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*ORIGINAL STUDY*

# Fibromatosis: A review of the risk factors for recurrence and outcomes

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**Aggressive fibromatosis is a rare condition. These benign fibrous tumours can develop in connective tissue. Wide-margin resection is the favoured method of treatment, however, radiotherapy and chemotherapy can also be used, to reduce the rate of recurrence.**

**We undertook a retrospective analysis of case notes of patients who had been diagnosed with aggressive fibromatosis. Data regarding treatments received and whether the tumours had recurred was collected. We also evaluated any other factors that may have influenced the risk of recurrence in these patients.**

**The recurrence rate was 47% overall, with the main risk factors being a younger age (below 30 years), being female and larger size of tumour. Patients were also more likely to have a recurrence if their original tumour was in the lower limb.**

**We conclude that high recurrence rate, may be reduced in future with patient-specific treatments based on patient characteristics, tumour histology and limb targeted therapies when a wider evidence base is achieved.**

**Keywords:** Fibromatosis ; desmoid ; fibrous ; tumour ; recurrence.

## INTRODUCTION

Aggressive fibromatosis is a condition characterised by formation of desmoid tumours within the body. These are benign tumours that arise from connective tissue, such as muscle aponeuroses and fascia; occurring anywhere within the body, with little malignant potential *(17)*. They account for 0.03% of all tumours and 3% of soft tissue tumours *(21)*. Associated morbidity and mortality is dependent upon location of the tumour and proximity to important structures. These tumours are locally invasive and have a high risk of local recurrence *(7,20,22)*. Aggressive fibromatosis is rare, with only 2-4 cases per million per year being seen commonly between the ages of 15 and 60 with an average

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age of presentation of 40 years *(2)*. The disease is slightly more common in females, with a female to male ratio of 5:1 *(2)*. They can arise either in the abdominal wall, within the abdominal cavity itself, the trunk or in the extremities, which is where the majority of tumours occur.

Treatment for desmoid tumours depends more on the symptoms that they cause as well as the size and location of the lesion itself. Although first-line treatment is usually wide-resection surgery, in cases where there is a high-risk of recurrence or surgery is not likely to achieve negative resection margins, then adjuvant therapy (either radiotherapy or chemotherapy) may be used; more recently biological agents, anti-inflammatories and anti-hormonal therapy have been used in experimental settings with variable results *(1,3-6,12,18,19)*. Due to the growth pattern of desmoid tumours, there may be no need for treatment as some lesions remain the same size for long periods and in time they may regress *(11)*.

## AIMS

Desmoid tumours pose a difficult question to clinicians treating axial fibromatosis due to high recurrence rates, with tumours in the extremities. Therefore it is important to understand, firstly, which is the best treatment for people who present with these tumours, and secondly if there are any risk factors that can predict recurrence and thus, where more aggressive treatment regimens may be required.

## MATERIALS AND METHODS

A retrospective analysis was performed on patients who had histologically confirmed diagnosis of aggressive fibromatosis at our centre. A manual search of the identified patient's case-notes allowed us to extract and analyse details of their diagnosis, treatment and any recurrences, which allowed us to deduce whether an association could be made with specific risk factors such as family history or any medications they may have been taking at the time.

Once the rate of recurrence had been established, we split the data into two groups, one with patients that had no recurrence following treatment and the others that had a recurrence. For the recurrence group we used a statistical program (SPSS) to determine the statistical significance between certain risk factors and recurrence.

We evaluated case notes of 23 patients, however, two of the patients had non appendicular tumours and were excluded. Another two patients had very little information in their case-notes and so we decided not to include them either. The average age of patients was 36 years, with the range being 19-67 years. The female: male ratio in this study was 14:5.

## RESULTS

The average volume of the tumours was 183.7ml, ranging from 0.12ml to 882ml; 8 of these tumours were located in the upper limbs and 11 in the lower limbs.

The most common presenting feature in our patient group was pain and swelling. Two of the patients had no treatment, because of the size and position of the tumour and so neither of these patients had a recurrence of the disease. Out of the 17 patients in the study that were treated we found that 8 of the patients had a recurrence, meaning that there was a recurrence rate of 47%.

It was found that 50% of the recurrences occurred within a year following surgery, 75% had recurred within two years, 88% had recurred within 3 years and all of them had recurred within four years. From the results we collected therefore, the chance of recurrence after 1, 2, 3 and 4 years were 24%, 35%, 41% and 47% respectively.

7 of the patients who had recurrence were treated with surgery only; 1 was treated with tamoxifen and radiotherapy. 2 patients (25%) then had a re-recurrence and 1 patient had only 1 further recurrence, which went untreated. 1 patient had 4 further recurrences.

The patients were then split into two groups, those with and without recurrence (Tables I and II). The variables that were found to be different in the two groups were then analysed using the paired t-test. The level of significance used in the analysis was set at 5%, with a p value of 0.05. Therefore the confidence interval was 95%.

Table I — Patients without recurrence of disease

| Sex | Age | Presenting Feature | Length of Illness (months) | Location | Biopsy Done | Type of Biopsy | Size (cm) | Volume (ml) | Surgery | Radiotherapy | Chemotherapy | Previous Malignancy | Family History |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| F | 31 | Swelling | 1 | Right medial calf | Yes | US guided | 10 x 5 x 4.5 | 225 | Yes | Yes | No | No | No |
| F | 44 | Swelling | 24 | Left proximal forearm | Yes | 16 gauge tru-cut | 5 x 2.5 x 2 | 25 | Yes | No | No | No | No |
| M | 30 | Swelling and pain | 24 | Anterolateral shoulder | Yes | Excision | 6.5 x 3.5 x 2 | 45.5 | Yes | No | No | No | No |
| F | 53 | Pain and swelling | 1 | Dorsum of left little finger | Yes | Excision | 0.8 x 0.5 x 0.3 | 0.12 | Yes | No | No | No | No |
| M | 67 | Swelling | 1 | Postero-lateral to right distal femur | Yes | Core | 5 x 3.5 x 2 | 35 | Yes | No | No | Carcinoma of the prostate | No |
| F | 36 | Pain and swelling | 24 | Right shoulder | Yes | Trucut | 7 x 8 | 56 | Yes | No | No | No | No |
| M | 58 | Swelling and burning sensation | 2 | Left upper arm | Yes | CT guided | 3 x 2 | 6 | Yes | No | No | No | No |
| F | 19 | Right lower back pain | 12 | Buttock | Yes | US guided | 9 x 5 x 8 | 360 | No | No | No | No | No |
| M | 44 | Swelling | 120 | Outer aspect of left forearm | Yes | US guided | 4 x 1.5 x 1 | 6 | Yes | No | No | No | No |
| F | 45 | Left hip pain and sciatica | 60 | Left gluteal region | Yes | US guided | 13 x 10 x 5.3 | 689 | No | No | No | No | No |
| F | 27 | Pain and swelling | Unknown | Left sacro-coccygeal region | Yes | US guided | 7 x 5 | 35 | Yes | No | No | No | No |

Statistically significant results were seen when patients who had a recurrence were younger on average than those who had no recurrence (30 years vs. 41.3 years), or if the volume of tumours that recurred was larger than in those that did not (255.4ml vs. 48.2ml). Other notable but statistically not significant results included a higher ratio of females: males in the group with recurrence (7:1 vs. 5:4), lower limb lesions were more likely to recur (67% vs. 25%) and the length of illness was lower on average in those who had a recurrence than those that did not (14 months vs. 21.6 months) (Table III). If the patient had a tumour less than 100ml in volume, they had a 27% chance of recurrence, compared to a 100% chance if the tumour was over 300ml.

Specific data for resection margins was not collected as obtaining wide resection in fibromatosis is not always possible due to permeative nature of the pathological process and evidence of skip lesions. Nevertheless there was no difference in the two groups as for as resection margins were concerned.

## DISCUSSION

Fibromatosis is a rare condition, therefore, it is difficult to collect a large sample of patients to analyse. Wide local resection is the treatment of choice for most patients with aggressive fibromatosis. Due to the fact that these tumours are not encapsulated, it is difficult to access the full extent of the lesion intra operatively.

The standard used in this study was based upon the current evidence from similar studies on the recurrence rates of limb fibromatosis patients. From the studies we looked at, we took an average of 40-50% recurrence rates as the standard for this study *(11,13,23)*.

Table I — Patients without recurrence of disease

| Sex | Age | Presenting Feature | Length of Illness (months) | Location | Biopsy Done | Type of Biopsy | Size (cm) | Volume (ml) | Surgery | Radiotherapy | Chemotherapy | Previous Malignancy | Family History | Recurrence | Time between Biopsy and Recurrence | Treatment for Recurrence | Re-recurrence |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| F | 21 | Pain and swelling | 18 | Left hip | Yes | Excision | 10 x 5 x 5.5 | 275 | Yes | No | No | No | No | Yes | 14 | Surgery | No |
| F | 38 | Pain and swelling | Unknown | Sole of right foot | Yes | Excision | 3.5 x 2.5 x 1.1 | 9.625 | Yes | No | No | No | Dupuytren's contracture and plantar fibromatosis | Yes | 42 | Surgery | No |
| F | 26 | Pain and swelling | 5 | Left hip | Yes | Open | 14 x 9 x 7 | 882 | Yes | No | No | No | No | Yes | 12 | Surgery | Yes |
| M | 21 | Swelling | 10 | Right popliteal fossa | Yes | Excision | 10 x 6 x 3 | 180 | Yes | No | No | No | No | Yes | 34 | Surgery | No |
| F | 46 | Swelling | 3 | Right calf | Yes | Open | 3.5 x 8.4 x 12.6 | 370.44 | Yes | No | No | No | No | Yes | 13 | Surgery | Yes |
| F | 24 | Swelling | 24 | Right upper arm | Yes | Excision | 6.5 x 4.5 x 3 | 87.75 | Yes | No | No | No | No | Yes | 10 | Surgery | No |
| F | 23 | Pain and swelling | 24 | Behind knee | Yes | Trucut | 8 x 6.5 x 4 | 208 | Yes | Yes | No | No | No | Yes | 8 | Sulindac, Tamoxifen and Radiotherapy | Yes |
| F | 38 | Pain and swelling | Unknown | Left shoulder | Yes | Excision | 10 x 3 | 30 | Yes | No | No | No | No | Yes | 6 | Surgery | No |

There is a difference between recurrence rates in patients with positive resection margins and negative resection margins, with recurrence rates being between 42-68% and 12-22% respectively *(11,13,23)*. It can be difficult to be sure how many of these are residual tumours rather than a recurrence. A comparison of negative margins, where they were divided into close (<1mm) and wider (>1mm) found that as long as surgeons achieve a negative margin, then there is no difference in the rate of recurrence *(25)*. Even if surgery can establish negative margins there is still a high risk of recurrence.

Another factor associated with higher chance of recurrence is the location of the tumour, with tumours on the extremities being more likely to recur, which could partly be due to close proximity to the neuro-vascular structures and difficulty in attaining sufficient resection margins in these areas *(10)*.

Radiotherapy can be used in the management of extra-abdominal desmoid tumours either as an adjuvant following surgery in patients where there is a positive margin (one where there is still fibromatosis present at the borders of surgery), or when surgery is not possible due to its position or size. Nuytten found that the local control rates of surgery alone were 61% compared with 75%, when radiotherapy was added and for radiotherapy on its own the rates were 78% *(21)*. This shows that radiotherapy can be very effective in the management of desmoid tumours even without surgical intervention.

Cytotoxic chemotherapy has been used for some years as an alternative treatment to surgery and radiotherapy, in cases where these would not be

Table I — Patients without recurrence of disease

| | Recurrence | Non-recurrence | p-Value |
|---|---|---|---|
| Number | 8 | 9 | - |
| Mean Age | 30 | 41.3 | 0.033 |
| Length of Illness | 14 | 24.6 | 0.54 |
| M:F | 1:7 | 4:5 | 0.169 |
| Upper Limb (UL) | 25% | 67% | 0.096 |
| Lower Limb (LL) | 75% | 33% | (LL vs UL recurrence) |
| Proximal Limb | 50% | 56% | - |
| Distal Limb | 50% | 44% | - |
| Mean Volume | 255.4 | 48.2 | 0.096 |
| Surgery | 8 | 9 | - |
| Radiotherapy | 1 | 1 | - |
| Chemotherapy | 0 | 0 | - |

feasible. In patients with desmoid tumours on the limbs, isolated limb perfusion can be used as an alternative to systemic chemotherapy. Melphalan and tumour necrosis factor were shown to achieve response rates of 83%, with 33% being complete responses and no limb amputations were required.16

The recurrence rate of the 17 patients that were given treatment in this study was found to be 47%. This was within the acceptable standards previously reported. The factors that seemed to be important to recurrence were; being female, a younger age, a larger tumour and the tumour being located in the lower limb.

Previously published studies have shown similarly higher rates of recurrent fibromatosis in females *(14)*. The data we collected supports this fact and suggests that recurrence is nearly three times more common in females. This may represent a hormonal aetiology but further research is required.

The average age of first presentation in the literature is between 30 and 40 years 21; in our study this was 36 years of age and thus within this range. Furthermore, our data supports the idea that tumours are more active in females of child-bearing age because of the lower average age and higher female: male ratio in the recurrence group.

We were unable to find any previous studies in the English language literature to evaluate the effect of location of tumour on rate of recurrence however, we found that patients with lower limb tumours had a much higher recurrence rate compared with upper limb tumours (67% vs. 25%).

In conclusion, the data presented in this study has shown that although our current recurrence rates fall within the same range as previously published, they are still high. There is not one single risk factor that has been shown to predict recurrence; however, we did find that a combination of factors can contribute to an increased likelihood of recurrence.

The factors we found to be important to this were; age at presentation, volume of tumour, gender and location of tumour. 83% of patients under the age of 30 years had a recurrence, 100% of tumours larger than 300ml recurred, 58% of females had a recurrence and 67% of tumours presenting in the lower limb recurred.

Although this a retrospective analysis and collection of resection margin data was not possible due to the nature of the samples included, we would expect the rate of recurrence to increase with positive margins like in the abdomen *(8)*.

Our findings highlight key factors that need to be taken into account when managing patients with fibromatosis, in future it may be possible to treat this group of patients with a higher risk of recurrence with more aggressive treatments but further research into this is required.

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