



ORIGINAL ARTICLE

Risk factors for recurrence of abdominal aggressive fibromatosis after radical surgery: An 8-year observational study from a chinese high-volume sarcoma center

Mingkun Zhao^{1†}, Guanghui Zhu^{2†}, Aobo Zhuang^{1†}, Hanxing Tong^{1,3}, Yuan Fang^{1*}, Yong Zhang^{1,3*}

¹Department of General Surgery, Shanghai Public Health Clinical Center, Fudan University, Shanghai, China, ²Department of Gastrointestinal Surgery, Shanghai Municipal Hospital of Traditional Chinese Medicine, Shanghai University of Traditional Chinese Medicine, ³Department of General Surgery, Zhongshan Hospital, Fudan University, Shanghai, China

[†]These authors contributed equally to this work

ARTICLE INFO

Article history:

Received: June 14, 2022

Revised: July 26, 2022

Accepted: July 27, 2022

Published online: August 12, 2022

Keywords:

aggressive fibromatosis

local recurrence

progression-free survival

radical surgery

*Corresponding authors:

Yuan Fang, Department of General Surgery,

Shanghai Public Health Clinical Center,

Fudan University, Shanghai, China.

E-mail: fangyuan@shphc.org.cn

Yong Zhang, Department of General Surgery,

Shanghai Public Health Clinical Center, Fudan

University, Shanghai, China.

Department of General Surgery, Zhongshan

Hospital, Fudan University, Shanghai, China.

E-mail: zhangyong1@zs-hospital.sh.cn

Abstract

Background: There are lacking standard treatment guidelines for aggressive fibromatosis (AF) because of its rarity.

Aim: This study aimed to investigate the risk factors for recurrence and survival of abdominal AF after radical surgical resection.

Methods: From August 2012 to December 2020, a retrospective analysis was conducted on the clinical data of 69 AF in Shanghai Public Health Clinical Center Affiliated to Fudan University, with the tumor locating either in the abdominal wall or in the abdominal cavity. The main observation end point was progression-free survival time (PFS) and overall survival time (OS).

Results: All 69 patients achieved microscopic R0 resection, 10 (14.5%) had local recurrence, and 3 (4.3%) died. The PFS rate after 1, 3, 5, and 10 years was 96.8%, 87.7%, 78.8%, and 78.8%, respectively. The OS rate after 1, 3, 5, and 10 years was 100%, 100%, 92.9%, and 81.3%, respectively. In 10 patients with recurrence, the median recurrence time was 17.6 months. Concomitant familial adenomatous polyposis (FAP) and history of previous recurrence were independent risk factors of post-operative recurrence.

Conclusion: After radical surgery of abdominal AF, the local recurrence rate was 15%. Concomitant FAP and a previous history of recurrence were independent risk factors of post-operative recurrence. R0 and a combined organ resection should be performed especially in FAP patients to minimize the recurrence and improve the prognosis.

Relevance for Patients: The present study identifies the risk factors of recurrence in AF and suggests R0 resection especially in concomitant FAP patients. A wait-and-see strategy should not be generally implemented and radical surgery will bring clinical benefits to patients with such kind of rare disease.

© 2022 Author(s). This is an Open-Access article distributed under the terms of the Creative Commons Attribution-Noncommercial License, permitting all non-commercial use, distribution, and reproduction in any medium, provided the original work is properly cited.

1. Introduction

Aggressive fibromatosis (AF), also known as desmoid fibromatosis, is a deep soft-tissue tumor with malignant potential originating from fibroblasts/myofibroblasts. First reported in 1832 by Mac-Farlane [1], its incidence rate reached 5 per 1,000,000 population/year, and comprised 3% of all the soft tissue tumors [2]. AF is divided into sporadic and hereditary types [3], with sporadic type being more common in extra-abdominal location and associated with mutations in the β -catenin gene [4], while hereditary type were more common in patients with familial adenomatous polyposis (FAP) and usually in the abdominal (AD) wall or intra-abdominal (I-AD) mesenteric and visceral locations. AF rarely

develops metastases and is characterized by locally aggressive growth and unpredictable recurrence, with the recurrence rate reached 20–30% after surgical resection [5]. Due to disease rarity, clinicians often perform surgical treatment and adjuvant treatment through personal experience. Our center is the highest-volume sarcoma Center in Southern China, and now we collected the clinicopathological, surgical, and adjuvant treatment data of abdominal AF in the past 10 years, and analyzed the risk factors for recurrence and survival, aiming to reduce the post-operative recurrence rate and improve the survival and clinical efficacy.

2. Materials and Methods

This retrospective study was conducted at the Shanghai Public Health Clinical Center, Fudan University. As approved by the ethics committee of Shanghai Public Health Clinical Center (No. 2021-Y01-01), this study analyzed the clinicopathological data of patients pathologically diagnosed with AF either in the abdominal (AD) wall or I-AD location from August 2012 to December 2020. All patients signed an informed consent form before the surgery. The principle of surgery was to ensure the margin at least 3 cm or more from the tumor. After complete resection of the tumor, larger defects on the abdominal wall were appropriately selected for biological mesh or peduncle flap transplantation. According to the patient's surgical margin, tumor size and history of recurrence, post-operative supplementary radiotherapy, and chemotherapy were implemented. The collected data included gender, age, symptoms, maximum diameter, presentation status (primary or recurrence), tumor location (AD or I-AD), multifocality, Ki-67 staining, neoadjuvant treatment and adjuvant radiotherapy, and chemotherapy. Follow-up was until April 30, 2022, and recurrence was assessed every 3 months by computed tomography or magnetic resource imaging. New lesions or significant enlargement of the original lesions were defined as disease progression. The main observation indicators were progression-free survival time (PFS) and overall survival time (OS).

All data were analyzed using the Statistical Package for the Social Sciences (SPSS version 26.0, IBM Corp., Armonk, NY, USA). Quantitative data were expressed as the mean±standard deviation and compared with paired Student's *t*-tests and Mann–Whitney *U*-tests for normally and non-normally distributed values, respectively. Qualitative data and ordinal data were presented as the number of cases and percentages, and the groups were compared using χ^2 tests or Mann–Whitney *U*-tests, as appropriate. Kaplan–Meier method and Cox proportional-hazards regression were used to analyze univariate and multivariate risk factors for post-operative recurrence and survival. $P < 0.05$ was considered statistically significant.

3. Results

3.1. Demographic and clinicopathological characteristic

Among the 69 patients, 20 (29%) were males and 49 (71%) were females; the average age was 37.3 ± 13.2 years. Three (4.3%) of these cases were hereditary type with FAP. Moreover, 64 (92.8%)

patients were operated for the first time and 5 patients (7.2%) were reoperated after recurrence. Forty-nine patients were treated immediately in our center after the onset of the disease, including four cases of surgery after neoadjuvant treatment and 45 cases of upfront surgery. Twenty patients had a history of treatment in the other hospital, of which five patients received surgery after recurrence. The other 15 patients had surgery after tumor biopsy. In terms of clinical symptoms, 18 (26.1%) of the 69 patients had symptoms: 16 cases had abdominal pain or distension, one case had lower limb pain, and one case had fever. Forty-one (59.4%) cases were asymptomatic and symptoms of the other 10 cases were unknown.

When we were exploring the abdomen, 63 (91.3%) cases were single and 6 (8.7%) were multiple lesions; the average tumor diameter was 9.22 ± 5.70 cm. There were 32 (46.4%) AD and 37 (53.6%) I-AD patients. It is interesting that in the female patients with the AD type, we only observed the tumor site near the scar in two patients. The position of I-AD included 13 cases at mesentery, 11 cases at retroperitoneum, six cases at pelvic cavity, two cases at right lower quadrant, and two cases at left upper quadrant. Thirty-two (46.4%) patients underwent combined organ resection and 37 (53.6%) cases received tumor resection.

After radical surgery, 13 (18.8%) patients developed post-operative complications. There were seven cases of complications < Clavien-Dindo Grade 3 and 6 cases of complications \geq Grade 3, all of which were treated by percutaneous drainage or other interventional therapy. The immunostaining results showed that all tumor tissues were nuclear-positive for β -catenin. Ten cases were negative and 51 cases were positive in 61 cases of Ki-67 staining. In terms of 14 cases with CTNNB1 gene mutation sequencing, there were T41A mutations in nine cases and S45P mutations in five cases (Table 1).

3.2. Post-operative treatment

Thirteen patients selected post-operative adjuvant therapy, of which nine cases underwent radiotherapy with the regimen: 50 Gy in 28 fractions; whereas two cases had adjuvant chemotherapy using epirubicin plus dacarbazine for four cycles. One patient received anti-endocrine therapy (tamoxifen) plus non-steroidal anti-inflammatory drugs (NSAIDs) (celebrex or meloxicam) while one patient only used NSAIDs.

3.3. Prognostic factors after radical surgery

Of the 69 patients undergoing radical surgery, 10 (14.5%) had recurrence, all of which were local recurrence. Five patients were treated with epirubicin combined with dacarbazine plus NSAIDs (celebride or meloxicam) for 2–8 cycles; two patients received surgery, one patient selected NSAIDs, and two patients selected only observation. There were only 3 (4.3%) patients who had died before the last day of follow-up.

The median follow-up time for all the patients was 49.4 months (1–153.6 months). The PFS in 1, 3, 5, and 10 years was 96.8%, 87.7%, 78.8%, and 78.8%, respectively. The OS at 1, 3, 5, and 10 years was 100%, 100%, 92.9%, and 81.3%, respectively. In

Table 1. Clinicopathological parameters in aggressive fibromatosis patients.

Clinicopathological parameters (n = 69)	n (%)
Age (years; mean ± SD)	37.3 ± 13.2
Gender	
Male	20 (29)
Female	49 (71)
FAP	
No	66 (95.7)
Yes	3 (4.3)
Reoperation after recurrence	
No	64 (92.8)
Yes	5 (7.2)
Symptom	
No	41 (59.4)
Yes	18 (26.1)
Unknown	10 (14.5)
Multifocality	
No	63 (91.3)
Yes	6 (8.7)
Tumor Site	
I-AD	37 (53.6)
AD	32 (46.4)
Combined organ resection	
No	37 (53.6)
Yes	32 (46.4)
Size (cm, mean ± SD)	9.2 ± 5.7
Adjuvant therapy	
Chemotherapy and Radiotherapy	11 (15.9)
Anti-endocrine and NSAIDs	2 (2.9)
Observation	56 (81.2)
Treatment after recurrence	
Surgery	2 (20)
Chemotherapy	5 (50)
NSAIDs	1 (10)
Observation	2 (20)
CTNBB1 mutation type	
T41A	9 (60)
S45P	6 (40)

FAP: Familial adenomatous polyposis; I-AD: Intra-abdominal; AD: Abdominal; NSAIDs: Non-steroidal anti-inflammatory drugs; CTNBB1: Catenin beta 1

10 patients with recurrence, the median recurrence time was 17.6 months.

According to Kaplan-Meier analysis, concomitant FAP, history of previous recurrence, multiple lesions, combined organ resection, and I-AD type were risk factors associated with recurrence, and Cox regression analysis showed that concomitant FAP and history of previous recurrence were independent risk factors associated with recurrence (Table 2). Finally, we divided the entire cohort into two groups: High-risk group was either FAP or history of previous recurrence and low-risk group was neither FAP nor history of previous recurrence. Again, we found

Table 2. Univariate and multivariate analysis of prognostic factors for PFS

Parameters	n	PFS		
		Univariate P-value	Multivariate P-value	HR (95% CI)
Age		0.687		
<37	40			
≥37	29			
Gender		0.362		
Female	49			
Male	20			
FAP		<0.001	0.004	2.428–100.333
No	66			
Yes	3			
Reoperation after recurrence		0.005	0.011	1.599–39.061
No	64			
Yes	5			
Multifocality		<0.001	0.081	0.849–17.246
No	63			
Yes	6			
Combined organ resection		<0.001	0.374	0.070–1196.129
No	37			
Yes	32			
Diameter >9 cm		0.06		
No	33			
Yes	25			
Tumor site		0.012	0.871	0.011–195.027
AD	32			
I-AD	37			
Chemoradiotherapy		0.986		
No	58			
Yes	11			
CTNBB1 mutation		0.617		
T41A	9			
S45P	5			

FAP: Familial adenomatous polyposis; I-AD: Intra-abdominal; AD: Abdominal; NSAIDs: Non-steroidal anti-inflammatory drugs; CTNBB1: Catenin beta 1. Values in bold indicate statistically significant results ($P < 0.05$)

that there were significant differences of PFS between these two groups (Figure 1).

4. Discussion

Nowadays, the treatment of AF mainly includes active surveillance, surgery, radiotherapy, chemotherapy, targeted therapy, and hormonal therapy [6]. However, because of the rarity of AF, there is still lack of randomized and controlled trials focusing on AF and no standardized treatment of the disease.

Historical treatment of AF involved up-front surgical resection for symptomatic and asymptomatic patients [6]. However, in recent years, a number of studies have reported spontaneous regression of tumors and wait-and-see treatment became the

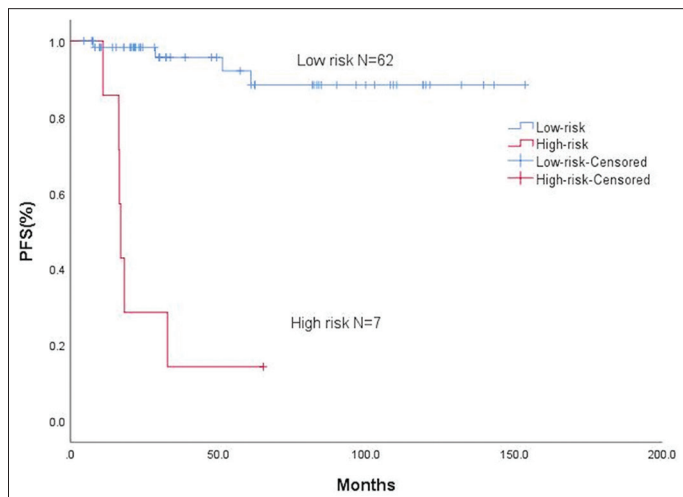


Figure 1. Progression-free survival between high- and low-risk groups in the 69 abdominal aggressive fibromatosis patients.

mainstay modes of AF [7]. One study [4] found that 36% of the included AF patients were stable; however, nearly half of the 168 patients included in the study located on the abdominal wall. Moreover, for I-AD type of AF, due to its aggressiveness to peripheral organs and the severe complications that may lead to perforation and obstruction, we believed that radical surgical resection is still needed. The National Comprehensive Cancer Network recommended the indications of non-surgical treatment of AF was that there were no clinical symptoms and the tumor location did not cause organ dysfunction due to tumor enlargement and infiltration [8]. Therefore, identifying factors predictive for the recurrence will help to choose the appropriate treatment strategy and personalized treatment.

As to the prognostic factors of AF, multiple studies and consensus suggest that abdominal AF, younger age, large tumor size, and β -catenin mutations were recognized risk factors for post-operative recurrence of AF [9]. In many surgical studies [10,11], margin status is the only independent risk factor of local recurrence according to multivariate analysis. Hence, in our study, we included all the R0 resection patients to analyze the risk factors after the radical surgery. In this study, it was discovered that the independent risk factors for recurrence were concomitant FAP and history of previous recurrence. Therefore, we suggested that during the first surgery, if the tumor was found to infiltrate the surrounding organs, especially in the patients with FAP history, R0 resection should be performed. Moreover, based on our experiences, combined organ resection should be performed to minimize the possibility of recurrence and improve the prognosis.

In addition, for patients who cannot be surgically resected or shortly experienced recurrence after surgery, adjuvant chemotherapy or radiotherapy should be considered. A case-control study [11] showed that 34 patients accepting surgery alone were matched with another 34 patients who underwent surgery combined with post-operative radiotherapy, and factors such as gender, age, tumor size, and incision margin were controlled

in the two groups. The results showed that post-operative combined radiotherapy could significantly improve the 3-year PFS of patients compared with surgery alone. At present, the recommended dose is 50~56 Gy while the single recommended dose is 1.8–2 Gy, and the long-term effective local control rate can reach 81% [12]. However, AF is mostly young patients with a long-expected survival, and side effect such as tissue fibrosis, ischemic necrosis, and even secondary malignancy caused by radiotherapy will occur in the long run. Besides, radiotherapy also carried the risk of radiation enteritis. Therefore, radiation therapy should be used as a supplementary treatment when the surgical margin was found positive [13].

In light of estrogen receptor (ER), subtype ERb is positive on the AF cells [1], so tamoxifen is sometimes used to bind to this receptor and block the estrogen signaling pathway. Moreover, non-steroidal drugs (NSAIDs) could inhibit the activation of Wnt/ β -catenin by inhibiting the activation of platelet-derived growth factor receptors (PDGFR) mediated by cyclooxygenase 2 (COX2), thus playing a role in inhibiting the proliferative growth of AF [14]. In terms of chemotherapy, methotrexate and vinblastine were commonly used chemotherapy regimens for AF. However, the side effects caused by chemotherapy, including nerve injury or myelosuppression, were far more than that of endocrine and non-steroidal drugs. Nonetheless, chemotherapy is used as a supplementary treatment after the surgical margin was found positive [15].

There were some limitations to our study. First, it was a retrospective study and there were still biases in statistical analysis. Second, because of its lower malignancy potential, some of the patients chose the wait-and-see strategy or only oral NSAIDs, which caused the regimen of neoadjuvant and post-operative chemotherapy and radiotherapy were inconsistent.

Generally speaking, the perspective for the future treatment of AF continues to be hopeful. For some small AD type of AF, the patient should receive a period of watchful waiting and make a careful deliberation of upfront surgery. However, to the I-AD type, especially concomitant with FAP, we believed that surgery is feasible with acceptable morbidity and long-term PFS. However, this conclusion still needs to be confirmed by the multi-institutional, large-scale, and prospective clinical study.

Acknowledgments

None.

Funding

This study was supported by Clinical Special Funding of the Shanghai Municipal Health Commission (202140083).

Conflict of Interest

The authors declare that they have no competing interests.

Ethics Approval and Consent to Participate

This retrospective study was conducted at the Shanghai Public Health Clinical Center, Fudan University and approved by the

ethics committee of Shanghai Public Health Clinical Center (No.2021-Y01-01). Written informed consent was obtained from the patient and legal guardian for the publication of these case reports.

Consent for Publication

Written informed consent was obtained from the patient and legal guardian for the publication of these case reports.

References

- [1] Ganeshan D, Amini B, Nikolaidis P, Assing M, Vikram R. Current Update on Desmoid Fibromatosis. *J Comput Assist Tomogr* 2019;43:29-38.
- [2] Ratan R, Roland CL, Bishop AJ. Desmoid Fibromatosis: Management in an Era of Increasing Options. *Curr Oncol Rep* 2021;23:41.
- [3] Villalobos VM, Hall F, Jimeno A, Gore L, Kern K, Cesari R, et al. Long-term Follow-up of Desmoid Fibromatosis Treated with PF-03084014, an Oral Gamma Secretase Inhibitor. *Ann Surg Oncol* 2018;25:768-75.
- [4] van Houdt WJ, Husson O, Patel A, Jones RL, Smith MJ, Miah AB, et al. Outcome of Primary Desmoid Tumors at all Anatomic Locations Initially Managed with Active Surveillance. *Ann Surg Oncol* 2019;26:4699-706.
- [5] Bonvalot S, Eldweny H, Haddad V, Rimareix F, Missenard G, Oberlin O, et al. Extra-abdominal Primary Fibromatosis: Aggressive Management could be Avoided in a Subgroup of Patients. *Eur J Surg Oncol* 2008;34:462-8.
- [6] Improta L, Tzanis D, Bouhadiba T, Abdelhafidh K, Bonvalot S. Desmoid Tumours in the Surveillance Era: What are the Remaining Indications for Surgery? *Eur J Surg Oncol* 2020;46:1310-4.
- [7] Seinen JM, Niebling MG, Bastiaannet E, Pras B, Hoekstra HJ. Four Different Treatment Strategies in Aggressive Fibromatosis: A Systematic Review. *Clin Transl Radiat Oncol* 2018;12:1-7.
- [8] Desmoid Tumor Working Group. The Management of Desmoid Tumours: A Joint Global Consensus-based Guideline Approach for Adult and Paediatric Patients. *Eur J Cancer* 2020;127:96-107.
- [9] Harati K, Jaenisch A, Behr B, Goertz O, Harati A, Hirsch T, et al. Effect of Surgical Margins on Prognosis in Aggressive Fibromatosis: A Single-institutional Analysis of 90 patients. *Oncol Lett* 2017;14:5129-34.
- [10] Zhou SC, Pei W, Sun Z, Zhou ZX, Wang S, Liang JW, et al. Clinicopathological Characteristics and Prognostic Factors for the Recurrence of Abdominal Desmoid Tumors: A Retrospective Study of 113 Patients from Two Chinese Hospitals. *Chin Med J (Engl)* 2020;134:1505-7.
- [11] Janssen ML, van Broekhoven DL, Cates JM, Bramer WM, Nuyttens JJ, Gronchi A, et al. Meta-analysis of the Influence of Surgical Margin and Adjuvant Radiotherapy on Local Recurrence After Resection of Sporadic Desmoid-type Fibromatosis. *Br J Surg* 2017;104:347-57.
- [12] Santti K, Beule A, Tuomikoski L, Rönty M, Jääskeläinen AS, Saarilahti K, et al. Radiotherapy in Desmoid Tumors: Treatment Response, Local Control, and Analysis of Local Failures. *Strahlenther Onkol* 2017;193:269-75.
- [13] Jelinek JA, Stelzer KJ, Conrad E, Bruckner J, Kliot M, Koh W, et al. The Efficacy of Radiotherapy as Postoperative Treatment for Desmoid Tumors. *Int J Radiat Oncol Biol Phys* 2001;50:121-5.
- [14] Cho JY, Gupta S, Cho HS, Park MS, Mok SJ, Han I, et al. Role of Nonsteroidal Anti-inflammatory Drug in Treatment of Extra-abdominal Desmoid Tumors. *Clin Orthop Surg* 2018;10:225-33.
- [15] Shimizu K, Hamada S, Sakai T, Koike H, Yoshida M, Nishida Y. Efficacy of Low-dose Chemotherapy with Methotrexate and Vinblastine for Patients with Extra-abdominal Desmoid-type Fibromatosis: A Systematic Review. *Jpn J Clin Oncol* 2020;50:419-24.

Publisher's note

Whioce Publishing remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.