

Desmoid Tumours

Effective Date: July, 2017

The recommendations contained in this guideline are a consensus of the Alberta Provincial Sarcoma Tumour Team and are a synthesis of currently accepted approaches to management, derived from a review of relevant scientific literature. Clinicians applying these guidelines should, in consultation with the patient, use independent medical judgment in the context of individual clinical circumstances to direct care.

BACKGROUND

Desmoid tumours (aggressive fibromatosis, deep musculoaponeurotic fibromatosis, and formerly fibrosarcoma grade I of the desmoid type), are locally aggressive tumours which do not metastasize or differentiate. Desmoids are locally aggressive and have a high rate of recurrence even after complete resection. Tumour-related destruction of vital organs can be fatal, particularly in patients with familial adenomatous polyposis (familial adenomatous polyposis (FAP); Gardner's syndrome).

Desmoid tumours are rare, accounting for approximately 0.03% of all neoplasms and less than 3% of soft tissue sarcomas (STS). The estimated incidence in the general population is 2-4 per million population per year ¹. Desmoids have no significant racial or ethnic predilection, occur most frequently in individuals between 15 and 60 years of age, and are more common in women than men ².

The risk of developing a desmoid is increased by approximately 850 times in patients with FAP versus the general population with the majority of desmoids being associated with the abdomen, although extremity desmoids can also occur ³. Other risk factors include family history of desmoid tumour, pregnancy, and APC mutation (3' of codon 1444)^{4,5}.

GUIDELINE QUESTIONS

- What is the appropriate diagnosis and work-up strategies for patients with desmoids?
- For desmoid patients, when is Surgery/ Systemic Therapy/ Radiotherapy/ Watch and Wait appropriate and when are these treatment strategies contraindicated?
- What is the appropriate follow-up protocol for patients with desmoid tumours who have been treated or are on watch and wait?

DEVELOPMENT AND REVISION HISTORY

This guideline was reviewed and endorsed by the Alberta Provincial Sarcoma Tumour Team. Members of the Alberta Provincial Sarcoma Tumour Team include surgeons, medical oncologists, radiation oncologists, nurses, pathologists, and pharmacists. Evidence was selected and reviewed by a working group comprised of members from the Alberta Provincial Sarcoma Tumour Team and a Knowledge Management Specialist from the Guideline Resource Unit. A detailed description of the methodology followed during the guideline development process can be found in the [Guideline Resource Unit Handbook](#).

This guideline was originally developed in April, 2017.

SEARCH STRATEGY

Evidence was gathered from experts in each respective field (Radiation Oncology, Medical Oncology, and Surgery). Additionally, a literature search was conducted from January 1, 2016 to August 20, 2016 in the PubMed database: ("fibromatosis, aggressive"[MeSH Terms] OR ("fibromatosis"[All Fields] AND "aggressive"[All Fields]) OR "aggressive fibromatosis"[All Fields] OR "desmoid"[All Fields]) AND ("2016/01/01"[PDAT] : "3000/12/31"[PDAT])). The search yielded 102 articles of which 7 were included for analysis.

TARGET POPULATION

Adult patients (17 years of age or older) who have been diagnosed with (or suspected) desmoid (aggressive fibromatosis) tumours.

RECOMMENDATIONS

Diagnosis

1. The diagnosis of a desmoid tumour can only be established by histological and radiological examinations. For a complete list of sarcoma biopsy recommendations, please refer to the Sarcoma Biopsy Guideline (www.ahs.ca/guru).

Staging

2. Upon diagnosis (prior to initiation of therapy), all patients should be evaluated and managed by a multidisciplinary team with expertise and experience in sarcoma. Patients should have a history and physical including evaluation for Gardner's syndrome and FAP. Discussions on sigmoidoscopy/ colonoscopy or genetic counselling may be appropriate.
3. Desmoid tumours lack the propensity for regional or distant spread. Imaging of the primary site with CT or MRI are appropriate and staging for distant disease is generally not clinically indicated.
4. There is no commonly agreed upon staging system for desmoids. The American Joint Committee on Cancer (AJCC) TNM staging system specifically excludes desmoids⁶.
5. Desmoids are characterized by variable clinical behaviour. Some desmoids may grow progressively larger over time, however, it is common for desmoids tumours to experience indolent growth, or periods of growth arrest and spontaneous regression⁷⁻¹¹.
6. Factors associated with increased recurrence rate include: site of disease (extremities having the worst prognosis, trunk/abdominal wall tumors have a lower rate of recurrence than either intraabdominal or extrabdominal disease¹², size >7cm, female gender, and younger age¹¹.

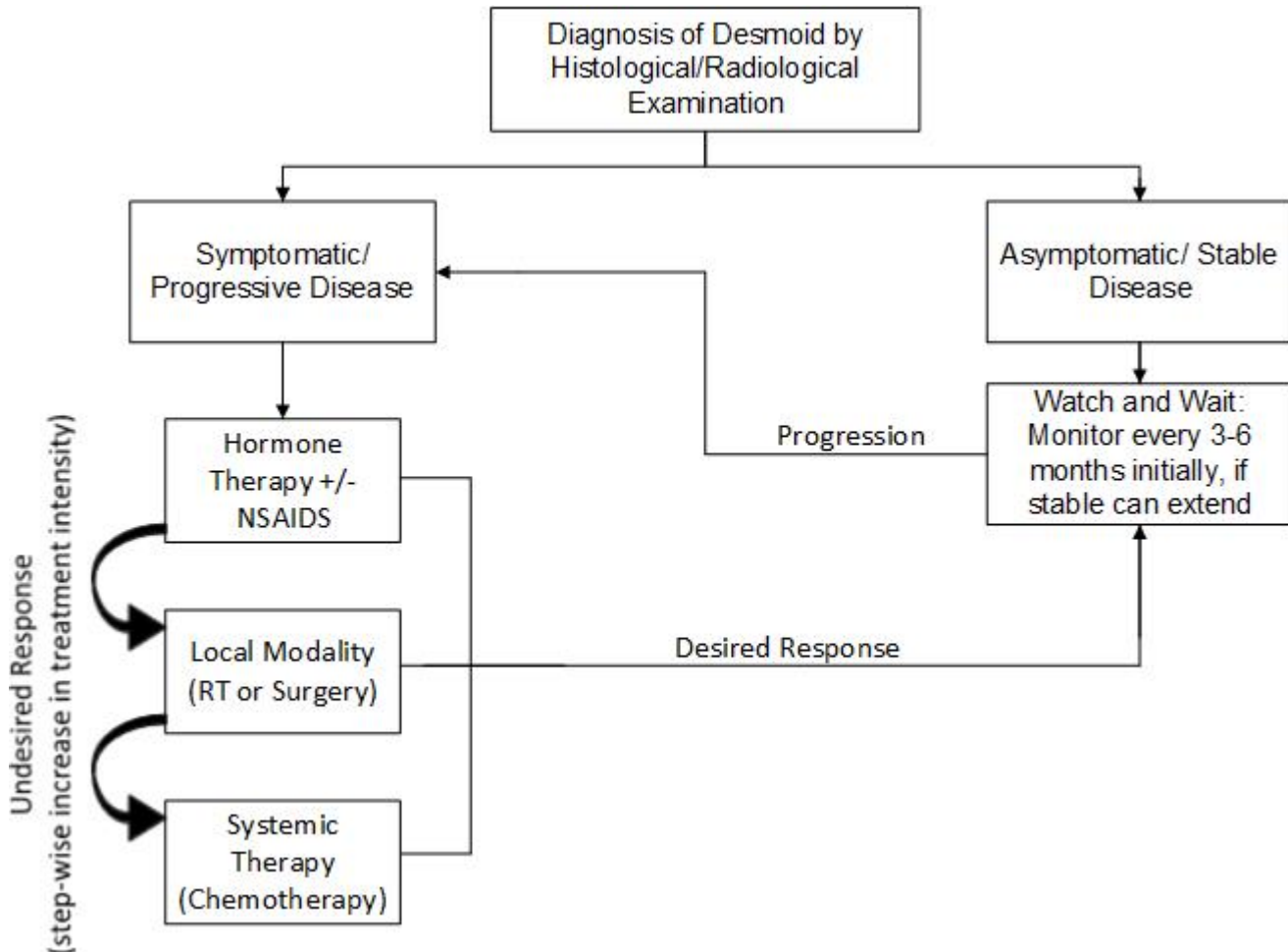
Treatment


Figure 1. Basic Treatment Flow Chart for Patients Diagnosed with a Desmoid Tumour.

Active Surveillance:

7. Active surveillance is increasingly being utilized as the treatment of choice especially for those patients with at worst minimally symptomatic disease. A retrospective study involving primary or recurrent desmoid patients using a deliberately conservative (no surgery/RT) management policy found that 5-year progression free survival was 49.9% for patients treated initially with medical therapy (n=59) and 58.6% for patients on a 'wait and see' policy (n=89)⁷. A study of 27 patients with newly diagnosed sporadic desmoids where patients went on attentive medical surveillance rather than active therapy reported 5 patients (18.5%) had spontaneous tumor regressions, 16 patients (59.0%) had stable disease, and 6 patients (22.2%) had progression at median 52-months follow-up¹¹. A higher rate of spontaneous regression was observed in a series of 102 patients with primary abdominal wall desmoids, where 29 (28.4%) experienced a median 66% decrease in tumour size, with 12 (11.8%) having no tumor detectable after median 32 months of follow-up⁸. Active surveillance may not be appropriate if progression could be life-threatening or pose a risk for mutilation (adjacent nerves or vessels).

8. Patients should be monitored every 3-6 months initially, and if disease is stable this can be extended. The total duration of follow-up should be determined through discussion between the physician and the patient.
9. All treatment modality beyond “wait and watch” approach in desmoid tumours can be considered in patients with progressive and/or symptomatic disease. The treatment recommendation should be discussed in multidisciplinary rounds.

Surgery:

10. Consider observation, if the tumor is stable, and continue observation until progression. Nonsurgical approaches are feasible for patients with abdominal wall desmoid tumours <7cms, followed by surgery based on tumour growth in select cases⁸.
11. Surgery, when complete resection with negative margins is technically feasible without undue morbidity and in symptomatic patients, can be considered as a local therapy option; however, RT may also be considered¹³. If progression or recurrence, consider systemic therapy, or resection, or radical RT alone (56-58 Gy) (if not previously irradiated) based on multidisciplinary input. Multidisciplinary input is especially important when patients are symptomatic or accelerated growth has been noted on imaging.
12. If R0 margins are achieved the patient should be observed. If R1 margins, generally consider observation. If R2 margins, multidisciplinary review and input is needed. There are mixed reports as to the importance of negative vs close or positive resection margins, with some studies showing higher recurrence rates when negative margins are not achieved¹³⁻¹⁷, and others showing risk of recurrence is independent of margin status^{12,18,19}.

Radiation Therapy:

13. Radiation therapy, is an effective primary treatment option in the treatment of desmoids, especially if they are symptomatic and progressing^{20,21}. Although controversial, there are some reports suggesting reduced efficacy of radiotherapy in young adult patients²², so this should be taken into consideration when management options are being discussed.
14. RT (50-60Gy) alone or in combination with surgery in patients with incomplete resection can achieve long-term local control in approximately 70-80% of patients²¹⁻²³. One study of 107 desmoid patients treated with surgery alone (n=51), RT alone (n=15) or surgery followed by RT (n=41) reported five-year actuarial local control rates of 69%, 93%, and 72%, respectively²⁴. A second similar study with n=381 surgery alone patients, n=102 RT alone patients and n=297 surgery plus RT patients reported local control rates of 61%, 78%, and 75%, respectively. Similar local control rates (81% at 3-years) were reported in a phase II trial utilizing RT (56Gy) in 44 patients with inoperable progressive primary, recurrent or incompletely resected desmoid tumours²¹.
15. Post-operative RT is not typically recommended in the adjuvant setting after complete surgical resection. Utilization of RT in patients with close or positive margins is controversial, with some studies showing superior outcomes^{13,24}, while others fail to demonstrate any benefit of RT in this setting^{18,19}.

16. Neoadjuvant RT may be utilized to increase resectability, and reduce rates of local recurrence in extra-abdominal desmoids, however, there is limited data to support this approach. One study of n=58 patients who underwent neoadjuvant RT reported 11 (19%) patients experienced local recurrence after a median 69 months, with 2 (3.4%) patients experiencing major wound complications²⁵. Currently there does not exist sufficient evidence to recommend neoadjuvant RT as standard of care.

Systemic Therapy:

17. Systemic therapy is typically reserved for those patients who have unresectable desmoids, multiple locoregional recurrences despite local therapy, symptomatic disease for which local therapy options are radical or morbid, or intraabdominal/mesenteric desmoids tumors in patients with FAP. Although data supporting neoadjuvant systemic therapy with or without RT is limited, it may have a role in avoiding debilitating local therapy²⁶.
18. Systemic therapy options include cytotoxic chemotherapy (single agent or combination), and less toxic target therapies such as hormonal therapy, nonsteroidal anti-inflammatory drugs (NSAIDs), and imatinib. Typically, hormonal therapy and/or NSAIDs should be attempted as first-line treatment for desmoids before attempting chemotherapy.
19. The choice of agent largely depends on the urgency of the clinical situation (patient co-morbidities, functional status, and interpretation of risk-to-benefit ratio), where more aggressive options (such as combination chemotherapy) should be reserved for patients with impending threat to life or function, while less aggressive options (hormonal therapy, NSAIDs, or imatinib) should be used when systemic treatment is warranted without threat to life or function. Response rates are highest with anthracyclines and hormonal therapy, and lower with single agent dacarbazine/ temozolomide or TKI; generally those patients with non-limb disease, macroscopic nodular morphology or Gardner syndrome are associated with greater time to disease progression after systemic treatment^{27,28}.

Table 1. Chemotherapy Protocols for Soft Tissue Sarcoma²⁸

Protocol	Drugs
Mesna, adriamycin, ifosfamide, dacarbazine	Doxorubicin 20 mg/m ² (day 1–day 3) Ifosfamide 2.5 g/m ² (day 1–day 3) Dacarbazine 300 mg/m ² (day 1–day 3) 21 days cycle
Adriamycin, dacarbazine	Doxorubicin 20 mg/m ² (day 1–day 3) Dacarbazine 300 mg/m ² (day 1–day 3) 21 days cycle
Metronomic etoposide	Oral etoposide 75 mg/day for 21 days of 28 days cycle
Metronomic cyclophosphamide	Oral cyclophosphamide 50 mg/day for 21 days of 28 days cycle
Doxorubicin	Doxorubicin 60–75 mg/m ² 21 days cycle
Pegylated liposomal doxorubicin	50 mg/m ² by a 1h intravenous infusion 28 day cycle
Methotrexate–vinblastine	Vinblastine 6 mg/m ² Methotrexate 30 mg/m ² (J1, J8, 15, 21) 28 days cycle
Methotrexate	Methotrexate 30 mg/m ² (J1, J8, 15, 21) 28 days cycle
Vinorelbine	Vinorelbine 20 mg/m ² (J1, J8) 21 days cycle

20. Response to systemic therapy can be slow, and may take up to eight months to become apparent^{29,30}. Patients who exhibit a delayed response may even experience an initial increase in tumor size followed by an objective decrease in size²⁹. Imaging is recommended ever 2-3 cycles (or every 2-3 months). If the tumour is stable or has increased in size only minimally than the response should not be considered treatment failure. Symptomatic or functional improvement warrants continued therapy even when changes to the tumour are not apparently on imaging.

Pregnancy

21. Extra-abdominal and abdominal desmoids occur more frequently in woman who are pregnant or shortly after pregnancy (up to 6 months), likely as a result of higher estrogen levels. The desmoid tumour typically presents as an abdominal wall mass which is separate from the uterus³¹, and is more common in pregnant woman with a history of desmoid tumors before conception. Overall, a non-aggressive approach is advocated in women with a desmoid during pregnancy. A retrospective study of 92 woman who developed a desmoid tumour during or shortly after pregnancy found that pregnancy-associated desmoids are typically associated with good outcomes, with no obstetric complications³². The study reported that amongst woman who presented during pregnancy without a history of desmoids, 12 of 15 on watchful waiting had progression. 4 continued watchful waiting, 4 had medical therapy, and 4 had surgery.. Overall, surgery was required in 4 of 16 patients on conservative management. Similar results were reported in those women who developed a desmoid within six months of delivery. Among those women with a history of desmoids prior to pregnancy (n=48), 42%

had relapse/progression; 94% were successfully managed with resection or watchful waiting, with 8 patients experiencing spontaneous regression (4 complete) after pregnancy. Among the 15 future pregnancies in all groups, only 4 (27%) progressed, and 3 required surgery³².

Pain Management

22. Patients with desmoids may have debilitating pain. Involvement (co-management) of a specialized pain clinic may be beneficial for the patient.

Rehabilitation

23. Patients can be referred to rehabilitation medicine (PT, OT etc) for functional and symptomatic assessment.

Follow-up

24. Patients should be monitored every 3-6 months initially, and if disease is stable this can be extended. Duration of follow-up thereafter will be subjected to the discussion between the physician and the patient.

GLOSSARY OF ABBREVIATIONS

Acronym	Description
FAP	Familial adenomatous polyposis
NSAID	Nonsteroidal anti-inflammatory drugs
RT	Radiotherapy

DISSEMINATION

- Present the guideline at the local and provincial tumour team meetings and weekly rounds.
- Post the guideline on the Alberta Health Services website.
- Send an electronic notification of the new guideline to all members of CancerControl Alberta.

MAINTENANCE

A formal review of the guideline will be conducted at the Annual Provincial Meeting in 2018. If critical new evidence is brought forward before that time, however, the guideline working group members will revise and update the document accordingly.

CONFLICT OF INTEREST

Participation of members of the Alberta Provincial Sarcoma Tumour Team in the development of this guideline has been voluntary and the authors have not been remunerated for their contributions. There was no direct industry involvement in the development or dissemination of this guideline. CancerControl Alberta recognizes that although industry support of research, education and other areas is necessary in order to advance patient care, such support may lead to potential conflicts of interest. Some members of the Alberta Provincial Sarcoma Tumour Team are involved in research funded by industry or have other such potential conflicts of interest. However the developers of this guideline are satisfied it was developed in an unbiased manner.

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