# Recent Trends in the Management of Desmoid Tumors

## *Summary of 19 Cases and Review of the Literature*

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**Recent advances in the understanding of desmoid tumor biology affect therapeutic choices. This series of 19 patients and review of the literature outlines historic perspectives and discusses the options in the management of these locally aggressive tumors. Desmoid tumors tend to grow steadily, regardless of tumor location. However differences in the aggressive nature of these tumors are seen when age and sex distributions are scrutinized. Although recurrence rates are high, excisional therapy is the best first approach. An exception is the case in which tumor excision is either particularly dangerous or likely to result in significant physical handicap. Radiation or drug therapy are most often used with recurrent disease or as an alternative to mutilating surgery. Although many pharmacologic approaches have been advocated, (including antiestrogen therapy, cyclic-AMP, and prostaglandin inhibition), results are anecdotal at best.**

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DESMOID TUMORS ARE infrequent. The descriptive name borrows from the Greek word "desmos," meaning band, or tendonlike. The world's collective literature to date records less than two thousand cases. However, because many surgeons see a scant number of these tumors during a routine career, the majority of isolated cases must certainly go unreported.

This collection of 19 patients and literature review that summarize recent developments in the understanding of desmoid tumor biology were stimulated by a patient with an abdominal wall desmoid tumor.

### Materials and Methods

All hospital discharge and clinic records from January 1978 to January 1988 were reviewed on patients with the ICD.9 codes 238.1, 238.2, and 235.4 from the U.C.S.D. Medical Center and City of Hope National Medical Center (Duarte, CA). Pathology reports were verified to include only those patients with desmoid tumors (*i.e.*, aggressive fibromatosis). Desmoid tumors were categorized according to those found in the extremities or girdle muscles, in the abdominal wall, and in the mesentery. Cases were then tabulated with special reference to the episodes of desmoid tumors per patient (*i.e.*, recurrences), location of tumor, number of months until surgical procedure, type of surgical procedure, pathologic margins, adjunctive nonsurgical therapy, number of months until recurrence (if applicable), current disease status, and other medical conditions temporally related to the appearance or recurrence of these tumors.

### Results

Table 1 summarizes our patient population. There were six male and 13 female patients. Twelve patients had extra-abdominal tumors, five had abdominal-wall tumors, and two had mesenteric desmoids. All but one of the male patients (with an abdominal-wall tumor) were in the extra-abdominal group. The mean age of the patients was 31.3 years (range, 5 to 59 years). The average age was 26.2 years for those with extra-abdominal desmoid tumors, 30.4 years for those with abdominal-wall tumors, and 36 and 59 years for the two patients with mesenteric tumors.

There were 42 surgical procedures performed on the 19 patients, six of which were limited to diagnostic incisional biopsies. The remaining procedures were attempts at surgical cures. All of the 19 patients are now alive. Six patients have recurrent disease, 12 are disease free at a follow-up of more than 6 months (probable cures), and one patient shows no evidence of recurrent disease at 1-month follow-up.

Five patients received radiation therapy in an effort to control recurrent extra-abdominal disease. None of these patients had control of their tumors after radiation therapy

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TABLE 1.

| Patient No./Sex | Location | Months Until Excision | Type of Surgery | Margins | Additional RX | Months Until Recurrence | Current Status | Other Conditions |
|---|---|---|---|---|---|---|---|---|
| 30F | Infrascapular | 49 | Excisional biopsy | Positive | Tamoxifen | 2 | | |
| | | 2 | Chest wall resection | Positive | | 50+ | No evidence of disease | Childbirth (9/87) |
| 30M | Finger | 4 | Excisional biopsy | Unclear | | 0 | | |
| | | 17 | Ray amputation | Negative | | 3+ | No evidence of disease | |
| 24F | Upper arm | 12 | Excisional biopsy | Positive | | 6 | | Pregnancy |
| | | 7 | Wide excision | Negative | | 6 | | |
| | | 6 | Shoulder disartic | Negative | | 31+ | No evidence of disease | |
| 49M | Chest wall | 1 | Chest wall resection | Unclear | Potaba ×5 years | 8 | | Gout, diabetes |
| | | 45 | Extended excision | Positive | (Same) | 1 | | |
| | | 115 | Chest wall resection | Negative | | 42+ | No evidence of disease | |
| 20F | Sternum | 3 | Excisional biopsy | Unclear | | 12 | | |
| | | 0 | Excision | Unclear | | 24 | | |
| | | 2 | Excision | Positive | XRT ("maximum") | 9 | | |
| | | 13 | Excision with flap | Positive | Flap coverage | 0 | | |
| | | 12 | Clavicle excision | Positive | | 0 | | |
| | | 38 | (re-excision planned) | — | | — | Alive with disease (>96 mo.) | |
| 20F | Calf | 0 | Biopsy | Positive | XRT (6600 cGy) | 0 | | |
| | | 54 | Excisional biopsy | Positive | Tamoxifen | 56 | Alive with disease (>7 mo.) | Pregnancy |
| 13F | Foot | 60 | Excisional biopsy | Positive | | 35 | | |
| | | 1 | Wide excision | Positive | | 1 | | |
| | | 10 | Wide excision | Negative | Scar revision | 82+ | No evidence of disease | |
| 5M | Neck/ mediastinum | 3 | Biopsy, tracheostomy | Positive | | 0 | | |
| | | 1 | Partial resection | Positive | Chemotherapy | 87 | Alive with disease (>12 mo.) | Sepsis |
| 37F | Subscapular | 0 | Biopsy | Positive | | 0 | | |
| | | 1 | Neck disection | Positive | XRT (7480 cGy) | 36 | | |
| | | 12 | Chest wall resection | Negative | | 16+ | No evidence of disease | |
| 17M | Upper arm | 36 | Biopsy ×2 | Positive | | 0 | | |
| | | 1 | Excisional biopsy | Positive | XRT (5500 cGy) | 0 | Alive with disease (>6 mo.) | |
| 14F | Hand | 1 | Excisional biopsy | Unclear | | 24 | | |
| | | 1 | Excision | Unclear | | 36 | | |
| | | 1 | Ray amputation | Positive | Scar revision | 2 | Alive with disease (>6 mo.) | |
| 55M | Scalp | 2 | Excisional biopsy | Unclear | | 7 | | |
| | | 1 | Excision | Positive | XRT (6000 cGy) | 27+ | No evidence of disease | |
| 33F | Rectus abdominis | 6 | Excision, mesh repair | Negative | | 7+ | No evidence of disease | Postpartum |
| 23F | Abdomen-RLQ | 17 | Excisional biopsy | Positive | | 46+ | No evidence of disease | |
| 33F | Abdomen-RLQ | 8 | Excisional biopsy | Unclear | | 25+ | No evidence of disease | |
| 31F | Abdomen-RLQ | 2 | Excisional biopsy | Positive | | 6+ | No evidence of disease | Appy scar site |
| 32M | Abdomen | 1 | Wide excision | Positive | Chemotherapy | 24+ | No evidence of disease | Germ-cell CA |
| 59F | Mesenteric | 30 | Biopsy | Positive | | 0 | | Rectal polyps |
| | | 19 | Radical excision | Negative | | 44 | No evidence of disease | |
| 36F | Mesenteric | 180 | Biopsy | Positive | Clinoril, tamoxifen Colectomy, TAHBSO | 0 | Alive with disease (>75 mo.) | Gardner's Syndrome |

Series of 19 patients. The data include the number of "tumor-burden" months before surgical procedure, the type of surgery performed, status of surgical margins, adjunctive therapy, the months until recurrence (or "disease-free" periods), current status of disease, and other medical conditions present.

alone. Of these five patients, three are alive with their disease and two are disease free 16 and 27 months after subsequent resectional therapy.

Two patients had chemotherapy, with no apparent effect on their tumor status. (A third patient with an abdominal-wall tumor had chemotherapy, but for an un-

related condition). Three patients had trials of the antiestrogen tamoxifen, with no apparent effect on their disease states. Only one patient had a trial of a nonsteroidal anti-inflammatory drug (Clinoril, Merck, Sharp, & Dohme, West Point, PA). She is now alive more than 6 years after total abdominal colectomy for polyposis coli (with Gardner's syndrome) and has confirmed residual mesenteric desmoid tumor.

Of the patients with no current evidence of disease, most have had a substantial period of tumor burden. In these 13 patients, who together had a cumulative disease time of 530 months, the average time from first symptoms until curative therapy was 40.8 months.

There were 20 episodes of tumor recurrence, all but one with positive surgical margins. (This represents the final pathologic reading, and not necessarily frozen section margins). Of the 12 patients without clinical evidence of tumor recurrence, five had positive tissue margins and seven had clear margins. These figures give an accuracy in predicting recurrence according to surgical margins of 81%, a sensitivity of 95%, and a specificity of only 58%. The positive predictive value of surgical margins was 79%, and the negative predictive value was 88%.

## Discussion

John MacFarlane, in a 1832 compendium of cases from the Glasgow Royal Infirmary, described a mass that later came to be recognized as the first recorded case of a desmoid tumor.[1] Common usage of the descriptive term "desmoid" followed the naming of these tumors in 1838 by J. Muller.[2] The association of intra-abdominal desmoid tumors with familial *polyposis coli* was made in 1923 by Nichols,[3] and later reinforced in a series by McAdam and Goligher in 1970.[4] Radiation therapy for the control of desmoid tumors was first advocated by Ewing in 1928.[5]

Desmoid tumors comprise approximately 0.03% of all solid tumors, and 3.6% of the fibrous-tissue neoplasms. The annual incidence of these tumors is only 2 to 5 per million persons.[6] Reitamo has outlined four age distribution peaks in his series of 89 Finnish patients, with markedly different tumor characteristics found within each group.[6] In the juvenile peak (4.5 ± 3.5 years), girls outnumbered boys by 3:1, and extra-abdominal tumors predominate. In the fertile group (27 ± 4 years), abdominal-wall tumors were 11 times more frequent than the other types of desmoids, with the female:male ratio of 1.8:1. The middle-aged group (44 ± 7 years) also had predominantly abdominal-wall tumors (2.6 times higher incidence than other types), and no sex predominance. Finally in the old-age group (68 ± 4 years), no one tumor type or sex predominated.

The symptoms associated with desmoid tumors are few. Nearly all patients present to their physician with a mass. Pain is less frequent (~33%), and occurs primarily when tumors encroach joint or muscle mobility.[7,8] Bowel obstruction is seen with mesenteric desmoid tumors, but is separate and distinct from retroperitoneal fibrosis. That these tumors are found in association with Gardner's syndrome, a variant of familial polyposis coli, raises the issue of a genetic abnormality in collagen turnover regulation.[6] Alternatively a separate gene defect predisposing to desmoid tumors may be juxtaposed to the abnormality that transmits familial polyposis syndromes.

Desmoid tumors are located within the abdomen or trunk musculature in approximately 50% of cases, in the extremities in approximately 40% (usually referred to as extra-abdominal), and are mesenteric in less than 10% of patients.[6] They are commonly found in areas of previous traumatic or surgical scarring, and have been found in such obscure locations as the sphenoid bone[9] and surrounding CSF shunt tubing.[10]

Pathologically these tumors show a characteristic mass of interwoven spindle cells in bundles. There are varying amounts of collagen found within their matrix, with occasional sarcolemmic giant cells. Not infrequently the centers of the larger tumors are acellular. This whole constellation of findings resembles a low-grade fibrosarcoma. Importantly, however, only normal mitoses are found within the tumor. This partly accounts, at least in theory, for the poor response of these tumors to modes of therapy relying on cell-cycle kinetics.

The differential diagnosis of these tumors includes mainly other soft-tissue neoplasms (fibrosarcoma, liposarcoma, lipoma, and so on). However hernias, especially Spiegelian or incisional, as well as rectus sheath hematomas, can conceivably give a confusing picture. Intra-abdominal/mesenteric desmoids may be confused with lymphomas and retroperitoneal fibrosis.

### *Tumor Biology*

Desmoid tumors are characterized by their propensity for slow, incessant growth and invasion of contiguous structures. Morbidity, while rarely associated with these tumors, occurs when there is encroachment on vital structures (*e.g.*, bowel obstruction by mesenteric desmoids, or invasion into the trachea or major blood vessels). Although locally aggressive, these tumors do not metastasize.

Many observers have noted that desmoid tumors show varying rates of growth. Whereas the growth rate of desmoids seems to be independent of the site of the tumor, the sex and the hormonal status of involved women affect the rate of growth.[6] Many have noted fast-growing tumors that are associated with pregnancy and tumor growth rates that seem to be lower in postmenopausal women. Desmoid tumors in male subjects average a growth rate of

approximately 7.4 cm per year.[6] In the four age groups identified by Reitamo et al.[6] (mean ages, 4.5, 27, 44, and 68 years), the growth rates of tumors in women were 4.3, 19, 33, and 13 cm per year, respectively. The high rate of growth in hormonally active women underscores the suggestion that these tumors may be estrogen responsive.

Estrogen-receptor assays can be difficult to interpret because most tissues and tumors nonspecifically bind estrogen. However in a variety of studies 25% to 67% of desmoid tumors have been shown to bind estrogens in the same range seen in other estrogen-target organs ($K_d$ = 0.44 − 3.97). Moreover, in one study, 79% of tumors bound antiestrogens (tamoxifen), whereas only 36% were estrogen-receptor positive.[11]

### *Control of Disease*

Most authors believe that the best hope for the primary cure of this disease rests in total excision of the tumor. Unfortunately even when surgical margins are clear of tumor, recurrence rates are high. Table 2 compiles data from five recent studies that have reported substantial numbers of patients.[6,12–15] The overall recurrence rate with surgical excision alone was 40%. This recurrence rate is highest with mesenteric desmoids, presumably due to their necessarily limited surgical margins, but possibly also due to a genetic predisposition for this disease (see above).

It is of some interest that clean surgical margins do not necessarily guarantee a lower risk of recurrence.[6] This observation, along with similar data for the efficacy of adjuvant radiation therapy, probably speaks more for the selected (nonrandomized) nature of these reports than for the actual behavior of the tumors. It stands to reason that those patients with questionable or involved surgical margins will tend to populate the trials of adjuvant therapy. It is clear that no one parameter can predict the tendency of these neoplasms to recur. Re-excision of residual or recurrent disease is valid because recurrence rates following second and third excisions are equal to or lower than after the first attempt.[6]

TABLE 2. *Desmoid Tumor Recurrences (%) (Recent Studies with More Than 15 Patients)*

| Reference | n | Tumor Location (%) | | | Treatment* (%) | |
|---|---|---|---|---|---|---|
| | | Abdominal | Extr'abd'l | Mesenteric | Surgery | Surg + XRT |
| Reitamo[6] | 89 | 44 (9) | 38 (45) | 7 (NA) | 74 (24) | 6 (50) |
| Markhede[12] | 44 | — | 44 (37) | — | 41 (39) | 3 (33) |
| Jones[13] | 25 | 5 (40) | 4 (50) | 16 (81) | 16 (81) | 2 (100) |
| Khorsand[14] | 19 | 5 (20) | 11 (45) | 3 (33) | 12 (50) | 6 (0) |
| Kiel[15] | 222 | 45 (40) | 172 (41) | 5 (100) | 222 (42) | 8 (38) |
| Current series | 19 | 5 (0) | 12 (83) | 2 (50) | 13 (54) | 5 (80) |
| Total | 428 | 104 (24%) | 281 (43%) | 33 (77%) | 378 (40%) | 30 (43%) |

* Not all patients received these treatment options, hence totals indicate fewer than all those with disease.

The number of patients at risk in each category is followed by the percent who had recurrent tumors (in parenthesis).

The literature on radiation therapy for desmoid tumors is largely addressed to extra-abdominal tumors. This is not only because of the difficult radiation fields with truncal and intra-abdominal desmoids, but also because radiation, as either adjunctive or primary therapy, is an attractive alternative to mutilating or debilitating extremity resections. Importantly because desmoid tumors grow slowly and do not metastasize, amputations and/or major muscle group excisions are considered too aggressive in certain cases. While most will have residual disease after radiation, many will have acceptable responses and potential control of their extra-abdominal disease.[15,16]

There have been a variety of pharmacologic approaches in the effort to control desmoid-tumor growth, especially for troublesome recurrences. These modes of therapy include c-AMP modulators (theophylline, chlorothiazide, ascorbic acid, testolactone), various chemotherapeutic agents, estrogen blockade, and prostaglandin manipulation.[17–20] There have been no convincing results from the conventional antineoplastic approach of either c-AMP or chemotherapy manipulations. This is probably due to the low mitotic index seen in these tumors. In uncontrolled studies, there have been reports of regression of tumors with estrogen blockade.[19] This is presumably a result of restricted RNA synthesis and altered gene transcription, but may also be an indirect effect through the inhibitory effect of estrogens on prostaglandin synthesis.[20]

The use of prostaglandin manipulation for desmoid tumors began with the observation that experimentally induced fibrosarcomas in rats regress with prostaglandin blockade.[21] Since then a variety of agents have been tried (again in poorly controlled studies with few cases), with hopeful response rates, including a recent case report regarding the use of Clinoril (sulindac).[20]

The most successful method of control, and best hope for cure of desmoid tumors, is complete excision. Re-excision of recurrent tumors is clearly warranted. Estrogen-receptor levels are of academic interest, but may justify hope for noninvasive therapy in the case of recurrent desmoid tumors. High-dose radiation therapy is also useful in the attempt to control recurrent disease, and may be appropriate as the primary therapy when the only alternative is a mutilating resection. Similarly trials of antiestrogens (even if receptor assays are low) and prostaglandin inhibitors may postpone, or possibly obviate, the need for aggressive surgical intervention when recurrent disease is encountered.

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