Tailoring Desmoid Treatment

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Op maat gemaakte behandeling voor desmoid tumoren

Proefschrift

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Contents

Chapter 1

Introduction

Desmoid-type fibromatosis (DF) is a rare disease, also known as aggressive fibromatosis or desmoid tumor. It is a fibroblastic proliferation arising in deep soft tissues. DF is characterized by infiltrative growth with a tendency towards local recurrence but an inability to metastasize[1]. Therefore, they are labeled as an "intermediate (locally aggressive)" tumor by the World Health Organization. These tumors typically present as a deep, firm mass which causes little or no pain.

Etiology

The pathogenesis of DF is not fully understood. Genetic mutations, hormonal influences and a history of trauma are all involved factors[2-4]. Genetic mutations are seen in the majority of patients, mostly in the *APC* and *CTNNB1* gene. Both genes are part of the canonical Wnt-pathway and influence gene transcription and cell adhesion[5]. A distinction is made between these types of mutations. In most cases of sporadic disease, the *CTNNB1* gene is involved, whereas mutations in the *APC* gene are associated with familiar adenomatous polyposis (FAP)[6,7]. This association is called Gardner syndrome. Approximately 7.5% of all desmoid patients have FAP, whereas approximately 14% of FAP patients develop DF[8,9].
Hormonal influences are implied by the peak occurrence of tumors among fertile females and the behavior of disease during pregnancies. Pregnant patients often report tumor growth during pregnancy, with spontaneous regression after delivery.
A history of trauma is documented in a large group of patients. In particular, surgical trauma is believed to influence pathogenesis, as DF often arises in scars.

Classification

There are three subgroups of DF:

- Extra-abdominal. A scale of anatomic locations can be involved, though mainly the extremities, chest wall, back, head and neck. The origin is mostly sporadic.
- Abdominal. Tumors arising from the abdominal wall. The origin is both sporadic and associated with FAP. Also associated with pregnancies and cesarean sections.
- Intra-abdominal. Tumors arising in the pelvis or mesentery. The origin is associated with FAP.

This thesis is focused on the extra-abdominal and abdominal DF. Due to the different

biology, treatment options and consideration in relation to FAP, intra-abdominal DF will not be discussed.

Part 1 - Epidemiology

DF accounts for approximately 0.03% of all neoplasms and less than 3% of all soft tissue tumors. Mostly females are affected by this disease, with a peak around 38 years of age. The incidence of DF is low. Descriptive articles by a Finnish group, dated around 1982, report an incidence of two to four individuals per million people per year[2,3]. They found different distributions of gender and tumor localization among age groups. In the pediatric population, extra-abdominal lesions prevailed, equally among the genders. Abdominal wall lesions were predominantly found in young adolescents till the age of 40. The majority of the group was female. Among older patients, tumors were distributed equally between abdominal and extra-abdominal lesions and equally among gender. These studies date three decades ago. More insight in current epidemiologic trends and treatment related trends was imperative. In **chapter 2** we analyzed the trends in incidence and treatment of extra-abdominal and abdominal DF in a population based study.

Part 2 – Treatment modalities

The treatment options for DF are dependent on the localization of the tumor. Extra-abdominal and abdominal disease is often treated similarly, whereas intra-abdominal disease poses different challenges. Organ involvement and the often large size of the tumor limit surgical and radiotherapeutic options for intra-abdominal disease. In addition, the frequent association with FAP in intra-abdominal disease is related to a high mortality rate, partially due to organ compression by the tumor[10].
The classical treatment of extra-abdominal and abdominal DF implies primary surgery, with radiotherapy on indication. During the past decade, this advice switched based on accumulating evidence to active surveillance and in case of progressive disease surgery, radiotherapy or systemic treatment based on localization.

Surgery

DF cannot metastasize and is therefore not considered malignant. However, the tumor can be locally aggressive and surgeons may be inclined to remove the tumor at the earliest possible stage. Complete resection is challenging due to the infiltrative growth pattern.

In addition, pathology characteristics mimic scar tissue, hindering evaluation of repeated surgery to achieve complete resection. Literature on the benefit of complete resection is ambivalent. Studies supporting the significance of resection margin on local control are reported by Ballo et al. and Huang et al.[11,12]. In contrast, Guadagnolo et al., Stoeckle et al. and Gluck et al. did not find statistical significant benefit of microscopic radical resection (R0) over microscopic irradical resection (R1)[13-15]. A large study by Gronchi et al. (n=203) reported a discrimination[16]. They found no benefit of radical resection on local recurrence for primary disease, but is was statistical significant for recurrent disease. Salas et al. described the largest study on the subject (n=426), reporting a significant benefit of R0/R1 over R2, but none for R0 over R1 and no statistical significance in multivariate analysis[17]. In **chapter 3** we describe a retrospective study among a large patient cohort. We analyzed the risk of recurrence following complete or incomplete resection, as well as the value of adjuvant radiotherapy.

Radiotherapy

Radiotherapy can be applied neo-adjuvant or adjuvant in candidates for surgery, or as an option for inoperable patients. The advised therapeutic dose is set at 56 Gy[18]. The benefit of radiotherapy is however disputed, in particular the value of (neo-) adjuvant radiotherapy. Whereas Ballo et al. and Baumert et al. described an added value for adjuvant radiotherapy on local control[11,19], Guadagnolo et al. and Gluck et al. did not find the same results[13,15]. The value of radiotherapy as primary treatment is more supported in the literature. Zlotecki et al. reported a 5-year local control rate of 96% for primary disease and 75% in recurrent disease among 72 patients[20]. EORTC study 92991-22998 reported by Keus et al. showed complete response in 13.6%, partial response in 36.4% and stable disease in 40.9% of patients after 3 years[18]. In addition, continuing regression was seen after 3 years of follow-up. Radiotherapy is a very aggressive treatment modality for a relatively benign disease, as it can induce malignancy and other complications. Therefore, careful considerations must be made before applying this treatment modality. The value of radiotherapy following surgery is discussed in **chapter 4**.

Isolated limb perfusion

Another form of local treatment is isolated limb perfusion (ILP). With this technique, high dose chemotherapy can be delivered to the tumor. During the procedure, the targeted blood circuit is isolated and connected to an oxygenated extracorporeal circuit. Tumor necrosis factor alpha and melphalan are injected into the limb vascular system. After

60-90 minutes of perfusion, the vascular system is rinsed and circulation restored. This technique is the European standard of care for patients with limb-threatening sarcoma. It is a highly aggressive treatment due to the toxicity. For patients with DF, this treatment is only considered for a very select group of patients. Patients need to have advanced disease, in which surgery would lead to severe mutilation or amputation. This treatment is only performed in specialized sarcoma centers after careful consideration, often in a multidisciplinary setting. In **chapter 5**, we report the outcome of this technique in DF in 3 specialized EORTC sarcoma centers.

Systemic treatment

Besides local treatment, several drugs have been applied as systemic treatment for DF. Anti-hormonal drugs, non-steriodal anti-inflammatory drugs (NSAIDs), tyrosine kinase inhibitors and several types of chemotherapy have been reported as treatment for DF. Literature on the outcome of these drugs in DF is very scarce. Usually small patient cohorts are described, with overall good response of treatment. A systematic review of systemic treatment has been reported by Janinis et al., concluding that the evidence in the literature supports the opinion that both non-cytotoxic and cytotoxic chemotherapies are effective against DF[21]. However, the lack of sufficient patient numbers and randomized trials compromises the validity of the reported results. Recently, an European consensus on the treatment of DF has been published[22]. Systemic treatment is mentioned among the options stating that '(...), it is reasonable to employ the less toxic therapies before the more toxic ones in a stepwise fashion. However, due to the lack of randomized or comparative data, we are not in the situation to propose a definitive order of the existing systemic treatment options.' Overall, toxicity of treatment is balanced against the intermediate nature of this disease.

Active surveillance

As DF is not an aggressive disease, active surveillance (also known as wait-and-see policy or watchful waiting) can be applied in patients with limited or no complaints. During active surveillance, frequent follow-up visits will be made, to monitor potential tumor growth. This treatment modality has gained popularity during the past decade. Reports from several research groups show promising numbers of disease stabilization and spontaneous regression[17,23]. This has led to a shift in treatment from primarily surgery and radiotherapy to more conservative management. Currently, active surveillance is advised as primary management for all DF by the European Organization for Research and Treatment of Cancer (EORTC)[22].

This shift has resounded in the Netherlands, where initial surgery for primary DF has decreased. In addition to the epidemiologic study described in chapter 2, we have traced treatment modalities for these patients. In **chapter 6** we report the results of first-line non-surgical management of DF in the Netherlands.

Part 3 – Predicting tumor behavior

The natural behavior of DF ranges from spontaneous regression to rapid invasive growth. It is challenging to predict the behavior of a tumor in an individual. Several factors have been analyzed, mostly related to risk of recurrence after surgery. Age, localization and size of the tumor are commonly accepted as predictive factors of recurrence, with young age, large tumors and localization in extremity or chest wall associated with high risk of recurrence. Crago et al. constructed an nomogram to predict risk of recurrence after surgery, based on data from 495 patients[24].

Mutations in the *CTNNB1* gene correlate to DF. As these mutations play a role in pathogenesis, a role in biologic behavior seems natural. Several groups have analyzed *CTNNB1* mutation as a predictive factor for recurrence after surgery. Although Mullen et al. did not find a statistical significant prognostic value[25], several other groups reported a higher risk of recurrence for patients with an S45F mutation[26-28], even in multivariate analysis[26]. We analyzed the predictive value of *CTNNB1* mutations on the risk of recurrence in **chapter 7**. For this study, the previously formed cohort of patients undergoing surgical treatment was used.

To tailor treatment of DF, a staging system is needed designed to be applied at diagnosis. Present knowledge is mostly based on retrospective data, with a lack of comparative research. As such, it is not sufficient to create a staging system. Knowledge on natural behavior can best be obtained during active surveillance. Three research groups have initiated prospective studies to provide insight on natural behavior; a French group (NCT01801176), an Italian group (NCT02547831) and our group (NTR4714). The study protocol for the Dutch study is presented in **chapter 8**. This protocol was designed in collaboration with the Italian group, in order to improve generalizability of the data.

Part 4 – General discussion, summary and appendices

This thesis is about tailoring the treatment of DF. Knowledge on DF has increased greatly during the last decade. More information is available on natural behavior, genetics and the effects of treatments. Current medical care is patient oriented, with a trend toward individualized treatment strategies. In addition, one must keep in mind the intermediate nature of DF. Mortality due to DF is reported for intra-abdominal disease, but not for extra-abdominal or abdominal tumors. Quality of life is very important when treating DF. Active surveillance is advised in a first-line setting, although surgery might be a better option for some patients. When DF has advanced, toxicity of treatment and expected results must be balanced. In **chapter 9 and 10** we discuss current knowledge, considerations for treatment strategies and provide our vision for the future.

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Part 1

Epidemiology

Chapter 2

Time trends in the incidence and treatment of extra-abdominal and abdominal aggressive fibromatosis: a population-based study.

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Abstract

Background

Aggressive fibromatosis (AF) is a locally infiltrating soft-tissue tumor. In a population-based study in the Netherlands, we evaluated time trends in the incidence and treatment of AF.

Methods

In PALGA: Dutch Pathology Registry, all patients diagnosed between 1993 and 2013 as having extra-abdominal or abdominal wall aggressive fibromatosis were identified and available pathology data of the patients were evaluated. Epidemiological and treatment-related factors were analyzed with Chi-square and regression analysis.

Results

During the study period, 1134 patients were identified. The incidence increased from 2.10 to 5.36 per million people per year. Median age at the time of diagnosis increased annually by B 0.285 (P=0.001). Female gender prevailed and increased over time (annual odds ratio (OR) 1.022; P=0.058). All anatomic localizations, but in particular truncal tumors, became more frequent.

During the study period diagnostic histological biopsies were performed more often (annual OR 1.096; P<0.001). The proportion of patients who underwent surgical treatment decreased (annual OR 0.928; P<0.001). When resection was preceded by biopsy, 49.8% of the patients had R0-resection versus 30.7% in patients without biopsy (P<0.001).

Conclusion

In this population-based study, an increasing incidence of extra-abdominal and abdominal wall aggressive fibromatosis was observed. The workup of patients improved and a trend towards a nonsurgical treatment policy was observed.

Introduction

Aggressive fibromatosis (AF; or desmoid-type fibromatosis) is a rare soft-tissue tumor that lacks the capacity to metastasize but may behave in a locally aggressive fashion. Knowledge on its epidemiology and etiology is limited. The Wingless/Wnt-pathway is involved although the mechanism is not fully understood[1-3]. Three different subtypes are recognized as entities in the WHO-classification of desmoid-type fibromatose: extra-abdominal, abdominal and intra-abdominal tumors[4]. The first two mostly occur sporadic whereas the latter has a correlation with familiar adenomatous polyposis (FAP)[5].

The incidence of AF was reported previously by Reitamo et al. in 1982, estimated at 2.4-4.3 per million people per year[6]. Their studies on the etiology and epidemiology are often referred to in the current literature[6-8]. The correlation of intra-abdominal AF with FAP has been subject of more recent studies[9-11]. Current research on AF mainly focuses on treatment strategies. Surgery has until recently been the primary treatment modality. Data regarding the prognostic value of surgical margins and adjuvant radiotherapy is conflicting[12-15]. New insights suggest that asymptomatic patients can be carefully watched without active treatment and this is suggested by international (NCCN and ESMO) guidelines[16,17]. Symptomatic patients with tumors that can be resected completely with acceptable morbidity should be offered surgery. In patients with symptomatic and "unresectable" disease, radiotherapy may be considered[18]. Isolated limb perfusion can be considered for irresectable AF of the extremities[19]. Systemic treatment can also be considered, although response rates are rather low[20-22].

We evaluated time trends of the incidence and treatment of extra-abdominal and abdominal wall AF within the Dutch population.

Methods

Data collection

The Dutch Pathology Registry PALGA was searched for patients with extra-abdominal or abdominal AF, whereas patients with intra-abdominal tumors were excluded[23]. The epidemiology and treatment of intra-abdominal tumors are linked to FAP and are considered a different entity. Data on this entity in the Dutch population have recently been

analyzed[9]. The PALGA database contains encoded excerpts of all pathology examinations obtained by a diagnostic procedure, including tissue biopsy or resection since 1979 in selected laboratories and expanded to nationwide inclusion in 1991. The conclusion sections of all pathology reports were queried for available information concerning patient, tumor and treatment characteristics. Age was categorized as <20, 20-44, 45-64, 65-79 and >80 years old. Tumor localization was categorized as head/neck, trunk (including breast, thoracic aperture and back), abdominal wall, extremity and others. Reports were scored based on the encoding of procedures and details in the report as biopsy, resection or re-resection and on manifestation of the tumor (primary or recurrence). All patients undergoing re-resection were considered to have had a prior resection, even when pathology reports of the resection were missing. In case of patient records documenting recurrent disease, an attempt was made to retrieve details on the primary tumor. Due to incomplete data registration, patients with disease presentation before 1993 were excluded. The years of diagnoses were categorized as 1993-1998, 1999-2003, 2004-2008, 2009-2013.

The primary objective was to analyze time trends in the incidence of AF. Trends of clinicopathological factors were analyzed as well as possible associations between the factors. The secondary objective was to analyze time trends in type of treatment, to which end the rate of resection was evaluated. Due to constrains in the pathology database structure, only data on pathology specimens such as biopsy of resection were available. Information on other treatment strategies or outcome was not available.
In order to compare the patient cohort with the Dutch population, data from Statistics Netherlands were obtained. This is a registry for all general population data. We used information on demographics to calculate annual incidence rates and information on surgical treatments, hormonal drugs and newborns to analyze possible etiological correlations.

Statistical analysis

Statistical analysis was performed using IBM SPSS Statistics 21. Continuous variables are shown as median with interquartile range (IQR), and categorical variables as numbers with percentages. Associations between clinicopathological variables were determined by Chi-square analysis. Univariate logistic and linear regression analysis was performed to analyze trends over time, results are shown as odds ratios (OR) or regression coefficient B (B) and with 95 % confidence intervals (CI). For all analyses, two-sided $P<0.050$ was considered statistically significant.

Results

A total of 1134 patients were diagnosed with extra-abdominal or abdominal wall AF between January 1993 and December 2013; there were 326 men and 808 women. Median age was 37 years (IQR 30-50). The distribution of demographic factors is shown in Table 1. In addition to the 1134 patients diagnosed as having AF, an uncertain diagnosis of AF was stated in the pathology excerpt in 213 patients. This latter group of patients did not change significantly over the years (P=0.730). These patients were not included in the analyses for the present series.

Table 1. Distribution of epidemiologic factors

	1993-1998		1999-2003		2004-2008		2009-2013	
	N	%	N	%	N	%	N	%
Gender								
Male	56	31.1	50	27.0	105	31.7	115	26.3
Female	124	68.9	135	73.0	226	68.3	323	73.7
Age (years)								
<20	18	10.0	14	7.6	29	8.8	39	8.9
20-44	115	63.9	124	67.0	170	51.4	239	54.6
45-64	37	20.6	33	17.8	85	25.7	112	25.6
65-79	10	5.6	11	5.9	39	11.8	43	9.8
80+	0	0.0	3	1.6	8	2.4	5	1.1
Localization								
Head/neck	14	8.0	13	7.1	20	6.1	27	6.2
Trunk	29	16.7	39	21.4	102	30.9	152	34.8
Abdominal wall	77	44.3	88	48.4	113	34.2	151	34.6
Extremity	45	25.9	32	17.6	68	20.6	85	19.5
Other	7	4.0	6	3.3	22	6.7	22	5.0
Unknown	2	1.1	4	2.2	5	1.5	0	0.0
Pathology reports								
Biopsy	13	7.2	39	21.1	69	20.8	130	29.7
Biopsy + Resection	39	21.7	40	21.6	98	29.6	161	36.8
Resection	114	63.3	101	54.6	163	49.2	147	33.6
Unknown	14	7.8	5	2.7	1	0.3	0	0.0

Epidemiologic factors

The incidence of extra-abdominal and abdominal wall AF increased over the study period, from 2.10 to 5.36 per one million people (P<0.001; Figure 1).

Figure 1. Incidence of aggressive fibromatosis, per million people.

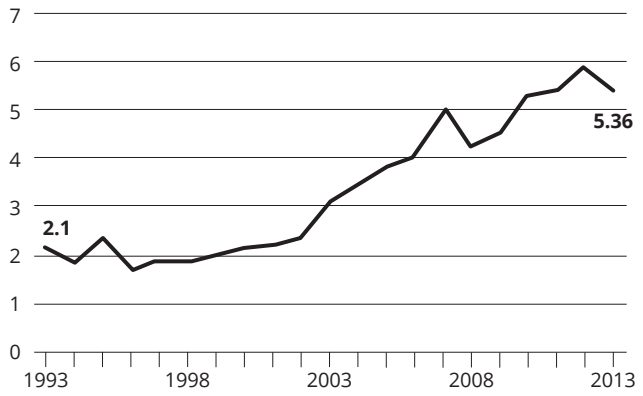


Figure 2a. Distribution among age during study period.

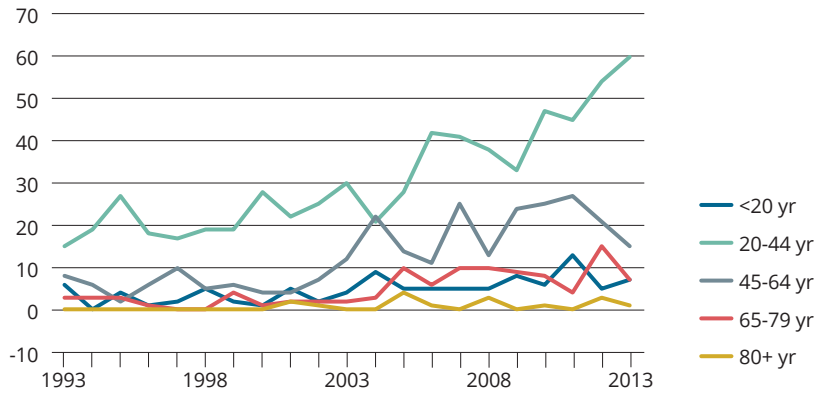


Figure 2b. Percentage of age distribution.

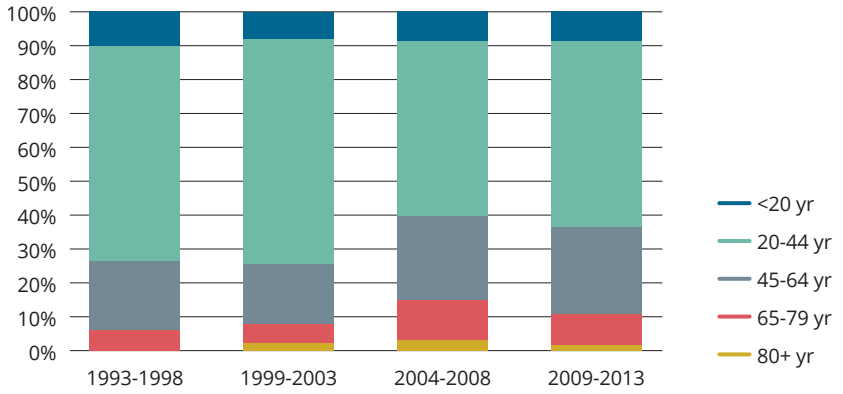


Figure 2c. Distribution among localization during study period.

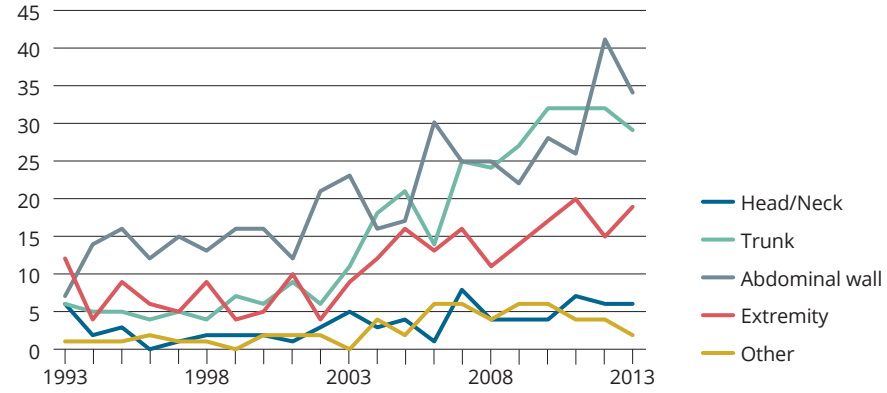
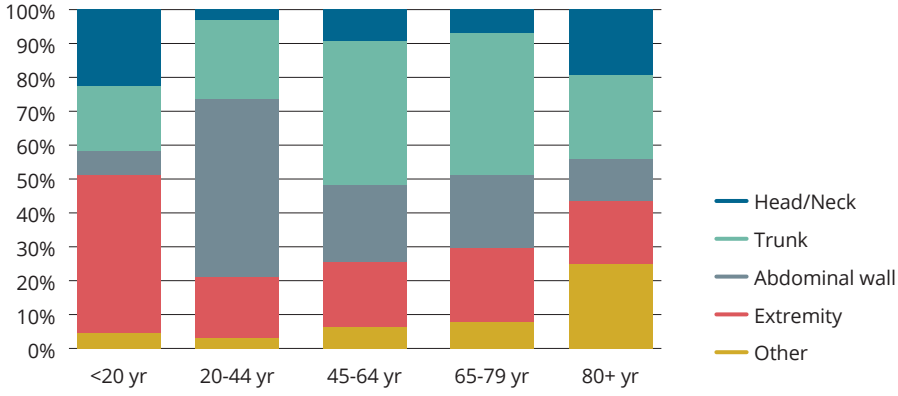


Figure 2d. Distribution of localization per age group.



Age

The median age increased annually by B 0.285 (95%CI 0.114-0.455; P=0.001). The median age in 1993-1998 was 34 years (IQR 27-45) and was 39 years (IQR 30-51) in 2009-2013. The absolute numbers increased in all age groups over time (Figure 2a). However, the percentage of patients per age groups changed, mostly in patients aged 20-79 years (Figure 2b). Analysis of the distribution among age groups showed a significant annual decrease in the percentage of patients aged 20-45 years (OR 0.977; 95%CI 0.957-0.997; P=0.027) and a trend towards an annual increase in the percentage of patients aged 45-65 years and 65-80 years (OR 1.017; 95%CI 0.993-1.042; P=0.173 and OR 1.035; 95%CI 0.997-1.074; P=0.069 respectively).

Figure 3. Type of pathology records per patient

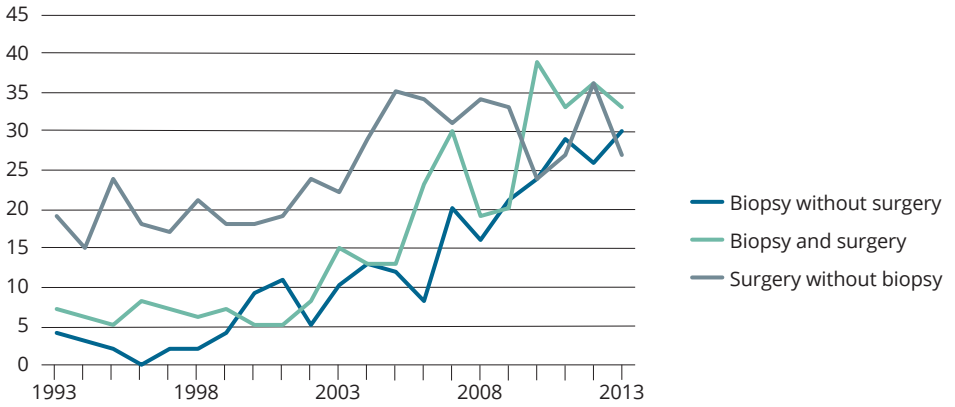
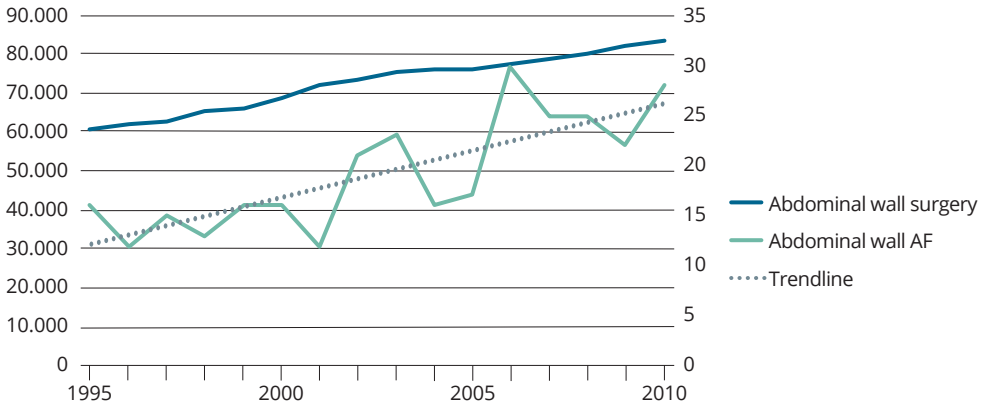


Figure 4. Absolute number of most common abdominal wall surgery, in relation to the absolute number of patients with abdominal wall AF (on secondary axis).



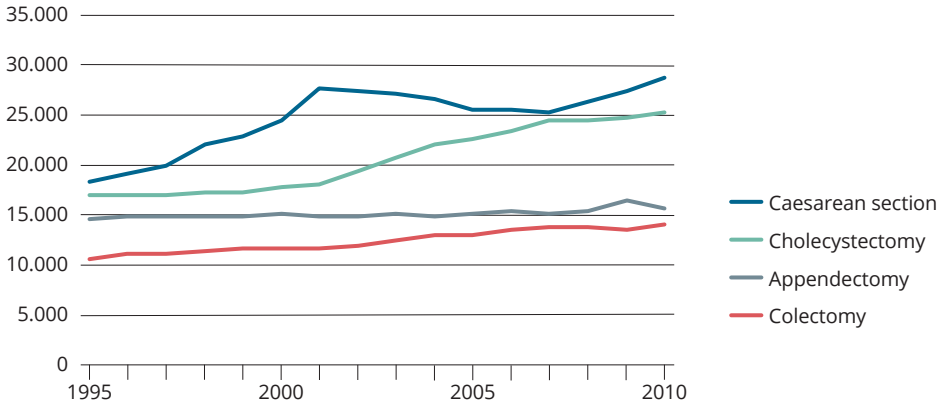
Gender

The absolute numbers of both male and female patients increased over the years. The male-female ratio showed an increasing female predominance, ranging from 68.6% in 1993-1998 to 73.6% in 2009-2013.

Anatomic tumor localization

Tumor localization was distributed as: 6.7% head/neck, 29.0% trunk, 38.6% abdominal wall, 20.7% extremity and 5.1% other (localization details were missing for 22 patients). Over the years, the absolute incidence in all groups increased (Figure 2c). Analysis of the distribution

Figure 5. Abdominal surgery in the Netherlands.



of tumor localization showed a significant proportional increase in the percentage of patients with truncal localization (OR 1.057; 95%CI 1.032-1.083; P<0.001) whereas the percentage of patients with tumors in the abdominal wall decreased (OR 0.972; 95%CI 0.952-0.993; P=0.008).

Associations between clinicopathological factors

The distribution of tumor localization varied per age group (Figure 2d). Extremity-based tumors were most common in patients under 20 years of age (45.0%), whereas patients between 20 and 45 years most commonly harbored abdominal wall tumors (52.6%); truncal tumors were predominantly seen in patients between 45 and 80 years of age (41.5%). For patients over 80 years of age, no dominant localization could be identified. The distribution of age groups and localization changed over the study period.

Workup and treatment

In 251 patients (22.1%) solely a biopsy report was retrieved; for 338 patients (29.8%) a biopsy report and a pathology resection specimen report was retrieved and for 525 patients (46.3%) solely a pathology resection specimen report was retrieved. For 20 patients, the type of report was unknown (Figure 3). From 1993-1998 to 2008-2013, the biopsy rate increased more than twofold: from 31.1% to 66.4% (OR 1.096; 95% CI 1.072-1.121, P<0.001). The proportion of patients who underwent surgical resection decreased annually (OR 0.928; 95%CI 0.902-0.954, P<0.001). It was not known what treatment was offered to the patients who did not undergo surgery due to the nature of the database. Over time, surgical resection was increasingly

preceded by biopsy. If a resection was preceded by biopsy, the resection margin status improved significantly (49.8% R0-resection versus 30.7% in patients without biopsy; P<0.001). Pathology reports did not discriminate between diagnostic or therapeutic resections. Median time between biopsy and resection was 1.6 months (IQR 0.9 -2.7). The date of either biopsy or resection was missing for 2 patients. A substantial number of patients (210; 18.5%) had a history of surgery in the same area where AF subsequently developed.

Dutch population

Since the abdominal wall was the most common tumor localization, we analyzed surgical trends in the Netherlands for the most common surgeries in this area (caesarean section, cholecystectomy, appendectomy and colectomy)[24]. During the study period, surgical trauma to the abdominal wall increased (Figures 4 and 5). Due to minimal invasive techniques for many surgical interventions, the rate of laparotomy decreased and the rate of laparoscopic surgery increased.

Data on hormonal drugs was available for the period 2006-2012. During this period, the overall use of hormonal medication in the Netherlands remained stable.

The number of pregnancies of any gestational age was not available. The number of newborns per year was used as a surrogate, and during the study period this number decreased from 195.748 in 1993 to 171.341 in 2013.

Discussion

The reference standard on the incidence and epidemiology of AF are Finnish studies by Reitamo et al[6-8]. An incidence of 2.4-4.3 per million people was reported in those studies, using 3 methods of estimation (local, regional and national). Distribution of disease was reported with a dominance of abdominal wall tumors (49%) with variations per age group. In the present population-based study, a rising incidence of extra-abdominal and abdominal wall AF was observed from 2.1 to 5.36 per million people during the period 1993 – 2013. The distribution among age groups was similar to the Finnish studies, with a predominance of abdominal wall tumors in females ages 20-44 years. Remarkably, median age and female predominance increased over the years and the distribution of tumor localization shifted. The driving factor for these observed changes is unclear.

The PALGA database provided an elaborate overview of AF in the Netherlands. The nationwide coverage enabled epidemiological research on this rare disease. Then again, the available information was limited to the date and conclusion of the pathology reports. Although there was information on biopsy and resection, no information was available for nonsurgical treatments, which is a limitation of the present study. Still, important information could be extracted.

Time trends in incidence

Explanations for the observed rising incidence of AF are not evident. If a rise in incidence occurs, this can be due to improved diagnostic modalities (i.e. for instance detection of previously unrecognized tumors by improved imaging, improved recognition of the disease by pathologists, or the start of a screening program), or due to a true rise in the incidence of the disease.

Improved registration and diagnostic tools are likely to have influenced the incidence figures to some extent. The changes in distribution of tumor localization might be an indication for a true change in disease. However, there are possible biases: other reasons could be an increased frequency of trunk computer-tomography scan or higher awareness due to screening programs.

Dutch guidelines on registration of neoplasms have changed over the years. The introduction of the third edition of the WHO Classification for Soft Tissue and Bone Tumours stimulated improvement of coding, enabling a better pathology registration[25]. Due to the benign nature, this neoplasm is not registered among soft tissue tumors in the national cancer registries precluding verification of our data. The overall incidence of sarcomas has remained stable over the years at approximately 30-35 patients per million people, with a slight increase to around 40 patients per million people over the past 5 years[26].

Knowledge on β-catenin and its application in the diagnostic setting around 2005 aided the pathologist in diagnosing AF with more confidence[27-29]. Nevertheless, the percentage of uncertain diagnoses has not changed significantly over the years, indicating that some difficulty to distinguish AF from low-grade and reactive spindle cell proliferations remains.

Awareness of the presence of AF and the realization of the importance of a correct diagnosis have improved. In addition, the association with FAP is better understood.

Lastly, screening programs may have influenced the stage of diagnosis, such as the breast cancer screening program in asymptomatic people.

Documented etiological factors are surgical trauma, hormonal influences and pregnancy[6-8]. National data on these factors was obtained to provide some context for the study data. A hypothesis could be that the increased rate of surgical trauma would lead to an increase in AF. On the contrary, a limitation of surgical trauma by means of minimal invasive techniques could possibly decrease the risk of AF. The analyses of abdominal surgery and abdominal AF both showed increasing rates over the study period, which might be supportive of the first hypothesis.

The peak in occurrence of AF among fertile females is supportive of hormonal influences as an etiological factor. To test the hypothesis that a rise in hormonal levels would lead to an increase in AF, we compared data on hormonal drug use from Statistics Netherlands with the data from PALGA. Although the information on drug use was from a small period (2006-2012), the incidence of AF was rising during this period while the rate of hormonal drug use remained stable.
Pregnancy is seen as an etiological factor within the hormonal influences. Because no data on pregnancies in the patient cohort was available, we obtained the rate of newborns in the Netherlands during the study period. The rate of pregnancies of any gestational age was not available. The hypothesis that an increase in pregnancies (represented by the number of newborns) would lead to an increase in AF was not supported, as the rate of newborns was decreasing.
A more sensitive approach to test hormonal influences on AF, like analyzing hormonal receptors on the tumor, could provide more information but was not possible for the current study.

We would like to emphasize that the presented comparisons between data from PALGA and Statistics Netherlands are all based on hypotheses. Direct correlations for these etiological factors could not be explored and possible biases should be taken into consideration.

Time trends in diagnosis and treatment

Despite the aforementioned advances in diagnostic tools, the diagnosis of AF poses remaining challenges to the treating physicians. Although the rising incidence is most likely biased by diagnostic modalities and improved registration, the presented results showed an increasing number of patients being treated for AF.
The presented results suggest an improved workup procedure of patients as histological biopsies were more often obtained. Surgical resection following a biopsy diagnosis

resulted in a significant higher rate of negative resection margins, underscoring the importance of the diagnostic process.

Treatment strategies changed in recent years and this is reflected in the present data. There has been a paradigm shift in the surgical treatment for AF patients. Before 2000, surgery with negative margins had been considered the standard of care for patients affected by AF, reflecting the same approach to extremity soft-tissue sarcomas. A reassessment has taken place by several groups, advocating a more conservative approach[30,31]. The European consensus is currently set at an initial wait-and-see approach[32]. The increasing number of patients undergoing nonsurgical treatment in the presented study indicated a tendency to adhere to this policy in the Netherlands. The growing knowledge and understanding of the etiology and involvement of *CTNNB1* mutations will improve the diagnostic process.

During the past 25 years, developments in the available diagnostic modalities and changing treatment insights had an impact on the workup and treatment of extra-abdominal and abdominal wall AF. More insight in current epidemiologic trends and treatment-related trends was imperative. This population-based study reflected these changes and showed an overall incidence rise of AF. The reasons for the changing incidence, age distribution and anatomic localization distribution remain to be further elucidated.

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Part 2

Treatment modalities

Chapter 3

Local recurrence following surgical treatment for primary extra-abdominal desmoid-type fibromatosis.

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Abstract

Background

Desmoid-type fibromatosis is a locally aggressive soft tissue tumour with a biological behavior that varies between relatively indolent and progressive growth. Although there is a trend towards conservative treatment, surgery remains the standard treatment.

Methods

Databases of three hospitals were searched to identify patients who had been treated for desmoid-type fibromatosis between November 1989 and May 2011. The risk of local recurrence was evaluated and predictive factors were assessed in patient who underwent surgical resection as initial treatment for a primary tumour.

Results

A total of 132 patients had surgical treatment for a primary tumour. A complete resection (R0) was achieved in 87 patients (65.9 per cent), macroscopic residual tumour remained in 4 patients. In addition to surgery, 54 patients received radiotherapy. During a median follow-up of 38 months, 18 local recurrences were detected. The estimated 5-year cumulative risk of local recurrence was 17.6 per cent. Univariable Cox regression demonstrated that the risk of local recurrence increased for extremity lesions compared with desmoids on the trunk (odds ratio 6.69, 95 per cent confidence interval 1.45 to 31.54). No significant influence of age, resection margins or adjuvant radiotherapy on the risk for local recurrence was observed.

Conclusion

Following surgical treatment of a primary extra-abdominal desmoid tumour, the 5-year risk of local recurrence is modest and not influenced by microscopically clear resection margins or adjuvant radiotherapy.

Introduction

Desmoid-type or aggressive fibromatosis involves rare, non-metastasizing, locally aggressive, soft tissue tumours that may occur in nearly any part of the body. Desmoid-type fibromatosis is usually sporadic, although several factors are associated with the development of the tumours. Abdominal wall involvement is frequently seen in women of reproductive age[1], and familial adenomatous polyposis is associated with an increased risk of developing desmoid tumours, particularly in the abdomen[2]. The biological behaviour is unpredictable and varies considerably between relatively indolent and progressive growth, which in turn may halt spontaneously[3]. The reported frequency of recurrence following local treatment ranges from 5 to 63 per cent[4,5].

Surgery is considered the standard treatment for desmoid-type fibromatosis[6], but radiotherapy and medical treatment have also been employed[7,8]. The influence of resection margin, tumour size and adjuvant radiotherapy on the risk of local recurrence is disputed[5,9–12]. The considerable number of patients who develop local recurrence represent, for some authors, a reason to advocate extensive local treatment[13], although others support a more conservative approach with a wait-and-see policy in the majority of patients[5].

In the present study, the 5-year cumulative risk of local recurrence after operative treatment for primary extra-abdominal desmoid-type fibromatosis was evaluated and the effect of possible risk factors for local recurrence was assessed.

Methods

Data collection

Patients with desmoid-type fibromatosis were identified from the institutional databases at University Medical Centre Utrecht, and the affiliated Diakonessenhuis, and at the Erasmus MC Cancer Institute in Rotterdam, The Netherlands. Patients diagnosed between November 1989 and May 2011 as having primary extra-abdominal desmoid-type fibromatosis were included in the study. Patients who did not undergo surgical resection as the initial treatment were excluded.

Patient and tumour characteristics

The following demographic and clinical variables were recorded: sex, age at diagnosis, localization of the tumour, tumour size and relation to the fascia (superficial or deep). Age was categorized into quartiles. Tumour localization was categorized as: trunk, extremity, head/neck/thoracic aperture, and other. Tumour size was categorized as 0–50, 51–100 or more than 100 mm. The soft-tissue pathology boards at University Medical Centre Utrecht and Erasmus MC Cancer Institute reviewed the histopathological diagnosis for all patients. The following information regarding primary treatment was recorded: number of operative procedures, surgical resection margins, and adjuvant radiotherapy.

The result of surgery was categorized based on the histological examination of surgical margins and the operative report, using the classification of the International Union Against Cancer (UICC), as R0 (microscopic radical resection), R1 (microscopic tumour-positive margins) or R2 (macroscopic residual disease). After the first operation in patients with microscopically involved margins (R1), reoperation was undertaken when re-resection was judged feasible without unacceptable morbidity or loss of function. In the case of multiple operations, surgical margins were classified according to histopathological findings after the last operation.

Local recurrence was the main endpoint, defined as tumour relapse following R0 or R1 excision of the primary tumour. For patients with an R2 resection, tumour progression was assessed. The end of follow-up was marked by tumour relapse (event), the last registered contact within the hospital or date of death (censored).

There were institutional differences regarding the follow-up strategy. At Erasmus MC Cancer Institute, patients were evaluated in accordance with the national guidelines, with physical examination every 3 months during the first year, every 6 months in the second year, and then once a year until 5 years after surgery. Magnetic resonance imaging (MRI) was performed only at 6 months after surgery, and in the event of symptoms suggestive of recurrence. At University Medical Centre Utrecht, and the Diakonessenhuis, the frequency of patient visits was the same, but MRI was performed additionally as part of the annual follow-up. After 5 years of follow-up, patients were encouraged to contact the hospital only in the case of local symptoms.

Statistical analysis

Continuous variables are shown as median with range, and categorical variables as numbers with percentages. Associations between clinicopathological variables were determined by Chi-square analysis. The overall cumulative 5-year risk of local recurrence following R0 or R1 resection was estimated using the Kaplan–Meier method, and differences between clinicopathological variables were analysed with the log rank test. To support these analyses, univariable Cox regression analysis was used; results are presented as hazard ratios (HRs) compared with a reference category and with 95 per cent confidence intervals (c.i.). The total number of local recurrences was too small to allow multivariable analysis. As the number of deceased patients also was very small, survival analysis was not performed. For all analyses, two-sided $P < 0.050$ was considered statistically significant.

Results

A total of 132 patients who underwent surgery as the initial treatment for primary extra-abdominal desmoid-type fibromatosis were identified (Table 1). Their median age was 36 (range 1–80) years, and 84 patients (63.6 per cent) were female. The most common localization of the tumour was the trunk (45.5 per cent); median tumour size was 53 mm.

Following attempted curative resection, additional operative procedures were performed in 33 patients (25.0 per cent). A complete resection (R0) was achieved in 87 patients (65.9 per cent); in 28 (32 per cent) of these patients, a second or third operation were performed to obtain microscopically clear resection margins. In 36 patients, surgery resulted in a microscopically incomplete resection (R1); in five patients, the tumour was removed completely according to the operative report but data regarding resection margins were lacking in the histopathological report. The tumour was macroscopically incompletely excised (R2) in four patients (3.0 per cent).

Postoperative radiotherapy was given to 54 patients (40.9 per cent). Data on definitive application of advised radiotherapy were lacking for three patients (2.3 per cent); in the other patients, doses of more than 50 Gy were given, in fractions of 2 Gy. Between the institutions, there were no differences in the proportions of patients who received radiotherapy (data not shown). Radiotherapy was applied following R1 or R2 resection

in 20 (50 per cent) of 40 patients following R1 or R2 resection versus 34 (39 per cent) of 87 patients who had an R0 resection (*P*=0.205).

The median length of follow-up was 38 (1–222) months. Forty-six patients (34.8 per cent) were followed beyond 5 years. During follow-up, three patients (2.3 per cent) died without recurrence from unrelated causes.

Table 1. Characteristics of patients operated on for primary extra-abdominal desmoid-type fibromatosis

	No. of patients (n=132)
Median age (years)	36
Age group (years)	
1–28	33 (25.0)
29–35	32 (24.2)
36–45	35 (26.5)
46–80	32 (24.2)
Sex ratio (M : F)	48 : 84
Involved anatomical area	
Trunk	60 (45.5)
Extremity	32 (24.2)
Head/neck/thoracic aperture	33 (25.0)
Other	7 (5.3)
Relation to fascia	
Superficial	24 (18.2)
Deep	108 (81.8)
Size of lesion (mm)	
0–50	74 (56.1)
51–100	43 (32.6)
> 100	11 (8.3)
Data missing	4 (3.0)

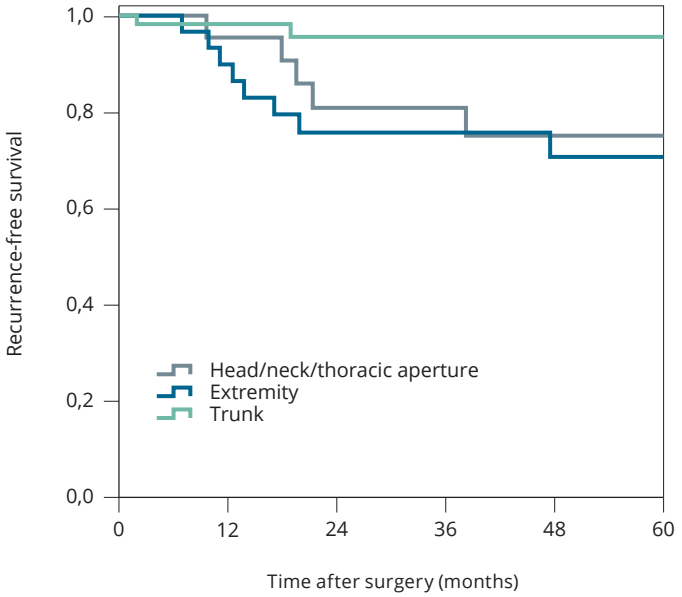
Values in parentheses are percentages.

Table 2. Risk of local recurrence after attempted curative surgery for primary extra-abdominal desmoid-type fibromatosis

			Kaplan-Meier analysis		Cox proportional hazards analysis	
	No. of subjects	**No. of events**	**5-yr local recurrence risk (%)**	**P-value[a]**	**Hazard ratio**	**P-value[b]**
Age group (years)				0.139		
1-28	31	7	34		1.00 (reference)	
29-35	34	3	10		0.28 (0.07-1.10)	0.068
36-44	30	3	14		0.36 (0.09-1.39)	0.139
45-80	33	3	15		0.35 (0.09-1.36)	0.129
Sex ratio				0.381		
M	46	8	23		1.00 (reference)	
F	82	8	14		0.65 (0.24-1.73)	0.384
Involved anatomical area				0.024[#]		
Trunk	59	2	4		1.00 (reference)	
Extremity	32	8	29		6.69 (1.42-31.54)	0.016
Head/neck/thoracic aperture	30	5	25		5.07 (0.98-26.13)	0.052
Other	7	1	20		3.50 (0.32-38.56)	0.307
Relation to fascia				0.300		
Superficial	24	1	11		1.00 (reference)	
Deep	104	15	19		2.79 (0.37-21.12)	0.321
Size of lesion (mm) *				0.761		
0-50	72	9	19		1.00 (reference)	
51-100	42	5	15		0.84 (0.28-2.52)	0.762
>100	10	2	25		1.56 (0.34-7.21)	0.571
Surgical margin **				0.736		
R0	87	10	15		1.00 (reference)	
R1	36	4	20		1.22 (0.38-3.90)	0.736
Radiotherapy ***				0.362		
No	74	10	21		1.00 (reference)	
Yes	51	6	13		0.63 (0.23-1.73)	0.366

Values in parentheses are 95 per cent confidence intervals. Data missing for * 4, ** 5 (with either R0 of R1 resection) and *** 3 patients. [a] Log rank test. [b] Wald test. [#] Excluding the "other" group; including this group of patients, P=0.056.

Figure 1. Kaplan–Meier analysis showing the association between the anatomical area and local recurrence following surgery for extra-abdominal desmoid-type fibromatosis. P=0·024 (log rank test)



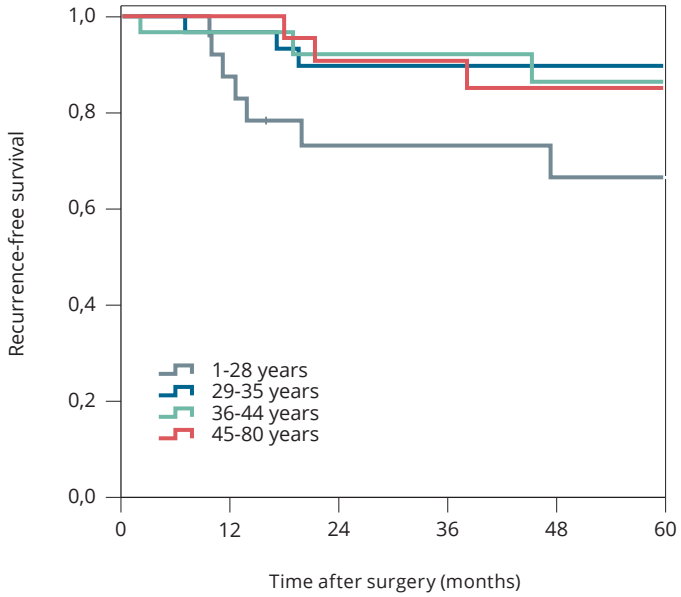
No. at risk

Head/neck/thoracic aperture	30	20	16	15	12	11
Extremity	32	26	19	16	14	12
Trunk	59	41	36	31	26	18

Local recurrence following R0/R1 resection

Local recurrence was observed in 18 patients (14.1 per cent) of 128 patients. The 5-year cumulative risk of local recurrence was 17.6 (95 per cent c.i. 9.9 to 25.6) per cent. The median time to recurrence was 18 months. Sixteen of the 18 diagnosed recurrences occurred before 5 years. Two of the 33 reoperated patients developed recurrent disease, both after R0 resection. Univariable analysis showed a difference in the risk of recurrence depending on tumour localization (*P*=0.024) (Table 2, Fig. 1), with a higher recurrence risk for lesions located on the extremities compared with the trunk (HR 6.69, 1.42 to 31.54); the 5-year risk of local recurrence was 29 per cent versus 4 per cent respectively. Of the 60 patients with desmoid-type fibromatosis on the trunk, 44 (73 per cent) had tumour

Figure 2. Kaplan–Meier analysis showing the association between age and local recurrence following surgery for extra-abdominal desmoid-type fibromatosis. P=0·139 (log rank test)



No. at risk						
1-28 years	31	19	14	12	10	8
29-35 years	34	29	23	21	18	15
36-44 years	30	22	20	18	14	9
45-80 years	33	23	19	16	14	12

localized in the abdominal wall. Thirty-nine of these 44 patients were female, compared with 84 in the entire cohort (P<0.001). None of these 44 patients developed a local recurrence during follow-up.

The youngest age group of patients had the highest risk of local recurrence (34 per cent), but this was not significant (Table 2, Fig. 2). Tumour size, sex, relation to the fascia, resection margins and adjuvant radiotherapy were not associated with the risk of local recurrence. Univariable analysis of the risk of local recurrence after an initial R0 resection with R0 resection following repeated surgery revealed no statistically significant difference in local recurrence (P=0.575, log rank test).

Disease progression following R2 resection

None of the four patients who had R2 resection developed tumour progression during follow-up. The patients initially had desmoid tumours localized on the left hemithorax (two patients), at the right scapula (one patient) and in the neck (one). R2 resection was accepted to avoid unacceptable morbidity following more extensive surgery with loss of arm function. Three of the patients with R2 resection received additional radiotherapy. During follow-up of 22, 37, 65 and 68 months respectively, stable disease was confirmed by annual computed tomography or MRI.

Discussion

After surgical treatment of aggressive extra-abdominal fibromatosis, the 5-year risk of local recurrence was 17.6 per cent. Tumour localization on the trunk was associated with a decreased risk, and patients with tumours of the abdominal wall did particularly well.

The present study evaluated the outcome of surgically treated patients without induction or neoadjuvant therapy. By excluding patients with intra-abdominal desmoid tumours, recurrent disease, and those in whom an initial wait-and-see policy was adhered to, a relatively uniform patient cohort has been presented. A strength of the study is also that the histopathology of the specimens was reviewed by experts in soft tissue pathology at two tertiary referral centres, thus enhancing the consistency of the diagnosis and report.

The study has several limitations inherent to retrospective research, such as the lack of information on the precise indications for radiotherapy and data regarding a history of pregnancy and caesarean section for the women included. The latter information could have contributed to a more thorough analysis of the risk of recurrence of tumours of the abdominal wall in women of reproductive age, as these factors appear to be of aetiological and prognostic significance[1,6,14]. A further weakness is the modest duration of follow-up (median 38 months), with different types of follow-up at the three participating centres for a disorder that may recur after many years.

The observed 5-year risk of local recurrence is modest in comparison with data reported by others. A systematic review reported recurrence rates varying between 6 and 59 per cent[9]. Many studies analyse primary and secondary tumours, or evaluate intra- and

extra-abdominal tumours together. However, recurrent and intra-abdominal tumours are to be considered distinct clinical entities, and are difficult to compare with primary musculoskeletal desmoid tumours. These tumours were, therefore, not included in the present investigation. In comparison with other reports that focus on primary extra-abdominal disease, the recurrence rate in the present study was still relatively low[5]. The limited follow-up period in the present study may have contributed to this finding, but only 18 (14.1 per cent) of the 128 patients with R0 or R1 resection had recurrence. The estimated 95 per cent c.i. of the 5-year cumulative recurrence rate was 9.9 to 25.6 per cent.

A significant influence of the involved anatomical area on the risk of local recurrence was observed. The trunk, and the abdominal wall in particular, were predictive of a low risk of recurrence, and have also been associated with a low risk of local recurrence by other investigators[5,13,14]. In the present study, abdominal wall tumours constituted the majority of the desmoid lesions on the trunk, and the patients were predominantly women. This finding supports an aetiological role for hormonal factors in desmoid tumours arising in the abdominal wall[1,6,15]. There was a trend towards a higher risk of recurrence in the youngest age group, confirming a higher risk of recurrence in younger patients, which has been found by several investigators[11,13,16].

Microscopically involved resection margins and the additional use of adjuvant radiotherapy were not identified as factors influencing the local recurrence rate. The number of events in the study may have been too low to reach statistical significance. In addition, the limited number of events precluded multivariable analysis for proper evaluation of the independent effect of these variables on the risk of recurrence.

It is important to emphasize that data regarding the precise indications for radiotherapy were lacking in the present study. The value of radiotherapy has been disputed in recent literature. Although a systematic review showed a decreased recurrence rate after postoperative radiotherapy[9], other studies have not demonstrated an effect[5,10–12,17]. More convincing data have been reported regarding the use of radiotherapy without surgery on response rates and progression-free survival[11,17,18]. A multicentre randomized clinical trial is currently investigating the effect of radiotherapy as a single treatment modality in patients with aggressive fibromatosis; data from this trial have demonstrated a 3-year progression-free survival of 81.5 per cent[19].

Surgical margin status was not associated with recurrence in the present investigation. Although some authors have reported better long-term local control following R0 resection[10,16], others have questioned the importance of microscopic tumour-free resection margins[5,11,12,17,20]. In a recent large cohort study, R2 resection was associated with a higher risk of tumour recurrence, but a microscopically tumour-free resection margin (R0 resection) was not associated with a better local control than R1 resection[5]. In agreement, Gronchi and colleagues[21] observed no additional benefit of microscopic tumour-free resection margins in patients treated for primary extra-abdominal desmoid-type fibromatosis.

The study by Salas and co-workers[5] has contributed to the current shift of paradigm towards less aggressive local surgical treatment in patients with extra-abdominal desmoid-type fibromatosis. A considerable proportion of patients who were not operated on had tumours that did not progress, whereas the recurrence rate following surgery was exceedingly high: half of all patients developed a recurrence within 5 years[5]. These findings are in line with the observation of Bonvalot et al.[22], who reported a tumour progression rate of 39 per cent in patients in whom a wait-and-see policy was adopted. Medical treatment versus a wait-and-see policy was compared in one investigation[23]. In this study, 47–53 per cent of the patients developed progressive disease. Again, in approximately half of the patients the tumour did not progress.

The effectiveness of medical therapy is beyond the scope of the present study, although several agents have been used, including cyclo-oxygenase 2 inhibitors[24], hormonal therapy[7,8], chemotherapy[25] and tyrosine kinase inhibitors[26]. Complete or partial tumour response varies in these studies between 6 and 36 per cent.

The cohort described in the present study was treated during a period when aggressive local surgical treatment for desmoid-type fibromatosis was performed routinely. The present data demonstrate that microscopically clear resection margins do not necessarily decrease the local recurrence rate and that adjuvant radiotherapy may be omitted in selected patients.

Disclosure

The authors declare no conflict of interest.

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Chapter 4

Meta-analysis of the influence of surgical margin and adjuvant radiotherapy on local control after resection of sporadic desmoid-type fibromatosis.

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Abstract

Background

Extra-abdominal desmoid-type fibromatosis (DF) is a rare, locally aggressive neoplasm that is managed primarily in a conservative manner. When treatment is indicated, it usually involves surgical resection, possibly with adjuvant radiotherapy. The indications for post-operative radiotherapy and its effectiveness are unclear. The objectives of this systematic review and meta-analysis are to estimate the effect of surgical resection margins and adjuvant radiotherapy on recurrence rates in DF.

Methods

Literature published between 1999 and 2015 was extracted from MEDLINE, EMBASE, Cochrane, Web of Science and Google Scholar. Recurrence rate was analysed by meta-analysis and compared between subgroups.

Results

Sixteen reports were included, consisting of a total of 1295 patients with DF. In patients treated by surgical resection only, the risk of local recurrence was almost two-fold higher for patients with microscopically positive resection margins (risk ratio (RR)=1.78, 95%CI 1.40-2.26). Adjuvant radiotherapy after surgery with negative margins showed no detectable benefit on recurrence. In contrast, after incomplete surgical resection with positive margins, adjuvant radiotherapy improved recurrence rates in both primary (RR=1.54, 95%CI 1.05-2.27) and recurrent patients (RR=1.60, 95%CI 1.12-2.28).

Conclusion

DF resected with microscopically positive margins has a higher risk of recurrence compared to negative resection margins. According to this analysis, adjuvant radiotherapy does not alter recurrence rates after complete surgical resection. Radiotherapy appears to reduce the recurrence rate for DF after incomplete surgical resection, mainly in recurrent tumours. Due to the benign nature of the disease, any invasive or harmful therapy should be carefully weighed in multidisciplinary teams in specialised centres.

Introduction

Desmoid-type fibromatosis (DF) is a locally aggressive tumour of fibroblastic origin that most commonly arises in young adults. With an incidence rate of approximately 5 cases per million people annually, it is uncommon (representing approximately 0.3% of all soft tissue neoplasms)[1,2]. The majority (approximately 85%) of sporadic tumours are characterized by mutations in the *CTNNB1* gene, whereas hereditary tumours often harbor mutations in the *APC* gene[3,4]. Syndromic cases are usually associated with intra-abdominal disease and familial adenomatous polyposis (FAP), and thus require a different therapeutic approach[5,6]. Distinction between intra-abdominal and extra-abdominal tumours (including abdominal wall tumours) is clinically important because of differences in etiology, biological behavior, and the morbidity associated with surgical resection[7-9].

Even though DF does not metastasize and is rarely lethal, patients suffer substantial morbidity due to the invasive growth and recurrence of the tumour[10]. A subset of DF patients have indolent disease, with spontaneous growth arrest or tumour regression[11-13].

Historically, complete surgical resection with negative resection margins was the standard of care, with or without adjuvant radiotherapy. Convincing evidence for this management protocol is lacking, as the results in the literature are conflicting. Since complete surgical resection may result in substantial morbidity due to sacrifice of critical musculoskeletal structures or peripheral nerves and retrospective analyses of patients managed expectantly show optimistic results, a conservative front-line approach has been advocated[11,12,14-18]. A recent consensus paper from Europe supported this strategy of expectant management with close observation for all patients with primary DF[18]. Prospective studies investigating this strategy are currently being conducted in France (ClinicalTrials.gov identifier: NCT01801176), Italy (ClinicalTrials.gov identifier: NCT02547831), and the Netherlands (Dutch Trial Registry identifier NTR4714)[19-21].

While there is an ongoing trend towards non-surgical management, especially in centres of expertise, surgery remains a therapeutic modality for symptomatic patients. The association between status of surgical resection margins and risk of local recurrence remains subject to discussion, as many studies have reported conflicting conclusions. Microscopic resection margin seems to influence recurrence rates in some series, but this association is disputed in others[22-27]. Similarly, supporting evidence for the effectiveness of

adjuvant radiotherapy after surgery is limited to several small studies with contradictory results[27-30]. Since DF lacks the capability to metastasize and most patients have a normal life expectancy, any possible therapeutic benefits should be weighed against the long term side effects associated with this treatment.

In order to critically reassess the therapeutic benefits of aggressive surgical resection with negative resection margins and adjuvant radiotherapy for extra-abdominal DF, this systematic review and meta-analysis was carried out. Specifically, local recurrence rates are compared between patients with surgery with (in)complete resection margins and adjuvant radiotherapy.

Methods

This study was reported according to the PRISMA guidelines for reporting systematic reviews and meta-analyses[31].

Literature search

A comprehensive literature search was last performed on September 3, 2015. The databases from MEDLINE via Ovid, EMBASE.com, Cochrane Central Registry of Trials, Web of Science, and Google Scholar were searched from inception. The following search terms, including synonyms and truncations, were applied: “extra-abdominal”, “desmoid tumour” or “aggressive fibromatosis”, and “radiotherapy” or “surgery”. The complete search is shown in the appendix.
According to protocol, inclusion criteria were papers written in English, reporting on extra-abdominal DF treated by surgical resection, with or without adjuvant radiotherapy, published from 1999 onwards. Data on referral status, use of adjuvant radiotherapy or not, and disease recurrence was also required for papers to be included. Articles specifically reporting on pediatric or syndromic patients, intra-abdominal or mesenteric tumours, or interventions other than surgery and external beam radiotherapy were excluded.

Assessment of study quality and bias

The level of evidence of each article was determined using the Oxford Centre for Evidence-Based Medicine level of evidence[32]. Quality assessment of included non-randomised studies was established according to the Newcastle-Ottawa Scale (NOS) criteria[33]. Funnel

plots were constructed in order to assess risk of several types of reporting bias, among which publication bias[34].

Data collection

Data was collected in standard forms by one researcher. In case of any doubts, a second researcher was consulted. Unpublished, but required data was requested from authors of eligible articles to assemble a complete and homogeneous cohort with minimal selection bias. This was done by sending a standard form which could be completed by the author. Patients were categorized based on referral status, treatment regimen, and surgical resection margin status. Referral status was considered primary when patients presented without history of prior therapeutic interventions. Patients were considered as having recurrent DF when presenting with regrowth of DF after at least one therapeutic intervention after which the tumour was removed. Prior treatment was unknown for most of cases of recurrent disease. Treatment was categorized as surgery alone (S) or surgery with adjuvant radiotherapy (S+R). Surgical resection margins were scored using AJCC guidelines as R0, R1, R2 or RX[35]. Patients were divided in subgroups according to the aforementioned treatment group (S or S+R), surgical resection margin and referral status (primary or recurrent DF at presentation), see also Table 3 for further clarification of the subgroups.

Outcome

The outcome of interest was recurrence rate. Recurrence was defined as local tumour regrowth after macroscopic complete surgical resection or tumour progression after macroscopic incomplete surgical resection. Recurrence rates were compared between subgroups by means of the risk ratio (RR) for recurrence. The RR for recurrence was calculated in meta-analysis. Event-free survival (EFS) was defined as period that patients were free of recurrence after surgical resection. Forest plots were constructed using Cochrane RevMan version 5.3 software[36].

Statistical Analysis

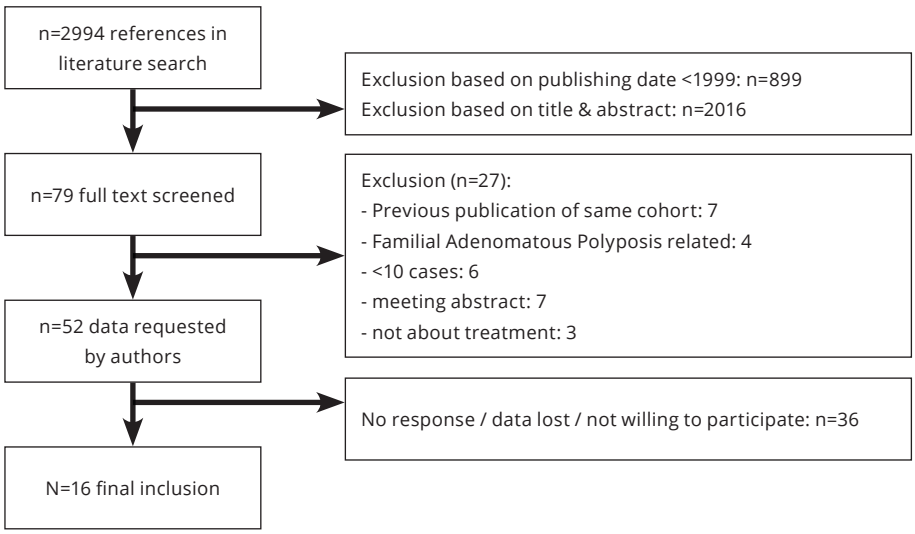
RR estimates were considered statistically significant when their 95% confidence interval (CI) excluded 1.0. Meta-analysis of RR of recurrence was calculated by pooled point estimates of Mantel-Haenszel weighted RR's. Both fixed effect (FE) and random effect (RE) models were used to account for inter-study heterogeneity[34]. Statistical analyses were conducted using IBM SPSS Statistics v20 and Cochrane RevMan v5.3[36,37].

Results

Literature search results and study characteristics

The database search yielded 2875 articles, of which 52 were eligible for inclusion. Those 52 studies described approximately 3500 potentially eligible patients in total. This number of 3500 patients included a significant amount of patients who violated at least one of the exclusion criteria. Sufficient data for analysis were published in 2 articles; authors from the other 50 articles were contacted and requested to provide the additional data needed for analysis. Of these 50 authors, 14 responded, bringing the total number of included studies to 16[11,22-25,38-48]. A flowchart which shows detailed description of the selection process is provided in Figure 1.

Figure 1: Flowchart of the selection process for inclusion



All included studies were retrospective cohort studies. According to the Oxford 2011 Levels of Evidence these references are assigned Level 2b evidence. All included studies scored between 5 and 7 on the NOS criteria and were included in the meta-analysis. Results from the quality NOS quality assessment are displayed in Table 1.

Assessment of publication bias across studies was done using funnel plots. Visual analysis of these funnel plots showed no big asymmetries, reflecting absence of any significant publication bias.

Table 1: Patient characteristics per inclusion

Publication	Primary patients	Recurrent patients	Surgery	Surgery & radio-therapy	Median dose (range), in Gy	Median follow-up, in months	Overall local control rate (%)
Baumert, 2007[35]	42	22	31	33	59.4 (3.4 - 72)	72.0	76.6
Bertani, 2012[36]	50	8	51	7	Unknown	66.0	89.7
Bonvalot 2008[11]	80	0	67	13	50.0 (45 - 60)	76.0	62.5
Cates, 2014[24]	98	0	83	15	Unknown (50 - 60)	38.4	70.4
Eastley, 2014[37]	38	0	36	2	60.0 (60.0)	58.8	78.9
Gronchi, 2003[22]	128	75	163	40	57.0 (45 - 65)	135.0	72.9
Huang, 2009[38]	97	29	106	20	Unknown (45 - 55)	102.0	81.7
Ihalainen, 2015[39]	76	28	82	22	Unknown	25.0	77.9
Kriz, 2014[40]	29	8	0	37	50.0 (50 - 65)	44.0	86.5
Pignatti, 2000[41]	35	46	64	17	Unknown (35 - 66)	134.4	55.6
Prodinger, 2013[42]	17	4	8	13	54.0 (50 -60)	39.0	57.1
Salas, 2011[25]	127	0	113	14	50.0 (Unknown)	52.0	33.9
Stoeckle, 2009[43]	42	21	61	2	Unknown	123.0	55.6
V.Broekhoven 2013[23]	129	0	75	54	Unknown	38.0	85.3
Wang 2006[44]	16	0	15	1	Unknown	38.0	87.5
Wilkinson 2014[45]	49	1	50	0	NA	72.0	92.0
Total	1053	242	1005	290	NA	NA	Median: 77.3

Description of patient characteristics of all included articles. Abbreviations: Gy: Gray, NA: Not applicable

Table 2: 5-year Event-free survival (in %) for different subgroups

Publication	Overall	Primary*	Surgery	Surgery Primary	Surgery Recurrent	S+R
Baumert, 2007[35]				63.5		
Bertani, 2012[36]				94.2	83.3	
Bonvalot, 2008[11]	47.0	47.0		50.0		60.0
Cates, 2014[24]						
Eastley, 2014[37]		81.0		81.0		
Gronchi, 2003[22]	73.0	81.0	71.7			78.3
Huang, 2009[38]	80.7	85.4 (rec. 63.7%)*	82.3	86.5	59.5	63.0
Ihalainen, 2015[39]	77.0	100.0	91.0	100.0	22.0	23.0
Kriz, 2014[40]	81.0					84.0
Pignatti, 2000[41]						
Prodinger, 2013[42]	70.7	64.2 (rec. 50.0%)*				64.5
Salas, 2011[25]	42.9					
Stoeckle, 2009[43]	57.1	84.5 (rec. 10.5%)*	57.1	84.5	10.5	
V.Broekhoven, 2013[23]	87.5	87.5		86.7		88.9
Wang, 2006[44]	100.0	100.0		100.0		
Wilkinson, 2013[45]	94.0					
Median	77.0	85.0	77.0	86.5	40.8	64.5

Description of follow-up data of all included articles.
Abbreviations: S+R=surgery with adjuvant radiotherapy.
*5-year event-free survival for recurrent tumors is also presented in 3 articles, in parentheses.

Overall study cohort

The 16 included studies constituted a total cohort of 1295 DF patients. Table 1 shows the total number of patients included per article. The majority of patients had primary disease (n=1053, 81%). Treatment consisted of surgery alone in 1005 patients (S group, 78%) and surgery with adjuvant radiotherapy in 290 patients (S+R group, 22%). Tumour recurrence developed in 376 patients (29%), of which 297 occurred in the S group and 79 in the S+R

group. The overall recurrence rate was 25% in patients with primary disease and 46% in patients with recurrent disease. Median follow-up time ranged between 25 and 135 months (Table 2).

Influence of surgical margin on recurrence

Risk ratio for recurrence

Forest plots showing the association between microscopic resection margin and recurrence risk from each individual study were constructed. Only patients treated with surgery alone (S) were included and patients with primary (n=761) or recurrent tumours (n = 133) were analysed separately (Figure 2a and Figure 2b). The point estimate of the pooled and weighted RR among all studies showed a significant relationship between microscopic surgical margin and the risk for recurrence of primary tumours (RR=1.51, 95% CI 1.13-2.01; Figure 2a). A similar analysis was performed for patients with recurrent DF (Figure 2b), although only 4 articles reporting on 133 patients were eligible for inclusion. Similar to primary tumours, the pooled and weighted RR showed a significant relation between microscopic surgical margin and the risk for recurrence in recurrent tumours (RR = 1.57, 95% CI 1.10-2.24). Comparison of results from random effects (RE) model is shown in the appendix. Pooled analysis with primary and recurrent tumours together showed an even stronger relationship between margin and recurrence risk (RR=1.78, 95% CI 1.40-2.26, plot not shown).

The role of adjuvant radiotherapy

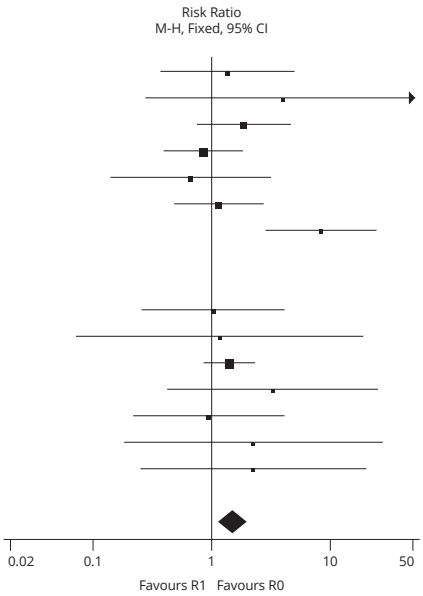
Risk ratio for recurrence

The RRs for S and S+R groups for 481 primary DF patients with positive or indeterminate resection margins are presented in Figure 3a, where Figure 3b shows the same analysis for 119 patients with recurrent DF. The pooled and weighted RRs showed a significant relationship between treatment regimen and recurrence rate, with a higher risk for recurrence in the S group in both primary (RR=1.54, 95% CI 1.05-2.27) and recurrent patients (RR=1.60, 95% CI 1.12-2.28). Comparisons between the FE and RE models are described in the appendix. The pooled and weighted RR for recurrence in 695 primary and recurrent patients with R0 resections are displayed in Figure 4, which showed a significantly lower risk for recurrence in the S group: RR=0.67, 95% CI 0.46-0.97. Because of considerable heterogeneity (I2=62%), results were compared with those from a RE model, which did not alter any conclusions: RR=0.50, 95% CI 0.26-0.94.

Figure 2a. Forest Plot comparing RR for recurrence between R0 and R1 margins in primary tumors treated with surgery alone

	R1		R0			Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% CI
Baumert et al.	2	5	5	17	4.4%	1.36 (0.37-5.00)
Bertani et al.	1	9	1	36	0.8%	4.00 (0.28-57.98)
Bonvalot et al.	22	50	4	17	11.4%	1.87 (0.75-4.66)
Cates et al.	9	36	10	34	19.7%	0.85 (0.39-1.83)
Eastley et al.	2	15	4	20	6.6%	0.67 (0.14-3.17)
Gronchi et al.	5	21	18	87	13.4%	1.15 (0.48-2.74)
Huang K et al.	8	17	4	71	3.0%	8.35 (2.84-24.53)
Ihalainen et al.	0	8	0	64		Not estimated
Kirz et al.	0	0	0	0		Not estimated
Pignatti et al.	2	7	5	18	5.4%	1.03 (0.26-4.12)
Prodinger et al.	0	1	1	6	1.3%	1.17 (0.07-18.96)
Salas et al.	14	22	14	31	22.3%	1.41 (0.85-2.32)
Stoeckle et al.	5	23	1	15	2.3%	3.26 (0.42-25.23)
Van Broekhoven et al.	2	16	7	53	6.2%	0.95 (0.22-4.11)
Wang CP et al.	1	4	1	9	1.2%	2.25 (0.18-27.66)
Wilkinson et al.	3	28	1	21	2.2%	2.25 (0.25-20.13)
Total (95% CI)		262		499	100.0%	1.51 (1.13-2.01)
Total events	76		76			

Heterogeneity: Chi²=15.57, df=13 (P=0.27); I²=16%
Test for overall effect: Z=2.82 (P=0.005)

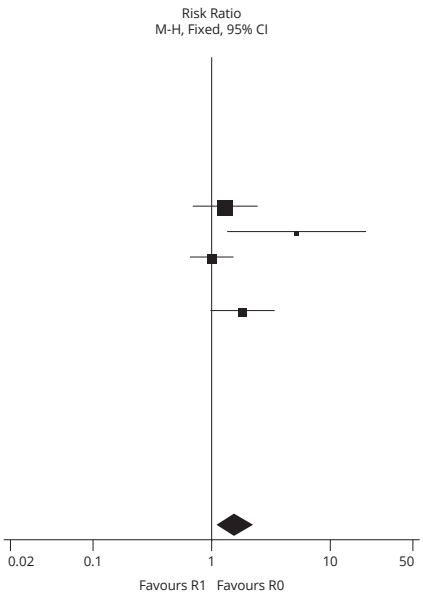


Abbreviations: RR: Relative Risk

Figure 2b. Forest Plot comparing RR for recurrence between R0 and R1 margins in recurrent tumors treated with surgery alone

	R1		R0			Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% CI
Baumert et al.	0	1	0	1		Not estimated
Bertani et al.	0	0	1	6		Not estimated
Bonvalot et al.	0	0	0	0		Not estimated
Cates et al.	0	0	0	0		Not estimated
Eastley et al.	0	0	0	0		Not estimated
Gronchi et al.	8	16	15	39	48.6%	1.30 (0.69-2.44)
Huang K et al.	4	5	2	13	6.2%	5.20 (1.35-20.02)
Ihalainen et al.	6	6	3	3	24.8%	1.00 (0.98-1.53)
Kirz et al.	0	0	0	0		Not estimated
Pignatti et al.	4	5	11	25	20.4%	1.82 (0.98-3.39)
Prodinger et al.	0	0	0	1		Not estimated
Salas et al.	0	0	0	0		Not estimated
Stoeckle et al.	11	11	0	0		Not estimated
Van Broekhoven et al.	0	0	0	0		Not estimated
Wang CP et al.	0	0	0	0		Not estimated
Wilkinson et al.	0	1	0	0		Not estimated
Total (95% CI)		45		88	100.0%	1.57 (1.10-2.24)
Total events	33		32			

Heterogeneity: Tau2=7.97; Chi2=7.97, df=3 (P=0.05); I2=62%
Test for overall effect: Z=2.50 (P=0.01)

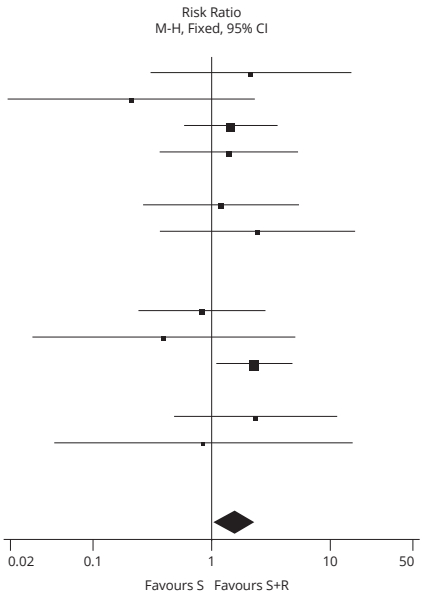


Abbreviations: RR: Relative Risk

Figure 3a. Forest Plot comparing RR for recurrence between S and S+R groups for primary patients with R1, R2 or RX margins

	S		S+R			Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% CI
Baumert et al.	5	12	1	5	4.2%	2.08 (0.32-13.61)
Bertani et al.	1	9	1	2	4.9%	0.22 (0.02-2.24)
Bonvalot et al.	22	50	4	13	19.0%	1.43 (0.60-3.42)
Cates et al.	15	49	2	9	10.1%	1.38 (0.38-5.02)
Eastley et al.	3	16	0	0		Not estimated
Gronchi et al.	5	21	2	10	8.1%	1.19 (0.28-5.11)
Huang K et al.	8	17	1	5	4.6%	2.35 (0.38-14.58)
Ihalainen et al.	0	9	0	1		Not estimated
Kirz et al.	0	0	3	29		Not estimated
Pignatti et al.	5	12	2	4	9.0%	0.83 (0.25-2.73)
Prodinger et al.	0	1	5	8	6.0%	0.41 (0.04-4.77)
Salas et al.	65	82	14	14	25.5%	2.22 (1.09-4.52)
Stoeckle et al.	6	26	0	0		Not estimated
Van Broekhoven et al.	5	22	2	20	6.3%	2.27 (0.50-10.43)
Wang CP et al.	1	6	0	1	2.3%	0.86 (0.05-13.93)
Wilkinson et al.	3	28	0	0		Not estimated
Total (95% CI)		360		121	100%	1.54 (1.05-2.27)
Total events	144		28			

Heterogeneity: Chi2=6.77, df=10 (P=0.75); I2=0%
Test for overall effect: Z=2.21 (P=0.03)

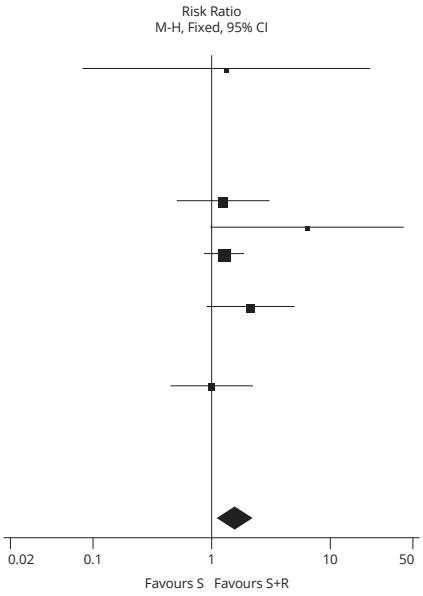


Abbreviations: RR: Relative Risk, S: Surgery, S+R: Surgery with adjuvant radiotherapy.

Figure 3b. Forest Plot comparing RR for recurrence between S and S+R groups for recurrent patients with R1, R2 or RX margins

	S		S+R			Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% CI
Baumert et al.	0	1	1	7	3.1%	1.33 (0.08-21.94)
Bertani et al.	0	0	2	2		Not estimated
Bonvalot et al.	0	0	0	0		Not estimated
Cates et al.	0	0	0	0		Not estimated
Eastley et al.	0	0	0	0		Not estimated
Gronchi et al.	8	16	4	10	25.5%	1.25 (0.51-3.09)
Huang K et al.	4	5	1	8	4.0%	6.40 (0.97-42.15)
Ihalainen et al.	6	6	9	12	34.5%	1.27 (0.86-1.87)
Kirz et al.	0	0	2	8		Not estimated
Pignatti et al.	7	9	4	11	18.7%	2.14 (0.91-5.04)
Prodinger et al.	0	0	1	2		Not estimated
Salas et al.	0	0	0	0		Not estimated
Stoeckle et al.	20	20	1	1	14.2%	1.00 (0.45-2.23)
Van Broekhoven et al.	0	0	0	0		Not estimated
Wang CP et al.	0	0	0	0		Not estimated
Wilkinson et al.	0	1	0	0		Not estimated
Total (95% CI)		58		61	100.0%	1.60 (1.12-2.28)
Total events	45		25			

Heterogeneity: Chi2=5.45, df=5 (P=0.36); I2=8%
Test for overall effect: Z=2.57 (P=0.01)

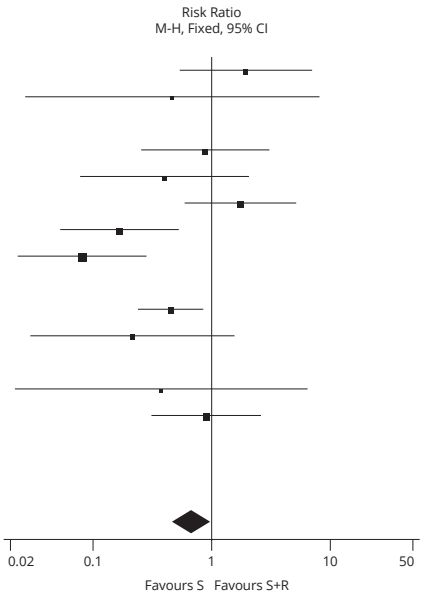


Abbreviations: RR: Relative Risk, S: Surgery, S+R: Surgery with adjuvant radiotherapy.

Figure 4. Forest Plot comparing RR for recurrence between S and S+R groups in primary and recurrent tumours

	S		S+R			Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% CI
Baumert et al.	5	18	3	21	6.5%	1.94 (0.54-7.03)
Bertani et al.	2	42	0	3	2.1%	0.47 (0.03-8.11)
Bonvalot et al.	4	17	0	0		Not estimated
Cates et al.	10	34	2	6	7.9%	0.88 (0.25-3.07)
Eastley et al.	4	20	1	2	4.2%	0.40 (0.08-2.06)
Gronchi et al.	33	126	3	20	12.1%	1.75 (0.59-5.16)
Huang K et al.	6	84	3	7	12.9%	0.17 (0.05-0.53)
Ihalainen et al.	3	67	5	9	20.6%	0.08 (0.02-0.28)
Kirz et al.	0	0	0	0		Not estimated
Pignatti et al.	16	43	2	2	10.9%	0.45 (0.24-0.85)
Prodinger et al.	1	7	2	3	6.5%	0.21 (0.03-1.56)
Salas et al.	14	31	0	0		Not estimated
Stoeckle et al.	1	15	0	1	2.1%	0.38 (0.02-6.44)
Van Broekhoven et al.	7	53	5	34	14.2%	0.90 (0.31-2.60)
Wang CP et al.	1	9	0	0		Not estimated
Wilkinson et al.	1	21	0	0		Not estimated
Total (95% CI)		587		108	100.0%	0.67 (0.46-0.97)
Total events	108		26			

Heterogeneity: Chi2=26.12, df=10 (P=0.004); I2=62%
Test for overall effect: Z=2.12 (P=0.03)



Abbreviations: RR: Relative Risk, S: Surgery, S+R: Surgery with adjuvant radiotherapy.

Discussion

In this systematic review and meta-analysis, the published outcomes of 1295 patients with extra-abdominal DF from 16 studies were combined to determine the effect of surgical resection margin and adjuvant radiotherapy on recurrence.

The current study suggests that the microscopic margin status does indeed influence the recurrence rate. Pooled results of patients treated with surgery alone demonstrate that recurrence rates were significantly lower after negative surgical resection margins (R0) for both primary and recurrent tumours. These results imply that a R0 resection is the desired situation, but when a R1 resection has been carried out, recurrence rates are still very acceptable in primary tumours. A conservative approach in such a situation seems preferable, given the benign nature of this disease. Especially in recurrent tumours, re-resection can be considered in cases where morbidity is expected to be little, given the significant difference in recurrence rate.

Several previous studies have addressed the issue of surgical resection margins for DF, with conflicting results. In some retrospective studies, microscopically negative margins were significantly associated with a better surgical outcomes[29-31]. On the contrary, other large retrospective studies show no overall positive effect of microscopically negative margins on recurrence rates[22,25,49,50]. Some of these reports did not separate intra-abdominal and extra-abdominal DF or account for different treatment regimens among study cases. Unfortunately, these studies could not be included in the present analysis, as additional data were not available. These studies might have had influence on the results of this analysis. Crago et al.[49] studied a single-centre cohort of almost 400 patients with extra-abdominal DF and showed that microscopic negative margins have a favourable recurrence rate in subgroups with small tumours. Ballo et al.[30] retrospectively reviewed 189 patients from the MD Anderson Cancer Centre, this report was updated by Lev et al.[50]. In the former study, negative microscopic resection margins were associated with lower recurrence rates, but this result was not repeated in the latter. In both reports, intra-abdominal tumours and FAP-related tumours were analysed together with extra-abdominal tumours.

Adjuvant radiotherapy appears to reduce the risk of local recurrence of DF after surgical resection with positive resection margins. Its effect in reducing the risk of local recurrence was particularly strong after R1/R2 resection of recurrent DF. Adjuvant radiation therapy is expected to be indicated in patients at risk for a poor outcome, thereby potentially causing indication bias. There appears to be no additional value of adjuvant radiotherapy in case of complete surgical resection.

Guadagnolo et al.[51] described 74 primary and recurrent cases of DF in which a 10-year local control rate of 78% was achieved with addition of adjuvant radiotherapy. Keus et al.[52] studied the effect of moderate dose radiotherapy for inoperable DF in a prospective cohort study. This pilot study showed a 81.5% 3-year local control rate and mild side effects after a median follow-up of 4.8 years. Nuyttens et al.[53] also reviewed this question among 381 patients treated with surgery alone and 297 with surgery and radiotherapy and concluded that adjuvant radiotherapy improved recurrence rates significantly. In the present study, the most pronounced benefit was observed among patients with positive surgical resection margins; similar findings were reported by Nuyttens. A systematic review conducted by Yao et al.[54] also concluded that surgery with adjuvant radiotherapy, compared to surgery alone, resulted in favourable recurrence rates. Therefore adjuvant

radiotherapy was recommended for all patients, even those with negative resection margins. In contrast to studies reviewed by Yao et al., the current review does not include any DF patients treated with systemic therapy, patients with intra-abdominal disease, or patients with FAP or Gardners syndrome. In this meta-analysis, stronger evidence was given for the absence of benefit of adjuvant radiotherapy for patients after R0 resection.

DF is a benign disease and resection does not alter survival in the majority of cases. The main reason for treatment is pain, discomfort and impairment of quality of life. Therefore, avoidance of morbidity of treatment is of utmost importance. In patients with symptomatic, disabling disease or progressive disease under non-surgical treatment, resection is still a valuable option, given that expected morbidity is little and patients are carefully counseled. Therefore, this systematic review and meta-analysis offers information for physicians and patients about the importance of surgical resection margins in their shared decision model in clinical practice, once surgery has been chosen as the primary treatment option.

Resection with the least morbidity should be the goal of surgical resection. Microscopic complete resection margins are associated with lower recurrence rates compared to microscopic residual disease, but may result in substantial morbidity due to sacrifice of critical musculoskeletal structures or peripheral nerves. R1 resection is preferable in such a case because a substantial proportion of these patients will not develop a significant recurrence according the current data. In case of an unexpected R1 resection, an expectant management, re-resection or adjuvant radiotherapy are optional. Given the current guidelines and acceptable recurrence rate, expectant management might be the most appropriate strategy. Nonetheless, patients should be discussed in a multidisciplinary team of specialised centres to carefully make these treatment decisions.

In agreement with current management guidelines for patients with DF[18], it is acknowledged that aggressive treatment can result in poor functional outcomes that may harm patients more than the disease itself. Re-operation and adjuvant radiotherapy is therefore not advised in patients in which this could result in mutilation, functional loss or cosmetic disfigurement. As DF usually has an indolent clinical behavior and is not a life-threatening disease complete eradication of disease should not be dogmatically pursued without regard for preservation of quality of life. Therefore, it may often be preferable to simply monitor patients with a primary close clinical observation, according to the

consensus[18]. Multiple retrospective studies have shown that an expectant management is suitable for many patients[11,12,14,15,17]. In case of symptomatic disease requiring treatment, recurrence, or progression of disease, local treatment can be applied as needed, including radiotherapy as single treatment. As earlier mentioned, Keus et al.[52] and Nuyttens et al.[53] conclude that radiotherapy can be applied as single treatment with acceptable morbidity and recurrence rates.

This systematic review and meta-analysis describes a large cohort of surgically treated DF patients from the literature. Many studies that were otherwise ineligible for inclusion were able to be incorporated after directly requesting additional data from the original authors, thereby minimizing selection bias. The status of surgical resection margins, referral status, and outcome data were available for all patients in both treatment groups. None of the prior studies, including a comprehensive comparative analysis performed by Leithner et al.[55] investigated the impact of surgical resection margins in a cohort of extra-abdominal DF as large as presented here.

It should be considered that most patients in this cohort received treatment before the general consensus of expectant management had become standardized. This has to be taken into account very carefully, as today's practice is to avoid any unnecessary invasive treatment in DF patients. As a corollary, patients presently undergoing surgical resection compose a selected population of progressive patients and thus are not completely equivalent to the cohort described in this paper.

The current study has other limitations. For instance, the magnitude of tumour clearance, or the distance from tumour to the resection margin was not accounted for in most studies. Thus, the group with negative resection margins surely encompass negative margins of variable extent (i.e., narrow margins <1 mm vs. wider margins of >1 mm). This factor could be related to recurrence rates[18,24]. Moreover, the group with negative resection margins might represent a selection of patients in which resection was less difficult than the groups with positive margins. This possibly explains the beneficial recurrence rate for negative compared to microscopically positive resection margins. The authors admit that carefully selected, more comparable patient groups would be favourable to answer this question, but such cohort is not available. Second, although all patients in the cohort have extra-abdominal or abdominal wall tumours, this paper does not include data on other important parameters who have showed to be of influence on recurrence rate,

such as age, tumour size and precise anatomic location[25,49]. These data were lacking in the vast majority of the described cohort and therefore this is considered as a significant limitation of the study. Thus, the inferences made here may not necessarily be applicable to other patient cohorts. On the other hand, the present cohort is large enough such that patient age and tumour size and localization may be assumed to be distributed normally. Furthermore, the length of follow-up intervals varied among different investigations, which perhaps influenced reported recurrence rates. However, most relapses of DF occur within 2 years of surgical resection[12,25]. Since only one paper included in this analysis reported a median follow-up interval less than 3 years, the follow-up is considered sufficient to observe recurrences[42]. Another point of consideration is the wide variation in the origin of study cases. This cohort consists of patients treated in a variety of countries and hospitals. Different management protocols in these various treatment centres may have resulted in treatment heterogeneity. For recurrent patients in particular, information regarding the initial treatment modality was unavailable. Treatment heterogeneity is almost inherent to literature studies describing patients from many different centres. Another weakness of the study is that the radiation dose is not reported for 121 of the 290 patients (42%) who received postoperative radiotherapy. A radiation dose below 50 Gy is considered ineffective and current recommendations advise a dose of 56 Gy in 2 Gy per fraction. Finally, only retrospective observational studies were included, as there are few if any prospective, experimental studies on surgery and radiotherapy for DF patients. It is recognised that meta-analysis in itself has limited power to answer clinical issues as in the present study. A meta-analysis of retrospective studies with all their inherent biases it subject to bias itself. The lack of prospective series makes that a careful analysis of all known data may give the best available guidance for clinical management.

In conclusion, microscopic residual disease after surgical resection of primary or recurrent DF is associated with higher recurrence rates than complete surgical resection. Adjuvant radiotherapy improves recurrence rates after incomplete surgical resection of DF, but does not appear to be of additional value after surgical resections of primary or recurrent DF with negative resection margins. Due to the benign nature of the disease, any invasive or potentially harmful therapy should be carefully weighed in a multidisciplinary team and only be offered in specialised centres.

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Appendix

Complete Search

Embase.com

('desmoid tumor'/exp OR (((aggressive* OR extra-abdominal OR extraabdominal) NEAR/3 (fibromatos*)) OR desmoid*)) AND ('radiotherapy'/exp OR radiotherapy:lnk OR 'surgery'/exp OR surgery:lnk OR (radiotreat* OR radiotherap* OR operati* OR resect* OR surg* OR ((irradiation OR radiation OR fractionated OR radio) NEAR/3 (therap* OR treat*))):ab,ti)

Medline (OvidSP)

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Cochrane

((((aggressive* OR extra-abdominal OR extraabdominal) NEAR/3 (fibromatos*)) OR desmoid*)) AND ((radiotreat* OR radiotherap* OR operati* OR resect* OR surg* OR ((irradiation OR radiation OR fractionated OR radio) NEAR/3 (therap* OR treat*))):ab,ti)

Web-of-science

TS=(((((aggressive* OR extra-abdominal OR extraabdominal) NEAR/3 (fibromatos*)) OR desmoid*)) AND ((radiotreat* OR radiotherap* OR operati* OR resect* OR surg* OR ((irradiation OR radiation OR fractionated OR radio) NEAR/3 (therap* OR treat*)))))

PubMed publisher

(Fibromatosis, Aggressive[mh] OR (((aggressive*[tiab] OR extra-abdominal OR extraabdominal) AND (fibromatos*[tiab])) OR desmoid*[tiab])) AND (radiotherapy[mh] OR radiotherapy[sh] OR Surgical Procedures, Operative[mh] OR surgery[sh] OR (radiotreat*[tiab] OR radiotherap*[tiab] OR operati*[tiab] OR resect*[tiab] OR surg*[tiab] OR ((irradiation OR radiation OR fractionated OR radio) AND (therap*[tiab] OR treat*[tiab])))) AND publisher[sb]

Google scholar

"aggressive|extraabdominal fibromatosis|fibromatoses" | "extra abdominal fibromatosis | fibromatoses" | desmoid radiotreatment | radiotherapy | operation | operative | resection | surgery | surgical | "irradiation | radiation | fractionated | radio therapy | treatment"

Influence of surgical margin: Meta-analysis with random effects model

Here we compare results from the fixed effects (FE) model from Figure 2a and Figure 2b to the random effects (RE) models (Figures not shown). The results were not different from the analysis in the FE model in case of primary tumors with R0 and R1 resection margins (risk ratio (RR) =1.51, 95% CI 1.07-2.14). In recurrent tumors, using the RE model did show a similar effect estimate but had lower confidence (RR=1.53, 95% CI 0.89-2.63). The RE model gives in this case higher weight to studies with smaller sample size and shorter follow up period. This explains the difference in results between the RE and FE analyses. Since the study from Ihalainen et al.(42) has the shortest follow-up period, but is assigned the highest weight factor in the RE model, the FE model is preferable in this case.

Role of adjuvant radiotherapy: Meta-analysis with random effects model

Here we compare results from the FE model from Figure 3a and Figure 3b to the random effects RE model (Figures not shown). The results were not different from the analysis in the FE model in case of primary tumors with positive or indeterminate resection margins (RR=1.48, 95% CI 1.00-2.18). In recurrent tumors, using the RE model did show a similar effect estimate but had lower confidence (RR=1.38, 95% CI 0.99-1.94). The results from the meta-analysis with a RE model did not alter any conclusion in case of primary tumors. In recurrent tumors, a different result was obtained with the RE model. But, in this case a FE model is preferable because of the very low heterogeneity between studies (I2=8%).

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Chapter 5

Isolated limb perfusion by tumor necrosis factor alpha and melphalan in patients with advanced aggressive fibromatosis

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Abstract

Background

Aggressive fibromatoses (desmoid tumours) may be locally aggressive, but do not metastasize. Although a conservative approach is advocated for most patients, pain and functional impairment are indications for active treatment. Tumour necrosis factor (TNF) α and melphalan-based isolated limb perfusion (TM-ILP) is a limb-saving treatment modality for soft tissue tumours. This study reports the results of TM-ILP treatment in patients with aggressive fibromatosis.

Methods

Institutional databases of three European centres were searched. All patients who received TM-ILP treatment for aggressive fibromatosis between 1990 and 2012 were included. Before therapy, the patients were discussed at multidisciplinary tumour board meetings.

Results

Twenty-five patients received 28 TM-ILP treatments. The median age of patients was 28 (i.q.r. 19–34) years and median hospital stay was 8 (7–12) days. Median follow-up was 84 (34–114) months. A complete response was achieved after two TM-ILP treatments, and a partial response after 17 treatments in 16 patients. Stable disease was reported after eight treatments in seven patients, including a patient with stable disease after the first treatment and progression after the second TM-ILP. Toxicity was modest after most treatments; Wieberdink grade IV (extensive epidermolysis, and threatening or manifest compartment syndrome) was seen after two TM-ILP treatments. Systemic leakage was reported after one treatment, but did not lead to systemic toxicity. Functional outcome was good; 16 patients had no physical limitations, and six patients had some limitations but did not need medical aids. Amputation was prevented in all but three patients.

Conclusion

TNF-α-based ILP is effective in patients with aggressive fibromatosis.

Introduction

Aggressive fibromatosis, or desmoid tumour, is a rare benign soft tissue tumour that is localized throughout the body. Aggressive fibromatosis does not metastasize, but locally advanced or recurrent disease is frequently seen in tumours localized in the extremities[1–3]. Extra-abdominal aggressive fibromatosis is not associated with mortality, unlike intra-abdominal tumours[4]. Current literature advocates a conservative approach for these benign tumours, owing to compelling evidence of disease stabilization and spontaneous tumour regression in many patients[5,6]. Despite the benign nature, some tumours behave aggressively, leading to pain and functional impairment. In patients with severely impaired quality of life, a conservative approach may no longer be an option. The choice of treatment depends on many factors, and an algorithm was proposed recently[6]. Involvement or proximity of vital structures, for instance major nerves and vessels, may lead to mutilating surgery or even amputation. In these patients, a limb-saving strategy that results in relief of symptoms should be preferred.

In 1958, isolated limb perfusion (ILP) was introduced as a treatment modality for extremity malignancies, such as locally advanced sarcomas and melanoma in-transit metastases[7]. In patients with sarcoma this technique appeared ineffective with cytostatics alone, but gained markedly in efficacy when tumour necrosis factor (TNF) α was added[8,9]. Currently, TNF-α and melphalan-based ILP (TM-ILP) is the standard of care in Europe for patients with limb-threatening sarcomas, and leads to limb salvage in up to 89 per cent of patients[10]. The present study reports data from three sarcoma centres of the European Organization for Research and Treatment of Cancer (EORTC) relating to patients with locally advanced aggressive fibromatosis treated with TM-ILP to avoid limb amputation.

Methods

Consecutive patients with aggressive fibromatosis who underwent treatment with TM-ILP in participating EORTC centres between 1990 and 2012 were included in the study. Participating centres were: Gustave Roussy Cancer Campus, Villejuif, Paris, France, Fondazione IRCCS Istituto Nazionale dei Tumori, Milan, Italy, and Erasmus Medical Centre Cancer Institute, Rotterdam, The Netherlands.

Owing to the benign tumour biology of aggressive fibromatosis, only patients suffering from intolerable pain or functional impairment are considered for surgical treatment in

these institutions. The safety and efficacy of conservative treatment is currently being evaluated in prospective trials in all three centres. For patients in the present study, a variety of treatments had been performed previously, and radical resection was deemed possible only with mutilating surgery or amputation. In these patients, TM-ILP treatment was considered. Before TM-ILP, all patients were discussed at a multidisciplinary tumour board meeting.

Perfusion

The ILP technique has been described extensively[8,11]. The procedure is performed under general anaesthesia. After heparinization, the targeted blood circuit is isolated by clamping and cannulation of the major artery and vein, and connected to an oxygenated extracorporeal circuit. A tourniquet compresses collateral vessels to prevent leakage. Using a precordial scintillation probe to detect technetium-labelled albumin, leakage is monitored throughout the procedure. TNF-α and melphalan are used; after 60–90min of perfusion, the active compounds are rinsed from the vascular system of the limb and the circulation is restored. There were minimal differences in the ILP protocols of the contributing institutions; details of the procedures have been described previously[9,12,13].

Response and toxicity

Response was evaluated by clinical examination and MRI 4–8 weeks after ILP treatment, and reported according to World Health Organization criteria[14]. Complete response (CR) was defined as complete disappearance of the tumour; partial response (PR) was a decrease in tumour size of more than 50 per cent; and stable disease (SD) was recorded when the criteria for neither PR nor progressive disease were met. Disease progression was defined as a 25 per cent increase in tumour size with no initial documentation of CR, PR or SD. In patients with incomplete radiographic measurements, the response was based on available radiological information and clinical judgement.

Acute regional toxicity after perfusion was classified according to Wieberdink et al.[15]: grade I, no reaction; grade II, slight erythema or oedema; grade III, considerable erythema or oedema with some blistering, slightly disturbed motility permissible; grade IV, extensive epidermolysis, and threatening or manifest compartment syndrome; and grade V, reaction that may necessitate amputation.

Functional outcome was based on clinical assessment and categorized as perfect, impairment without the necessity for medical aids, and impairment with the need for medical aids or amputation. Continuous data are presented as median (i.q.r.).

Results

A total of 25 patients received 28 TM-ILP treatments. The median age of the patients at the time of TM-ILP was 28 (19–34) years and median hospital stay after treatment was 8 (7–12) days. The majority of patients were female. Median length of follow-up was 84 (34–114) months. Baseline characteristics of the patients are summarized in Table1. Five patients were treated for a primary tumour; two of these had previously received systemic anti-inflammatory treatment for inoperable disease, but this did not lead to sufficient reduction or relief of complaints. The indication for choosing ILP as a primary treatment in the other three patients was bone involvement, sciatic nerve involvement, and refusal of systemic treatment by the patient.

Table 1. Baseline characteristics of patients with aggressive fibromatosis

	No. of patients (n= 25)
Sex ratio (M : F)	8 : 17
Age (years)†	28 (19–34)
Localization	
Arm	4
Leg	21
Size of lesion (cm)†	12 (8.5–15)
No. of tumours	
Single	14
Multiple	11
Tumour treated	
Primary tumour	5
Primary recurrence	10
Secondary recurrence	10
Previous treatment	
None	3
Surgery	7
Radiotherapy	2
Systemic treatment	2
Surgery + radiotherapy	3
Surgery + radiotherapy + systemic treatment	4
Surgery + systemic treatment	4

†values are median (i.q.r.).

Treatment outcomes

An overall response was seen after 19 of 28 TM-ILP treatments (Table2). CR was achieved in two patients; both patients had TM-ILP as a single treatment modality for recurrent disease after previous surgical resections, and one patient had also undergone radiotherapy. These two patients had a sustained CR to the end of follow-up at 94 and 36 months.

PR was recorded after 17 TM-ILP treatments in 16 patients. For 11 patients, TM-ILP led to control of disease and symptoms that was sustained to the end of follow-up with no need for additional treatment; an example is shown in Fig.1. Of the other five patients, one received adjuvant radiotherapy to achieve disease control. Surgical resection of residual disease was performed after the first TM-ILP in one patient presenting with recurrent disease. A second recurrence, treated by further TM-ILP 32 months after the first treatment, also resulted in a PR and disease control to the end of follow-up. Three patients with an initial PR after TM-ILP developed progression of remaining disease during follow-up. One of these patients had tumour deposits throughout one leg and had previously undergone extensive radiotherapy. The patient was included in a phase I study (GW786034) of treatment with paclitaxel and pazopanib. During this treatment, the patient developed necrosis of the foot and a below-knee amputation was performed 3years after TM-ILP. Several tumour deposits were still insitu and stable at the end of follow-up. The other two patients with progression received systemic treatment for the progressive disease, which led to disease control.

SD was recorded after eight TM-ILP treatments in seven patients. The response to TM-ILP was sufficient to achieve disease control in four of these patients, which was sustained in two to the end of follow-up. One patient with initial disease control developed tumour progression after 24 months and received systemic treatment; the other developed a new lesion after 57 months, with SD of the primary tumour. After systemic treatment, both lesions remained stable to the end of follow-up. In the other three patients with SD, the response was sufficient to perform limb-sparing surgery. One of these patients, with a 30 per cent tumour response after TM-ILP, had macroscopically negative margins after surgical (R1) resection. Four years after resection, disease progression led to a second treatment with TM-ILP. After treatment, the leg was amputated above the knee owing to healing problems. However, a new recurrence occurred in the stump, for which exarticulation of the hip was performed with postoperative adjuvant radiotherapy.

At the end of follow-up, the patient was free from disease. Another patient, who had an R1 resection after TM-ILP, developed recurrence that was treated successfully with chemotherapy.

Table 2. Characteristics of the 28 treatments with isolated limb perfusion

	No. of treatments
Type of ILP	
Axillar	3
Brachial	1
Iliacal	10
Femoral	10
Popliteal	4
Response	
Complete	2
Partial	17
Stable disease	8
Progression	1
Wieberdink grade	
I	4
II	16
III	6
IV	2
Duration of hospital stay (days)†	8 (7–12)
Treatment after ILP‡	
None	21
Resection	3
Radiotherapy	2
Amputation	3
Local recurrence after ILP	
No	17
Yes	11
Limb function§	
Perfect	16
Limited	6
Amputated	3

†values are median (i.q.r.). ‡One patient had both amputation and radiotherapy. §For the 25 patients at end of follow-up. ILP, isolated limb perfusion.

In the last patient with SD, disease control was achieved after surgery (R1 resection). After 19 months a second recurrence was diagnosed. Systemic treatment was ineffective, and a second TM-ILP was performed 56 months after the first. Owing to continued disease progression, the patient underwent above-knee amputation and radiotherapy of the stump, which resulted in disease stabilization. The patient developed yet another recurrence, which was treated with systemic therapy. This was the only patient with progressive disease at the end of follow-up.

Toxicity and function

Local and systemic toxicity were modest. Wieberdink grade I was recorded after four procedures, grade II after 16 procedures and grade III after six procedures. More severe toxicity (Wieberdink grade IV) was seen after two TM-ILP treatments: one patient required fasciotomy and necrosectomy, and the other needed amputation as a result of rapid disease progression.

Leakage of perfusate to the systemic circulation was seen after one treatment. The leakage was managed conservatively and did not result in systemic toxicity.

Functional outcome was good. Sixteen patients had no limitations of physical function; six had some limitations of the limb, but without the need for medical aids. Amputation could not be prevented in three patients (Table2).

Recurrence and survival

Local recurrence or disease progression after initial disease control was documented following 11 of the 28 TM-ILP treatments. The median time for tumour recurrence or progression was 27 (17–44) months. No patient died during follow-up.

Discussion

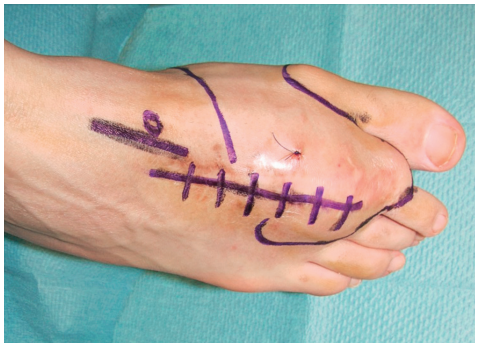
This multicentre study indicates that treatment with TM-ILP may be a limb-saving strategy for aggressive fibromatosis in patients for whom previous therapy has failed or where surgical treatment might result in severe limb impairment. A tumour response was seen after 19 of 28 TM-ILP treatments, and amputation was avoided in all but three of the 25 patients.

A limitation of this study is the absence of pain scores before treatment, as a result of the retrospective study design. Although details are lacking, the indication for TM-ILP for each patient was assessed carefully during a multidisciplinary board meeting, which included evaluation of pain due to tumour growth.

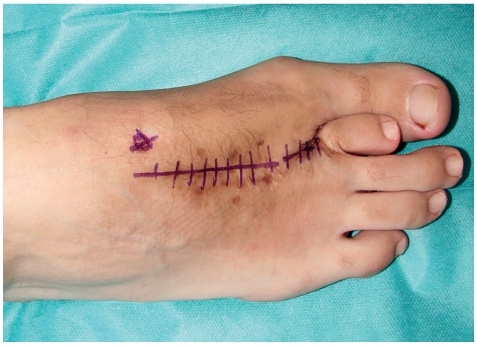
Tumour behaviour of aggressive fibromatosis varies greatly. At the time of diagnosis, a conservative approach with careful follow-up only is advocated, in agreement with a recent study[6]. Even minor tumour progression in the absence of patient complaints may justify a conservative approach. Aggressive local tumour growth or intolerable pain are reasons for active therapy. In these patients, surgery is the mainstay of treatment, but adequate surgical resection may lead to severe impairment of the limb or even amputation. In these

Fig. 1 Patient with recurring aggressive fibromatosis of the right foot.

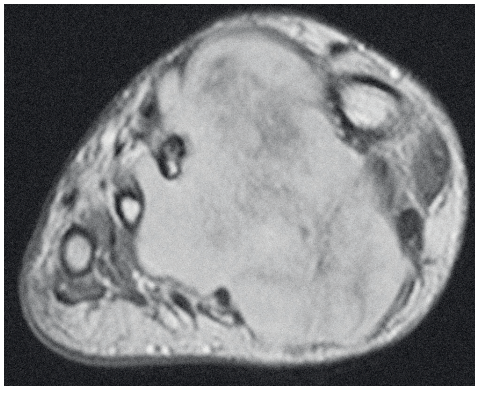
a. Appearance before ILP



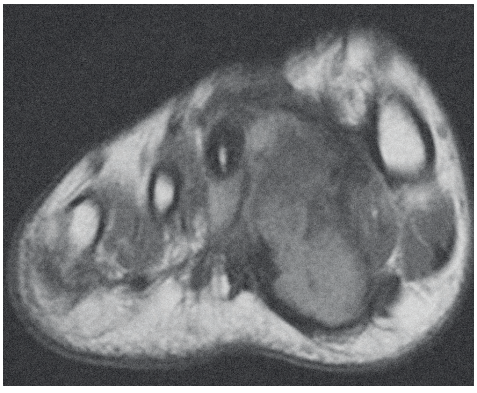
c. Appearance 2 years after ILP



b. MRI before ILP



d. MRI 2 years after ILP



a. Macroscopic appearance and b. axial view of contrast-enhanced, T1-weighted MRI before isolated limb perfusion (ILP); c. macroscopic appearance and d. axial view of contrast-enhanced, T1-weighted MRI 24 months after ILP.

patients, treatment with TM-ILP might be successful and achieve an excellent limb salvage rate, as shown in the present series.

Chemotherapy, non-cytotoxic systemic treatment and radiotherapy are other options when the extent of disease excludes surgery as a primary treatment modality. Several different chemotherapy regimens have been proposed, with varied response rates[16]. In an overview by the French Sarcoma Group[17], 62 patients were analysed after treatment with various regimens; the overall response rate was 21 per cent. The systemic side-effects of chemotherapy for a localized tumour disease warrant careful consideration before treatment.

Less aggressive systemic treatment options are hormone therapy, non-steroid anti-inflammatory drugs or the tyrosine kinase inhibitor imatinib. Response rates of approximately 50 per cent have been reported[18,19], but only small groups of patients were studied and with limited follow-up time. Side-effects vary depending on the type of treatment, but often include gastrointestinal complaints and fatigue. Long-term side-effects are unknown and follow-up protocols have yet to be established.

Most of the experience with radiotherapy has been acquired in the adjuvant setting. Few reports discuss radiotherapy as a single-modality treatment for aggressive fibromatosis. Ballo and colleagues[20] showed a 5-year progression-free survival rate of 69 per cent. A review[21] reported local tumour control rates of 78 per cent. The most compelling data are from a recent EORTC study[22], which included 44 patients with inoperable or incompletely resected disease with a median follow-up of 4-8 years; all patients received a dose of 56 Gy in 28 fractions. The 3-year local control rate was 81.5 per cent. A further response with tumour regression was seen after 3 years in three patients; two patients had a CR and one had a PR.

Acute grade 3 side-effects were limited to the skin, mucosa and pain, whereas mild oedema was the late toxic effect in ten patients[22].

In the present study, nine patients had received radiotherapy before TM-ILP, excluding radiotherapy as a treatment option. For patients without previous radiotherapy, the present authors advocate treatment with TM-ILP because of the potential for surgical resection, and radiotherapy, or even repeat TM-ILP, after the initial treatment. In areas that are not amenable to TM-ILP, such as the groin or buttocks, radiotherapy might be an attractive alternative for unresectable and limb-threatening tumours.

Local and systemic toxicity was limited in the present series. Toxicity in these patients was comparable to that reported in previous series[9,10,12] of nearly 400 TM-ILP treatments of extremity sarcomas.

Patient selection is essential in the current era of tailored treatment strategies. TNF-α-based ILP is an aggressive treatment for this relatively benign disease. Patients who are considered for TM-ILP have tumours with aggressive tumour biology and severe symptoms.

Aetiological studies[23,24] have shown the importance of the Wnt pathway and β-catenin in the development of aggressive fibromatosis. Specific mutations of the *CTNNB1* gene (which encodes β-catenin) have been associated with aggressive fibromatosis[25–27]. The

precise mechanism and the different effects exerted by the specific mutations are not well understood. Several studies[28–31] have demonstrated a predictive value for the mutations on the risk of tumour recurrence after surgery. Whether the mutational status of the tumour has an effect on the outcome after TM-ILP is unknown.

TNF-α-based ILP is an effective limb-sparing technique for the treatment of aggressive fibromatosis in selected patients. It should be considered after failure of initial therapy and where surgery for recurrent or progressive disease would lead to functional loss or amputation.

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Chapter 6

Outcome of non-surgical management of extra-abdominal, trunk and abdominal desmoid-type fibromatosis: a population-based study in the Netherlands.

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—— Submitted

Abstract

Background

Non-surgical management of patients with desmoid-type fibromatosis (DF) is increasing. Aim of the present study is to provide insight on type, usage and outcome of first-line non-surgical management strategies.

Methods

From the Dutch Pathology Registry (PALGA) patients with extra-abdominal or trunk/abdominal wall DF, diagnosed between 1993 and 2013, were identified. First-line treatment was analyzed. Best response using RECIST-criteria and time to progression (TTP) from start of treatment/surveillance until change of treatment or last documented follow-up visit.

Results

1134 patients were identified, 91 patients had first-line non-surgical management. During the study period, the percentage of patients treated non-surgically increased from 0.6% in 1993-1998 to 12.8% in 2009-2013. Best response (BR) for surveillance was complete response (CR) in 2/37, partial response (PR) in 4/37, stable disease (SD) in 21/37, progressive disease (PD) in 5/37 and unknown in 5/37 patients. During follow-up, 13 patients developed PD with median TTP of 7 months. BR for radiotherapy was CR in 4/35, PR in 11/35, SD in 16/35 and unknown in 4/35. During follow-up, 2 patients developed PD after 31 and 47 months. BR for systemic treatment was CR in 1/19, PR in 1/19, SD in 10/19, PD in 2/19 and unknown in 5/19. During follow-up, 3 patients developed PD with median TTP of 7 months (range 6-7 months).

Conclusion

Over a 20-year period, the percentage of patients with primary non-surgical management for extra-abdominal and trunk/abdominal wall DF increased from 0.6% up to 12.8%. Given the low percentage of early PD, this policy deserves further exploration prospectively.

Background

Desmoid-type fibromatosis (DF or aggressive fibromatosis) is an intermediate grade soft tissue tumor that does not metastasize, but can be locally aggressive[1]. For long, surgery has been the primary treatment for resectable tumors, with or without additional radiotherapy. Currently, a more conservative approach is applied based on reports of disease stabilization and spontaneous regression and on progression after surgery because complete resection is sometimes difficult to achieve[2,3]. An epidemiological study conducted in extra-abdominal and trunk/abdominal wall DF patients in the Netherlands reported an increase in the use of non-surgical modalities over the past decade[4].

An European consensus on the management of DF has recently been published, advocating active surveillance as the initial treatment modality, with systemic treatment, surgery or radiotherapy in case of tumor progression[5]. Despite a trend towards conservative treatment, knowledge on the outcome of different management modalities as first-line treatment is limited. We conducted this nationwide retrospective study to report on the prevalence of used treatment modalities, especially active surveillance, for extra-abdominal and trunk/abdominal wall desmoid-type fibromatosis in the past 20 years. Moreover, we used this retrospective study to gain more insight in the application and outcome of all first-line treatment modalities in a cohort of DF patients during routine clinical care.

Studies on radiotherapy have described disease stabilization and tumor regression[6-8]. Literature on systemic treatment is limited, with a variety of treatment regimes, often applied at different stages of disease presentation. Active surveillance is currently being investigated in a prospective setting by three different groups; a French group (NCT01801176), an Italian group (NCT02547831) and a Dutch group (NTR4714)[9]. Non-surgical management of patients with DF is increasing. Population-based studies are needed to gain insight into the actual implementation of non-surgical treatment in daily practice. Since these studies are lacking for patients with DF, the present study reports type and outcome of first-line non-surgical treatments in a nationwide population based study. Because this study is a retrospective study, it is not designed to compare the outcomes of the different non-surgical treatments. Moreover data regarding symptoms in relation to the disease status were not sublet to this analysis.

Methods

From the Dutch national pathology database (PALGA) patients diagnosed between 1-1-1993 and 31-12-2013 having extra-abdominal or trunk/abdominal wall DF were identified. The PALGA database contains encoded excerpts of all nationwide pathology examinations obtained by diagnostic procedure, including tissue biopsy or resection since 1971 in selected laboratories and expanded to nationwide inclusion in 1991[10]. Due to incomplete data registration, patients with disease presentation before 1993 were excluded. Specialists from PALGA reviewed the study design before providing excerpts. Excerpts contained standardized information: an encrypted patient identification, date of pathology report, age and gender of the patient, and the conclusion of the pathology reports. Reports were scored as biopsy, resection or re-resection. Patients with diagnostic biopsy of DF, without excision specimens were selected. Exclusion criteria were intra-abdominal DF, recurrent disease at presentation, uncertain diagnosis and initial surgical treatment. Hospitals with more than 10 patients were contacted for information. Data collection was performed in seven centers, as most patients were referred after diagnosis. In addition to the PALGA registration, center-based registrations were searched for patients. Medical records were retrieved for patient characteristics, tumor characteristics and details on treatment modalities. Only the first-line of treatment was documented.

Tumor localization was categorized as: head/neck, trunk (including thoracic wall, breast and back), abdominal wall, extremity or groin. Type of systemic treatment was categorized as: non-steroidal anti-inflammatory drug (NSAID), anti-hormonal (HT), chemotherapy (ChT) or tyrosine kinase inhibitors (TKI).

Reports from all available imaging studies were reviewed. Best response to treatment was classified using RECIST 1.1 as complete response (CR), partial response (PR) in case of >30% decrease of the largest diameter, stable disease (SD) or progressive disease (PD) in case of >20% increase of largest diameter based on reported measurements[11]. Date for the start of treatment was defined as the date of visit with the physician, in which the treatment modality was initiated. In most patients, active surveillance was initiated within 3 weeks after diagnosis. Results are shown as best response and time to progression (TTP). Time to progression was defined as the period from start of treatment to radiological progressive disease as classified by RECIST 1.1. Follow-up period for each treatment was documented as time of start treatment or active surveillance until change of treatment or last documented follow-up visit, whichever came first.

To evaluate the changes in the approach and choice of non-surgical management over time, the results are presented in 5-year cohorts. Late toxicity after radiotherapy was retrospectively scored using RTOG-EORTC criteria[12].

Statistical analysis was performed using IBM SPSS Statistics 21. Continuous variables are shown as median with interquartile range (IQR), and categorical variables as numbers with percentages. Associations between clinicopathological variables were determined by Chi-square analysis. For all analyses, two-sided $P<0.05$ was considered statistically significant.

Results

The PALGA search covering the period between 1-1-1993 and 31-12-2013, identified 1134 patients with extra-abdominal and trunk/abdominal wall DF. Patients were selected using in- and exclusion criteria (see Figure 1). Hospital records could be traced for 181 patients. Their files were reviewed for details on tumor characteristics and treatment modalities. Centre-based registrations provided data on additional patients (diagnosed in 2014). In total, 91 patients were included for further analysis. Baseline characteristics are listed in Table 1. Median follow-up was 37 months (IQR 20–62). Details on beta catenin (*CTNNB1*) and *APC* gene mutation status were reported sporadically. To our knowledge, 6 patients with *APC* gene mutation were included. Due to the scarce data, these factors were not included in further analyses.

Based on initial management patients were divided in 3 groups: active surveillance, radiotherapy and systemic treatment. Outcome for each group is listed in Table 2. Median follow-up after active surveillance, radiotherapy and systemic treatment was 16 months (IQR 7-31), 44 months (IQR 24-62) and 5 months (IQR 2-12) respectively.

There is a clear increase in the use of non-surgical management over the years, from 0.6% in 1993-1998 up to 12.8% in 2009-2013 (Table 3).

Figure 1. CONSORT diagram of patient selection

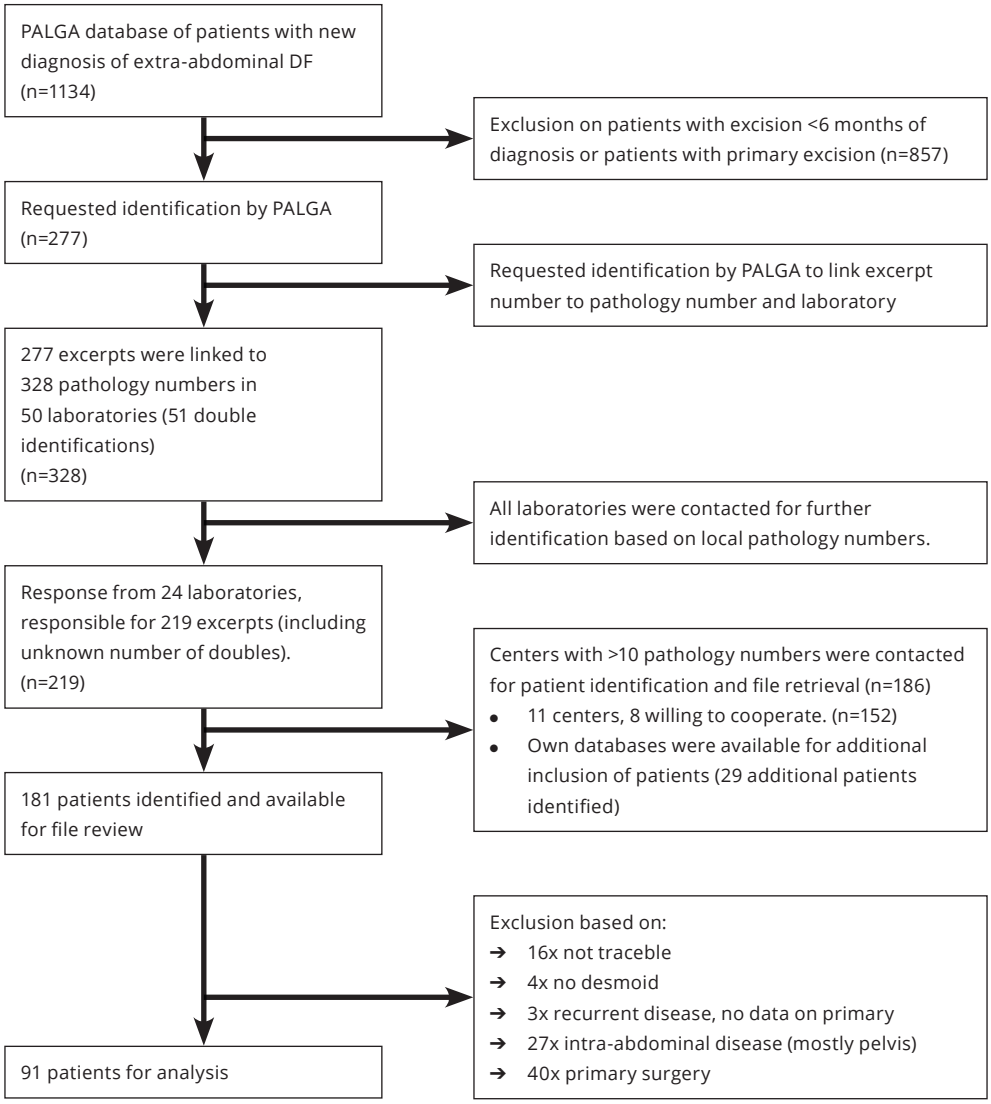

Table1. Baseline characteristics

	All patients		Active surveillance		Radiotherapy		Systemic treatment	
	N	%	N	%	N	%	N	%
Gender								
Male	30	33	9	24.3	12	34.3	9	47.4
Female	61	67	28	75.7	23	65.7	10	52.6
Age								
Median (IQR)	39 (33.1-52.2)		36 (31.2-51.6)		43,6 (39.4-52.4)		34.8 (23.3-46.3)	
Localization								
Head/Neck	9	9.9	3	8.1	6	17.1	-	-
Thorax/back	35	38.5	13	35.1	13	37.1	9	47.4
Abdominal wall	25	27.5	17	45.9	1	2.9	7	36.8
Extremity	21	23.1	4	10.8	15	42.9	2	10.5
Other*	1	1.1	-	-	-	-	1	5.3
Size								
<5 cm	25	27.5	16	43.2	7	20.0	2	10.5
5-10 cm	48	52.7	18	48.6	19	54.3	11	57.9
>10 cm	15	16.5	2	5.4	8	22.9	5	26.3
Missing data	3	3.3	1	2.7	1	2.9	1	5.3
Beta-catenin (nuclear)								
Positive	56	61.5	28	75.7	16	45.7	12	63.2
Negative	10	11	3	8.1	6	17.1	1	5.3
Unknown	25	27.5	6	16.2	13	37.1	6	31.6

N=number of patients. Cm=centimeters. IQR=interquartile range. *groin.

Table 2. Outcome of non-surgical treatment, using best response according to RECIST

	CR		PR		SD		PD		Unknown		Total
	N	%	N	%	N	%	N	%	N	%	N
Active surveillance	2	5.4%	4	10.8%	21	56.8%	5	13.5%	5	13.5%	37
Radiotherapy	4	11.4%	11	31.4%	16	45.7%	0	0%	4	11.4%	35
Systemic treatment	1	5.3%	1	5.3%	10	52.6%	2	10.5%	5	26.3%	19

N=number of patients. CR=complete response. PR=partial response. SD=stable disease. PD=progressive disease.

Table 3. First-line non-surgical management per 5 year time period

	1993-1998	1999 - 2003	2004 - 2008	2009 - 2013	2014	Total
	N	N	N	N	N	N
PALGA registration[4]	180	185	331	438		1134
First-line treatment	1	5	22	56	7	91
Stratified treatment						
Active surveillance	0	0	5	26	6	37
Radiotherapy	0	1	13	20	1	35
Systemic treatment	1	4	4	10	0	19
Percentage*	0.6 %	2.7%	6.6%	12.8%		8.0%

N=number of patients. *Percentage of non-surgical treatment compared to overall diagnoses as documented in the PALGA registration

Active surveillance

Thirty-seven patients were directed to active surveillance after diagnosis. Tumor localization was as follows: 3 patients with head/neck tumors, 13 patients with truncal tumors, 17 patients with abdominal wall tumors and 4 patients with extremity tumors. Best response during that period was spontaneous CR for 2 patients (5%), PR for 4 patients (11%), SD for 21 patients (57%) and PD for 5 patients (14%). For 5 patients, images required for RECIST were not available. During the follow-up period, 13 patients had progressive disease with a median TTP of 7.3 months (IQR 4.1-11.9). In total, 22 patients (63%) were still under active surveillance at the date of last of follow-up after a median of 16 months, including all patients with CR or PR (median duration of active surveillance for patients with CR and PR was 22 months, IQR 13-46). Of the 21 patients with SD, 3 ended active surveillance due to complaints related to the tumor and 5 patient had tumor growth of which 1 patient with <20% increase. Of the 5 patients with PD, 4 patients remained under active surveillance.

Radiotherapy

Initial treatment was radiotherapy for 35 patients. Tumor localization was categorized as follows: 6 patients with head/neck tumors, 13 patients with truncal tumors, 1 patient with abdominal wall tumor and 15 patients with extremity tumors.
Most patients (n=34) received 56 Gy in 28 fractions of 2 Gy or 25 fractions of 2 Gy and 2 fractions with 3 Gy. One patient with a tumor on the head/neck received 54 Gy over 30 sessions of 1.8 Gy.

Ten patients had no toxicity, 11 patients had grade 1, 10 patients had grade 2 and one patient had grade 3 toxicity. Data used for scoring was too limited in 3 patients.
Best response to radiotherapy was CR in 4 patients (11%), PR in 11 patients (31%) and SD in 16 patients (46%). For 4 patients, no images were available to determine outcome using RECIST. During follow-up, 2 patients developed PD with TTP of 31 and 47 months. Median follow-up after radiotherapy was 44 months (IQR 24-62).

Systemic treatment

A total of 19 patients received initial systemic treatment. Type of systemic treatment was non-steroid anti-inflammatory drugs (NSAID) in 10 patients, anti-hormonal therapy (HT) in 5 patients, chemotherapy (ChT) in 1 patient, tyrosine kinase inhibitor (TKI) in 1 patient and a combination of HT and TKI in 1 patient. Details were missing for 1 patient.
Tumor localization was categorized as follows: thoracic/back in 9 patients, abdominal wall in 7 patients, extremity in 2 patients and groin in 1 patient.
Median duration of initial systemic treatment was 5 months (IQR 2-12). Best response during initial systemic treatment was CR for 1 patient (5%), PR for 1 patient (5%), SD for 10 patients (53%), PD for 2 patients (11%) and unknown for 5 patients (26%). The female patient with CR received HT. The patient with PR received a NSAID. The 10 patients with SD had received NSAIDs (n=7), HT (n=2) and TKI (n=1). PD was seen after NSAID (n=1) and ChT (n=1). During follow-up, 3 patients developed PD with TTP of 6.3, 7.1 and 7.2 months.
After initial systemic treatment, multiple regimes of systemic treatments were given to 10 patients. Overall, NSAIDs were given in 14 regimes, HT was given in 7 regimes, ChT was given in 7 regimes, TKIs were given in 1 regime, a combination of TKI with HT was given in 1 regime and a combination of NSAIDs and HT was given in 4 regimes.

Discussion

The change in treatment strategies from initial surgery with or without radiotherapy to initial non-surgical treatment has been fueled by several studies and increasing expertise about this disease with its unpredictable behavior. Reports on outcome of initial non-surgical treatment are limited. The Dutch PALGA registration provided data to analyze treatment strategies in the Netherlands over the last 20 years. Overall trends have been recently described, reporting a decrease in surgery as initial treatment[4]. The present study describes the first-line non-surgical management modalities, including 37 patients

receiving surveillance (41%), 35 patients receiving radiotherapy (38%) and 19 patients receiving systemic treatment (21%). Overall, patients had a 25% response rate and 52% stable disease rate. This study was not designed to compare the outcome of the different treatment modalities, merely to report common practice over the years.

Over the past 20 years, first-line non-surgical management has increased to up to 12.8%. Although the ratio between the time periods might be biased by several factors (such as limited numbers and registration), the trend towards non-surgical management is evident and is expected to increase, as more specialists adhere to the current guidelines.

Literature on first-line non-surgical management is limited. Moreover, all studies are reports from specialized centers. Retrospective studies with combined data from the French and Italian research groups reported promising results for all tumor localizations. Even a predictive value to switch to non-surgical management was found: tumor size[13,14]. The present study was designed to provide more insight in common practice for this rare disease on a population based level. Using a national database of 1134 patients, the number of patients treated non-surgically, is still very small, but increasing. This indicates that surgery remained the first-line treatment over the last 20 years. The paradigm shift towards active surveillance could be observed in the present study, as these patients represent the largest group among non-surgical management. Radiotherapy comes second, possibly due to available knowledge on efficacy, a study that has run within participating centers in this analysis and the often irresectable cases where radiotherapy is the only treatment of choice. The small numbers of systemic treatment reflect the limited evidence for any of those and lack of clinical studies in the Netherlands.

Overall, outcome of first-line non-surgical treatment was good. Among patients under active surveillance, 16% showed spontaneous regression and 57% disease stabilization. These results might be biased because in many cases choice for first-line treatment was made after referring the patient to a tertiary referral center which enabled the physicians to observe the natural behavior of the tumor, thereby selecting patients for active surveillance or more aggressive treatments. For radiotherapy, the patients in the present study received radiotherapy at the recommended dose of 50-56 Gy[6-8,15]. Results showed response in 43% and SD in 46% of the patients. During the follow-up period (median of 44 months (IQR 24-62) only 2 patients had disease progression with long TTPs of 31 and 47 months. These results are promising and might seem to advocate radiotherapy.

However, radiotherapy might be considered an aggressive treatment for this intermediate grade tumor, usually reserved for patients with advanced disease. Especially in younger patients, given the low, but present long term risk on irradiation induced sarcomas radiotherapy is not deemed as first line treatment. When systemic treatment is chosen, a large variety of possible agents and regimes are available, such as hormonal agents, NSAIDS, chemotherapy and angiogenesis inhibitors, making comparison impossible. Although the group in the present study was small and diverse, results show stabilization and response in 63% of patients. Again, due to the large variety, no conclusions can be made for on preference of specific agents or regimes.
For each type of active treatment, the possible results should be weighed against adverse events. In particular, the small risk of secondary tumors should be taken into account for this relatively young patient group. Treatment decisions should therefore always be made during multidisciplinary expert meetings.

The optimal first-line non-surgical management of DF has been discussed by many groups, predominantly based on expert opinions and specific treatment modalities. The European consensus, reported by Kasper et al.[5] advises to start with active surveillance and switch to active treatment in case of 3 subsequent reports of progression, and that treatment should be guided by tumor localization. This advice is consensus-based. There is no staging system available to predict outcome at the time of diagnosis. Predictive factors have been described, such as age, tumor localization and *CTNNB1* mutations[16-21]. Recent data on *CTNNB1* mutations show different behavior for tumors with different mutations. In the future, these mutations could play an important role when deciding to initiate specific treatment modalities. Moreover, it is increasingly important to recognize the lack of correlation between radiological volume and symptoms. Given the chronic condition and the spontaneous fluctuations of the disease this should be taken into account in any decision that will be taken.

By the use of PALGA, the Dutch pathology registry, and the long study period, we have tried to be as inclusive as possible. Because referral for a desmoid-type fibromatosis to one of the sarcoma referral centers is standard practice in the Netherlands, the study is unbiased by clinical behavior.

Finally, a limitation of the study is it retrospective nature. As a result, details on symptoms during or after treatment are lacking, which could have provided insight in the way decisions to either management had been taken. Therefore, no comparisons can be made

between the different strategies. The natural behavior of these tumors is variable, varying from spontaneous regression to long-term disease stabilization and rapid progression. In the absence of randomization, no clear recommendations can be given. Desmoid-type fibromatosis remains a rare disease, for which several treatment modalities are available. Active surveillance is a good and safe initial treatment, with options for adjuvant treatment in case of progression. Importantly, expected benefits from therapy should be well balanced against potential treatment-induced untoward effects.

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Part 3

Predicting behavior

Chapter 7

Prognostic value of *CTNNB1* gene mutation in primary, sporadic aggressive fibromatosis

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Abstract

Background

Aggressive fibromatosis (AF) comprises tumors with a varying biological behavior. Genetic tumor characteristics may be predictive of recurrence; hence the prognostic value of three specific mutations on the *CTNNB1* gene was evaluated in relation to known clinicopathological risk factors in patients with primary, sporadic AF.

Methods

In a multi-institutional retrospective cohort study of patients with primary extra-abdominal and abdominal wall AF who underwent surgical treatment, the original pathology specimens were reviewed for the presence of a T41A, S45F and 45P mutations on the *CTNNB1* gene. For these mutations the risk of recurrence was analyzed using the Kaplan-Meier method with log-rank test. Univariable and multivariable Cox-regression was performed to calculate hazard ratio's.

Results

A total of 101 patients were analyzed. During a median follow-up of 41 months, 17 recurrences were detected; the cumulative 5-year recurrence rate was 22.8%. A specific *CTNNB1* mutation was found in 76 patients, the majority of patients having a T41A mutation (n=49). *CTNNB1* mutations were associated with the risk of recurrence: the presence of a S45F mutation was associated with a 5-year cumulative risk of recurrence of 63.8% (P<0.001). Multivariable analysis showed that young age and S45F mutation were independent risk factors (P=0.011 and P<0.001).

Conclusion

The presence of specific *CTNNB1* mutations was predictive for recurrence in patients after surgical treatment for primary, sporadic extra-abdominal and abdominal AF.
A S45F mutation increased the risk of recurrence significantly.

Introduction

Aggressive fibromatosis (AF) is a soft tissue tumor that does not metastasize, but frequently recurs following surgical excision[1,2]. On the other hand, the growth of these tumors may halt spontaneously in a substantial proportion of patients[2,3]. Because of this heterogeneity of biological behavior, the course of the disease is difficult to predict and the benefit of aggressive treatment modalities is unclear. On a cellular level the beta-catenin protein level is elevated in these tumors, and the demonstration of mutations in two mediators in the Wnt-*APC*-beta-catenin pathway implicates beta-catenin stabilization as the key factor in the pathogenesis of AF[4,5]. The *CTNNB1* gene encodes for β-catenin and literature suggests the involvement of *CTNNB1* gene mutations in sporadic AF[6,7].

Three particular mutations on the *CTNNB1* gene have been associated with AF, namely T41A, S45F and 45P[5,8]. Although it remains unclear how these mutations precisely affect the aforementioned pathway in these tumors, the presence or absence of a specific mutation appears to be predictive of recurrence. A number of studies observed a prognostic impact of *CTNNB1* mutations; in particular S45F mutations were associated with a high risk of recurrence following surgical excision[9-11]. Others, however, have failed to demonstrate this increased risk[12].

We recently analyzed clinicopathological factors for their prognostic significance in a multi-institutional cohort of patients who underwent surgery for primary, sporadic AF[13]. The original pathology specimens of the patients in this cohort were collected and reexamined for the presence of the specific *CTNNB1* gene mutations. The association with other clinicopathological factors was evaluated in an attempt to use mutation status in addition to clinical factors to stratify the risk of recurrence in patients with AF.

Methods

Data collection

The institutional databases of patients with soft tissue tumors at the University Medical Center Utrecht, the affiliated Diakonessenhuis in Utrecht and the Erasmus MC Cancer Institute in Rotterdam were searched. Patients diagnosed between November 1989 and October 2013 as having a a first manifastation of sporadic extra-abdominal or abdominal

wall AF were included if original pathology specimens were available for mutation analysis[14]. Patients who underwent incomplete (R2) tumor resection were excluded. None of the patients had undergone previous surgery for AF.

Mutation Analysis

The soft tissue pathology boards at the University Medical Center Utrecht or the Erasmus MC Cancer Institute reviewed the histopathological diagnosis for all patients at the time of treatment. The available pathology specimens of the patients were collected and analyzed in one laboratory. Tumor areas as identified on serial H&E sections were harvested from 4 µm thick formalin fixed paraffin embedded sections (corresponding to approximately 1 square cm tumor tissue) with a scalpel. Tumor percentages of all samples were estimated before DNA isolation and only samples with tumor percentages of at least 10% were used. DNA was isolated from these tissue fragments with the Cobas® DNA Sample Preparation kit (Roche Diagnostics).

For the detection of *CTNNB1* mutations, 1 µl of DNA (10-50 ng/µl) was amplified with primers positioned in exon 4, flanking codons 41 and 45 (forward PCR primer: 5` AAA-GCG-GCT-GTT-AGT-CAC 3`, reverse PCR primer: 5` TCC-CTG-TTC-CCA-CTC-ATA 3`, 35 cycles, annealing temperature 55 ºC). After subjecting to agarose gel electrophoresis, 1-2 µl of viable PCR product was sequenced (forward sequence primer: 5` ACT-GGC-AGC-AAC-AGT-CTT 3`, reverse sequence primer: 5` ACA-GGA-CTT-GGG-AGG-TAT-C-3`, 25 cycles, annealing temperature 50 ºC) in both sense and antisense directions, using the BigDye Terminator v1.1 sequencing kit on an ABI 3730 capillary sequencer (Life technologies) according to the manufacturer's instructions. Only mutations that could be confirmed in both sequencing directions were taken into account.

Patient and tumor characteristics

Age was categorized into quartiles. Tumor localization was categorized as extra-abdominal (head/neck, extremity, chest wall/back, other) and abdominal (abdominal wall) in accordance with the WHO Classification of Tumours[14]. Tumor depth was categorized as superficial or deep, in relation to the fascia. The result of surgery was categorized based on the histological examination of surgical margins and the operative report, using the classification of the International Union Against Cancer (UICC), as R0 (microscopic negative resection) or R1 (microscopic tumor positive margins). In case of more than one operation on the primary tumor, surgical margin status was classified based on the histopathological findings after the last operation. The type of *CTNNB1* gene mutation was categorized based on the three

known mutations related with aggressive fibromatosis: T41A, S45F and 45P mutation. Other deletions or mutations on the *CTNNB1* gene were categorized as "other". Specimens without a mutation were considered to be 'wild type' and were categorized as such.

Local recurrence was the main endpoint, defined as radiological and/or pathological evidence of tumor recurrence established during follow-up after resection. The end of follow-up was marked by local recurrence, the last registered contact between surgeon and patient or death. The follow-up protocol was not identical in the different institutions. The Erasmus MC Cancer Institute performed physical examination of patients every three months in the first year, every six months during the second year and then yearly until a five year follow-up. In addition to physical examination, magnetic resonance imaging (MRI) was performed routinely six months postoperatively and from then on indication only. At the University Medical Center Utrecht and the Diakonessenhuis, patients were evaluated at the same intervals postoperatively. In addition, MRI was performed routinely on an annual basis. Regular follow-up was ended after five years. Patients were encouraged to contact the hospital if symptoms occurred.

Statistical analysis

Categorical variables are shown as numbers and percentages, continuous variables as median and interquartile range (IQR). Associations between variables were explored by Chi-square analysis. The Kaplan-Meier method was used to estimate the 5-year cumulative risk of recurrence and differences in the risk of recurrence between the *CTNNB1* mutations as well as for the other clinicopathological variables were analyzed with the log-rank test. To support these analyses, univariable Cox regression analysis was used, and results are presented as hazard ratios (HR) compared to a reference category and with 95% confidence interval. Multivariable Cox regression was performed using variables that were statistically significant in univariable analysis. The association between the *CTNNB1* mutation that was most predictive for recurrence and the other clinicopathological factors was explored by Chi-square analysis. For all analyses, two-sided $P < 0.050$ was considered statistically significant.

Results

There were 101 patients who were surgically treated for primary, sporadic extra-abdominal and abdominal AF and for whom pathology specimens were available for *CTNNB1* mutation

analysis. Median age at the time of treatment was 36 years (IQR 28-44). The majority of patients were female (65.3 percent; see Table 1).

Table 1. Baseline characteristics of patients with primary sporadic aggressive fibromatosis.

	No. of patients
Sex ratio (M : F)	35:66
Median age (years)	36
Age (years)	
0-27	24
28-35	25
36-44	27
45-80	25
Extra-abdominal localization	
Head/Neck	10
Chest wall/back	23
Extremity	26
Other*	7
Abdominal localization	
Abdominal wall	35
Size (mm)	
0-50	61
51-100	32
>100	8
Depth	
Superficial	21
Deep	80
***CTNNB1* mutation**	
Wild type	25
T41A	49
S45F	18
Other	9

* Groin (n=4), retroperitoneal (n=3)

Treatment

R0 resection was achieved in 64 patients, 17 of these patients underwent a second operation to obtain this result. A total of 32 patients underwent R1 resection as a definitive operative treatment (including 3 patients who underwent a re-excision). In 5 patients, the tumor was completely removed according to the operative report but information regarding resection margins was lacking in the histopathological report. Medical therapy

was provided to five patients (chemotherapy n=4; sulindac n=1) as induction treatment in order to improve the feasibility of a complete tumor resection. One patient had a partial response. Forty patients received postoperative radiotherapy, twenty-six of them after microscopically radical surgery (R0), fourteen following an R1 resection. No patient received adjuvant medical therapy.

CTNNB1 gene analysis

A specific *CTNNB1* gene mutation was found in 76 patients (75%): a T41A mutation was most common (n=49), an S45F mutation was present in 18 patients and a 45P mutation was seen in three patients. A mutation or deletion on the *CTNNB1* gene other than T41A, S45F or 45P was found in 6 patients. Due to the limited number of patients with a 45P mutation, these patients were categorized in the group "other" for the analyses. Wild type was documented for 25 patients.

Recurrences

After a median follow-up period of 41 months (IQR 18-71), 17 patients developed recurrent disease. Median time till recurrence was 20 months (IQR 13-45). The 5-year cumulative risk of recurrence was 22.8%. Three patients died during follow-up, in two cases due to unrelated causes. One patient died at the age of 4 after extensive treatment of a tumor located in the head and neck.

Table 2. Univariate analysis of factors predictive of recurrence after R0/R1 resection of AF.

	No. of recurrence	Kaplan-Meier 5-year risk of recurrence %	P (log-rank)	Cox HR (95% CI)	P (Wald)
Age			0.001		
0-27	10/24	60.5		Reference	
28-35	2/25	10.3		0.16 (0.04-0.74)	0.019
36-44	3/27	11.2		0.20 (0.05-0.73)	0.015
45-80	2/25	11.8		0.15 (0.03-0.69)	0.015
Localizationa			0.006		
Extra-abdominal	17/66	31.0			
Abdominal	0/35	0			
Extra-abdominal			0.463		
Head/Neck	4/10	40.0		Reference	
Chest wall/Back	4/23	22.5		0.33 (0.08-1.34)	0.122
Extremity	7/26	33.6		0.56 (0.16-1.92)	0.357
Other	2/7	40.0		0.52 (0.09-2.84)	0.449
Size			0.323		
0-50 mm	7/61	19.1		Reference	
51-100 mm	8/32	26.5		1.68 (0.61-4.64)	0.318
>100 mm	2/8	37.5		3.04 (0.63-14.68)	0.167
Depth			0.109		
Superficial	1/21	9.1		Reference	
Deep	16/80	26.3		4.51 (0.60-34.07)	0.144
Resection margin			0.219		
R0	9/64	16.9		Reference	
R1	6/32	31.2		1.85 (0.65-5.26)	0.248
Rx[b]	2/5	50.0		3.22 (0.69-14.95)	0.136
Adjuvant radiotherapy			0.213		
No	11/61	29.7		Reference	
Yes	6/40	15.7		0.53 (0.20-1.46)	0.220
Mutation			0.248		
Negative	2/25	13.4		Reference	
Positive	15/76	25.6		2.33 (0.53-10.18)	0.262
Mutation			<0.001		
Wild Type	2/25	13.4		Reference	
T41A	4/49	12.2		0.86 (0.16-4.73)	0.866
S45F	10/18	63.8		8.50 (1.85-39.00)	0.006
Other/45P	1/9	16.7		1.47 (0.13-16.26)	0.751

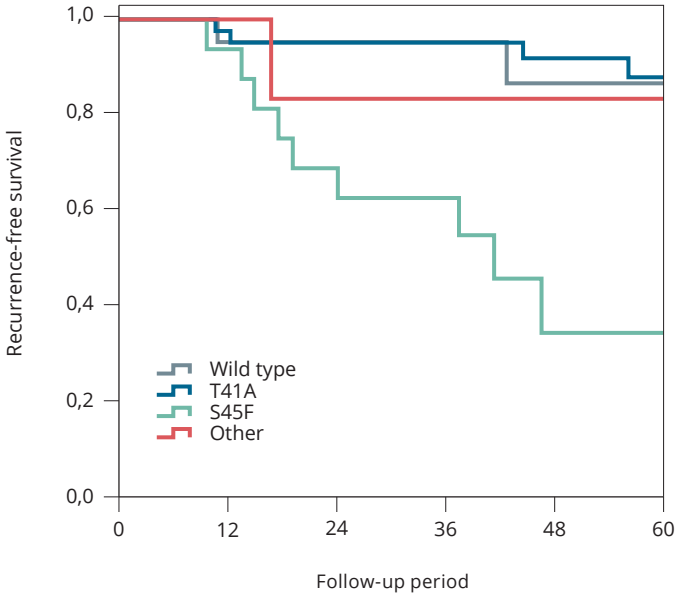
[a] Cox regression was not possible due to no events in the abdominal group. [b] Missing data on resection margin, operative report states macroscopic radical resection. No=number, KM=Kaplan Meier, Cox=Cox regression, HR=Hazard Ratio, CI=confidence interval

Factors affecting recurrence

Univariable analysis of factors affecting the risk of recurrence showed a statistically significant effect of age (P=0.001), tumor localization (P=0.006) and the presence of a *CTNNB1* mutation (P<0.001), see Table 2. Young age (< 28 years) and the presence of a S45F mutation were associated with an increased risk of recurrence. Tumor localization in the abdominal wall was associated with a decreased risk of recurrence. The highest risk of local recurrence was observed in patients with a S45F mutation. These patients had a 5-year recurrence risk of 63.8% and a 8.5 fold higher risk of recurrence (95% CI 1.85-39.00; P=0.006) than patients with tumors that were wild type. The 5-year risk of recurrence for wild type, T41A- or other mutations was 13.4%, 12.2% and 16.7% respectively (Figure 1).

Multivariable analysis was performed using age and *CTNNB1* mutations (Table 3). Both the presence of S45F mutation and young age (under 28 years) proved to be independent risk factors (P<0.001 and P=0.011 respectively). The association between the presence of a S45F mutation and the conventional clinicopathological factors is presented in Table 4. A significant association with tumor depth was observed (P=0.021) as S45F mutations did not occur in superficial tumors.

Figure 1. Recurrence- free survival of the specific *CTNNB1* mutations



No. at risk						
Wild type	25	20	17	11	10	8
T41A	49	40	34	30	28	20
S45F	18	15	11	8	3	3
Other	9	8	5	4	4	2

Table 3. Multivariate analysis of factors predictive for recurrence following R0/R1 resection of AF.

	Cox HR (95% CI)	P (Wald)
Age: 0-27 year vs other age groups*	3.70 (1.34-10.19)	0.011
Mutation: S45F vs no S45F*	6.20 (2.24-17.15)	<0.001

*Reference. Localization was not included due to the statistical limitation of Cox regression when no events occur in a group. Cox=Cox regression, HR=hazard ratio, CI=confidence interval

Table 4. Association between S45F mutation and other clinicopathological factors by Chi-square analysis.

	S45F mutation (n=18)	No S45F mutation (n=83)	P (Pearson)
Sex ratio (M : F)	9:9	26:57	0.109
Median age (years)	35	36	
Age (years)			0.407
0-27	7	17	
28-35	3	22	
36-44	4	23	
45-80	4	21	
Localization			0.103
Extra-abdominal	15	51	
Abdominal	3	32	
Extra-abdominal			0.440
Head/Neck	3	7	
Chest wall/Back	3	20	
Extremity	8	18	
Other	1	6	
Size (mm)			0.366
0-50	8	53	
51-100	8	24	
>100	2	6	
Depth			0.021
Superficial	0	21	
Deep	18	62	
Resection margin			0.161
R0	8	56	
R1	9	23	
Rx*	1	4	
Postoperative radiotherapy			0.605
No	12	49	
Yes	6	34	

*missing data on resection margin; operative report states macroscopic radical resection

Discussion

In patients with primary, sporadic extra-abdominal and abdominal AF, the 5-year cumulative risk for recurrence was 22.8%. The presence of a S45F mutation and age <28 years were independent predictors of recurrence. Both were associated with a 60% risk of developing recurrence within five years.

The present study evaluated the prognostic value of specific *CTNNB1* gene mutations in a uniform cohort of patients with primary, sporadic AF who underwent a macroscopic complete tumor resection. A strength of the present study is the verification of pathology specimens by experts on soft tissue tumors and the central pathologic analysis of the *CTNNB1* mutations and the homogeneous inclusion of primary, sporadic extra-abdominal and abdominal tumors. Because intra-abdominal AF is considered a different biological entity with a deviating treatment protocol, this category of patients was excluded from the study. All patients were treated in specialized centers.

This study has some limitations too, mostly inherent to the retrospective study design, such as the small sample size and the different follow-up schemes in the respective institutions. Information on postoperative radiotherapy (indications, precise doses and effects) was limited. In addition, the median follow-up period of 41 months may cause underreporting of recurrences for a disease which can recur after several years. However, the observed difference in recurrence rates between mutations is evident with this modest follow-up.

The impact of clinicopathological factors on recurrence has recently been used to construct a nomogram for predicting recurrence[15]. In this nomogram, age, localization and tumor size are important predictive factors. The present data confirms the high risk associated with young age, while the predictive value of tumor size was not. The low risk associated with abdominal wall localization was confirmed by the present study: no recurrences were observed in the abdominal wall group (n=35).

In the present study, desmoid-specific *CTNNB1* mutations significantly influenced the risk of recurrence. A study by Lazar et al. also reported a significantly increased risk of recurrence associated with a S45F mutation with a relative risk of 3.5[9]. Colombo et al. observed comparable results with a S45F mutation as a significant predictor for recurrence

in a multivariable analysis[11]. In these studies the 5-year risk of recurrence was 77% and 54% respectively for patients with an S45F mutation, underscoring the overall high risk of recurrence after surgery in this group. In addition, Bo et al. found a predominance of S45F mutations in the group of patients with recurrent disease, whereas T41A mutation was observed more often in primary disease, also suggesting an increased recurrence risk in the former mutation[16]. Discordant findings have been reported by Mullen et al[12]. In their analysis on 115 patients with primary and recurrent AF the difference in recurrent free survival (RFS) for patients with *CTNNB1* mutations was modest (58,0% vs 73.6% for wild type) and did not reach statistical significance. The frequency of S45F mutations varied between the studies and was 28%, 22%, 22% and 25% in the studies by Lazar, Colombo, Bo and Mullen respectively[9,11,12,16] compared to 18% in the present study. Differences between these studies and the present study are mainly explained by inclusion criteria. We applied a strict selection of primary sporadic (extra-abdominal and abdominal) tumors to present a uniform cohort. The exclusion of recurrent disease will lower the frequency of S45F, as this mutation has a predominance in recurrent tumors[16].

Other than the knowledge that *CTNNB1* mutations can lead to increased beta-catenin levels, the exact mechanism and the different effects exerted by the specific mutations on the same gene are not well understood. Other enzymes within the Wingless/Wnt-pathway can have the same effect, whereas mutations in the *APC* gene can cause increased beta-catenin levels too, as is most often seen in intra-abdominal aggressive fibromatoses[6,7]. On the other hand *CTNNB1* mutations have been found in beta-catenin negative tumors also, suggesting a more elaborate role of mutational status over beta-catenin levels[17].

The effect of mutation status on the risk of recurrence fuels the discussion about the indications for surgery and other treatment options. In this context we would like to emphasize that the presented results are based on a modest number of eighteen S45F patients. Yet when confirmed by larger studies, the extra information gained by determination of *CTNNB1* gene mutation, will play a valuable role in treatment choices. Patients with a low risk of recurrence are likely to benefit most from primary surgical treatment. As such, patients with abdominal tumors, superficial tumors and S45F-negative tumors appear to be good candidates for an upfront surgical approach. Given the high risk of recurrence after surgery in young patients (<28 years) and in patients with S45F-positive tumors, upfront surgical treatment is disputable in these patients. Aggressive treatment by repeated surgery and postoperative radiotherapy has been standard of care until recently.

Therefore, in the latter high risk categories other treatment options should be taken into consideration.

Currently there is a trend towards a more conservative treatment strategy in patients with AF[18]. The high risk of recurrence associated with a particular mutation suggests a more aggressive behavior of the primary tumor. Although conceivable that this is associated with a higher progression rate in untreated AF, this remains to be established. It is too early to advise a watchful waiting approach based on a particular mutation. Still, patients with S45F mutations and young patients have such a high absolute risk of recurrence following radical surgery that they still may be considered eligible for other treatment modalities than surgery. Radiotherapy as a single treatment modality has shown promising results in patients with AF with an objectified response or stabilization in up to 80% of patients after three years[19]. It appears to work better as an upfront approach than as an adjunct to surgery[13,20,21]. Although no information exists about the effect of radiotherapy in relation to mutation status, it appears an attractive treatment option in a category of tumors that, more likely than not, will recur after surgery. Various regimes of chemotherapy have shown an overall response rate of 21% in an unselected group of patients[22,23]. It would be worthwhile to conduct studies analyzing the effect of systemic therapy and radiotherapy in relation to the *CTNNB1* mutation.

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Chapter 8

Tailored Beta-catenin mutational approach in extra-abdominal sporadic desmoid tumor patients without therapeutic intervention.

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Abstract

Background

The efficacy of the classical treatment modalities surgery and radiotherapy in the treatment of aggressive fibromatosis is presently disputed and there is a shift towards a more conservative approach. The aim of the present study is to objectify tumor growth in patients with extra-abdominal or abdominal wall aggressive fibromatosis, while adhering to a "watchful waiting" policy. Other objectives are to investigate quality of life and to identify factors associated with tumor growth, in particular the relation with the presence of a *CTNNB1* gene mutation in the tumor.

Design and methods

GRAFITI is a nationwide, multicenter, prospective registration trial. All patients with extra-abdominal or abdominal wall aggressive fibromatosis are eligible for inclusion in the study. Main exclusion criteria are: history of familiar adenomatous polyposis, severe pain, functional impairment, life/limb threating situations in case of progressive disease. Patients included in the study will be treated with a watchful waiting policy during a period of 5 years. Imaging studies with ultrasound and magnetic resonance imaging scan will be performed during follow-up to monitor possible growth: the first years every 3 months, the second year twice and then yearly. In addition, patients will be asked to complete a quality of life questionnaire on specific follow-up moments. The primary endpoint is the rate of progression per year, defined by the Response Evaluation Criteria In Solid Tumors (RECIST). Secondary endpoints are quality of life and the rate of influence on tumor progression for several factors, such as *CTNNB1* mutations, age and localization.

Discussion

This study will provide insight in tumor behavior, the effect on quality of life and clinicopathological factors predictive of tumor progression.

Trial registration

The GRAFITI trial is registered in the Netherlands National Trial Register (NTR), number 4714.

Background

Biological behavior

Desmoid-type fibromatoses are rare, non-metastasizing, locally aggressive soft tissue tumors. Aggressive fibromatoses can be located in every part of the body and are classified as extra-abdominal, abdominal wall or intra-abdominal[1,2]. The abdominal wall is a predilection site in women of reproductive age[3]. Sporadic onset of the tumor is common, but an association with familiar adenomatous polyposis (FAP) has been documented, in particular in intra-abdominally localized aggressive fibromatoses[4]. The course of the disease is unpredictable and varies between relatively indolent, i.e. stabilization of the tumor, and progressive growth, which may halt spontaneously[5]. The reported frequency of recurrence following local treatment ranges from 5 to 63%[6].

Genetic markers in tumor tissue have been analyzed, in particular the *CTNNB1* gene. *CTNNB1* gene encodes beta-catenin, a proto-oncogene involved in cell adhesion and cell transcription. Beta-catenin is a key factor in the Wnt-*APC*-beta-catenin pathway. On a cellular level the beta-catenin protein level is elevated in these tumors, implicating beta-catenin stabilization as a key factor in the pathogenesis of aggressive fibromatosis[7,8]. Nuclear overexpression of beta-catenin is a histological condition used in a diagnostic setting. The diagnostic value is sensitive, but not specific[8-10]. Research on the *CTNNB1* gene revealed 3 specific mutations, namely T41A, S45F and 45P[8,10]. While it is yet unclear how these mutations precisely affect the aforementioned pathway in these tumors, a role in biologic behavior seems natural according to their role in pathogenesis. Several groups have analyzed *CTNNB1* mutation and these mutations appear to have a prognostic value in determining the risk of recurrence in retrospective series of surgically treated patients[11-15]. Although Mullen et al. did not find a statistical significant prognostic[15], several other groups reported a higher risk of recurrence for patients with an S45F mutation[11-13], even in multivariate analysis[12]. In addition, (surgical) trauma and hormones presumably play a role in the genesis of this tumor, as aggressive fibromatosis is known to arise in scars and in fertile females[16] .

Treatment

Treatment of aggressive fibromatosis classically involves surgery, combined with radiotherapy on indication. Literature on the effects of surgery and radiotherapy on the rate of recurrence is conflicting[17-19]. While these effects are still being questioned,

treatment policies have recently turned towards a more conservative approach. Nowadays, a watchful waiting approach is being advocated by various authors and is currently the standard in European care[20-25]. Retrospective studies showed that progression usually occurs within 2 years of diagnosis. Fiore et al.[22] reported a median time till progression of 14 months, with 89% of progression observed within 2 years, while Salas et al.[18] described a median time till progression of 20 months. In addition, these studies have also reported spontaneous regression in up to 18.5% of the patients[18,22].

The ability to predict tumor behavior would enable tailoring individual patient treatment. Little is known about tumor growth. Available literature is dated and descriptive, without objective measurements[16].

Study aim

The GRAFITI study will evaluate a watchful waiting approach as an initial treatment for patients with extra-abdominal or abdominal wall aggressive fibromatosis. The primary objective is to assess tumor progression using the Response Evaluation Criteria In Solid Tumors (RECIST)[26]. We will attempt to identify patient and tumor characteristics related to growth. A twin study is ongoing in Milan, Italy (NCT02547831). The present study proposal was designed in collaboration with the Italian study group, to facilitate a possible future merger of data.

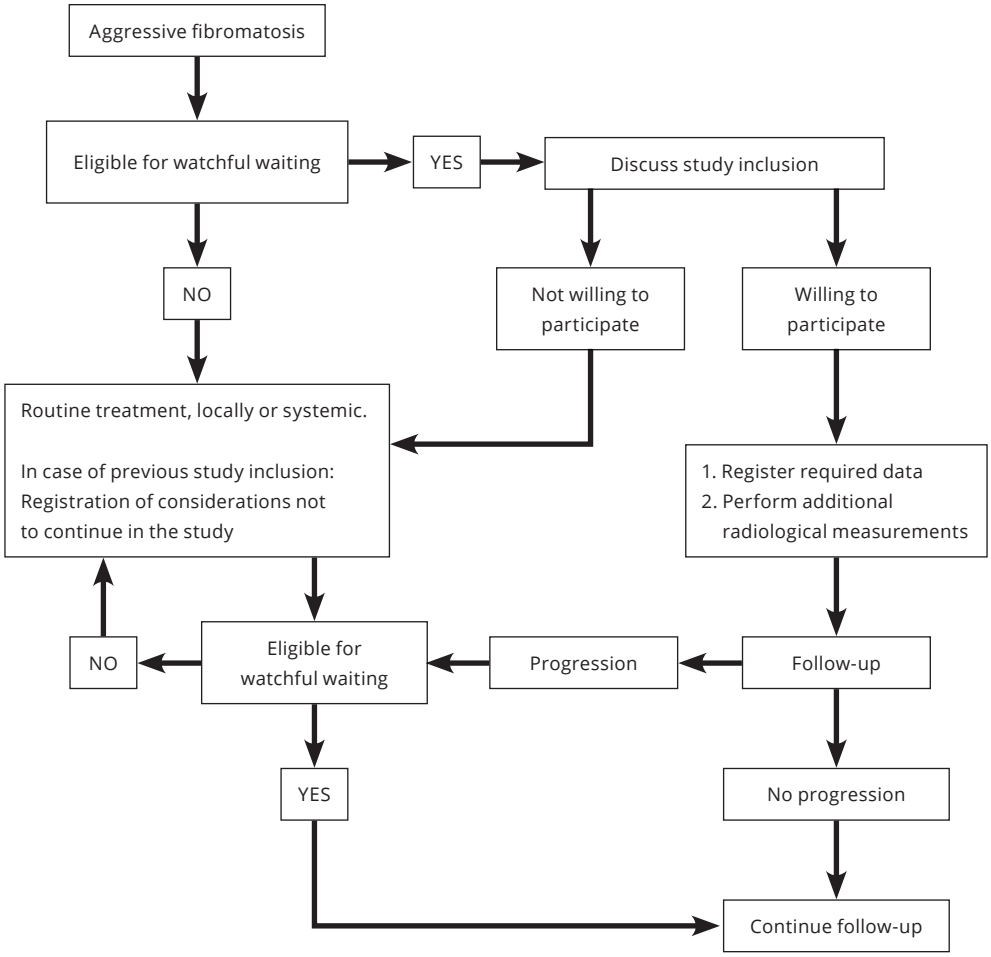
Design and methods

Study design

GRAFITI was designed in collaboration with experts in sarcoma care throughout the Netherlands as a nationwide prospective observational study. All patients with extra-abdominal or abdominal wall aggressive fibromatosis are eligible for participation. Inclusion and exclusion criteria are discussed below. If not included, treatment options will be discussed by the local multidisciplinary teams. Treatment modalities include systemic treatment, surgery and radiotherapy, and individualized treatment will be chosen based on patient characteristics, tumor localization and predicted outcome.
Patients will be treated by a watchful waiting policy and asked to complete quality of life questionnaires. During follow-up, imaging studies will be performed to monitor tumor growth. In case of growth, all treatment options will be evaluated, including continuation

of watchful waiting. A switch in treatment strategy will be monitored and reasons for this switch documented (see Figure 1).

Figure 1. Flowchart



Primary objective

The primary objective is to assess tumor progression in terms of objectifying and monitoring growth during watchful waiting policy as an initial treatment. Ultrasound and MRI imaging will be used to determine tumor size. Tumor behavior will be scored using RECIST. Primary endpoint is the rate of progression per year, which will be measured after 5 years of follow-up.

Secondary objectives

The secondary objective is to investigate the effect of treatment on the quality of life. During the study period, patients will be asked to complete the EORTC QLQ-C30 questionnaire five times: at inclusion and after 6, 12, 24 and 60 months. After a switch to active treatment, patients will remain on-study for the questionnaires. The scores will be evaluated and related to treatment policy.

Other objectives are to analyze the value of clinicopathological factors, including *CTNNB1* gene mutation, in predicting progression. The reasons and considerations for active treatment will be analyzed in relation to the applicability of a watchful waiting policy.

Study population

The study will take place in the Netherlands. All patients with extra-abdominal or abdominal wall aggressive fibromatosis are eligible for inclusion in the study. Primary and recurrent disease will be included, stratification will be done for analyses.

Inclusion criteria

Histological evidence of aggressive fibromatosis. Capable to undergo MRI-scans and ultrasounds. Capable to understand and sign informed consent.

Exclusion criteria

Age <18 years. Personal or family history of FAP. Intra-abdominal tumor localization. Previous treatment for the current manifestation (recurrent lesions without previous treatment are included). Severe pain or functional impairment due to the tumor (as indicated by the patient. The use of painkillers is not an exclusion criterion). Tumor progression leading to mutilation or life/limb-threatening situations, as assessed by the attending physician.

Sample size

Based on the incidence of sporadic aggressive fibromatosis and tumor localization, we expect to include 20 patients annually, we aim to include 100 patients in 5 years. Loss to follow-up or death is not to be expected. Under the most adverse conditions, a progression rate of 50% would result in a 95% confidence interval (95% CI) of 40-60%. A progression rate of 25% would result in a 95% CI of 18%-34%. We consider the presented 95% CI to be acceptable for the study.

Methods

Participation in the study implies that the work-up does not deviate from present common practice. A contrast enhanced MRI-scan (T1 and T2 weighted) is used to determine the precise localization, size and involved structures. Subsequently, and also in line with national guidelines, the patient will undergo an ultrasound-guided, histological needle-biopsy of the soft tissue tumor, with a 14 G needle. Preferably 3 biopsies will be obtained. During the ultrasound, tumor size will be measured in three dimensions. In addition, as part of this study a quality of life questionnaire is completed by the patient.

Table 1. Follow-up schedule

Assessment	Enrollment	Year 1				Year 2		Year 3-5		
Month		3	6	9	12	18	24	36	48	60
History and Physical examination	x	x	x	x	x	x	x	x	x	x
MRI-scan	x		x		x		x	x		
Ultrasound	x	x		x		x			x	x
QoL questionnaire	x		x		x		x			x

QoI=Quality of life

The follow-up schedule is set for 9 outpatient-clinic visits (see Table 1).
During each visit imaging studies will be performed to monitor possible growth. In addition, patients will be asked to complete a questionnaire during 5 follow-up visits.
The radiology report of the ultrasound or MRI-scan will specify the maximum diameter in all 3 dimensions and the growth in relation to previous radiological examinations.
When ultrasonography suggests tumor progression, an MRI-scan is additionally made as standard care and considered as the golden standard for detecting changes within the tumor.

In case of tumor progression, the patient will be re-evaluated. If the patient is still eligible, watchful waiting policy will be continued. If not, local or systemic treatment will be started and considerations to switch treatment strategies will be documented.
After inclusion of all patients, pathology specimens will be collected by one pathology laboratory and *CTNNB1* gene analysis will be performed for all patients. If *CTNNB1* mutation status is already known, this procedure will not be repeated.

Statistical considerations

Statistical analysis will be carried out using IBM SPSS Statistics 21. Radiological measurements will be registered as a continuous variable at ratio. The average progression rate per year will be analyzed using data of all patients. The progression rate per year, defined as increase in size per tumor, using RECIST criteria, with the associated range and confidence interval, will be registered as the primary outcome. The QLQ-C30 questionnaire results in a score to classify the quality of life. This score will be registered as discrete data at ratio scale. If a score cannot be rewarded, the data of the questionnaire will be regarded as missing data. If a score is missing, but later registered scores are available, the later scores will be used in assessment of the quality of life. The overall quality of life will be calculated using data of all patients at the end of follow-up. The median value will be extracted with the associated range.

The possible influence of patient and tumor related factors on the progression rate and the quality of life are analyzed using the Kaplan-Meier method and univariable Cox regression. Associations between variables will be explored by Chi-square analysis. Multivariate analysis will be performed if possible by means of Cox regression. Those factors which prove to have statistical significance in univariate analyses, will be included in the multivariate analysis. The considerations for treatment will be categorized and analysis will show the occurrence of specific considerations.

The interim analysis of both primary and secondary parameters will be done after one year of follow-up on 20 patients. The analyses will be the same as described above and will be performed by the principal investigator. For all analyses, two-sided $P < 0.050$ is considered statistically significant.

Discussion

During the last decade, there has been a shift in treatment strategy for aggressive fibromatosis from aggressive to conservative modalities. A watchful waiting policy is currently advised for extra-abdominal and abdominal wall aggressive fibromatosis[25]. Research validating the efficacy and applicability of a watchful waiting policy is limited. Mitchell et al. were the first to describe a stable phase for aggressive fibromatosis[5]. In a retrospective study of 17 patients under medical observation, all experienced at least one period of stable disease for over 6 months. A larger study by Fiore et al. evaluated 142 patients with primary and recurrent aggressive fibromatosis, treated with initial conservative treatment retrospectively[22]. Approximately 50% of the patients did not have tumor progression after 1 year. Spontaneous regression has been reported by Salas et al[18]. In a retrospective study analyzing 426 patients with aggressive fibromatosis, 27 patients were treated with a watchful waiting policy. Five of these patients had spontaneous remission, 16 patients stable disease and 6 patients had progressive disease. The median time to progression was 19.7 months. A recent study by Colombo et al. reported 216 patients with primary extra-abdominal (n=188) and intra-abdominal (n=28) disease undergoing a diversity of treatments[24]. Initial wait-and-see policy was applied in 70 patients (60 extra-abdominal) and continued till the end of follow-up in 60%. Progression occurred in 16 of the 70 patients, mostly treated with systemic modalities. These results demonstrate the potential safety of a watchful waiting policy.

Current knowledge on predictive factors is mostly based on surgical cohorts. Age, tumor localization and tumor size have been reported as predictive factors for the risk of recurrence following surgery. A nomogram was proposed by Crago et al.[27] using all these factors in a postoperative setting.
In addition, *CTNNB1* mutations are found to be a predictive factor for the risk of recurrence following surgery[12-14,16]. The value of these factors in a postoperative setting cannot be extrapolated to a watchful waiting setting. The present study was designed to evaluate the role of these factors in relation to the progression rate in a watchful waiting setting. This information would help in determining which patients can safely undergo a watchful waiting policy, and which patients would benefit most from active treatment. The ability to predict tumor behavior would enable tailoring individual patient treatment and prevent over- or undertreatment.

The low incidence of aggressive fibromatosis presents a challenge for quality research. Collaborations between specialized institutions is essential. The prospective evaluation of predictive factors in a watchful waiting setting has been initiated by two other research groups. In France, Bonvalot et al. are conducting a similar study (ClinicalTrials.gov identifier NCT01801176). They have finished the inclusion process and are now conducting the final follow-up. In Italy, a similar study is coordinated by Colombo et al. (ClinicalTrials.gov identifier NCT02547831). This study is still open and we encourage inclusion. The present study was designed to resemble the French and Italian study, to facilitate a possible merging of the data if the inclusion rate in the studies would be disappointing. Main inclusion and exclusion criteria match for all three studies, though our study also includes patients presenting with recurrent disease.

The occurrence of aggressive fibromatosis has been related to hormonal influences and pregnancy by Häyry and Reitamo et al.[16,28]. Although hormonal levels and receptors on the tumor have not been investigated, the occurrence of disease among fertile females is very suggestive. A recent study by van Broekhoven et al. evaluated time trends in the Dutch population[29]. Their analysis between incidence and hormonal influences did not show a positive correlation. In an attempt to evaluate the hormonal influence, data on the use of hormonal medication and history of pregnancy will be collected during the present study.

Intra-abdominal tumor depositions and personal or family history of FAP are among the exclusion criteria for the presented study. Intra-abdominal desmoid tumors are associated with FAP[30]. This association is suggestive of a different tumor biology compared to sporadic disease. In addition, intra-abdominal disease is related to a high mortality among FAP-patients and as such treated differently. To limit the risks associated with the present study, these patients are excluded from participation.

The occurrence of progression does not necessitate a switch to active treatment. In case the safety of the patient is compromised, for example due to organ involvement or increased pressure, a switch to active treatment will be recommended. In order to minimize the risk of compromised abilities due to tumor growth, the follow-up schedule allows for timely detection of tumor progression and patients with vital structures at risk will not be included in the study. The exclusion criteria prevent life threaten of functional impairment in case of tumor growth. Severe pain is considered to require continuous pain medication. Active treatment does not guarantee pain relief. As such, a watchful

waiting policy should be considered and discussed in patients experiencing degrees of pain. During the study period, we will monitor the considerations in switching treatment strategies.

An interim analysis will be performed after 1 year follow-up from the first 20 patients. This analysis is designed to validate the safety of the study. If too many patients deviate from the watchful waiting policy, this policy should be questioned. Due to the benign nature of this disease, we consider it safe if over 50% of the patients is still undergoing watchful waiting after 1 year of follow-up.

This study will provide insight in tumor behavior and clinicopathological factors predictive of tumor progression. The ability to predict tumor behavior would enable tailoring individual patient treatment.

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Funding

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Availability of data and materials

Information on the study can be found on www.grafiti-trial.nl (Dutch website). The datasets obtained during the study are available from the corresponding author on reasonable request.

Authors' contributions

A writing committee was formed for this study, to ensure a nationwide acceptance of the protocol and to facilitate implementation of the results. Specialists were asked to participate based on their role of expert in the Dutch sarcoma centers. They have given approval of the final study protocol before evaluation by the ethics committee. Three specialists will not act as principal investigator at their center and are mentioned under "Acknowledgements". CV is the project leader. DG, TvD and FvC were part of the writing

committee and are principal investigators. HB, LB, SD and MD are principal investigators. CC and AG have contributed to the study outline and are the principal investigator and project leader for the twin study in Milan. DvB is responsible for data collection and analysis. All authors have been involved in facilitating participation of the sarcoma centers. All read and approved the final manuscript.

Competing interests

The authors declare that they have no competing interests.

Ethical approval and consent to participate

The study has ethical approval from the Erasmus MC medical-ethical committee. Analysis of the manuscript was performed and approval for participation in the study was given by each center, based on either ethical approval or other guidelines in the specific centers. The study will be conducted in accordance with the ethical principles of the Declaration of Helsinki. The local investigator is responsible for the proper conduct of the study at the study site. Informed consent will be obtained for each participant at inclusion.

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Part 4

General discussion and future perspectives

Chapter 9

General discussion

(adjusted from “Abdominal Desmoid Tumors: Hands Off?”)

Epidemiology

Desmoid-type fibromatosis (DF) is a challenging disease. Insight in biology and understanding of epidemiology, incidence and treatments started over 30 years ago, when Finnish studies provided a foundation[1-3]. This foundation was dated and more insight in current epidemiologic trends and treatment related trends was imperative. Analysis of the Dutch population (reported in **chapter 2**) showed an increase from about two cases per million people in 1993 to about five cases per million people in 2013. Explanations for the rising incidence are not evident. Improved diagnostic modalities, better registration, awareness and screening programs are likely to influence these numbers. The possibility of a true rise in the incidence is made more likely by the observed changes of increased median age and female predominance, with a shift in tumor distribution. The driving factor for these observed changes is unclear. Direct correlations for etiological factors could not be explored and possible biases should be taken into consideration.

Treatment modalities

Treatment strategies for DF were similar to (malignant) soft tissue tumors. Radical surgery used to be the standard treatment, often combined with radiotherapy. The evidence for these aggressive treatment modalities is ambiguous. Reports of disease stabilization and spontaneous regression has tempered the use of surgery and radiotherapy. In addition, it underscores the poor understanding of the natural history of DF[4-6]. These reports have fueled the trend for primary conservative management, that is, an active surveillance approach. No established or evidence-based approach for the management of this neoplasm is available as of today. In order to interpret results of active surveillance in DF, the context of all treatment modalities is important.

Surgery has been the cornerstone in treatment of DF. The reported recurrence rate following resection varies greatly from 5 to 63 per cent [5,7], with most studies reporting recurrence rates around 20-25% [8-11]. In an attempt to predict the risk of recurrence, several study groups have analyzed patient and tumor characteristics for prognostic value. The reported results about importance of age, location, resection margins and adjuvant radiotherapy are conflicting[7,10,12-14]. In **chapter 3**, we report our results from a large Dutch cohort. The patients in the cohort were treated in a period of time when aggressive local treatment was routinely

performed. The 5-year risk of local recurrence was 18%. This relatively low percentage is partially explained by the uniform cohort of patients with primary disease, located in the abdominal wall or extra-abdominal structures. Many studies analyze primary and recurrent disease combined, or evaluate intra-abdominal DF as part of the cohort. Results should be stratified for these subgroups. Primary and recurrent disease are two different subtypes, as recurrent disease has already shown its nature to recur. Intra-abdominal disease has a different tumor biology and behavior, with a high mortality rate and should therefore be analyzed apart from extra-abdominal or abdominal wall disease.
Our results showed resection margin did not have an significant influence on the risk of recurrence, whereas age and localization did have a significant influence. These results underscore the nomogram drafted by Crago et al.[14].
The ambivalent results in several studies fuel the discussion on adjuvant treatment following microscopically irradical resection (R1). Radical resection (R0) is always strived for by the surgeon, sometimes by performing several surgeries to achieve radical resection margins. Our data provides an argument not to pursue microscopically tumor free resection margins (R0) at all (functional) costs.

Radiotherapy has been widely applied for desmoid tumors, both in primary and adjuvant settings. Results have been ambiguous, especially for adjuvant radiotherapy[7,11,13,15]. A comparative review by Nuyttens et al. showed significantly better local control rates with adjuvant radiotherapy, irrespective of resection margin width, in both primary and recurrent disease[16]. Despite these convincing results, the therapeutic benefits should be weighed against long term side effects of radiotherapy. In an attempt to provide more guidance, we performed a systematic review as described in **chapter 4**. Results showed improved local control rates for adjuvant radiotherapy in patients with microscopically irradicale resection (R1) in both primary and recurrent disease. These results support the use of adjuvant radiotherapy for local control after incomplete resection, with the nuances that in case of R1-resection, patients must be discussed in a multidisciplinary setting. Several adjuvant treatment strategies are possible, including the preferred active surveillance instead of radiotherapy.
A study by Keus et al. addressed the role of radiotherapy in a primary setting[17]. They reported partial and complete response in 50% of patients and stable disease in 41% of patients, with ongoing effect of radiotherapy after 3 years of follow-up. In **chapter 6**, we addressed the use of radiotherapy in the primary setting for patients with extra-abdominal DF. Complete or partial response was documented in 43% and stable disease

in 46% of patients. Progression of disease did not occur in the first 30 months of follow-up. Again, these results are promising for the effect of radiotherapy on DF and underscore its potential value. However, the possible long term effects should not be taken lightly in this intermediate grade disease.

Isolated limb perfusion (ILP) is reserved for patients with advanced disease in which surgery would lead to severe loss of function. This procedure is only performed in specialized centers. ILP is mostly applied in patients with sarcoma or melanoma and rarely used for DF. We combined data from three European sarcoma centers to evaluate the effect in DF, as described in **chapter 5.** Limb preservation was achieved in up to 88% of patients. The small number of patients (N=25) underscores the limited use of ILP in DF. Besides the needed experience to perform the procedure, it is also an indication that most patients do not have disease as advanced that they qualify. The aim of ILP is limb preservation with adequate function. Toxicity is often accepted to some degree, as amputation remains an option after ILP.

Literature on systemic treatment for DF is heterogeneous and limited. Anti-hormonal drugs, non-steroid anti-inflammatory drugs (NSAID's), chemotherapy and tyrosine kinase inhibitors have been applied in different regimes. Most studies consist of small cohorts, with a variation of systemic regimes. Randomised controlled trials are currently running with sorafenib (NCT 02066181) and pazopanib (NCT01876082).
With increasing knowledge on biology in DF and involved pathways, systemic treatment gains interest. As described in **chapter 6**, the use in common practice is very limited, thus hampering research. Selection bias should be taken into consideration when interpreting results. As first-line management, good results for systemic treatment were achieved with overall response and stabilization in 63% of patients. Patients in our cohort mostly received anti-hormonal drugs and NSAID's. Again, similar to radiotherapy, possible side effects and toxicity must be taken into account when considering systemic treatment.

Predicting behavior

The WHO is very clear in discriminating 3 subtypes of DF: extra-abdominal, abdominal (or abdominal wall) and intra-abdominal[18]. The biology and natural behavior for each subtype is different and thus requires different treatment. In addition, discrimination

between primary and recurrent disease is essential as recurrent disease has already proved to be more aggressive by recurring. Most studies in existing literature have mingled intra- abdominal tumors, tumors on the trunk, extremities and head/neck as well as primary and recurrent lesions and familial adenomatous polyposis (FAP) and non- FAP related. These heterogeneous reports lead to conflicting results regarding the biology and recommendations regarding management of these tumors.
Since the European consensus, an increasing number of centers have implemented active surveillance as primary treatment[19]. A recent article by Burtenshaw et al describes the effect of active surveillance on intra-abdominal and abdominal disease[20]. While they do stratify for primary and recurrent disease, intra-abdominal and abdominal DF, with or without FAP or pregnancy, were analyzed as one entity.

Literature consistently reports that patients with abdominal tumors have ideal outcomes regardless of treatment strategy. Intra-abdominal and abdominal DF likely have different inherent biology and distinction between these two subsets of patients is evolving in the literature. It is very likely that this is not one entity to treat; intra-abdominal DF need another approach. A recent study by Huss et al. investigated clinico-pathological and genetic features of intra-abdominal DF[21]. They found a difference in biology, as intra-abdominal tumors were solid, bulky, localized and originated from mesentery, whereas extra-abdominal and abdominal wall tumors were flat and growing in an infiltrating manner. Patient characteristics were different, as intra-abdominal tumors presented mostly in men, with a median age of 50. Abdominal tumors occur predominantly in fertile women.
Within the intra-abdominal disease, there is a difference between FAP and non-FAP related DF. In several publications of FAP associated intra-abdominal DF, surgical resection is associated with morbidity rates of 22–60%, perioperative mortality rates of up to 36% and recurrence rates of 65–88% [22-24]. Non-FAP-associated intra-abdominal DF can be resected with low morbidity and mortality rates in specialist centers, and is associated with low rates of local recurrence[25].
In non-FAP related DF, mutations in the *CTNNB1* gene are mostly present.
This distinction in subtypes might be applicable for more types of DF, such as pregnancy and non-pregnancy related DF[26].

Knowledge on genetic aspects of DF have increased our understanding of this disease. Patients with FAP have a genetic mutation in the *APC* gene. This gene is also involved in bowel cancer. FAP related DF harbor more genetic changes compared to sporadic DF, which

predominantly present *CTNNB1* mutations[27]. Three disease-specific *CTNNB1* mutations are recognized (T41A, S45F, 45P), each with their own characteristics and recurrence risks[28,29]. As such, genetics have become essential in predicting outcome of treatment. In **chapter 7** we reported results on the predictive value of *CTNNB1* mutations for recurrence after surgery. The differences in recurrence rates is remarkable and underlines the different behavior based on biology. Tumors with an S45F mutation have a higher risk of recurrence, which could be a sign of generally more aggressive behavior. The exact mechanism of different pathways in the pathogenesis of DF are not well understood. *CTNNB1* mutations can lead to increased beta-catenin levels, though these mutations have also been found in beta-catenin negative tumors. Perhaps the mutational status has a more elaborate role over beta-catenin levels[21].

Biological behavior remains a subject for future studies. Several study groups are investigating the behavior under active surveillance in a prospective manner [NCT01801176, NCT02547831]. In **chapter 8**, the Dutch study protocol is presented [NTR4714]. All specialized centers in the Netherlands are participating in this project. The protocol was drafted in collaboration with the Italian study group [NCT02547831]. The information from the studies will provide guidance to an individualized treatment strategy. The recent European consensus is the result of such collaboration and is now the guideline for treating desmoid tumors[19]. All types and locations are included. Different treatments are advised based on tumor location. In the European consensus, intra-abdominal tumors are included and regarded as different from all other types of locations, in line with WHO classification[18].

Knowledge on biology, epidemiology and treatment modalities for DF has greatly increased. Guidelines have been formed, weighing the prognostic value of several characteristics to assist decision making in disease management. A staging system that can stratify patients according to the severity of disease, is a prerequisite to understand the natural history, compare treatments, and delineate guidelines for a specific disease as DF. An attempt has been done by the Collaborative Group of the Americas on Inherited Colorectal Cancer (CGA-ICC) in 2005 for the management of patients with intra-abdominal DF[30]. There are additional variables that may interact with outcome (FAP, pregnancy associated, beta-catenin status, etc.). Larger multi-institutional experience must be gathered in the future for desmoid patients, which would be able to provide a more accurate assessment of different sites and clinico-pathological features as it pertains to outcome.

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Chapter 10

Future perspectives

Future perspectives

Knowledge on DF is improving, and improved knowledge is accompanied by more questions. The reasons for the rising incidence remain unclear. Diagnostic modalities will certainly improve and screening programs are likely to find more asymptomatic lesions. Along with the shift in tumor distribution, this will effect treatment strategies. In a young population, curative treatment with low toxicity is pursued. An older population might have a different interpretation of quality of life. As management of DF is changing, discrimination for age groups should be taken into account. Factors such as cosmetic results, duration of treatment and possible long term effects might be weighed differently by patients in different age groups. Although research is hampered by the low incidence, international collaborations will aid to improve high quality research and enrich knowledge.

Surgery has a risk of recurrence, which might be minimal in selected patients. As such, it could be an early and definite treatment, without extensive follow-up.
Radiotherapy has added value but the long term effects prevent physicians from using it frequently. Prediction tools are needed to predict the effect of radiotherapy in an individual. As *CTNNB1* mutations are a predictive tool for the effect of surgery, so might they be for radiotherapy or systemic treatment. In addition, tumor growth might be a predictor. More aggressive tumors are more likely to respond to radiotherapy or systemic treatment.
Insight on involved pathways in the pathogenesis of DF is increasing. Untouched subjects, such as mRNA, might be the key to understanding the mechanisms of systemic treatment. For now, it is a good option for patients with progressive disease who are not eligible for radiotherapy. The preferable duration of treatment remains unclear, though it is an important factor in the young population. As such, radiotherapy might be more appealing.
ILP should be reserved for patients with advanced disease. As this option should be evaluated, it is important patients should be treated in specialized centers. Current trends show a better concentration for care within specialized centers. In the future this will only increase, improving quality of care and facilitating high quality research.
Active surveillance is currently advised for all patients. This is generally a safe option, considering the intermediate nature of DF and generally slow growth. In addition, it helps the physician to select patients for further treatment and buys time for multidisciplinary evaluations.

Key questions in managing DF are when and how to treat. Importantly, expected benefits from therapy should be well balanced against potential treatment-induced untoward effects. The GRAFITI study is designed to better understand tumor behavior and to find factors which influence this behavior. If we are able to discriminate between aggressive and indolent behaving tumors at diagnosis, appropriate treatment strategies can be selected for the best result with minimal untoward effects.
A better understanding of tumor behavior leads to different goals of treatment. As DF behaves non-malignant in most patients, it is not essential to aggressively pursue total tumour irradication. Preservation of function and quality of life become the real goals of treatment and should be a key outcome in future studies. A possible framework could be provided by the PROFILES registry, which is a registry for the study of the physical and psychosocial impact of cancer and its treatment from population-based cohort of cancer survivors[1].

Treatment of DF has been and will remain a focus point for future research. The paradigm shift from surgery to conservative treatment was radical, but will balance itself out. Toxicity is a driving factor for current guidelines. In the future, guidelines will be more focused on the expected effect of treatment and quality of life. When analyzing common practice, it is noted that the paradigm shift is not as visible as advocated in the literature. Over the past 20 years, first-line non-surgical management has increased to up to 12.8% of Dutch DF patients. This indicates that until recently, surgery was considered the first-line treatment. Awareness of the paradigm shift in treating DF is indispensable, so centralization of these patients is mandatory.

Experience is essential in treating patients with DF. The years of experience with surgery and radiotherapy are not lightly put aside. Specialized centers are gaining experience by applying different treatment modalities and investigating clinico-pathogenetic factors. Combined, this will lead to a staging system that can stratify patients according to the severity of disease and thus create an individualized treatment strategy for each patient.

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Chapter 11

Nederlandse samenvatting

Epidemiologie

Desmoid-type fibromatose (DF) is een gecompliceerde en uitdagende ziekte. Inzicht in biologie en begrip van de epidemiologie, incidentie en behandelingen begon ruim 30 jaar geleden, toen Finse studies de fundamenten hebben gelegd[1-3]. Dit fundament was gedateerd en meer inzicht in de hedendaagse trends van epidemiologie en soorten behandelingen was noodzakelijk. In **hoofdstuk 2** beschrijven we een analyse van de Nederlandse bevolking. Er is een stijging van incidentie van circa 2 patiënten per miljoen mensen in 1993 naar circa 5 patiënten per miljoen mensen. Verklaring voor deze stijging is niet evident. Verbeterde diagnostische technieken, betere registratie, betere bekendheid van ziekte en diverse screening programma's dragen hoogstwaarschijnlijk bij aan deze stijging. De mogelijkheid van een ware incidentie stijging wordt meer aannemelijk gemaakt door de veranderingen in gemiddelde leeftijd, man-vrouw verhouding en de verandering in distributie van ziekte. De drijvende factor achter deze veranderingen is niet duidelijk. Directe correlaties tussen etiologische factoren konden niet worden uitgezocht en er moet rekening worden gehouden met mogelijke vertekeningen.

Behandelmodaliteiten

Behandelstrategieën voor DF waren gelijk met (kwaadaardige) weke delen tumoren. Radicale chirurgie was de standaard behandeling, vaak gecombineerd met radiotherapie. Het bewijs voor deze agressieve behandelingen is niet eenduidig. Berichten van stabilisatie van ziekte en spontane regressie hebben het gebruik van chirurgie en radiotherapie verminderd. Tevens onderschrijven deze berichten het slechte begrip van het natuurlijk beloop van DF[4-6]. Deze onderzoeken voeden de trend voor een primair conservatieve behandeling, namelijk actieve observatie[4-6]. Er is momenteel geen bewezen of wetenschappelijk onderbouwde benadering beschikbaar. Om de resultaten van de actieve observatie goed te interpreteren, is begrip en context van alle behandelmodaliteiten belangrijk.

Chirurgie is de hoeksteen in de behandeling van DF geweest. Het aantal recidieven na resectie varieert enorm, van 5 tot 63% [5,7], waarbij de meeste studies een recidiefpercentage van circa 20% beschrijven[8-11]. De prognostische waarde in de voorspelling van recidieven is onderzocht voor diverse factoren. Uitkomsten met betrekking tot leeftijd, locatie,

snijmarges en adjuvante radiotherapie zijn tegenstrijdig[7,10,12-14]. In **hoofdstuk 3** beschrijven we de resultaten van een Nederlands cohort. De patiënten werden behandeld in een tijd waar chirurgie de eerste keuze was in de behandeling. De kans op een recidief na 5 jaar was 18%. Dit relatief lage percentage is deels verklaarbaar door het uniforme cohort van patiënten met primaire ziekte, gelokaliseerd in de buikwand of extra-abdominale structuren. Andere studies beschrijven vaak een combinatie van primaire en recidiverende ziekte, of includeren patiënten met intra-abdominale ziekte. De resultaten moeten worden gestratificeerd voor deze subgroepen. Primaire en recidiverende ziekte zijn twee verschillende subgroepen, aangezien recidiverende ziekte al een agressiever gedrag vertoont door te recidiveren. Intra-abdominale ziekte heeft een afwijkende tumor biologie en gedrag, met een hoge mortaliteit en moet daarom apart worden geanalyseerd.
Onze resultaten toonden dat een radicale snijmarge geen significant effect had op het recidiefpercentage. Leeftijd en lokalisatie waren in univariate analyse wel van invloed, wat het nomogram opgesteld door Crago et al. onderstreept[14].
De tegenstrijdige resultaten voeden de discussie van adjuvante behandeling na irradicale resectie (R1). Een chirurg zal altijd streven naar een radicale resectie (R0), soms door meerdere operaties uit te voeren. Onze data bieden een argument om de radiale resectie niet ten koste van alles na te streven.

Radiotherapie wordt vaak gebruikt in de behandeling van DF, zowel in primaire als adjuvante setting. Ook hierin zijn de resultaten tegenstrijdig, met name voor adjuvante radiotherapie[7,11,13,15]. Een vergelijkende studie van Nuyttens et al. toonde een significant betere lokale controle met de toepassing van adjuvante radiotherapie, voor alle snijmarges en in zowel primaire en recidiverende ziekte[16]. Ondanks deze overtuigende resultaten moeten de therapeutische voordelen worden afgewogen tegen de lange termijneffecten van radiotherapie. In een poging om meer duidelijkheid hierin te krijgen, hebben we een systematische review gedaan van de recente literatuur, zoals beschreven in **hoofdstuk 4**.
De resultaten lieten verbeterde lokale controle zien bij gebruik van adjuvante radiotherapie in patiënten met een irradicale resectie (R1), zowel bij primaire als recidiverende ziekte. Deze resultaten ondersteunen het gebruik van adjuvante radiotherapie na incomplete resectie, met de nuance dat patiënten met een irradicale resectie moeten worden besproken in een multidisciplinaire setting. Verschillende adjuvante behandelingen zijn mogelijk, inclusief actieve monitoring in plaats van radiotherapie.
De rol van radiotherapie als primaire behandeling werd onderzocht door Keus et al.[17]. Zij rapporteren een partiële en complete respons in 50% van patiënten, en stabilisatie van

ziekte in 41%, met tevens een continuerend effect van de radiotherapie na 3 jaar controle. In **hoofdstuk 6** beschrijven we het gebruik van radiotherapie in de primaire setting voor patiënten met extra-abdominale DF. Complete of partiële respons werd gezien in 43% en stabilisatie in 46% van patiënten. Progressie van ziekte werd niet gezien in de eerste 30 maanden na bestraling. Opnieuw zijn deze resultaten veelbelovend en bevestigen het effect van radiotherapie. Echter moeten de lange termijneffecten niet worden onderschat bij deze niet-maligne ziekte.

Geïsoleerde ledemaat perfusie (ILP) is een behandeling welke enkel wordt toegepast in patiënten met vergevorderde ziekte, die kandidaat zijn voor amputatie. Deze behandeling wordt alleen toegepast in gespecialiseerde centra. ILP wordt vaker gebruikt in patiënten met sarcomen of melanomen, maar zelden voor DF. We hebben data gecombineerd van 3 gespecialiseerde, Europese centra en de resultaten beschreven in **hoofdstuk 5**. Het ledemaat kon behouden worden in 88% van de patiënten. De kleine groep patiënten (N=25) bevestigt het beperkte gebruik van ILP voor DF. Naast de benodigde ervaring om de behandeling uit te voeren, is dit ook een indicatie dat de ziekte vaak niet dusdanig vergevorderd is om patiënten in aanmerking te laten komen. Het doel van ILP is ledemaat behoud met een acceptabele functie. Toxiciteit wordt veelal in bepaalde mate geaccepteerd, omdat amputatie de enige andere optie is.

Literatuur betreffende de systemische behandeling is wisselend en beperkt. Anti-hormonale medicatie, niet-steroïde anti-inflammatoire medicatie (NSAID's), chemotherapie en tyrosine kinase remmers zijn beschreven in diverse combinaties. De meeste studies beschrijven kleine patiënt cohorten, met een variatie aan medicatie. Momenteel lopen er 2 gerandomiseerde studies naar het gebruik van sorafenib (NCT 02066181) en pazopanib (NCT01876082). Door toename van kennis op het gebied van biologie en pathogenese van DF, neemt de interesse in systemische behandelingen toe. Het gebruik van deze medicatie in de primaire setting is zeer beperkt. In **hoofdstuk 6** wordt het gebruik binnen Nederland beschreven. Het beperkte gebruik bemoeilijkt onderzoek. Vertekeningen in de selectie van patiënten moet worden meegewogen bij het interpreteren van de resultaten. Onze resultaten in de primaire setting waren goed, met respons en stabilisatie in 63% van de patiënten. Er werd meestal gebruik gemaakt van anti-hormonale medicatie en NSAID's. Echter moet ook hier worden gekeken naar de mogelijke bijwerkingen en toxiciteit van de middelen, wanneer deze behandeling wordt overwogen.

Gedrag voorspellen

De WHO is zeer duidelijk in het onderscheiden van 3 subtypes van DF: extra-abdominaal, abdominaal (buikwand) en intra-abdoinaal[18]. De biologie en het natuurlijk gedrag van elk subtype is anders en daarom is er een andere behandeling nodig. Daarnaast is onderscheid tussen primaire en recidiverende ziekte essentieel omdat recidiverende ziekte al bewezen agressiever is door te recidiveren. De meeste studies in de huidige literatuur combineren intra-abdominale tumoren, tumoren op de romp, ledematen en het hoofd/hals gebied, net als primaire en recidiverende laesies en familiaire adenomateuze polyposis (FAP) en niet-FAP gerelateerde ziekte. Deze heterogene verslagen leiden tot tegenstrijdige resultaten met betrekking tot de biologie en aanbevelingen voor de behandelingen van deze tumoren.
Met het vormen van een Europese consensus is er een stijgend aantal centra welke de actieve monitoring gebruiken als primaire behandeling[19]. Een recent artikel van Burtenshaw et al. beschrijft het effect van actieve monitoring op intra-abdominale en abdominale tumoren. Hoewel zij wel onderscheid maken tussen primaire en recidiverende ziekte, worden intra-abdominale en abdominale ziekte als 1 entiteit geanalyseerd, ongeacht FAP.

De literatuur beschrijft herhaaldelijk dat patiënten met abdominale tumoren een ideale uitkomst hebben, ongeacht de behandeling. Intra-abdominale en abdominale DF hebben zeer waarschijnlijk een andere biologie en onderscheid tussen deze subtypes van patiënten ontwikkelt zich in de literatuur. Het is zeer waarschijnlijk niet één entiteit om te behandelen: intra-abdominale DF heeft een andere benadering nodig. Een recente studie door Huss et al. onderzocht de clinicopathologische en genetische kenmerken van intra-abdominale DF[21]. Zij vonden een verschil in biologie; intra-abdominale tumoren waren solide, omvangrijk en mesenteriaal gelokaliseerd en ontstaan, terwijl extra-abdominale en abdominale tumoren plat waren en groeiden op een infiltratieve manier. Patiënt karakteristieken waren ook anders; intra-abdominale tumoren kwamen het meest voor in mannen, met een gemiddelde leeftijd van 50 jaar, terwijl abdominale tumoren voornamelijk ontstaan in vruchtbare vrouwen.
Binnen de intra-abdominale ziekte is er een onderscheid te maken tussen FAP en niet-FAP gerelateerde DF. Meerdere publicaties beschrijven een morbiditeitskans van 22-60% bij chirurgie, een kans op perioperatieve mortaliteit tot 36% en een recidiefkans van 65-88% voor FAP-gerelateerde intra-abdominale DF[22-24]. Niet-FAP gerelateerde intra-abdominale DF kan worden geopereerd met een lage morbiditeit- en mortaliteitkans in gespecialiseerde

centra, en is geassocieerd met een lagere recidiefkans[25].
In niet-FAP-gerelateerde DF komen vaak mutaties in het *CTNNB1*-gen voor.
Dit onderscheid in subtypes is mogelijk toepasbaar voor meerdere types van DF, zoals zwangerschap of niet-zwangerschap gerelateerde DF.

Kennis van de genetische aspecten van DF hebben ons begrip van deze ziekte vergroot. Patiënten met FAP hebben een genetische mutatie in het *APC*-gen. Dit gen is ook betrokken bij darmkanker. FAP-gerelateerde DF heeft meer genetische afwijkingen vergeleken met DF welke spontaan is ontstaan. Bij deze laatste groep is er vaak sprake van een mutatie in het *CTNNB1*-gen[27]. Er zijn drie *CTNNB1*-mutaties welke specifiek zijn voor DF (T41A, S45F, 45P), elk met eigen karakteristieken en recidiefkansen[28,29]. Deze genetische afwijken zijn een belangrijk onderdeel geworden in het voorspellen van de uitkomsten van behandelingen. In **hoofdstuk 7** beschrijven we de voorspellende waarde van *CTNNB1*-mutaties op de recidiefkans na chirurgie. De verschillen in recidiefkansen zijn opvallend en onderschrijven het verschil in gedrag gebaseerd op biologie. Tumoren met een S45F-mutatie hebben een hogere kans op recidieven. Dit kan een aanwijzing zijn voor een algeheel agressiever gedrag. Het exacte mechanisme van diverse wegen binnen de pathogenese van DF wordt nog niet goed begrepen. *CTNNB1*-mutaties kunnen leiden tot verhoogde beta-catenine spiegels, terwijl deze mutaties ook worden gezien in tumoren met lage beta-catenine spiegels. Wellicht heeft de mutatie een belangrijkere rol vergeleken met de beta-catenine spiegel[21].

Het biologisch gedrag blijft een belangrijk onderwerp voor toekomstige studies. Enkele studiegroepen onderzoeken momenteel het natuurlijke gedrag van DF tijdens actieve monitoring in een prospectieve setting [NCT01801176, NCT02547831]. In **hoofdstuk 8** is het Nederlandse studieprotocol beschreven [NTR4714]. Alle gespecialiseerde centra binnen Nederland doen mee aan dit onderzoek. Het protocol is opgesteld in samenwerking met de Italiaanse studiegroep [NCT02547831]. De informatie uit deze studies zal richting geven aan patiënt-specifiek behandelplannen. De Europese consensus is ook de uitkomst van een dergelijke samenwerking, en is nu de richtlijn voor de behandeling van DF[19].
Alle types en lokalisaties van DF worden geïncludeerd. Verschillende behandelingen worden geadviseerd, afhankelijk van tumor lokalisatie. In deze consensus worden intra-abdominale tumoren ook meegenomen, maar worden beschouwd als anders ten opzichte van de andere lokalisaties, in overeenstemming met de WHO classificatie[18].

Kennis van biologie, epidemiologie en behandelmodaliteiten is aanzienlijk toegenomen. Er zijn richtlijnen gevormd, waarbij de prognostische waarde van diverse karakteristieken wordt meegenomen in het maken van beslissingen over de behandelstrategie. Een stadiëringssysteem wat patiënten kan verdelen op basis van ernst van de ziekte, is een voorwaarde om het natuurlijk beloop te begrijpen, behandelingen te vergelijken en richtlijnen op te stellen voor een zeldzame ziekte als DF. Een opzet hiervoor is gemaakt voor intra-abdominale DF in 2005 door de Samenwerkende Groep van de Amerikanen voor Erfelijke Colorectaal Kanker (Collaborative Group of the Americas on Inherited Colorectal Cancer; CGA-ICC)[30]. Er zijn aanvullende waarden die mogelijk invloed hebben op de uitkomst (FAP, zwangerschap, beta-catenine status, et cetera). Grote multi-institutionele onderzoeken moeten worden uitgevoerd waarbij de ervaring moet worden verzameld voor DF patiënten. Daarmee zijn we in staat om een meer nauwkeurige evaluatie van de verschillende lokalisaties en clinicopathologische kenmerken uit te voeren, welke van invloed zijn op de uitkomst van behandelingen.

Toekomst perspectieven

De kennis over DF neemt toe, en hiermee nemen ook de vragen toe. De oorzaken van de toegenomen incidentie zijn onduidelijk. Diagnostische modaliteiten zullen zeker verbeteren en screening programma's zullen waarschijnlijk meer asymptomatische laesies vinden. Samen met de verandering van ziektedistributie tussen de leeftijds-groepen, zal dit effect hebben op de behandelstrategieën. In een jonge populatie wordt een curatieve behandeling met lage toxiciteit nagestreefd. Een oudere populatie heeft mogelijk een andere interpretatie van kwaliteit van leven. Nu de behandeling van DF aan het veranderen is, moet een onderscheid tussen de leeftijdsgroepen worden meegenomen. Factoren zoals cosmetische resultaten, duur van de behandeling en mogelijke lange termijneffecten hebben wellicht een andere waarde voor patiënten in andere leeftijdsgroepen. Hoewel het onderzoek wordt bemoeilijkt door de lage incidentie, zullen de internationale samenwerkingen bijdragen aan een hoge kwaliteit van onderzoek en toename van kennis.

Chirurgie heeft een recidiefkans, welke mogelijk minimaal is bij een specifieke groep patiënten. Voor hen zou chirurgie een vroege en definitieve behandeling kunnen zijn, zonder langdurige controles.

Radiotherapie heeft een toegevoegde waarde in de behandeling, maar de lange termijneffecten zorgen ervoor dat artsen terughoudend zijn in het gebruik hiervan. Er zijn handvaten nodig om het effect van radiotherapie bij patiënten te voorspellen. Waar *CTNNB1*-mutaties een dergelijk handvat bieden voor chirurgie, kunnen ze dat wellicht ook voor radiotherapie en systemische therapie. Daarnaast zou de mate van groei een voorspellende factor kunnen zijn. Agressievere tumoren zijn doorgaans gevoeliger voor radiotherapie of systemische therapie.
Inzicht in de verschillende wegen van pathogenese van DF neemt toe. Nog niet besproken factoren, zoals mRNA, kunnen de sleutel zijn voor het begrijpen van de werkings-mechanismen van systemische behandelingen. Momenteel is de systemische behandeling een goede optie voor patiënten met progressieve ziekte die geen kandidaat zijn voor radiotherapie. De gewenste duur van de behandeling is nog onduidelijk, hoewel dit vaak wel belangrijk is voor de jonge populatie. Daardoor kan radiotherapie mogelijk een aantrekkelijkere optie zijn.
Actieve monitoring wordt momenteel geadviseerd voor alle patiënten. Het is in het algemeen een veilige optie, gezien de niet-maligne aard van de ziekte en doorgaans trage groei. Daarbij helpt het de arts om patiënten te selecteren voor aanvullende behandelingen en om tijd te winnen voor multidisciplinaire besprekingen.
ILP dient te worden gereserveerd voor patienten met vergevorderde ziekte. Omdat deze optie wel meegenomen moet worden, horen patienten te worden behandeld in gespecialiseerde centra. Huidige trends tonen een betere concentratie van zorg binnen gespecialiseerde ziekenhuizen. In de toekomst zal dit nog verder toenemen, wat de kwaliteit van de zorg bevordert en kwalitatief onderzoek faciliteert.

Sleutelvragen in de behandeling van DF zijn wanneer en hoe te behandelen. Het is belangrijk om de verwachtte voordelen af te wegen tegen de potentiele gevolgen van de behandeling. De GRAFITI studie is opgezet om een beter begrip van het natuurlijk beloop van ziekte te krijgen en om factoren te identificeren welke het beloop beïnvloeden. Als we onderscheid kunnen maken tussen agressieve en indolente tumoren ten tijde van de diagnose, kunnen gerichte behandelingen worden toegepast voor het beste resultaat met minimale risico's. Een beter begrip van het natuurlijk gedrag leidt tot andere doelen van de behandeling. Omdat DF zich in de meeste patiënten niet kwaadaardig gedraagt, is het niet essentieel om agressief de tumor volledig te verwijderen. Behoud van functie en kwaliteit van leven worden de nieuwe doelen van de behandeling en zouden de belangrijkste uitkomst moeten zijn in toekomstige onderzoeken. Een mogelijk raamwerk wordt geboden door

het PROFILES register. Dit is een register om te kijken naar de fysieke en psychosociale gevolgen van kanker en de behandeling van kanker vanuit een landelijke groep van kankerpatiënten[31].

De behandeling van DF is en blijft een aandachtspunt voor toekomstige onderzoeken. De fundamentele verandering van chirurgie naar conservatieve behandeling was zeer radicaal, maar zal zichzelf uitbalanceren. Toxiciteit is de leidende factor binnen de huidige richtlijnen. In de toekomst zullen de richtlijnen zich meer richten naar de verwachtte uitkomst van behandelingen en kwaliteit van leven. Kijkend naar de huidige praktijk wordt duidelijk dat de fundamentele verandering niet zo zichtbaar is als wordt geadviseerd in de literatuur. Gedurende de afgelopen 20 jaar is het percentage van niet-chirurgische behandeling als eerste behandeling toegenomen tot 12.8% in Nederland. Dit geeft aan dat chirurgie als eerste behandeling werd toegepast tot recent. Bewustwording van deze fundamentele verschuiving is onmisbaar in de behandeling van DF patiënten, waarbij de centralisatie van zorg een vereiste is.

Ervaring is essentieel bij het behandelen van patiënten met DF. De jaren ervaring met chirurgie en radiotherapie worden niet makkelijk opzij geschoven. Gespecialiseerde centra verwerven meer ervaring met diverse behandelmodaliteiten en onderzoeken daarnaast de clinicopathologische factoren. Deze combinatie zal leiden tot een stadiëringssysteem waarbij een onderscheid kan worden gemaakt in de ernst van ziekte per patiënt. Zo kan een geïndividualiseerde behandelingsstrategie voor elke patiënt worden opgesteld.

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Appendices

List of publications

van Broekhoven DLM, Verhoef C, Elias SG, Witkamp AJ, van Gorp JMHH, van Geel BAN, Wijrdeman HK, van Dalen T. Local recurrence following surgical treatment for primary extra-abdominal desmoid-type fibromatosis. British Journal of Surgery 2013 Aug; 100(9): 1214–19.

van Broekhoven DLM, Deroose JP, Bonvalot S, Gronchi A, Grünhagen DJ, Eggermont AMM, Verhoef C. Isolated limb perfusion by tumor necrosis factor alpha and melphalan in patients with advanced aggressive fibromatosis. British Journal of Surgery 2014 Dec; 101(13):1674-80.

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van Broekhoven DLM, Grünhagen DJ, van Dalen T, van Coevorden F, Bonenkamp HJ, Been LB, Bemelmans MH, Dijkstra SD, Colombo C, Gronchi A, Verhoef C. Tailored Beta-catenin mutational approach in extra-abdominal sporadic desmoid tumor patients without therapeutic intervention. BMC Cancer 2016 Aug;16:686

van Broekhoven DLM, Grünhagen DJ, Verhoef C. Abdominal demoid tumors: Hands off? Annals of Surgical Oncology 2016 Jul;23(7):2128-30.

van Broekhoven DLM, Verschoor AJ, van Dalen T, Grünhagen DJ, den Bakker MA, Gelderblom AJ, Bovee JVMG, Haas RLM, Bonenkamp JJ, van Coevorden F, ten Oever D, van der Graaf WTA, Flucke UE, Pras E, Reyners AKL, Westermann AM, Oldenburger F, PALGA group, Verhoef C, Steeghs N. Outcome of non-surgical management of extra-abdominal, trunk and abdominal desmoid-type fibromatosis: a population based study in the Netherlands. *Submitted.*

Janssen ML, **van Broekhoven DLM**, Cates JMM, Bramer WM, Nuyttens JJME, Gronchi A, Baumert BG, Salas S, Bonvalot S, Ihalainen HR, Grünhagen DJ, Verhoef C. The influence of surgical margin and adjuvant radiotherapy on local control after resection of sporadic desmoid-type fibromatosis: a systematic review and meta-analysis. *Accepted for publication in British Journal of Surgery.*

PhD portfolio

Name PhD student: D.L.M. van Broekhoven
Erasmus MC Department: Surgical Oncology
Promotor: prof.dr. C. Verhoef, MD, PhD
PhD period: August 2013 – July 2015
Supervisors: dr. D.J. Grünhagen, MD, PhD, dr. T. van Dalen, MD, PhD

	Year	ECTS
PhD training		
General academic skills		
BROK 'Basiscursus Regelgeving Klinisch Onderzoek'	2014	1.5
Cursus Wetenschappelijke Integriteit	2013	0.3
Oral presentation		
CTOS Annual Meeting. Salt Lake City, Utah, USA	2015	2.0
SPAEN Annual Meeting. Amsterdam	2014	1.0
CTOS Annual Meeting. Berlin, Germany	2014	2.0
ESSO / BASO Conference. Liverpool, UK	2014	2.0
SSO Annual Meeting. Phoenix, Arizona, USA	2014	2.0
SSO Annual Meeting. Orlando, Florida, USA	2012	2.0
Daniel den Hoed Research Meeting. Rotterdam	2013	1.0
NVvH Najaarsdag. Veldhoven	2013	1.0
Sarcomendag NL. Leiden	2013	1.0
Regionale refereeravond. Utrecht	2012	1.0
Poster presentation		
NVvP Pathologendagen. Amsterdam	2014	1.0
NVvH Najaarsdag. Veldhoven	2011	1.0
Teaching activities		
Supervising Master's thesis Graduate student	2015	5.0
Other		
Reviewer Tumori	2015	1.0

Curriculum vitae

Danique Louise Maria van Broekhoven werd geboren op 21 juni 1987 te Rijen. Ze groeide op als jongste van het gezin, met een oudere zus en broer. In 2005 ronde ze het eindexamen af aan de Nassau Scholengemeenschap in Breda. Datzelfde jaar werd ze ingeloot voor de studie Geneeskunde in Utrecht en kon ze aan haar droomopleiding beginnen: dokter worden. Haar afstudeeronderzoek bij de chirurgie werd een samenwerking van het Diakonessenhuis te Utrecht en het Erasmus MC te Rotterdam. In 2012 behaalde ze het artsenexamen. Aansluitend werkte ze als arts-assistent in het Diakonessenhuis te Utrecht.

In 2013 werd de samenwerking van het afstudeeronderzoek uitgebreid en startte ze met het promotieonderzoek naar desmoid tumoren, onder supervisie van prof.dr. C. Verhoef, dr. T. van Dalen en dr. D.J. Grünhagen. Dit proefschrift is hiervan het resultaat. Na 2 jaar fulltime onderzoek, werkte ze een jaar in het RadboudUMC als assistent orthopedie.

In 2017 hoopt ze te starten met de opleiding tot orthopedisch chirurg.

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