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Release date: December 10, 2020; Expiration date: December 10, 2021

Learning Objectives:

Upon completion of this activity, participants will be able to:

- Integrate into professional practice the updates to the NCCN Guidelines for Soft Tissue Sarcoma
- Describe the rationale behind the decision-making process for developing the NCCN Guidelines for Soft Tissue Sarcoma

Disclosure of Relevant Financial Relationships

The NCCN staff listed below discloses no relevant financial relationships:

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Soft Tissue Sarcoma, Version 1.2021

Featured Updates to the NCCN Guidelines

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ABSTRACT

The NCCN Guidelines for Soft Tissue Sarcoma provide recommendations for the diagnosis, evaluation, treatment, and follow-up for patients with soft tissue sarcomas. These NCCN Guidelines Insights summarize the panel discussion behind recent important updates to the guidelines, including the development of a separate and distinct guideline for gastrointestinal stromal tumors (GISTs); reconception of the management of desmoid tumors; inclusion of further recommendations for the diagnosis and management of extremity/body wall, head/neck sarcomas, and retroperitoneal sarcomas; modification and addition of systemic therapy regimens for sarcoma subtypes; and revision of the principles of radiation therapy for soft tissue sarcomas.

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Category 1: Based upon high-level evidence, there is uniform NCCN consensus that the intervention is appropriate.

Category 2A: Based upon lower-level evidence, there is uniform NCCN consensus that the intervention is appropriate.

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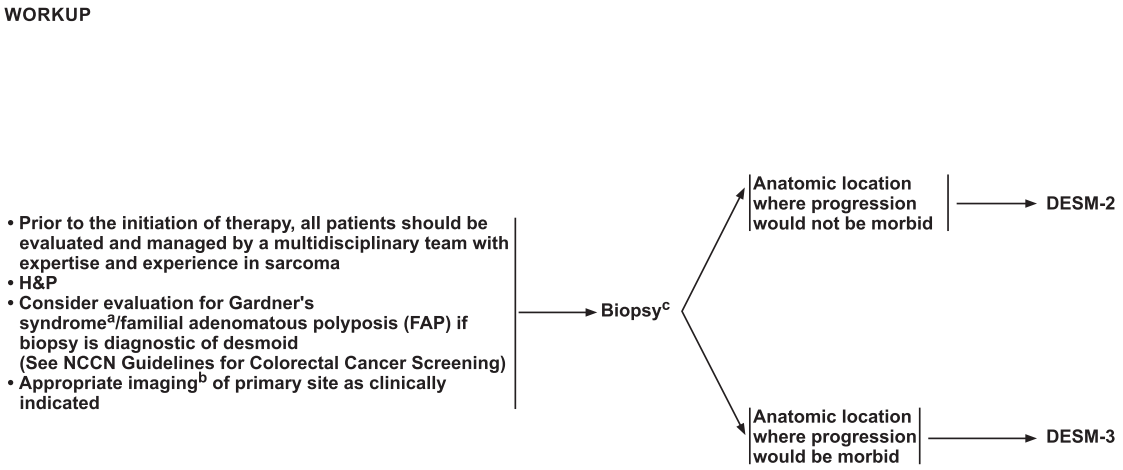


[a]Gardner's syndrome is an autosomal dominant disorder characterized by a triad of colonic polyposis, osteoma, and soft tissue tumors. (Traill Z, et al. AJR Am J Roentgenol 1995;165:1460-1461).
[b]See Principles of Imaging (SARC-A).
[c]See Principles of Pathologic Assessment of Sarcoma Specimens (SARC-B).

DESM-1

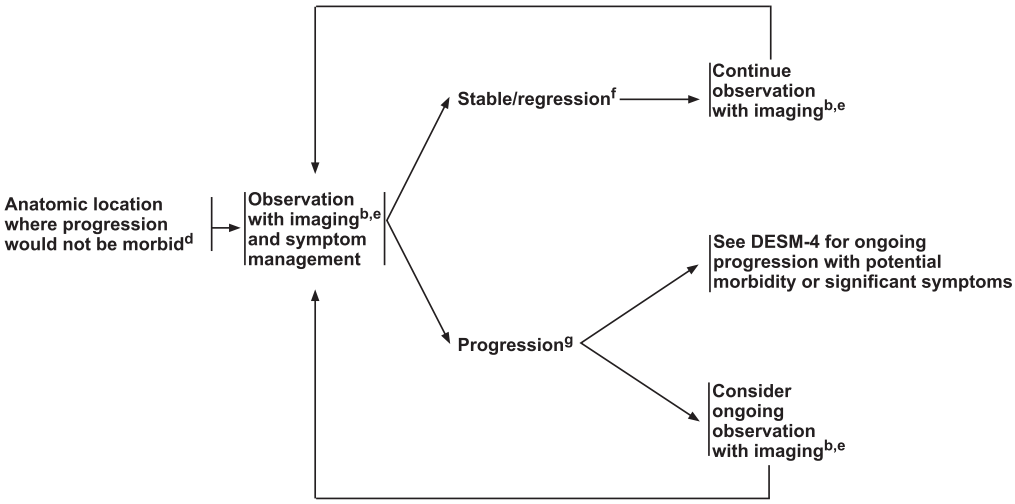
Overview

Collectively, sarcomas are a heterogenous group of solid tumors of mesenchymal origin. They can be divided broadly into sarcomas arising from soft tissues (such as fat, muscle, blood vessels, nerve/nerve sheath, and other connective tissues) and those arising from bone. Although bone sarcomas are covered in the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines) for Bone Cancer, and Gastrointestinal Stromal Tumors (GISTs) are now detailed in their own separate NCCN Guidelines, the NCCN Guidelines for Soft Tissue Sarcoma address in depth the following soft tissue sarcoma (STS) subtypes: STS of extremity/body wall, head/neck, retroperitoneal and intraabdominal STS, desmoid tumors (aggressive fibromatosis), and rhabdomyosarcoma (RMS).

Sarcomas are relatively rare, accounting for only 1% of all adult malignancies and 15% of childhood malignancies.[1] It is estimated that in 2020, 13,130 people in the United States will be diagnosed with STS, with approximately 5,350 deaths.[2] There are estimated to be >50 different histologic subtypes of STS with varying clinical and biologic characteristics.[3]

Characterized by local infiltration rather than distant metastasis, desmoid tumors (DTs), or aggressive fibromatosis (AF), are a unique soft tissue tumor subtype.[4] They are rare, thought to affect only 1 to 2 per 500,000 individuals worldwide, with approximately 900 to 1,500 new cases diagnosed annually within the United States.[5] Peak incidence occurs among individuals aged 25 to 35 years.[4] They most often occur sporadically (>90%)[6] and in postpartum females, or may be diagnosed in association with familial adenomatous polyposis (FAP) or its variant, Gardner syndrome.[5]

Although reports of fatality outside of individuals with FAP are infrequent, DTs may cause significant morbidity, including chronic pain, functional impairment, disfigurement, and numerous psychological ramifications (eg, depression and anxiety). Therefore, an optimal treatment plan determined by a multidisciplinary team of providers with experience and expertise in the management of sarcomas is recommended. Due to the possibility of spontaneous regression, an initial period of observation, or active surveillance, has now been adopted as the first-line approach for many patients. In the event of disease progression, a short course of observation may again be considered if the patient is minimally symptomatic or the



[b]See Principles of Imaging (SARC-A).
[d]For tumors that are symptomatic, or impairing or threatening in function, patients should be offered therapy with the decision based on the location of the tumor and potential morbidity of the therapeutic option.
[e]Optimal frequency for imaging depends on the anatomical location of tumor, risk of progression, and symptoms of disease progression. Imaging every 3 months is recommended. More frequent imaging may be indicated in symptomatic patients.
[f]Spontaneous regression has been reported in 20% of patients, supporting an initial period of observation in patients with newly diagnosed desmoid tumors (Gounder MM, et al. N Engl J Med 2018;379:2417-2428).
[g]A course of ongoing observation is an appropriate option even for patients with disease progression, if the patient is minimally symptomatic and the anatomical location of the tumor is not critical.

DESM-2

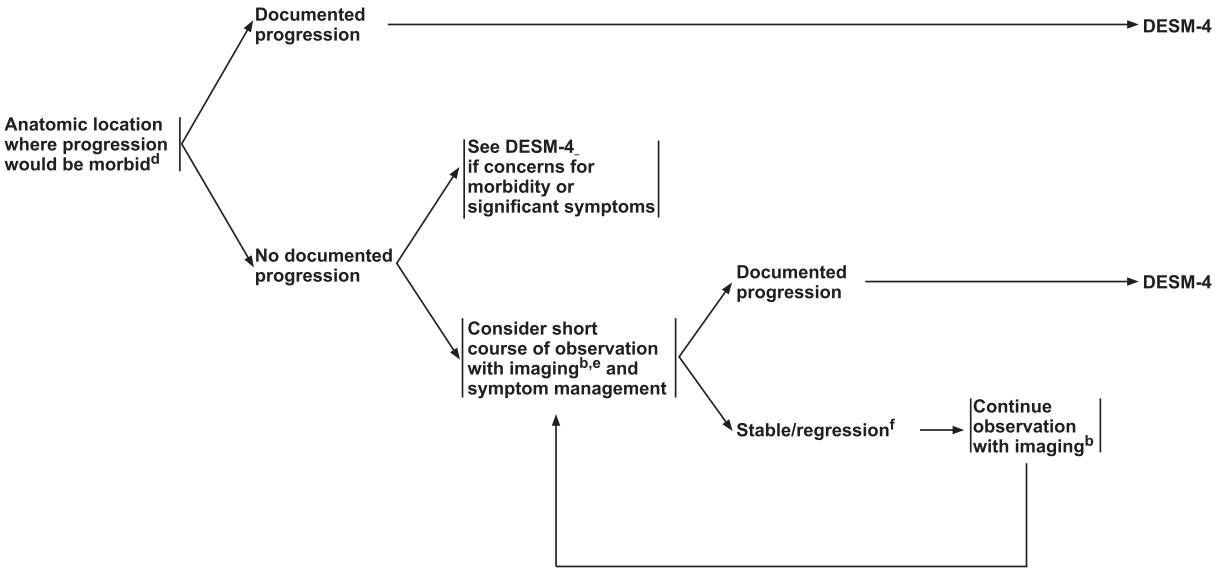
anatomic location is not critical. For patients who exhibit ongoing progression with potential morbidity and significant symptoms, intervention is recommended. Treatment options include surgery (if resectable), systemic therapy, definitive radiation therapy (RT), ablation procedures, or surgery with RT. Choice of therapy is dependent upon the anatomic location (ie, abdominal wall, intra-abdominal/retroperitoneal/pelvic, truncal/extremity, or head/neck/intrathoracic) and institutional expertise.

The NCCN Guidelines for STS provide recommendations for the diagnosis, evaluation, treatment, and follow-up of patients with soft tissue sarcomas. These NCCN Guidelines Insights summarize the panel discussion behind recent important updates to the guidelines, including the development of a separate and distinct guideline for GISTs; reconception of the management of DTs; inclusion of further recommendations for the diagnosis and management of extremity/body wall, head/neck sarcomas, and retroperitoneal sarcomas; modification and addition of systemic therapy regimens for sarcoma subtypes; and revision of the principles of RT for STS.

Genetics and Risk Factors

Grossly, DTs are locally invasive with infiltration into surrounding tissues. Microscopically, they are characterized by fascicles of low-grade appearing fibroblasts and myofibroblasts.[7] As mentioned earlier, DTs can occur either sporadically or in association with FAP or Gardner syndrome. Inherited in an autosomal dominant manner, FAP is characterized by mutations in the adenomatous polyposis coli (*APC*) tumor suppressor gene. Individuals with FAP are predisposed to the development of >100 adenomatous polyps, most commonly in the colon and rectum, as well as the occurrence of DTs.[8] DTs are reported to occur in 7.5% to 16% of patients with FAP,[9,10] and more commonly arise in the intra-abdominal region in these individuals.[8,11] Research suggests that previous surgery (especially open as opposed to laparoscopic procedures) in individuals with FAP is a risk factor for desmoid formation.[8] In individuals with FAP who have undergone surgery, intra-abdominal DTs are reported to be among the leading causes of mortality (due to bowl obstruction or ulceration).[12,13] Other risk factors for sporadic DTs include a positive family history for DTs, hormonal exposure (estrogens), trauma, and previous pregnancy or abdominal surgery.[10,14] Gardner syndrome is a subtype of FAP characterized by a triad of colonic polyposis, osteomas, and soft tissue tumors (epidermoids and desmoids).[15,16]

Although mutations in the *APC* gene are responsible for hereditary DTs, mutations in the *CTNNB1* gene encoding β-catenin have been implicated in sporadic



[b]See Principles of Imaging (SARC-A).
[d]For tumors that are symptomatic, or impairing or threatening in function, patients should be offered therapy with the decision based on the location of the tumor and potential morbidity of the therapeutic option.
[e]Optimal frequency for imaging depends on the anatomical location of tumor, risk of progression, and symptoms of disease progression. Imaging every 3 months is recommended. More frequent imaging may be indicated in symptomatic patients.
[f]Spontaneous regression has been reported in 20% of patients, supporting an initial period of observation in patients with newly diagnosed desmoid tumors (Gounder MM, et al. N Engl J Med 2018;379:2417-2428).

DESM-3

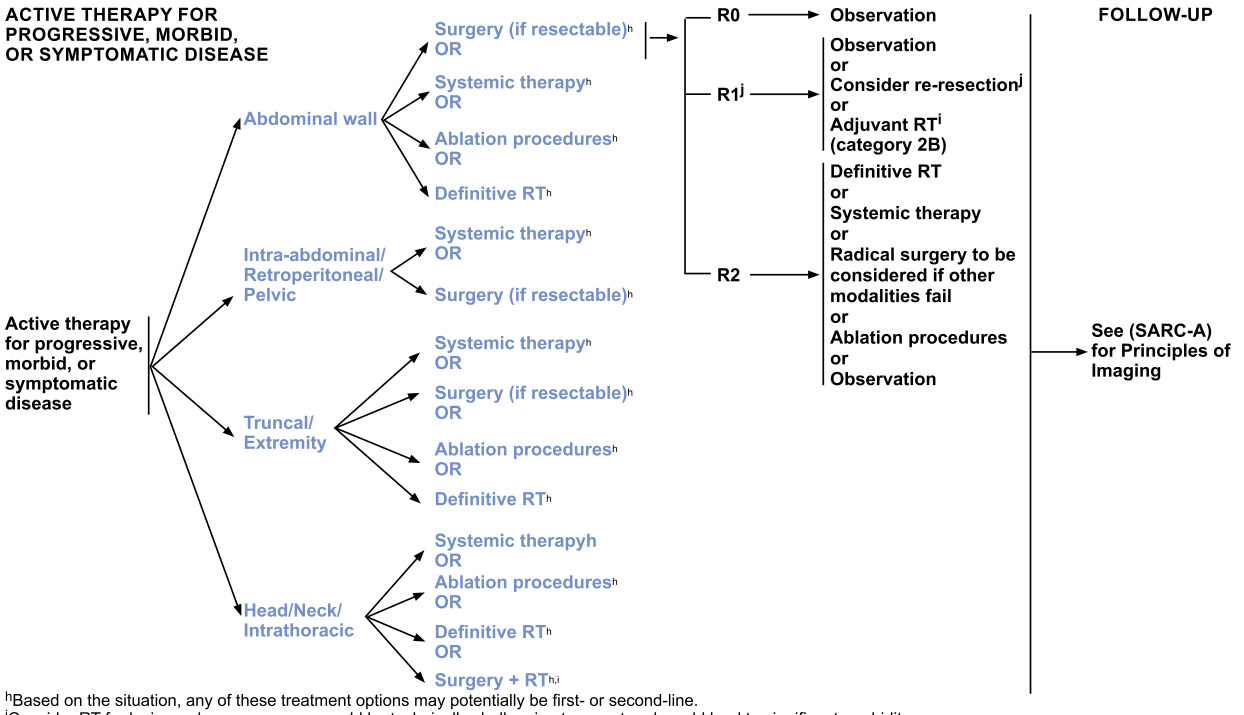
desmoids.[17] The *APC* and *CTNNB1* mutations are mutually exclusive; hence, recognition of a somatic *CTNNB1* mutation excludes syndromic origin.[18] Three distinct mutations in the *CTNNB1* gene have been identified: T41A, S45F, and S45P.[19] Several studies have reported an increased risk of recurrence associated with the S45F mutation.[20,21] Although further research is required to confirm the prognostic significance of genotyping, DTs are characterized ultimately by aberrant Wnt signaling.[19] Diagnosis of DT requires a thorough patient history and physical examination (with evaluation for FAP/Gardner syndrome) followed by imaging of the primary site (using either CT or MRI) and a biopsy for confirmation.

Observation: An Initial Management Approach

The treatment paradigm of AF has shifted in recent years from active intervention to initial observation in the absence of progressive, morbid, or symptomatic disease. Although historically surgery (ie, wide local excision) has been the primary modality of treatment of DTs, given that spontaneous regression has been reported in 20% of cases,[6] an initial period of observation is permissible in many patients with newly diagnosed DTs. In an institutional analysis involving 213 patients with pathologically confirmed DTs that were either sporadic (48%), associated with pregnancy (14%), or affiliated with FAP (38%), individuals were divided into 3 groups: A (untreated patients), B (patients with desmoids that were resected elsewhere), and C (patients with recurrent tumors). It was reported that of the 176 individuals in group A, 109 underwent initial observation. Of this subset, 51 individuals required intervention, whereas 93% of the remaining 58 patients who underwent observation demonstrated spontaneous regression or stable disease.[22]

In a more recent study, active surveillance was used for the initial management of 168 patients with primary DTs. A total of 36% of patients displayed progressive disease radiographically, whereas 36% exhibited stable disease and 27% showed regression. Progression was more often noted in patients aged <50 years. Overall, 46% of patients required treatment following a median initial surveillance period of 31 months. The most common indications for treatment included pain (32%), progression (31%), or both. It was concluded that although nearly 50% of patients with desmoids may eventually require treatment, an initial period of active surveillance may be appropriate for many patients given the rate of spontaneous regression and stabilization.[23]

The Desmoid Tumor Working Group, as published in their 2020 global consensus paper, also supports an



[h]Based on the situation, any of these treatment options may potentially be first- or second-line.
[i]Consider RT for lesions where recurrence would be technically challenging to resect and would lead to significant morbidity.
[j]R1 margins are acceptable if achieving R0 margins would produce excessive morbidity (Cates JM, et al. Am J Surg Pathol 2014;38:1707-1714; Crago AM, et al. Ann Surg 2013; 258:347-353; and Salas S, et al. J Clin Oncol 2011;29:3553-3558).

DESM-4

initial active surveillance approach as the first step in the management of DTs.[18] The group cites a comparative study conducted by Penel et al[24] in which event-free survival (EFS) rates showed little difference between patients managed with initial observation (58%) and those managed with surgery (53%). They found that for favorable anatomic locations (eg, abdominal wall, lower limb), 2-year EFS was comparable in individuals treated surgically (70%) and conservatively (63%); whereas for unfavorable anatomic locations (eg, head/neck, chest wall), 2-year EFS was superior in those managed conservatively (52% vs 25%).[24] Several other studies also support an initial period of active surveillance for asymptomatic or nonprogressive disease.

Given the evidence for a conservative approach, the NCCN panel now recommends that patients confirmed to have a DT undergo an initial period of observation in the absence of progressive, morbid, or symptomatic disease. In the case of progressive disease, a short course of observation may again be considered if the patient is minimally symptomatic or the anatomic location is not critical. Intervention is recommended for patients who exhibit ongoing progression with potential morbidity and significant symptoms.

Active Therapy for Progressive, Morbid, or Symptomatic Disease

Choice of therapy for progressive, morbid, or symptomatic disease depends upon the site of origin (eg, abdominal wall, intra-abdominal/retroperitoneal/pelvic, truncal/extremity, or head/neck/intrathoracic) and institutional expertise. For patients with DTs arising from the abdominal wall, treatment consists of either surgery (if resectable), systemic therapy, ablation procedures, or definitive RT. For DTs originating from an intra-abdominal, retroperitoneal, or pelvic region, the NCCN panel recommends systemic therapy or surgery (if resectable). RT and ablation procedures should be avoided in such sites. Systemic therapy, surgery (if resectable), ablation procedures, or definitive RT may be considered for DTs arising from the trunk or extremity. Finally, for head, neck, or intrathoracic DTs, the panel recommends treatment in the form of systemic therapy, ablation procedures, definitive RT, or surgery with adjuvant RT.

Although upfront surgery was formerly the mainstay of treatment of DTs, the postoperative recurrence rate was found to be unacceptably high (>40%).[6] Risk factors associated with recurrence included larger tumor size,

SYSTEMIC THERAPY

Desmoid Tumors (Aggressive Fibromatosis)

	Preferred Regimens	Other Recommended Regimens	Useful in Certain Circumstances
• Time to response less critical	• Methotrexate and vinorelbine • Methotrexate and vinblastine		• Sulindac or other nonsteroidal anti-inflammatory drugs (NSAIDs), including celecoxib (for pain)
Time to response more critical	• Sorafenib (category 1) • Imatinib • Pazopanib[38] • Liposomal doxorubicin • Doxorubicin ± dacarbazine		

SARC-F 2 OF 9

younger age, and the presence of a *CTNNB1* S45F mutation.[13] Similar rates of recurrence were found following R0 and R1 resections, and therefore the significance of margin status is debated.[4] Regardless, surgery may be considered a treatment option for progressive, morbid, or symptomatic disease that is resectable. Although the goal of surgery in such cases is a complete microscopic resection, if an R0 resection would lead to undue morbidity, an R1 resection may be acceptable. Following an R1 resection, observation or further treatment in the form of reresection or adjuvant RT may be considered. Treatment options following an R2 resection include definitive RT, systemic therapy, radical surgery, ablation procedures, or observation.

RT may be administered definitively or in the adjuvant setting (following an R1/R2 resection). The NCCN panel has included definitive RT as a treatment option for progressive DTs, except for those arising from an intra-abdominal, retroperitoneal, or pelvic site. Previous studies have reported good long-term local control rates with RT (70%–93%).[25] In a study of patients with AF treated with RT, overall survival (98% at 5 years) and local control (82% at 5 years) were reported to be exceptional. However, it was found that younger patients (aged <20 years) demonstrated significantly poorer 5-year local control than older patients (72% vs 97%, respectively).[26] Similarly, in a review of 209 patients with DT treated with either RT alone or with surgery, it was found that among both treatment arms, individuals aged ≤30 years and those who had larger tumor size (>10 cm) exhibited poorer local control.[27] Thus, although RT may be an effective local control modality for DTs, caution must be exercised with its use in younger patients given their unique tumor biology and associated radioresistance and future risk for radiation-induced malignancies.

The panel has included ablation procedures as a treatment option for desmoids. A retrospective study of 23 patients with extra-abdominal DTs who received either initial or salvage CT-guided percutaneous cryoablation reported a 90% clinical response rate. The average tumor volume reduction at 12 months was 81%, and 71% of individuals exhibited complete response or partial response (based on modified RECIST criteria).[11] Other studies have also published favorable outcomes for percutaneous image-guided cryoablation, although its use is not advisable in larger tumors or in desmoids abutting critical structures.[28,29] Several studies have also

reported good local control with radiofrequency ablation (RFA).[30–32] In one study of 4 patients treated with RFA and followed for a mean duration of 30 months, no recurrence was reported and complications included skin ulceration and cellulitis.[30] High-intensity focused ultrasound (HIFU) is another emerging treatment alternative for progressive or symptomatic desmoids. In a multicenter study of 15 patients with DTs treated with MR-guided focused ultrasound, median viable targeted tumor volume was reduced to 63% after treatment, with significant improvement in pain.[33] Similar outcomes with minimal complications (eg, superficial burns) have also been reported by others supporting the use of HIFU in the treatment of extra-abdominal desmoids.[34–37] Thus, ablative therapies offer novel treatment approaches and may be considered as an alternative to RT; however, data supporting the safety and efficacy are still limited at this time.

The panel has organized the systemic therapy regimens for desmoids according to treatment urgency: "time to response more critical" and "time to response less critical." The regimens have been preference-stratified according to the NCCN Categories of Preference. Preferred agents under "time to response more critical" include sorafenib, imatinib, liposomal doxorubicin, doxorubicin ± dacarbazine, and finally, pazopanib. Hormonal (antiestrogen) agents have been removed by the NCCN panel due to lack of meaningful response, unpleasant side effects (eg, hot flashes), and the potential risk for thrombotic events or uterine malignancies. Preferred regimens under "time to response less critical"' include methotrexate/vinblastine and methotrexate/vinorelbine. Nonsteroidal anti-inflammatory drugs, including sulindac and celecoxib, have been included under "useful in certain circumstances" for patients experiencing pain.

Pazopanib was added to the NCCN Guidelines following the noncomparative, randomized, open-label, multicenter phase II DESMOPAZ study, in which patients were randomized to receive either pazopanib or methotrexate/vinblastine. The primary endpoint was the proportion of patients with no progression after 6 months who completed 1 cycle or 2 incomplete cycles of pazopanib or methotrexate/vinblastine. Among the first 43 patients in the pazopanib treatment arm, 83.7% (95% CI, 69.3%–93.2%) showed no progression at 6 months, whereas only 45% (95% CI, 23.1%–68.5%) of those in the methotrexate/vinblastine treatment arm exhibited no progression at 6 months. Based on its efficacy and tolerable safety profile (most common grade 3/4 adverse effects were hypertension and diarrhea), pazopanib has been included as a treatment option for progressive, symptomatic, or morbid desmoids with an NCCN category 2A recommendation.[38]

Following treatment, follow-up should include history and physical examination accompanied by imaging (CT or MRI) every 3 to 6 months for 2 to 3 years, and then every 6 to 12 months thereafter to assess for recurrence. Ultrasound may be an alternative imaging modality for select locations (eg, abdominal wall).

Summary

Given the rate of spontaneous regression and high postoperative recurrence rate, the NCCN panel has adopted a treatment strategy of initial observation for patients with asymptomatic and nonprogressive desmoids. This preference for a first-line active surveillance approach obviates unnecessary surgery and any associated complications. In the event of progressive, morbid, or symptomatic disease, the panel has delineated treatment options according to the disease site. Treatment options include surgery (if resectable), systemic therapy, definitive RT, ablation procedures, or surgery with RT. Finally, pazopanib has been added to the systemic therapy options for DTs, which have since been reorganized according to treatment urgency and preference-stratified according to the NCCN Categories of Preference.

To participate in this journal CE activity, go to https://education.nccn.org/node/89065

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