

β-Catenin Mutation Status and Outcomes in Sporadic Desmoid Tumors

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Disclosures of potential conflicts of interest may be found at the end of this article.

Key Words. Desmoid tumor • Beta-catenin • Mutation status • CTNNB1 • Fibromatosis

Learning Objectives

Describe the frequency of *CTNNB1* mutations in sporadic desmoid tumors.

Summarize findings regarding *CTNNB1* mutation status and disease outcome.

ABSTRACT

Background. Mutations in the gene-encoding β-catenin, *CTNNB1*, are highly prevalent in sporadic desmoid tumors and may predict the risk for recurrence. We sought to determine the prevalence of *CTNNB1* mutations in a large cohort of sporadic desmoid tumors and to determine whether *CTNNB1* mutation status correlates with disease outcome.

Methods. Single-base extension genotyping of the *CTNNB1* gene was performed on 145 sporadic, paraffin-embedded desmoid tumor specimens. Correlation of mutation status with outcome was performed on a subset of 115 patients who underwent macroscopically complete surgical resection.

Results. *CTNNB1* mutations were detected in 106 of 145 (73%) tumor specimens and in 86 of 115 (75%) specimens from patients who underwent curative-intent surgical resection, including discrete mutations in the following codons of *CTNNB1*

exon 3: T41A (46%), S45F (25%), S45P (1.7%), and S45C (0.9%). Desmoid tumors of the superficial trunk were significantly less likely to harbor *CTNNB1* mutations than tumors located elsewhere, but none of the other examined clinicopathologic factors were found to be associated with *CTNNB1* mutation status. At a median follow-up of 31 months, 5-year recurrence-free survival was slightly, although not statistically significantly, worse for patients with β-catenin-mutated tumors than for those with wild-type tumors (58% vs. 74%, respectively). The specific *CTNNB1* codon mutation did not correlate with the risk for recurrence.

Conclusion. *CTNNB1* mutations are indeed common in sporadic desmoid tumors. However, our study did not detect a statistically significant difference in recurrence risk according to either the *CTNNB1* mutation status or the specific *CTNNB1* mutation. *The Oncologist* 2013;18:1043–1049

Implications for Practice: Mutations in the gene-encoding β-catenin, *CTNNB1*, are highly prevalent in sporadic desmoid tumors, yet whether mutation status and/or type predict outcome is not certain. In contrast to recently published studies from other groups, we did not detect a significant difference in recurrence risk according to either the *CTNNB1* mutation status or the specific mutation. Accordingly, the impact of *CTNNB1* mutation status in the treatment algorithm of these enigmatic tumors is uncertain at present. However, with the acquisition of further data, and as the efforts to target β-catenin as a therapy mature, knowledge of the *CTNNB1* mutation status may eventually permit a much more rational, individualized treatment approach to desmoid tumors.

INTRODUCTION

Desmoid tumor, also known as aggressive fibromatosis, is a mesenchymal tumor that arises from fascial or deep musculoaponeurotic structures [1, 2]. Although desmoid tumors do not metastasize, they can be locally invasive and exhibit a propensity to recur despite aggressive surgical resection. Desmoid tumors may arise sporadically or in association with

familial adenomatous polyposis (FAP), caused by a germ-line mutation in the adenomatous polyposis coli (APC) gene. Treatment consists of surgery, radiation therapy, and systemic therapies in various combinations. However, a consensus understanding of optimal treatment approaches and their outcomes is confounded by the rarity of desmoid tumors as

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well as by their unpredictable natural history, including the spontaneous regression of some desmoid tumors in the absence of treatment [3, 4].

The occurrence of desmoid tumors in patients with FAP, along with cytogenetic studies of aggressive fibromatoses from patients without FAP that showed the frequent loss of a portion of the long arm of chromosome 5, suggested the potential role of APC mutations and β -catenin dysregulation in sporadic desmoid tumorigenesis [5]. APC controls the cytosolic levels of β -catenin, a cadherin-binding protein involved in cell-cell adhesion and a transcriptional activator of genes such as *c-MYC* that promote cellular proliferation and survival [6]. The APC protein complex marks β -catenin for degradation by the proteasome by sequential phosphorylation of four critical amino acids (serines 45, 37, and 33 and threonine 41), all encoded by exon 3 of the β -catenin gene [7, 8]. Most *CTNNB1* mutations occur within this exon of the gene in the region encoding for the β -catenin protein sequence that contains the serine and threonine residues listed above. These mutations lead to stabilization of the β -catenin protein, translocation from the cytoplasm to the nucleus, and transcriptional activation of target genes [9]. Indeed, several recent studies have demonstrated that the vast majority of sporadic desmoid tumors harbor mutations in the *CTNNB1* gene and not in the *APC* gene, and only three specific mutations in the *CTNNB1* gene have been identified, one at threonine 41 (T41A) and two at serine 45 (S45F and S45P) [5, 10–14]. Furthermore, two recent studies have shown that *CTNNB1*-mutated desmoid tumors have a significantly worse recurrence-free survival (RFS) than wild-type tumors [15, 16]. However, Lazar et al. [16] found that the S45F mutation in particular predicts a higher risk for recurrence; whereas, Domont et al. [15] found that no specific mutant genotype predicts outcome. These discrepant results may be the result of differences in the patient cohorts studied, as Domont et al. only considered extra-abdominal tumors and included a high percentage of recurrent tumors, whereas Lazar et al. included intra-abdominal desmoid tumors and a higher percentage of primary tumors.

In this study, we sought to determine the prevalence of *CTNNB1* mutations in a large cohort of sporadic desmoid tumors, including both primary and recurrent tumors and both intra-abdominal and extra-abdominal sites, and to determine whether *CTNNB1* mutation status correlates with disease outcome.

PATIENTS AND METHODS

Patients and Tumor Samples

A total of 160 formalin-fixed, paraffin-embedded desmoid tumor specimens collected between 1984 and 2009 were retrieved from the pathology archives of the Massachusetts General Hospital. All specimens were evaluated by an experienced soft tissue pathologist (G.P.N.), and a histologic diagnosis of desmoid tumor was confirmed in each case. Clinical data, including demographic, treatment, tumor, and outcome variables were collected and tabulated. To investigate the correlation between β -catenin mutation status and outcome, we included only those patients undergoing macroscopically complete surgical resection (R0 and R1 resections), and we excluded those patients lost to follow-up and for whom complete clinicopathologic data were lacking. This study was

approved by the institutional review board of the Massachusetts General Hospital.

Patient age was defined as the age at initial presentation to Massachusetts General Hospital. This definition was used for patients with both primary and recurrent tumors, because the date of initial diagnosis was not always available for patients who presented with recurrent tumors. Tumor size was determined by pathology reports. Tumor site was categorized as intra-abdominal or extra-abdominal, with the latter further categorized as extremities, girdles (shoulder/axilla and hip/buttock/groin), head and neck, or superficial trunk. Microscopic margin status was retrieved from the final pathology reports and was considered positive if the tumor was identified at the inked margin of the pathologic specimen. Radiation therapy was delivered in an adjuvant fashion at the discretion of the surgeon and radiation oncologist when a higher risk for recurrence was predicted on clinical grounds. In general, patients were seen for follow-up after definitive treatment every three months for the first two years, then every 6 months until year five, and thereafter patients were either seen on a yearly basis or were considered cured, depending on the anticipated risk for recurrence (e.g., higher risk for extremity tumors and lower risk for abdominal wall tumors). Imaging studies were typically obtained with each visit or with every other visit and included an abdominopelvic computed tomography scan for intra-abdominal tumors and a magnetic resonance imaging scan for extremity and body wall desmoid tumors.

Single-Base Extension Mutational Analysis of *CTNNB1* Codons 41 and 45

The histologic diagnosis of desmoid tumor was confirmed by a soft tissue pathologist (G.P.N.), and tumor-rich formalin-fixed paraffin-embedded blocks were identified for DNA extraction, as described previously [17]. Genotyping with a slightly modified protocol was then performed. Briefly, tumor DNA samples were analyzed for recurrent point mutations in *CTNNB1* codons T41 and S45 using the single-base extension SNaPshot assay. *CTNNB1* exon 3, which contains both target codons 41 and 45, was amplified in a single PCR reaction. After thermocycling 38 cycles, PCR were cleaned up by adding 2 μ L of an exonuclease I (Exo) and shrimp alkaline phosphatase (SAP) mixture. The extension primer pool mixed with RR mix (2 μ L) was added directly to the cleaned up PCR amplification product for single-base extension. The extension primers were designed to interrogate four bases corresponding to the two target codons, all in the reverse direction: *CTNNB1* c.121A, c.122C, c.133T, and c.134C. The extension products were treated with SAP using the same procedure used in the Exo-SAP step and then analyzed with the ABI 3500xL Genetic Analyzer (Applied Biosystems, Foster City, CA <http://www.appliedbiosystems.com>). Detailed primer information is available upon request to the authors.

Statistical Methods

Binary and categorical comparisons were made using the chi-squared test. Medians were compared using the Kruskal-Wallis test. Time to local failure and RFS were calculated from the time of surgery at our institution to first local recurrence. Patients who did not have a local recurrence at or before their date of last contact or death were censored at this date. Local recurrence was defined as clinical or radiologic evidence of tu-

Table 1. Patient and disease characteristics ($n = 115$)

Variable	Overall ($n = 115$) n (%) or median (range)	Primary ($n = 95$) n (%) or median (range)	Recurrent ($n = 20$) n (%) or median (range)
Median follow-up (months)	31	28.6	36.9
Gender: female	85 (74%)	69 (73%)	16 (80%)
Age at diagnosis (years); median (range)	36.0 (3–76)	35.0 (3–76)	40.0 (21–76)
Age at diagnosis ≥ 30 years	73 (63%)	58 (61%)	15 (75%)
Disease presentation: primary	95 (83%)	95 (100%)	0 (0%)
Tumor size (cm); median (range)	7.0 (0.8–29.0)	7.0 (0.8–26.6)	6.5 (2.8–29.0)
Tumor size ≥ 5 cm	86 (75%)	70 (74%)	16 (80%)
Tumor site: girdle	18 (16%)	12 (13%)	6 (30%)
Tumor site: head and neck	4 (3.5%)	2 (2.1%)	2 (10%)
Tumor site: extremity	36 (31%)	29 (31%)	7 (35%)
Tumor site: trunk–intra-abdominal	14 (12%)	13 (14%)	1 (5.0%)
Tumor site: trunk–superficial	43 (37%)	39 (41%)	4 (20%)
Resection type: R0	52 (45%)	41 (43%)	11 (55%)
Resection type: R1	63 (55%)	54 (57%)	9 (45%)
Radiation therapy: yes	10 (8.7%)	4 (4.2%)	6 (30%)
S45C mutation	1 (0.9%)	1 (1.1%)	0 (0.0%)
S45F mutation	29 (25%)	23 (24%)	6 (30%)
S45P mutation	2 (1.7%)	2 (2.1%)	0 (0.0%)
T41A mutation	53 (46%)	43 (45%)	10 (50%)
T41A / S45P double mutation	1 (0.9%)	1 (1.1%)	0 (0.0%)
Wild type	29 (25%)	25 (26%)	4 (20%)

mor regrowth at the primary site. RFS curves were estimated using Kaplan-Meier methodology, and comparisons were made using the log-rank test. Univariate and multivariate Cox proportional hazards modeling was used to estimate hazard ratios for RFS. Logistic regression modeling was used to determine factors associated with *CTNNB1* mutations. Two-sided p values are provided. All statistical analyses were performed using SAS version 9.2 (SAS Institute, Inc., Cary, NC, <http://www.sas.com>).

RESULTS

CTNNB1 Mutations are Common in Sporadic Desmoid Tumors

Of the 160 desmoid tumor samples (from 160 patients) that had sufficient DNA extracted for *CTNNB1* exon 3 gene sequencing, results were definitive in 149 (93%). After excluding 4 patients with a history of FAP (none with *CTNNB1* mutations), 145 patients remained. A mutation in exon 3 of the *CTNNB1* gene was identified in 106 (73%) of the 145 samples, and all mutations were found at codons 41 and 45. These were identified as c.121 A > G, or pThr-41-Ala (T41A), which was identified in 65 samples (61%); c.134 C > T, or pSer45Phe (S45F), identified in 35 tumor samples (33%); c.133 T > C, or pSer45Pro (S45P), found in 3 samples (2.8%); and c.134 C > G, or pSer45Cys (S45C), identified in 1 tumor (0.9%) sample. Mutations in both T41A and S45P were identified in the 2 (1.9%) remaining samples.

Patient Characteristics According to *CTNNB1* Genotype

After excluding 30 patients who did not undergo macroscopically complete surgical resection or who had incomplete clinical

copathologic and/or follow-up data, 115 patients remained and were included in the study (Table 1). Of these 115 patients, 85 (74%) were female and 30 (26%) were male. Median age was 36 years. Primary desmoid tumors were present in 95 patients (83%) at presentation, and 20 patients (17%) presented with recurrent tumors. Median tumor size was 7.0 cm (range, 0.8–29.0 cm). Surgical margins were microscopically negative in 52 cases and positive in 63 cases. Adjuvant radiation therapy was administered to 10 patients. The *CTNNB1* mutation rate detected in this cohort (75%, or 86 of 115 cases) was similar to that identified for the entire series, as was the distribution of the specific mutations (T41A, 62%; S45F, 34%; S45P, 2.3%; S45C, 1.2%; and T41A and S45P double mutant, 1.2%). *CTNNB1* mutation status was negatively associated with superficial trunk location (odds ratio = 0.31 [95% confidence interval, 0.13–0.73], $p = .008$), but it was not significantly associated with any other clinicopathologic factor examined, including age, sex, tumor site, presentation status, microscopic margin status, or receipt of radiation therapy. Tumor size, considered to be either a continuous variable or a binary variable (<5 cm or ≥ 5 cm), was also not significantly associated with *CTNNB1* mutation status.

CTNNB1 Mutation Status Does Not Significantly Correlate With Outcome

We sought to determine whether *CTNNB1* mutation status correlated with clinical outcome; namely, RFS. There were a total of 31 local recurrences (27% of the cohort), 5 of which occurred in patients with wild-type tumors and 26 of which occurred in patients with *CTNNB1*-mutated tumors. Five-year RFS was slightly, although not significantly, worse in the

CTNNB1-mutated tumors (58.0%) than in the wild-type tumors (73.6%) ($p = .285$) (Fig. 1). Five-year RFS did not differ significantly among the different *CTNNB1* genotypes (Fig. 2). The estimated 5-year RFS rate was 59.8% (95% CI, 35.4%, 77.5%) for patients with the 45F mutation, 54.9% (35.6%, 70.5%) for patients with the 41A mutation, and 73.6% (46.7%, 88.4%) for patients with wild-type tumors. Because only four samples harbored S45P, S45C, or double mutations, these tumors were excluded from the analysis. In a multivariate Cox regression model that included all patients, girdle/extremity tumors were associated with a shorter time to local recurrence, whereas advanced age and R0 resection status were associated with longer RFS (Table 2). Given the small proportion of patients treated with adjuvant radiation and systemic therapies as well as the diversity and highly variable start and stop dates of the systemic agents, we could not legitimately analyze these data in a time-to-event statistical analysis.

Because of the potential prognostic impact of presentation status (primary vs. recurrent) on outcome, we analyzed the *CTNNB1* genotype in patients with primary tumors ($n = 95$) and found slightly higher 2-year rates of recurrence in patients with mutated tumors (RFS, 64%) compared with rates in patients with wild-type tumors (RFS, 77%); however, this failed to reach statistical significance ($p = .128$) (Fig. 3). Similarly, *CTNNB1* mutation status failed to predict outcome for patients with recurrent desmoid tumors. Because of the potential prognostic impact of surgical margin status on outcome, we also analyzed the *CTNNB1* genotype in patients who underwent R0 resection ($n = 52$), and we found the risk for recurrence to be similar in patients with *CTNNB1*-mutated tumors and in those with wild-type tumors (Fig. 4).

DISCUSSION

In this study, we identified a high frequency (~75%) of *CTNNB1* mutations in a large cohort of sporadic desmoid tumors, including both primary and recurrent tumors at both intra-abdominal and extra-abdominal sites. This mutation rate is considerably higher than the rate of 39% to 54% reported in some of the earliest studies [11, 12, 14], but is quite consistent with that reported in three recent large series, all of which identified *CTNNB1* mutations in 85% of their respective series of sporadic desmoid tumors [10, 15, 16]. Similarly, we also found that all of the mutations are clustered in exon 3 of the *CTNNB1* gene at threonine 41 and serine 45, emphasizing the crucial role that these residues play in the *Wnt* signaling pathway. Although we identified a very limited *CTNNB1* mutational spectrum in our series of desmoid tumors, including high percentages of T41A and S45F mutants, we also identified one patient with an S45C mutation and another patient with a T41A/S45P double mutation. To our knowledge, these two *CTNNB1* mutations have not been described previously in desmoid tumors.

We also sought to determine whether *CTNNB1* mutation status predicted disease outcome in a subset of 115 patients who underwent macroscopically complete surgical resection. We found that 5-year RFS was slightly, although not significantly, worse in mutated tumors (58%) compared with wild-type tumors (74%). This conclusion is true even

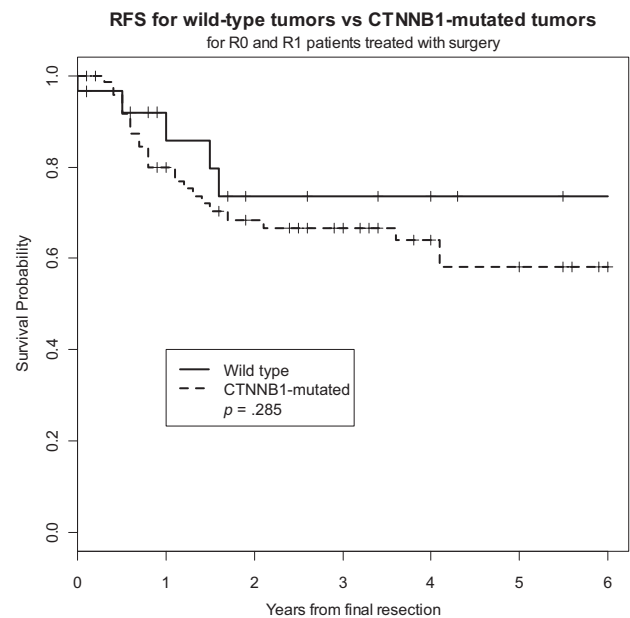


Figure 1. Recurrence-free survival for wild-type tumors versus *CTNNB1*-mutated tumors in all patients.

Abbreviation: RFS, recurrence-free survival.

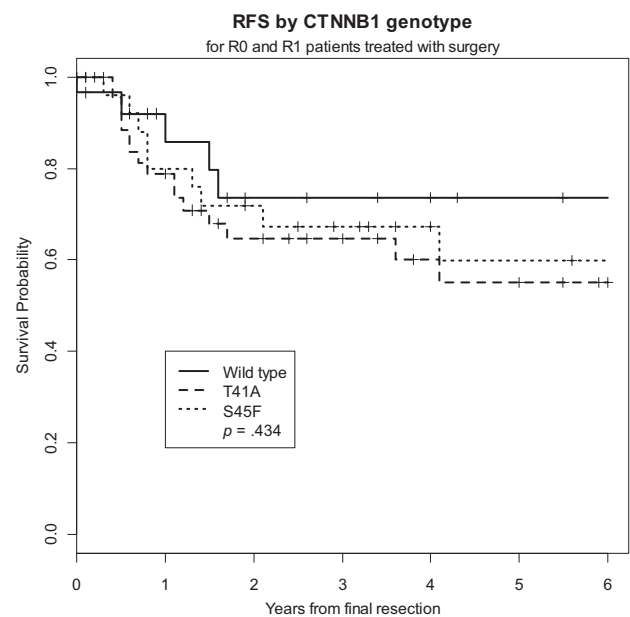


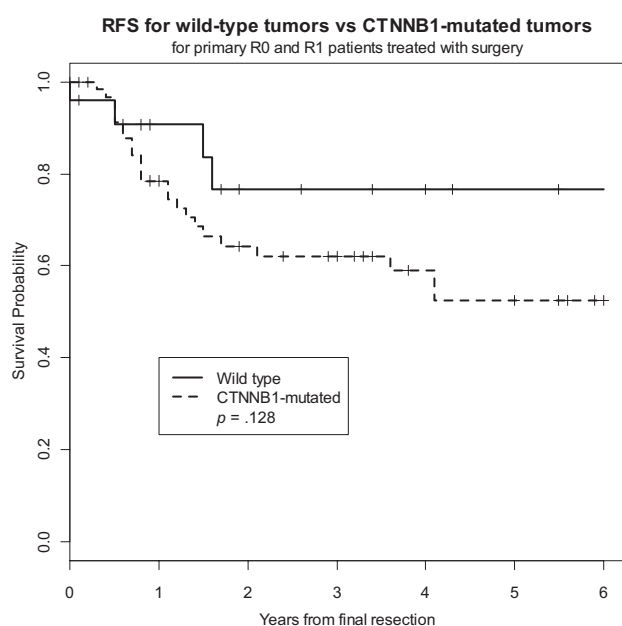
Figure 2. Recurrence-free survival by *CTNNB1* genotype.

Abbreviation: RFS, recurrence-free survival.

when considering only primary tumors (i.e., not including recurrent tumors) and when considering only those tumors resected with negative margins (R0 resections). These results contrast those reported by Domont et al., who found a statistically significant difference in 5-year RFS between wild-type tumors and mutated tumors (75% vs. 43%; $p = .02$) [15]. It should be noted, however, that these authors included eight patients, all of whom had *CTNNB1* mutations, who underwent R2 resections, and we reasonably suspect that all of them subsequently had recurrence, no doubt influencing the conclusions of the study. Nevertheless, our finding that no specific *CTNNB1* mutation geno-

Table 2. Cox regression models for all patients ($n = 115$)

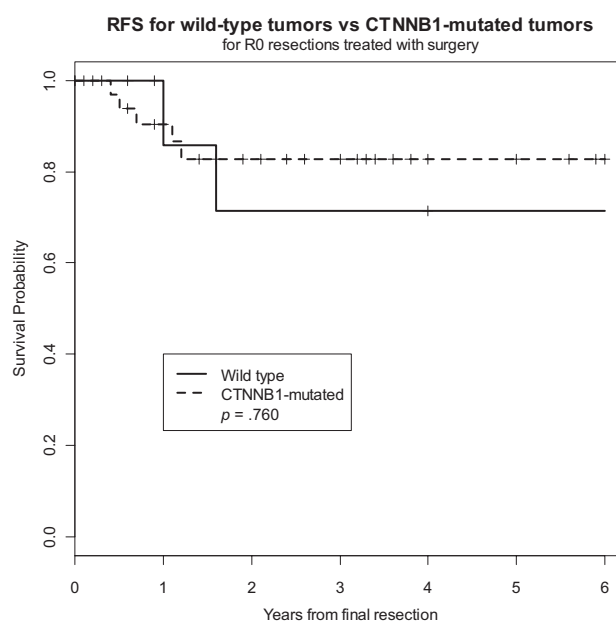
Model	Variable	Hazard ratio (95% confidence interval)	<i>p</i> value
Univariate	Age at diagnosis (years)	0.98 (0.96, 1.00)	.074
	Age at diagnosis ≥ 30 years	0.51 (0.25, 1.03)	.062
	Male	1.25 (0.54, 2.91)	.602
	Tumor location: Girdle or extremities	2.66 (1.23, 5.79)	.013
	Tumor location: Trunk–intra-abdominal	0.58 (0.18, 1.91)	.369
	Tumor location: Trunk–superficial	0.38 (0.15, 1.00)	.050
	Tumor size ≥ 5 cm	1.00 (0.45, 2.24)	.999
	Primary tumor	2.33 (0.70, 7.75)	.166
	Resection type: R0	0.33 (0.14, 0.77)	.010
	Mutation status: Wild-type	0.59 (0.23, 1.56)	.290
Multivariate	Age at diagnosis (years)	0.97 (0.95, 1.00)	.034
	Tumor location: Girdle or extremities	2.93 (1.32, 6.51)	.008
	Resection type: R0	0.38 (0.16, 0.88)	.025

**Figure 3.** Recurrence-free survival for *CTNNB1*-mutated tumors versus wild-type tumors in patients with primary tumors.

Abbreviation: RFS, recurrence-free survival.

type (e.g., T41A or S45F) predicts outcome is in agreement with the findings reported by Domont et al., who found a statistically nonsignificant trend toward a higher risk for recurrence for S45F-mutated tumors. These data contradict the results of Lazar et al., who reported that the risk for recurrence in desmoid tumors was strongly associated with the S45F mutation [16].

These discrepancies may be because each of these studies included distinct populations of patients with desmoid tumors, included variable percentages of patients with primary versus recurrent tumors, included patients with intra-abdominal versus extra-abdominal tumors, and included patients with R0 versus R1 versus R2 resections. Furthermore, the therapies rendered to patients in these studies, including adjuvant radiation and medical therapies, are highly variable. Moreover, the recurrence rates reported in

**Figure 4.** Recurrence-free survival for wild-type tumors versus *CTNNB1*-mutated tumors in patients undergoing R0 resection.

Abbreviation: RFS, recurrence-free survival.

each of these three studies vary quite markedly. These significant differences in recurrence rates may be the result of any of a number of factors, including differences in tumor location, R0 resection rates, and patient age, and may mask the effect that *CTNNB1* mutation status might have on risk for recurrence. For instance, in this study we report 5-year RFS rates of 58% and 73.6% for wild-type and mutated tumors, respectively. Domont et al. reported 5-year RFS rates of 43% and 75%, respectively, and Lazar et al. reported 5-year RFS rates of 23% for S45F-mutated tumors, 57% for T41A-mutated tumors, and 65% for wild-type tumors. Finally, our study is underpowered to show a 15%–20% difference in RFS according to mutation status. Specifically, this study has only 29% power to detect the 16% difference in 5-year RFS (58% vs. 74%) that we identified at a two-sided significance level of 5%. Thus, with greater patient numbers, perhaps by combining our population of patients with

those from other centers, we may be able to demonstrate a statistically significant difference in RFS according to *CTNNB1* mutation status.

Given that there is significant controversy about the true prognostic impact of *CTNNB1* mutation status in desmoid tumors, one might reasonably question what role, if any, this factor plays in the treatment algorithm of these complicated tumors. Certainly, genotyping of *CTNNB1* exon 3 is useful as a diagnostic test to distinguish a desmoid tumor from an otherwise pathologically confusing entity such as postsurgical scar. However, it is not clear what impact *CTNNB1* mutation status might have on the current “watch and wait” posture that many surgeons now take in the treatment of desmoid tumors in light of at least two recent studies supporting the safety of this more conservative approach [3, 18]. These studies confirm that up to 50% of patients with extra-abdominal desmoid tumors will exhibit spontaneous tumor growth arrest after initial progression, and that many if not most of these patients will not require any treatment whatsoever. Clearly, because up to 85% of sporadic desmoid tumors harbor a *CTNNB1* exon 3 mutation, a large proportion of these tumors exhibiting growth arrest are in fact mutated tumors. This finding suggests that β -catenin mutation status, rather than trumping all other clinicopathologic factors, is just one of the many clinical, pathologic, and molecular factors to consider in the management of these tumors. In addition, there is no shortage of controversy when it comes to the prognostic impact of margin status, adjuvant radiation therapy, and other factors on desmoid tumor outcome.

Our practice at Massachusetts General Hospital is to perform *CTNNB1* exon 3 genotyping on every desmoid tumor we biopsy, and we store these data in our clinical outcomes database. A large proportion of these patients, especially those patients who are asymptomatic or who have tumors in anatomically challenging locations, are simply followed expectantly on no therapy at all or on a medical therapy of low toxicity, such as sulindac. Another subset undergo surgical resection and/or radiation therapy, but these decisions are currently made on clinical grounds alone (i.e., degree of symptoms, tumor growth rate, estimated morbidity of the

therapy in question), with little if any consideration given to the *CTNNB1* mutation status. However, the knowledge that a given desmoid tumor harbors a *CTNNB1* mutation, regardless of the type, and thus has elevated levels of nuclear β -catenin, may prove useful as the efforts to target β -catenin as a therapy mature. With the acquisition of further data, especially those garnered through a prospective trial, we hope to acquire a more refined understanding of the molecular determinants of outcome for these tumors to permit a more rational, individualized treatment approach.

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DISCLOSURES

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