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Radiotherapy of Aggressive Fibromatosis

G. Schmitt, E.E.D. Mills, V. Levin, B.J. Smit, H. Boecker and H. Pape

The long term results of 24 patients treated with postoperative irradiation for aggressive fibromatosis are presented. Tumour sites were the pelvis (8), chest wall (5), shoulder (5), extremities (4) and head and neck (2). Macroscopic complete resection (R1) was performed in 3 cases. 17 patients presented postoperatively with gross disease (R2), 8 of which were recurrent tumours. 4 patients with inoperable disease had biopsies only. Radiation doses ranged from 28 to 64 Gy at a fractionation of 5 × 2 or 4 × 2,5 Gy/week. 4 patients had external irradiation in combination with ^{192}Ir implants, 2 were irradiated with implants alone. In the combined treatment group, external doses ranged from 28 to 52 Gy and additional interstitial doses from 35 to 50 Gy. ^{192}Ir treatment alone was given with 45 and 57 Gy to the contour of the target volume. The 10 year recurrence free survival rate is 75%. A dose response relationship has been established in the dose range of 30–60 Gy revealing an expected 80% persistent tumour control rate at 60 Gy. A dose volume relationship however, could not be derived from our data. Moderate fibrosis without functional impairment developed in 5 patients (21%). These data support a policy of postoperative radiotherapy with 60 Gy in patients with incompletely excised or gross residual tumour following surgery.
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INTRODUCTION

AGGRESSIVE FIBROMATOSIS or desmoid tumour is a non-metastasing, locally infiltrative lesion of heterogeneous fibroblastic origin derived primarily from fascial sheaths and musculo-aponeurotic structures. The histological picture comprises uniformly elongated, slender cells with few mitoses, interspersed in abundant collagen. The incidence is 0.03% of all neoplasms with a predilection for young females [1]. The tumour characteristically infiltrates surrounding vital tissues causing severe morbidity and if untreated, may ultimately be the cause of death. Local resection results in a 25–58% failure rate. Radiotherapy, first suggested by Ewing in 1929 [2], has been shown to substantially reduce the recurrence rate in incompletely resected tumours. This report of 24 cases supports these data and updated our long term results.

PATIENTS AND METHODS

Between 1972 and 1983, 24 patients with histologically proven aggressive fibromatosis were treated at the departments of radiotherapy, Groote Schuur Hospital and University of Düsseldorf. There were 13 females and 11 males including 6 black and 18 white patients. The age distribution was 10–62 years (mean: 25 years). Tumour sites were the pelvis (8), chest wall (5), shoulder (5), extremities (4) and head and neck (2).

Macroscopic complete resection was performed in 3 cases. However, margins were histologically doubtful in these cases (R1). 17 patients presented postoperatively with gross disease (R2), 8 of which were recurrent tumours. 4 patients with inoperable disease had biopsies only. The time interval from surgery to radiotherapy ranged from 0.5 to 108 months.

External beam irradiation was administered with ^{60}Co-gamma rays, 5.7 and 12 MV photons as well as 15 MeV electrons as a boost. 4 patients received external irradiation in combination with ^{192}Ir implants, 2 were irradiated with implants alone. The treatment volume included the tumour or tumour bed with a safety margin of 2–3 cm. Parallel opposed isocentric fields were used for the extremity and head and neck lesions whereas

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Table 1. Persistent local control rate of 24 patients with aggressive fibromatosis with respect to tumour volume at the beginning of radiotherapy

Tumour Size	No. of patients	Recurrence free (%)	Failures (%)	Lost to follow-up
Microscopic tumour residuum (R1)	3	3 (100)	0	0
Gross tumour residuum (R2)	9	8 (88)	1	3*
Recurrent tumour	8	5 (62)	3	0
Inoperable tumour with biopsy only	4	3 (75)	1	0
Total	24	19 (79)	5 (21)	3

* Lost to follow-up at 0.5, 1 and 2.5 years after completion of radiotherapy and scored as recurrence free

computerised treatment plans were preferred for tumours of the pelvis and the chest wall. In these cases computed tomography scans were obligatory for delineating the target volume. Dose inhomogeneity in the target volume met the requirements of ICRU Report 29 [3] in all patients treated with external beam irradiation. Doses ranged from 30 to 64 Gy (mean: 47 Gy) specified at the 100% isodose at a fractionation of 5 × 2 or 4 × 2.5 Gy/week. The target volume was enclosed in all cases by the 95% isodose. The maximum target absorbed dose did not exceed 110%. Interstitial treatment alone was given with 45 and 57 Gy to the contour of the target volume. In the combined treatment group, external doses ranged from 28 to 52 Gy and interstitial doses from 35 to 50 Gy. The low doses had been given in the early years of treatment when dose response relationships were not yet established for desmoid tumours.

RESULTS

Treatment outcome of all patients with respect to tumour size at the beginning of radiotherapy is summarised in Table 1. 3 patients with macroscopic complete resection of small tumours (R1, ≤ 5 cm) are disease free at a minimum of 10 years. One received 57 Gy with a ^{192}Ir implant and 2 others had received external doses of 52 and 56 Gy, respectively (Table 2).

9 patients with tumours of 6–19 cm in diameter underwent macroscopic subtotal resection. 4 of them received doses of 34, 50 and 64 Gy, respectively. 3 of them are free of recurrence at 5, 8 and 14 years. The fourth patient experienced minor response with symptomatic improvement but died from another malignancy 6 months after the end of treatment. 4 other patients had combined interstitial and external irradiation. 2 of them are free of recurrence at 9 and 10 years, 2 others were lost to follow-up at 1 and 2.5 years. The ninth patient who had interstitial irradiation with 45 Gy was lost to follow-up 6 months after the end of treatment. No gross tumour was detectable at last review in these 3 patients who were all referred from remote African homelands.

Of these 9 patients 8 finally achieved complete tumour resolution by postoperative radiotherapy, the ninth had relief from pain.

8 other patients had repeated resections at 2–108 months after the first operation. Radiation doses ranged from 30 to 56 Gy in this group with a mean value of 42 Gy. 4 patients experienced complete remission. One of them, a female, received a dose of 40 Gy at the retroperitoneal area and pelvis together with actinomycin D, 500 μg per day for the first 5 days of treatment. 2 patients achieved partial remission. 1 other patient had partial remission and relief of pain but died 1 year later from a secondary malignancy. The remaining patient underwent three courses of radiotherapy following repeated resections for recurrence. Doses ranged from 15 to 40 Gy. He is now tumour free 4.5 years after the last treatment.

5 of these 8 patients who had recurrent disease are in complete remission, 2 are in partial remission and 1 has pain palliation.

In the last 4 patients biopsies only were taken. 2 of them who had gross tumour of > 15 cm received external irradiation with 40 and 50 Gy, respectively and remain disease free at 10 years. 1 patient showed minor response at 40 Gy. The last one had minimal response at 30 Gy and withdrew from further treatment to return 2 years later with progressive disease necessitating repeated surgery and additional radiotherapy up to 50 Gy. The patient remains disease free 4 years after the second treatment.

Data of all patients with gross tumour did not allow to derive a dose–volume relationship.

19 of 24 patients are free of recurrence at last review (Table 1), resulting in a 10 year disease free survival probability of 75% (Fig. 1). A dose-response relationship has been established in the dose range of 30–60 Gy with an expected 80% persistent tumour control rate at 60 Gy (Fig. 2).

No serious side reactions according to grade 3 and 4 of the EROTC RTOG late morbidity scoring system, namely pronounced oedema, joint contractures or ulcerations, were recorded. Slight fibrosis developed in 14 (58%) and moderate fibrosis without functional impairment in another 5 patients (21%).

Table 2. Complete tumour resolution according to radiation technique

Type of resection			Radiation technique	No. of patients	Dose (Gy)	Complete tumour resolution
Microscopic tumour residuum	(R1)	1	^{192}Ir implant	2	57	100% (2/2)
Gross tumour residuum	(R2)	1			45	
Microscopic tumour residuum	(R1)	2	External beam irradiation	2	52, 56	100% (2/2)
Gross tumour residuum	(R2)	4	^{192}Ir implant and external beam irradiation	4	35–50 28–52	100% (4/4)
Gross tumour		16	External beam irradiation	16	30–64	69%(11/16)

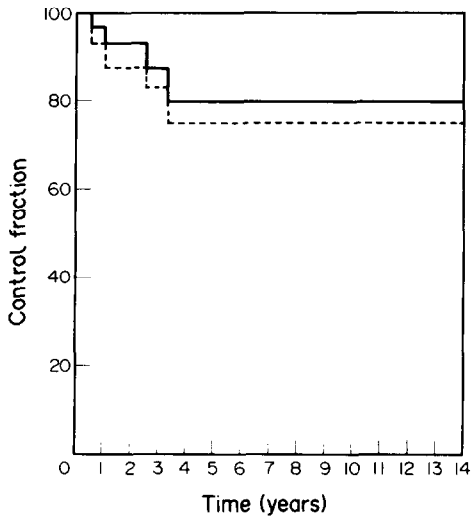

Fig. 1. Probability of local control and survival (Kaplan–Meier method) of 24 patients with aggressive fibromatosis. —— overall survival; ---disease free survival.

Table 3. Results of radiotherapy with or withour surgery of aggressive fibromatosis in recent literature

Reference	No. of patients	No. of recurrences: Tumour volume: Macroscopic	Microscopic	Dose < 50 Gy	Total recurrence rate
19	9	1/9	–	1	1 (11%)
5	19	4/13	2/6	1	6 (32%)
4	17	2/10	2/7	2	4 (24%)
6	21	0/4	2/17	1	2 (10%)
7	29	5/21	2/8	4	7 (24%)
9	45	4/14	7/31	0*	11 (24%)
This paper	24	5/21	0/3	5†	5 (21%)‡
Total	164	21/92 (23%)	15/72 (21%)	14	36 (22%)

* No. of patient treated with < 50 Gy.
† All patients with gross disease.
‡ Including 2 cases of minor response for the whole follow-up period.

DISCUSSION

Surgical treatment of aggressive fibromatosis results in a local failure rate of approximately 45% (99/222; [4]), which is mainly attributed to an inadequate clearance of extended tumours.

Substantial data have been accumulated during the past decade on the effectiveness of radiotherapy in this disease. Long term local control rates ranging from 60–90% have been reported [4–9], when radiotherapy was given after complete or bulk reduction surgery.

A correlation has been established for dose and local control probability. Kiel and Suit [4] achieved a local control rate of 82% when applicating ≥ 60 Gy. Our cumulative control rate is in agreement with these results (Fig. 2) and those of Keus and Bartelink [6]. Patients treated for recurrent gross disease fared worst in our series with a local control rate of 62% compared with 88% for primary tumours. A significant difference between these groups was also noted by Miralbel *et al.* [8].

As reported, local control could not be clearly correlated with tumour size at the time of radiotherapy. Our results and collected data from the recent literature show a local control rate of 79% (57/72) following radiotherapy for microscopic residuum compared with 77% (71/92) for gross disease (Table 3). Corresponding data, which have recently been published by Sherman *et al.* [9], are 77% and 71% respectively. In a series of 21 patients, who were only observed following R_1 resection, 17 (81%) remained free of recurrence after a median follow up 70 months [8]. However, the minimum follow-up period of these patients was only 12 months. These data indicate that incomplete clearance of all gross disease does not necessarily prejudice prognosis.

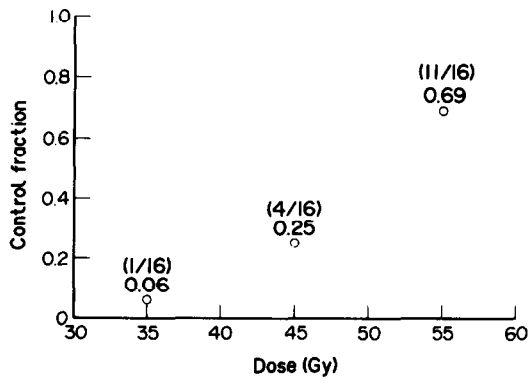

Fig. 2. Dose–response relationship for persistent local control of aggressive fibromatosis in 16 patients with gross tumour.

Some few observations on chemotherapy should also be mentioned: Stein [10] and Hutchinson *et al.* [11] reported on successful chemotherapy of aggressive fibromatosis in children. 2 other patients with recurrent disease have been treated by Leibel and co-workers [5] with vincristine, actinomycin D and cyclophosphamide (VAC). Surgical removal of recurrence had been performed in both and subsequent radiotherapy in one of these cases before initiation of chemotherapy. Both patients, 1 male and 1 female remained free of disease at 3 and 6 years after completing chemotherapy.

A further report on successful treatment of extensive aggressive fibromatosis in a 7-year-old girl has been published by Atahan and co-workers [12]. These authors also used a VAC regimen followed by a 52 Gy course of radiotherapy. However, the same treatment failed in a 3-year-old boy.

One of our female patients who had received 40 Gy to the retroperitoneal area and pelvis in combination with actinomycin D for inoperable disease is free of recurrence 11 years after treatment. These data demonstrate that chemotherapy may also be effective in aggressive fibromatosis and might be advocated in recurrent disease particularly in young females. Whether this is a direct effect on the tumour or an indirect hormonal effect has not yet been established.

Some observations do give support to the theory of endocrine predisposition of the development of desmoid tumours: the incidence of abdominal desmoid tumour is four times higher in females than in males and extra-abdominal desmoids occur twice as often in females as in males. 70% are seen in females following pregnancy [13].

Other reports exist on the regression of desmoid tumours at menopause [14] or following irradiation of the ovaries [15], as well as appearance of desmoids after injection of oestrogens [16].

Prednison was also shown to be effective in the treatment of a

recurrence in a 22-month-old girl [17]. Likewise complete tumour involution has been reported in a 21 year old female [18].

On this basis one might conjecture that at least part of the chemotherapy effect is attributable to a reduced ovary function. Ovarian suppression could therefore also be considered in the treatment of recurrent desmoid tumours. The unexpected tumour regression in one of our female patients following pelvic irradiation might be attributed to this effect.

In summary, our data are in agreement with the recent literature and support a policy of postoperative radiotherapy with 60 Gy in established cases of incomplete excision or gross residual disease following surgery. A policy of watchful expectancy might be considered in young patients with minimally positive or uncertain margins where it is assured that any recurrence will be readily resectable.

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Chronic Oral Etoposide in Non-small Cell Lung Carcinoma

J. Estapé, H. Palombo, J. Sánchez-Lloret, C. Agustí, J.J. Grau, M. Daniels, N. Viñolas, C. Solá, A. Biete and J. Ramirez

25 consecutive inoperable or extended non-small cell lung cancer (NSCLC) patients (19 non-chemotherapy pretreated, 6 non-heavily pretreated) were given oral etoposide, 50 mg/m²/day for 21 successive days, every 4 weeks. 5 partial responses (PR), 9 disease stabilisations were achieved; the overall response rate of 20% (95% confidence interval, 4% to 36%) or 26% in non-pretreated patients. Median survival and PR duration probabilities were 6.7 months and 6.3 months, respectively. Alopecia excepted (96% of patients), non-haematological toxicity was mild. Haematological toxicity WHO grade II+III mainly consisted of leukopenia (28%).
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INTRODUCTION

ETOPOSIDE IS a schedule-dependent drug in preclinical systems [1] and in human oncology [2]. In small cell lung cancer (SCLC) the etoposide 5-day schedule has achieved a higher survival rate than the 1-day course [3]. The 8-day schedule has shown similar rate and duration of responses but lower toxicity than the 5-day course [4]. Based on the etoposide mechanism of action, preclinical studies and clinical data, Greco *et al.* started clinical research of a new schedule they called "chronic oral etoposide", in which etoposide is given orally for 21 consecutive days [5]. This new schedule has given promising results in SCLC, germ-cell tumours and non-Hodgkin lymphomas [6, 7]. The present study describes our experience with chronic daily oral etoposide in the treatment of advanced non-small cell lung cancer (NSCLC).

PATIENTS AND METHODS

25 consecutive NSCLC patients were entered into this trial from March to November 1990. Eligibility criteria were age,