

Management of Desmoids



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KEYWORDS

• Desmoid fibromatosis • Beta-catenin • Management • Margins • Observation

KEY POINTS

- Desmoid fibromatosis is an infiltrative tumor that can be aggressive in nature because of its ability to locally invade adjacent structures.
- Mutations in β -catenin and APC genes are responsible for the development of most desmoid tumors.
- Wide local excision with negative margins is the standard surgical treatment of desmoid tumors.
- A variety of nonsurgical therapies are useful in the management of desmoid tumors, including radiation, chemotherapy, nonsteroidal antiinflammatory drugs, and hormonal therapy.
- Treatment algorithms are evolving with the observation that many tumors remain stable under a program of watchful waiting, and spontaneous regression has been observed.

INTRODUCTION

Desmoid tumors (also known as aggressive fibromatosis) are rare, with an incidence of 0.03% of all neoplasms and 3.0% of soft tissue tumors.¹ They are seen more commonly in women than men with a 2:1 predilection for women.²⁻⁴ Young adults are the most commonly affected, and it is frequently in the 25- to 35-year-old demographic.^{2,3} Most desmoid tumors occur sporadically, but they can be associated with familial adenomatous polyposis syndrome (FAP). In the FAP patient population there is not a sex predilection for these tumors.⁵ Mutations in either the β -catenin or APC genes are usually the cause for the development of these tumors. Sporadic development of desmoid tumors has been associated with β -catenin mutations, whereas mutations in the APC gene pathway are associated with development of desmoids in the setting of FAP syndrome. It seems that these mutations are mutually exclusive.⁶ Other factors that have been associated with development of desmoids include

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pregnancy, hormonal exposure, and physical factors, such as trauma and/or surgery.^{3,4} Although desmoid tumors cannot be considered a true malignancy because of their inability to metastasize, they are aggressive in their ability to locally invade adjacent structures. Surgical resection has been the mainstay of treatment; however, recurrence rates range from 20% to 45%.⁷⁻⁹ Because of the propensity for recurrence, multimodal therapies have been used, including hormonal therapy, nonsteroidal antiinflammatory drugs (NSAIDs), chemotherapy, and radiation. Recently the surgery-first approach has begun to evolve into a movement of watchful waiting, as observational studies have shown long-term stability of some tumors without treatment and even spontaneous regression in 5% to 10%^{6,10} of cases.

Pathogenesis

Alterations in the Wnt signaling pathway seem to be the mechanism of tumorigenesis in the development of desmoid fibromatosis.¹¹ Genetic mutations that alter this pathway and are associated with the development of desmoid tumors have been identified in the β -catenin and APC genes. Both β -catenin and APC are part of the Wnt pathway suggesting that 2 separate mutations affecting the same end point are involved with the development of desmoid fibromatosis.¹² These mutations result in the development of intranuclear accumulation of β -catenin, which stimulates DNA transcription and cell proliferation.¹¹ Eighty-five percent of sporadic desmoid tumors have an activating mutation in the CTNNB1 gene coding for β -catenin, whereas the germline mutation of the APC gene leads to the development of desmoid tumors for patients with FAP.^{11,13} More recently a genetic analysis looking at wild-type desmoids or those without the aforementioned known mutations found that with deep sequencing 95% of desmoids may have mutations that affect the Wnt/ β -catenin pathway suggesting a near-universal relationship between desmoid tumors and the Wnt signaling.¹⁴

In sporadic desmoid tumors, mutations in the gene coding for β -catenin, CTNNB1, occur in 71% to 91% of tumors. The highest rate of mutation is found in intra-abdominal tumors.^{13,15-19} The most common mutations are T41A and S45F. The discovery of genetic mutations in the development of desmoid tumors has been an important advancement as they have also been associated with prognosis, providing the opportunity to improve the ability to risk stratify patients. Several studies have shown a significantly higher chance of disease recurrence at 5 years despite complete resection for patients harboring a S45F mutation, which is likely exclusive to extra-abdominal desmoids.^{13,17,19} The growing amount of data suggests that specific mutations within this gene do play a role in disease recurrence and provide the opportunity to influence clinical care in the future.

For those without a β -catenin gene mutation, APC gene mutations are suspected to be the source of development of desmoid tumors. APC mutations are most common among patients with FAP. Approximately 10% to 15% of patient with FAP develop desmoids, and intra-abdominal tumors have become the primary cause of death in patients with FAP who have previously had a prophylactic colectomy.^{11,20} Despite a similar molecular end point for APC and β -catenin mutations, the phenotype between the two is different, as most tumors in FAP are intra-abdominal with involvement of the small bowel mesentery.⁵

Presentation

Desmoid tumors can occur anywhere in the body. They are divided into 3 general anatomic locations: extra-abdominal, intra-abdominal, and abdominal wall. There

are important behavioral differences related to location that may affect specific treatment algorithms.

Extra-abdominal desmoid tumors are composed of tumors in the pelvic and shoulder girdles, head, neck, and extremities (**Fig. 1A**). They arise from deep fascia or within muscle, have an infiltrative growth pattern, and are often poorly circumscribed.²¹ This location has been associated with a 2- to 3-fold increased rate of recurrence and 20% decrease in recurrence-free survival when compared with intra-abdominal or abdominal wall/trunk lesions.^{6,7,22,23}

Intra-abdominal desmoids often arise in the mesentery of the small bowel or are located in the pelvis (see **Fig. 1B**). This location is more commonly associated with FAP but can also occur sporadically. In patients less than 40 years old found to have an intra-abdominal or abdominal wall desmoid, a colonoscopy should be performed to rule out polyposis.⁶ Overall, FAP-associated desmoid tumors represent a small proportion (2%–15%) of all patients with desmoid tumors.^{2,5,6,12} The management of intra-abdominal desmoids can be quite difficult because of size and location and frequently require resection of large amounts of small bowel for complete removal. In a study of patients with FAP and mesenteric desmoids that were treated surgically, small bowel resections were necessary in 87.5% of cases with an average of 45.6 cm of bowel removed.²⁴ In extreme cases this can lead to intestinal failure, chronic total parenteral nutrition, and possible need for small bowel transplantation. This location in particular may be optimal for nonsurgical approaches first in asymptomatic patients, as the consequences of extended resections can be devastating.

Lesions of the abdominal wall or trunk seem to have the most favorable prognosis of the 3 groups (see **Fig. 1C**). They have been associated with the lowest recurrence rates of 6% to 20%^{7,25} and the highest likelihood of spontaneous regression.^{10,26}

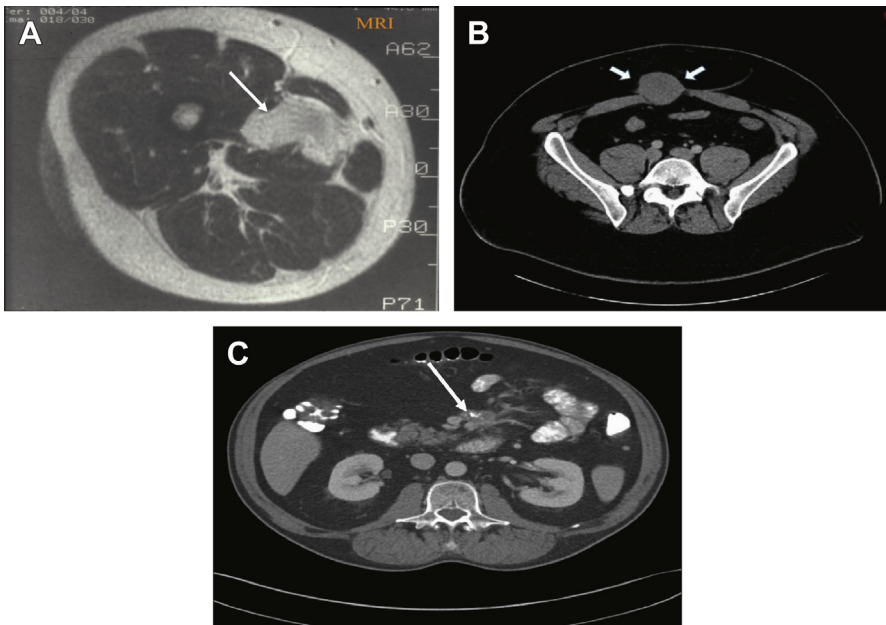


Fig. 1. Desmoid tumors can be divided into 3 anatomic locations: (A) extra-abdominal, (B) abdominal wall (C) intra-abdominal. Arrows depict tumor.

This location is also the most common for pregnancy-related desmoid tumors. There has been a reported association between pregnancy and the development or progression of desmoids. It is thought that this is related to the observation that these tumors stain strongly positive for estrogen-receptor β on immunohistochemistry.²⁷ In a recent study that evaluated desmoid fibromatosis and pregnancy, the investigators found that, although there was an increased risk of progression during pregnancy, patients could still be managed with standard therapies with minimal risk to the mother or child. The risk of progression was more prominent in patients who were diagnosed with desmoid fibromatosis before pregnancy (42%) versus the patients whose disease presented during pregnancy (13%). The rate of spontaneous regression in this population was 14%, which is higher than what is seen in other patient populations. They concluded that desmoid tumors during pregnancy have an indolent course, do not increase risk of obstetric complications, and should not be a contraindication for subsequent pregnancies.²⁸

EVALUATION

Radiologic Evaluation

Imaging modalities useful in the diagnosis and surveillance of desmoid tumors include ultrasound, computed tomography (CT) scan, and MRI. For initial evaluation, cross-sectional imaging is most appropriate to evaluate tumor size and local invasion of adjacent anatomic structures. Contrast-enhanced CT scan is the preference for intra-abdominal tumors to evaluate proximity to adjacent intra-abdominal vasculature and organs. CT scan of intra-abdominal lesions reveals a soft-tissue density with radiating strands typically located in the mesenteric fat. MRI is the modality of choice for evaluating extremity and soft-tissue tumors often demonstrating a heterogeneous pattern due to the mixed fibrous and cellular components. Tumors appear as low intensity signals on T2-weighted images.²⁹ Linear extension along fascial planes known as the fascial tail sign is common. Ultrasound can be used to survey for recurrence or to follow lesions in the extremities and abdominal wall. Appearance on ultrasound is that of a hypoechoic lesion with posterior acoustic shadowing. They are often vascular, and a fascial tail sign may also be seen with this modality.

Diagnosis

Biopsy is mandatory to confirm the diagnosis before treatment is discussed. Image-guided core biopsies are the recommended approach with ultrasound being useful in performing biopsy of soft-tissue lesions and CT-guided biopsy for intra-abdominal disease. Pathologically desmoid fibromatosis appears as a low cellularity proliferation of fibroblasts and myofibroblasts that are infiltrative into surrounding tissues. The differential diagnosis of desmoid tumors includes scar tissue, low-grade fibromyxoid sarcoma, nodular fasciitis, and other benign fibroblast proliferations. Immunohistochemical stains aid in confirming the diagnosis. In particular intranuclear staining of β -catenin has been shown to be positive in 67% to 80% of cases.³⁰ As previously mentioned, these tumors also stain strongly positive for estrogen receptor β .²⁷ Cyclooxygenase-2 expression may also be present and can be useful to determine desmoid from healing scar.³¹

TREATMENT

The management of desmoid tumors has traditionally been a surgery-first approach. For patients whereby surgical removal would lead to significant morbidity or lesions that are unresectable on initial presentation, there are several nonoperative strategies.

A recent development in management includes watchful waiting as an initial approach, as studies have shown 50% progression-free survival (PFS) as well as spontaneous regression of tumors with no treatment.³² Because of the complexity of management and the variety of treatment options as outlined later, treatment recommendations are best determined in a multidisciplinary setting.

Surgery

Wide local excision with negative margins has been the standard treatment of desmoid tumors. This treatment can prove to be challenging because of the infiltrative nature of these tumors. Retrospective studies have shown recurrence rates for margin negative (R0) resection ranging from 16% to 22% and 19% to 48% for microscopically positive margin (R1) resection.^{22,23,33–35} The frequency of recurrences after surgical resection has led to multiple studies that have evaluated margin status as a prognostic indicator of recurrence. When examining the prognostic significance of microscopic margin status, the data are mixed; some have found it to be significantly associated with recurrence-free survival, whereas others have shown no prognostic significance when comparing R0 versus R1 resections in desmoid tumors (Table 1).^{9,33,36–38} A study from the MD Anderson Cancer Center compared desmoid outcomes from 2

Table 1
Selected studies evaluating R0 versus R1 as prognostic factor for recurrence in desmoid tumor

Author	No. Patients	Tumor Types	Univariate Analysis	Multivariate Analysis
Mullen et al ³³	177	Intra-abdominal and Extra-abdominal	HR 0.42 (95% CI 0.22–0.79) <i>P</i> = .008	HR 0.39 (95% CI 0.19, 0.82) <i>P</i> = .012
Gronchi et al ²³	203	Extra-abdominal	—	Primary tumors HR 0.76 (95% CI 0.31, 1.88), recurrent tumors HR 1.92 (95% CI 0.80, 4.64) <i>P</i> = .14
Bertani et al ³⁹	62	Intra-abdominal and Extra-abdominal	—	HR 2.94 (95% CI 0.47, 18.20) <i>P</i> = .25
Huang et al ⁹	198	Extra-abdominal and abdominal wall	—	HR 3.11 (95% CI 1.40, 6.93) <i>P</i> = .005
Peng et al, ⁷ 2012	211	Intra-abdominal and Extra-abdominal	HR 2.16 (95% CI 1.17, 4.01) <i>P</i> = .01	HR 1.51 (95% CI 0.85, 2.66) <i>P</i> = .16
Crago et al ³⁷	495	Intra-abdominal and Extra-abdominal	HR 1.18 (95% CI 0.78, 1.80) <i>P</i> = .42	HR 0.99 (95% CI 0.65, 1.52) <i>P</i> = .97
van Broekhoven et al ⁴⁰	132	Extra-abdominal	HR 1.22 (95% CI 0.38, 3.90) <i>P</i> = .736	—
Spear et al, ³⁵ 1998	107	Extra-abdominal	NS	HR 3.00 <i>P</i> = .046

Abbreviations: CI, confidence interval; HR, hazard ratio.

distinct time frames: the first is 1965 to 1994 and a more modern cohort from 1995 to 2005. Interestingly, margin status was a significant predictor of disease recurrence in the older cohort but that significance was lost in the modern cohort despite similar rates of margin positive resections between the two groups (46% vs 47%).²² Evaluating the current data, it is not clear that recurrence rates are significantly different with microscopically positive margins. The inability to clearly define margin status as a prognostic factor has led to the recommendation that effort should be made to perform an R0 resection but not at the expense of organ or limb function. Re-resection for recurrent disease has similar cure rates as those achieved for primary resection, even in multiply recurrent patients.³⁴ Thus, for recurrent disease that is technically resectable without unreasonable morbidity, surgery should still be offered as a viable option for cure.

Frozen-section analysis has been used to help improve margin clearance.^{39,41} It is not clear whether this technique has led to improved R0 resection rates.⁴¹ In cases of recurrence it is difficult to distinguish desmoid fibromatosis from scar on frozen section. Based on these findings, the use of intraoperative frozen-section analysis is not recommended for confirmation of margin negative resection, as it is unreliable.

The surgical challenges of desmoid tumors extend beyond their infiltrative nature and ability to adequately obtain clear margins. Removal of these tumors in the abdominal wall or extremity locations can leave large anatomic defects. The goal in these locations is to restore skin and musculofascial integrity. This restoration often requires myocutaneous flaps and/or mesh for the abdominal wall. The safety of mesh closure was demonstrated in a study of 50 patients with abdominal desmoid tumor. Although more than half had an R1 resection, the recurrence rate was low at 8% and repairs were durable.²⁵ For those tumors that extend into the intra-abdominal space, care must be taken to close the peritoneum to prevent fistulas; alternatively staged reconstruction with bioprosthetic mesh may be appropriate. For extremity tumors limb-salvage is the standard. In a review of 15 patients who would require amputation for resection of limb recurrence, patients were treated with a variety of adjuvant therapies as well as observation alone. No one developed significant disease progression requiring amputation supporting the recommendation that function-preserving management is safe.⁴² Tumors of the extremity not amenable to R0 resection due to neurovascular involvement can often be resected in an R1 fashion using adjuvant systemic therapy or radiation to help achieve local control and avoid amputation. Multidisciplinary surgical approaches, including plastic and reconstructive surgery, are important in preoperative planning. Regional therapy with isolated limb infusion or perfusion has been used in a variety of skin and soft-tissue extremity tumors to control disease while avoiding amputation when other more conservative approaches have failed. The use of limb perfusion with tumor necrosis factor alpha and melphalan in desmoid tumors has been described and led to a response in 19 of 28 treatments in a cohort of 25 patients. Limb preservation was achieved in all but 3 patients.⁴³ This technique seems to be a viable approach for symptomatic, progressive tumors of the extremity. Given all of the aforementioned information, amputation is still appropriate in a select group of patients, including those with intractable pain, loss of function of the extremity, or complicated wounds.

Intra-abdominal tumors present a separate set of challenges, particularly those located in the mesentery of the bowel. Proximity to the superior mesenteric artery and vein may limit resectability. Efforts to obtain histologically negative margins can lead to significant loss of bowel length and does not improve recurrence rates or overall survival.⁴⁴ Surgical bypass may be preferable in symptomatic patients with extensive vascular involvement in an effort to limit morbidity and mortality.⁴⁵

Historical data have suggested that recurrence rates for intra-abdominal tumors in patients with FAP were higher than those with sporadic disease; however, more recent data suggest that there is no difference.²⁴ The propensity for the FAP population to develop mesenteric tumors that are diffuse and difficult to resect may be the reason for previous findings. With more modern surgical and nonsurgical strategies, the algorithm for patients with FAP is the same as those with sporadic disease. Treatment decisions should be made in the context of a multidisciplinary review and use multimodality therapy with surgery reserved for those with impending loss of critical structures or symptoms.

Surgical resection with wide local excision can achieve cure or local control of disease for most desmoid tumors. The goal of surgical resection should be a margin negative resection with the preservation of function of surrounding involved organs and structures.

Systemic Therapy

Because of the propensity for recurrence and the morbidity of repeat resections, there has been a multitude of therapies used to treat desmoid tumors either in the adjuvant setting or as definitive treatment. Traditionally the use of systemic therapy has been in the unresectable, recurrent, or progressing desmoid tumors; but this is changing.

Hormonal and nonsteroidal antiinflammatory drugs

Antiestrogen agents and NSAIDs are considered first-line agents because of their effectiveness and relatively low side-effect profile.^{2,38,46–48} Based on the observation that many desmoid tumors stain strongly positive for estrogen receptor, the use of antiestrogen therapy may have a biological basis. The most common antiestrogen agents are tamoxifen and raloxifene. Response rates to these agents are approximately 40% to 51%.^{20,49} Sulindac is the most commonly used NSAID. The response rate to this NSAID is approximately 28%.²⁰

To improve response rates, hormonal therapies and NSAIDs are typically used in combination. A report of 134 patients treated with both an antiestrogen agent and sulindac achieved an 85% response rate when used as either adjuvant or definitive therapy. In patients who had previously been resected, therapy could eventually be tapered with only one long-term recurrence.⁵⁰ This group contained patients with sporadic and FAP-related tumors. The high response rate and durability is encouraging for nonsurgical management of these tumors. However, an objective response may take several months to achieve stability of disease and decrease in associated symptoms.^{46,47,50}

Chemotherapy

The response rate of chemotherapy in desmoid tumors has been reported to be as high as 79%.^{20,47,51} Similar to hormonal and NSAID therapy, time to response can be variable. Because of the associated side effects, chemotherapy is generally considered second-line systemic therapy. For those with rapidly progressive disease, impending destruction of critical anatomic structures, or symptomatic, unresectable tumors, it should be considered as a first-line therapy.^{20,47,51–53} Combinations using anthracyclines seem to be the most effective. Other commonly used agents include methotrexate, vinblastine, and cisplatin.

Anthracycline-based regimens have resulted in long PFS and even complete responses. In a retrospective study by the French Sarcoma Group evaluating the role of chemotherapy in desmoid tumors, response rates favored anthracycline-based regimens compared with other systemic therapies (54% vs 12% $P = .0011$). The

anthracycline group contained only 13 patients; all experienced stable disease (46%) or a partial response (PR) (54%).⁵⁴ Others have confirmed these results with a PFS of 74 months in anthracycline-based therapy.⁵¹ Toxicity is higher with this regimen resulting in grade 3 to 4 hematological toxicities in approximately 31% to 43% of patients.^{51,54} Cardiotoxicity is a concern for this regimen particularly because of the young patient population. A pegylated liposomal formulation of doxorubicin, which improves drug delivery with decreased cardiotoxicity, has been reported. A small series has shown similar efficacy as all patients had either PR (36%) or stable disease (64%) with decreased toxicity.⁵⁵

Another commonly used regimen for desmoids is termed low-dose chemotherapy, which consists of methotrexate and vinblastine. This regimen has consistently resulted in stable or responding disease in 67% to 100% of patients treated.^{47,54,56} Low-dose chemotherapy has been associated with a durable response and 5-year PFS as high as 67%.⁵⁶ Similar to anthracycline-based regimens, toxicity results in patient intolerance and a 50% attrition rate. Neurotoxicity related to vinblastine is the most common side effect resulting in patient intolerance. Another Vinka alkaloid, vinorelbine, has been described as an effective alternative to vinblastine with less long-term neurotoxicity.^{57,58} This alkaloid is also given with methotrexate and may be a useful regimen in patients who do not tolerate vinblastine.

Targeted therapy

The tyrosine kinase inhibitors (TKI) have been used for the treatment of desmoids resulting in stability of disease, limited toxicity, but low response rates. A phase II trial using imatinib reported a 1-year PFS of 66% but an objective response rate of only 6%.⁵⁹ In a heavily pretreated group of patients using higher doses of imatinib, Heinrich and colleagues⁶⁰ saw a 15.7% PR rate ($\geq 50\%$ tumor shrinkage). The duration of response was greater than 1.5 years for all patients. In a third phase II trial using imatinib patients experienced progression free survival of 67% at 1 year.⁶¹ Toxicity for all 3 of these trials was acceptable with very few grade 4 toxicities, which were treated effectively with dose reduction. In addition to these phase II trials, other small retrospective reviews have revealed stable or PR in 36% to 80% of patients treated with TKI and a median PFS of nearly 27 months by Response Evaluation Criteria in Solid Tumors (RECIST) criteria.⁴⁷

Sunitinib, another TKI that also blocks vascular endothelial growth factor receptors, has also been investigated for use in the treatment of desmoid tumors. A phase II study showed an overall response rate of 26.3% and a 2-year PFS rate of 74.7%. Importantly, 3 of the 12 patients with mesenteric disease developed serious adverse events with the first dose of treatment, which presented as tumor bleeding, bowel perforation, and entero-tumoral fistula formation. The investigators postulate that all of these events could be explained by the drugs antiangiogenic affect with resultant tumor necrosis.⁶² Although this report may signify sunitinib as a potent treatment of desmoids, the significance of adverse events with this therapy should be noted.

Other TKI and antiangiogenic drugs that have been evaluated and shown to have efficacy in treating desmoid tumors are sorafenib and pazopanib.^{63,64} In a retrospective review of 26 patients treated with sorafenib, 70% of patient-reported improved symptoms and 95% of patients had either a PR or stable disease at 6 months.⁶³ Following the response seen from sorafenib, the antiangiogenic drug pazopanib has also shown promise as a potential option in treating desmoid tumors. Two case reports show that patients treated with pazopanib had improved symptoms, tumor shrinkage, and decreased tumor cellularity similar to results seen with sorafenib.⁶⁴

Conclusions regarding these drugs' efficacy must be interpreted with caution until larger prospective clinical trials are performed to validate initial findings.

Novel therapies

Therapies are evolving as new information emerges on the pathophysiology of desmoid tumors. The NOTCH pathway drives several cancer-related processes in solid tumors and has recently been recognized as a potential therapeutic target in desmoid tumors. It can be blocked by γ -secretase inhibition. Desmoid tumor cell lines treated with a γ -secretase inhibitor showed decreased cell growth, migration, and invasion.⁶⁵ In an open-label phase I dose-escalation trial of a γ -secretase inhibitor, 5 of 7 patients with desmoid tumors that were treated showed an objective response rate of 71.4% with some patients achieving durable response.⁶⁶ These promising early data have led to an ongoing phase II trial.⁶⁷ Recently another target, hyaluronan (HA), a glycosaminoglycan in the stromal microenvironment involved with normal wound healing, has also been associated with desmoid tumorigenesis.⁶⁸ HA levels were shown to be overexpressed in desmoid tumor surgical specimens as well as in immortalized cell lines. By using an inhibitor of HA, tumor proliferation rates as well as HA levels were decreased, suggesting a novel therapeutic target in treating desmoid fibromatosis. As the pathways in desmoid tumorigenesis are elucidated, novel therapeutic targets will continue to emerge.

Radiation Therapy

The use of radiation therapy in desmoid tumors has been evaluated in several settings. It has been used as adjuvant therapy for margin positive resections and to decrease recurrence of completely resected tumors. Radiation has also been used successfully as a definitive treatment of unresectable tumors or for tumors whereby resection would be associated with unacceptable morbidity or functional deficit.

In a large meta-analysis of 22 studies evaluating patients treated with surgery, surgery plus radiation, or radiation alone revealed a superior local control rate with radiation or radiation plus surgery (78% and 75%, respectively) than patients treated with surgery alone (61%).⁶⁹ The investigators suggested that all patients with desmoid be treated with radiation. However, the radiation doses in this study were highly variable; this recommendation does not take into consideration the morbidity associated with radiation. Complication rates related to radiation for desmoid fibromatosis are 17% to 23%.^{21,69,70} Radiation-induced malignancies are particularly relevant in a disease that often affects a younger cohort of patients.⁷⁰ In a more recent single-institution retrospective review of 95 patients, investigators found no difference in the rate of recurrence for surgery alone (14.8%), radiation alone (15.4%), and surgery plus radiation (32.1%) ($P = .300$). There was also no association between local control and radiation therapy in those patients with a positive margin.⁷¹ They did find that the head and neck location was associated with increased recurrence in their patient population. The investigators concluded that a subset of patients with high risk for local failure can be identified that may benefit from adjuvant radiation, including those with head and neck location, recurrent disease after surgery, and possibly those with positive margins. Although there seems to be a real benefit of radiation for some patients, the true utility of radiation as an adjuvant therapy in desmoid fibromatosis has not been evaluated in a prospective, randomized trial. Most studies are small, retrospective, and do not have standardization of patient selection. Because of the lack of clearly defined indications for radiation, it is critical to make these decisions in large-volume multidisciplinary centers to properly select patients to optimize benefit and avoid unnecessary exposure and morbidity from this treatment.

Definitive radiation seems to be as effective as surgery for those that would otherwise need radical and disfiguring surgery. Radiation as the primary mode of therapy for unresectable disease offers a 70% to 80% chance of local control in retrospective studies.^{21,72,73} The European Organization for Research and Treatment of Cancer conducted a phase II study that standardized treatment of 44 patients with unresectable disease to 56 Gy received in 28 fractions. At 3 years, local control was 81.5% with 13.6% of patients having a complete response. Notably, radiation response will continue beyond 3 years in some patients promoting the durability of this therapy for unresectable disease.⁷³ For patients treated unsuccessfully with definitive radiation, surgery or systemic therapy may be an option as salvage therapy.

The use of radiation for desmoid tumors in a neoadjuvant setting has not been investigated in a trial but has been reported. The proposed benefit would be for those patients who are initially deemed unresectable or when a response would allow preservation of critical structures decreasing the morbidity of surgical resection. Because of the small numbers of patients treated with neoadjuvant radiation followed by surgery, it is difficult to evaluate the true benefit of this approach, although it seems to be similar to either modality alone.²¹ Radiation has also been used in combination with chemotherapy in the neoadjuvant setting in small series and was associated with a control rate of 85% to 90%.^{74,75}

Watchful Waiting

The heterogeneous nature of desmoids has led to a variety of therapies used to treat and control the disease. In many large databases, there are patients who receive no treatment of their tumors but have shown no progression and sometimes even spontaneous regression. While evaluating the best initial therapy for primary desmoid tumors, Bonvalot and colleagues²⁶ compared a group of patients who were treated nonsurgically with those who underwent surgery as their initial therapy. Three-year event-free survival was similar between the groups (68% no surgery vs 65% surgery). The nonsurgical group included medically treated patients and patients who underwent observation only. To understand this observation further, a multi-institutional study to evaluate the wait-and-see approach was undertaken. Patients were stratified into an observation group or a medical therapy group from a prospective database. In the 83 patients treated with observation, the 5-year PFS was 49.9%, which was not different from the 58.6% PFS in the 59 medically treated patients.³² Significant prognostic factors to identify progression were not identified. When progression occurred, it was in the first 2 years for most patients (89%). Based on these findings, the investigators have proposed close disease surveillance for 24 months. These data led to several notable European groups developing proposals to standardize desmoid tumor management such that a watchful-waiting strategy is the first step for all new tumors.^{6,46} Patients will be followed closely by a multidisciplinary team, with escalation of care only if the tumor declares an aggressive phenotype and spare patients with indolent tumors the morbidity of aggressive therapy (**Fig. 2**).

This approach should not be confused with doing nothing and may not be appropriate for every tumor. It requires close follow-up and monitoring of the disease with appropriate imaging based on tumor location. The recommended imaging schedule is every month for 2 months, every 3 months for the first year, then every 6 months up to 5 years, and yearly thereafter.⁴⁶ It is most appropriate in patients with tumors that are asymptomatic and free of anatomically critical structures. For those with tumor adjacent to critically important anatomy, frequent imaging is critical so as to not lose an operative window.

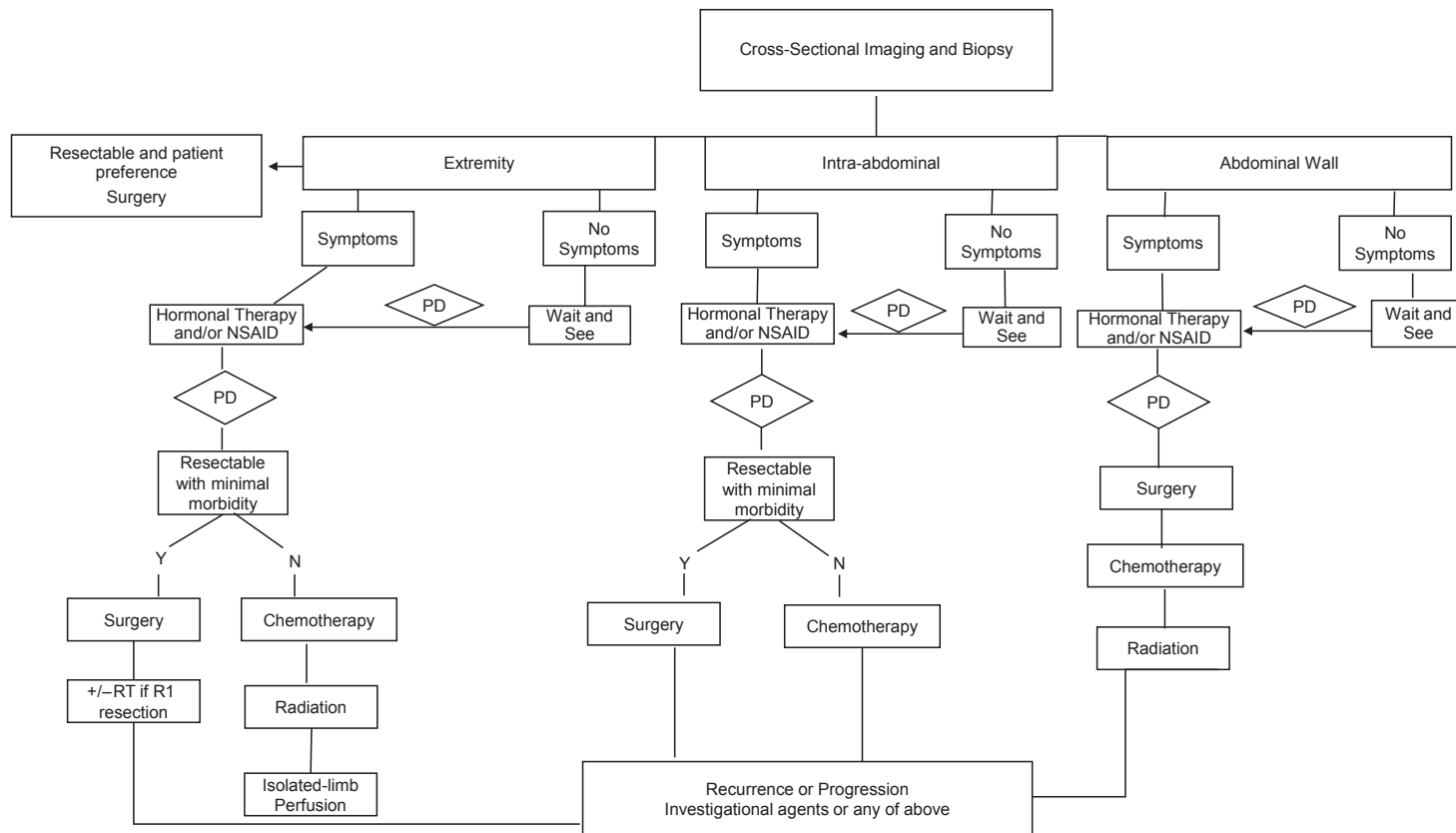


Fig. 2. Management algorithm for treatment of desmoid tumors. PD, progressive disease; RT, radiation therapy.

SURVEILLANCE

Recurrence for desmoid tumor typically occurs within the first 2 years.²² After complete surgical resection or other definitive therapy, patients should be surveyed with appropriate imaging every 3 to 6 months for 2 to 3 years and then annually.⁷⁶

SUMMARY

Because of the rarity of the disease and most data being retrospective, it is difficult to define a clear treatment algorithm. Many studies have had differing results in determining prognostic factors that lead to recurrence. Overall the treatment must be individualized and is best accomplished at large-volume centers with a multidisciplinary approach.

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