THE MANAGEMENT OF DESMOID TUMORS: A JOINT GLOBAL EVIDENCE-BASED CONSENSUS GUIDELINE APPROACH FOR ADULT AND PEDIATRIC PATIENTS

Sarcoma Patients EuroNet (SPAEN) & EORTC / Soft Tissue and Bone Sarcoma Group (STBSG)

Bernd Kasper & Peter Hohenberger

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on behalf of The Desmoid Tumor Working Group

sos desmoid

EORTC European Organization for Research and Treatment of Cancer

UMM UNIVERSITÄTSMEDIZIN MANNHEIM

European Reference Network for rare or low prevalence complex diseases

Network Adult Cancers (ERN EURACAN)

Sarcoma Patients EuroNet

DTRF THE DESMOID TUMOR RESEARCH FOUNDATION

Background

- Desmoid tumor (DT) is a monoclonal, fibroblastic proliferation characterized by a variable and often unpredictable clinical course.
- The incidence is ~5-6 cases per 1 million of the population per annum.
- There has been no level I/II evidence for the DT treatment approach available; there were only few prospectively conducted studies / meta-analysis.
- Initially, The Desmoid Tumor Working Group published a **Position Paper** in the *European Journal of Cancer** based on a **joint SPAEN & EORTC/STBSG Roundtable Meeting held in May 2014** in Frankfurt, Germany.

European Journal of Cancer (2015) 51, 127–136

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journal homepage: www.ejcancer.com

ELSEVIER

EJC

Position Paper

Management of sporadic desmoid-type fibromatosis: A European consensus approach based on patients' and professionals' expertise – A Sarcoma Patients EuroNet and European Organisation for Research and Treatment of Cancer/Soft Tissue and Bone Sarcoma Group initiative

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* *Kasper B et al. Eur J Cancer 2015; 51: 127-136.*

Joint SPAEN & EORTC/STBSG Initiative

Sarcoma Patients EuroNet

What can Patients and Patient Advocates provide?

- Are a helpful voice in really understanding patients' problems and needs and avoid some misunderstanding ("active surveillance").
- May focus on issues of DT patients which experts hardly see (such as "pain").
- Help to identify experienced experts, centers or networks of excellence.
- Play a fundamental role in connecting contributors & resources and in disseminating information.
- Can jointly develop together with the medical experts a consented treatment approach and therapeutic algorithm.

EORTC European Organization for Research and Treatment of Cancer

The (European) Desm… …up

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ESMO GOOD SCIENCE BETTER MEDICINE BEST PRACTICE

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)

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†Additional Members of Desmoid Working Group are listed in the Acknowledgements.

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The Desmoid Tumor Working Group went global!

EORTC
European Organization for Research and Treatment of Cancer

18th of June 2018, Istituto Nazionale dei Tumori, Milan, Italy

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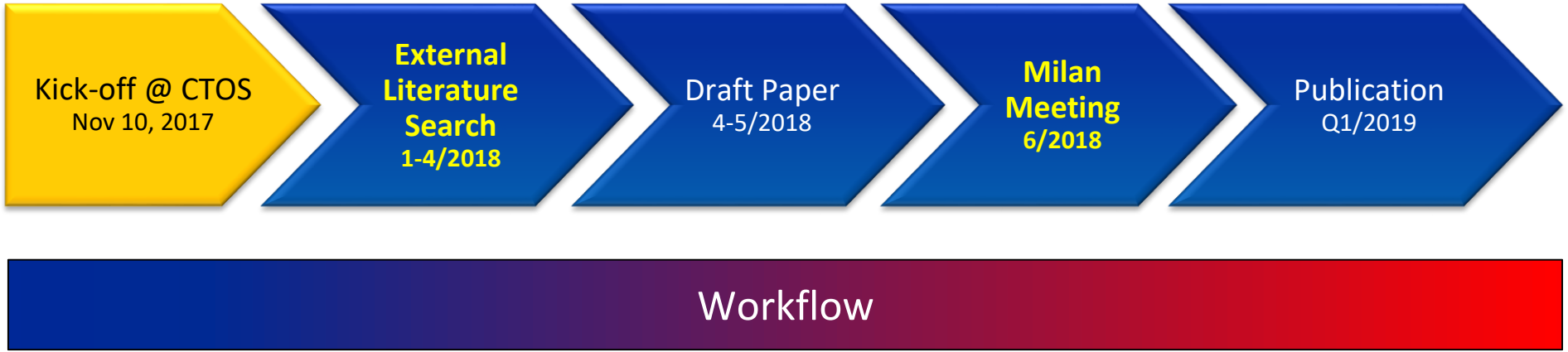
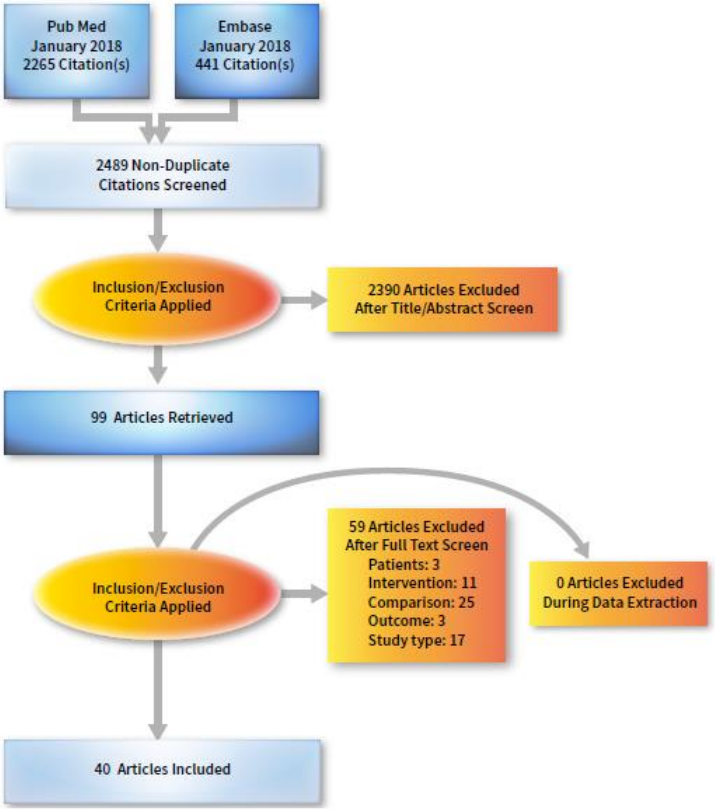
Medizinische Fakultät Mannheim der Universität Heidelberg
Universitätsklinikum Mannheim

Desmoid Meeting 2018 - Methodology & Workflow



Desmoid Meeting 2018 - Methodology



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Desmoid Meeting 2018 - Topics Covered

- Pathology & Molecular Genetics
- Indications for an Active Treatment incl. Radiotherapy
- Available Medical Therapies in Different Indications
- Assessment of Treatment Effects
- Pain, Quality of Life, Fertility & Pregnancy
- Which Endpoints, Study Designs & Regulatory Requirements do we need for Desmoids?

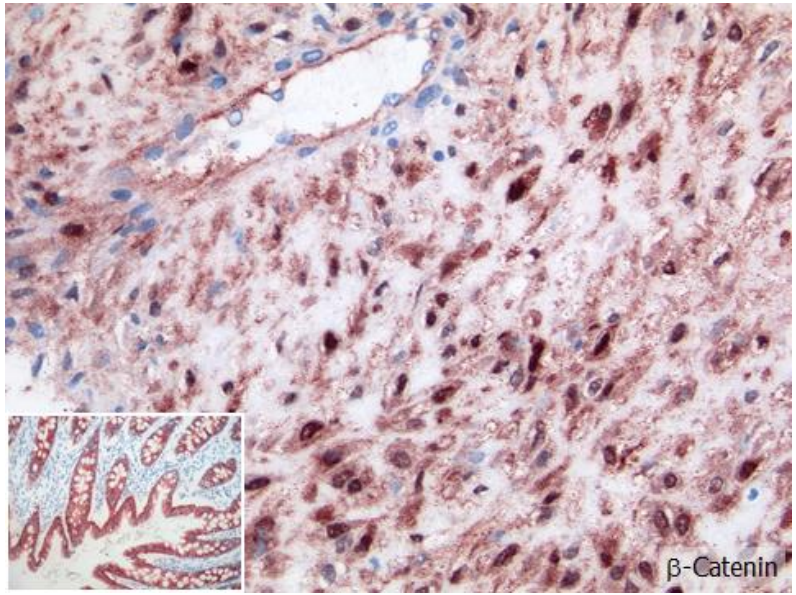
Desmoid Meeting 2018 - Funding

- Initial Meeting & Idea 10th November 2017, CTOS, Maui, Hawaii

▪ Kick-off/Seeding Grant: sos desmoid, Germany	10.000 €
▪ The Desmoid Tumor Research Foundation (DTRF)	30.000 $
▪ Sarcoma Patients EuroNet (SPAEN)	6.000 €

Desmoid Global Consensus - Molecular Genetics

- Diagnosis of DT should be confirmed by an expert soft tissue pathologist.
- *CTNNB1* mutations and *APC* mutations are mutually exclusive in DT, thus, detection of a somatic *CTNNB1* mutation can help to exclude a syndromic condition.
- Therefore, our group gives a strong recommendation to perform a mutational analysis in DT biopsy specimens to confirm diagnosis and guide the work-up.



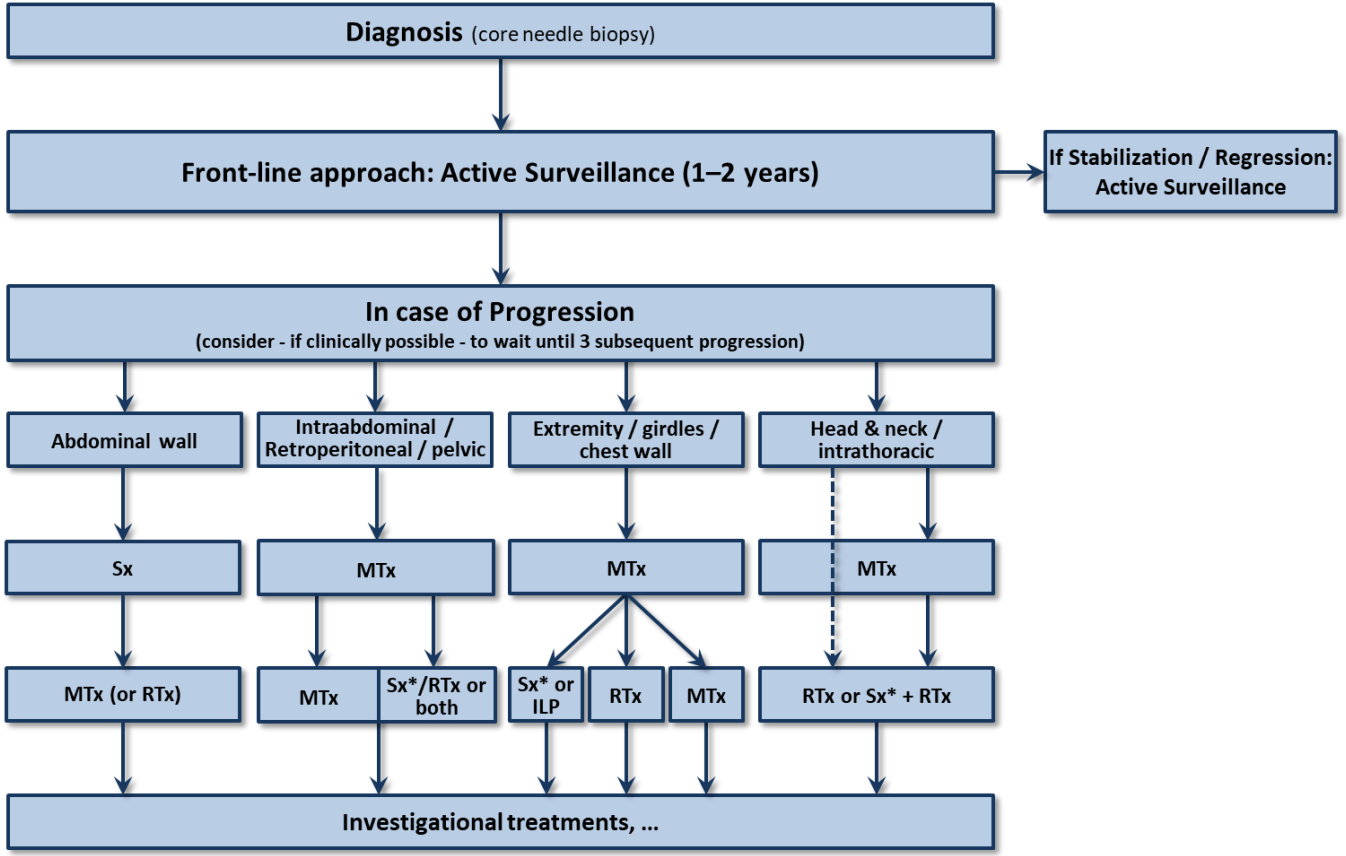
Desmoid Global Consensus - Active Surveillance

- **An initial "Active Surveillance" approach does not appear to influence the efficacy of further treatments when needed.**
- Thus being cautious and avoiding potential harm in experienced hands, **this approach is now considered the first step after diagnosis** in the majority of patients.
- **Neither surgery nor other forms of active treatments are proposed as primary therapy at diagnosis.**
- Progression at a single assessment, especially in the absence of specific symptoms and in non-critical anatomic sites, should not per se be considered as an indication to start an active treatment immediately.
- **Active surveillance** means that patients need to be continuously monitored with a first MRI (or alternatively CT if MRI is not possible) within 1-2 months, then in 3-6 months intervals.
- A decision towards an active treatment should be postponed until the occurrence of subsequent progression or increase of symptoms burden, assessed with **at least two further assessments** and possibly not before one year from diagnosis.
- This **policy avoids overtreatment** in patients who could spontaneously regress and discourages treatment for stable and pauci-symptomatic patients.

Desmoid Global Consensus - Type of Therapy

As depicted in the **Treatment Algorithm**, the type of further treatment is generally guided according to the **anatomical site** and the decision should be taken with the patients in a stepwise approach:

- For **abdominal wall DT**, surgery is still the first option in case of progression.
- For **intraabdominal / retroperitoneal / pelvic DT**, systemic therapy should be considered as the first treatment option.
- For **extremity / girdles / chest wall DT**, again surgery should not be the first treatment option unless the expected morbidity is very low (and only following MDT discussion); medical therapy should be administered preferably. Besides surgery, radiotherapy and medical therapy, isolated limb perfusion (ILP) may be part of the further treatment strategy in this location.
- For **head & neck / intrathoracic DT**, medical therapy is generally considered the first line option. However, in selected conditions (elder age, patient intolerance / preference, comorbidities, lesion growing rapidly and threatening vital organs, etc.) radiotherapy is a reasonable and effective first line alternative.



Abbreviations: Sx: Surgery; Sx*: Surgery is an option if morbidity is limited; MTx: Medical treatment; RTx: Radiotherapy; ILP: Isolated limb perfusion.

Desmoid Global Consensus - FAP-associated and Pediatric DT

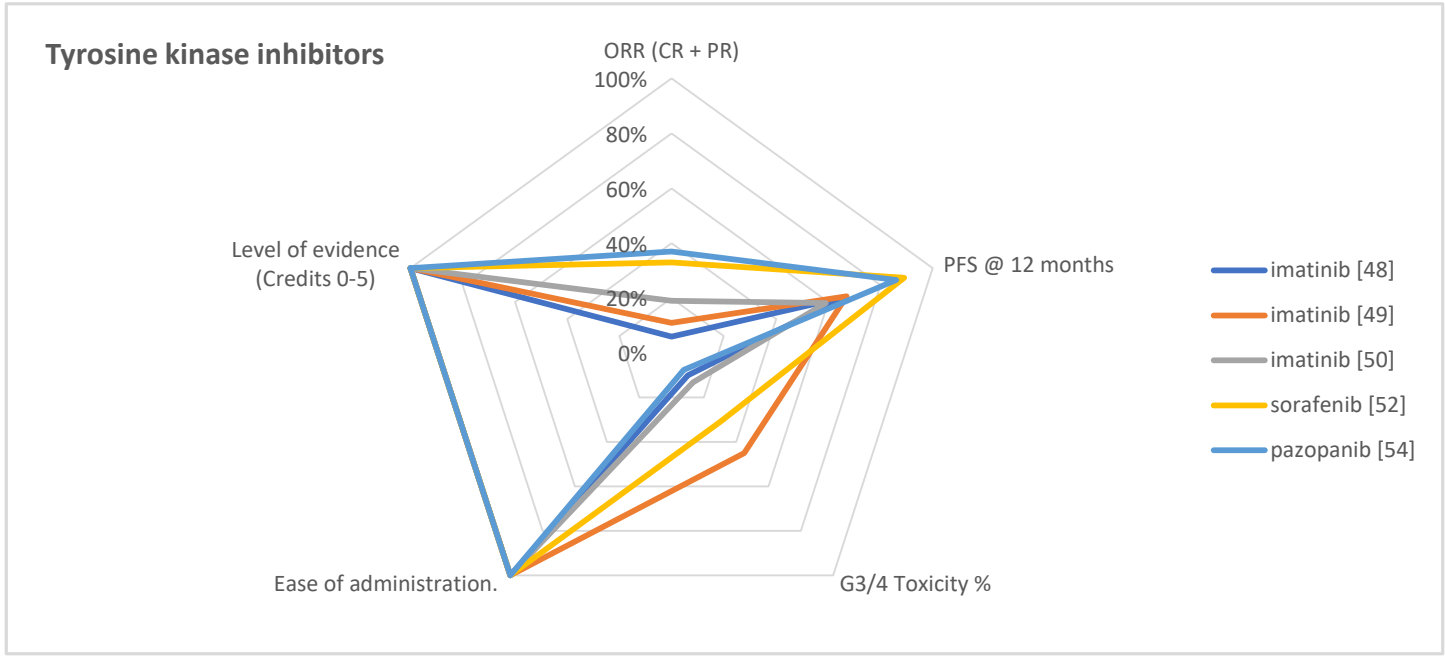
- **FAP-associated DT (Gardner syndrome) seems to be more aggressive and multifocal and, therefore, tends to be treated more aggressively in terms of medical management.**
- **Act with caution regarding performing a biopsy; however, currently there are insufficient data to totally exclude performing a biopsy.**
- **In the setting of a confirmed *APC* mutation, a mesenteric mass may likely be a DT, particularly if the patient had prior surgery.**
- **FAP patients should be jointly managed by sarcoma specialists and experts in gastrointestinal cancer. Surgery should be performed by an experienced surgeon; small bowel transplantation should be discouraged.**

- **There is a lack of evidence that pediatric patients need to be treated differently compared to adults. Thus, the management approach is very similar to that of adult patients and should follow the same treatment algorithm.**

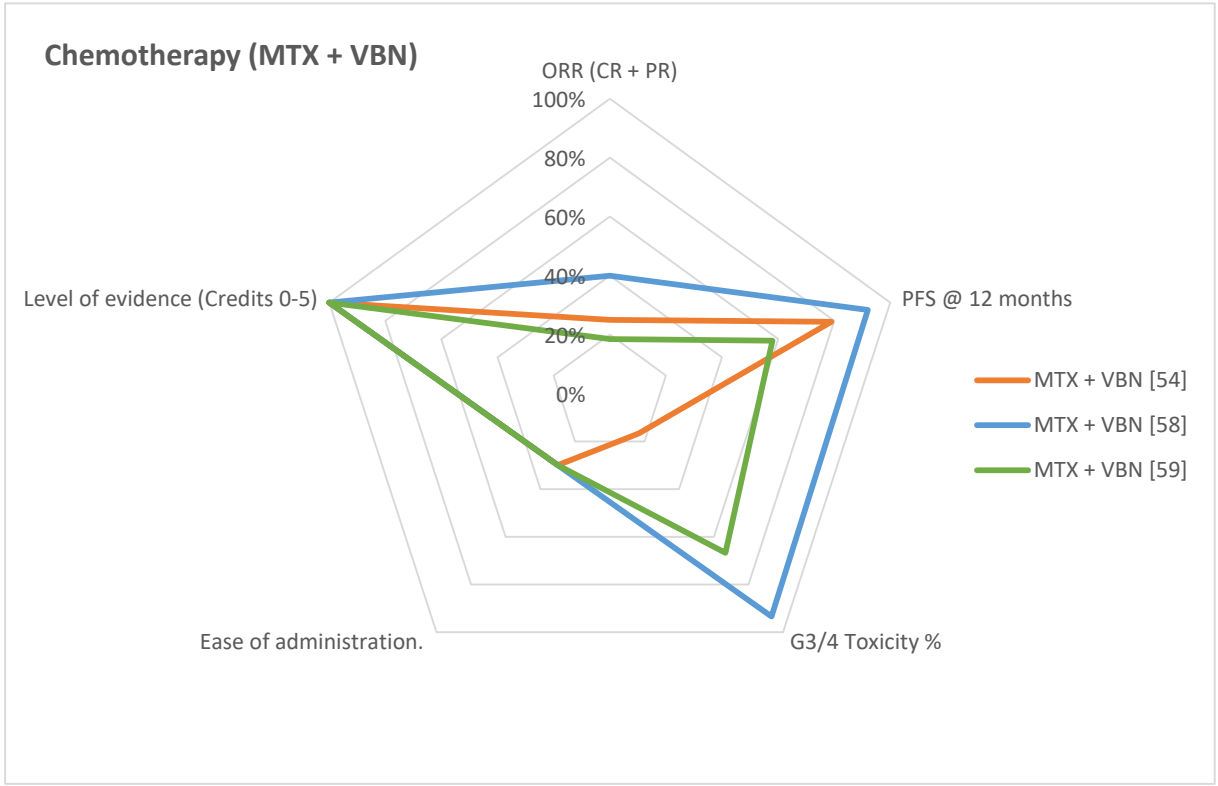
Desmoid Global Consensus - Available Medical Therapies

- In summary, due to the lack of comparative studies we are still not able to propose a definitive sequence of the existing systemic treatment options.
- Randomized data only exist for sorafenib, pazopanib and methotrexate plus vinblastine.
- Prospective phase II studies do exist for the administration of low-dose chemotherapy with methotrexate plus vinblastine and for the use of imatinib.
- In general, it is reasonable to employ less toxic therapy initially followed by more toxic agents in a stepwise fashion.
- Out of the variety of possible systemic treatment options, one can be chosen taking into account the (1) level of evidence, the (2) overall response rate, the (3) PFS rate, the (4) ease of administration, and the (5) expected toxicity of the administered drug following a 5-dimensional model.

Desmoid Global Consensus - Available Medical Therapies

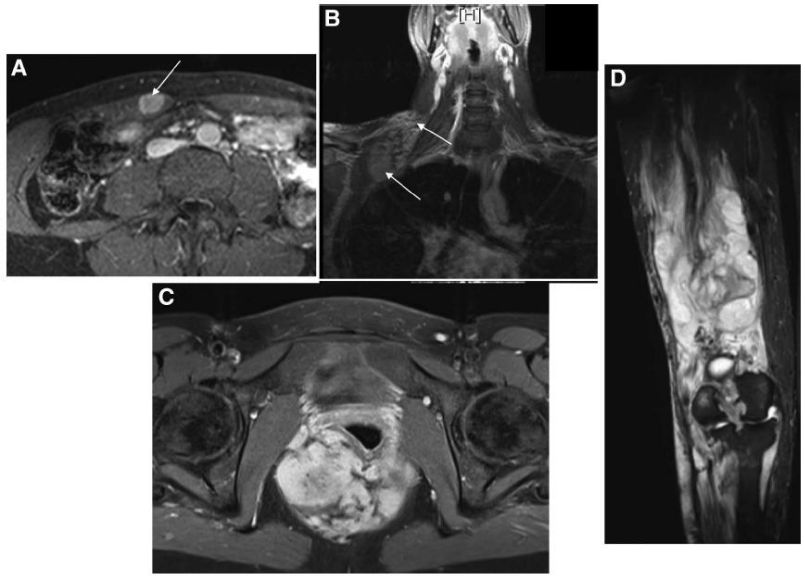


Desmoid Global Consensus - Available Medical Therapies



Desmoid Global Consensus - Assessment of Treatment Effects

- Assessment of treatment effects in DT remains an unresolved issue and **no standard validated response criteria** are available.
- **RECIST** does not robustly identify all clinically relevant responses.
- Contrast-enhanced **MRI** or alternatively CT are the preferred modalities for monitoring DT. No role for FDG-PET in DT evaluation.
- **Circulating tumor DNA** is presently under evaluation and may become a valid biomarker of response / progression.
- **HRQoL evaluation** should be included in any assessment of clinical benefit; validation of a specific tool for DT patients is under way.

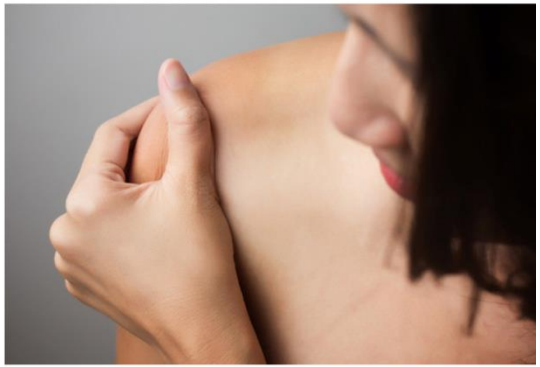


Desmoid Global Consensus - Quality of Life & Pain

- The evidence in this clinical setting is scarce and further clinical trials must integrate HRQoL as an endpoint including levels of functioning and symptoms (most importantly pain).
- Management of pain or functional impairment urgently needs specific research.
- Comprehensive programs for DT patients should include physical, psychological and social support.
- DT is not a contraindication for future pregnancies in favorable evolution and pregnant DT patients should be followed closely by obstetricians and desmoid clinicians.

Desmoid Global Consensus - Publication

The Management of Desmoid Tumors:
A joint global evidence-based consensus guideline approach for adult and pediatric patients



The Desmoid Tumor Working Group

Supported by:

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Thank you!

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