

DT DESMOID TUMOR
RF RESEARCH FOUNDATION

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Desmoid Tumor: Pathobiology and Treatment

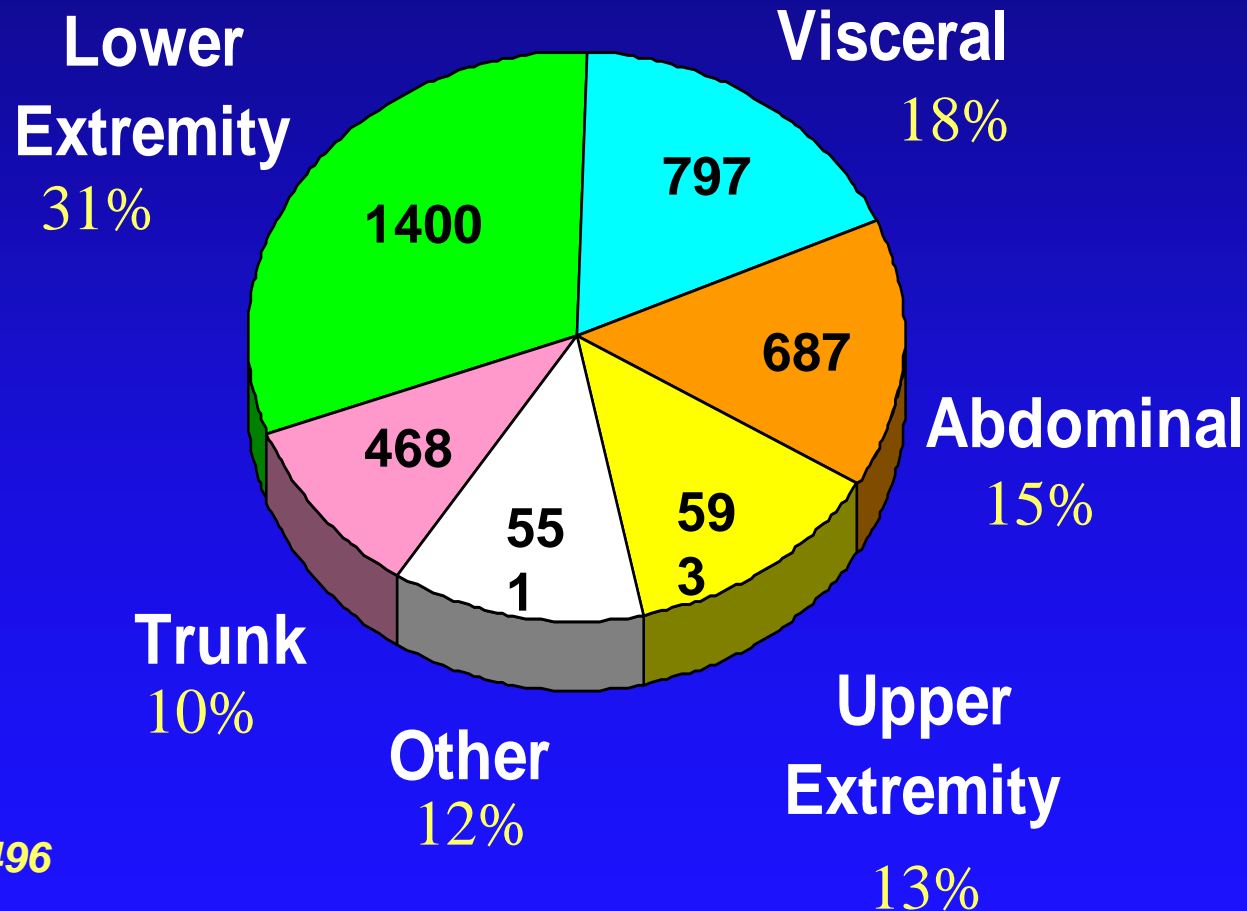
Desmoid Tumor Research Foundation
October 22, 2011

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Overview of Sarcomas

- “Incidence”: 11,000/year in USA
 - 1% of cancers in adults
 - 15% of cancers in pediatric malignancies
- Not restricted to any organ site
- Resemble connective tissue with mesenchymal origin
 - Bone and cartilage
 - Blood vessels, lymphatics
 - Skeletal and smooth muscle
 - Fat
 - Neural crest and perineural cells

Sarcomas can occur anywhere in the body



n = 4496

Courtesy of M. Brennan MSKCC

Classification of Sarcomas by Lineage of Differentiation

- **Adipocytic:** *Liposarcoma*
- **Myogenic:** *Leiomyosarcoma, Rhabdomyosarcoma*
- **Vascular:** *Angiosarcoma, Hemangioendothelioma*
- **Neural:** *Ewing/PNET, MPNST*
- **Fibroblastic:** *Synovial Sarcoma, Fibrosarcoma, **Desmoid**, Myofibroblastic, Myxofibrosarcoma, Endometrial Stromal Sarcoma*
- **Chondrocytic:** *Chondrosarcoma*
- **Osteogenic:** *Osteosarcoma*
- **Unclassifiable**

Approach to Patients with Sarcomas

- Multidisciplinary Teamwork Required
 - Specialty expertise in multiple fields
e.g. surgery, pathology, medical oncology, radiation oncology, psychosocial support, plastic and reconstructive surgery, physical therapy
- Definitive referral center disease

Choosing the Optimal Primary Management of a Newly Diagnosed Localized Sarcoma

- Pathology review is often critical
- Every patient is unique
 - Complex decisions based on anatomic site, tumor behavior, co-morbid factors, etc.

Same Issues Apply to Desmoid Tumor

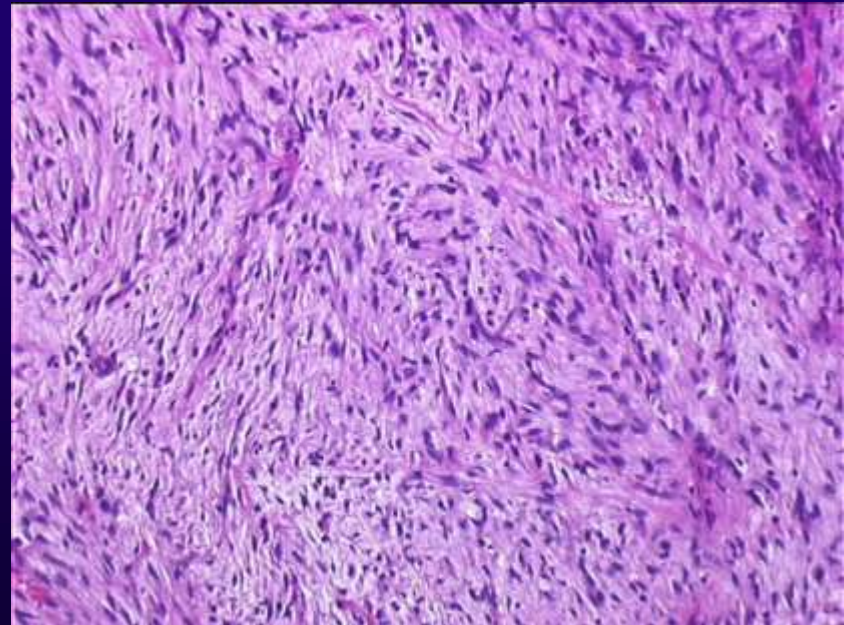
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- Fibroblastic monoclonal proliferation arising from musculo-aponeurotic structures, constituted by spindle cells in a collagen matrix, without atypical, pleomorphic or hyperchromatic nuclei typical of malignancy.

- 0.2-0.4/100,000

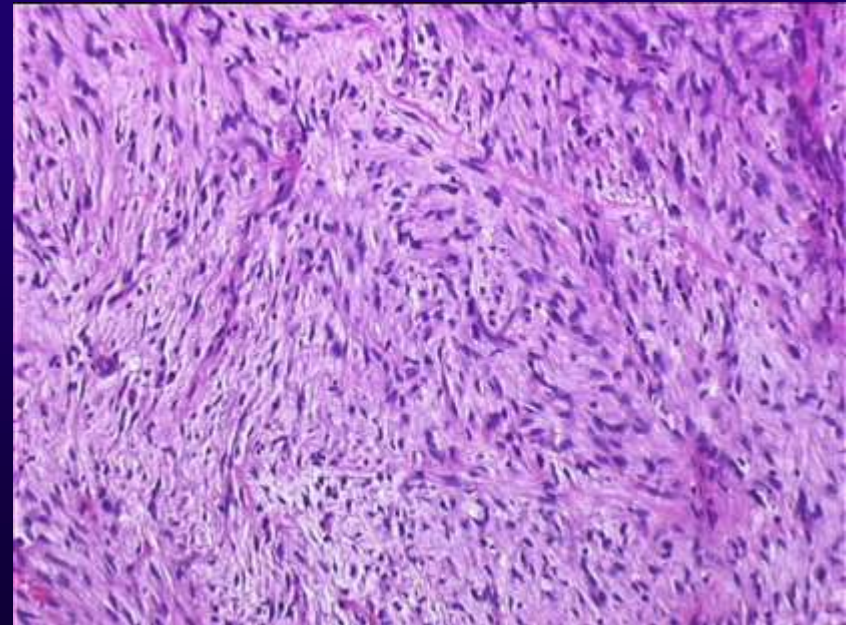
Li et al., Hum Pathol 1996

Alman et al., Diagn Mol Pathol, 1997



- Fibroblastic **monoclonal** proliferation arising from **musculo-aponeurotic** structures, constituted by spindle cells in a collagen matrix, **without** atypical, pleomorphic or hyperchromatic **nuclei typical of malignancy**.

Scar formation that the body isn't turning off



Desmoid Tumor/ Aggressive Fibromatosis

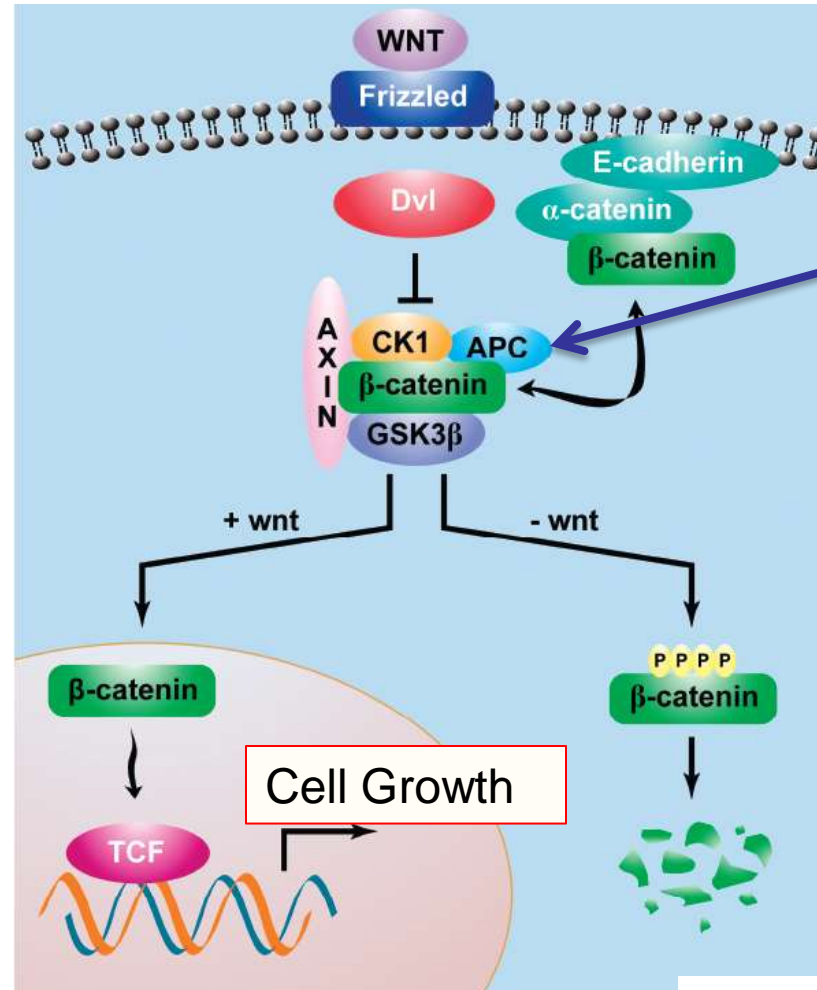
- Not a cancer, but can cause morbidity and mortality
- 95% Sporadic
- 5% FAP-Associated (Familial Adenomatous Polyposis = Gardner syndrome)

Gardner Syndrome

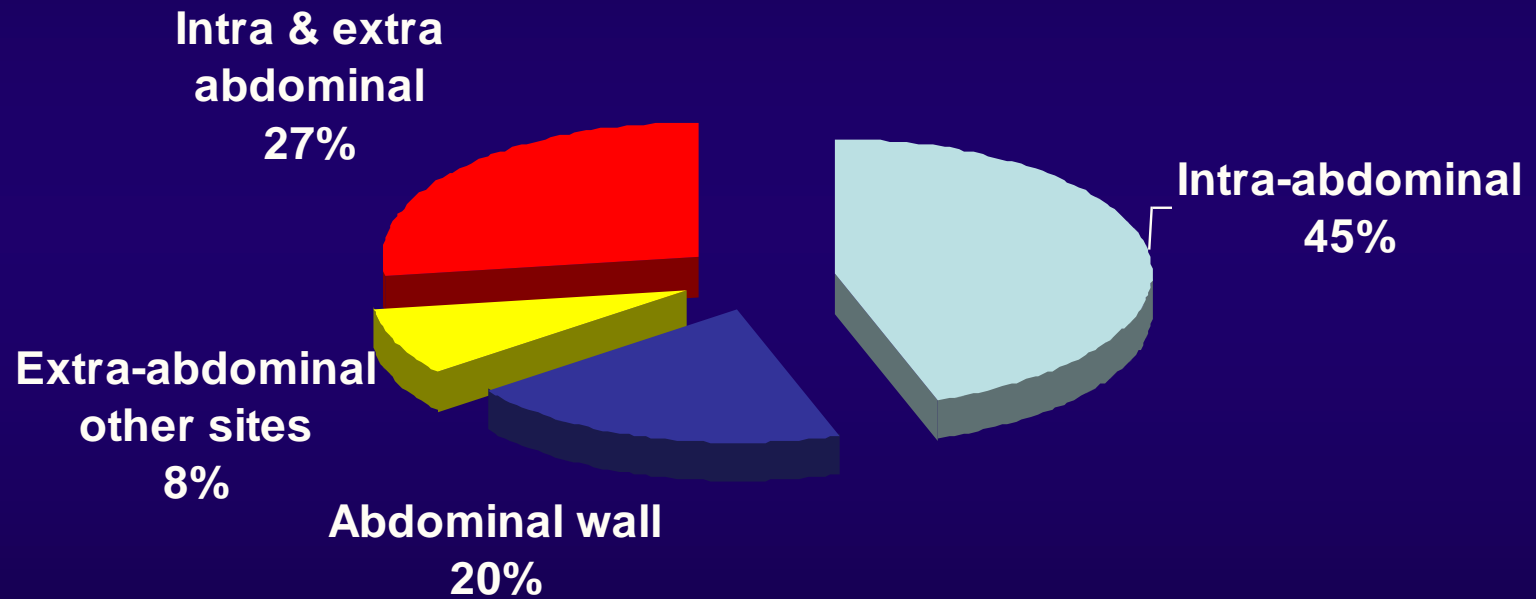
- Autosomal dominant syndrome (50% chance of passing it on to children)
- 1000s of bowel polyps and high risk of colon cancer if colon is not removed
- Mutation in FAP “tumor suppressor gene” in all cells in body
- 10% lifetime risk of desmoid tumors

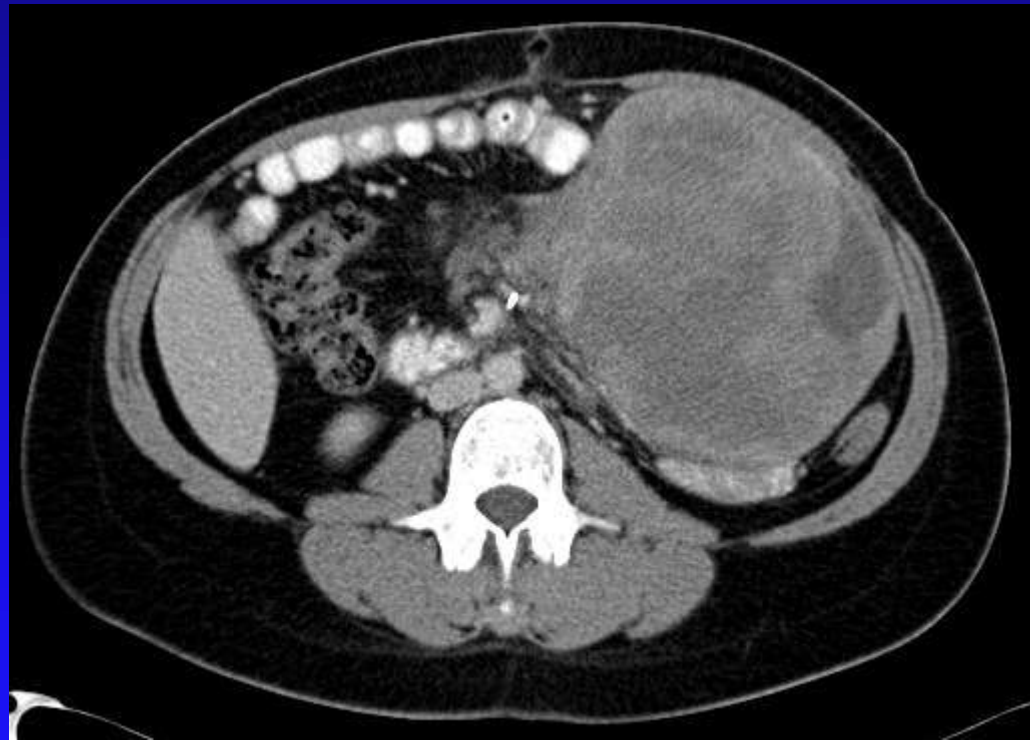
Desmoid tumor: a disease opportune for molecular insights

D. Kotiligam¹, A.J.F. Lazar², R.E. Pollock³ and D. Lev¹



SITES: FAP-Associated





Follow up of 897 FAP patients

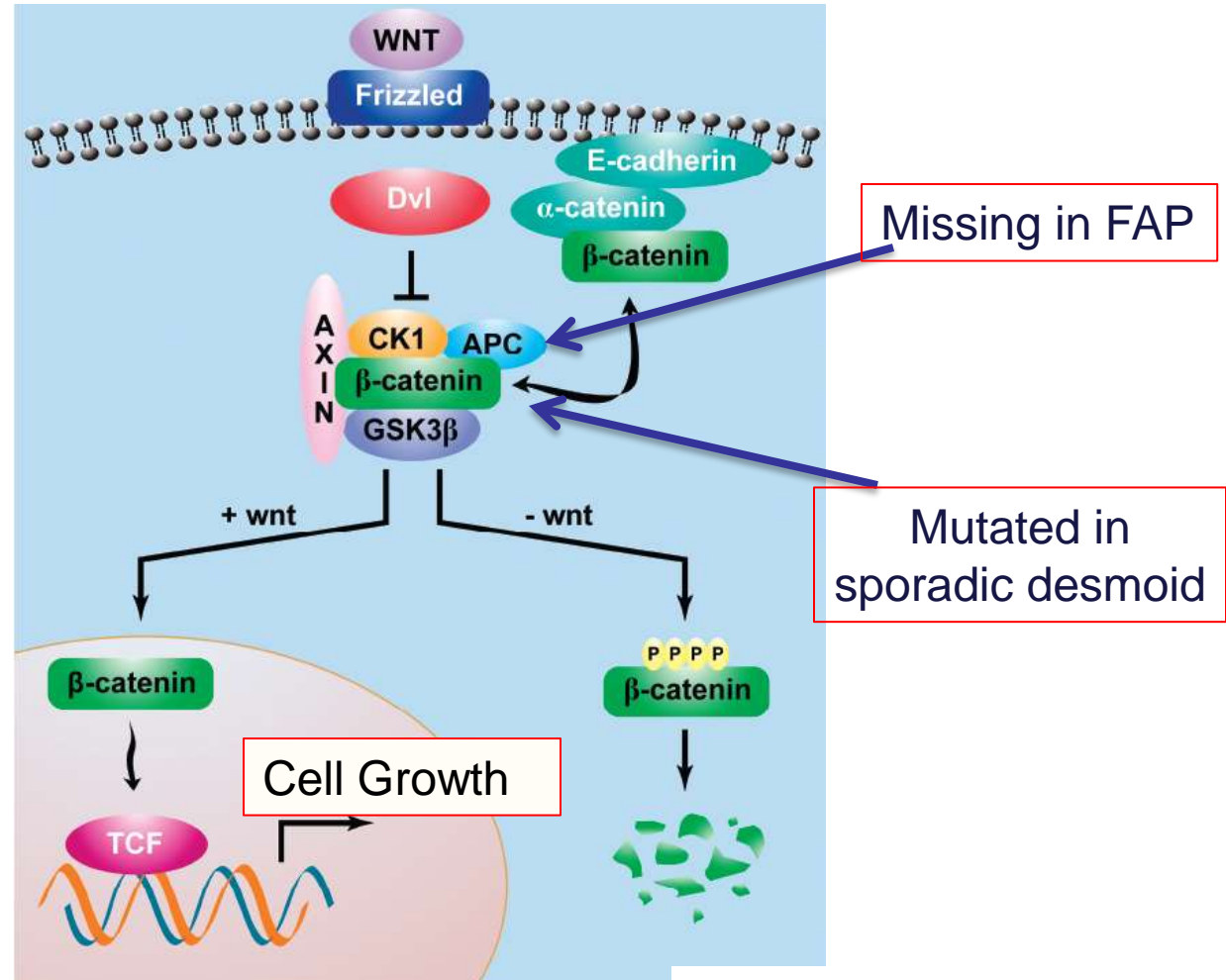
	No	Desmoids			All
		<i>Abdominal</i>	<i>Extra-abdominal</i>	<i>Abdominal and extra-abdominal</i>	
Alive	602 (76.2)	37	28	24	89 (83.2)
Causes of death					
Colorectal cancer	160 (20.3)	3 (6.3)	1 (3.3)	3 (10.3)	7 (6.5)
Other neoplasm	16 (2.0)	-	1 (3.3)	-	1 (0.9)
Fibromatosis	-	7 (14.6)	-	2 (6.9)	9 (8.4)
Other causes	12 (1.5)	1 (2.1)	-	-	1 (0.9)
Total	790	48	30	29	107

Sporadic Desmoid

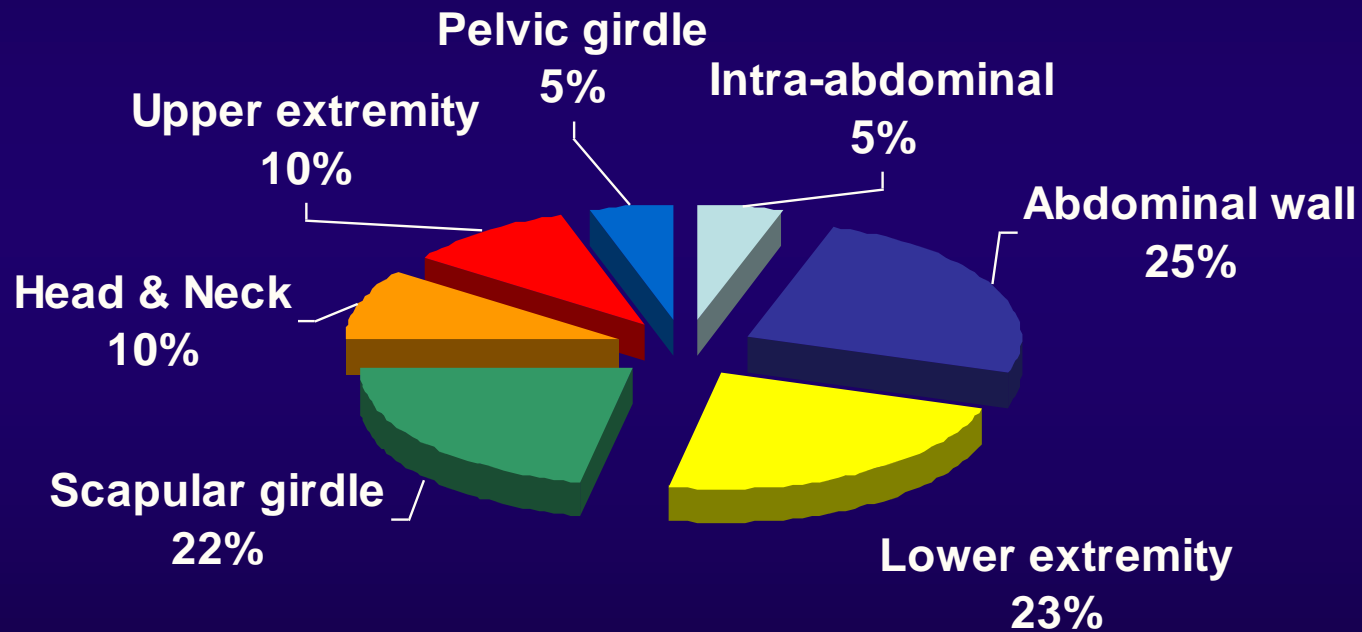
- 85% of the cases harbor a mutation in *CTNNB1*, encoding for β -Catenin protein
- Occurs just in the tumor cells; not in normal tissue
- **Not** hereditary
- Rarer *APC* (chromosome 5) deletion in *CTNNB1* WT tumors may occur

Desmoid tumor: a disease opportune for molecular insights

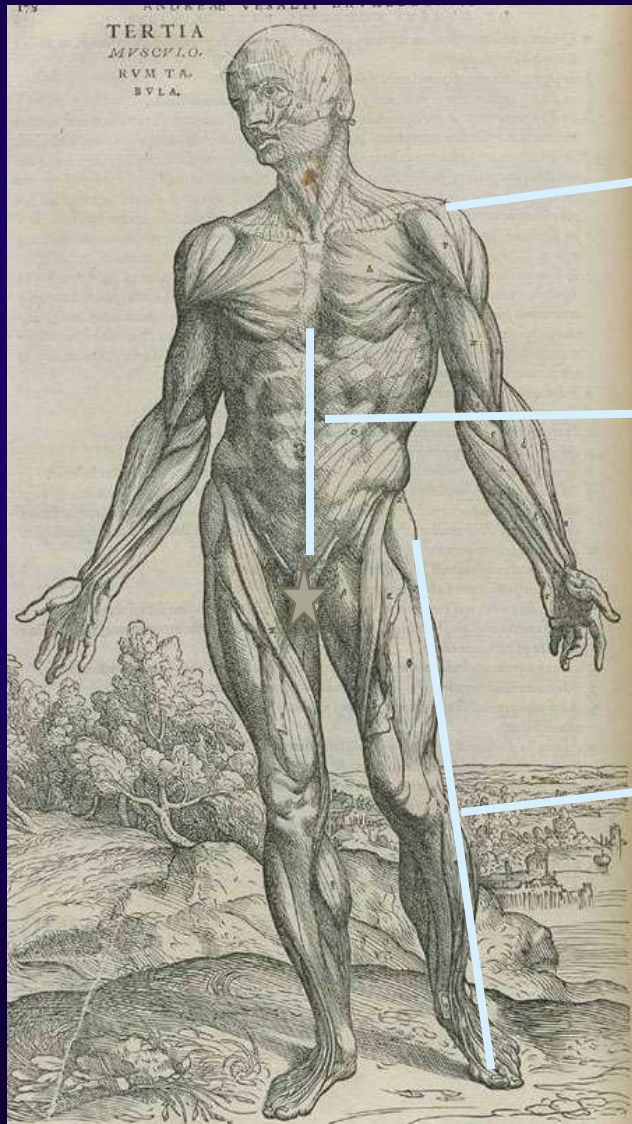
D. Kotiligam¹, A.J.F. Lazar², R.E. Pollock³ and D. Lev¹



SITES: Sporadic Desmoid



Most common sites

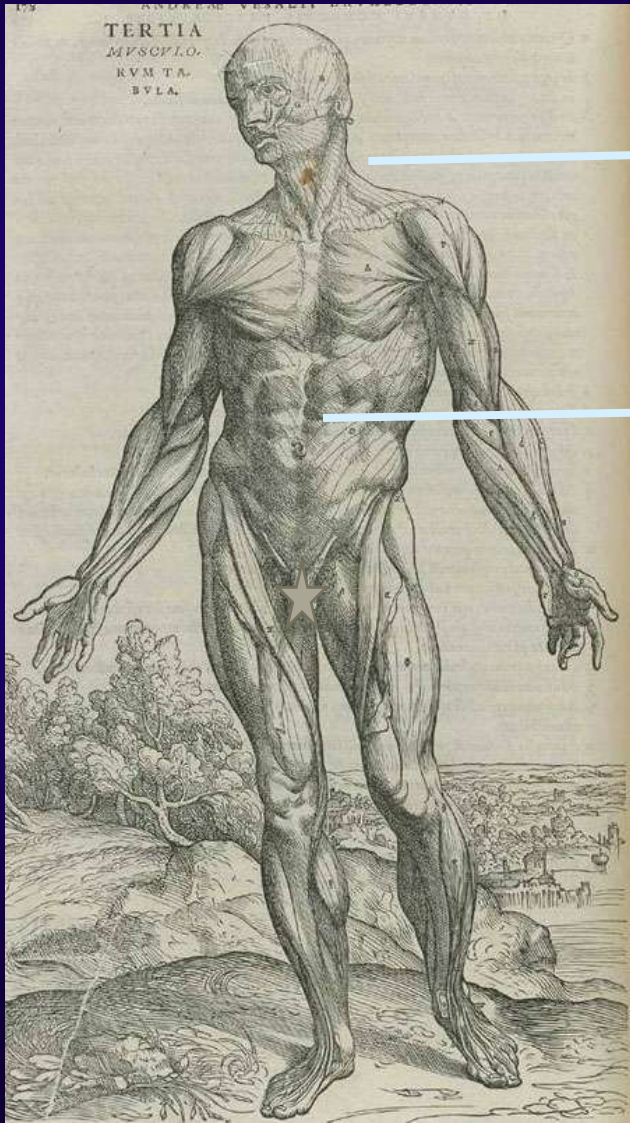


22 %

29 %

24%

Threatening locations



10 %

5 %

Management

- Observation
 - Some spontaneously recede
 - Some grow and then stop growing
- Surgery
 - Only known curative therapy
 - Role of “margins”?
 - Need to balance consequence of disease with consequence of surgery

Management - 2

- Radiation Therapy
 - Unclear role for “positive margins”
 - Can be helpful for unresectable and growing or symptomatic disease

Management - 3

- Medical Treatment
 - NSAIDs (eg Sulindac)
 - Hormonal Therapy (eg tamoxifen)
 - Targeted therapy (imatinib/Gleevec)
 - Chemotherapy
 - Liposomal doxorubicin (Doxil)
 - Methotrexate and Vinblastine (Velban)
- Need to determine need for and goals of treatment!

Clinical Study Designs

- Retrospective Case Series
 - “In the last 10 years we treated 30 patients with drug X. Looking back at their medical records, here is what happened to the tumors.”
 - Require Institutional Review Board approval for medical record review (with or without signed consent of patient)
 - Biased by case selection and lack of direct comparator

Clinical Study Designs

- Prospective Studies
 - Enrollment of patients as research subjects/participants in study of drug(s)
 - Requires permission of IRB and often the FDA
 - Requires signed informed consent of patient

Types of Prospective Studies

- Phase I

- New drug or combination of drugs
- Designed primarily to test **safety and toxicity**, and to establish appropriate dose
- Often multiple (or any) tumor types
- Enroll very small numbers of patients at one dose level; if safe, increase dose in new group of patients
- Everyone gets drug but may not be at effective (too low) or safe (too high) dose
- Frequent visits for safety evaluation and determination of drug blood levels

Types of Prospective Studies

- Phase II

- Designed primarily to **test efficacy** of drug
- Dose determined from prior Phase I studies
- Often one tumor type
- Enrolls moderate number of patients
- Everyone gets drug
- Everyone gets same dose of drug
- Outcome measured as “response rate” or “progression free survival (PFS)”

Types of Prospective Studies

- Phase III

- Designed primarily to **test if one treatment is better** than another
- One tumor type
- Enrolls large number of patients
- Requires national/global effort for rare disease
- Everyone gets drug
- Everyone gets same dose of drug
- Outcomes: “Response rate”, “PFS”, “Overall Survival”, or “Hazard Ratio”
- If positive results, can lead to FDA approval

Recent Very Promising Retrospective Study

(Drs. Gounder, Maki, and others;
Memorial Sloan-Kettering Cancer Center)

- Sorafenib (Nexavar)
 - Oral medicine
 - Blocks key pathways in many tumors
 - Approved for treatment of kidney and liver cancers
 - Side effects can include high blood pressure, painful rash on hands/feet, diarrhea, nausea, fatigue, low blood counts, and others

Activity of sorafenib against desmoid tumor/deep fibromatosis (DT/DF)

Gounder MM, Lefkowitz RA, Hameed MR, D'Adamo DR, Keohan ML,
Singer S, Brennan MF, Antonescu CR, Ahn L and Maki RG.

Departments of Medicine, Pathology, and Surgery,
Memorial Sloan-Kettering Cancer Center, New York, NY

Sorafenib and DT/DF

CELLULAR PROPERTIES:

- Sorafenib inhibits VEGFR, PDGFR, KIT, RET and RAF.
- Exhibits anti-angiogenic, antiproliferative and/or pro-apoptotic effects.

INDEX CASE:

- 19 year old female with progressive and symptomatic supraclavicular desmoid that was initially resected, however recurred within 24 months and deemed unresectable.
- Imatinib was unavailable for this patient. She was started on Sorafenib 400 mg BID through an expanded access program from the manufacturer.
- Symptomatic relief of pain and improvement in shoulder mobility within weeks of starting; the tumor has been only stable by MRI at 24 months, however.

GOAL:

We herein report our retrospective experience of 14 DT/DF patients treated with sorafenib.

Sorafenib:

INDICATION:

-- Progression by imaging: 12, stable scans but worsening pain : 2 and maximum benefit in 1 patient who had received prior doxorubicin.

-- 10/14 pts with prior chemotherapy (median 3 lines) started on sorafenib after a median of 17.5 mo after initial presentation.

-- 4/14 pts had first-line therapy with sorafenib after a median of 4 mo (1-12) after initial presentation.

DURATION

-- Sorafenib was given for a median of 14 months (range 2 – 24) mo.

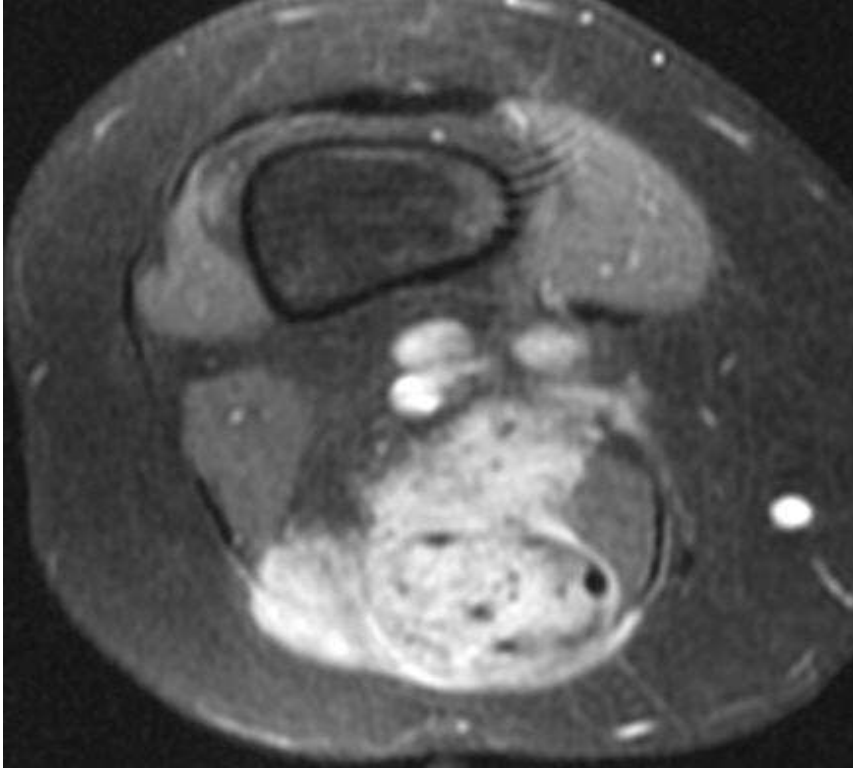
DOSE

-- Patients were started at a median dose of 400 mg PO daily, decreased for symptoms.

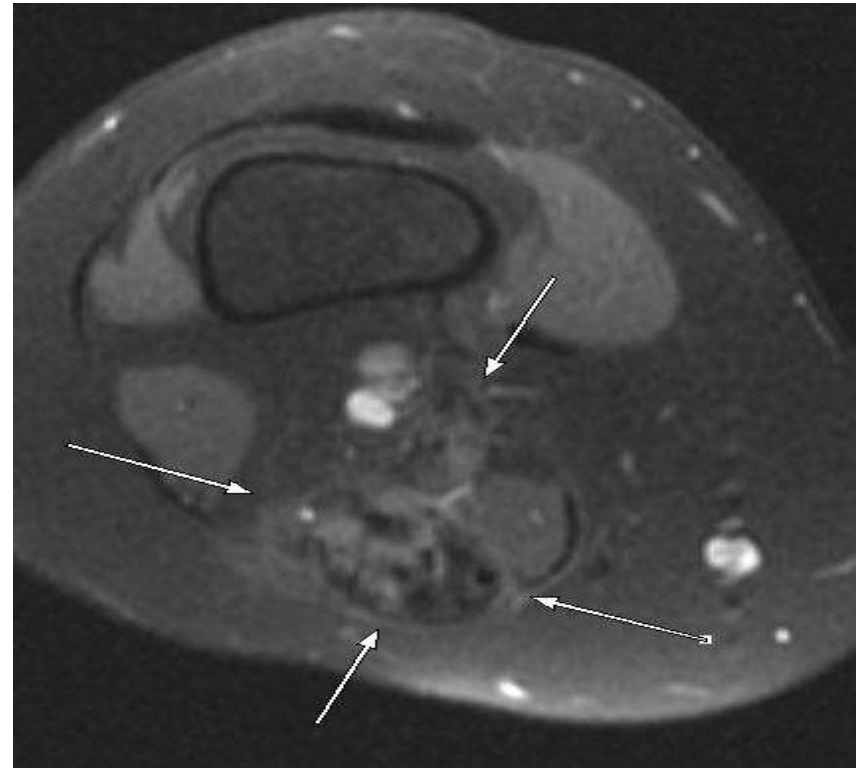
-- Symptoms included: included hand-foot syndrome, fatigue, rash, a sensation of scalp burning, hypertension, mild alopecia and diarrhea.

-- Severity of symptoms were not quantified.

Pt #1: Pre- and Post MRI w/ contrast

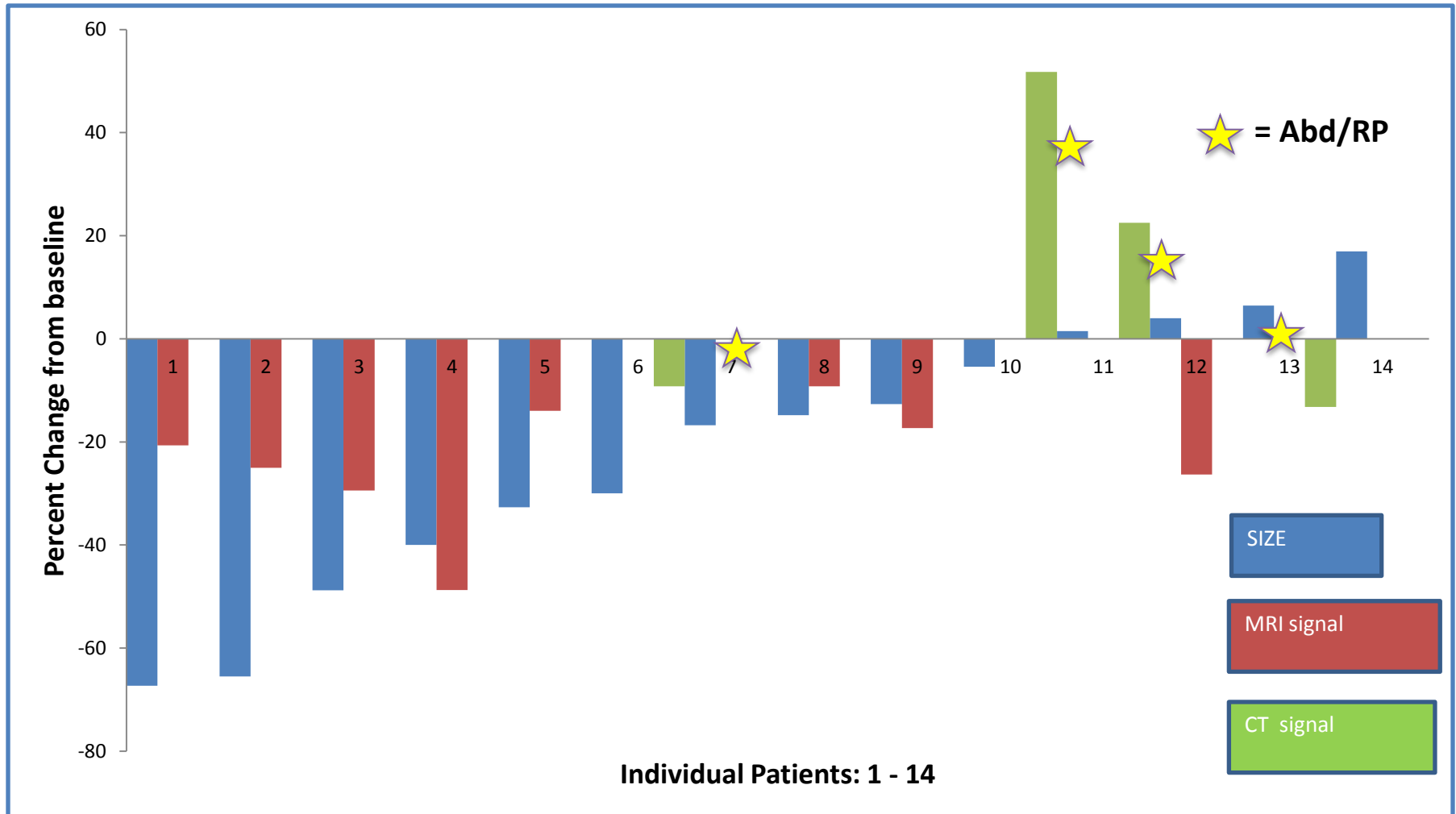


7/9/09: Post Gadolinium (popliteal surface)



12/11/09: Post Gadolinium

RECIST Response (BLUE) Signal Change (RED and GREEN)



Conclusions

- Desmoid Tumors are caused by mutations in the **APC/beta-catenin** pathway
- Although not strictly cancers, desmoids can cause **significant illness or death**
- **Treatment plans must be individualized** and can include observation, surgery, radiation, and medical therapy
- A variety of medical therapies can be effective, and **promising new treatments are coming!**

THANK YOU!

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