

Outcome of Aggressive Fibromatosis Treated with Radiation Therapy

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Abstract

Introduction.

The purpose of this study is to report the clinical course and outcome in 7 patients with aggressive fibromatosis.

Material and Methods.

Between the years 2000 and 2003, 7 patients who were treated with combined modalities were evaluated retrospectively. Patients' demographic information, including age and gender, tumour characteristics, surgical resection, and the use of radiotherapy were recorded and evaluated.

Results.

The mean patient age was 34 years. The median time to follow-up was 15.5 months. Resection was performed with positive surgical margins in three cases. Three patients were evaluated as inoperable and one patient was treated with debulking surgery. All patients received radiation therapy with a median dose of 51 Gy. At follow-up, three patients had no evidence of disease, three patients were alive with disease, and one patient died 15 days after radiotherapy.

Conclusion.

Local control is the primary problem in aggressive fibromatosis. There is no appropriate treatment for aggressive fibromatosis and the type of treatment depends on tumour characteristics and location as well as patient characteristics.

Introduction

Aggressive fibromatosis is characterised by benign, slow-growing tumours without metastatic capability. Aggressive fibromatosis causes fibroblastic proliferation and behaves locally in an aggressive and infiltrating manner. Fibromatosis therefore causes local growth and tissue invasion that may result in pain, organ dysfunction, and deformity. Pregnancy, soft-tissue trauma, and Gardner's syndrome are associated with this tumour.^{1,2,3,4} Aggressive fibromatosis may be seen anywhere in the body but is mainly found at five sites: the proximal extremities, neck, trunk, abdominal wall and mesentery. Local recurrence may occur even after a wide resection. Although the role and precise indication of radiation therapy has not been clearly defined, radiotherapy is helpful in the management of aggressive fibromatosis.^{5,6}

The purpose of this study is to report the outcome of 7 patients treated with radiotherapy and with/without surgery for aggressive fibromatosis.

Material and Methods

Seven patients with aggressive fibromatosis had radiation treatment in our department between 2000 and 2003. In all the cases, the diagnosis of aggressive fibromatosis was confirmed histologically and the patients were referred to our department with their primary tumours. Patients' demographic information, including age and gender, tumour characteristics, surgical resection, and the use of radiotherapy were recorded. The most common location for tumours was in the extremities. The other locations were intracranial, the axilla, and the mediastinum. Ultrasound, computerised tomography (CT) scan, and magnetic resonance imaging (MRI) were used according to the location of the tumour for evaluation of both staging and response.

Tumours were classified into the following three categories. A tumour in the first category is characterised as having a microscopic positive margin (R1 resection), in which margins are microscopically tumour positive after surgery. A tumour in the second category has a macroscopic residue (R2 resection), which can be recognised visually. The third category consists of inoperable tumours which cannot be resected because the tumour has invaded vital organs.

Radiotherapy was used as either the primary treatment or as an adjuvant therapy after surgery. For adjuvant treatment, the entire operative bed with a margin was included in the radiotherapy volume. Radiotherapy was given using 6 MV photons or γ rays from Co-60. Fractionation schedules were five days per week with a daily fraction of 2 Gy.

The patients were treated with a median dose of 51 Gy (range 39.6 to 62 Gy) in fractions of 2 Gy per day. The patients with microscopic tumour positive margins were treated with curative intent, but for the patients with the macroscopic residue tumours and the inoperable patients, the aim of the treatment was mainly to stop progression. For curative intent, total doses of 50-62 Gy were used. The 5 year old paediatric patient was given a relatively low total dose (39.6Gy) because of his age and prior chemotherapy. After the completion of radiation therapy, the patients were evaluated every three months for the first two years and every six months after that.

Results

The mean age of the 7 patients was 34 years (range 5 to 52). The male to female ratio was 3:4. The median follow-up time was 15.5 months. Patient characteristics are detailed in Table I. At the time of diagnosis, the mean tumour diameter size was 7 cm (with a range of 2.5 to 11 cm). Only one tumour was less than 5 cm. Three tumours ranged between 5 cm and 10 cm, and the remaining three tumours were greater than 10 cm. Three patients had gross measurable disease prior to radiotherapy.

Table I. Clinical Data of Reported Patients

	Gender/Age	Site	Presentation	Treatment mode	Residual status	Tumour size	RT dose	Last known status
Case 1	F/44	Upper arm	Primary	Postoperative RT	Microscopic	3x2.5 cm	56 Gy	NED;21 months
Case 2	F/52	Axilla	Primary	Postoperative RT	Microscopic	5x4 cm	62 Gy	NED; 37 months
Case 3	F/15	Leg	Primary	Postoperative RT	Microscopic	7x11 cm	50 Gy	NED;12 months
Case 4	M/34	Intracranial	Primary	Postoperative RT	Gross residue	11x8 cm	50 Gy	AWD;11 months
Case 5	M/49	Mediastinum	Primary	Primary	Inoperable	8x8 cm	50 Gy	EX;15 days
Case 6	F/40	Popliteal fossa	Primary	Primary	Inoperable	5x5 cm	50 Gy	AWD;28 months
Case 7	M/5	Buttock	Primary	Primary	Inoperable	11x5 cm	39.6 Gy	AWD;41 months

AWD: alive with disease, NED: no evidence of disease

RT: radiation therapy, EX: exitus

The anatomic distribution of tumours is as follows: four patients had tumours located in the extremities (tumours located in the upper arm, the leg, the axilla, and the popliteal fossa for the four patients, respectively), one patient with a tumour in the cranium, one patient with a tumour in the buttock, and one patient with a tumour in the mediastinum.

Curative resection was attempted for three patients (cases 1, 2, and 3), but they were found to have a positive microscopic margins upon pathologic evaluation. All three patients received adjuvant radiotherapy. Despite the positive margin, no local recurrence developed during follow-up.

Another patient (case 4) who had intracranial aggressive fibromatosis was treated with debulking surgery. The tumour was located in the infratemporal fossa, invading the pterygoid muscles, sphenoid sinus and cavernous sinus, up to the apex of the orbita and the optic chiasm. The patient's condition was stable after radiotherapy.

Three patients (cases 5, 6, and 7) had tumours close to vital structures and in locations which made resection impossible. Primary radiotherapy was planned for these cases. One patient (case 5) with the tumour in the mediastinum died 15 days after completion of radiotherapy. This patient had an oesophageal stricture and a stent had been placed in order to provide nutrition. The lesion had extended through the oesophagus and the descending aorta, invading the pericardium and the inferior vena cava. Only one patient (case 7), the 5 year old who had a tumour on the buttock, had received chemotherapy. The combined chemotherapy regimens were comprised of vincristine and actinomycin D. After chemotherapy treatment, this patient received radiotherapy. After a follow-up period of 24 months, tumour progression occurred and subtotal excision was performed.

No patients revealed metastatic disease at follow-up. No serious toxicities (grade 3-4) were observed. However, in the patient with the axillary tumour localisation, grade 2 arm oedema and subcutaneous fibrosis were observed. The five other patients showed grade 1-2 skin toxicity.

Discussion

Fibromatosis is a tumour-like fibroblastic proliferation without metastatic capability but with a tendency to infiltrate surrounding

tissues.^{7,8} Fibromatosis commonly occurs in 20 to 40 year olds with a female predominance. It may originate from any place in the body, but it is mainly found in the extremities and the girdle, the chest and abdominal wall, and the neck.⁹

No single appropriate treatment for aggressive fibromatosis exists. The type of treatment depends on tumour characteristics and location, as well as patient characteristics and preferences. Only 50% of tumours recurred after wide local excision, compared to a recurrence rate of 90% after incomplete excision.¹⁰ However, the true effect of the surgical resection margin on local recurrence rates remains difficult to evaluate, as most studies include a small number of patients treated with variable treatment combinations for different indications (Table II).

Most studies have found the extent of initial excision to be prognostically significant. Mehrotra et al. reported 36 patients who were initially treated by surgical excision. Seventy one per cent of patients with positive surgical margins had local recurrence, compared to only 31% of patients who had negative surgical margins ($P < 0.05$).¹¹ Gronchi et al⁹ reported that marginal status was not a significant prognostic factor in this subset of tumours. Patients with positive margins had a 5 year disease-free survival rate of 79% and a 10 year disease-free survival rate of 74%, whereas those with negative margins had a 5 year disease-free survival rate of 82% and a 10 year disease-free survival rate of 77%. Results of the National Patterns of Care study demonstrated no statistical correlation between resection and margin status.¹² In another study using multivariate analysis, margin status was the single most significant determinant of recurrence in patients treated with surgery.¹³ The sufficient margin width for safe resection has not been determined. The primary therapeutic approach is always radical surgical resection with a wide safety margin (2-3 cm). However, Spear and colleagues did not find any difference in outcome when tumours with negative margins were subdivided into those with close (< 1 mm) and wider (> 1 mm) margins.¹⁴ In another study, they found significantly better local control for patients receiving radiotherapy (RT) after surgery regardless of the marginal or residual status.¹⁴ In our study, three cases with microscopic residue tumours received adjuvant irradiation after surgery and had no evidence of disease at follow-up. Nuytters et al. showed in a comparative review of 22 articles that surgery alone is not adequate, but surgery plus radiation therapy is a good option.¹⁵

Table II. End Points Rates in Published Series

		Primary Surgery		p		Primary RT	Surgery+RT
		(+) margin	(-) margin				
Mehrotra et al. ¹¹	Local Recurrences	%71	%31	< 0.05			
Gronchi et al. ⁹	DFS (5 yr-10 yr)	%79-%74	%82-77	NS			
National Patterns of Care ¹²	Local control			NS	Local control	%81.4	%79.6
Ballo et al ¹³	Local recurrences (10 yr)	%54	%27	0.003	Long term control	%76	
Spear et al ¹⁴	Local control	%69			Local control	%93	%72
Pritchard et al ¹⁵	Local control(5yr)	%65				%65	
Keus et al ¹⁶					DFS (5yr)		%90
Leibel et al ¹⁷					RFS (5yr)		%72
McCullough et al ¹⁸					Local control (6yr)		%79
Miralbell et al ¹⁹	Local control (5yr)	%68			Local control	19/24 (patient)	
Sherman et al ²⁰					Local control (7.6yr)		%77

RT: radiation therapy

DFS: disease free survival

RFS: relaps free survival

Yr: years

Radiotherapy has been shown to improve local control of aggressive fibromatosis. The long-term control rate of 76% in Ballo's series was reported.¹³ Pritchard et al reported the results of surgery alone or combined with radiation, and showed that the local control rate was 65% for 5 years.¹⁰ The combined results of multiple studies show that radiation therapy, with or without subtotal resection, resulted in local control of 78%.^{16,17,18,19,20}

Radiation therapy alone is preferred for patients who have an inoperable tumour or who proceed to gross residual disease after operative debulking, and for those in whom operative management would lead to major morbidity or loss of function. In this study, four patients (cases 4, 5, 6, and 7) were treated with radiation therapy due to inoperability or gross residual disease. Only one died from the disease, the other three were alive with disease and two of them were stable during follow-up.

Although it is difficult to find the exact origin of the aggressive fibromatosis, most authors tend to agree that intracranial fibromatosis arises from the dura.^{7,21,22} In our intracranial case it was not possible to determine the origin of the lesion because the huge tumour had invaded most of the intracranial structures. Rock et al identified the calf, foot, supraclavicular fossa, and buttock as sites which were resistant to treatment.²³ Most authors advised a dose between 50 Gy and 60 Gy.¹³ Radiation dose correlated with the incidence of complications. Doses of 56 Gy or less produced a 5% 15-year complication rate, compared to a 30% incidence with higher doses ($p < 0.05$).²⁴ Primary tumours and recurrent lesions treated with radiation therapy showed 5 year and 10 year local control rates of 93% and 76% respectively, compared with rates for surgery of 69% and 62%, respectively.¹³

Many studies showed that local control was better for patients with fewer than two operations versus patients with more than three operations. Recurrence was a significant unfavourable risk factor.¹⁵ In locations where surgical extirpation is difficult or unfeasible, or in case of recurrence, primary radiation therapy, hormonal therapy, chemotherapy and nonsteroidal anti-inflammatory agents should be considered.^{25,26} The use of combination chemotherapy with vinblastine sulfate and methotrexate or doxorubicin and dacarbazine has been reported to be effective in adults as well as in children.^{27,28,29,30} In some series, chemotherapy has been mostly used in children as the first treatment modality.³¹ Case 7, who had an unfavourable presentation, a gross mass, and three recurrences despite chemotherapy and radiotherapy, was determined to have local progression. Because of high recurrence rates despite radical surgery plus radiotherapy in recurrent patients, different combinations of chemotherapy and radiotherapy have been tested in some studies. Baliski et al determined low recurrence rates with neoadjuvant radio-chemotherapy in recurrent patients in a small series.³²

Although mortality is rare and is usually due to local complications, patients with unresectable aggressive fibromatosis often die because of the locally aggressive nature of the tumour. One of our patients, who had a mediastinal tumour, died because the tumour invaded the pericardium and inferior vena cava.

Complications of surgery have seldom been reported in contrast with radiotherapy complications, which have been frequently reported. However, while mild and moderate complications were more frequent in the radiotherapy group, severe complications were reported, especially in the surgery group.¹⁵ In the present study, no serious toxicities (grade 3-4)

were observed. However in the patient with the axillary tumour localisation, grade 2 arm oedema and subcutaneous fibrosis were observed, and five other patients have showed grade 1-2 skin toxicity.

Multiple modalities may be necessary in some patients. The entire clinical picture and the patient's preferences must be taken into account when deciding on an appropriate treatment plan. The current study supports the utility of primary radiation therapy in the treatment of these tumours with some localisation to stop progression. Patients with tumours amenable to surgery with a good functional and cosmetic outcome are treated with resection alone if negative margins can be achieved. Patients with predictable microscopic residual disease should be considered for adjuvant RT to decrease the recurrence rate. Patients with gross residual disease after surgery, unresectable tumours, and those for whom resection would result in a significant functional deficit should be treated with RT alone. The results of our cases treated with primary or adjuvant radiotherapy also supports the utilization of irradiation as reported elsewhere in the literature, although our number of patients was quite low.

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