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Does the Addition of Mutations of *CTNNB1* S45F to Clinical Factors Allow Prediction of Local Recurrence in Patients With a Desmoid Tumor? A Local Recurrence Risk Model

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Abstract

Background The initial approach to the treatment of desmoid tumors has changed from surgical resection to watchful waiting. However, surgery is still sometimes considered for some patients, and it is likely that a few patients would benefit from tumor removal if the likelihood of local recurrence could be predicted. However, to our knowledge, there is no tool that can provide guidance on this for clinicians at the point of care.

Question/purpose We sought to explore whether a combined molecular and clinical prognostic model for relapse

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in patients with desmoid tumors treated with surgery would allow us to identify patients who might do well with surgical excision.

Methods This was a retrospective, single-center study of 107 patients with desmoid tumors who were surgically treated between January 1980 and December 2015, with a median follow-up of 106 months (range 7 to 337 months). We correlated clinical variables (age, tumor size, and localization) and *CTNNB1* gene mutations with recurrence-free survival. Recurrence-free survival was estimated using a Kaplan-Meier curve. Univariate and multivariable analyses of time to local recurrence were performed using Cox regression models. A final nomogram model was constructed according to the final fitted Cox model. The predictive performance of the model was evaluated using measures of calibration and discrimination: calibration plot and the Harrell C-statistic, also known as the concordance index, in which values near 0.5 represent a random prediction and values near 1 represent the best model predictions.

Results The multivariable analysis showed that S45F mutations (hazard ratio 5.25 [95% confidence interval 2.27 to 12.15]; $p < 0.001$) and tumor in the extremities (HR 3.15 [95% CI 1.35 to 7.33]; $p = 0.008$) were associated with a higher risk of local recurrence. Based on these risk factors, we created a model; we observed that patients considered to be at high risk of local recurrence as defined by having one or two factors associated with recurrence (extremity tumors and S45F mutation) had an HR of 8.4 compared with patients who had no such factors (95% CI 2.84 to 24.6; $p < 0.001$). From these data and based on the multivariable Cox models, we also developed a nomogram to estimate the individual risk of relapse after surgical resection. The model had a concordance index of 0.75, or moderate discrimination.

Conclusion *CTNNB1* S45F mutations combined with other clinical variables are a potential prognostic biomarker associated with the risk of relapse in patients with desmoid tumors. The developed nomogram is simple to use and, if validated, could be incorporated into clinical practice to identify patients at high risk of relapse among patients opting for surgical excision and thus help clinicians and patients in decision-making. A large multicenter study is necessary to validate our model and explore its applicability.

Level of Evidence Level III, therapeutic study.

Introduction

Desmoid tumors are rare neoplasms characterized by fibroblast proliferation and represent only 0.03% of all neoplasms and approximately 3% of all soft tissue tumors [25, 34]. Desmoid tumors display aggressive infiltrative growth, with high rates of local recurrence after surgery and no distant metastasis. Beta-catenin, a protein encoded by the *CTNNB1* gene, was found to be overexpressed in approximately 75% of patients with desmoid tumors [16]. Desmoid tumors are clinically characterized as large masses that are usually painful with varying growth patterns. Most patients experience a period of symptomatic growth; however, long periods of stabilization and spontaneous regression are also observed [29].

Most desmoid tumors are sporadic and result from a mutation in the *CTNNB1* gene. Recent studies demonstrated three hotspot mutations in exon 3 of *CTNNB1* in the two codons 41 and 45—one mutation in 41 (T41A) replacing threonine for alanine and two mutations in 45 (S45F and S45P), replacing serine for phenylalanine and proline, respectively [3, 4, 43]. The prevalence of *CTNNB1* mutations in sporadic desmoid tumors ranges from 73% to 92% [2, 31, 33] and there are many publications demonstrating that the S45F betacatenin gene mutation is related to worse prognosis and higher risk of relapse [9, 31, 44, 46].

Complete surgical resection with wide margins has been the main treatment modality for desmoid tumors [1, 14, 18, 28, 35, 37-39, 42, 47]. However, because of the high recurrence rate and poor functional results after aggressive surgery, a watch-and-wait approach is generally recommended for most patients with slow-growing asymptomatic tumors, and some studies have shown long progression-free survival with this less-aggressive approach [5, 7, 15].

Although an expectant approach is advocated for most patients at first diagnosis, surgery could be helpful for some patients with symptomatic lesions because systemic and local therapy could impair the patient's quality of life. Additionally, the psychologic burden of an incurable disease in young patients should not be neglected and must be incorporated into the therapeutic decision-making process. In other words, patients should actively participate in the decision process, and if more reliable methods to predict disease evolution are available, these could be helpful. Many prognostic factors associated with relapse after surgical resection have been described [10, 24, 31]. No single factor seems dominant, so prediction models or nomograms might prove helpful. Crago et al. [12] developed a relapse prediction model based on an evaluation of the clinical variables of 495 patients with desmoid tumors. However, this model did not include the molecular profile of *CTNNB1* mutations. Consequently, a more robust and accurate model is needed to predict the risk of relapse and better select patients who undergo surgical resection of desmoid tumors.

We sought to explore whether a combined molecular and clinical prognostic model for relapse in patients with desmoid tumors treated with surgery would allow us to identify patients who might do well with surgical excision.

Patients and Methods

Study Design and Setting

Patients who underwent surgical resection and had a pathologic diagnosis of desmoid tumor between December 1980 and December 2015 were identified and retrospectively reviewed from the database of a single tertiary cancer center (A. C. Camargo Cancer Center) in São Paulo, Brazil.

The inclusion criteria were diagnosis of desmoid tumor, patients undergoing macroscopically complete surgical resection, available paraffin-embedded material for diagnostic review, a minimum follow-up time of 24 months for patients whose tumors did not relapse, and available clinical data. We excluded patients with familial adenomatous polyposis syndrome, whose prognoses are reported to be significantly different from those with sporadic desmoid tumors [24, 40, 46].

Patients

The search resulted in the identification of 169 patients with desmoid tumors over a period of 35 years. Ninety-four percent (158 of 169) of patients were considered to have sporadic tumors and 7% (11 of 169) had tumors that met the criteria for familial polyposis adenomatosis and were excluded. Ninety-one percent (144 of 158) of patients with sporadic disease were treated with surgery. Thirty-eight percent (55 of 144) of these patients had local recurrence, and in 62% (89 of 144), no recurrence was observed. All patients with recurrence were included in our analyses, and the shortest follow-up was in one of these patients with relapse (7 months). However, patients without recurrence with less than 24 months of follow-up were excluded from the final sample because they did not meet one of the inclusion criteria. Therefore, there were 126 patients. For 19 patients, data could not be collected properly or a histologic review could not be performed, so these patients were also excluded.

The final sample consisted of 107 patients with a follow-up time ranging from 7 to 337 months, with a mean follow-up time of 134 months and a median of 106 months. At the final assessment, 70% (75 of 107) of patients were alive without disease and 18% (19 of 107) were alive with disease. Among them, 1.9% (two of 107) of deaths were linked to desmoid tumors, 0.9% (one of 107) of deaths were not linked to a desmoid tumor, and 7.5% (eight of 107) of patients were lost to clinical follow-up after a minimum of 32 months after surgery to remove the tumor.

Table 1. Frequency of demographic, clinical, treatment, and molecular variables

Variable	Value (n = 107)
Women gender	
Age in years	59 (63)
< 25	33 (35)
25 to 49	59 (63
50 to 75	8 (9)
Nonextremity location	63 (68)
Site	
Intraabdominal	10 (11)
Abdominal wall	20 (21)
Head and neck	14 (15)
Chest wall and back	20 (21)
Extremities	36 (39)
Tumor size in cm	
< 5	32 (34)
≥ 5 and < 10	32 (34)
≥ 10	20 (21)
Unknown	16 (18)
Type of treatment	
Surgery	83 (89)
Surgery and chemotherapy	6 (6)
Surgery and radiotherapy	4 (4)
Surgery, chemotherapy, and radiotherapy	4 (4)
Unknown	4 (4)
Surgery	
Wide resection	86 (92)
Amputation	1 (1)
Excisional biopsy	3 (3)
Unknown	10 (11)
Surgical margins	
Free (R0)	58 (62)
Compromised (R1 or R2)	31 (33)
Unknown	11 (12)
Mutation	
Wild type	14 (10 of 71)
T41A	47 (33 of 71)
S45F	23 (16 of 71)
S45P	9 (6 of 71)
T41A and S45F	7 (5 of 71)
T41A and S45P	1 (1 of 71)
Mutation other than S45F	78 (55)
Allele frequency > 10%	70 (43)

Data presented as % (n).

Table 2. Simple Cox regression model fitted to dataset

Variable	Coefficient	Standard error	HR (95% CI)	p value
Age in years				
> 31			Reference	
≤ 31	0.78	0.34	2.19 (1.11 to 4.3)	0.02
Men gender	0.57	0.33	1.77 (0.93 to 3.39)	0.08
Site				
Extremities			Reference	
Intraabdominal	-1.21	0.74	0.29 (0.07 to 1,26)	0.10
Abdominal wall	-1.22	0.54	0.29 (0.1 to 0.85)	0.02
Head and neck	-0.91	0.54	0.40 (0.13 to 1.16)	0.09
Chest wall and back	-1.05	0.49	0.34 (0.13 to 0.92)	0.03
Location				
Nonextremities			Reference	
Extremities	1.09	0.33	2.98 (1.54 to 5.77)	0.001
Treatment type				
Surgery and chemotherapy and/or radiotherapy			Reference	
Surgery	1.96	1.01	7.09 (0.97 to 51.82)	0.05
Tumor size in cm				
≤ 10			Reference	
> 10	0.87	0.45	2.39 (0.97 to 5.89)	0.05
Tumor size in cm				
≥ 10			Reference	
< 5	-0.77	0.48	0.46 (0.17 to 1,19)	0.11
≥ 5 and < 10	-1.33	0.55	0.26 (0.08 to 0.79)	0.01
Margin				
Compromised (R1 or R2)	0.37	0.38	1.45 (0.68 to 3.07)	0.32
Allele frequency				
≤ 10%			Reference	
> 10%	0.94	0.54	2.57 (0.88 to 7.5)	0.08
Allele frequency				
≤ 10%			Reference	
10% to 20%	1.05	0.58	2.86 (0.91 to 9.02)	0.07
> 20%	0.83	0.59	2.30 (0.72 to 7.36)	0.15
Mutation type				
S45F			Reference	
Wild type	-0.75	0.51	0.46 (0.17 to 1,27)	0.13
T41A	-1.84	0.46	0.15 (0.06 to 0.39)	< 0.001
S45P	-1.71	0.76	0.18 (0.04 to 0.81)	0.02
Mutation type				
Other			Reference	
S45F	1.48	0.38	4.42 (2.1 to 9.31)	< 0.001
Mutation type (free margin)				
Other			Reference	0.003
S45F	1.80	0.61	6.10 (1.82 to 20.41)	

Variables Considered in the Model

Clinical and demographic variables were age (grouped as 0 to 24 years, 25 to 49 years, and 50 to 75 years), tumor size (grouped as < 5 cm, ≥ 5 and < 10 cm, and ≥ 10 cm), site (extremities and nonextremities; the nonextremities were subdivided into intraabdominal, abdominal wall, head or neck, and chest or backwall). The treatment variables were surgery (in 83% [89 of 107]), surgery and systemic therapy (5.6% [six of 107]), surgery and radiotherapy (3.7% [four of 107]), and surgery with systemic therapy and radiotherapy (3.7% [four of 107]). In 3.7% (four of 107), the exact treatment could not be confirmed, and these patients were classified as having unknown treatment (Table 1). Additional treatment variables were type of surgery (wide resection, amputation, or excisional biopsy) and follow-up time. Surgical margins are a controversial issue for patients with desmoid tumors, although most of the data indicate that negative margins (R0 resection) are associated with a better outcome [8, 12, 24, 48]. Additionally, data show that R1 or R2 resections tend behave differently from R0 resection [8, 24]. In the current study, the surgical margins were free in 44 nonrelapsed patients and 18 relapsed patients and were compromised (positive) in 21 nonrelapsed and 12 relapsed patients (p = 0.62) (Supplemental Table 1; http://links.lww.com/CORR/B67). The log-rank analysis for the survival curves related to the surgical margins (Supplemental Fig. 1; http://links.lww.com/CORR/B68) and simple Cox model (Table 2) allowed us to infer recurrence had no influence on the surgical margins.

Cates et al. [8] observed that some of the surgical margins analyzed in their study that were considered free but close (less than 1 mm) are actually compromised margins. Further, inadequate samples of surgical margins sent to pathologists may be the real reason why the surgical margin variable cannot to predict the risk of local recurrence.

He et al. [24] evaluated patients with grossly and microscopically compromised margins versus those with free margins. Their study demonstrated that compromised margins are predictors of local recurrence (relative risk = 2.64; p = 0.027) and, in their discussion on margins, concluded that there is difficulty in achieving an adequate margin during surgery for resection of desmoid tumors. Further, in that study, it was very difficult to obtain an adequate surgical margin in patients with desmoid tumors; it was perhaps even more difficult to know microscopically and when they were adequate.

Faced with these controversies, we chose to characterize the surgical margins of our patients as free margins (R0 resection) and positive margins (R1 if microscopically positive and R2 if macroscopically positive), classified as suboptimal resection; therefore, these patients were separated from those with R0 resection.

Clinical and Demographic Characteristics

The median age was 31 years, and 59% (63 of 107) of the patients were women. Sixty-four percent (68 of 107) of patients had nonextremity tumors and 36% (39 of 107) had extremity tumors. Sixty-four percent (68 of 107) had tumors less than 10 cm. Eighty-three percent (89 of 107) were treated solely with surgery and 86% (92 of 107) had macroscopically wide resections. Fifty-eight percent (62 of 107) had negative surgical margins (R0), and 31% (33 of 107) had positive margins (R1 or R2) (Table 1). Tumor relapse was observed in 39% (42 of 107) of patients, and 83% (35 of 42) of relapses occurred in the first 24 months after the first surgery (median 15 months). There was no association between surgical margins (R0: noncompromised; X R1/R2: compromised) and relapse (hazard ratio = 1.45 [95% confidence interval 0.68 to 3.07]; p = 0.32) (Table 2). The univariate analysis showed that age younger than 31 years (HR 2.19 [95% CI 1.11 to 4.30]; p = 0.02), tumor size > 10 cm (HR 2.39 [95% CI 0.97 to 5.89]; p = 0.05), tumor in the extremities (HR 2.98 [95% CI 1.54 to 5.77]; p = 0.001), and the S45F mutation (HR 4.42 [95% CI 2.1 to 9.31]; p < 0.001) were associated with relapse (Table 2).

DNA Extraction and DNA Amplicon Sequencing of Exon 3 of CTNNB1

CTNNB1 mutations were analyzed by next-generation sequencing. Paraffin-embedded samples were reviewed by a specialized pathologist (IWC) to confirm the original diagnosis. Samples with > 95% viable tumor cells were selected, and DNA was extracted according to the standard operating protocol of the A. C. Camargo Biobank. Amplicon sequencing was performed using the Ion Proton platform after direct amplification of the target region using specific primers designed to detect point mutations in codons 41 or 45 of *CTNNB1* exon 3. The allelic frequency was estimated and characterized as ≤ 10%, > 10% ≤ 20%, and > 20% of the allele fraction. The selection criteria for variant calling were a minimum coverage of 500 reads and a frequency of at least 1% for the altered base. CLC Genomics Workbench software (Quiagen) was used to compare the generated sequences with the *CTNNB1* genomic reference sequence (NG_013302) to identify variants. Samples with no detectable mutation on *CTNNB1* sequencing were further analyzed using a comprehensive gene sequencing panel with the Ion AmpliSeq™ Comprehensive Cancer Panel (Thermo Fisher Scientific), with 409 genes related to cancer.

Proportion of Tumors With Mutations in CTNNB1

Next-generation sequencing was performed on 71 samples (Supplemental Table 2; http://links.lww.com/CORR/B69),

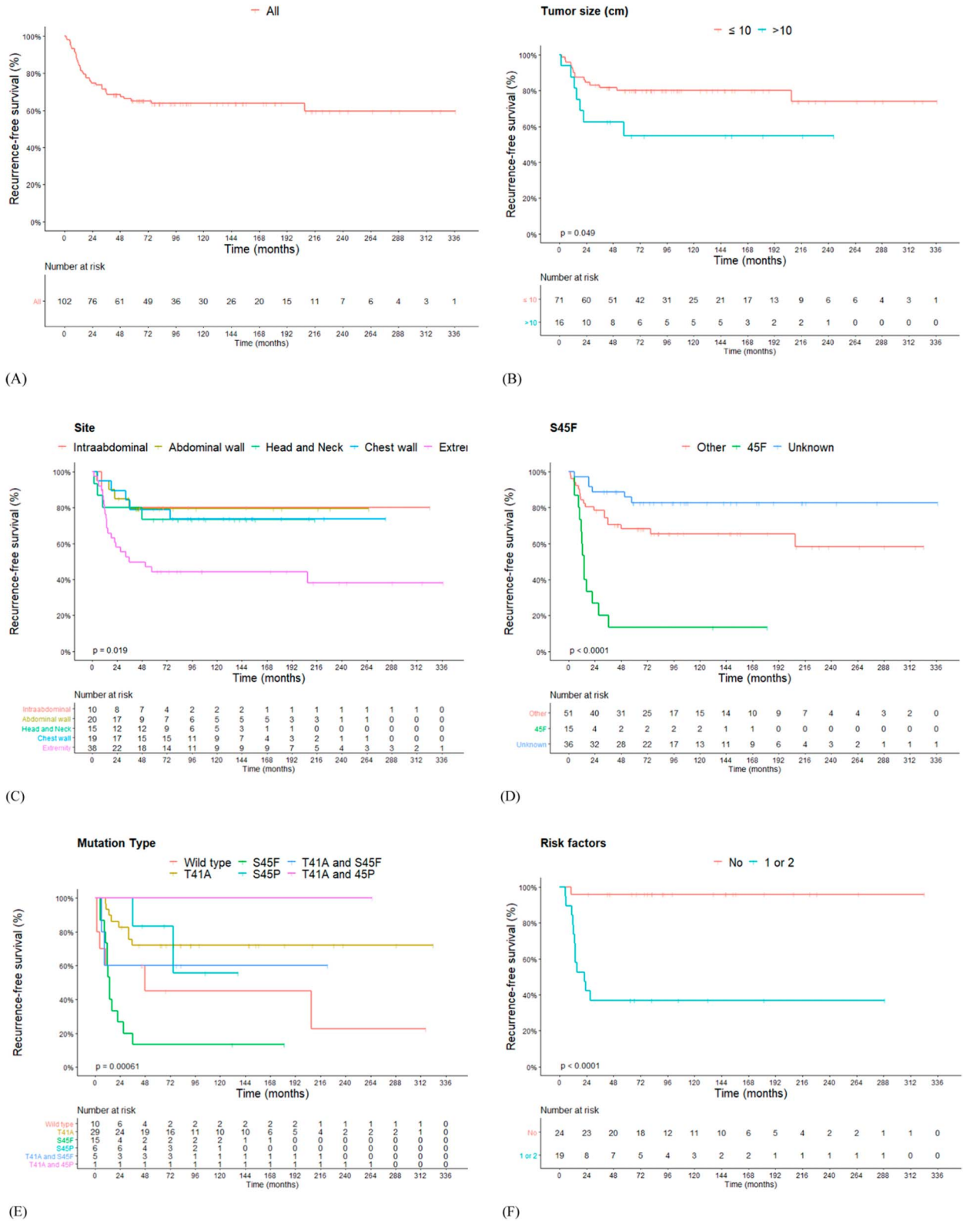

Fig. 1 These figures show the (**A**) RFS for 102 sporadic desmoid tumor patients who were treated surgically; (**B**) RFS according to tumor size (≤ 10 cm and > 10 cm); (**C**) RFS according to specific anatomic site; (**D**) RFS according to the specific mutation in the beta-catenin gene grouped as the S45F mutation, other (wild type and non-S45F mutations), and unevaluated mutation (unknown); (**E**) RFS according to all specific mutations found; and (**F**) RFS according to the number of risk factors (no risk factors and one to two risk factors).

Table 3. Multiple Cox regression model fitted to dataset

Variable	Coefficient	Standard error	HR (95% CI)	p value
Nonextremities			Reference	
Extremities	1.14	0.43	3.15 (1.35 to 7.33)	0.008
Other mutation type			Reference	
S45F	1.65	0.42	5.25 (2.27 to 12.15)	< 0.001

Independent variables considered in the model: localization, allele frequency (cutoff), and mutation type.

and 86% (61 of 71) had at least one mutation in *CTNNB1* at codons 41 and 45 of exon 3. No mutation was found in 14% (10 of 71) of the samples. The mutation distribution was 47% (33 of 71) for T41A, 23% (16 of 71) for S45F, 8.5% (six of 71) for S45P, 7% (five of 71) for T41A and S45F, and 1.4% (one of 71) for T41A and S45P. The mean allele frequency was 17% (Table 1).

Ethical Approval

Ethical approval for this study was obtained from the institutional review board of the Antônio Prudente Foundation, A. C. Camargo Cancer Center (number 2.091/15).

Statistical Analysis

Baseline patient characteristics are expressed as a percentage with absolute number. Associations between qualitative variables were evaluated with the chi-square test or Fisher exact test. The main endpoint was local relapse confirmed by imaging examinations. Recurrence-free survival (RFS) was calculated from the date of operation until the date of relapse or date of the last follow-up assessment in event-free patients (follow-up time > 24 months). Regarding age and tumor size, simple cutoff points were estimated using the maximum of the standardized log-rank statistics proposed by Lausen and Schumacher [30].

Survival curves were estimated by the Kaplan-Meier estimator, and the log-rank test was applied to compare survival distributions between groups. The Cox semiparametric proportional hazards model was fitted to describe the relationship between independent variables and RFS [11]. Variables with a p value < 0.2 in the univariate Cox regression models were selected for the initial multivariable Cox regression model. The final multivariable Cox model was selected using backward stepwise variable selection. The proportional hazards assumption of the Cox model was assessed based on a statistical test and graphical diagnostics based on Schoenfeld residuals [19]. In all analyses, the proportional hazards assumption was satisfied. Calibration and discrimination were used to assess the predictive performance of the model using the calibration plot and Harrell C-statistic [23]. One hundred bootstrap resamples were considered to evaluate the predictive performance of the model. The discrimination power of the model, which is the model's ability to correctly and reliably rank survival times based on individual risk scores, was evaluated with the Harrell C-index (also known as the concordance index). C-index values near 0.5 represent a random prediction, whereas values near 1 represent the best model predictions. The nomogram was constructed based on the final model using the mutation, tumor site, tumor size, and age. The significance level was fixed at 5%. Data were analyzed using R software version 3.5.

Results

What Was the Relapse-free Survival From Recurrence in Patients With and Without Mutations of CTNNB1*?*

We found that overall 2-, 5-, 10-, and 20-year local RFS was 74.5%, 65.1%, 63.7%, and 59.5%, respectively (Fig. 1). Patients with the S45F mutation had 2-, 5-, and 10-year lower RFS than patients without the S45F mutation (26.7%, 13.3%, 13.3% versus 78.4%, 68.1%, 65.4%, respectively; p < 0.001) (Fig. 1D). A multivariable analysis was performed for 56 patients with available clinical and molecular variables and showed that S45F mutation (HR 5.25 [95% CI 2.27 to 12.15]; p < 0.001) and tumor in the extremities (HR 3.15 [95% CI 1.35 to 7.33]; p = 0.008) were independent risk factors for relapse (Table 3).

Model to Assess Local Recurrence Risk After Surgical Resection (Prognostic Model)

Based on these risk factors, we created a model to evaluate the risk of tumor relapse after surgical resection. The model demonstrated that patients considered to be at high risk of local recurrence as defined by having one or two factors

Table 4. Cox regression model with the number of prognostic factors for local relapse

Number of factors	Estimate	Standard error	HR (95% CI)	p value
0	Reference			
1 or 2	2.12	0.55	8.36 (2.84 to 24.60)	< 0.001

Table 5. Multiple Cox regression model fitted to dataset (n = 87)

Variable	Coefficient (β)[a]	Standard error	HR (95% CI)	p value
Mutation				
Unknown			Reference	
Wild type or other mutation (other)	1.13	0.62	3.10 (0.92 to 10.49)	0.06
S45F	3.13	0.62	23.07 (5.47 to 97.32)	< 0.001
Tumor site				
Extremities			Reference	0.015
Intraabdominal	-2.15	1.12	0.11 (0.01 to 1.04	0.055
Abdominal wall	-1.33	0.79	0.26 (0.05 to 1.25)	0.093
Head and neck	-0.84	0.80	0.42 (0.08 to 2.08)	0.293
Chest wall and back	-3.13	1.12	0.04 (0.005 to 0.39)	0.005
Tumor size > 10 cm	1.75	0.55	5.77 (1.94 to 17.18)	0.002
Age in years				
Continuous	0.01	0.01	1.01 (0.97 to 1.04)	0.54

Index C (Harrell C-statistic) = 0.75. [a]Coefficient (β) = estimated Cox model coefficient.

associated with recurrence (extremity tumors and S45F mutation) had an HR of 8.4 compared with patients who had no such factors (95% CI 2.84 to 24.6; p < 0.001) (Table 4).

The estimated 2-, 5-, and 10-year local RFS values were 47.4%, 36.8%, and 11.07%, respectively, for patients who had one or two factors associated with recurrence. The value for local RFS was 95.8% for 2, 5, and 10 years (p < 0.001) for patients without any factors associated with recurrence (Fig. 1F).

Calculation of Relapse-free Survival

Evaluating the identified risk factors and the risk model data for local recurrence after surgery, and based on the multivariable Cox models (Table 5), we also developed a calculator to estimate the individual risk of relapse after surgery (nomogram) based on tumor size (< 10 cm or > 10 cm), tumor location (intraabdominal, abdominal wall, head and neck, chest wall, or extremities), age (continuous variable in years), and the S45F mutation (present, absent, or unknown) (Fig. 2). The nomogram calculation table helps to estimate the RFS of a patient according to their specific characteristics in a predetermined time. For example, a patient who has the S45F mutation is assigned 100 points; if his age is 60 years, another 20 points is added; if the lesion is on the abdominal wall, approximately 57 points are added; and 0 points are added if the tumor is smaller than 10 cm. The total points equal 177. This value is placed on the line that totals the points, and estimates of RFS in the desired period of time are observed through a normal line to this line. In this example, we have RFS at 2 years of 50%, and at 5 and 7 years the RFS is approximately 35%. The model has a concordance index of 0.75, or moderate discrimination. The actual incidence of recurrence was plotted against the predicted recurrence and the results showed that the model was a good predictor of 7-year RFS (Supplemental Fig. 2; http://links.lww.com/CORR/B70).

Discussion

Desmoid tumors are rare mesenchymal neoplasms with uncertain behavior [16]. Patients can present with fast growing and symptomatic tumors, or the disease can remain stable for a long time. Some patients undergo spontaneous regression even without active treatment [17]. Thus, an active surveillance strategy is recommended for most patients with a new diagnosis of desmoid tumor [13]. However, during the disease, surgery can be considered to control the disease and relieve symptoms in patients who have tumor progression or symptoms that are uncontrolled with other treatment types. Unfortunately, the local recurrence rate after surgery can be very high in some patients, and a method capable of predicting these high rates of recurrence could help better guide the patient and surgeon in deciding whether to choose a surgical treatment. Our study showed that the combination of clinical and molecular parameters is associated with local recurrence after tumor resection. Tumor size, age, tumor location, and the *CTNNB1* mutation could help the surgeon evaluate the possibility of local recurrence in patients treated with surgical resection.

Limitations

First, because this was a retrospective analysis, many selection biases could have been involved in the patient inclusion and exclusion process. We tried to minimize this

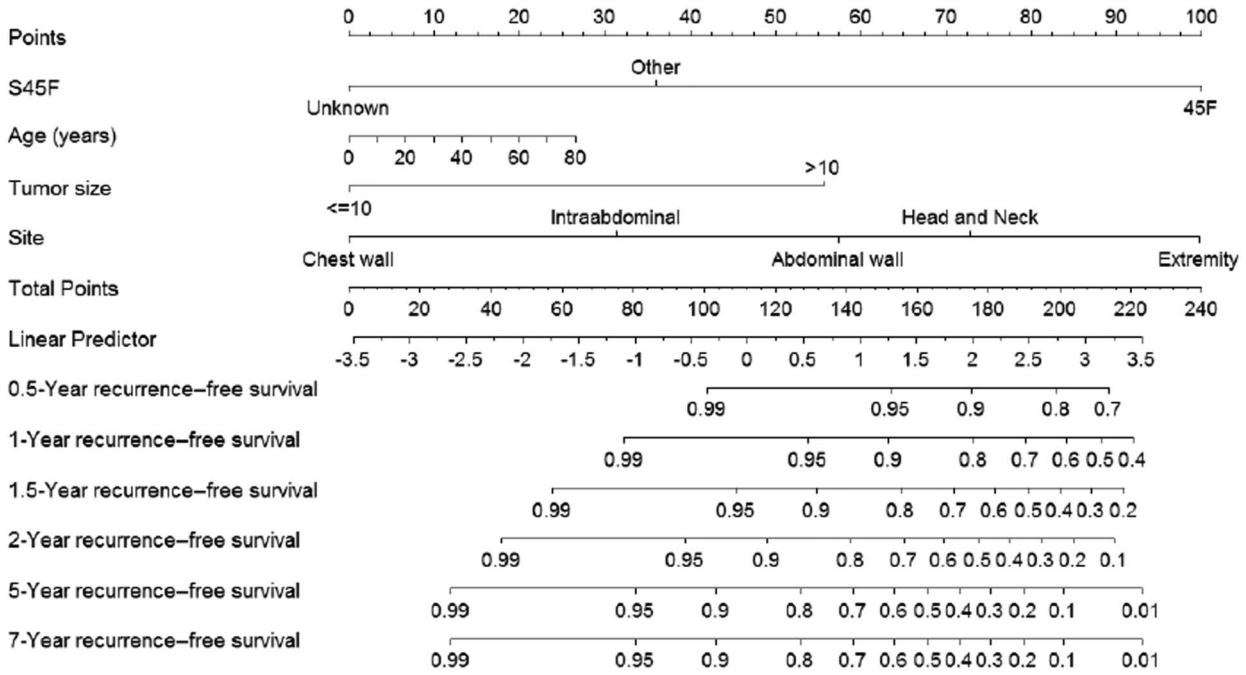

Fig. 2 This nomogram estimates the probability of RFS at 0.5, 1, 1.5, 2, 5, and 7 years.

type of bias by selecting all patients who met all of the inclusion and exclusion criteria. Second, the limited number of patients treated in a single center did not allow an external validation of our prediction model. However, we believe our data, even though they are based on a small sample, show that a combined clinical and molecular predictive model could be used to better select patients for surgery or active surveillance. Third, we could not provide a report of the symptoms and quality of life of patients spared from radical surgery. Schut et al. [41] demonstrated that the disease and treatment impact many aspects of the patients' quality of life, and it is very important in prospective studies to evaluate the real impact of surgery on global quality of life. Moreover, although surgical resection of desmoid tumors is not used very often in patients without symptoms, there are still patients with progressive symptomatic disease who do not respond well to drug treatment and could undergo surgical treatment. Additionally, these patients and their physicians could benefit from more data on the risk of recurrence after surgery. These risk assessments would allow both to choose between the different therapeutic modalities such as surgery, radiotherapy, and drug treatment, for example, in a more conscious and technical way. Thus, a patient with a very high risk of local recurrence postoperatively would not benefit from being operated on, and therefore, the doctor and patient would choose another therapeutic modality. On the other hand, a symptomatic patient with progressive disease with a low risk score could be considered for surgical treatment. Therefore, we sought to collect data at our institution that would allow us to better understand these risks and perhaps encourage other centers to perform these types of studies.

Prognostic Factors

Over the past decades, many prognostic factors such as age, tumor size, tumor location, and surgical margins have been evaluated to predict recurrence after surgical resection [8, 10, 21, 26, 33, 34, 35, 36, 37, 38, 39,40, 42, 48]. Nevertheless, there is no universal consensus. In our study, the multivariable analysis showed that patients with tumors larger than 10 cm had a higher risk of relapse, and this finding is in accordance with that of Crago et al. [12]. Numerous studies have shown that the tumor site is associated with prognosis [10, 21, 24-26, 30, 31, 32, 34, 36, 37, 39, 45]. Bonvalot et al. [5] showed worse prognoses for patients with tumors in the extremities. We found that patients with abdominal wall and chest wall lesions had lower risks of relapse than patients with lesions in their extremities. The value of attaining negative surgical margins has been debated because of controversial study results [28, 38]. Our data showed no correlation between the microscopic margin status and local relapse; the outcome of patients with R0 resection was similar to that of patients treated with R1 or R2 resection, and the behavior of desmoid tumors is very distinct from that other soft tissue

malignancies. High local relapse rates are observed even after wide surgical margins [22].

Proportion of Tumors With Mutations in CTNNB1

In our study, only 14% of our patients did not have a mutation in the *CTNNB1* gene (wild type), and the frequencies of the three specific point mutations were very similar to the frequencies in an important meta-analysis [44] based on individual patient data from all published studies that analyzed *CTNNB1* mutations. This study analyzed seven retrospective studies; the *CTNNB1* gene of 329 patients was sequenced and 25.1% of patients had wild-type *CTNNB1* genes without mutations, and the T41A, S45F, and S45P mutations were found in 46.8%, 20.1%, and 7.3% of patients, respectively. Many factors could impact the process by which the mutation is determined, one of which is the sensitivity of the sequencing method used. Most of the initial studies used methods with low sensitivity, and in our study, we used next-generation sequencing, which could explain the smaller percentage of patients with the wild type in our current study.

What Was the Relapse-Free Survival From Recurrence in Patients With and Without Mutations of CTNNB1*?*

Many advances have been made in understanding the biology of desmoid tumors, and *CTNNB1* mutations have been correlated with the risk of recurrence. The S45F mutation was correlated with a higher risk of local recurrence after desmoid tumor resection. However, most studies that evaluated the *CTNNB1* mutation had a limited number of patients. In our study, the multivariable analysis showed that the S45F mutation was associated with an increased risk of relapse after surgical treatment, which is in agreement with Timbergen et al. [44].

Prognostic Model

Prognostic models that predict disease relapse or progression provide important information to guide treatment decisions. It is valuable to have prediction tools for rare diseases such as sarcomas and desmoid tumors because large prospective trials are not feasible. Patients at a high risk of relapse could be spared from radical procedures, and adjuvant therapy could be discussed. Imaging studies could also be personalized based on an individual risk of progression or relapse. Additionally, if a reliable prognostic or risk predictive tool is available, patients with desmoid tumors who are pregnant or have psychologic stressors could be counseled better. This would be especially useful because the incidence of desmoid tumor is higher in women who are of childbearing age. Additionally, surgery could be avoided in patients with a high risk of disease recurrence or pregnancy, and these patients would thus have a lower risk of relapse. Crago et al. [12] developed a nomogram with clinical variables to predict the individual risk of relapse after surgery, but the model was not adjusted for the beta-catenin mutation status.

Calculation of Relapse-free Survival

We created a nomogram with clinical variables including tumor size, tumor site, and *CTNNB1* mutation sequencing to predict recurrence after complete surgical resection. Patients with one or two risk factors had an approximately eightfold increase in the risk of relapse compared with patients who have no risk factor. The 5-year local RFS was only 36.8% for patients at high risk for local recurrence. Our nomogram can identify very high–risk patients who could be spared radical surgical procedures that impair function. For these patients, alternatively, radiation or systemic treatment could be recommended instead of surgery to relieve symptoms and control disease. The *CTNNB1* mutation, especially the S45F mutation, has been shown to be a strong prognostic factor associated with poor RFS [9, 10, 31, 45, 46], and recently, Braggio et al. [6] demonstrated that the *CTNNB1* S45F mutation in a cell line model incites resistance against apoptosis. Although single-gene sequencing may be an affordable test, it is not universally available. Our prediction model has the advantage of using clinical variables with and without an analysis of *CTNNB1* mutations. In a scenario in which sequencing is not accessible or a tumor specimen is not available, it is still possible to predict the risk of recurrence with our model.

The incorporation of genomic profiling of tumors using large next-generation sequencing multigene panels has changed the management of many sarcomas and neoplasms [20] but remains costly. Thus, predictive tools such as our nomogram that combine clinical variables and hotspot *CTNNB1* mutation analysis are very important to improve the selection of patients for surgery, sparing those who need radical surgery with no clear benefit. Recent trials have demonstrated that multi-tyrosine kinase inhibitors shrink tumors and provide symptom relief; thus, systemic treatment with these inhibitors and other agents could be an effective initial approach for patients with desmoid tumors [17, 46].

One important aspect in the management of desmoid tumors is the psychologic distress of patients and social impact of this disease in young patients. In a recent study conducted in Canada with 94 patients with desmoid tumors, the authors found a high prevalence of emotional distress, with anxiety, depression, and poor well-being as

the most frequent disorders [27]. Additionally, the burden of a chronic disease in young, active patients should be measured because problems with interpersonal relationships (such as marriage) and socioeconomic problems such as job absenteeism are frequently reported by patients [41]. Consequently, it is not uncommon to see patients who seek surgery as the primary treatment to eliminate the disease.

Conclusion

We developed a combined clinical and molecular predictive model of disease relapse for patients with resected desmoid tumors. This tool is simple to use and, if validated, could be incorporated into clinical practice guidelines to identify patients at high risk of relapse after surgery. A large multicenter study is necessary to validate our model and explore its applicability in unresectable or relapsed disease to predict the evolution of desmoid tumors.

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