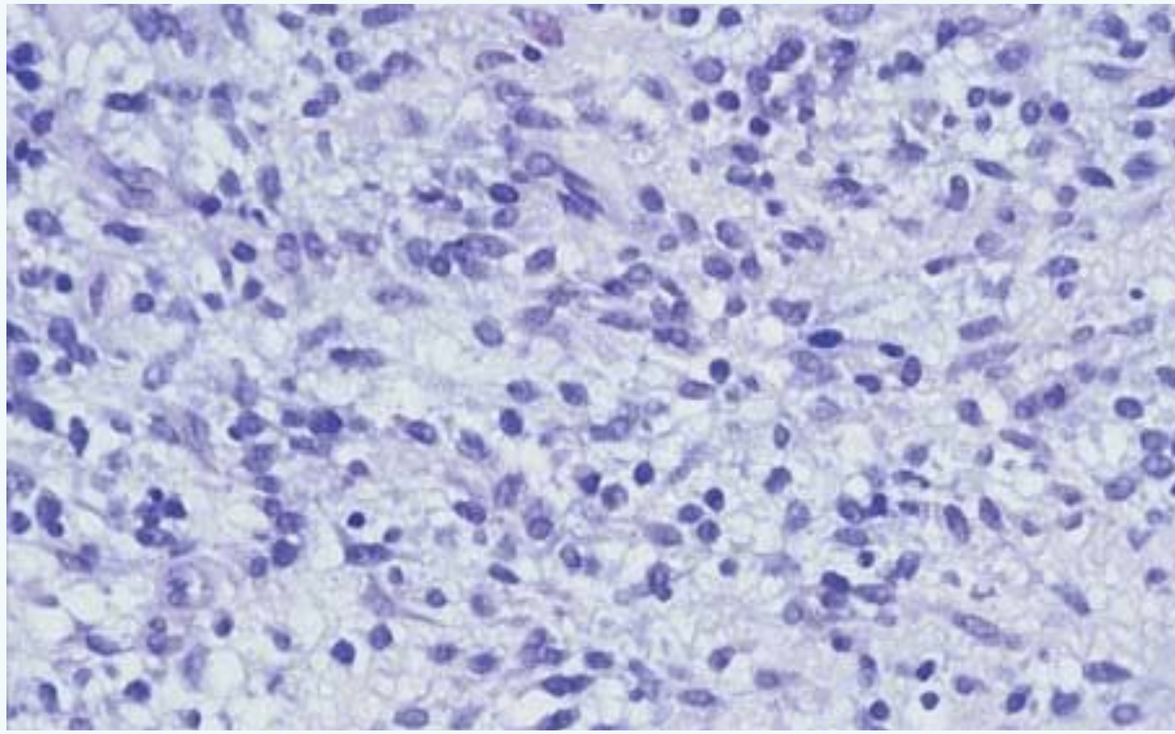
FLASCO 2026

DESMOID TUMORS:
TO TREAT OR NOT TO TREAT



Controversies in the Management of Desmoid Tumors

Joanne P. Lagmay MD

August 22, 2026

ADOLESCENT YOUNG ADULT (AYA) CANCER

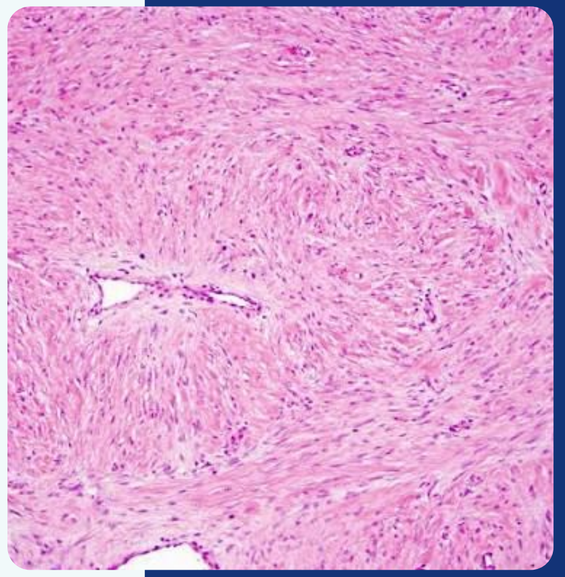
- 15-39 years old
- Distinct tumor biology
- 90K diagnosed in US per year
- AYA cancer incidence increased 30% (1973–2015); breast, colorectal and other carcinomas
- **Desmoid tumors** peak age 30–40 years

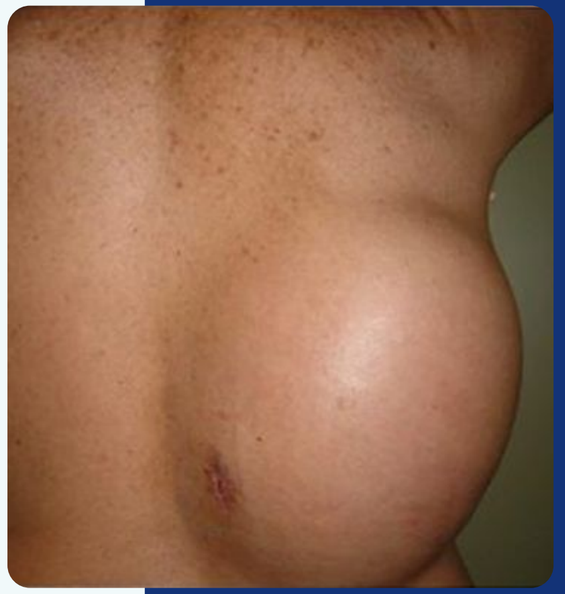
UFHealth | AYA CANCER PROGRAM

DESMOID TUMORS

- Benign, do not metastasize
- Locally aggressive fibroblastic neoplasms
- Associations
  - CTNNB1 (β-catenin) mutations (85%), T41A and S45F
  - APC mutations (FAP) (10-20%)
  - Hormonal- pregnancy and contraception use
  - Trauma- surgery
- Unpredictable and variable clinical course

One disease, many behaviors.
No one-size-fits-all treatment.

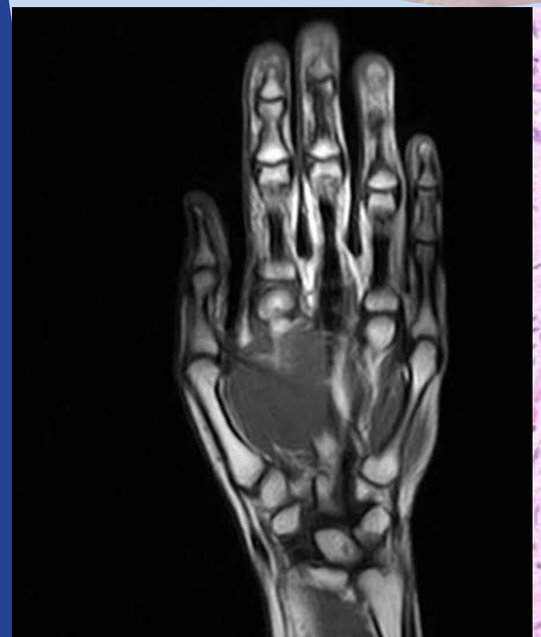


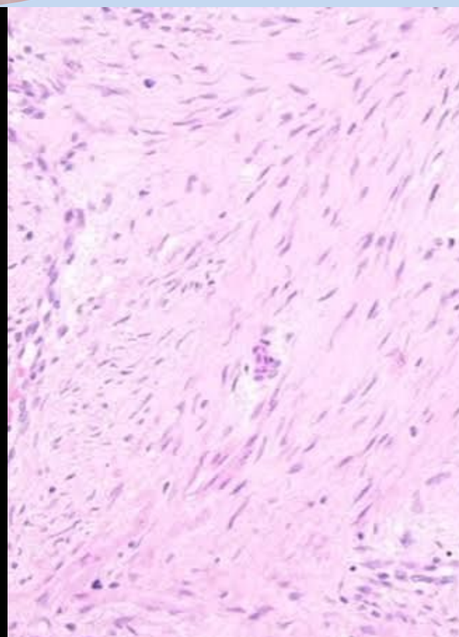


CASE 1 Hand mass

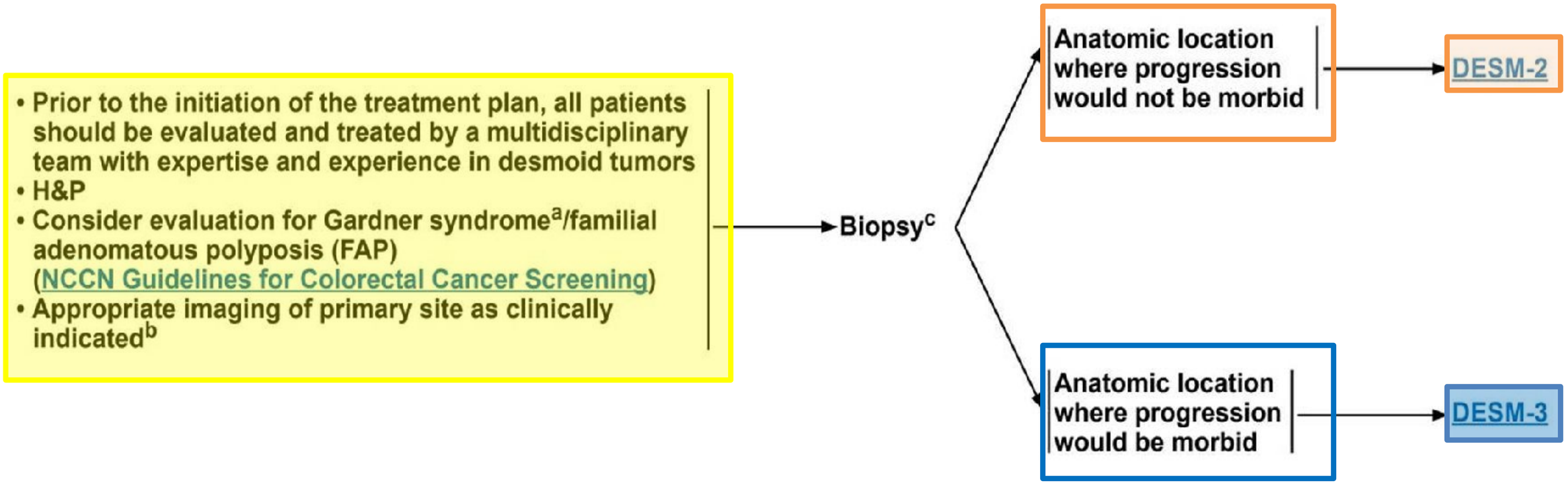
A 34y/F right hand-dominant noted a firm, non-tender mass on her left palm 4 months ago while gardening. She reports no pain, no limitation in grip strength, no numbness or tingling, and no functional impairment. She works as a high school teacher and is fully active without restrictions.

- *Observe or treat?*
- *How to predict which patients will likely be OK with active surveillance?*





NCCN GUIDELINES 2026: ACTIVE SURVEILLANCE

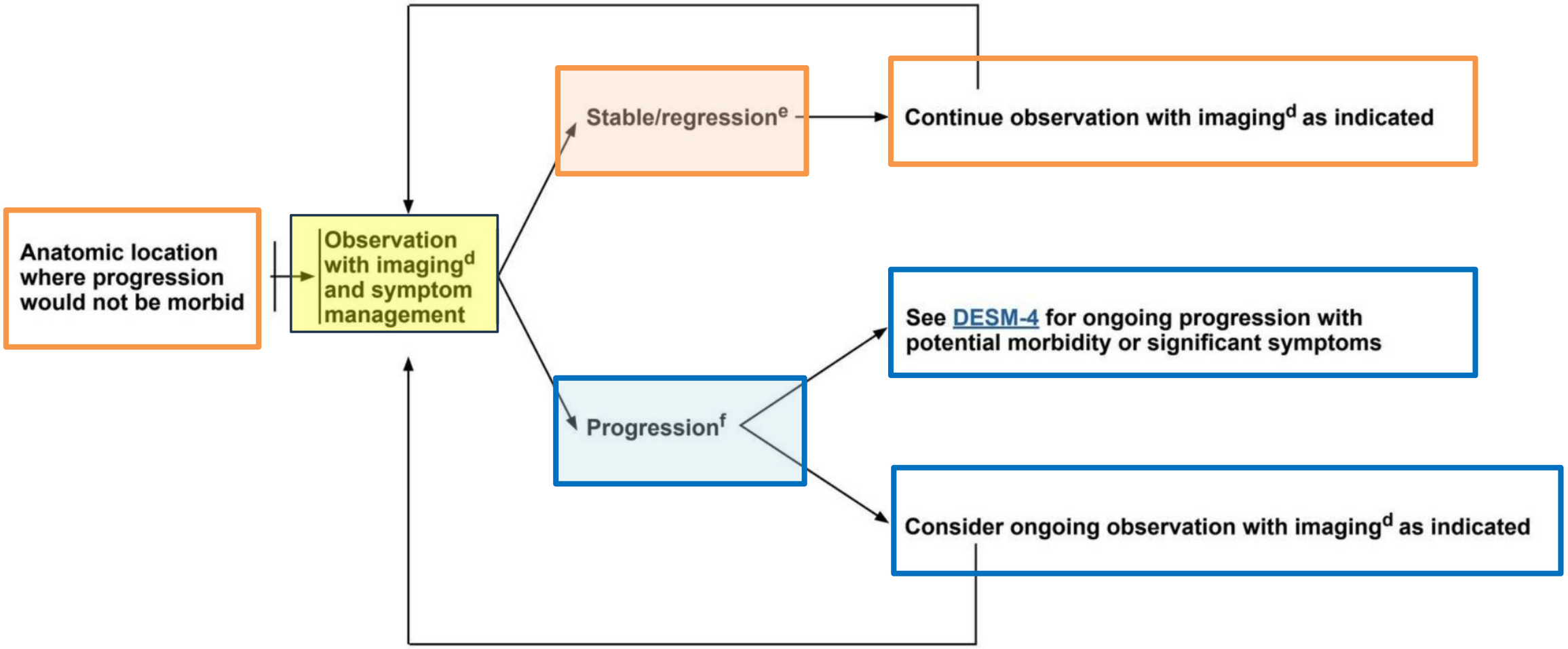


DESM-2 Desmoid Tumors (Aggressive Fibromatosis): Observation Management for Anatomic Location Where Progression WOULD NOT Be Morbid

DESM-3 Anatomic site where progression WOULD be morbid

NCCN Guidelines® — Soft Tissue Sarcoma (v3.2026)

NCCN GUIDELINES 2026: ACTIVE SURVEILLANCE

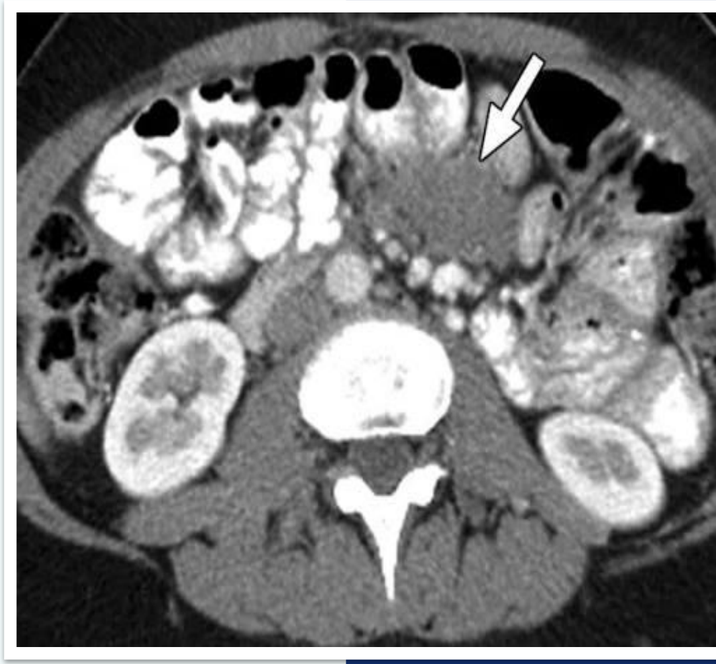


DESM-4 *Desmoid Tumors (Aggressive Fibromatosis): Treatment Based on Anatomic Location and Follow-Up for Active Therapy for Progressive, Morbid, or Symptomatic Disease, NCCN Guidelines® — Soft Tissue Sarcoma p. 25 (v4.2026)*

Desmoid tumors spontaneous regression

Clinical course is unpredictable.

- Spontaneous regression in **~30%**
- **50%** on active surveillance stabilize or regress
- Long-term tumor stability w/o treatment
  - ~**70%** GRAFITI trial (n=105)
  - 3 prospective studies (n=282) 3y PFS **53–58%** with **66%** treatment free at 5y
- Progress then stabilize or regress **~40%**
- French study (n=100) median time to PR **31.7 mos**
- First **2–3y** represent the critical observation period



Bonvalot S, Miah A, Kasper B. Current Opinion in Oncology. 2024;36(4):263-268
National Comprehensive Cancer Network. Updated 2026-03-12;
Schut AW, Timbergen MJM, van Broekhoven DLM, et al. Annals of Surgery. 2023;277(4):689-696. .
Colombo C, Fiore M, Grignani G, et al. Clinical Cancer Research : An Official Journal of the American Association for Cancer Research. 2022;28(18):4027-4032.

DT progression risk stratification

Risk Category	Biological Features	Clinical Implication
Very high	S45F mutation Extremity location Size >5–6 cm Age ≤ 30y	Lowest probability of spontaneous regression, favor early treatment
High	APC mutation (FAP)	Worse biology; inferior systemic therapy outcomes
Intermediate	T41A mutation Extra-abdominal	Standard observation appropriate; intervene for progression
Low	Wild-type CTNNB1/T41A abdominal wall Age ≥ 30y	Highest probability of spontaneous regression; observation strongly favored

Bonvalot S, Cozic N, Le Cesne A, et al. Annals of Surgical Oncology. 2023;30(13):8653-8659; Colombo C, Hakkesteegt S, Le Cesne A, et al. Clinical Cancer Research 2025;31(3):603-610; Timbergen MJM, Schut AW, Grünhagen DJ, Sleijfer S, Verhoef C. European Journal of Cancer (Oxford, England : 1990). 2020;137:18-29; Salas S, Dufresne A, Bui B, et al. Journal of Clinical Oncology: 2011;29(26):3553-86; Annals of Surgery. 2013;258(2):347-53The GRAFITI Trial. Schut AW, Timbergen MJM, van Broekhoven DLM, et al. Annals of Surgery. 2023;277(4):689-696; M, Grignani G, et al. Clinical Cancer Research. 2022;28(18):4027-4032.

Active Surveillance

Key principles

1. **Individualized active patient surveillance**
   - Avoid overtreatment for tumors, may spontaneously regress or stabilize
   - Consider: location of tumor, morbidity if with progression and clinical symptoms
   - Risk / benefit ratio

2. **Defer treatment decisions until clear progression documented**
   - Be patient!

CASE 1

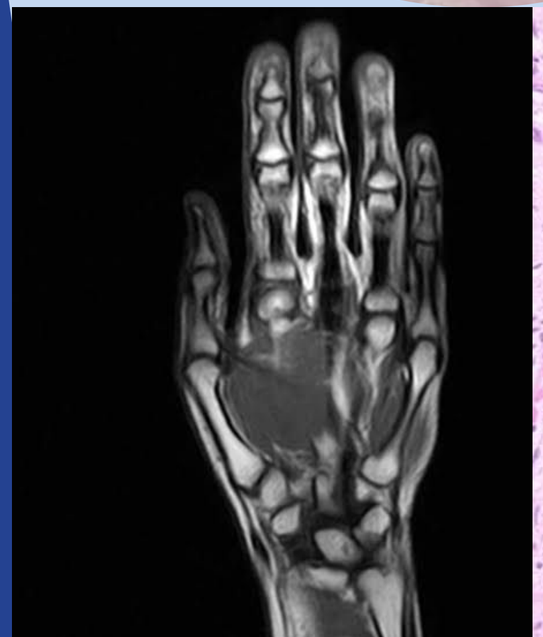
A 34y/F R hand-dominant with firm, non-tender mass on her L palm, fully functional

1. Why not treat?

- Spontaneous regression ~ 30%
- ~2/3 on active surveillance treatment-free at 5y

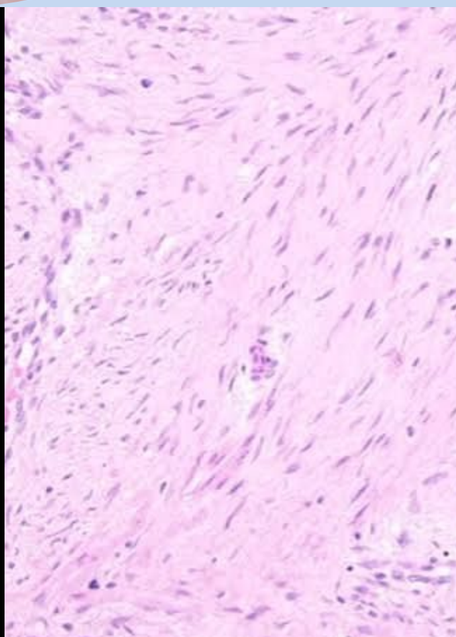
2. Why not operate?

- Surgery risks
- High surgical recurrence rates for extremity desmoids
- Asymptomatic
- Non-dominant hand



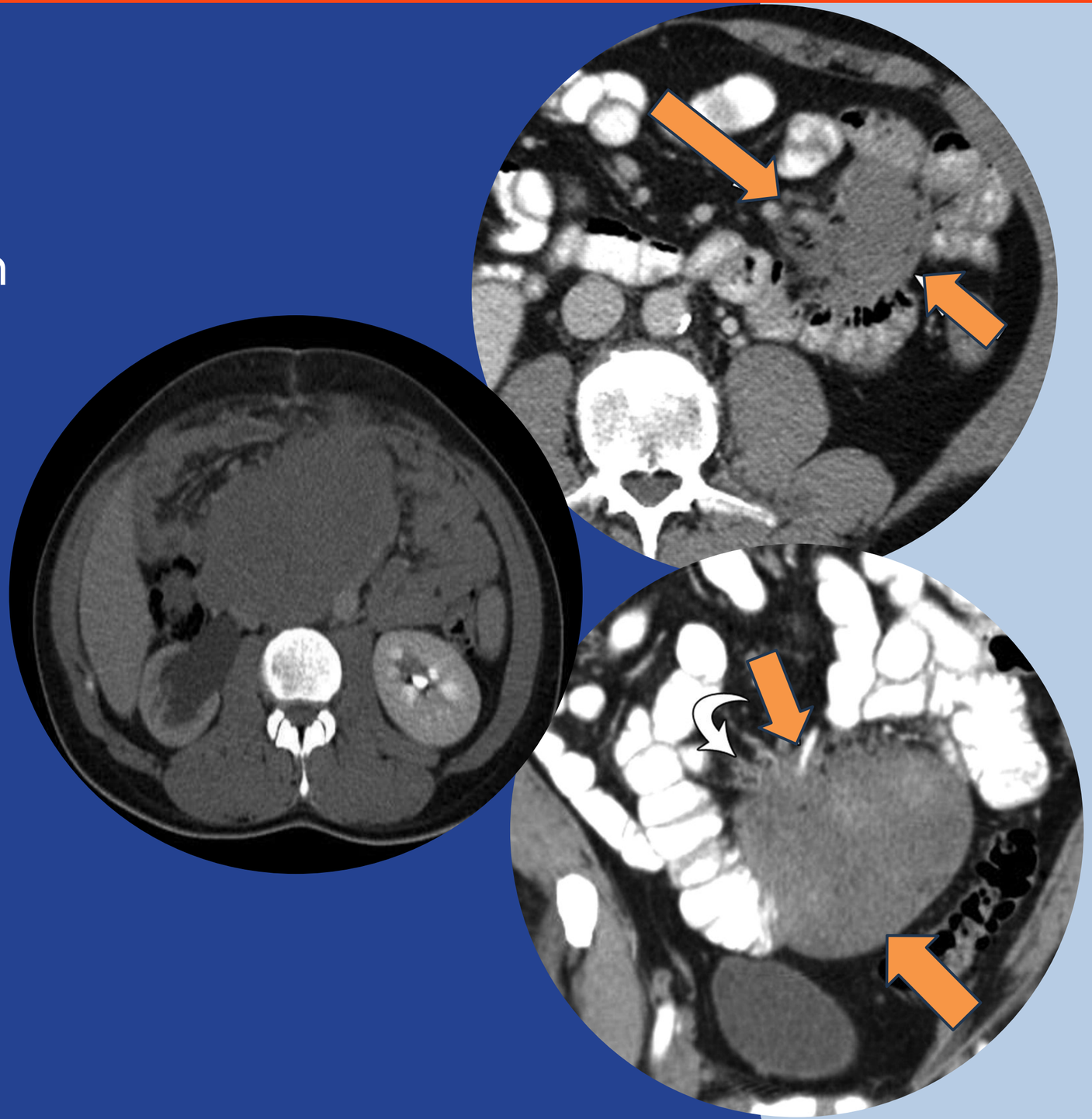
3. Why not start systemic therapy?

- No symptoms
- No functional impairment
- No documented progression
- Treatment side effects

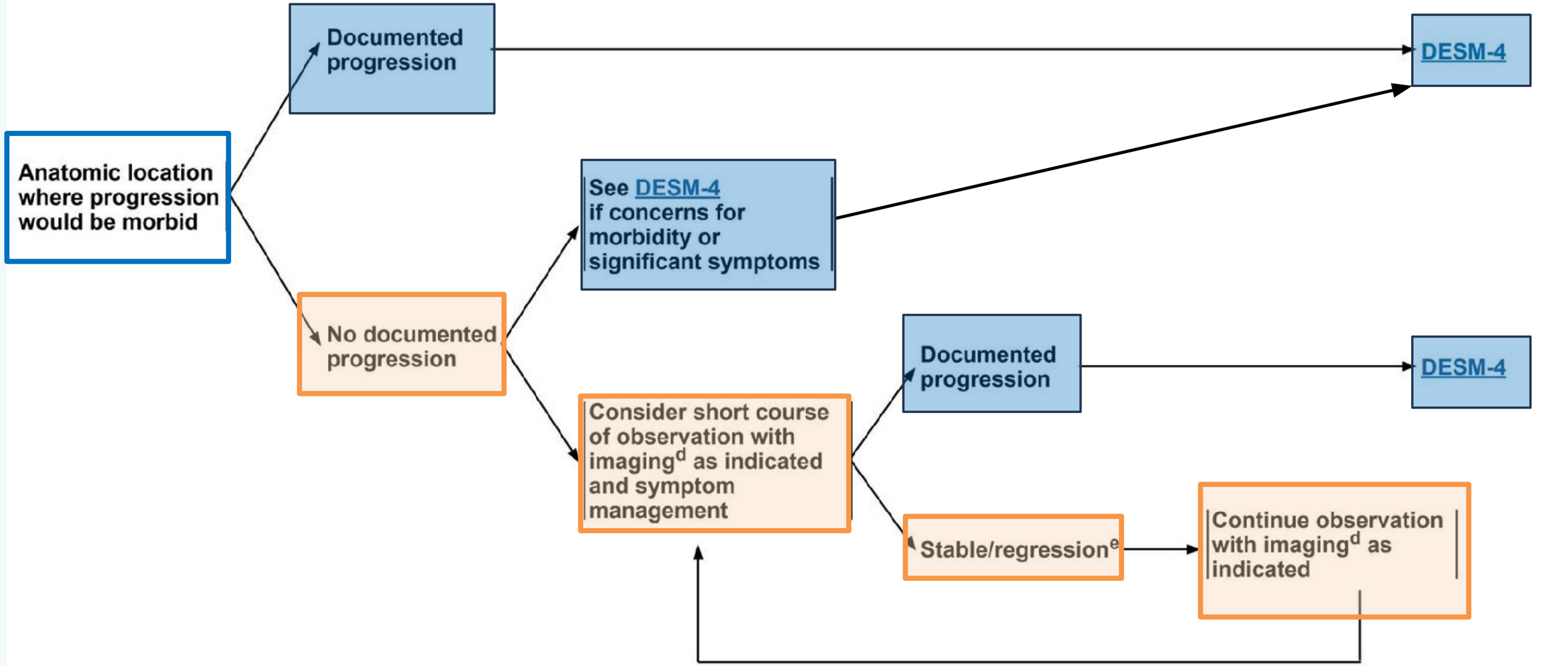


CASE 2

A 25y/F with a growing 12 cm pelvic desmoid causing ureteral obstruction without renal insufficiency and mild pelvic pain

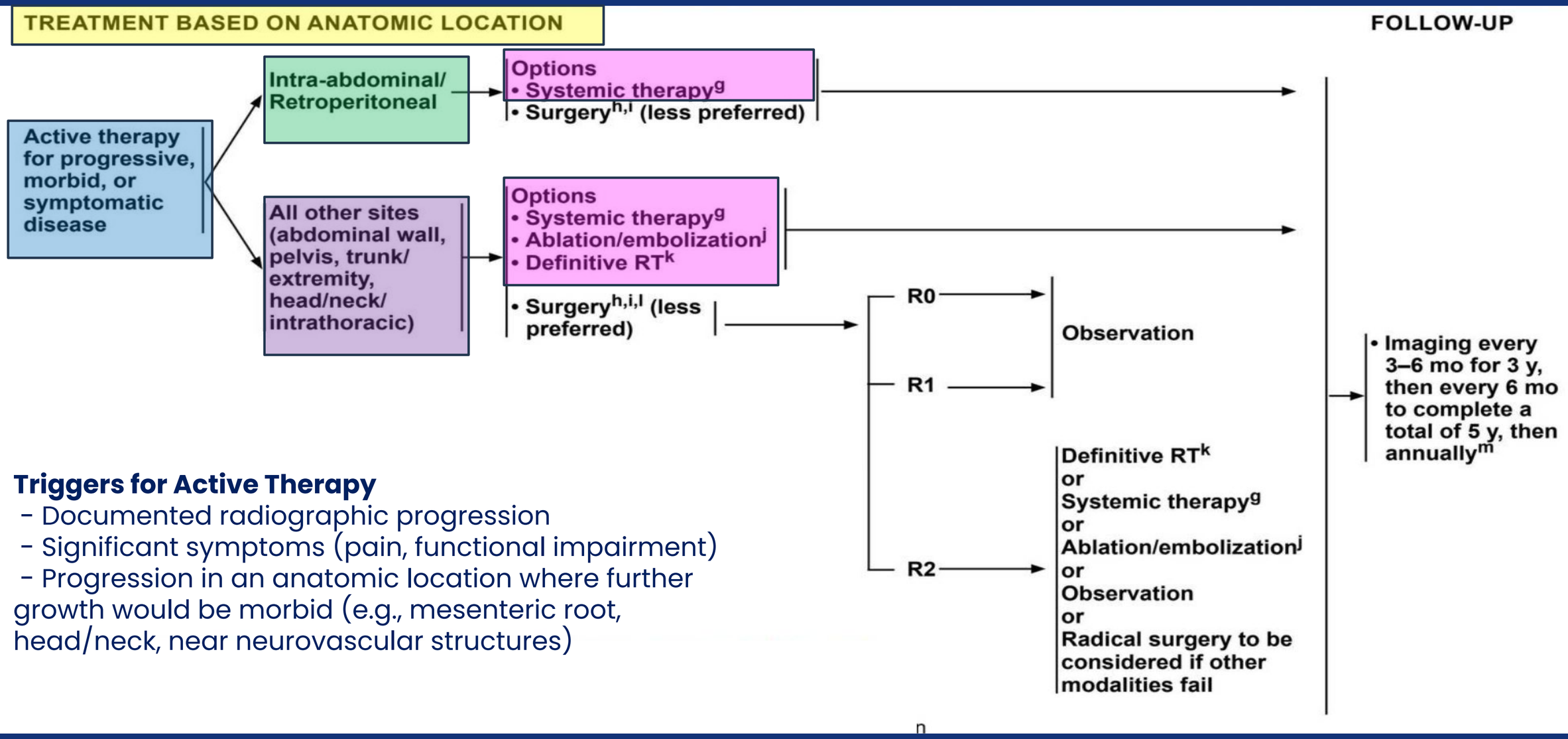


NCCN GUIDELINES 2026: TREAT



DESM-4 *Desmoid Tumors (Aggressive Fibromatosis): Treatment Based on Anatomic Location and Follow-Up for Active Therapy for Progressive, Morbid, or Symptomatic Disease — NCCN Guidelines® — Soft Tissue Sarcoma p. 25 (v4.2026)*

NCCN GUIDELINES 2026: TREAT



Triggers for Active Therapy

- Documented radiographic progression
- Significant symptoms (pain, functional impairment)
- Progression in an anatomic location where further growth would be morbid (e.g., mesenteric root, head/neck, near neurovascular structures)

n

__DESM-4__ Desmoid Tumors (Aggressive Fibromatosis): Treatment Based on Anatomic Location and Follow-Up for Active Therapy for Progressive, Morbid, or Symptomatic Disease — NCCN Guidelines® — Soft Tissue Sarcoma p. 25 (v4.2026)

Desmoid Tumors (Aggressive Fibromatosis)[o]

Preferred

- Nirogacestat (category 1)[45]
- Sorafenib (category 1)[46]
- Methotrexate/Vinorelbine[47]
- Methotrexate/Vinblastine[48]
- Imatinib[49,50]
- Liposomal Doxorubicin[51]
- Doxorubicin[52-54]
- Dacarbazine/Doxorubicin[52-54]
- Pazopanib[55]

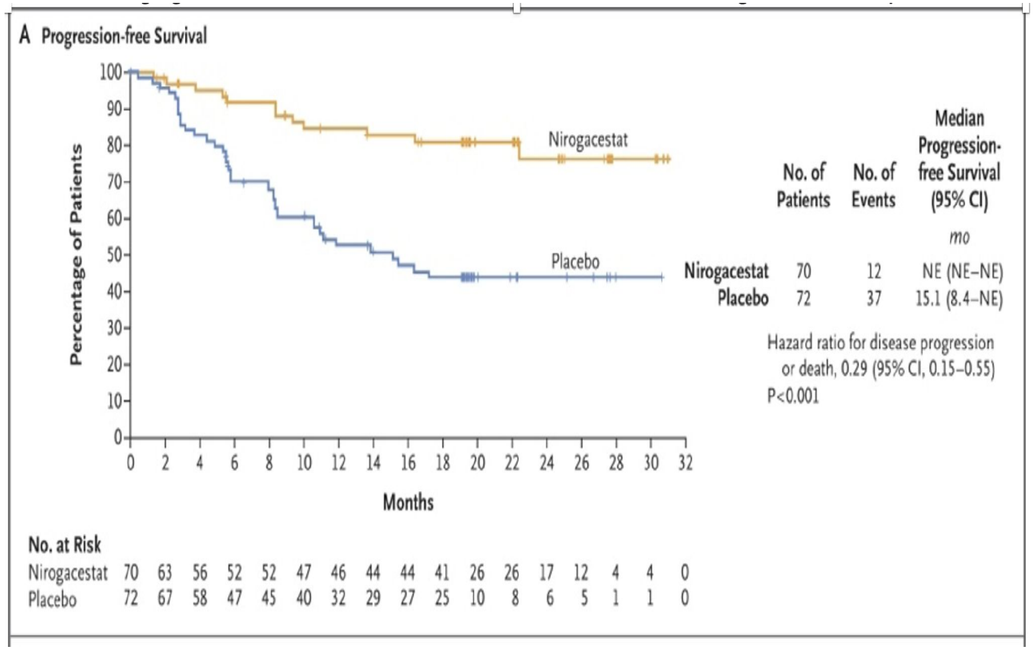
Useful in certain circumstances

- Sulindac[56] or other nonsteroidal anti-inflammatory drugs (NSAIDs), including Celecoxib (for pain)

TIER 1 : HIGHEST-EVIDENCE AGENTS (PHASE III RCT)

1. *Nirogacestat*

- Only FDA-approved drug for DT
- DeFi trial (≤ 18y)
  - ORR of **41%- 45.7%** vs. 8% placebo
  - Reduction in risk of progression **71%**
  - Clinical response **78%**
  - Median ffup **33.6mos**
  - Time to response **5-6 mos**
  - Benefits across all groups, including FAP-associated tumors
  - Ovarian dysfunction in **75%**, resolved in 74%



Nirogacestat, a γ-Secretase Inhibitor for Desmoid Tumors. Gounder M, Ratan R, Alcindor T, et al. The New England Journal of Medicine. 2023;388(10):898-912. doi:10.1056/NEJMoa2210140.

TIER 1: HIGHEST-EVIDENCE AGENTS (PHASE III RCT)

2. Sorafenib

- **87%** reduction in risk of progression
- 2y PFS of **81%** (vs 36%), ORR of **33%** (vs 20%)
- Dose 400 mg daily, manageable toxicity profile

(ALLIANCE phase III trial) Gounder MM, Mahoney MR, Van Tine BA, et al. The New England Journal of Medicine. 2018;379(25):2417-2428.

3. Pegylated liposomal doxorubicin (PLD)

- 2y PFS **90.4%** vs. 19.6% placebo, ORR **40.4%**
- favorable safety profile
- high disease control: intra-abdominal site (**76.2%**) and FAP-associated (**73.7%**) desmoids

Xu H, Hu Y, Zhang S, et al. Clinical Cancer Research : An Official Journal of the American Association for Cancer Research. 2026;32(11):2198-2205; Wytiaz V, Dorand RD, Cohen S, et al. Expert Review of Anticancer Therapy. 2025.

TIER 2 : ESTABLISHED AGENTS (PHASE II /LARGE RETROSPECTIVE)

1. *Methotrexate + vinblastine/vinorelbine*

- Most established low-dose chemotherapy regimen
- ORR of **31–54%**, clinical benefit rate **95–100%**
- Median PFS **75 months**
- FAP-associated desmoids ORR 54.1%, median PFS 6.5 years
- Well tolerated
- Successfully rechallenge upon progression

Azzarelli A, Gronchi A, Bertulli R, et al. Cancer. 2001;92(5):1259-64.; Palassini E, Frezza AM, Mariani L, et al. Cancer Journal (Sudbury, Mass.). 2017 Mar/Apr;23(2):86-91; Napolitano A, Provenzano S, Colombo C, et al. ESMO Open. 2020;5(1):e000604.

2. *Pazopanib*

- 6-month non-progression rate of **84%**
- ORR of **37%**

DESMOPAZ phase II trial Toulmonde M, Pulido M, Ray-Coquard I, et al. The Lancet. Oncology. 2019;20(9):1263-1272.

TIER 2 : ESTABLISHED AGENTS (PHASE II /LARGE RETROSPECTIVE)

3.Anthracycline-based regimens (doxorubicin ± dacarbazine)

- higher 1-year ORR **37%** (vs sorafenib 13%)
- faster TTR **5.6 mos** (vs sorafenib 8.7 mos)
- higher grade 3 AEs (27% vs. 14%)

Costa PA, Arora A, Fernandez Y, et al. Cancer. 2025;131(1):e35647. doi:10.1002/cncr.35647.

4. Imatinib

- lowest ORR among preferred agents (<10% tumor shrinkage)
- 6-month progression rate of **65%**
- well tolerated

Kasper B, Gruenwald V, Reichardt P, et al. European Journal of Cancer (Oxford, England : 1990). 2017;76:60-67. doi:10.1016/j.ejca.2017.02.001; Toulmonde M, Pulido M, Ray-Coquard I, et al. The Lancet. Oncology. 2019;20(9):1263-1272. doi:10.1016/S1470-2045(19)30276-1.

KEY PRINCIPLES FOR SYSTEMIC THERAPY

1. **No single agent is universally superior**
   - Nirogacestat and sorafenib have the strongest evidence *(Category 1)*

2. **Choice depends on patient-specific factors**
   - Gender, age, reproductive status, clinical urgency, tumor location

3. **Be patient**
   - Response is SLOW across all agents: *TTR* ***5.6 mos*** *(nirogacestat, anthracyclines) to* ***9.6–15.2 mos*** *(sorafenib)*
   - Treatment duration matters *(**minimum 1 year**)*
   - Continuing regression occurs off therapy

4. **Rechallenge is effective** (MTX/vinca alkaloids and sorafenib)

PRIORITIZATION BY CLINICAL SCENARIO

Clinical Scenario	Drug of Choice
Progressive desmoid in a male or postmenopausal female	Nirogacestat or Sorafenib
Premenopausal F, fertility preservation critical	Sorafenib 400 mg
Rapidly progressive, threatening vital structures	Anthracycline-based regimen or PLD
FAP-associated, intra-abdominal	PLD or MTX/vinca alkaloid
Pediatric/AYA (age ≤30)	PLD or Sorafenib Nirogacestat
Elderly or comorbid, poor tolerance for toxicity	Sorafenib 200 mg or Imatinib
Failed sorafenib	Nirogacestat
Failed nirogacestat	Sorafenib or anthracycline-based regimen or PLD

UNRESOLVED CONTROVERSIES

1. Optimal duration of systemic therapy is unknown

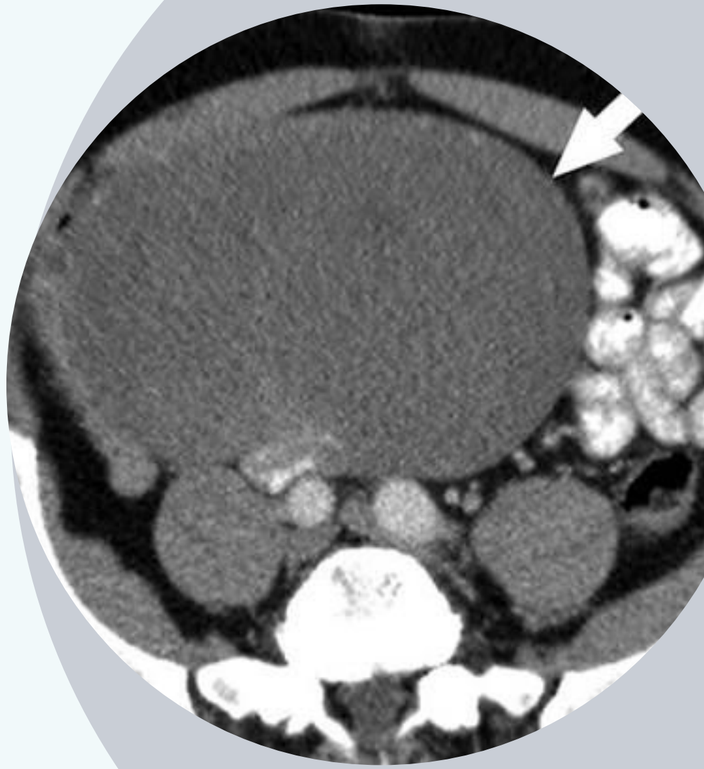
- Sorafenib **<1 year** higher risk of needing further therapy (**2y TFS 60%** vs 87.5%)
- SORASTOP trial stopping **≥1 year**, 12-month PFS **90.8%**

2. Sequencing of systemic agents is undefined

- No head-to-head trials nirogacestat vs. sorafenib

3. Anthracycline-based chemotherapy vs. TKIs

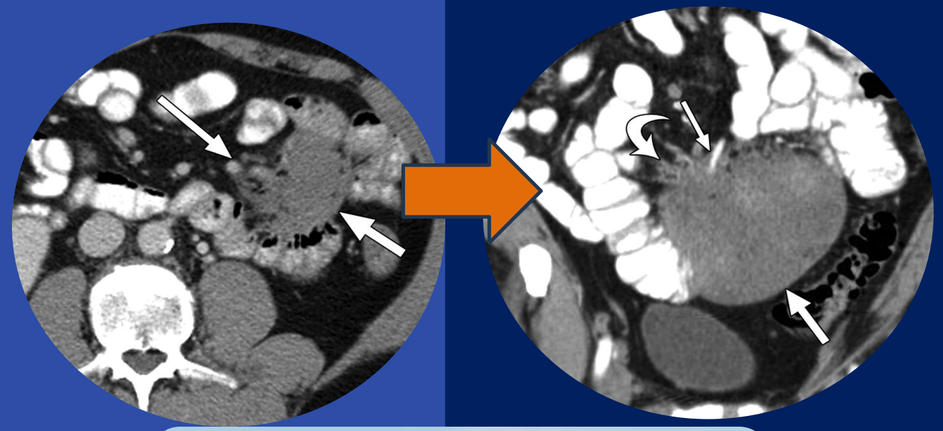
- Anthracyclines - faster/ deeper responses (1y **ORR 37%** vs. 13%), but higher grade 3 toxicity (**27%** vs. 14%)



Costa P, Yi I, Arora A, et al. Journal of Clinical Oncology. 2024;42(Suppl 16):11585; Phase-Ii SORASTOP Study From India. Singh K, Rastogi S, Singh A, et al. European Journal of Cancer (Oxford, England : 1990). 2026;235:116253; HeeKyung Kim and Warren Chow. Journal of Clinical Oncology. 2026;44(Suppl 16):e23542; Costa PA, Arora A, Fernandez Y, et al. Cancer. 2025;131(1):e35647; Prendergast K, Kryeziu S, Crago AM. The Surgical Clinics of North America. 2022;102(4):667-677; Dilley R, Al-Jazrawe M, Greenberg A, et al. Journal of Clinical Oncology. 2026;44(Suppl 16):11583.; Smith S, Sweeney K, Elliott A, et al. Journal of Clinical Oncology. 2025;43(Suppl 16):11547.

CASE 2

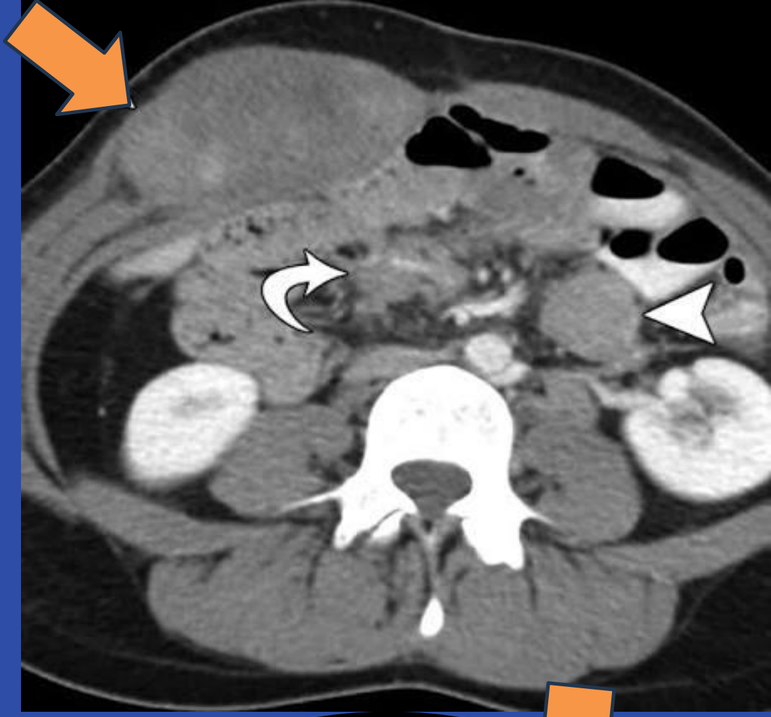
A 25y/F with a growing 12 cm pelvic desmoid causing ureteral obstruction without renal insufficiency and mild pelvic pain

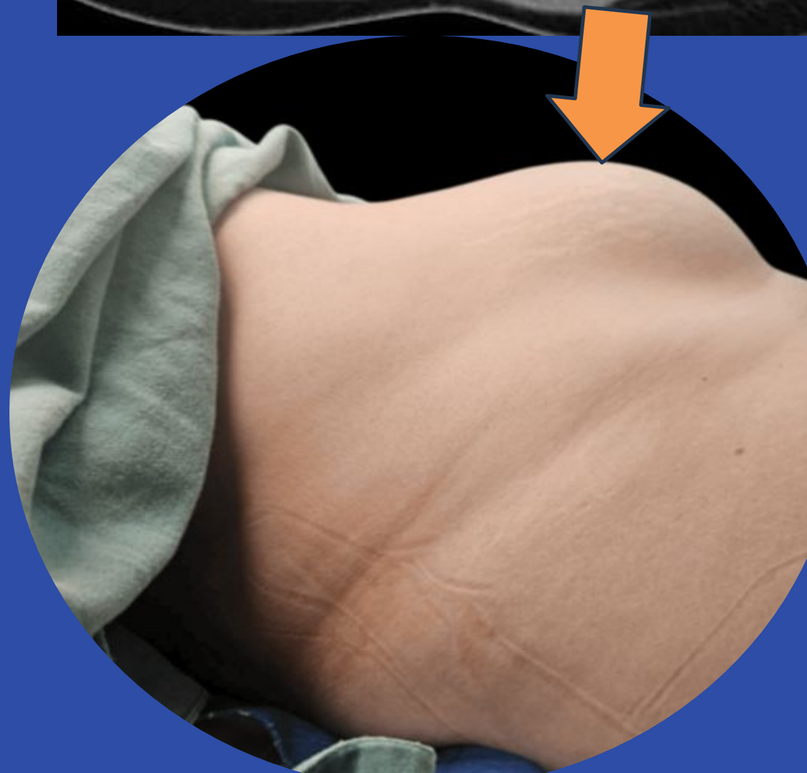


- *Nirogacestat TTR 5.6 mos with 41% ORR, 75% ovarian dysfunction*
- *Sorafenib 80% 2y PFS, 30% ORR*
- *If with rapid growth, anthracycline-based therapy or Nirogacestat*
  - *TTR 5.6 mos vs. 5-6 mos Niro vs 10 mos TKI*

CASE 3

A 25y/F presents with a recurrent 5 cm desmoid tumor of the anterior abdominal wall. She was initially managed with active surveillance, then progressed on sorafenib after 12 mos of treatment. Now with worsening pain and abdominal wall deformity. The tumor is superficial, well-localized, and amenable to complete resection with acceptable functional outcomes.





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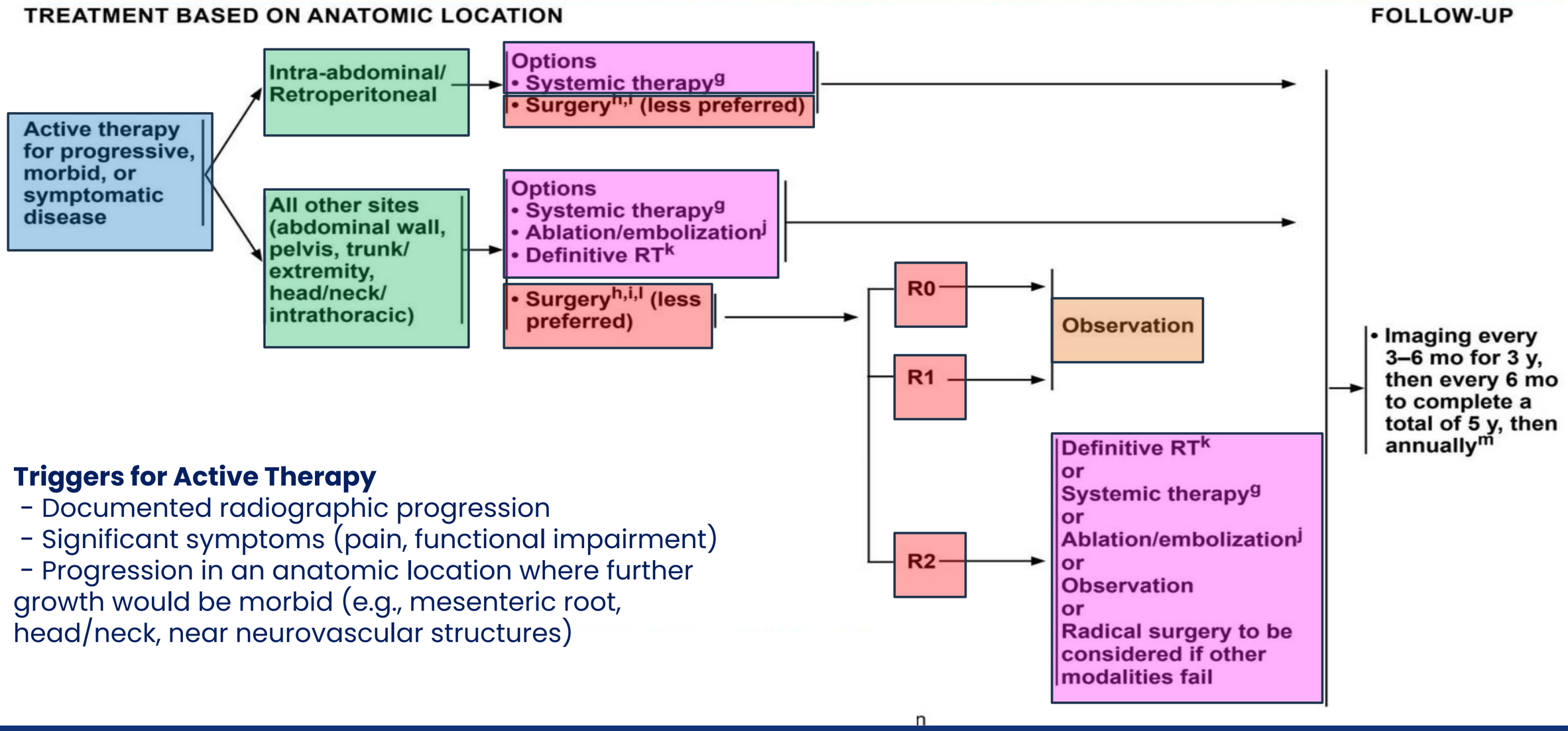

Triggers for Active Therapy

- Documented radiographic progression
- Significant symptoms (pain, functional impairment)
- Progression in an anatomic location where further growth would be morbid (e.g., mesenteric root, head/neck, near neurovascular structures)

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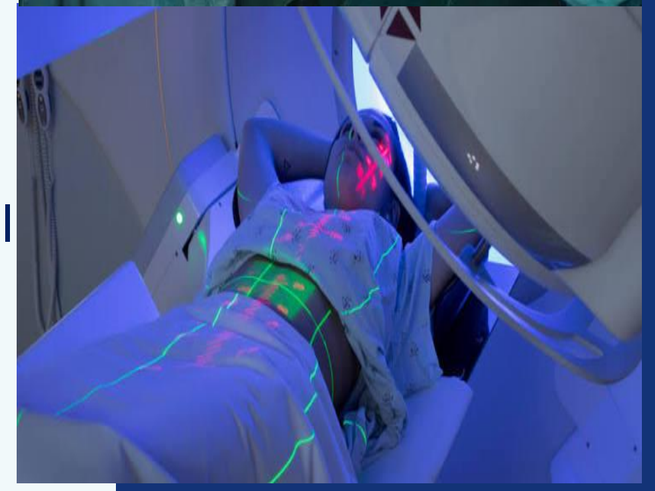
KEY PRINCIPLES FOR LOCAL CONTROL

1. Active surveillance first, local therapy second or third

- Always the first-line!
- Local therapy
  - progressive, symptomatic tumors
  - morbid progression on observation
  - after systemic therapy

2. Anatomic location is the primary determinant of local therapy choice

- **Surgery** - abdominal wall, intraabdominal/mesenteric (emergent)
- **Radiation**- Extremity, head/neck, intrathoracic, NOT intra-abdominal
- Trunk and pelvis- depends on morbidity



Kasper B, Baldini EH, Bonvalot S, et al. JAMA Oncology. 2024;10(8):1121-1128; Sarcoma. National Comprehensive Cancer Network. Updated 2026-07-08; Crago AM, Denton B, Salas S, et al. Annals of Surgery. 2013;258(2):347-53; Bishop AJ, Landry JP, Roland CL, et al. Cancer. 2020;126(14):3265-3273; Keus RB, Nout RA, Blay JY, et al. Annals of Oncology : Official Journal of the European Society for Medical Oncology. 2013;24(10):2672-2676; Nuyttens JJ, Rust PF, Thomas CR, Turrisi AT. Cancer. 2000;88(7):1517-23; Hunt JL, et al. Head & Neck. 2014;36(10):1517-26; Neck. Niu X, Jiang R, Hu C. Cancer Investigation. 2019;37(8):387-392.

KEY PRINCIPLES FOR LOCAL CONTROL

3. KEY Surgical principles for DT

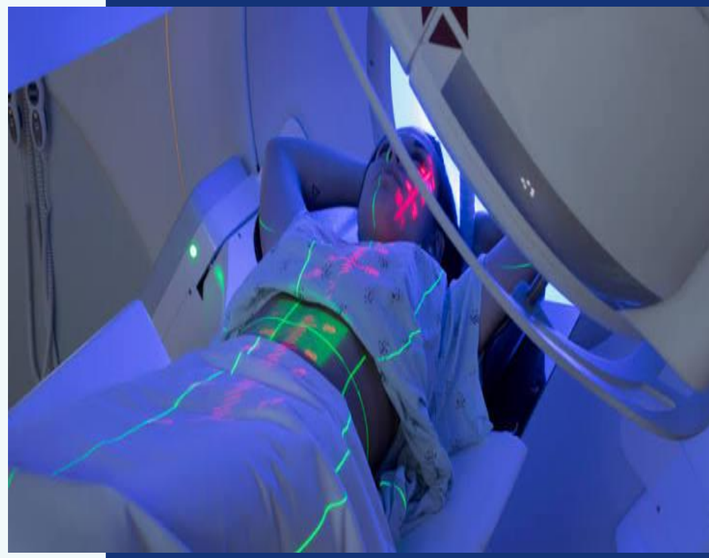
- ”Less preferred" per NCCN
- superficial sites with low morbidity, R0 margins
- Prefer function-preserving surgery with narrow negative margins
- Do not pursue R0 at the cost of major morbidity- ***OBSERVE!***
- Do not reoperate after unplanned excision – ***OBSERVE!***
- Do not operate on stable residual disease after systemic! therapy- ***OBSERVE!***

A Review. Kasper B, Baldini EH, Bonvalot S, et al. JAMA Oncology. 2024;10(8):1121-1128; National Comprehensive Cancer Network. Updated 2026-07-08; Crago AM, Denton B, Salas S, et al. Annals of Surgery. 2013;258(2):347-53.; Cates JM, Stricker TP. The American Journal of Surgical Pathology. 2014;38(12):1707-14.

KEY PRINCIPLES FOR LOCAL CONTROL

4. Key RT principles for DT

- Best when surgery is too morbid or has already failed
- Definitive RT (56 Gy/28 fractions) is the standard approach
  - ✔ NO preoperative/neoadjuvant role for DT
  - ✔ RT alone is equivalent to surgery + RT
  - ✔ Postoperative RT after R0 resection provides NO benefit
  - ✔ Postoperative RT after R1 resection improves outcomes, but observation is a reasonable alternative
  - Intra-abdominal/retroperitoneal sites
- Response is SLOW (14 mos)
  - ✔ continuing regression beyond 3 years



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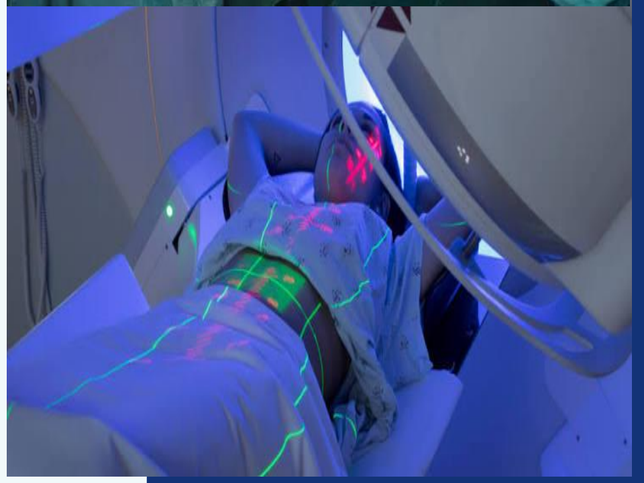
KEY PRINCIPLES FOR LOCAL CONTROL

5. Age significant factor for local therapy outcomes

- **Age >30–40 years**
  - ✔ RT excellent outcomes (5y LCR 75–97%)
  - ✔ surgery also performs well

- **Age ≤30 years**
  - ✔ Both surgery and RT have poor outcomes (5-yr LC 43–57%)
  - ✔ Systemic therapy as primary approach
  - ✔ local therapy reserved for refractory cases



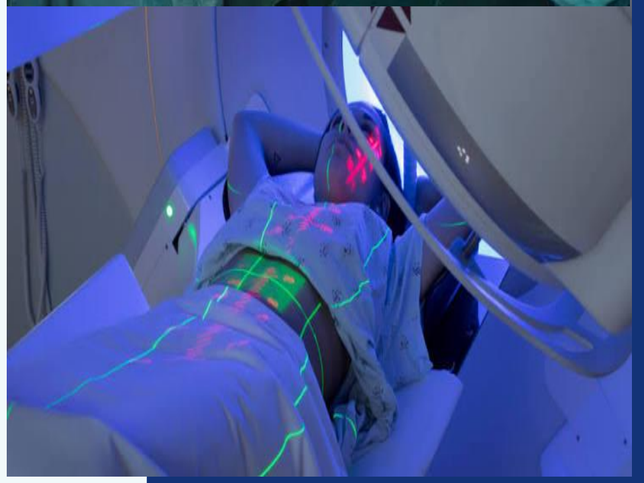
Bishop AJ, Landry JP, Roland CL, et al. Cancer. 2020;126(14):3265-3273.; Bishop AJ, Zarzour MA, Ratan R, et al. International Journal of Radiation Oncology, Biology, Physics. 2019;103(5):1167-1174; Bates JE, Morris CG, Iovino NM, et al. International Journal of Radiation Oncology, Biology, Physics. 2018;100(4):997-1003.

KEY PRINCIPLES FOR LOCAL CONTROL

6. Recurrence risk stratification should guide treatment modality selection

Clinical predictors

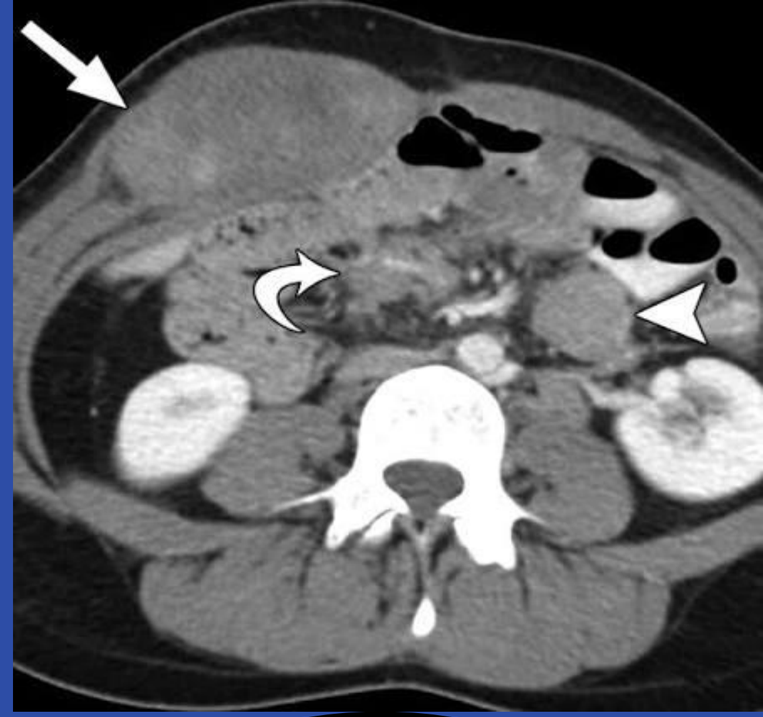
- Extremity location → **RT** > surgery
- Recurrent disease → **RT** (LCR ~80%) > re-excision (LCR 47%)
- Age ≤30 → **systemic therapy** > RT/surgery
- Size >10 cm → **systemic therapy** > RT > surgery
- CTNNB1 S45F mutation → **RT or systemic therapy** over surgery

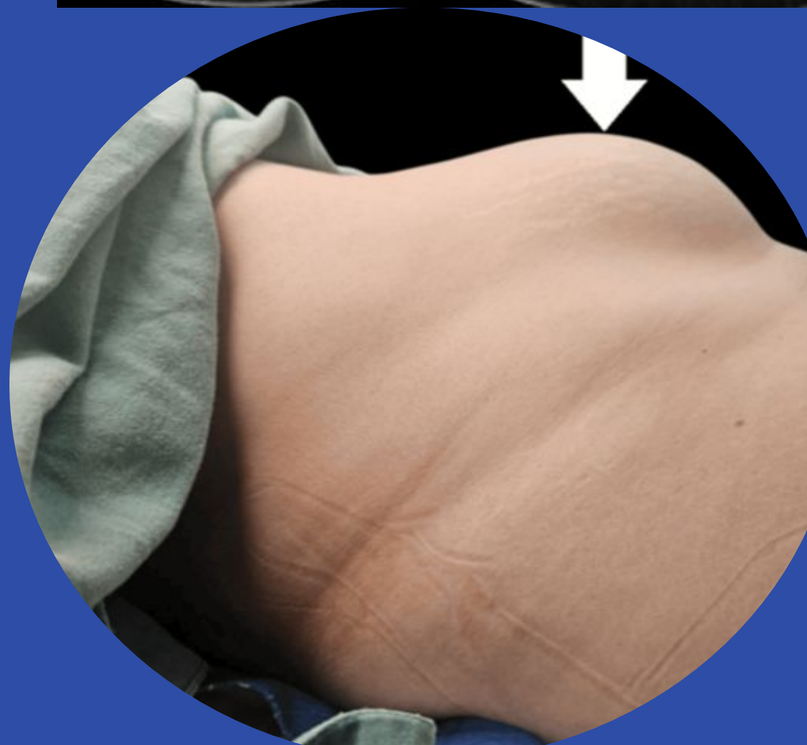


Crago AM, Denton B, Salas S, et al. Annals of Surgery. 2013;258(2):347-53; Bishop AJ, Landry JP, Roland CL, et al. Cancer. 2020;126(14):3265-3273; Nishida Y, Hamada S, Kawai A, et al. Cancer Science. 2020;111(8):2935-2942; Peng Y, Liu S, Li Y, et al. Frontiers in Oncology. 2025;15:1677325; Pinto FFE, Mello CAL, Nakagawa SA, et al. Clinical Orthopaedics and Related Research. 2023;481(10):1978-1989.

CASE 3

A 25y/F presents with a recurrent 12 cm desmoid tumor of the anterior abdominal wall. She was initially managed with active surveillance, then progressed on sorafenib after 12 mos of treatment. Now with worsening pain and abdominal wall deformity.



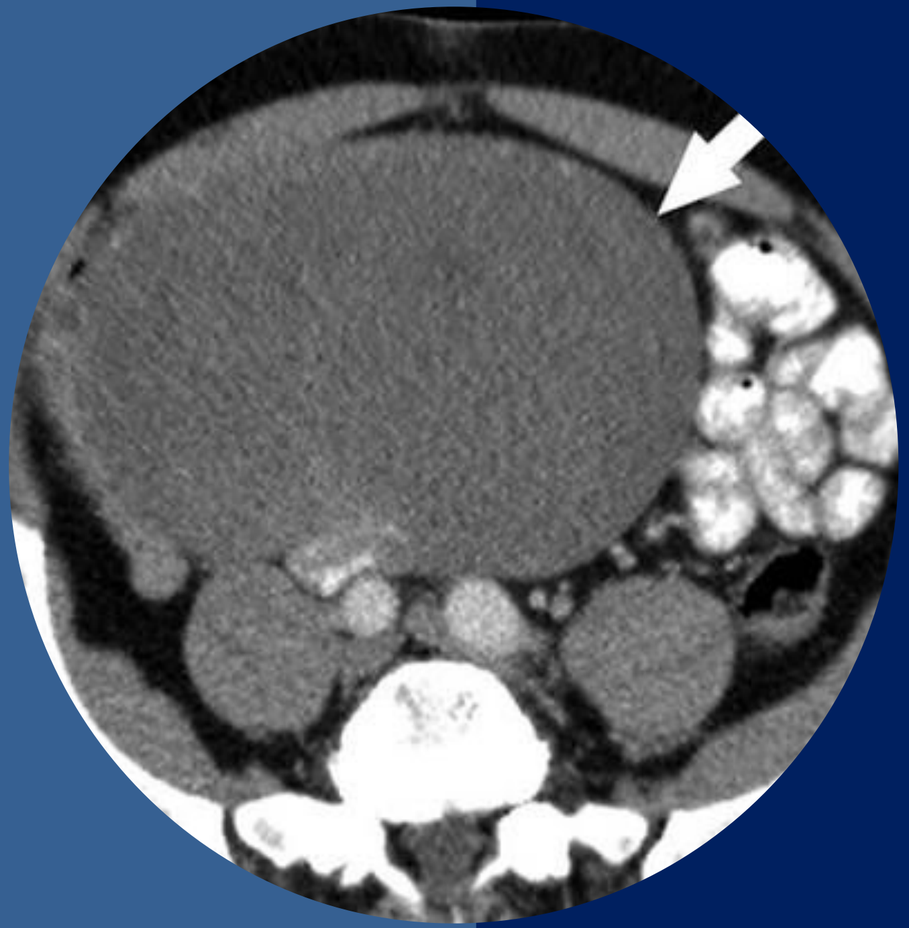


- ✔ *Wide local excision performed with R0 margin*
- ✔ *observation with imaging per NCCN guidelines every 3–6 months for 3 years, then every 6 months to complete 5 years, then annually.*

CASE 4

A 25y/F with a rapidly growing 12 cm pelvic desmoid causing ureteral obstruction with renal insufficiency and pelvic pain.

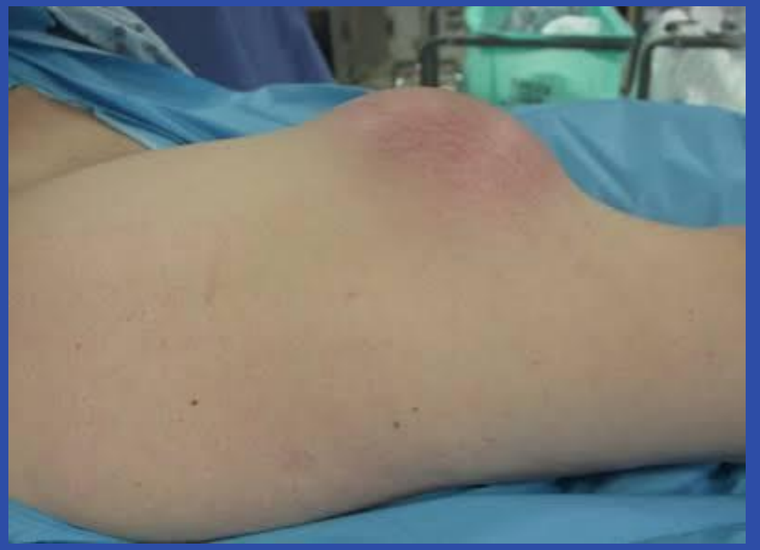
✔ Surgery

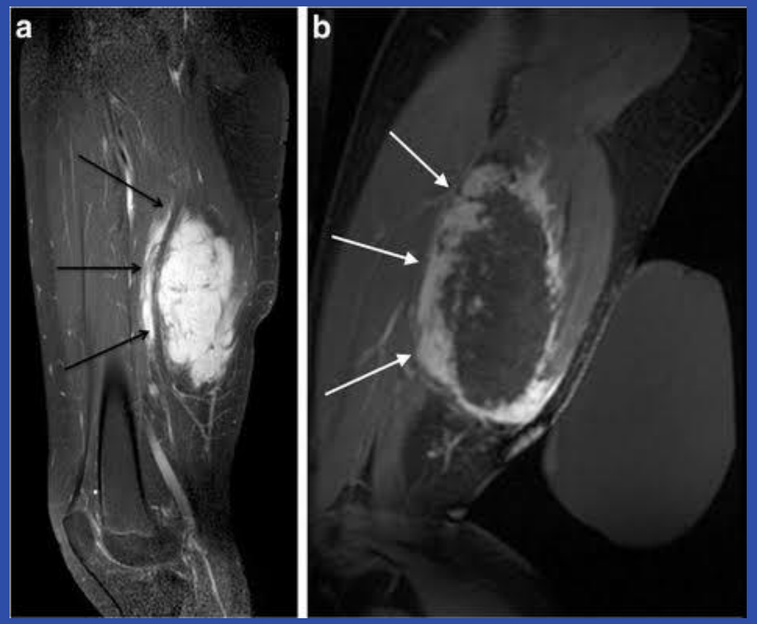


CASE 5

A 40y/F with a recurrent 10 cm desmoid tumor of the thigh. She was initially managed with surgery (R1 resection) 2y ago. She progressed and was started on Nirogacestat 8mos ago with continued worsening of pain and deformity.

✔ *Definitive XRT*



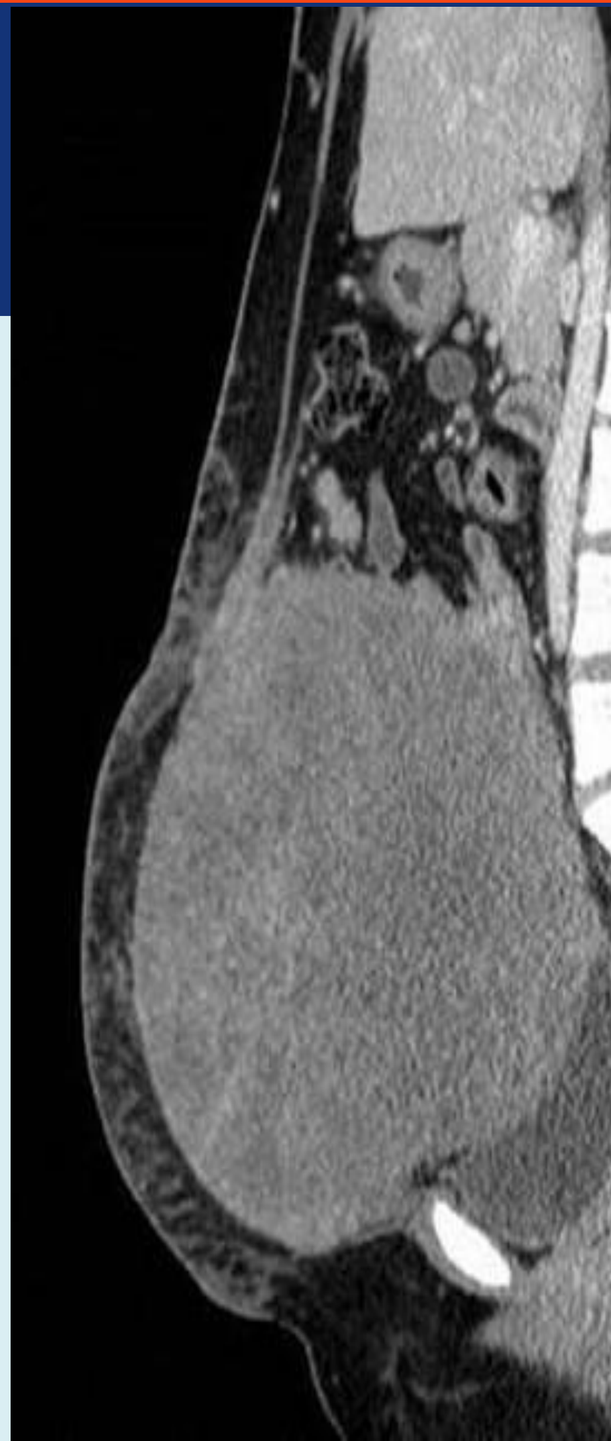


TREATMENT PRIORITIZATION

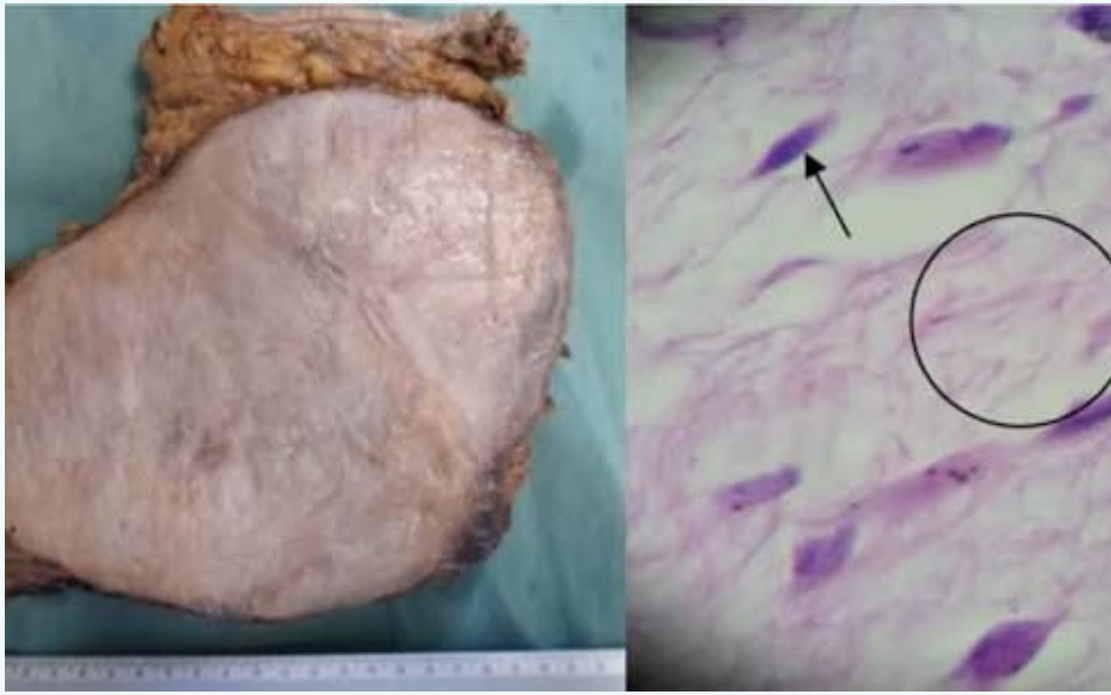
Clinical Scenario	Preferred Approach
FAP, abdominopelvic	Systemic therapy
Age ≤30, any site	Systemic therapy
Mesenteric, non-emergent	Systemic therapy
Mesenteric, acute complication	Surgery
Abdominal wall, resectable	Surgery
Deep extremity	Definitive RT
Head/neck	Definitive RT
Recurrent after prior surgery	Definitive RT
R1 margins after surgery	Observation (preferred) or Adjuvant RT
R2 margins after surgery	Definitive RT or systemic therapy

TAKE AWAY POINTS

1. **WATCH IT** when it's behaving.
2. **DRUG IT** when it's progressing or causing trouble.
3. **ZAP IT** when it matters and surgery is costly.
4. **WHACK IT** *only* when you can remove it without creating a bigger problem.



QUESTIONS ?



Thank you for your attention.