
DT
RF
DESMOID TUMOR
RESEARCH FOUNDATION
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Desmoid Tumor: Pathobiology and Treatment

Desmoid Tumor Research Foundation
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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

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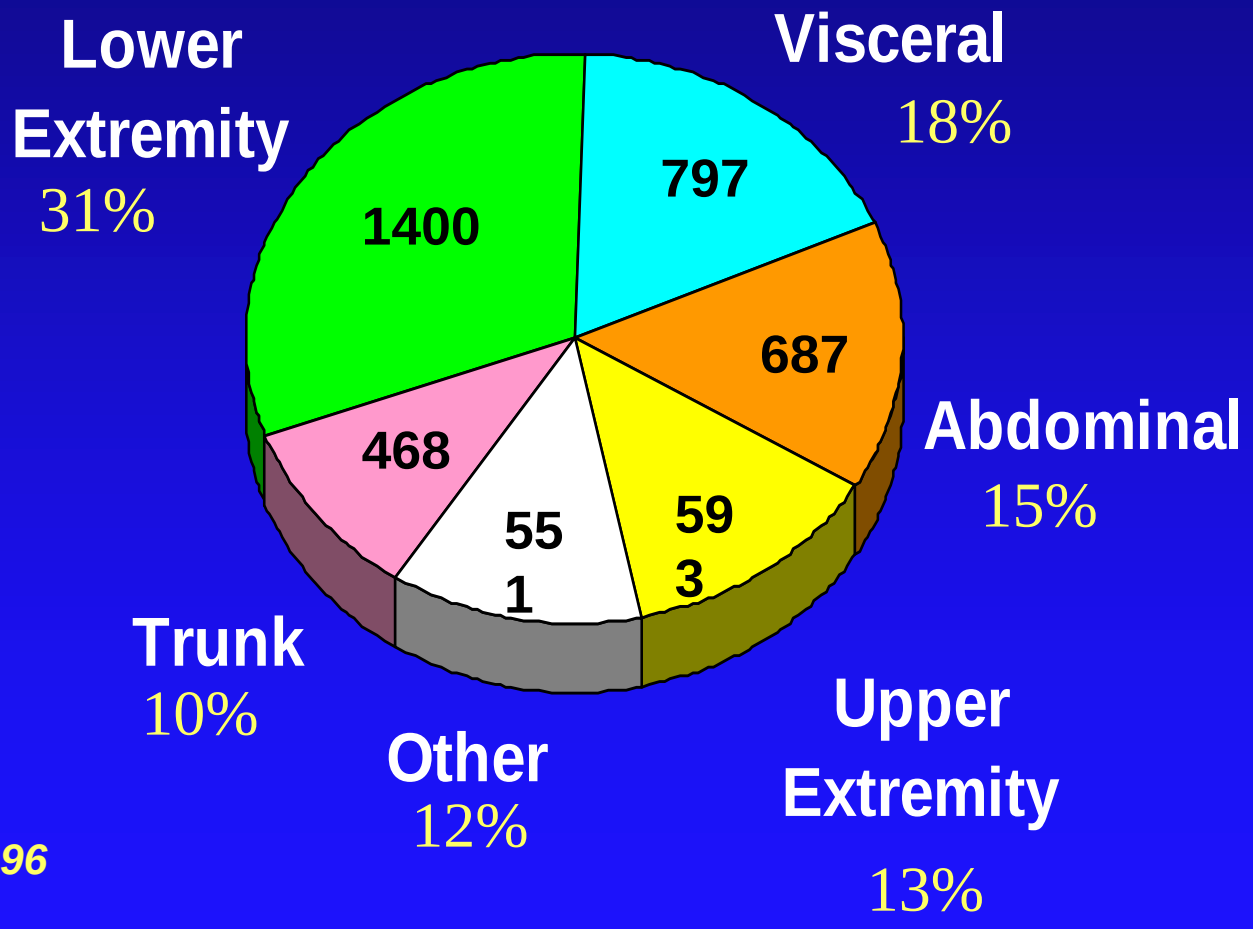
Sarcomas can occur anywhere in the body



n = 4496

Courtesy of M. Brennan MSKCC

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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

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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

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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.

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Same Issues Apply to Desmoid Tumor

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

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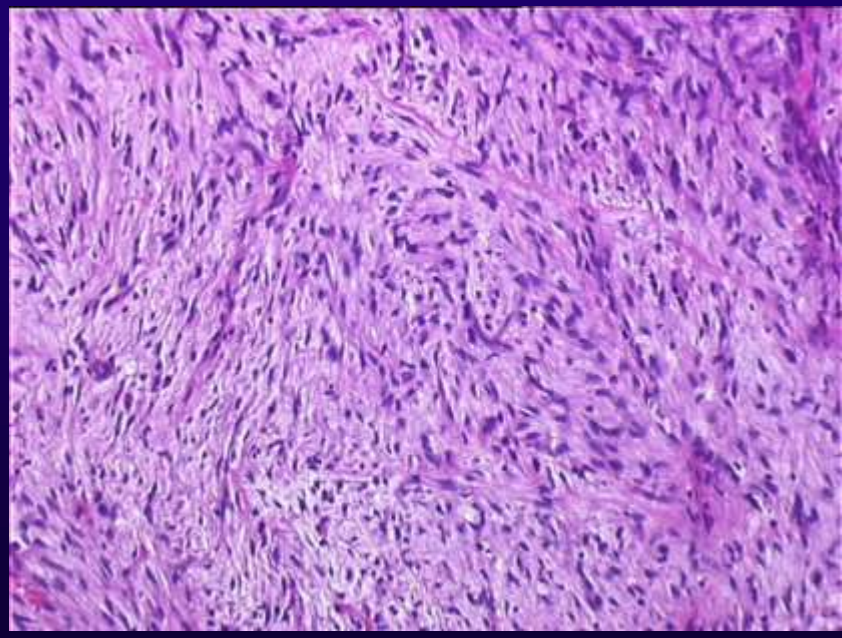
- Fibroblastic monoclonal proliferation arising from musculo-aponeurotic structures, constituted by spindle cells in a collagen matrix, without atypical, pleomorphic or hypercromatic nuclei typical of malignancy.

- 0.2-0.4/100,000

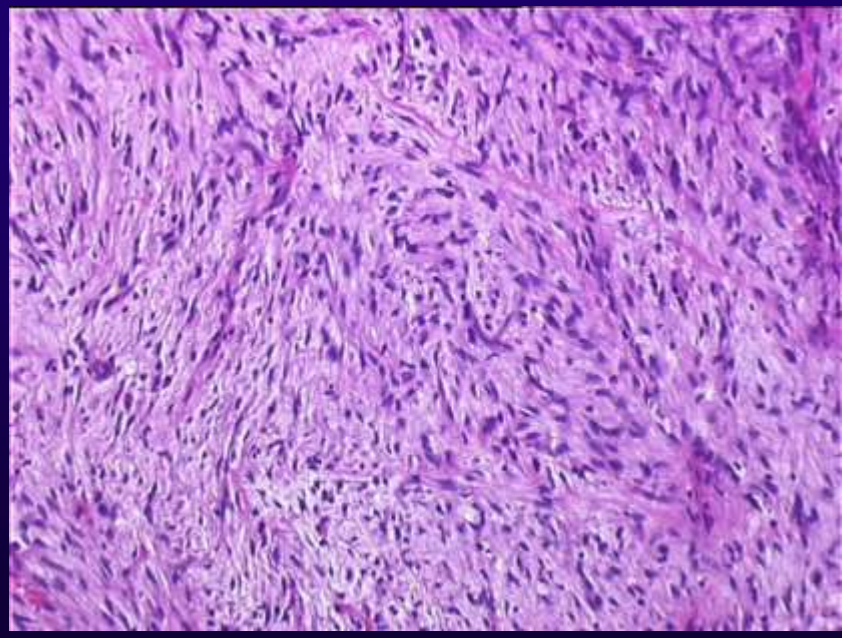
Li et al., Hum Pathol 1996

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 hypercromatic 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)

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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

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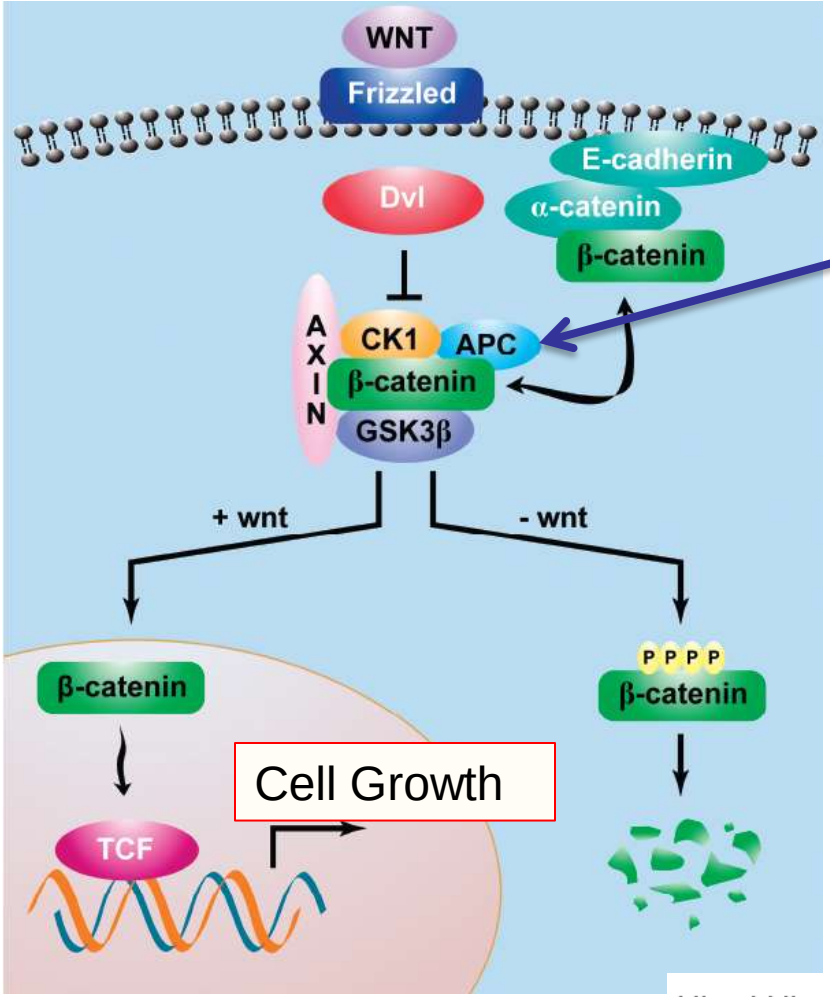
Desmoid tumor: a disease opportune for molecular insights

D. Kotiligam[1], A.J.F. Lazar[2], R.E. Pollock[3] and D. Lev[1]

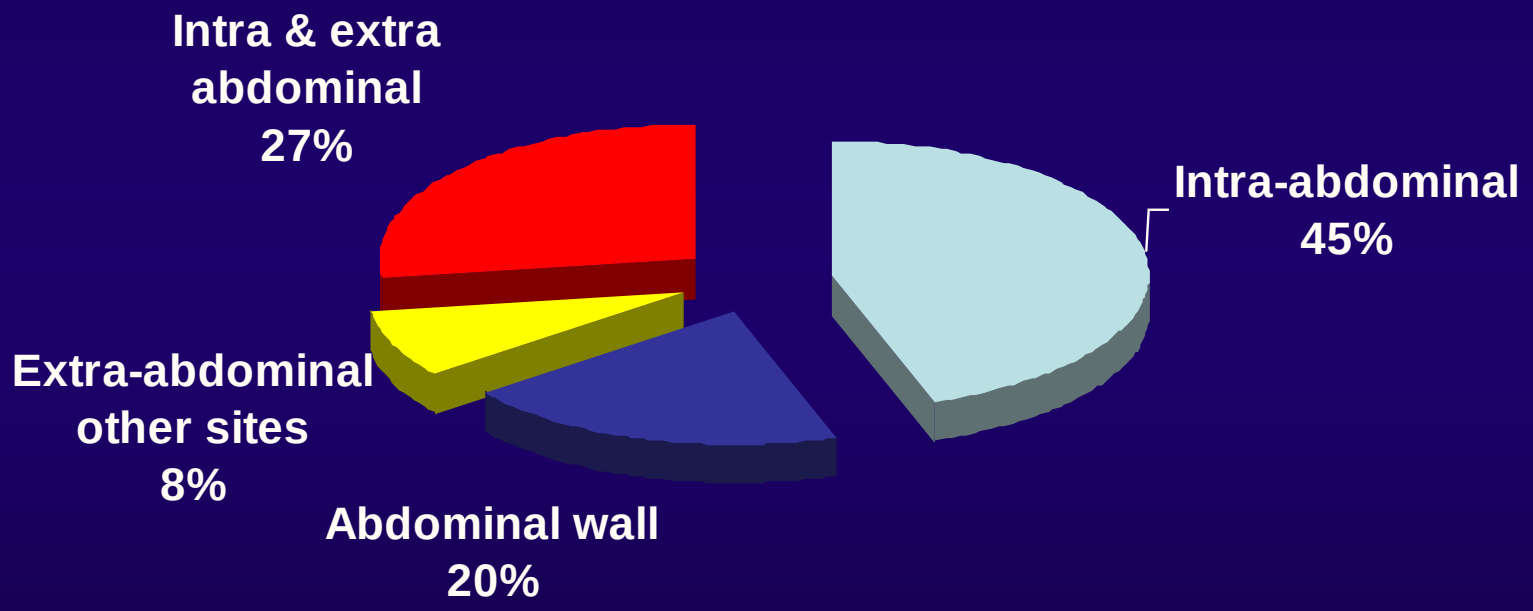


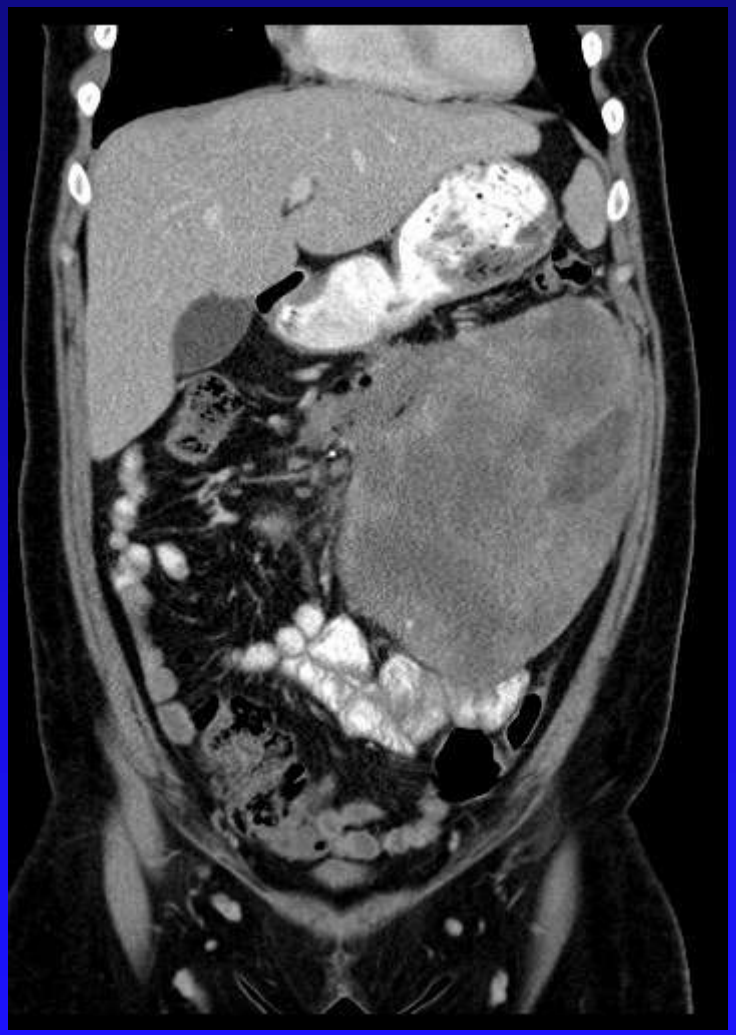
Missing in FAP

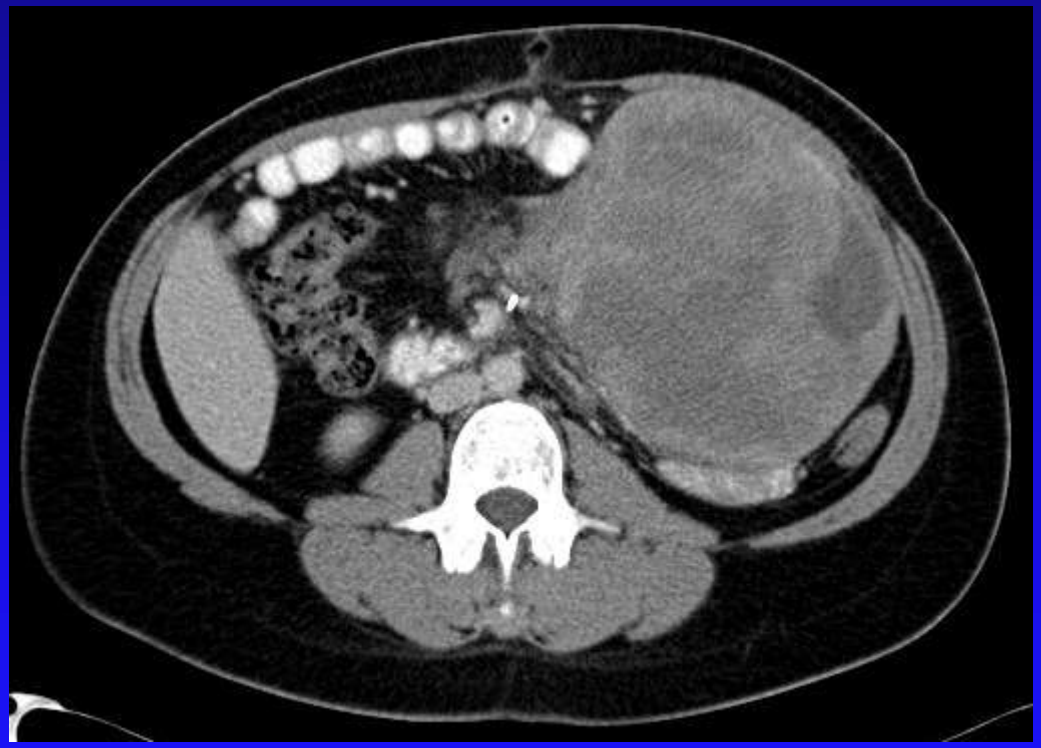
Histol Histopathol (2008) 23: 117-126

SITES:

FAP-Associated







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Follow up of 897 FAP patients

	No	Desmoids			
		Abdominal	*Extra-abdominal*	*Abdominal and extra-abdominal*	*All*
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

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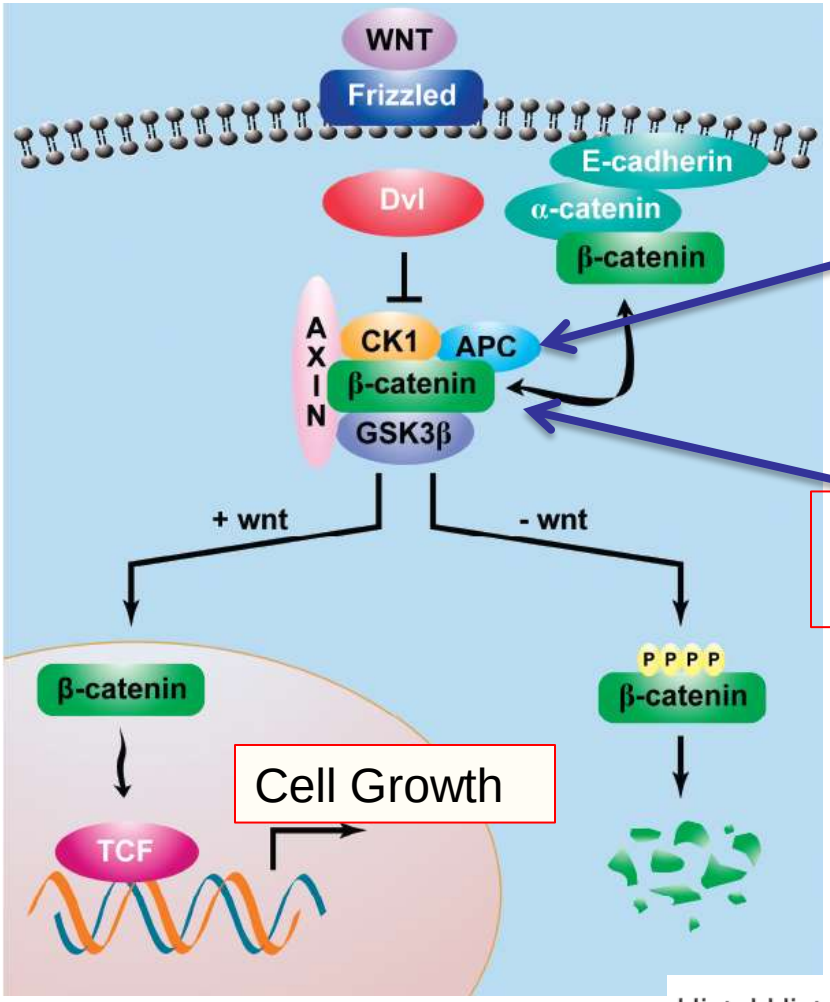


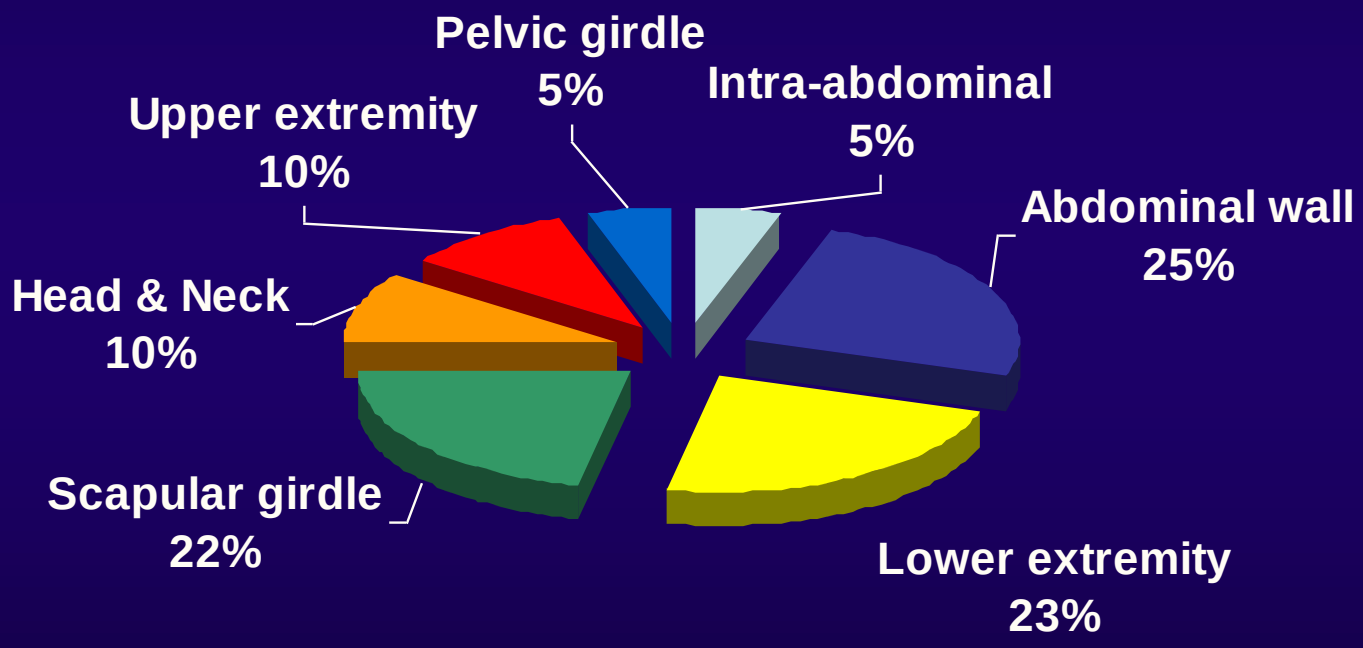
Missing in FAP

Mutated in sporadic desmoid

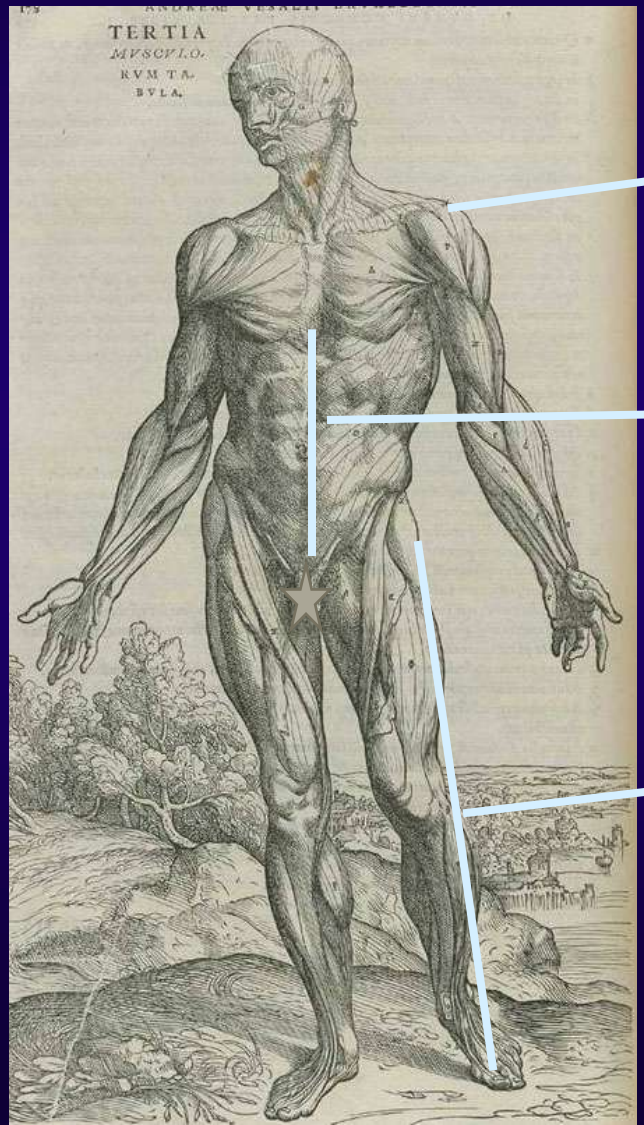
Histol Histopathol (2008) 23: 117-126

SITES:

Sporadic Desmoid



Most common sites

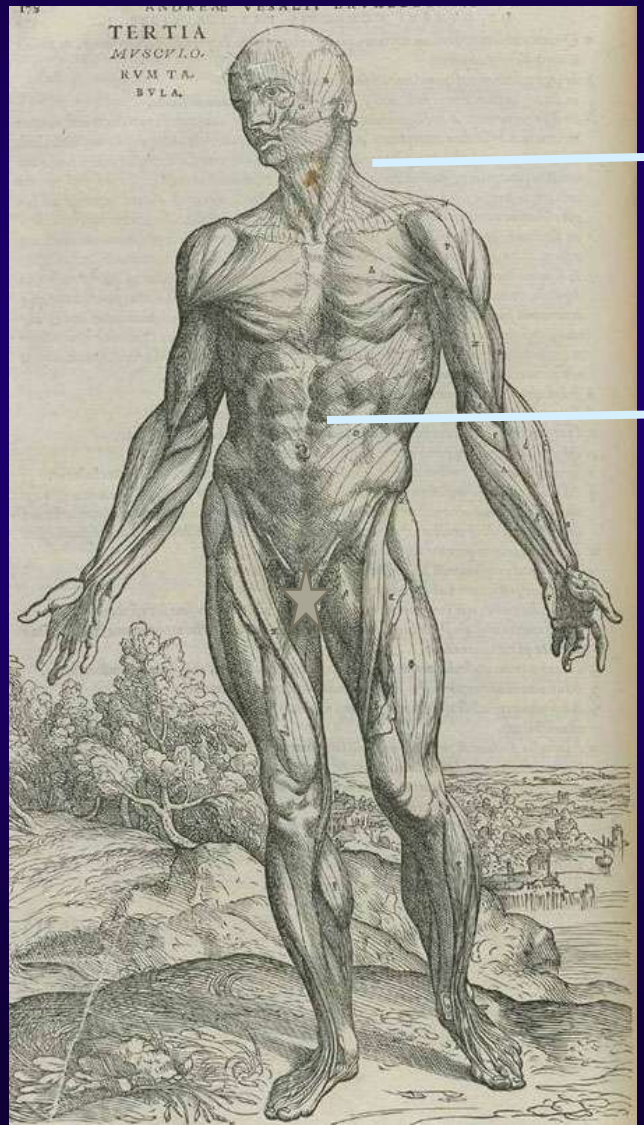


22 %

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

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Management - 2

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

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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!

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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

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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

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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

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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)”

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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

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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

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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

ASCO
American Society of Clinical Oncology

Memorial Sloan-Kettering Cancer Center

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.

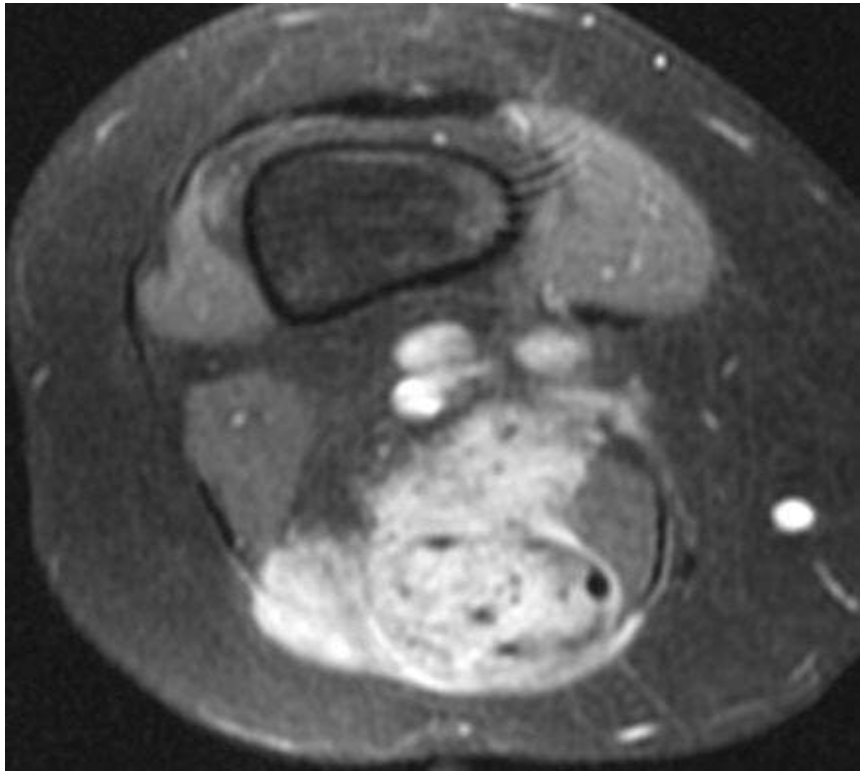
DURATION

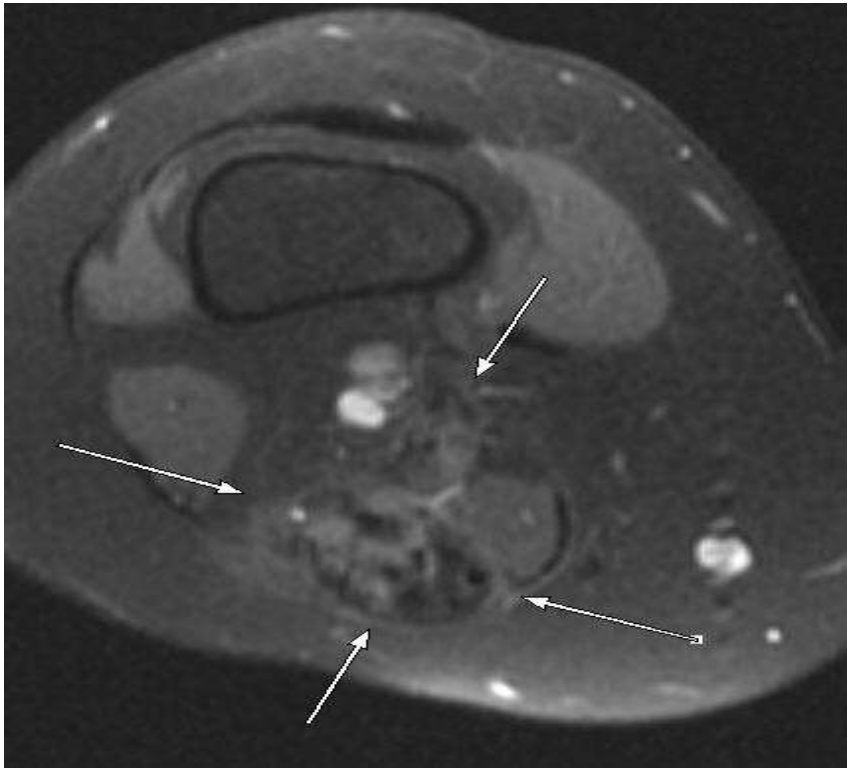
-- Sorafenib was given for a median of 14 months (range 2 – 24) mo.

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.

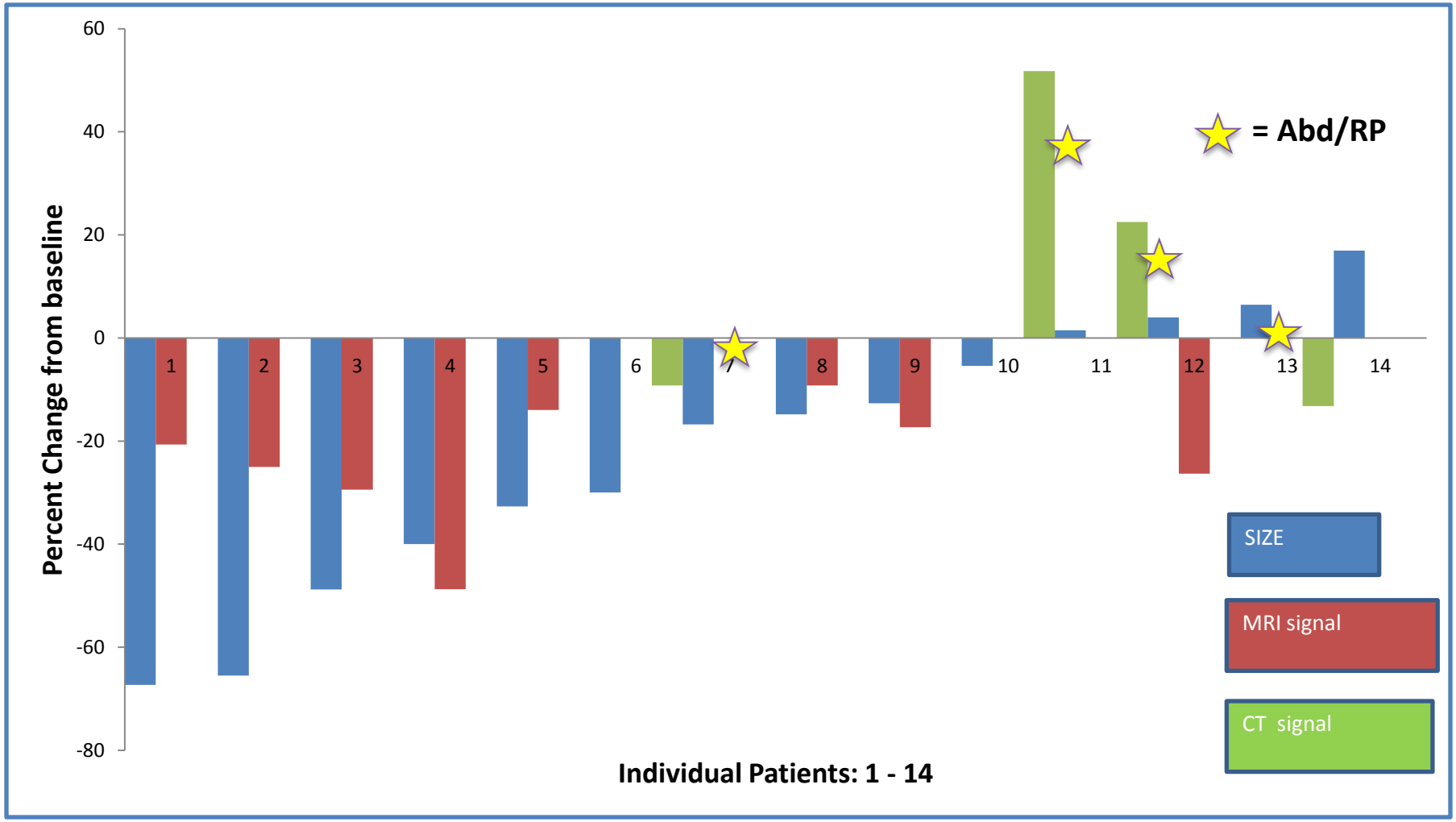
Pt #1: Pre- and Post MRI w/ contrast





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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