



The Challenge in the Management of Extremity Fibromatoses: Our Experience

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Abstract

Desmoid tumours are known for their varied clinical behaviour. Hence, choosing an ideal treatment protocol remains challenging. This is further complicated by the rarity of these neoplasms and high recurrence rates following treatment. In our study, we tried to answer these questions in the background of Indian scenario. This is a retrospective study of 41 patients with extremity fibromatoses who were operated between June 2002 and November 2012. The mean age for all patients was 29.2 years with 30 females and 11 males. The mean duration of follow-up was 4.37 years. Eight patients were margin-positive on final histopathology. Seventeen developed recurrences (41.4%). Ten of these 17 patients underwent repeat surgery. The remaining 7 patients with inoperable recurrence were put on metronomic chemotherapy. The DFS for patients treated with surgical management was 62.6% at 3 years, 54.4% at 5 years and 44% at 10 years. The enigmatic nature of the tumour biology, natural history and optimal management of fibromatoses continue. Surgery remains the standard treatment and should be attempted only if R0 resection is possible without much morbidity to the patient. Non-surgical modalities also have their role to play in the management of these neoplasms.

Keywords Fibromatoses · Treatment options · Surgery · Recurrence

Introduction

Fibromatoses are rare soft-tissue neoplasms that are known for their varied clinical behaviour. Histologically, these tumours are poorly circumscribed with infiltration of adjacent tissue. They may undergo spontaneous resolution, remain static over years, grow slowly over a period of time or grow rapidly to invade adjacent structures leading to substantial morbidity, but they never metastasize to the distant organs [1–3]. This diversity in their tumour biology makes the management of

fibromatoses highly challenging [1, 4]. These tumours tend to recur in spite of multimodal management. Adding to this complexity is the rarity of these neoplasms which make randomised controlled trials on their treatment even more difficult. Current treatment modalities in the armamentarium of fibromatoses management include wait and watch policy, surgery, radiation therapy, hormone therapy and chemotherapy [1–3, 5, 6]. The varied options itself speak for the confusion existing in managing these neoplasms. Currently, there are no clear-cut guidelines regarding their optimal management strategy.

Researchers have tried to identify the factors that contribute to the varied biological behaviour of these neoplasms. Numerous variables including age, sex, previous history of surgery, tumour size, site of occurrence, resection margins, treatment modality used and use of adjuvant therapy were studied extensively to correlate their association with tumour behaviour including their high incidence of recurrence [5, 6]. Predictive nomograms to identify the risk of local recurrence have also been devised [7]. To date, all these efforts are in vain and no single parameter was found to be highly predictive of their exact natural history.

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Materials and Methods

This is a retrospective study of our hospital tumour registry. Standard demographic and clinic-pathologic data were collected. Data were collected on primary desmoid tumour location and size. Data on treatment-related variables, such as the type of surgery and adjuvant therapy, were also obtained. Operative procedure details were collected, including the intent of surgery (curative vs palliative/debulking) and need for soft-tissue reconstruction when primary closure was not possible. Margin status was ascertained based on final pathologic assessment. Data on operative morbidity and mortality were recorded. A total of 41 patients with biopsy-proven extremity fibromatoses were operated between June 2002 and November 2012. Fourteen patients were less than 20 years, while the remaining 27 were above the age of 20. The mean age for all patients was 29.2 years (median, 25 years). There were 30 female and 11 male patients. Seventeen patients had tumour involving the upper limb including the parascapular area, while the remaining 24 had lower limb involvement which included patients with pelvic fibromatoses. The presenting symptom was a swelling or a mass that was noted by all the patients, with only 10 patients mentioning pain as a dominant presenting symptom. Functional deficit was common in patients with involvement of the upper limb. Three patients had presented with neurological deficit. All patients had a biopsy diagnosis of fibromatoses prior to treatment. Thirty-seven patients had a needle biopsy, while 2 patients had an open biopsy done at a different hospital prior to treatment here. Two patients had only FNAC done prior to treatment. Local failure and recurrence-free survival were calculated from the time of operation. Local failure was defined as local recurrence occurring after a complete surgical resection or the presence of clinically or radiographically appreciable disease after an incomplete surgical resection with macroscopically positive margins. Local recurrence rates and recurrence-free survival were calculated by the Kaplan–Meir method. Comparisons between groups were performed by log-rank analysis for statistical significance. A p value of <0.05 was considered statistically significant.

Results

The mean duration of follow-up was 4.37 years (median, 3 years). Twenty-four patients were operated de novo, while 17 patients had prior surgery done elsewhere and presented to our institute with recurrence. Three patients underwent limb ablative procedure as the tumour was involving vital neurovascular structures and due to the presence of neurological deficit at presentation. The remaining 38 patients underwent wide local excision with removal of a cuff of normal tissue for clearance. Patients operated after 2008 had an

intraoperative frozen section done as per our institute protocol. So, a total of 18 patients had intraoperative frozen section. Eight patients were margin-positive on final histopathology or had intraoperative tumour spill. The minimum margin was determined by the pathologist after the operation on close examination of the tissues around the tumour mass. Five among them were having margin less than 0.5 cm but were microscopically free. Twenty-four patients had tumour size greater than 8 cm, and 17 had tumour less than 8 cm. Thirteen patients received postoperative external beam radiotherapy after discussion in the multi-speciality board of our institute. This included all the 8 patients with positive margins and the remaining 5 patients had margins less than 0.5 cm but were microscopically free of tumour.

Among the 41 patients operated at our institute, 17 had recurrence (41.4%). The mean time to recurrence was 15 months; 10 out of these 17 patients with recurrence were deemed to be operable and underwent repeat wide local excision for the recurrence. The remaining 7 patients with inoperable recurrence were put on metronomic chemotherapy, and these patients are currently having stable disease except for 1 patient with a large forearm lesion. Six patients who underwent re-excision for recurrence also received adjuvant external beam radiotherapy. The remaining 4 had already received it following the index surgery. Among these 10 patients who had re-excision for recurrence, 4 had developed a second recurrence. All these patients are currently on oral metronomic chemotherapy Table 1.

The disease-free survival for patients treated with surgical management was 62.6% at 3 years, 54.4% at 5 years and 44% at 10 years. The mean duration to develop recurrence from the index procedure was 15 months (median, 16 months). Age, sex, type of presentation (primary or recurrent), addition of adjuvant radiotherapy and negative frozen section had no influence on disease-free survival on statistical analysis. Only margin-positive resections had a statistically significant effect on recurrence ($p = 0.05$). Five out of 8 patients with margin-positive resection had recurrence. The disease-free survival for these patients was 29% at 3 years Figs. 1 and 2.

Discussion

Most series on desmoid tumours are small, adding to the problems in the management of these rare neoplasms. Ours is a single institutional tertiary care centre retrospective data that includes a total of 41 patients who were treated with surgery as the primary modality of treatment. Our study had a female preponderance who accounted for 73% of the study population as is shown by most series [1–3, 7, 8]. This female preponderance also attributed to the role of oestrogen probably having a role in the pathophysiology of these tumours. Various study groups using tamoxifen in the management of

Table 1 Patient, disease, treatment characteristics and outcome

	Total no. of patients (<i>n</i> = 41)
1. Age	Mean–29.2 years (median–25 years)
a. < 20 years	14 (34%)
b. > 20 years	27 (66%)
2. Sex	
a. Male	11 (27%)
b. Female	30 (73%)
3. Tumour site	
a. Upper limb	17 (41%)
b. Lower limb	24 (59%)
4. Type of presentation	
a. De novo	24 (59%)
b. Recurrent	17 (41%)
5. Type of surgery	
a. Wide local excision	38 (93%)
b. Amputation	3 (7%)
6. Intraoperative frozen section	<i>n</i> = 38
a. Yes	18 (47%)
b. No	20 (53%)
7. Margin positivity	<i>n</i> = 38
a. Yes	8 (20%)
b. No	30 (80%)
8. Tumour size	<i>n</i> = 41
a. < 8 cm	17 (41%)
b. > 8 cm	24 (459%)
9. Adjuvant radiotherapy	<i>n</i> = 41
a. Yes	13 (31%)
b. No	28 (69%)
10. Recurrence and its management	17 (41%)
a. Surgery	10 (59%)
b. Metronomic chemotherapy	7 (41%)
11. Disease-free survival	Median follow-up = 4.37 years
a. 3 years	62.6%
b. 5 years	54.4%
c. 10 years	44%

these rare neoplasms can be accounted for this gender preponderance [9, 10].

The mean age of presentation was 29.2 years (median, 25 years) as is reported by most other series [4, 11, 12]. Peng et al. [3] and Crago et al. [13] predicted that the recurrence rate after surgical resection was higher among younger age group. However, in our series, we were unable to correlate the recurrence rate with age.

Fifty-nine percent of the patients presented with a tumour size of more than 8 cm at presentation, but the size of the tumour was not a predictive factor for local recurrence. The same is confirmed by the series from Merchant et al. and

Lewis et al. who also showed that risk of local recurrence after treatment was not dependant on tumour size [1, 4]. However, in one of the largest recent series from MSKCC, size of the tumour was used as one of the predictive factor for local recurrence after surgical resection of desmoid fibromatoses [7]. Another series from Bertani et al. also found that larger tumour size was associated with increased local recurrence [2].

Surgery was the primary modality of treatment for all the patients who presented either de novo or with recurrence. Majority of patients underwent limb sparing procedures with 3 patients requiring limb ablative procedures in order to achieve an R0 resection. In the majority of patients, we were able to achieve an R0 resection (30 out of 38 patients). Our ability to achieve R0 resection through limb sparing procedures was at par with most other studies [2, 7, 13].

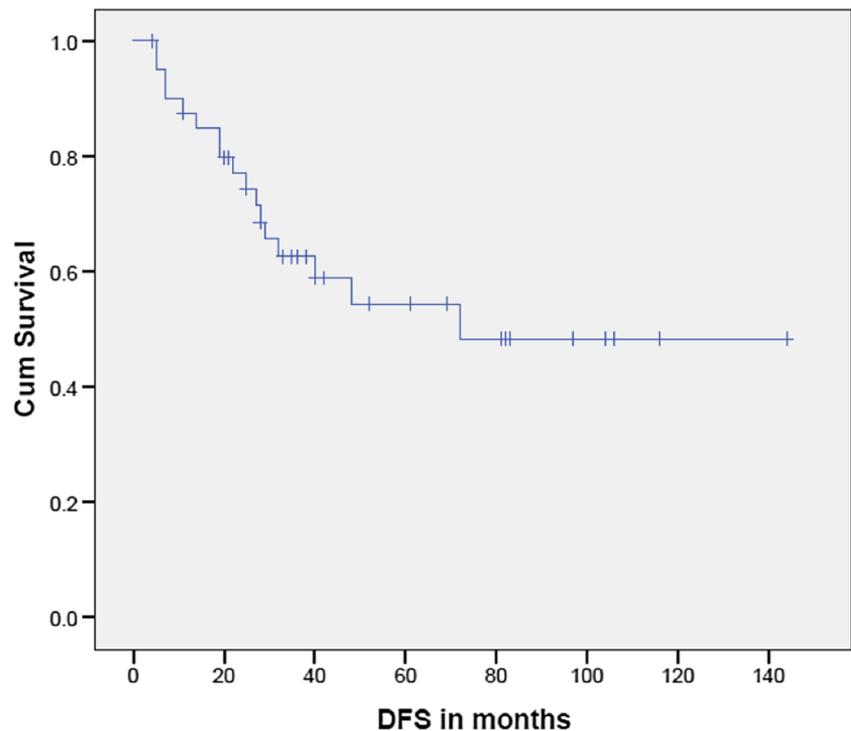
Nearly 41% of patients recurred after surgical treatment that was offered either de novo or presented with recurrence to our institute. The recurrence rate at our institute was on par with most other reported studies. Most studies reported a recurrence rate of 17 to 77% despite the use of any form of therapeutic modality [1, 2, 8, 11, 13, 14]. Multiple studies attempted to figure out factors that are responsible for this high recurrence rates. The comparison is shown in Table 2.

The mean duration for the patients to develop recurrence in our series was 15 months (median, 16 months). Most authors reported similar duration for local recurrence: Merchant et al. [1], 18 months; Lewis et al. [4], 17 months; Karakousis et al. [8], 17 months; Peng et al. [13], 13.6 months; and Mehrotra [15], 23 months.

Of the total 41 patients who have undergone resection, 8 (20%) patients had margin-positive resection on final histopathological examination. Our series had a low margin-positive rate compared to most other series (Merchant et al. reported a margin-positive rate of 43% [1], Salas et al. 38% [3], Mehrotra et al. 60% [7], Peng et al. 40% [13]). This could be accounted to the use of intraoperative frozen section for assessment of margin status because Bertani et al. also reported a margin-positive rate of 20% with the use of intraoperative frozen section [2].

As with most tumours, margin-positive resection clearly increases the risk of local recurrence. Five out of 8 (62%) patients with positive margins presented with local recurrence during follow-up. This was found to be statistically significant. The disease-free survival for patients with margin-positive resection was 29% at 3 years. Margin-positive resection significantly increases the risk of local recurrence. The same is confirmed by most other series [2, 3, 5, 6, 12, 13, 16–19]. However, some series have shown that the impact of margin status as a risk factor for local recurrence is questionable [1, 4, 7, 20–22]. There is no doubt that whenever possible, the aim is to achieve R0 resection; but the morbidity that would result from this R0 resection has to be outweighed with the risk of local

Fig. 1 Kaplan–Meir curve for disease-free survival



recurrence. The role of margin status on local recurrence still remains debatable.

All patients with positive margin or close margin (31%) were treated with adjuvant radiotherapy. Statistical significance could not be reached between the use of adjuvant RT and prevention of local recurrences on follow-up. Similar

conclusions have been reported by Merchant et al. [1], Crag et al. [7], Mehrotra et al. [15], Barry et al. [23], and Gronchi et al. [24]. However, some authors claim that the use of adjuvant radiotherapy following surgical resection significantly reduced the local recurrence rates (Karakousis et al. [8], Mankin et al. [11], Lev et al. [25], Spear et al. [26], Nuytens

Fig. 2 Kaplan–Meir curve for patients with margin-positive resection

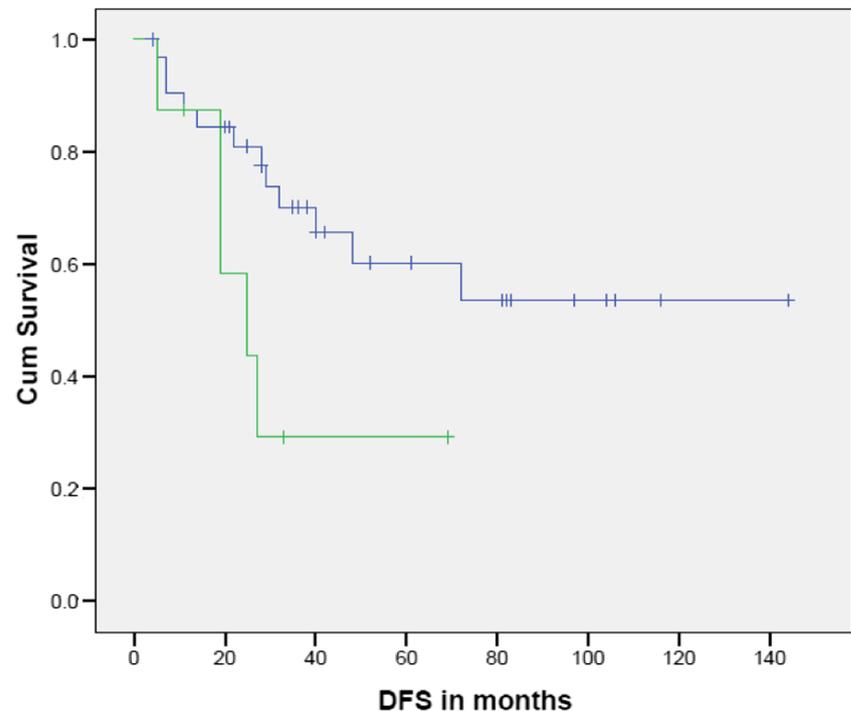


Table 2 Comparison of various study group parameters

Study	No. of patients	Mean age	% of female population	Recurrence rate (%)	Margin positivity (%)	Mean duration to recurrence	Did margin positivity affected recurrence?	Did use of adjuvant RT reduced recurrence?	DFS
Merchant et al. [1]	105	35	74	23	45	18 months	No	No	80% (2 years) 75% (5 years)
Bertani et al. [2]	63	36	69	16	20	–	Yes	No	–
Salas et al. [3]	426	37	67	50	38	–	No	No	35% (5 years) 22.8 (10 years)
Mehrotra et al. [7]	36	35	55	56	60	23 months	Yes	No	–
Peng et al. [13]	211	36	68	50	40	13.6 months	Yes	No	81% (1 year) 53% (5 years)
Current study	41	29.2	73	41	20	15 months	Yes	No	62.6% (3 years) 54.4% (5 years) 44% (10 years)

et al. [27]). In the present study, adjuvant radiation was delivered selectively depending on margin status. Whether this positive margin status masked the beneficial effect of adjuvant radiation on local recurrence has to be further studied. Those patients who presented with recurrences were either operated if operable or started on metronomic chemotherapy if the surgery entailed a major resection. Most of these patients had a stable disease. However, one patient had a progressive disease. The same strategy was followed for management of recurrent tumours in the series by Merchant et al. [1], Lewis et al. [3], Salas et al. [4], and Mehrotra et al. [15]. Whether this could be attributed to the highly variable natural course of the disease remains an enigma. The question of why most tumours have an indolent course and few have rapid progression remains unanswered and could be due to tumour biology.

None of the patients died of the disease during follow-up; the disease-free survival reported in our study (62.6% at 3 years, 54.4% at 5 years and 44% at 10 years) was comparable to most other reported studies where surgery was performed as a primary treatment modality: Merchant et al. [1] 2- and 5-year DFS rates were 80% and 75%, respectively; Salas et al. [3] 5- and 10-year DFS rates of 35% and 22%; and Peng et al. [13] 1-, 3- and 5-year DFS was 81.3%, 57.0% and 52.8%, respectively.

There are certain limitations in the current study. As with most studies on fibromatoses, this is a single institutional, retrospective study. The number of patients included was small. All patients were offered the treatment option of surgery at presentation. Whether non-surgical treatment modality like wait and watch policy, hormone therapy, chemotherapy and radiotherapy would have played a role in the management of fibromatoses remains unanswered, although these options were explored in the recurrent setting in our series. These limitations precluded us from identifying the natural course of the disease and ideal management protocol.

Conclusion

Despite several studies, the enigma on the tumour biology, natural history and optimal management of fibromatoses continues. To date, surgery remains the standard treatment and should be undertaken only if R0 resection is possible without much morbidity to the patient. Non-surgical modalities including wait and watch policy also have their role to play in the management of these neoplasms. However, large prospective studies are needed to identify factors that help us to guide the treatment options and predict recurrence to each subset of patients. Until then, the treatment has to be tailored to individual patients outweighing the risks and benefits of treatment modality in individual patients.

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