

Value of imaging findings in predicting post-operative recurrence of desmoid-type fibromatosis

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Received March 4, 2018; Accepted October 1, 2019

DOI: 10.3892/ol.2019.11129

Abstract. Desmoid-type fibromatosis is a rare type of soft-tissue tumor originating from connective tissue of the fascia or aponeurosis, which exhibits aggressive growth, high likelihood of relapse and less frequent distant metastasis. The present study aimed to predict the recurrence rate and time by retrospectively analyzing the clinical data (sex, age and recurrence time), imaging findings [tumor location, maximum diameter, border, computed tomography (CT) enhancement ratio, magnetic resonance enhancement ratio and T2 signal ratio] and pathological features (Ki-67 and microscopic margin) in a total of 102 cases of pathologically confirmed desmoid-type fibromatosis. The risk ratio of each factor was calculated using the Cox proportional hazards regression model and the cumulative recurrence-free survival rate was determined using the Kaplan-Meier method and the log-rank test. The cohort comprised of 73 females and 29 males, with mean age of 32.86±12.64 years (range, 6-78 years). The 1-year and 2-year recurrence rate was 31 and 54%, respectively. The median age at recurrence was 29 years. Univariate analysis indicated that sex, maximum tumor diameter, CT enhancement ratio and Ki-67 had a significant effect on the recurrence time. Furthermore, multivariate analysis revealed that sex, maximum tumor diameter, Ki-67 and T2 signal ratio were independently associated with the time of recurrence, and the risk ratios were 0.424, 1.100, 1.084 and 1.268, respectively. Therefore, in male

patients with a larger maximum tumor diameter, positivity for Ki-67 and a higher T2 signal ratio, desmoid-type fibromatosis was more likely to recur after surgery.

Introduction

Desmoid-type fibromatosis is a tumor-like proliferating fibrous tissue disorder, composed of clonal proliferation of fibroblasts and myofibroblasts (1). It is a rare soft-tissue tumor originating from connective tissue of the fascia or aponeurosis. Genetic, endocrine and physical factors, such as pregnancy and trauma, play an important role in the etiology of the disease (2). Desmoid-type fibromatosis is characterized by aggressive growth, high likelihood of relapse and less frequent distant metastasis (3). The recurrence rate after complete tumor resection is between 20 and 60%, about 8% of patients die due to rapid recurrence, and 20 to 30% of patients achieve tumor stabilization or spontaneous remission (4). The peak incidence of desmoid-type fibromatosis is from 35-40 years old, whereas for women it is mainly during the reproductive age (5). Although rare, it is a highly atopic tumor with unpredictable biological behavior that may occur in any part of the body (6). According to its anatomic location, desmoid-type fibromatosis is generally divided into three types: Abdominal external type (trunk and limbs), abdominal wall type and intra-abdominal type (7). Due to the variety of location and clinical symptoms of desmoid-type fibromatosis, it often leads to difficult diagnosis, and there are many diseases that need to be differentiated, such as inflammatory lesions, liposarcoma and fibrosarcoma (8). The most common complaints of patients are painless progressive growth of the mass, neurological dysfunction, joint stiffness and abdominal discomfort due to the tumor growth (9). The imaging findings of desmoid-type fibromatosis depend on the number of fibroblasts proliferating in the tumor, as well as the fiber composition, collagen content and tumor supply (10). Areas of dense fibrous tissue and scar-like collagen fiber deposition usually show low signal for T1WI and T2WI, and no enhancement after injection of contrast agent (11). In areas where tumor cells are concentrated, there is a moderate to significant enhancement following the injection of contrast agent, whereas the matrix portion is weakly enhanced (12). Certain cases of desmoid-type fibromatosis remain stable following surgery, while others progress rapidly (13). Therefore, it is important to choose the

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Key words: desmoid-type fibromatosis, recurrence, imaging findings, sex, tumor maximum diameter, Ki-67, T2 signal ratio

appropriate treatment. Currently, treatments for desmoid-type fibromatosis include surgical tumor resection, radiation therapy, hormonal therapy, and non-steroidal anti-inflammatory therapy. Surgery is currently the preferred treatment for desmoid-type fibromatosis. The incidence of desmoid-type fibromatosis is ~2-4 cases per 1 million, accounting for 0.03% of all tumors (14,15). Since the cases are rare, the factors that can accurately predict tumor recurrence have not been confirmed. In the present study, through the assessment of tissue samples and regression analysis using the Cox proportional hazards model, factors significantly affecting the recurrence rate and time of desmoid-type fibromatosis were identified.

Materials and methods

General patient data. A total of 102 cases of pathologically confirmed desmoid-type fibromatosis were collected from Jiaxing Traditional Chinese Medicine Hospital between January 2011 and May 2017. The cohort comprised of 73 females and 29 males, with mean age of 32.86 ± 12.64 years (range, 6-78 years). The data collected included clinical data [sex, age, relapse status at the end of the follow-up (every 3 months) in May 2017 and recurrence time], imaging data [tumor type, maximum diameter, tumor margin, computed tomography (CT) enhancement ratio, magnetic resonance (MR) enhancement ratio and T2 signal ratio] and pathological data (Ki-67 and endoscopic margin). Among them, 71 cases (21 males and 50 females) experienced a relapse and 31 cases (8 males and 23 females) had no relapse. A total of 89 cases had an unexplained mass, 2 had a mass identified on physical examination, 7 cases were identified after trauma, 23 cases had pain associated with the lesions, 2 cases had joint deformities, 5 cases had limited joint activity, 5 cases had abdominal pain and 2 cases had intestinal obstruction. Furthermore, 2 cases were identified during pregnancy, 1 case following surgical resection of the thyroid carcinoma, 1 case following surgical resection of endometrial carcinoma, 1 following surgical resection of ovarian cyst, 2 after appendectomy, 1 after splenectomy and 1 following intestinal polyp removal on colonoscopy. Ethics approval was obtained from the Medical Ethics Committee of Jiaxing Chinese Medicine Hospital (no. 2016-JZLK-005). All patients were informed and provided oral consent to participate.

CT examination. CT scans were performed using a Siemens SOMATOM Sensation 16-slice spiral CT (Siemens AG) with a layer thickness of 2.5 mm and a layer spacing of 2.5 mm. The 0.625-mm standard algorithm was used for reconstruction. The coronal plane and sagittal plane were reconstructed with a layer thickness of 2.0 mm. Enhanced scanning was performed at 25, 70 and 300 sec, respectively, after injection of ioversol (300 mg/100 ml; Medtronic Ltd.) at a rate of 2.5 ml/sec and a dose of 80 ml.

MR imaging (MRI) examination. MRI was performed with a GE Signal 1.5T or 3.0T MRI scanner (GE Healthcare Life Sciences). TOSOPA phased array coils, EXTREM surface coils or GPFLEX surface coils were used, depending on the scan site. The scanning sequences were: T1-weighted imaging [(T1WI) Repetition time (TR), 360-560 msec; echo

time (TE), 9-18 msec]; T2WI (TR, 2,200-3,600 msec; TE, 108-127 msec); proton density-WI (TR, 2,200-3,600 msec; TE, 11-29 msec); and short time inversion recovery (TR, 4,500-5,400 msec; TE, 48-53 msec), including sagittal, coronal and transverse sections, with a layer thickness of 4.0 mm, layer spacing of 1.0 mm, a field of view of 18x18 cm and a matrix of (160-192) x (200-256). Coronary, transverse and sagittal T1WI and T1WI fat-suppressed scanning were performed after injection of Gd-diethylenetriamine penta-acetic acid (0.2 mmol/kg).

Image data collection methods and measurement standards.

The following parameters were used. The maximum diameter of the tumor was measured after an enhanced scan. The CT enhancement ratio was defined as $(CT \text{ value}_{\text{enhanced scan}} - CT \text{ value}_{\text{plain scan}}) / CT \text{ value}_{\text{plain scan}}$. The signal intensity (SI) prior to and after the MR enhanced scan of the same region of interest (ROI) was measured by 3-dimensional localization. The ROI (away from cystic change, calcification and fat area) was enhanced in the lesion. The MR enhancement ratio was defined as $(SI_{\text{enhanced scan}} - SI_{\text{plain scan}}) / SI_{\text{plain scan}}$. The SI of the most enhanced region of the lesion (away from cystic change, calcification and fat area) and adjacent muscle on the T2WI fat-suppressed sequence was measured. The T2 signal ratio was defined as $(SI_{\text{tumor}} - SI_{\text{muscle}}) / SI_{\text{muscle}}$. Low, high and iso-density were all relatively defined by CT examination, when the major parts of the tumor (non-necrotic sites) were compared with that in the surrounding muscle or other soft tissue. Lesions were considered as mildly, moderately or significantly enhanced after CT enhanced scan when the CT values of the lesions were increased by 0-20, 21-40 or >40 Hounsfield unit (HU), respectively. The MR signal level was the signal within the tumor relative to the surrounding muscle. Tumor recurrence was defined as the original pathologically confirmed desmoid-type fibromatosis relapsing after surgery, confirmed by imaging and pathology. A new tumor was defined as the first appearance of desmoid-type fibromatosis. Recurrence-free survival was defined as the absence of recurrence from the time the lesion was surgically removed to the end of follow-up. The recurrence time was the time between the surgery and the time-point when a recurrent tumor was identified by the patient. All the measurements were performed by two experienced radiologists who had no prior knowledge of the relapse status of the patients, and the results were subsequently analyzed.

Histopathological analysis. All the tissues were fixed with 3.7% neutral buffered formalin, routinely dehydrated, embedded in paraffin and serially sectioned. Cells positive for the Ki-67 protein were observed by immunohistochemical staining. The 3- μ m-thick sections were blocked with 3% hydrogen peroxide at room temperature for 6 min. The primary antibody (MyoD1; ready-to-use, no dilution; clone number: EP212; Beijing Zhongshang Jinqiao Biotechnology Co., Ltd.) was incubated overnight at 4°C. The secondary antibody (Envision Immunochromogenic Reagent; ready-to-use, no dilution; cat. no. K-5007; Zhejiang Medical Biotechnology Co., Ltd.) was incubated for 30 min at room temperature and developed for 5 min. Positivity for Ki-67 was confirmed by the presence of brown stained nuclei. A DP70 Digital Camera

(Olympus Corp.) image acquisition system was used to select 2-5 high-power fields of view (magnification, x200) to capture images. The number of Ki-67 positive tumor cells and the total number of tumor cells were counted using the Image-pro Plus image analysis software (v6.0; Media Cybernetics Inc.). The Ki-67 positive index was calculated as: (number of Ki-67 positive tumor cells/total number of tumor cells) x100%.

Statistical analysis. SPSS (v19.0; IBM Corp.) was used for all statistical analyses. The Kaplan-Meier method and log-rank test were used for univariate analysis to identify significantly associated indicators. By using the Cox proportional hazard regression model, stepwise regression analysis was used to determine the independent risk factors of recurrence time, while the hazard ratio and 95% confidence interval were also calculated. All values were expressed as the mean \pm standard error of the mean.

Results

Recurrence time and rate. Of the 102 patients, 71 exhibited local recurrence (70%) with a recurrence time of 20.59 ± 23.98 months (range, 3-123 months), including 21 males for whom the recurrence time was 23.04 ± 23.48 months (range, 3-73 months) and 50 females with a recurrence time of 19.53 ± 24.69 months (range, 4-123 months). The overall 1-year recurrence rate was 31% and the 2-year recurrence rate was 54%. The median age at recurrence was 29 years. In all cases of relapse, the recurrence occurred *in situ*.

Clinicopathological data. A total of 67 lesions were located outside of the abdomen, of which 27 lesions were located in the limbs (6 in the upper limbs and 21 in the lower limbs), 25 in the joint girdle (13 in the shoulder girdle and 12 in the pelvic girdle), 12 in the trunk (4 cases in the chest wall and 8 cases in the back) and 3 in the head and neck. A total of 28 lesions were located in the abdominal wall, including 19 lesions in anterior lower abdominal wall. Furthermore, 7 lesions were located inside of the abdomen, including 3 cases in the mesentery of the small intestine, 1 case in the small intestine, 1 case in the ileocecal region and 2 cases in the anterior bladder. Relapse of desmoid-type fibromatosis occurred in 71 cases (70%). The follow-up time was 30.53 ± 22.57 months (range, 24-123 months). The tumor size was 7.71 ± 3.59 cm (range, 1.6-19.0 cm). The tumor margin was clear in 29 cases and unclear in 73 cases visually. Of the 19 cases that were positive for desmoid-type fibromatosis in the margin, based on histology with hematoxylin and eosin (H&E) staining, 16 cases relapsed. Of the 83 cases that were negative on histology with H&E staining, 55 cases relapsed. A total of 87 cases of hard-textured lesions and 15 cases of medium-grade lesions were encountered. A total of 35 lesions invaded the peripheral vessels. Envelopes on the lesions were seen in 1 case. In 19 cases, pathologically positive margins of desmoid-type fibromatosis were observed. On microscopy, the sections exhibited a bundle of spindle-shaped cells with uniform nuclei and clear nucleoli (Figs. 1A and 2A). A total of 60 cases had positive staining for Ki-67, with the positive index ranging between 1 and 20%. Representative images for Ki-67 staining are presented in Fig. 3.

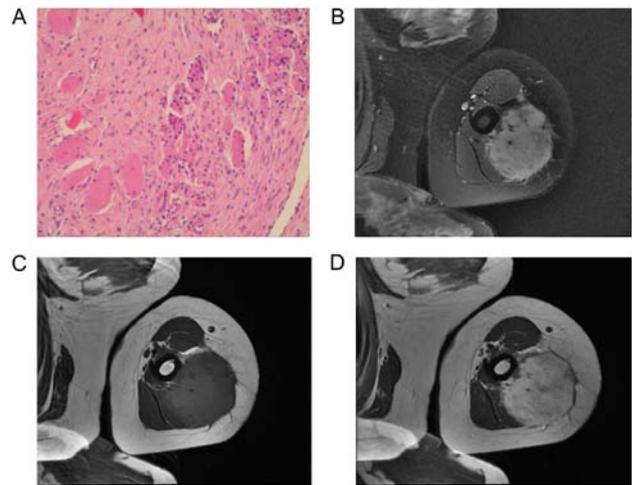


Figure 1. A 42-year-old female relapsed 4 months after surgery. (A) Hematoxylin and eosin staining (magnification, x100) of a pathological section of desmoid-type fibromatosis indicated that the tumor cells surrounded and invaded striated muscle tissue, causing striated muscle tissue atrophy and accumulation of myonuclei. (B) The lesion exhibited high SI on the T2WI fat-suppressed sequence. (C) The lesion exhibited low SI on T1WI. (D) The lesion was markedly enhanced on the T1WI enhancement scan. T1WI, T1-weighted imaging; SI, signal intensity.

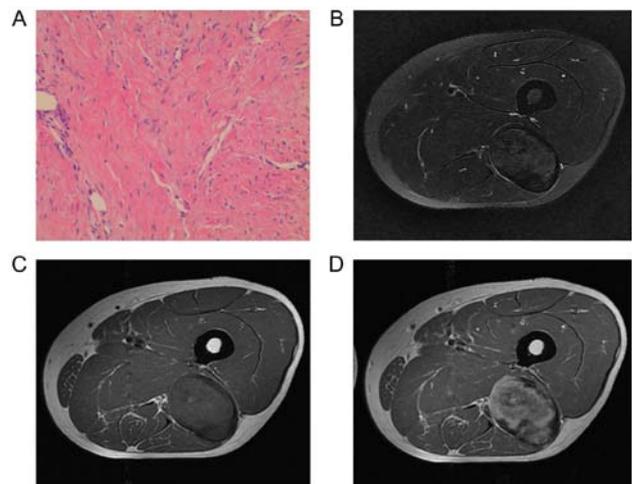


Figure 2. A 33-year-old male did not relapse for 33 months up to the end of the follow-up in May 2017. (A) Hematoxylin and eosin staining (magnification, x100) of pathological section of desmoid-type fibromatosis revealed a bundle of spindle-shaped cells and an area of collagenization. (B) The lesion exhibited high SI on the T2WI fat-suppressed sequence. (C) The lesion had low SI on T1WI. (D) The edge of the lesion was not enhanced, while the center of the lesion was map-like enhanced on the T1WI enhancement scan. T1WI, T1-weighted imaging; SI, signal intensity.

Imaging data. The minimum size of the tumors was 1.3x2.1x2.0 cm and the maximum size was 15x14x8 cm. The lesions included calcification in 8 cases, cystic degeneration in 3 cases, fat in 1 case, peripheral nerve and vessel invasion in 35 cases, bone destruction in 17 cases and ascites in 1 case. Lesions displayed using CT had a lower density compared with that of the muscles. The CT value ranged between 33 and 47 HU, and the mean CT value was 39.0 ± 2.0 HU. The CT enhanced scan exhibited mild enhancement in 11 cases, moderate enhancement in 69 cases and marked enhancement in 22 cases. With MRI, the SI of the lesions on the T2WI

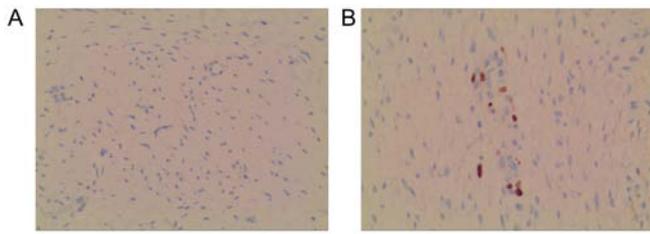


Figure 3. Immunohistochemistry images for staining of Ki-67. (A) Negative Ki-67 staining with blue nuclei. (B) Positive Ki-67 staining with brown nuclei. Magnification, x200.

fat-suppressed sequence was higher (Fig. 1B) or slightly higher (Fig. 2B) compared with that of the surrounding muscle. The SI of the lesions on T1WI was equal to or lower compared with that of the surrounding muscle, and the SI was at times uneven with a clear or blurred margin (Figs. 1C and 2C). The lesions exhibited a marked and non-uniform enhancement in the arterial phase of the enhanced scan (Figs. 1D and 2D), which was higher compared with that of the surrounding muscle. The lesions continued to intensify in the delayed phase and were still partially enhanced until 600 sec later. The area of low SI on T1WI and the T2WI fat-suppressed sequence corresponded to the higher collagen content. Of the 102 cases, 25 of the lesions were uniformly enhanced (24.5%).

Measurement indices. The maximum diameter of the tumors was 7.71 ± 3.59 cm (range, 2-19 cm) and the CT enhancement ratio was 0.78 ± 0.38 (range, 0.18-1.88). Furthermore, the T2 signal ratio was 2.32 ± 1.42 (range, 0.13-5.05) and the MR enhancement ratio was 1.17 ± 0.77 (0.14-4.62).

Univariate analysis. Kaplan-Meier survival analysis was used to analyze 10 variables to investigate recurrence time (Table I). The differences between 1-year and 2-year postoperative tumor-free survival rates were analyzed by the log-rank test. The results revealed that sex ($P=0.038$), tumor diameter ($P=0.005$), CT enhancement ratio ($P=0.016$) and Ki-67 status ($P<0.001$) had a significant effect on the recurrence time (Table II).

Multivariate analysis. The 10 variables (Table I) were analyzed using the multivariate Cox regression model, and the stepwise regression method to eliminate the mutual influence among the various factors to obtain four independently associated variables with recurrence (Table III). These four variables were sex, maximum diameter, Ki-67 status and T2 signal ratio.

Recurrence-free survival. The Kaplan-Meier curve for cumulative recurrence-free survival time within the study population is presented in Fig. 4. The number of recurrence-free patients decreased over time. At the median of 35 months, 50% of the patients had relapsed. As males had a higher risk of recurrence compared with that in females ($P=0.032$), recurrence-free survival was stratified by sex (Fig. 5). Furthermore, the recurrence-free survival curves for patients with Ki-67-positive and -negative lesions are presented in Fig. 6. At the same time-points on the horizontal axis, the number of Ki-67-positive cases without recurrence was significantly lower compared with that in the Ki-67-negative cases ($P=0.001$).

Discussion

Desmoid-type fibromatosis is also known as invasive fibromatosis. Under normal physiological conditions, fibroblasts have a crucial role in wound healing and protecting vital organs, including the lung, liver, blood vessels, heart and kidney, but when certain cells undergo gene mutations, neoplasms may be formed, leading to the occurrence of desmoid-type fibromatosis (16,17). With an incidence rate of approximately five per million people annually, it is uncommon, representing approximately 0.3 per cent of all soft tissue neoplasms (18,19). While the exact causes remain elusive, desmoid-type fibromatosis is currently considered to be associated with surgical history, traumatic injury, familial adenomatous polyposis and Gardner's syndrome (10). Women were more likely to develop the disease compared with men (20), and therefore, estrogen is an influencing factor. The most common sign is a painless, progressive mass, but symptoms/complaints including neurological disorders, joint stiffness or abdominal discomfort due to tumor growth may also occur (9). Desmoid-type fibromatosis is likely to recur after surgery. Despite complete resection of the tumor, the recurrence rate remains 20-60% (21). The overall recurrence rate in the present study was 70%, which is higher than that reported by previous studies (3,22-24). Whether gender affects the recurrence of desmoid-type fibromatosis is also controversial. A study by Wang *et al* (25) indicated that sex and recurrence of desmoid-type fibromatosis had no significant association. In the present study the overall incidence in females (73/102; 71.6%) was higher than that in males (29/102; 28.4%), but the two-year recurrence rate was higher in males (57%) compared with that in females (51%), and male gender was a significant risk factor for recurrence. Multivariate analysis also revealed that sex was a major influencing factor of tumor recurrence. Female patients had a 0.424-fold risk of recurrence compared with that for male patients. Analysis of the reasons suggested that this may be due to hormone levels. This may also be associated with each patient's individual genetic mutations, and genetic studies with this regard are therefore desirable. It has also been reported that age may be a prognostic factor (26). However, in the present study, the patient age had no effect on the prognosis.

The present study indicated that the maximum diameter of the tumor affected postoperative recurrence. A larger primary tumor in size was significantly associated with a higher probability of recurrence and a shorter recurrence time. Furthermore, larger lesions tended to invade the surrounding vessels and nerves, therefore the lesion was not completely removed during surgery to preserve the local tissue function, and some tumor cells remained in the surrounding tissue, leading to short-term recurrence. Multivariate analysis revealed the CT enhancement and the MR enhancement ratios were not significantly associated with postoperative tumor recurrence. The imaging findings of desmoid-type fibromatosis were dependent on the number of proliferating fibroblasts in the tumor as well as the fibrous, collagen and vascular components (11). The CT value mainly reflects the difference in tissue density. Differences in the CT values of the fibrous, collagen and vascular components within the tumor were small, as all of them are soft tissues. The difference in the increase of CT values after the enhanced scan

Table I. Influencing factors on the recurrence rate of desmoid-type fibromatosis.

Variables	Score		
	1	2	3
Sex	Male	Female	
Age, years	<20	20-40	>40
Tumor location	Abdominal external	Abdominal wall	Intra-abdominal
Maximum tumor diameter, cm	<5	5-9	>9
Border	Clear	Unclear	
CT enhancement ratio	<0.6	0.6-0.9	>0.9
MR enhancement ratio	<0.8	0.8-1.5	>1.5
T2 signal ratio	<1.8	1.8-2.5	>2.5
Ki-67	Negative	Positive	
Pathological margin	Negative	Positive	

was small and not sufficient to reflect the difference between these tissues. On plain scanning, it was difficult to display the exact border of the desmoid-type fibromatosis, but on the CT enhancement scan, the border was clearly visible. Although the MR enhancement ratio had no effect on postoperative tumor recurrence, an MR enhanced scan is important, as it may help determine the size of the tumor, tumor composition and infiltration of the surrounding tissue, as well as to identify the presence of a tumor envelope and edema around the tumor, the observation and comprehensive evaluation of which is important for the surgical treatment and prognostication of the patient. On T2WI, the SI of desmoid-type fibromatosis was higher compared with that of the surrounding muscle, whereas on T1WI, the SI was equal to or lower compared with that of the surrounding muscle. The lesions exhibited invasive growth with unclear margins. The internal lesion with low SI (lower compared with that of the muscle) was unevenly enhanced, while the remainder of the lesion was consistently enhanced. Different modes of MR help distinguish the internal tissue components of the tumor. The area of band-shaped low SI on T1WI was usually not enhanced on the T1WI enhanced scan, corresponding to the dense fibrous tissue and scar-like collagen deposition area, and the results were similar to those studied by Xu *et al* (12). After injection of the contrast agent, the lesion was moderately to markedly enhanced, particularly in the concentration area of the tumor cells, while the stromal area exhibited mild enhancement and the results were similar to those studied by Kim *et al* (27). The T2WI SI was associated with the number of tumor cells in the collagen matrix (27). A stronger T2WI SI was associated with a higher cell proliferation and a shorter time to tumor recurrence (27). The results from the present study suggested that the T2 signal ratio was a risk factor affecting recurrence time. An increase of the T2 signal ratio was significantly associated with an increase in the risk of recurrence.

It is controversial whether the pathological margin of desmoid-type fibromatosis has any effect on recurrence. A multidisciplinary research institute in France (15) retrospectively analyzed and demonstrated that an infiltrated margin, including tumor cells of desmoid-type fibromatosis, had

no significant effect on the prognosis of patients. However, Wang *et al* (25) reported that invasion of major vessels and nerves and invasion of the surgical margin were risk factors for postoperative recurrence. In the present study, univariate and multivariate analyses indicated no association between the pathological margin and tumor recurrence. This may be due to the small number of samples. Ki-67 is a proliferating cell-associated nuclear antigen that is a marker for cell proliferation (26). The present study demonstrated that Ki-67 is a key factor influencing tumor recurrence time. Patients with positive Ki-67 are more likely to relapse.

The causes of recurrence of desmoid-type fibromatosis are complex and diverse and may be affected by numerous factors. A number of imaging findings that may affect the recurrence were assessed in the present study, which revealed that sex, maximum tumor diameter, T2 signal ratio and Ki-67 were independent risk factors using the Cox proportional hazard regression analysis; sex and Ki-67 status were not associated with imaging. Therefore, when imaging findings are used to predict the recurrence of desmoid-type fibromatosis, clinical and pathological indicators must be combined.

While having identified several factors that affect postoperative recurrence, it must be noted that the present study had certain limitations. Due to the different locations of the tumors, it was not possible to measure the SI in the same muscle. Only the corresponding SI around the lesion was selected as a reference. Furthermore, as the size of the lesions was inconsistent, it was not possible to uniformly determine the ROI, which may have affected the present results. In addition, as the present study was retrospective, patients were lost to follow-up and/or their clinical data were incomplete.

At present, MRI is the preferred method for the preoperative evaluation of tumors and postoperative detection of recurrence. Based on the results of the present study, an objective assessment of postoperative recurrence of desmoid-type fibromatosis may be made based on the imaging findings. The sex of the patients, tumor diameter, Ki-67 expression status and T2 signal ratio were identified to affect postoperative recurrence. The T2 signal ratio and the maximum diameter of the tumor were the most significant indicators of post-operative

Table II. Univariate analysis of each variable on recurrence time.

Variables	Number	Postoperative tumor-free survival rate, %		P-value
		1-year	2-year	
Sex				0.038
Male	29	57	43	
Female	73	73	49	
Age, years				0.208
<20	15	71	57	
20-40	62	64	42	
>40	25	82	55	
Types				0.159
Abdominal external	67	64	24	
Abdominal wall	28	46	38	
Intra-abdominal	7	86	71	
Maximum diameter, cm				0.005 ^a
<5	24	75	50	
5-9	49	68	56	
>9	29	64	29	
Border				0.591
Clear	29	64	50	
Unclear	73	70	46	
CT enhancement ratio				0.016 ^a
<0.6	27	65	50	
0.6-0.9	37	56	39	
>0.9	38	84	53	
MR enhancement ratio				0.759
<0.8	29	79	64	
0.8-1.50	42	62	43	
>1.50	31	69	38	
T2 signal ratio				0.073
<1.8	32	87	69	
1.8-2.50	36	50	33	
>2.50	34	71	41	
Ki67				<0.001 ^a
Negative	42	79	74	
Positive	60	63	31	
Pathological margin				0.068
Negative	83	71	52	
Positive	19	44	11	

^aP<0.05. MR, magnetic resonance.

recurrence. Long-term follow-up after surgery is necessary. Clinical and imaging examination should be performed every 3-6 months for 2-3 years prior to annual follow-up. For high-risk cases with a Ki-67-positive status or a high T2 signal ratio, close follow-up with short intervals is required.

Table III. Data from multivariate Cox proportional hazard regression model.

Variables	HR (95% CI)	P-value
Sex	0.424 (0.203-0.938)	0.032
Maximum tumor diameter	1.100 (1.001-1.218)	0.045
T2 signal ratio	1.268 (0.993-1.560)	0.044
Ki-67	1.084 (1.003-1.139)	0.001

HR, hazard ratio; CI, confidence interval.

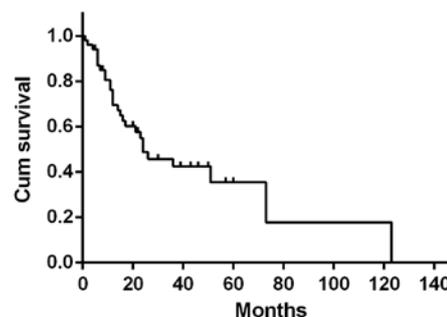


Figure 4. Cumulative recurrence-free survival function. The number of recurrence-free patients decreased over time. At the median of 35 months, 50% of the patients had relapsed. Cum survival, cumulative recurrence-free survival.

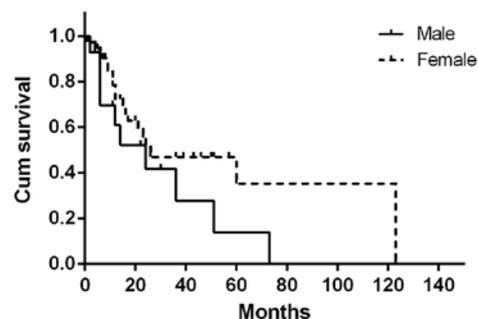


Figure 5. Cumulative recurrence-free survival function stratified by sex. At various time-points, the number of men without recurrence was significantly lower compared with that of women. P=0.032. Cum survival, cumulative recurrence-free survival.

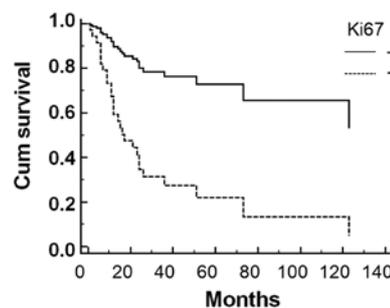


Figure 6. Cumulative recurrence-free survival function compared with Ki-67 status (positive and negative) of the patients. At various time-points, the number of Ki-67-positive cases without recurrence was significantly lower compared with that in Ki-67-negative cases. P=0.001. Cum survival, cumulative recurrence-free survival.

Acknowledgements

Not applicable.

Funding

The present study was supported in part by Zhejiang Provincial Natural Science Foundation of China (grant. no. LQ19H220001).

Availability of data and material

The datasets used and/or analyzed during the present study are available from the corresponding author on reasonable request.

Authors' contributions

Study design, data collection, statistical analysis, data interpretation, manuscript preparation and literature search was performed by JW. Statistical analysis, data interpretation, manuscript preparation, manuscript revision and the literature search were performed by YH. Data collection, statistical analysis, data interpretation, literature search and manuscript revision were performed by YS. Statistical analysis, data interpretation and the literature search were performed by YG. Study design, statistical analysis and data interpretation were performed by MZ. All authors read and approved the final manuscript.

Ethics approval and consent to participate

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. Ethics approval was obtained from the Medical Ethics Committee of Jiaying Chinese Medicine Hospital (no. 2016-JZLK-005).

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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