

Surgery versus Radiation Therapy for Patients with Aggressive Fibromatosis or Desmoid Tumors

A Comparative Review of 22 Articles

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BACKGROUND. Desmoid tumors (aggressive fibromatoses) are benign neoplasms with high rates of recurrence after surgery. Radiotherapy is sometimes reported to prevent recurrences, but not in all studies. In order to evaluate the effect of radiation, comparative analysis was performed.

METHODS. The authors conducted a MEDLINE search and collected all articles in the English language on the treatment of "desmoid tumor" or "aggressive fibromatosis" from the years 1983–1998. They categorized treatment into three groups: surgery alone (S), surgery with radiotherapy (S + RT), or radiotherapy alone (RT). The S and S + RT groups were each subdivided according to whether margins were free (–), positive (+), or unknown. Each subgroup was divided into cases with primary, recurrent, or unknown tumor.

RESULTS. The local control rates after treatment for cases in the S group with (–) margins, (+) margins, and overall were 72%, 41%, and 61%, respectively. For the S + RT group the local control results were 94%, 75%, and 75%, respectively, significantly different when compared with the results for the S group. For the RT group, the local control was 78%, significantly superior to that of the S group (61%). Cases with primary and recurrent tumors had significantly superior local control rates with S + RT or RT versus S. Radiotherapy complications noted were fibrosis, paresthesias, edema, and fracture.

CONCLUSIONS. RT or S + RT results in significantly better local control than S. Even after dividing the groups into cases with free and positive margins and cases with primary and recurrent tumors, the best local control is achieved with RT or S + RT. *Cancer* 2000;88:1517–23. © 2000 American Cancer Society.

KEYWORDS: desmoid tumor, aggressive fibromatosis, surgery, radiotherapy, complications.

Aggressive fibromatosis is a benign neoplasm that arises from fascial and musculoaponeurotic tissues. These tumors lack a capsule, infiltrate along fascial planes, and invade adjacent neurovascular structures.¹ Local recurrences may occur even after a wide resection. Some resections may be mutilating. Disfigurement may be avoided in some instances by radiotherapy, either alone or after conservative surgery, without compromise in local control. Radiotherapy has a relapse rate of 31% for unresectable tumors.² There seems to be evidence that radiotherapy is helpful in the management of aggressive fibromatosis, although the role and precise indication for this modality has not been defined clearly. In an attempt to put the multimodal management of the desmoid tumor in some perspective, a comparative review of 22 articles regarding the roles of surgical and radiotherapy for aggressive fibromatosis was performed.

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TABLE 1
Reasons for Exclusion of Articles from This Study

Author	Reason of exclusion
Assad ²⁷	Had an update in 1991
Atahan ²⁸	Four case reports of desmoid tumors in children
Goy ²⁹	Comparison between radiotherapy and observation Some patients with resection could have been the same as in a previous article
Khorsand ³⁰	Had an update in 1993
Kiel ³¹	Had an update in 1998
Lopez ³²	Two desmofibrosarcoma protuberans tumors were included, but no distinction in results between this tumor and desmoid tumor
McCullough ³³	Had an update in 1996
Mirabell ³⁴	Had an update in 1998
Posner ³⁵	Had an update in 1991
Reitamo ⁴	Review article without individual patient results
Rock ⁵	Patients from 1908–1980 were included
Sherman ³⁶	Had an update in 1998
Suit ³⁷	Review article without individual patient results

MATERIALS AND METHODS

A MEDLINE search obtained all articles in the English language on the treatment of desmoid tumors or aggressive fibromatosis from the years 1983–1998. The search was done first for treatment with surgery, as follows: (desmoid[All Fields] OR aggressive fibromatosis[All Fields]) AND surgery[All Fields] AND English[Language] NOT pediatric[All Fields] NOT case report[All Fields] NOT (soft[Title Word] AND tissue[Title Word]) NOT polyposis[Title Word]. The same words were used for radiotherapy, substituting the word “surgery” with “radiotherapy.” From this list, we excluded all the articles with “children,” “Gardner syndrome,” or “familial polyposis coli” as subjects, because pediatric patients have a high recurrence rate and often are treated with chemotherapy,³ and because desmoid tumors in Gardner syndrome can be considered a different category due to the genetic linkage. The articles with desmoid tumors isolated to one anatomic region, such as “abdominal” or “head and neck,” were excluded because certain anatomic regions have been described as having a higher or lower recurrence rate.^{4,5} Thirty-four articles,^{2,4–37} including all anatomic sites, were found, but only 22 articles^{2,6–26} were used. The reasons for exclusion are shown in Table 1. Twenty-two articles, in which a total of 780 desmoid tumors were discussed, were reviewed for this study. Any patient treated with hormonal therapy or chemotherapy was excluded.

The remaining patients were categorized by treatment: 1) surgery alone (S), 2) surgery with radiotherapy (S + RT), or 3) radiotherapy alone (RT). The S and S + RT groups were divided into three subgroups based on margins: 1) free, 2) positive, or 3) unknown. The group with positive margins was subdivided into undetermined, marginal, microscopic, and macro-

scopic margins. The following were considered resections with positive margins: “unclear” or “close” margins, “inadequate” margins, “probably adequate” margins, “marginal” or “intralesional” resection, minimal surgical resection, and subtotal or incomplete resection. All patients treated with RT had macroscopic disease. Every group or subgroup was divided according to treatment as primary, recurrent tumor, or unknown tumor status.

The mean or median follow-up ranged between 2 and 10.4 years. In two articles^{9,10} the follow-up period was not reported, but there was a high recurrence rate within the first 2 years after resection. The number of patients evaluated per study and the follow-up is shown in Table 2.

Statistical Methods

Chi-square statistics were used to assess the significance of differences between rates and proportions. In all cases there was a single degree of freedom, and *P* values were computed without respect to the directionality of any differences. Moreover, because the *P* values were not altered with the Bonferroni method, they were considered marginally significant if $0.01 < P < 0.05$. Most of the detected differences met a more stringent value of $P < 0.01$.

It is recognized that chi-square analyses performed on data collected within a particular study are appropriate for independent observations. Correspondingly, meta-analyses employing chi-square statistics are appropriate when the data collected across studies are independent, and when conditions under which the many studies are conducted are reasonably comparable. Although we are not claiming perfection here, we did eliminate about a dozen studies that may have compromised one of the above guidelines.

TABLE 2
Number of Patients Included Per Article and Per Treatment and Associated Mean and Median Follow-Up in Years

Author	Surgery alone	Surgery + RT	RT alone	Dose range (Gy)	Median follow-up	Mean follow-up
Acker ⁶	16	0	16	49.6–56.2		4.5
Ballo ²	0	52	23	46–75	7.5	10.4
Bataini ⁷	8	8	9	45–65		6.3
Catton ⁸	4	26	8	36–60	7.1	
Easter ⁹	9	2	1	55–74.8		
Gansar ¹⁰	15	0	0	/		
Goy ¹¹	45	11	0	49.6–70	6	
Higaki ¹²	39	1	0	/		10
Kamath ¹³	0	45	8	35–70	5	
Karakousis ¹⁴	16	10	0	32–64 ^a	6.7	7
Keus ¹⁵	0	19	2	60	5	
Kofoed ¹⁶	15	0	0	/		4.6
Leibel ¹⁷	0	6	13	40.8–61.2	8	
Markhede ¹⁸	42	3	0	30–40	5	
McKinnon ¹⁹	29	4	0	50–60	2	3.4
Plukker ²⁰	32	5	1	50–60	6	
Pritchard ²¹	34	10	2	/		4
Schmidt ²²	0	16	4	30–102 ^b	10	
Shpitz ²³	8	0	0	/		7.5
Spear ²⁴	41	41	15	10–72	5	
Taylor ²⁵	28	0	0	/		7.6
Zelevsky ²⁶	0	38	0	20–60.5 ^b	5.5	
Total	381	297	102	/	6.0	7.3

RT: radiotherapy.

^aOne patient received intra-operative radiotherapy with a dose of 10 Gy.^bSome patients received brachytherapy.**TABLE 3**
Local Control for Free Margins, Positive Margins, or Unknown Margins Treated with Surgery Alone, Surgery with Radiotherapy, or Radiotherapy Alone

	Surgery alone		Surgery + RT			RT alone ^a		
	No.	%	No.	%	<i>P</i> value ^b	No.	%	<i>P</i> value
Free margins	171/237	72	33/35	94	0.0048			
Positive margins	50/121	41	174/232	75	4×10^{-10}	80/102	78	NA
Unknown margins	13/23	56	14/26	54	NA			
Total	234/381	61	223/297	75	0.0002	80/102	78	0.023

RT: radiotherapy; No.: number of patients with local control, NA: not available.

^aAll patients treated with radiotherapy alone had macroscopic disease.^b*P* value in comparison with surgery alone.

RESULTS

Treatment Results

The local control rates with S, S + RT, and RT were 61%, 75%, and 78%, respectively. The local control after RT or S + RT was significantly superior to that after S. The influences of margins are shown in Table 3. For patients treated by S and stratified by free or positive margins, salvage rates of 72% and 41%, respectively, were observed. When RT was added to S, the local control increased to 94% and 75% for the free and positive margin

cohorts, respectively. After S with positive margins, the addition of RT significantly improved local control compared with S alone (75% vs. 41%).

When positive margins were subdivided into marginal, microscopic, and macroscopic, the local control after S was 45%, 41%, and 33% but with S + RT, the rates improved to 89%, 79%, and 69%, respectively. The comparison between S and S + RT was significantly different for the 3 subgroups (0.0025, 5×10^{-8} , and 0.038, respectively).

TABLE 4
Local Control after Treatment of Primary, Recurrent, and Unknown Tumor Status

Treatment	Surgery		Surgery + RT			RT alone			Treatment with RT ^a		
	No. ^b	%	No. ^b	%	<i>P</i> value ^c	No. ^b	%	<i>P</i> value ^c	No. ^b	%	<i>P</i> value ^c
Primary tumor	164/263	62	45/58	78	0.027	25/30	83	0.022	70/88	80	0.0031
Recurrence	29/62	47	80/101	79	2 × 10 ⁻⁵	19/26	73	0.238	99/127	78	2 × 10 ⁻⁵
Unknown status	41/56	73	98/138	71	NA	36/46	78	NA	134/184	73	NA

RT: radiotherapy; NA: not available.

^a The no. in column 4 is the sum of columns 2 and 3.

^b No. of patients with local control.

^c *P* value in comparison with surgery alone.

TABLE 5
Local Control after Treatment of Primary and Recurrent Tumors with Free or Positive Margins

		Surgery (%)	Surgery + RT (%)
Free margins	Primary tumor	126/180 (70)	4/4 (100)
	Recurrence	24/34 (71)	13/14 (93)
Positive margins	Primary tumor	38/33 (46)	46/59 (78) ^a
	Recurrence	5/28 (18)	62/82 (76) ^b

RT: radiotherapy.

^a *P* = 0.0001, in comparison with surgery.

^b *P* = 6 × 10⁻⁸, in comparison with surgery.

For a primary tumor treated with S, S + RT, or RT, local control was 62%, 78%, and 83%, respectively. After recurrence, local control was 47%, 79%, and 73% for S, S + RT, and RT, respectively (Table 4). These results for treatment of a primary tumor and recurrence with RT were significantly different when compared with S alone. Primary tumors and recurrent lesions treated with RT produced local control rates of 80% and 78%, respectively, compared with S, which resulted in local control of only 62% and 47%, respectively. These differences, which involved pooling radiotherapy groups, were highly significant.

The results after S for primary and recurrent tumor with free margins were 70% and 71%, respectively (Table 5). However, if the margins were positive, the local control rates diminished to 46% and 18%, respectively. This difference in the margin positive S group was highly significant (*P* = 0.008). With postoperative radiotherapy supplements, the local control rate for positive margins increased from 46% to 78% for primary and from 18% to 76% for recurrent tumors. This difference between S and S + RT groups was highly significant when the margins were positive. The trend for free margins was the same but did not attain statistical significance.

Tests stratified by treatment were performed to

TABLE 6
Locations and Frequency of Recurrences after Radiotherapy

Treatment	In-field	Marginal	Out-of-field
RT alone	10	1	1
Surgery + RT	16	10	7
Surgery + RT or RT alone	11	10	3
Total	37 (54%)	21 (30%)	11 (16%)

RT: radiotherapy.

compare free margins with positive margins for local control. Comparisons within the S group (*P* = 0.0001) and within the S + RT group (*P* = 0.010) showed significant differences.

Radiotherapy Failure

The failure rate after RT or S + RT was 23%, as reported in 11 articles (Table 6).^{6-8,13,14,17,20,21,24,26,36} Fifty-four percent of the failures occurred in-field. The marginal and out-of-field failure rates were 30% and 16%, respectively. Of the patients who experienced failure, the group treated with RT had an in-field failure rate of 83% for the S + RT group, this rate was 54%.

We also looked for a dose response. Forty-two in-field failures of 188 patients were documented in 10 articles,^{6,7,12,14,15,17,21,26,31,36} as seen in Table 7.

Complications after Treatment with Radiotherapy

Nine articles reported complications.^{6,7,11,13,17,20,22,26,34} Complications included edema, cellulitis, fibrosis, ulcers, paresis, pathologic fractures, and second malignancy (Table 8). Fibrosis was the most common complication, and causes sometimes limited motion.¹⁷ Paresis was often caused when the tumor was adherent to the nerve.²⁶ Cellulitis was predominantly seen in obese female patients.³³ When bones were included within the portals of radiotherapy, stripping of the periosteum could cause pathologic fracture.^{11,13} One

TABLE 7
Number of In-Field Recurrences According to Dose and Treatment

Treatment	< 50 Gy (%)	50–59 Gy (%)	> 60 Gy (%)
RT alone	3/5 (60) ^a	3/24 (13)	4/26 (15)
Surgery + RT	6/50 (12)	3/30 (10)	5/48 (10)
Total	9/55 (16)	5/54 (11)	9/74 (12)

RT: radiotherapy.

^a *P* = 0.038, in comparison with dose higher than 50 Gy.

osteosarcoma was reported after irradiation of a perimandibular tumor,²⁰ and 1 uterine sarcoma developed 9 years after radiotherapy in a patient with an abdominal desmoid tumor.³⁴

DISCUSSION

Desmoid tumors are rare. The incidence is 0.03% of all neoplasms³⁷ or 3% of the soft tissue tumors.^{20,25} For that reason, large or randomized series do not exist. Different modalities have been utilized, including surgical resection, radiotherapy, anti-inflammatory agents, hormonal therapy, and chemotherapy. Most reports of the latter are case reports with varying success,^{5,6,8,11,13,34,37–39} and systemic therapy was mostly used if there was a recurrence after surgery and/or radiotherapy. It is noteworthy that spontaneous regressions were reported,²⁴ even in a case of multicentric lesions.⁴⁰

This analysis shows that surgery alone is not adequate, but surgery supplemented with radiotherapy is a good option. Radiotherapy alone provided a local control rate of 78% among 102 patients. This was significantly better than surgery alone (381 patients). If anything, there was adverse selection for patients who received radiotherapy. Patients who received radiotherapy alone tended to have larger tumors; tumors adjacent to joints, nerves, or major vessels; or tumors not considered resectable. Posner et al.³⁵ reported that radiotherapy for gross residual disease following inadequate resection reduced the rate of local control. Spear et al.²⁴ found significantly better local control for patients with gross residual disease or with microscopic positive or negative margins after surgery if they were treated with radiotherapy afterwards. Ballo et al.² reported that the disease control for gross residual or unresectable disease was about 70%. On the other hand, one author reported no cure with radiotherapy.⁹ Before amputative or mutilating surgery that compromises cosmesis of function, radiotherapy alone or debulking surgery followed by radiotherapy provides a very reasonable alternative.

We gathered the reports of local failure after ra-

TABLE 8
Reported Types and Frequency of Complications

Complication	%	Comment
Fibrosis	9.0	Mostly mild but sometimes with limited motion
Paresthesias	3.0	Often associated with growth of tumor into a nerve
Edema	2.2	Mostly mild
Fracture	2.2	After stripping of periosteum or curettage
Skin ulcers	1.9	Sometimes required surgery to heal
Cellulitis	1.5	Only in obese patients
Miscellaneous	2.2	Disfigurement, surgical reconstruction, enteritis
Malignancy	0.7	Mandibular osteosarcoma, uterine adenocarcinoma
Total	22.8	

diotherapy and found that 46% of 69 failures happened at the margin or outside the radiation field. This suggests that field sizes must be sufficient (\approx 5 cm margin) and need to cover at least the total scar tissue. A dose response curve was only found in the group that received radiotherapy alone, with the result that doses higher than 50 Gray (Gy) had fewer failures. Most authors proposed a dose between 50 and 60 Gy.^{1,6,23,33,37,38,40} Ballo et al.² reported a significant difference in local control for doses < 50 Gy versus > 50 Gy. However, a complete response has been seen with a dose as low as 35 Gy,¹¹ and recurrences have been seen with doses higher than 60 Gy.^{21,31,36}

We looked at two prognostic factors: the margins after surgery and primary or recurrent tumors. Other prognostic factors are tumor size, site, age, and gender. Catton et al.⁸ indicated that tumor size greater than 8 cm was predictive of relapse. Other authors found that positive margins were negative prognostic factors.^{24,35} Reitamo et al.,⁴ however, described a low relapse rate for those with incomplete resections, compared with a 24% rate with complete resections. On the other hand, we found significantly better local control for free margins versus positive margins in the group that had surgery alone and the group that had surgery plus radiotherapy. Rock et al.⁵ described sites resistant to cure: calf, foot, supraclavicular fossa, popliteal fossa, and buttock. Ballo et al.² found no difference among sites. Suffice it to say that no site can be excluded from consideration for radiotherapy.

Local control was better for patients with fewer than two operations versus more than three operations.³⁶ Recurrence is a significant unfavorable risk factor.³⁵ Despite this, we found no significant difference in local control for primary versus recurrent tumors, except for the positive margins within patients treated with surgery alone. Others failed to note any significant difference.^{2,8,24,30} Some have observed a higher risk of failure for patients younger than 30 years,^{5,13,33} whereas other authors have not.^{2,20}

Complications of surgery are seldom reported. Operations include amputation or other procedures that compromise appearance and function. In contrast with the radiotherapy, complications often are reported. Only one article¹¹ makes a comparison between the two treatments. Goy et al.¹¹ reported that mild complications (edema, pain paresthesias, stiffness, and weakness) and moderate complications (reconstructive surgery) were more frequent in the radiotherapy group (20% vs. 36% and 7% vs. 9%, respectively). Severe complications, such as disability or amputation, were only present in the surgery group (4%). The complications reported in this article were often moderate, caused no major disability, and were sometimes required to avoid an amputation. Two malignancies were reported in the nine articles^{6,7,11,13,17,20,22,26,34} that described side effects. However, Rock et al.⁵ mentioned two other radiation-induced malignancies: a fibrosarcoma and a lymphoma.

It is important to note that surgical techniques were not clearly outlined in these articles and were not the subject of this analysis. It is plausible and likely that surgical technique may be very important to outcomes in cases like these. Nevertheless, the data in hand from the published literature suggests that radiotherapy adds to the efficacy surgery even when margins are evaluated as adequate.

CONCLUSIONS

Because outcomes are not improved with radical surgical procedures, and because radiotherapy improves control, this analysis provides evidence that more modest surgical procedures followed by radiotherapy or even radiotherapy alone may be preferable. The upcoming American College of Surgeon Oncology Group Phase III trial will test the efficacy of postoperative radiotherapy. This also should clarify the best treatment for these tumors.

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