

AGGRESSIVE FIBROMATOSIS: TREATMENT MODALITIES AND RESULTS

By

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Aggressive fibromatosis are rare neoplasms with unpredictable behavior and high local relapse rate following surgical resection. This, together with the lack of large randomized trials, have resulted in much debate in evaluation of alternative therapeutic intervention. We have reviewed our results of treatment of these lesions in an attempt to define guidelines of treatment and patterns of failure.

Material and Methods: We reviewed the records of 149 patients diagnosed as aggressive fibromatosis in our institute between January 1992 and January 2001. Twelve records were discarded due to incomplete data thus leaving 137 records for evaluation (89 females, 48 males; mean age 26.4 years). Patients were divided into two groups according to the treatment modality; surgery alone group and combined surgery and radiation therapy group. Evaluation included local control rates and analysis of failure as regards therapeutic modality used, margin status, and presentation status (primary or recurrent)

Results: Ninety eight patients were treated with surgery alone. The initial local control rate was 62.2% with a median time to recurrence of 25.4 months. Thirty nine patients received adjuvant radiation therapy with a local control rate of 82.1%. The difference in the local control rates between the two groups was statistically significant ($p = 0.014$). Margin status was the most important predictor of failure. The local recurrence rates for positive and close margins (<0.5 cm) were 50% and 40.9% respectively in the surgery alone group. Previous recurrence had a significant negative impact on patients' outcome. The local control rates for primary and recurrent cases were 75.6% and 46.8% respectively.

Conclusion: Surgical resection with wide safety margin whenever feasible is the appropriate initial therapy for these group of lesions. In case, wide margins could not be achieved and for recurrent disease, the addition of radiation therapy will improve the final outcome of these patients.

Keywords: Aggressive fibromatosis, Desmoid tumor

INTRODUCTION

Aggressive fibromatosis (desmoid tumors) are rare tumors with a reported incidence of 0.03% of all neoplasms and 3% of soft tissue tumors. For that reason large or randomized trials do not exist ⁽¹⁾. This group of tumors possess unique pathological features that tend to add to the dilemma encountered in their management. The term basically denotes fibroblastic proliferation with a monoclonal pattern, that are locally malignant and do not metastasize. These tumors lack a capsule and tend to grow along the tissue planes with a peculiar infiltrative-like

pattern toward mesenchymal tissues. Such features account for the high incidence of local failure despite adequate pathologically documented free margin resection ⁽²⁾. They express a high propensity for local infiltration that could be significant in terms of deformity, morbidity and occasional mortality due to pressure effects and obstruction of vital structures and organs. Surgical extirpation has always been the first line of treatment but the high local failure rate depicted in the range of 30-40% have prompted the use of other treatment modalities, mainly radiation therapy ⁽³⁾. We have reviewed our experience over the past nine years, comparing the results of therapeutic modalities used,

patterns of recurrence and reasons for treatment failure.

PATIENTS AND METHODS

Records of 149 patients diagnosed as aggressive fibromatosis treated at the National Cancer Institute, Cairo University between January 1992 and January 2001 were retrospectively analyzed. Twelve records were discarded due to incomplete data (unspecified site, no pathology report available) thus leaving 137 records available for analysis. There were 89 females and 48 males. Mean age was 26.4 years (range 1–60). For the purpose of evaluation patients have been divided into two groups according to the treatment modality: Surgery group and combined treatment group which included surgery and radiation therapy. Patients who received radiation therapy during their treatment were evaluated as the combined modality group regardless of prior or subsequent surgical intervention. According to the pathology reports reviewed, margins were classified as either negative, close (within 0.5 cm of the tumor margin) or positive. Such margins pertain to the first definitive surgical treatment or the procedure that resulted in patient's referral to radiation therapy.

Surgical resection with clear margins (2 cm) was the preferred initial treatment unless limited by proximity to vital structures or expected major functional loss. For intra-abdominal lesions, wide local excision removing involved organs was carried out. The general indications for radiation therapy included those with positive margin or recurrent disease. Tumors located at sites where no margin could be achieved (abdominal, head and neck) were also referred to radiation therapy department. Patients with close margin were placed under close follow up.

Radiation treatment was planned to deliver 45 to 70Gy, 180 cGy/fraction, and 5 fractions per week. Radiation field was designed to encompass the surgical scar with a clear 2-3 cm margin around. All were treated with megavoltage external beam photons \pm electrons.

Determination of local outcome was largely dependent on clinical examination for superficial lesions and on CT examination for deep lesions (intra-abdominal and intra-thoracic). The average follow up period was 36 months (range 8 to 108 months). Failure rates have been compared based on therapeutic modality, surgical margin, tumor location, and recurrent vs. primary disease. Fisher's exact test was used for statistical analysis.

RESULTS

One hundred and thirty seven patients with histological diagnosis of aggressive fibromatosis were available for evaluation between January 1992 and January 2001. (Fig.1) illustrates tumor site distribution among the whole group. Extremity lesions were the most common

accounting for 59% of all cases (80/137), followed by abdominal wall lesions (18%). Ninety eight patients were treated with surgery alone and thirty nine patients received adjuvant radiation therapy. Demographic and tumor characteristics of the two groups are presented in (Table 1). Extremity lesions predominated the surgery group (69/98, 70.4%) while in the combined modality group abdominal and head and neck lesions were the most frequent sites (24/39, 61.5%). Local failure per treatment modality, margin status and presentation status are shown in (Table 2).

Surgery Group: Of the ninety eight patients who were treated with surgery alone, thirty seven patients developed recurrence at one point of time during their follow up, thus the initial local control was 62.2%. Seven patients were subsequently managed with re-excision bringing the total failure rate for the surgery group to 31.6%. Three patients eventually required amputation for progressive disease; one above elbow and two above knee and all were disease free thereafter. The median time to recurrence was 25.4 months (range 4 – 54 months). Analysis of recurrence according to margin status was as follows; of the fourteen patients with positive margins seven developed recurrence (50%). For patients with close margins (twenty two), nine developed recurrence (40.9%). In the remaining sixty two patients with negative margins, twenty one patients developed recurrence of which six cases had the recurrent tumor outside the primary surgical field, thus bringing the local recurrence rate for negative margins to 22.4% (15/62). Comparison of the recurrence rate between patients with negative margins and those with close or positive margins was statistically significant ($p = 0.02$).

Of the 31 patients who presented with recurrent disease following previous excision outside our institute, recurrence was encountered in sixteen patients (51.6%) compared to 31.3% for those presenting with primary disease ($p = 0.028$). Patients with recurrent disease tended to develop more than one recurrence and they fared worse than those with primary lesions; local control rate for recurrent cases by surgery alone was only 18.9% (7/37).

Combined Modality Group: The local control rate for the 39 patients who received combined treatment was 82.1% (32/39) which was higher than surgery alone and the difference was statistically significant ($p=0.014$). Of the seven patients who developed recurrence, five had positive margins and two had close margins. Two patients went on and had an amputation (one above elbow and one above wrist) and they eventually became disease free (the total amputation rate for the surgery and combined modality groups was 3.6%). In the remaining five patients, three received chemotherapy (single agent; methotrexate) and two received combination of non-steroidal anti-inflammatory agents and tamoxifen. Although the disease was stable with these regimens, the small number does not allow for

conclusions. The local control rate for primary disease was significantly better than that for recurrent lesions (1/23 vs 6/16 respectively) ($p=0.011$). Addition of radiation therapy was significantly better than surgery alone in patients with positive or close margins ($p=0.01$ and $p=0.02$ respectively) but the significance was lost for recurrent lesions ($p=0.07$).

Margin analysis for the entire group revealed positive margins in forty eight patients (35%), and close margins in twenty seven patients (19.7%), and tumor site was an important predictor of margin status. Intra-abdominal and head and neck sites had the highest incidence of positive margins (100%; 8/8 and 58.3%; 7/12 respectively), while extremity lesions had the lowest incidence (15.9%; 11/69).

Data analysis according to presentation status (primary vs. recurrent) for the whole group demonstrated an adverse effect for recurrent lesions on the overall outcome. The control rates for primary and recurrent disease were 75.6% (68/90) and 46.8% (22/47) respectively.

Major morbidity was encountered in only seven patients (5.1%) in both groups. They included five patients where amputation was done to control the disease and two patients with recurrent intra-abdominal lesions that led to renal failure.

DISCUSSION

Aggressive fibromatosis continues to be controversial in terms of management (4). The benign nature of the disease together with the young age at presentation coupled with the unpredictable behavior are among the principal factors that add to the confusion in treatment (5). Rarity of the disease and lack of large prospective randomized trials are additional parameters (3). Surgery had always been used as the initial treatment modality, however the extent of surgery required to control the disease remains to be settled. Several factors undermine the significance of the margins required to control the disease; positive margins do not always predict recurrence and spontaneous regression had been reported especially in the pediatric age group (6). Different series reported variable policies with some reporting simple excision to more extensive compartmental resections (7,8). Our data agree with others as regards relation between margin and recurrence with positive margins being an important predictor of failure (6,9). The reported local control rate with negative margins is 80 – 85% (10,11). The local control for negative margins in our group was 77.6%. Fifty percent of patients with positive margins in the surgery alone group developed local recurrence. The aggregate control rate for positive margins in most series is in the range of 50-60% (7,12,13). Our data tend to favor a more aggressive approach in terms of margin extent with local control rates falling to 40.9% in patients with close margins. There was a tendency for better outcome in patients with

negative margins than in those with close margins (15/62 (22.4%), 9/22 (40.9%)) respectively) but it did not reach statistical significance ($p=0.07$) which could be related to sample number. Our policy was to attempt at least one cm margin whenever feasible. There was a statistically significant difference in the local control rate between negative margins and close/positive margins ($p = 0.02$). This contradicts results reported in most series that fail to demonstrate similar conclusion if close margins were added to the data analysis (10, 11,14). However, it remains unclear, the reasons for failure to obtain free margins despite the high relapse rate for these lesions (15). Extremity lesions dominated our series (58.4%) and it is usually easier to obtain wider margins in these sites. That site is an important predictor of local failure, had been demonstrated by others (16,17, 18), and was evident in our series which again could be attributed to failure to obtain wide margins in selected sites. Intra-abdominal and head and neck regions had the highest incidence of failure in our data (100% and 58.3% respectively). Most authors agree that a negative margin short of major functional loss would be appropriate (5).

The exact role of radiation therapy in the management of aggressive fibromatosis remains to be defined (3). The initial local control rate in our series with surgery alone was 62.2%, which improved to 82.1% with the addition of radiation therapy. The difference was statistically significant ($p = 0.014$). These figures are consistent with data reported elsewhere; Spear et al (6), reported 93% control for the combined modality group. McKinnon et al (8), proposed that addition of radiation therapy appeared to abrogate much of the margin dependence. Only one author reported no response with radiation therapy (5). The last major factor that we examined was the effect of previous recurrence on the final outcome of patients. Our control rates for primary and recurrent lesions were 75.6% and 46.8% respectively which again was attributed to margin status. Nuyttens et al (13) in their review demonstrated better local control for patients with fewer than two operations but failed to maintain this difference when margin status was excluded. The median time to recurrence in our series was relatively short (25.4 months) compared to 54 months in most series (9).

Several issues remain to be investigated including management of recurrences following maximum surgery and radiation therapy and other alternative treatment modalities particularly in the pediatric age group where treatment toxicity would be a major issue. We had a very small number in that age category (six patients) which does not permit conclusions. Current trials are addressing the use of chemotherapeutic agents, non-steroidal anti-inflammatory agents and the estrogen receptor modulators (Tamoxifen) (19).

The analysis of our data and comparison with the others reported, provide certain guidelines for treatment of

this category of lesions. Initial surgical resection is detrimental for patient's outcome. Margin is the single most important predictor of relapse. Wide surgical resection short of major functional loss or cosmetic deformity should be

attempted. For bulky disease, inadequate margin, and for recurrent cases, addition of radiation therapy will significantly improve the local control rates.

Table (1): Demographic and tumor characteristics stratified by group.

	Surgery	Combined Modality
Number	98	39
Mean age (years)	27.4	24.3
Gender (male:female)	1:1.6	1:1.7
Site		
Head and Neck	6	7
Thorax	7	4
Upper Extremity	27	5
Lower extremity	42	6
Abdominal wall	13	12
Intra-abdominal	3	5
Presentation status		
Primary	67	23
Recurrent	31	16
Margin status		
Positive	14	34
Close (0.5 cm)	22	5
Negative	62	0

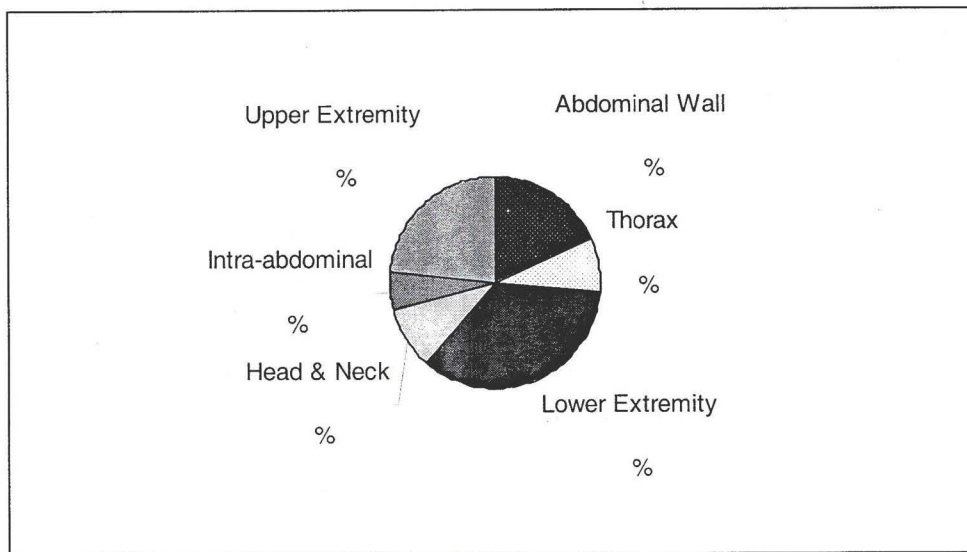


Fig. (1): Distribution of tumor sites among the whole group

Table (2): Local failure per treatment modality, margin status, and presentation status.

	SURGERY	SURGERY + RTH	P-VALUE
Total number	37/98 (37.8%)	7/39 (17.9%)	P=0.014
Margin Status			
Positive margin	7/14 (50%)	5/34 (14.7%)	P=0.01
Close margin	9/22 (40.9%)	2/5 (40%)	P=0.02
Negative margin	15/62 (22.4%)	0*	
Presentation status			
Primary	21/67 (31.3%)	1/23 (4.3%)	P=0.005
Recurrent	16/31 (51.6%)	6/16 (37.5%)	P=0.16**

*None of the patients with negative margins received adjuvant radiation therapy

**Statistically insignificant

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