraabdominal	2.79 (1.03, 7.55)	0.043	2.73 (0.98, 7.59)	0.054
Other	1.52 (0.31, 7.56)	0.61	1.54 (0.31, 7.63)	0.6
Size (>10 cm vs. <10 cm)	1.87 (1.22, 2.86)	0.005	1.94 (1.23, 3.05)	0.004
Age (vs. >65 y.o.)				
≤25 y.o.	4.27 (1.51, 12.2)	0.006	3.55 (1.23, 10.3)	0.013
26-65 y.o.	1.99 (0.72, 5.48)	0.19	2.02 (0.72, 5.70)	0.21



No impact of margins
All treatments will be efficient
No treatment could be enough

Negative impact of positive margins
Need for adapted treatment

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EJSO 34 (2008) 462–468
www.ejso.com

Extra-abdominal primary fibromatosis: Aggressive management could be avoided in a subgroup of patients☆

S. Bonvalot [a,*], H. Eldweny [a], V. Haddad [b], F. Rimareix [a], G. Missenard [a], O. Oberlin [c], D. Vanel [d], P. Terrier [e], J.Y. Blay [f], A. Le Cesne [g], C. Le Péchoux [h]

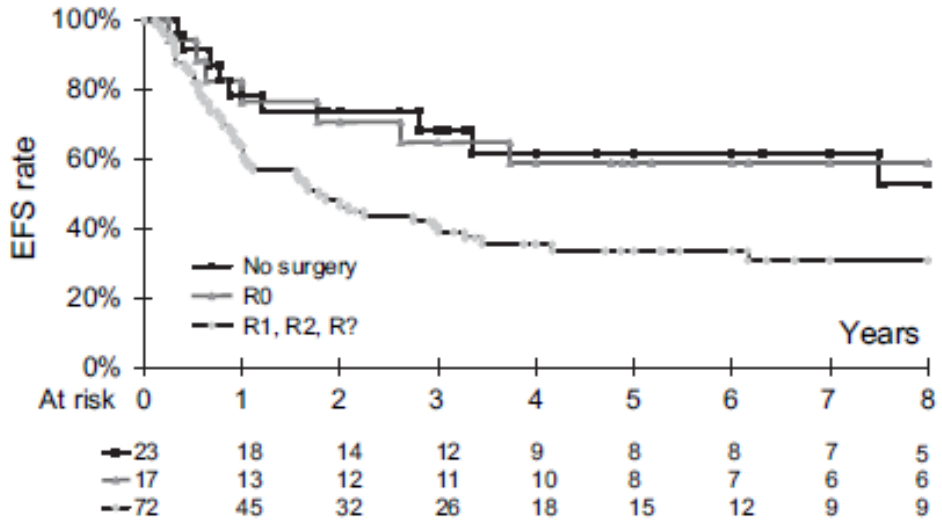

Figure 2. Event-free survival according to the quality of surgery (R0 versus no-surgery versus R1, R2, R not evaluated) (R? = R not evaluated).

Observation

- 5-year PFS: 49.9% for the W&S group (these pts were over treated before)
- 5-year PFS: 58.6% for the medical therapy group
- 50 % pts with primary avoid any treatment
- For pts who progressed, median TTP: 14 months

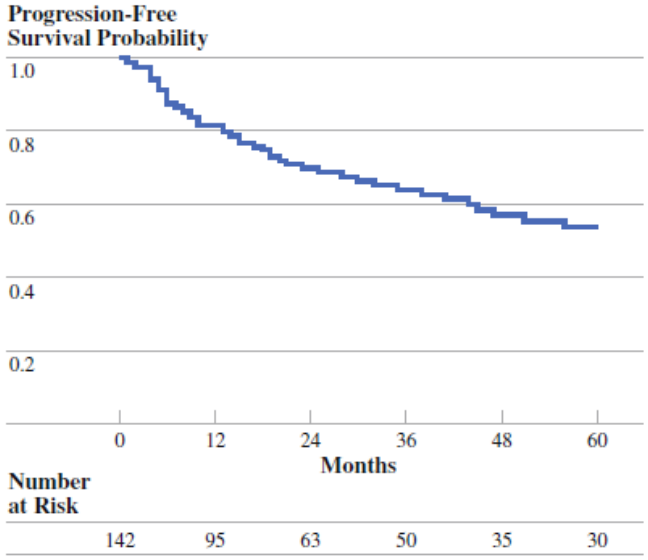

FIG. 1 Progression-free survival in the whole series

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Annals 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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ABSTRACT

Purpose. Surgery is still the standard treatment for desmoid-type fibromatosis (DF). Recently, the Institut Gustave Roussy (IGR), Villejuif, France, reported a series of patients treated with a front-line conservative approach (no surgery and no radiotherapy). The disease remained stable in more than half of patients. This study was designed to evaluate this approach on the natural history of the disease in a larger series of patients.

Methods. A total of 142 patients presenting to the IGR or Istituto Nazionale Tumori (INT), Milan, Italy, were initially treated using a front-line deliberately conservative policy. Their progression-free survival (PFS) was observed and a multivariate analysis was performed for major clinical variables.

Results. Seventy-four patients presented with primary tumor, 68 with recurrence. Eighty-three patients received a "wait & see" policy (W&S), whereas 59 were initially offered medical therapy (MT), mainly hormonal therapy and chemotherapy. A family history of sporadic colorectal cancer was present in 8% of patients. The 5-year PFS was 49.9% for the W&S group and 58.6% for the medically treated patients ($P = 0.3196$). Similar results emerged for primary and recurrent DF. Multivariate analysis identified no clinical variables as independent predictors of PFS. In the event of progression, all patients were subsequently managed safely.

Conclusions. A conservative policy could be a safe approach to primary and recurrent DF, which could avoid unnecessary morbidity from surgery and/or radiation therapy. Half of patients had medium-term stable disease after W&S or MT. A multidisciplinary, stepwise approach should be prospectively tested in DF.

Data were presented at the Connective Tissue Oncology Society (CTOS) 14th Annual Meeting, London, UK, November 14–17, 2008.

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Desmoid-type fibromatosis (DF) is a clonal fibroblastic proliferation marked by an infiltrative growth and an inability to metastasize.[1,2] For decades, standard treatment has been complete macroscopic surgical resection. However, sizable rates of local recurrences have been reported (range 20–60% at 5 years in major retrospective studies).[3–6] Given the unpredictable outcome of the disease and the lack of metastatic potential, the aggressiveness of surgery has evolved over time. Currently, it differs from that of soft tissue sarcomas.[4–8] In fact, until 1998 the standard treatment for DF consisted of primary resection with wide margins, possibly with radiotherapy when negative margins could not be achieved or surgery would have resulted in major functional or cosmetic defects.[9] Later, function-preserving surgery was advocated for DF, with particular emphasis on limiting unnecessary morbidity.[4–6] A "wait & see" (W&S) policy alone was first proposed for recurrent but stable lesions.[10] An initial period of observation also was considered for unresectable primary tumors.[11] Furthermore, DF may respond to chemotherapy or other systemic treatments

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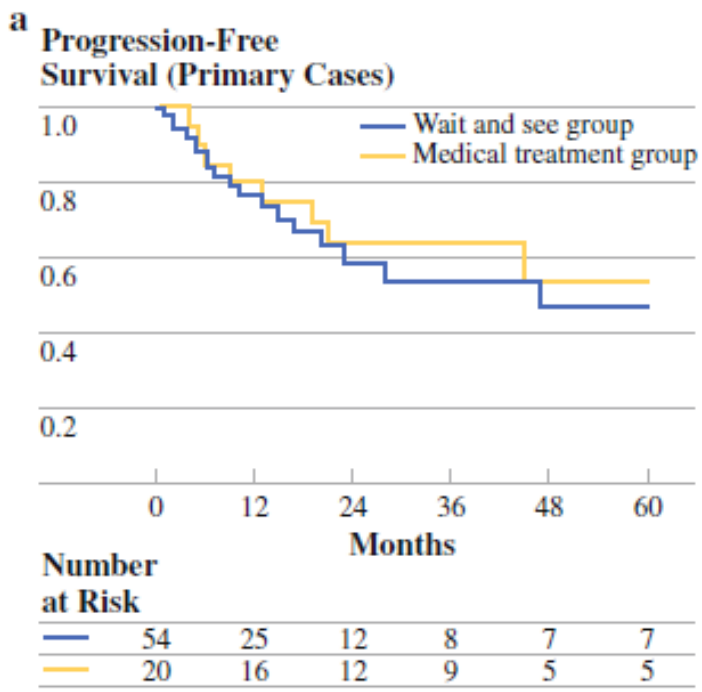

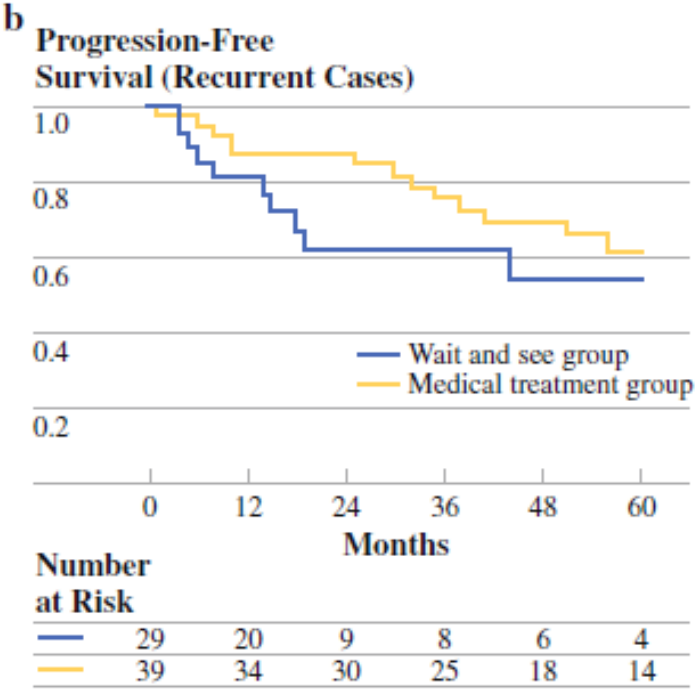

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ORIGINAL ARTICLE – BONE AND SOFT TISSUE SARCOMAS

Spontaneous Regression of Primary Abdominal Wall Desmoid Tumors: More Common than Previously Thought

Sylvie Bonvalot, MD, PhD[1], Nils Ternès, MS[2], Marco Fiore, MD[3], Georgina Bitsakou, MD[1], Chiara Colombo, MD[3], Charles Honoré, MD[1], Andrea Marrari, MD[4], Axel Le Cesne, MD[5], Federica Perrone, MD[6], Ariane Dunant, MS[2], and Alessandro Gronchi, MD[3]

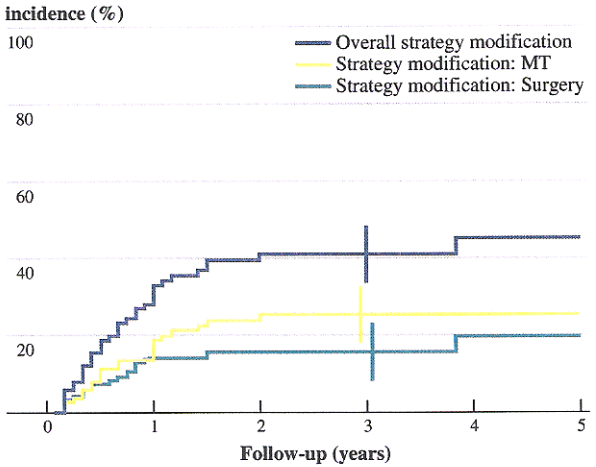

FIG. 2 Cumulative incidence of overall strategy modification, switch to medical treatment with no further switch, and final switch to surgery

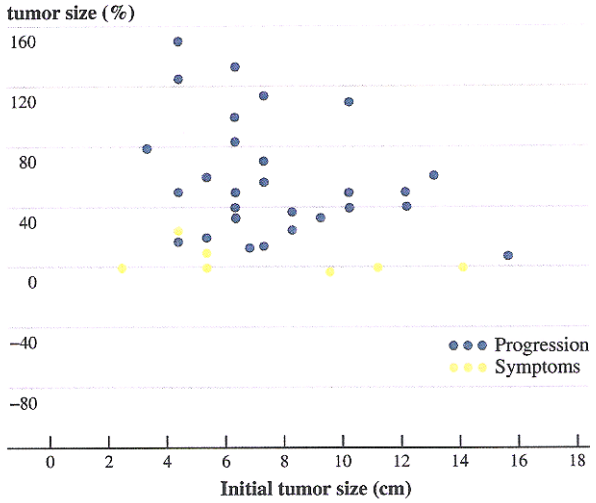

FIG. 3 Change in tumor size for patients with modification strategy (each *point* represents a patient)

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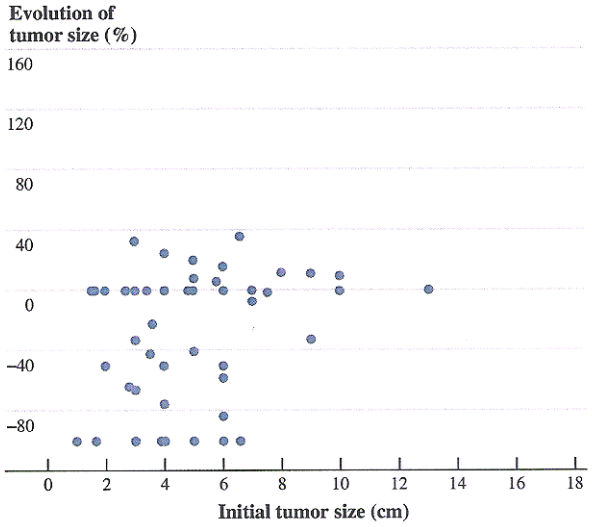

FIG. 4 Change in tumor size for patients without modification strategy (each *point* represents a patient)

147 patients

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Sporadic extra abdominal wall desmoid-type fibromatosis: Surgical resection can be safely limited to a minority of patients

C. Colombo [a], R. Miceli [b], C. Le Péchoux [c], E. Palassini [d], C. Honoré [e], S. Stacchiotti [d], O. Mir [f], P.G. Casali [d], J. Dômont [f], M. Fiore [a], A. Le Cesne [f], A. Gronchi [a,*], S. Bonvalot [e]

Table 1
Patients and tumour characteristics in the two treatment groups.

	Surgery group ($n = 94$)	Non-surgery group ($n = 122$)			
		CT ($n = 19$)	Medical treatment ($n = 29$)	W&S ($n = 70$)	RT ($n = 4$)
Sex					
Female	51 (54%)	11 (58%)	23 (79%)	48 (69%)	2 (50%)
Male	43 (46%)	8 (42%)	6 (21%)	22 (31%)	2 (50%)
Age (median)	43	30	43	41	31
Size (median)	7	10	9	7	10
Site					
Intra-abdominal	28 (30%)	6 (32%)	9 (31%)	10 (14%)	2 (50%)
Extremity/girdles	25 (27%)	6 (32%)	10 (35%)	26 (37%)	1 (25%)
Head/neck	10 (10%)	2 (10%)	3 (10%)	2 (3%)	0
Trunk	31 (33%)	5 (26%)	7 (24%)	32 (46%)	1 (25%)
Strategy modification					
Yes	NA	7 (37%)	18 (62%)	28 (40%)	0
No	NA	12 (63%)	11 (38%)	42 (60%)	4 (100%)

CT, chemotherapy; W&S, wait and see; RT, radiotherapy; NA, not applicable; ILP, isolated limb perfusion.

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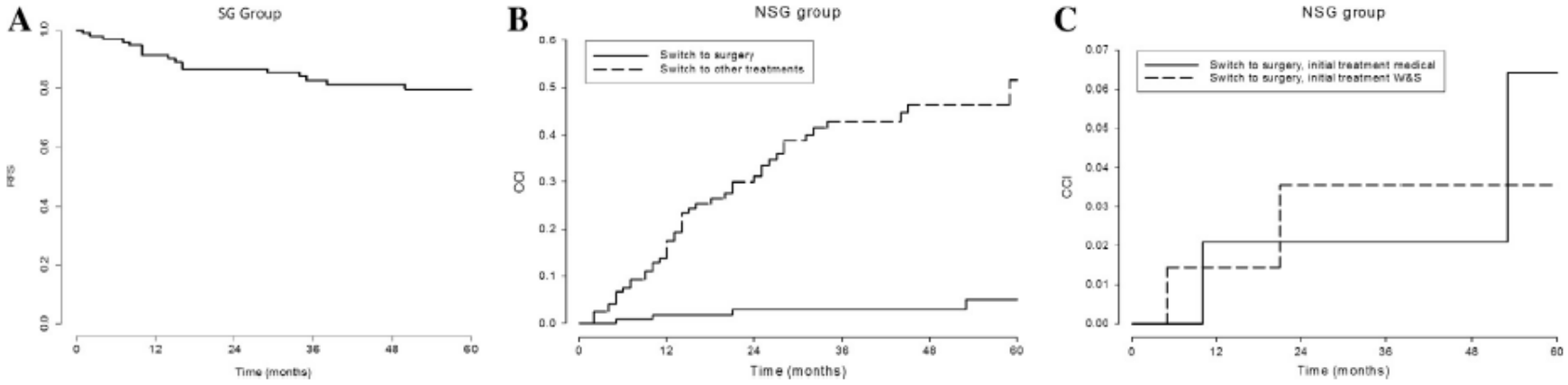

Fig. 1. Recurrence free survival for patients in surgical (SG) (panel A); crude cumulative incidence (CCI) of switch strategy in non-surgical (NSG) group: switch to surgery versus other treatments (Panel B) and switch to surgery if initial treatment was wait and see (W&S) versus medical treatments (Panel C).

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Toward a new strategy in desmoid of the breast?

S. Roussin [b], C. Mazouni [a], F. Rimareix [a,b], C. Honoré [b], P. Terrier [c], O. Mir [d], J. Dômont [d], C. Le Péchoux [e], A. Le Cesne [d], S. Bonvalot [b,*]

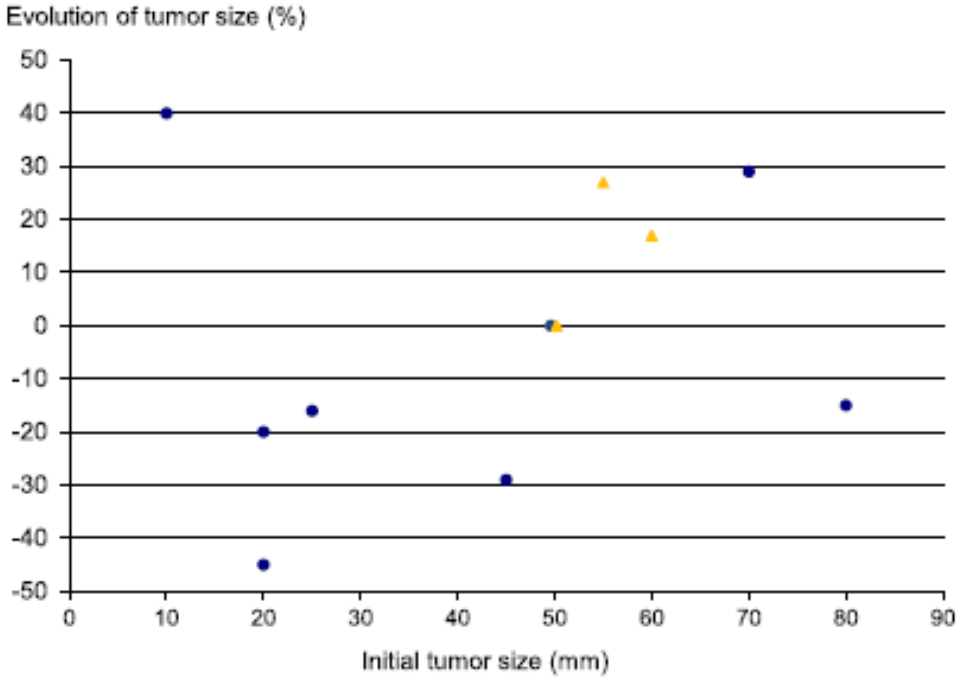

Figure 1. Evolution of tumor size (each point represents a patient) in the Non Surgery/Radiotherapy Group. Each point represents one patient. Yellow triangle: modification of strategy. Blue circle: no modification strategy.

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British Journal of Cancer (2011) 104, 37 – 42

www.bjcancer.com

Evaluation of management of desmoid tumours associated with familial adenomatous polyposis in Dutch patients

MH Nieuwenhuis*[,1], EM Mathus-Vliegen[2], CG Baeten[3], FM Nagengast[4], J van der Bijl[5], AD van Dalsen[6], JH Kleibeuker[7], E Dekker[2], AM Langers[8], J Vecht[9], FT Peters[7], R van Dam[3], WG van Gemert[3], WN Stuifbergen[10], WR Schouten[11], H Gelderblom[12] and HFA Vasen[1,8]

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

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

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

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

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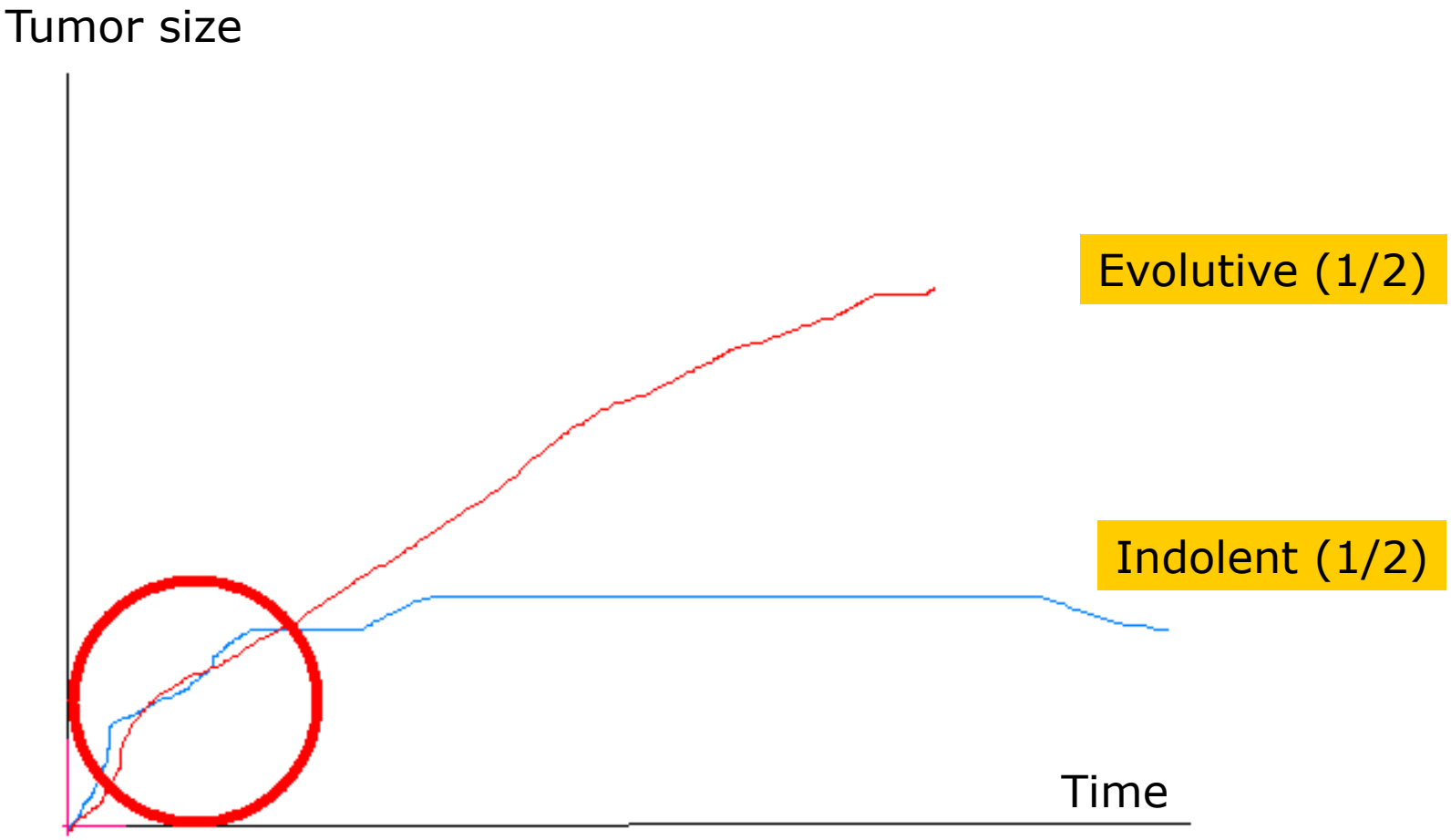
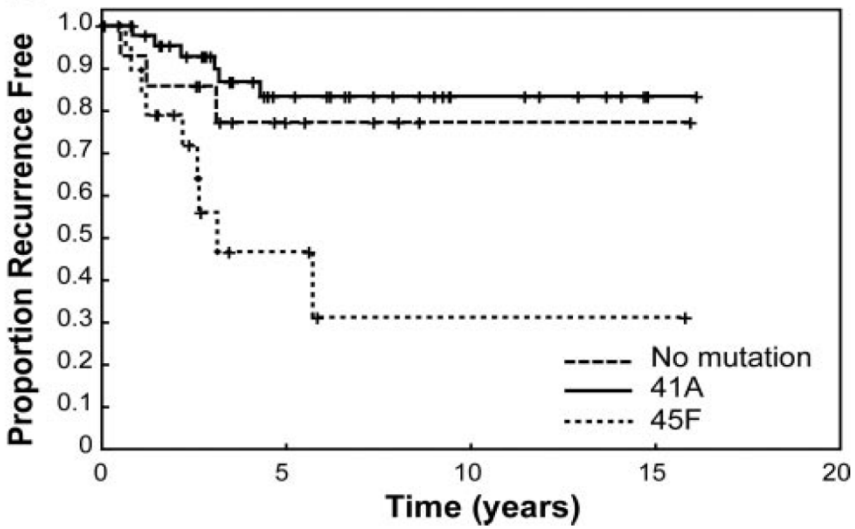
CONCLUSION: For intra-abdominal desmoids, a conservative approach and surgery showed comparable outcomes.

How to make the difference between the 2 groups?



Specific Mutations in the *β-Catenin* Gene (*CTNNB1*) Correlate with Local Recurrence in Sporadic Desmoid Tumors

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



The American Journal of Pathology, Vol. 173, No. 5, November 2008

DOI: 10.2353/ajpath.2008.080475

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JOURNAL OF CLINICAL ONCOLOGY

ORIGINAL REPORT

Prognostic Factors Influencing Progression-Free Survival Determined From a Series of Sporadic Desmoid Tumors: A Wait-and-See Policy According to Tumor Presentation

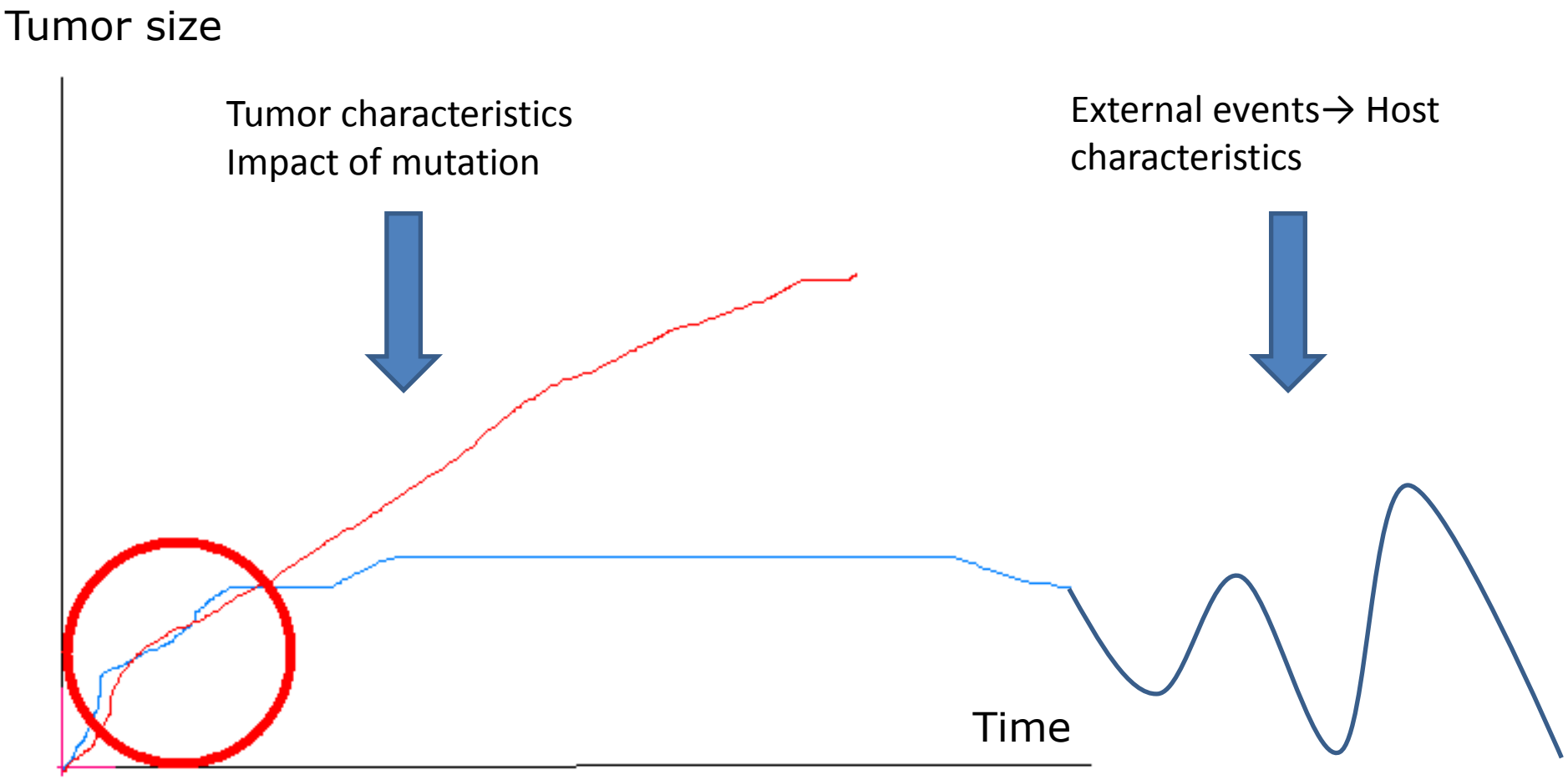
Sébastien Salas, Armelle Dufresne, Binh Bui, Jean-Yves Blay, Philippe Terrier, Dominique Ranchere-Vince, Sylvie Bonvalot, Eberhard Stoeckle, Louis Guillou, Axel Le Cesne, Odile Oberlin, Véronique Brouste, and Jean-Michel Coindre

Table 4. Multivariate Progression-Free Survival Analysis

Variable	Crude HR	95% CI	*P*
Median age	1.97	1.36 to 2.84	< .001
Median size	1.64	1.13 to 2.36	.008
Tumor site			
Abdominal wall			
Intra-abdominal tumor	1.95	0.92 to 4.15	.084*
Extra-abdominal tumor	2.55	1.48 to 4.4	< .001

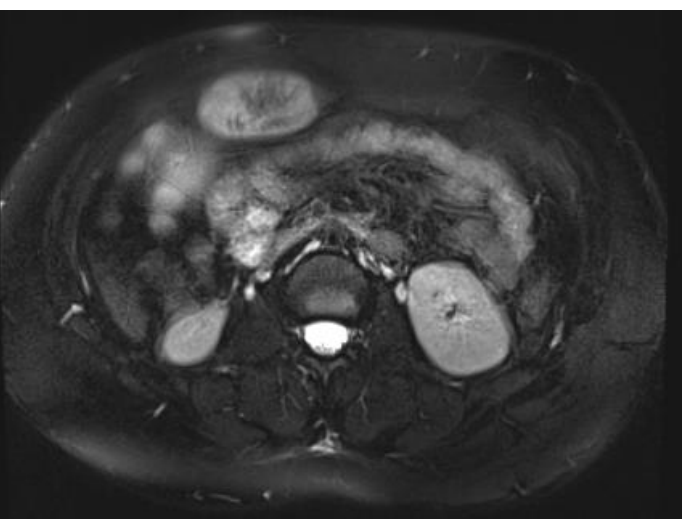
Abbreviation: HR, hazard ratio.
*Not significant.

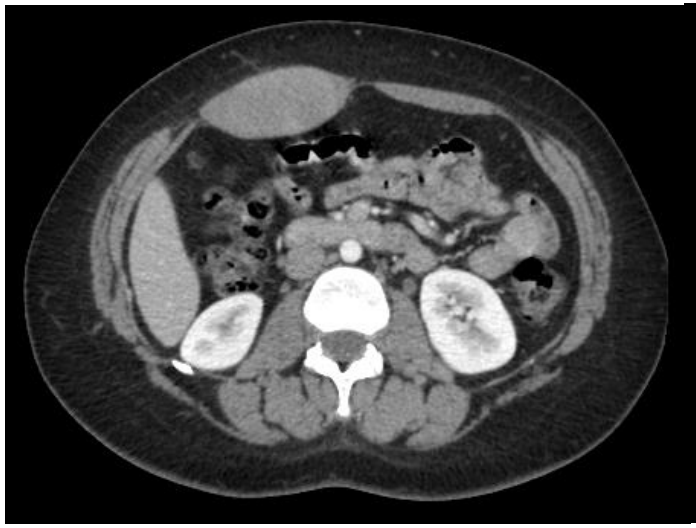
Evolution

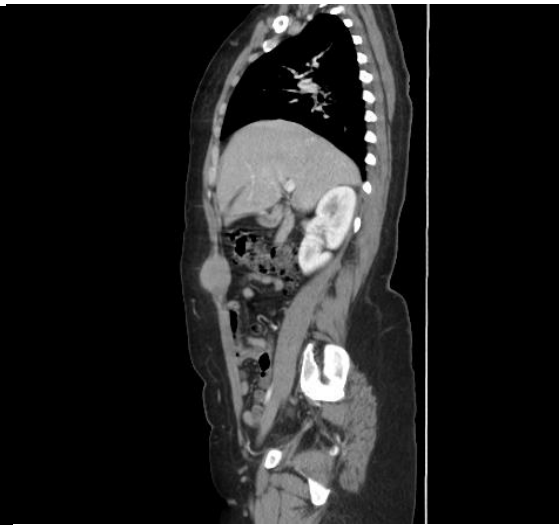

Tumor size
Tumor characteristics
Impact of mutation
External events→ Host characteristics
Time

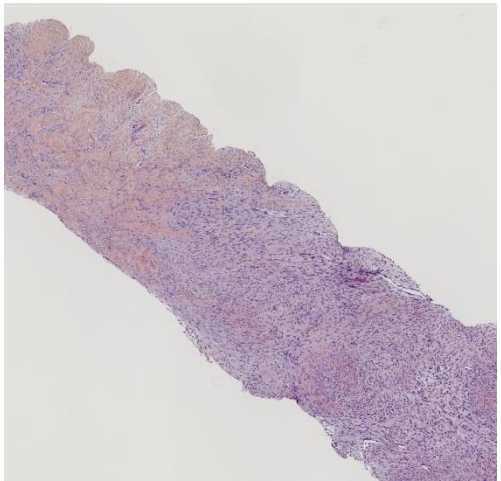
- 29 year-old woman, No past history
- Right parietal mass increasing in size (8 cm) for 5 months
- Percutaneous needle core biopsy / sonography
- Desmoïd tumor, Somatic mutation CTNNB1 T 41 A

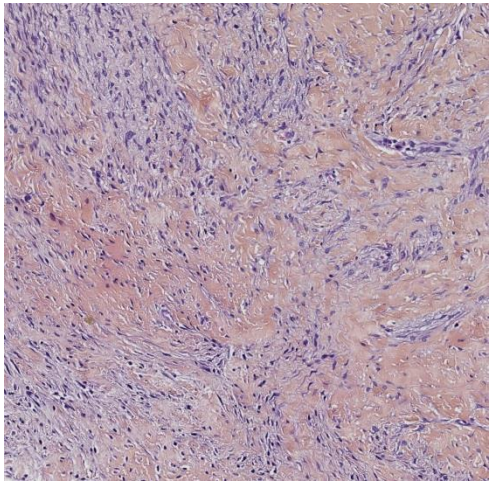
April 2012

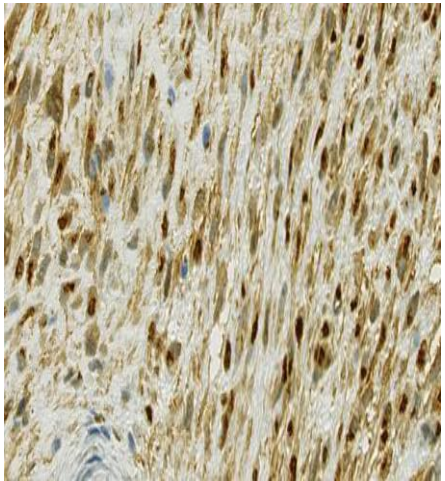




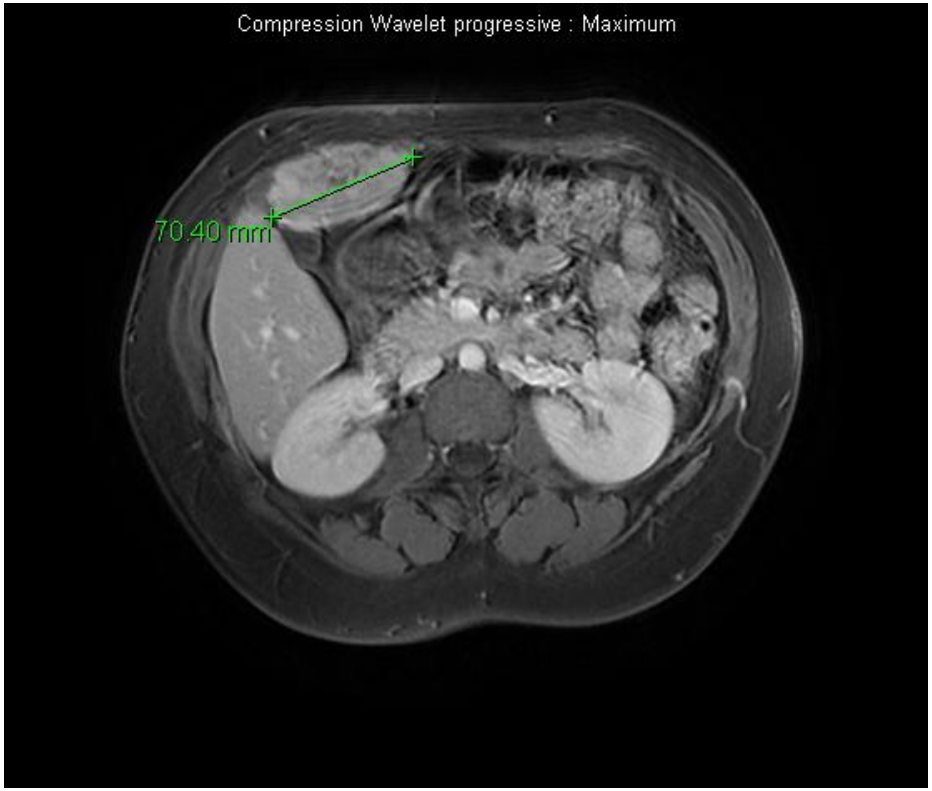


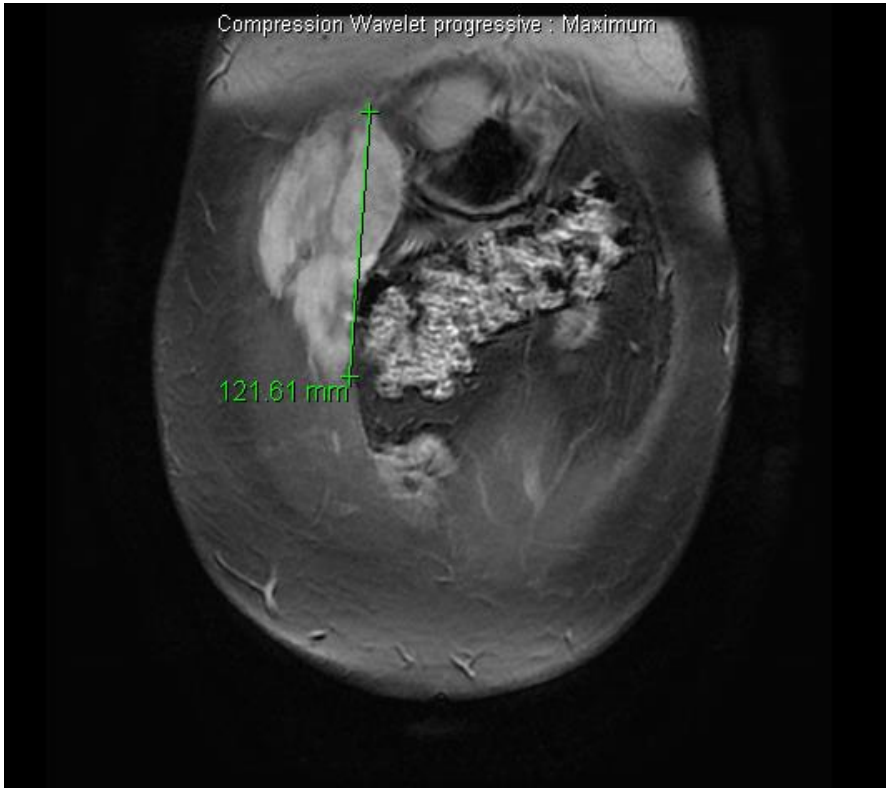




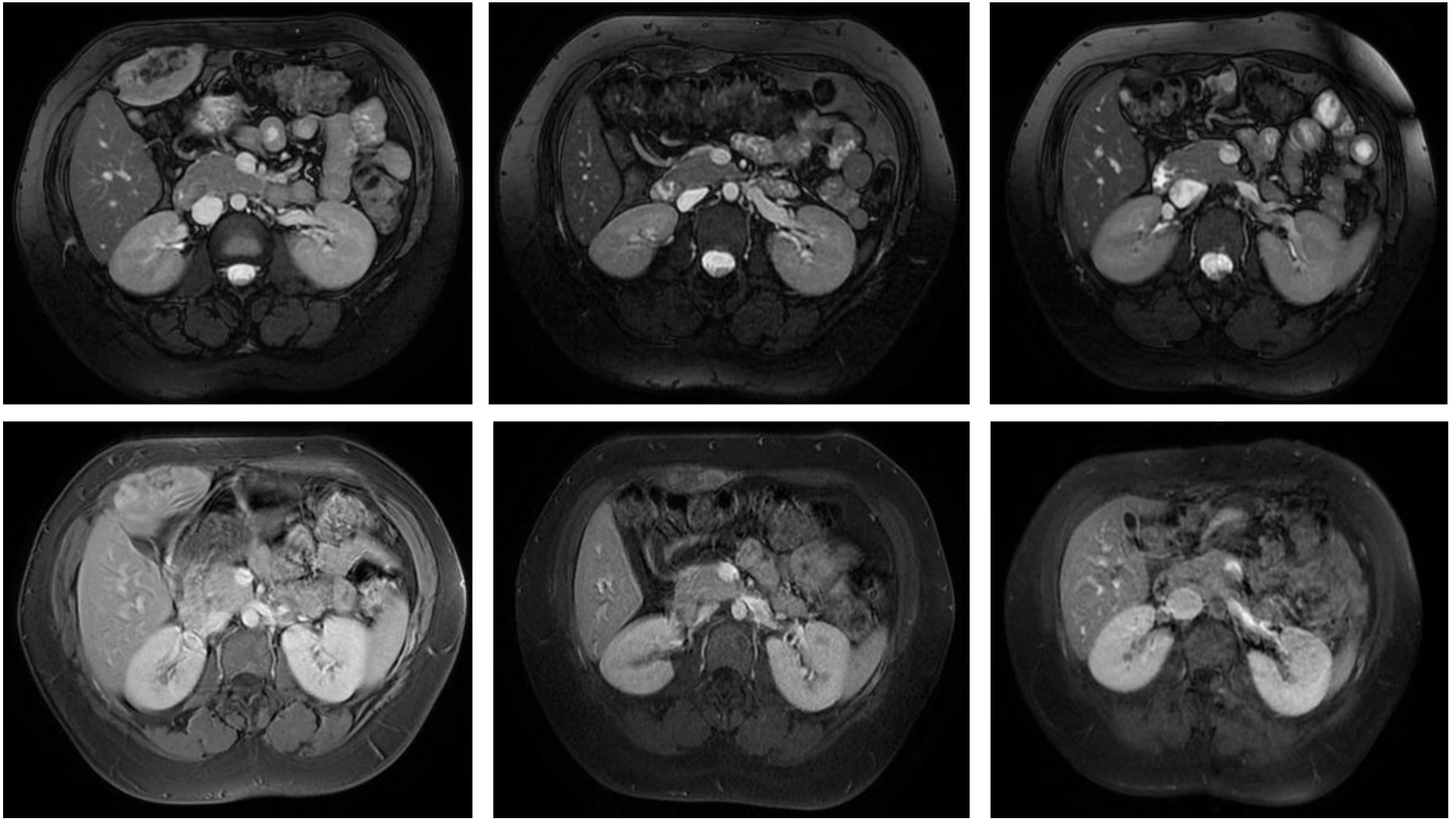


- Gave birth to a healthy baby april 2013
- Clinically: ± 12 cm mass (+50%)





April 2013 +1Year + 50%



April 2013

November 2013

May 2014
+2 years ≈ 0

symposium article

Annals of Oncology 23 (Supplement 10): x158–x166, 2012
doi:10.1093/annonc/mds298

The treatment of desmoid tumors: a stepwise clinical approach

S. Bonvalot[1]*, A. Desai[1], S. Coppola[1], C. Le Péchoux[2], P. Terrier[3], J. Dômont[4] & A. Le Cesne[4]

[1]*Departments of Surgery;* [2]*Radiotherapy;* [3]*Pathology;* [4]*Medical Oncology, Institut Gustave Roussy, Villejuif, France*

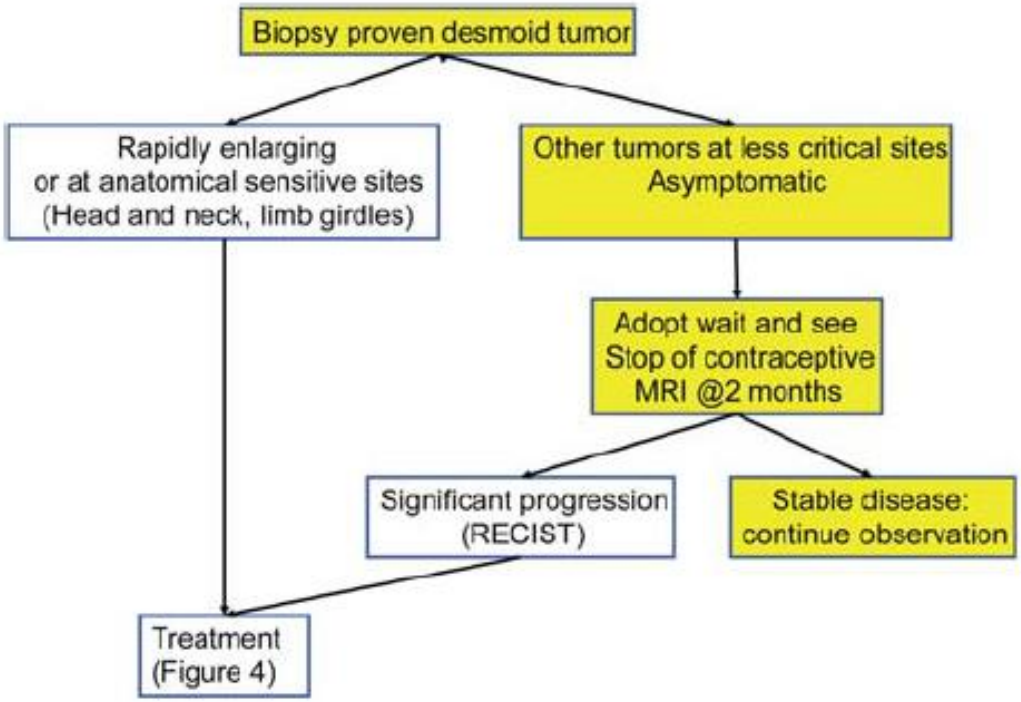


Figure 3. Initial treatment algorithm for primary desmoids.

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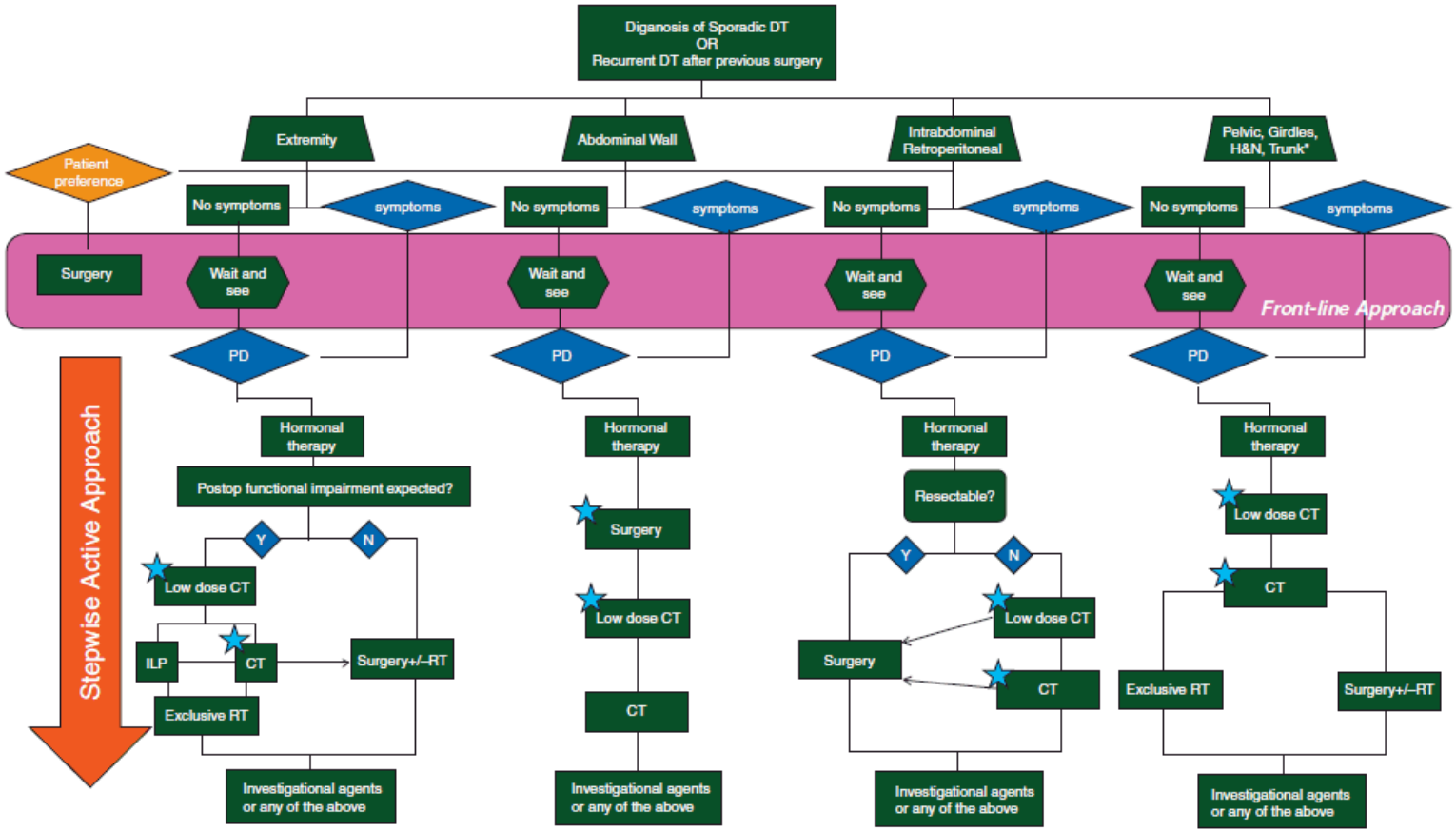
Annals of Oncology 00: 1–6, 2013
doi:10.1093/annonc/mdt485

Sporadic desmoid-type fibromatosis: a stepwise approach to a non-metastasising neoplasm—a position paper from the Italian and the French Sarcoma Group

A. Gronchi[1*], C. Colombo[1], C. Le Péchoux[2], A. P. Dei Tos[3], A. Le Cesne[4], A. Marrari[5], N. Penel[6], G. Grignani[7], J. Y. Blay[8], P. G. Casali[5], E. Stoeckle[9], F. Gherlinzoni[10], P. Meeus[11], C. Mussi[12], F. Gouin[13], F. Duffaud[14], M. Fiore[1], S. Bonvalot[15] & on behalf of ISG and FSG



H&N=head and neck *abdominal wall excluded ★ first choice in case of rapid PD

European Journal of Cancer (2015) 51, 127–136

Available at www.sciencedirect.com

ScienceDirect

journal homepage: www.ejcancer.com

Position Paper

Management of sporadic desmoid-type fibromatosis: A European consensus approach based on patients' and professionals' expertise – A Sarcoma Patients EuroNet and European Organisation for Research and Treatment of Cancer/Soft Tissue and Bone Sarcoma Group initiative

B. Kasper[a,*], C. Baumgarten[b], S. Bonvalot[c], R. Haas[d], F. Haller[e], P. Hohenberger[a], G. Moreau[f], W.T.A. van der Graaf[g], A. Gronchi[h], on behalf of the Desmoid Working Group[1]

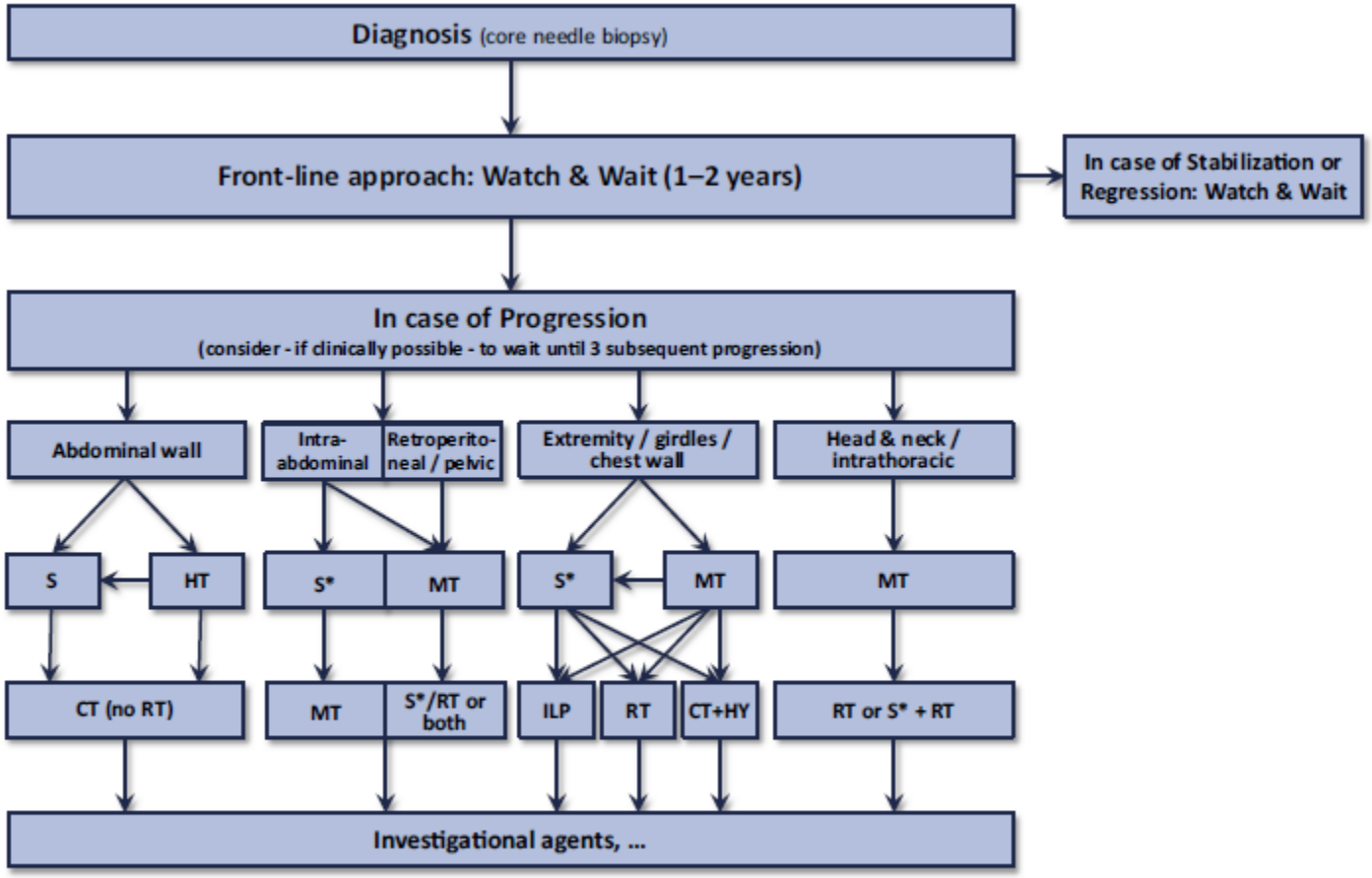
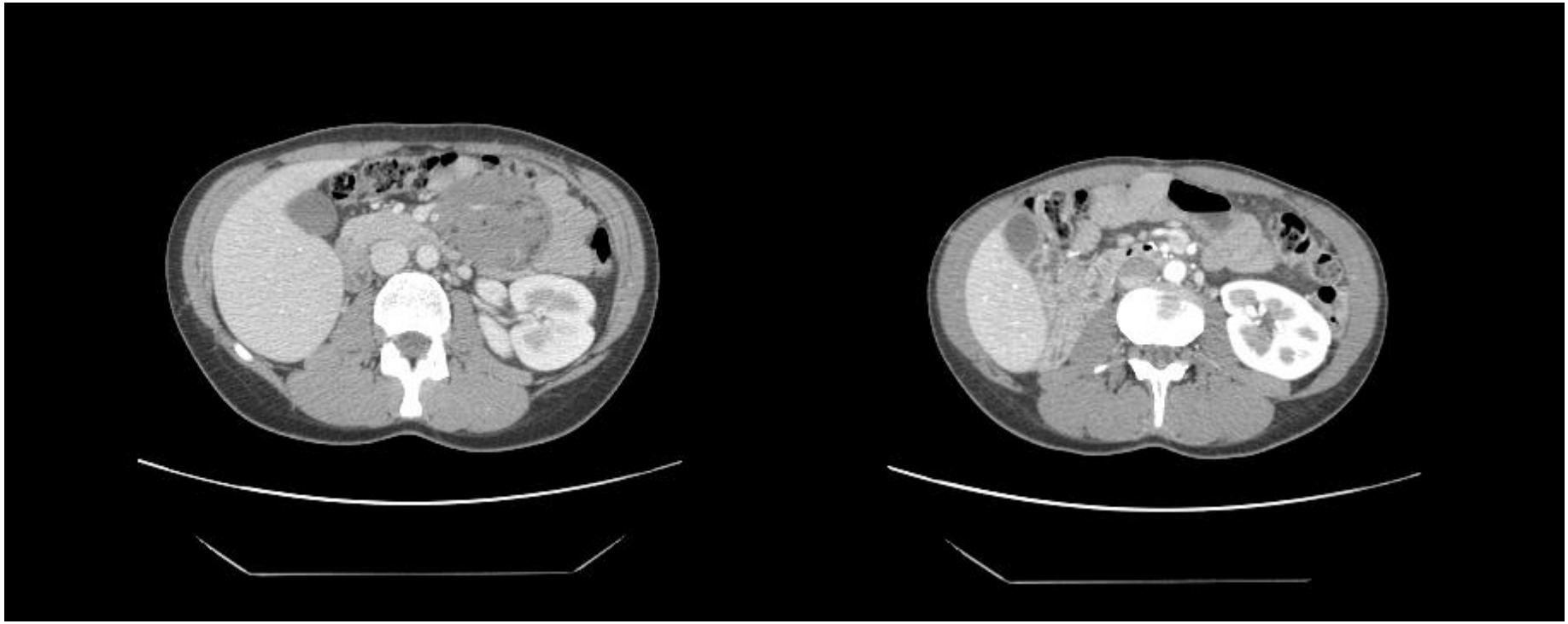


Fig. 1. Consensus algorithm. *Abbreviations:* HT, hormonal therapy; S, surgery; S*, surgery is an option if morbidity is limited; MT, medical therapy; RT, Radiotherapy; CT, chemotherapy; ILP, isolated limb perfusion; HY: hyperthermia.

No proven diagnosis

2007

2015



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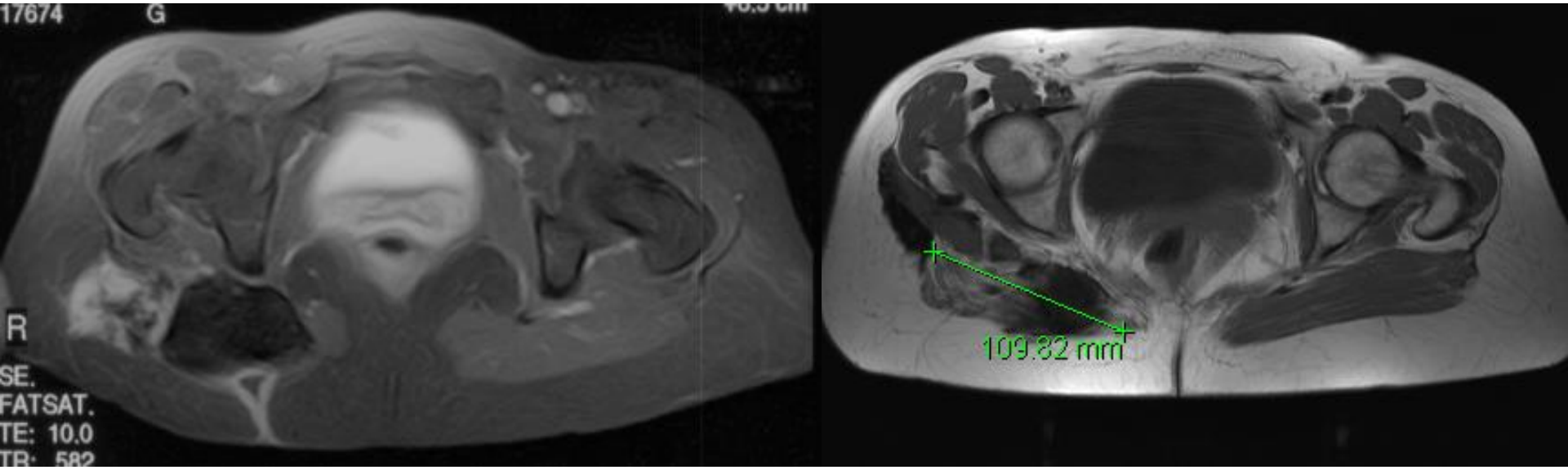
Exemple of « wait and see » policy on a resectable AF

MRI 1998 MRI 2012



36-year-old woman
Primary fibromatosis (surgical biopsy)
No treatment
No change

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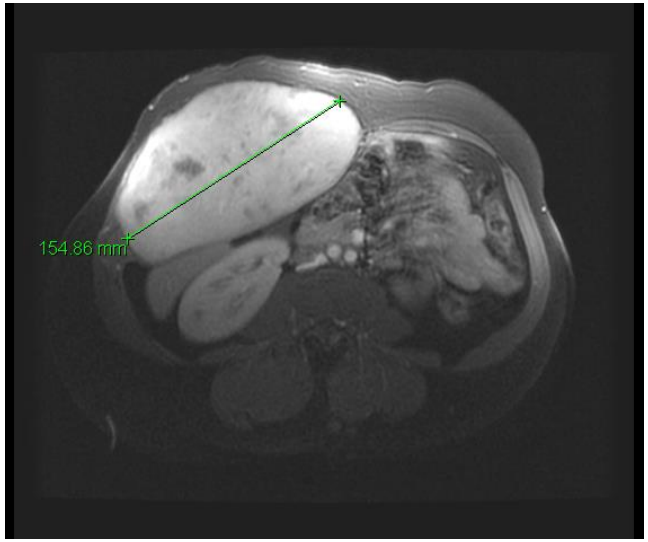
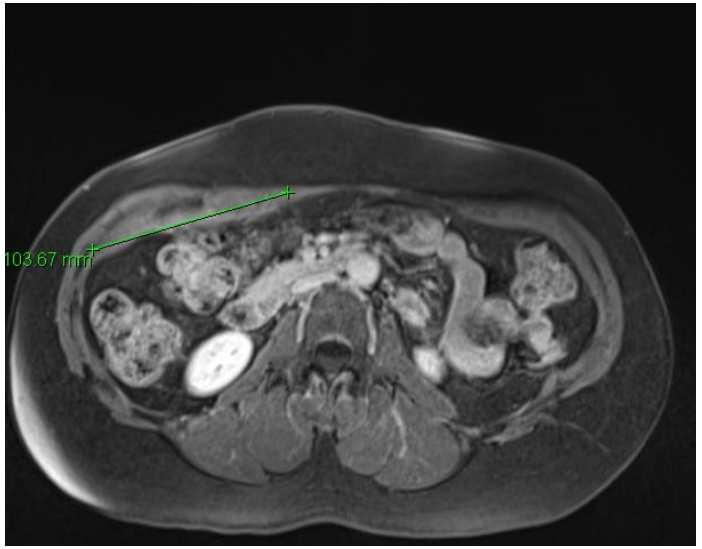
Wait and see



May 2005
Female: 50 years old
Biopsy: Desmoid (review FSG)



Oct 2015

- Size criteria is not sufficient…
- Regression/Stabilisation in desmoids is likely to have been underestimated as it has been calculated in a group of patients with recurrences where surgical options have been exhausted…

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symposium article

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The treatment of desmoid tumors: a stepwise clinical approach

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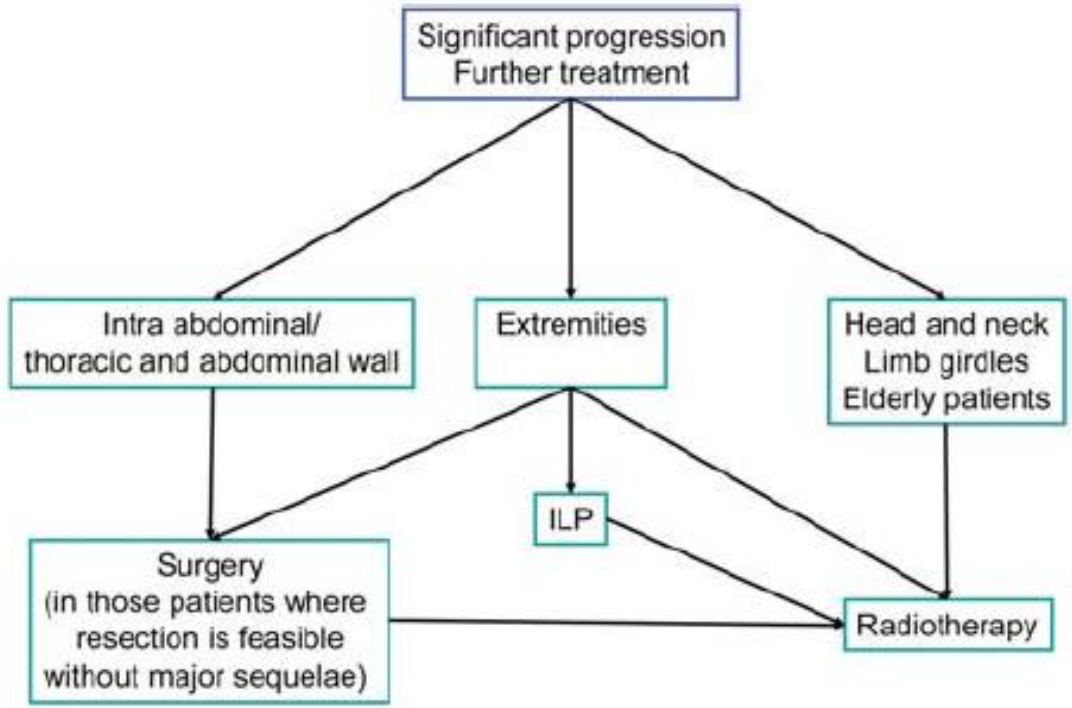

Figure 6. Treatment algorithm in cases of documented progression on MRI (part 2).

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Medical options

- Non-steroidal anti-inflammatory drugs (Sulindac, Meloxicam…)

  COX-2 partially regulates proliferation because of beta-catenin stabilization in AF. COX-blocking agents results in reduced proliferation.

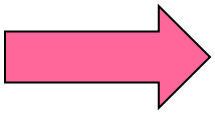
- Hormone therapy (Tamoxifen, Toremifene, Gn-RH analogues)

  Antiestrogen treatment could be mediated by estrogen receptor (ER) beta (Deyrup AT et al. Cancer. 2006)

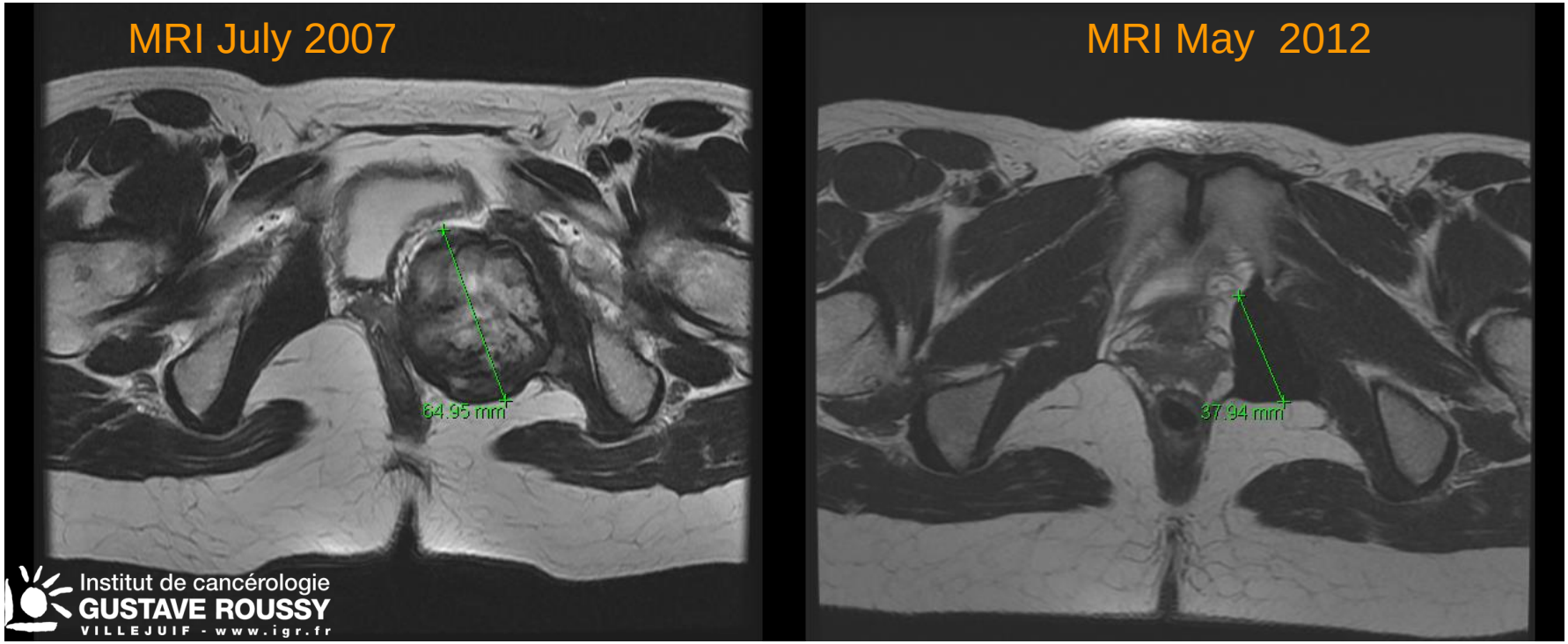
- Tyrosine kinase inhibitors

- Interferon

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

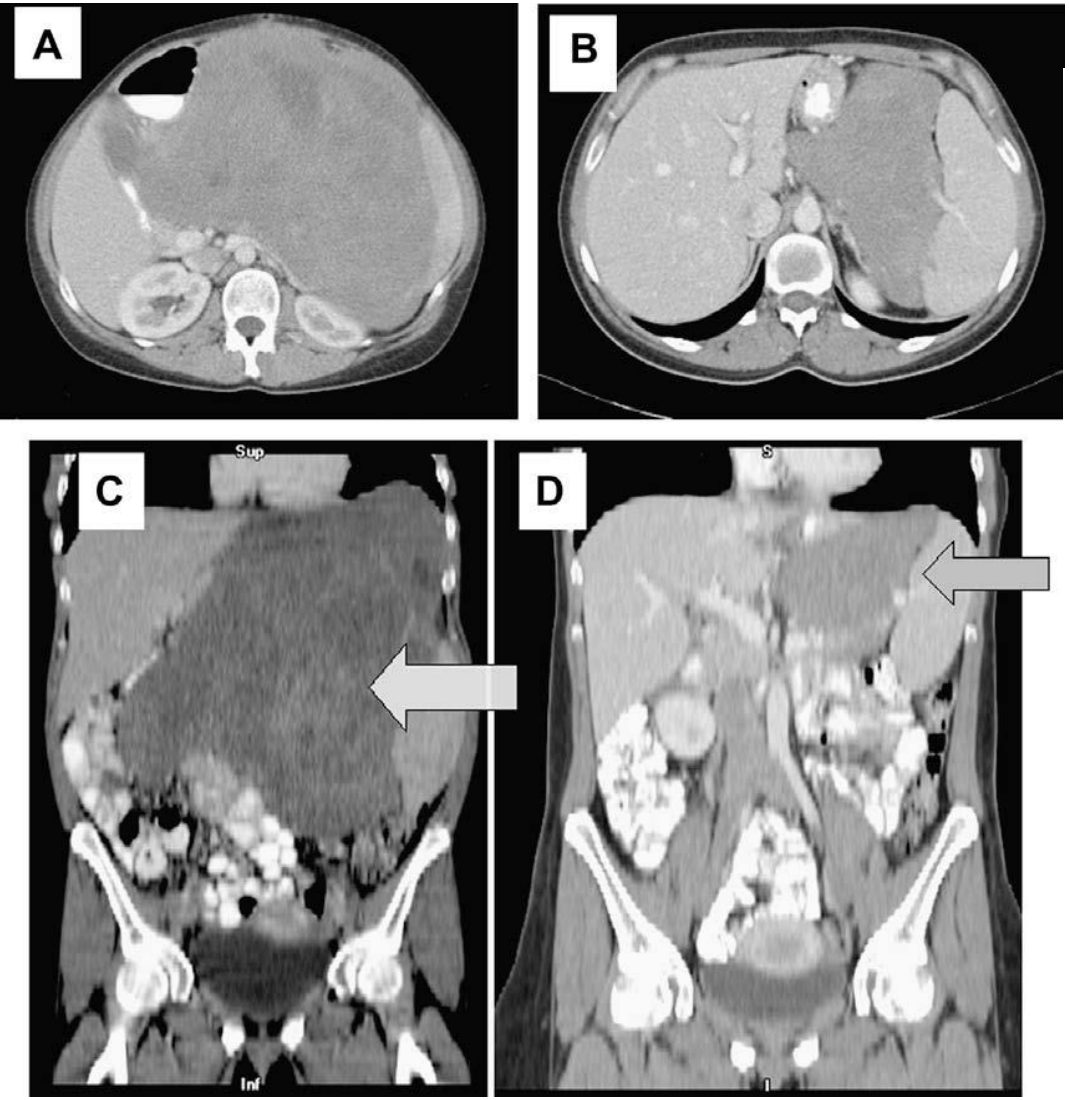


No randomized trial



34 years old female: post partum
Percutaneous biopsy: Desmoid
Tamoxifen and agonist LHRH: 18 months

- The surgery would have been mutilating
- The radiation source of sequelae in this young patient



Response to liposomal doxorubicin
CT scan before (A,C) and after (B,D) 9 cycles of liposomal doxorubicin

EUROPEAN JOURNAL OF CANCER 44 (2008) 2404–2410

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journal homepage: www.ejconline.com

Multimodality treatment of mesenteric desmoid tumours

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ABSTRACT

Background: Desmoid tumours are rare neoplasms characterised by clonal proliferation of myofibroblasts that do not metastasise, but often exhibit an infiltrative pattern and functional impairment. When desmoids arise in the intestinal mesentery, surgical resection is seldom possible without life-altering loss of intestinal function.
Methods: Retrospective review of the clinical management of 52 consecutive patients treated for desmoids of the intestinal mesentery from January 2001 to August 2006. A multidisciplinary treatment plan was developed based on primary disease extent, tumour behaviour and resectability. Patients with stable but unresectable disease were observed without treatment. Patients with resectable disease underwent surgery, and patients with unresectable progressing disease received chemotherapy, most commonly liposomal doxorubicin, followed by surgery if chemotherapy rendered the disease resectable.
Results: At a median follow-up of 50.0 months (range 4.6–212), 50 patients (96%) have either no recurrence or radiographically stable disease. No patient requires total parenteral nutrition.
Conclusion: These data indicate that the extent of disease, tumour behaviour and resectability are the important factors when defining a treatment plan for mesenteric desmoid tumours. A multidisciplinary approach of surgery combined with chemotherapy is an effective and function-sparing strategy for managing this disease.

1. Background and aims

Desmoid tumours, also known as desmoid fibromatoses, are uncommon soft tissue neoplasms. Although they do not metastasise, desmoids often exhibit an infiltrative pattern of spread in an abundant collagen matrix, giving them a dense, fibrotic character.[1] As a result, these tumours can produce local tissue destruction leading to significant morbidity and

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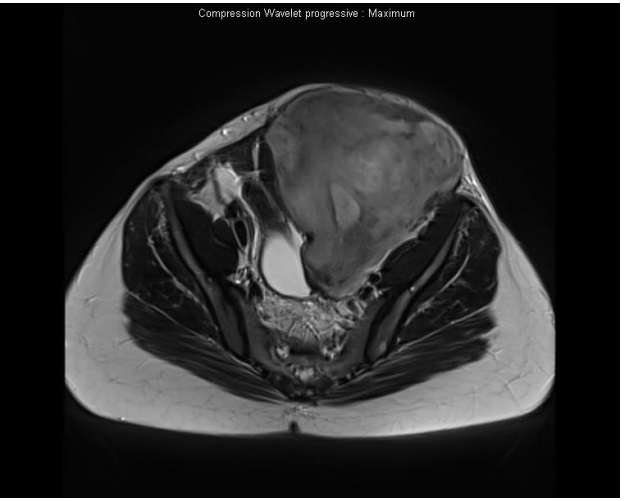
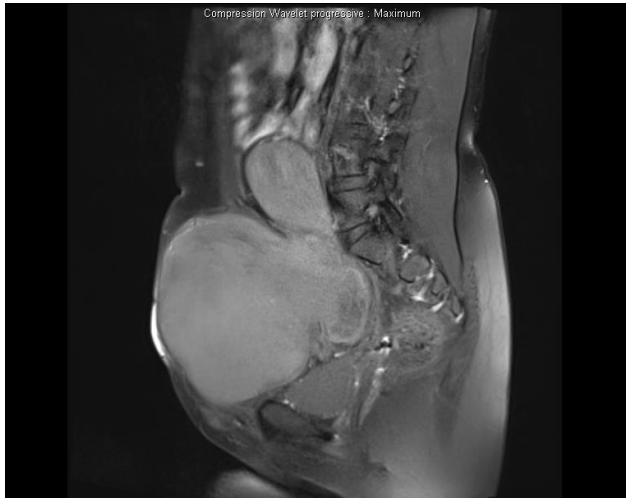
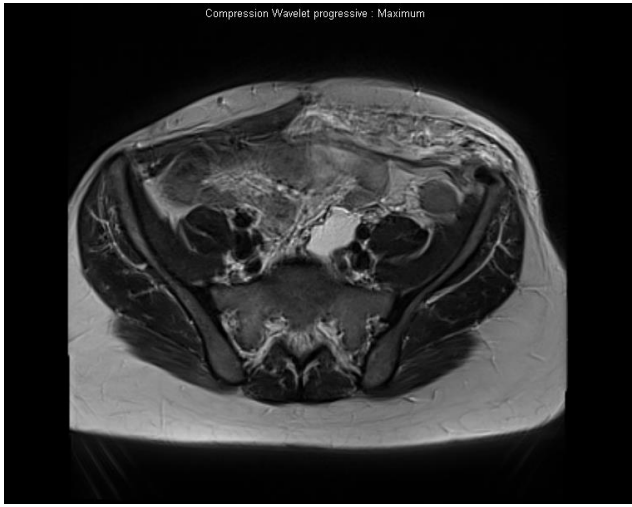
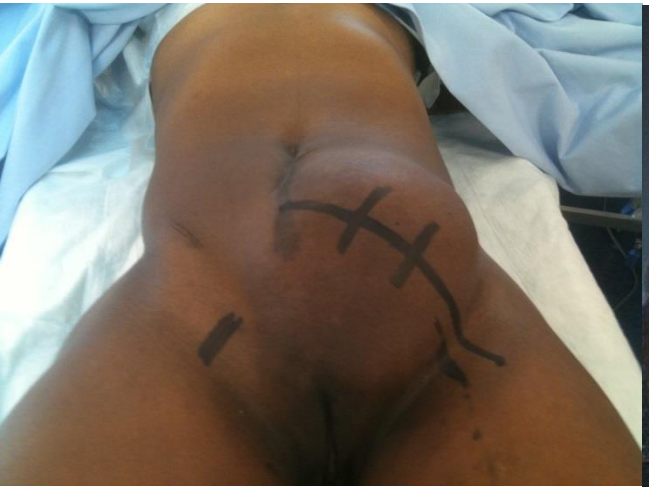
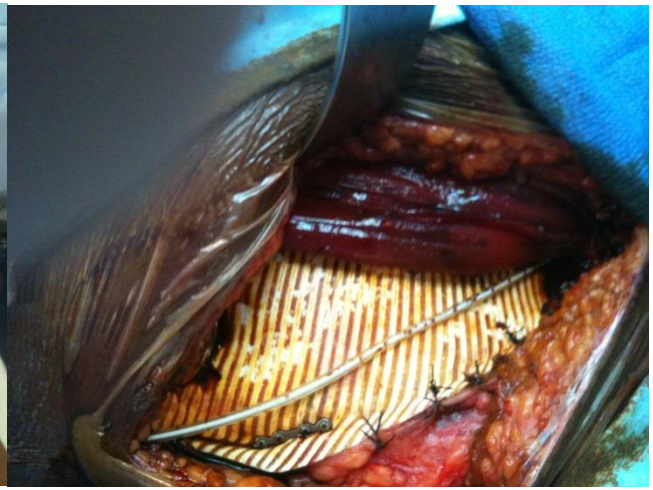
doi:10.1016/j.ejca.2008.06.038

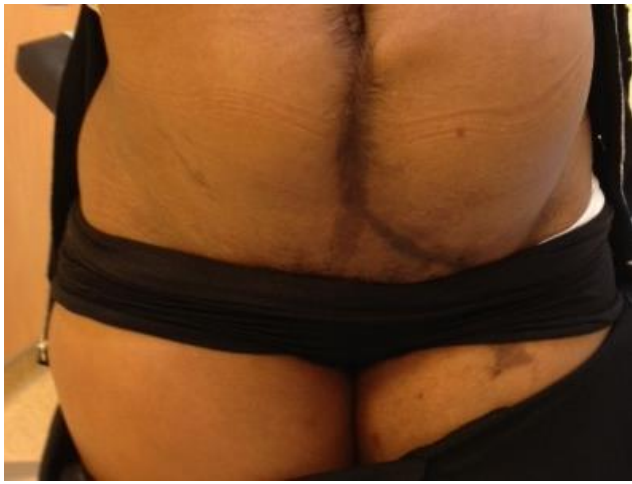












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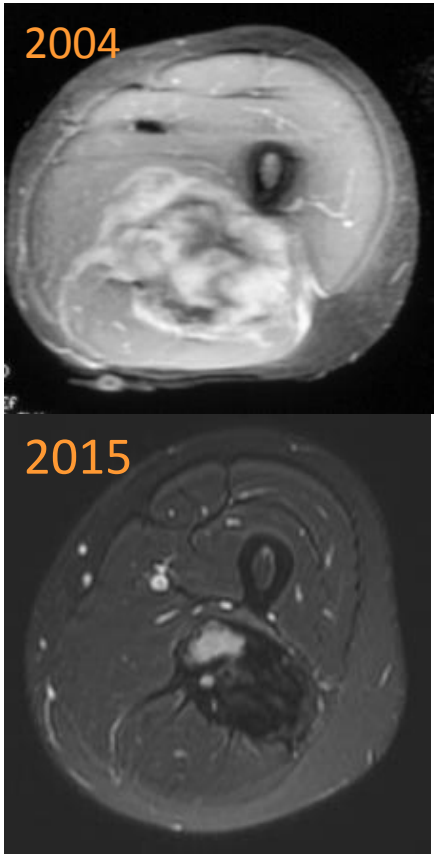
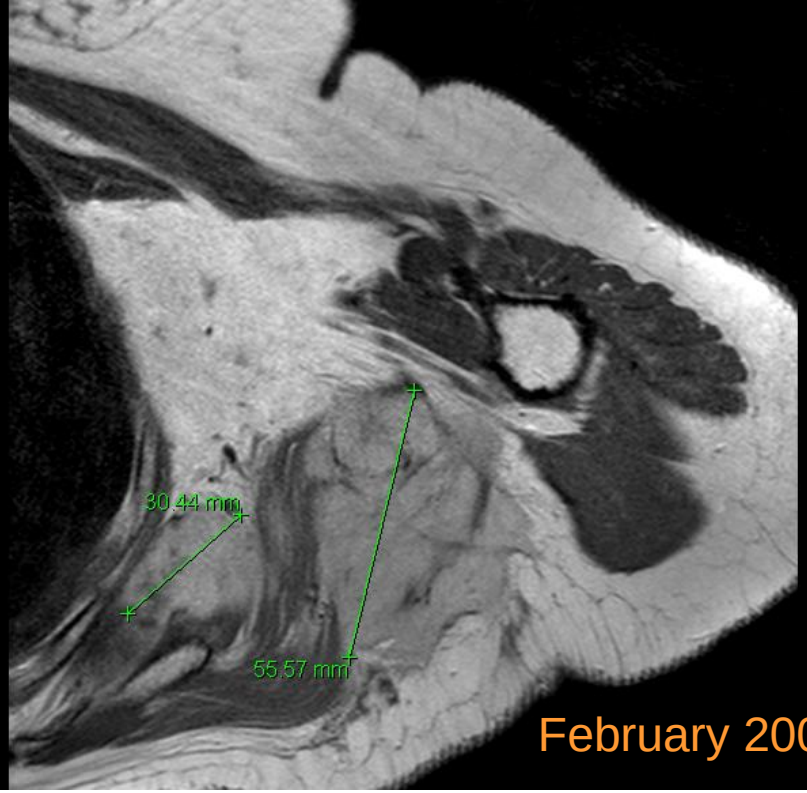
Isolated limb perfusion with tumor necrosis factor-alpha and melphalan has a possible role

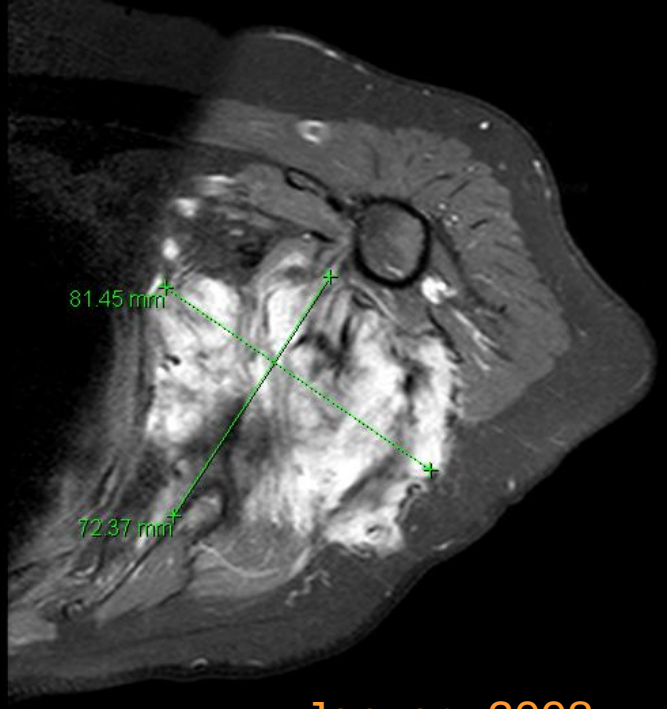
	N	CR	PR	Stable	Local progression
Lev- chelouche (Surgery 1999)	6	2	3		2 (Follow up 45 months)
Bonvalot (Ann Surg Oncol 2010)	8	1	6		1 (Follow up 27 months)
van Broekhoven (BJS 2014)	25	2	16	7	Amputation 3 pts (Follow up 84months)



20 years old Female Fibromatosis of the thigh

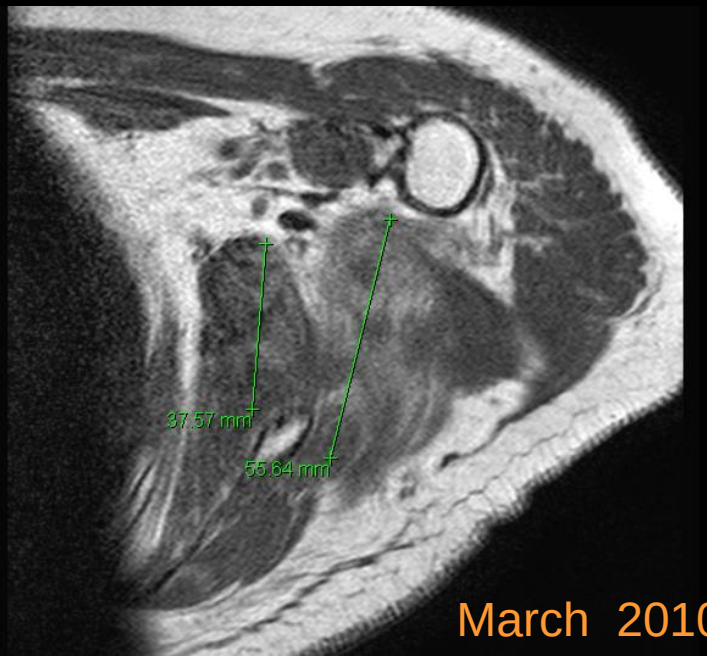


February 2007



January 2008

Female 59 years old
Surgical biopsy: desmoid
Initial wait and see
Progression
Exclusive radiotherapy 60 Gy



March 2010

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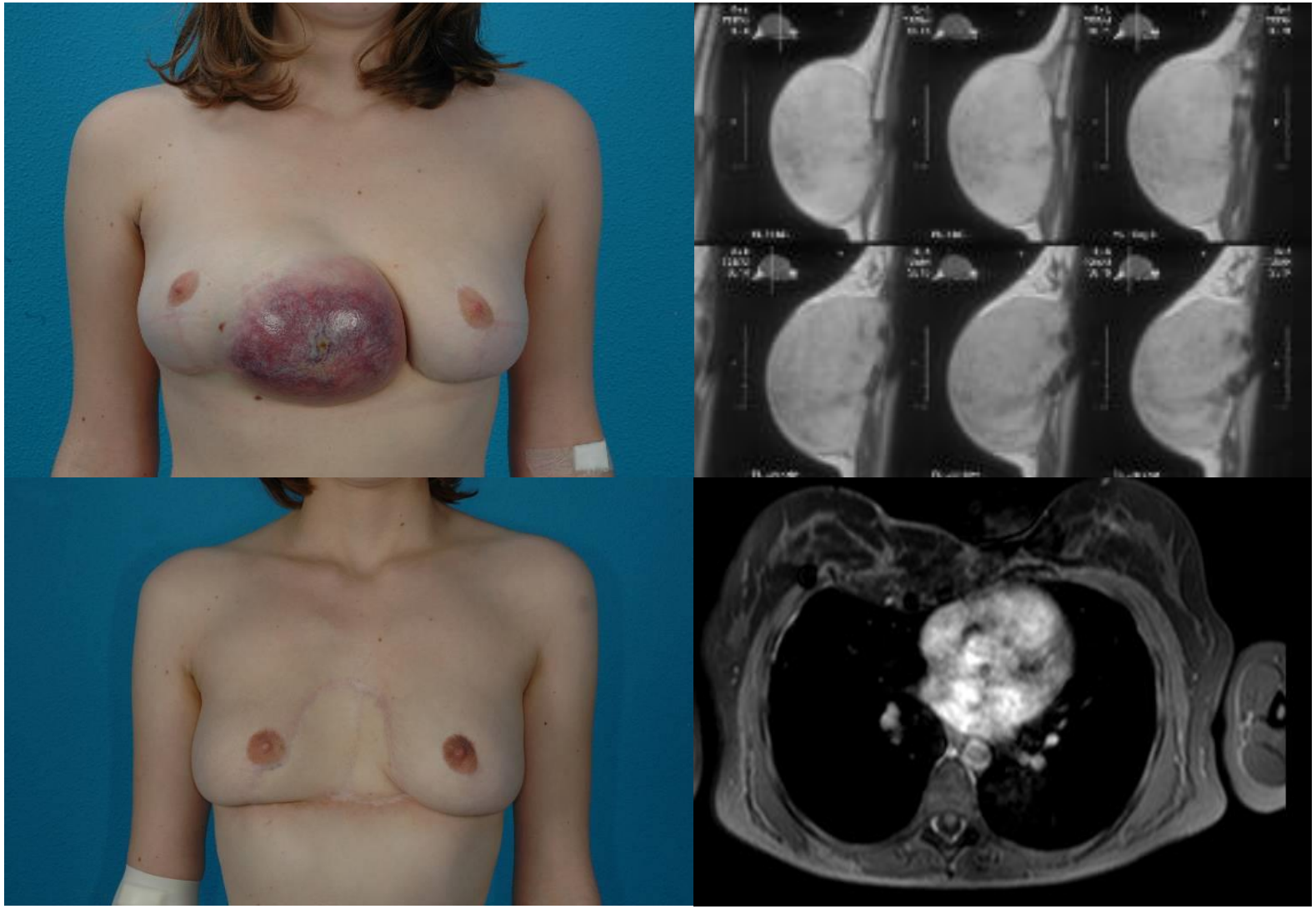
Surgery versus radiation therapy for patients with aggressive fibromatosis or desmoid tumors
A comparative review of 22 articles

1983 1998	Surgery + RT			RT alone
Local Control rate	Margins			
	-	+	overall	
	94%	75%	75%	78%

- RT alone or S + RT results in significantly better local control than S alone
- When radiotherapy is expected feasable and necessary, why to operate the patient if RT alone seems equivalent to S+RT??

Nuyttens JJ et al Cancer. 2000

Surgery and Radiotherapy



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Conclusions

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

- Observation alone could be considered for primary tumors
  - In case of diagnosis certitude (biopsy)
  - located such that progression would not cause significant morbidity
  - Surgery is not the best treatment of pain

- In cases of RECIST progression, treatment is tailored according to age, gender, location, symptoms…in specialized team

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