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A prognostic nomogram for prediction of recurrence in desmoid fibromatosis

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Abstract

Objective—To construct a postoperative nomogram to estimate the risk of local recurrence for patients with desmoid tumors.

Background—The standard management of desmoid tumors is resection, but many recur locally. Other options include observation or novel chemotherapeutics, but little guidance exists on selecting treatment.

Methods—Patients undergoing resection during 1982–2011 for primary or locally recurrent desmoids were identified from a single-institution prospective database. Cox regression analysis was used to assess risk factors and to create a recurrence nomogram, which was validated using an international, multi-institutional dataset.

Results—Desmoids were treated surgically in 495 patients (median follow-up 60 months). Of 439 patients undergoing complete gross resection, 100 (23%) had recurrence. Five-year local recurrence-free survival (LRFS) was 69%. Eight patients died of disease, all after R2 resection. Adjuvant radiation was not associated with improved LRFS. In multivariate analysis, factors associated with recurrence were extremity location, young age, and large tumor size, but not margin. Abdominal wall tumors had the best outcome (5-year LRFS 91%). Age, site, and size were used to construct a nomogram with concordance index 0.703 in internal validation and 0.659 in external validation. Integration of additional variables (R1 margin, gender, depth, and primary

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vs. recurrent presentation) did not importantly improve concordance (internal concordance index 0.707).

Conclusions—A postoperative nomogram including only size, site, and age predicts local recurrence and can aid in counseling patients. Systemic therapies may be appropriate for young patients with large, extremity desmoids, but surgery alone is curative for most abdominal wall lesions.

Introduction

Desmoid tumors are clonal proliferations that may arise from mesenchymal stem cells.^{1, 2} Desmoids are associated with β -catenin mutations in over 75% of cases; a smaller proportion are associated with *APC* mutations and familial adenomatous polyposis.³⁻⁷ The lesions do not have the ability to metastasize, but progressive disease and local recurrence can lead to significant morbidity.⁸ Intraabdominal tumors may cause intestinal obstruction or fistulization and extremity tumors may result in neuropathic pain and limited mobility. For these reasons, aggressive treatment strategies were historically employed to completely extirpate disease. Patients were often managed with radical surgery and adjuvant or definitive radiation therapy. For many tumors, however, the anatomic location can make resection impossible or extremely morbid, and post-operative recurrence rates have been reported at over 70% in some series.⁸⁻¹⁵

The clinical course of desmoid fibromatosis varies widely; in some instances, the lesions remain stable for long periods with no intervention, while in others the tumors grow rapidly.^{8, 16, 17} The difficulty of surgical eradication of desmoids, together with their variable clinical course, has led to exploration of alternative treatment strategies. In instances where operation carries substantial risk, systemic therapies have been prescribed.¹⁸ Up to 70% of patients treated with novel systemic therapies may have improvement of desmoid-related symptoms.¹⁹ In several series, asymptomatic desmoid patients were observed for three to six months after presentation.¹⁶ In these series, up to 65% of patients did not progress, suggesting that some desmoid patients do not require any intervention.

Although observation, systemic therapy, and surgery are currently options for management of desmoid tumors, an optimal management strategy and how best to select patients for therapy have yet to be defined. We sought to identify patients ideally suited for surgical intervention versus those who might be candidates for neoadjuvant/definitive systemic therapies or non-operative management. To do so, we examined characteristics of a large cohort of patients with surgically resected desmoids. We identify characteristics that predict local recurrence, and we construct a clinical nomogram that predicts postoperative tumor recurrence.

Methods

Patient cohort

Approval for evaluation of desmoid patients managed at MSKCC was obtained from the institutional review board. Patients who underwent surgical resection between July 1, 1982, and November 1, 2011, were identified from the institutional soft tissue sarcoma database,

in which clinicopathologic characteristics and survival outcomes were prospectively recorded. Diagnosis and margin status were determined by a sarcoma pathologist at the time of surgical resection.

Clinicopathologic characteristics were defined as follows. Lesions at the axilla, shoulder joint, buttock, and groin were classified as extremity. Lesions at the neck, because of their small number in our cohort (n=29), were considered collectively with extremity lesions. Chest wall and abdominal wall lesions were differentiated based on their position relative to the tenth rib. Visceral, intraabdominal, and retroperitoneal lesions were considered collectively; each of these lesions was considered deep to the fascia. Tumor depth in the extremity or trunk was defined as superficial or deep according to the relationship to the investing fascia. Margin was classified as gross positive (R2), microscopic positive (R1), or negative (R0).

An external validation set included 274 patients who underwent complete surgical resection between February 1, 1965, to March 6, 2008 in 24 cancer centers from the French Sarcoma Group; clinicopathologic correlates were entered into the European database (www.conticabase.org).²⁰

Statistical methods

Characteristics of primary vs. recurrent tumors and tumors with complete vs. incomplete gross resection were compared using chi-squared analysis. Local recurrence-free survival (LRFS) was defined from the time of first surgery at MSKCC. Patients who underwent R2 resection were not included in the analysis of LRFS. Deaths in patients without documented recurrence were considered events; patients who were alive at most recent follow-up were censored. LRFS probabilities were estimated by the Kaplan-Meier method and stratified according to various clinicopathologic variables. Age and tumor size (at primary presentation) were considered on a continuous scale for nomogram construction and were considered by category (age: 16-25, 26-45, 46-65, and over 65 years; size: 5, 5-10, and >10 cm) in the univariate and multivariate analyses; the categories were chosen before modeling.

Cox proportional hazards regression was used to perform univariate and multivariate analyses; all variables (excluding treatment-related variables) were included in the multivariate analysis. No correlation was found between significant variables when evaluated by Spearman's rank correlation. Two nomograms were constructed, one including only those variables significant to 0.05 on multivariate analysis and the second including all variables. The Cox model of nomogram construction has been described.²¹ Validation, in this case, was performed internally by creating 100 bootstrap resamples and externally on the European database set. Nomogram calibration was checked using the calibration plot.

Results

Characteristics of surgically resected patients

The study cohort consisted of 495 individual patients who underwent surgical resection of a desmoid tumor at MSKCC (Table 1). The cohort was predominantly female (67%, n=329). Overall, 382 patients (77%) had primary disease, while 113 (23%) had recurrent disease.

Patients with primary and recurrent disease were similar in terms of gender and depth. Patients with recurrent disease tended to be younger (79% vs 66% younger than 45, $p=0.074$; median age 34 vs. 38 years). They more commonly presented with extremity or chest wall lesions (83% vs. 54%, $p<0.001$). Patients presenting with primary disease were more likely to undergo complete microscopic resection (57% vs. 45% in recurrent disease, $p=0.05$). They were less likely to undergo treatment with radiation (12% vs. 32%, $p<0.001$) or chemotherapy (9% vs. 19%, $p=0.002$) than were patients presenting with recurrent disease.

Familial adenomatous polyposis (FAP) had been documented in 15 patients, 6 of them male and 9 female. Their age at resection ranged from 16 to 43 years. Ten had intra-abdominal lesions, 4 had chest wall desmoids, and one had a paraspinal lesion.

Determinants of complete gross resection

Complete gross resection was confirmed in 440 patients (89%), whereas 53 patients (11%) underwent R2 resection with gross residual disease in place after surgery. The R2-resected tumors were more commonly large (38% vs. 24% were >10 cm; $p=0.001$) and located in the abdomen (47% versus 17%, $p<0.001$). Twenty-five percent of R2 resections were in extremity tumors. Of 15 patients with documented FAP, 8 underwent incomplete gross resection.

Predictors of local recurrence

Median follow-up of the cohort was 60 months (range 0-327 months). Overall, 44 patients were dead at last follow-up, but only 8 died of disease. All of these patients had undergone R2 resection; 6 of them had intra-abdominal tumors and 3 were FAP patients. Two patients died following intestinal transplant.

Of 439 patients undergoing complete gross resection, 100 had recurrence. Among these, 92 (92%) had their recurrence within 5 years. Five-year local recurrence-free survival (LRFS) was 69% (Figure 1).

The clinicopathologic characteristics were examined for association with LRFS after complete gross resection (Table 2). Patient gender, tumor depth, and presentation status (primary vs. recurrent) were not associated with LRFS. However, patients aged under 26 years at time of diagnosis had a significantly higher rate of local recurrence (HR 4.27, $p=0.006$; Figure 2A). Five-year LRFS among these patients was 52% compared to 81% among patients over 65 y.o.

Size of the patient's primary tumor was associated with outcome. Tumors over 10 cm in largest diameter were associated with 5-year LRFS rates of 57% compared to 72% for tumors ≤ 5 cm and 74% for tumors >5 cm and ≤ 10 cm (Figure 2B). There was a striking association between site and LRFS. Intraabdominal, chest wall, and extremity tumors had relatively poor outcomes (5-year LRFS 76%, 72%, and 60% respectively). Desmoids in the neck, which were considered collectively with extremity lesions in the main analyses, behaved nearly identically to extremity tumors (5-year LRFS 43% for neck versus 47% for lower extremity). Abdominal wall tumors had the best outcome (5-year LRFS 90% [Figure

2C] vs. 34% in patients ≥ 25 y.o. with large, extremity tumors [$n=11$]). Only 8 of 79 patients with abdominal wall tumors had recurrence. All were 40 or younger, and 3 of the 8 had tumors over 10 cm. Only one abdominal wall tumor that recurred, a rectus sheath lesion, was <5 cm.

A multivariate analysis demonstrated that age, tumor size, and tumor site are independent predictors of recurrence (Table 2). Margin status (R1 vs. R0) was not associated with altered outcome in the cohort as a whole or in subgroups defined by age or tumor site. However, among patients with small tumors (<5 cm), R0 resection was associated with longer LRFS compared to R1 resection (76 vs. 60%, $p=0.007$). Margin was not associated with recurrence in larger lesions.

Adjuvant radiation therapy

The role of radiation therapy in desmoid fibromatosis has been debated. In our series, there was no improvement in outcomes in patients who had received radiation therapy during the course of their treatment (5-year LRFS 68% vs 72% without radiation; Figure 3A).

Additionally, adjuvant radiation therapy was not significantly associated with improved LRFS in any subset of tumors (stratified by size, site, and patient age at diagnosis) except extremity tumors. Adjuvant radiation was most commonly used for extremity tumors (in 23% of these patients), and radiation for extremity tumors was associated with a 15% absolute reduction in local recurrence; LRFS among patients with extremity tumors was 71% with radiation vs. 56% without ($p=0.029$).

To eliminate the contribution of selection bias to analysis of the role radiation plays in management of desmoid tumors, we analyzed outcomes over time. Prior to 1997, 30% of patients received adjuvant radiation therapy, but in 1997 and later, only 7% of patients received this treatment ($p<0.0001$). The decreased use of radiation was not accompanied by a statistically significant change in LRFS (71 vs. 70%; Figure 3B).

A nomogram to predict local recurrence following surgical resection

Based on the univariate and multivariate models, we integrated clinicopathologic risk factors into a nomogram to predict post-operative recurrence of desmoid tumors at 3, 5, and 7 years after surgery. Because prescription of radiation had no association with outcome, we retained patients receiving this therapy in our analysis. Included in the model were the significant predictors of local recurrence on univariate analysis, i.e., patient age and tumor site and size. The nomogram is shown in Figure 4. The bootstrapping concordance index of this model was 0.703. Addition of margin, depth, gender, or presentation status to the model did not improve concordance significantly (0.707). Actual incidence of recurrence was plotted versus predicted recurrence, confirming good calibration of the nomogram (Figure 5).

External validation of this nomogram was performed on a cohort of patients ($n=274$) treated at sarcoma specialty centers in Europe. Patients within this cohort were of similar age as those treated at MSKCC (mean 38.6 versus 37.5 y.o.). Tumors in the validation set were slightly smaller (mean 6 vs. 7 cm; $p=0.001$), and were more commonly seen in the chest wall (27 vs. 16%) and less often in the extremity (36 vs. 41%; $p=0.009$). The concordance

index in the validation set was 0.659 (confidence interval 0.598-0.712). The external validation set was previously used to create a 3-point scoring system to predict progression-free survival following desmoid resection. Compared to the nomogram, the 3-point tool had substantially lower concordance index for both in the MSKCC cohort (0.532) and in the external validation cohort (0.570). Calibration of the nomogram in the validation cohort demonstrated that the tool is particularly accurate for high-risk lesions (predicted versus actual 3-year survival in the quintile with poorest prognosis being 51 vs. 49%). The tool overestimated recurrence-free survival in the tumors with good prognosis (89% predicted vs. 69% actual risk of local recurrence at 5 years in the upper quintile).

Discussion

Desmoid tumors can be managed by observation, surgery, or chemotherapy, but little information exists on how to select the best treatment for the individual patient. Given promising responses to some novel chemotherapies and the high rate of local recurrence following resection, we sought to define subgroups of patients with desmoid tumors who should be considered for surgical resection and subsets in whom a multimodality approach to management can be explored. To accomplish this, we have used a large, prospectively collected database to find risk factors for local recurrence after complete gross resection and to create a clinical nomogram that predicts risk of recurrence.

In a multivariate analysis, only tumor site and size and patient age were associated with recurrence. A nomogram that uses these three variables predicts local recurrence-free survival, exhibiting good concordance in internal and external validation (concordance indices 0.70 and 0.66, respectively). While the concordance indices are lower than observed with our institution's nomograms for outcome after surgical resection of liposarcoma and synovial sarcomas,^{22, 23} they suggest that the desmoid nomogram's predictive ability is better than those describing prognosis in pancreatic cancer (concordance index 0.64) and melanoma (concordance 0.69) as well as FIGO staging for ovarian cancer (0.62) and AJCC staging systems (e.g., colon with concordance of 0.60).²⁴⁻²⁷

Although the concordance index was lower in the validation data than in the test set, this is not overly concerning for two reasons. First, performance on a validation set is generally worse than on the test set used to develop a given tool. This phenomenon was also observed in validating the three-point scoring system describing desmoid outcome (concordance index 0.57 in the dataset on which it was developed vs. 0.53 in the MSKCC dataset). Second, as noted above, the concordance for the validation set suggests that the desmoid nomogram is better than staging systems routinely applied to more common cancers. We did note that calibration of the predicted outcome to actual outcome among the patients treated at the European centers is more accurate in high-risk tumors than in the low-risk tumors, where the nomogram may underestimate local recurrence rates. The tool persists in being an excellent means in this second population for performing its purpose, i.e., identifying high-risk patients who may be candidates for non-operative management.

All of these predictors of recurrence can be evaluated preoperatively, allowing efficient preoperative estimation of risk and counseling of patients using the nomogram. For

example, abdominal wall tumors have less than ten percent risk of recurrence while extremity lesions recur often. In this context, we currently recommend surgical intervention for abdominal wall lesions if they are symptomatic or progressing. Patients with large extremity lesions are ideal candidates for enrollment in clinical trials examining neoadjuvant or definitive systemic treatment. While easily resectable lesions in the extremity are still approached surgically, we believe that the high risk of local recurrence justifies discussion with the patient regarding alternative therapies including definitive or neoadjuvant therapy with sorafenib or other investigational agents, particularly in patients where resection may result in significant morbidity. In analysis of factors associated with incomplete resection, we noted that patients with large, intraabdominal tumors were prone to R2 resection. This is likely related to the risk of mesenteric vessel involvement, and the surgeon should carefully consider the anatomy before recommending surgery to these patients, despite the fact that their predicted risk of local recurrence is characteristically in the intermediate range (e.g., 10-cm lesions in 25-year-old patients are predicted to recur in ~30% of patients).

This single-institution series of surgically resected desmoids, the largest reported to date, enables examination of the role of margin status and radiation in the clinical management of these tumors. In the cohort as a whole, we observed no association between R0 vs. R1 margin of resection and recurrence. In a sub-group analysis of small tumors (<5 cm), those excised with R1 margins had an increased risk of local recurrence compared with R0 excisions (76% vs 60%, $p = 0.007$). Regardless, most patients with small tumors undergoing R1 resection did not have recurrence, and therefore it seems reasonable to employ a period of observation in this clinical scenario rather than aggressive attempts to achieve complete microscopic resection.

While prior studies have suggested that adjuvant radiation may be of benefit in desmoids, no randomized trials have been performed. Selection bias and recent data regarding the role of stable disease even in untreated tumors make historical reports describing the role of adjuvant radiation difficult to interpret. In small case series, local control rates of 75% and 81% for patients receiving radiation are comparable to the overall risk of recurrence observed here even in the absence of such treatment.^{28, 29} A retrospective review of 189 patients at a single specialty center showed no association between adjuvant radiation and improved outcomes.³⁰ In updated data, an increased rate of local recurrence associated with R1 margins was abrogated by prescription of adjuvant radiation.³¹ In our study, margin of resection did not alter outcomes, and radiation treatment was not related to statistically significantly better overall LRFS, despite the large number of patients studied. Moreover, over the duration of our series the frequency of patients receiving adjuvant radiation dropped from 30% to 7%, but this has resulted in no increase in the local recurrence rate. In extremity lesions the use of radiation was associated with a statistically lower rate of recurrence, with absolute risk reduction of 15%. Balancing this scant evidence of benefit against the short- and long-term complications associated with radiation (wound complications, fibrosis, edema, bone fracture, radiation-associated sarcoma) in what is a young patient population, we have now removed radiation from our treatment algorithm for patients with resectable desmoids.

Our results are concordant with the proposal that among patients with desmoid tumors, there exists a spectrum of disease biology. Patients undergoing resection for an abdominal wall desmoid have a long-term disease-free survival rate over 90%, while in young patients with large extremity lesions the rate is less than 40%. Given the very different rates of local recurrence of abdominal wall lesions compared to extremity and chest wall tumors, these tumors may have a different biology or a different host–tumor-site interaction. Similarly, the worse outcomes for younger patients, which has been reported previously,²⁰ suggests differences in tumor biology. In addition to providing insight into patient risk, these data provide a framework in which we can examine the molecular biology of desmoid fibromatosis. Recent data suggest that genomic factors, such as the exact mutation in β -catenin (*CTNNB1*) associated with a given desmoid, help stratify patient risk.⁶ The nomogram could potentially be used as a basis for investigating whether such determinants are independent predictors of local recurrence or whether they are associated with clinical factors that we already define as contributing to risk. Future work will entail examining whether inclusion of genetic markers of disease may allow us to identify molecular characteristics of desmoid tumors that can be integrated into the nomogram to improve its concordance.

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Figure 1. Recurrence-free survival in 439 patients undergoing complete gross resection of a desmoid tumor analyzed by the Kaplan-Meier method.

Figure 2.

Recurrence-free survival in 439 patients undergoing complete gross resection of a desmoid tumor stratified by (A) patient age, (B) tumor size, and (C) tumor location.

Figure 3.

(A) Recurrence-free survival in patients receiving adjuvant radiation versus those not treated with radiation. (B) Recurrence-free survival in patients treated before 1997, when 30% of patients received adjuvant radiation, versus during 1997 and later, when only 7% of patients received adjuvant radiation.

Figure 4.

A nomogram estimating the probability of local recurrence-free survival at 3, 5, and 7 years following desmoid resection. Desmoids at the axilla, shoulder joint, buttock, groin, and neck are classified with extremity desmoids. LR, local recurrence.

Figure 5.

Calibration of the nomogram shown in Figure 4 in predicting 5-year recurrence-free survival following resection of a desmoid tumor. Solid line indicates performance of the nomogram; vertical bars 95% confidence interval; O, subcohorts of the database; x, bootstrap-corrected estimate of the nomogram's performance.

Table 1**Characteristics of patients**

Characteristic	Primary (n=382)	Recurrent (n=113)	p-value
Gender			0.734
Male	130 (34%)	36 (32%)	
Female	252 (66%)	77 (68%)	
Age, years			0.074
15-25	67 (18%)	28 (25%)	
26-45	184 (48%)	60 (53%)	
46-65	92 (24%)	18 (16%)	
>65	39 (10%)	7 (6.2%)	
Location of primary tumor			<0.001
Abdominal wall	77 (20%)	11 (9.7%)	
Chest wall	50 (13%)	26 (23%)	
GI/intraabdominal	94 (25%)	6 (5.3%)	
Extremity	138 (36%)	68 (60%)	
Other	23 (6.0%)	2 (2%)	
Depth			0.914
Superficial	28 (7.3%)	7 (6.2%)	
Deep	351 (92%)	105 (93%)	
Unknown	3 (0.79%)	1 (0.88%)	
Margin status			0.05
R0	216 (57%)	51 (45%)	
R1	130 (34%)	43 (38%)	
R2	35 (9.2%)	18 (16%)	
Unknown	1 (0.26%)	1 (0.88%)	
Size of primary tumor			<0.001
5 cm	112 (29%)	36 (32%)	
>5 cm, 10 cm	155 (41%)	45 (40%)	
>10 cm	113 (30%)	12 (11%)	
unknown	2 (0.52%)	20 (18%)	
Any chemotherapy	34 (8.9%)	22 (19%)	0.002
Adjuvant RT	46 (12%)	36 (32%)	<0.001

RT, radiation therapy

Table 2
Analysis of factors predicting local recurrence after desmoid resection

Factor	Univariate		Multivariate	
	Hazard ratio (95% CI)	p-value	Hazard ratio (95% CI)	p-value
Margin status (R1 vs. R0)	1.18 (0.78, 1.80)	0.42	0.99 (0.65, 1.52)	0.97
Presentation status (recurrent vs. primary)	1.32 (0.82, 2.14)	0.28	1.16 (0.70, 1.90)	0.57
Depth (deep vs. superficial)	1.56 (0.63, 3.84)	0.34	1.37 (0.54, 3.45)	0.51
Gender (female vs. male)	1.17 (0.75, 1.84)	0.49	1.32 (0.82, 2.10)	0.25
Location (vs. abdominal wall)				
Extremity	5.21 (2.25, 12.1)	<0.001	5.02 (2.14, 8.42)	<0.001
Chest wall	3.31 (1.27, 8.62)	0.014	3.12 (1.20, 8.42)	0.02
Intraabdominal	2.79 (1.03, 7.55)	0.043	2.73 (0.98, 7.59)	0.054
Other	1.52 (0.31, 7.56)	0.61	1.54 (0.31, 7.63)	0.6
Size (>10 cm vs. <10 cm)	1.87 (1.22, 2.86)	0.005	1.94 (1.23, 3.05)	0.004
Age (vs. >65 y.o.)				
25 y.o.	4.27 (1.51, 12.2)	0.006	3.55 (1.23, 10.3)	0.013
26-65 y.o.	1.99 (0.72, 5.48)	0.19	2.02 (0.72, 5.70)	0.21