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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