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Outcome of surgery for primary and recurrent desmoid-type fibromatosis. A retrospective case series of 174 patients

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HIGHLIGHTS

- Primary excision with clear margins is associated with superior local control.
- Localization in the extremities is associated with higher recurrence rate.
- Surgery for recurrent disease carries a very high risk of local relapse, irrespective of surgical margins.
- Adjuvant radiotherapy or chemotherapy do not affect local control rate of recurrent disease.

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ABSTRACT

Background: The best management of relapsing desmoid-type fibromatosis, a benign but locally infiltrative soft-tissue tumour, is largely undecided. Our aim was to investigate the incidence and the factors influencing local relapse after surgery for primary and recurrent disease of the trunk and extremities.
Patients and Methods: Retrospective analysis of 174 patients who had surgical treatment for desmoid-type fibromatosis. The quality of the surgical margins and use of adjuvant radiotherapy or chemotherapy were analysed regarding local recurrences in primary and recurrent disease.
Results: Clear margins were achieved in 41% of cases. 10-year local control rate was 58% for clear primary resections as compared to 37% with intralesional primary resections ($p = 0.030$). Extremity tumours had a higher risk of local recurrence compared to trunk and pelvic ones ($p < 0.001$). Attempted resection of recurrent disease was associated with an approximately 90% incidence of relapse after each procedure, despite the quality of the surgical margins being equivalent to primary resections. Quality of surgical margins was not important for local control of recurrent lesions. Adjuvant treatments (radiotherapy and chemotherapy) had a no significant effect on the local control rate of recurrent disease (odds ratio 0.693 and 0.969 respectively).
Conclusions: A complete primary excision is the best window of opportunity to achieve local control of desmoid-type fibromatosis. Once the disease relapses, surgical intervention is accompanied with a high risk of failure, irrespective of the quality of the margins and adjuvant treatment given.

1. Introduction

Desmoid-type fibromatosis is a benign soft tissue tumour which displays infiltrative growth but never metastasizes. It is a clonal proliferation of fibroblastic cells in a dense extracellular matrix, attributed to underlying beta-catenin, CTNBB1 or APC mutations [1]. A minority of patients are diagnosed with the Gardner syndrome, having germ-line mutations of the adenomatous polyposis coli (APC) gene [2].

Management of desmoid-type fibromatosis is controversial since it has an unpredictable natural history. As stable disease or even spontaneous regression is seen even in the absence of any treatment [3–5] an initial watchful waiting strategy should be

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discussed [6]. Treatment is generally offered to patients with progressive or symptomatic disease. Medical therapy relies on non-steroidal anti-inflammatory drugs, hormonal treatment, low-dose or conventional chemotherapy based on anthracycline compounds, methotrexate, and vinca alkaloids, as well as targeted treatment with kinase inhibitors [7–13]. The role of non-invasive ablative therapies to control the extent of disease has yet to be determined [14]. Surgery was in the past regarded as the mainstay of treatment, but the locally invasive pattern makes complete surgical resection challenging, which in turn contributes to the high risk of local recurrence. Furthermore, the extent of lesional soft-tissue involvement can be so extensive that complete resection would result in mutilating surgery. Conflicting evidence exists to support the use of adjuvant radiotherapy after intralesional resections, since it has shown to improve local control but on is also accompanied by significant adverse effects such as wound healing problems and late fibrosis [15–18]. Clearly, an individualised, multidisciplinary and stepwise approach to each patient should be pursued [19], where surgery should be considered for symptomatic patients where resection is not expected to cause significant morbidity [20].

While the outcome of primary surgical resection has been addressed in many retrospective studies, there is still conflicting evidence regarding the importance of surgical margins [15,16,21–26], location of the disease [15,21,25,27] and other prognostic factors such as patient age and gender [21,24,28,29]. Local recurrence is expected in 25–53% of surgically treated patients [15,19,26,28,30]. Importantly, the characteristics and management of recurrent disease are still unknown. For patients with desmoid-type fibromatosis of the trunk and extremities, we aimed to investigate (1) the incidence of local recurrence after surgical excision for primary and recurrent disease (2) the factors influencing local recurrence after each surgical resection.

1.1. Patients and methods

The prospectively collected departmental database was interrogated to identify desmoid-type fibromatosis of the extremities and the trunk: There were 388 patients between 1981 and 2015; 213 of them underwent surgical excision. Of these, 174 were primarily treated at our centre and 39 were referred after inadvertent surgery ("whoops" procedures) with residual or recurrent lesions. The former were finally included for analysis in this study.

Median age was 34 (1–75) years and mean age 35 years. There were 77 male and 97 female patients. Anatomical locations included the, trunk (33%)-of whom the rectus abdominis in 9%, lower extremities (31%), upper extremities (30%) and pelvis (6%). There was no significant difference between male and female patients regarding age ($\chi^2 = 0.646$) and location ($\chi^2 = 0.693$). Median follow-up was 38 (1–290) months.Diagnosis was achieved in a multi-disciplinary setting based on typical radiographical findings and either a tru-cut or open biopsy for histological analysis. The treatment plan was individualised, taking into account the clinical symptoms, the location, size and growth of the tumour, the potential to achieve a complete resection without significant morbidity and the patient's preference. Often, this was based on a multidisciplinary team meeting of the orthopaedic, pathology, radiology and oncology department members. Mutation analysis was not routinely done.

All operations were performed by a consultant grade surgeon and the median volume of the surgically resected primary tumours was 41 (12–2964) cubic centimetres. 17 patients had adjuvant radiotherapy (4 in a preventive setting, i.e. before the detection of any local recurrence), 4 adjuvant chemotherapy, and 14 a combination of both. Follow-up was individualised, and relied on clinical examination for the detection of recurrence. Due to the benign nature of the disease, and the availability of a reliable primary community care, there was no minimum surveillance period within the sarcoma centre, or standardized scheme. Local recurrences could either detected by the patients themselves, primary care physicians or during the follow-up in the sarcoma centre. For this reason, there was no minimum follow-up time as an inclusion criterion. MRI and/or biopsy were used to verify the presence of locally recurrent disease when evident clinically.

SPSS was used for statistical analysis (version 20, SPSS Inc, Chicago, IL). Variables used for analysis were the quality of surgical margins (clear, intralesional), the ebent and time to local recurrence, any adjuvant therapy (radiotherapy, chemotherapy), any late (secondary surgery). The Kaplan-Meier method was used to generate survival plots, and comparisons were done using the log-rank test, and p values are presented according to the univariate log-rank method unless otherwise stated. Arithmetic values are given as median and the range of values is shown in brackets, unless stated otherwise. Analysis of possible prognostic factors was performed using the cox-proportional hazard test. The Pearson's chi-square (χ^2) test was used for comparisons between groups. All tests were double-sided, and a p or χ^2 value of $\leq$0.05 was considered statistically significant. The work is reported according to the PROCESS guidelines [31] and has been registered at the Research Registry (1801).

2. Results

2.1. Incidence of local recurrence after primary surgical excision and factors influencing it

Clear resection margins were achieved in 41% of the cases. Only a minority of clear resections were wide (4%), the rest being marginal. The incidence of local recurrence after primary resection was 44% for the whole cohort. A clear resection (R0) had a significantly lower risk of local recurrence as compared to an intralesional (R1/R2) one. Indeed, the 5-year 10-year local control rate was 58% for clear resections as compared to 37% with intralesional resections ($p = 0.030$) (Fig. 1).

In both univariate and multivariate analysis, age and gender of the patient, plus size of the lesion did not influence the rate of local recurrence (Table 1). Extremity lesions had a higher rate of local recurrence compared to the ones located in the trunk and pelvic regions ($p < 0.001$) (Fig. 2). This could not be attributed to the quality of surgical margins, which did not differ significantly (51% clear margins in trunk and pelvis, 35% for extremities, $\chi^2 = 0.084$), neither to a more indolent biological behaviour of rectus abdominis desmoids, since the effect was present ($p = 0.005$) even when these lesions were excluded from the analysis. Within the same extremity, proximal, joint-near or distal location did not affect the recurrence rate in the lower extremity ($p = 0.381$), whereas proximal and elbow-near lesion had a lower recurrence rate as compared to forearm and hand ones ($p = 0.038$) (see Fig. 3).

2.2. Outcome of treatment of recurrent disease

Of the patients that presented with first-time recurrence, 61% were treated surgically, and this was the case for 37% and 73% of the patients after a second and a third recurrence. The median number of surgical procedures for recurrent disease was 2 (range 1–6). Resection of recurrent fibromatosis was associated with a 93% risk of further recurrence (Tables 2a and 2b). Likewise, after a second recurrence, surgery had a 88% of resulting in a third relapse. Lastly, of the 8 patients that were operated for third relapse, 5 had a further relapse. Recurrence after primary resection was observed

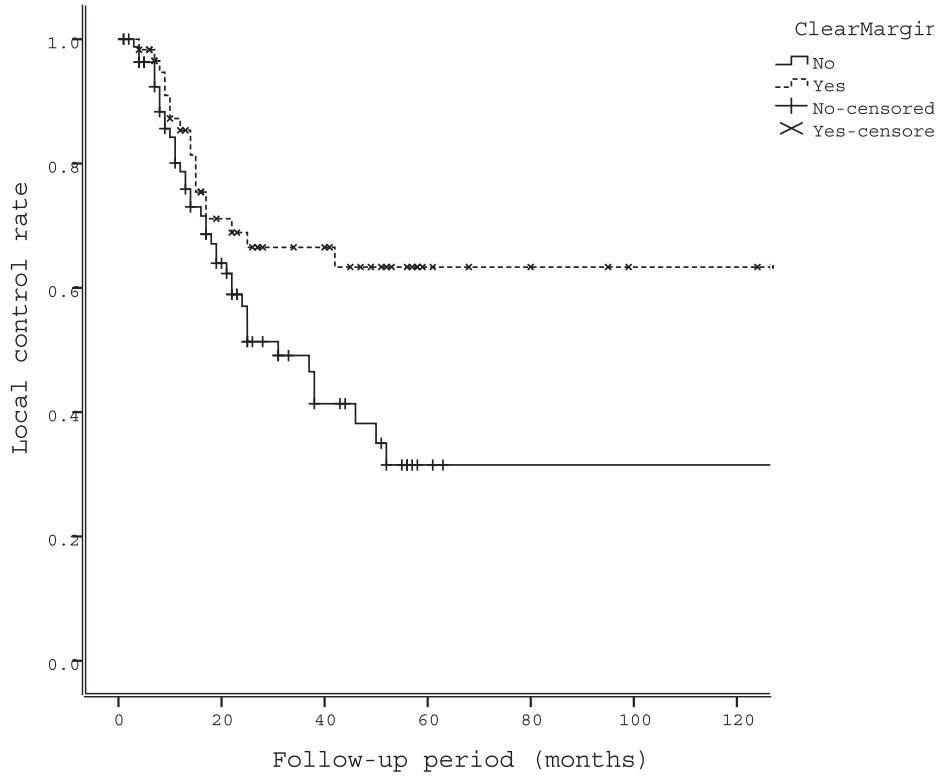

Fig. 1. Kaplan-Meier analysis for local control rate in 174 surgically treated patients with desmoid-type fibromatosis of the trunk and the extremities. Clear surgical margins were associated with a superior local control rate ($p = 0.003$).

Table 1
Univariate (left) and multivariate (right) cox-regression analysis of correlation of possible prognostic factors associated with primary recurrence of surgically treated desmoid-type fibromatosis of the trunk and the extremities. Median age of the patients that had surgical treatment was 34 years and the median size of the primary tumour was 41 cm^3. 95% confidence intervals of hazard ratio (C.I.) and p value for significance are displayed.

	C.I.	p	C.I.	p
Age				
>34 years	0.438–1.140	0.127	0.350–1.383	0.696
≤34 years				
Gender				
Male	0.732–1.824	0.535	0.645–2.455	0.501
Female				
Volume				
>41 cm^3	0.399–1.495	0.442	0.467–1.771	0.901
≤41 cm^3				
Location				
extremity	1.531–4.274	<0.001	1.270–5.888	0.010
trunk and pelvis				

after a median of 17 months (range 1–209 months), whilst re-recurrence was detected after a median of 12 months (range 1–131 months) following the second surgery. The likelihood of obtaining a clear margin did not differ significantly between the primary operation and operation for recurrent disease (Tables 2a and 2b).

2.3. Factors affecting the local control rate after surgery for recurrent disease

Recurrent desmoid-type fibromatosis displayed a different biological behaviour than primary disease. Contrary to the initial resection, quality of surgical margins had no effect on local control rate, and this was the case for the first ($p = 0.327$) as well as further recurrences ($p = 0.828$ and $p = 0.157$ for second and third respectively). In both univariate and multivariate analysis, age and gender of the patient, as well as size of and location of the lesion did not influence the local recurrence rate (Table 2b). Localization of the tumour within the same extremity (proximal, joint-near or distal) was not an important prognostic factor in the case of surgically treated recurrent disease ($p = 0.614$ for the upper extremity and $p = 0.928$ for the lower one).

Spontaneous regression or response to medical treatment and/or radiotherapy was documented in a minority (4 out of 26) of patients with a local recurrence who were managed non-operatively. Of the patients who were treated surgically for recurrence, 61% were disease-free at last follow-up, although multiple surgeries were eventually required for 37% of these patients. The effect of surgery on the oncological outcome was statistically superior compared to non-surgical treatment for patients with a first-time recurrence ($\chi^2 < 0.001$). However, when the disease relapsed again, surgical excision of further recurrences (second and third) was not associated with an improved local control ($\chi^2 = 0.343$ and $\chi^2 = 1.000$ respectively). Radiotherapy was performed in 36% of the cases of recurrent disease, and had no effect on the local control rate (odds ratio 0.693, 0.370–1.299). Chemotherapy on the other hand was given to 22% of the recurrent disease cases, and also had no significant effect on subsequent local recurrence (odds ratio 0.969, 0.402–2.338).

3. Discussion

Management of desmoid-type fibromatosis remains a challenge, due to the high risk of local recurrence resulting from the infiltrative growth pattern of the tumour. Surgery was initially the standard mode of treatment, although its necessity was later on

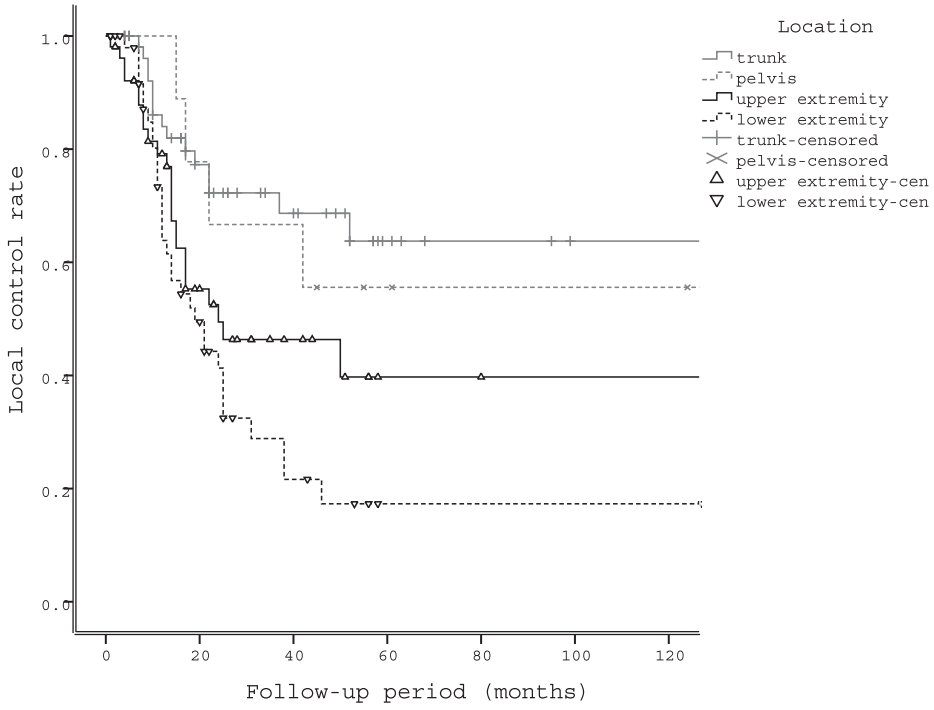

Fig. 2. Kaplan-Meier analysis for local control rate in 174 surgically treated patients with desmoid-type fibromatosis. Tumour localization in the trunk and the pelvis was associated with a lower risk for local recurrence ($p < 0.001$).

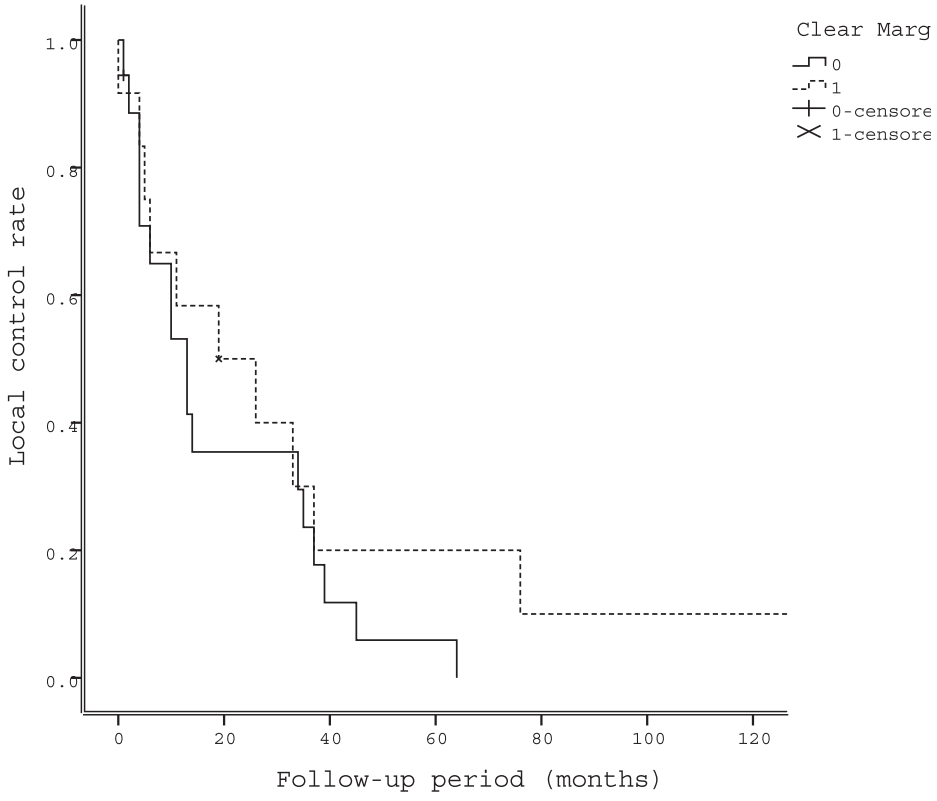

Fig. 3. Secondary local recurrence rate for desmoid-type fibromatosis following surgical excision of recurrent tumours analysed according to the Kaplan-Meier method. Clear margins had no effect on the outcome after surgery following secondary local recurrence ($p = 0.327$).

questioned in view the associated morbidity [32], the existence of medical therapies including the response of the tumour to non-steroidal anti-inflammatory drugs [4,19] and the fact that the disease often displays a stable pattern or even spontaneous regression in rare occasions [5,11,13]. Indeed, the latest European Society of Musculoskeletal Oncology (ESMO) guidelines suggest a

Table 2a
Quality of surgical margins and incidence of local recurrence (LR) after primary as well as surgery for first (LR1) and second (LR2) local recurrence for surgically treated desmoid-type fibromatosis of the trunk and the extremities. Actual percentages as well as 95% confidence intervals of hazard ratio (C.I.) are displayed.

	% clear margins	C.I.	% incidence of LR	C.I.
Primary surgery	41	37–49	44	36–52
Surgery for LR1	39	21–57	93	85–100
Surgery for LR2	44	9–89	88	70–100

Table 2b
Univariate (left) and multivariate (right) cox-regression analysis of correlation of possible prognostic factors associated with secondary recurrence of surgically treated desmoid-type fibromatosis of the trunk and the extremities. Median age of the patients that had a local recurrence was 33 years and the median size of the recurrent tumour was 142 cm^3. 95% confidence intervals of hazard ratio (C.I.) and p value for significance are displayed.

	C.I.	p	C.I.	p
Age				
>33 years	0.474–1.870	0.864	<0.001 - >100	0.964
≤33 years				
Gender				
Male	0.620–2.314	0.590	<0.001 - >100	0.904
Female				
Volume				
>142 cm^3	0.072–2.234	0.282	0.067–5.944	0.687
≤142 cm^3				
Location				
extremity	0.437–1.976	0.848	0.119–12.168	0.875
trunk and pelvis				

'watchful waiting' policy for many cases of this disease [6], but the results from this series predate this guidance.

The importance of the quality of surgical margins has been a matter of debate, as some studies have reported that clear margins are associated with improved local control [15,16,23,25,26] and others have failed to confirm this relationship [21,22,24]. This may be explained by the volume of the cohort studied and the follow-up period, the sensitivity of the method to detect local recurrence, the presence of confounding factors, as well as by how strong is the effect of a clear surgical resection on local control of the disease. In our series, clear (R0) resections were associated with a lower local recurrence rate, supporting the view that one should aim for uninvolved resection margins if the associated morbidity is acceptable. Our data corroborate the view that local recurrence of desmoid-type fibromatosis is a major concern, as the high recurrence rate observed after the primary resection in this series was in line with previous data [15,19,30]. Microscopically complete resections are difficult to achieve due to the infiltrative growth pattern of the lesion and most resections were intralesional.

Factors such as patient age and gender, tumour location and size have been proposed as prognostic factors by some authors whilst their importance has been disputed in other studies. We found that extremity lesions, especially those of the lower extremity, had a higher risk for recurrence as compared to trunk and pelvic ones. This was previously recognized in other large series [15,19,24], whereas other authors failed to confirm such a relationship [21]. Although the aetiology is largely unknown, it appears not to be a result of the quality of the resection, and may be attributed to the fact that extremity lesions may involve more anatomical compartments than axial ones. Moreover, there is conflicting evidence as to the significance of age on the clinical outcomes of desmoid-type fibromatosis. Age has generally not been shown to affect outcome in the majority of the studies [11,15,21,25], whereas some authors have shown a positive [27] or negative [19,29] effect of younger age. Female gender on the other hand has occasionally been shown to have a more favourable outcome [23], the majority of studies however showing no effect [11,19,21,24]. Both these parameters did not significantly influence outcomes in the present series. A meta-analysis of the available data may shed more light on this matter.

The patient characteristics and management outcomes of recurrent fibromatosis have not been adequately addressed to date. In cases of recurrent disease surgical excision was associated with a very high risk for re-recurrence, of approximately 90%, despite the fact that the probability of achieving a clear margin did not differ from primary resections. Surgical margin quality after re-resection was unrelated to the incidence of relapse, possibly due to microscopic residual disease in the surgical bed after the primary resection i.e. the surgical field being contaminated by the tumour. Despite the high risk of failure, surgery still has a role in first-time recurrence, but does not appear to offer significant advantage when the patients present with further recurrences.

The use of adjuvant radiotherapy reportedly improves local control, particularly with involved surgical margins [15–18]. We did not observe an advantage with prophylactic adjuvant radiotherapy, which is most likely due to the fact that the number of treated patients was limited. However, the side effects of radiation therapy are well-described and not dismissible given the low median age of the patients with desmoid-type fibromatosis [16–18]. Furthermore, since radiotherapy induces secondary fibrosis, it may render small areas of recurrent or residual disease non-detectable both clinically and radiologically. A baseline MRI after surgery, allowing a reasonable time interval for post-surgical oedema to settle, should thus be considered to facilitate interpretation of radiological findings in case of suspected recurrence.

Limitations of this study include the retrospective nature and the absence of a standardize surveillance schema, as well as the fact that it extends over many years. Its strengths are the fact that surgical techniques have remained constant throughout the years, that only patients primarily operated at a tertiary sarcoma centre were included, and the volume of the cohort studied.

The results of this study support the notion that a primary surgical resection with clear margins has the best chance of local control. Our policy is to recommend surgery for symptomatic cases which are resectable with the possibility of achieving adequate margins and limited morbidity. We acknowledge that the infiltrative growth pattern of the disease often results in contaminated margins, even in the hands of experienced surgeons. Given the rarity of the disease, the challenges in excising the lesion, and the need for multidisciplinary diagnosis and treatment, it should be best dealt in tertiary centres. If the patient is symptomatic and complete resection carries a significant morbidity, observation or medical treatment is preferable. We show for the first time that once the tumour relapses, local control is very difficult to achieve, as the incidence of recurrence after secondary surgery is very high, irrespective of the quality of surgical margins. Asymptomatic patients with recurrent tumours should not undergo surgical treatment as stable disease is very common, and spontaneous regression may occur in a small number of patients. Based on our findings, we advocate that second excision is considered in symptomatic recurrent patients if the morbidity is low, but accept that in this scenario, repeated surgical excisions (debulking) are often necessary to maintain 'local control'. Surgeon and patient awareness of these data can contribute to sound decision-making and realistic expectations in this challenging situation.

Ethical approval

Not required.

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None.

Author contribution

PT: study design, data collection and analysis, writing.
JS: writing.
RG: writing.
SC: study design, writing.

Conflicts of interest

None.

Research registration unique identifying number (UIN)

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