General Surgery

Aggressive fibromatosis – impact of prognostic variables on management

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Summary

Objective. To determine the impact of prognostic variables on local control in patients with aggressive fibromatosis treated with or without radiation.

Materials and methods. Forty-two patients presenting to the combined sarcoma clinic at Johannesburg Hospital with aggressive fibromatosis from 1990 to 2003 were analysed retrospectively. There were 14 males and 28 females. The lesions involved the head and neck in 6 cases (14%), the thorax in 6 (14%), the extremities in 19 (45%) and the abdomen in 11 (26%). Thirty-seven patients (88%) presented to the clinic for the first time, whereas 5 (12%) had recurrent disease at presentation. Fifteen patients (36%) underwent excision only, 15 (36%) had excision followed by postoperative radiation, 8 (19%) had biopsy only, and 4 (9%) had radiation only. The median dose of radiation was 60 Gy (range 9 - 70 Gy).

Results. One patient had local failure following excision and postoperative radiation therapy. The local control was 100% for surgery alone and 86% for surgery followed by postoperative radiation at ≥ 24 months. On univariate analysis, age, sex, positive margins, primary or recurrent presentation, site of involvement and initial treatment did not affect local control significantly. Eight of 19 patients (42%) receiving radiation developed severe moist desquamation following treatment, and all these patients had doses of 60 Gy or more.

Conclusion. Surgery with or without radiation therapy gave excellent local control. The addition of radiation therapy to surgery as well as other known prognostic parameters did not impact on local control. The morbidity of radiation treatment is considerable, as noted in this series, and adjuvant radiation therapy should therefore be considered only in situations where the risk of recurrence and the morbidity of re-excision are high.

Aggressive fibromatosis or desmoid tumours are heterogeneous benign tumours that originate from deep musculo-aponeurotic structures. They display local infiltrative growth but do not metastasise. Desmoid tumours are non-encapsulated and tend to extend along the fascial planes. They also have the potential to erode bone, surrounding blood vessels and nerves. Microscopically they are associated with an abnormal proliferation of connective tissue but lack the cytological features of malignancy. The proliferation of the lesion is composed of interlacing fascicles of elongated relatively uniform spindle cells (Fig. 1) with vesicular ovoid to tapering nuclei with 1 - 3 small nucleoli present (Fig. 2). Desmoid tumours can be distinguished from low-grade fibrosarcomas by a lack of mitotic activity, metastatic potential and nuclear or cytoplasmic features of malignancy. They accounted for 0.05% of all patients with solid tumours and 3.7% of those with fibrous tissue neoplasms attending the Department of Radiation Oncology at Johannesburg Hospital in 2001. They account for approximately 0.03 - 0.1% of all solid tumours and 3.6% of fibrous tissue neoplasms. The most common locations for desmoid tumours include the shoulder, chest wall and thigh. Males and females of all ages can be affected, but a propensity for fertile women has been noted by many authors.

Fig. 1. Low-power view demonstrating the typical interlacing fascicles of fibroblasts separated by collagen.
Recurrence of desmoid tumours may be related to the age of the patient, the site of the tumour and the initial form of treatment. The primary mode of treatment for desmoid tumours is surgical excision. However, high recurrence rates (39 - 79%) have been reported when surgery is used alone. The goal of surgical excision is gross total resection with negative margins, but approximately one-third of desmoid tumours are not amenable to gross total resection. Local control rates have been reported to be a function of tumour location, ability to obtain negative margins and adjuvant radiotherapy. With regard to adjuvant radiation, there is controversy surrounding the dose, timing and indication for treatment of desmoid tumours.

We examined our experience from 1990 to 2003 with the intent of rationalising therapy based on individual characteristics such as location, age, recurrence status and surgical margins.

Materials and methods

The records of 42 patients diagnosed with fibromatosi sreferred to our hospital for treatment were analysed retrospectively. There were 14 males and 28 females. The mean age was 33 years and the median age was 32.7 years for the whole group. The patients presenting with recurrent tumours had 1 - 3 excisions (median of 2) before radiation.

All patients were evaluated jointly by surgeons and radiation oncologists. Surgery was usually the preferred initial treatment unless limited by proximity to vital structures or a poor expected functional outcome. The patients were managed over 14 years by multiple surgeons and radiation oncologists with varying and dynamic policies regarding radiation therapy for recurrent disease and positive margins. The analysis was therefore conducted based on the treatment rendered and outcome. Tumours thought to be at higher risk of failure or of significant morbidit y associated with failure tended to receive combined modality treatment. The group of patients receiving radiation therapy had a significantly higher percentage of grossly or microscopically positive margins than the group treated with surgery alone.

Fifteen patients underwent excision of the lesion alone and 15 had excision followed by radiation. Four patients were treated with radiation alone as they refused surgery, and 8 had a biopsy for diagnosis only but did not receive any further treatment. These 12 patients were not considered further in the analysis.

The patient and tumour characteristics for the surgery-alone patients (N = 15) and the surgery-plus-radiation patients (N = 15) were compared as matched groups as these form the two main alternative treatments. Their characteristics are shown in Table I.

There was no significant difference in presentation between the treatment groups with regard to age at presentation, sex distribution, site of lesions, and primary or recurrent disease. The mean diameter of the lesions was similar in the two groups.

Nineteen patients received radiation. Four patients had radiation alone and 15 patients had postoperative radiation. The radiation was delivered as megavoltage external-beam photons, electrons or a combination of electrons and photons. External-beam treatments were given at 1.8 - 3 Gy per fraction (1 patient had 2.5 Gy/fraction and another 3 Gy/fraction) with a median dose of 2 Gy/fraction given 5 days per week. Three patients received low doses of external-beam radiation ranging from 9 Gy to 34 Gy. The treatment margins given were 3 - 5 cm from the tumour or resection bed in the planes having potential for disease extension. Shrinking field techniques were used as applicable. Doses were prescribed based on the estimated extent of disease (gross or microscopic) in situ at the time of treatment.

Ten patients received external-beam radiation with Co\textsuperscript{60} gamma-rays, 2 patients received 6 MeV photons, 6 patients received electrons alone, and 1 patient received a photon and electron combination. The median dose was 60 Gy (9 - 70 Gy). Seven of 8 patients receiving more than 60 Gy had grossly positive margins.

Statistical analysis

Determination of local outcome was based on clinical examination or computed tomography (CT) as appropriate for tumour location. Freedom from local failure was defined as an absence of post-treatment tumour growth and was
evaluated at last follow-up after initiation of the indicated treatment modality. Local failure-free survival curves were generated using the Kaplan-Meier method, and the p-values to compare various prognostic variables were calculated using the log-rank method. The data were analysed using the SPSS-1.5 package. Failure rates were compared based on the surgical margins, radiation dose, age, tumour location and recurrent versus primary disease.

All patients who had surgery with or without radiation therapy were included for the local control and survival analysis. Others have excluded patients receiving inadequate doses.

**Results**

**Surgery with or without radiation therapy**

Of the 30 patients who received surgery with or without radiation therapy, 1 patient failed locally. This patient presented with microscopically positive margins and had 60 Gy postoperatively. Recurrence occurred at 11 months and was salvaged by surgery and the patient remains controlled at 65 months.

None of the following prognostic variables was significant for local control: sex (p = 0.36), primary v. recurrent disease (p = 0.64), extremity v. non-extremity (p = 0.18), diameter of disease (≤ 10 cm v. > 10 cm) (p = 0.61), and radiation v. no radiation (p = 0.44).

Using the Kaplan-Meier method local control was 100% with surgery and 86% with surgery followed by postoperative radiation therapy at more than 24 months’ follow-up.

**Radiation alone (4 patients)**

Two of the 4 patients receiving radiation therapy only had lesions of the extremity where surgery would have entailed amputation. The doses given were 50 Gy and 66 Gy respectively. Of the remaining 2 patients, 1 child aged 1 year had a mediastinal lesion that was inoperable, and received 30 Gy in 16 fractions, and the second patient had an inoperable scapular lesion and received 30 Gy in 10 fractions for palliation.

Two of 4 patients who were treated with radiation alone developed a recurrent lesion at 3 months and 29 months respectively. One had received a total dose of 30 Gy for a mediastinal lesion and the other 66 Gy for a lesion of the extremity. The disease was controlled in the remaining 2 patients at 44 and 40 months’ follow-up respectively.

**Biopsy-alone group (8 patients)**

Long-term follow up was available for only 1 patient in this group who was disease-free at 44 months.

**Radiation toxicity**

Of the 19 patients who received radiation, 8 patients (42%) developed moist desquamation during the treatment. All 8 patients received 60 Gy or more. Four of 10 patients who received radiation with Co\(^{60}\) gamma-rays developed moist desquamation. Three of 6 patients who were treated with electrons had moist desquamation. One patient treated with photons and electrons developed moist desquamation. These skin reactions resolved completely in 7 patients. One patient developed a chronic ulcer for a period of 1 year that was managed conservatively.

**Discussion**

Desmoid tumours are unpredictable and are often locally aggressive, with a high potential for recurrence and may invade adjacent vital structures if left untreated. A review of recent literature on the management of aggressive fibromatosis revealed a wide range of treatment outcomes and heterogeneous treatment strategies. After surgery alone, local recurrences ranged from 20% to 80%, whereas others describe no significant improvement compared with surgery alone. In this study the local control of patients receiving surgery with or without radiation therapy was excellent, with only 1 patient failing in the combined modality arm. Because there was only 1 event in this study, a definitive comment on the impact of prognostic variables cannot be made from these data. A recent meta-analysis of 22 studies, Nuyltens et al. reported a local control of 61% with surgery alone and 75% with surgery and postoperative radiation whereas radiation alone had a local control of 78%. Mickey and Seegenschmiedt reported the results of a multicentre German study of 204 patients treated primarily with radiation and 141 patients who received postoperative radiation therapy and reported an overall local control of 81.4% for unresectable disease and 79.6% for the postoperative group.

Speet et al. reported 5-year control rates for surgery, radiation therapy and combined modality groups as being 69%, 93% and 72% respectively. Their analysis of 107 patients identified recurrent disease, positive surgical margins, treatment with surgery alone and age < 18 years as predictors of failure. They recommended doses of 60 - 65 Gy for gross disease and 50 - 60 Gy for microscopic residual. In a study of 54 patients Jelinek et al. reported a 5-year actuarial local control rate of 81% for patients receiving radiation with a median dose of 55 Gy in addition to surgery compared with 53% for surgery alone (p = 0.018).

Complete responses have been seen even with a total dose as low as 35 Gy, whereas recurrences have been seen with doses higher than 60 Gy. The appropriate radiation dose is unclear, with most authors indicating a minimum of 50 Gy and recommending 60 Gy or more for gross disease. Lower doses of up to 55 Gy that were also recommended by other authors may be adequate even for the positive margins. Sherman et al. also did not find any correlation.
between dose of radiation and local control. In the present study no correlation could be found between the dose of radiation and local control. Merchant et al.\(^9\) reported no benefit with the postoperative radiation therapy.

Various groups\(^{11,13,28}\) have reported a 5-year overall control rate of 52% for inadequate or positive margins, compared with 81% for negative margins. Patients whose treatment included radiation usually for unresected or residual disease also appeared to have a higher aggregate control rate of approximately 77%\(^{1,13,16,20,35}\). In the present series positive margins did not have an impact on the local control.

Reitamo et al.\(^7\) reported a local recurrence rate of 50% following a combination of resection and radiation therapy compared with 24% after complete excision of the tumour. In our series, 1 of 15 patients receiving surgery plus radiation therapy failed compared with 0 of 15 with surgical excision alone. All 15 patients receiving radiation therapy had positive margins (10 macroscopic and 5 microscopic), whereas 9 of 15 patients (60%) in the surgery-only group had positive margins. McKinnon et al.\(^10\) also reported that postoperative radiation did not reduce the local recurrence as in their series 2 of 4 patients with positive margins relapsed following radiotherapy compared with 3 of 7 with positive margins and no treatment. In the present series also no patient presenting with grossly positive margins failed, but failure was noted in 1 patient who presented with microscopically positive margins. Kirscher and Sauer\(^{14}\) reported the results of a meta-analysis showing an improvement of local control by 17% in postoperative irradiation for \(R_1\) resections and 40% and 28% improvement after \(R_2\) and \(R_3\) resections.

Spear et al.\(^{12}\) have recommended a margin of 5 - 7 cm in planes having potential for disease extension. Micke and Seegenschmiedt\(^2\) reported that a range of field margins of 2 - 8 cm (median 4 cm) were used by different groups but this did not impact on the treatment failures. In the present series the margin used was 3 - 5 cm. The patient with treatment failure had a margin of 3 cm and the recurrence was noted to be at the edge of the field.

To date no benefit of delivering a tumour dose exceeding 60 Gy has been demonstrated, while an increased risk of radiation-induced toxicity has been documented.\(^{19,26,33,34,35}\) Sherman et al.\(^3\) have also reported a significant correlation between the complications and dose. In the present study, 42% of patients who developed moist desquamation during treatment had at least 60 Gy total dose. One patient had a non-healing ulcer for 1 year, although with no definite evidence of recurrent disease.

There was no impact of site of lesion on local control in the present series (75% for lesions of the extremity compared with 100% for non-extremity lesions (not significant)). Micke and Seegenschmiedt\(^2\) also did not find an effect of site of lesion on local control in their study.

Local control was similar for tumours \(\leq\) 10 cm in diameter and those \(>\) 10 cm. Other authors\(^{2,27}\) have also not reported tumour size as a prognostic indicator for local control following radiation therapy.

The median age was 32 years in our patients. Age did not have an impact on local control in this report but Spear et al.\(^{12}\) did report that age \(<\) 18 years was a predictor of failure.

The time to recurrence for desmoid tumours is considered to be relatively short. Posner et al.\(^11\) noted that 80% of recurrences occur within the first 2 years. Catton et al.\(^11\) noted that all relapses occurred within 5 years of treatment. In the present series the recurrence was noted at 11 months in the patient receiving postoperative radiation.

Spear et al.\(^11\) have reported 100% local control in patients presenting with primary disease and 90% in those presenting with recurrent disease when using radiation alone. Catton et al.\(^17\) reported a 75% relapse-free rate with radiation alone compared with 54% with combined therapy. Leibel et al.\(^2\) reported a local control of 68% for 19 patients receiving between 50 Gy and 55 Gy. In the present series, 2 of 4 patients (50%) receiving radiation alone to doses of 30 - 66 Gy were controlled for more than 2 years.

**Conclusion**

This series showed that surgery with or without radiation therapy gave excellent local control. Radiation therapy and other known prognostic parameters did not impact on local control but on the basis of this study it is difficult to determine which patients, if any, may require radiation therapy. The toxicity associated with the addition of radiation therapy was high, with over 40% of patients developing grade 3 or higher skin toxicity. We therefore recommend that even though adjuvant radiation therapy is recommended by various authors for positive margins and recurrent desmoid tumours, it should be considered only in situations where resection would be difficult or impossible. Primary radiation therapy for inoperable tumours may be effective in a high proportion of cases as evidenced by this study and by studies from the literature.

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Frequent hand washing and use of alcohol-based disinfectants can attack
the natural moisturisers present in the skin. In many cases this barrier
breakdown results in irritant contact dermatitis, with redness and swelling
of the skin and associated itching or burning. With chronic exposure,
symptoms may worsen, with the skin thickening, drying or cracking, opening
a migration path for irritants, allergens and micro-organisms. Extended glove
wearing and hyperhydration (resulting from skin being bathed in perspiration
for long periods) render skin soggy and easily eroded. The combined
action of scrubbing with soaps and antiseptics, and continued glove use,
contribute to attacking the protective barrier constituted by healthy skin.
This in turn affords a portal of entry for allergens.

A survey showed that 43% of UK NHS staff had signs or symptoms of
irritant dermatitis or allergic contact dermatitis, and 10% showed latex
hypersensitivity.

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**Gammex PF HydraSoft**

Ansell Healthcare Europe, the global leader in hand protection solutions,
has launched HydraSoft, an innovative hydrating coating technology
for surgical gloves. Designed to retain moisture and rehydrate users’ skin,
HydraSoft has been developed specifically for surgeons’ hands, to help maintain the skin’s natural barrier function.

Frequent hand washing and use of alcohol-based disinfectants can attack

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