Management of desmoids

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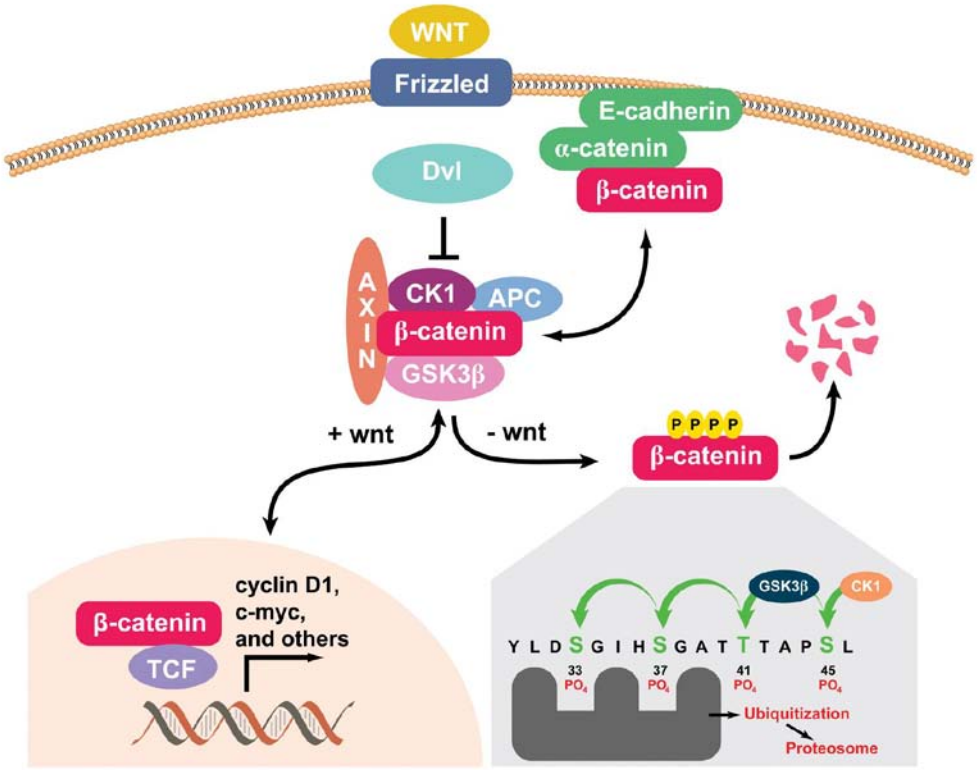
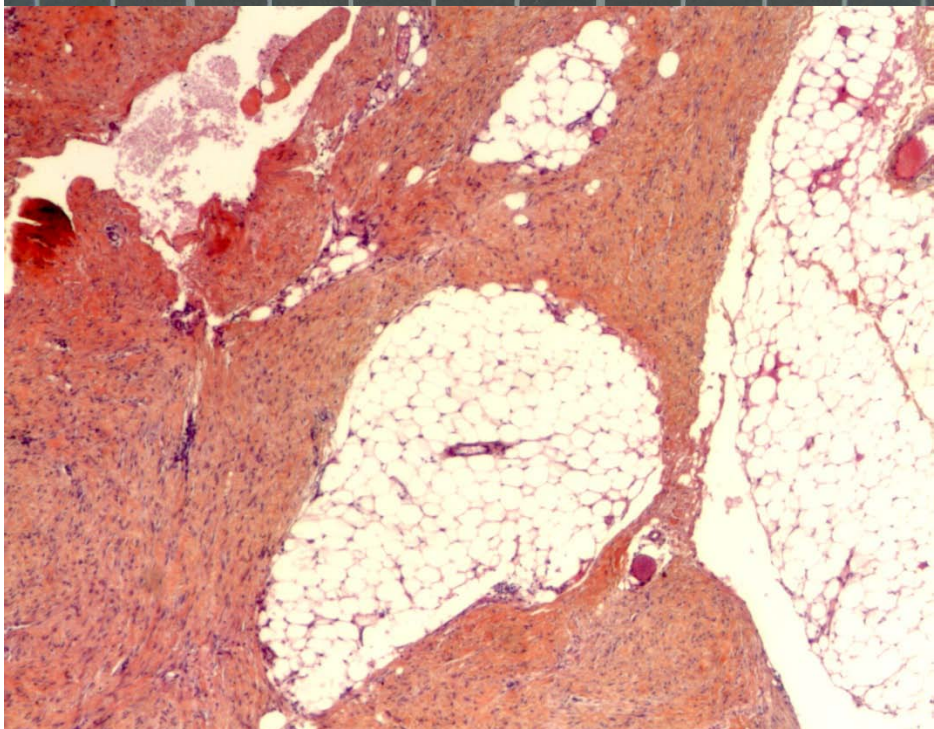
Desmoid Tumors - overview

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



AF: Clinical Properties

- Does not metastasize
- Does not de-differentiate to a high-grade malignancy in case of recurrence
- No “grading”: unpredictable clinical course with a same histologic morphology
- Infiltrative growth: the resection that is needed to achieve clear margins is often larger than for the same-sized sarcoma
- Desmoid = cause of death 10% FAP

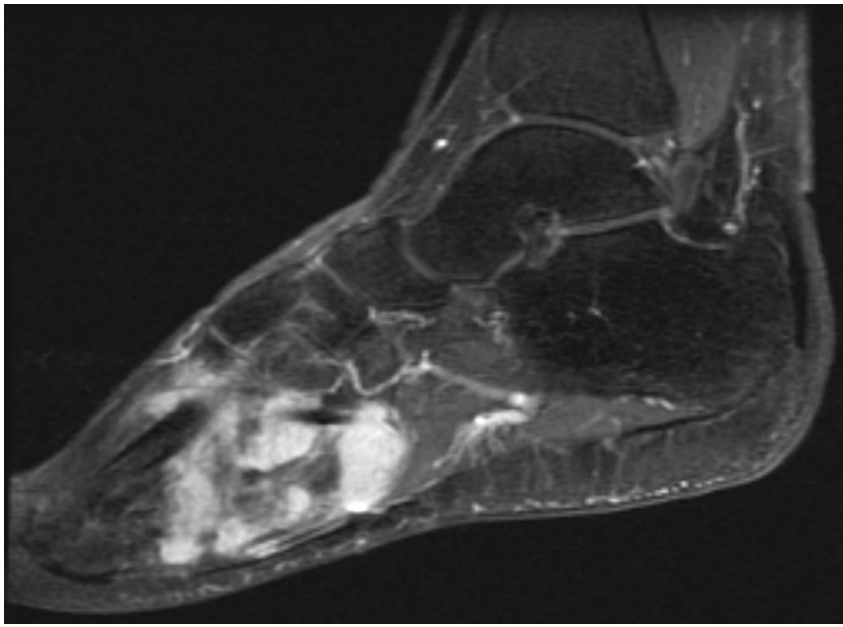


INDICATIONS OF AGGRESSIVE AND "DEFINITIVE" TREATMENTS (SURGERY AND RADIOTHERAPY) CHANGE OVER TIME

1980

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

2013



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

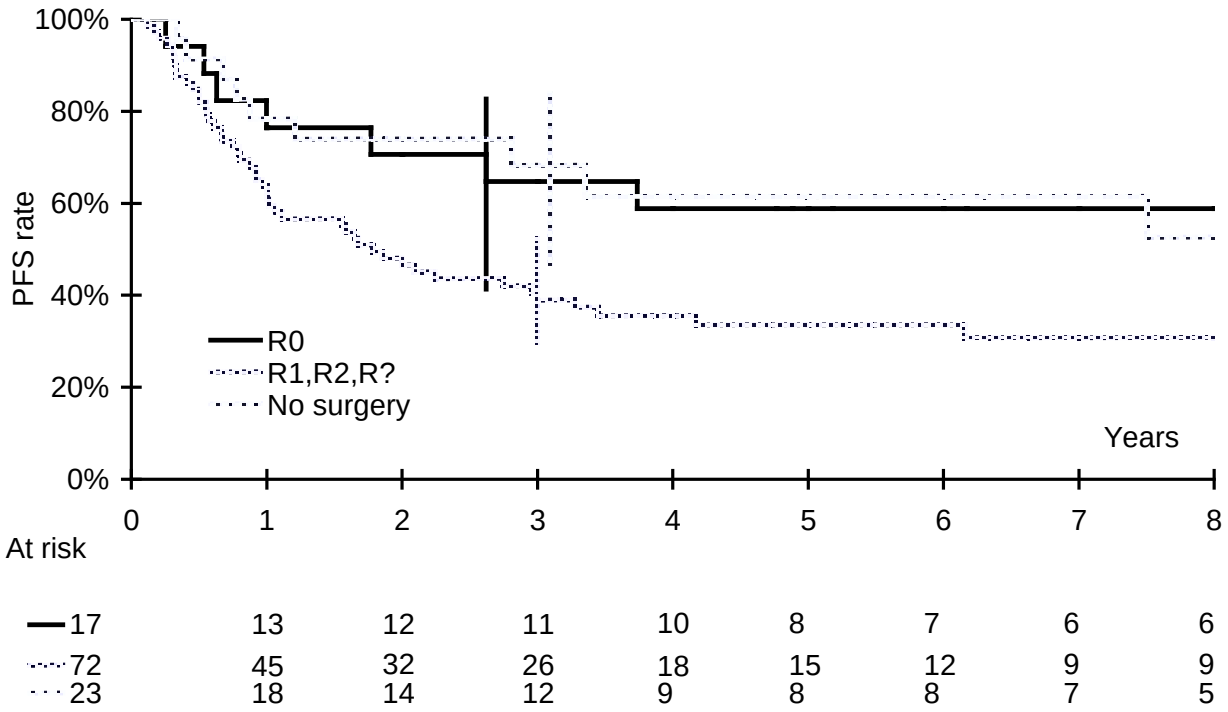
Lev JCO 2007, Bonvalot EJSO 2008, Fiore ASO 2009, Salas JCO 2012, ESMO 2012

Treatment options

1. Observation
2. Medical treatment
3. ILP
4. Radiotherapy
5. Surgery

1) Observation

Primary AF: Disease-free survival according to surgery



No surgery
R0

R1,R2,R?

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

Bonvalot et al. EJSO 2008

Observation

- 5-year PFS: 49.9% for the W&S group (these pts were over treated before)
- 5-year PFS: 58.6% for the medical therapy group
- 50 % pts with primary avoid any treatment

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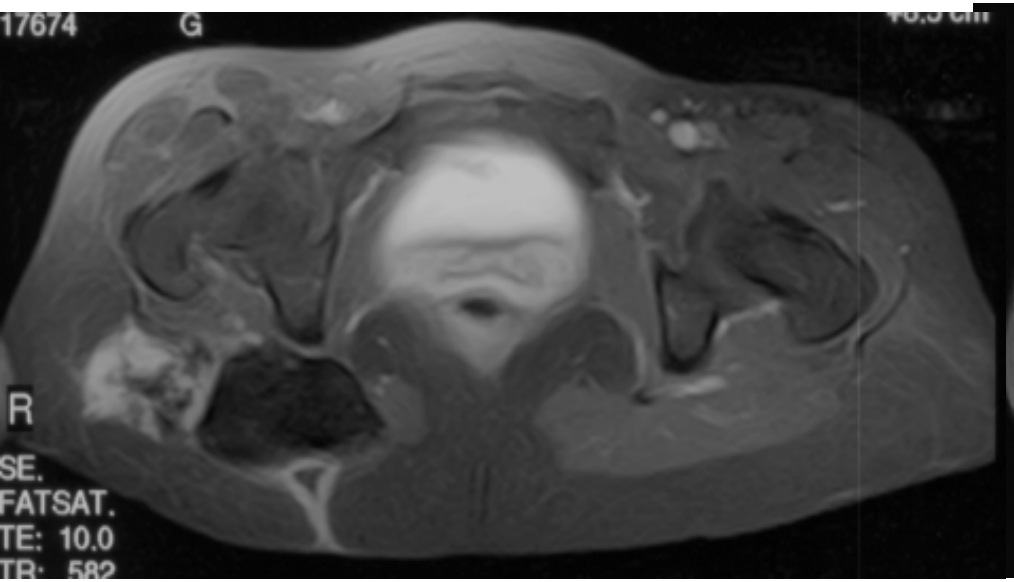
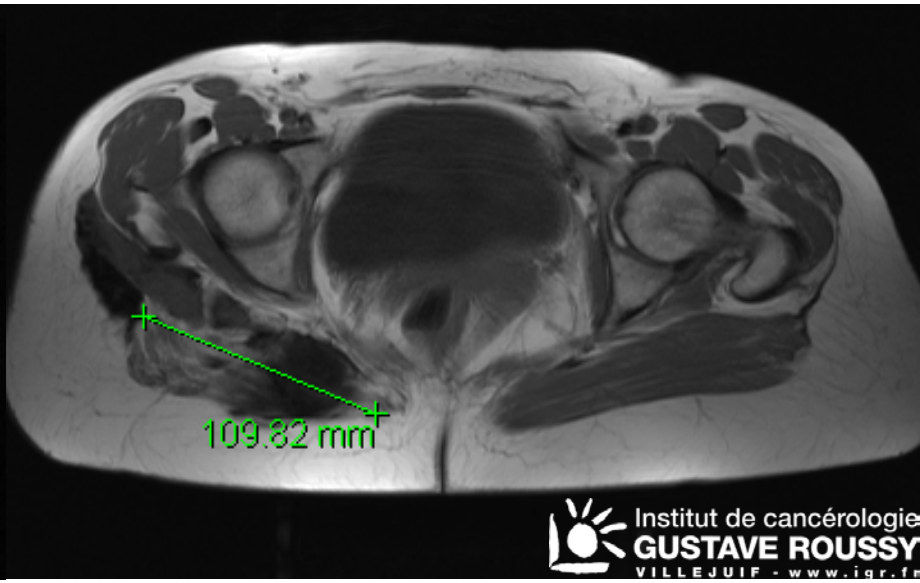
Exemple of « wait and see » policy on a resectable AF

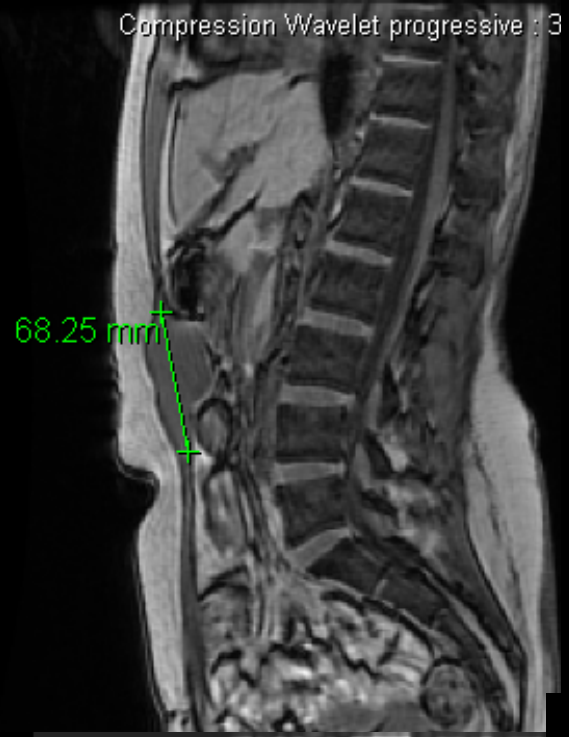
MRI 1998



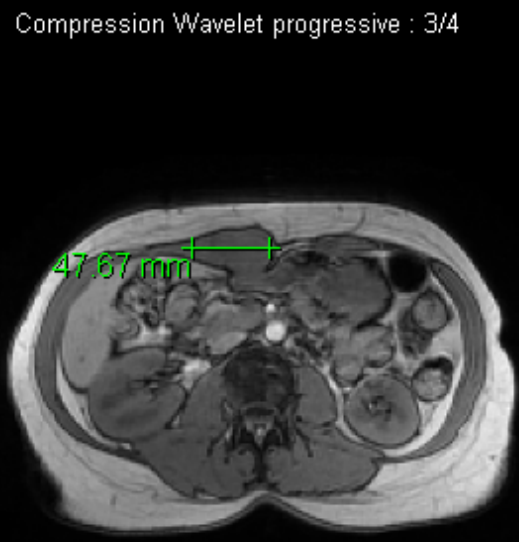
MRI 2010



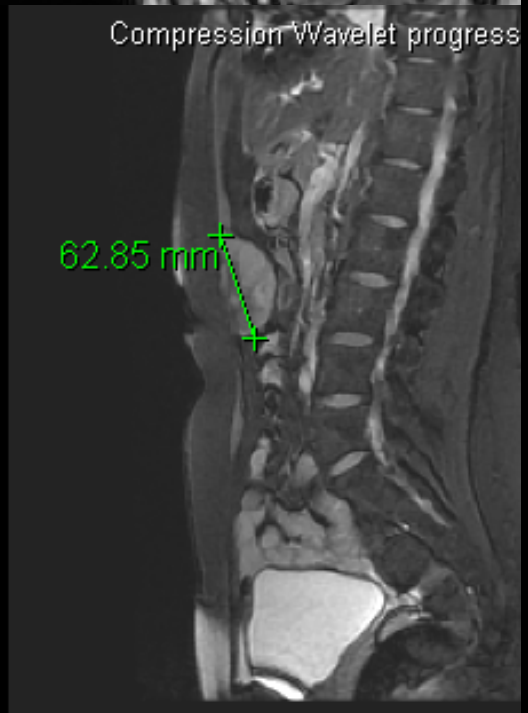
36-year-old woman
Primary fibromatosis (surgical biopsy)
No treatment
No change after 12 years



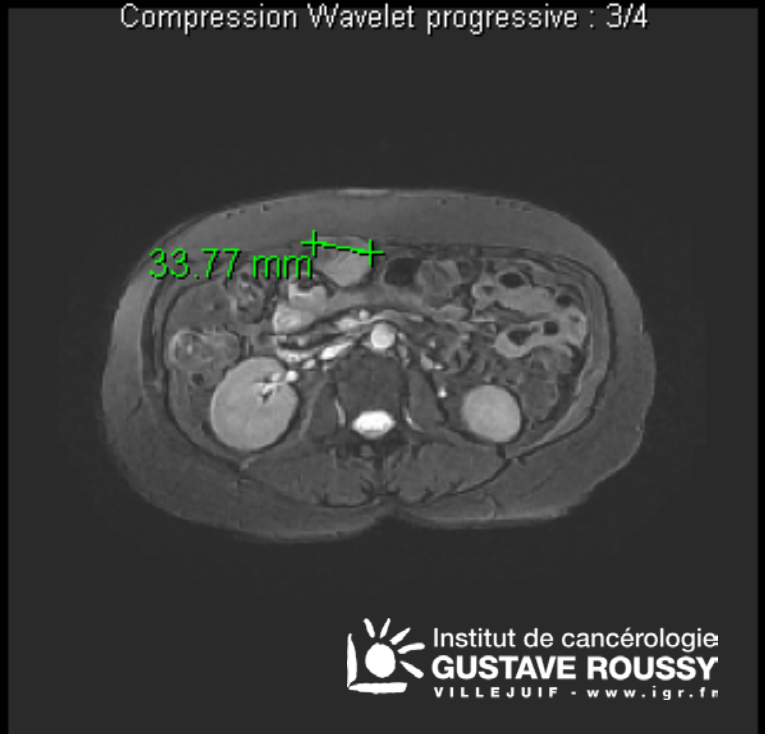
2004



27 years old female



2011



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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]

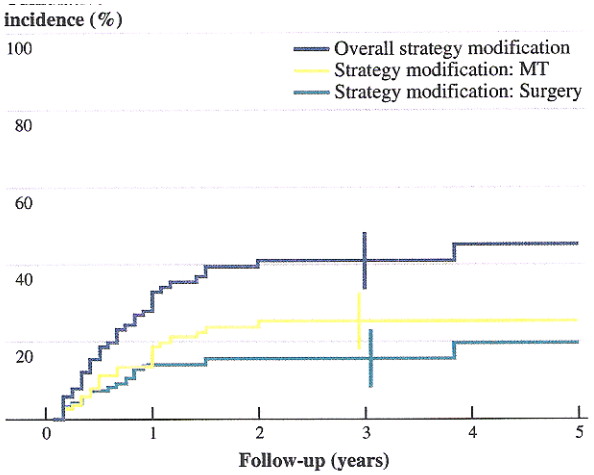


FIG. 2 Cumulative incidence of overall strategy modification, switch to medical treatment with no further switch, and final switch to surgery

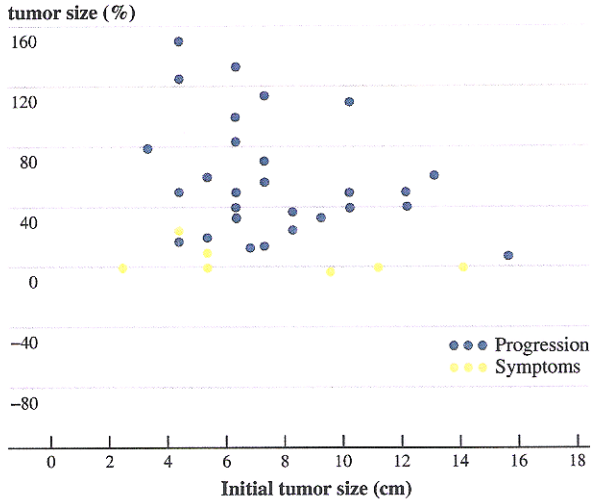


FIG. 3 Change in tumor size for patients with modification strategy (each *point* represents a patient)

(

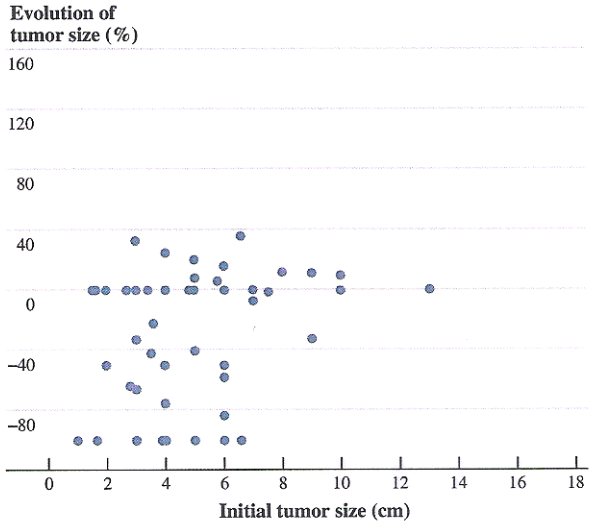


FIG. 4 Change in tumor size for patients without modification strategy (each *point* represents a patient)

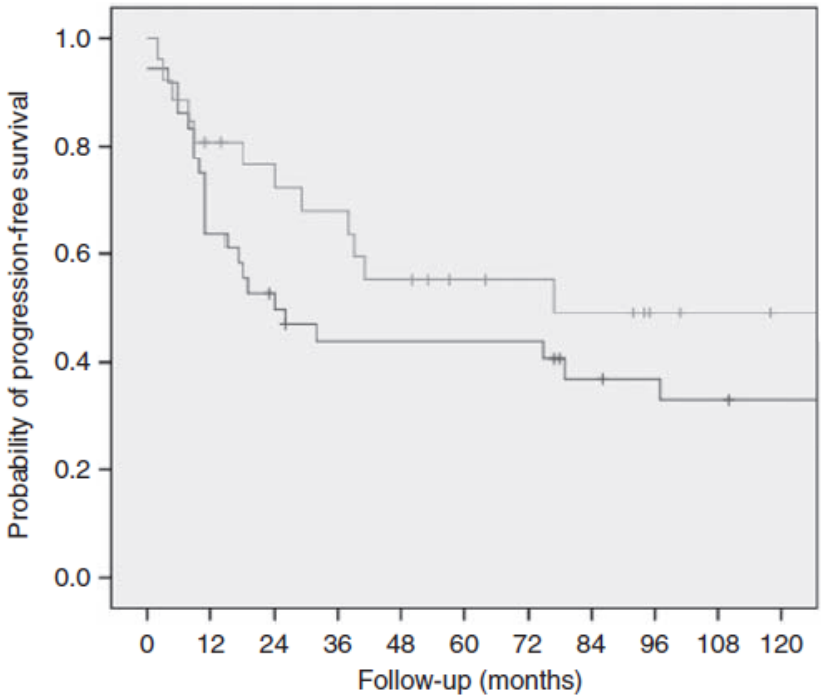
147 patients

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]



Time	0	12 (1 year)	60 (5 years)	120 (10 years)
N patients surgery	36	23	14	7
N patients non-surgery	26	20	10	3

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

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

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

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

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

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

2) Medical treatment

Medical options

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

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

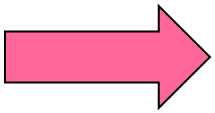
- Hormone therapy (Tamoxifen, Toremifene, Gn-RH analogues)

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

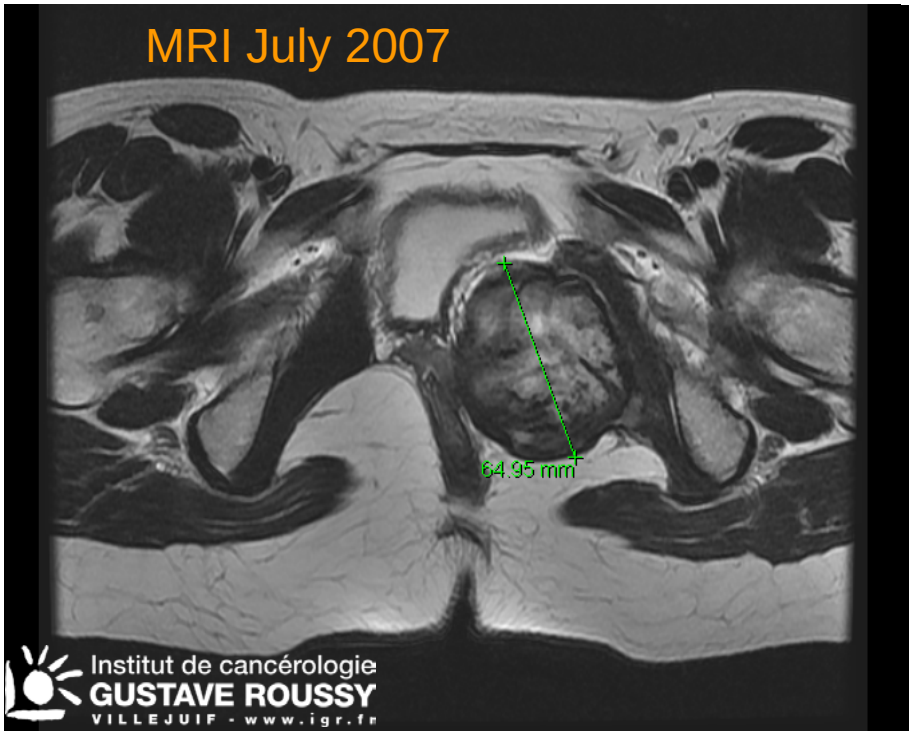
- Tyrosine kinase inhibitors

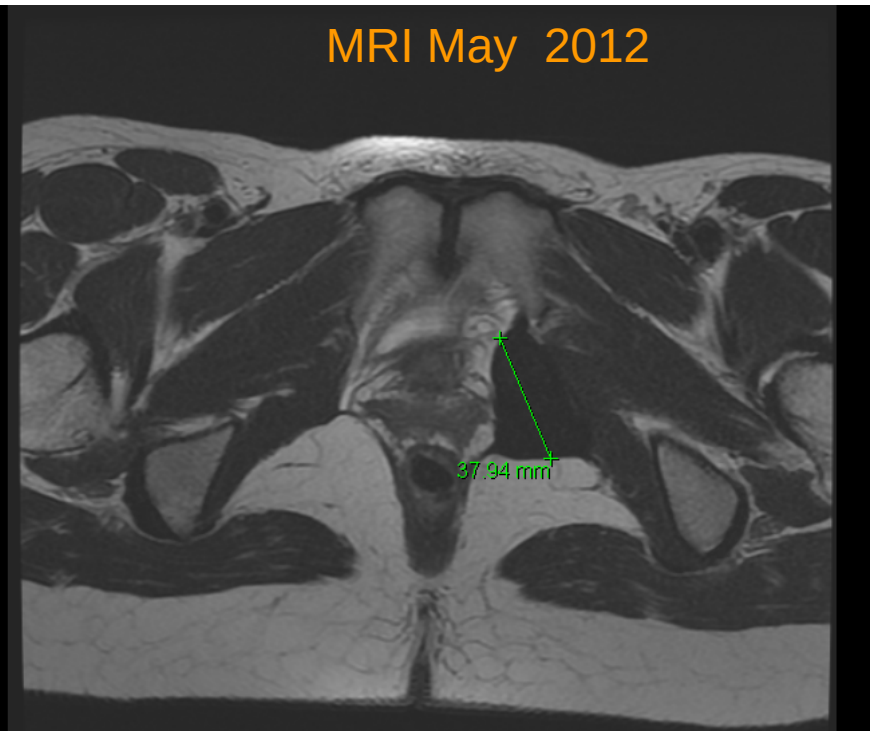
- Interferon

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



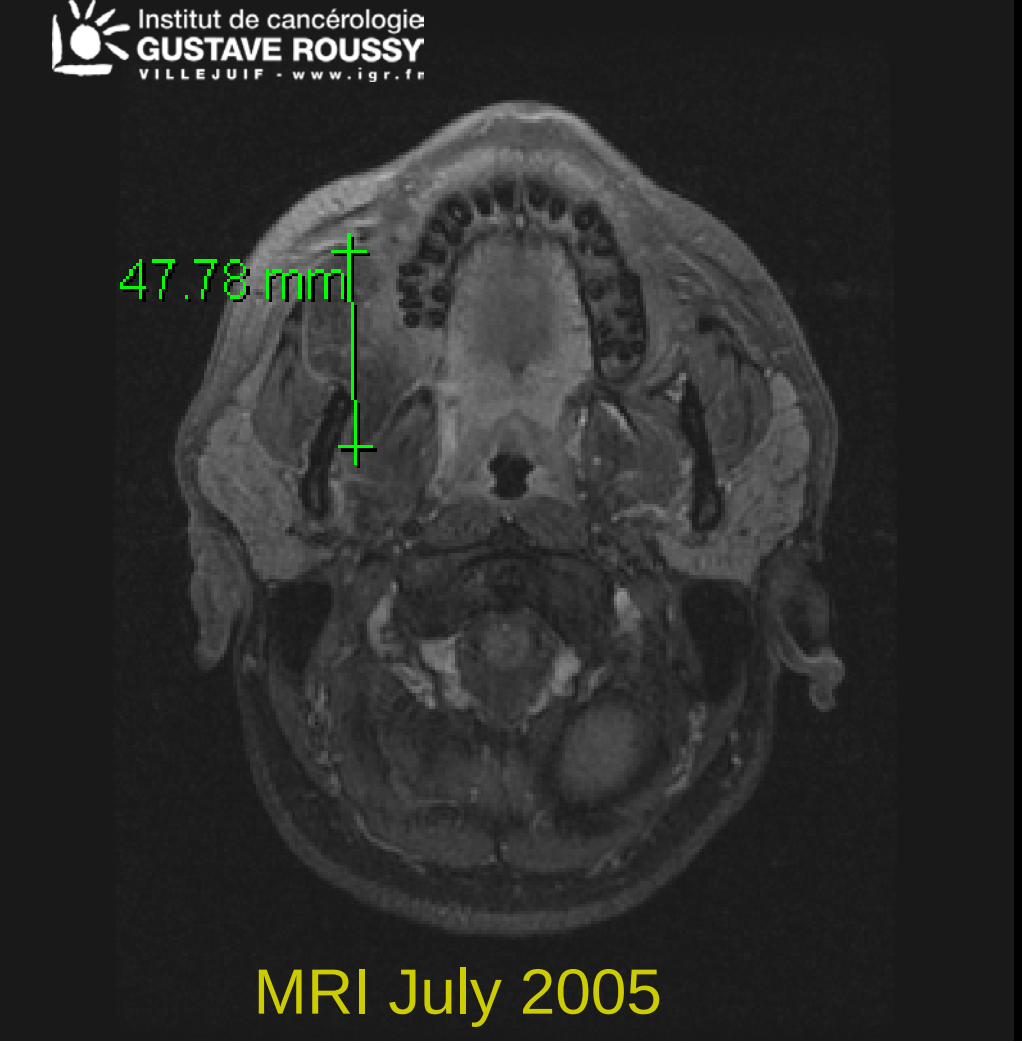
No randomized trial

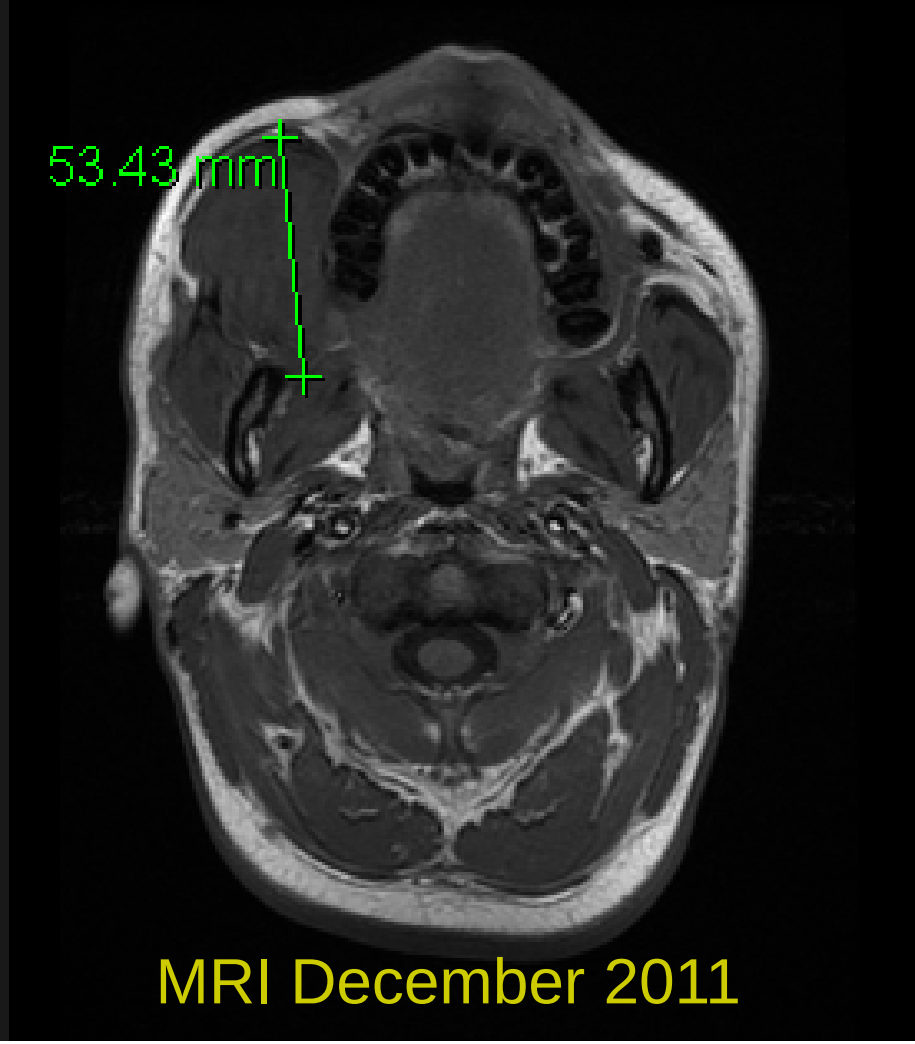




34 years old female: post partum
Percutaneous biopsy: Desmoid
Tamoxifen and agonist LHRH: 18 months

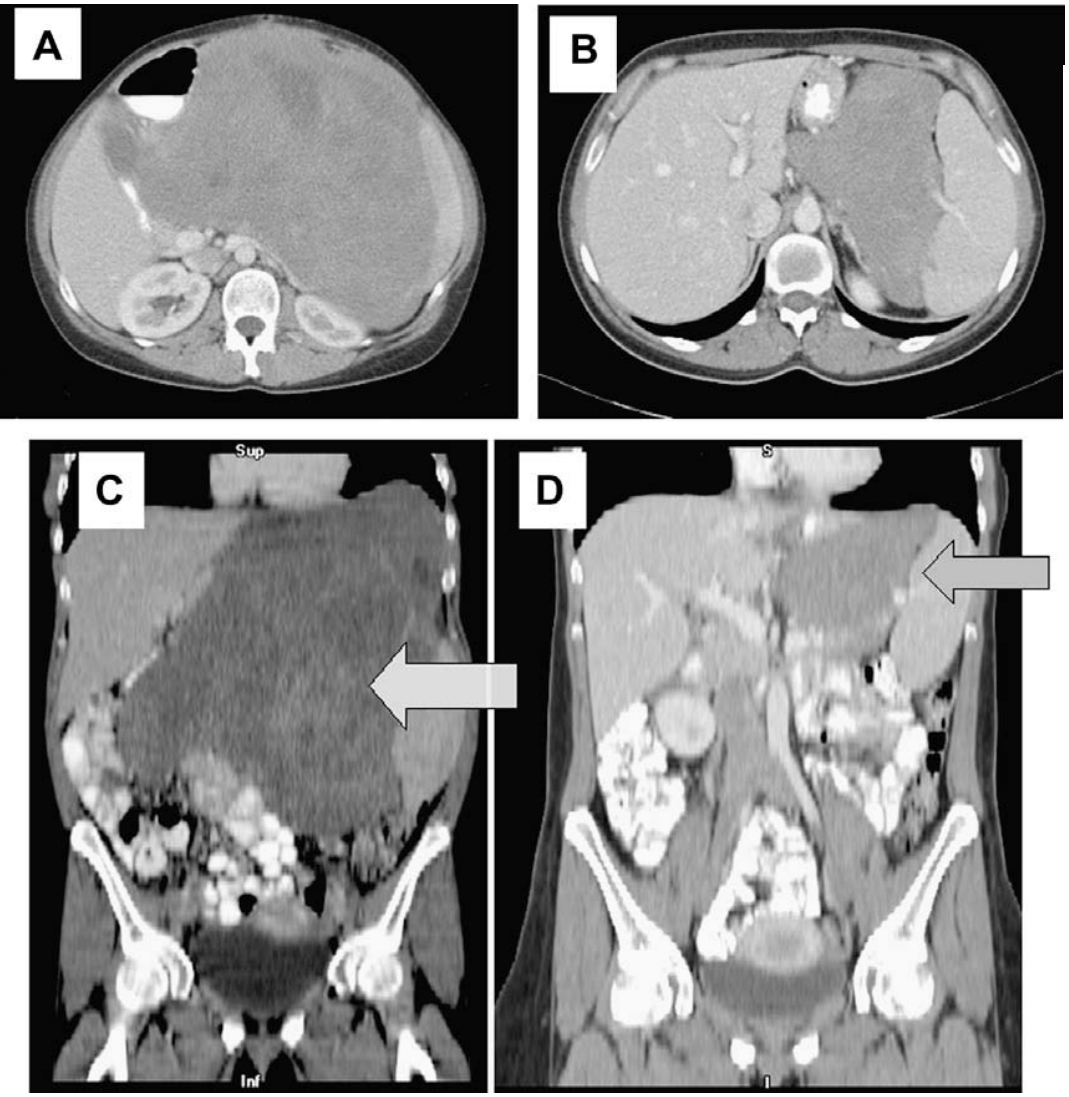
- The surgery would have been mutilating
- The radiation source of sequelae in this young patient





23-year-old man
Vinorelbine (12 months)
Glivec (8 months)

- Hormonal therapy: side effects/activity? on male
- Surgery: mutilating
- Radiation: source of sequelae (young patient)



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

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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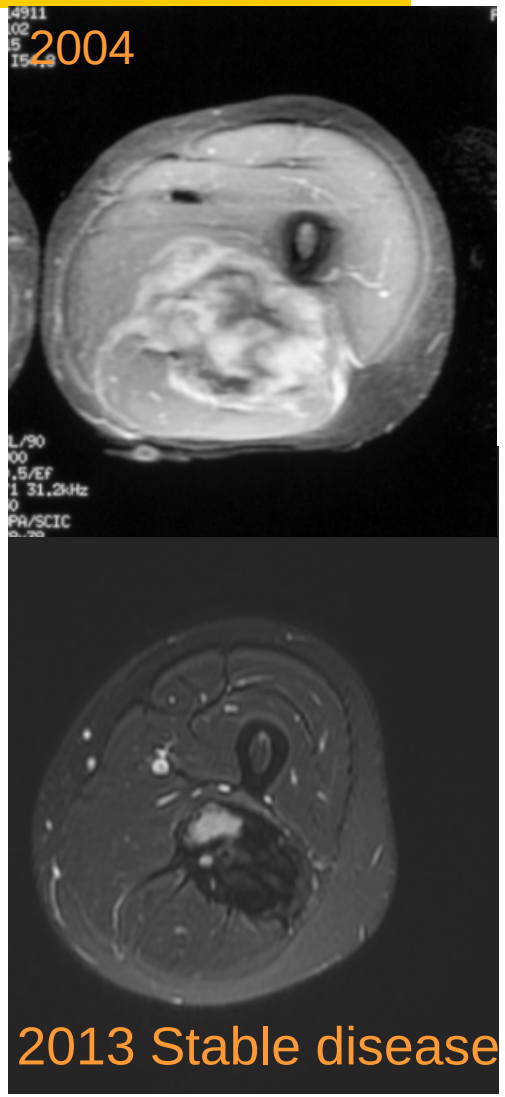
3) Isolated limb Perfusion

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

	N	CR	PR	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)
Grunhagen (EJSO 2005)	12	3	9	?



20 years old Female Fibromatosis of the thigh

4) Radiotherapy

Local Recurrence rates following RT alone

Author	N pts	RT dose	Recurrence rate
Leibel 83	**13**	**40-61 Gy**	**31%**
Schmitt 92	**21**	**30-64 Gy**	**24%**
Acker 93	**16**	**50-56 Gy**	**7%**
Catton 95	**8**	**50 Gy**	**25%**
Kamath 96	**24**	**33-70 Gy** **med 54**	**12%**
Spear 98	**15**	**10-70 Gy**	**7%**
Ballo 98	**23**	**<50 Gy** **>50 Gy**	**60%** **23%**
Nuyttens 00 **(Review of 22 studies)**	**102 (lary T or R)**	**10-74 Gy** **Better results if Dose>50 Gy**	**22% (54% In-field failures)**
Guadagnolo 07	**41**	**50-75** **<56 Gy** **>56 Gy**	**32%** **10Yr LC:62%** **10yr LC:75%**

Recommended dose for desmoid tumors: 50 to 56 Gy

Local Recurrence rates following RT alone

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Recurence rate ≈ 20%

Recommended dose for desmoid tumors: 50 to 56 Gy

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

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

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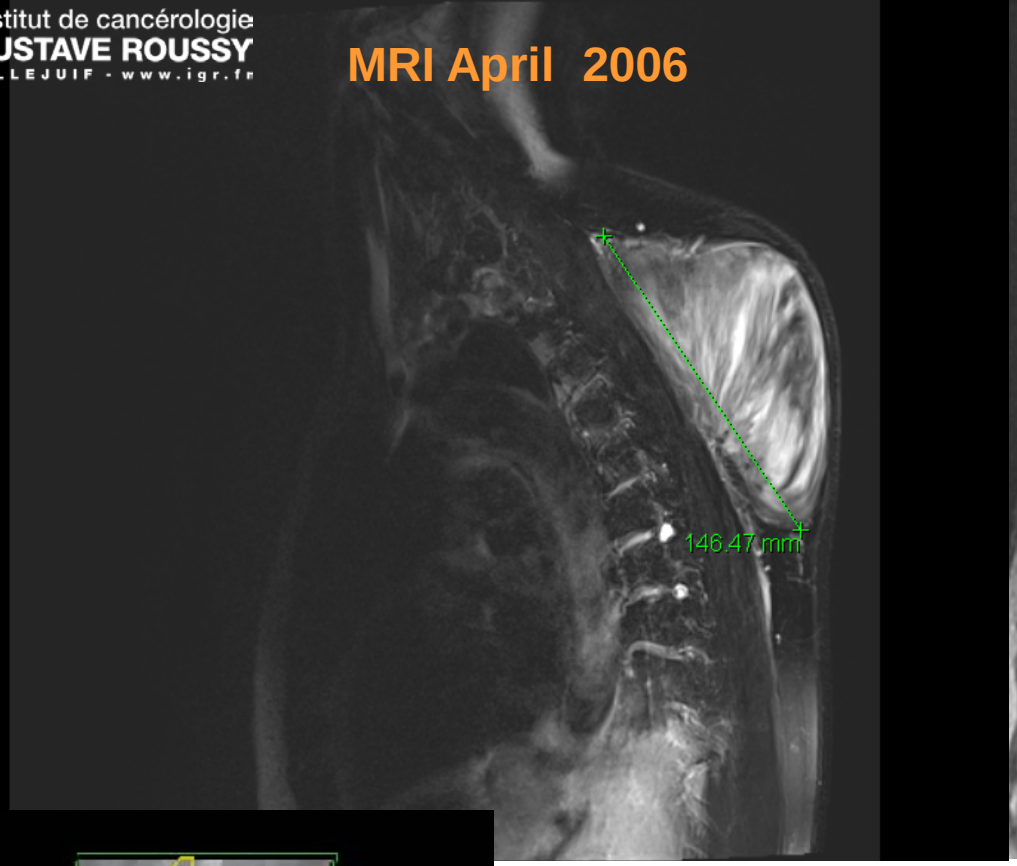
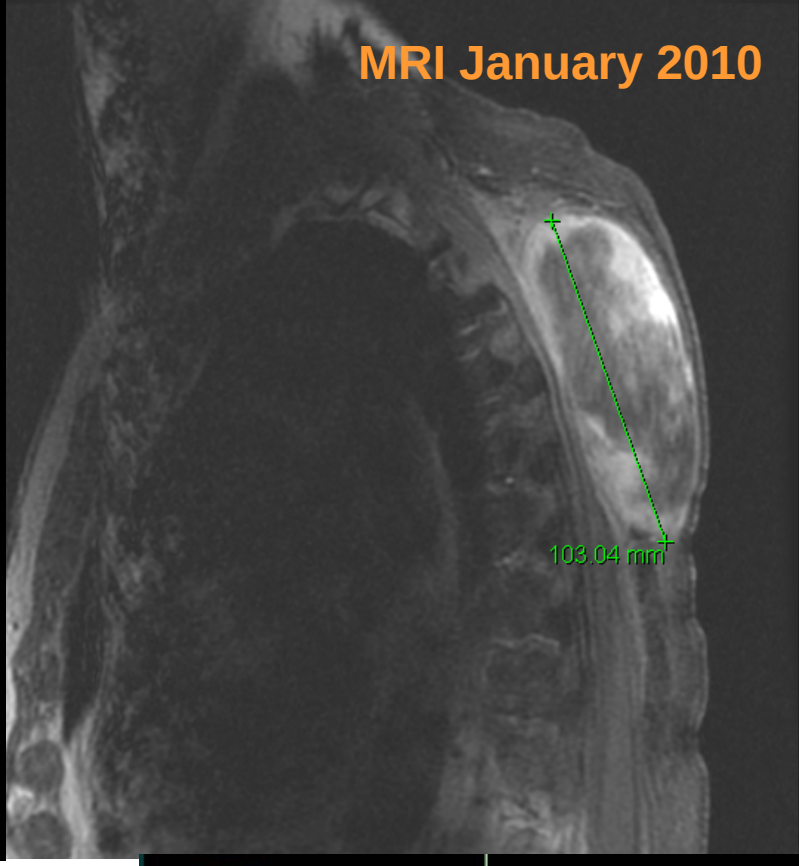
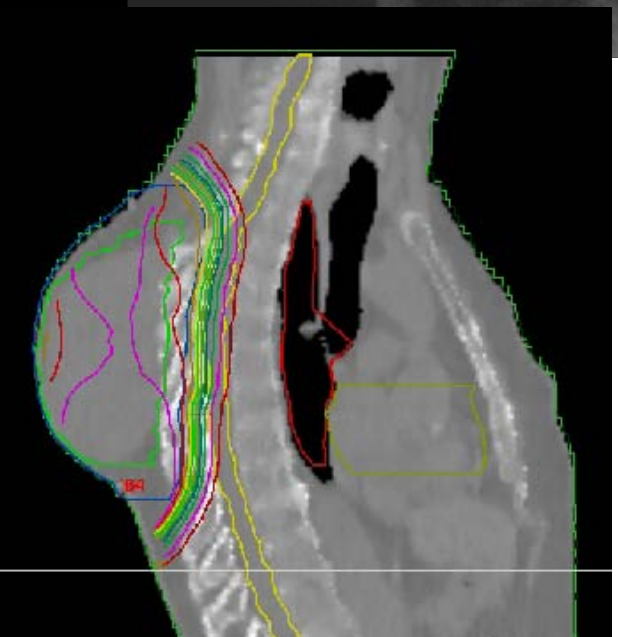
MRI April 2006

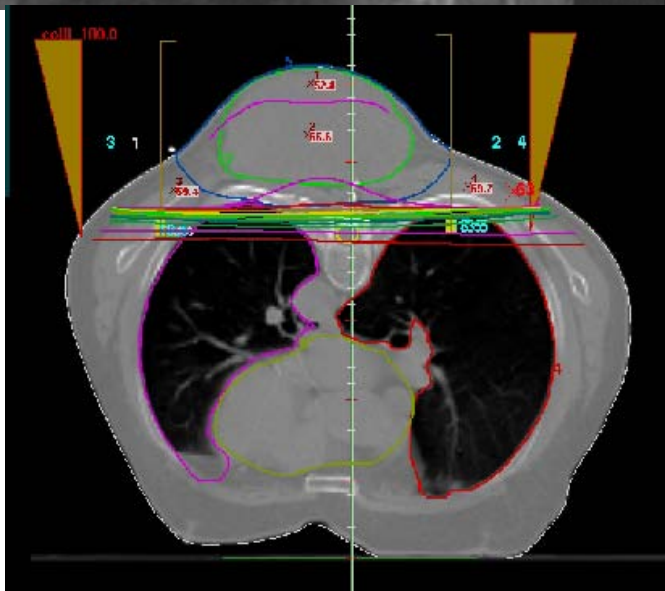


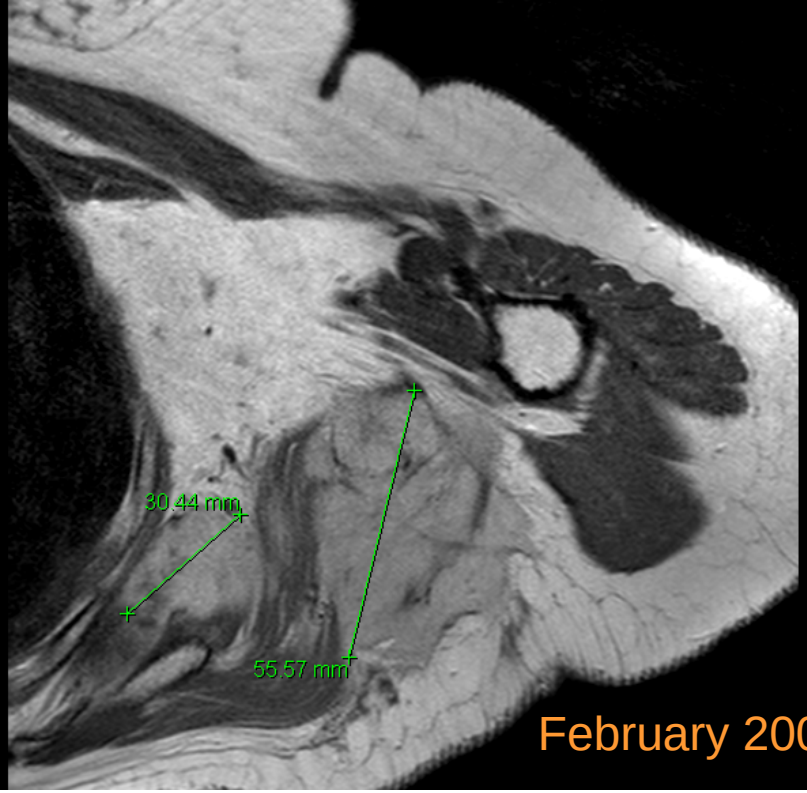
MRI January 2010



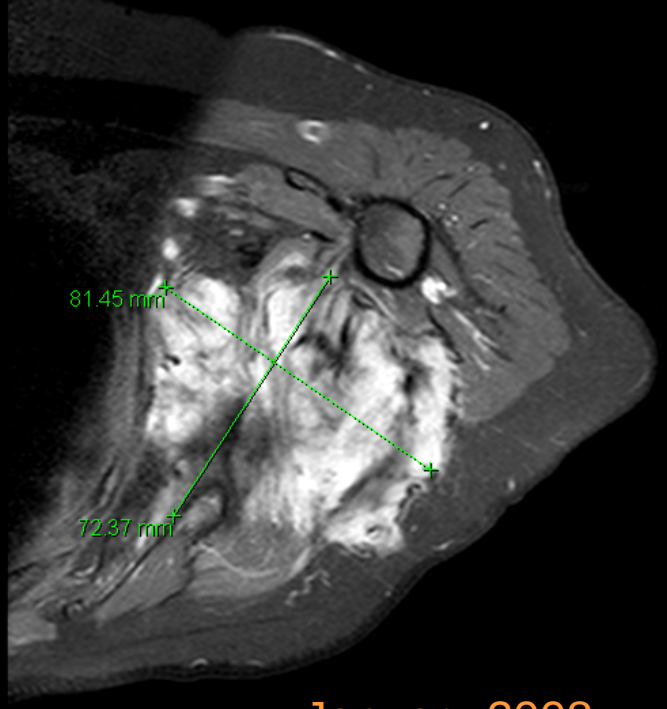


Male 71 years old;
Parkinson
Percutaneaous biopsy: desmoid
Pain ++
Exclusive RX 54 Gy



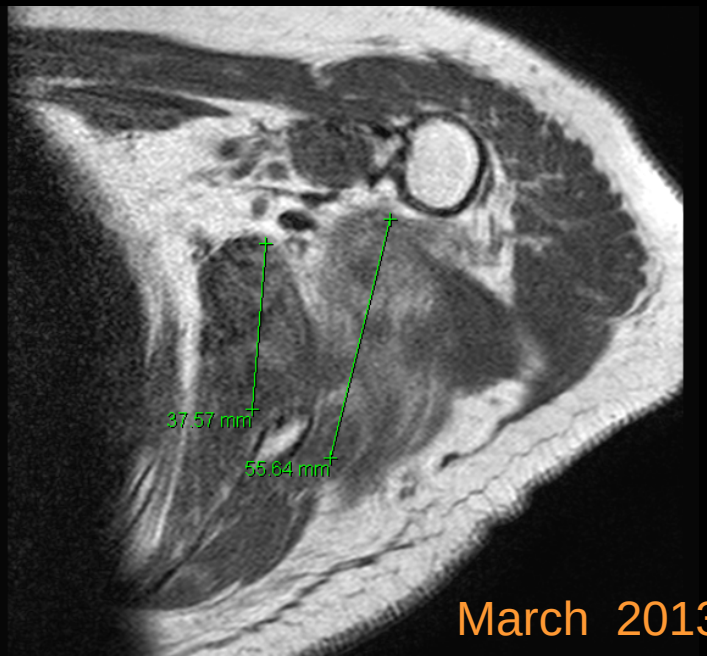


February 2007



January 2008

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



March 2013

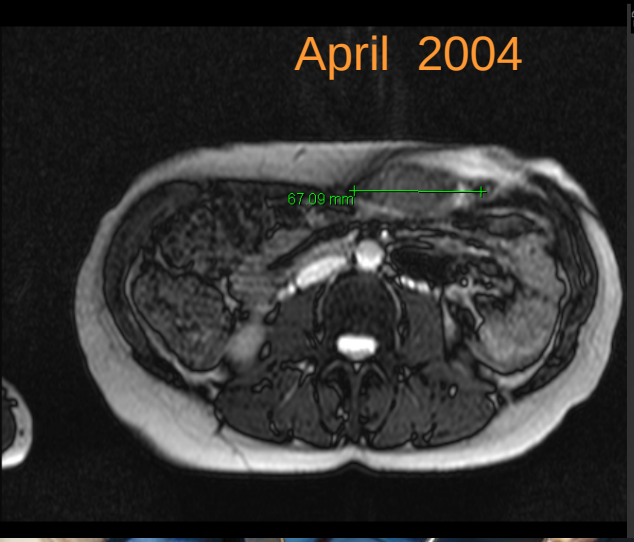
5) Surgery

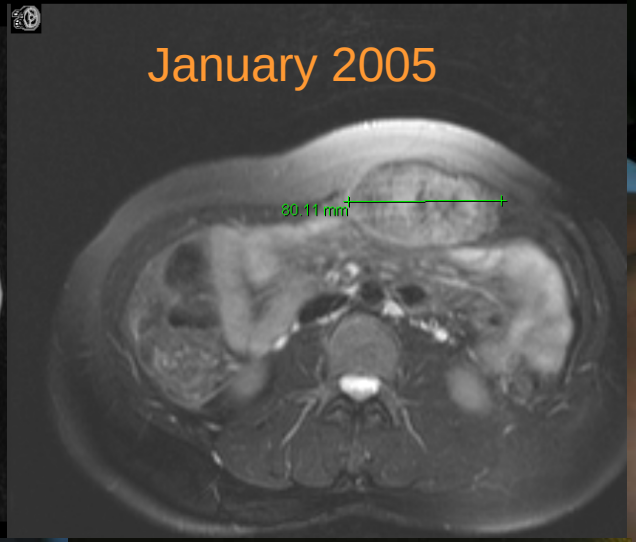
Surgery versus radiation therapy for patients with aggressive fibromatosis or desmoid tumors
A comparative review of 22 articles

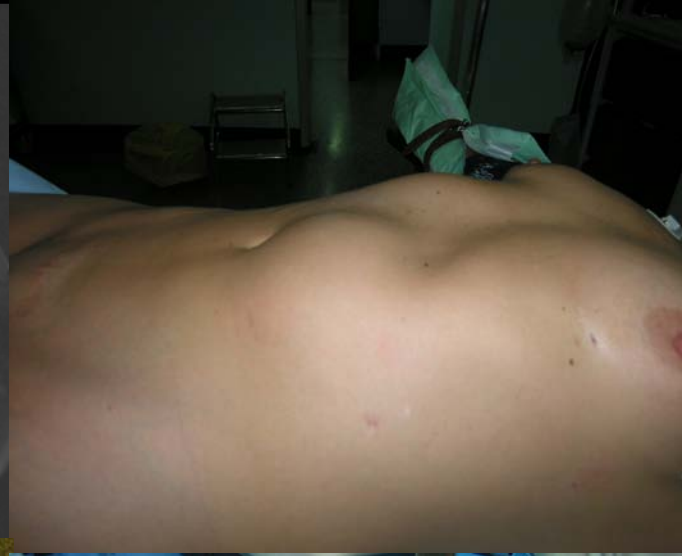
1983 1998	Surgery alone		
Local Control rate	Margins		
	-	+	overall
	72%	41%	61%

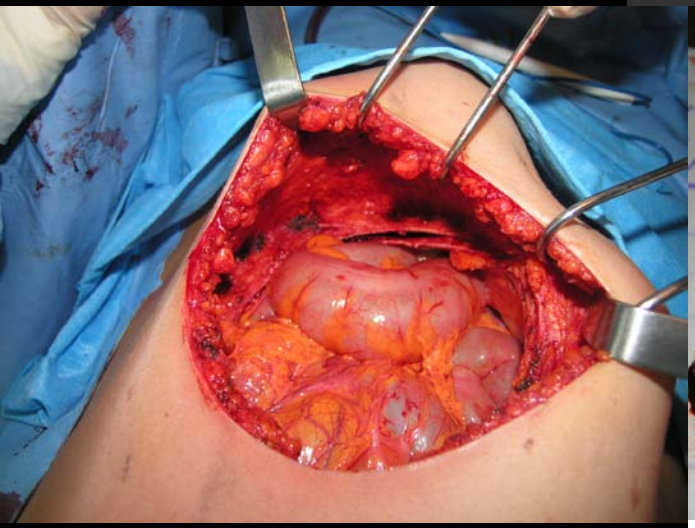
Approximately 60% of the patients are controlled by surgery <u>alone</u>

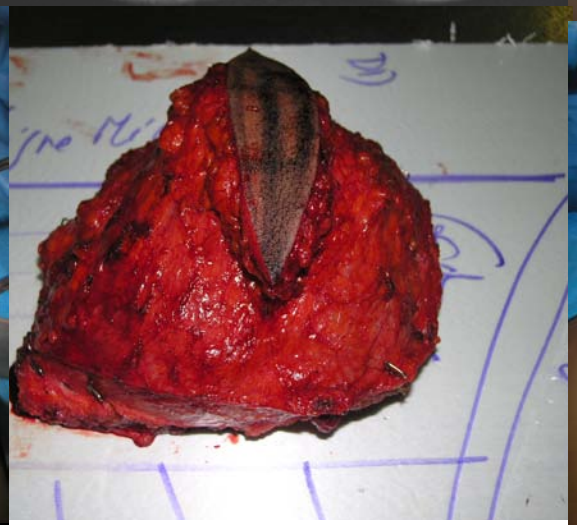
Nuyttens JJ et al Cancer. 2000

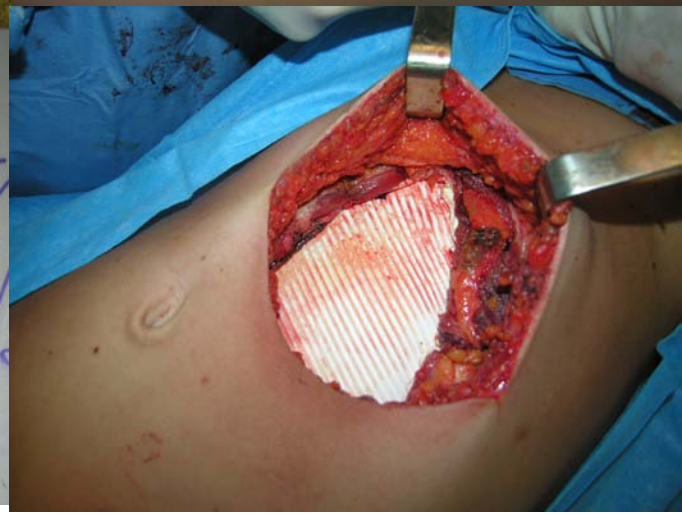


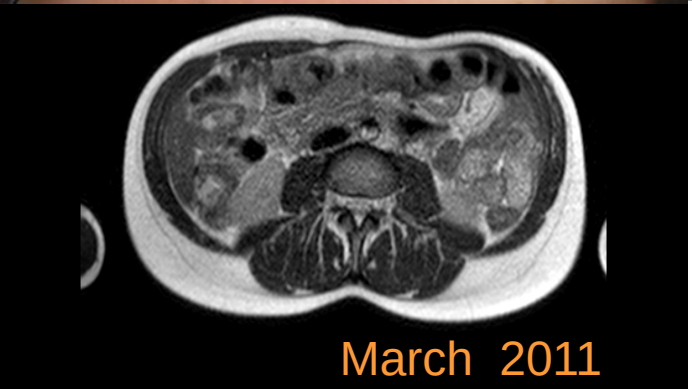








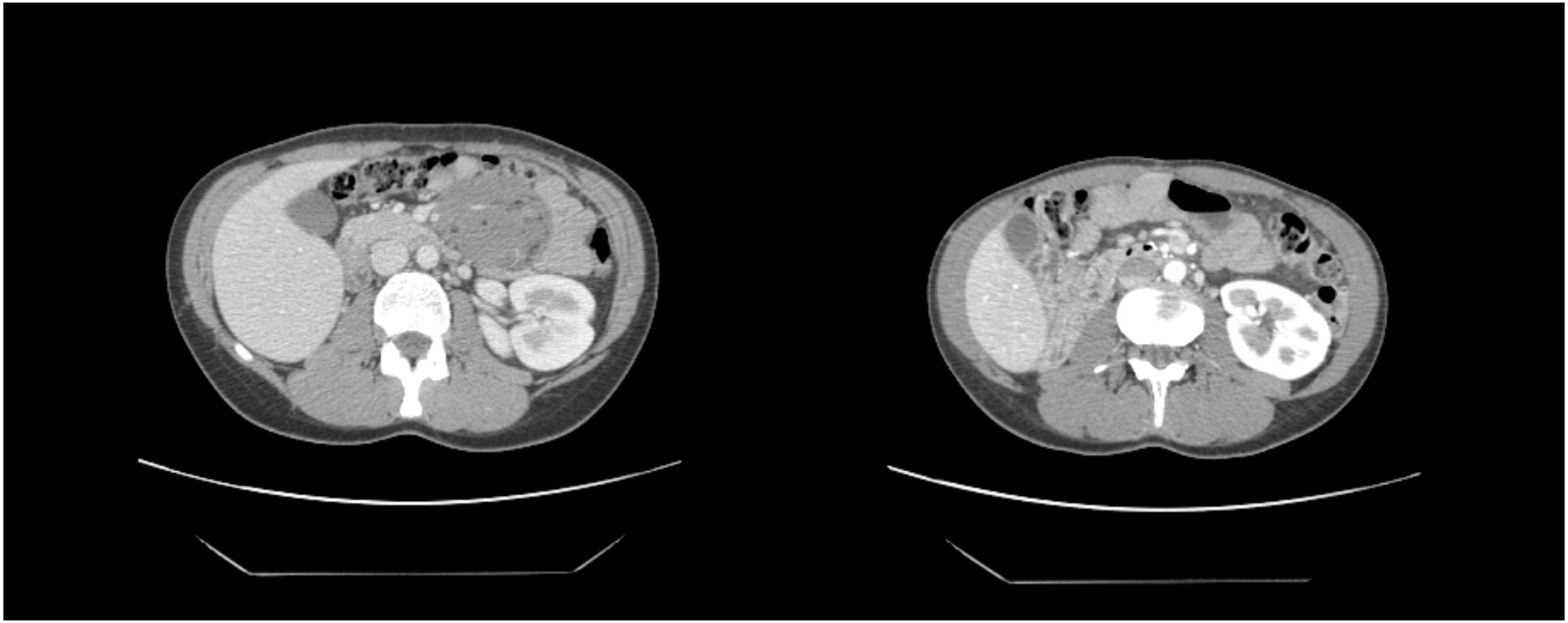




- 31 years old female
- AF (biopsy)
- Evolutive after 9 months including 6 mths TAM
- Parietectomy

2007

2010

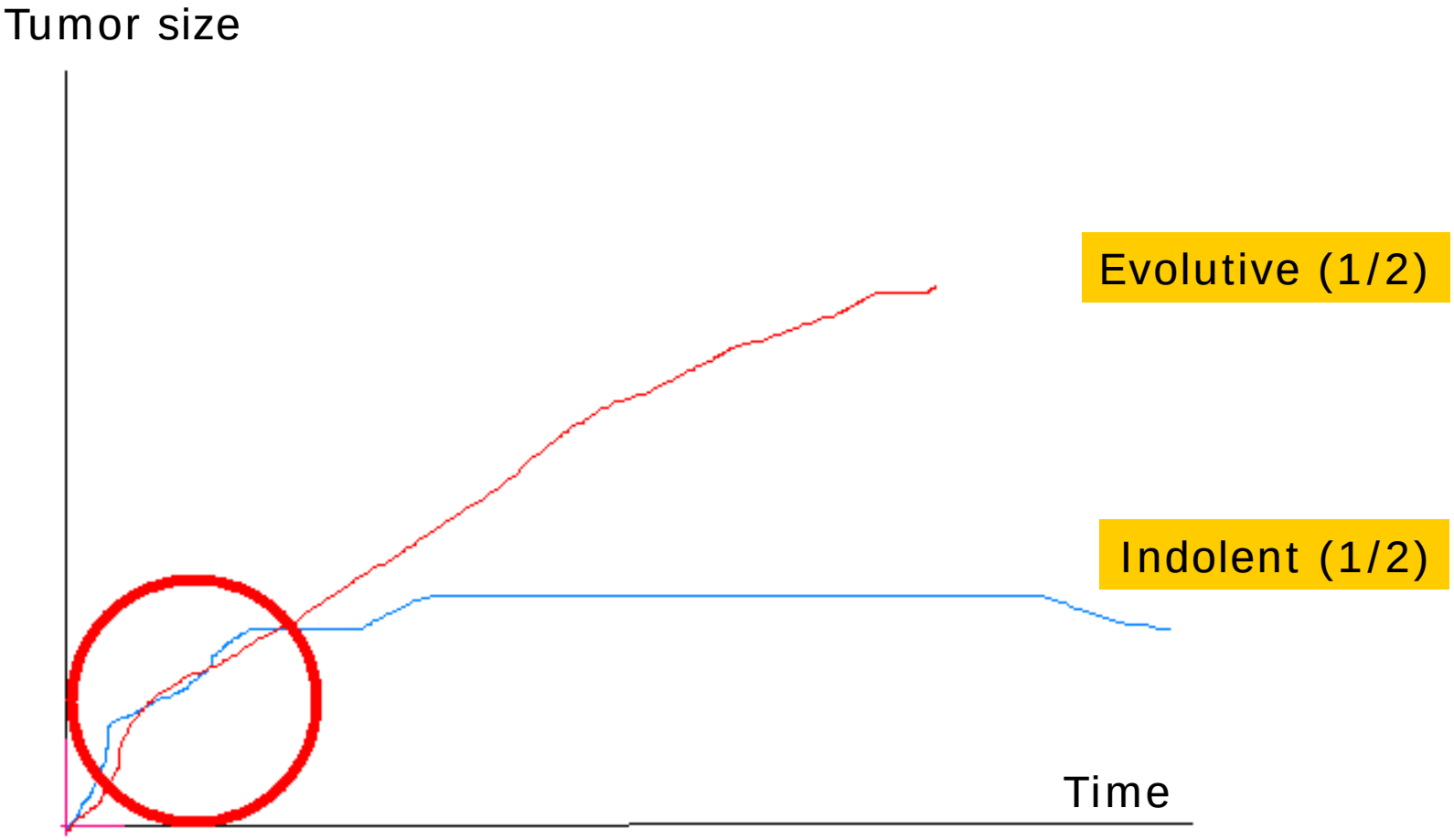


A stepwise clinical approach to desmoids

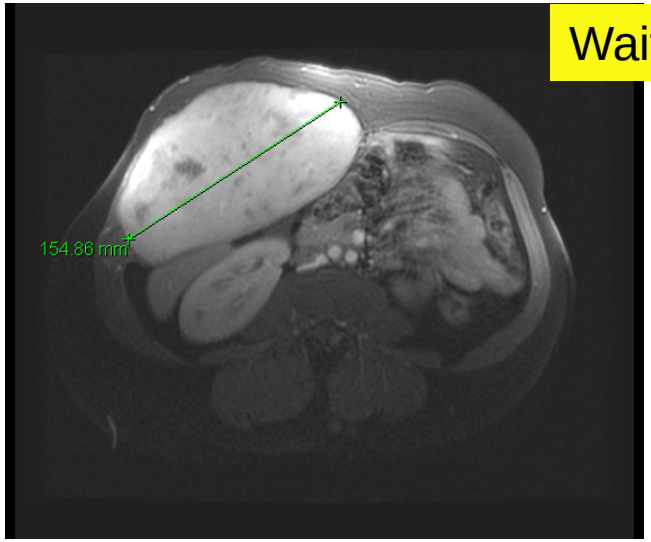
Institut de cancérologie
GUSTAVE ROUSSY
VILLEJUIF - www.igr.fr

Bonvalot S et al. The treatment of desmoid tumors: a stepwise clinical approach. Ann Oncol. 2012

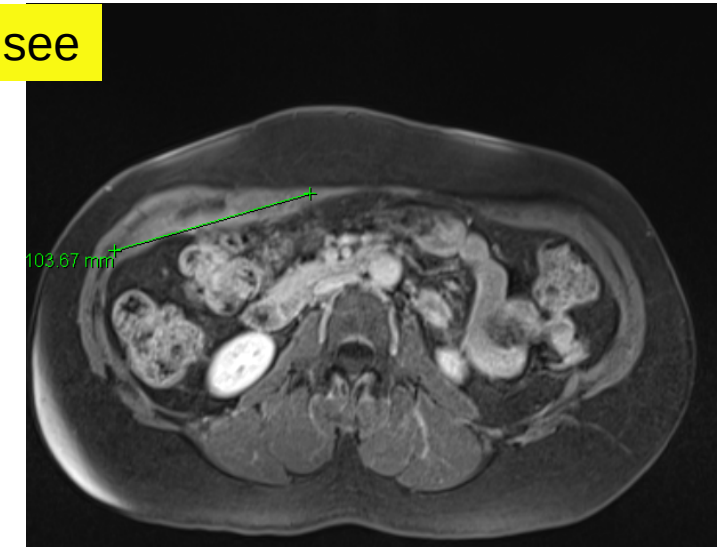
How to make the difference between the 2 groups?



Wait and see



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



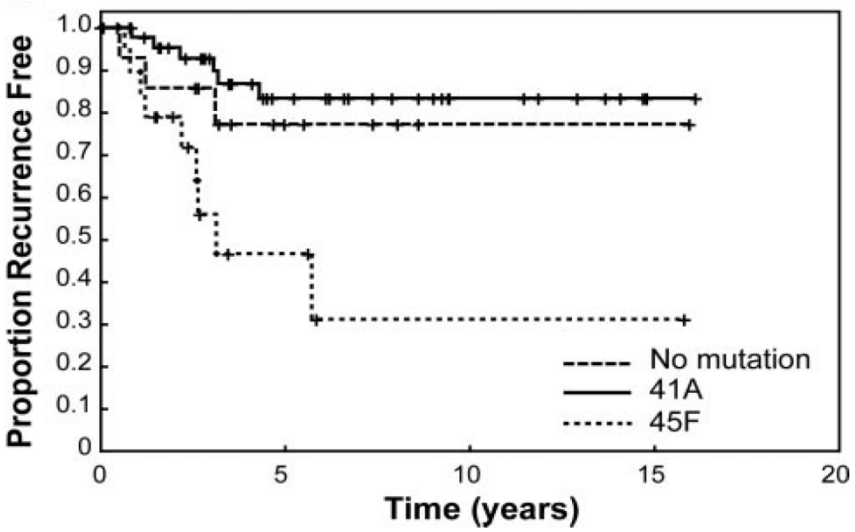
Oct 2011

- 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…

Institut de cancérologie
GUSTAVE ROUSSY
VILLEJUIF - www.igr.fr

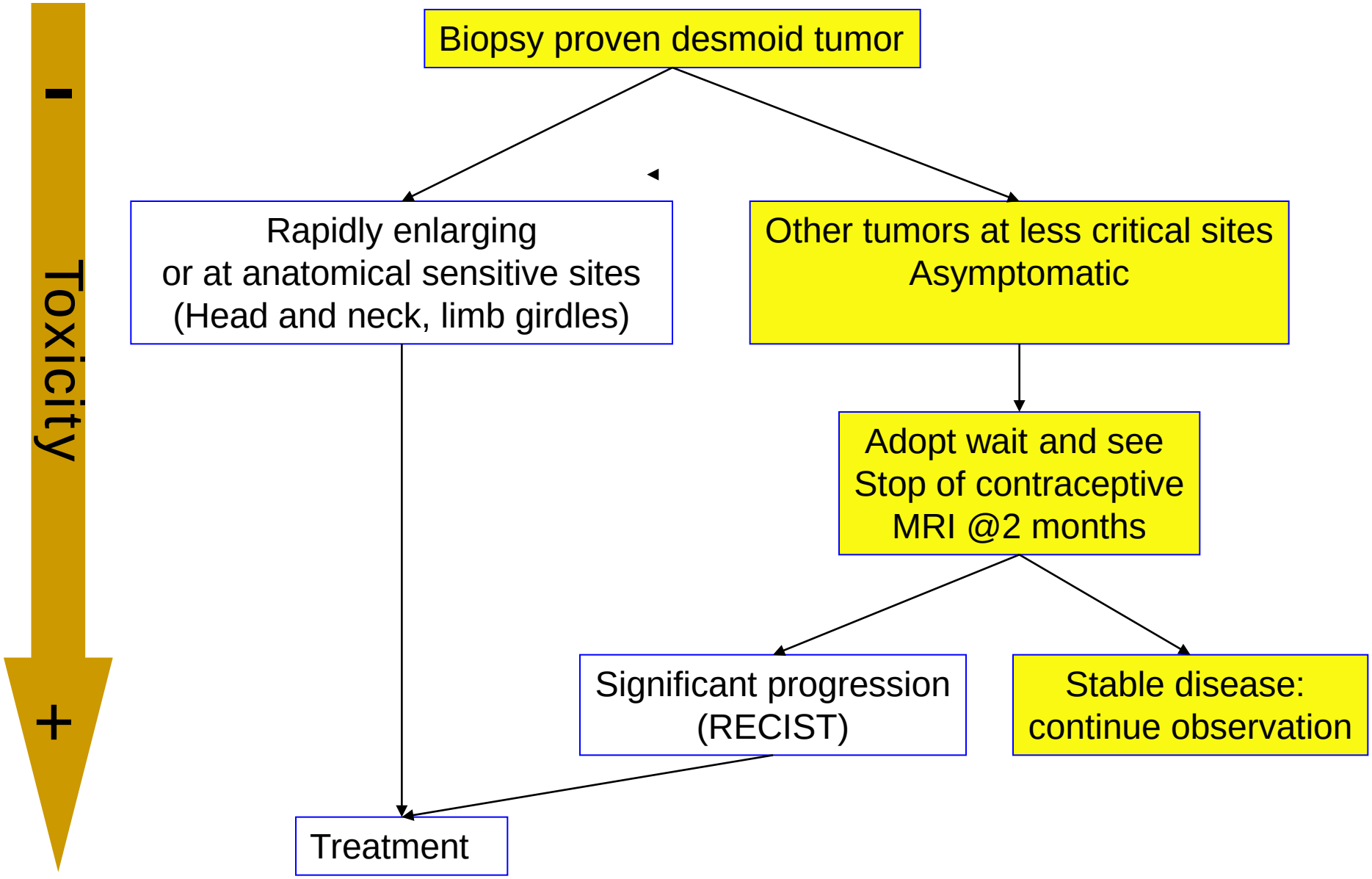
Specific Mutations in the *β-Catenin* Gene (*CTNNB1*) Correlate with Local Recurrence in Sporadic Desmoid Tumors

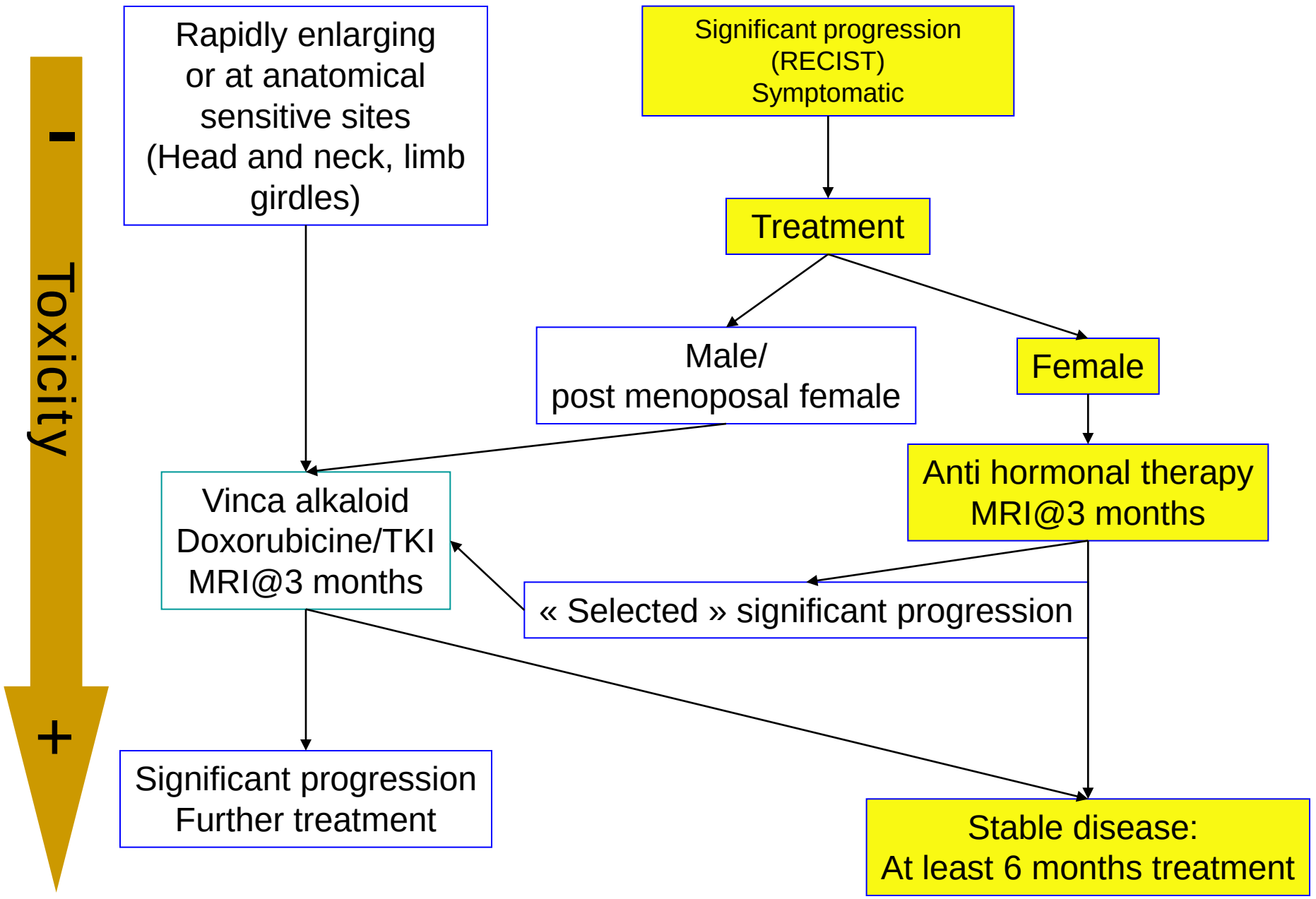
Alexander J.F. Lazar,*† Daniel Tuvin,*‡
Shohrae Hajibashi,*§ Sultan Habeeb,¶
Svetlana Bolshakov,*‡ Empar Mayordomo-Aranda,¶
Carla L. Warneke,‖ Dolores Lopez-Terrada,¶
Raphael E. Pollock,*‡ and Dina Lev*§

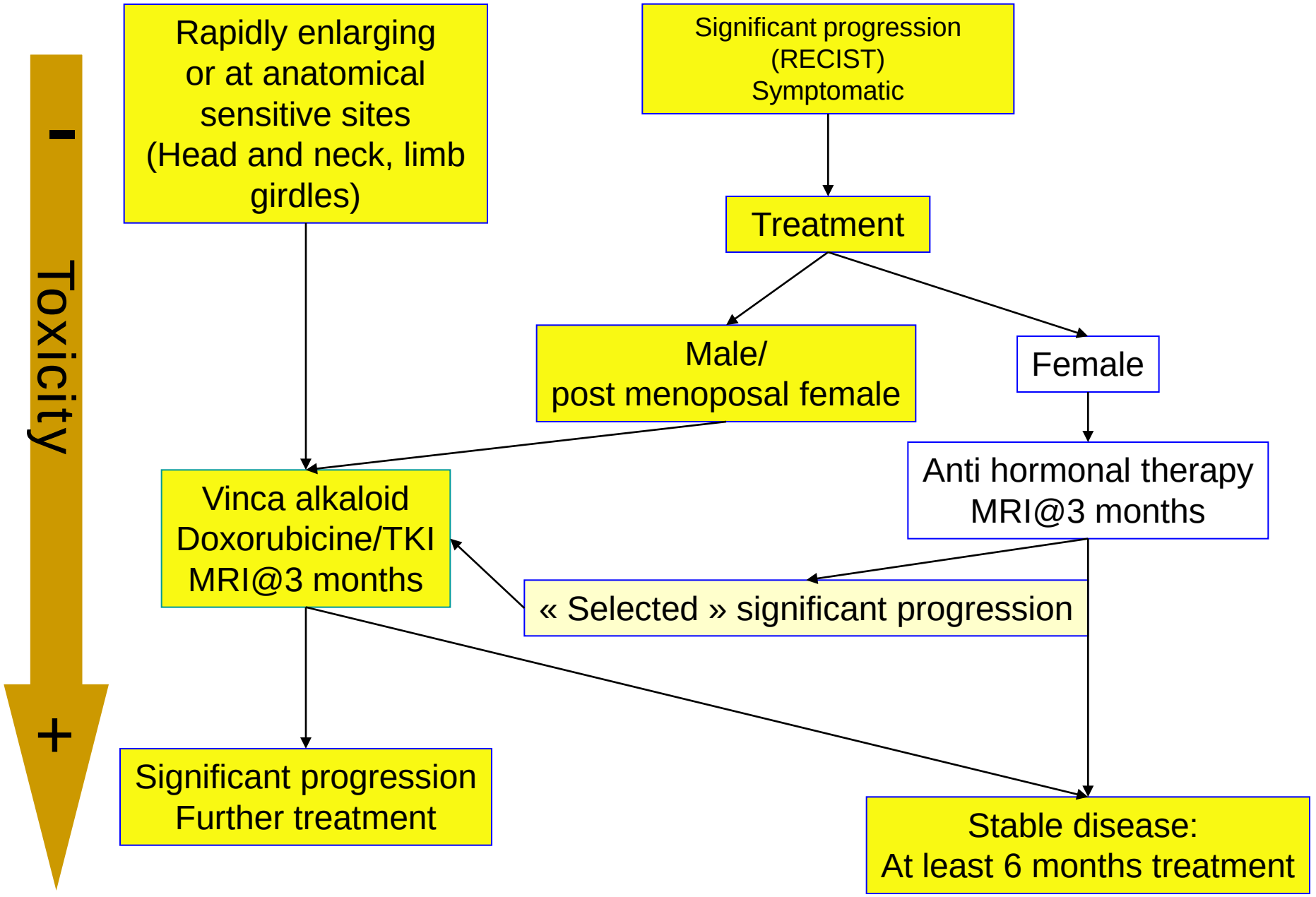


The American Journal of Pathology, Vol. 173, No. 5, November 2008

DOI: 10.2353/ajpath.2008.080475


-
Toxicity
+
Biopsy proven desmoid tumor
Rapidly enlarging
or at anatomical sensitive sites
(Head and neck, limb girdles)
Other tumors at less critical sites
Asymptomatic
Adopt wait and see
Stop of contraceptive
MRI @2 months
Significant progression
(RECIST)
Stable disease:
continue observation
Treatment


Rapidly enlarging or at anatomical sensitive sites (Head and neck, limb girdles)
Significant progression (RECIST) Symptomatic
Treatment
Male/ post menoposal female
Female
Anti hormonal therapy MRI@3 months
Vinca alkaloid Doxorubicine/TKI MRI@3 months
« Selected » significant progression
Significant progression Further treatment
Stable disease: At least 6 months treatment
- Toxicity +


Rapidly enlarging or at anatomical sensitive sites (Head and neck, limb girdles)
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Male/ post menoposal female
Female
Anti hormonal therapy MRI@3 months
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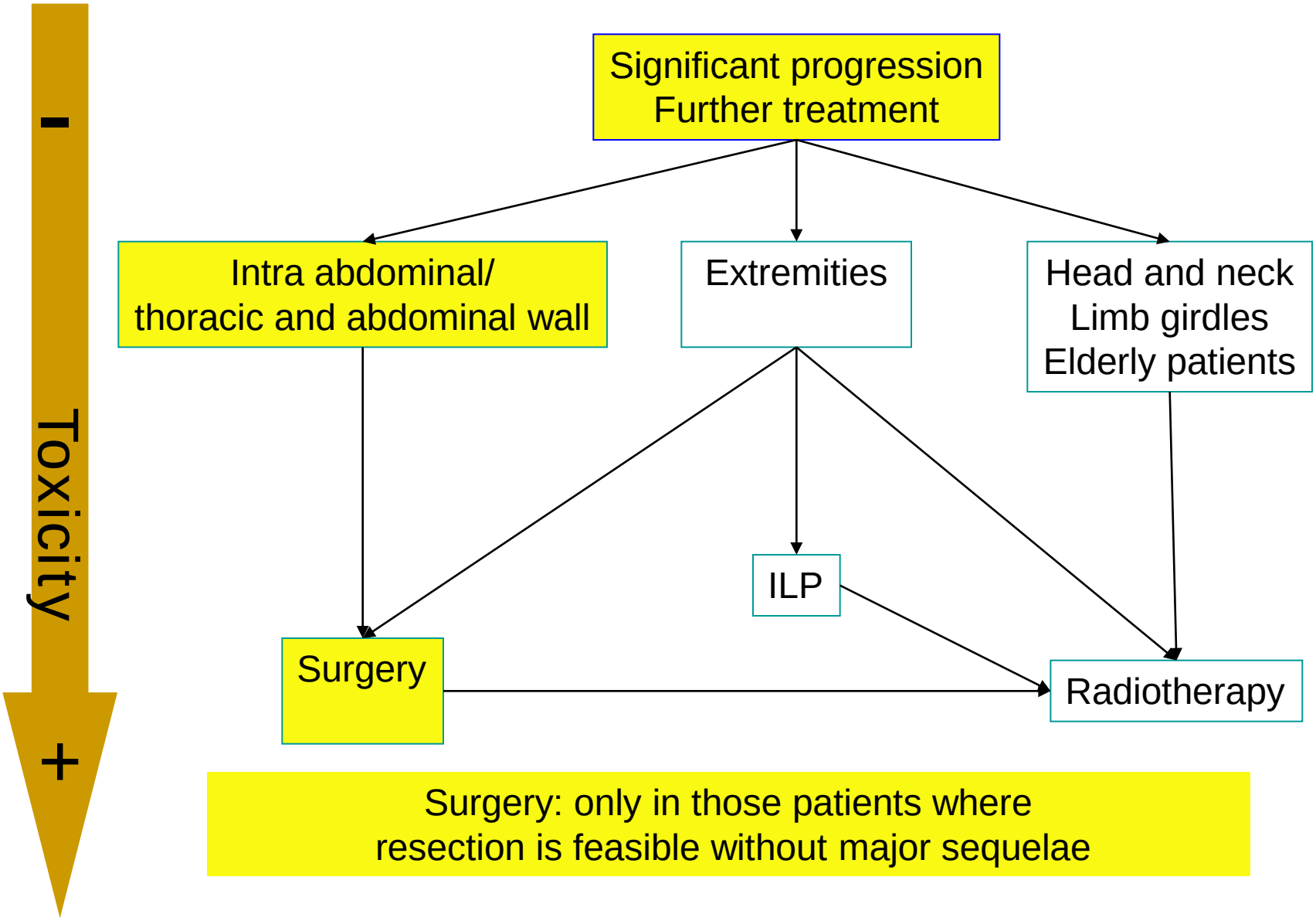
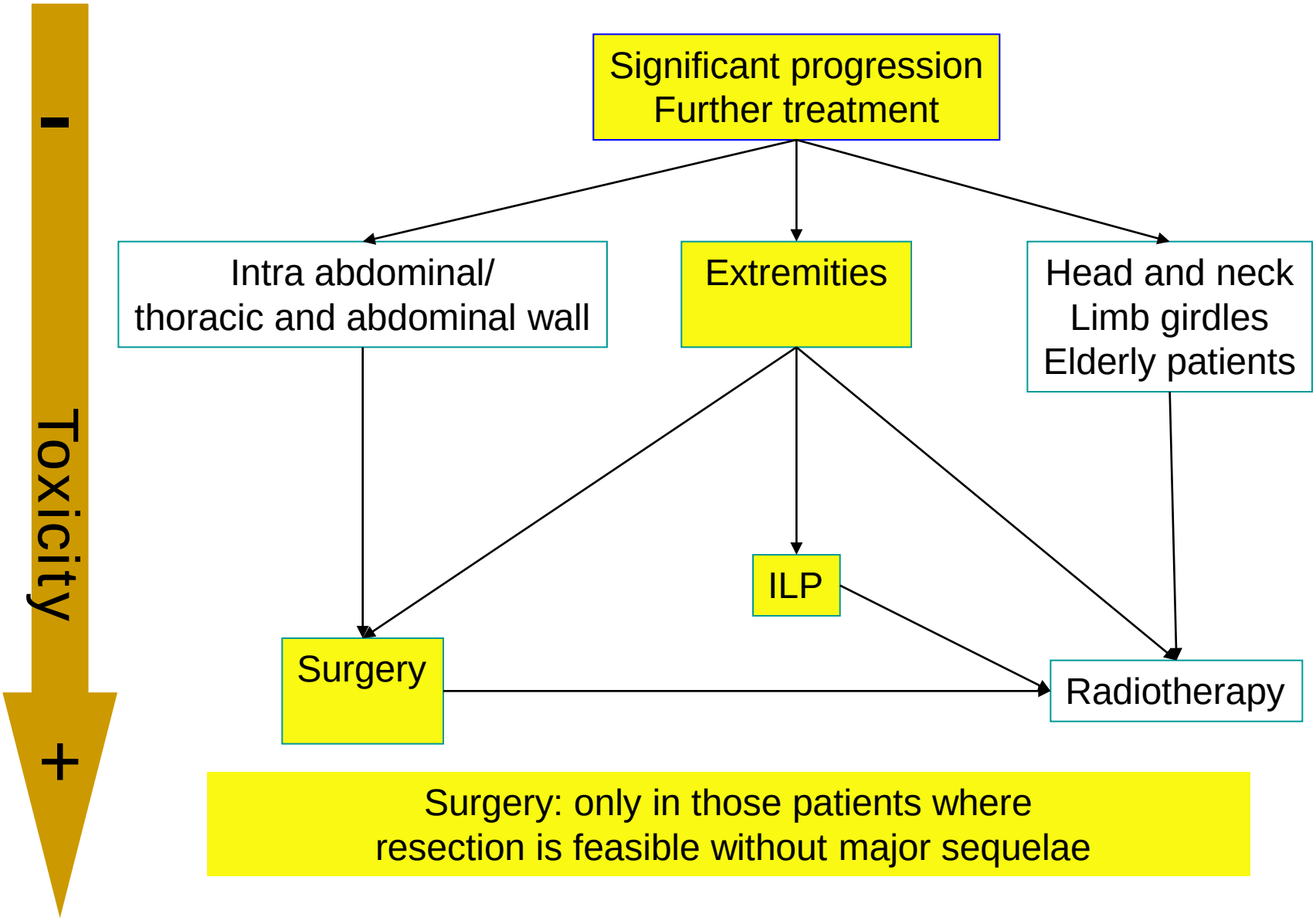
« Selected » significant progression
Significant progression Further treatment
Stable disease: At least 6 months treatment
Toxicity
-
+


-
Toxicity
+
Significant progression
Further treatment
Intra abdominal/
thoracic and abdominal wall
Extremities
Head and neck
Limb girdles
Elderly patients
ILP
Surgery
Radiotherapy
Surgery: only in those patients where
resection is feasible without major sequelae


-
Toxicity
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Head and neck
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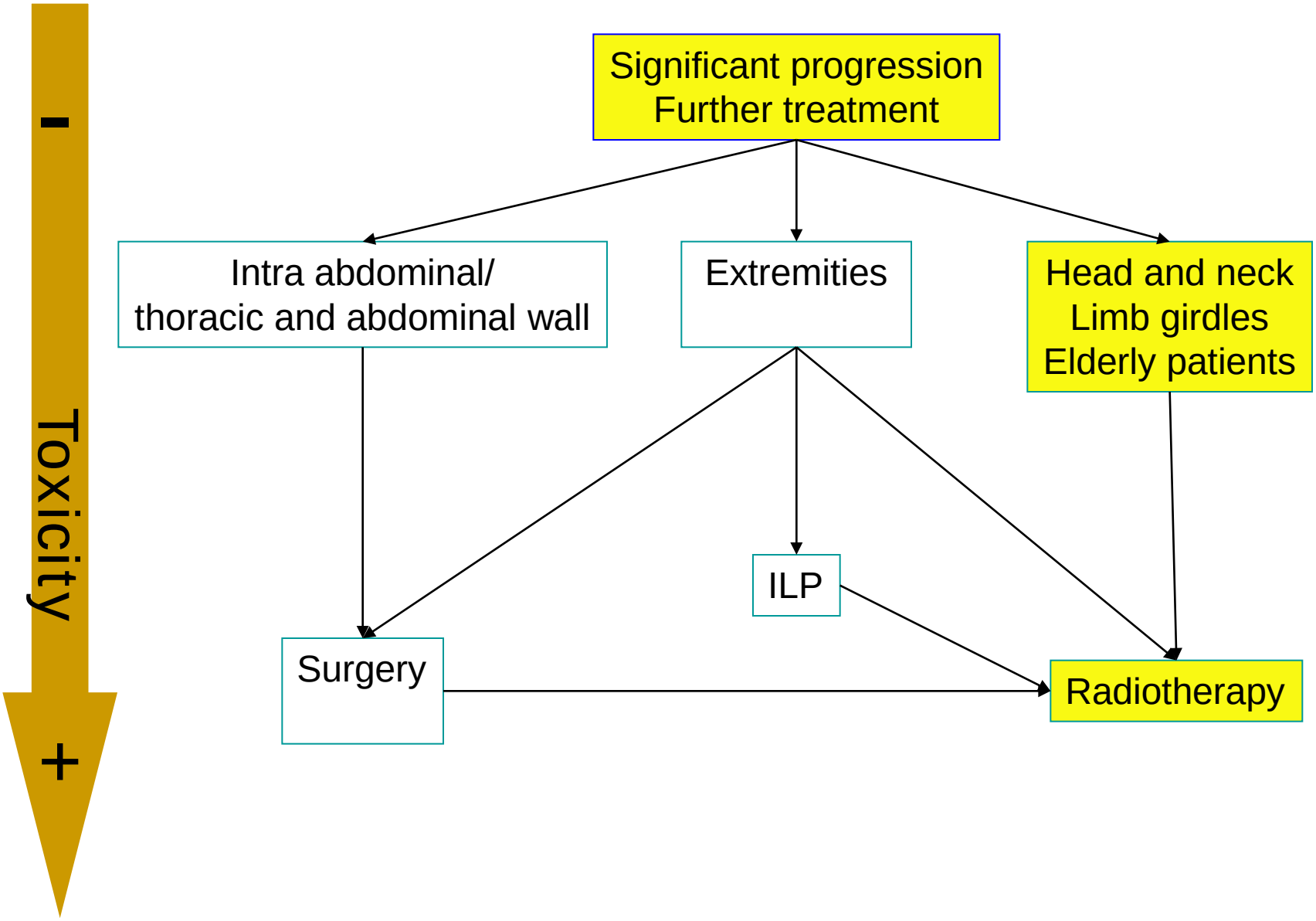
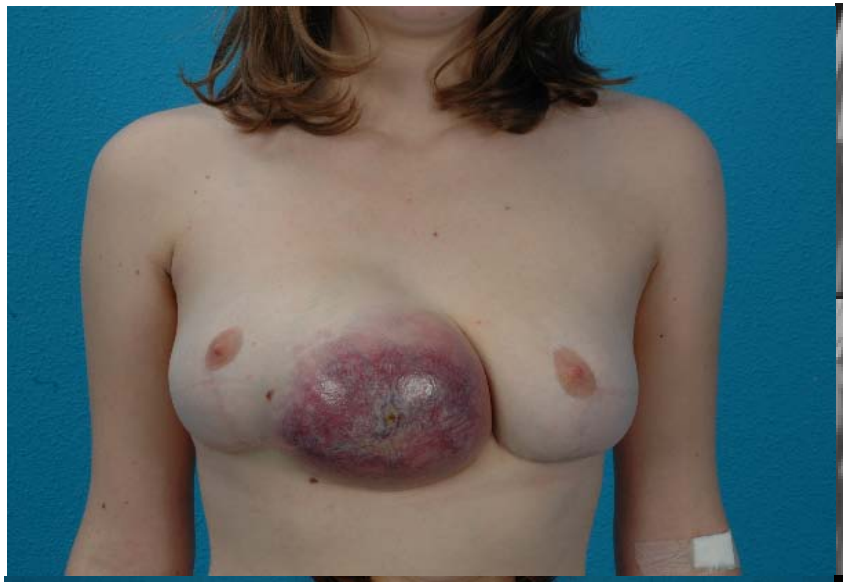
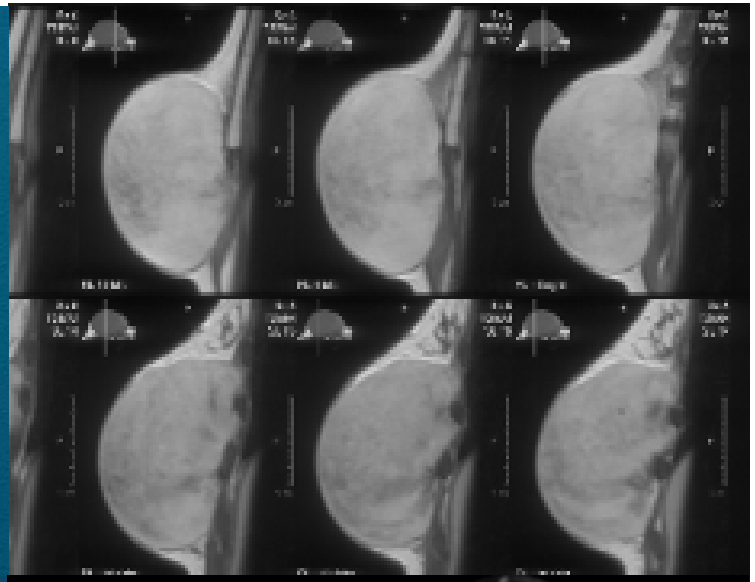
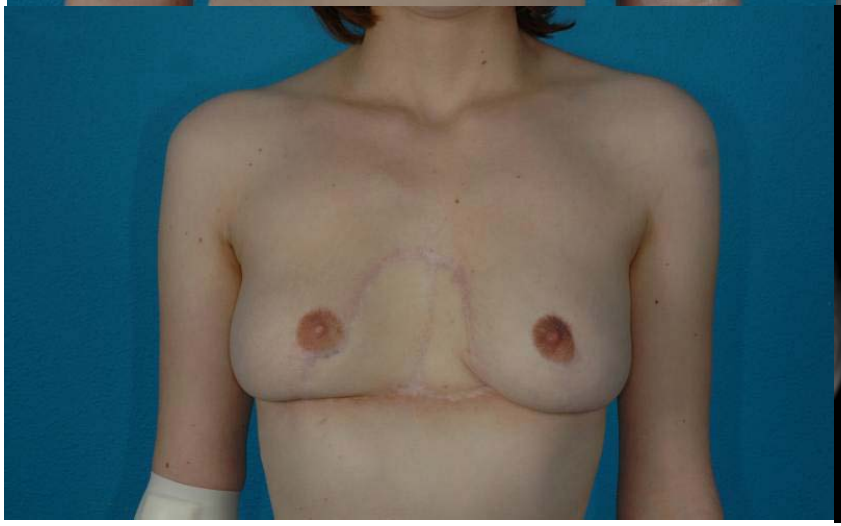
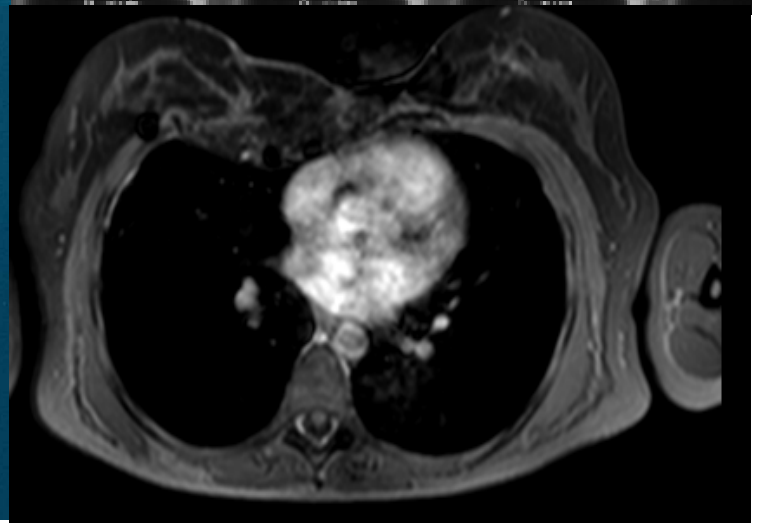

-
Toxicity
+
Significant progression
Further treatment
Intra abdominal/
thoracic and abdominal wall
Extremities
Head and neck
Limb girdles
Elderly patients
ILP
Surgery
Radiotherapy

Combination of treatments









Desmoid and Pregnancy

	A	B	C	D
Total number	17	10	29	19
DF progression during or after P	12 (70%)	-	16 (55%)	4 (21%)
Treatment after progression	9 (53%)	-	8 (28%)	3 (16%)
Surgery	5	-	6	2
Medical therapy	4	-	2	1
Spontaneous regression	1 (5%)	1 (10%)	7 (24%)	1 (5%)

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

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

ASCO 2012
Ann Surg 2013

Istituto Nazionale dei Tumori, Milan, Italy
Institute Gustave Roussy, Villejuif, France
Brigham and Women's Hospital, Dana-Farber Cancer Institute

Conclusions

- Aggressive treatments that take their indications from retrospective studies should be re evaluated in the light of new data
- Observation alone could be considered for primary tumors
- In cases of RECIST progression, treatment is tailored according to age, gender, location, symptoms…in specialized team

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Thanks for your support!!!