Management of aggressive fibromatosis (Review)

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Abstract. Aggressive fibromatosis or desmoid tumor is a rare disease resulting from fibroblasts which do not metastasize. However, desmoid tumors belong to low-grade malignant tumors since they have high potential to infiltrate surrounding tissues, causing high local recurrence rates and may affect surrounding organs, threatening life quality and expectancy. Although surgery, watch and wait, radiotherapy, chemotherapy, high intensity focused ultrasound, ablation techniques or several agents have all been frequently investigated for the treatment of this type of disease, none are deemed as standard therapy for high recurrence rates that have been supported by any data. The present review retrieved literature on treatment options for desmoids to summarize the latest treatment modalities and refine their efficacy, as well as their side effects, in order to provide a more comprehensive treatment reference for clinicians.

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Abbreviations: LRR, local recurrence rate; PLD, pegylated liposomal doxorubicin; HIFU, high intensity focused ultrasound; RFA, radiofrequency ablation; NSAIDS, non-steroid anti-inflammatory drugs; COX-2, cyclooxygenase-2; MTX/VBL, 'low-dose' chemotherapy with methotrexate and/or vinblastine/vinorelbine; PLD, pegylated liposomal doxorubicin; LD, liposomal doxorubicin; VAC, vincristine and actinomycin±cyclophosphamide

Key words: desmoid tumor, aggressive fibromatosis, treatment, regimen

1. Introduction

Aggressive fibromatosis (AF), also known as desmoid tumor, is a rare type of fibrous tumor with low-grade malignancy and high potential of recurrence (25-77%) (1,2), although it usually recurs *in situ* and does not metastasize distantly. Etiological factors include injury, endocrine disorders (estrogen) and chromosome abnormalities, although familial adenomatous polyposis (FAP) or Gardner's syndrome are all hypothetical (3).

Fibromatoses can be classified by their location into superficial and deep (3-5). Deep fibromatoses usually refer to desmoid tumors (3). This type of tumor may occur from head to foot, which is clinicopathologically categorized into three types: Extra-abdominal (60%), abdominal wall (25%) and intra-abdominal (8-15%) (6).

Pathogenesis-associated molecules are centered on the cascade reaction of nuclear β-catenin that is encoded by the catenin b-1 (CTNNB1) gene. The adenomatous polyposis coli (APC) complex induces the degradation of β-catenin by phosphorylating it, which can be inhibited by the Wnt pathway. Either mutations of exon 3 of the CTNNB1 gene and the 3' position in codon 1444 of the APC gene or APC dysfunction can result in the accumulation of β-catenin (7-10).

The most commonly used imaging techniques for desmoids are computed tomography (CT) and magnetic resonance imaging (MRI). Desmoids show similar or slightly higher attenuation compared with skeletal muscle in a non-contrast CT scan and contrast-enhanced CT generally exhibits mild-to-moderate enhancement (11,12). Mesenteric desmoids are typically characterized as a soft tissue mass with radiating spicules extending into the adjacent mesenteric fat at CT (13). As for MRI, desmoids commonly show a heterogeneous pattern appearance, with iso-to hyper-intense signals to skeletal muscle on T2-weighted images and isointense to muscle on T1-weighted images (14). Additionally, 90% of desmoids demonstrate moderate-to-marked enhancement at gadolinium-based contrast-enhanced MRI (15).

According to The National Comprehensive Cancer Network (NCCN) guidelines, the use of surgery, radiotherapy, systemic therapy and observation are recommended for both

primary and recurrent aggressive fibromatosis (16). However, the treatment of AF is still controversial since infrequent evidence can validate the satisfactory effects of any treatment means on avoiding local recurrence following administration (6). In this setting, the present review comprehensively retrieved literatures relevant to treatments to summarize the latest treatment modalities or drugs listed in the following chart and detailed the efficacy of each modality along with side effects or limitations, which would facilitate in attaining a better clinical decision.

The treatment modalities of desmoids discussed include: i) Surgery and watch and wait; ii) radiotherapy; iii) chemotherapy [tyrosine kinase inhibitors (imatinib, sunitinib, sorafenib), methotrexate and vinblastine (MTX/VBL), conventional chemotherapy with doxorubicin (including PLD; LD) ± dacarbazine, loco-regional chemotherapy, vincristine and actinomycin and cyclophosphamide (VAC), other agents (cyclophosphamide, pazopanib, hydroxyurea]; iv) hormonal therapy and non-steroidal anti-inflammatory drugs (NSAIDs) [selective estrogen receptor modulators (tamoxifen, raloxifene, toremifene) with or without NSAIDs, luteinizing hormone-releasing hormone analogue (leuprolide), other hormones that could antagonize estrogen (medroxyprogesterone, testosterone, progesterone]; v) high intensity focused ultrasound (HIFU) treatment; vi) ablation technique [radiofrequency ablation (RFA), CT-guided percutaneous cryoablation]; vii) non-NSAIDS (sulindac, indomethacin, meloxicam, celecoxib); viii) other agents in clinical trials [1,25-(OH)2-vitamin D3 treatment, interferon-α, retinoic acid, tranilast, predinisolone].

2. Surgery and watch and wait

Surgery. Surgery has been widely used in all types of resectable desmoid tumors. Surgery is the first-line treatment for tumors with a clear margin in most cases (17). It was found that patients in case reports with intra-abdominal desmoids attain a non-recurrent duration varying from <12 months (18) to 30 months (19), excluding those who were lost to follow up and cases that were not mentioned. In addition, the local recurrence rate is 8-31% (20,21) after surgery with a clear margin. A study involving 176 patients receiving a complete excision with a clear margin showed a 10-year local recurrence rate of 58% (22). A meta-analysis containing 1,005 patients receiving surgery alone showed a recurrence of 30% (23). Other reported recurrence rates are even higher. It was reported that local recurrence rates still range between 19-77% with a wide excision (24,25). However, according to a systemic review (26), the local control rate of desmoids with R0 excision from several studies vary from 47-86%, which is not so disappointing.

As for the impact of margin on prognosis, there are different views (16). Several studies (27-29) favored that negative excision did not make a difference in prognosis, however others (16) did not discover such an association. For example, R0 excision did not favor R1 excision in progressive-free survival (PFS) in a univariate analysis (16), but a multivariate proportional hazards regression analysis revealed that state of margin significantly impacted the prognosis (positive vs. negative; P=0.001; relative risk, 2.9) (30). Considering its infiltrate characteristics, it is difficult to distinguish the boundaries of desmoids. Simultaneously, an aggressive excision for negative margin cannot exactly assure a better outcome, which may sacrifice important function or even lives. Hence, the benefits and faults of excision should be carefully considered. In addition, post-operational radiotherapy is supposed to improve the prognosis of those with a positive margin after excision; the 10-year recurrence rates for patients treated with surgery alone and patients treated with combined surgery and radiation therapy were 54% (95% CI; 37-69%) and 31% (95% CI; 15-53%), respectively (P=0.007) (30). Overall, it is risky and difficult to perform complete excision.

Surgery has substantial limitations. To begin with, although wide local excision is the gold-standard treatment for desmoid tumors in the past, no solid evidence has affirmed that surgery yielded superior outcomes over other treatments (16). Even other conservative measures are favored as these measures have lower complication rates. Secondly, scientists have found that in a series of 203 patients with extra-abdominal desmoid tumors treated with surgery over a 35-year period, patients without antecedent interventions had longer disease-free survival and presence of recurrence was the prognostic factor indicating strong recurrence (31). Given that surgery, as a type of trauma, is an etiological factor for desmoid tumors and long-term recurrence rates of surgery are quite high, surgery should be treated with caution. Simultaneously, the boundaries of the tumors are hard to distinguish intraoperatively from scars and connective tissue, causing difficulty in R0 resection (32). Recurrence after surgery not only occurs *in situ* but also in adjacent areas, as it is unable to preserve connective tissues well (33). Under these conditions, repeated recurrent desmoid tumors would tend to invade surrounding tissues in a concentric way if treated with surgery, which would gradually invade more tissues and important organs or major vessels. Radical surgery is always infeasible in mesenteric desmoid disease as the mortality of surgery is 10-60% and the recurrence rate is 78% (34). Surgery itself subjects patients to post-operational risks in addition to its high recurrence rate (up to 40%) (3).

Watch and wait. With multi-institutional studies having demonstrated spontaneous regression rates of 28-50% in recent years (35-37), interventions should be treated discreetly. The effect of the watch-and-wait policy is endorsed by the number of cases. A clinical study demonstrated growth arrest in two thirds of the nonsurgical group (38). In a study (16) involving 27 patients with sporadic desmoid tumors treated with the watch-and-wait policy, only six progressed with a delay to progression ranging from 7.8 to 46.2 months. The remaining 21 patients avoided surgery with an ideal outcome, in which the disease attained a stable course, and even five cases regressed spontaneously. Cho *et al* (39) reviewed five studies in which desmoids are managed by the watch-and-see policy with varying rates of spontaneous regression from 65.1-96.1%.

The watch-and-wait policy is recommended by NCCN 2018 guidelines where observation applies to selected patients in non-life-threatening situations. However, it is confusing to judge the criterion for 'selected patients', and Zhao *et al* (40) believes that surgery should be performed once the disease has progressed. Others believe that the endpoint of this type of modality depends on the patient's symptoms, medical status and the biological properties of the tumor (41). Briand *et al* (42)

reported a low probability of transiting to other salvages which was only 5.7% at 1 year and 9.6 at 5 years. Hence, it seems that watch and wait is quite safe and may be a promising treatment for first-line therapy, especially considering the high local recurrence rate of other interventions, along with its low rates of dropping out.

3. Radiotherapy

Radiation therapy has been used in patients with inoperable desmoid tumors, local recurrence or incompletely excised lesions (43-45). The results from radiation therapy demonstrated local recurrence rates of ~25% (46). A systemic review revealed a control rate following radiotherapy varying from 65-83% (26). Bishop *et al* (47) reported 5- and 10-year local recurrence rates of 71 and 69%, respectively. Smith *et al* (26) found that the local control rates of desmoid tumors treated with radiotherapy ranged between 65 and 83% during a reported follow-up of 105 months (range, 72-120). Hence, it seems that exclusive radiotherapy cannot attain satisfactory local control, although a systemic review revealed a control rate after radiotherapy varying from 65-83% (26).

According to the guidelines from the NCCN, radiotherapy is often a supplementary treatment indicated in cases of AF that present as large tumors or with positive margins (48). Nuyttens *et al* (49) noted that the local control rate of surgery combined with post-operational radiotherapy group was 75%, which is better compared with the exclusive surgery group while both margins are positive.

Radiotherapy for desmoids has several disadvantages. Firstly, it can decrease local recurrence, but may account for post-irradiation fibrosis, joint contracture and neuropathy. Moreover, the duration to achieve complete resolution may be as long as several months (50). Secondly, Chen *et al* (48) reported a desmoid tumor developed from radiation treatment for keloids, which indicated that radiotherapy may be a causal factor of AF. Thirdly, some studies cannot validate the efficacy of adjuvant radiotherapy for desmoids following incomplete surgical resection (51,52). Fourthly, radiotherapy is effective for both extra-abdominal and abdominal wall tumors as relevant side effects are quite less compared with radiation enteritis that is in high risk, which occurs at mesenteric desmoids if treated by radiation (53).

4. Chemotherapy

Chemotherapy is used for inoperable progressive lesions in occasions where surgery or radiotherapy would cause morbidity (50,54). The overall response rates to combination chemotherapy are 17-100% (55). The duration of response to chemotherapy in pain relief is usually short, while longer in radiological tumor shrinkage or stabilization, which may continue for months before an expectant response (56). Chemotherapy is used for primary or recurrent desmoids and adjuvant treatment ahead of operation or after operation.

According to literature, agents used in DT chemotherapy include tyrosine kinase inhibitors (TKIs), methotrexate, vinblastine, vinorelbine, doxorubicin, dacarbazine, carboplatin, melphalan, vincristine, actinomycin, cyclophosphamide and hydroxyurea. They are used alone or in combination with one another. Different combination chemotherapies constitute various regimens that apply to different situations and characterize a variety of features. The present review summarized the present common regimens and their efficacy to assist in clinical decisions.

TKIs. TKIs were found to have response rates of 5-20% at 1 year, and the rate of progression-free disease varies between 60-70% (57,58). An uncontrolled, non-randomized, phase III study showed high rates of stable disease up to 50-80% (59,60). Imatinib, sorafenib and sunitinib are common TKI drugs targeted for desmoids, which have been extensively studied (60-66).

Imatinib therapy has a response rate of <10% for solid tumors (41). Imatinib treatment is reported to attain progression-free survival (PFS) rates of 58% at 24 months and 55% at 36 months (59,60). A prospective phase II trial demonstrated that PFS rates were 94% at 2 months, 88% at 4 months and 66% at 1 year. However, it is associated with toxicities such as grade 3/4 neutropenia, rash, fatigue, abdominal pain, diarrhea, myalgias and asthenia (59,60).

Skubitz *et al* (67) reported a case of multifocal desmoids that was refractory to imatinib but responded well to sunitinib. Based on the aforementioned study, a prospective multicenter phase II study (68) evaluated the efficacy of sunitinib, in which the rates of partial response and stable disease were 26.3 and 42.1%, respectively. Additionally, the 2-year progression-free and overall survival rates were 74.7 and 94.4%, respectively. Side effects that occurred in >5% of patients included neutropenia (33.3%), diarrhea (5.3%) and hand-foot syndrome (5.3%). In the early phase of sunitinib, mesenteric mass bleeding, bowel perforation along with bowel fistula due to bowel mass necrosis were respectively observed in three patients. The author believed sunitinib to be a useful management of non-mesenteric desmoids.

A study elucidated the efficacy of sorafenib and its side effects (69). Sorafenib is administered as the first-line or substitute treatment with a striking clinical benefit comprising 16 of 22 patients. Moreover, no difference was found in radiological benefit (P=0.9). Toxicities include hand-foot syndrome, fatigue, skin rash, trichodynia, hypertension, mild alopecia and diarrhea, which can be controlled with dose reductions and the use of antidiarrhea and antihypertensive drugs. However, another double-blind, phase III trial study comparing the efficacy of sorafenib vs. placebo demonstrated objective response rates [sorafenib vs. placebo: 33% (95% CI, 20-48%); 20% (95% CI, 8-38%)]. In addition, the 2-year PFS rate was 81% (95% CI, 69-96%) in the sorafenib group and 36% (95% CI, 22-57%) in the placebo group (hazard ratio for progression or death, 0.13; 95% CI, 0.05-0.31; P<0.001). The sorafenib group has similar side effects as the previous study. In addition, desmoids harboring the S45F mutation with anti-cytotoxic effects caused by autophagy may respond well to sorafenib and hydroxychloroquine (an autophagy inhibitor), as reported by Braggio *et al* (70).

MTX and VBL. The combination of MTX and VBL (MTX/VBL) were studied for desmoid treatment and yielded a promising effect (54,71-74). According to the literature, the response rate for MTX/VBL varied from 31-52% (72,75),

but the data is too conservative if more prognosis data are included. A systematic review that evaluated the efficacy of MTX/VBL combination chemotherapy on primary or recurrent desmoids showed a mean response rate of 36% (11-57%) or 85% in patients with stable disease (71). In addition, it was reported that patients with stable disease progression accounted for >35 and >28% attain a PFS duration of a mean of 43.4 months in a phase II study examining the effect of MTX/VBL therapy on children (72). Another similar phase II study (73) focusing on adults showed a 100% rate of clinical benefit with ratios of stable disease and partial response accounting for 60 and 40%, respectively. The percentage of patients with a 10-year PFS interval was up to 67%. As reported, young age is an indicator of bad prognosis, which applies to those treated with chemotherapy according to aforementioned studies.

This combination modality also has some side effects, although the rates of adverse effects are low according to studies on children (54,72,75). Neutropenia (myelosuppression or myelotoxicity) (71,72) was reported to be the main adverse effect. Moreover, anemia, nausea, mild alopecia, vomiting and elevation in hepatic transaminases, which were reversible with interruption of chemotherapy, are all common side effects (54,72,73). The duration of response to MTX/VBL is longer in children, typically ~9 months (76). Due to toxicities of this modality, the combination of vinorelbine and MTX can substitute the previous regimen for decreasing toxicities without sacrificing the response rate (77). Considering its low rates of side effects which are dominantly due to myelotoxicity, which would make it feasible to impose prophylaxis ahead of time, the MTX/VBL modality is a promising and safe modality.

Conventional chemotherapy with doxorubicin, including pegylated liposomal doxorubicin (PLD) and liposomal doxorubicin (LD) with or without dacarbazine. Conventional chemotherapy is generally applied to patients who fail the 'low-dose' regimen (78). PLD or LD is a variant of doxorubicin (a type of topoisomerase II inhibitor), which is decorated by liposomes with or without polyethylene glycol for decreasing the cardiotoxicity of doxorubicin (79). Several studies have shown its high rates of response. A study reported that four patients with advanced desmoids responded well to PLD without significant toxicities (80). Another study involving 12 patients demonstrated satisfactory results in which the rate of stable disease was up to 64, and 75% of patients did not attain progression during the entire follow up with a median duration of 14 months (81). A retrospective review of pediatric patients analyzed the effects of LD and an average 4.5% reduction of tumor size and a median PFS time of 29 months, which showed more ideal results (76). In addition, doxorubicin can also be used to assist carboplatin in further reducing the tumor size by intralesional injection, which was reported in a cohort study (82). Additionally, some researchers have discontinued doxorubicin or adjusted the dose of carboplatin to a cumulative of 400-500 mg/m^2, due to its cardiotoxicity. Although promising, doxorubicin also has some side effects, such as palmar-plantar erythema, mucositis, cardiotoxicity (83) and dose-relevant reduction (81).

Loco-regional chemotherapy. Loco-regional chemotherapy is rarely reported in some cases, in which TNF-α and melphalan is perfused into isolated limbs (84). Data from three sarcoma centers of the European Organization for Research and Treatment of Cancer indicated that TNF-α and melphalan could prevent amputation in 88% of patients with advanced disease. Up to 61% showed regression or stabilization of disease during a median follow-up of 84 months and the PFS time was as long as 27 months (85). It acts as a substitute in patients affected by carcinoma in extremities, especially for those who have multifocal desmoids of hand or foot (84). This regimen helps patients avoid routine operation since state of stable disease or slow regression is often observed in patients after therapy (84).

VAC regimen. The VAC regimen was firstly reported by Raney (86) to treat fibromatosis in a series of cases including six patients aged 3 months to 7 years with primary or recurrent desmoid tumors. This regimen is an alternative to doxorubicin-based chemotherapy with comparable responses, particularly in pediatric patients. The main side effects of VAC are sterility and carcinogenesis (55,87). The duration from the first administration of the VAC regimen to response is estimated to be at least 12 weeks, according to the Intergroup Rhabdomyosarcoma Study (88). However, others (89) believed that VAC regimens should be given up if no response was observed within a duration of 16-20 weeks following the initial administration. Additionally, most clinical reports regarding the VAC regimen involve children. Prognostic data are not available considering the rare cases and clinical reports, which can be supplemented by more trials.

The present review listed five different regimens that are formed by combinations of different agents and commonly used in desmoid chemotherapy, although other agents such as hydroxyurea (76), γ-secretase inhibitor (90) and pazopanib (91) are also involved in chemotherapy trials. These five combinations are mainstream chemotherapy regimens whose efficacy and side effects have not been comprehensively reviewed in previous literatures.

5. HIFU

HIFU is a novel, minimally invasive treatment based on thermal ablation. Adjacent tissues are not involved in this treatment as it is based on ultrasound beams that are precisely focused on the target locations to produce thermal coagulation necrosis (92,93). No virtual insertion operation, as well as energy that is highly centralized, guarantee normal tissues out of iatrogenic trauma, which may contribute to desmoid tumors (94). Facial tissues, unlike the targeted area (where the rate of absorption exceeds the rate of heat emission and would undergo necrosis due to accumulation of heat) can be passed through by focused ultrasound energy, hardly harming the patient (95).

Several studies have illuminated the efficacy of HIFU treatment on desmoid tumors. Zhao *et al* (40) reported the first case of HIFU treatment in aggressive breast fibromatosis with multiple recurrence following surgery. Ghanouni *et al* (96) applied HIFU treatment to 15 selected patients with extra-abdominal desmoids. The mean tumor volume decreased to 63% with

significant improvement in pain. HIFU treatment can also be used to treat intra-abdominal desmoid tumors. Shi *et al* (97) reported four patients with intra-abdominal desmoid tumors treated with HIFU treatment. The MRI showed at least 80% ablation in all cases and one patient showing 100% ablation during a follow up for 19-46 months (mean, 34 months). Similarly, abdominal wall desmoid tumors are treated in the study by Wang *et al* (98), aiming to evaluate the therapeutic efficacy of HIFU ablation for the treatment of extra-abdominal desmoid tumors. It seems that HIFU more often served as a salvage for recurrent desmoid tumors. However, the present study found two cases where HIFU treatments are used to treat primary desmoid tumors with ablation ratios of 100%. Hence, the present study proposes that HIFU can be a curative treatment. In contrast, for recurrent desmoid tumors, HIFU treatment is performed as palliative treatment (98).

In fact, this type of minimally invasive treatment modality does have some side effects. Zhao *et al* (99) reported acroparaesthesia of the lower limb and platelet decrease in patients after treatment. Wang *et al* (98) reported swollen skin, first-degree skin burns, mild pain and low-grade fever in HIFU-treated patients. In addition, similar adverse events, such as those in surgery, including adjacent important vessels or organ injuries that affect functions or even life-threatening may occur. Therefore, a balance should be struck between eradication and decreasing side effects. According to different goals of HIFU treatment, a margin of at least 1 cm can satisfy curative *in situ* eradication for primary desmoid tumors not involving major neurovascular structures. Additionally, ablation areas should include as much planned areas without injuring major neurovascular structures as possible, which can achieve better local control, taking side effects of palliative treatment outcome in recurrent desmoid tumors in consideration (98).

HIFU treatment is a promising means in desmoid tumor treatment. Although it has side effects, it is characterized as highly 'precise excision' and relatively minimally invasive. More research should focus on its potential as a curative means, based on presently rare primary cases in which patients are cured.

6. Cryoablation technique

Percutaneous cryoablation. Percutaneous cryoablation currently delivers room temperature argon gas through a sealed, segmentally insulated probe to cause rapid cooling locally due to the Joule-Thomson effect (100). According to Kurup and Callstrom (101), percutaneous cryoablation is a less-invasive treatment potential to cure desmoid tumors. A study (33) was performed to evaluate the efficacy, safety and advantages of cryoablation for both first-line treatment and remedial treatment of extra-abdominal desmoid tumors. A total of 89% of patients reported improvement and the average change in viable volume was -80% (range, -100 to +10%) with complete response of 36%, partial response of 36% and stable disease of 28% after a 1-year follow-up. The high rate of incomplete ablation, achieving a 90% clinical response rate as well as its less-invasive feature suggested that percutaneous cryoablation is a promising modality to cure extra-abdominal desmoid tumors. Similar results affirmed the efficacy of cryoablation for its high rate of local control (102,103). In addition, cryoablation has been investigated as both first-line and salvage treatment modality (33) and an ideal outcome has affirmed its reliability.

Cryoablation owns several advantages over other therapies. In contrast to a 23% recurrence rate in a 2-year follow-up after R0 excision by imaging, complete A0 ablation extinguishes diseases (16). Moreover, it was reported that the recurrence after cryoablation often occurs *in situ*. However, recurrence sites after surgery are located in adjacent tissue, complicating further therapy by causing neurovascular injury. This is due to connective tissues or compartments being well-preserved in cryoablation, unlike in surgery (33). Cryoablation has better local control which may substitute surgery or radiotherapy, neither of which alone could attain an ideal local control (47). Finally, nearly all cryoablation is less invasive and patients would return home within one or two weeks, unlike in the surgery group depending on the complexity of excision and recovery state (33).

Percutaneous cryoablation owns several limitations or side effects. Mostly, this type of modality applies to extra-abdominal and abdominal wall desmoid tumors and no reports reported treating intra-abdominal desmoid tumors with this modality. Furthermore, longer term follow up is needed to assess how A0 cryoablation compares to the R0 5-year recurrence rate of almost 40% (47). Injury to skin and nerves are the most common complications caused by cryoablations.

7. RFA

RFA exploits high-frequencies (375-500 kHz) that are delivered by a special electrode to cause local heating effect of tumors, which would result in protein denaturation and coagulation necrosis in order to decrease or exterminate tumors (100). It is a minimally invasive therapy widely applied to treat unresectable, malignant tumors and some benign lesions using a fine needle electrode inserted into lesions with imaging guidance (100,104,105), which requires a shorter anesthetic time without using an operating room compared with surgery (19). RFA can be applied in abdominal wall desmoids (106).

Some studies have tried this modality on recurrent desmoid tumors which failed to response to surgery. Complete ablation without any relapse was observed in all four patients during a mean 30-month follow-up (107). Tsz-Kan *et al* (108) reported a case of successful long-term local control of recurrent fibromatosis treated by RFA. Barrow *et al* (106) used RFA to treat a patient with desmoid tumors in familial adenomatous polyposis (FAP) which caused a decrease in tumor size and relief of symptoms.

RFA has some advantages in treating desmoids in FAP, such as aversion of surgery, tumor reduction, inhibition of growth and symptom relief (106). Simultaneously, this type of modality also has several shortcomings. Firstly, RFA has the potential to cause some side effects associated with ablation. For example, cellulitis and soft tissue necrosis were both mentioned in a study by Ilaslan *et al* (107), who applied CT guidance for assistance in RF ablation. Ko and Kang (109) suggested that CT showed untidy margins of desmoid tumors with the same density as muscles, which potentially resulted in over-ablation-induced skin burns. This can be improved by transition to using MRI guidance that

can image a definite margin. Real-time ultrasound images, especially combined with the 'moving tip' technique, have been investigated for their ability to assist in ablation to treat superficial lesions. Secondly, it was reported that RFA can cause some common complications such as pain, bleeding, infection and visceral injury while desmoid tumors exist in abdominal walls (106,107). Thirdly, RFA may stimulate tumor growth (106).

8. Hormonal therapy and NSAIDs

Either hormonal treatments or NSAIDs were reported to be used for first-line therapy or unresectable, recurrent or progressing desmoids, solely or in combination (77,110-113). Common hormonal treatments used for desmoids include selective estrogen receptor modulators (tamoxifen, raloxifene and toremifene), leuprolide, medroxyprogesterone, testosterone and progesterone. The corresponding NSAIDs contain sulindac, indomethacin, meloxicam and celecoxib.

Hormone-based therapy. Hormonal therapy typically consists of the use of selective estrogen receptor modulators (tamoxifen, raloxifene and toremifene) and occasionally involves the use of luteinizing hormone-releasing hormone analogues (leuprolide) and other hormones that antagonize estrogen (medroxyprogesterone, testosterone and progesterone).

Tamoxifen, raloxifene and toremifene are all anti-estrogen agents that are used for desmoids. Lackner *et al* (114) described the efficacy of tamoxifen and toremifene with a response rate of 65% and scarce side effects in treating desmoids. According to a systemic review, the overall response (complete plus partial response) rates and disease stabilization rates are similar in tamoxifen and toremifene (115), which are 58 and 18% vs. 56 and 19%, respectively. Moreover, according to Okuno (116), dosage increases of tamoxifen are not more effective although some clinical trials elevate the dosage of tamoxifen when its effects are not satisfactory. Toremifene is effective in some cases refractory to tamoxifen. Toremifene does not exhibit long-term complications (117-120), however it should be reserved for patients with a history of venous thromboembolism or pulmonary embolism given the risk of thromboembolic events observed following long-term treatment with raloxifene.

Some reports have demonstrated the effects of anti-estrogens combined with other drugs. Hormone-based treatment showed a response in 40-51% of cases (115,121). It was reported that ~50% of patients with mesenteric desmoids respond to anti-estrogens (108). In addition, a systemic review focused on the effects of anti-estrogen with or without other drugs, such as NSAIDs, concluded that overall response (complete response plus partial response) rates and disease stabilization rates are 51% (46/91) and 27% (24/91), respectively in desmoids with FAP, and 48% (24/50) and 38% (19/50), respectively, in sporadic desmoids (115). The author of this review also found a higher rate of complete or partial response in anti-estrogen alone compared with in combination with NSAIDs ($P<0.001$). In addition, the regimen that combined sulindac (an NSAID) with anti-estrogen agents was tapered after a median duration of medication of 42.4±24.3 months, which could not be influenced by genetic state, sex or a concrete type of anti-estrogen agent applied to desmoids (122).

The most common hormone-based therapy is tamoxifen in combination with or without other drugs. Bauernhofer (123) reported a female patient with FAP suffering from recurrent unresectable intra-abdominal desmoids. Tamoxifen with subsequent goserelin acetate (an analogue of the luteinizing hormone-releasing hormone) attained a PFS duration of up to 17 months, and tumor progression was again inhibited by goserelin acetate combined with IFN-γ. Tamoxifen combined with sulindac have been well investigated in clinical trials. A phase II study within the Children's Oncology Group demonstrated overall response, 2-year PFS and survival rates of 36% (95% CI, 0.23-0.48) and 96%, respectively (124). This study also reported relevant side effects including gastritis, emesis, hemorrhage events, ocular problems, pain in the abdomen or head, embolism-related events, tinnitus, prolonged QTc interval, fever, fatigue, skin breakdown/decubitus, nausea, elevated alanine transaminase/aspartate transaminase ratio, hypomagnesemia, ovarian cysts and dizziness. Another systemic review revealed that the side effects of anti-estrogen occur at a lower rate compared with surgery and chemotherapy (125). Simultaneously, selection of drugs was significantly impacted in cases of side effects of corresponding drugs (122); raloxifene was preferred in female patients in order to reduce the risk of endometrial cancer and ovarian cysts, while male patients were preferably administered with tamoxifen.

NSAIDs. NSAIDs used to be the first-line therapy due to their low toxicity (39). Common NSAIDs used for desmoids include meloxicam, indomethacin, sulindac and celecoxib.

Sulindac is always used in combination with tamoxifen. Tsukada *et al* (126) found that the overall response rate was up to 57% with a mean response time lag of 24 months in assessing the efficacy of sulindac in 14 patients with FAP suffering from recurrent desmoids. Quast *et al* (122) reported common side effects of sulindac such as high elevation in liver function tests which occurred in 1.5% of patients and venous thrombosis in 2.2% of patients.

Meloxicam, which belongs to the cyclooxygenase-2 (COX-2) inhibitor agent group, has shown its effects in managing extra-abdominal desmoid tumors (127). A retrospective review analyzing the outcomes of primary or recurrent extra-abdominal desmoid tumors treated with meloxicam showed state of partial relief or stability in 65% of patients. The rates of dropping out from this treatment remain at 35% at both 1 or 5 years (39). Meloxicam efficacy was demonstrated by Nishida, who followed 20 patients treated for 3-81 months; over the 44 months of follow up, 95% of patients experienced equal to or better than stable disease (128).

Yang *et al* (129) first reported a case of patients with aggressive fibromatosis (desmoid tumor) treated with celecoxib (a type of NSAID) under the guidance of genetic testing, in which the patients demonstrated significant regression without any signs and symptoms during a 20-month follow-up. They recommend this modality under the condition that genetic testing showed the presence of p.T41A mutations on the CTNNB1 gene, which could predict whether the patient is sensitive to the COX-2 inhibitor celecoxib or not. A previous study used celecoxib

combined with excision, in which complete remission without local recurrence was accomplished within a duration of a 24-month follow-up (130). However, multicenter randomized controlled trials are required in the future.

An early report indicated that indomethacin at an oral dose of 100 mg/d caused resolution of the tumor (131). According to the report, this drug caused complete resolution of desmoids which was partially responsive to radiotherapy in one previous case. Another case showed immediate but short response and resumed resolution for 14 months with large doses of ascorbic acid being supplemented with indomethacin. The remaining two cases received combination indomethacin from the beginning and showed shrinkage of tumors during the entire follow-up.

In addition, other drugs used for the attempted treatment of desmoids showed certain efficacy such as 1,25-(OH)2-vit amin D3 (132,133), IFN-α (134), retinoic acid, tranilast (135), predinisolone (136,137) and ascorbate (138,139). These strategies are not included in conventional therapy but may act as second line therapies. Ferah *et al* (133) reported a female patient with a huge desmoid mass in the right shoulder region, resistant to radio-chemo-hormonal therapy, that eventually responded to radio-chemo-hormonal therapy. A clinical trial including 13 patients who previously received surgery for desmoids were recruited to examine the efficacy of further management of IFN-α with or without tretinoin (134). The results (seven patients had no evidence of disease and a mean disease-free interval of 22±18 months; in two patients, progressive disease occurred after only 7 and 9 months, respectively, during observation) revealed that this regimen could significantly prolong the disease-free interval. Tranilast was administered to a Japanese male with desmoid tumors on his chest wall who refused to surgery-radio-chemical therapy and the tumor was successfully controlled (135). Predinisolone was reported to induce intra-abdominal desmoids with FAP to regress or even disappear in an unresectable case (137).

9. Summary

As aforementioned, the present review comprehensively summarized the efficacy of recent interventions on desmoids along with their side effects or limitations. Surgery, NSAIDs, hormonal therapy, chemotherapy and radiation therapy have all been recommended as either first-line or alternative treatments. However, neither treatment modality could exhaustively eradicate tumors without recurrence supported by sufficient evidence. An increasing number of clinical trials aim to supplement existing evidence and continue to investigate novel potential drugs for the treatment of desmoids, which are necessarily characterized to provide pivotal information in order to serve in clinical practice better.

Some crucial points should be supplemented. Firstly, surgery, chemotherapy or radiotherapy should be used with caution. Patients with recurrent desmoids after excision and/or radiation have poor response to broad spectrum chemotherapy. In addition, taking into consideration that ~50% primary desmoids would recur and young age is indicative of a high chance of relapse, it is unwise to treat children with chemotherapy alone (21,140,141). Simultaneously, radiation is a clear carcinogenic factor, increasing risk of tumors, especially in children (48). Hence, children with desmoids should be treated synthetically with much caution, while surgery, chemotherapy or radiation is necessary.

This review also has some limitations. To begin with, crucial indices such as local recurrence rates cannot be compared directly among different treatment modalities, due to unignorable heterogeneity. For example, prognostic factor criteria are judged by various means, from imaging to symptoms. In addition, heterogeneity in population characteristics such as sex or age can significantly impact prognosis. The present review proposes that multicenter cooperation should constitute a unified research strategy to eliminate heterogeneity in order to yield convincing evidence, which would decide the best modality to treat desmoids. Secondly, data from different reports with varying levels of evidence inevitably caused some biases. With more evidence emerging, it would make systematic research possible to sift out high-quality data while simultaneously not leaving out too much information.

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ZZ initially started this review, organized the literature and drafted the article. JS made critical revisions and contributed to drafting parts of the manuscript. TY retrieved literatures, collected and sorted crucial information. KZ and TL provided instructions on writing, as well as retrieving literatures, and made insightful revisions. All authors read and approved the final manuscript.

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Competing interests

The authors declare that they have no competing interests.

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