Desmoid Fibromatosis and Dermatofibrosarcoma Protuberans

8

Ricky Jrearz, Samir Fasih, Brendan C. Dickson, Abha A. Gupta, and Rebecca A. Gladdy

Introduction

Desmoid tumors (DTs, also known as desmoid-type fibromatosis) and dermatofibrosarcoma protuberans (DFSP) are rare mesenchymal neoplasms of fibroblastic/myofibroblastic derivation.

DT can be locally invasive, but has no metastatic potential. They account for 0.03% of all neoplasms with an annual incidence of 2–4 per 1,000,000 individuals [3, 10, 37]. The peak age of presentation is between 30 and 40 years of age. In contrast to its superficial counterpart, palmer/planter fibromatosis, DT typically occurs in the deep soft tissues. Most desmoids arise sporadically, although some may be associated with trauma or pregnancy. Approximately 5–10% of desmoids occur in patients that have familial adenomatous polyposis (FAP); 10–20% of FAP patients will develop DT [52]. Nuchal fibromas (Gardner's syndrome) can occasionally transform into desmoids [53].

R. Jrearz
General Surgical Oncology, University of Toronto, Toronto, ON, Canada

S. Fasih
Medical Oncology, University of Toronto, Toronto, ON, Canada
e-mail: samir.fasih@uhn.ca

B. C. Dickson
Department of Laboratory Medicine and Pathobiology, University of Toronto, Toronto, ON, Canada
e-mail: BDickson@mtsinai.on.ca

A. A. Gupta
Division of Medical Oncology, University of Toronto, Toronto, ON, Canada
e-mail: abha.gupta@sickkids.ca

R. A. Gladdy (✉)
Department of Surgery, University of Toronto, Toronto, ON, Canada
e-mail: rgladdy@mtsinai.on.ca

F. C. Wright et al. (eds.), *Surgical Oncology Manual*,
https://doi.org/10.1007/978-3-030-48363-0_8

DFSP is a soft tissue neoplasm that is locally invasive and a subset have metastatic potential. They account for less than 0.1% of all malignancies, but are the most common sarcoma of the skin [54]. The annual incidence of DFSP is 1–4 per 1,000,000 individuals [6, 7]. It is most commonly seen between 20 and 50 years of age. Most DFSPs are low grade tumors. However, fibrosarcomatous transformation (FS-DFSP) occurs in 5–15% of tumors. FS-DFSP is an intermediate grade sarcoma that has a 10–15% chance of metastasis [8]. The presence of a positive surgical margin significantly increases the risk of local recurrence in DFSP [9, 24, 40].

Histology and Molecular Genetics

DT

DTs are characterized histologically by infiltrative fascicles of monomorphic spindle cells. The majority (85%) of sporadic tumors contain mutations in exon 3 of the CTNNB1 gene which encodes for β-catenin [1, 2, 22]. Recent studies have shown that many of the so-called "wild-type" (15%) DT will actually contain mutations in *CTNNB1* with deeper sequencing [55]. Familial DT and a subset of sporadic DT display mutations in the adenomatous polyposis coli (*APC*) gene [56, 57].

DFSP

DFSP originates superficially in the dermis or subcutis. Histologically it is characterized by storiform whorls of monomorphic spindle cells [58]. FS-DFSP is associated with architectural transformation into a herringbone pattern, and greater pleomorphism and mitotic activity; frequently, these tumors will also lose expression of CD34, an immunohistochemical marker typical of DFSP. Greater than 90% of tumors exhibit a translocation resulting in *COL1A1-PDGFB* gene fusion [5], which renders the tumor sensitive to imatinib.

Staging and Prognosis (See Table 8.1)

DT

DT is not included in the most recent American Joint Committee on Cancer AJCC 8th edition staging system as it is considered a benign neoplasm. Staging systems

Table 8.1 Prognosis of DT and DFSP

	Prognosis [9–17]	
	5-year overall survival (OS) (%)	5-year local recurrence (LR) (%)
DT	76[a] – 100	20–47
DFSP	98–100	3–25

[a]Intra-abdominal DT in FAP patients – deaths due to complications of DT treatment or other causes

for intra-abdominal DT in the context of FAP has been proposed based on size, symptoms, growth, and complications [59].

DFSP

The AJCC 8th edition is the current recommended staging system for DFSP. Staging differs based on location of the primary tumor; extremities and trunk vs. head and neck.

Management (See Table 8.2)

DT

There has been a paradigm shift in the management of DT from upfront surgical resection to upfront active surveillance [18, 19, 25, 65]. A large recent prospective French

Table 8.2 Management, workup, and follow-up for DT

Workup	Management	Follow-up
History and physical exam Imaging: MRI preferred for abdominal wall, trunk, and extremity (CT if MRI not available) CT for intra-abdominal lesions Investigations: Percutaneous core biopsy MCC discussion Consider colonoscopy to r/o FAP (higher risk in <40, multifocal, intra-abdominal/retroperitoneal DT, family hx of colon cancer)	Trial of active surveillance to assess growth rate (1–2 years) Ensure discontinuation of all exogenous estrogen (i.e., oral contraception) Consider active treatment if: Progression over at least 2 subsequent assessments Increase of symptom burden Disease close to critical structure (mesentery, head and neck) Initial medical treatment on progression: Intra-abdominal/retroperitoneal DT Head and neck, extremity, chest wall DT Abdominal wall DT Medical treatment options: Consider targeted agents[a] or cytotoxic chemotherapy[b] [26–31] Consider for a clinical trial or trial of NSAIDs[c] or antiestrogens[d] if the above options not possible Surgical resection can be considered at all DT sites if progression on medical treatment; the aim is for gross resection with preservation of function Radiotherapy can be first-line alternative in highly selective cases (age, comorbidities, etc.)	History and physical exam every 3–6 months to establish pattern of growth MRI or CT every 3–6 months for first 2 years If stabilization/regression ➔ active surveillance with annual MRI/physical exam Can consider US if demonstrated long-term stability In case of progression, consider medical or surgical treatment

ER/PR estrogen receptor/progesterone receptor, MCC multidisciplinary cancer conference, NSAIDs nonsteroidal anti-inflammatory drugs, US ultrasound, TKIs tyrosine kinase inhibitors

[a]For example, sorafenib, pazopanib

[b]For example, Methotrexate plus vinca alkaloid, doxorubicin, liposomal doxorubicin, dacarbazine

[c]For example, sulindac, indomethacin

[d]For example, tamoxifen, raloxifene, toremifene

study showed no difference in surgery vs. active surveillance in 2-year event-free survival [60]. Similar results have been observed in studies comparing initial active surveillance to upfront medical therapy [63]. Studies have demonstrated through multivariate analysis and predictive nomograms that age (<37), tumor site (non-abdominal wall), and tumor size (>7 cm) are independent risk factors for local recurrence after resection [20, 21]. Specific mutations in exon 3 such as S45T have also been associated with increased risk of recurrence after resection [22, 23]; whether this mutation is associated with tumor progression during active surveillance is currently being prospectively studied.

Special Notes

Recurrence:
- Recurrent DT should be managed in a similar fashion to primary DT with consideration to previous therapies, tumor location, and biology
- Patients with multiple recurrences after adequate resections should be considered for medical therapy

Margins:
- The aim of surgical resection should be negative histologic margins with preservation of function. Despite this, 25% of cases with negative margins will recur locally.
- The evidence is controversial on margin status and recurrence. Therefore, unlike sarcomas, positive margins should be followed and not necessarily re-excised [65].

Imaging:
- A baseline MRI and assessment of T2 hyperintensity within the tumor may be predictive of desmoid progression during active surveillance [64].

Medical Therapy:
Several options and considerations for medical therapy are listed in Table 8.3. The discussion of pros/cons of various therapies with the patient will aid in decision-making.

Regression:
- Spontaneous regression has been reported in 19–28% of cases [20, 32]; this is seen predominately in abdominal wall DT.

FAP:
- Younger patients (<40 years) with a new diagnosis of DT should be screened for FAP with colonoscopy.
- Intra-abdominal or retroperitoneal DT, multifocal disease, and positive family history are associated with FAP.

Table 8.3 Type of medical therapy for DT

Type of therapy	Number of patients	Objective response rates	Considerations	Reference
Targeted therapy			Total duration of therapy remains unclear	Gounder MM; 2018 [41] Maud T; 2018 [42] Chugh R; 2010 [43]
1. Sorafenib 2. Pazopanib 3. Imatinib	87 72 51	33% 37% 5%		
Cytotoxic chemotherapy			1. Intravenous therapy, prolonged course 2. Hair loss with doxorubicin	Azzarelli A; 2001 [44] Patel S; 1993 [45] Constantinidou A; 2010 [46]
1. Methotrexate/ vinblastine or vinorelbine 2. Doxorubicin/ dacarbazine 3. Pegylated liposomal doxorubicin (PLD)	30 11 14	40% 54% 33%		
Nonsteroidal anti-inflammatory drugs (NSAIDs)			May be considered in patients with FAP	Nishida Y; 2012 [47] Tsukada K; 1992 [48]
1. Meloxicam 2. Sulindac	20 14	40% 57%		
Antiestrogen therapy			Use with caution in premenopausal women due to ovarian cyst development	Brooks M; 1992 [49] Fiore M; 2011 [50]
1. Toremifene or tamoxifen 2. Toremifene	20 27	65% 26%		
Gamma-secretase inhibitors			Duration of therapy unclear. Diarrhea can be problematic.	Kummar S; 2017 [51]
1. Nirogacestat	17	29%		

- FAP patients with DT have a higher rate of recurrence and nonsurgical options should be strongly considered prior to resection [11].

Pregnancy:

- Disease progression often occurs during pregnancy but can generally be managed safely with close observation with serial US in most cases [33].
- The risk of adverse obstetric events is not increased in DT [33].
- DT should not be a contraindication to future pregnancies [33].
- Tumors arise in previous caesarian-section sites.

Table 8.4 Workup, management, and follow-up for DFSP

Workup	Management	Follow-up [62]
History and physical exam Investigations: Percutaneous or excisional biopsy MRI in selected cases to assess extent/depth/multifocality Routine staging not indicated unless: Clinical signs of metastases Recurrent disease Fibrosarcomatous transformation MCC discussion	Surgical resection Wide local excision (WLE) 2–3 cm Plastic surgery consultation if primary closure is anticipated to be challenging[a] Medical treatment: Imatinib (inoperable tumors or preoperative downstaging to preserve function, limit extent of soft tissue reconstruction)	Low risk DFSP (wide R0, no FS changes) Routine self-examination Np formal follow-up Low risk DFSP (close R0, R1, no FS, difficult to examine locations, i.e., axilla, perineum, etc.) Annual clinical exam × 10 years No routine imaging High risk DFSP (FS changes) Clinical exam + CXR q3–6 months × 2–3 years then annually × 10 years total

[a]Approximately 30% of reconstructions require plastic surgery techniques [35]

- 17% of pregnancy induced DT experience spontaneous regression [33].
- Discontinue the use of exogenous hormones as they can impact growth.

Radiation Therapy:
- In selected circumstances such as age, patient intolerance/preference to surgical/medical therapy, comorbidities, rapidly growing lesion threatening vital structures (head and neck, limb salvage, etc.), radiation can be considered in as a treatment for DT [65].
- May be considered in patients with multiple local recurrences or unresectable disease, but MCC discussion should be conducted prior to treatment [34].

Primary DFSP (See Table 8.4)

The primary treatment modality for localized DFSP is surgical resection with negative margins. Local recurrence has been associated with depth of invasion, anatomical location, margin status [40], and FS status [61].

Special Notes

Imatinib:
- Consider neoadjuvant imatinib for large, borderline resectable, or complex recurrent lesions in order to downsize prior to surgery.
- Can also use imatinib to help with function preservation.

Resection:

- Wide local excision is preferred, 2–3 cm in non-critical areas. Margins may be limited in facial resections.
- Mohs micrographic surgery (MMS) is not recommended in the treatment of DFSP.

Margins:
- Negative histologic margins should be the goal of surgical resection (R0).
- The ideal planned margins are 2–3 cm radially in the dermis with fascial clearance deep to tumor.

Reconstruction:
- Delayed definitive reconstruction for complex resections until margin status is confirmed can be considered in some cases.

Recurrence:
- Treat with surgical resection if possible.
- Local recurrence rates have been reported between 1% and 22% [35, 40, 61].

Lymph Nodes:
- Assessment of regional lymph nodes is not required in the absence of clinically or radiologically apparent disease.

FS-DFSP:
- Approximately 10–15% of DFSP contain fibrosarcomatous progression that behaves more aggressively (i.e., widespread metastasis) than classic DFSP [36].

Radiation Therapy:
- May be useful for recurrent tumors when surgical morbidity limits ability to re-excise. Delivery of radiation is considered only after multidisciplinary discussion [62].

Metastatic DFSP (See Table 8.5)

Special Notes

Metastases
- Most commonly occur in lungs.
- Can also occur in pancreas, liver, and bone [61].

Medical Therapy:
- Imatinib can be used for unresectable, recurrent, or metastatic disease.
- >90% of DFSP are characterized by the t(17;22) chromosomal translocation and may be susceptible to targeted platelet-derived growth factor inhibition [38].
- Response rate has been reported at 50%.

Table 8.5 Workup, management, and follow-up for metastatic DFSP

Workup	Management	Follow-up
History and physical exam CT chest/abdo/pelvis Case discussion at MCC	Systemic therapy with imatinib Consider resection (lung, liver) if: R0 resection can be achieved Favorable biology (slow growing, long disease-free interval) Primary tumor is resected or resectable Isolated/few metastases Radiation therapy for unresectable, progressive, or bony metastases	As clinically warranted

- There is limited data on cytotoxic chemotherapy and its utility in DFSP; when transformation has occurred, traditional cytotoxic therapies may be considered in the palliative setting.

Landmark Publications

There are limited prospective randomized control trials (RCT) on the management of DT (see Table 8.6) or DFSP (see Table 8.7). Management is largely dictated by consensus statements formed by expert, high-volume centers [65].

DT

DFSP

Referring to Medical Oncology

DT

1. Patients with progressive or recurrent disease.
2. Multifocal disease.
3. FAP patients.

Table 8.6 Landmark publications for DT

Study	Methods	Results
Burtenshaw et al. [15]	Retrospective review $n = 213$ Abdo wall DTs Primary DT with no prior treatment (Group A) vs. previously resected DT (Group B) vs. recurrent DT (Group C)	Abdo wall (48%) or intra-abdominal (43%) Group A ($n = 176$) 93% of patients who underwent observation alone (54/58) had stable disease or spontaneous regression 38% (67) overall required surgery (primary treatment or second line after observation/medical tx) 24% recurrence after surgery (med f/u 22 months) Abdo wall DT >7 cm and intra-abdo DT more likely to recur Group B ($n = 19$) 95% managed with upfront observation despite 63% having had R1/R2 resection Group C ($n = 18$) 61% managed non-operatively
Gronchi et al. [39]	Retrospective review $n = 203$ All patients treated with surgical resection All patients had complete macroscopic resection	DFS better in primary disease than recurrent disease (76% vs. 59% at 10 years)
Nieuwenhuis Et al. [4]	Retrospective population-based review $n = 519$ All Dutch patients with DT over a 10-year period	7.5% of DT associated with FAP factors identified with FAP-associated DT: Male, age < 60, intra-abdominal location
Gounder et al. [41]	Phase III RCT $n = 87$ Progressive, recurrent, or symptomatic DT Sorafenib vs. placebo	2-year PFS 81% vs. 36% Of note, objective response in placebo arm of 30%, consistent with spontaneous regression rates
Penel et al. [60]	Prospective randomized study Initial surgery vs. initial observation $n = 771$	Overall 2-year EFS 53% vs. 58% Favorable location DT (abdo wall, intra-abdo, breast, digestive viscera, lower limb) similar 2-year EFS (70% vs. 63%) Unfavorable location (chest wall, upper limb, head and neck) 2-year EFS significantly better in observation group (25% vs. 52%)
Salas et al. [20]	Multi-institution retrospective review $n = 426$ All patients had sporadic DT	Subgroup of patients treated with wait-and see (policy 19% spontaneous remission) Age, tumor size, tumor site (extra-abdominal) predictive of PFS on multivariate analysis

RT radiation therapy, *DFS* disease-free survival, *PFS* progression-free survival, *EFS* event-free survival

Table 8.7 Landmark publications for DFSP

Study	Methods	Results
Bowne et al. [9]	Retrospective review *N* = 159 All patients treated with WLE 16% had FS-DFSP	Positive margins and FS-DFSP predictors of poor outcome 2% of patients developed metastases and died of disease
Fiore et al. [16]	Retrospective review *N* = 218 All patients treated with WLE	Low rate of LR at 5 years (3%) Rate of distant metastases at 5 years (2%)
Huis in't Veld et al. [61]	Retrospective review *N* = 357 87.5% treated with WLE 11.5% treated with MMS 17.4% presented with local recurrence 11.4% had FS-DFSP	LR rate 22.7% Median time to recurrence 55.5 months FS-DFSP and positive margins prognostic for recurrence 61.7% of LR identified by self-examination Rate of distant metastases 1.1% at median time of 68 months
Fields et al. [40]	Retrospective review *N* = 244 All patients treated with WLE	Depth and margin status predictive of DFS Low LR with WLE (92% DFS at 5 years)

FS-DFSP DFSP with fibrosarcomatous transformation, *DFS* disease-free survival, *WLE* wide local excision, *LR* local recurrence

DFSP

1. All patients with metastatic, recurrent, or unresectable disease.
2. Patients considered for neoadjuvant therapy to downstage bulk of disease or to preserve function.

Referring to Radiation Oncology

DT

1. Patients with multiple local recurrences for consideration of combined pre- or postoperative treatment.
2. Patients with unresectable disease that has progressed on medical therapy.
3. Patients with progressive disease not amenable to frontline medical or surgical therapy due to comorbidities/preferences.

DFSP

1. Patients with positive margins after maximal surgical resection.
2. Patients with DFSP-FS progression not amenable to surgery.
3. Patients with disease not amenable to frontline medical or surgical therapy due to comorbidities/preferences.

Referring to Multidisciplinary Cancer Conference (MCC)

DT

All cases should be discussed.

DFSP

All cases should be discussed.

Toronto Pearls

DT

- The biology and behavior of DT can be greatly varied between growth, stabilization, or regression. Non-aggressive interventions including active observation are increasingly employed in DT patients. Systemic therapy choices must balance quality of life, drug access, and symptoms.
- Percutaneous core biopsies should ideally be done with image guidance at sarcoma centers with specialized radiologists. A minimum of 4 good quality tissue cores should be obtained for accurate diagnosis.
- Pathology review should be performed by expert pathologists experienced in sarcoma.
- DT is commonly seen in young patients and has no metastatic potential. Surgical resection, if undertaken, should focus on preservation of function to avoid significant morbidity.
- DT is rarely a cause for mortality except in large, recurrent intra-abdominal tumors (particularly in FAP). Consequently, a multidisciplinary approach should be considered before embarking on extensive surgical resection.

DFSP

- Pathology review should be performed by expert pathologists experienced in sarcoma with access to appropriate molecular diagnostic techniques for accurate diagnosis.
- Definitive treatment is surgical resection in DFSP. A wide local excision should be performed to minimize local recurrence.
- Patients with DFSP-FS progression should be followed closely as they have a higher propensity for metastatic disease.
- Consider the use of imatinib in the neoadjuvant setting for locally advanced disease or in the management of metastatic disease.

References

1. Fletcher CDM, Bridge JA, Hogendoorn PCW, Mertens F. WHO classification of tumours of soft tissue and bone. 4th ed. Lyon: IARC; 2013.
2. Huss S, Nehles J, Binot E, et al. β-Catenin (CTNNB1) mutations and clinicopathologic features of mesenteric desmoid-type fibromatosis. Histopathology. 2013;62(2):294–304.
3. Reitamo JJ, Hayry P, Nykyri E, et al. The desmoid tumor I: incidence, sex-, age- and anatomical distribution in the Finnish population. Am J Clin Pathol. 1982;77(6):665–73.
4. Nieuwenhuis MH, Casparie M, Mathus-Vliegen LM, et al. A nation-wide study comparing sporadic and familial adenomatous polyposis-related desmoid-type fibromatoses. Int J Cancer. 2011;129:256–61.
5. Patel KU, Szabo SS, Hernandez VS, et al. Dermatofibrosarcoma protuberans COL1A1-PDGFB fusion is identified in virtually all dermatofibrosarcoma protuberans cases when investigated by newly developed multiplex reverse transcription polymerase chain reaction and fl uorescence in situ hybridization assays. Hum Pathol. 2008;39:184–93.
6. Koh CK, Ko CB, Bury HP, et al. Dermatofibrosarcoma protuberans. Int J Dermatol. 1995;34(4):256–60.
7. Criscione VD, Weinstock MA. Descriptive epidemiology of dermatofibrosarcoma protuberans in the United States, 1973 to 2002. J Am Acad Dermatol. 2007;56(6):968–73.
8. Stacchiotti S, Pedeutour F, Negri T, et al. Dermatofibrosarcoma protuberans-derived fibrosarcoma: clinical history, biological profile and sensitivity to imatinib. Int J Cancer. 2011;129:1761–72.
9. Bowne WB, Antonescu CR, Leung DH, et al. Dermatofibrosarcoma protuberans: a clinicopathologic analysis of patients treated and followed at a single institution. Cancer. 2000;88(12):2711–20.
10. Quintini C, Ward G, Shatnawei A, et al. Mortality of intra-abdominal desmoid tumors in patients with familial adenomatous polyposis: a single center review of 154 patients. Ann Surg. 2012;255:511–6.
11. Clark SK, Neale JC, Landgrebe JC, et al. Desmoid tumours complicating familial adenomatous polyposis. Br J Surg. 1999;86:1185–9.
12. Spear MA, Jennings LC, Mankin HJ, et al. Individualizing management of aggressive fibromatoses. Int J Radiat Oncol Biol Phys. 1998;40(3):637–45.
13. Lev D, Kotilingam D, Wei C, et al. Optimizing treatment of desmoid tumors. J Clin Oncol. 2007;25(13):1785–91.
14. Peng PD, Hyder O, Mavros MN, et al. Management and recurrence patterns of desmoids tumors: a multi-institutional analysis of 211 patients. Ann Surg Oncol. 2012;19:4036–42.

15. Burtenshaw SM, Cannell AJ, Mcalister ED, Siddique S, Kandel R, Blackstein ME, et al. Toward observation as first-line management in abdominal desmoid tumors. Ann Surg Oncol. 2016;23(7):2212–9.
16. Fiore M, Miceli R, Mussi C, et al. Dermatofibrosarcoma protuberans treated at a single institution: a surgical disease with a high cure rate. J Clin Oncol. 2005;23(30):7669–75.
17. Chang CK, Jacobs IA, Salti GI. Outcomes of surgery for dermatofibrosarcoma protuberans. Eur J Surg Oncol. 2004;30:341–5.
18. Bonvalot S, Edlweny H, Haddad V, et al. Extra-abdominal primary fibromatosis: aggressive management could be avoided in a subgroup of patients. Eur J Surg Oncol. 2008;34:462–8.
19. Fiore M, Rimareix F, Mariani L, et al. Desmoid-type fibromatosis: a front-line conservative approach to select patients for surgical treatment. Ann Surg Oncol. 2009;16:2587–93.
20. Salas S, Dufresne A, Bui B, et al. Prognostic factors influencing progression-free survival determined from a series of sporadic desmoid tumors: a wait-and-see policy according to tumor presentation. J Clin Oncol. 2011;29(26):3553–8.
21. Crago AM, Denton B, Salas S, et al. A prognostic nomogram for prediction of recurrence in desmoid fibromatosis. Ann Surg. 2013;258(2):347–53.
22. Lazar AJF, Tuvin D, Hajibashi S, et al. Specific mutations in the β-catenin gene (CTNNB1) correlate with local recurrence in sporadic desmoid tumors. Am J Pathol. 2008;173(5):1518–27.
23. Colombo C, Miceli R, Lazar AJ, et al. CTNNB1 45F mutation is a molecular prognosticator of increased postoperative primary desmoid tumor recurrence. Cancer. 2013;119:3696–702.
24. Cates JM, Stricker TP. Surgical resection margins in desmoid-type fibromatosis: a critical reassessment. Am J Surg Pathol. 2014;38(12):1707–14.
25. Gronchi A, Colombo C, Le Pechoux C, et al. Sporadic desmoid-type fibromatosis: a stepwise approach to a non-metastasising neoplasm – a position paper from the Italian and the French sarcoma group. Ann Oncol. 2014;25:578–83.
26. Janinis J, Patriki M, Vini L, et al. The pharmacological treatment of aggressive fibromatosis: a systematic review. Ann Oncol. 2003;14:181–90.
27. Garbay D, Cesne AL, Penel N, et al. Chemotherapy in patients with desmoid tumors: a study from the French sarcoma group (FSG). Ann Oncol. 2012;23:182–6.
28. de Camargo VP, Keohan ML, D'Adamo DR, et al. Clinical outcomes of systemic therapy for patients with deep fibromatosis (desmoid tumors). Cancer. 2010;116(9):2258–65.
29. Gega M, Yanagi H, Yoshikawa R, et al. Successful chemotherapeutic modality of doxorubicin plus dacarbazine for the treatment of desmoid tumors in association with familial adenomatous polyposis. J Clin Oncol. 2006;24(1):102–5.
30. Heinrich MC, McArthur GA, Demetri GD, et al. Clinical and molecular studies of the effect of Imatinib on advanced aggressive fibromatosis (desmoid tumor). J Clin Oncol. 2006;24(7):1195–203.
31. Gounder MM, Lefkowitz RA, Keohan ML, et al. Activity of Sorafenib against desmoid tumor/deep fibromatosis. Clin Cancer Res. 2011;17:4082–90.
32. Bonvalot S, Ternes N, Fiore M, et al. Spontaneous regression of primary abdominal wall desmoid tumors: more common than previously thought. Ann Surg Oncol. 2013;20:4096–102.
33. Fiore M, Coppola S, Cannell AJ, et al. Desmoid-type fi bromatosis and pregnancy: a multiinstitutional analysis of recurrence and obstetric risk. Ann Surg. 2014;259:973–8.
34. Gluck I, Griffith KA, Biermann JS, et al. Role of radiotherapy in the management of desmoid tumors. Int J Radiat Oncol Biol Phys. 2011;80(3):787–92.
35. Farma JM, Ammori JB, Zager JS, et al. Dermatofibrosarcoma protuberans: how wide should we resect? Ann Surg Oncol. 2010;17:2112–8.
36. Mendenhall WM, Zlotecki RA, Scarborough MT. Dermatofibrosarcoma protuberans. Cancer. 2004;101:2503–8.
37. Shields CJ, Winter DC, Kirwan WO, Redmond HP. Desmoid tumours. Eur J Surg Oncol. 2001;27:701–6.
38. McArthur GA, Demetri GD, van Oosterom A, et al. Molecular and clinical analysis of locally advanced dermatofibrosarcoma protuberans treated with imatinib: imatinib target exploration consortium study B2225. J Clin Oncol. 2005;23(4):866–73.

39. Gronchi A, Casali PG, Mariani L, et al. Quality of surgery and outcome in extra-abdominal aggressive fibromatosis: a series of patients surgically treated at a single institution. J Clin Oncol. 2003;21(7):1390–7.
40. Fields RC, Hameed M, Qin L, et al. Dermatofibrosarcoma protuberans (DFSP): predictors of recurrence and the use of systemic therapy. Ann Surg Oncol. 2011;18:328–36.
41. Gounder MM, Mahoney MR, Van Tine BA, Ravi V, Attia S, Deshpande HA, et al. Sorafenib for advanced and refractory desmoid tumors. N Engl J Med. 2018;379(25):2417–28.
42. Toulmonde M, Ray-Coquard IL, Pulido M, Andre T, Isambert N, Chevreau C, et al. DESMOPAZ pazopanib (PZ) versus IV methotrexate/vinblastine (MV) in adult patients with progressive desmoid tumors (DT) a randomized phase II study from the French Sarcoma Group. J Clin Oncol. 2018;36(15_suppl):11501.
43. Chugh R, Wathen JK, Patel SR, Maki RG, Meyers PA, Schuetze SM, et al. Efficacy of imatinib in aggressive fibromatosis: results of a phase II multicenter Sarcoma Alliance for Research through Collaboration (SARC) trial. Clin Cancer Res. 2010;16(19):4884–91.
44. Azzarelli A, Gronchi A, Bertulli R, Tesoro JD, Baratti D, Pennacchioli E, et al. Low-dose chemotherapy with methotrexate and vinblastine for patients with advanced aggressive fibromatosis. Cancer. 2001;92(5):1259–64.
45. Patel SR, Evans HL, Benjamin RS. Combination chemotherapy in adult desmoid tumors. Cancer. 1993;72(11):3244–7.
46. Constantinidou A, Jones RL, Scurr M, Al-Muderis O, Judson I. Advanced aggressive fibromatosis: effective palliation with chemotherapy. Acta Oncol (Madr). 2011;50(3):455–61.
47. Nishida Y, Tsukushi S, Shido Y, Urakawa H, Arai E, Ishiguro N. Transition of treatment for patients with extra-abdominal desmoid tumors: Nagoya university modality. Cancers (Basel). 2012;4(1):88–99.
48. Tsukada K, Church JM, Jagelman DG, Fazio VW, McGannon E, George CR, et al. Noncytotoxic drug therapy for intra-abdominal desmoid tumor in patients with familial adenomatous polyposis. Dis Colon Rectum. 1992;35(1):29–33.
49. Edmonson JH, Ryan LM, Blum RH, Brooks JS, Shiraki M, Frytak S, et al. Randomized comparison of doxorubicin alone versus ifosfamide plus doxorubicin or mitomycin, doxorubicin, and cisplatin against advanced soft tissue sarcomas. J Clin Oncol. 1993;11(7):1269–75.
50. Fiore M, Colombo C, Radaelli S, Prestianni P, Sanfilippo R, Morosi C, et al. Activity of toremifene in sporadic desmoid-type fibromatosis. J Clin Oncol [Internet]. 2011;29(15_suppl):10033.
51. Kummar S, O'Sullivan Coyne G, Do KT, Turkbey B, Meltzer PS, Polley E, et al. Clinical activity of the γ-secretase inhibitor PF-03084014 in adults with desmoid tumors (aggressive fibromatosis). J Clin Oncol. 2017;35(14):1561–9.
52. Righetti AEM, Jacomini C, Parra RS, De Almeida ALNR, JJR R, Féres O. Familial adenomatous polyposis and desmoid tumors. Clinics. 2011;66(10):1839–42.
53. Allen PW, Hasan N, Thorburn M. Nuchal-type fibroma appearance in a desmoid fibromatosis. Am J Surg Pathol. 2001;25(6):828–9.
54. Mullen JT. Dermatofibrosarcoma protuberans. Surg Oncol Clin N Am. 2016;25(4):827–39.
55. Crago AM, Chmielecki J, Rosenberg M, Oconnor R, Byrne C, Wilder FG, et al. Near universal detection of alterations inCTNNB1and Wnt pathway regulators in desmoid-type fibromatosis by whole-exome sequencing and genomic analysis. Genes Chromosom Cancer. 2015;54(10):606–15.
56. Zreik RT, Fritchie KJ. Morphologic spectrum of desmoid-type fibromatosis. Am J Clin Pathol. 2016;145(3):332–40.
57. Salas S, Chibon F, Noguchi T, Terrier P, Ranchere-Vince D, Lagarde P, et al. Molecular characterization by array comparative genomic hybridization and DNA sequencing of 194 desmoid tumors. Genes Chromosom Cancer. 2010;49(6):560–8.
58. Choi JH, Ro JY. Cutaneous spindle cell neoplasms: pattern-based diagnostic approach. Arch Pathol Lab Med. 2018;142(8):958–72.

59. Church J, Berk T, Boman BM, et al. Staging intra-abdominal desmoid tumors in familial adenomatous polyposis: a search for a uniform approach to a troubling disease. Dis Colon Rectum. 2005;48(8):1528–34.
60. Penel N, Cesne AL, Bonvalot S, Giraud A, Bompas E, Rios M, et al. Surgical versus non-surgical approach in primary desmoid-type fibromatosis patients: a nationwide prospective cohort from the French Sarcoma Group. Eur J Cancer. 2017;83:125–31.
61. Eva A, In'T Veld H, Coevorden FV, Grünhagen DJ, Smith MJ, ACJV A, MWJM W, et al. Outcome after surgical treatment of dermatofibrosarcoma protuberans: is clinical follow-up always indicated? Cancer. 2019;125(5):735–41.
62. Gladdy RA, Wunder JS. Risk-stratified surveillance in dermatofibrosarcoma protuberans: less is more. Cancer. 2019;125(5):670–2.
63. Colombo C, Miceli R, Le Pechoux C, et al. Sporadic extra abdominal wall desmoid-type fibromatosis: surgical resection can be safely limited to a minority of patients. Eur J Cancer. 2015;51:186–92.
64. Cassidy MR, Lefkowitz RA, Long N, Qin L-X, Kirane A, Sbaity E, et al. Association of MRI T2 signal intensity with desmoid tumor progression during active observation. Ann Surg. 2018;271:748.
65. Kasper B, Gronchi A, et al. The management of desmoid tumours: A joint global consensus-based guideline approach for adult and paediatric patients. Desmoid Tumor Working Group. Eur J Cancer. 2020;127:96–107. https://doi.org/10.1016/j.ejca.2019.11.013. PMID: 32004793.