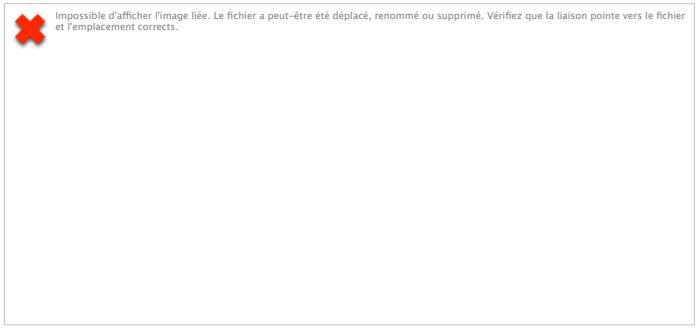
Les essais qui vont changer nos pratiques

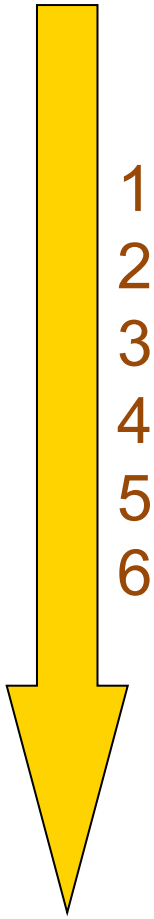
Tumeurs desmoides

Sylvie Bonvalot



LES INDICATIONS DES TRAITEMENTS AGRESSIFS DEFINITIFS (CHIRURGIE ET RADIOTHERAPIE) ONT EVOLUE RECEMMENT

2000



1. Chirurgie large « pour tous » si tumeur résécable
2. + Radiothérapie si R1
3. Impact marges variable, privilégier chirurgie fonctionnelle
4. Surveillance pour des récidives ou tumeurs non résécables
5. Surveillance pour des tumeurs résécables
6. 2012: Recommandation NCI et ESMO

2012

Bonvalot EJSO 2008, Fiore ASO 2009, Salas JCO 2012

Available online at www.sciencedirect.com
ScienceDirect
EJSO
the Journal of Cancer Surgery
ELSEVIER
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]

[a] *Department of Surgery, Institut Gustave Roussy, 39 rue Camille Desmoulins, 94805 Villejuif, France*
[b] *Department of Biostatistics, Institut Gustave Roussy, Villejuif, France*
[c] *Department of Pediatric Oncology, Institut Gustave Roussy, Villejuif, France*
[d] *Department of Radiology, Institut Gustave Roussy, Villejuif, France*
[e] *Department of Pathology, Institut Gustave Roussy, Villejuif, France*
[f] *Medical Oncology, Centre Léon Bérard, Lyon, France*
[g] *Department of Medical Oncology, Institut Gustave Roussy, Villejuif, France*
[h] *Department of Radiotherapy, Institut Gustave Roussy, Villejuif, France*

Accepted 20 June 2007.

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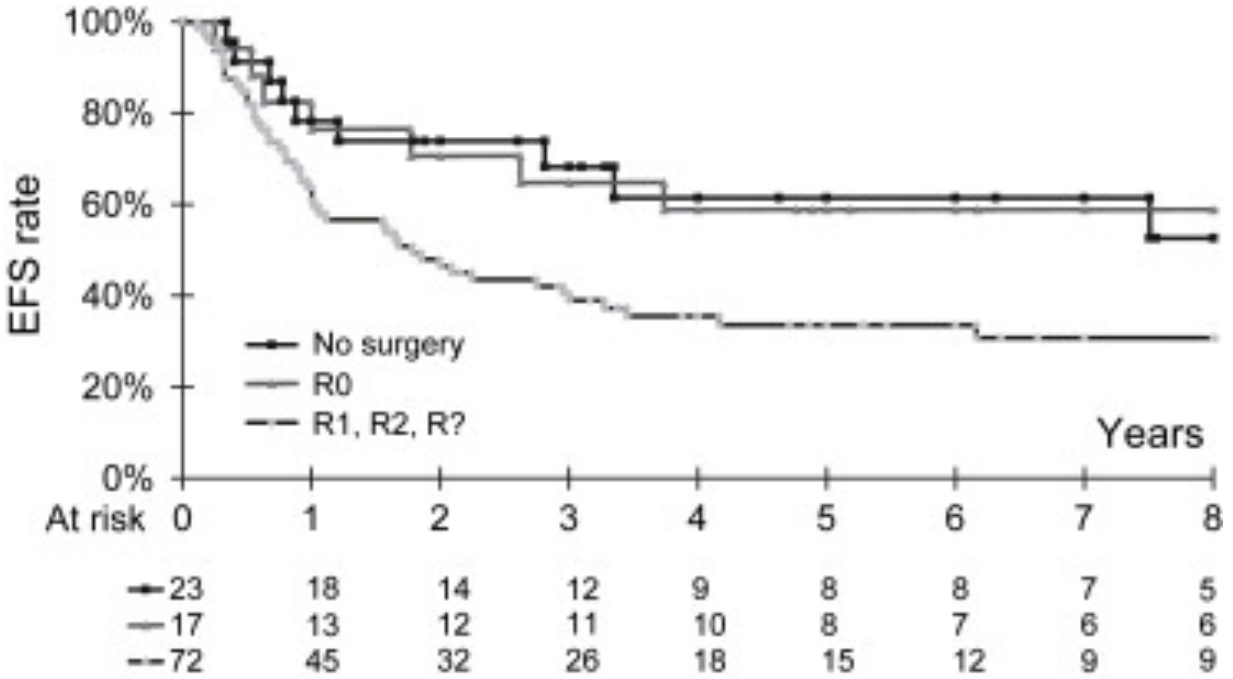
Extra-abdominal primary fibromatosis: Aggressive management could be avoided in a subgroup of patients☆



Observation

- Surveillance: 5-year PFS: 49.9%
- Traitement médical: 5-year PFS: 58.6%
- 50 % pts avec T primitive n' ont pas reçu de traitement
- Pts "progressifs": median TTP: 14 mois

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

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]

[1]Department of Surgery, Istituto Nazionale Tumori, Milan, Italy; [2]Department of Surgery, Institut Gustave Roussy, Villejuif, France; [3]Department of Biostatistics, Istituto Nazionale Tumori, Milan, Italy; [4]Department of Medical Oncology, Institut Gustave Roussy, Villejuif, France; [5]Department of Pathology, Istituto Nazionale Tumori, Milan, Italy; [6]Department of Radiotherapy, Institut Gustave Roussy, Villejuif, France; [7]Department of Cancer Medicine, Istituto Nazionale Tumori, Milan, Italy

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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Published Online: 1 July 2009

A. Gronchi, MD
e-mail: alessandro.gronchi@istitutotumori.mi.it

S. Bonvalot, MD, PhD
e-mail: sylvie.bonvalot@igr.fr

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

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

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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Published online 9 November 2010

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

VOLUME 29 · NUMBER 26 · SEPTEMBER 10 2011

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.

Ann Surg Oncol
DOI 10.1245/s10434-013-3197-x

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

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]

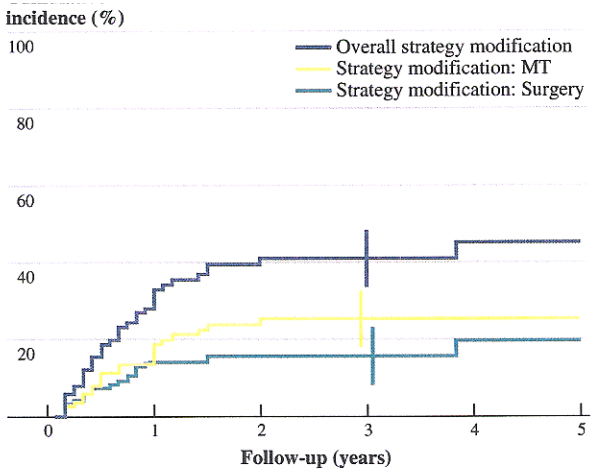

FIG. 2 Cumulative incidence of overall strategy modification, switch to medical treatment with no further switch, and final switch to surgery

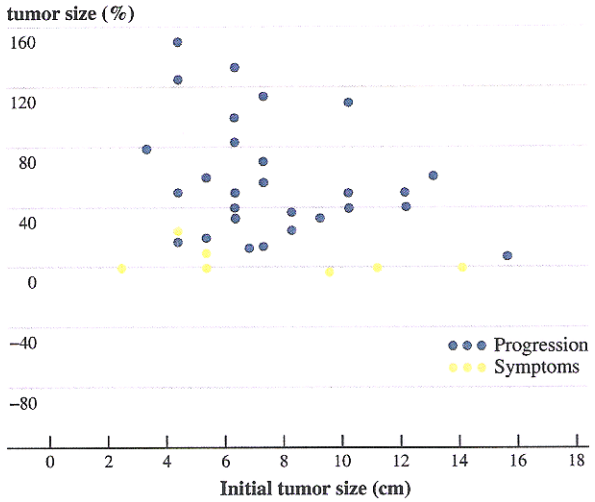

FIG. 3 Change in tumor size for patients with modification strategy (each *point* represents a patient)

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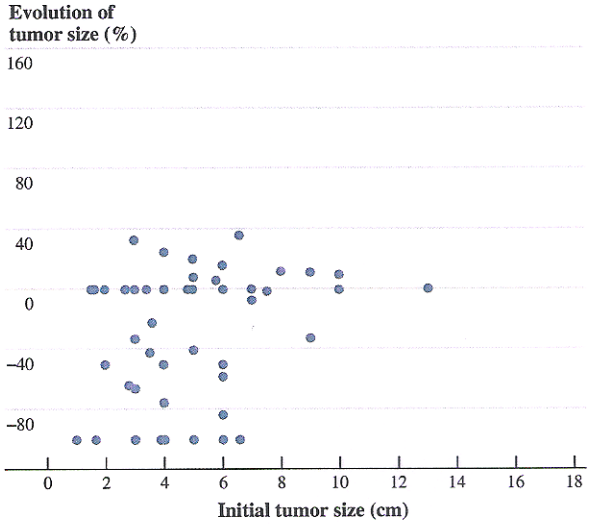

FIG. 4 Change in tumor size for patients without modification strategy (each *point* represents a patient)

147 patients présentant T desmoide primitive de paroi abdominale

British Journal of Cancer (2010) 102, 1032–1036

www.bjcancer.com

High frequency of β-catenin heterozygous mutations in extra-abdominal fibromatosis: a potential molecular tool for disease management

J Dômont[1,13], S Salas[2,13], L Lacroix[3,4], V Brouste[2], P Saulnier[3], P Terrier[1], D Ranchère[5], A Neuville[6], A Leroux[7], L Guillou[8], R Sciot[9], F Collin[10], A Dufresne[5], J-Y Blay[5], A Le Cesne[1], J-M Coindre[*,2,11], S Bonvalot[*,1] and J Bénard[*,1,4,12]

[1]Sarcoma Committee, Institut Gustave Roussy, Villejuif, France; [2]Institut Bergonié, Bordeaux, France; [3]Translational Laboratory, Institut Gustave Roussy, Villejuif, France; [4]Department of Clinical Biology and Pathology, Institut Gustave Roussy, Villejuif, France; [5]Centre Léon Bérard, Lyon, France; [6]Department of Pathology, Hôpital Hautepierre, Strasbourg, France; [7]Department of Pathology, Centre Alexis Vautrin, Nancy, France; [8]University Institute of Pathology, Lausanne, Switzerland; [9]Department of Pathology, KU Leuven, Belgium; [10]Department of Pathology, Centre Georges-François Leclerc, Dijon, France; [11]INSERM U916, Pathology Department, University Victor Ségalen, Bordeaux, France; [12]CNRS-UMR 8126, IFR54, Institut Gustave Roussy, Villejuif, France

British Journal of Cancer (2010) 102, 1032 – 1036

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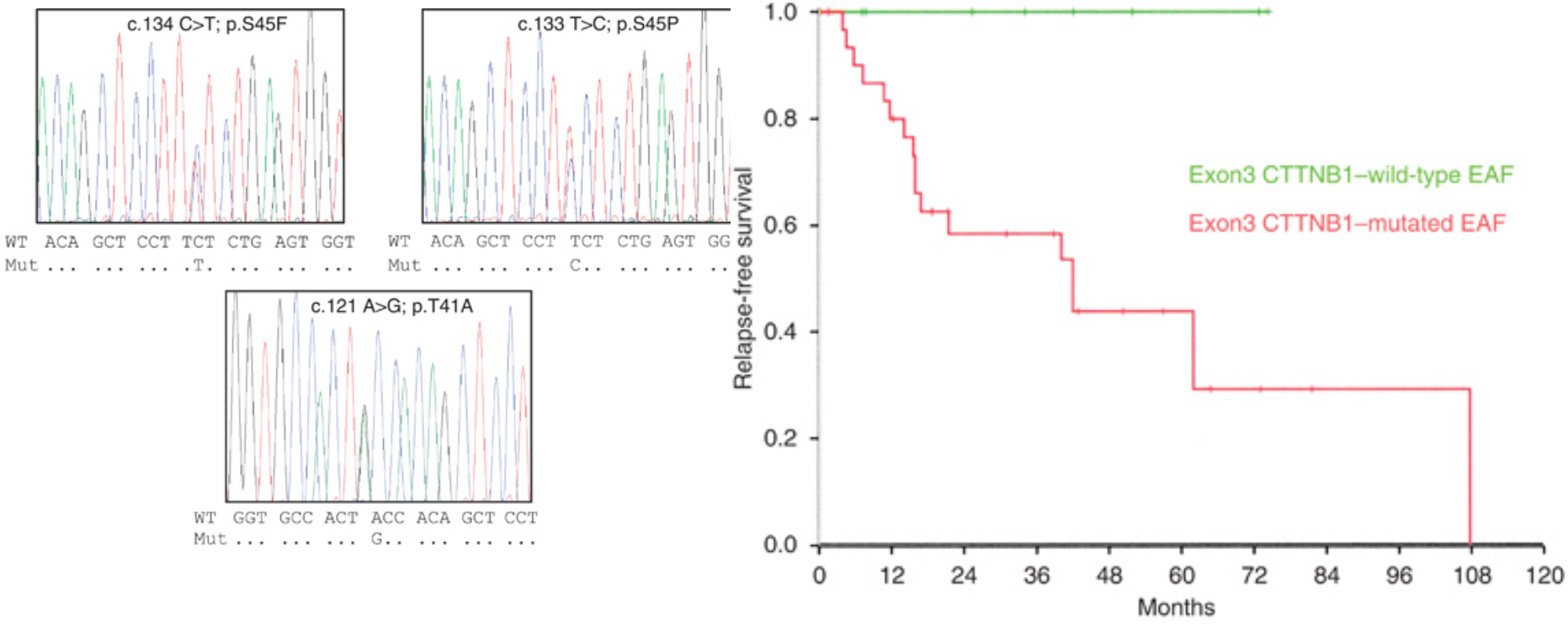
High frequency of β-catenin heterozygous mutations in extra-abdominal fibromatosis: a potential molecular tool for disease management



Original Article

CTNNB1 45F Mutation Is a Molecular Prognosticator of Increased Postoperative Primary Desmoid Tumor Recurrence

An Independent, Multicenter Validation Study

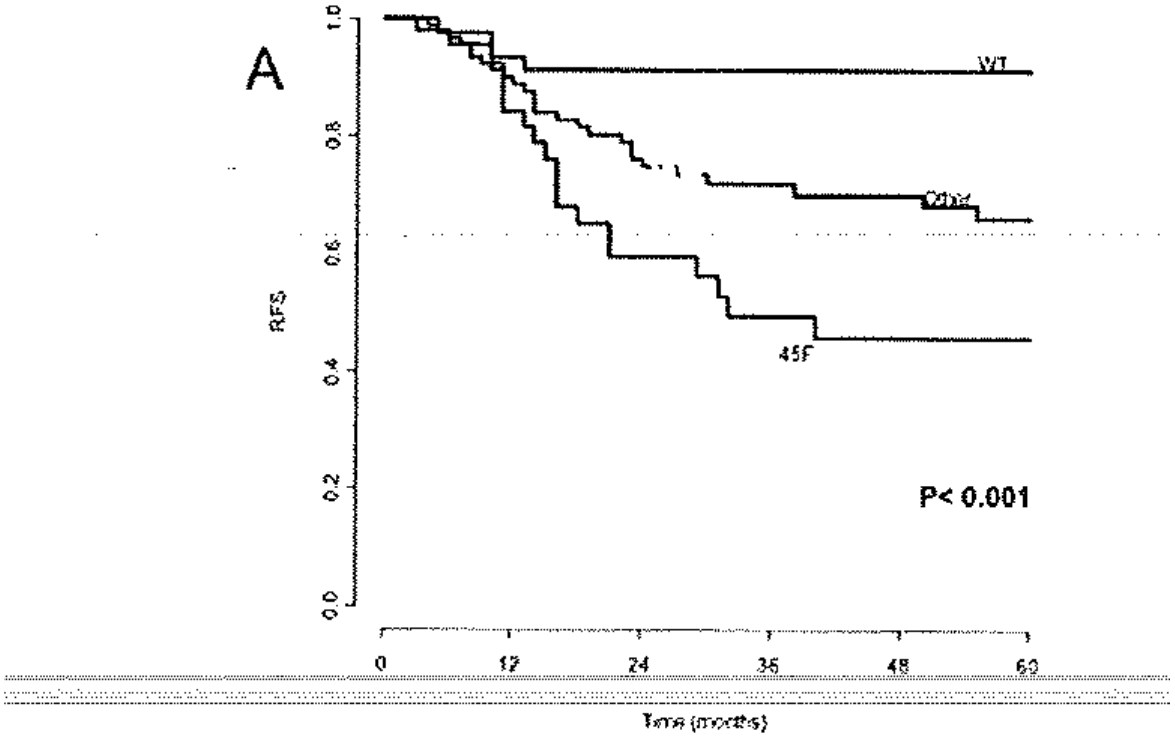
Chiara Colombo, MD[1]; Rosalba Miceli, PhD[2]; Alexander J. Lazar, MD, PhD[3,4]; Federica Perrone, PhD[5]; Raphael E. Pollock, MD, PhD[4,6]; Axel Le Cesne, MD[7]; Henk H. Hartgrink, MD[8]; Anne-Marie Cleton-Jansen, PhD[9]; Julien Domont, MD[7]; Judith V. M. G. Bovée, MD[9]; Sylvie Bonvalot, MD[10]; Dina Lev, MD[4,11]; and Alessandro Gronchi, MD[1]

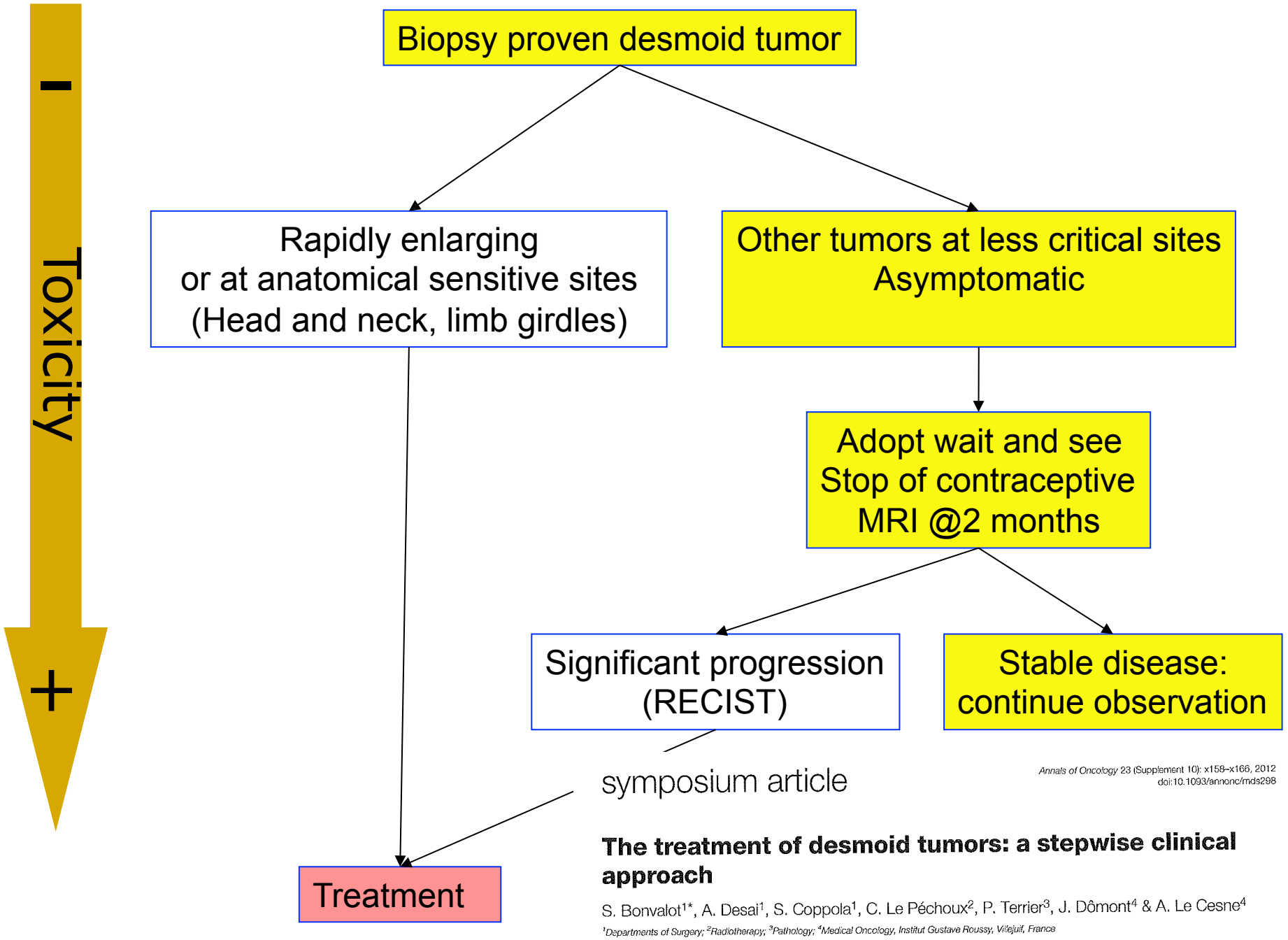
BACKGROUND: A role for the serine to phenylalanine substitution at codon 45 (the S45F mutation) in the catenin (cadherin-associated protein) β-1 (*CTNNB1*) gene as a molecular predictor of local recurrence in patients with primary, sporadic desmoid tumor (DT) has been reported. To confirm the previous data, the authors evaluated the correlation between *CTNNB1* mutation type and local recurrence in this multi-institutional, retrospective study. **METHODS:** Patients with primary, sporadic DT who underwent macroscopic complete surgical resection were included. Recurrence-free survival (RFS) analyses were conducted using the Kaplan-Meier method and log-rank tests to compare strata. **RESULTS:** In total, 179 patients were identified, including 65% females and 35% males (median age, 39 years; median tumor size, 7 cm). Most DTs were located in the abdominal/chest wall (42%) followed by extra-abdominal sites (40%) and intra-abdominal sites (18%). All patients underwent either R0 resection (62%) or R1 resection (38%), and most underwent surgery alone (80%). The tyrosine to alanine substitution at codon 41 (T41A) was the most frequent mutation (45%), but the S45F mutation was more prevalent in extra-abdominal DTs compared with other sites ($P<.001$). At a median follow-up of 50 months, 86% of patients remained alive without disease. The estimated 3-year and 5-year RFS rates were 0.49 and 0.45, respectively, for patients who had tumors with the S45F mutation; 0.91 and 0.91, respectively, for patients who had wild-type tumors; and 0.70 and 0.66, respectively, for all others ($P<.001$). A similar trend was observed for patients who underwent surgery alone ($P<.001$). On multivariable analysis, mutation remained the only factor that was prognostic for local recurrence. **CONCLUSIONS:** This series confirmed that primary, completely resected, sporadic DTs with the S45F mutation have a greater tendency for local recurrence. With increasing implementation of "watchful-waiting" for DT management, it will be important to determine whether mutation type predicts outcome for these patients. ***Cancer* 2013;119:** 196-702. © *2013 American Cancer Society.*

Original Article

CTNNB1 45F Mutation Is a Molecular Prognosticator of Increased Postoperative Primary Desmoid Tumor Recurrence

An Independent, Multicenter Validation Study





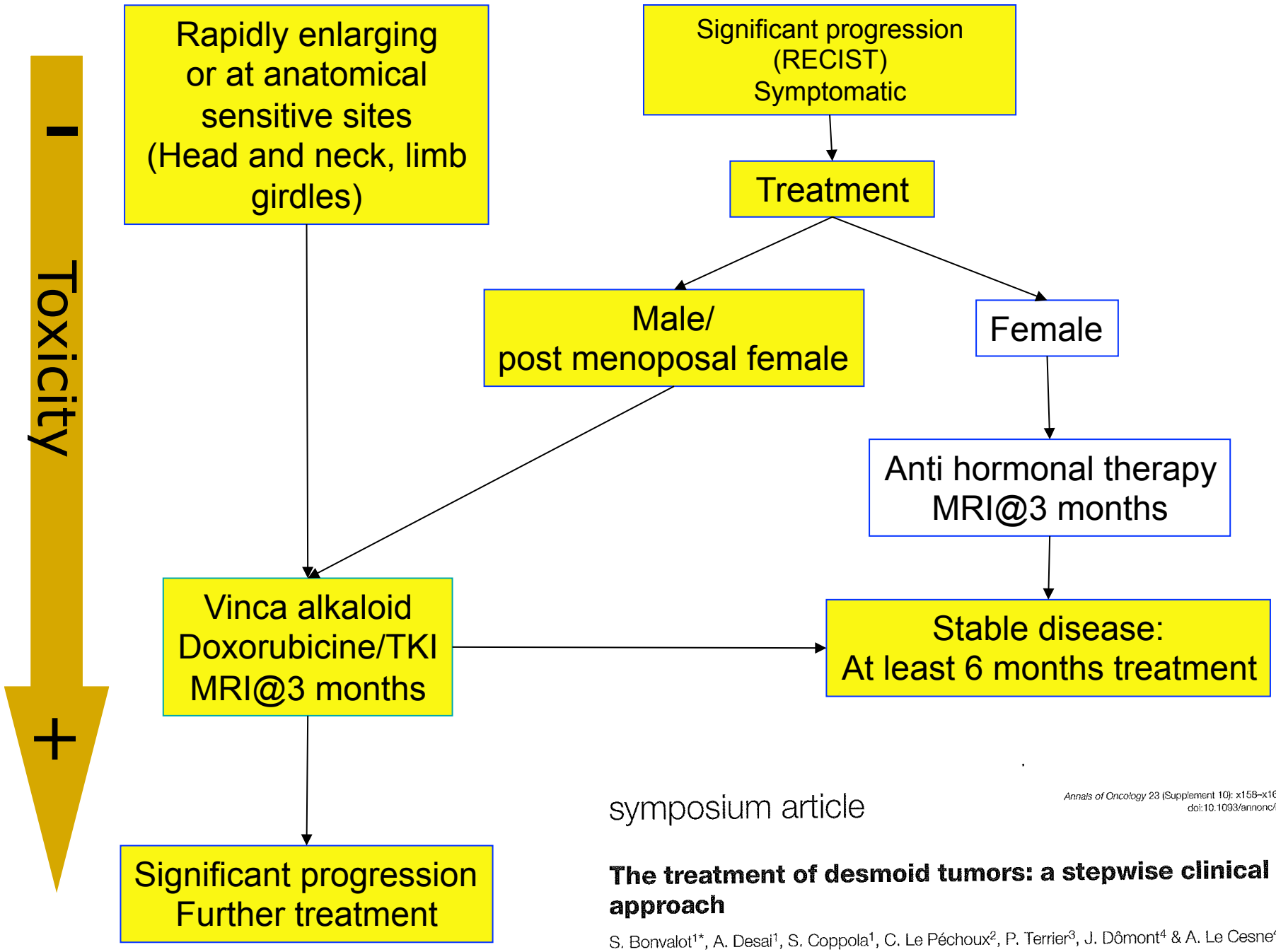
symposium article

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*



symposium article

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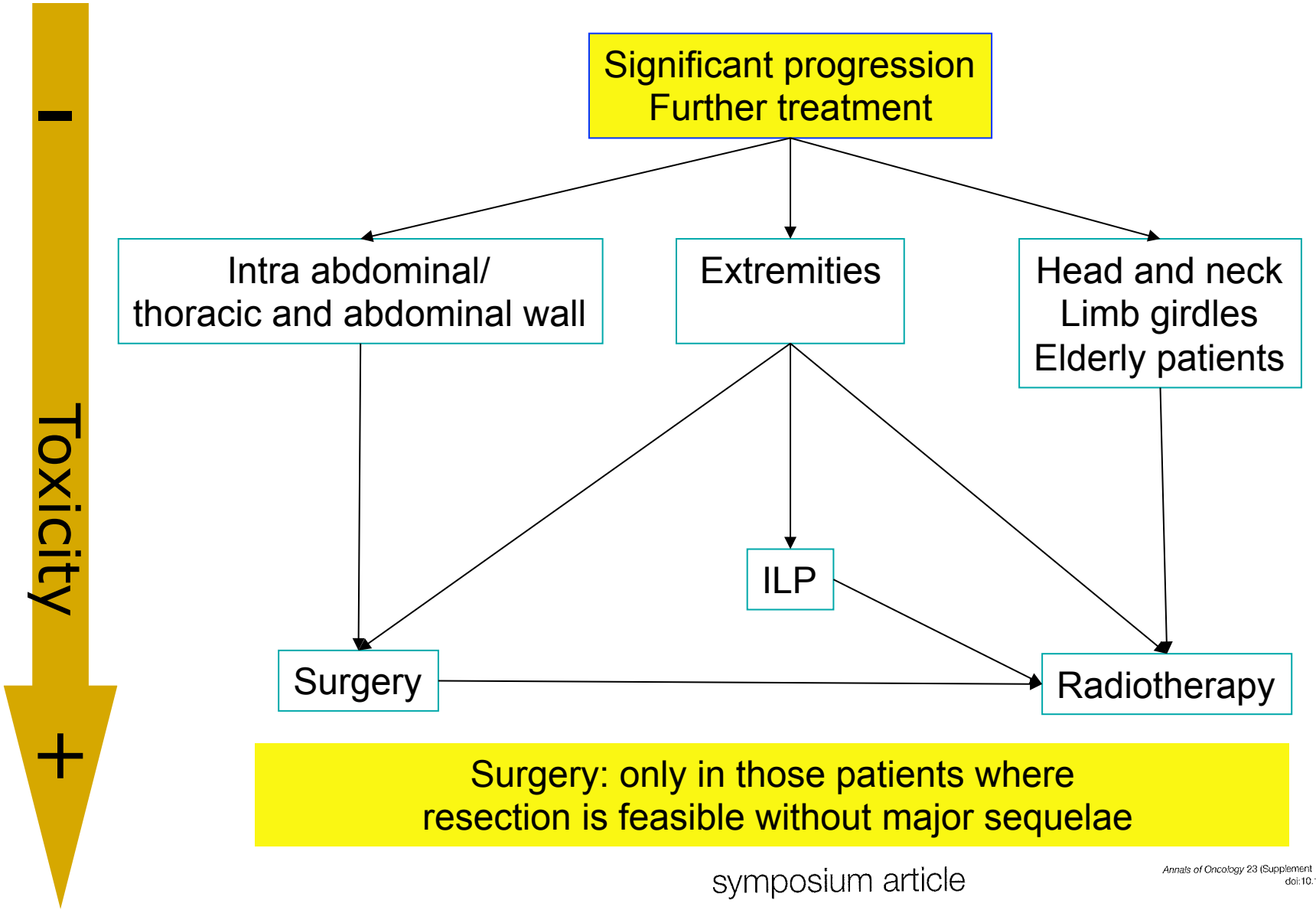

Surgery: only in those patients where resection is feasible without major sequelae

symposium article

Annals of Oncology 23 (Supplement 10): x158–x166, 2012
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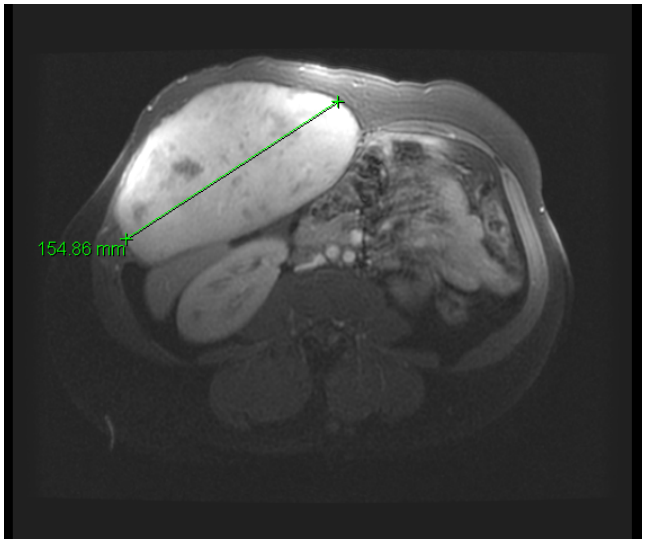
The treatment of desmoid tumors: a stepwise clinical approach

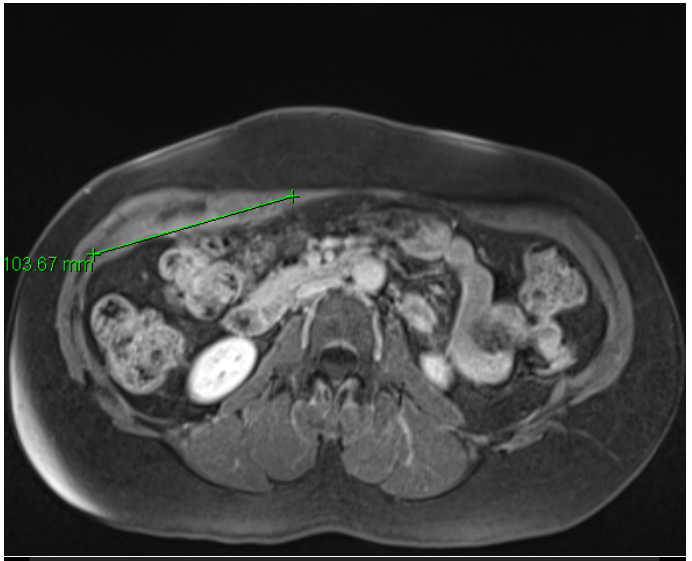
S. Bonvalot[1*], A. Desai[1], S. Coppola[1], C. Le Péchoux[2], P. Terrier[3], J. Dômont[4] & A. Le Cesne[4]

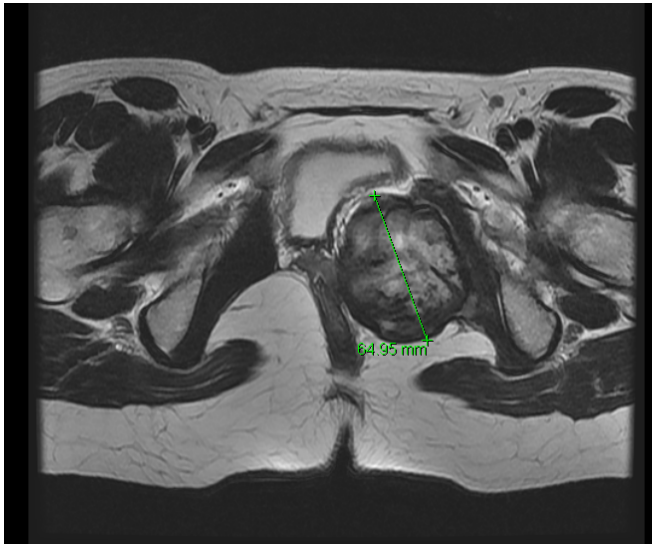
[1]*Departments of Surgery;* [2]*Radiotherapy;* [3]*Pathology;* [4]*Medical Oncology, Institut Gustave Roussy, Villejuif, France*

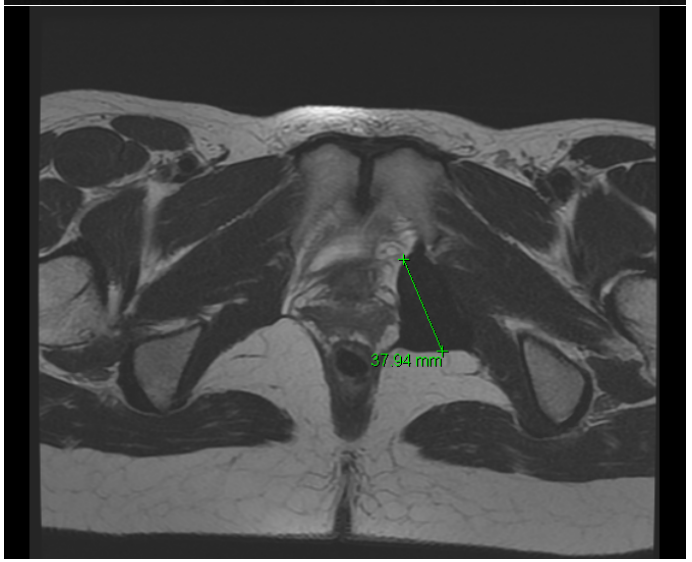
2005: Femme: 50 ans
Biopsie: Desmoide (revue GSF)

Wait and see
IRM 2012



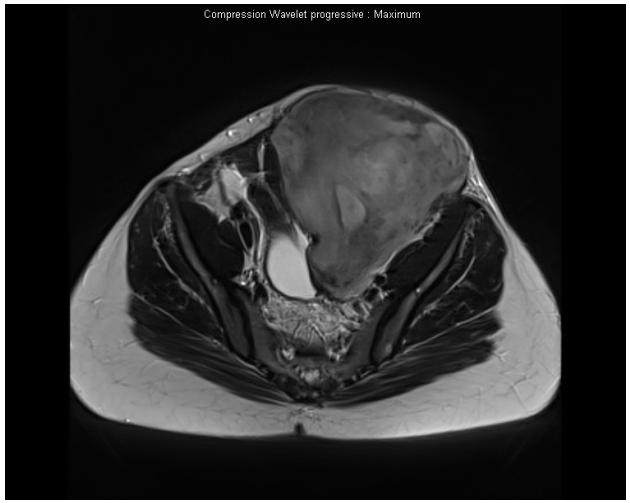


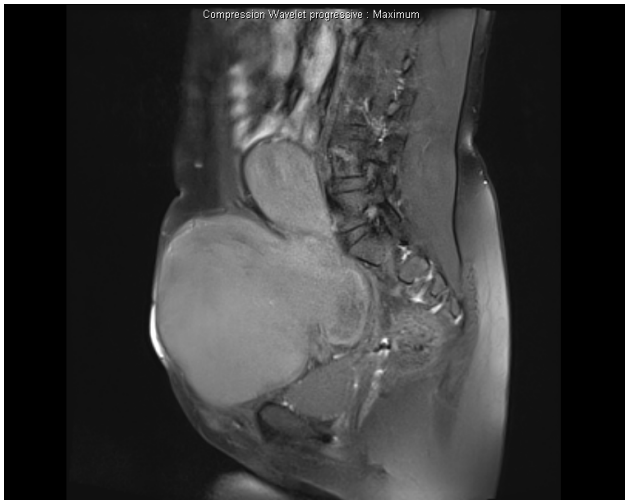


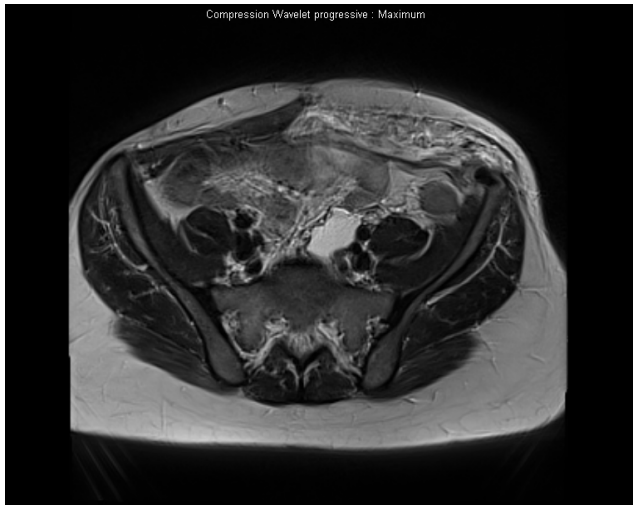


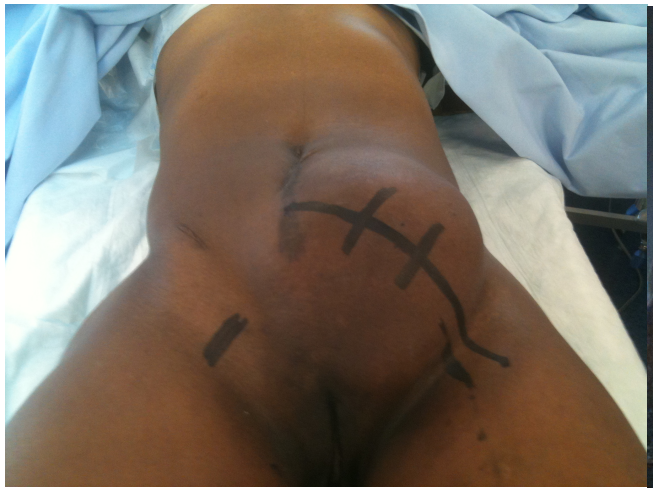
2007: Femme 34 ans post partum
Biopsie pertucanée 16G: desmoide

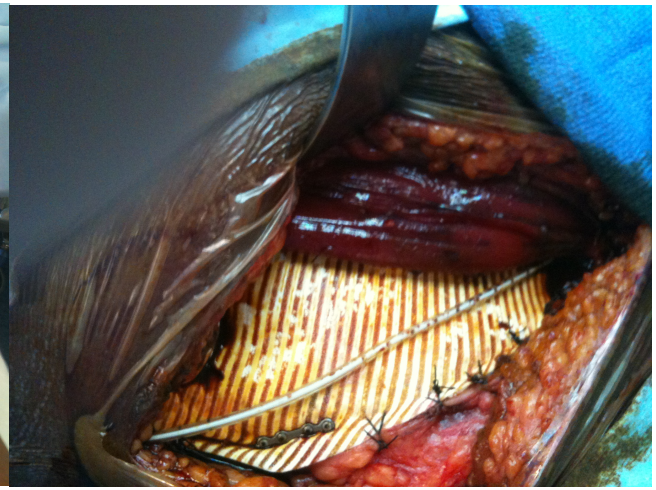
Tamoxifène 18 mois
IRM: 2012

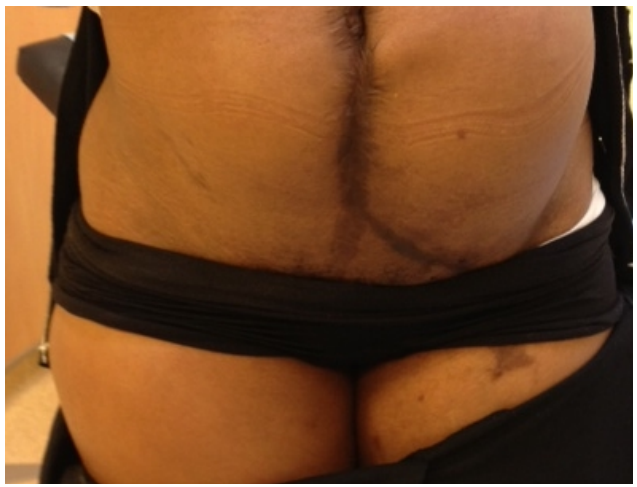

Compression Wavelet progressive : Maximum


Compression Wavelet progressive : Maximum


Compression Wavelet progressive : Maximum







Fibromatoses primitives périphériques

Etude de phase 2 évaluant une surveillance simple initiale avec
Recherche des facteurs prédictifs d'évolutivité et Enregistrement des traitements en cas de progression

- Fibromatoses périphériques primitives (membres et parois abdominale ou thoracique) prouvées par biopsie
- Tous les patients sont surveillés initialement
- Objectif Principal: Survie sans évènement local (progression) à 3 ans
- Objectif(s) secondaire(s):
  - Résultat fonctionnel (CTCAE-V3)
  - Etude des facteurs biologiques (hôte et tumeur) prédictifs de l'évolution
- Enregistrement des traitements en cas de progression
- Stat: le taux de survie sans progression à 3 ans est estimé à 60% (Fiore 2009). Avec 100 patients, l'intervalle de confiance à 95% du taux de survie sans progression s'étendra sur +/- 10% par rapport au taux observé

- Financement: PHRC National 2011
- 10 centres du GSF GETO participent
- Juin 2012: inclusion 1er patient
- Septembre 2013: 24/100 pts inclus

Conclusions

- L'observation a permis de remarquer l'évolution clinique très particulière des « desmoides »
- Les collaborations Nationale et Internationale ont permis de confirmer par des études rétrospectives que la moitié des desmoides a une évolution indolente et était sur traitée
- Le type de mutation du gène β-cathénine apparait pronostic dans les études rétrospectives internationales
- L'objectif de l'essai prospectif en cours est de déterminer sur des critères biologiques, dés le diagnostic, une stratégie thérapeutique actuellement basée sur l'évolutivité clinique