Role of Imaging in Management of Desmoid-type Fibromatosis: A Primer for Radiologists[1]

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Desmoid-type fibromatosis (DF) is a locally aggressive fibroblastic neoplasm that has variable clinical and biologic behaviors ranging from indolent tumors that can undergo spontaneous regression to aggressive tumors with a tendency toward local invasion and recurrence. The management of DF has evolved considerably in the last decade from aggressive first-line surgery and radiation therapy to systemic treatment (chemotherapy, hormonal therapy, and targeted therapy) and symptomatic local control (surgery and radiation therapy). Imaging plays an important role in each of these treatment settings. In surgical candidates, computed tomography (CT) and magnetic resonance (MR) imaging are the modalities of choice for assessing resectability and surgical planning. For evaluating recurrence, MR imaging is the modality of choice for extra-abdominal recurrence, whereas CT is the preferred modality for intra-abdominal recurrence. Signal intensity changes at MR imaging can be used to monitor the biologic behavior of certain DFs chosen for expectant management. Response to systemic treatment with anti-inflammatory agents, hormonal therapy (eg, tamoxifen), cytotoxic chemotherapy (eg, doxorubicin, vinblastine, methotrexate), and targeted therapy (eg, sorafenib), as well as to radiation therapy, can be assessed at CT by monitoring size and attenuation changes or at MR imaging by monitoring size, T2 signal intensity, and degree of enhancement. Several patterns of response can be seen at imaging. Imaging also helps in detecting complications associated with systemic therapy and radiation therapy.

Abbreviations: DF = desmoid-type fibromatosis, FAP = familial adenomatous polyposis, FDG = fluorodeoxyglucose, NCCN = National Comprehensive Cancer Network, RT = radiation therapy

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SA-CME LEARNING OBJECTIVES

After completing this journal-based SA-CME activity, participants will be able to:

- Illustrate common and uncommon imaging appearances of desmoid-type fibromatosis.
- Review the role of imaging in surgical and nonsurgical management of desmoid-type fibromatosis.
- Describe the patterns of tumor response at CT and MR imaging.

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Introduction

Desmoid-type fibromatosis (DF), also known as aggressive fibromatosis, is a locally aggressive fibroblastic neoplasm with no potential for metastasis. It can arise anywhere in the body. Its high tendency to recur after surgical resection makes DF an important cause of morbidity and, occasionally, mortality. DF is rare, with an estimated annual incidence of 2–4 new cases per million people, accounting for approximately 0.03% of all neoplasms and less than 3% of all soft-tissue tumors (1,2). DF frequently affects individuals between the ages of 15 and 60 years, with a peak incidence in the third and fourth decades of life. The vast majority of DF occurs sporadically; however, it may also occur in association with the hereditary syndrome familial adenomatous polyposis (FAP); the combination of FAP with DF is known as Gardner syndrome (3). DF can be classified, in accordance with its location, as extra-abdominal, intra-abdominal, or abdominal wall. The majority of DF is represented by sporadic extra-abdominal lesions, the most commonly involved sites being the extremities, head,

TEACHING POINTS

- During the past decade, there has been a paradigm shift in treatment, which has evolved from aggressive first-line therapy (surgery and radiation therapy [RT]) to expectant management, systemic treatment (chemotherapy, hormonal therapy, and/or targeted therapy), and symptomatic local management focused on the best functional result (surgery, RT). Hence, treatment stratification requires a multidisciplinary approach, with close collaboration between medical oncologists, surgeons, radiation oncologists, and radiologists. Imaging plays an important role in the management of DF.
- CT and MR imaging are the modalities of choice for assessing resectability and surgical planning. As DF does not metastasize, a whole-body staging workup is not required. Neurovascular structure encasement as well as invasion of the viscera and bones should be detectable and reported in this locally aggressive disease.
- MR imaging signal intensities may evolve on the basis of the phase of tumor.
- Because DF may have a relatively indolent course with low mortality, symptomatic improvement and absence of progression at imaging are the primary endpoints for outcome. Imaging plays an important role in the assessment of tumor response as well as in early detection of complications associated with systemic treatment.
- Patients with DF on systemic treatment are usually monitored with CT and MR imaging. Changes in DF size and attenuation should be assessed at CT, whereas size, T2 signal intensity, and degree of enhancement are relevant at MR imaging. Enhancement changes at CT are not easily appreciated.

neck, and chest wall/breast. They usually present as slow-growing painless or minimally painful soft-tissue masses. Intra-abdominal DF may occur sporadically or in association with FAP as Gardner syndrome; it is typically represented by slow-growing masses and can present with complications that can include intestinal obstruction and bowel ischemia. FAP-associated DF may be multifocal at both intra- and extra-abdominal sites (particularly the abdominal wall) (3) The abdominal wall is the most common location for pregnancy-associated DF (4) (Fig 1).

At pathologic examination, DF is grossly firm and white, resembling scar tissue. Histologically, DF is composed of long fascicles of bland, uniform fibroblasts with low cellularity, in a dense collagenous stroma (Fig 1). The cells lack nuclear and cytoplasmic features of malignancy; mitotic activity is sparse, and necrosis is absent. Sporadic DF and FAP-associated DF are histologically indistinguishable from each other (5). Understanding the pathologic appearance of DF is of considerable interest given the fact that imaging findings, particularly at MR imaging, closely reflect the histologic components (6). Immunohistochemistry can help confirm the diagnosis. The spindle cells are positive for smooth-muscle actin, and usually show nuclear staining for β_1-catenin (reflecting an underlying *CTNNB1* or *APC* mutation, resulting in nuclear accumulation of β_1-catenin). Nuclear immunoreactivity for β_1-catenin supports the diagnosis but is not pathognomonic for this disease because other entities, including superficial fibromatosis, low-grade myofibroblastic sarcomas, and solitary fibrous tumors, may also show nuclear staining for β_1-catenin (7–9). Furthermore, β_1-catenin negativity does not preclude a diagnosis of fibromatosis.

The clinical behavior of DF is not uniform, varying from indolent to aggressive, with some indolent tumors demonstrating spontaneous regression. The primary goal of treatment in DF is disease control, without appreciable functional impairment. Before 2000, radical surgical resection was the standard of care of DF. During the past decade, there has been a paradigm shift in treatment, which has evolved from aggressive first-line therapy (surgery and radiation therapy [RT]) to expectant management, systemic treatment, and symptomatic local management focused on the best functional result (surgery, RT) (8,10,11). Hence, treatment stratification requires a multidisciplinary approach, with close collaboration between medical oncologists, surgeons, radiation oncologists, and radiologists. Imaging plays an important role in the management of DF. In surgical candidates, imaging is key in assessing resectability and in detecting postsurgical complications and recurrences. The role of imaging in nonresectable tumors is to evaluate changes in size and/or morphology, detect complications, and assess the response to systemic treatments.

Although there are a number of studies describing the imaging features of DF, there is limited literature focused on the role of imaging during the course of treatment and expected post-therapy appearance. The purpose of this article is to provide a comprehensive review of imaging of DF, with a focus on the treatment-related aspects. We will briefly describe the multimodality imaging findings of aggressive fibromatosis, review the various treatment options, discuss in detail the role of imaging in both surgical and nonsurgical management, and review the various patterns of tumor response to nonsurgical therapies.

Imaging Features of DF

The most commonly employed imaging modalities for DF are computed tomography (CT) and magnetic resonance (MR) imaging, as well as ultrasonography (US) in selected cases. Plain radiography, skeletal scintigraphy, and positron emission tomography (PET)/CT have limited roles in the diagnosis and management of DF. Imaging characteristics of DF at various modali-

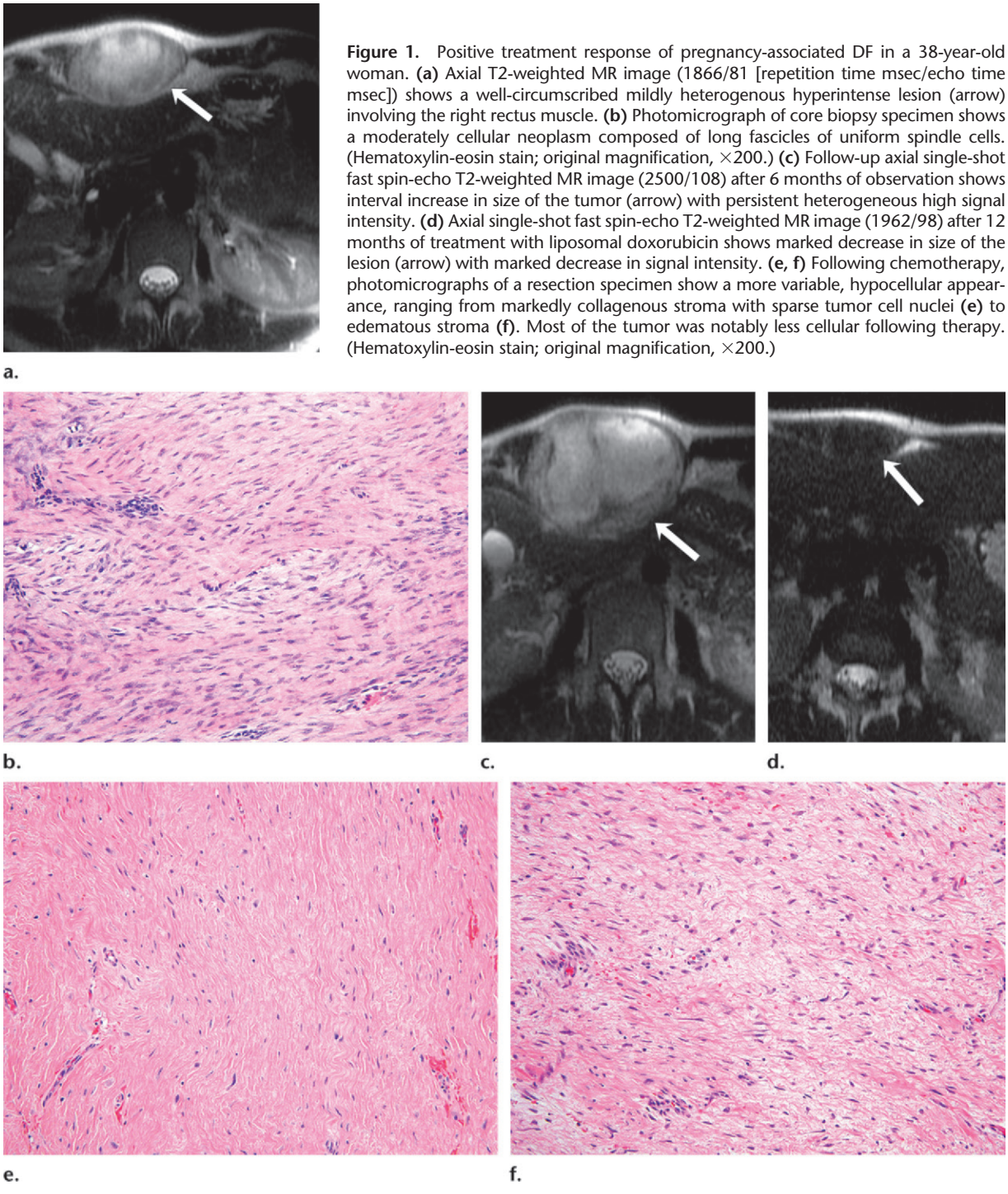
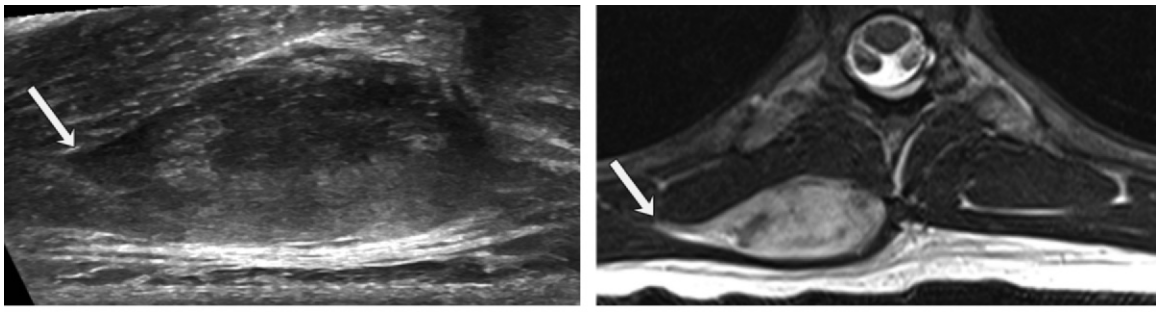


Figure 1. Positive treatment response of pregnancy-associated DF in a 38-year-old woman. **(a)** Axial T2-weighted MR image (1866/81 [repetition time msec/echo time msec]) shows a well-circumscribed mildly heterogenous hyperintense lesion (arrow) involving the right rectus muscle. **(b)** Photomicrograph of core biopsy specimen shows a moderately cellular neoplasm composed of long fascicles of uniform spindle cells. (Hematoxylin-eosin stain; original magnification, ×200.) **(c)** Follow-up axial single-shot fast spin-echo T2-weighted MR image (2500/108) after 6 months of observation shows interval increase in size of the tumor (arrow) with persistent heterogeneous high signal intensity. **(d)** Axial single-shot fast spin-echo T2-weighted MR image (1962/98) after 12 months of treatment with liposomal doxorubicin shows marked decrease in size of the lesion (arrow) with marked decrease in signal intensity. **(e, f)** Following chemotherapy, photomicrographs of a resection specimen show a more variable, hypocellular appearance, ranging from markedly collagenous stroma with sparse tumor cell nuclei **(e)** to edematous stroma **(f)**. Most of the tumor was notably less cellular following therapy. (Hematoxylin-eosin stain; original magnification, ×200.)

ties, particularly at MR imaging, closely reflect the distribution of its histologic components: spindle cells, myxoid matrix, and surrounding collagenous stroma (6).

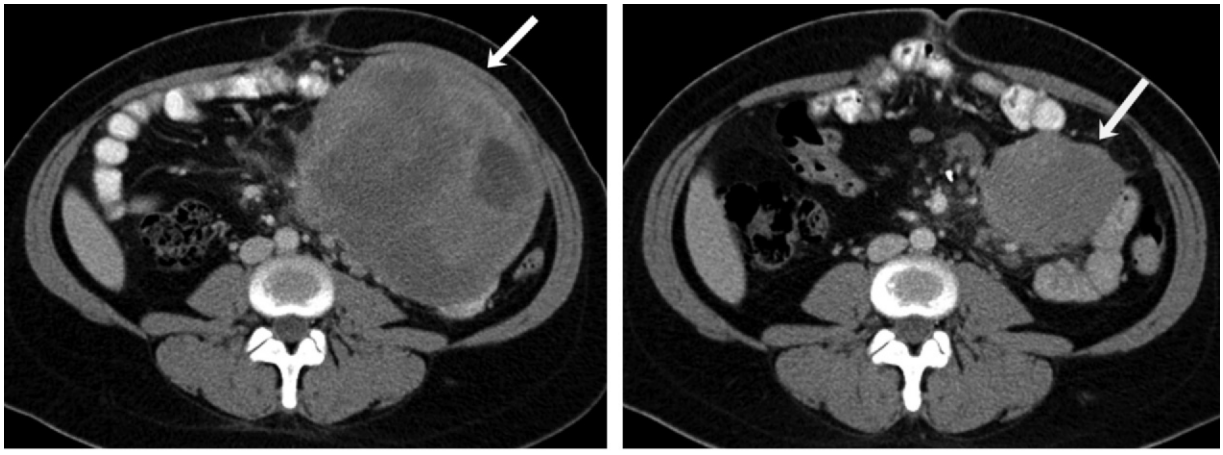
Imaging Features at US

US is an inexpensive and widely available imaging tool that is useful in the evaluation of DF in certain clinical settings, especially in initial screening of palpable masses of the extremities and in lesions involving the abdominal wall (12) and the chest wall/breast (13). The sonographic appearance of DF is variable: It may appear as oval, smooth, and/or poorly marginated solid soft-tissue mass or masses with variable echogenicity (Fig 2). Alternate layers of hypo- and hyperechogenicity may be visualized, correlating with heterogenous tissue composition, comprising cells (hyperechoic), matrix (hypoechoic), and collagen (hypoechoic). Vascularity is variable, as manifested at color Doppler US (14). DF may be associated with the *fascial tail sign* (or simply, tail sign), indicating thin



a. b.

Figure 2. US appearance of a sporadic right paraspinal musculature extra-abdominal DF in a 26-year-old woman. **(a)** Transverse US image shows an oval well-marginated heterogeneously hypoechoic mass. Note the linear fascial extension (tail sign) (arrow) along the periphery of the lesion. **(b)** Axial T2-weighted MR image (3066/106) shows a predominantly hyperintense well-defined mass with linear extension (arrow) along the deep intermuscular fascia. This was a superficial desmoid that was resected without any functional impairment.



a. b.

Figure 3. Positive treatment response to chemotherapy in a 27-year-old woman with a nonresectable solitary intra-abdominal DF not associated with FAP. **(a)** Axial contrast-enhanced CT image shows an oval well-defined large heterogeneous mesenteric mass (arrow) adherent to the small bowel and mesenteric vessels. Surgery was deferred, and the patient was started on chemotherapy. **(b)** Follow-up axial contrast-enhanced CT image, after 6 months of treatment with vinorelbine, shows decrease in size of the mass (arrow) with minimal change in attenuation.

linear extension along fascial planes (15) (Fig 2) and the *staghorn sign*, from intramuscular fingerlike extensions of the tumor (12,16). US is particularly well-suited for follow-up of pregnancy-associated DF due to its lack of ionizing radiation and the superficial abdominal wall location of the lesions.

Imaging Features at CT

At CT, DF appears as a soft-tissue mass, either sharply marginated, as most commonly seen in abdominal-wall tumors, or with ill-defined infiltrative margins, as seen in extra-abdominal or mesenteric tumors (17) (Fig 3). DF shows variable attenuation, similar to or slightly higher than that demonstrated by skeletal muscle, with hyper- and hypoattenuation, probably reflecting collagen and myxoid elements, respectively (18). Enhancement is variable, with the majority of the masses demonstrating mild-to-moderate enhancement. Necrosis and calcifications are extremely rare (19). Mesenteric DF, most commonly encountered with FAP in Gardner syndrome, is typically seen at CT as a soft-tissue mass with radiating spicules extending into the adjacent mesenteric fat (20). CT is the most commonly used imaging modality for the diagnosis and follow-up of patients with intra-abdominal DF and for the detection of associated complications such as small bowel obstruction (21).

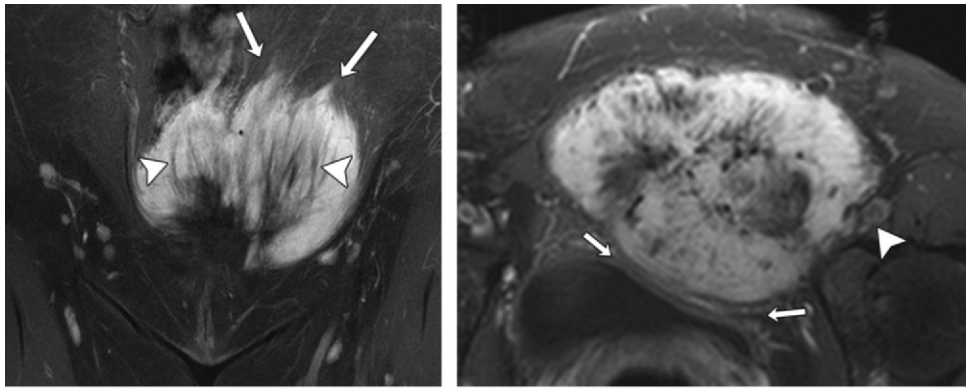
Imaging Features at MR Imaging

MR imaging is preferable for the evaluation of abdominal wall and extra-abdominal DF (18). Signal intensity of DF at MR imaging, in the various imaging sequences, is reflective of the proportion of collagen fibers, spindle cells, and extracellular matrix present (22,23). The most commonly observed MR imaging appearance of DF is a heterogeneous pattern, with signal iso- to hyperintense to skeletal muscle on T2-weighted

Table 1: Correlation between MR Imaging Signal Intensity and Histologic Components in DF

Histologic Components	T1 Signal Intensity	T2/PD/STIR Signal Intensity	Contrast Enhancement
Myxoid matrix	Low	High	Intense
Cellular stroma	Intermediate to low	Intermediate to high	Moderate
Fibrous tissue/ collagen bands	Low	Low	Absent

Note.—PD = proton density, STIR = short inversion time inversion-recovery.



a. **b.**

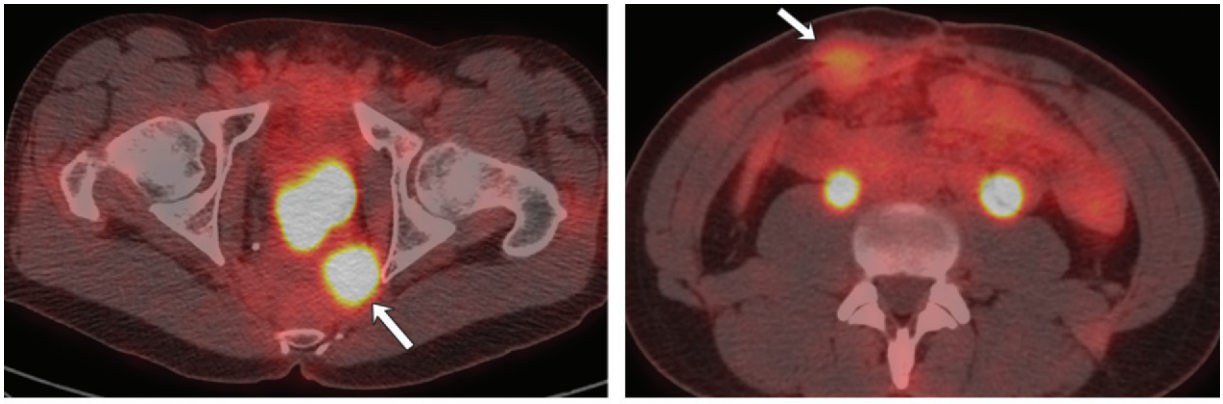
Figure 4. MR imaging appearance of a pregnancy-associated abdominal-wall DF in a 34-year-old woman. **(a)** Coronal post–contrast medium fat-suppressed T1-weighted MR image (417/14) shows a large enhancing mass with linear low-signal-intensity bands (band sign) (arrowheads), and feathery margins along the superior aspect of the mass resembling a fire (flame sign) (arrows). **(b)** Corresponding axial postcontrast fat-suppressed T1-weighted MR image (582/18) shows a heterogeneously enhancing mass, closely related to the left external iliac vein (arrowhead). A clear fat plane (arrows) between the mass and the urinary bladder is also evident.

images, and isointense to muscle on T1-weighted images (15). Decreased signal intensity on T2-weighted images most likely results from dense collagen and hypocellularity; conversely, increased T2 signal intensity reflects a high content of spindle cells (8,24) (Table 1). Low-signal-intensity nonenhancing linear bands (known as the *band sign*) have been described in DF for all sequences (ranging from 60% to 90% of tumors), likely corresponding to the dense collagenous stroma often found at histologic examination (Fig 4) (6). Although this is a characteristic finding, it is not specific for DF, as it may be seen in other benign (giant cell tumor of tendon sheath) and malignant (myxofibrosarcoma) soft-tissue tumors. DF commonly (90%) demonstrates variable, moderate-to-marked enhancement after administration of gadolinium-based contrast material, especially in the more cellular, less fibrotic regions (25). Although nonenhancing areas may be present in DF, necrosis is very rare, even in large tumors. There is little data supporting the routine use of diffusion-weighted MR imaging in DF, although a small study found the apparent diffusion coefficient (ADC) values of DF to be higher than those of other soft-tissue sarcomas.

Extra-abdominal DFs typically occur in the intermuscular location along deep fascia, may show a thin rim of surrounding fat (*split fat sign*), linear enhancing extension along the fascial planes (Fig 2), and feathery margins resembling a flame (*flame sign*) (Fig 4). Despite the characteristic imaging findings of DF at MR imaging, biopsy is often performed to distinguish this entity from other soft-tissue tumors. The histologic features of desmoid tumors can change over time, and the alterations can be depicted at MR imaging, as detailed in the section on treatment (15,22).

Imaging Features at Fluorodeoxyglucose PET/CT

DF is not typically very metabolically active and often demonstrates standardized uptake values (SUV_{max}) of less than or equal to 4.8 (26). The pattern of uptake is commonly heterogeneous, reflecting the histologic composition,



a. b.

Figure 5. FDG PET/CT imaging appearance of synchronous recurrent rectal cancer and DF in a 32-year-old man with a history of resected colorectal cancer in the setting of FAP syndrome. **(a)** Axial fused FDG PET/CT image shows an intensely FDG-avid focus (arrow) in the left pelvic sidewall. Biopsy showed recurrent rectal cancer. (Tracer also manifests within the ureters bilaterally.) **(b)** Section at a superior level shows a small focus (arrow) of low-level FDG uptake in the right anterior abdominal wall. Due to the differential FDG uptake, biopsy was performed, which revealed DF.

with increased uptake in more cellular areas (27,28). Mesenteric fibromatosis may present as a mildly fluorodeoxyglucose (FDG)–avid mass mimicking metastatic disease at routine imaging surveillance in FAP patients with a history of colorectal cancer. In FAP patients (in whom the incidence of mesenteric fibromatosis is increased severalfold [3]) presenting with an intra-abdominal mass, differential uptake at PET/CT (moderately intense in recurrent cancer versus mild uptake in DF) may be helpful in distinguishing between the two entities (Fig 5).

Management of DF

DF has variable clinical presentation and biologic behavior; hence a multidisciplinary approach personalized to the individual patient, requiring close collaboration between medical and surgical oncologists, radiologists, and radiation oncologists, is required for optimal care (8,29). Although DF is histologically benign and does not metastasize, it can be locally aggressive. Therefore, the main goal of treatment is local control, while minimizing functional impairment and morbidity.

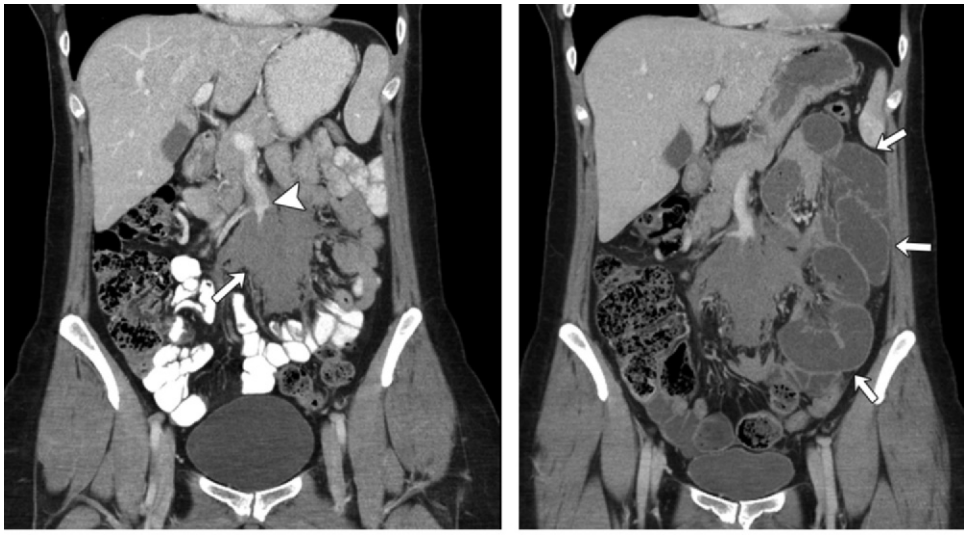
Surgery

Surgical resection has been the cornerstone of treatment for DF, which can be resected without marked functional impairment or cosmetic disfigurement (30). Local control can be achieved in 75%–80% of DF, especially extra-abdominal DF involving the extremities (31,32). Surgery is still recommended when the tumor is easily resectable without associated morbidity (33). Although patients with tumors close to vital organs or neurovascular structures were previously offered initial surgery, many centers now would defer to systemic therapy (34). In this setting, optimization of multidisciplinary care ultimately will determine the treatment plan for an individual's clinical situation. Surgery may be employed to treat complications related to DF and in recurrent DF, whenever feasible, as local control rates are similar to those of first-line surgical intervention (8,35). In extremity tumors, function-preserving procedures usually take precedence over radical resection.

Role of Imaging in Presurgical Planning

CT and MR imaging are the modalities of choice for assessing resectability and surgical planning. As DF does not metastasize, a whole-body staging workup is not required. Neurovascular structure encasement as well as invasion of the viscera and bones should be detectable and reported in this locally aggressive disease. The nature and scope of surgery depends on tumor location. For example, a superficial extra-abdominal DF may be amenable to surgical resection with no resulting functional impairment (Fig 2). Conversely, an infiltrative abdominal mass at the base of the bowel mesentery might not be resectable without compromise of vital anatomic structures (35) (Fig 6). We will discuss the key role of imaging in surgical planning in the three main subgroups of DF, which are based on location: abdominal-wall, intra-abdominal, and extra-abdominal DF.

With abdominal-wall DF, surgery is often the primary treatment option for progressive or symptomatic lesions, particularly in sporadic cases where the risk of recurrence is likely to be low. Involvement of the rectus abdominis muscle is the most common. Lesions tend to be solitary and fairly well circumscribed, both at CT and MR imaging, showing moderate-to-marked



a. b.

Figure 6. Unresectable sporadic mesenteric DF, on observation, causing bowel obstruction in a 30-year-old woman. **(a)** Coronal contrast-enhanced CT image reveals a solitary large ill-defined mesenteric mass (arrow) encasing the superior mesenteric vessels (arrowhead). **(b)** After 3 months on observation, the patient presented to the emergency department with abdominal pain, nausea, and vomiting. Coronal contrast-enhanced CT image obtained at the emergency visit reveals unchanged size and attenuation of the mass; however, there is new dilatation of the small bowel loops (arrows), suggesting bowel obstruction. There was angulation and tethering of the jejunal bowel loops by the infiltrative mesenteric mass.

post–contrast medium enhancement. Pertinent imaging findings with surgical implications to be described in the radiology report include the longitudinal extent and depth of the tumor (particularly intraperitoneal extension), involvement of internal organs such as the bowel and urinary bladder, and proximity to/involvement of the costochondral junction or the lower ribs (Fig 4). Although CT or MR imaging may be considered for the surgical evaluation, MR imaging is optimal due to its superior soft-tissue resolution.

Intra-abdominal DF occurs most commonly in the small-bowel mesentery, but also in the retroperitoneum and the pelvis. Lesion location, multiplicity, infiltrative margins, and relationship with mesenteric vessels and intra-abdominal organs are important surgical considerations. Intra-abdominal DF may present as a well-circumscribed mass or masses or as infiltrative soft tissue encasing mesenteric vessels (Fig 6), or a combination. CT with oral and intravenous contrast medium is optimally suited for the detection and presurgical evaluation, as intra-abdominal fat acts as excellent contrast for delineation of the lesions. Unlike at MR imaging, bowel- and breathing-motion artifacts do not limit CT evaluation. Excellent spatial resolution with multiplanar CT reformation allows for detailed visualization of the tumor and its relationship with mesenteric vessels.

Although extra-abdominal DF can occur anywhere from head to toe, it is most common in the extremities (60%), chest wall/paraspinal region (25%), and head and neck (15%). In extremity lesions, the entire limb should be imaged to evaluate for potential synchronous multifocal tumors (Fig 7). Due to its superior soft-tissue resolution, MR imaging is optimally suited for tumor delineation and tumor relationship to critical structures, including to the neurovascular bundle (Fig 8). MR imaging clearly depicts fascial extension, which is a characteristic finding in extra-abdominal DF. This is seen at MR imaging as linear, enhancing tissue at the periphery of the tumor (tail sign) (Fig 2) (18). It is important to describe fascial extension, which is not a limitation to resection, when present, in order for the surgeon to widen the resection margin and thereby decrease the chance of recurrence. When tumor abuts the neurovascular bundle, function-preserving surgery is performed (with or without postoperative RT) or nonsurgical approaches are considered.

Bone involvement may be seen in 5%–30% of DFs, especially in recurrent tumors. CT is the best option for detection of bone involvement, which may present at CT as scalloping, frondlike periosteal reaction, and/or frank bone destruction (36,37) (Fig 9). It is important to provide the surgeon with the degree and type of involvement, to enable complete resection (36). For lesions involving the ribs or iliac bones, a segmental osseous resection can be performed. In cases of extensive vertebral body involvement, incomplete resection or curettage may be performed. Only rarely does the presence of bone involvement preclude surgery.

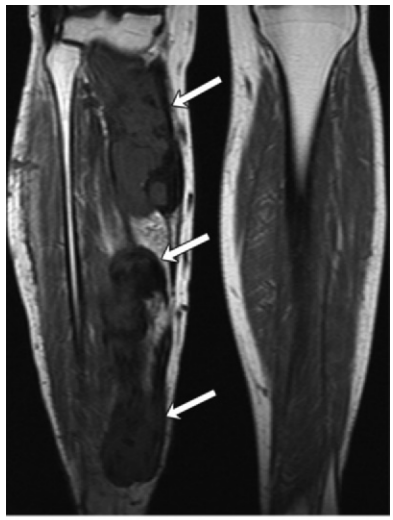
Limitations of Surgical Resection

Complete resection of the tumor with negative microscopic margins (R0) is often limited by anatomic considerations and the infiltrative nature of DF, leading to a high incidence of recurrence. Major factors limiting resectability include deep location (Fig 9), involvement of critical structures (including the viscera and neurovascular bundle) (Figs 7, 8), and multifocality (Fig 7). Surgical resection is also associated with peri- and postoperative morbidity and mortality, an important consideration for a usually nonfatal tumor. Resection of large abdominal-wall DF requires abdominal-wall reconstruction to minimize the risk of hernias; likewise, removal of infiltrative intra-abdominal DF often requires concomitant bowel resection.

Recurrence

Recurrence is seen in 20%–68% of patients, typically occurring within the first 1.5–5 years after treatment (31,38,39) (Fig 10). High recurrence rates are partly due to the difficulty in obtaining negative margins because of the infiltrative nature of DF (40). Many studies cite positive margins as a negative prognostic factor (31,41), whereas other series report no significant differences in recurrence rates with positive or negative margins (11,42). The role of the margin status should be considered with caution (43). Tumor location influences outcomes, with the highest rate of recurrence seen in extra-abdominal tumors, especially limb and girdle tumors (Fig 10), and lowest recurrence rates with abdominal-wall tumors (44). Mesenteric DF, and DF arising in association with FAP/Gardner syndrome, have also been reported to have greater potential for local recurrence (11,45).

MR imaging is the modality of choice for evaluating local recurrence in extra-abdominal locations, whereas CT is the preferred modality for intra-abdominal locations. Surveillance should be frequent in the first 12–18 months after surgery, when the incidence of local recurrence is at its highest (Fig 10). Recurrent DF frequently shows imaging characteristics similar to those of the original lesion, but at times the recurrence may be more aggressive and infiltrative than the original tumor (6). Recurrent tumors are commonly seen as nodular enhancing masses along areas of fascial extension, where surgical resection tends to be incomplete. However, it is not always easy to distinguish postoperative fibrosis from recurrent desmoids; serial follow-up or biopsy may be required in questionable cases. Management of recurrent DF is similar to that of primary tumor, although it is to be noted that recurrences tend to become more frequent and aggressive with each surgical intervention (5,40,46).



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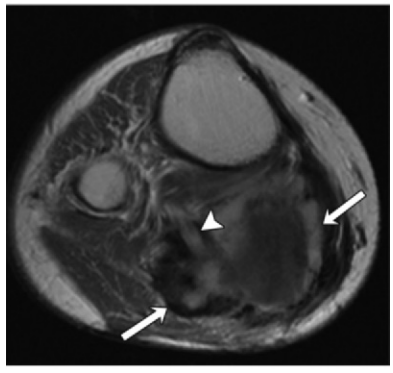


b.

Figure 7. MR imaging appearance of a multifocal sporadic extra-abdominal DF of the right calf in a 40-year-old woman. **(a)** Coronal T1-weighted MR image (500/15) reveals multiple heterogeneous soft-tissue masses (arrows) infiltrating the right calf region posteromedially. The masses show signal intensity similar to the muscle with peripheral low-signal-intensity linear bands. **(b)** Axial contrast-enhanced T1-weighted MR image (500/15) shows a heterogeneously enhancing mass (arrow) at the level of the popliteal fossa with encasement of the popliteal artery (arrowhead). Surgery was not feasible due to the extensive multifocal involvement and vascular encasement, and the patient was started on systemic therapy.

Nonsurgical Management

Given the limitations of surgical resection and that resection does not affect survival (due to the nonmetastatic nature of desmoids), nonsurgical options have gained more attention in recent years (33).

Observation/Expectant Management

The latest consensus guidelines from the National Comprehensive Cancer Network (NCCN) recommend observation as a primary

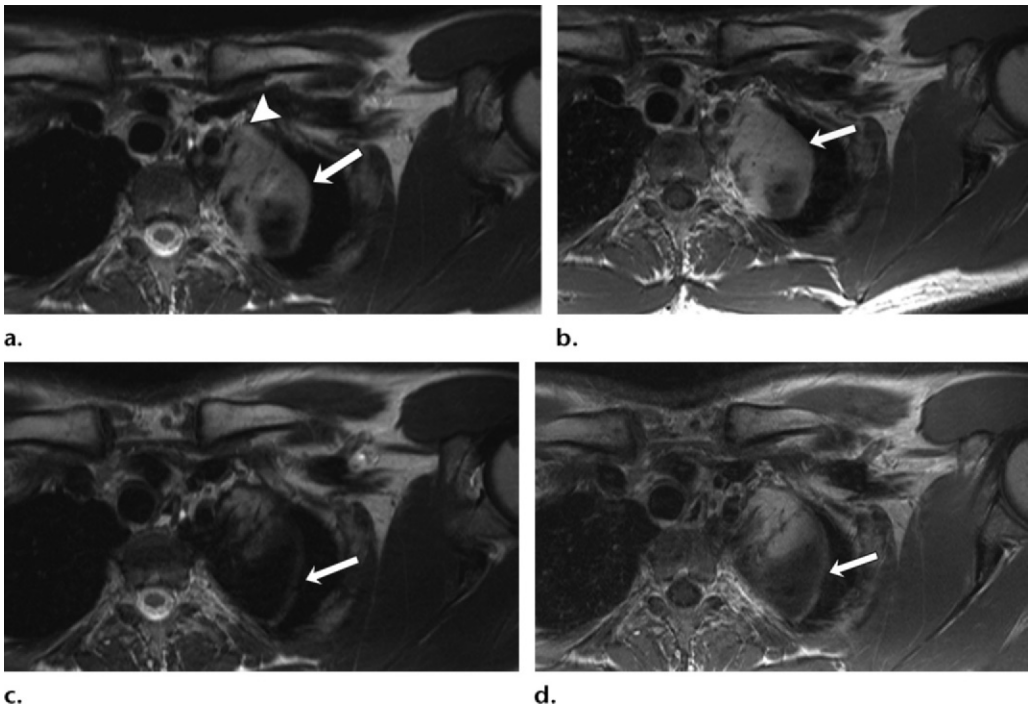


Figure 8. Positive response to systemic therapy with sorafenib of an unresectable extra-abdominal left apical thoracic DF in a 27-year-old man. **(a)** Axial T2-weighted MR image (8300/63) shows a well-defined heterogeneously hyperintense left apical thoracic mass (arrow) with involvement of the neurovascular bundle (arrowhead). **(b)** Axial postcontrast T1-weighted MR image (796/11) shows heterogeneous avid enhancement of the mass (arrow). **(c, d)** Axial T2-weighted (8390/63) **(c)** and postcontrast T1-weighted (648/12) **(d)** MR images after 9 months of therapy with sorafenib show a slight interval increase in size, but a marked decrease in signal intensity (arrow in **c**) and in enhancement (arrow in **d**), especially the posterior component.

treatment option for surgically unresectable tumors or resectable tumors that are not symptomatic, life threatening, or causing notable impairment (34,47). A wait-and-see policy (expectant management) alone was first proposed for recurrent but stable lesions in 2000, where, in an 83-patient study, an initial period of observation was considered for unresectable primary tumors (48–50). Two additional recent studies have shown a high rate of spontaneous tumor growth cessation (37,38).

A conservative approach to primary and recurrent DF is a safe and acceptable option if continued growth, surgical resection, or RT would lead to unnecessary morbidity, particularly in infiltrative mesenteric tumors or deeply located tumors such as pelvic or neck tumors adjacent to vital structures (33). A conservative approach entails close imaging follow-up, especially in anatomic locations adjacent to critical structures, in which an increase in size of the tumor would indicate a need for surgery or other therapy (51). CT is used for monitoring intra-abdominal DF and the majority of abdominal-wall DF. MR imaging is the modality of choice for the follow-up of nonresectable extra-abdominal DF of the extremities, head and neck, chest wall, and deep pelvic locations (19).

Although DF shows unpredictable biologic behavior, after an initial growth phase (Fig 1) there is a propensity toward stabilization or a "plateau phase" and even spontaneous regression, the so-called biologic burn-out. MR imaging signal intensities may evolve on the basis of the phase of the tumor (Table 2) (6).

The growth phase may be associated with a sudden increase in symptoms and pain aggravation. No clear data support MR imaging being useful for predicting biologic behavior or clinical outcome. In a study of 15 patients with FAP-associated DF, lesions with high signal intensity on T2-weighted images showed notable growth at follow-up (52). In a retrospective study of 27 patients with DF at observation or systemic therapy, the initial MR imaging signal intensity was not predictive of change in size over time (53).

Systemic Therapy

Systemic therapy is used for tumors for which surgery would cause unnecessary morbidity due to infiltrative margins or deep location, tumors with multiple locoregional recurrences, tumors that demonstrate marked growth on observation, and tumors with imaging findings suggestive of aggressive behavior or risk of invasion of critical structures. Systemic therapy can also be used in the

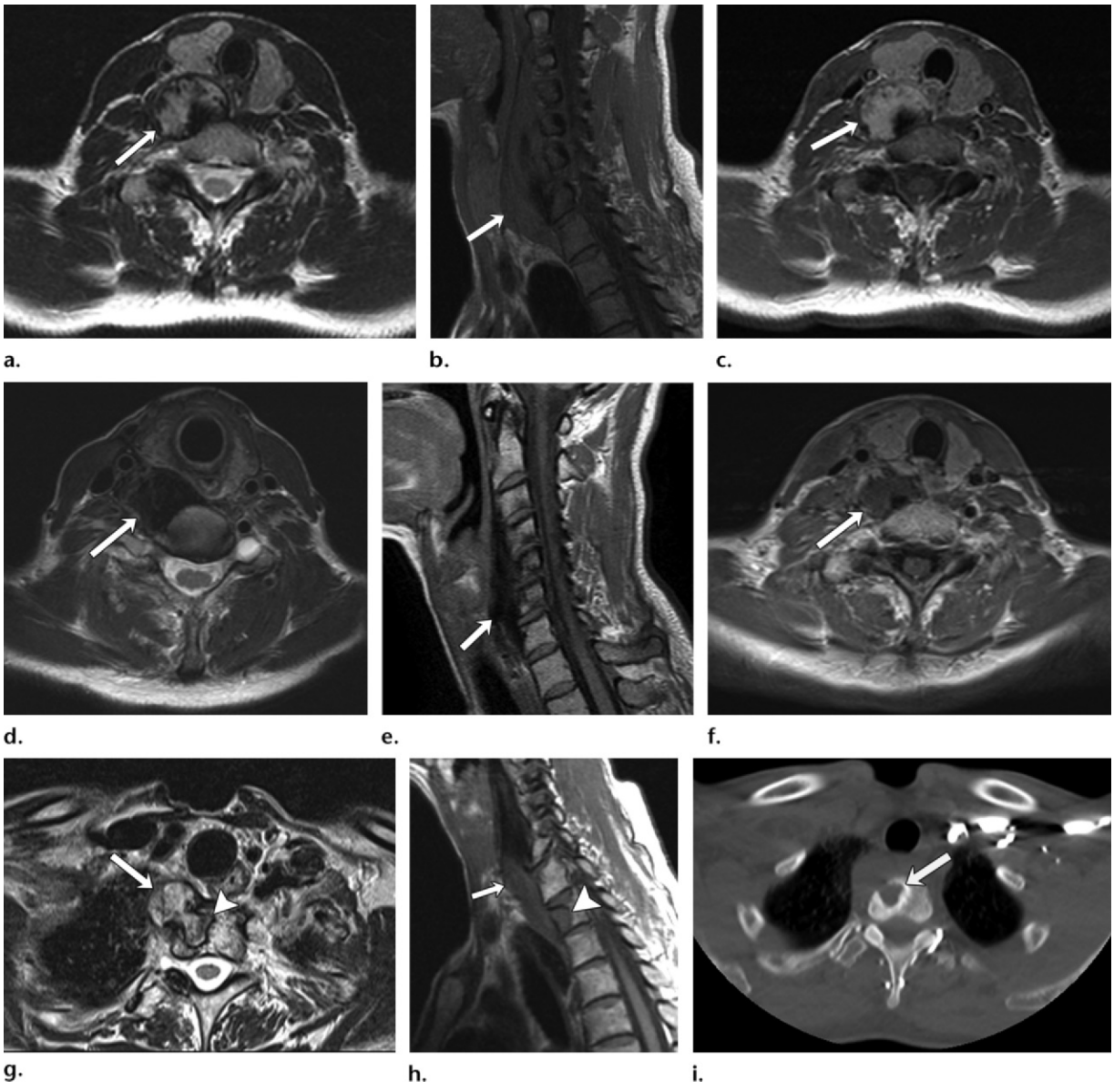
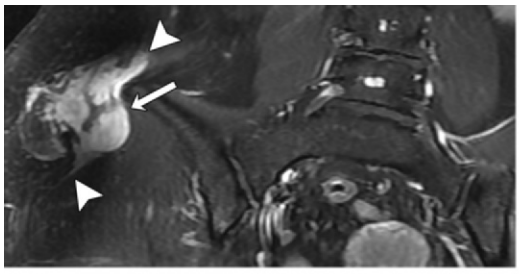


Figure 9. Positive response to RT of an unresectable extra-abdominal DF of the right neck in a 45-year-old woman, with subsequent locally aggressive disease. **(a)** Axial T2-weighted MR image (3100/98) shows a well-defined heterogeneously hyperintense right neck mass (arrow) posterior to the thyroid gland abutting the esophagus and the upper thoracic vertebral body. **(b, c)** Sagittal precontrast **(b)** and axial postcontrast **(c)** T1-weighted MR images (583/17) show a hypointense mass (arrow) with avid enhancement corresponding to the T2-hyperintense areas. **(d–f)** Axial T2-weighted (3800/80) **(d)**, sagittal T1-weighted precontrast (550/15) **(e)**, and axial T1-weighted postcontrast (530/14) **(f)** MR images, after RT, demonstrate slight decrease in tumor size but notable decrease (arrow in **d, e**) in signal intensity and decrease (arrow in **f**) in enhancement. **(g, h)** Axial T2-weighted (2900/106) **(g)** and sagittal T1-weighted (560/17) **(h)** MR images 7 years later demonstrate recurrent DF in the form of an increasing T2-hyperintense, T1-intermediate-signal-intensity component (arrow) along the inferior aspect of the main mass (arrowhead) with extension into the vertebral body. The superior component of the mass remains T1 hypointense. **(i)** Axial CT image (bone window) at the same level helps to confirm the osseous destruction (arrow).

neoadjuvant setting. Currently available systemic therapies include hormonal agents, anti-inflammatory drugs, cytotoxic agents, and molecular targeted therapies. Because DF may have a relatively indolent course with low mortality, symptomatic improvement and absence of progression at imaging are the primary endpoints for outcome. Imaging plays an important role in assessment of tumor response as well as in early detection of complications associated with systemic treatment (22). In this section, we discuss the most commonly used drugs and describe the rationale for use of specific agents. We also describe the typical imaging manifestations of response to treatment and progression of disease, as evidenced by size and morphologic changes in the masses that are not class- or drug-specific.

Anti-inflammatory Drugs

DF has been shown to overexpress cyclooxygenase (COX), specifically cyclooxygenase 2



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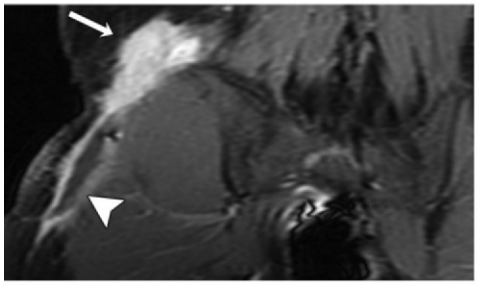
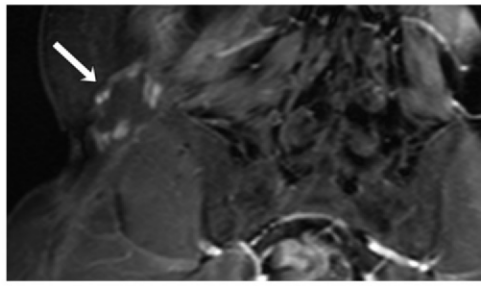




b. c.

Figure 10. Positive treatment response to systemic therapy of a recurrent sporadic right flank DF in a 41-year-old woman after surgical resection. **(a)** Coronal contrast-enhanced fat-suppressed T1-weighted MR image (660/15) shows an irregular heterogeneously enhancing mass (arrow) abutting the right iliac crest. Note linear extension along the superior and inferior margins (arrowhead). **(b)** Coronal contrast-enhanced fat-suppressed T1-weighted MR image (300/2.5) 1 year after surgical resection shows a postsurgical seroma (arrowhead) with rim enhancement and recurrent desmoid tumor seen as a homogeneous enhancing mass (arrow) along the superior margin of the resection site. **(c)** Coronal contrast-enhanced fat-suppressed T1-weighted MR image (3.1/1.3) after 2 years of chemotherapy that included liposomal doxorubicin and sorafenib shows mild decrease in size and marked decrease in enhancement (arrow).

Table 2: Correlation between MR Imaging Signal Intensity and Phases of DF

MR Imaging Signal Intensity	Growth Phase	Plateau Phase	Regression Phase
T1-weighted	Low	Low	Very Low
T2-weighted	High	Low	Very Low
Enhancement	Mild to moderate	Mild	Absent

(COX-2); nonsteroidal anti-inflammatory drugs (NSAIDs) are therefore used in the management of DF (54). NSAIDs (sulindac, celecoxib) are most commonly used as single agents for prophylaxis after surgical resection or, in combination with hormonal therapy, for the treatment of unresectable tumors.

Hormonal Therapy

DFs have been associated with high estrogen states (55), especially in women during or following pregnancy. This is the rationale for the use of tamoxifen, a selective estrogen receptor modulator, as a therapeutic agent. Tamoxifen, with or without anti-inflammatory agents, has been found to be helpful in the treatment of DF (56). Current studies vary widely on dosages used and outcomes. As DF can occur in young men and women, both the negative effects of estrogen suppression, and the toxic effects of tamoxifen, can be marked. Therefore, hormonal suppression, although an option, is used less frequently than it has been in the past.

Cytotoxic Therapy

Cytotoxic chemotherapy is usually reserved for symptomatic or progressive disease not amenable to surgery (57,58). Although slow-growing neoplastic processes are generally unresponsive to cytotoxic chemotherapy, DF has been shown to respond to cytotoxic chemotherapy, with response rates exceeding 75% in some studies (57). Cytotoxic chemotherapy in the treatment of DF includes drug combinations mainly based on doxorubicin, vinorelbine, vinblastine, and/or methotrexate. Liposomal doxorubicin has been shown to be particularly effective in DF of both intra- and extra-abdominal locations (Fig 1). Importantly, disease stability is typically the

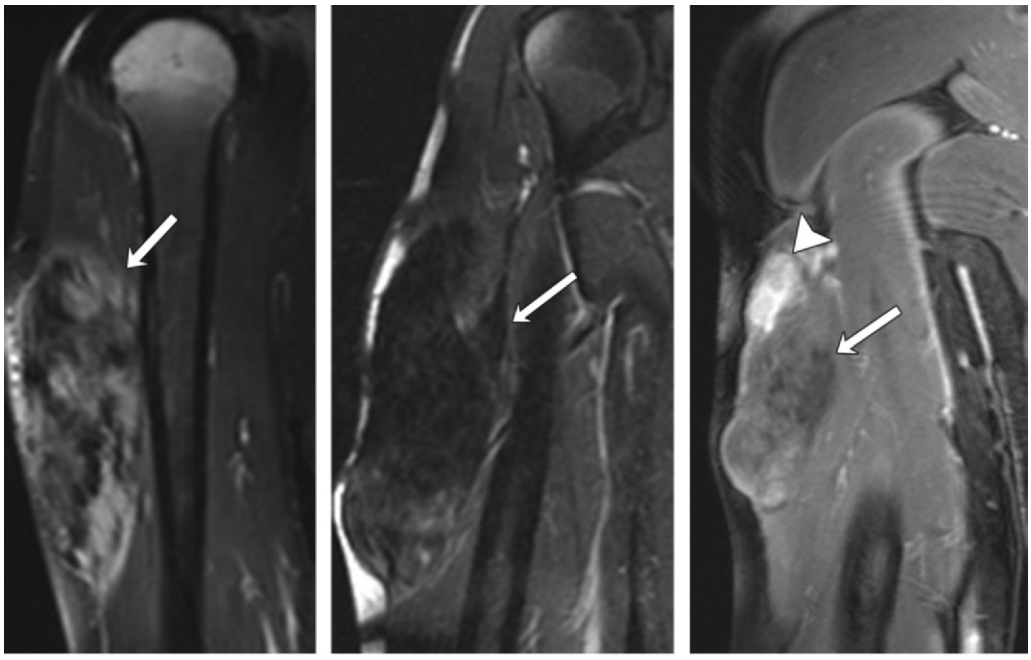


Figure 11. Positive treatment response to chemotherapy with imatinib of an unresectable sporadic extra-abdominal DF of the right triceps region in a 22-year-old man. **(a)** Coronal contrast-enhanced fat-suppressed T1-weighted MR image (550/18) at diagnosis shows a heterogeneous avidly enhancing intramuscular mass (arrow) in the right arm. **(b)** Coronal contrast-enhanced fat-suppressed T1-weighted MR image (800/14) after 2 years of systemic therapy with imatinib demonstrates slight interval increase in tumor (arrow) size but a marked decrease in enhancement. **(c)** Coronal contrast-enhanced fat-suppressed T1-weighted MR image (14/5), 24 months after cessation of imatinib therapy, reveals a new nodular enhancing focus (arrowhead) along the superior aspect of the tumor (arrow), indicating an aggressive component of the tumor.

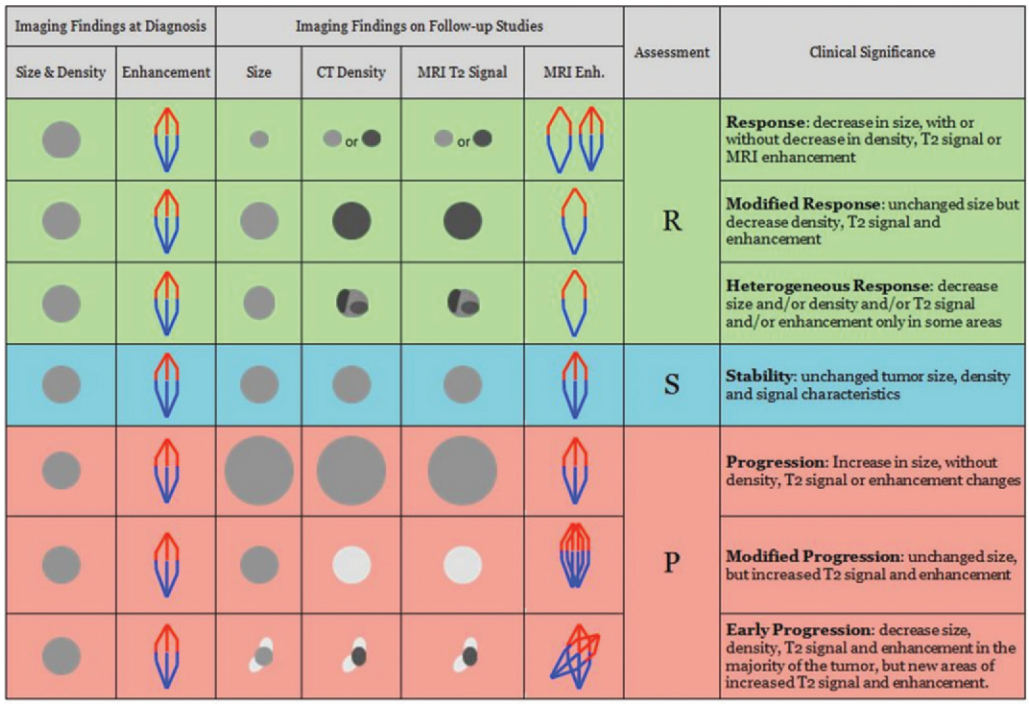
first indication of benefit. Bidimensional reduction in tumor size can occur and persist even after a course of therapy has been completed. Prolonged stable disease after completion of treatment is common. Vinorelbine is often used in patients when anthracyclines are not considered an optimal option (Fig 3). In pediatrics, the combination of vinblastine and methotrexate has demonstrated notable benefit as well. Doxorubicin-containing regimens have higher response rates than monotherapy or non–anthracycline-containing regimens but are also more toxic.

Molecular Targeted Therapies

There has been recently increased interest in the potential role of tyrosine kinase inhibitors (TKIs) in the treatment of extra-abdominal DF. Some data support increased production of platelet-derived growth factor (PDGF) in DF, which provides a potential rationale for the use of TKIs, although the true target remains unknown. The most common molecular targeted therapies used are imatinib and sorafenib. Imatinib was the initial TKI used in DF, with very modest effects (Fig 11). Sorafenib is a multitargeted TKI that inhibits, among others, vascular endothelial growth factor receptor (VEGFR) (Fig 8). Activity against DF was seen in a review of 26 patients who received sorafenib 400 mg daily (59). In that study, the clinical benefit with the use of sorafenib was seen within 2 weeks in 70% of symptomatic patients. Longer radiologic follow-up of a smaller cohort within the study demonstrated that 92% of patients exhibited greater than 30% reduction in lesion size. The majority of responses were in extra-abdominal DF as opposed to intra-abdominal DF. There is an ongoing phase 3 trial evaluating sorafenib in DF to further define benefit.

Systemic Treatment

Patients with DF on systemic treatment are usually monitored with CT and MR imaging. Changes in DF size and attenuation should be assessed at CT, whereas size, T2 signal intensity, and degree of enhancement are relevant at MR imaging. Enhancement changes at CT are not easily appreciated. Although the degree of response may vary, response manifests similarly with all systemic therapies as decreased size, attenuation, and/or signal intensity. Conventional response criteria, such as Response Evaluation Criteria in Solid Tumors (RECIST) or World Health Organization (WHO), may not truly reflect the tumor biology and the effectiveness of treatment in DF. We present seven clinically relevant imaging patterns of change that can be



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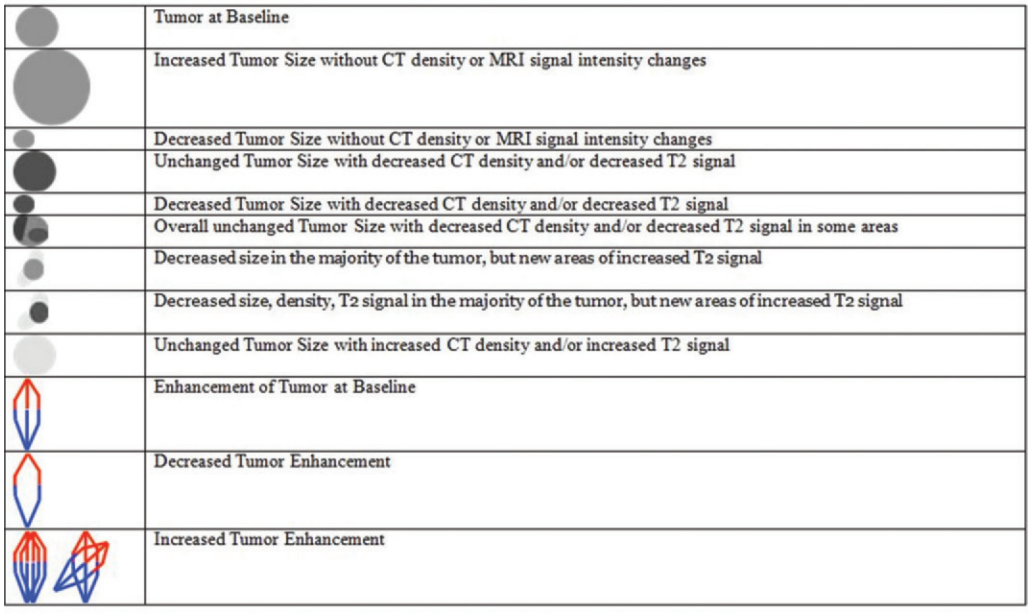

b.

Figure 12. Schematic representations of response patterns of DF at MR imaging.

seen at CT and/or MR imaging, and we propose a conventional nomenclature (Fig 12) as follows:

1. Treatment response (R): Decrease in size of the tumor with or without change in attenuation at CT or signal intensity at MR imaging (Figs 1, 3).

2. Modified response (mR): Unchanged/increased tumor size but decreased attenuation, T2 signal intensity, and enhancement at MR imaging, suggesting increased fibrotic component and decreased cellularity (Figs 8, 10).

3. Heterogeneous response (hR): Decreased size, attenuation at CT, and/or T2 signal intensity and enhancement at MR imaging in some areas of the tumors, indicating response, but increased attenuation at CT and T2 signal intensity and enhancement at MR imaging in other areas (Fig 9).

4. Stability (S): Unchanged size, attenuation, and signal intensity characteristics.

5. Progression (P): Increase in size without attenuation changes at CT or signal intensity changes at MR imaging (Fig 1).

6. Modified progression (mP): Unchanged tumor size but increased T2 signal intensity and

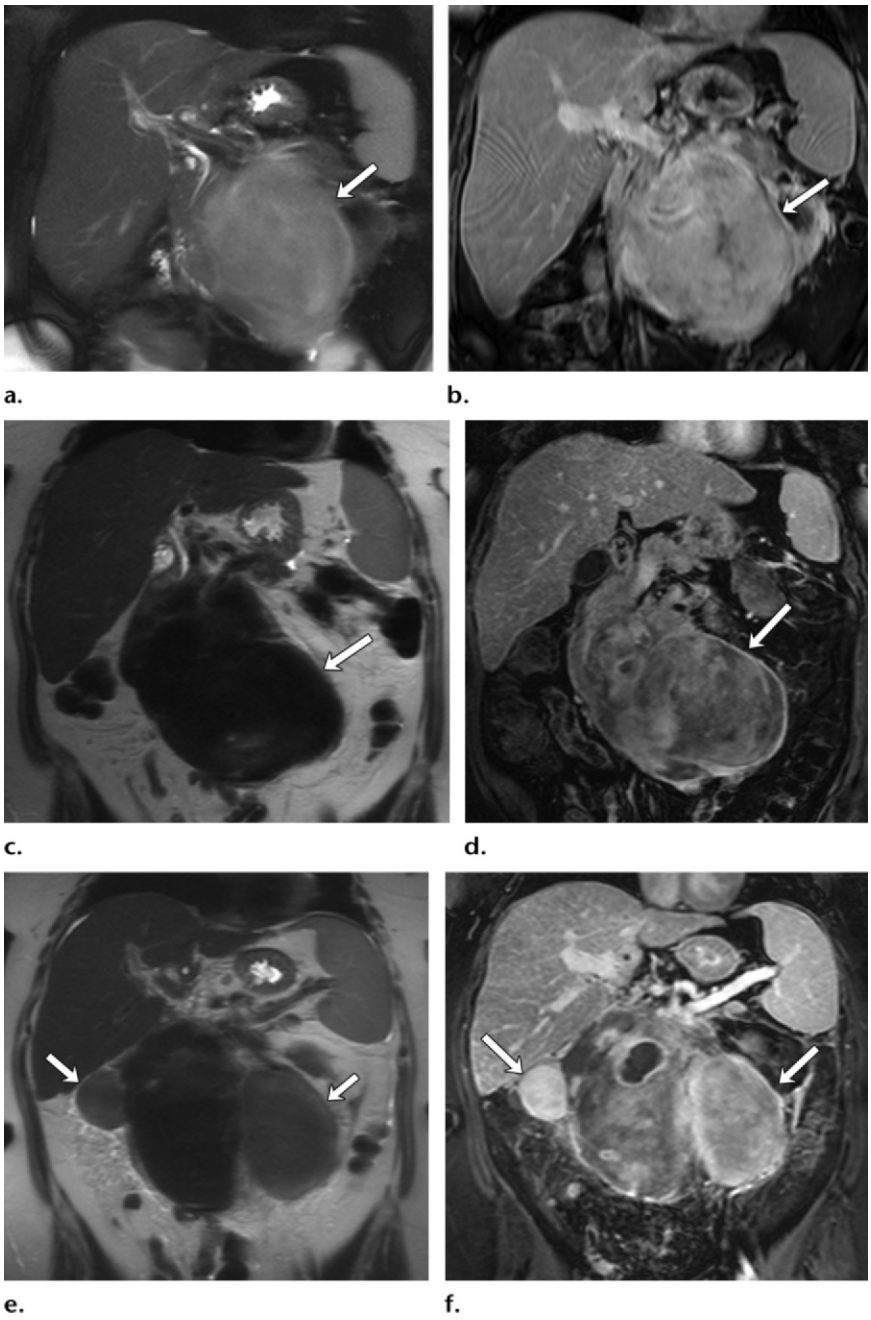

Figure 13. Unresectable sporadic intra-abdominal DF in a 46-year-old woman at presentation and then showing early progression pattern. **(a)** Coronal fat-suppressed T2-weighted MR image (2500/90) at presentation shows a large solitary homogeneously hyperintense intra-abdominal mass (arrow). **(b)** Coronal contrast-enhanced fat-suppressed T1-weighted MR image (4.5/2.3) at presentation shows homogeneous enhancement of the mass (arrow). **(c)** Coronal T2-weighted MR image (1000/103) after 12 months of therapy with liposomal doxorubicin shows slight interval increase in size of the tumor but marked homogeneous decrease in signal intensity (arrow). **(d)** Coronal contrast-enhanced fat-suppressed T1-weighted MR image (3.1/1.4) after 12 months of therapy with liposomal doxorubicin shows slight interval increase in size of the tumor but diffuse heterogeneously decreased enhancement (arrow). The patient continued the same treatment for another 12 months. **(e, f)** Follow-up coronal T2-weighted (1000/101) **(e)** and contrast-enhanced fat-suppressed T1-weighted (3.1/1.2) **(f)** MR images after 24 months of therapy with liposomal doxorubicin show decrease in size in the dominant T2-hypointense central component of the tumor but new T2 intermediate signal intensity left para-aortic and right retroperitoneal components (arrows in **e**) before contrast enhancement along the periphery of the mass, and which show avid enhancement (arrows in **f**) after contrast material administration.

enhancement at MR imaging, suggesting increased cellularity, hence increased aggressiveness of the tumor (Fig 11).

7. Early progression (eP): Decreased size, attenuation, T2 signal intensity, and enhancement in the majority of the tumor, but demonstration of new areas of increased T2 signal intensity and enhancement corresponding to new areas of aggressive disease (Fig 13).

Any of the pattern change must take into account the occasional patient with spontaneous regression or delayed response from prior therapy. For example, response to chemotherapeutic agents such as liposomal doxorubicin has been found even 6 months after completion of treatment (57).

Radiation Therapy

RT is a treatment option in extra-abdominal DF (extremities, superficial trunk, head and neck) in the adjuvant setting or as a primary treatment when surgical resection is not feasible or may result in marked functional limitations (2,60). RT is not recommended for patients with DF that is retroperitoneal and/or intra-abdominal. Postoperative RT (in the form of brachytherapy or external-beam irradiation) has been associated with increased local control in patients with positive margins from 4% to 75% (61,62). The role of adjuvant RT, however, is unclear, because there is no consensus on whether positive surgical margins are of prognostic significance,

making it difficult to determine the benefit of RT after surgery (63,64). The recommended dose of adjuvant/postoperative RT is 50 Gy in 2-Gy fractions (34). The dose for definitive RT without surgery, according to the most recent NCCN guidelines, is 54–58 Gy in the absence of any prior RT (34). Imaging, primarily CT and MR imaging, can provide important information for evaluation of response to therapy in this setting. Response to RT can be delayed, appearing a long time after the completion of treatment. Hence, initial scans following the treatment may not provide accurate information regarding tumor response. As in response to medical treatments, lesions that respond to RT can demonstrate decrease in size, lower attenuation at CT, and lower T2-weighted signal intensity at MR imaging (Fig 9). Imaging is key in detecting immediate treatment-related toxic effects, such as fibrosis, pathologic/insufficiency fractures, fistulas with adjacent organs (particularly for deep pelvic tumors), and also late radiation effects, including second malignancies (61). Because RT may be associated with delayed sequelae, including secondary cancers, the use of RT for this benign condition varies widely across the major international DF centers.

Conclusion

DF has variable clinical presentations and biologic behavior; hence, a multimodality approach, personalized to the individual patient, is required for optimal care. Imaging plays a critical role in the management of DF. In a surgical setting, imaging helps in determining the location, multicentricity, and involvement of any vital structures, including the neurovascular bundles, bones, and viscera, which are key points in assessing surgical resectability. In nonsurgically managed patients, imaging is critical in assessing rate of growth, detecting potential complications, and evaluating response in patients on systemic therapy. Changes in size and density at CT and changes in signal intensity at long-TR imaging and in enhancement pattern at MR imaging reflect tumor biology and response. PET/CT may be helpful in FAP patients with resected colorectal cancer to differentiate tumor recurrence from DF. Response to RT may be delayed and tumor shrinkage may manifest years after treatment.

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