Familial Cancer (2016) 15:31–40
DOI 10.1007/s10689-015-9830-z

ORIGINAL ARTICLE

Long-term outcome of sporadic and FAP-associated desmoid tumors treated with high-dose selective estrogen receptor modulators and sulindac: a single-center long-term observational study in 134 patients

Daniel Robert Quast[1] · Ralph Schneider[2] · Emanuel Burdzik[3] · Steffen Hoppe[4] · Gabriela Möslein[2]

Published online: 15 August 2015

Abstract Aim of this study is to evaluate the outcome of long-term conservative treatment with sulindac and high-dose selective estrogen receptor modulators (SERMs) for sporadic and FAP-associated desmoid tumors. Desmoids are very rare tumors in the general population but occur frequently in FAP patients, being encountered in 23–38 %. Treatment of desmoids is still most controversial since response cannot be predicted and they are prone to develop recurrence. This study included all desmoid patients that were treated and followed at our institution and had completed at least 1 year of treatment. Response was defined as stable size or regression of desmoid size between two CT or MRI scans. A total of 134 patients were included. 64 (47.8 %) patients had a confirmed diagnosis of FAP, 69 (51.5 %) patients were sporadic. Overall 114 (85.1 %) patients showed regressive or stable desmoid size. Patients with previous history of multiple desmoid-related surgeries showed less-favorable response. The mean time to reach at least stable size was 14.9 (±9.1) months. After regression or stabilization, medication was tapered in 69 (60.5 %) of the treated patients with only one long-term recurrence after >10 years. The results of this study fortify the role of sulindac and high-dose SERMs as an effective and safe treatment for both, sporadic and FAP-associated desmoid tumors. While invasive treatment frequently results in high recurrence rates, high morbidity and high mortality, this conservative treatment is successful in most patients. The recurrence rate is negligible with no desmoid-related mortality in this large series. Therefore surgical resection, especially for mesenteric desmoids, should be deferred favoring this convincingly effective, well tolerated regimen.

Keywords Desmoid · Aggressive fibromatosis · Fap · Familial adenomatous polyposis · Tamoxifen · Sulindac

Introduction

Desmoids (also referred to as aggressive fibromatosis) are rare tumors deriving from the mesenchymal sheath, known for aggressive growth and, despite lacking frequent mitotic forms and cellular atypia, locally fulfill the malignant criteria of invasive growth. They are unable to metastasize but frequently develop life threatening infiltrative growth and may lead to severe morbidity and also mortality. Sources estimate that desmoids account only for 0.03 % of all tumors [1]. Their incidence is estimated to be 2–4 cases per one million per year [2]. Patients diagnosed with familial adenomatous polyposis (FAP) are known to be predisposed for desmoid tumors with a 1000-fold higher risk compared to the normal population [3, 4]. FAP is an autosomal dominant syndrome caused by a germline mutation of the adenomatous polyposis coli (APC) gene and is characterized by hundreds to thousands of colorectal adenomas and frequent

✉ Daniel Robert Quast
Daniel.quast@rub.de

Gabriela Möslein
gabriela.moeslein@helios-kliniken.de

1 Klinik für Allgemeine Innere Medizin - Medizinische Klinik I, St. Josef-Hospital, Gudrunstr. 56, 44791 Bochum, Germany

2 Klinik für Hereditäre Tumorerkrankungen, HELIOS-Klinikum Wuppertal, Heusnerstr. 40, 42283 Wuppertal, Germany

3 Klinik für Allgemein- und Viszeralchirurgie, Evangelisches Krankenhaus Bethesda zu Duisburg, Heerstraße 219, 47053 Duisburg, Germany

4 Klinik für Radiologie, HELIOS St. Josefs-Hospital Bochum-Linden, Axstr. 35, 44879 Bochum, Germany

extracolonic manifestations [5]. Although the true prevalence of desmoids among these patients remains unclear, studies report an overall prevalence of up to 30 %, rising to 38 % in high risk sub-groups [1, 6–13].

The underlying pathogenetic mechanism has yet to be identified. However, several risk factors are well established. Trauma, including surgical interventions such as prophylactic colorectal surgery in FAP patients, is known to trigger desmoid growth. The prevalence of desmoids in FAP patients increases after surgical interventions [14]. When desmoids are removed surgically, a positive surgical resection margin is a risk factor for recurrence [11, 15]. Generally, high estrogen levels are suspected to promote growth since desmoid incidence is significantly higher in young females. Desmoid prevalence is lower in males and postmenopausal women and when they occur in these patients, their growth pattern is generally slower [16, 17]. Furthermore, pregnancy or the use of oral contraceptives increase the risk of desmoid development in the general population [16, 18]. The role of gender and pregnancy for desmoid occurrence in FAP-patients remains controversial with some studies contradicting female predominance [19, 20]. However, most studies describe female gender or pregnancy as predisposing risk factors [8, 10, 21–23].

Sporadic desmoids often present in the abdominal wall, extremities and head and neck area [24, 25], whereas FAP-associated desmoids are found mostly in the small bowel mesentery after prophylactic colectomy or in the abdominal wall, mainly close to the incision line [9, 11, 14, 21]. The site of the genetic mutation in FAP patients seems to influence desmoid localization, while this effect appears to be of more importance in female patients [23]. Generally, a 3′ mutation beyond codon 1444 was reported to be associated with increased desmoid occurrence [26–28]. In families with a positive history of desmoids there is a higher desmoid incidence even when a mutation in the high-risk location for desmoids of the APC gene is lacking [10, 21]. Therefore a positive family history is regarded as independent risk factor.

Well-established treatment of desmoids includes surgery, radiation and pharmacological approaches. Surgery is performed especially in localized extra-abdominal or abdominal wall tumors [29, 30]. Small series report a low rate of recurrence or low morbidity after surgical desmoid resection [30, 31]. By contrast, other studies describe high recurrence rates from up to 85 % and recurrent and increasingly aggressive growth after surgical interventions [1, 32–35]. Primary or adjuvant radiotherapy is mainly applied in extra-abdominal tumors and/or a positive surgical margin after resection, leading to reduced recurrence rates in these cases [35, 36]. Pharmacological approaches include cytotoxic chemotherapy [37], imatinib [38], interferones [39], sorafenib [40], non-steroidal anti-inflammatory drugs (NSAIDs) [41] and Selective Estrogen Receptor Modulators (SERMs) [42].

FAP associated desmoids are known to express cyclooxygenase 2 [43]. Sulindac is a NSAID akin with indomethacin and inhibits the cyclooxygenase via its active metabolite sulindac-sulfide. Temporary reduction of adenomas in the colon and rectum has been described in FAP-patients [5]. Several case reports and small series reporting successful treatment of desmoids with sulindac as a monotherapy may be found in literature. A characteristically delayed response is observed in these cases. However, to our knowledge no randomized-controlled study has been published [4, 44, 45].

Tamoxifen, raloxifene and toremifene are SERMs, demonstrating both selective agonistic and antagonistic effects on estrogen receptors, depending on the target tissue. Whilst endometrial cancer is described to be a major side effect of tamoxifen in the mouse model, raloxifene lacks estrogen-like stimulation of the uterus, therefore preventing an increased endometrial cancer risk [46]. For toremifene epidemiological studies display slightly less side effects than tamoxifen at comparable response rates [47].

Brooks et al. [48] described the therapeutic use of SERMs in desmoids, using tamoxifen and toremifene dosages up to 200 mg per day with a response rate of 65 % and only few side effects. Further literature reports comparable observations with high-dose tamoxifen and raloxifene [49–52]. According to these studies, high-dose SERMs are more effective than lower dosages.

Desmoids were analyzed histopathologically in order to identify the mechanism of SERMs in desmoid response. Most desmoids were estrogen receptor (ER) alpha negative, whereas ER beta was identified in up to 100 % of investigated desmoids [53–55]. Interestingly in both, ER alpha negative and positive desmoids, therapy with SERMs proved effective on inhibiting desmoid growth [42, 55]. Possible explanations for response to SERMs despite negative ER alpha status could be either the finding of a large number of anti estrogen binding sites in microsomal fractions of ER alpha negative desmoids or the indirect influence on growth factors [56, 57]. Expression of ER beta might also explain the inhibiting influence of SERMs on the tumor [54, 55]. Nonetheless the exact mechanism leading to response remains unknown.

Patients and methods

Patients

In our institution, all patients with the diagnosis of a desmoid tumor were treated following the guidelines for

clinical management for FAP [5]. FAP patients with a small (<1 cm) asymptomatic extraabdominal desmoid detected at follow up post colectomy were subjected to a watch and wait approach and therefore not treated and not included in this series. All other patients with the diagnosis of a desmoid tumor received medication unless an absolute contraindication was identified (e.g. advanced liver disease), following the principle of a primary standardized approach. The dosage was administered regardless of initial size, location, or previous treatment including previous desmoid surgeries. No difference was made regarding presence or absence of FAP. A minimum treatment period of 1 year was defined as inclusion criteria, since a characteristic prolonged time to response is known and has been described by our group in a preceding paper. This study also includes the long-term follow-up of the patients reported by our group in 2003 [4].

Diagnosis

In FAP-patients clinical diagnosis during follow-up with CT- or MRI-imaging or intraoperative diagnosis was regarded as sufficient, following the guidelines for clinical management for FAP [5]. In sporadic desmoid patients a histopathological confirmation of the diagnosis was obligatory, particularly with regard to differential diagnoses such as malignant mesenchymal tumors.

Drug regimen

Our standard treatment is based on our initial results published by Hansmann et al. [4]. We follow the algorithm as proposed in 2003 which implies incremental dosage of SERMs as shown in Table 1 and a dosage of 300 mg sulindac per day (100 mg 3x/day) [58]. The theory behind incremental dosing is to allow hormonal regulatory circuit adaptation and to ease potential side effects. Tapering of medication was initiated after at least 1 year of quiescent disease or continuing reduction in size, allowing approximately 3 months for each of the total of three steps of reduction. The dosage of the specific SERM was halved until the starting dosage was reached, then medication was discontinued. Tapering medication enables early detection of recurrent growth and allows the patient's hormonal balance to adjust. Tamoxifen, raloxifene and toremifene were regarded as equally potent in treatment [48–52]. The selection of the drug was done in consideration of possible side-effects: female patients were preferably treated with raloxifene, reducing the risk of endometrial cancer and ovarian cysts. In male patients, treatment with tamoxifen was favored.

Statistic methods

Categorical data was analyzed using two-sided Fisher's exact test. Confidence interval (CI) was calculated using the modified Walt method. Level of significance $\alpha = 0.05$, 95 % CI respectively. Age is reported as mean (±SD). Continuous data was analyzed using unpaired t test. Statistical analyses were performed using SPSS Version 19 (SPSS Inc., Chicago, IL, USA).

Outcome

Outcome was categorized in desmoid-related death (DD, invasive growth or other complications leading to death), progressive disease (PD, every radiologically confirmed increase of size compared with the previously recorded imaging), stable disease (SD, no radiologically confirmed increase or decrease of size compared with the previously recorded imaging), partial regression (PR, every radiologically confirmed decrease of size compared with the previously recorded imaging) and complete remission (CR, no radiological correlate of a former described desmoid). When a patient suffered from multiple desmoids or diffuse growth, e.g. in mesenteric desmoids, the outcome was categorized using cross sectional area. Complications such as bowel obstruction were always regarded as progressive disease. If a patient deceased of other etiology than a desmoid-associated cause, the last recorded staging was considered for outcome. Staging was performed according to the DES classification [4]. In all cases we performed a regular follow-up via CT- or MR-imaging at least every 6 months during the first 2 years of treatment and every 12 months in the further follow-up until sustained stable disease was documented or the patient deceased. Clinically, for this study, stable disease was regarded as response and therapeutic success.

Table 1 SERM dosing

	Dose/day Week 1 (mg)	Dose/day Week 2 (mg)	Dose/day Week 3 (mg)	Dose/day Week 4 (target dose) (mg)
Tamoxifen	30	60	90	120
Raloxifene	60	120	180	240
Toremifene	30	60	90	120

Results

Patients

A total of 134 patients were included of which 64 (47.7 %) had the diagnosis of FAP. 70 (52.3 %) patients were sporadic patients. One male patient had an MSH-2 mutation, leading clinically to the diagnosis of Muir–Torre syndrome and was regarded as sporadic. 46 (71.9 %, CI 0.598–0.814) FAP-patients were female and 18 (28.1 %, CI 0.185–0.402) were male whereas in the sporadic group 44 (62.9 %, CI 0.511–0.732) were female and 26 (37.1 %, CI 0.267–0.488) male. The higher percentage of males in the sporadic group was not statistically significant ($p = 0.27$). Overall, a female: male ratio of approximately 2:1 with 90 female (67.2 %, CI 0. 588–0.745) and 44 (32.8 %, CI 0.254–0.411) male patients was noted. Patients' age at diagnosis deviated significantly ($p = 0.04$) between these groups. FAP-patients were diagnosed at an earlier age of 39.69 (±13.6) years while patients without FAP were diagnosed at 44.61 (±14.3) years. For the whole cohort the mean age at diagnosis was 35.54 (±13.7) years. The longest desmoid follow-up patient included was diagnosed in January 1989. Overall patients had a mean follow-up after diagnosis of 7.12 (±4.5) years. Non-FAP-patients had a mean follow-up of 7.9 (±4.0) years, resulting in a significantly longer period than FAP-patients' follow-up [6.3 (±5.0) years] ($p = 0.0001$).

Pregnancy

Five (5.6 %) of all female patients developed desmoids after delivery. The mean time from delivery to the diagnosis of a desmoid was 15.4 (±8.3) months. 3 (60 %) women had underlying FAP; all of these presented with mesenteric desmoid formation. Only one (20 %) of these patients had previous colectomy, 5 years before delivery. Of the 2 (40 %) women without FAP, one also developed an intraabdominal desmoid whereas the other had an abdominal wall desmoid only. Raloxifene was administered in all five cases. All patients responded to treatment [2 (40 %) with SD, 3 (60 %) with PR] in a mean time of 13.4 (±6.8) months, independently of c-section or vaginal birth.

Localization

In FAP-patients, 38 (59.4 %) had intraabdominal, 33 (51.6 %) had abdominal wall and 11 (17.2 %) had extraabdominal manifestations. 15 (23.4 %) of all FAP patients had desmoids in at least two separate sites. For patients with sporadic tumors the main localization was extraabdominal with 46 (65.7 %) whereas 21 (30 %) of these patients had abdominal wall and only 5 (7.1 %) had intraabdominal desmoids. 15 (88.3 %) of the total 17 (12.7 %) patients with multiple tumors had underlying FAP. In the entire cohort 57 (42.5 %) had extraabdominal manifestations, abdominal wall desmoids were present in 54 (40.3 %) and intraabdominal desmoids in 43 (32.1 %) of patients. FAP patients demonstrated a statistically significantly increased manifestation of intraabdominal desmoids ($p < 0.01$) and multiple occurrences of desmoids ($p < 0.01$). Sporadic patients had significantly more extraabdominal desmoids ($p < 0.01$). No difference was found between the groups for the localization of abdominal wall desmoids ($p = 0.17$).

Prophylactic surgery in FAP patients

Prophylactic colorectal surgery had been performed prior to desmoid diagnosis in 59 (92.2 %) of the FAP patients at a mean age of 29.7 (±12.4) years. Proctocolectomy (PCE) predominated the surgical procedures with a total of 50 (84.7 %) patients. Initially 14 (23.7 %) of the FAP patients had an ileorectal anastamosis (IRA) but 7 (50 %) required completion surgery due to excessive polyp growth in the remaining rectal remnant. These patients were included in the pouch group, but numbers of prior surgeries take this condition into account. The mean time between IRA and secondary PCE was 148.3 (±105.5) months. Of the patients with PCE, 4 (8 %) underwent a redo pouch reconstruction after the primary operation. Of these patients three had an unsatisfactory pouch function while one patient developed multiple pouch adenomas. The mean time to pouch resection or reconstruction in this group was 147.7 (±129.5) months. PCEs overall had significantly less secondary surgeries than IRAs ($p < 0.01$). Primary end-ileostomy (IST) was performed in 2 (3.4 %) patients only. Symptomatic desmoid occurrence was noted in 8 (13.6 %) FAP patients prior to any abdominal surgery, mean 73 (±63.1) months before prophylactic colectomy. The other 51 (86.4 %) FAP patients developed desmoid growth following prophylactic surgery, in average 64.1 (±80) months after surgery and ranging from 0 (intraoperative diagnosis of asymptomatic desmoid) to 309 months. 51 (73.9 %) of the sporadic desmoid patients have a documented history of previous surgery close to the site of desmoid development.

Previous desmoid treatment

Overall 31 (48.4 %) of FAP patients were referred to us with history of desmoid-related surgical interventions. 33 (51.6 %) patients had been managed conservatively without desmoid surgery and/or were diagnosed at our

institution. The attempt of surgical resection was more frequent in the sporadic setting, affecting 50 (71.2 %) of sporadic desmoid patients leaving 20 (28.8 %) without a surgical intervention other than biopsy. All sporadic desmoid patients had been subjected to histological verification of the diagnosis. Surgical desmoid treatment was attempted less frequently in the group of known FAP patients ($p < 0.01$). The total number of patients treated surgically for their sporadic or FAP-related desmoid at least once (not including biopsies) was 81 (60.4 %).

Before referral, 23 (17.1 %) were treated with radiotherapy and 14 (10.4 %) had other chemotherapeutic agents. 27 (20.1 %) of the reported patients were treated with a combination of chemotherapy, radiotherapy or surgery before referred to us with recurrent disease. The total number of patients with previous treatment and recurrent disease before being referred to our institution was 91 (67.9 %).

Sulindac and SERMs

Three different estrogen receptor-modulating agents were administered in this study: 68 (50.7 %) patients received tamoxifen, 61 (45.5 %) received raloxifene and 5 (3.7 %) received toremifene. In three (2.2 %) patients the medication was changed for better tolerability due to hot flashes and nausea. Among FAP-patients, 27 (42.2 %) were treated with tamoxifen, 33 (51.6 %) were treated with raloxifene and 4 (6.3 %) were treated with toremifene. In the sporadic patients 41 (58.6 %) received tamoxifen, 28 (40 %) patients received raloxifene and one (1.4 %) patient received toremifene. With 60 (66.7 %) the majority of female patients (premenopausal) received raloxifene, while 25 (27.8 %) were treated with tamoxifen (postmenopausal) and 5 (5.6 %) received toremifene. By contrast 43 (97.7 %) of the male patients received tamoxifen leaving one (2.3 %) of the male patients treated with raloxifene.

Common side effects attributed to SERMs were ovarian cysts, detected with significant size in 9 (10 %) of all female patients. Two (2.9 %) patients suffered tamoxifen-induced retinopathy but had already reached stable disease, so that medication was successfully discontinued without desmoid recurrence. Other minor side effects encountered were nausea, hot flushes and dyspepsia. For sulindac, 2 (1.5 %) of the patients showed high elevations in liver function tests, leading to dose reduction. Generally, venous thrombosis was found in 3 (2.2 %) patients in long-term hospitalized conditions.

Outcome

The response to therapy was analyzed accounting for the genetic status, assuming differing response rates related to a different underlying etiology. There were no statistically significant differences except for the outcome of complete remission (CR), which was significantly more frequent in non-FAP patients ($p < 0.01$) as illustrated in Fig. 1. Accounting SD, PR and CR as response and PD and DD as non-response, an overall success rate of 114/134 (85.1 %) was achieved. Comparison of response and non-response between FAP and sporadic patients as defined above did not demonstrate a statistically significant difference: (85.9 %) in the FAP-group versus 84.3 % in the non-FAP group, $p = 0.81$). Outcome was statistically independent of the SERM applied, with no statistically significant difference between tamoxifen, raloxifene or toremifene. The mean period to respond with at least stable disease was 14.9 (±9.1) months (Table 2). Until the cut-off date of the study, medication was tapered in 69 (60.5 %) of patients. The mean duration of treatment with sulindac and SERMs when medication was tapered was 42.4 (±24.3) months (Table 2). Genetic status, gender or the SERM applied did not influence these intervals significantly. One FAP patient had recurrent growth or rather new mesenteric desmoid growth 10 years after cessation of therapy. This patient had severe post-colectomy desmoid disease and medication was resumed.

Outcome of surgical desmoid resection was analyzed without accounting for prior prophylactic FAP-surgery compared to any other surgery. Patients after surgical desmoid resection, especially after repetitive surgery, demonstrated a significantly higher rate of progressive disease ($p = 0.03$; Table 3). Patients with a primary surgical approach were as a rule initially treated by other institutions and then referred to us after recrudescence. As displayed in Table 3, patients that did not undergo desmoid surgery had a higher percentage of response (92.5 %) than patients that underwent at least one surgical desmoid intervention (81.5 %), although this trend did not reach statistical significance ($p = 0.08$).

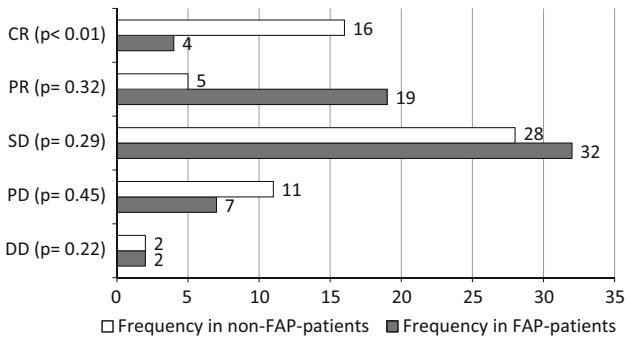

Fig. 1 Outcome considering genetic status. *CR* complete remission, *PR* partial regression, *SD* stable disease, *PD* progressive disease, *DD* desmoid related death

Table 2 Time to respond to medication

	Patients responding	Mean time to response (months)	Medication discontinued after response	Mean time to discontinuation (months)
General	114 (85.1 %)	14.9 (±9.1)	69 (51.5 %)	42.4 (±24.3)
FAP patients	55 (85.9 %)	16.0 (±9.8)	26 (40.6 %)	45.5 (±32.2)
Non-FAP patients	60 (85.7 %)	13.6 (±8.4)	43 (61.4 %)	40.6 (±18.1)
Female	79 (87.8 %)	15.2 (±9.2)	51 (56.7 %)	44.3 (±25.2)
Male	36 (81.8 %)	13.8 (±9.1)	18 (40.9 %)	37.1 (±20.9)
Sulindac + tamoxifen	59 (86.8 %)	15.4 (±9.2)	34 (50 %)	42.5 (±23.6)
Sulindac + raloxifene	55 (90.2 %)	13.7 (±7.8)	34 (55.7 %)	41.6 (±25.2)
Sulindac + toremifene	3 (60 %)	21.0 (±25.2)	1 (20 %)	68

Table 3 Outcome after repeated surgery

Outcome	DD	PD	SD	PR	CR	Number of patients
Surgeries						
0	1 (50 %)	3 (16.6 %)	29 (48.3 %)	15 (44.1 %)	5 (25 %)	53 (39.6 %)
1	0	10 (55.5 %)	15 (25 %)	13 (38.2 %)	9 (45 %)	47 (35.1 %)
2	0	2 (11.1 %)	9 (15 %)	3 (8.8 %)	6 (30 %)	20 (14.9 %)
≥3	1 (50 %)	2 (11.1 %)	7 (11.7 %)	3 (8.8 %)	0	14 (10.4 %)
	2 (1.5 %)	18 (13.4 %)	60 (44.8 %)	34 (25.4 %)	20 (14.9 %)	134

DD desmoid related death, *PD* progressive disease, *SD* stable disease, *PR* partial regression, *CR* complete remission

Mortality

Seven (4.5 %) patients deceased until the end of the study. Five (71.4 %) patients died of unrelated causes, such as trauma or other malignant disease. In two (28.6 %) of the deceased patients, desmoids or related complications were regarded as cause of death. This corresponds to an overall desmoid mortality of 1.5 %. These patients were both characterized by rapid mesenteric desmoid growth and reduced general physical condition. Both patients were referred to us after having undergone radio- and chemotherapy in addition to 5 desmoid surgeries per patient beforehand. In a palliative setting, both were treated with sulindac and raloxifene. Causes of death were infiltrative growth and port sepsis after port implantation required for parenteral nutrition.

Discussion

Although well described as trigger of desmoid growth, the role of surgery in desmoid therapy is discussed controversially. In this study, history of previous surgery was evident in 92.2 % of the FAP and 73.9 % of the sporadic desmoid patients, underlining the role of surgical trauma in desmoid progression. Studies supporting a primary non-surgical approach are increasing for both, FAP-associated and sporadic desmoid patients [59, 60]. For isolated sporadic desmoids, Lahat et al. [31] reported a series of successful surgery without any recurrence, but without reporting the long-term outcome or investigating patients' long-term morbidity. In FAP-patients, there are only case reports of surgical desmoid resection without recurrence. Larger cohorts and long-term studies always reported patients with recurrent disease or high mortality after surgical treatment [32–34, 61]. Several authors recommend non-invasive first line therapies, especially for FAP-associated desmoid patients [5, 33, 62]. These include sulindac and SERMs with well-documented success. Tonelli et al. described successful treatment of FAP-related desmoids with high dose raloxifene in 2003. Of the 13 FAP-patients treated, 12 (92.3 %) responded at least with partial response. 61.5 % had a complete remission [52]. Tamoxifen and toremifene were also administered by Brooks et al. [48] with an overall response rate of 65 %. Sulindac as a single agent is reported to show lower response rates. Tsukada et al. [44] reported a 57 % response rate in a series of 14 patients. The combination of sulindac and SERMs in treating sporadic and FAP-related desmoids was reported successful as first and second line treatment previously by our group [4]. None of these studies report such a large cohort combined with such an extensive long-term follow-

up combined with a standardized, non-invasive treatment for sporadic and FAP-related desmoids as the present study. Nonetheless, the present study is not a randomized-controlled trial and there is no control group. But these limitations are found in the majority of studies reporting or evaluating treatment options for desmoid tumors. Moreover, smaller desmoids (<1 cm) were excluded in this study as in these patients a watch-and-wait policy was pursued. Spontaneous regressions or stable disease are more common in these smaller lesions and they are known to frequently regress spontaneously. Due to our role as referral center, a high percentage of recurrent or large desmoids were included in our series. Before being included, two-thirds of the reported patients had recurrent disease following other treatment strategies. Patients diagnosed during FAP-follow-up at our institution were selected towards larger size or mesenteric desmoids. Therefore the results of this study document a surprisingly high rate of response to the reported treatment, despite the flaw of not having a control arm or being randomized. In this set of patients with documented progression of desmoid a subselection of particularly difficult to treat desmoids has been accumulated. The substantial difference in response depending on the amount of desmoid surgeries previously performed is illustrated by the decreasingly favorable outcome reported in this study. Therefore, despite the discussed limitations, the reported results support studies recommending a non-invasive first and also second line therapy. Taking into account the heterogeneity of desmoid disease, beginning with the different aetiology, localization, duration of disease, rate of growth, previous surgeries, gender etc. a truly prospective randomized study will always have serious limitations.

Long-term combination therapy resulted in higher response rates without increasing toxicity compared to literature reports with single agent strategies. Only in three cases, medication had to be adapted and overall toxicity and side effects were minor, especially when compared to other treatment strategies. Morbidity in this series was very low. Further evidence supporting the role of surgery as a trigger for desmoid growth and increasing aggressive growth was identified. Patients had better outcome and higher response rates to medication when fewer surgical interventions for desmoids were performed. A history of surgical resection was linked to a more progressive course of the disease as well as a deteriorated and delayed response to medication. The overall response rate to conservative therapy of >85 % can be improved by avoiding any desmoid surgery in the first place (>92 % response) as demonstrated in our series. Although the trend of higher response rates in patients that had never been exposed to desmoid surgery did not reach statistical significance ($p = 0.08$), it must be considered that our watch-and-wait patients were excluded for this study. We reported a significant coherence to therapy including these cases with a total number of 154 patients at the InSiGHT (International Society for Gastrointestinal Hereditary Tumours Incorporated) Meeting in San Antonio, Texas, in 2011 [63]. In patients that developed desmoids after delivery, the described regimen showed good results with no non-responders. An association between delivery and desmoid occurrence was documented in this study. This supports the thesis of estrogen-triggered desmoid growth described in literature [8, 10, 21–23].

In 60.5 % of the responding patients medication was tapered following the described algorithm. Recurrence was observed only once and medication was resumed in this particular case. The mean treatment time until medication was tapered was almost 4 years. This led us to the conclusion that tapering medication after an intake of at least 2 years, depending on the individual situation, is reasonable and safe. As long as growth is observed between two imaging examinations, we recommend continuing the high-dose medication to be pursued. Nevertheless this raises more questions on the underlying mechanism leading to response, especially when considering that the response rate was not dependent on the SERM applied.

Overall 14.9 % of the patients in this study did not respond until cut-off date. Since the mean time to response is 14.9 (±9.1) months in this study, medication is continued in these patients. A very low morbidity and an exceptionally low mortality of overall 1.49 % were documented in the long-term outcome of the series. It must be considered that larger desmoids with complicated course are usually more frequently treated surgically than smaller lesions. It still remains unclear whether surgery is the consequence of a complicated course or its cause. For FAP-associated tumors not responding to a first line approach with sulindac and SERMs, Latchford et al. concluded from a series of 20 patients that surgery for abdominal wall and extra-abdominal desmoids is safe and less hazardous than previously reported in intra-abdominal tumors. This conclusion was drawn although the clinically significant recurrence rate was over 40 % and up to 200 cm of small bowel was resected in intra-abdominal desmoids [30], clearly accounting for high morbidity with short bowel syndrome and the need for parenteral nutrition with all known morbidities and complications. This shows that even in a second-line situation surgery often causes very high morbidity. We thereby concluded that surgery in general should be avoided if possible. Nonetheless, individual decision of desmoid removal in specific constellation may be justified, weighting the respective risks and benefits. As Kasper et al. [35] pointed out perfectly "the consequences of radical excision may be worse than the disease itself".

The results of this study led us to the conclusion that between the varieties of treatments reported for desmoids, SERMs and sulindac is a promising option. Nonetheless, Skapek et al. [64] published rather disappointing results of a study investigating the efficacy of high-dose tamoxifen and sulindac for desmoid tumors in children, while only few serious side effects were noticed. However, the cohort reported by Skapek et al. is not comparable with the present cohort and it must be considered that desmoids in children usually grow more aggressively compared with desmoids of the adult. Other authors still recommend a conservative treatment in children [65]. Because of the ongoing discussion in literature we concluded that treatment with the reported regimen is an efficient first-line option but all other options should always be considered when progression continues or complications due to further growth arise.

The secondary finding that IRAs in FAP patients overall had significantly more secondary surgical interventions such as surgical revision than PCEs ($p = 0.004$) is of special interest for centers treating FAP patients. Although the number of patients was very limited, it raises the question whether IRA is equivalent to PCE in the long-time outcome of prophylactic FAP surgery. Since Burgess et al. [66] found no difference in desmoid associated morbidity after restorative PCE or IRA, we can only encourage further studies on the comparability of both techniques in prophylactic FAP surgery.

In FAP-associated, sporadic tumors and even pediatric tumors deregulation of the β-catenin pathway is currently investigated [67–69]. In this study patients' β-catenin status was not evaluated. CTNNB1 mutations are reported to be very frequent in sporadic tumors, but have been shown to be mutually exclusive with APC gene mutations in all tumor types studied so far [70]. For sporadic desmoids, literature reports no significant difference in recurrence risk according to either CTNNB1 mutation status or the specific CTNNB1 mutation [71]. We therefore concluded that for the lack of reliable markers, clinical features are currently of significantly higher importance in general. Nonetheless, further investigation of the role of β-catenin, especially in FAP-patients, is one of the promising topics in desmoid treatment, which we would encourage to evaluate in future studies.

In literature an obvious lack of randomized-controlled studies evaluating current treatment options for desmoids is striking. The desmoid population itself proves to be very diverse, making it virtually impossible to compare treatment success between individuals. Consequently a randomized, controlled multicentre study must be the long-range objective for not leaving patients and physicians in uncertainty about the optimal treatment. Beforehand, a standardized staging system for desmoids should be established to enable comparable results. The DES-staging applied in this study is favored by our group, with simple and comparable parameters and good clinical correlation to the aggressiveness of the disease [4].

The present long-term observational study has limitations, as it does not meet the high scientific standard of a randomized-controlled study. Nonetheless the success rate between 85.1 and 92 % in a cohort with a high percentage of recurrent desmoids and the very low morbidity and mortality rate compared to all other treatment modalities in literature fortify the role of the combination of sulindac and SERMs as treatment of choice for both FAP-associated and sporadic tumors.

References

1. Robanus-Maandag E, Bosch C, Amini-Nik S, Knijnenburg J, Szuhai K, Cervera P et al (2011) Familial adenomatous polyposis-associated desmoids display significantly more genetic changes than sporadic desmoids. PLoS One 6(9):e24354
2. Litchman C (2012) Introduction. In: Litchman C (ed) Desmoid tumors. Springer, Dordrecht, pp 1–2
3. Church JM (1995) Desmoid tumors in patients with familial adenomatous polyposis. Semin Colon Rectal Surg 6(1):29–32
4. Hansmann A, Adolph C, Vogel T, Unger A, Moeslein G (2004) High-dose tamoxifen and sulindac as first-line treatment for desmoid tumors. Cancer 100(3):612–620
5. Vasen HFA, Möslein G, Alonso A, Aretz S, Bernstein I, Bertario L et al (2008) Guidelines for the clinical management of familial adenomatous polyposis (FAP). Gut 57(5):704–713
6. Garzón-Benavides M, Pizarro-Moreno A, García-Lozano R, Herrero-Garrido MI, Hervás-Molina AJ, Márquez-Galán JL et al (2010) Andalusian registry for familial adenomatous polyposis. Analysis of patients included. Rev Esp Enferm Dig 102(11):653–657
7. Friedl W, Caspari R, Sengteller M, Uhlhaas S, Lamberti C, Jungck M et al (2001) Can APC mutation analysis contribute to therapeutic decisions in familial adenomatous polyposis? Experience from 680 FAP families. Gut 48(4):515–521
8. Sinha A, Tekkis PP, Gibbons DC, Phillips RK, Clark SK (2011) Risk factors predicting desmoid occurrence in patients with familial adenomatous polyposis: a meta-analysis. Colorectal Dis 13(11):1222–1229
9. Knudsen AL, Bülow S (2000) Desmoid tumor in familial adenomatous polyposis. Ugeskr Laeg 162(42):5628–5631
10. Sturt NJH, Gallagher MC, Bassett P, Philp CR, Neale KF, Tomlinson IPM et al (2004) Evidence for genetic predisposition to desmoid tumours in familial adenomatous polyposis independent of the germline APC mutation. Gut 53(12):1832–1836
11. Nieuwenhuis MH, Lefevre JH, Bülow S, Järvinen H, Bertario L, Kernéis S et al (2011) Family history, surgery, and APC mutation are risk factors for desmoid tumors in familial adenomatous polyposis: an international cohort study. Dis Colon Rectum 54(10):1229–1234
12. Church J (2012) Desmoid disease in familial adenomatous polyposis. In: Litchman C (ed) Desmoid tumors. Springer, Dordrecht, p 147
13. Bertario L, Russo A, Sala P, Varesco L, Giarola M, Mondini P et al (2003) Multiple approach to the exploration of genotype–phenotype correlations in familial adenomatous polyposis. J Clin Oncol 21(9):1698–1707

14. Lynch HT, Fitzgibbons R Jr (1996) Surgery, desmoid tumors, and familial adenomatous polyposis: case report and literature review. Am J Gastroenterol 91(12):2598–2601
15. Zeng W-G, Zhou Z-X, Liang J-W, Hou H-R, Wang Z, Zhou H-T et al (2014) Prognostic factors for desmoid tumor: a surgical series of 233 patients at a single institution. Tumour Biol 35(8):7513–7521
16. Reitamo JJ, Scheinin TM, Häyry P (1986) The desmoid syndrome. New aspects in the cause, pathogenesis and treatment of the desmoid tumor. Am J Surg 151(2):230–237
17. Reitamo JJ, Häyry P, Nykyri E, Saxén E (1982) The desmoid tumor. I. Incidence, sex-, age- and anatomical distribution in the Finnish population. Am J Clin Pathol 77(6):665–673
18. Posner MC, Shiu MH, Newsome JL, Hajdu SI, Gaynor JJ, Brennan MF (1989) The desmoid tumor. Not a benign disease. Arch Surg 124(2):191–196
19. Gurbuz AK, Giardiello FM, Petersen GM, Krush AJ, Offerhaus GJ, Booker SV et al (1994) Desmoid tumours in familial adenomatous polyposis. Gut 35(3):377–381
20. Nieuwenhuis MH, Cappel WDVTN, Botma A, Nagengast FM, Kleibeuker JH, Mathus-Vliegen EMH et al (2008) Desmoid tumors in a dutch cohort of patients with familial adenomatous polyposis. Clin Gastroenterol Hepatol 6(2):215–219
21. Bertario L, Russo A, Sala P, Eboli M, Giarola M, D'amico F et al (2001) Genotype and phenotype factors as determinants of desmoid tumors in patients with familial adenomatous polyposis. Int J Cancer 95(2):102–107
22. Durno C, Monga N, Bapat B, Berk T, Cohen Z, Gallinger S (2007) Does early colectomy increase desmoid risk in familial adenomatous polyposis? Clin Gastroenterol Hepatol 5(10):1190–1194
23. Schiessling S, Kihm M, Ganschow P, Kadmon G, Büchler MW, Kadmon M (2013) Desmoid tumour biology in patients with familial adenomatous polyposis coli. Br J Surg 100(5):694–703
24. Nieuwenhuis MH, Casparie M, Mathus-Vliegen LMH, Dekkers OM, Hogendoorn PCW, Vasen HFA (2011) A nation-wide study comparing sporadic and familial adenomatous polyposis-related desmoid-type fibromatoses. Int J Cancer 129(1):256–261
25. Lewis JJ, Boland PJ, Leung DH, Woodruff JM, Brennan MF (1999) The enigma of desmoid tumors. Ann Surg 229(6):866–872 **(discussion 872-873)**
26. Caspari R, Olschwang S, Friedl W, Mandl M, Boisson C, Böker T et al (1995) Familial adenomatous polyposis: desmoid tumours and lack of ophthalmic lesions (CHRPE) associated with APC mutations beyond codon 1444. Hum Mol Genet 4(3):337–340
27. Davies DR, Armstrong JG, Thakker N, Horner K, Guy SP, Clancy T et al (1995) Severe Gardner syndrome in families with mutations restricted to a specific region of the APC gene. Am J Hum Genet 57(5):1151–1158
28. Church J, Xhaja X, LaGuardia L, O'Malley M, Burke C, Kalady M (2015) Desmoids and genotype in familial adenomatous polyposis. Dis Colon Rectum 58(4):444–448
29. Stoeckle E, Coindre JM, Longy M, Binh MBN, Kantor G, Kind M et al (2009) A critical analysis of treatment strategies in desmoid tumours: a review of a series of 106 cases. Eur J Surg Oncol 35(2):129–134
30. Latchford AR, Sturt NJH, Neale K, Rogers PA, Phillips RKS (2006) A 10-year review of surgery for desmoid disease associated with familial adenomatous polyposis. Br J Surg 93(10):1258–1264
31. Lahat G, Nachmany I, Itzkowitz E, Abu-Abeid S, Barazovsky E, Merimsky O et al (2009) Surgery for sporadic abdominal desmoid tumor: Is low/no recurrence an achievable goal? ISR Med Assoc J 11(7):398–402
32. Berk T, Cohen Z, McLeod RS, Stern HS (1992) Management of mesenteric desmoid tumours in familial adenomatous polyposis. Can J Surg 35(4):393–395
33. Fiore M, Rimareix F, Mariani L, Domont J, Collini P, Le Péchoux C et al (2009) Desmoid-type fibromatosis: a front-line conservative approach to select patients for surgical treatment. Ann Surg Oncol 16(9):2587–2593
34. Shido Y, Nishida Y, Nakashima H, Katagiri H, Sugiura H, Yamada Y et al (2009) Surgical treatment for local control of extremity and trunk desmoid tumors. Arch Orthop Trauma Surg 129(7):929–933
35. Kasper B, Ströbel P, Hohenberger P (2011) Desmoid tumors: clinical features and treatment options for advanced disease. Oncologist 16(5):682–693
36. Nuyttens JJ, Rust PF, Thomas CR Jr, Turrisi AT 3rd (2000) Surgery versus radiation therapy for patients with aggressive fibromatosis or desmoid tumors: a comparative review of 22 articles. Cancer 88(7):1517–1523
37. Garbay D, Le Cesne A, Penel N, Chevreau C, Marec-Berard P, Blay J-Y et al (2012) Chemotherapy in patients with desmoid tumors: a study from the French Sarcoma Group (FSG). Ann Oncol 23(1):182–186
38. Chugh R, Wathen JK, Patel SR, Maki RG, Meyers PA, Schuetze SM et al (2010) Efficacy of imatinib in aggressive fibromatosis: results of a phase II multicenter Sarcoma Alliance for Research through Collaboration (SARC) trial. Clin Cancer Res 16(19):4884–4891
39. Leithner A, Schnack B, Katterschafka T, Wiltschke C, Amann G, Windhager R et al (2000) Treatment of extra-abdominal desmoid tumors with interferon-alpha with or without tretinoin. J Surg Oncol 73(1):21–25
40. Gounder MM, Lefkowitz RA, Keohan ML, D'Adamo DR, Hameed M, Antonescu CR et al (2011) Activity of Sorafenib against desmoid tumor/deep fibromatosis. Clin Cancer Res 17(12):4082–4090
41. Clark SK, Neale KF, Landgrebe JC, Phillips RK (1999) Desmoid tumours complicating familial adenomatous polyposis. Br J Surg 86(9):1185–1189
42. Bocale D, Rotelli MT, Cavallini A, Altomare DF (2011) Anti-oestrogen therapy in the treatment of desmoid tumours: a systematic review. Colorectal Dis 13(12):e388–e395
43. Colombo C, Foo WC, Whiting D, Young ED, Lusby K, Pollock RE et al (2012) FAP-related desmoid tumors: a series of 44 patients evaluated in a cancer referral center. Histol Histopathol 27(5):641–649
44. Tsukada K, Church JM, Jagelman DG, Fazio VW, McGannon E, George CR et al (1992) Noncytotoxic drug therapy for intra-abdominal desmoid tumor in patients with familial adenomatous polyposis. Dis Colon Rectum 35(1):29–33
45. Belliveau P, Graham AM (1984) Mesenteric desmoid tumor in Gardner's syndrome treated by sulindac. Dis Colon Rectum 27(1):53–54
46. Cohen FJ, Watts S, Shah A, Akers R, Plouffe L Jr (2000) Uterine effects of 3-year raloxifene therapy in postmenopausal women younger than age 60. Obstet Gynecol 95(1):104–110
47. Shanle EK, Xu W (2010) Selectively targeting estrogen receptors for cancer treatment. Adv Drug Deliv Rev 62(13):1265–1276
48. Brooks MD, Ebbs SR, Colletta AA, Baum M (1992) Desmoid tumours treated with triphenylethylenes. Eur J Cancer 28A(6–7):1014–1018
49. Lackner H, Urban C, Kerbl R, Schwinger W, Beham A (1997) Noncytotoxic drug therapy in children with unresectable desmoid tumors. Cancer 80(2):334–340
50. Bauernhofer T, Stöger H, Schmid M, Smola M, Gürtl-Lackner B, Höfler G et al (1996) Sequential treatment of recurrent mesenteric desmoid tumor. Cancer 77(6):1061–1065
51. Kinzbrunner B, Ritter S, Domingo J, Rosenthal CJ (1983) Remission of rapidly growing desmoid tumors after tamoxifen therapy. Cancer 52(12):2201–2204

52. Tonelli F, Ficari F, Valanzano R, Brandi ML (2003) Treatment of desmoids and mesenteric fibromatosis in familial adenomatous polyposis with raloxifene. Tumori 89(4):391–396
53. Leithner A, Gapp M, Radl R, Pascher A, Krippl P, Leithner K et al (2005) Immunohistochemical analysis of desmoid tumours. J Clin Pathol 58(11):1152–1156
54. Deyrup AT, Tretiakova M, Montag AG (2006) Estrogen receptor-beta expression in extraabdominal fibromatoses: an analysis of 40 cases. Cancer 106(1):208–213
55. Santos GAC, Cunha IW, Rocha RM, Mello CAL, Guimarães GC, Fregnani JH et al (2010) Evaluation of estrogen receptor alpha, estrogen receptor beta, progesterone receptor, and cKIT expression in desmoids tumors and their role in determining treatment options. Biosci Trends 4(1):25–30
56. Lim CL, Walker MJ, Mehta RR, Gupta TK (1986) Estrogen and antiestrogen binding sites in desmoid tumors. Eur J Cancer Clin Oncol 22(5):583–587
57. Benson JR, Baum M (1993) Breast cancer, desmoid tumours, and familial adenomatous polyposis—a unifying hypothesis. Lancet 342(8875):848–850
58. Moeslein G (2006) Invited commentary. Fam Cancer 5(3):287–288
59. Colombo C, Miceli R, Le Péchoux C, Palassini E, Honoré C, Stacchiotti S et al (2015) Sporadic extra abdominal wall desmoid-type fibromatosis: surgical resection can be safely limited to a minority of patients. Eur J Cancer 51(2):186–192
60. Desurmont T, Lefèvre JH, Shields C, Colas C, Tiret E, Parc Y (2015) Desmoid tumour in familial adenomatous polyposis patients: responses to treatments. Fam Cancer 14(1):31–39
61. Quintini C, Ward G, Shatnawei A, Xhaja X, Hashimoto K, Steiger E et al (2012) Mortality of intra-abdominal desmoid tumors in patients with familial adenomatous polyposis: a single center review of 154 patients. Ann Surg 255(3):511–516
62. Bonvalot S, Ternès N, Fiore M, Bitsakou G, Colombo C, Honoré C et al (2013) Spontaneous regression of primary abdominal wall desmoid tumors: more common than previously thought. Ann Surg Oncol 20(13):4096–4102
63. Quast D, Schneider C, Burdzik E, Möslein G (2011) Abstracts of 2011 InSiGHT-Meeting: long-term outcome of FAP-associated and sporadic desmoid tumours in 154 patients. Fam Cancer 10(4):713–743
64. Skapek SX, Anderson JR, Hill DA, Henry D, Spunt SL, Meyer W, et al. (2012) Safety and efficacy of high-dose tamoxifen and sulindac for desmoid tumor in children: results of a Children's Oncology Group (COG) Phase II Study. Pediatr Blood Cancer 60(7):1108–1112
65. Honeyman JN, Theilen T-M, Knowles MA, McGlynn MM, Hameed M, Meyers P et al (2013) Desmoid fibromatosis in children and adolescents: a conservative approach to management. J Pediatr Surg 48(1):62–66
66. Burgess A, Xhaja X, Church J (2011) Does intra-abdominal desmoid disease affect patients with an ileal pouch differently than those with an ileorectal anastomosis? Dis Colon Rectum 54(11):1388–1391
67. Lazar AJF, Tuvin D, Hajibashi S, Habeeb S, Bolshakov S, Mayordomo-Aranda E et al (2008) Specific mutations in the beta-catenin gene (CTNNB1) correlate with local recurrence in sporadic desmoid tumors. Am J Pathol 173(5):1518–1527
68. Bo N, Wang D, Wu B, Chen L, Ma R (2011) Analysis of β-catenin expression and exon 3 mutations in pediatric sporadic aggressive fibromatosis. Pediatr Dev Pathol [Internet]. [cited 2012 Aug 9]; http://www.ncbi.nlm.nih.gov/pubmed/21323417
69. Matono H, Tamiya S, Yokoyama R, Saito T, Iwamoto Y, Tsuneyoshi M et al (2011) Abnormalities of the Wnt/β-catenin signalling pathway induce tumour progression in sporadic desmoid tumours: correlation between β-catenin widespread nuclear expression and VEGF overexpression. Histopathology 59(3):368–375
70. Kattentidt Mouravieva AA, Geurts-Giele IRR, de Krijger RR, van Noesel MM, van de Ven CP, van den Ouweland AMW et al (2012) Identification of familial adenomatous polyposis carriers among children with desmoid tumours. Eur J Cancer 48(12):1867–1874
71. Mullen JT, DeLaney TF, Rosenberg AE, Le L, Iafrate AJ, Kobayashi W et al (2013) β-Catenin mutation status and outcomes in sporadic desmoid tumors. Oncologist 18(9):1043–1049