EVOLVING TREATMENT STANDARDS IN FIBROMATOSIS

BC CANCER | SURGICAL ONCOLOGY Network
Provincial Health Services Authority

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SON Update
5 October, 2019

DISCLOSURES

- None

OBJECTIVES

- To understand the natural history of Desmoid Fibromatosis (DF)
- To understand the roles of surgery, medical therapy, and local therapies in the treatment of DF
- To avoid overtreatment of patients with DF by endorsing an upfront watchful waiting approach
- To appreciate the complexity of DF necessitating multidisciplinary evaluation and treatment

DESMOID FIBROMATOSIS (DF)

- Clonal fibroblastic proliferation that arises in the deep soft tissues and is characterised by infiltrative growth and a tendency toward local recurrence but an inability to metastasise
- Incidence 5-6 cases per million with peak age 30-40 years
- Patient populations:
  1. Occur sporadically
  2. In association with FAP (5-10%)
  3. Within 2 years of pregnancy – abdominal wall
- Important to differentiate FAP-associated from sporadic DF

TREATMENT CHALLENGES

- Lack of prospective evidence
- Variable biological behaviour (eg by anatomic location)
- Treatment can cause considerable morbidity
  - Young patients
  - Benign disease
  - Long life expectancy
- Propensity to recur
- Difficult to evaluate treatment response
  - Functional outcomes more important than “oncologic” outcomes (PROs)
  - Confounding natural history (20-30% spontaneous regression)
  - Limitations of validated imaging systems (RECIST)

SURGERY

- Historically, primary surgery with negative margins considered standard of care
- Paradigm shift toward nonoperative management due to:
  - Infiltrative growth pattern requiring more extensive resection than sarcoma
  - Significant functional and cosmetic implications
  - Young patients
  - Recurrence rate 20-60%
  - Risk of recurrence not clearly related to margin status
  - Surgery over-treatment for many patients

MARGINS

- Lack of concordance between margin status and recurrence rates
  - Recurrence despite negative margins
  - No recurrence in context of positive margins
- Prioritize preservation of function
  - Aim for R0 resection but above all minimize morbidity
- Principles of sarcoma treatment do not apply to fibromatosis

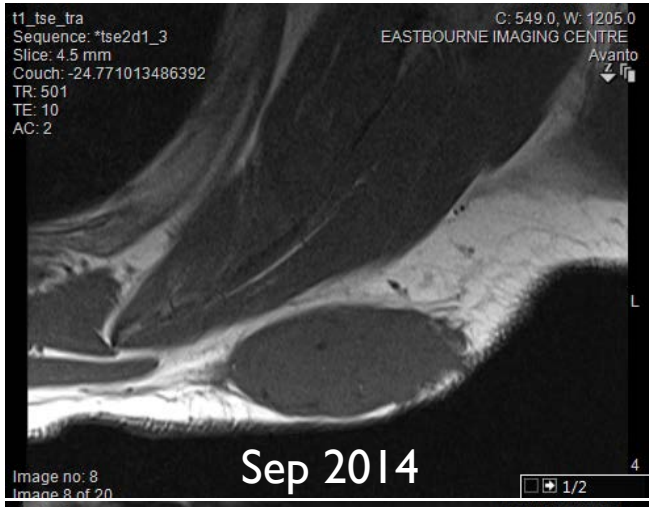
Gronchi et al. JCO 2003;21:1390–1397
Lev et al. JCO 2007;25:1785–1791
Salas et al. JCO 2011;29:3553–3558

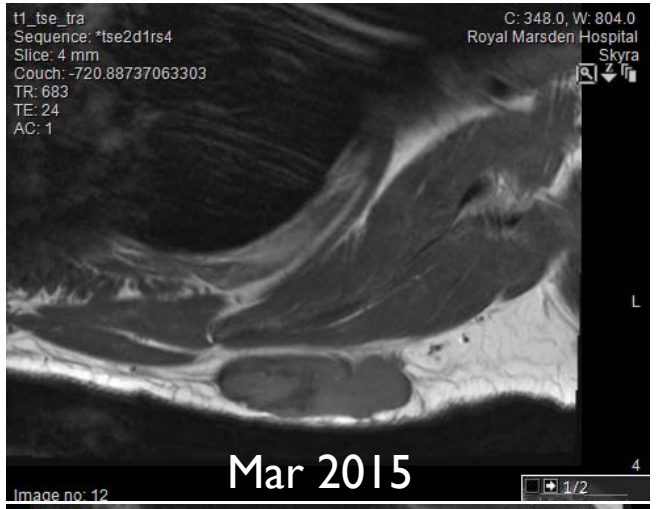
WATCHFUL WAITING

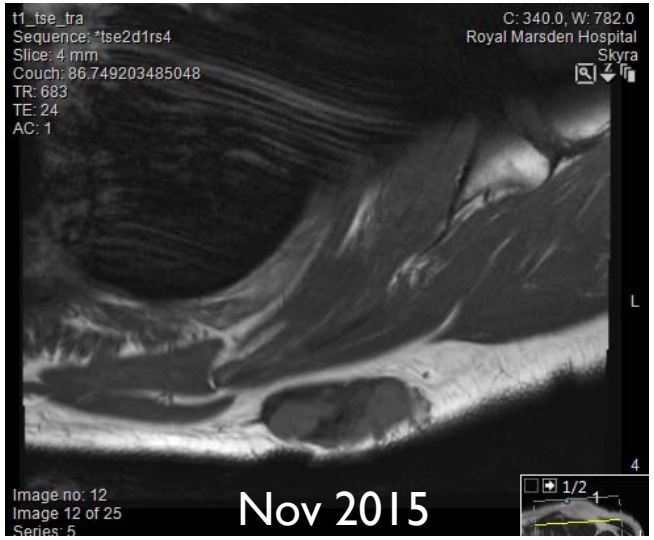
- 5Y PFS 50% with watchful waiting[1]
- Spontaneous arrest of tumour growth in 85% of extra-abdominal DF[2]
  - 10% failed watchful waiting
  - Progression after 3 years highly unlikely
- Up to 28% spontaneous regression over mean 32 months[3]
  - Abdo wall > other anatomic locations
  - 1- and 3-year incidences of switch to surgery 14% and 16%, respectively
  - Initial tumour size >7 cm associated with strategy modification

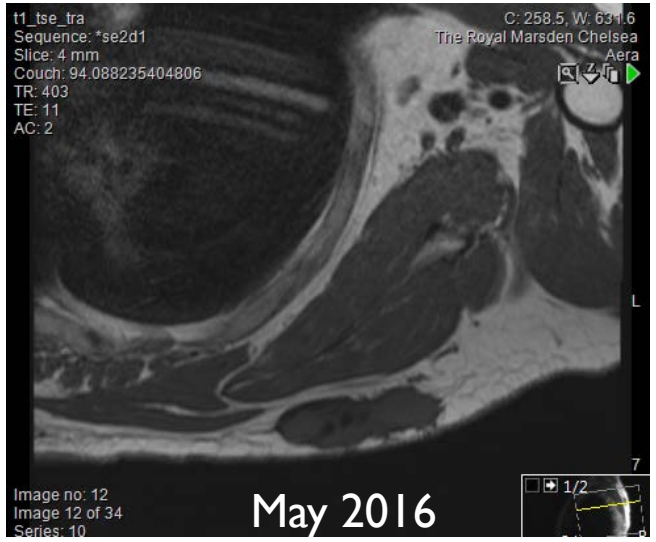
[1]Fiore M et al. Ann Surg Oncol 2009;16:2587–93.
[2]Briand S et al. J Bone Joint Surg Am 2014;96:631–8.
[3]Bonvalot S et al. Ann Surg Oncol. 2013;2013:4096-102.

SPONTANEOUS REGRESSION









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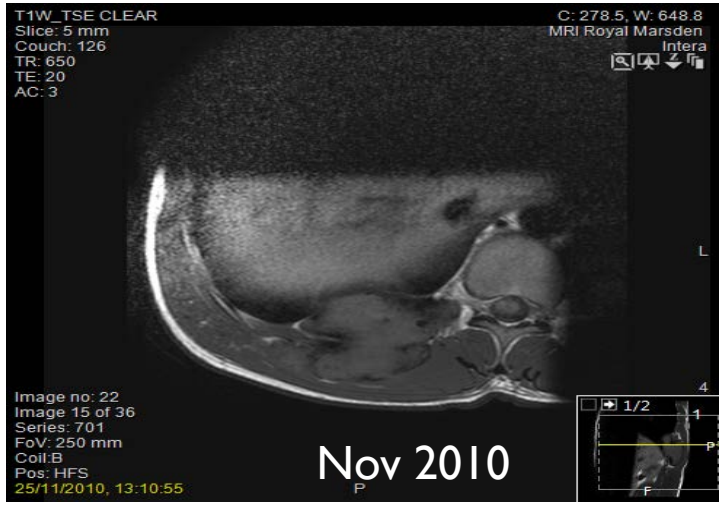

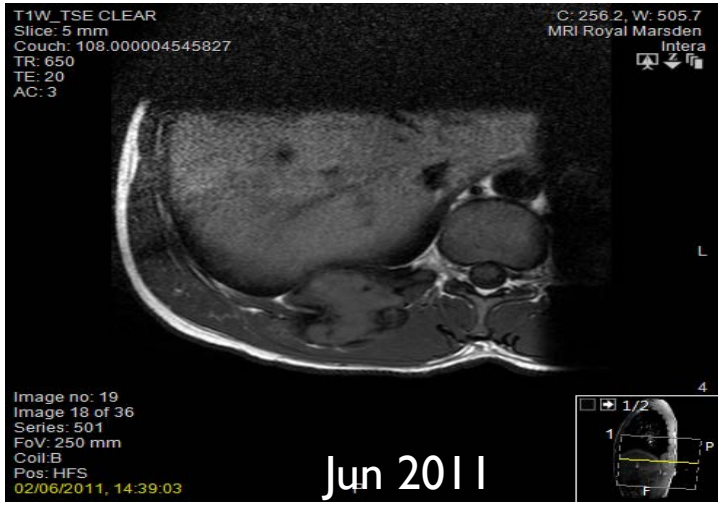

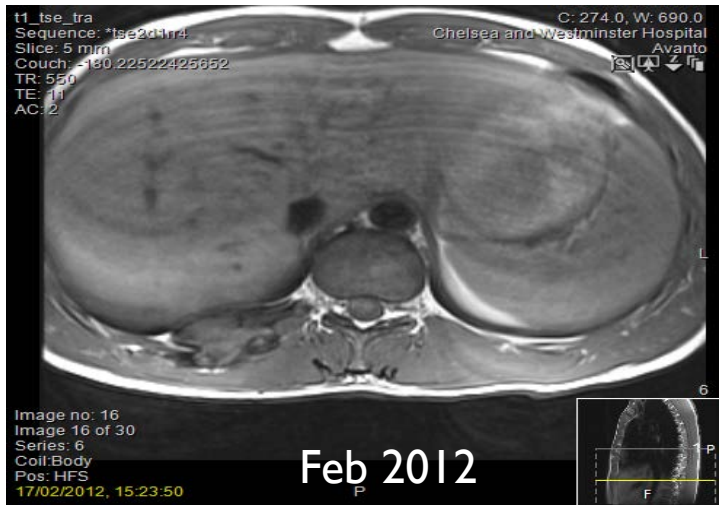

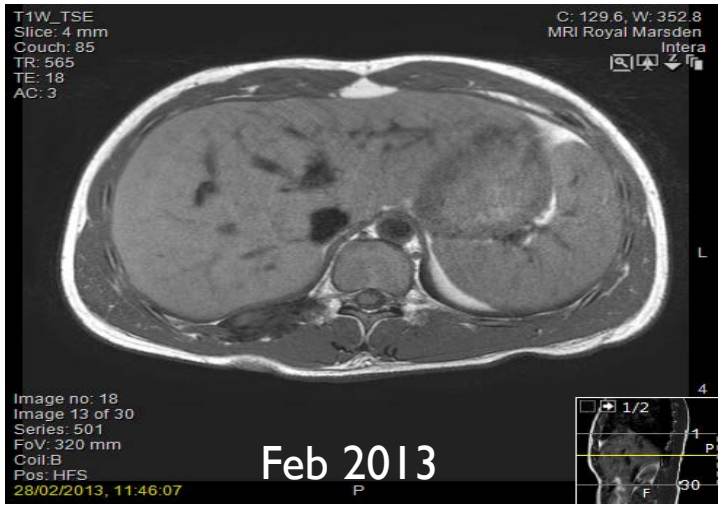

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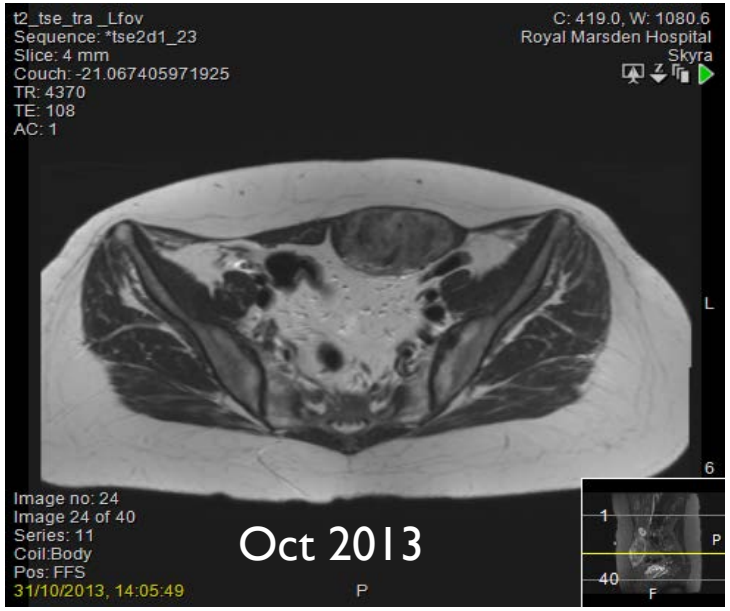
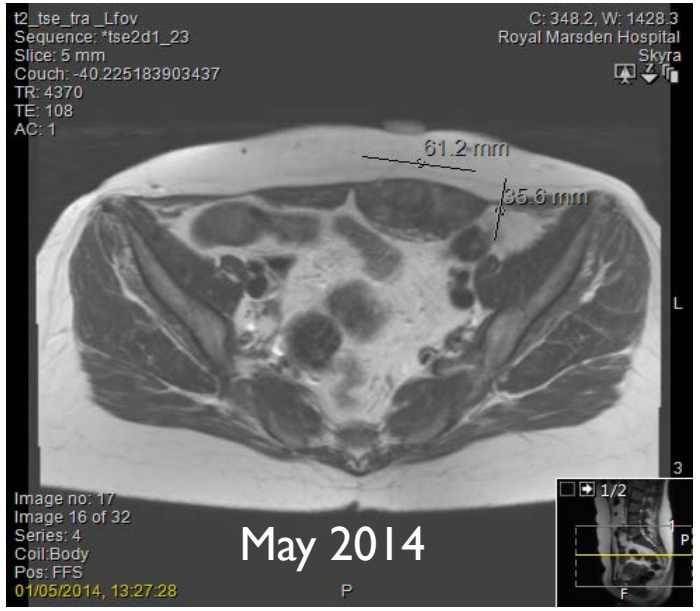
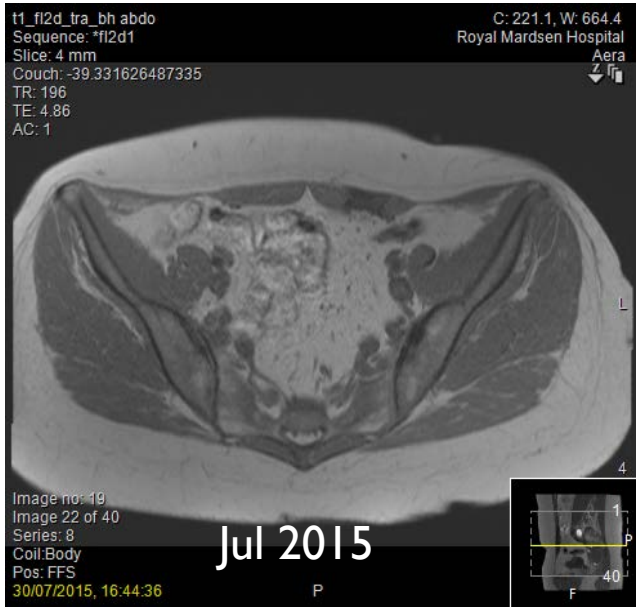






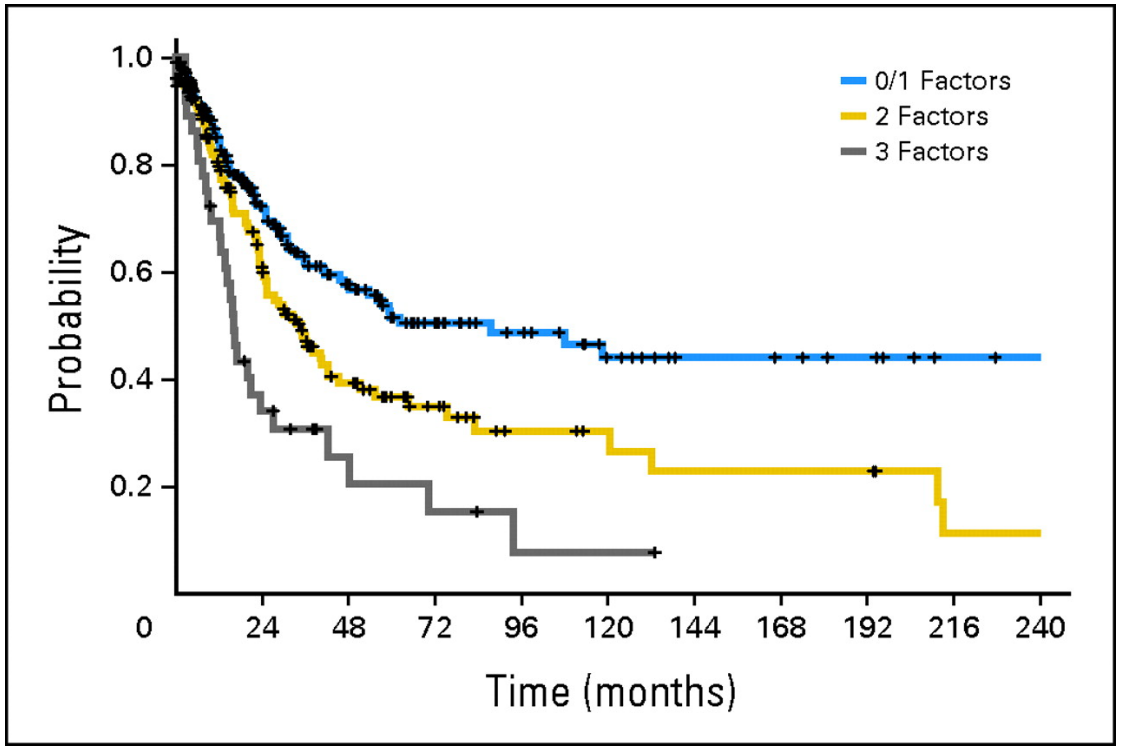
PROGNOSTIC FACTORS

Factors associated with decreased PFS:

- Age ≤ 37
- Size > 7 cm
- Extra-abdominal site
- Margins NOT significant

Conclusions:

- Different prognostic groups
- Consider different treatment strategies including watchful waiting



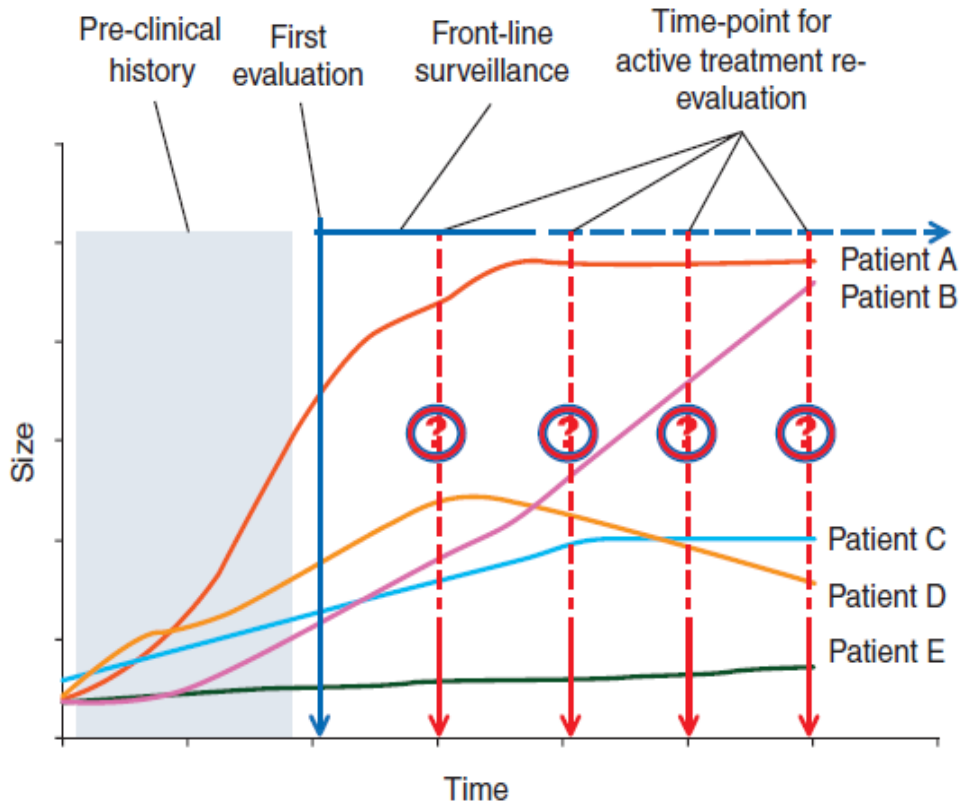
Salas S et al. J Clin Oncol. 2011;29(26):3553-8.

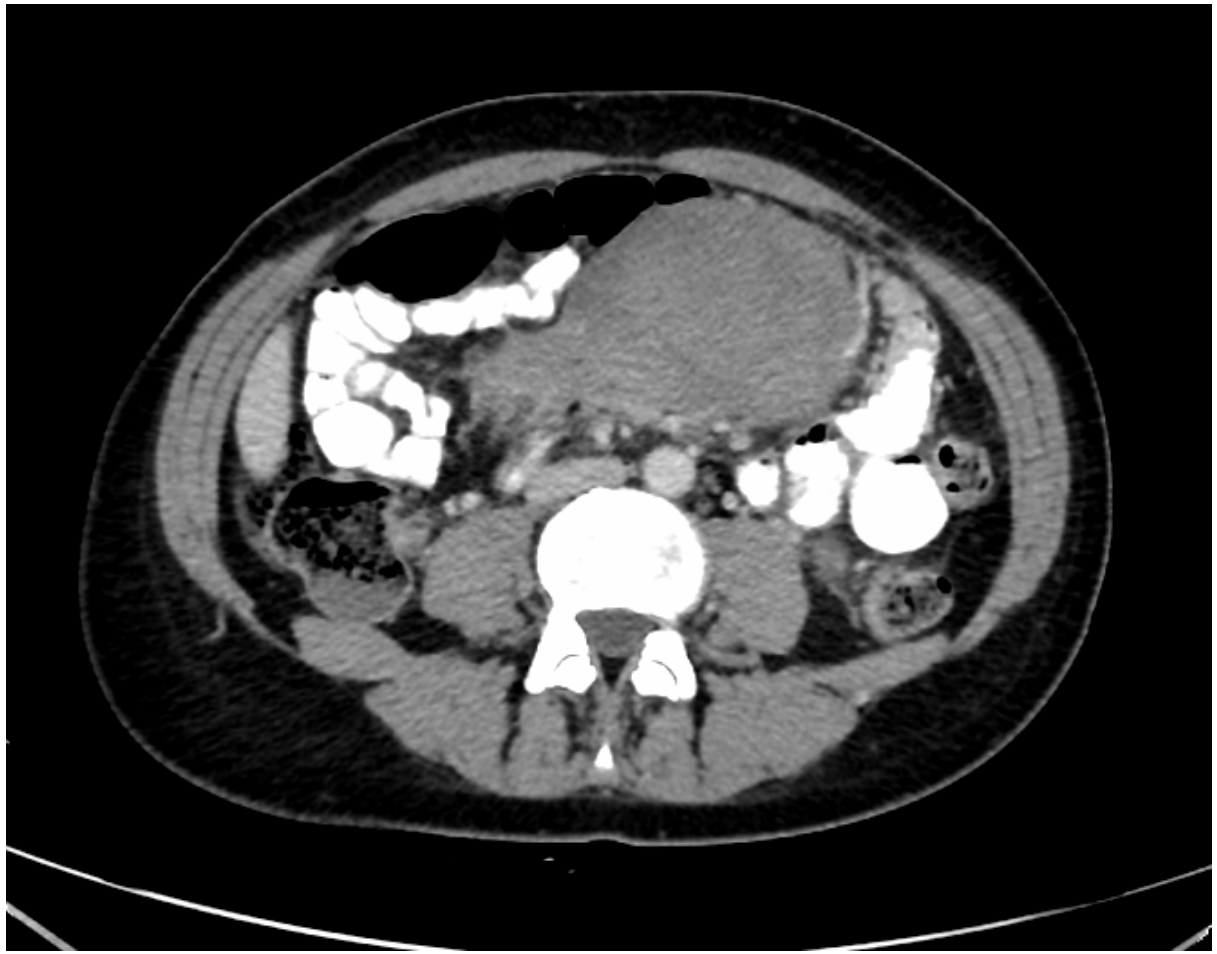
PROGNOSTIC RELEVANCE OF B-CATENIN MUTATION

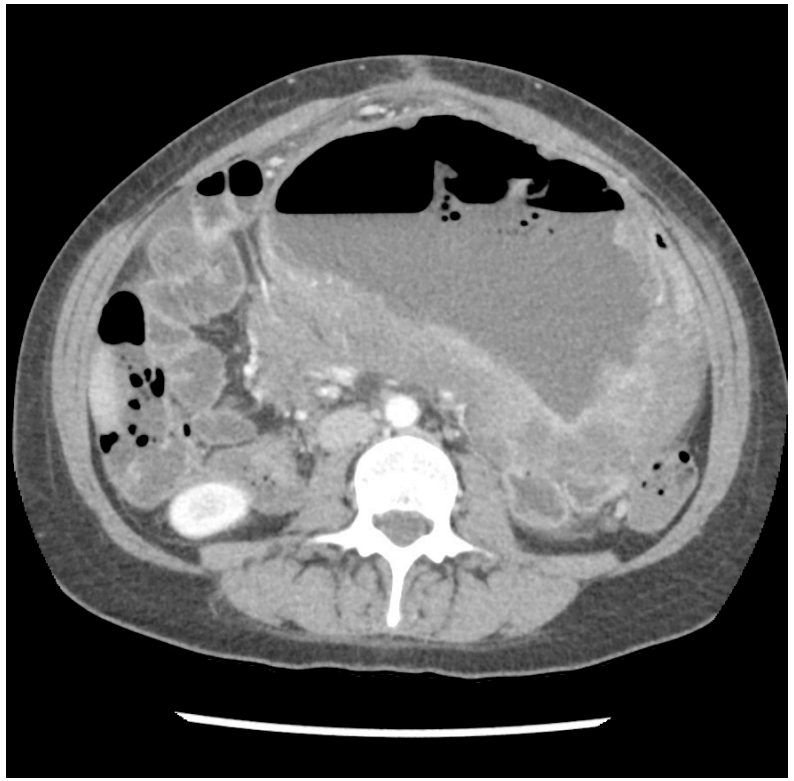
- Most common *CTNNB1* mutations:
  - T41A (50%)
  - S45F (25%)
  - S45P (9%)
- Significant correlation between mutation and recurrence after resection
- Evidence of more aggressive biological behaviour of S45F
- Possible predictive value in estimating response to therapy (e.g. S45F much more likely to respond to imatinib)

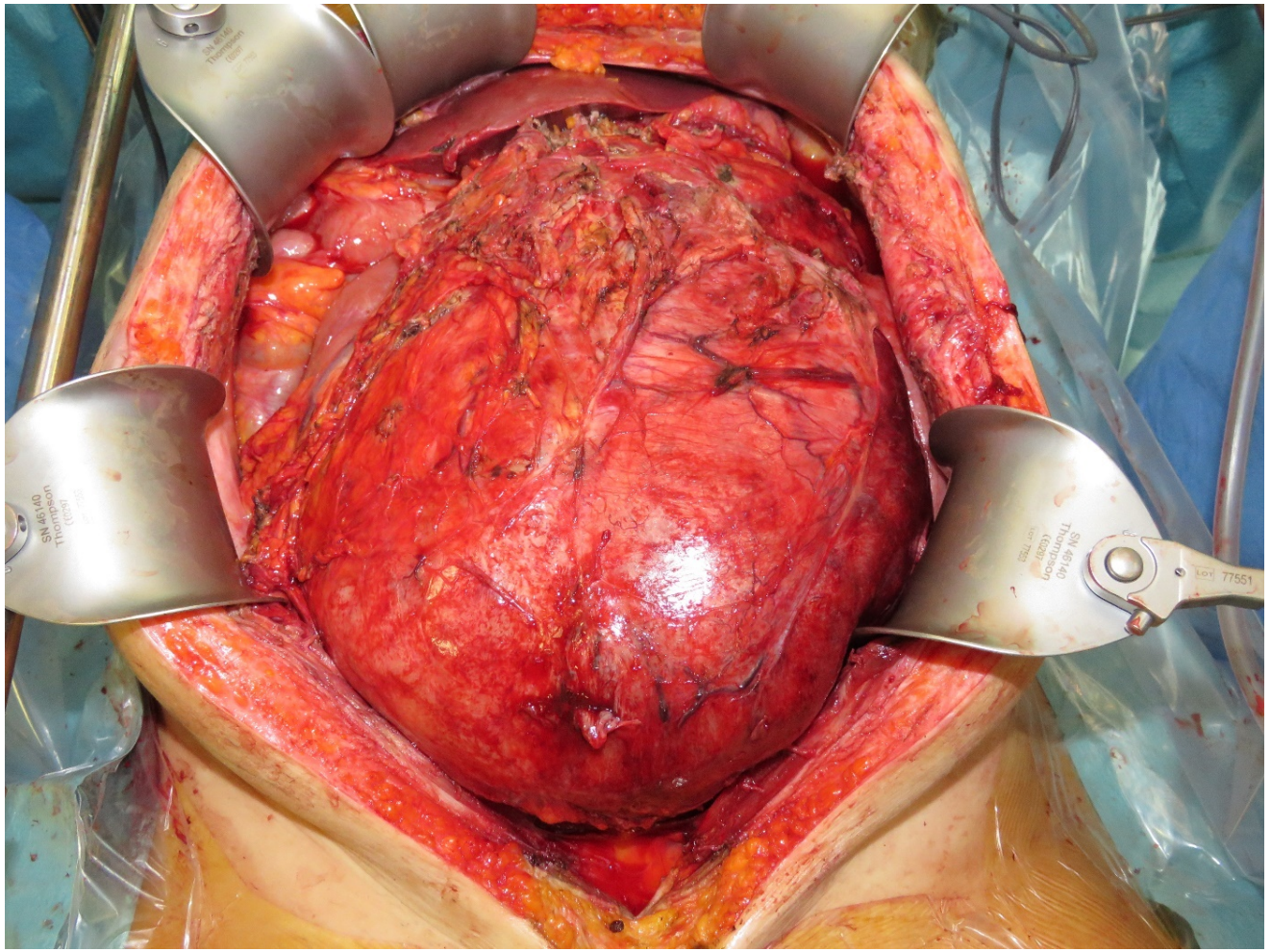
WATCHFUL WAITING

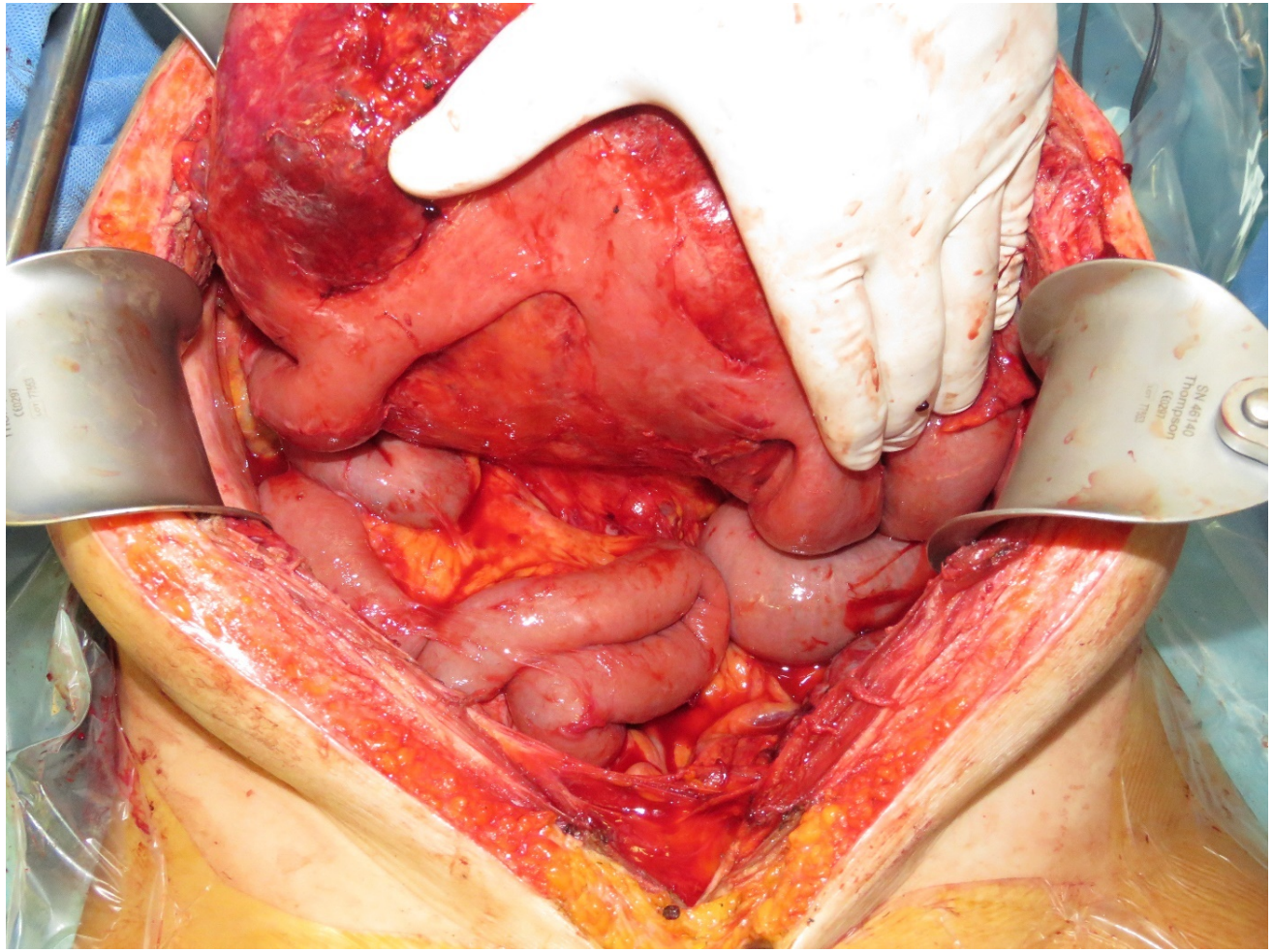
- Trial of surveillance for all patients to determine location on curve except for:
  - Close proximity to critical structures such that progression would preclude resection/pose considerable risk
  - Symptoms necessitate treatment
- Three prospective observational studies underway comparing upfront watchful waiting to active treatment
  - NCT01801176 (French)
  - NCT02547831 (Italian) – tailored based on mutational status
  - NTR4714 (Netherlands)

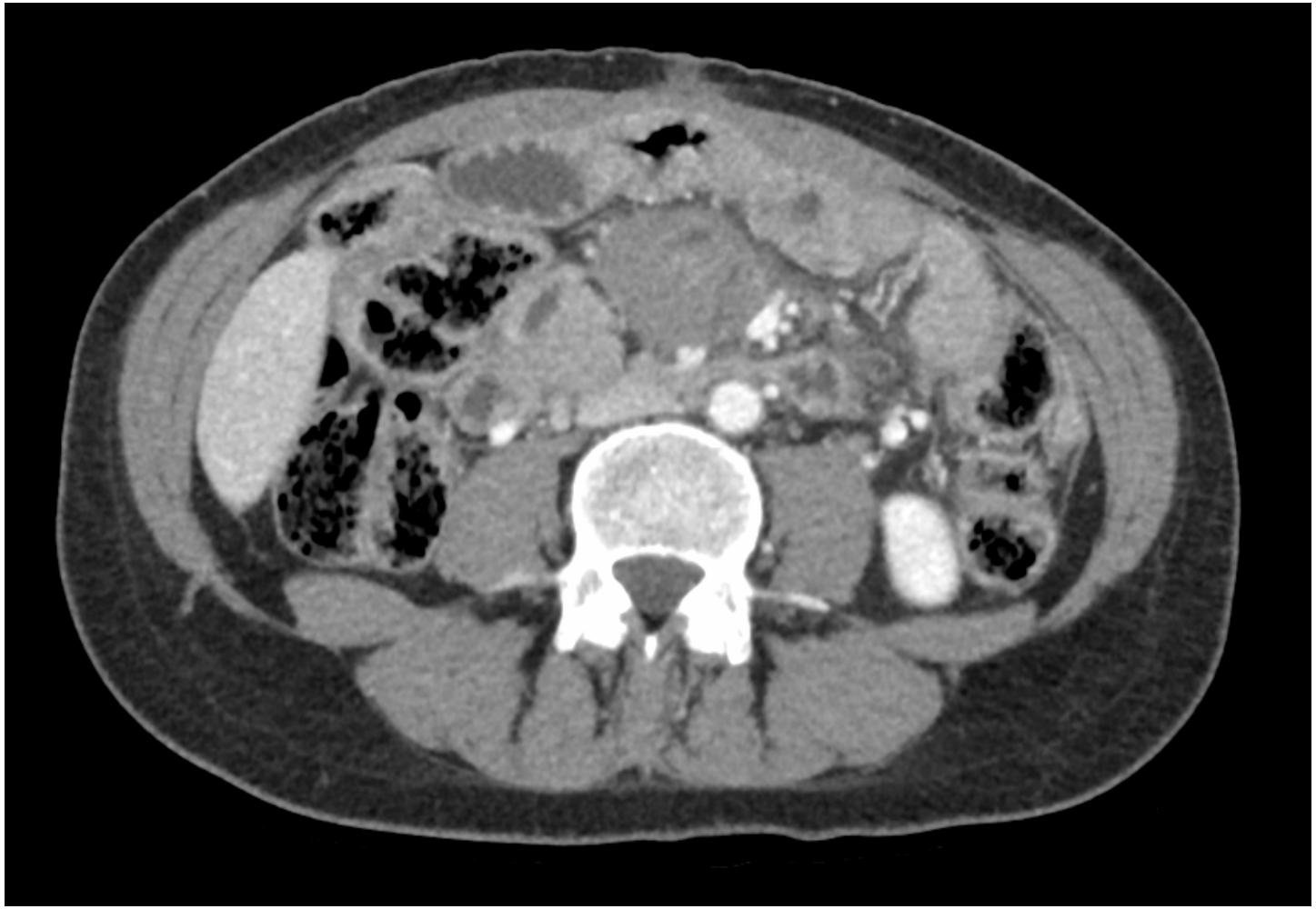












WATCHFUL WAITING STRATEGY

- MRI q3mo x 1yr, q6mo until 5yr, annually thereafter
- Dimensional changes reported according to RECIST criteria (PD, SD, PR, CR)
- MRI T2 signal intensity may be better reflection of biological behaviour
- Progression defined as increase on 3 successive scans, unless urgent intervention is required
- Assess symptoms/functional limitations at each time point
- Initiate treatment based on clear progression or disability

MEDICAL THERAPY

ANTIHORMONE THERAPY

- Tamoxifen/toremifene
- Only case reports and small series available[1]
- Response rates vary, up to 50%
- No correlation to ER/PR status
- Low cost
- Favourable side effect profile

Indication: Possible use for progressing, unresectable DF with or without mild symptoms (preferably FAP-associated)[2]; BUT no general recommendation

[1] *Janinis J et al. Ann Oncol 2003; 14: 181-190*
[2] *Hansmann A et al. Cancer 2004; 100: 612-620*

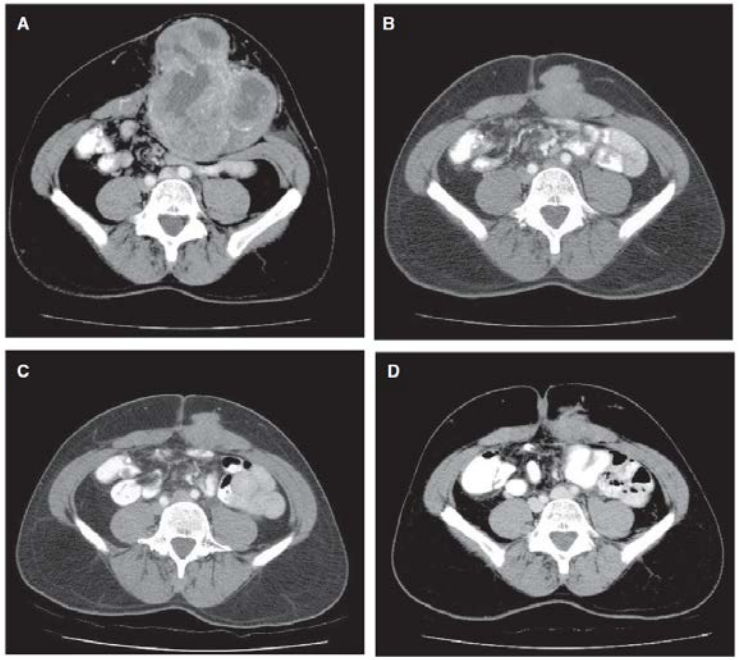
ANTIHORMONE THERAPY + NSAIDS

- Retrospective evidence for efficacy of sulindac, indomethacin, celecoxib, meloxicam
- Prospective phase II study of the Children Oncology Group (COG): **Tamoxifen + Sulindac**
  - N = 59 (< 19 years) between 2004 – 2009
  - Only 10 patients completed therapy without PD or withdrawal
  - Response rate **8 %** (5/59)
  - 2-years PFS rate **36 %**

First and only prospective study evaluating this combination with relatively low activity in terms of RR and PFS

CHEMOTHERAPY

- MTX + vinorelbine/vinblastine
  - Effective (CR 42%, PR 39%, SD 17% = clinical benefit 98%)
  - Slow but durable responses
  - Well tolerated (low doses)
  - Prolonged duration of treatment (at least one year) → variable compliance
  - Chemotherapy of choice in paediatric population
- Liposomal doxorubicin
  - Effective (response rate 54%[2])
  - Early responses – symptomatic relief precedes radiologic response
  - Less cardiotoxicity than conventional doxorubicin
  - Limited duration of treatment (6 months)
  - Anthracycline-based regimens preferred when rapid response required



[1]*Ingley et al. Cancer Med 2019; 8: 5047-5057*

[2]*Garbay D et al. Ann Oncol 2012; 23: 182-186*

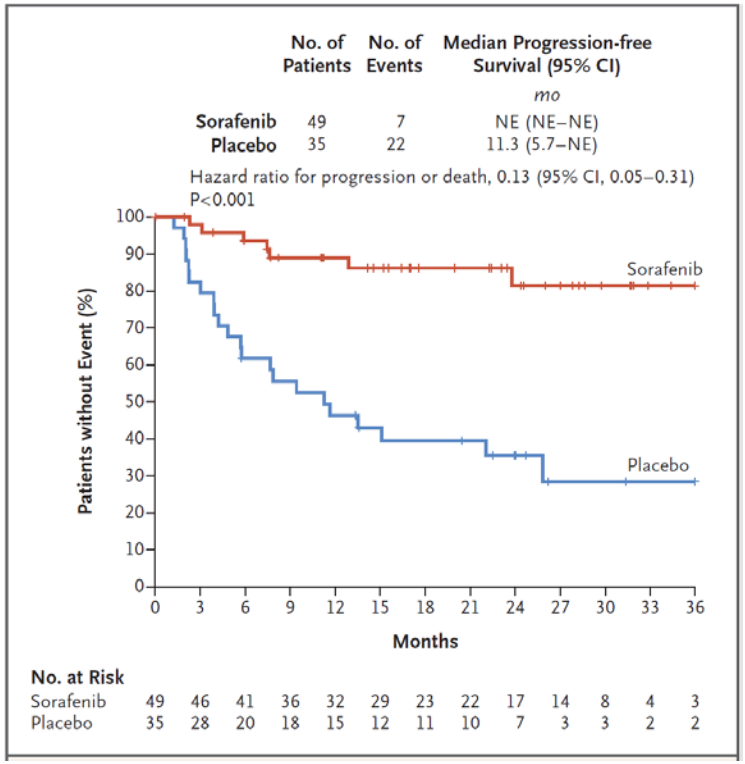
TARGETED THERAPIES

- US phase II study (n = 19) with **800 mg** Imatinib daily[1]
  - Response rate **16%** (3 PR and 4 SD)
  - No mutations of KIT, PDGFRA or PDGFRB
- FSG phase II study (n = 35) with **400 mg** Imatinib daily[2]
  - Response rate **11%** (1 CR, 3 PR and 28 SD)
  - 2-year PFS rate 55%
- GISG phase II study (n=38) with **800 mg** Imatinib daily[3]
  - Response rate **18%**
  - 1-year PFS rate 59%

[1] *Heinrich MC et al. J Clin Oncol 2006; 24: 1195-1203*
[2] *Penel N et al. Ann Oncol 2011; 22: 452-457*
3 Kasper B et al. Ann Oncol 2014; 25(suppl4):iv494

SORAFENIB

- Phase III, randomized, double-blind, placebo-controlled US study
- 87 patients randomized 2:1 to sorafenib 400mg daily vs placebo
- PFS at 2 years 81% in sorafenib group vs 36% in placebo
- ORR 33% (sorafenib) vs 20% (placebo)
- Skin disorders most common toxicity – led to discontinuation of sorafenib in 20%
- Exploratory imaging analysis – MRI T2-weighted signal intensity may be better indicator of treatment effect than RECIST



Gounder MM et al. NEJM 2018; 379:25

GAMMA SECRETASE INHIBITORS

Original Article

Targeting the Notch Pathway: A Potential Therapeutic Approach for Desmoid Tumors

Hui Shang, MD[1,2]; Danielle Braggio, PhD[1,3,4]; Ya-Jung Lee, PhD[1]; Ghadah A. Al Sannaa, MD[5]; Chad J. Creighton, PhD[6]; Svetlana Bolshakov, MSc[1]; Alexander J. F. Lazar, MD, PhD[1,5,7]; Dina Lev, MD[8]; and Raphael E. Pollock, MD, PhD[1,3,7]

Editorial

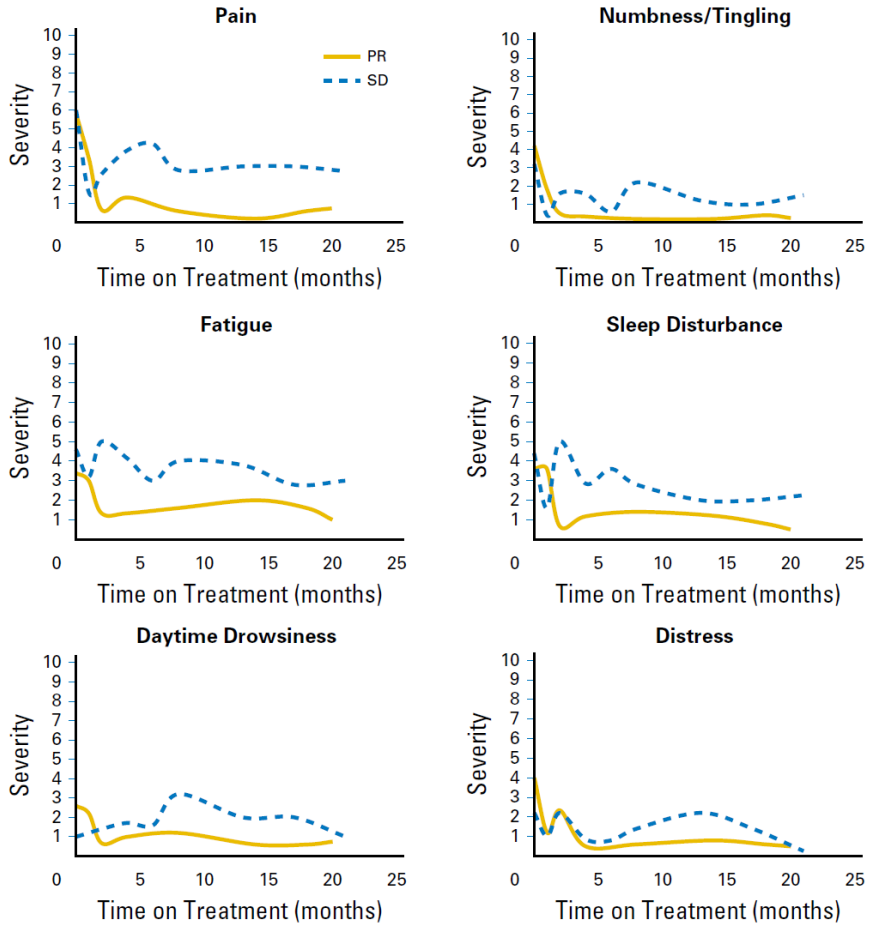
Notch Inhibition in Desmoids: "Sure It Works in Practice, but Does It Work in Theory?"

Mrinal M. Gounder MD[1,2]

Gounder MM Cancer 2015; 121: 3933-3937
Shang H et al. Cancer 2015; 121: 4088-4096

PF-03084014

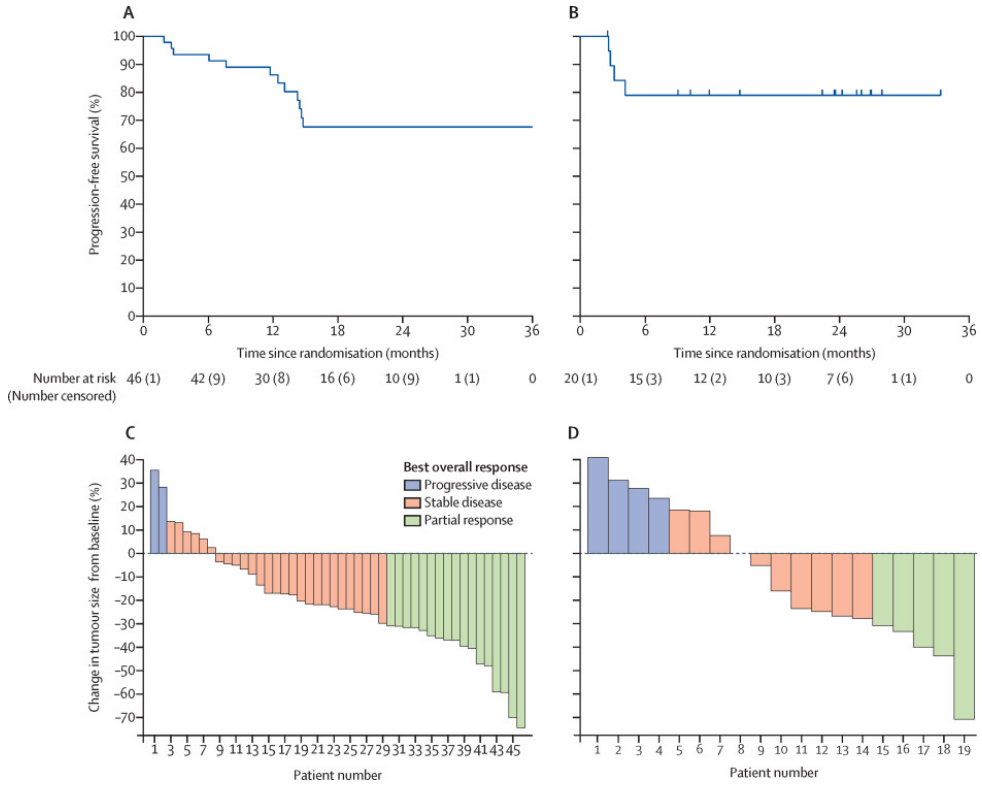
- **Phase II** study in symptomatic, progressive desmoid tumours (n = 17) after median of 4 prior lines of therapy
- PR in 5 (31%), SD in 11 (69%), no PD
- Well-tolerated (worst toxicity grade 2 diarrhea)



Kummar S et al. J Clin Oncol 2017. 35:1561-1569

PAZOPANIB

- DESMOPAZ trial
- Non-comparative phase II randomized trial of pazopanib vs MTX/vinorelbine in progressive DF
- Pazopanib (N=46): 37% PR, 59% SD, 4% PD
- MTX/vinorelbine (N=20): 25% PR, 50% SD, 20% PD
- 23% serious adverse events with pazopanib (HTN, diarrhea)



Toulmonde M et al. Lancet Oncol 2019. 20(9):1263-1272

MEDICAL THERAPY CONCLUSIONS

- Limited randomized/prospective data precludes recommendations regarding sequence of agents
- Decision regarding systemic treatment options should take into account:
  - dynamic growth of tumour
  - expected response rate
  - planned treatment duration
  - toxicity of the administered drug

Kasper et al. Eur J Cancer 2015;52(2):127-36

RADIATION THERAPY

- Consider for borderline/unresectable disease that is symptomatic and/or progressing
- Highly effective
  - Stable disease/partial response 51-77%
  - Complete response 13-17%
- Careful consideration of risks/benefits required
- No role for adjuvant RT following resection

Guadagnolo, et al. Int J Radiat Oncol Biol Phys. 2008;71:441–447
Keus et al. Ann Oncol. 2013;24:2672–2676

LOCAL THERAPIES

- ILP
  - TNF-alpha + melphalan
  - For extremity DF in which resection would be highly morbid
  - French Sarcoma Group study – 88% stable disease or partial response[1]
- Cryoablation
  - Retrospective series of cryoablation as both first-line and salvage therapy (N=23)[2]
    - 36% CR, 36% PR, 28% SD
    - Average change in viable tumour volume at 12 months – 80%
    - Symptomatic improvement in 89%
    - Major adverse events (neuropraxia) in 2 (8.6%)
  - BCCA experience promising – increasingly first-line treatment

[1]Bonvalot et al. Ann Surg Oncol 2009;16:3350–57
[2]Trembley et al. J Surg Oncol 2019. 120:366-375

TREATMENT ALGORITHM

ESMO GOOD SCIENCE BETTER MEDICINE BEST PRACTICE

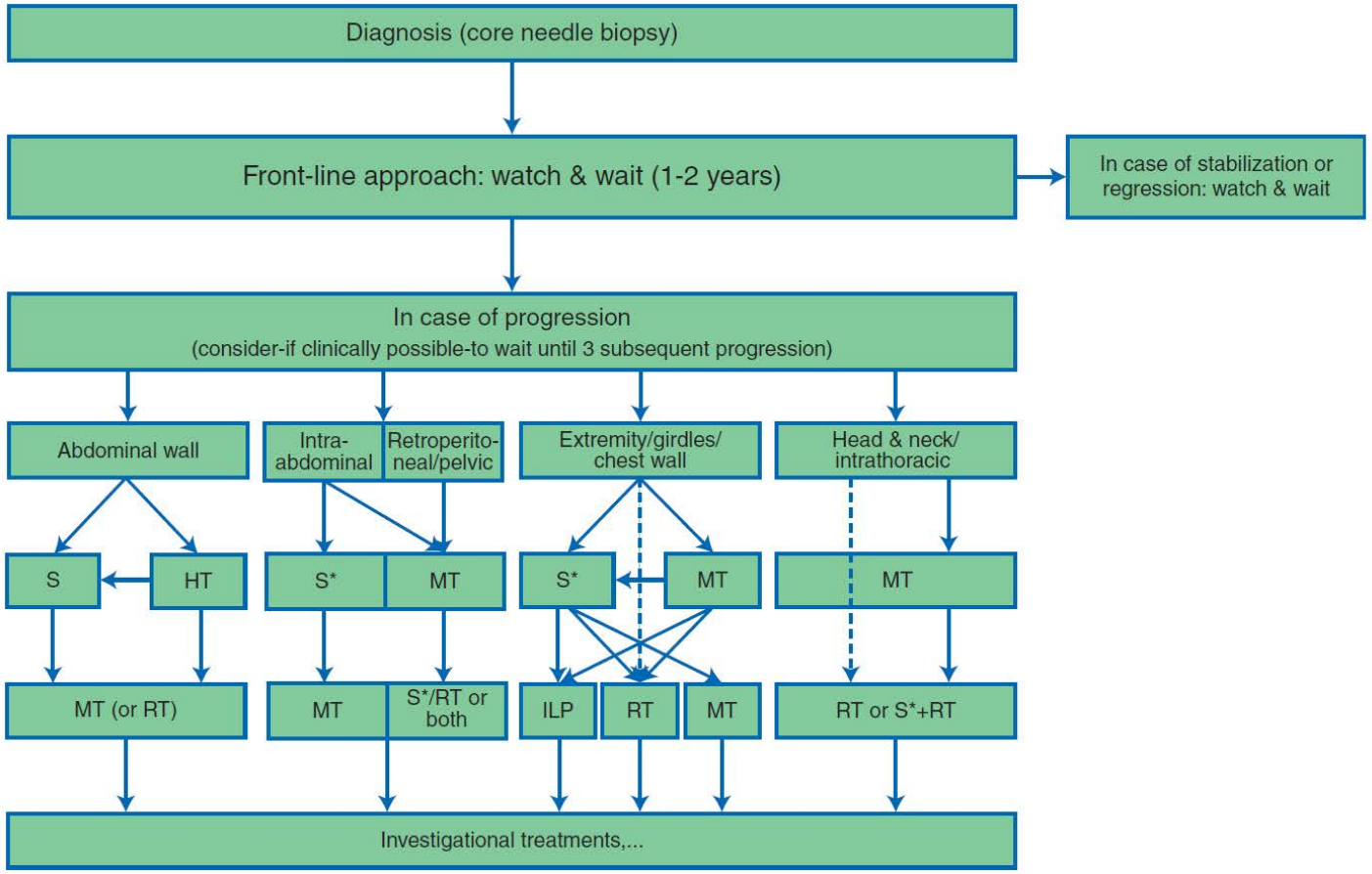
Annals of Oncology 28: 2399–2408, 2017
doi:10.1093/annonc/mdx323
Published online 23 June 2017

REVIEW

An update on the management of sporadic desmoid-type fibromatosis: a European Consensus Initiative between Sarcoma PAtients EuroNet (SPAEN) and European Organization for Research and Treatment of Cancer (EORTC)/Soft Tissue and Bone Sarcoma Group (STBSG)

B. Kasper[1*], C. Baumgarten[2], J. Garcia[2], S. Bonvalot[3], R. Haas[4,5], F. Haller[6], P. Hohenberger[1], N. Penel[7], C. Messiou[8], W. T. van der Graaf[9] & A. Gronchi[10*], on behalf of the Desmoid Working Group[†]

TREATMENT ALGORITHM



Abbreviations: HT: hormonal therapy; S: surgery; S*: surgery is an option if morbidity is limited; MT: medical therapy; RT: radiotherapy; ILP: isolated limb perfusion

DF AND PREGNANCY

- Expect progression during pregnancy
- No increased obstetrical risk
- Multicentre observational study:
  - 54% managed post-partum with watchful waiting
  - 14% spontaneous regression
  - 17% progression
- Not contraindication to pregnancy
- Progression can be managed → good outcomes

Fiore et al. Ann Surg 2014;259:973–78

Journal of Clinical Oncology
An American Society of Clinical Oncology Journal

SARCOMA

Prospective development of a patient reported outcomes (PRO) tool in desmoid tumors: A novel clinical trial endpoint.

Jean Paty, Leanne Maddux, Mrinal M. Gounder

CONCLUSIONS

- DF is a rare, complex and highly variable disease that should be treated by an experienced multidisciplinary team
- Vast majority of patients should be managed with an upfront watchful waiting strategy to determine biological behaviour
- Treatment can be avoided in most patients with appropriate counselling and supportive care
- Selection and sequencing of appropriate local/systemic treatment(s) should take into consideration tumour site and size, relationship to critical structures, symptoms, anticipated functional impairment of disease progression, toxicity/morbidity of proposed treatment in context of patient age and functional status
- PROs are imperative and treatment must include appropriate psychological support