Burden of Surgery in Desmoid Tumors

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BACKGROUND AND OBJECTIVES

- Desmoid tumors (DT), or aggressive fibromatosis, are soft-tissue tumors with locally aggressive, infiltrative, and destructive growth. DT can arise as extra-abdominal (extremities, chest wall, head and neck, or intrathoracic regions), abdominal wall (potentially occurring in women during or following pregnancy), and intra-abdominal (either a pelvic or mesenteric location) tumors[1-3]
- DT have a broad, negative impact on patients' lives. Patients experience symptoms of pain and impaired mobility, which limit their everyday activities and can lead to deterioration in physical, social, and emotional functioning domains[4-6]
- Treatment goals should not focus solely on clinical markers such as progression-free survival but also consider patient-relevant endpoints such as reduction in DT-specific symptom burden (e.g., pain) and DT impact on patients' lives, improvement in functioning on daily activities, and overall quality of life[7-11]
- Historically, surgery has been the standard of care, but the rates of recurrences after surgery can be high depending on age, tumor location, and tumor size.[12-17] In patients with DT, surgery can lead to significant complications[18]
- The functional impairment and high local recurrence rates observed after surgery for DT have contributed to a paradigm shift over the last 2 decades toward more conservative management
  - Resection needed for clear margins is often large and may require radical surgery, which can lead to functional impairment or morbidity[19]
- The aim of this research was to assess the burden of surgery in patients with DT, focusing on recurrence rates and functional deficits resulting from procedures such as limb amputation. Additionally, the cost of surgery in soft-tissue sarcoma (STS) and the general cost of amputation, a potential outcome of DT surgeries, were evaluated
  - Based on feedback from several surgical oncology experts in the United States and European Union, STS may be considered a valid analog to estimate the costs of surgery in DT. Of note, costs of surgical resections can vary based on the tumor size, location, extent of involvement, complexity of the case, and other factors

METHODS

- To identify publications written in the English language describing recurrence rates and functional outcomes after surgery in patients with DT, searches of the PubMed, Embase, and the Cochrane Library databases for studies published in English were conducted from November 2011 to November 2021 and updated in December 2022
- Given the lack of economic data related to DT surgeries, additional reviews of STS surgery costs and amputation general costs were conducted
- Costs of amputation were derived from studies in patients with other comorbidities (e.g., diabetes, peripheral artery disease, coronary artery disease).

RESULTS

RECURRENCE AFTER SURGERY AND KEY RISK FACTORS

- Recurrence rates of DT after surgery vary depending on the site of the tumor (Table 1)

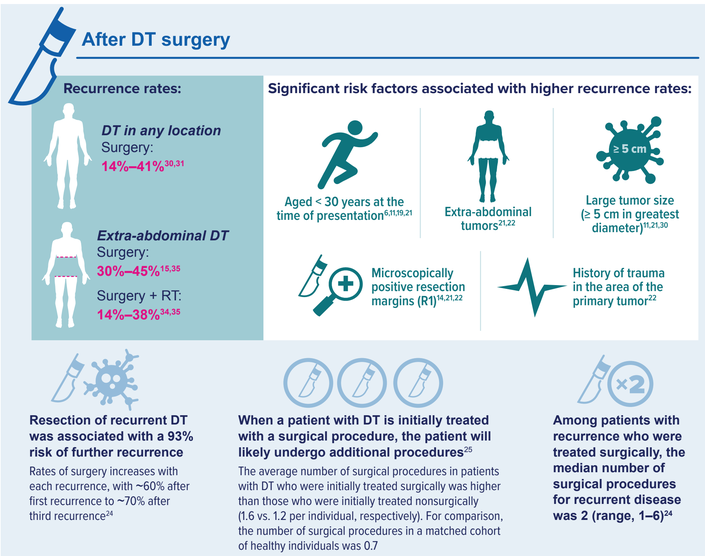
Table 1. Postsurgical Recurrence Rates in Patients With DT Reported in Retrospective Studies

Reference	Country years	Population characteristics	Tumor location	Patients who underwent surgery: Primary	Patients who underwent surgery: Recurrent	Median follow-up (months)	Recurrence rates: Surgery only	Recurrence rates: Surgery + RT	5-year RFS/EFS (%)
All subtypes of tumors (extra-abdominal, abdominal wall, intra-abdominal)									
He et al.[21]	China 1985–2014	N = 114[a] 69% female Median age, 33 years	AW: 35% Extra-A: 48% Intra-A: 17%	89	25	72.5	35/114 (31%)		72
Cates et al.[26]	US 1983–2011	N = 92[a] 69% female Median age, 40 years	AW: 22% Extra-A: 78%	92	0	38.4	25/92 (27%)		
Colombo et al.[27]	France and Italy 1992–2012	N = 216[a] 63% female Median age, 41 years	Extra-A: 75% Intra-A: 25%	94	0	76	18/94 (19%)		80
de Bruyns et al.[28]	Canada 1990-2013	N = 227 68% female Median age, 40 years FAP, 6%	AW: 22% Extra-A: 61% Intra-A: 17%	132		77	29/108 (27%)	4/24 (17%)	
Huang et al.[29]	China 1987–2009	N = 214 77% female Median age, 33 years	AW: 43% Extra-A: 51% Intra-A: 6%	153	61	55.5	42/214 (20%)		79
Zhao et al.[30]	China 2012–2020	N = 69 71% female Average age, 37.3 years	AW: 46% Intra-A: 54%	64	5	49.4	10/69 (14%)		79
Mueller et al.[31]	Germany 2000–2015	N = 32[a] 58% female Median age, 36 years	AW: 27% Extra-A: 58% Intra-A: 15%	26	6	65	13/32 (41%)		64–69
Nishida et al.[32]	Japan NR	N = 85[a] 66% female Age, 53% > 36 years	AW: 15% Extra-A: 85%	73	12	10	32/85 (38%)		53
Peng et al.[22]	US 1983–2011	N = 211 68% female Median age, 36 years FAP, 8%	AW: 21% Extra-A: 56% Intra-A: 23%	179	0	25.7	42/179 (23%)		53
Turner et al.[33]	Canada 2004–2015	N = 53[a] 74% female Mean age, 43 years	AW: 30% Extra-A: 53% Intra-A: 17%	53		35	8/53 (15%)		
Yang et al.[23]	China 2007–2019	N = 267 70% female Age, 65% > 30 years	Extremity: 38% Nonextremity: 62%	207	60	NR	29/141 (21%)	24/126 (19%)	
Extra-abdominal tumors									
van Broekhoven et al.[34]	Netherlands 1989–2011	N = 132 64% female Median age, 36 years	Extra-A: 100%	128[b]	0	38	18/128 (14%)		
Janssen et al.[15]	SLR and meta-analysis 1999–2015	N = 1,295	Extra-A: 100%	1,053	242	25–135	297/1005 (30%)	79/290 (27%)	
Krieg et al.[35]	Switzerland NR	N = 96 64% female Mean age, 38.9 years	Extra-A: 100%	96		100.8	20/44 (45%)	6/16 (38%)	
Tsagozis et al.[24]	Sweden 1981–2015	N = 174 56% female Mean age, 35 years	Extra-A: 100%	174		38	44%		

AW = abdominal wall; EFS = event-free survival; extra-A = extra-abdominal; FAP = familial adenomatous polyposis; intra-A = intra-abdominal; NR = not reported; RFS = recurrence-free survival; RT = radiation therapy; SLR = systematic literature review; US = United States

[a] Patients with FAP were excluded

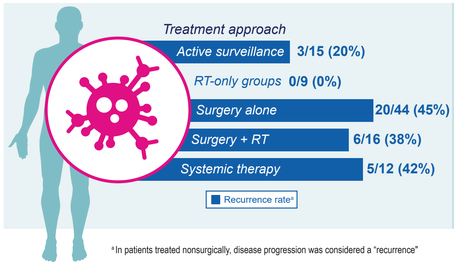
[b] 132 patients were treated, but data on recurrences are available for only 128 patients



FUNCTIONAL AND PATIENT-REPORTED OUTCOMES AFTER SURGERY

- Some studies have reported an increase in major functional limitations in the limbs among patients with DT after surgical resections of their tumors, with > 40% suffering functional loss or amputation of the involved limb[36,37]
- Patients undergoing 2 or more surgical interventions or those treated with surgery + radiotherapy (RT) at any time had lower functioning scores, indicating that a more aggressive local treatment may be associated with poorer long-term functional outcomes[38]
- Patients undergoing amputation may suffer from painful, functionless, or infected extremities as a result of a recurrent DT or local complications of treatment[39]
- Patient-reported outcome scores as measured using the Patient-Reported Outcomes Measurement Information System (PROMIS) were lowest (higher scores indicate better functioning) among patients who underwent 2 or more surgical interventions and among those treated with surgery + RT at any time, indicating that a more aggressive local treatment may be associated with poorer long-term functional outcomes.[38] Mean PROMIS function scores were 39 for ≥ 2 resections versus 51 for 1 resection versus 47 for 0 resections ($P = 0.025$). For both patients with primary and patients with recurrent tumors, event-free survival did not improve compared with those treated without local modalities[38]

EFFECT OF TREATMENT ON RATE OF RECURRENCE/PROGRESSION[35]



[a] In patients treated nonsurgically, disease progression was considered a "recurrence"

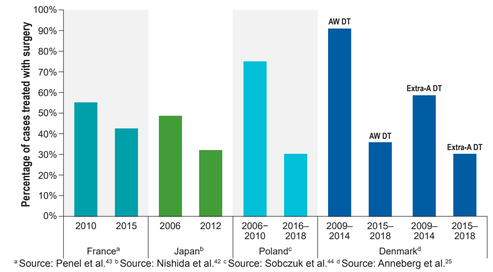
In a systematic review of studies published from 1999 to 2017, local recurrence was more common after surgery with positive margins than after surgery with negative margins[14]

Patients with recurrent disease who were on active surveillance had a better local control rate than patients treated with surgery alone ($P = 0.001$)[14]

TRENDS IN SURGICAL INTERVENTIONS

- Guidelines from the National Comprehensive Cancer Network, version 1.2023[40] recommend active surveillance with continuous monitoring for asymptomatic tumors not leading to functional limitations
- Surgery is no longer recommended as first-line treatment in most clinical situations
- Surgery is recommended by the Desmoid Tumor Working Group for abdominal wall tumors if morbidity is limited[41]
- Given the evidence that an active surveillance strategy is associated with a lower recurrence rate and better functional outcomes than a surgical strategy in many patients with DT, use of surgery as initial treatment has decreased in the last 10 years (Figure 4).[42-45] There may be selection bias in the choice of treatment, medical condition, and physician/patient preference[44]

Figure 4. Changes in the Percentage of DT Cases Treated With Surgery as Initial Treatment



[a] Source: Penel et al.[43] [b] Source: Nishida et al.[42] [c] Source: Sobczuk et al.[44] [d] Source: Anneberg et al.[25]

COSTS OF STS SURGERIES AND AMPUTATIONS

- Among 4 US studies reporting cost of tumor surgeries in people with STS, cost of surgery ranged from $18,151 in 2013 US dollars[45] to $55,801 in 2008–2013 US dollars.[46] Among 6 US studies reporting costs of amputations (mostly lower-extremity, nontraumatic amputations resulting from comorbidity complications), acute inpatient care costs varied from $30,573 to $43,030 (in 2022 US dollars) in patients with diabetes (used as proxy due to a lack of available costs of amputations for DT). Costs per patient per year (in 2022 US dollars) for nontraumatic amputations varied from $70,944 in patients with coronary artery disease to $112,751 in patients with peripheral artery disease.[47] Costs depend on the type of amputation; for example, in veterans with diabetes, total direct medical cost in 2022 US dollars for a toe amputation was estimated at $54,046, whereas costs of $92,588 and $107,819 were estimated for amputations below and above the knee, respectively[48]
- The estimated lifetime, all-cause (including any condition being treated) direct cost for lower-extremity amputation is approximately $1 million in 2022 US dollars[49]

CONCLUSION

Surgery is no longer recommended as first-line treatment in most clinical situations of DT, as it can be associated with poor long-term functional outcomes and high economic costs. Alternative treatments with improved benefit-risk profiles (i.e., that preserve limb function and improve quality of life) compared with current treatment options are needed for patients with DT

LIMITATIONS

- Other relevant studies may have been missed due to limiting the search to the past 10 years and to publications in English
- Few studies were available reporting on the functional outcomes of surgeries, and no studies evaluated the economic burden of surgery and amputations in patients with DT
- Due to the rarity and long natural history of DT, some studies could have reduced statistical power and estimate precision. Selection bias could occur among different treatment modalities caused by the selection of tumors with different patterns of progression

DISCLOSURES: Timothy Bell, Ana B. Oton, Shengfan Zhou, and Brad Tumminello are employees of SpringWorks Therapeutics, Inc., Stamford, CT, USA, and have equity in SpringWorks Therapeutics, Inc. Shahnaz Khan and Meryem Bektas are employees of RTI Health Solutions (Maria Fernandez is a former employee), Research Triangle Park, NC, USA.

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