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CLINICAL TRIAL

Breast desmoid tumor management in France: toward a new strategy

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Abstract

Purpose Desmoid tumors (DTs) are rare tumors that originate from myofibroblastic tissue. Recently, initial wait and see was recommended (ESMO guidelines Ann Oncol 2017) in the most frequent locations. This study investigates the outcome of breast desmoid tumor (BDT) according to the initial strategy.

Method Data from all consecutive patients treated from a BDT in four referral centers were collected. Only intra-mammary desmoid tumors were included. A pathological review and a molecular analysis (*CTNNB1* gene mutation) were performed (National re-reading network of sarcomas-RRePS). Patients were grouped according to initial strategy: surgery group (SG) and active surveillance group (ASG).

Results A total of 63 patients (61 women, 2 men) met the inclusion criteria. Median age was 50 years (16–86). *CTNNB1* mutation was found in 61% ($n=36$). SG included 46 patients (73%) (41 partial mastectomies, 2 mastectomies, and 3 mastectomies associated to parietectomies). Surgical margins were positive in 15 patients (33.3%). Median follow-up of SG was 24.9 (0.5–209) months; and 4 patients (8.7%) developed recurrence. ASG included 17 patients (27%). Their median follow-up was 42.2 (0–214) months, and 15 patients (88.2%) did not require any additional treatment. Six patients (35%) had a spontaneous regression, 9 patients (52%) were stable, and 2 patients presented a significant progression that was treated by partial mastectomy.

Conclusion This study supports an initial nonsurgical approach to BDTs followed by surgery based on tumor growth in select cases, which is consistent with current ESMO recommendations.

Keywords Desmoid tumor · Breast · Active surveillance · Surgery · Fibromatosis

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Introduction

Desmoid tumors (DTs) are benign monoclonal fibroblastic or myofibroblastic non-metastastic neoplasms originating from the musculo-aponeurotic structures. They are locally invasive and have a high recurrence rate but no metastatic potential [1]. They develop virtually at any site and are divided into two categories: those associated with Gardner's syndrome and those with the sporadic form associated with the *CTNNB1* gene mutation, which is more common [2]. The incidence rate is 2.4–4.3 new cases per 1 million individuals per year, while breast desmoids represent fewer than 10% of all DT, so they are still relatively uncharacterized [3–5].

Before the 2000s, systematic R0 (negative margins) surgery was the gold standard for DTs [6–9]. Their stellar shape resulted in wide resections with functional and aesthetic sequelae. Moreover, the observation of their spontaneous regression led to the emergence of the active surveillance (AS) approach. Bonvalot et al. demonstrated in 112 patients diagnosed with extra-abdominal primary fibromatosis that the outcome was similar between patients who underwent microscopically complete surgery and those with no surgery, suggesting the viability of AS [10]. Further support for AS was provided by Fiore et al. in 142 patients with desmoid-type fibromatosis [11]. DTs stabilize and regress in almost 50% of cases [5, 12–15]. This initial AS strategy is now recommended by ESMO guidelines, which are based on the outcome observed in the most frequent locations [16]. Due to the very low incidence of breast desmoid tumor (BDT), there is no clear recommendation for this specific location.

The risk factors for DT recurrence after resection in the majority of series include young age (under 26 years), tumor location, and tumor size as defined in Crago's nomogram [17]. The impact of margins on progression or recurrence is variable [10, 18, 19]. Since their clinical evolution is unpredictable, the challenge with BDT is to identify new early factors of progression using molecular biology [12] on blood samples [20] to adjust the treatment. Due to the lack of data on BDT, the objective of this large retrospective study was to describe the outcome according to the initial strategy.

Patients and methods

Characteristics of population

Ethics approval from the appropriate committees was obtained. Retrospectively, from January 1, 1998 to December 31, 2016, data of patients with BDT treated at the four participating cancer centers (Bergonié Institute–Bordeaux, Curie Institute–Paris, Gustave Roussy Institute–Villejuif, and Institut Universitaire du Cancer de Toulouse-Oncopole–Toulouse (IUCT-O)) were entered either in the Conticabase (European retrospective clinicopathologic database on sarcomas, https://conticabase.sarcomabcb.org) or in the NetSarc (National prospective database, https://netsarc.sarcomabcb.org).

We included patients with BDT addressed to referral centers, whose DT was localized in the intra-mammary parenchyma at the time of diagnosis. As previously described, the epicenter of the BDT could be located within the breast parenchyma itself, pectoralis muscle, or subcutaneous breast fat [21], and some BDTs were invading the skin, the pectoral muscle, or the thoracic wall, showing an infiltration along the fascia (fascia tail) in 80% of the cases [22]. We excluded all thoracic DTs with breast extension. The following clinical data were collected: Gardner Syndrome context, history of breast trauma or surgery, clinical tumor size, year of diagnosis, and follow-up.

We recorded all imaging data with tumor size as extension, as soon as it was available. Ultrasound, mammography, MRI (magnetic resonance imaging), and PET scan (positron emission tomography scan) were used to determine the tumor location and invasion. We used the Breast Imaging Reporting and Data System (BI-RADS) classification developed by the American College of Radiology (ACR) to standardize the interpretation of the results. Available MRI was re-read, double-blinded by radiologists at the IUCT-O in Toulouse in order to differentiate BDT and thoracic wall DTs, using the tumor gravity center as the initial location). In the event of BDT, they sought whether the thoracic wall was secondarily involved. If not, they measured the healthy tissue between the tumor and the thoracic wall.

We also collected histologic data such as tumor size and resection margins (R0: negative margins, R1: microscopically positive margins, R2: gross residual disease and *CTNNB1* mutation).

Treatments were recorded: surgery group (SG) (partial mastectomy, mastectomy, mastectomy, and parietectomy), and active surveillance group (ASG). Adjuvant (or neoadjuvant) treatments were recorded: external beam irradiation or tomotherapy and site of treatment, dose in Gray (Gy)), chemotherapy, immunotherapy, and non-steroidal anti-inflammatory drug (NSAID, inhibitor COX-2).

Statistical analysis

The data were summarized by median and range [min–max] for quantitative variables and by frequency and percentage for categorical variables. Comparisons between two therapeutic groups (SG and ASG) were assessed using the

Mann–Whitney test for quantitative variables and the Chi-squared test or Fisher's exact test for qualitative variables. Tests were two sided, and p-values < 0.05 were considered significant. Statistical analysis was conducted using Stata version 13.

Results

Patient characteristics

One hundred twenty-three patients with BDT were collected. Sixty were excluded: 57 because of loss to follow-up and three because the BDT were not in the mammary parenchyma (two under the area of the inferior breast in contact with the rib and one within a breast dorsal flap reconstruction). Among the 63 included patients, the SG included 46 patients (73%), and the ASG included 17 patients (27%). Patient characteristics are presented in Table 1.

The median clinical tumor size was 20 mm [range: nonpalpable-150 mm], and there were 33 left BDTs (52.4%) and 30 right BDTs (47.6%). All cases were reviewed and confirmed by an expert pathologist. The *CTNNB1* mutation gene was found in 61% of the cases ($n = 36$ patients). Only 4 tumors did not receive mutation analysis. There were no clinico-histologic features evoking Gardner's Syndrome with familial adenomatous polyposis suggesting the APC gene mutation (Table 1).

Thirty-two patients out of 41 (78%) had breast ultrasound, 22 out of 40 (55%) had mammography, and 20 out of 40 (50%) received MRI. The ACR classification identified 24 patients (57.1%) as BI-RADS 4; 11 (26.2%) as BI-RADS 5; and 6 (14.3%) as BI-RADS 6. Only one lesion was classified as BI-RADS 3. None was considered as benign (21 missing data).

Of the 15 MRI reviewed by the radiologists, 11 (73.3%) tumors seemed to emerge from the mammary parenchyma, but 4 (26.7%) had a gravity center within the thoracic wall. For the confirmed BDT, the healthy tissue between the tumor and thoracic wall was measured when feasible, i.e., without thoracic wall tumor invasion. It measured from 0–62 mm. The rest of them ($n = 7/11$; 63.6%) were invading the thoracic wall by local extension.

Surgery group

Among the 35 (76.1%) patients who had a preoperative biopsy, the *CTNNB1* mutation was found in 28 (63.6%). Only 10 patients (35.7%) had MRI. The MRI was reviewed for 7 patients and showed 5 tumors (71.4%) with a center of gravity within the breast parenchyma and 2 tumors (28.6%) apparently originating from the chest wall. Of the 5 intramammary cases, only one was in contact with the chest wall and four were distant with healthy tissue intervals ranging from 10 to 62 mm.

Partial mastectomy was performed in 45 cases (97.8%) and total mastectomy in one case. The median tumor size of the pathological specimen was 20 mm [range: 6–65 mm]. In 30 cases (66.7%), a clear margin (R0) was found. Positive margins (R1) were identified in 28.9% ($n = 13$), and R2 in

Table 1 Demographics and tumor characteristics, overall and by treatment (surgery/active surveillance), presented as median (range: min–max) or *n* (%)

Characteristics	Total $n = 63$ *n* (%)	ASG $n = 17$ (27%) *n* (%)	SG $n = 46$ (73%) *n* (%)	*p* value
Age at diagnosis (years), median (range)	50 (16–86)	59 (18–86)	49 (16–77)	0.154
Female	61 (96.8)	16 (94.1)	45 (97.8)	
Male	2 (3.2)	1 (5.9)	1 (2.2)	
History				
Breast Cancer	9 (14.3)	3 (17.6)	6 (13.0)	0.692
Breast benign surgery	16 (25.4)	4 (23.5)	12 (26.1)	1.000
Initial clinical tumor size (mm), median (range), n = 58	20 (6–150)	20 (10–80)	20 (6–150)	0.965
≤ 20 mm	36 (62.1)	9 (56.3)	27 (64.3)	
[20–50] mm	19 (32.8)	6 (37.5)	13 (31.0)	
> 50 mm	3 (5.2)	1 (6.3)	2 (4.8)	
Nonpalpable	4	0	4	
Missing	1	1	0	
Mutation CTNNB1	36 (61)	8 (53.3)	28 (63.6)	0.480
Missing	4	2	2	
Follow-up (months), median (range)	27.9 (0–214.4)	42.2 (0–214.4)	24.9 (0–209.2)	

ASG active surveillance group; *SG* surgery group, *mm* millimeters

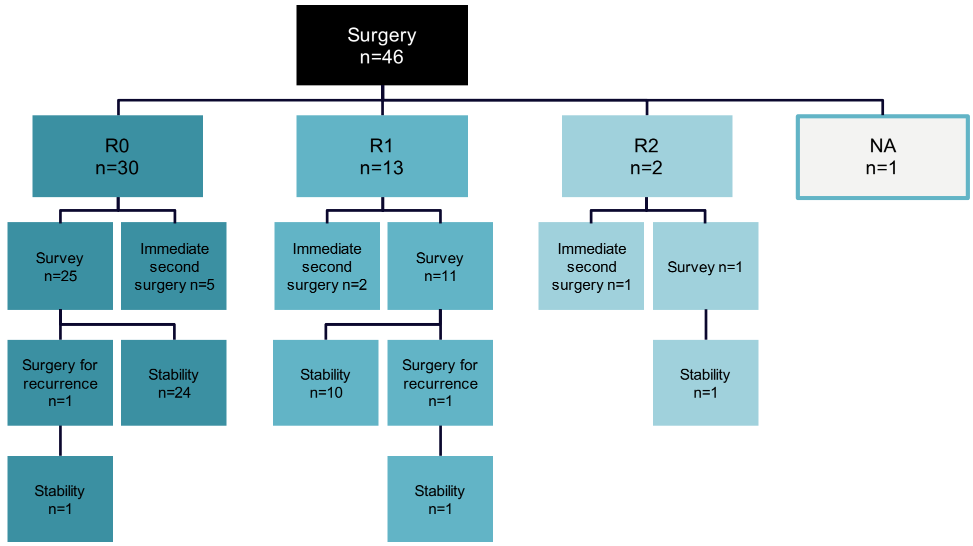


Fig. 1 Management of breast desmoid tumors within surgery group

4.4% ($n=2$). In 77.8% ($n=35$), no further excision was performed. Among these 35 patients, 24 cases (68.6%) had R0 margins, 10 (28.6%) were R1, and 1 (2.8%) was R2. Eight patients (17.8%) had an immediate re-excision, and the final margins were R0 $n=5$, R1 $n=2$, R2 and $n=1$.

Among the eight patients who had an immediate re-excision for positive or negative (R1/R2) margins but which were considered insufficient (infra-millimetric), four had a partial mastectomy, one had a radical mastectomy, and three a parietectomy with an autologous flap reconstruction.

The median follow-up in the SG was 24.9 months [range: 0.5–209.2 month] (Fig. 1, Tables 2, 3). Four patients (8.7%) developed a local recurrence. The delay between diagnosis and recurrence varied from 7.3 to 61.6 months. Two were operated for the local recurrence (one had initial R0 margins and the other had initial R1 margins) (one breast conservation and one with mastectomy) and two were observed. The disease stabilized in the two latter patients and had regressed after one year of surveillance, thus avoiding mutilating surgery.

None of the patients received radiotherapy or systemic treatment in a neoadjuvant setting. Two patients received systemic treatment after surgical treatment. One patient presenting explosive growth received high-dose methotrexate (120 mg/day) before second surgery with no effect on the growth kinetic. One patient with local recurrence was treated by NSAID (celecoxib 200 mg/day for 3 month) for a post-surgery recurrence. The disease then regressed.

Active surveillance group

All patients ($n=17$) in this group had a biopsy to confirm the diagnosis and 8 (53.3%) had the *CTNNB1* gene mutation. At physical examination, the median tumor size was 20 mm [range: 10–80 mm]. Ten patients (58.8%) received MRI.

Table 2 Characteristics of breast desmoid tumor management within surgery group

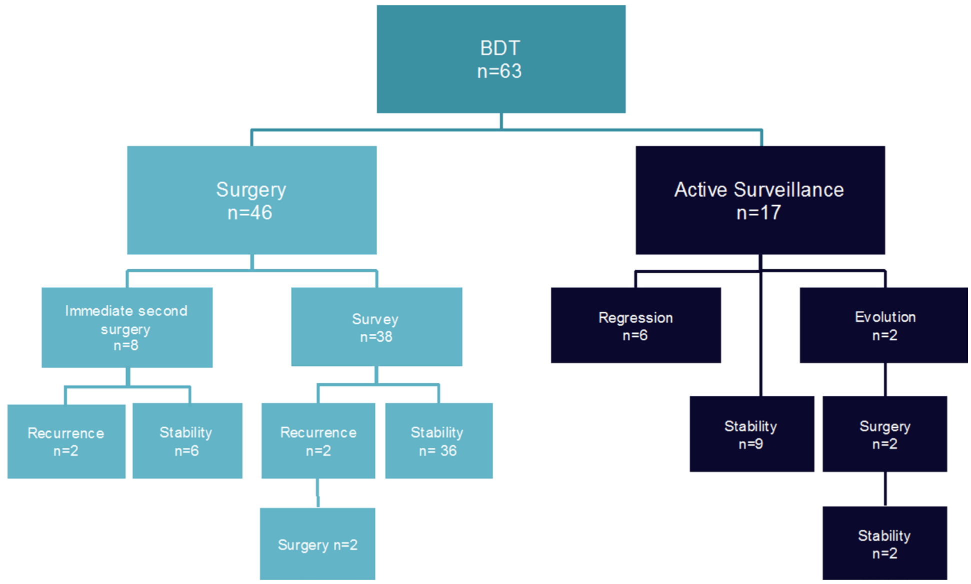
Characteristics	Surgery group, $n=46$ n (%)
Initial treatment	
Conservative surgery	45 (97.8)
Mastectomy	1 (2.2)
Pathological characteristics	
Tumor size (mm), median (range)	20 (6–65)
Margins (1 missing data NA for initial mastectomy)	
R0	30 (66.7)
R1	13 (28.9)
R2	2 (4.4)
Immediate second surgery, $n=8$	
Conservative surgery	4 (50)
Mastectomy	1 (12.5)
Pariectectomy	3 (37.5)
Evolution	
Stability	42 (91.3)
Recurrence	4 (8.7)
Second surgery post-recurrence, $n=2$	
Conservative surgery	1 (50)
Mastectomy	1 (50)

mm millimeters; *NA* not applicable

Table 3 Evolution according to treatment group (Surgery *vs* Active surveillance)

Characteristics	Total, $n=63$ n (%)	Surgery group, $n=46$ n (%)	Active surveillance, $n=17$ n (%)
Regression	6 (9.5)	0 (0)	6 (35.3)
Stability	51 (81.0)	42 (91.3)	9 (52.9)
Recurrence	6 (9.5)	4 (8.7)	2 (11.8)

Fig. 2 Management of breast desmoid tumors



This group received MRI more frequently than patients in the SG (83.3% versus 35.7% $p = 0.005$). The median radiologic tumor size was 16 mm [range: 10–50 mm]. The MRI was reviewed in eight patients. Six tumors appeared to have a center of gravity in the breast parenchyma, and two were emerging from the chest wall. Among the six tumors involving the mammary parenchyma, three were infiltrating the thoracic wall, and three were at a distance with clear tissue intervals ranging from 6 to 22 mm. The median follow-up in the ASG was 42.2 months [range: 0–214.4] (Fig. 2, Table 3). Among the ASG, seven patients had large tumors (> 20 mm). Among tumors measuring between 20 and 50 mm, 3 (50%) regressed, 2 (33.3%) remained stable, and 1 (16.7%) progressed. Also, the only patient with a tumor > 50 mm progressed. In total, the tumor regressed spontaneously in six patients (35.3%), was stable in 9 (52.9%), and progressed in 2 (11.8%) requiring a partial mastectomy. These two patients were subsequently stable. One of these two patients did not have a *CTNNB1* gene mutation, but the case was independently reviewed and was confirmed by two referent pathologists from the pathology subcommittee of the French Sarcoma Group (nuclear beta-catenin immunohistochemistry expression was present). The case of the second patient (arising on a plastic surgery reduction scar) who progressed was also reviewed and confirmed by a referent pathologist from the French Sarcoma Group, but the *CTNNB1* gene mutation was not sought (case too old dating from 1998).

Discussion

Currently, there is no consensus about the management of BDT. In this paper, we show that AS, which has recently been recommended in more frequent locations [8], may be applied safely in BDT, thereby avoiding mutilating surgery in some cases [16]. The initial diagnosis may be difficult since mammography and ultrasound images can mimic cancer [23]. MRI is the gold standard to evaluate BDT spread in the breast parenchyma and thoracic wall [24–26], but it may lead to the wrong diagnosis with a high rate of BI-RADS 4 or BI-RADS 5 (false-positive). Half of our patients had MRI, more frequently in the ASG (83.3%) than in the SG (35.7%). All patients with lesion ≥ BI-RADS 3 at imaging were biopsied. The identification of the exon 3 *CTNNB1* mutation, especially on core needle biopsies, can confirm the diagnosis of DT and rule out several spindle cell lesions such as low-grade sarcomas or reactive benign lesions such as nodular fasciitis and scars, which could appear similar to DTs. Exon 3 *CTNNB1* mutations are highly prevalent and are detected in up to 94% of sporadic DTs [6]. This high rate of exon 3 *CTNNB1* mutation is found for DTs whatever their location, except the breast, for which the rate of mutation is around 40–50% [27]. For this reason, a collegial review was done by expert soft tissue tumor pathologists to confirm the diagnosis when no exon 3 *CTNNB1* mutation was identified in BDT. This allowed us to establish a robust diagnosis, which is essential for appropriate management. Moreover, the challenge is to find predictive factors of progression, especially when AS is decided on the basis of the new recommendations [16]. Recent data obtained with emerging molecular biology techniques suggested the putative role of *CTNNB1* detection in circulating cell-free DNA at the time of diagnosis, which was able to predict DT evolution in 65% of patients [20]. These preliminary results opened the way for using cell-free DNA as a biomarker to predict progression for selecting the right patients for surgery.

Because this study is retrospective and strategy evolved during the study period, roughly three quarters of patients received surgery, of whom five had radical resections. This type of surgery may be very mutilating (five patients had mastectomy associated in two cases with parietectomy) (10.8%) in our series, which is less than in the studies by Roussin or Neuman [5, 28]. In the study by Roussin et al., six patients in the SG (30%) received a mastectomy, and seven patients (35%) received a thoracic wall resection [5]. In Neuman's study, eight patients (29%) had a chest wall resection that had a major aesthetic and functional impact for a nonmalignant tumor. Furthermore, the rate of positive margins within SG remained high with 34.3% R1 in our study. This was due to stellar extensions and is consistent with the literature [9, 13, 17]. This confirms that the necessarily wide surgical margins in DTs have a potential cosmetic impact according to the tumor/breast volume ratio. In fact, 17.8% of our patients in the SG had a surgical re-excision in primary care for positive or insufficient margins, which generated more radical surgery. Moreover, Janssen et al., in a meta-analysis including 16 studies with a total of 1295 patients suffering from extra-abdominal DTs, showed that risk of local recurrence in the SG was almost twofold higher for patients with R1 margins (RR = 1.78, 95% [1.40–2.26]) [13]. Adjuvant radiotherapy after surgery with positive margins is no longer recommended, especially in young patients [16]. On the other hand, the rate of recurrence was low (8.7%) in the SG compared to the rates of 17.9, 28.6, and 40% in the studies by Wargotz, Neumann, and Roussin, respectively [3, 5, 28]. The difference may be due to patient characteristics, tumor size being a prognostic factor [17].

The first study comparing AS to surgery in BDT included 31 patients of whom 11 were treated by AS [5]. In the ASG, only 27% (3/11) had to change treatment strategies during the observation period. Only one received surgery, and two were offered anti-hormonal treatment. Most of the patients (88.2%) had a BDT that was either stable (35.3%) or spontaneously regressed (52.9%) with a longer median follow-up than that of patients in the SG (42.2 months). The stability rate was consistent with the literature [15, 29–31] and the tumoral spontaneous regression rate (35%) observed was in the same range as that found for abdominal wall DT [32]. In a cohort of 102 patients suffering from an abdominal wall DT and placed under AS, 29 (28.4%) exhibited spontaneous regression with a median follow-up of 32 months [32]. The follow-up in our ASG (42.2 months) is sufficient since the vast majority of progressions appeared in the three years after diagnosis [3, 4, 11, 28]. Remarkably, 10 of our cases were stable after surgery with R1 margins, so second surgery should not be recommended [16].

Medical options in DTs can often be used in a stepwise fashion in the event of progressing or symptomatic lesions [16], according to the expected side effects, patient status, and the objectives (symptom relief or higher response rate). However, AS means that the patient is monitored actively, particularly at the beginning of follow-up. Based on the experience of this study, a clinical and radiologic exam with MRI should be performed within 4–6 weeks after diagnosis, then every 3 months in the first year, then every 6 months the next 2 years, and then yearly as recommended as in other locations [16]. Pregnancy is not recommended during the first year after diagnosis, because it is a known factor for progression [33]. Therefore, the disease should be stable or regressive status before pregnancy [16].

This is the first large cohort study to evaluate BDT management thanks to multi-institutional collaboration between referral centers. Although retrospective, it sheds light on this rare disease. A high rate of regression/stabilization (88.2%) was observed after the AS strategy, and the findings confirm that it is a pragmatic method to select patients who require surgery in the breast. Initial active monitoring by MRI is essential to identify patients whose disease is progressing. The strategy is safe for BDT as in other locations, provided decisions are taken on a multidisciplinary basis. In the event of progression, surgery is the gold standard. As in other rare tumors, national registration, data centralization, and multidisciplinary tumor board meetings are mandatory to improve our understanding of this rare disease.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no competing interests.

Ethical approval This article does not contain any studies with animals performed by any of the authors. 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.

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