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Preoperative Radiotherapy is Effective in the Treatment of Fibromatosis

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The use of preoperative radiation is well-established for soft tissue sarcoma, but its use in fibromatosis is not well-characterized. The purpose of this study was to examine the impact of preoperative radiotherapy on the local control of fibromatosis and to assess treatment-related morbidity in this setting. In particular we assessed complication rates in comparison with soft tissue sarcoma treatment. All patients with fibromatosis referred to this unit who received preoperative radiotherapy (50 Gy in 25 fractions) from 1988 to 2000 and who had at least 2 years of followup were included in this study. The rate of recurrence in this group was ascertained. Similarly constructed datasets from all patients with soft tissue sarcomas of the extremities who received preoperative radiation from 1986 to 1997 also were analyzed. The rates of complications in the two groups were compared. Fifty-eight patients were treated with preoperative radiation for fibromatosis and the median followup was 69 months. There were 11 local recurrences (19%). Major wound complications manifested in two patients (3.4%). Wound-related complications arose in 89 of 265 patients with soft tissue sarcomas (33.5%). There was a significant difference in the rate of major wound complications observed in the two groups. The use of radiotherapy before surgery is effective in the combined treatment of fibromatosis.

Fibromatosis is a histologic benign soft tissue tumor arising from mesenchymal tissues, which affects approximately 750 people in North America annually.[1] Despite the benign histologic appearance, it can act in extremely aggressive fashion at the local site.[7,8] Historically, recurrence rates of 50% to 70% with surgical treatment alone fostered the use of radiotherapy in an attempt to decrease the rate of recurrence.[9,20] Contemporary recurrence rates of 15% to 25% are expected after combined radiotherapy and surgery.[3,4,9,11–13] The available evidence suggests that radiotherapy plays a valuable role in large, deep, recurrent lesions or in those that involve critical structures.[3,4,9,11,12,16,22]

It was reported previously that preoperative versus postoperative radiation in the treatment of patients with soft tissue sarcomas of the extremity provided equivalent high local control (93%) in both groups.[18] Although short-term wound complications arose less frequently in the patients who received postoperative radiation, prospectively determined long-term functional status was better in the patients who received preoperative radiation. Multivariate analysis strongly

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indicated that the difference in late morbidity assessment was strongly associated with smaller radiation fields and lower radiation dose in the preoperative radiation group[18] confirming previous single institution nonrandomized data in cohorts treated with radiation doses of 60 Gy or greater.

Radiotherapy in the treatment of fibromatosis has been limited to postoperative or radiation alone except in a few isolated cases.[3,17] Because of the experience with preoperative radiotherapy with soft tissue sarcoma, preoperative radiation now is used in the treatment of fibromatosis in our center. Specifically, it is used in most patients with deep or recurrent lesions and in patients in whom the lesion develops adjacent to critical structures such as nerves or blood vessels. In large part the decision to use preoperative radiation was governed by our reported results of patients with fibromatosis who received postoperative radiotherapy who had disappointing functional outcomes.[6] In the current protocol, when it was apparent after multidisciplinary assessment that combined treatment with surgery and radiotherapy would be required to successfully treat the patient, preoperative radiotherapy generally was prescribed because the smaller radiotherapy fields possible with preoperative treatment might decrease normal tissue morbidity.

This study is the first to report the use of preoperative radiation in the treatment of patients with fibromatosis. We hypothesized that the use of preoperative radiation would have a local recurrence risk equal to the rate of recurrence seen with postoperative radiation. Furthermore, we hypothesized that preoperative radiation in patients with fibromatosis would be associated with a lower risk of wound complications than observed in patients with soft tissue sarcomas.

MATERIALS AND METHODS

From 1988 to 2000, all patients with histologically confirmed fibromatosis who received preoperative radiation at our unit were identified and prospectively entered into a data bank. We excluded patients who had head and neck, intraabdominal, or intrathoracic disease. Preoperative radiation with a total dose of 50 Gy was given over 25 fractions. The radiotherapy technique followed the principles that were described previously for preoperative radiotherapy of soft tissue sarcoma.[18,19] Approximately 4 weeks after the completion of radiotherapy, patients had definitive excision of the tumor in an attempt to achieve negative resection margins.

All patients were followed up prospectively for a minimum of 2 years. Patient demographics, tumor characteristics, treatment, and outcome data were stored in the prospective database.

Recurrence was determined by clinical examination, MRI, or CT scanning and was defined as absence of tumor growth. Wound complications were characterized using the same criteria developed in a prospective randomized trial of preoperative versus postoperative radiotherapy in soft tissue sarcoma.[19]

From 1986 to 1997, all patients with a soft tissue sarcoma of the extremity who had received preoperative radiation were identified. Tumor characteristics and complication data were analyzed. A comparison between the patients with soft tissue sarcomas and the patients with fibromatosis then was done to determine differences in complication rates between the two groups.

RESULTS

Fifty-eight patients (35 females, 23 males) were identified as receiving preoperative radiation in the fibromatosis group with an average age of 40.7 years (range, 16–74 years). Patients were followed up for a median of 69 months (range, 26–157 months). One patient died of unrelated causes 24 months postoperatively.

All fibromatosis lesions were deep to the fascia and had an average size of 8.6 cm. The upper extremity accounted for 51% of lesions, the lower extremity accounted for 37% of lesions, and the trunk accounted for 12% of lesions (Table 1). Thirty-three patients presented with primary tumors without prior surgery, seven

TABLE 1. Anatolmic Site of Presentation of Fibromatosis Lesions

Site of Lesion	Number of Lesions
Wrist or hand	2
Elbow	7
Shoulder	21
Pelvis	3
Hip	5
Knee	8
Ankle or foot	6
Trunk	6

patients had incomplete excision before referral, and 18 patients had recurrent disease at presentation to our unit.

At surgery, microscopically negative resection margins were achieved in 21 patients (36.2%), microscopically positive margins were achieved in 28 patients (48.3%), and grossly positive margins were achieved in nine patients (15.5%). The grossly positive margins all occurred in the shoulder, knee, and hip regions.

There were 11 local recurrences (19%) after the initial surgery (Table 2). The mean time to recurrence was 24 months. In univariate analysis, none of the tested variables (margin status, gender, anatomic site, and a history of prior surgery) were associated with the risk of recurrence.

Four patients who had local recurrence after protocol treatment had additional salvage surgery. One patient had an above-knee amputation at another institution, one patient had a reexcision with an additional course of preoperative radiotherapy, and one patient had a reexcision without adjunctive treatment. All three of these patients are alive with no additional evidence of disease. The other patient had two subsequent operations and is alive with stable disease. Eight patients did not have additional surgery and all are alive with disease. Four of these patients had medical therapy (methotrexate, antiinflammatory medications, or tamoxifen) and have stable disease at followup.

Complications arose in nine patients with fibromatosis. Two patients had complications unrelated to radiation; one patient had acute perioperative anterior interosseous nerve palsy (with later resolution) and a second patient had a pulmonary embolus. Seven patients had radiation-related complications. One patient had a fibrosarcoma develop in the radiated field 5 years after protocol treatment. One patient sustained an insufficiency fracture of the femur and subsequent bending of a femoral nail. Wound-related complications arose in five patients. Minor wound complications requiring no treatment occurred in three patients (one in the upper extremity and two in the lower extremity) whereas two (3.4%) patients had deep wound complications develop in the lower extremity necessitating additional surgical treatment.

There were 265 patients who received preoperative radiation for soft tissue sarcoma (117

TABLE 2. Summary Table of Local Recurrence Data

Patient	Gender	Margin	Site	Previous Surgery
1	Male	Gross +	Hip	No
2	Female	Negative	Knee	No
3	Male	Negative	Wrist	Yes
4	Female	Microscopic +	Shoulder	Yes
5	Female	Microscopic +	Shoulder	Yes
6	Female	Microscopic +	Hip	Yes
7	Female	Microscopic +	Shoulder	No
8	Female	Microscopic +	Shoulder	No
9	Male	Microscopic +	Ankle	Yes
10	Female	Negative	Shoulder	Yes
11	Male	Microscopic +	Knee	No

females and 148 males). The lower extremity accounted for 197 sarcomas (74.3%) and the upper extremity accounted for 68 sarcomas (26%). The median size of the tumors was 8.9 cm. There were 232 deep lesions and 33 superficial lesions. The difference in lesion depth was significantly different between the patients with fibromatosis and the patients with soft tissue sarcoma ($p < 0.05$; chi square) although lesion size was not different.

Major wound complications requiring additional treatment developed in 89 patients (33.5%). Seventy-eight (87.6%) of the 89 wound-related problems occurred in the lower extremity and 11 occurred in the upper extremity (12.4%). Patients with soft tissue sarcoma in the lower extremity were significantly more likely to have a wound-related complication than patients with fibromatosis of the lower extremity ($p < 0.001$). The proportion of patients having wound complications and the proportion of patients with tumors of the lower extremity who had wound complications were significantly higher in patients with soft tissue sarcoma than in patients with fibromatosis ($p < 0.0001$, $p < 0.005$; chi square).

DISCUSSION

This is the first investigation of the effect of preoperative radiation in the treatment of patients with fibromatosis. The use of postoperative radiation in the treatment of fibromatosis lesions that are deep, locally recurrent, or adjacent to critical structures is well-established. Recurrence rates less than 20% to 25% can be expected with the combined use of radiation and surgery.[3,4,9,11,12,21,23] In fact, Jelinek et al[11] suggested that radiation is the most important factor in reducing local recurrence.

We report a recurrence rate of 19%, suggesting that preoperative treatment is as effective as postoperative therapy. Although numerous risk factors for recurrence have been identified historically,[6,9,10,15,23] we could not identify any factors that affected outcome in the current series. In the eight patients who had recurrence and did not receive additional surgical treatment, four received medical therapy in the form of methotrexate, tamoxifen, or antiinflammatory medication. As reported previously, medical treatment may result in stable disease in some patients with recurrent or unresectable lesions.[5,25]

Some studies indicated that radiation therapy poses an unnecessary risk for patients with benign diseases.[16,21] Certainly wound-related complications, fracture risk, long-term stiffness, edema, and functional loss have been problematic in patients receiving postoperative radiotherapy.[6,18,19] These patients are subjected to radiation doses of as much as 66 Gy, which Ballo et al[3] have shown to be a definite risk factor for having radiation-induced sequelae. Furthermore, it has been shown that as many as 46% of patients receiving postoperative radiation for fibromatosis had long-term functional deficits.[6]

O'Sullivan and Davis[18] reported that the lower dose of radiation (50 Gy) given to patients receiving preoperative radiation for soft tissue sarcoma was shown to have fewer long-term functional complications but a higher incidence of early wound problems when compared with a postoperative group of patients who received 66 Gy of postoperative radiation.

The second hypothesis of this study was that patients treated with preoperative radiation for fibromatosis would have a lower risk of wound complications than patients receiving the same treatment for soft tissue sarcoma. The results of this study indicate that wound complications arose less frequently in patients with fibromatosis as compared with patients with soft tissue sarcoma overall and for patients with lower extremity lesions. This observation is even more notable because patients with fibromatosis had a greater percentage of deep lesions and each group had identical radiation and surgical treatment goals. This suggests that patients with fibromatosis may have an inherent wound healing advantage over patients with soft tissue sarcoma. Therefore, biologic differences may exist between the groups that have not been explored previously. For example, beta-catenin (a molecular substrate involved in cellular proliferation and differentiation) levels are higher in

fibromatosis lesions than in any other tumor type.[24] It also has been shown that beta-catenin is a potent regulator of the wingless (WnT) molecular signaling pathway that is involved in wound healing.[2,14] One hypothesis that would explain the differences in wound complications seen in this study is that patients with fibromatosis have regionally elevated beta-catenin levels at the local tumor site and that this confers a wound healing advantage after radiation in patients with fibromatosis.

Two treatment-related complications of concern in patients in our study are the development of an insufficiency fracture of the femur and the development of a radiation-induced fibrosarcoma in the radiation field. These are recognized complications of radiotherapy. Nevertheless, before initiating combined radiation and surgical treatment for readily resected lesions, consideration should be given to surgical treatment aloneand reserving radiotherapy for lesions that are difficult to resect completely, recurrent lesions, and those that initially present along critical structures.

Fibromatosis is an aggressive disease at the local site of origin. Combined treatment with preoperative radiation and surgery is effective therapy that can reliably prevent recurrence in 80% of patients. In this study, radiation-related wound complications were less prevalent in patients with fibromatosis compared with patients treated for soft tissue sarcoma suggesting a possible healing advantage. Because radiation poses a risk for the development of malignancy its use in patients with fibrolmatosis should be reserved for deep lesions that are difficult to completely resect, those that involve critical structures, or in recurrent lesions where surgery alone would result in major functional disability.

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