AOSIS

The management of desmoid tumours at Groote Schuur Hospital: A retrospective review of current practice

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Background: Desmoid tumours (DT) are rare soft tissue tumours that do not metastasise but are locally aggressive. Management options are varied and the response to treatment can be unpredictable.

Aim: The aim of this study was to describe the clinical presentation, management strategies and outcomes for adult patients who were treated for DT.

Setting: The study was conducted at Groote Schuur Hospital in Cape Town, South Africa, and all patients from 2003 to 2016 who presented with DT were included.

Method: This was a retrospective review of records. Data collected included: demographics, DT-associated conditions, site and size of tumour, histological findings, treatment modalities, follow-up and outcomes.

Results: Seventy patients with histologically confirmed DT were identified. The majority were women (86%) and 77% presented with a painless mass. The commonest site was the anterior abdominal wall (47%). Definitive surgery was performed in 46 (66%) patients, whereas 13 (19%) had definitive radiotherapy. Nine patients received adjuvant radiotherapy post-surgery for involved or close margins. Recurrence developed in 20% of patients post-surgery. In the primary radiotherapy group, one patient had disease progression. Two patients with mesenteric DT died because of bowel obstruction.

Conclusion: This retrospective review of patients affected by DT at a single centre demonstrates the rarity of the condition, the unpredictable natural history and the variety of treatment options available. Many of our findings are similar to other published studies, except the mean size of DT which was bigger. Treatment outcomes following surgery or radiotherapy seem acceptable, although study limitations are noted.

Keywords: desmoid tumour; desmoid fibromatosis; review; management; recurrence; outcome.

Introduction

Desmoid tumours (DT), also known as fibromatosis (aggressive, deep or desmoid-type), are a rare and unusual soft tissue neoplasm. Desmoid tumours result from monoclonal proliferation of myofibroblastic tissue which tends to infiltrate and recur locally, but never metastasise.[1,2] Despite their classification as a benign neoplasm, their capacity for local invasion may cause significant morbidity and even death. Therefore, appropriate and timeous treatment is essential. McFarlane first described the condition in 1832[3] and the term 'desmoids' (from the Greek 'desmos', meaning band- or tendon-like) was coined by Müller in 1838.[4] Desmoid tumours account for 0.03% of all neoplasms and 3% of soft tissue tumours[5,6] and have an estimated incidence of 2.4–4.3 per million people per year in the general adult population.[1] They commonly originate from deep musculo-aponeurotic structures, but also develop intra-abdominally.[2]

Desmoid tumours can occur sporadically (around 85%[7]) or in association with familial adenomatous polyposis (FAP),[1] the latter combination being termed Gardener's syndrome.[8] Pregnancy is an associated condition (either during or following a pregnancy), suggesting high oestrogen states as contributory.[5] The association with antecedent trauma or previous surgery[9] may implicate a dysregulated wound healing process in the pathogenesis of this condition.[8]

Treatment of DT is complicated by the heterogeneity of the condition with regard to natural history, location and symptomatology. Surgery aims to completely excise the tumour with limited functional or cosmetic morbidity, and is generally indicated for symptomatic or progressive DT.[10]

However, recurrence post-surgery is common and is higher in patients with macroscopically positive margins.[7] Radiotherapy (RT) can be used as a definitive treatment modality with results that compare favourably to surgery.[11] Also, when used in combination with surgery, RT appears to decrease local recurrence rates in patients with incomplete surgical excision, particularly following surgery for recurrent tumours.[7] Systemic therapies, including cytotoxic therapies, hormonal therapies, anti-inflammatory agents and biologicals, are also occasionally used.[12] Recently, practice guidelines in many countries have shifted to more expectant management of DT because of increasing evidence that a significant percentage of these tumours may regress or remain stable without any intervention.[10,13,14]

There are limited published data on this condition in low- and middle-income countries. As part of a review of local treatment protocols, the study was conducted to assess the demographics, clinical characteristics, treatment modalities and outcomes of adult patients who were diagnosed with DT, over a 13-year period. This study aims to describe the demographic and clinical characteristics, management strategies, local recurrence and outcomes for all patients treated with DT over this period.

Methods

This was a retrospective review of all patients with histologically confirmed DT who were managed at a single tertiary referral hospital from the 01 January 2003 to 31 December 2016. Patients younger than 18 years of age were excluded and there were no patients identified who had recurrence at initial presentation.

Eligible patient records were identified using established databases from the departments of General Surgery (Surgical Oncology Unit) and Radiation-Oncology. National Health Laboratory Services (NHLS) pathology records were also obtained for all patients diagnosed with this condition during the study period. Data collected included: patient demographics, site and size of DT (combination of clinical, imaging and operative specimen measurement), presenting symptoms, biopsy technique used, associated conditions or risk factors, β-catenin status on immunohistochemistry, primary and other treatment modalities, recurrence rates following surgery, post-operative complications according to Clavien–Dindo classification,[15] mortality events and total duration of follow-up for each patient from the time of diagnosis. Response to definitive RT was assessed according to the response evaluation criteria in solid tumours (RECIST) criteria.[16] Data were stored in a password-protected Microsoft Excel© Spreadsheet.

Statistical considerations

Univariate analyses were conducted given the descriptive nature of the study. Numerical variables were described using measures of central tendency and dispersion, depending on the distribution of the data. Categorical variables were analysed using proportions and two-way frequency tables.

Ethical considerations

Ethical clearance for the study was granted by the Human Research Ethics Committee of the Faculty of Health Sciences at the University of Cape Town (HREC REF: 679/2017).

Results

Patient and tumour characteristics

A total of 70 records of patients who had DT were identified for analysis, as presented in Table 1. The majority of patients (86%) were female. The median age at diagnosis was 36.5 years. The majority of DT, 65/70 (93%), were extra-abdominal, and of these, mainly in the anterior abdominal wall (51%), trunk (29%) and limbs (15%).

The most common presenting symptom was a painless mass, 54/70 (77%). Nine (13%) patients presented with painful mass, three (4%) with bowel obstruction, two (3%) reported

TABLE 1: Demography and clinicopathological findings in patients who had desmoid tumours.

Variables	Value	%	Range
Age			
Median age	-	-	36.5 years
Interquartile range (IQR)	-	-	27.3–45.0 years
Sex			-
Female	60/70	86	-
Male	10/70	14	-
Site			-
Extra-abdominal	65/70	93	-
Abdominal wall	33/65	51	-
Trunk	19/65	29	-
Limbs	10/65	15	-
Head and neck	3/65	5	-
Intra-abdominal	5/70	7	-
Associated conditions			
Familial adenomatous polyposis (FAP)	6/70	9	-
Pregnancy	17/70	24	-
Previous regional surgery	12/70	17	-
Trauma	4/70	6	-
Pregnancy-related desmoid tumours	17/70	24	-
Pregnant – 6-months post-partum	7/17	41	-
> 6-months – 2-years post-partum	10/17	49	-
Presenting symptoms			
Painless mass	54/70	77	-
Painful mass	9/70	13	-
Bowel obstruction	3/70	4	-
Local pain only	2/70	3	-
Unknown	2/70	3	-
Tumour size (N = 58)†	9 cm	-	2 cm – 29 cm
Diagnosis			
Core biopsy	45/70	64	-
Incisional biopsy	13/70	19	-
Excisional biopsy	10/70	14	-
Unknown	2/70	3	-
β-catenin staining			
Positive	36/38	95	-
Negative	2/38	5	-

†, Combination of clinical, imaging and operative specimen measurement.

pain localised to the mass and the symptom was not recorded in two (3%) patients. Six (9%) of the cohort were known to have FAP. Of the other factors known to be associated with DT, 7/70 (24%) were pregnancy-related, 12/70 (17%) had previous regional surgery and 4/70 (6%) had a history of previous trauma to the area. Of the 17 patients with pregnancy-related DT, 7/17 (41%) were pregnant or up to 6-months post-partum (one of these patients was noted to have had regional surgery prior to this pregnancy) and the remaining 10/17 (51%) were diagnosed between 6 and 24 months after delivery. Thirty-one patients (44%) had no known associated condition.

The diagnosis was based on histological samples obtained by core-needle biopsy in the majority of cases 45/70 (64%), whereas excisional biopsy was relied on in 13/70 (19%) and incisional biopsy in 10/70 (14%). The original diagnostic investigation was not specified in 2/70 (3%) of the records. Immunohistochemistry staining for β-catenin was performed in 38/70 (54%) cases and 36/38 (95%) of these were positive (thus only 51% of the total cohort were positive). Tumour size was known in 58/70 (83%) patients and ranged from 2.0 cm to 29.0 cm at greatest dimension, with an average size of 9.0 cm.

Treatments and outcomes

The majority of patients, 58/70 (83%), were managed by the Endocrine and Oncology Surgery Unit within the Division of General Surgery and by the Radiation Oncology Department, the remainder having been managed by the Gynaecological and Orthopaedic services. Thirty-six (51%) patients were formally reviewed within a multidisciplinary team (MDT) context, which varied in terms of relation to primary treatment intervention, with many having had primary surgery prior to MDT. The definitive treatment modalities are depicted in Figure 1.

Surgery

Surgery was the primary treatment in 46/70 (66%) patients; 44/70 of these were surgery performed with curative intent and 2/70 were palliative debulking procedures. Of the 44 patients who underwent surgery with curative intent, 28/44 (64%) had clear (R0) margins, 11/44 (25%) had microscopic (R1) involved margins and 2/44 (4%) had macroscopic (R2) involved margins; in the remaining 3 (7%), the final histology report was not available. Twenty-six

patients had wide local excisions of abdominal wall DT and of these 23 required mesh reconstruction of the abdominal wall defect. The surgical complications are shown in Table 2.

Surgery and radiotherapy

Combination treatment with surgery and RT was used in 11 cases. Nine received adjuvant RT and 2/11 neo-adjuvant RT. In the adjuvant category, 8/9 cases had involved margins (7 = R1, 1 = R2) and one case had a close margin (2 mm). In the neo-adjuvant category (to downsize the tumour prior to surgery), one had macroscopically involved (R2) margins at surgery and progressed (this patient had the debulking surgery for tumour necrosis), and the other had clear (R0) margins at surgery.
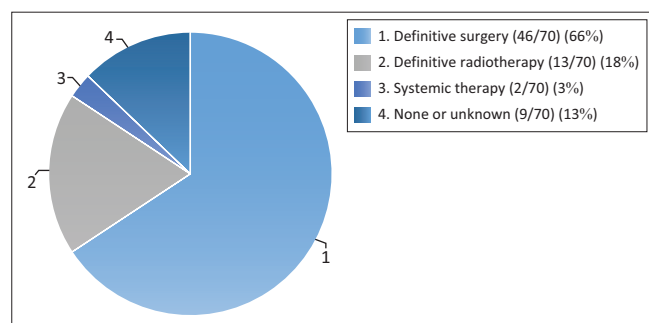
Radiotherapy as definitive treatment

Definitive RT was employed in 13 patients in whom the DTs were deemed irresectable. Of the patients who received RT as definitive treatment, nine (69%) had a partial response, one (8%) had a complete response, two (15%) had stable disease and one (8%) had progressive disease as assessed using the RECIST criteria.[11] See Figure 2.

These patients were all followed up for more than 1-year post-RT, with an average follow-up of 57 months (range: 13–133 months). Radiation complications included six cases of skin fibrosis. The median RT dose delivered (including definitive, adjuvant and neo-adjuvant) was 55.0 Gy (range: 46.8 Gy–62 Gy) given in 2 Gy fractions.
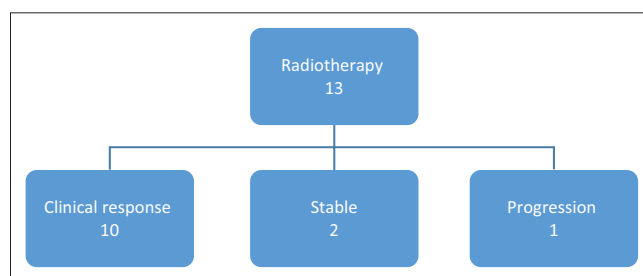
TABLE 2: Surgical complications (early or late) Clavien–Dindo classification system.[15]

Grade	Complications	Management	No. of patients
Grade 1	Seroma	Conservative	6
	Chronic pain syndromes	Anaelgesia	2
	Surgical site infection	Standard wound care	1
	Incisional hernia	Conservative	1
Grade 2	Surgical site infections	Oral antibiotics (in addition to standard wound care)	2
Grade 3a	Seroma	Percutaneous drain placement	1
Grade 3b	Incisional hernia	Repair with mesh	4
	Enterocutaneous fistula	Surgical resection	1
Grade 4a	-	-	-
Grade 4b	-	-	-
Grade 5	Bowel obstruction	-	2

No., number.

FIGURE 1: Breakdown of definitive treatment modality used.

Legend:
1. Definitive surgery (46/70) (66%)
2. Definitive radiotherapy (13/70) (18%)
3. Systemic therapy (2/70) (3%)
4. None or unknown (9/70) (13%)

FIGURE 2: Response to definitive radiotherapy treatment.

Radiotherapy 13 → Clinical response 10 / Stable 2 / Progression 1

Systemic treatments

Of the six patients who received systemic therapy, four had this in combination with RT. Only two patients had systemic therapy as their only treatment modality with one receiving imatinib with a good response and one received tamoxifen and non-steroidal anti-inflammatory drugs (NSAIDs) with no demonstrable response. Two patients received chemotherapy (six cycles of doxorubicin), and two tamoxifen, as an adjunct to definitive RT. Active observation alone was not formally used as a primary management strategy in any of our patients.

Follow-up

Forty-two patients had adequate follow-up of more than 1 year and 15 had follow-up for less than 1 year. The median follow-up for this combined group of patients was 29 months, with one patient having been followed up for 295 months (almost 25 years). For the remaining 13 patients, follow-up length could not be determined because of missing clinical notes.

Recurrence post-surgery

Local recurrence after surgery (surgery alone or surgery with RT) was only analysed in those patients who followed up for a year or more. This consisted of clinical examinations and radiological imaging. The outcomes are summarised in Figure 3. The total number of patients in this category was 25/44 (57%) who had surgery, with 19/44 (43%) patients considered as 'unknown' in terms of recurrence because of inadequate follow-up. None of the patients with inadequate follow-up was noted to have evidence of recurrence at last follow-up. Of the 25 patients with adequate follow-up, 5/25 (20%) had proven recurrence, and 20/25 (80%) had no evidence of recurrence. All patients with recurrence had either microscopically (three patients) or macroscopically (two patients) involved margins. Of the patients with no recurrence, 15/20 (75%) had clear (R0) resection margins and 5/20 (25%) had microscopically involved (R1) resection margins, as depicted in Figure 4. The average age at presentation of patients who had recurrence post-surgery was 25 years (range: 18–32).
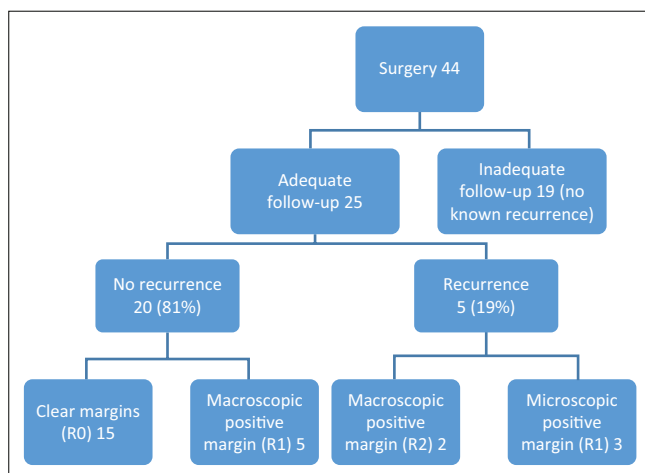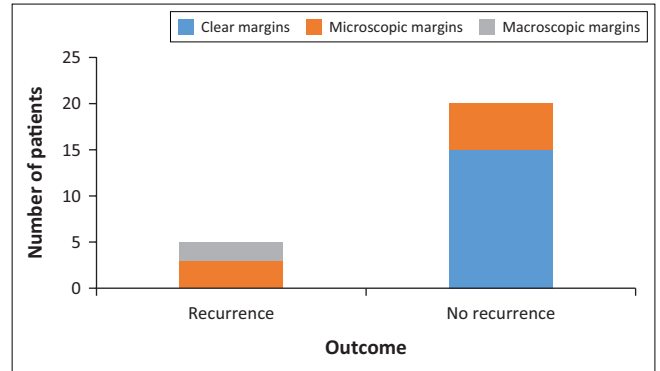

FIGURE 3: Outcome of surgical management.

FIGURE 4: Surgical margins and recurrence.

Mortality

Four patients in our cohort are known to have died, two of unrelated medical causes, while the other two were as a result of the DT. Both of the patients who had died of DT had intra-abdominal disease with bowel obstruction because of disease progression.

Discussion

The demographic profile of study patients with DT is similar to other published studies with the majority being female with a median age in the fourth decade and the majority being sporadic DT.[17,18,19,20] Sporadic DT affects β-catenin production with the mutation being in the CTNNB1 gene, whereas in FAP-related DT, the mutation is in the adenomatous polyposis coli (APC) gene.[12] Positive β-catenin immunohistochemistry in those tested (38/70 – 54%) in this study was much higher (95%) than the reported rate (67% – 80%) in other studies.[21] The average size of desmoids in the current study was 9.0 cm (range: 2.0 cm – 29.0 cm), which is larger than other similar reports, where the mean was between 6.3 cm and 7.7 cm.[2,20] Larger size at presentation is significant as size greater than 7 cm has been shown to be a poor prognostic factor for progression-free survival.[13]

In terms of the location, the majority (93%) of patients had extra-abdominal DT which is similar to a report from a study involving 426 patients by Salas et al.,[13] which showed 87% of DT to be extra-abdominal. Interestingly, only one of the six confirmed FAP-associated DT cases was intra-abdominal (four were located in the abdominal wall and one in the neck region). This preceding finding is unusual as the majority of reported DT associated with FAP are intra-abdominal, followed by the anterior abdominal wall. Pregnancy (previous or current) was noted in close to 25% patients. Similar to what is reported in the literature,[22] over two-thirds of pregnancy-related DTs occurred in the anterior abdominal wall and this group had a good outcome with a local recurrence below 5%.

The majority of patients underwent surgery as their primary treatment with the aim of achieving clear surgical margins. The rates of R0 and R1 surgical resections rate in our cohort are comparable to published studies despite relatively late presentation and large tumour size. However, the clinical

relevance of achieving clear surgical margins and its impact on local recurrence is not clearly proven and is the subject of conflicting reports in the literature.[7] In a series by Gronchi et al.[23], there was no significant difference in disease-free survival in those with microscopically negative or positive surgical margins, although there was a trend towards significance in patients with microscopically positive margins after repeat surgery for local recurrence. In a systematic review in 2017 which included 16 studies and 1295 patients,[7] microscopic margins did seem to be an important factor with an almost twofold increase in risk of recurrence for patients treated with surgery alone and positive microscopic margin. In our series, there was no local recurrence detected in those with negative surgical margins; however, the sample was too small to prove statistical significance. There were three local recurrences in patients with microscopically positive margins and two local recurrences in patients with macroscopically positive margins.

Another subject of contention in the management of DT is the role of adjuvant RT following surgery with involved margins, with some series showing a local control benefit[11,24,25,26] and others showing no clear benefit.[23,27] In our series, the effect of adjuvant RT cannot be determined because of the small sample size, heterogeneous treatment regimens and lack of adequate follow-up.

Factors associated with recurrence noted in published literature include age < 37 years, tumour size > 7 cm in diameter and extra-abdominal location.[13] The average age of patients with recurrence in our series was 25 years compared to the overall mean age of 37 years. Neo-adjuvant RT has been used with promising results in some centres,[28] but in our series, only two patients received neoadjuvant RT with one proceeding to an R0 resection with no recurrence and the other with no response to RT.

Radiotherapy as definitive treatment is an acceptable alternative treatment to surgery, with local control rates as high as 90.9% at 3 years, including 13.6% complete responses, 36.4% partial responses and 40.9% stable cases being reported.[29] Our results showed local control rates well over 90% in patients treated primarily with RT, with over 77% of cases attaining either complete or partial response. The average follow-up was close to 5 years, and it is important to note that the effects of RT can be slow and ongoing even beyond 3 years.[29] This response was measured according to the RECIST criteria despite its limitations in assessing the slow response of some tumours to RT.[16]

Systemic therapy, previously employed only in situations where surgery was not an option (e.g. intra-abdominal FAP-associated DT), is becoming a more commonly used option in the management of DT.[12] It consists of non-cytotoxic therapy and cytotoxic therapy. The non-cytotoxic therapies include hormonal agents (e.g. tamoxifen), anti-inflammatory agents (NSAIDS) or biologicals (imatinib, sorafenib).[12,30] The cytotoxic therapies include chemotherapy agents such as doxorubicin, vinblastine and methotrexate.[1] Other newer local treatments include local ablative therapies using thermal or chemical means (e.g. isolated limb perfusion with tumour necrosis factor alpha),[31] particularly in those poorly suited to surgery.[10] The use of systemic therapy in our setting was limited to only a few patients and in heterogeneous treatment settings. Only doxorubicin had a clinically significant impact with a good response in one of the patients managed with this agent.

Active surveillance for 1–2 years for DT is a management strategy that has been adopted by many guidelines in recent years.[7,10,14,32,33] This strategy has developed because of reports that up to 15% of DT regress spontaneously and a significant number remain stable with a progression-free survival of up to 50% at 5 years.[34,35,36] These findings have brought into question traditional therapies, primarily surgery, as the mainstay of treatment, particularly in cases where surgical excision results in significant morbidity.[13] The aim of active surveillance is to determine which DTs are aggressive and will progress and which are indolent, slow-growing or may regress. Unfortunately, to date, there are no reliable biological markers to distinguish these two groups although genetic mutations in the CTNNB1 gene are being investigated.[37] Because of the time frame of our study, none of the patients in our study underwent an active surveillance strategy, although it is clearly a preferable option to reduce patient morbidity and also to limit unnecessary procedures in our resource-limited setting. When considering the safe implementation of this strategy in our local context, the issues of late clinical presentation, delay in referral pathways, larger tumour size and poor follow-up will need to be taken into consideration.

Limitations

This study has many obvious weaknesses, including being retrospective, small sample size, poor follow-up, heterogeneous treatment regimens and missing or incomplete patient records. This impacts the external validity of the study findings. Associations between clinical characteristics and outcomes could not be explored further because of the small sample size.

Conclusion

This retrospective review of patients affected by DT demonstrates the rarity of the condition, the unpredictable natural history and the variety of treatment options available. While many of our findings mirror previously published studies, the mean size of DT in this series was greater, possibly because of later presentation or delayed referral. The majority of patients in this series underwent surgical management and a subset of patients were treated with adjuvant or definitive RT. Systemic treatments played a minor role. While surgical and RT treatment outcomes in this series were acceptable, strong conclusions cannot be drawn because of small numbers and inadequate follow-up. Newer treatment approaches emphasising active surveillance may need to be incorporated into our management protocols but

with an awareness of the specific clinical context and through an individualised multidisciplinary decision-making process.

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Competing interests

The authors declare that they have no financial or personal relationships that may have inappropriately influenced them in writing this article.

Authors' contributions

Research topic and initial planning were done by E.P. Data collection, analysis and manuscript composition were performed by H.P., with guidance from L.C., E.P., N.J. and T.N. Senior review, expert consultation and final documentation approval were performed by L.C., E.P., N.J., F.M. and T.N.

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Data availability statement

The data that support the findings of this study are available from the corresponding author, upon reasonable request.

Disclaimer

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