

# Treatment of aggressive fibromatosis

## A retrospective study of 72 patients followed for 1–27 years

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**ABSTRACT** – We evaluated prognostic factors for local recurrence-free survival, including expression of estrogen receptors, after surgical treatment of aggressive fibromatosis in 72 patients (53 women) having primary tumors between 1970 and 1998. Their median age at diagnosis was 31 (1 month–77 years) years. 50 patients had extraabdominal and 22 abdominal fibromatosis. Median tumor size was 4 (1–27) cm. 8 patients were treated with an intralesional resection, 32 with marginal, 31 with wide and 1 with radical resection. They were followed for a median of 8 (1–27) years.

The overall and local recurrence-free 5-year survival rates were 98% and 73%, respectively. Univariate analysis identified age, compartmentalization and tumor size as prognostic factors for local recurrence-free survival as well as radiotherapy in extraabdominal tumors. In the multivariate analysis, tumor size > 4 cm, extracompartmental location, inadequate margin and age < 32 years were independent negative prognostic factors for local recurrence.

None of the tumors expressed estrogen receptors.

In conclusion, aggressive fibromatosis has a high local recurrence rate, but a good prognosis, since almost no patients die of their tumor.

Fibromatosis is a rare soft tissue tumor with an incidence of 2–4 per million population a year (Dahn et al. 1963, Reitamo et al. 1982). The benign histopathological appearance cannot be used to predict a local recurrence of the tumor. The tumor has no capsule and may infiltrate the surrounding tissue up to 2–3 cm outside the palpable tumor (Mackenzie 1972, Antal et al. 1994, Enzinger and Weiss 1995). Fibromatosis therefore poses a prob-

lem of local control, but it does not disseminate. Unresectable tumors have been treated with radiotherapy although the effect is unclear. Anti-estrogens have also been used with variable success (Wilcken and Tattersall 1991, Brooks et al. 1992). This type of treatment is based on finding estrogen receptors in the tumor (Lim et al. 1986, Alman et al. 1992) in a few patients, but none are conclusive.

We evaluated the overall and local recurrence-free survival after surgery on aggressive fibromatosis, including an analysis of the influence of preoperative and treatment-related prognostic factors as well as the expression of estrogen receptors (ER).

## Patients and methods

### Patients

We reviewed histopathological slides of patients with fibromatosis between 1970 and 1998 and found 77 cases of musculoaponeurotic fibromatosis. The patients' records were in the files of the Pathology Institute, Aarhus Amtssygehus and in the sarcoma database at the Sarcoma Center in Aarhus. Palmar and plantar fibromatosis, penile fibromatosis, retroperitoneal fibrosis, mesenteric fibromatosis and other conditions with fibrosis (keloid) were excluded.

Of the 77 patients with aggressive fibromatosis, 5 were excluded—i.e., 3 were inoperable and 2 had no follow-up. Of the 72 patients in this study, 50 had extraabdominal and 22 abdominal tumors.

A prospective registration of all patients was introduced at our Center for Bone and Soft Tissue Sarcomas in the beginning of 1993. In patients who were first diagnosed as having fibromatosis

before this date or who had been treated outside the Center for Bone and Soft Tissue Sarcomas, data were obtained retrospectively from their medical records. Inclusion of patients in the study dated from their primary operation. 27 were treated outside the center, but of 45 treated at the center, 18 patients were referred before surgery, 8 after biopsy and 19 after inadequate surgery.

The study included 72 patients (53 women) with a median age on admission of 31 (1 month–77 years) years. The abdominal tumors usually occurred in patients between 21 and 40 years of age, but the extraabdominal tumors were more equally distributed. No men had abdominal tumors. The thorax was the commonest extraabdominal location. The upper and lower extremities were equally affected. Median tumor size was 4 (1–27) cm.

The median follow-up of the 69 patients who were alive was 8 (1–27) years, 3 patients died after 3, 8 and 10 years. 5 patients had Gardner's syndrome: in 1, the disease was first diagnosed at autopsy, in another, 13 years after presentation of the primary tumor, in the other 3, it was present before the diagnosis of fibromatosis. 2 were excluded from the study because of mesenteric fibromatosis.

### **Treatment**

The tumors were categorized as intra- or extracompartmental. The abdominal tumors situated in the rectus abdominis muscle were considered intracompartmental. The surgical margin was classified as intralesional, marginal, wide or radical (Enneking 1990). A wide margin required a minimum of 1 cm of fat or muscle around the tumor or an intact fascia. Intralesional and marginal margins were regarded as inadequate, but wide and radical margins were adequate.

Adjuvant radiotherapy was given to 28 patients of whom 27 had extraabdominal tumors and 1 abdominal. 4 of the 27 treated outside the center had postoperative radiotherapy, but 24 of the 45 patients in the center were irradiated before (10 patients) or after surgery (14 patients). Preoperative radiotherapy was given using a protocol which aimed to reduce the size of the tumor before surgery.

### **Estrogen receptor assay**

Expression of estrogen receptors (ER) was determined by an immunohistochemical assay in formalin-fixed, paraffin-embedded tissue. This method was preferred since aggressive fibromatosis contains remnants of infiltrated normal tissue. Moreover, two studies have shown that immunohistochemical determination of ER is equivalent to biochemical assays (Alberts et al. 1996, Molino et al. 1997). All 72 tumors were analyzed for expression of ER. The ER determination was done on deparaffinized slides pretreated (boiled) with a Tris-EGTA buffer (0.5 mmol, pH 9) twice for 5 min in a microwave oven. Then the slides were incubated with primary antibody complex (DAKO M7047) for 30 min at room temperature. Positive and negative controls were treated the same way, although in the case of the negative controls the primary antibody was omitted. Tissue from a breast cancer served as a positive control. To be classified as positive, a minimum of 10% tumor cells had to be positive. This is also accepted for classifying breast cancer.

### **Statistics**

Local recurrence-free and overall survival curves were generated using the Kaplan-Meier method. P-values were calculated using the log rank method. The multivariate analysis was done with Cox regression analysis. These tests were carried out by programs in the database Medlog and by SAS. The  $\chi^2$ -test and Spearman's correlation coefficient were used with the SPSS-program.

### **Results**

3 patients died before the evaluation. 1 died of another disease with a tumor, 1 of another disease without a tumor and 1 of unknown cause. No patients died of metastases. The local recurrence-free 5-year survival was 73% (Figure 1).

#### **Local recurrence**

The local recurrence rate was 19/72 (0.3). The median time to local recurrence was 17 (3–86) months. The frequency was 10/27 (0.3) in patients treated outside the center and 9/45 (0.2) in patients treated in the center. Most of the local recurrences occurred within three years after surgery. 4/8

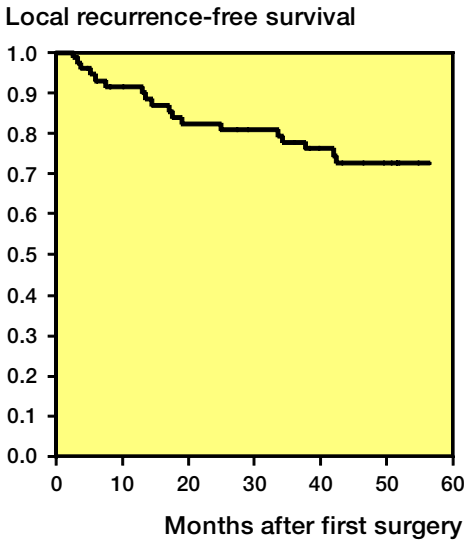


Figure 1. Actuarial relapse-free survival curves.

patients treated with an intralesional resection had a local recurrence, 9/32 with a marginal and 6/31 with a wide margin. One patient treated with radical resection by means of a myectomy had no recurrence. These differences were not significant (Spearman's correlation coefficient 0.2 and  $p = 0.09$ ). No patient had an amputation. 3 of the 22 abdominal and 16 of the 50 extraabdominal tumors recurred. Of the 27 patients with extraabdominal tumors who received adjuvant radiotherapy, 5 tumors recurred. A wide margin was achieved much oftener at the tumor center (n 27) than outside the center (n 4).

### Prognostic factors

Of the patient characteristics, age, compartmentalization and tumor size significantly affected the local recurrence-free survival (Table 1, Figure 2). Tumor size and age were categorized according to the median value.

Table 1. Univariate analysis of the effect of various prognostic factors on local recurrence-free survival. All patients

Factor	Criteria	No. of local recurrences/ no. of patients	5-year relapse-free survival (%)	P-value (log rank)
Sex	women	12/53	77	} 0.3
	men	7/19	62	
Age	< 31 years	13/36	63	} 0.04
	> 31 years	6/36	82	
Location	abdominal	3/22	85	} 0.2
	extraabdominal	16/50	68	
Compartmentalization	intra	4/34	87	} 0.02
	extra	15/38	60	
All	intra	1/16	94	} 0.2
	extra	2/6	67	
Extraabdominal	intra	3/18	83	} 0.1
	extra	13/32	60	
Tumor size	< 4 cm	4/38	89	} 0.002
	> 4 cm	15/34	54	
Margin	intralesional	4/8	50	} 0.2
	All	marginal	9/32	
	wide	6/31	80	} 0.6
	radical	0/1	100	
Abdominal	inadequate	13/40	66	} 0.3
	adequate	6/32	81	
Extraabdominal	inadequate	2/11	82	} 0.6
	adequate	1/11	86	
Radiotherapy	inadequate	11/29	60	} 0.3
	adequate	5/21	79	
All	yes	5/28	78	} 0.2
	no	11/44	69	
Extraabdominal	yes	5/27	77	} 0.05
	no	11/23	57	

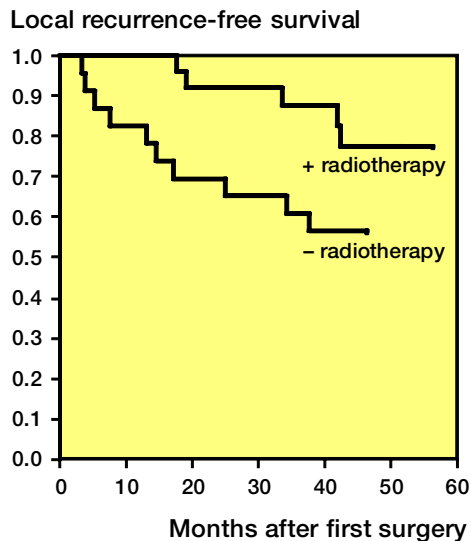
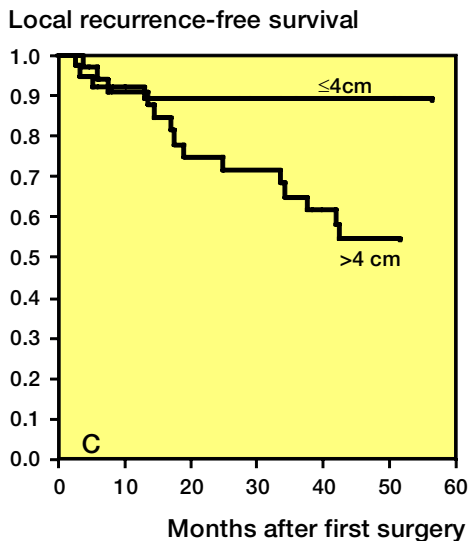
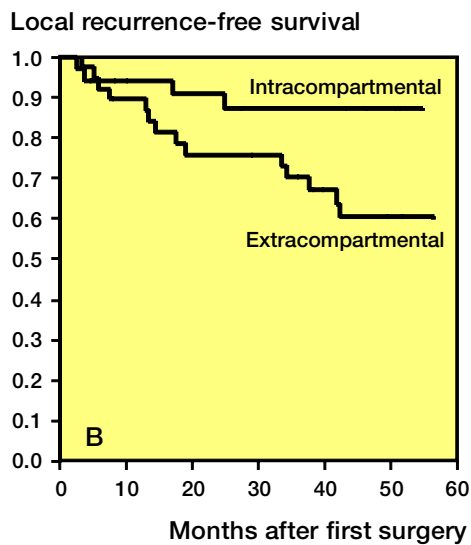
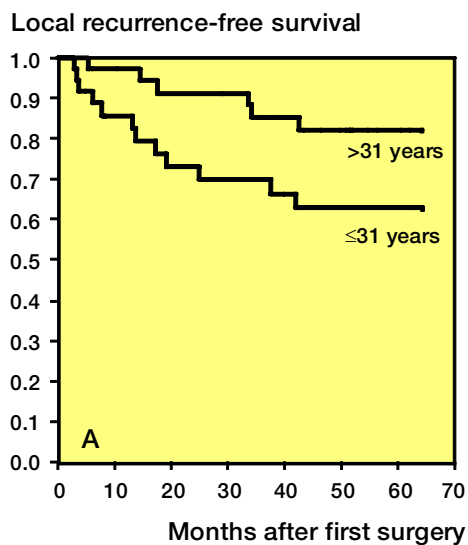


Figure 2. The dependence of actuarial relapse-free survival on A—age ( $p = 0.04$ ), B—surgical classification ( $p = 0.02$ ) and C—tumor size ( $p = 0.002$ ).

Figure 3. The dependence of actuarial relapse-free survival of extraabdominal tumors on radiotherapy ( $p = 0.05$ ).

Surgical margin had no significant effect on the local recurrence-free survival, but radiotherapy had a significant influence in patients with extraabdominal tumors (Figure 3).

Age, compartmentalization, tumor size, margin, radiotherapy, location and gender were included in the multivariate analysis since some data indicated that these were prognostic factors. Tumor size  $> 4$  cm, an extracompartmentally situated tumor, inad-

equately margin and age  $<$  the median (31 years) were all independent negative prognostic factors (Table 2).

#### Estrogen receptor assay

None of the 72 tumors was ER positive, since the number of positively stained nuclei was far less than 1%.

Table 2. Multivariate analysis of the effect of prognostic factors on local recurrence-free survival. All patients

Factor	RR	95% – lower limit	95% – upper limit	P-value
Tumor size (> 4 cm vs. < 4 cm)	4.64	1.48	14.56	0.009
Margin (sufficient vs. insufficient)	0.48	0.24	0.98	0.04
Surgical classification (extracompartmental vs. intracompartmental)	3.82	1.22	11.94	0.02
Age (> 31 years vs. < 31 years)	0.21	0.073	0.61	0.004
Location (women extraabdominal vs. women abdominal)				0.6
Gender (men extraabdominal vs. women)				0.2
Radiotherapy (yes vs. no)				0.1

## Discussion

Our findings agree with various reports regarding the age of diagnosis and gender distribution of aggressive fibromatosis (Reitamo et al. 1982, Posner et al. 1989, McCollough et al. 1991, Schmitt et al. 1992, Acker et al. 1993, Karakousis et al. 1993, Catton et al. 1995, Pritchard et al. 1996, Spear et al. 1998).

We found a difference in location of the tumor between men and women. Most abdominal tumors developed in women 21–40 years of age. Reitamo et al. (1986) noted a similar difference and that the abdominal tumors predominated in the fertile and middle-aged patients. The observation that patients with abdominal tumors were mainly fertile women suggests that a high level of hormones and pregnancy may be important in the development of aggressive fibromatosis.

The thorax was the most frequent extraabdominal location in our study. Acker et al. (1993) found that the retroperitoneal region and thorax are the most frequent locations. There is no agreement in the literature as regards the most frequent location of aggressive fibromatosis (Reitamo 1983, Acker et al. 1993).

None of our patients died of the tumor. This agrees with the findings of other authors (Posner et al. 1989, Karakousis et al. 1993). The local recurrence rate was 27%, which resembles that reported by others. The reported local recurrence rate of primary (extraabdominal) tumors ranges between 11% and 64% (Posner et al. 1989, Spear et al. 1998, Acker et al. 1993, Karakousis et al. 1993, Yokoyama et al. 1989). Unlike Reitamo (1983), we found no difference in the local recurrence-free survival rate between abdominal and extraabdominal tumors.

Age affected the local recurrence-free survival in both the univariate and multivariate analyses in agreement with other studies (Posner et al. 1989, Spear et al. 1998).

We found that patients with an intracompartmental tumor had a significantly better local recurrence-free survival than those with a tumor situated extracompartmentally. A similar conclusion has been drawn concerning soft tissue sarcomas as well (Vraa et al. 1998).

A tumor size more than 4 cm had a negative effect on the local recurrence-free survival in the multivariate analysis. In contrast, Posner et al. (1989) found no correlation between tumor size and recurrence, but they used 10 cm as the cut-off point.

The surgical margin was found to be an independent prognostic factor in the multivariate analysis, but not in the univariate analysis. The findings of other studies agree with this (Posner et al. 1989, Spear et al. 1998). Bearing in mind the invasive nature of the tumor, we recommend that surgeons pay great attention to the margin. Although the univariate analysis showed that adjuvant radiotherapy has a positive effect on extraabdominal tumors, this was not confirmed with the multivariate analysis. In a univariate analysis, Spear et al. (1998) found that adjuvant radiotherapy had no effect, but in a multivariate analysis, radiotherapy significantly affected the relapse-free survival. Irradiation of gross residual tumor had a significant positive effect on the relapse-free survival, but it did not have an effect on microscopic residual (Posner et al. 1989). Reitamo (1983) also reported that combined surgery and radiotherapy improved local control. Data from prospective studies are needed to clarify the role of adjuvant irradiation in aggressive fibromatosis. An international study addressing this question is planned.

In our study, no tumors expressed ER. On the basis of a few studies (Häyry et al. 1982, Lim et al. 1986, Alman et al. 1992) showing that biochemically one fourth to one third of the tumors express ER, aggressive fibromatosis is generally regarded as an ER positive tumor. Fong et al. (1993) analyzed 6 multifocal tumors immunohistochemically for expression of ER and found that all tumors were negative. The view that aggressive fibromatosis is an ER positive tumor has served as the basis for treating non-resectable tumors with anti-estrogens like tamoxifen. Many studies have reported successful treatment of aggressive fibromatosis with anti-estrogens (Thomas et al. 1990, Wilcken and Tattersall 1991, Brooks et al. 1992). This has been ascribed to the effect of anti-estrogen on the estrogen receptors within the tumor. However, we found no ER expression in any of 72 consecutive aggressive fibromatosis tumors. This suggests that the effect is due to other factors (Colletta et al. 1990).

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