Clinicopathological and molecular characteristics of abdominal desmoid tumors in the Chinese population: A single-center report of 15 cases

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Abstract. Desmoid tumors (DTs), derived from the abdomen, are a type of rare and aggressive borderline tumor exhibiting high recurrence and malignant potential. The aim of the present study was to investigate the clinicopathological and molecular characteristics of abdominal DT in a Chinese population and to provide clues for selecting the optimal treatment strategy for different types of abdominal DT. The clinicopathological data of 15 consecutive patients with DT was collected. Matched fresh-frozen tumor tissues and peripheral blood samples were used to detect mutations of adenomatous polyposis coli gene (*APC*), β-catenin (*CTNNB1*) and MutY DNA glycosylase (*MUTYH*) using Sanger sequencing. Pearson's test was conducted to analyze the differences between sporadic DT and familial adenomatous polyposis (FAP) associated with DT. Time to progress (TTP) and overall survival curves were estimated using the Kaplan-Meier method and compared using the log-rank test. A review of the patient clinicopathological characteristics revealed that FAP-associated DT exhibited a higher rate of abdominal surgery history (P=0.011), with no significant differences in any other characteristics. Sequencing revealed that mutations in the *APC*, *CTNNB1* and *MUTYH* genes were common in DT, and only one patient harbored no mutations in these genes. Survival analyses revealed that patients with FAP exhibited shorter TTP (P=0.030). Log-rank test demonstrated a tendency towards shorter TTP in the cases where an R2 resection was performed (P=0.072) and a tendency towards poor prognosis in the cases of DT associated with FAP (P=0.087). In conclusion, Abdominal DTs were prone to occur in patients with FAP with a history of abdominal surgery. Mutations in the *APC*, *CTNNB1* and *MUTYH* genes were detected in patients with DTs. To the best of our knowledge, this is the first study of abdominal DT occurrence in patients with *MUTYH*-associated FAP. The prognosis of DT associated with FAP may be worse compared with that of sporadic DT.

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Abbreviations: DT, desmoid tumor; FAP, familial adenomatous polyposis; TTP, time to progress; OS, overall survival

Key words: desmoid tumors, familial adenomatous polyposis, β-catenin, adenomatous polyposis coli gene, MutY DNA glycosylase, prognosis, treatment

Introduction

Desmoid tumors (DTs), also known as aggressive fibromatosis, are rare, locally infiltrative mesenchymal neoplasms that are associated with high rates of local recurrence, but do not possess the potential to metastasize (1). DTs account for <3% of all soft tissue tumors (2) and have an estimated incidence rate of 2-5 individuals per million per year in Europe (3). The exact etiology of DTs is currently unknown, but hormonal, genetic and physical factors all serve roles in their development and growth. Two different types of DTs have been described: Sporadic tumors and familial adenomatous polyposis (FAP)-associated DTs (4). Regardless of type, an important part of the biology is the disruption of the Wnt signaling pathway, leading to the accumulation of nuclear β-catenin and the inappropriate stimulation of downstream genes (4). In sporadic DT, this is often caused by a mutation in the β-catenin gene (*CTNNB1*) (5), whereas in FAP-associated DT, the loss of adenomatous polyposis coli (*APC*) function serves a role (6). Recently described biallelic mutations of

MutY DNA glycosylase (*MUTYH*) have been demonstrated to be responsible for adenomatous polyposis with an increased risk of colorectal cancer and have been observed in 30-40% of adenomatous polyposis cases in which an *APC* mutation was not identified; however, no evidence has indicated thus far that *MUTYH* serves a role in DT (7). Further studies have revealed that the mutation site of *APC*, as well as that of *CTNNB1*, may impact the incidence, severity and prognosis of DT (8-10). This may be significant for the prevention and treatment of DTs.

DT can occur in any location, often involving the extremities, the trunk, including the pelvic and shoulder girdles, and the abdomen (4). For abdominal DTs, the clinical presentation depends on its primary site. In the present study, according to its location, abdominal DTs are classified into two types: Peripheral and central DT. The clinicopathological and molecular characteristics were collected from a group of patients with abdominal DTs and analyzed to explore the optimal strategies for diagnosing and management of different types of abdominal DTs.

Materials and methods

Study design, patients and samples. Tumor samples, peripheral blood samples and matched clinical data from 15 patients with DT were retrospectively collected from the Zhongshan Hospital (Shanghai, China) with informed consent. The present study was approved by the Committee for Ethical Review of Research Involving Human Subjects of Zhongshan Hospital Affiliated with Fudan University. All 15 patients received surgery and were diagnosed with DT consecutively between July, 2009 and January, 2016; no patients were excluded from the study. DTs were diagnosed by an experienced pathologist based on tumor morphology and immunohistochemistry. The expression levels of *APC*, *CTNNB1* and *MUTYH* genes of 15 patients were analyzed by direct sequencing of tumor and blood samples. The clinicopathological data and follow-up outcomes were collected and analyzed.

Data retrieved included age, sex, date of surgery, anatomic site, tumor size and margin status. The results of the *APC*, *CTNNB1* and *MUTYH* mutational analysis were recorded along with the type of treatments administered prior to and/or following surgery. Patients were followed to record any future recurrence of disease with the date of recurrence, treatment following recurrence, date of the last follow-up and status at last follow-up. According to the anatomic site, abdominal DTs were classified as either peripheral (derived from the abdominal wall) or central (derived from the retroperitoneal space and mesentery). Tumor size was defined as the greatest DT dimension in the surgical specimen reported by the original pathologists. Surgical excisions were considered macroscopically complete in the absence of gross residual disease. All macroscopically complete resections were classified according to the closest surgical margin, which was microscopically categorized as positive (R1, tumor within 1 mm from the inked surface) or negative (R0, the absence of tumor within 1 mm from the inked surface). Non-surgical treatments were administered in the primary or recurrent phase of the disease on an individualized basis. These included radiotherapy, chemotherapy (methotrexate and vinorelbine in the majority of cases), medical therapy/hormone agents (tamoxifen, toremifene) and non-steroidal anti-inflammatory drugs (cyclooxygenase-2 inhibitors).

Telephone and outpatient follow-up were used to collect the data. The median follow-up time following the diagnosis of DT was 60 months (range, 20-90 months), and all follow-up data were complete.

Mutational analysis. Genomic DNA was extracted from peripheral blood using a TIANamp Blood DNA kit (Tiangen Biotech Co., Ltd.) and tumor samples using a TIANamp Genomic DNA kit (Tiangen Biotech Co., Ltd.). Primers flanking all coding exons and intron-exon boundaries of *APC*, *CTNNB1* and *MUTYH* were designed using Primer Premier (version 5.0; Premier Biosoft) and are presented in Table SI. Genomic DNA samples were amplified using PCR. The thermocycling conditions were as follows: Denaturation at 94˚C for 5 min; 31 cycles of denaturation at 94˚C for 30 sec, annealing for 30 sec (temperature was set according to the primers of each fragment) and an extension at 72˚C for 1 min. A final extension step was performed at 4˚C for 5 min, and the experiment was repeated 10-20 times. The PCR products were evaluated by a 2% agarose gel electrophoresis and were further purified using an AxyPrep DNA Gel Extraction kit (Corning Life Sciences) according to the manufacturer's protocol. Sanger sequencing was subsequently performed using an ABI PRISM 3730 automated sequencer (Applied Biosystems; Thermo Fisher Scientific, Inc.). Sequencing results were analyzed by Geneious software (version 5.6.7; Biomatters Ltd.). An identified mutation was verified in the corresponding region of the unaffected parents of the proband and 100 population-matched healthy controls. The mutation was described by comparison with the NCBI cDNA reference sequences (11) NM_001354897.1 for APC, NM_001098209.1 for CTNNB1 and NM_012222.2 for MUTYH.

Statistical analysis. All statistical analyses were performed using SPSS software (version 18.0; SPSS, Inc.). The primary endpoint was the time to progress (TTP) and overall survival (OS), and the event time was calculated as the time between the date of surgery and the date of relapse or death, whichever occurred first, or was censored at the date of last follow-up assessment in event-free patients. TTP curves were estimated using the Kaplan-Meier method and were compared statistically using the log-rank test. Multivariate Cox model analyses were also performed using following characteristics: Sex, tumor site, tumor size and margin status. A Fisher's exact test was performed to analyze the differences between sporadic DT and FAP-associated DT. $P<0.05$ was considered to indicate a statistically significant difference.

Results

Patient demographics and disease characteristics. Between July, 2009 and January, 2016, 15 patients, including nine female and six male patients, were enrolled in the present study. The demographic and disease characteristics are presented in Table I and Fig. 1. In total, nine patients were ≥30 years, and the median age was 32 years (range, 26-47 years). According

Table I. Clinical characteristics of 15 patients with DT.

Characteristics	Cases, n (%)
Type of DT	
FAP-associated	6 (42.86)
Sporadic	9 (57.14)
Age, years	
<30	6 (42.86)
≥30	9 (57.14)
Sex	
Male	6 (42.86)
Female	9 (57.14)
History of abdominal surgery	
Yes	6 (42.86)
No	9 (57.14)
Site	
Central	12 (80)
Peripheral	3 (20)
Tumor size	
<10	5 (33.33)
≥10 cm	10 (66.67)
Margin status for primary surgery	
R0/R1	9 (60)
R2	6 (40)
Recurrence or progression after primary surgery	
No	3 (20)
Yes	12 (80)
Treatment after primary surgery	
Radiotherapy	2 (13.33)
Chemotherapy	6 (40)
Other (COX-2I, TAM or wait and see)	7 (46.67)
Type of treatment for recurrence	
Surgery	6
Radiotherapy	3
Chemotherapy	6
Other (COX-2I, TAM or none)	8

DT, desmoid tumor; FAP, familial adenomatous polyposis syndrome; COX-2I, cyclooxygenase-2 inhibitor; TAM, tamoxifen.

Table II. Differences between sporadic and FAP-associated desmoid tumors.

Characteristics	FAP-associated, n	Sporadic, n	Fisher's exact test P-value
Sex			
Male	2	4	>0.999
Female	4	5	
Age, years			
20-30	3	3	0.622
≥30	3	6	
History of abdominal surgery			
Yes	5	2	0.011[a]
No	1	7	
Site			
Central	6	6	0.229
Peripheral	0	3	
Tumor size, cm			
<10	1	4	0.580
≥10	5	5	
Margin status			
R0/R1	4	7	0.136
R2	2	2	
Recurrence after R0/R1 resection			
Yes	4	4	0.236
No	0	3	

[a]P<0.05. FAP, familial adenomatous polyposis syndrome.

to the primary site of DT, the central type accounted for 80% (12/15), whereas the peripheral type accounted for 20% (3/15) of the cases. The median size of the primary lesions was 10 cm (range, 4-17 cm). Of the 15 cases, nine were sporadic (four male and five female patients), whereas six patients had a family history of FAP and a history of abdominal injury, including surgery.

All the patients accepted surgical resection as a treatment course, with a number of patients undergoing multiple surgeries due to recurrence. Overall, nine patients underwent complete surgical excision (R0/R1), and six patients underwent R2 resection. Due to variations in the anatomic site of the tumor, the extent of surgery was different for each case. The three patients with peripheral-type sporadic DTs underwent R0/R1 resection without combined organ resection. Among the 12 patients with central type DTs, 50% (6/12) underwent R0/R1 resection, whereas 50% (6/12) underwent R2 resection. For the central type group, combined evisceration was performed in 75% (9/12) of patients, and the resected organs included the small intestine (66.67%, 6/9), colon (33.33%, 3/9), ureter (22.22%, 2/9), appendix (11.11%, 1/9), ovary (11.11%, 1/9) and pancreas (11.11%, 1/9). Following primary surgery, only three patients did not experience recurrence or progression. In addition, six patients who underwent R2 resection received chemotherapy, two patients received radiotherapy and seven patients received Tamoxifen, a non-steroid anti-inflammatory drug (NSAID; COX-2 inhibitor) and/or waited for the outcome. Of patients who experienced recurrence and progression following primary resection, six cases underwent additional surgery, three received radiotherapy and six received chemotherapy; eight patients received Tamoxifen, NSAID (COX2 inhibitor) or waited for the outcome.

Difference between sporadic and FAP-associated DT. To reveal the differences between sporadic and FAP-associated

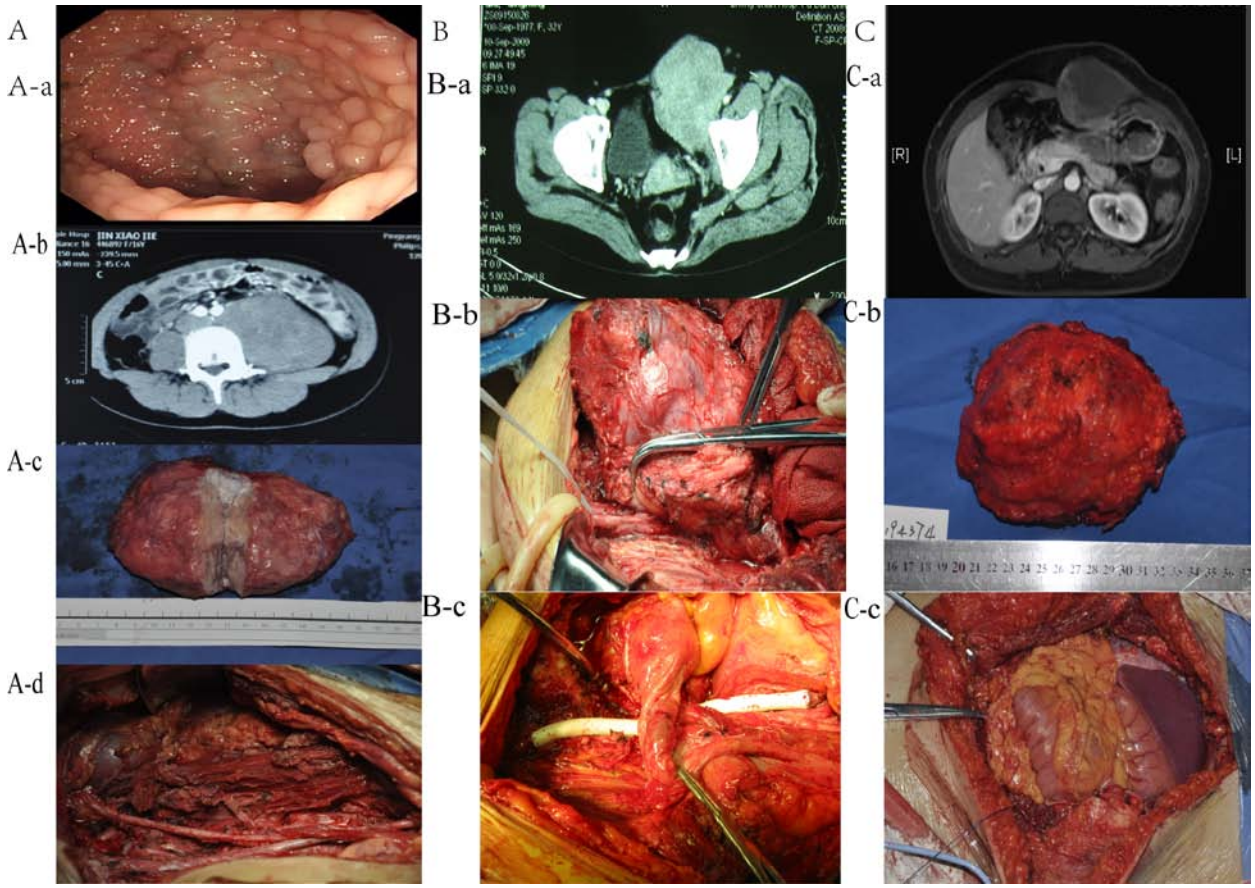

Figure 1. Characteristics of different types of DT. (A) A patient with FAP-associated DT. (A-a) Polyps in the large intestine. (A-b) Tumor localized in the retroperitoneum. (A-c) Resected tumor. (A-d) The surgical field. (B and C) Patients with sporadic DT. (B-a and C-a) Tumors derived from the abdominal wall. (B-b, B-c, C-b and C-c) Tumors and the surgical fields. DT, desmoid tumor; FAP, familial adenomatous polyposis.

DT, clinicopathological characteristics between the two groups were compared. The results revealed a significant difference between the two groups in past history of abdominal surgery, with patients with FAP-associated DT exhibiting a higher rate of abdominal surgery. This may suggest an increased susceptibility to the development of DT in patients with FAP that had a history of abdominal surgery. No significant differences were identified in the other characteristics (Table II).

Mutations in the study cohort. Among the 15 patients with DT, only one patient did not exhibit any mutations in *CTNNB1*, *APC* or *MUTYH*. Of the six patients with FAP-associated DT, one patient harbored a *MUTYH* gene mutation, whereas the others possessed *APC* gene mutations. In the nine patients with sporadic DT, analysis of the tumor samples revealed six mutations in the *CTNNB1* gene, four mutations in the *APC* gene and one mutation in the *MUTYH* gene. In the group of patients with sporadic DT, one harbored mutations in *CTNNB1*, *APC* and *MUTYH* genes, whereas another carried *CTNNB1* and *APC* mutations (Table III).

Survival analysis. In the follow-up to December 2016, two patients with FAP-associated DT succumbed to disease, six patients survived with progression and seven exhibited disease-free survival. The median TTP was 13 months, and median OS time was 57 months. Survival analysis revealed that patients with FAP-associated DT exhibited shorter TTP (P=0.030). Log-rank test revealed a tendency for shorter TTP in the cases that underwent R2 resection (P=0.072) and poor prognosis in the cases with FAP-associated DT (P=0.087) (Table IV; Fig. 2). In the multivariate Cox regression analysis, FAP-associated DT was revealed to be associated with a higher risk of recurrence following resection (Table V).

Discussion

DTs are heterogenous borderline lesions that originate from mesenchymal fibroblastic proliferation with an incidence rate of 0.03% of all neoplasms and 3.00% of soft tissue tumors (12). It is a rare condition that typically infiltrates surrounding structures and tends to recur with minimal metastatic potential (12). The majority of DTs occur sporadically, but a number of DTs are associated with FAP syndrome (13). In the present study, when clinicopathological characteristics were compared between the sporadic and FAP-associated groups, the history of abdominal surgery and prognosis were notably different. Among the 15 patients, all patients with FAP-associated DTs had a history of abdominal surgery. Clark *et al* (14) reported that 82% of patients with FAP-associated DTs had predisposing surgery. It has been hypothesized that surgical trauma and the process of tissue repair by fibroblasts contribute to DT development following injury. The risk of tumor development among patients with FAP following injury or surgical trauma remains unknown.

Table III. Mutations identified in *APC, CTNNB1 and MUTYH* in the present study.

No.	Incidence	Gene	Location	Mutation	Mutation type
1	Familial	*APC*	E15	c.1875_1878delGACA	Frameshift
2	Familial	*APC*	E09	c.904C>T:p.R302X	Missense
3	Familial	*MUTYH*	E15	c.1005G>C:p.Q335H	Missense
4	Familial	*APC*	E16-9	c.3927_3931delAAAGA	Frameshift
5	Familial	*APC*	E16	c.3927-3931delAAAGA	Frameshift
6	Familial	*APC*	E16-10	c.4429C>T:p.Q1477X	Missense
7	Sporadic	*APC*	E16	c.5465T>A:p.V1822D, c.1635G>A	Missense, synonymous
8	Sporadic	*APC*		c.1458T>C, c.1635G>A	Synonymous
9	Sporadic	*CTNNB1*	E3	c.133T>C:p.S45P	Missense
10	Sporadic	*APC*		c.1458T>C, c.1488A>T, c.1635G>A	Synonymous
		CTNNB1	E15	c.2340C>T	Synonymous
		MUTYH	E12	c.1005 G>C	Synonymous
11	Sporadic			None	
12	Sporadic	*APC*		c.1458T>C, c.1635G>A	Synonymous
		CTNNB1	E15	c.2340 C>T	Synonymous
13	Sporadic	*CTNNB1*	E3	c.134C>T:p.S45F	Missense
14	Sporadic	*CTNNB1*	E3	c.121:A>G:p.T41A	Missense
15	Sporadic	*CTNNB*1	E3	c.121:A>G:p.T41A	Missense

APC, adenomatous polyposis coli; *CTNNB1*, β-catenin; *MUTYH*, MutY DNA glycosylase.

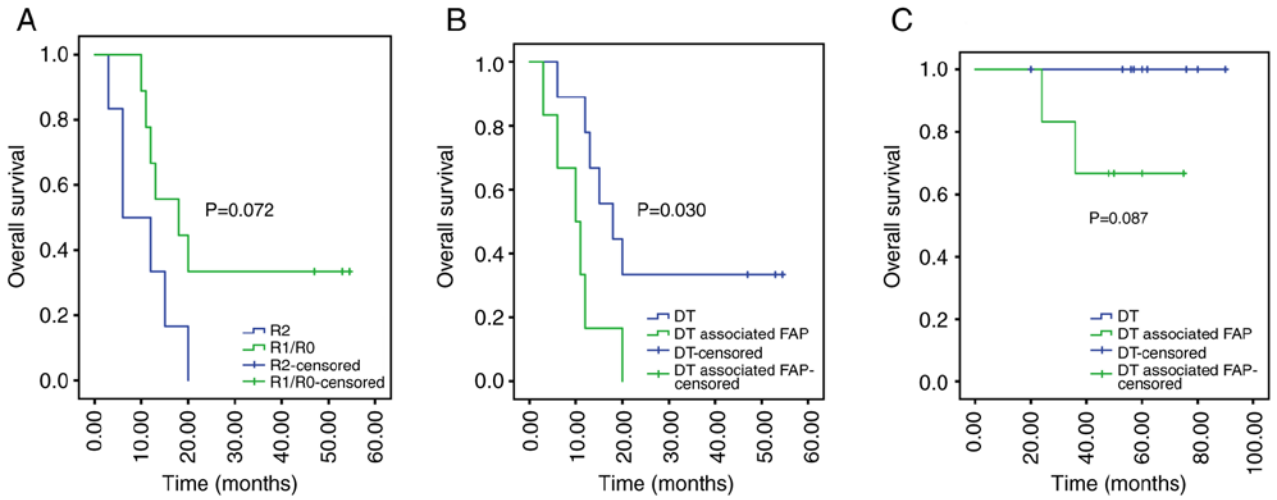

Figure 2. Survival analysis by log-rank tests. (A) A tendency towards shorter TTP was observed in the cases that underwent R2 resection. (B) Compared with patients with FAP associated with DT, patients with sporadic DT exhibited longer TTP. (C) A tendency towards poor prognosis was observed in the cases of DT associated with FAP. DT, desmoid tumor; FAP, familial adenomatous polyposis.

Among patients with FAP, DT is one of the most common causes of death after colorectal cancer (15). Due to the high local recurrence rate, recurrence and survival are of equal importance in the management of DT. In the present study, 2 patients with FAP-associated DTs succumbed to complications associated with the tumor. Survival analysis revealed that patients with FAP-associated DT exhibited shorter TTP and a relatively poor prognosis compared with those with sporadic DTs. These results suggest a more aggressive pathology and poor prognosis in patients with FAP-associated DT, but more evidence is required to support this hypothesis.

Alterations in the Wnt/β-catenin signaling pathway have been reported as the likely driving mechanism of tumorigenesis in the development of the disease; mutations in the β-catenin gene occur in the majority of sporadic cases, as well as mutations in *APC*, which regulates β-catenin degradation in FAP-associated DTs (16). In the present study, *APC*, *CTNNB1* and *MUTYH* mutational analyses were performed in 15 patients, and only one patient did not exhibit any muta-

Table IV. Univariate analysis of TPP and OS.

A, Univariate analysis of TTP

Variables	Log-rank test	
	χ^2	P-value
Sex (male vs. female)	1.401	0.236
Age, years (20-30 vs. ≥30)	0.242	0.623
Tumor size, cm (<10 vs. ≥10)	0.787	0.375
Site (central vs. peripheral)	2.658	0.103
Margin status (R0/R1 vs. R2)	3.227	0.072[a]
FAP-associated (yes vs. no)	4.684	0.030[a]
Systematic therapy (yes vs. no)	0.003	0.959

B, Univariate analysis of OS

Variables	Log-rank test	
	χ^2	P-value
Sex (male vs. female)	1.606	0.205
Age, years (20-30 vs. ≥30)	0.072	0.788
Tumor size, cm (<10 vs. ≥10)	0.143	0.705
Site (central vs. peripheral)	0.573	0.449
Margin status (R0/R1 vs. R2)	0.072	0.788
FAP-associated (yes vs. no)	2.925	0.087
Systematic therapy (yes vs. no)	1.180	0.277

[a]P<0.05. TTP, time to progress; OS, overall survival; FAP, familial adenomatous polyposis syndrome.

Table V. Cox regression analysis of risk factors for recurrence.

Risk factor	HR	95% CI	P-value
Sex	1.404	0.188-10.474	0.740
Age	1.015	0.151-6.821	0.998
Site	0.090	0.003-2.297	0.145
FAP-associated	0.086	0.006-1.283	0.075[a]
Margin status	0.410	0.062-2.703	0.354
Systematic therapy	15.367	0.325-726.452	0.165

[a]P<0.05. FAP, familial adenomatous polyposis syndrome; CI, confidence interval. HR, hazard ratio.

tions in these genes. Of the six patients with FAP-associated DT, five harbored *APC* mutations, of which 80% were located downstream from codon 1444. Previous studies have reported that FAP-associated DTs are associated with mutations toward the 3' end of the gene, distal to codon 1444, compared with the general FAP population, where 90% of mutations are located upstream from codon 1444 (17,18). A novel finding from the present study was that one patient with FAP-associated DT exhibited *MUTYH* mutations within the tumor tissues. Mutations in the MUTYH gene have been previously demonstrated in a type of colorectal polyposis referred to as MUTYH-associated polyposis (MAP), which has a relatively mild phenotype, exhibiting <100 adenomas per patient and an average age at diagnosis of 45 years (19). In certain patients with MAP, the extracolonic manifestations can also be demonstrated, but DTs are not part of the MAP tumor spectrum (20). To date, *MUTYH* mutations in FAP-associated DTs have not been reported in published literature or in any database. The mutation c.1005G>C has also not yet been reported. Whether it is meaningless or functionally associated with the development of DT will require further investigation. In tumors of the nine patients with sporadic DT, six mutations in the *CTNNB1* gene, four mutations in the *APC* gene and one mutation in the *MUTYH* gene were identified. Three particular mutations in the *CTNNB1* gene have been reported (and associated) with DT: T41A, S45F and S45P (6). A number of studies have demonstrated a significantly increased risk of disease recurrence in patients harboring an S45F mutation compared with those who had either tumors with a T41A mutation of WT tumors (21,22); however, the association between genotype and phenotype has not yet been determined. In the present study, two T41A, one S45F and one S45P mutations were identified in *CTNNB1*. However, due to the small sample size of the present study, the association between particular gene mutations and prognosis could not be confirmed.

Due to the lack of prospective cohort studies for rare conditions such as DTs, the optimal treatment remains to be elucidated. Surgery is the primary treatment for patients with resectable DTs (23). According to the results of the present study, resection of central-type DTs is more difficult compared with that of peripheral-type DTs due to organ involvement. Although margin status remains a controversial topic in the management of DTs (24,25), the present study demonstrated a tendency towards shorter TTP in the patients that underwent R2 resection, which may be due to the small sample size. DTs behave in an unpredictable manner, as they may remain stable, grow aggressively or even regress without intervention (26,27). Due to the heterogeneity, unpredictable natural biology and high recurrence rate of DTs, the benefit of aggressive treatment modalities remains unclear. A move towards conservative management strategies has emerged over the past decade, including hormonal therapy, NSAIDs, chemotherapy and a 'wait and see' approach. In the present study, following primary surgery, seven patients who accepted R0/R1 or R2 resection, received Tamoxifen, NSAID (COX2 inhibitor) and/or waited for the outcome remained alive by the end of the follow-up period. Bonvalot *et al* (28) revealed that patients with extra-abdominal DT with a microscopically complete surgery had a similar outcome compared with patients in a no-surgery group. However, abdominal DT has different characteristics, particularly for retroperitoneal and intra-abdominal cases, and may lead to severe morbidity, functional impairment and even mortality due to its anatomic site (12). In certain cases, resectable tumors may progress to be unresectable or involve additional viscera (12). Therefore, it is currently unknown when a 'wait and see' approach may be the best treatment strategy. More prospective trials are required to provide a basis for clinical management. A

number of systemic therapies have been used for DT, ranging from those with low toxicity such as hormonal therapy or NSAIDs (29,30) to combination chemotherapy (31,32). In the present study, hormonal therapy, NSAIDs and chemotherapy were used alone or in combinations to treat patients with primary or recurrent DTs, but the effect was difficult to evaluate. Potential complications should be carefully considered when systemic therapy is used as, In the present study, two patients experienced gastrointestinal perforation due to chemotherapy (33).

For abdominal DTs, which are a rare condition, the management remains controversial due to the high number of variations, such as the incisional margin, site of tumor and genotype. However, surgery remains the preferred treatment for DTs. Although the present study comprised a small sample size, the analysis revealed a number of meaningful results, such as mutations in *APC*, *CTNNB1* and *MUTYH*. To the best of our knowledge, the present study is the first to report a patient with *MUTYH*-associated FAP and an abdominal DT; abdominal DT was prone to occur in patients with FAP who had undergone abdominal surgery, and the prognosis of patients with FAP-associated DT was poor. The present study may contribute to the future development of optimal strategies for diagnosing and management of different types of abdominal DTs.

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Availability of data and materials

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

Authors' contributions

JYW, NJ, QWL, YH, YZ and HXT conceived and designed the study. JYW and HXT drafted the manuscript. QWL, JLL, QJ and WSL performed the mutation analysis. YFH and JL collected the samples and performed pathological analysis. YH performed the enteroscopy. NJ, JX and ML collected clinical data and assisted in the follow-up. WQL and YHZ assisted in data analysis and interpretation. YZ revised the manuscript critically. All authors read and approved the final manuscript.

Ethics approval and consent to participate

The study was approved by the Committee for Ethical Review of Research Involving Human Subjects of Zhongshan Hospital affiliated with Fudan University. Informed consent was acquired from all patients.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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