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RESEARCH

Prognostic factors for second recurrence after surgical resection of recurrent desmoid-type fibromatosis

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Abstract The optimal management of recurrent desmoid-type fibromatosis is undefined. This study was performed to determine what factors, if any, predict second recurrence after surgical resection of recurrent desmoid tumors. Of 41 patients with recurrent desmoid-type fibromatosis, 29 underwent surgical resection and 8 were followed by observation. Four others received adjuvant chemo/pharmacotherapy. Clinicopathologic features were assessed as prognostic factors for second recurrence after surgical resection of recurrent desmoid tumors by Cox proportional hazards regression. Nine of 29 patients who underwent surgical resection of recurrent desmoid tumor developed a second recurrence. Larger size of recurrent tumor was associated with increased risk of second recurrence (hazard ratio, 1.09; P=0.006). Treatment of the primary tumor with adjuvant radiation therapy also increased risk of re-recurrence (3.41; P=0.032). Second recurrence of desmoid-type fibromatosis after surgical resection is, much like recurrence of primary desmoid tumor, difficult to predict with current prognostic indicators.

Keywords Aggressive fibromatosis · Local recurrence · Prognosis · Second recurrence

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Introduction

While the treatment of primary desmoid-type fibromatosis is becoming more standardized, optimal management of recurrent disease remains highly varied [1–4]. Although this is partly because therapeutic decisions are individualized based on practice-specific and patient-dependent factors, it is also because there are few data available upon which to make informed treatment decisions in this patient population.

The three predominant approaches to the patient with recurrent desmoid tumor include surgical resection, cytotoxic or pharmacologic therapy, and simple observation. Previous studies have reported 5-year second recurrence-free survival rates of 47–80 % after surgical resection of recurrent tumors [5–10], compared to 5-year progression-free survival of 61 % for medical therapy and 54 % for observation alone [11]. Currently, there is no way to predict response to medical therapy or observation and risk factors for re-recurrence after surgical resection of recurrent desmoid tumor remain poorly defined. Although adjuvant radiotherapy appears to increase second recurrence-free survival after surgical resection [5, 7], less is known about other factors, such as the size of the recurrent tumor or the status of surgical resection margins [6, 9]. This study was performed to determine what factors, if any, predict second recurrence after surgical resection of recurrent desmoid tumor.

Patients and Methods

All primary and recurrent desmoid-type fibromatosis specimens resected at Vanderbilt University Medical Center between 1983 and 2011 were identified in the surgical pathology archives (N=122). Hematoxylin and eosin-stained slides were reviewed to confirm the histopathologic diagnosis and

resection margin status (tumor extending to an inked tissue edge was considered a positive margin). For cases with negative margins, the distance between tumor and resection margin (tumor clearance) was measured microscopically. Tumor size and anatomic location were recorded from pathology reports. Clinical records were reviewed for demographic (patient age and sex), adjuvant treatment, and patient outcome information (interval from resection of recurrent desmoid tumor to second recurrence or last clinical follow-up). Median follow-up time from the date of resection of recurrent disease for all patients was 3.6 years (range 2.5 months—22.3 years).

Differences in clinicopathologic variables were compared using Fisher's Exact test or the Mann–Whitney U test. Cox proportional hazards regression was used to evaluate clinicopathologic variables on the likelihood of second recurrence of desmoid tumor after surgical resection. Estimated standard errors were obtained using the method of Huber and White [12, 13]. Given the limited number of events (there were 9 second recurrences), multivariate regression was not performed. All reported *P* values were derived from two-tailed hypothesis tests. All statistical analyses were performed using the Stata® software package (v13, StataCorp, College Station, TX).

The study protocol was approved by the Institutional Review Board at Vanderbilt University Medical Center.

Results

Clinicopathologic Characteristics of Patients with Recurrent Desmoid-Type Fibromatosis

Of 122 patients who underwent resection of primary desmoid tumor, 43 (35 %) developed a local recurrence. Of these 43 patients, 29 underwent resection of recurrent tumor, 4 selected

Table 1 Clinicopathologic characteristics of patients who underwent surgical resection of locally recurrent desmoid-type fibromatosis

	No 2nd recurrence (*N*=20)	2nd recurrence (*N*=9)	*P*[a]
Time to 1st LR (years)	3.0±3.8	2.6±3.0	0.64
Age at diagnosis (years)	33.8±24.3	34.3±20.0	0.92
Age at recurrence (years)	36.9±24.7	38.2±19.0	0.81
Female	12	4	0.69
Male	8	5	
Anatomic site[b]			
High-risk	16	8	1.00
Low-risk	4	1	
Non-syndromic	20	8	0.31
FAP/Gardner syndrome	0	1	
No associated GF	9	1	0.11
Associated GF	11	8	
Size of primary desmoid (cm)	7.1±3.0	12.6±7.0	0.22
Size of recurrence (cm)	6.2±2.8	9.3±6.1	0.34
Tumor clearance (mm)	1.2±0.9	0.7±0.3	0.32
Resection margin negative	7	3	1.00
Resection margin positive	10	5	
Margin negative & ≥1 mm	4	1	0.63
Margin positive or <1 mm	12	7	
No XRT of primary desmoid	19	6	0.08
XRT of primary desmoid	1	3	
No chemotherapy for LR	14	5	0.68
Chemotherapy for LR	6	4	
No XRT of LR	12	6	1.00
XRT of LR	8	3	

Abbreviations: *LR* local recurrence, *FAP* Familial Adenomatosis Polyposis, *GF* Gardner fibroma; XRT, adjuvant radiotherapy

[a] Categorical variables were compared using Fisher's Exact test. Continuous variables were compared using the Mann–Whitney U test

[b] High-risk anatomic sites include the extremities, shoulder/buttock areas, head/neck, and deep trunk. Low-risk sites included the abdominal wall and the superficial soft tissues of the trunk

to receive adjuvant chemotherapy (vinblastine and methotrexate) or pharmacotherapy (COX2 inhibitor and tamoxifen), and 8 declined further therapy. Follow-up information was not available for the other 2 patients. Nine of the 29 patients (31 %) who had resection of recurrent desmoid tumor developed a second recurrence; the median time to second recurrence was 25 months (range, 4 months to 21 years). Clinicopathologic characteristics of patients with second recurrence of resected locally recurrent desmoid tumor are compared to those of patients without re-recurrence in Table 1. For re-recurrent cases, only prior treatment of the primary tumor with radiotherapy approached statistical significance for association with second recurrence.

Risk Factors for Second Recurrence of Desmoid Tumor

Prognostic markers for second recurrence after surgical resection of recurrent disease were assessed using Cox proportional hazard regression (Table 2). Re-estimations including interactions between variables and analysis time and examination of Schoenfeld residuals disclosed no evidence that the assumption of proportional hazards was violated for any of the variables. For every 1 cm increase in tumor size, the risk of second recurrence increased nearly 10 % (Fig. 1). The estimate of the effect of size of recurrent desmoid tumor was not notably different (1.10; 95 % CI 1.03–1.18) when 5 missing values were imputed using partial means matching (40 imputations). Furthermore, additional estimates obtained after stratification by anatomic site, sex, or adjuvant radiotherapy of primary or recurrent tumors were similar to unstratified estimates (data not shown), suggesting that the estimates are fairly robust and not affected by confounding.

Table 2 Univariate analysis of second recurrence-free survival after surgical resection of recurrent desmoid-type fibromatosis

	Hazard ratio (95 % CI)	*P*
Primary resection at outside hospital	0.93 (0.27–3.14)	0.91
Age at diagnosis	0.99 (0.96–1.02)	0.48
Age at recurrence	0.99 (0.97–1.02)	0.47
Size of recurrent tumor	1.09 (1.03–1.17)	0.006
Surgical resection margin	0.97 (0.27–3.55)	0.97
Tumor clearance	0.80 (0.29–2.16)	0.66
Radiotherapy of primary desmoid	3.41 (1.11–10.4)	0.032
Radiotherapy of local recurrence	0.41 (0.08–2.15)	0.29
Chemotherapy for local recurrence	1.71 (0.48–6.10)	0.40
High-risk anatomic site	1.17 (0.12–11.6)	0.89
Sex (male)	3.08 (0.87–10.8)	0.08
Time to 1st recurrence	0.95 (0.80–1.12)	0.53
Associated Gardner fibroma	2.69 (0.35–21.0)	0.35

Abbreviations: *CI* confidence interval

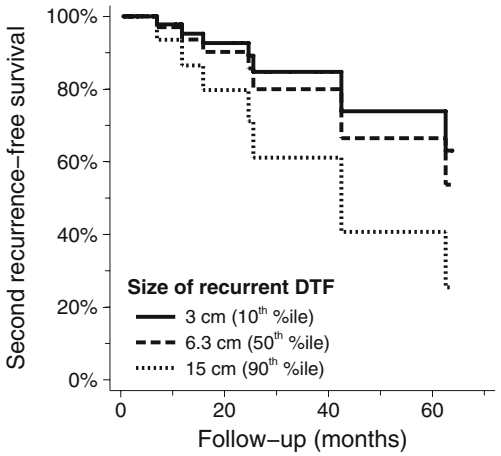

Fig. 1 Second recurrence-free survival after surgical resection of recurrent desmoid-type fibromatosis by size of recurrent tumor (plots for recurrent tumors at the 10th, 50th and 90th percentiles [%ile] of size are shown)

Treatment of the primary tumor with adjuvant therapy was also associated with an increased risk of second recurrence. To determine whether radiation therapy was administered preferentially to patients with high-risk primary tumors, associations between radiotherapy and known poor prognostic indicators were examined. Radiation treatment of the primary tumor was not significantly associated with patient age at diagnosis, tumor size, anatomic location, or surgical resection margin status by exact logistic regression or standard bivariate methods (Fisher's exact test and Student's t-test with unequal variances; data not shown). However, patients whose tumors had been resected at referring institutions were over five times more likely to have been irradiated, likely reflecting referral bias for positive or indeterminate surgical resection margins.

Male sex showed a trend for an increased risk of re-recurrence as well. Other variables associated with increased risk of recurrence after primary resection (age, anatomic site, resection margin status) failed to reach statistical significance in predicting second recurrence. Some variables (race, Familial Adenomatosis Polyposis/Gardner's syndrome, and adjuvant chemotherapy for primary desmoid tumor) were excluded from the analysis because there were limited numbers of patients in comparison groups. There were also too many missing values for the size and resection margin status of primary desmoid tumors (N=11 and N=14, respectively) to use multiple imputation.

Duration of initial disease-free interval was not associated with second recurrence (Table 2). Moreover, the time to second recurrence was not strongly correlated with the initial disease-free interval (Fig. 2). One tumor that initially recurred after 6 months and subsequently recurred almost 21 years after resection of recurrent disease was considered an outlier (and possibly representing a second primary tumor), and therefore was omitted from the regression analysis.

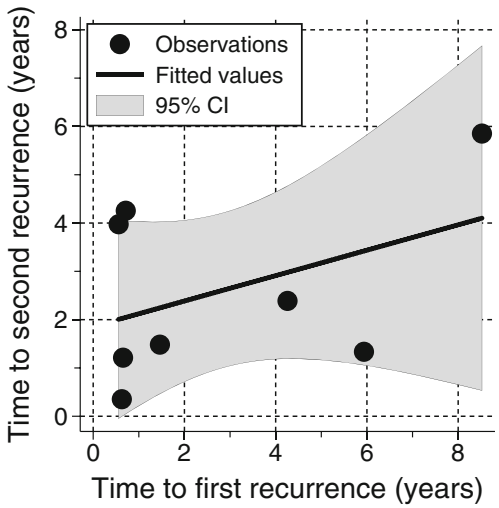

Fig. 2 Linear regression of time to second recurrence of desmoid-type fibromatosis after surgical resection by time to first recurrence. Time to second recurrence was not significantly correlated with time to first recurrence (Spearman's ρ=0.36; *P*=0.39). *Line* represents the linear regression fit; shaded area represents the 95 % confidence interval (CI) for the regression line

Comparison to Non-Surgical Treatment

Disease progression rates for both non-surgical therapy (2 of 4) and simple observation (4 of 8) were comparable to the re-recurrence rate after surgical resection (9 of 29). Although there were too few patients treated non-surgically (*N*=4) to consider this group further, median progression-free interval for patients followed by observation alone was 14 months, compared to median second recurrence-free survival of 192 months for patients who underwent surgical resection of recurrent disease (Fig. 3). However, given the limited sample numbers, this difference failed to reach statistical significance.

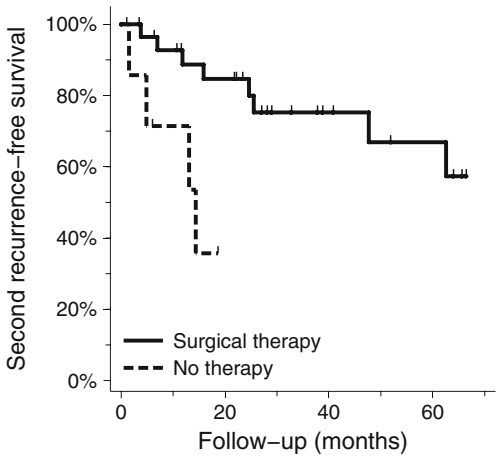

Fig. 3 Comparison of second recurrence-free and progression-free intervals of patients with recurrent desmoid-type fibromatosis after surgical resection or observation only. The hazard ratio for observation was not significantly increased compared to surgical resection (2.81, 95 % confidence interval 0.69-11.5; *P*=0.15)

Discussion

Prognostic factors for second recurrence of desmoid-type fibromatosis after surgical resection of recurrent tumor have not been studied extensively. The results of this study and others suggest that second recurrence of desmoid tumor after surgical resection is, much like recurrence of primary tumors, difficult to predict with current prognostic indicators. In this series, only the size of recurrent tumor and treatment of the primary tumor with adjuvant radiotherapy were associated with an increased risk of second recurrence.

Why radiation therapy of the primary tumor impacts the likelihood of re-recurrence is unclear, but may reflect clinical concern regarding the recurrent potential of the primary tumor or adequacy of the initial surgical resection. This could not be confirmed, however, since neither patient age, anatomic location or resection margin status of the primary desmoid affected the risk of second recurrence or likelihood of receiving radiation treatment for primary disease. Although adjuvant radiotherapy of recurrent disease did not reach statistical significance in this study (due to small sample sizes), other

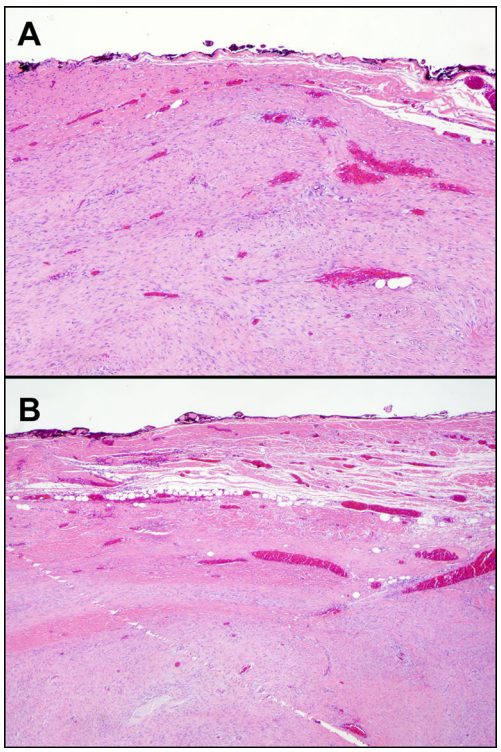

Fig. 4 Representative positive (**a** 40×) and negative (>1 mm) (**b** 20×) surgical resection margins of desmoid-type fibromatosis

studies have reported that adjuvant radiation prolongs second recurrence-free survival [5, 7].

In the current series, surgical resection margin status had no influence on the risk of second recurrence. While achieving negative surgical resection margins has been associated with slightly decreased risk of second recurrence in other studies [5, 6, 9], the reported effect sizes in each of these cohorts failed to reach statistical significance. The importance of adequate surgical resection margins in predicting initial recurrence of primary desmoid tumor has been re-evaluated recently [14]. In contrast to primary tumors, neither tumor clearance nor classification of resection margins as negative and ≥1 mm from tumor vs. positive or <1 mm from tumor (Fig. 4) had significant predictive value for the risk of second recurrence. Although some pathologists advocate the use of β-catenin immunohistochemistry to document resection margin status, others (including the author) feel that this assay is not accurate enough to be applied in this manner. Moreover, nuclear accumulation of β-catenin can be focal in desmoid-type fibromatosis, and may not be present within an area desmoid tumor at the resection margin.

Other prognostic factors that impact the risk of recurrence of primary desmoid tumor, such as age or anatomic site [15] did not affect the risk of second recurrence in this series. There were too few cases in this cohort to adequately assess whether co-existing Gardner fibroma [16] or Familial Polyposis Adenomatosis / Gardner syndrome [17] were associated with increased risk of second recurrence. Duration of the initial disease-free interval did not correlate with recurrence-free survival after resection of recurrent disease, but this is likely due to insufficient sample size (N=9). Other authors have reported that second or third recurrences, when they occur, do not appear to be more aggressive than primary tumors [2, 3, 5, 8].

While second recurrence-free survival after surgery in this cohort was similar to that reported by another institution [5], progression-free survival rates for the non-surgical groups were lower [11, 18]. Though not the primary objective of this study, the results fail to provide evidence that any one of these therapeutic options is significantly better than the others. However, although functional or patient-reported outcomes were not assessed in this study, other investigators have shown that morbidity increases with subsequent surgical procedures [8, 19].

The size of recurrent desmoid-type fibromatosis and administration of adjuvant radiotherapy to primary desmoid tumors seem to affect the rate of second recurrence after surgical resection. All studies reporting risk factors for second recurrence or progression of recurrent desmoid-type fibromatosis, including this one, are affected by limited sample sizes. A systematic review and meta-analysis may be warranted to further define risk factors for second recurrence of desmoid tumor after surgical resection and provide a basis for data-driven clinical management decisions for these patients.

Compliance with Ethical Standards

Funding The author has no relevant sources of funding to disclose.

Conflicts of Interest The author declares that he has no conflict of interest.

Ethical Approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. For this type of study formal consent is not required. A waiver of informed consent was obtained from the Institutional Review Board at Vanderbilt University.

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