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Surgical excision versus observation as initial management of desmoid tumors: A population based study

Benjamin Turner [h, *], Mohamed Alghamdi [b, g], Jan-Willem Henning [b], Elizabeth Kurien [c], Don Morris [b], Antoine Bouchard-Fortier [a], Daniel Schiller [f], Shannon Puloski [d], Michael Monument [d], Doha Itani [e], Lloyd A. Mack [a]

[a] Department of Surgery, University of Calgary, Calgary, AB, Canada
[b] Division of Medical Oncology, University of Calgary, Calgary, AB, Canada
[c] Division of Radiation Oncology, University of Calgary, Calgary, AB, Canada
[d] Division of Orthopedic Surgery, University of Calgary, Calgary, AB, Canada
[e] Department of Pathology, University of Calgary, Calgary, AB, Canada
[f] Department of Surgery, Royal Alexandra Hospital, Edmonton, AB, Canada
[g] Department of Medical Oncology, King Saud University, Riyadh, Saudi Arabia
[h] Head and Neck Oncologic Surgery & Microvascular Fellowship, 2nd Floor, Faculty Clinics Building University of Florida, Jacksonville 653-1 West 8th Street, Jacksonville, FL, 32209, United States

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ABSTRACT

Synopsis: Desmoid tumors can be safely managed with watchful waiting, including either observation alone or tamoxifen/NSAIDs. Surgery at first presentation can be associated with significant treatment burden.

Background: Immediate surgery was historically recommended for desmoid tumors. Recently, watchful waiting, (tamoxifen/NSAIDs or observation alone), has been advocated.

Methods: All diagnoses of desmoid tumor within the Alberta Cancer Registry from August 2004 to September 2015 were identified. Patients with FAP were excluded. Demographics, tumor characteristics and treatment and outcome data were collected. Outcomes were compared between immediate surgery and watchful waiting. The effect of abdominal wall site on progression and recurrence and the effect of microscopic margin on recurrence were assessed with Fisher's exact test.

Results: We identified 111 non-FAP patients. Median follow-up was 35 months from diagnosis. 74% were female. Mean age was 42. Fifty (45%) underwent watchful waiting, of whom 21(42%) progressed, with median PFS of 10 months. Fifty-three (48%) underwent resection at presentation, of whom 8 (15%) recurred, with median disease-free survival of 22 months.

Abdominal wall lesions were equally represented in both groups, and equally likely to progress on watchful waiting (50% vs 39%, $p = 0.53$), but there was a trend toward decreased recurrence after surgery. (5% vs 23%, $p = 0.08$).

Microscopic margin had no effect on recurrence (14% of margin negative vs 20% of margin positive, $p = 1.0$).

Conclusions: Watchful waiting was successful in 58% of patients, and a further 28% only required one aggressive treatment thereafter, for a total of 86%. Surgery had a favorable recurrence rate (15%), but some recurrences were associated with significant treatment burden. Treatment should be tailored to individual patients in a multidisciplinary setting. A trial of observation appears warranted in most patients.

Recurrence rate was not affected by positive margins.

* Corresponding author.
E-mail address: Benjamin.turner@jax.ufl.edu (B. Turner).

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Introduction

Desmoid tumors (aggressive fibromatosis) are a subtype of mesenchymal neoplasia, thought to arise from deregulated scar formation [1] and associated with abnormalities of Wnt signaling mediated by the APC/β-catenin pathway [2]. The latter explains the association of desmoids with familial adenomatous polyposis coli (FAP, Gardner's syndrome), which is caused by germline loss of function of APC. Desmoids have no potential for distant metastasis or malignant transformation, but can be locally aggressive and have a high recurrence rate post-resection [3]. Both tumor and treatment can cause significant local morbidity and even mortality depending on tumor location.

While the traditional approach favored surgery at presentation, more recent long-term studies have demonstrated that many desmoids remain stable or even regress with observation, or with hormonal or anti-inflammatory treatment [4,5]. An approach of initial watchful waiting has therefore been advocated, reserving chemotherapy, radiation and surgery (hereafter 'aggressive treatment') for progressive disease [4,6,7]. This approach is further supported by the observation that trauma, and surgery in particular, is sometimes an inciting event for the de novo development of desmoids [8]. We sought to compare outcomes between patients initially observed and those treated with surgery at presentation.

There is some evidence that desmoids arising in the abdominal wall have a more benign natural history than those in other sites [9]. We therefore compared progression and recurrence in abdominal wall desmoids vs all other sites.

The importance of negative microscopic margins in desmoids has been extensively investigated. Some series have demonstrated increased recurrence with positive margins, and others no effect [3,10–13]. We sought to determine the effect of positive microscopic margin, if any, in our population.

Methods

The study was approved by the research ethics board of the University of Calgary. All patients within the Alberta Cancer Registry diagnosed with desmoid tumor between August 2004 and September 2015 were identified. In addition, the tertiary referral pathology repository at Foothills Medical Centre in Calgary was reviewed for any cases not captured by the Registry. All patients with the diagnosis were included. Patients with a concurrent diagnosis of FAP were excluded from the comparison of surgery vs watchful waiting, but described separately. All data were abstracted from the electronic medical record. Patient age and gender were recorded, as well as risk factors for desmoids (FAP, pregnancy within the year prior to diagnosis, prior surgery in the area, and inflammatory bowel disease). Tumor characteristics collected included site, size and presentation (index vs recurrence). The type and timing of all treatment were recorded. Date of diagnosis was analyzed dichotomously as early (2004–2009) or late (2010–2015).

Patients were deemed to have recurred or progressed if so determined by the radiologist of record on interval cross-sectional imaging or by the treating physician based on symptoms. RECIST score was recorded, but was not used to arbitrate progression when discordant with clinical impression. A patient was considered to have had a trial of watchful waiting when this was stated as the plan in a clinic note at presentation, or when more than 180 days elapsed between diagnosis and index aggressive treatment. Conversion from no treatment to hormonal therapy was not considered a failure of watchful waiting.

Similarity of baseline characteristics was compared between groups with Fisher's exact test for dichotomous variables and chi-squared test for categorical variables. Outcomes in each group were reported with descriptive statistics.

The impact of abdominal wall site on progression and recurrence was analyzed with Fisher's exact test.

The effect of positive microscopic margin on recurrence was analyzed with Fisher's exact test. To rule out any possible effect from resections with unspecified margins, the analysis was repeated on the assumption that all recurrences with unspecified margins had been positive.

Results

We identified 117 patients, 90 through the registry and 27 through the pathology repository review. Six had FAP, and were excluded from the comparison. Median follow-up was 35 months from diagnosis. (Range: 1–137). Baseline characteristics of both groups are listed in Table 1. Average age was 42 years (range 17–83). Median lesion size was 5 cm (range 0.7–23). The most common site was the abdominal wall (31, 28%), followed by the lower extremity (20, 18%). Most patients (86, 79%) had no documented risk factors for desmoids. There were no statistically significant differences between the surgery and watchful waiting groups with respect to age, sex, date of diagnosis or site, whether considered individually or dichotomously (abdominal wall vs all others). Average size was statistically significantly greater in the patients treated with watchful waiting (6.2 vs 4.9 cm, $p = 0.08$).

Fifty-three (48%) patients underwent immediate resection, and eight (15%) of these cases recurred. In this group, no recurrences were noted in patients with an abdominal wall site ($p = 0.09$). For

Table 1
Demographic and pathological characteristics of surgery and watchful waiting groups, non FAP patients only.

	Surgery	Watchful waiting	p value
Cohort	53	50	
Male	14 (26%)	13 (26%)	
Female	39 (74%)	37 (74%)	1.0[a]
Average Age	43	41	0.49[b]
Head and Neck	2 (4%)	3 (6%)	0.78[c]
Upper extremity	2 (4%)	4 (8%)	
Lower extremity	6 (11%)	14 (28%)	
Abdominal wall	16 (30%)	14 (28%)	
Intra-abdominal	9 (17%)	3 (6%)	
Chest wall	8 (15%)	6 (12%)	
Breast	7 (13%)	2 (4%)	
Limb girdle	2 (4%)	2 (4%)	
Other	1 (2%)	2 (4%)	
Abdominal wall	16 (30%)	14 (28%)	0.83[a]
All others	37 (70%)	36 (72%)	
Median diam (cm)	4.9	6.2	0.08[b]
<5 cm	31 (58%)	24 (48%)	0.74[c]
5–10 cm	15 (28%)	16 (32%)	
>10 cm	5 (9%)	9 (18%)	
Unknown	2 (4%)	1 (2%)	
Risk Factors			
None	45 (85%)	40 (80%)	[d]
Pregnancy	2 (4%)	4 (6%)	
Previous surgery	5 (9%)	6 (12%)	
IBD	1 (2%)	0	
Date of Diagnosis			
2004–2009	12 (23%)	11 (22%)	1.00[a]
2010–2015	41 (77%)	39 (78%)	

[a] Fisher's exact test.
[b] Student's *t*-test.
[c] Chi squared test.
[d] Chi squared test not possible for risk factors because of cell with zero value.

the surgical group, median disease-free survival was 22 (1–77) months, and 3 year DFS was 65%. Of the 8 recurrences, 4 were treated with re-resection as first salvage therapy, 2 with radiation, and 2 with tamoxifen/NSAID. One additional patient underwent repeat resection of an intra-abdominal desmoid after hormonal therapy. Three recurrences were ultimately deemed unresectable (chest wall, extremity, head), and 4 were rendered disease-free after repeat surgery (breast, intra-abdominal, extremity, chest wall). Four patients received three or more interventions after first recurrence. There was one death in this group, with no evidence of disease.

Fifty patients (45%) underwent watchful waiting, 40 with no treatment and 10 with tamoxifen with or without NSAID. Of these 10, 4 had an intra-abdominal site and 2 had extra-abdominal lesions >10 cm. No specific indication for hormonal therapy was documented in the remaining 4. Five of the patients who started with no treatment went on to receive tamoxifen. Twenty one (42%) of the patients undergoing watchful waiting were later deemed to have progressed. In 13 patients, progression was supported by MRI according to RECIST criteria. In 5, MRI demonstrated a size increase, but not sufficient to meet RECIST criteria. In 1 patient with a desmoid of the neck, this determination was based only on increasing pain in spite of stable findings on MRI. Indications for progressing to aggressive treatment were not documented in 2 patients. Median progression-free survival was 10 (2–94) months, and 3 year PFS was 38%. Abdominal wall site was not associated with progression (50% vs 39%, $p = 0.53$, see Table 2). Ten patients had surgery after progression, nine underwent definitive radiation, one continued observation without further progression over a further 14 months (21 months total follow-up from diagnosis) and one was lost to follow-up. Disease was stable after the first intervention in 14/21 (67%). In 1 patient with a desmoid of the lower extremity, three interventions were required after progression (surgery preceded by neoadjuvant RT, followed by recurrence after 10 months, then two lines of chemotherapy). No patient required more than three interventions after progression. No patient in this group died, either with or without disease. There were no documented cases of desmoid regression.

There was a non-significant trend toward decreased recurrence in the abdominal wall site, both in the surgery-first group (0% vs 22%, $p = 0.09$) and when considering both index and salvage surgery together (5% vs 23%, $p = 0.08$, see Table 2).

Four patients received neoadjuvant radiation and four received radical intent radiation. These were excluded from analysis, as there were too few for meaningful comparison with either the surgery or the observation group. No patient underwent cytotoxic chemotherapy before surgery or a trial of observation.

For the purposes of microscopic margin analysis, all non-FAP patients who ever underwent surgery were considered, including patients who failed watchful waiting, patients in the surgical group, and the four patients who received neoadjuvant RT at presentation. There were 69 patients over all. Microscopic margin status was not available for 14 (20%), of whom disease recurred in 3. Margin was negative in 21 (30%) and positive in 34 (50%). There were 3 recurrences in the margin negative group (14%) and 6 in the margin positive group (20%, $p = 1.0$). The analysis was repeated on the assumption that all three recurrences in the non-reported group had been margin positive, still yielding a non-significant p value of 0.50.

Six patients had a concurrent diagnosis of FAP. The desmoid was located in the mesentery in four, abdominal wall in one and both abdominal wall and retroperitoneum in one. The patient with a single lesion in the abdominal wall was treated with tamoxifen for six months, progressed, and went on to resection, without recurrence. The patient with abdominal wall and retroperitoneal lesions was diagnosed at laparotomy for a perforated viscus, and progressed on tamoxifen and three lines of chemotherapy before dying of disease. At no point were the lesions thought resectable. Two patients never received any systemic treatment or surgery, and never progressed. Two patients were treated with tamoxifen. Both progressed. One of these proceeded to one line of chemotherapy, without progression at 71 months from diagnosis. The other was ultimately treated with two lines of chemotherapy, and was pending further imaging at the close of the study, 93 months from the time of diagnosis.

Six patients were pregnant or had been within the year before diagnosis. Two patients (one ischiorectal fossa, one abdominal wall) never received treatment, and did not progress over 20 and 48 months, respectively. Two patients (one axilla, one abdominal wall) underwent surgery at presentation. Both were lost to follow-up. One (breast) was started on tamoxifen at presentation, and did not progress over 7 months. One (abdominal wall) progressed after 6 months without treatment, and then underwent surgery. Disease recurred after 13 months, and was again observed without treatment and without progression for 4 months before the conclusion of the study.

Table 2
Distribution of abdominal wall desmoids and effect on outcome.

	Abdominal Wall	Any Other Site	p value
Surgery	16 (53%)	37 (51%)	0.83[a]
Watchful Waiting	14 (47%)	36 (49%)	
Progression on WW	7 (50%)	14 (39%)	0.53[a]
Recurrence (Immediate surgery)	0	8 (22%)	0.09[a]
Recurrence (Surgery at any time)	1 (5%)	10 (23%)	0.08[a]

[a] Fisher's exact test.

Discussion

Our series suggests that desmoids observed for a period after diagnosis frequently do not require treatment. This is in concert with the majority of recent literature, some of which has had yet more encouraging results than ours. In the large series ($n = 142$) presented by Fiore et al. [4], five year PFS in the watchful waiting arm ($n = 83$) was 49.9%, whereas our 3 year PFS was 38%. The most promising result of which we are aware belongs to Briand et al. [14], who found that only 9.6% of patients in a series of 55 patients offered watchful waiting for extremity desmoids progressed, after a median follow-up of 73 months. Neither Briand's nor Fiore's series included tamoxifen as part of watchful waiting, while ours did in 10/50 patients. Thus, while observing the caveats of comparison between studies, it might still be pointed out that tamoxifen did not improve the success rate in our watchful waiting group.

It appears that even those patients ultimately requiring treatment do not suffer additional morbidity as a consequence of progression during observation. This is an important question, as intuition suggests that delaying treatment might risk the loss of a therapeutic window [15]. However, the existing literature supports our suggestion that watchful waiting does not increase risk among patients who progress to aggressive treatment. For example, a recent multi-institutional review showed no evidence of harm as a result of watchful waiting even in pregnant patients, in spite of a high progression rate (63% in cases diagnosed during or after pregnancy) [16]. In Fiore's series [4], none of the patients who progressed after initial non-operative management suffered significant morbidity as a result, although the authors conceded that the study was not designed to form robust conclusions on the question. The present series gives the same qualitative picture,

susceptible of the same criticism. Guidelines published by the European desmoid working group in 2015 [6] and updated in 2017 [7] support the safety of watchful waiting, and suggest that it is often the best strategy at presentation.

The recurrence rate in the surgery-first group was 15%, although again this may be affected by the follow-up interval. The rate in the existing literature varies, but is generally 20–60% [10–12,17,18]. The most compelling reason for hesitation before surgery is the small number of patients whose recurrences are much more difficult to treat than the primary. In our series, 4/8 recurrences required three or more interventions (surgical or other), and 3/8 were eventually deemed unresectable. In contrast, in the observation-first group, only 2/24 patients required three interventions after progression, and none required more. The concerns regarding up-front resection are augmented by the fact that the average size of lesions in the surgery-first group was smaller than those in the watchful waiting group, suggesting a selection bias favoring surgery.

The effect of abdominal wall site should be noted. While this site was equally represented in the two groups, and there was no effect on risk of progression in the observation group, there was a strong trend against recurrence when the desmoid was located in the abdominal wall. This was true both for patients in the surgery-first group and for all patients in either group who underwent surgery. Since the recurrence rate was low (11 patients in all), it is possible that the failure to achieve significance was an effect of sample size.

With respect to the prognostic value of negative microscopic margins, our series falls among the many which do not indicate an effect. Our data suffer from a high rate (20%) of unreported margins, but this does not affect our result. Even if all three recurrences in the non-reported group are added to the margin positive group, the p value against the margin negative group remains non-significant, at 0.50. The literature to date is divided on this question. A recent meta-analysis does demonstrate increased recurrence rate for resected extra-abdominal lesions, (RR 1.78, 95% CI 1.40–2.26) [19]. However, for procedural reasons, the review did not include at least two large series (n = 439 and 189) which had demonstrated no effect [20,21]. In Gronchi's series of 203 patients treated with surgery [22], no statistically significant difference in recurrence rate was demonstrated, although there was a trend in favor of negative margins among patients having surgery for recurrent disease. Peng et al. [3] demonstrated improved recurrence-free survival with negative margins, and offered the following interpretation of the conflicting literature: Negative margins should be the goal, but should not be pursued at the expense of significant functional loss. We agree with this approach, and suggest one additional consideration, namely tumor behavior. It should be presumed that any residual from an aggressive tumor is at high risk for regrowth, and that therefore negative margins are more important in this group. On the other hand, more indolent disease may shift the balance in favor of minimizing surgical morbidity, in those cases that still require surgery.

Although the behavior of disease was expectedly different in patients with FAP, there were no findings to suggest that any patient suffered harm from a non-surgical approach in this subgroup. The one patient who died was never a surgical candidate, and the other four non-surgical patients have done generally well.

The chief potential criticism of this series is the relatively short follow-up period. (Median 35 months). In such an indolent disease, it might be expected that some patients who progress will do so after a longer interval. On the other hand, Fiore et al. demonstrated that most progression (89%) occurs within two years [4], so our series likely captures the majority of progression.

Our study is also limited by our inability to discuss regression. No cases of regression were documented, whereas the existing literature would suggest a rate of approximately 15%. It is possible that patients who experienced regression were lost to follow-up when they no longer required treatment. Given the concern discussed above, that patients with smaller and less complex lesions might have been offered surgery more often, it is also possible that the patients who would have regressed simply went to surgery instead.

The current study is also subject to the inherent limitations of its retrospective design, especially the risk of selection bias. Our population is drawn from a population-based central cancer registry, but the capture rate of desmoid tumors is not known, and it might be expected that a registry designed to capture malignant diseases might have suboptimal capture for a benign one. As discussed above, review of our tertiary referral centre's pathological records revealed 27 cases that were not identified by the registry. It is therefore virtually certain that a proportion of the desmoids in the province were not included in this study. Some of these may have been uncomplicated desmoids treated successfully in the community with surgery at presentation.

Conclusion

The current series confirms that management of desmoids by watchful waiting is safe and effective. A trial of observation to determine biology appears warranted in most cases. Treatment should be tailored to individual patients in a multidisciplinary setting. While our post-surgical recurrence rate was lower than the general range in the literature, a large proportion of these recurrences were associated with significant morbidity. Non-operative management appeared to have good results in FAP patients as well, but there were too few to draw any strong conclusions. There was a trend toward lower recurrence rate in patients with abdominal wall desmoids. Microscopic margin did not affect recurrence rate.

Potential conflicts of interest statement

SP has done consultation work for DePuy, a division of Johnson and Johnson, in an area unrelated to the present topic. All other authors declare that they have no conflicts of interest.

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