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Review

Active surveillance in desmoid-type fibromatosis: A systematic literature review

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Treatment outcome

Abstract ***Background:*** This study evaluates the results of the active surveillance (AS) approach in adult patients with desmoid-type fibromatosis (DTF) because AS is advocated as a front-line approach for DTF in the European consensus guidelines.
Methods: A systematic literature search was conducted (December 19th, 2019, updated on April 14th, 2020). Studies describing the outcomes of the AS approach were included. The PRISMA guidelines were used.
Results: Twenty-five articles were included for data retrieval. Forty-two percent of reported patients (1480 of 3527 patients) received AS, the majority were women and the majority had a primary tumour. The median age at diagnosis ranged from 28 to 59 years. Common tumour sites were the extremities/girdles (n = 273), the abdominal wall (n = 253) and the trunk (n = 153). The median reported percentage of progressive disease, stable disease and partial response was 20% (interquartile range [IQR]: 13–35%), 59% (IQR: 37–69%) and 19% (IQR 3–23%), respectively. In 640 patients, the outcome was not specified. The median reported percentage of shifting to an active form of treatment was 29%, most commonly to systemic treatment (n = 195) and surgery (n = 107). The reported median follow-up time ranged between 8 and 73 months. The reported median time to progression and/or initiation of the subgroup shifting from AS to 'active' therapy ranged from 6.3 months to 19.7 months.
Conclusion: The majority of patients undergoing AS have either stable disease or a partial response, and about one-third of patients shift to an active form of treatment. Selecting

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patients who will benefit from active surveillance upfront should be the priority of future studies.
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1. Introduction

Desmoid-type fibromatosis (DTF) is an uncommon, soft-tissue tumour arising in musculoaponeurotic structures and mainly affecting young adults aged between 20 and 40 years [1]. DTF is characterised by unpredictable, invasive growth. Rapid growth is often seen in the early phase of the disease, but also in response to pregnancy or hormonal manipulation [2,3]. After an initial period of growth, many patients experience prolonged stabilisation of the desmoid tumour.

Up to ten years ago, surgical treatment was the mainstay of treating DTF leading to significant morbidity and high recurrence rates [4–6]. Other forms of active treatments, such as radiotherapy and systemic therapy, mainly have a role in case of progressive and symptomatic tumours located at sites which are difficult to treat surgically [7]. However, these therapies can lead to treatment-related toxicities [7]. The term 'active surveillance' (AS) for the management of DTF was introduced in the 1990s. Initially, AS was only offered to patients with recurrent tumours, but after 2005 also patients with primary tumours were exposed to this approach [8,9]. As a result, a decrease in the use of these 'active treatments' over the past years has been reported in several nation-wide cohort studies [4,5]. AS for DTF is justified as it has no metastatic potential and spontaneous tumour regression is reported in up to 30% of patients who undergo initial AS [10]. A large retrospective study showed no difference in event-free survival (EFS) comparing surgery with the AS approach (53% versus 58%, $p = 0.415$) [6]. The first European consensus guideline dates from 2015, and advocates using AS as an upfront approach, to minimise overtreatment and to prevent unnecessary morbidity [11]. This recommendation was based on the results of several retrospective series [8,10,12–14]. A systematic review to summarise and to evaluate the published results of the AS approach can be helpful to select patients who benefit from this approach, while awaiting the results of three ongoing, prospective clinical trials from Europe (NCT01801176, NCT02547831, and NTR 4714) [15–17].

The aim of the current study was to systematically review published studies reporting the results of the AS approach in adult DTF patients. Furthermore, Response Evaluation Criteria in Solid Tumours (RECIST) classification of DTF tumours during the AS approach was evaluated, prognostic factors for a successful AS approach were identified, the median time to shift to an active form of treatment and the median duration of the AS approach were analysed and lastly, the forms of active treatment after the initial AS approach were assessed.

2. Material and methods

This study uses the PRISMA guidelines for reporting a systematic literature review.

2.1. Information sources

On December 19th 2019, a systematic literature search was performed by an expert librarian. The search was updated on April 14th which yielded one additional inclusion. Used databases include Embase.com, Ovid MEDLINE, Web of Science, Cochrane CENTRAL, PsycInfo Ovid and Google Scholar. Duplicated records were removed. Case reports were excluded, and an English language filter was applied. There were no constrains on publication dates. Appendix 1 depicts the search strategy.

2.2. Eligibility criteria

Studies with sporadic DTF as a main subject and full-text availability were included by two researchers (MJMT, AWS). Papers reporting outcomes (either using RECIST [18] or number of patients shifting to 'active treatment') were included in this systematic literature review. Cross-referencing was carried out ensuring inclusion of all relevant articles. The flowchart depicting the study selection procedure is available in Appendix 2.

2.3. Study selection

The retrieved articles were assessed for potential inclusion by the first and second author based on the review of title and abstract. Next, full-text articles were evaluated in accordance with the predetermined inclusion criteria and exclusion criteria for this systematic literature review (listed in Table 1).

2.4. Data extraction

Data was collected by two researchers (MJMT, AWS) using a predefined Excel sheet stating the year of publication, the first author, the journal, the publication title, whether the publication fulfilled the inclusion criteria, the inclusion period, the type of study, the total number of participants, the number of participants

receiving AS, the number of patients with familial adenomatous polyposis (FAP)/Gardner syndrome, the number of primary tumours, and the number of recurrent tumours. Of the AS group, the following variables were extracted: the reported mean/median follow-up (range, interquartile range [IQR], 95% confidence interval [CI]), the reported median/mean age (with range or IQR), the sex distribution, the tumour sites, the number of patients with progressive disease (PD), stable disease (SD), partial response (PR), complete response (CR), the number of patients who shifted to active treatment, reasons for shifting to an active form of treatment, and whether RECIST were used for determination of these outcomes. For responses not evaluated by RECIST but by using similar terms, tumour response was categorised based on the RECIST categories; PD, SD, PR and CR. PD included the terms 'increase', 'evolution' and 'enlarged'; SD included the terms 'stable', 'arrested' and 'non-progressive'; PR included the terms 'decreased', 'regressed', 'disease free survival', 'responding disease' and 'spontaneous remission'; and CR included the terms 'disappeared', and 'complete regression'. Not specified (NS) was used in case a variable was missing.

Tumour sites were classified as the extremity/girdle region (including upper extremity, lower extremity, shoulder, buttock, thigh and hip), intra-abdominal (including mesenteric), trunk (including paraspinal and thoracic wall) abdominal wall, head/neck region and other (including inguinal region and not further specified sites). When age and follow-up (in months of years) were reported for each individual patient, the median age and median follow-up with range were extracted and calculated from these data.

A shift to 'active treatment' was defined as 'ceasing active surveillance'. The following therapies were categorised as 'active treatments': systemic treatment (including hormonal treatment, chemotherapy and tyrosine kinase inhibitors), surgery, radiotherapy, combination therapies and local therapies such as radiofrequency or cryotherapy. The category of 'NS' was used when information was lacking about the type of active treatment. Shift to 'active treatment' is reported as the percentage of patients shifting to active treatment from each separate study, and compiled as an overall median percentage of patients shifting to active treatment with IQR, compiling all study results. The same was done for the types of active treatments. Variables such as median follow-up of the AS group, the time to intervention, the time to progression, the time to stabilisation, the time to regression, progression-free survival (PFS), and EFS were extracted in case they were stated by the included studies.

3. Results

3.1. Systematic literature search

The search was performed on December 19, 2019 and updated on April 14, 2020. The search strategy yielded a total of 940 papers; after deduplication, 589 papers remained. Title and abstract were screened leading to the exclusion of 551 papers. A total of 38 papers were reviewed based on full-text, and 25 studies were finally included for further analysis. The study selection procedure is depicted in Appendix 2. No randomised controlled trials reporting about AS in DTF were identified. Several reviews, discussing the current status and treatments of DTF addressed the AS approach, but none of these reviews included a systematic literature review solely focussing on the outcomes of the AS approach.

3.2. Study design and quality assessment

All included studies were published after 2005. All studies were retrospective case series, which are generally considered to have a high risk of bias and a low certainty [19,20]. Of note, nine studies potentially used overlapping patient cohorts based on author names,

Table 1
Inclusion and exclusion criteria of study selection procedure.

Inclusion criteria	Exclusion criteria
• Primary and recurrent DTF • Active surveillance (or other similar terms such as wait and see, expectative management, etc.) as a primary treatment • Adult (aged $\geq$ 18 years) patients • English language • Reporting the outcomes of active surveillance in terms of reporting the success rate of active surveillance, numbers of patients needed to shift to active treatment, RECIST outcomes during active surveillance	• Studies with patients receiving solely active forms of treatment such as surgery, systemic treatment, local therapy (e.g. cryotherapy) and radiotherapy • Case reports, case series $\leq$5 patients • Preclinical studies describing molecular features of DTF • Diagnostic studies describing imaging features of DTF • Non-original reports (e.g. editorials, study protocols, reviews etc.) • Non–full-text availability (e.g. conference abstracts, etc.) • Studies describing solely paediatric cohorts • Studies describing solely FAP or Gardner syndrome • Other subjects than DTF (e.g. soft tissue sarcoma) • Languages other than English

DTF, desmoid-type fibromatosis; FAP, familial adenomatous polyposis; RECIST, Response Evaluation Criteria in Solid Tumours.

Table 2
Overview of studies reporting the results of the active surveillance approach in desmoid-type fibromatosis.

First author, year of publication, inclusion period	Total N	FAP/ Gardner N	P/R total	ASG N	P/R ASG	Median age ASG	Sex M/ F ASG	Site ASG	Median FU (r/IQR/95% CI) ASG	PD	SD	PR	CR	NS	Shift to AT	AT
Dalén, 2006 [24] NS	8	NS	6/2[a]	**8**	6/2[a]	32.5	3/5	5 AW 1 EG 2 TR	4.6 year (r 0.8–7.5)	2	1	2	3	0	NS	NS
Bertagnolli, 2008 [25] 2001–2006	52	21	NS	**4**	NS	NS	4 NS	4 IA	NS	0	4	0	0	0	0/4	NA
Bonvalot, 2008 [12] 1988–2003	112	NS	112/0	**11**	11/0	NS	11 NS	11 NS	NS	3	NS	NS	NS	8	3/11	1 ST 2 ST+SG
Nakayama, 2008 [26] 1992–2003	11	NS	9/2	**11**	9/2	28	2/9	2 AW 7 EG 2 HN	56 months (r: 16–132)	1	7	3	0	0	3/11	2 SG 1 ST
Fiore, 2009 [14] 1995–2008	142	6	74/68	**83**	54/29	NS	22/61	33 AW 27 EG 3 HN 6 IA 14 TR	NS	29	35	3	NS	16	26/83	10 NS 6 SG 10 ST
Barbier, 2010 [27] 1989–2009	26	0	11/15	**26**	11/15	34.5	5/21	26 EG	8 months (r: 0–80)	1	24	0	1	0	0/26	NA
Salas, 2011 [22] 1965–2008	426	0	426/0	**27**	27/0	NS	27 NS	27 NS	52 months (95% CI: 43.6–61.6%)	6	16	5	0	0	NS	NS
Bonvalot, 2013 [10] 1993–2012	147	0	147/0	**102**	102/0	NS	102 NS	102 AW	NS	NS	NS	NS	NS	102	37/102	15 SG 22 ST
Fiore, 2014 [2] 1985–2011	44[b]	0	44/0	**27**	27/0	NS	0/27	27 NS	NS	17	NS	NS	NS	10	12/44	6 SG 6 ST
Huang, 2014 [28] 1987–2009	214	NS	153/61	**20**	9/11	NS	20 NS	20 NS	45 months (r: 24–90)	4	14	2	0	0	NS	NS
Roussin, 2015 [23] 1992–2014	31	0	NS	**11**	NS	50	1/10	11 TR	23 months (r: 3–144)	2	NS	NS	NS	9	3/11	1 SG 2 ST
Colombo, 2015 [9] 1992–2012	216	0	216/0	**70**	70/0	41	22/48	26 EG 10 IA 2 HN 32 TR	39 months (r: 15–62)	28	24	15	NS	3	28/70	3 RT 3 SG 22 ST
Burtenshaw, 2016 [29] 1980–2012	194[c]	80	176/18[a]	**120**	109/11	NS	120 NS	120 NS	NS	NS	NS	NS	NS	120[d]	53/120	16 SG 33 ST 2 ST + SG 2 RT + SG
Park, 2016 [30] 2008–2015	47	NS	39/8	**20**	20/0	40.2	6/14	9 EG 1 HN 1 IA 9 TR	NS	1	13	5	1	0	1/20	1 SG
Cassidy, 2018 [31] 2008–2015	160	NS	118/42[a]	**72**	50/22[a]	NS	22/50	19 AW 21 EG 21 IA 6 NS 5 TR	25.1 months (r 1.8–177)	10	NS	NS	NS	62	42/72[e]	42 NS
Van Broekhoven, 2018 [32] 1993–2013	91	6	91/0	**37**	37/0	36	9/28	17 AW 4 EG 3 HN	16 months (IQR: 7–31)	5	21	4	2	5	15/37	15 NS

(*continued on next page*)

Table 2 (*continued*)

First author, year of publication, inclusion period	Total N	FAP/ Gardner N	P/R total	ASG N	P/R ASG	Median age ASG	Sex M/ F ASG	Site ASG	Median FU (r/IQR/95% CI) ASG	PD	SD	PR	CR	NS	Shift to AT	AT
								13 TR								
De Bruyns, 2019 [33] 1990–2013	227	14	NS	**59**	NS	NS	59 NS	59 NS	NS	NS	20	13	9	17	NS	NS
Duazo-Cassin, 2019 [21] 1998–2016	63	0	63/0	**17**	17/0	59	1/16	17 TR	42.2 months (r: 0–214)	2	9	6	0	0	2/17	2 SG
Krieg, 2019 [34] NR	96	NS	NS	**15**	NS	NS	15 NS	15 NS	3.4 year (r: 2.4–11.6)	3	9	3	0	0	3/15	1 SG+RT 2 NS
Shen, 2019 [35] 2010–2018	29	2	27/2	**3**	NS	NS	3 NS	3 NS	NS	3	0	0	0	0	1/3	1 SG
Van Houdt, 2019 [36] 1998–2016	168	0	168/0	**168**	168/0	42.2	50/118	61 AW 51 EG 15 IA 11 NS 30 TR	40.5 months	60	60	33	12	3	78/168	40 SG 36 ST 2 RT
Kim, 2020 [37] 1995–2015	76	0	46/30	**76**	30/46	30.2[f]	29/47	39 EG 37 NS	50.4 months (r: 12–226)[f]	NS	54	8	1	13	NS	NS
Reported concurrent use of NSAIDs and/or hormonal therapy during the AS approach																
Non-narcotic analgesics and non-steroidal anti-inflammatory drugs (NSAID's) were offered to symptomatic patients																
Briand, 2014 [8] NS	73	0	52/21	**55**	31/24	35	20/35	42 EG 1 HN 12 TR	73 months	7	42	NS	5	1	5/55	3 SG 1 ST 1 SG + RT
With or without administration of NSAID's																
Penel, 2017 [6] 2010–2016	771	NS	771/0	**388**	388/0	NS	388 NS	388 NS	NS	117	NS	NS	NS	271	71/338	3 CrT 2 SG 61 ST 1 RF 4 RT
Conversion to hormonal therapy was not considered failure of AS treatment																
Turner, 2019 [38] 2004–2015	103	0	103/0	**50**	50/0	41[f]	13/37	14 AW 20 EG 3 HN 3 IA 8 TR 2 NS	NS	21	29	0	0	0	19/50	9 SG 9 RT 1 SG+ RT + ST

ASG, active surveillance group; AT, active treatment; AW, abdominal wall; CrT, cryotherapy; EG, extremity/girdles; HN, head/neck; IA, intra-abdominal; IQR, interquartile range; NA, not applicable; NS, not specified; NSAIDs, non-steroidal anti-inflammatory drugs, P, primary disease; R, recurrent disease; RF, radiofrequency; RT, radiotherapy; SG, surgery; ST, systemic treatment; TTI, time to intervention; TR, trunk, r, range.

[a] including residual tumours.

[b] only group A, B and C included in this table.

[c] only group A (primary tumours) and C (recurrent tumours) included in this table.

[d] n = 51 shift due to tumour growth, symptom escalation or patient preference for intervention.

[e] n = 72 received AS, n = 37 patients had available Response Evaluation Criteria in Solid Tumours (RECIST).

[f] mean value instead of median.

affiliations and inclusion time period [2,6,9,10,12,14,21–23].

3.3. Clinical characteristics and outcomes of active surveillance

The clinical characteristics and outcomes of patients treated with AS of the included studies are shown in Table 2. Most studies only included sporadic DTF, whilst seven studies also included FAP-related DTF. It was mostly unclear whether these FAP-patients were included in the AS groups, and no study published separate results for the AS approach in FAP-related DTF patients. Treatment strategy comparisons included surgery with or without adjuvant radiotherapy, isolated limb perfusion, cryotherapy, radiotherapy and systemic treatments including chemotherapy, tyrosine kinase inhibitors, and hormonal treatment. One study compared three groups categorised by surgical margins [28], another study categorised groups based on their pregnancy status [2]. From the later, only groups A, B and C (representing patients with diagnosed during pregnancy [A], diagnosed within 6 months after delivery [B], and previously diagnosed and still in situ at the time of pregnancy [C]) were included in the analysis. Group D (resected before pregnancy without clinical evidence of residual or recurrent disease) was excluded from the results owing to lack of reporting of clinical outcome and shift to active treatment. One study only reported the outcome of 37 patients with RECIST whilst they had 72 patients undergoing AS (Table 2) [31]. Furthermore, one study also described a group of patients with resected tumours (group B). This group was excluded from analysis and only groups A and C from this study were included [29].

Few studies solely included patients receiving AS [26,27,36,37]. Ten studies provided the type and interval of imaging during the AS approach. Most studies used intervals of two to six months after the first evaluation with either computed tomography (CT) [25] or magnetic resonance imaging (MRI) [8,10,23,27,37], or a combination. Few studies used additional ultrasound [9,36,37]. Two studies stated to 'change to annual visits' after tumour stabilisation or after two years of follow-up [30,36].

3.4. Active surveillance as a single treatment

The total number of patients was 3527, of which 1480 (42%) received AS. Three studies allowed the use of non-steroidal anti-inflammatory drugs (NSAIDs) in symptomatic patients during the AS approach or did not consider shift to hormonal therapy as a 'failure of AS' (Table 2) [6,8,38]. As the use of NSAIDs could be under-reported by both patients and researchers, the results of these studies were included in the analysis of this paper.

The number of patients receiving the AS approach ranged from 3 to 388 per included study. The total group receiving AS consisted of 205 men and 526 women (reported in fifteen studies), for the remaining patients (n = 749), the sex was not further specified. The median percentage of women in each reported study was 72% (IQR: 67–78%). The reported median age at diagnosis of the AS group (available in twelve studies) ranged from 28 to 59 years. Twenty studies reported the number of primary and recurrent tumours included in their AS group (Table 2). In these studies, the majority of patients had a primary tumour with a median percentage of primary tumours of 100% (IQR: 68–100%). The remaining had a recurrent tumour. Based on the reported information, no distinction in numbers of patients needing shift to active treatment could be made between primary and recurrent tumours.

3.5. Tumour response to active surveillance

Fourteen out of twenty-five studies stated to use RECIST (either 1.0 or 1.1) [18] to objectively measure tumour response [2,6,8,14,23,25,29–33,35,36,38]; however only a part of those studies actually reported the radiological response per treatment type in accordance with RECIST. Other studies used similar approaches describing the disease outcome as PD, SD, PR or CR.

A total of 21 studies reported PD in 322 patients. The median percentage of PD reported in these studies was 20% (IQR: 13–35%). A total of eighteen studies reported SD in 382 patients. The median percentage of SD reported in these studies was 59% (IQR: 37–69%). Seventeen studies reported PR in 102 patients. The median percentage of PR reported in these studies was 19% (IQR: 3–23%). CR was reported sixteen studies in 34 patients. The median percentage of CR reported in these studies was 0% (IQR 0–6%) (Table 3).

3.6. Indications for start of treatment

Pain, with or without radiological evidence of progression, functional symptoms, or patient request, were frequently mentioned reasons for shifting to an 'active' treatment [10]. A total of 402 patients (reported in twenty studies) shifted to 'active' treatment. The median percentage of patients shifting in these studies was 29% (IQR: 17–40%). The type of 'active' treatment was systemic treatment in 195 cases, surgery in 107 cases, radiotherapy in 18 cases, a combination of therapies (e.g. systemic treatment with surgery, and systemic treatment with radiotherapy) in 8 cases and local therapy (e.g. radiofrequency and cryotherapy) in 4 cases. In 69 cases it was reported that patients shift to an active form of treatment but the type was unspecified (Table 3).

Table 3
Overview of RECIST outcomes and shift to active treatment.

	Number of studies reporting this variable	Number of patients	Median % of patients (IQR) reported in all studies
RECIST outcomes			
Progressive disease	21	322	20% (13–35%)
Stable disease	18	382	59% (37–69%)
Partial response	17	102	19% (3–23%)
Complete response	16	34	0% (0–6%)
Active treatment			
Shifting to an active form treatment	20	402	29% (17–40%)
Surgery	17	107	41% (11–62%)
Systemic treatment	17	195	33% (0–52%)
Local therapies[a]	16	4	0% (0%)
Radiotherapy	16	18	0% (0–1%)
Combination of therapies[b]	20	8	0% (0–3%)

IQR, interquartile range; RECIST, Response Evaluation Criteria in Solid Tumours.
[a] radiofrequency, cryotherapy.
[b] surgery + radiotherapy, systemic therapy + surgery.

3.7. Progression and change in treatment strategy

The median follow-up time of patients with the AS approach was reported by twelve studies and ranged between 8 months and 73 months (Table 4). Most studies reported the median time to progression (n = 5) [9,22,28,29,32], and solely two studies reported median time to shifting from AS to 'active' therapy [31,36]. Other studies used PFS [14,30,33,38] or EFS [6,28] to express the success rates of the AS approach. Two studies described time to SD [27,37].

Van Broekhoven et al. [32] described that the median duration of the AS approach was 22 months (IQR: 13–46) for patients with CR or PR. Kim et al. [37] reported that age younger than 40 and a recurrent tumour were significant predictive factors of longer time to disease stabilisation (p = 0.014 and p = 0.036, respectively). Penel et al. [6] reported that 30.1% of patients in the AS group experienced an event (progression during AS, change in treatment strategy and/or disease-related death). Briand et al. [8] reported a cumulative probability of dropping out from the AS approach of 5.7% (95% CI: 1.5%–14.2%) at one year and 9.6% (95% CI: 3.5%–19.6%) at 2, 5 and 10 years. Bonvalot et al. [10] stated that the percentage of patients shifting to another treatment was 33% (95% CI: 24–43) at 1-year and 41% at 3 years (95% CI: 31%–52%). Fiore et al. [14] reported that 89% of patients progressed within the first two years after referral and reported a 5-year PFS rate of 47% (standard error [SE] = 10.3%) for primary tumours and 54% (SE = 11.6%) for recurrent tumours (p = 0.48) (Table 4).

Table 4
Reported time intervals and survival data to express the success rate of the active surveillance approach.

References	Outcome
	Median time to intervention
Cassidy et al., 2018 [31]	11.7 months (±6.5 months)
Van Houdt et al., 2019 [36]	6.5 months
	Median time to progression
Salas et al., 2011 [22]	19.7 months (range: 7.8–46.2 months)
Huang et al., 2014 [28]	15.3 months (range: 7.8–41 months)
Colombo et al, 2015 [9]	16 months
Van Broekhoven et al., 2018 [32]	7.3 months (IQR: 4.1–11.9 months)
Krieg et al., 2019 [34]	1.2 years (range: 0.9–1.5 years)
	Median time to stable disease
Barbier et al., 2010 [27]	13.2 months (range: 6–30 months)
Kim et al., 2020 [37]	30.4 months (range: 7–112 months)[a]
	Median time to regression
Briand et al., 2014 [8]	54.8 months (range: 21–130 months)
	Median progression-free survival
Turner et al., 2019 [38]	10 months (range: 2–94 months)
	2-year progression-free survival
De Bruyns et al., 2019 [33]	71% (95% CI: 0.6%–0.84%)
	3-year progression-free survival
Turner et al., 2019 [38]	38%
Park et al., 2016 [30]	92%
	5-year progression-free survival
Fiore et al., 2009 [14]	47% (SE = 10.3%) primary tumours
	54% (SE = 11.5%) recurrent tumours
	2-year event-free survival
Penel et al., 2017 [6]	85.7 (±9.6) core needle biopsy
	52.8 (±4.6) open biopsy
	5-year event-free survival
Huang et al., 2014 [28]	71.2%

CI, confidence interval; IQR, interquartile range; SE, standard error.
[a] mean value instead of median.

A description of the risk factors for progression or a change in treatment strategy is reported in Table 5. A larger tumour size, >5 cmversus ≤5 cm, was associated with a shorter time to intervention (6.9 months versus 32.6 months, p = 0.02) [31], and shift to 'active' treatment was more likely in patients with 'larger' tumours (≥7 cm) with a hazard ratio (HR) of 2.0 (95% CI: 1.3%–3.2%, p = 0.002) [36] and >3.5 cm, p = 0.004 [10]. Furthermore, the initiation of 'active' treatment was more likely for patients with PD or SD than for patients with PR (p < 0.001) with a HR of 12.4 (95% CI: 4.9%–31.4%) and 4.8 (95% CI: 1.8%–12.6%), respectively [36]. Patients who experienced pain were also more likely (p < 0.001) to shift to an active form of treatment, with a HR of 2.55 (95% CI: 1.63%–3.99%) [36]. Cassidy et al. [31] found no association between intervention (i.e. shift to active treatment) and age (p = 0.22), as well as intervention and sex (p = 0.07).

Table 5
Published results regarding variables that are potentially associated with time to disease stabilisation, risk of progression or change in treatment strategy. Significant outcomes (p-value <0.05) are in bold.

First author, year of publication	Reference	Outcome	p-value	Statistically significant identified risk factor
Barbier, 2010	[27]	Time difference in evolution to stabilisation		Longer evolution time before stabilisation in recurrent tumours
		Primary versus recurrent disease	p = 0.0417	
Kim, 2020	[37]	Age	**p = 0.022**	Age, < 40 years and recurrent tumours are predictive factors of longer time to disease stabilisation
		Tumour status	**p = 0.041**	
		Tumour site (axial versus extremity)	p = 0.148	
Bonvalot, 2013	[10]	Change in treatment strategy		Larger tumour size (>3.5)
		Pregnancy before the development of DTF	p = 0.27	
		Age	p = 0.27	
		Tumour size	**p = 0.004**	
		3.5–5.0 cm (HR = 3.7, 95% CI: 1.0%–14%)		
		5–7 cm (HR = 4.0, 95% CI: 2.4%–2.8%)		
		7–15.6 cm (HR = 8.2, 95% CI: 2.4%–28%)		
Cassidy, 2018	[31]	Change in treatment strategy		
		Age	p = 0.22	
		Sex	p = 0.07	
		Documentation of symptoms at presentation	p = 0.35	
		PFS[a]		
		Age (HR = 0.99)	p = 0.31	
		Tumour size (HR = 1.027)	p = 0.13	
		Tumour site extremities/all other sites versus abdominal wall	p = 0.54/p = 0.38	
		Tumour site paraspinal/flank versus abdominal wall	**p = 0.01**	
Colombo, 2015	[9]	Change in treatment strategy		
		Sex	p = 0.565	
		Tumour site	p = 0.926	
		Size	p = 0.397	
Turner, 2019	[38]	Progression		
		Tumour site abdominal wall versus other sites	p = 0.53	
Van Houdt, 2019	[36]	Change in treatment strategy		
		Tumour size >7 cm (HR = 2.04, 95% CI: 1.29%–3.21%)	**p < 0.01**	Larger tumour size (>7 cm), reporting pain, and stable disease or progressive disease are associated with a higher risk of initiation of an active form of treatment
			p < 0.001	
		Reporting pain	**p < 0.001**	
		PR versus SD, PD	p = 0.13	
		Age	p = 0.36	
		Tumour site	p = 0.84	
		Sex		

CI, confidence interval; DTF, desmoid-type fibromatosis; HR, hazard ratio; PD, progressive disease; PFS, progression-free survival; PR, partial response; SD, stable disease.
[a] *only available for n = 37 patients with evaluable magnetic resonance imaging.*

3.8. The influence of the tumour site on initiation of active surveillance

Frequent reported tumour sites (available in sixteen studies) were the extremities/girdles (n = 273 patients, median percentage of incidence in studies = 31% [IQR: 3–68%]), the abdominal wall (n = 253 patients, median percentage of incidence in studies = 9% [IQR: 0–37%]) and the trunk (n = 153 patients, median percentage of incidence in studies = 17% [IQR: 0–37%]). Intra-abdominal (n = 60) and head/neck (n = 15) tumours were less common, with a median percentage of incidence in studies of 0% (IQR: 0–8%) and 0% (IQR: 0–4%), respectively. From a total of 1480 patients receiving AS, the tumour sites were not specified in 726 (49%) of patients (Table 2).

Cassidy et al. [31] described that patients with abdominal wall tumours were often managed with AS (61%), whereas those with chest wall and intra-abdominal tumours more often received active

treatment (80% and 60%, respectively). Fiore et al. [14] also described that patients who received AS commonly had abdominal wall tumours ($p < 0.0001$) compared with patients who received other treatments, whilst Park et al. [30] found no difference in tumour sites between groups managed with AS or surgery.

3.9. The influence of the tumour site on disease stabilisation, progression or a change of the treatment strategy

No differences in risk of progression during AS were found between abdominal wall tumours and other sites ($p = 0.53$) by Turner et al. [38] nor on a chance of spontaneous stabilisation among axial sites of extremity tumours ($p = 0.148$) by Kim et al. [37] (Table 5). The 5-year PFS of primary cases managed with AS of trunk/thoracic wall tumours and abdominal wall tumours was similar (53.9% [SE = 16.2%] versus 52.5%, [SE = 14.3%]) in the study from Fiore et al. [14]. Van Houdt et al. [36] concluded that upper extremity and chest wall DTF tumours have the highest percentage of progression (39% and 47%, respectively), although this difference was not significant compared with other locations.

Cassidy et al. [31] described that tumours located paraspinal or flank were more commonly associated with a change in treatment than abdominal wall tumours ($p = 0.01$), but no differences were found comparing extremity, intra-abdominal or abdominal wall tumours. Van Houdt et al. [36] concluded that there was no difference in initiation of active treatment between upper extremity and chest wall DTF ($p = 0.36$). This is in line with the findings of Colombo et al. [9] who did not identify the tumour site as a predicting factor for progression and/or change in the treatment strategy among tumour sites ($p = 0.926$). No single conclusion could be reached regarding the tumour site and the success or failure of the AS approach because of the heterogeneity of the cohorts of included studies.

4. Discussion

This systematic literature review evaluated the outcomes of the AS approach in sporadic DTF. Twenty-five articles, describing the outcomes of the AS in DTF, were identified. The majority of the reported patients experienced SD, and about one-third of the patients needed to shift to 'active' treatment. The median time of follow-up was reported by twelve studies and ranged between 8 months and 73 months, and the median time to shift from AS to active treatment or to progression ranged from 6.5 months to 19.7 months.

AS has increasingly been advocated in for sporadic DTF [39]. This is underlined by the number of publications about this subject since the year of 2006. In the most recent European consensus paper, published by the Desmoid Tumor Work Group in 2020, AS is advocated as a first-line treatment in symptomatic patients, independently of the tumour site or size. In case of progression, other treatments such as surgery or systemic therapies, and treatments (including AS), should preferably take place in an expert clinic with an experienced multidisciplinary sarcoma team [7]. A study by Eastly et al. [40] showed that almost half of the clinicians prefer AS an initial management strategy for primary DTF for which function-sparing surgery is possible. In case of recurrent DTF after a previous complete resection without adjuvant treatment, this rate dropped to 20%. This is illustrated by the current study as the majority of included patients have primary tumours.

The definition of AS varies widely between studies. Some studies also allowed the usage of non-narcotic analgesics, NSAIDs or hormonal treatment in the AS group [6,8,38]. Especially for NSAIDs, which are non-prescription drugs in many countries and mainly used for relieving pain symptoms, the usage of these drugs can be severely under-reported by patients, clinicians and researchers. Inclusion of these patients in studies evaluating the AS approach can distort the true outcomes because NSAIDs and hormonal treatment (e.g. tamoxifen) can be beneficial for DTF with a reported response rate of 85% [41].

The current study did not include the results of the phase 3 trial comparing sorafenib to placebo [42]. Whilst placebo treatment can be considered a form of AS, as patients do not receive an active form of treatment, we decided not to include this trial in the current study. This was because only patients with progressive, recurrent or primary disease which were deemed inoperable or required extensive surgical resection or were symptomatic were included in this clinical trial. In daily clinical practice, AS will not be offered as a front-line approach to these patients, and therefore, this study was not included in the current review.

The selection of patients suitable for the AS approach remains challenging. The results of this systematic review suggest that AS is mainly described as a treatment for tumours localised in the extremity/girdles and in the trunk. This might be due to the predilection sites of DTF tumours to these locations [43] or due to a selection upfront because of the higher risk of recurrence after surgery for these groups [12]. Based on the current systematic review, drawing a single conclusion with regard to tumour sites and the success of AS remains challenging. This is mainly due to the inclusion of studies with homogeneous cohorts in terms of tumour sites (e.g. mesenteric, or breast) or a preselection of patients upfront (e.g. inoperable tumours due to localisation adjacent to vital structures [e.g. nerves, blood vessels]). Furthermore, the exact tumour site was not specified in a large number of patients.

About one-third of the patients needed a shift to an 'active' form of treatment. Although no uniform results

could be drawn from the current studies, several studies reported that larger tumours were more likely to shift [10,36], whilst age, sex and pregnancy before the development of DTF were not associated with this shift [10,31,36]. Colombo et al. [9] reported that the sex, tumour site and tumour size did not predict progression and/or shift to change in treatment; the non-surgical group (n = 106) also contained patients receiving medical treatments (n = 4). Few studies described β-catenin mutation of the included cohort, and none of these studies analysed the influence of these mutations on the success or failure of the AS approach [6,21]. The same applies for FAP-related DTF tumours. The variable results from these retrospective studies highlight the need for the identification of predictive factors for progression and changes in treatment strategies.

In the current study, progression was often reported within two years after diagnosis [14]; however the length of follow-up of the included studies varied highly. Few studies reported the median follow-up duration of the AS subgroup, and time to intervention was often lacking. The minimal available information about the type and frequency of follow-up during AS underlines the need for standardisation of the AS approach. This includes defining a follow-up schedule with the use of MRI or CT, depending on the tumour site. As few studies reported progression after stabilisation, a maximum AS term should be discussed with the patient.

The major limitation of the current study is the inclusion of retrospective, small sample–sized studies, which often evaluate several treatment regimens, with various follow-up schedules and limited information about disease outcomes, or reasons for shifting to 'active' treatment. Only part of the studies used and reported disease response based on RECIST [18]. Some included studies selected patients for the AS approach based on the fact that the patients were unable to tolerate chemotherapy or radiotherapy [28], had unresectable asymptomatic mesenteric masses [25] or had masses that were not life-threatening or at risk for mutilation [22]. Moreover, some studies selected patients based on tumour sites (e.g. breast desmoids [21,23]) or were interested in other study end points than the results of the AS approach (e.g. pregnancy status [2], or imaging characteristics [24,31]). Another limitation is the relatively large number of studies included in this systematic review were there is potential cohort overlap (based on author names, affiliations and inclusion time period) [2,6,9,10,12,14,21–23]. Despite these limitations, this systematic literature review was able to compile the available evidence for the use of the AS approach in adult DTF.

Currently, the results of three prospective European studies evaluating the efficacy of AS in DTF are awaited. The French study (NCT01801176) and the Italian study (NCT02547831), which started in May 2012 and July 2013, respectively, both evaluate 3-year PFS [15,16]. The Dutch study (NTR 4714), which started in May 2014, evaluates tumour progression at 5-years follow-up [17]. These three studies will provide further insights into the natural growth of DTF, the differences in growth behaviour between various tumour sites, tumour sizes and β-catenin mutation types as well as the indications and considerations for the start of 'active' treatment.

5. Conclusions

Active surveillance is the mainstay of treatment for sporadic DTF. This systematic literature review underlined the ongoing trend of the AS approach and indicates that a minority of patients need shift to an active form of treatment avoiding overtreatment and minimising potential morbidity.

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Conflict of interest statement

Authors declare that there is no conflict of interest.

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List of abbreviations

AS	active surveillance
ASG	active surveillance group
AT	active treatment
AW	abdominal wall
CI	confidence interval
CR	complete response
CT	cryotherapy
DTF	desmoid-type fibromatosis
EFS	event-free survival
EG	extremity/girdles
FAP	familial adenomatous polyposis
HR	hazard ratio
IA	intra-abdominal
IQR	interquartile range
MRI	magnetic resonance imaging
NA	not applicable
NS	not specified
NSAID's	non-steroidal anti-inflammatory drugs
P	primary disease

PD progressive disease
PFS progression-free survival
PR partial response;
R recurrent disease
RECIST Response Evaluation Criteria in Solid Tumours
RF radiofrequency
RT radiotherapy
SD stable disease
SE standard error
SG surgery
ST systemic treatment
TR trunk
TTI time to intervention

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ejca.2020.06.022.

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