Author’s response to reviews

Title: Desmoid Tumours of the Extremity and Trunk. A retrospective Study of 44 Patients

Authors:

Laura Wirth (laurawirth@web.de)
Alexander Klein (Alexander.Klein@med.uni-muenchen.de)
Andrea Baur-Melnyk (Andrea.Baur@med.uni-muenchen.de)
Thomas Knösel (Thomas.Knoesel@med.uni-muenchen.de)
Lars Lindner (Lars.Lindner@med.uni-muenchen.de)
Falk Roeder (Falk.Roeder@med.uni-muenchen.de)
Volkmar Jansson (Volkmar.Jansson@med.uni-muenchen.de)
Hans Dürr (hans_roland.duerr@med.uni-muenchen.de)

Version: 1 Date: 14 Sep 2017

Author’s response to reviews:

Dear Editors,

Thank you very much for reviewing this manuscript. We think that the comments of the reviewer will greatly increase the clarity of this study.

As proposed by the reviewer we made the following corrections:

1.) Shorten the manuscript on focusing on your major endpoint

Our major endpoint is local recurrence. We shortened the manuscript as proposed.

2.) Present data more comprehensively, especially avoid the confusion between patient data (44 patients) and procedures (54 treatments). I suggest sticking to patient data.

As proposed we did a number of changes more clarified in the following details.
3.) Abstract/Methods/Endpoints. You mention secondary lesions being part of endpoints you looked for. Suppress-it as precisely you indicate in the Introduction/First sentence that DF will not metastasize.

“Endpoint was either local recurrence (LR), progression of residual disease or secondary lesions.” Was changed to “Endpoint was either local recurrence (LR), progression of residual disease or ra-re non-metastatic secondary lesions at the same extremity.”

4.) Shorten and specify the Introduction. It may be unnecessary for the general reader to learn when DF has first been described, what its cause is, or which events characteri-ze the Gardner syndrome. In contrast, clearly distinguish between PAF-associated DF (with a germline APC mutation) and sporadic DF (harboring the CTNNB1 mutation (be-ta-catenin) in the tumor), which are considered mutually exclusive. Prognosis is quite different between the groups. Then put the basis for the discussion concerning the ac-tual place of surgery in DF by replacing the sentence ” In recent years resection of the tumour and/or radiation were proposed as principal treatment” by "In former years re-section of the tumour and/or radiation were proposed as principal treatment." New text: “There are two group of patients with prognosis quite different between both. Pa-tients there DF is associated with the autosomal dominant familial adenomatous polyposis (FAP) syndrome characterized by a germline mutation of the adenomatous polyposis coli (APC) gene and a risk of 30% developing DF.[1] And patients with sporadic DF (harboring the CTNNB1 mutation (beta-catenin) in the tumor, which are considered mutually exclusive.” The Gardner syndrome was deleted. “In former years resection of the tumour and/or radiation were proposed as principal treatment.” was set instead of the former sentence.

5.) Active observation of DF has been has been suggested nearly a decade ago. You may cite:


We changed the sentence in the introduction to “Therefore the European Sarcoma Network Working Group (ESNWG), the European Organization for Research and Treatment of Cancer (EORTC) and others consider an initial period of active observation in extra abdominal DF as pro-posed already more than a decade ago by some authors.[2-6]” including the citations.
6. Specify patient data. For a better understanding, indicate numbers of patients, not percentages and stick to patient data, not treatments. It may avoid confusing sentences like: "37 patients had primary, 17 recurrent disease". This totals 54 patients. In reality, I guess, 27 patients had primary and 17 recurrent disease. You may put these data into a table.

Suggestion of Table:

<table>
<thead>
<tr>
<th>Age</th>
<th>Mean (range), y</th>
<th>39.4 (14 - 69)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex</td>
<td>F</td>
<td>25</td>
</tr>
<tr>
<td></td>
<td>M</td>
<td>19</td>
</tr>
<tr>
<td>Tumour size</td>
<td>Mean (range), mm</td>
<td>7.7 (1 - 25)</td>
</tr>
<tr>
<td>Tumour site n (%)</td>
<td>Upper limb</td>
<td>18 (40)</td>
</tr>
<tr>
<td></td>
<td>Lower limb</td>
<td>15 (35)</td>
</tr>
<tr>
<td></td>
<td>Trunk (wall?)</td>
<td>6 (14)</td>
</tr>
<tr>
<td></td>
<td>Pelvis</td>
<td>5 (11)</td>
</tr>
<tr>
<td>Presentation</td>
<td>Primary</td>
<td>27 (61)</td>
</tr>
<tr>
<td></td>
<td>Recurrent</td>
<td>17 (39)</td>
</tr>
<tr>
<td></td>
<td>PAF-associated</td>
<td>X</td>
</tr>
<tr>
<td></td>
<td>Sporadic</td>
<td>Y</td>
</tr>
</tbody>
</table>

In fact we had 44 patients. In those 44 patients we did 54 therapies. 37 of them primary, 17 on recurrent disease. If a patient was treated elsewhere first and had then therapy in our institution, this was also classified as recurrent disease. So as stated also in #2 we tried to clarify that more precisely and included, as proposed, a table for better understanding. We hence reduced the text and also used now numbers.

“The patients details are described in Table 1. In 4 cases, multiple lesions were evident. None of our patients had FAP-associated disease but routine GI screening (colonoscopy) was not done.”
7. How many patients had PAF-associated DF and how many sporadic?

Very important question. We had no patient with FAP- or PAF-associated disease. But we did no routine screening. We stated that as described above.

8. Treatment modalities remain unclear to me, even after several readings of the manuscript:

a. Surgery: 50 resections and 4 other treatments were given to 44 patients, the latter 4 all in recurrent DF (RecDF). Consequently, 13/17 RecDF were operated, leaving 37 surgeries for 27 primary DF (PrimDF). Right? Consequently 10 patients with PrimDF were operated twice. Why? For recurrence? In Results (Page 6, Alinea 52) you indicate that in a total 10 patients had a recurrence. Ciphers do not fit. Please specify.

b. Radiotherapy: 21 patients received radiotherapy. How many with PrimDF and RecDF, respectively?

A) 44 patients with 54 procedures. 50 surgeries, 4 non-surgical. Those 4 only in re-current cases. 37 primary, 17 recurrent disease. All patients with primary disease had surgery (37) in addition 13 surgeries in recurrent cases. The obviously mis-leading factor for the reader is, that some patients had more than 1 recurrence and so had surgery several times. 7 patients had first resections elsewhere and showed recurrent disease. From those 3 had then one resection 2 one resection and then second recurrence and conservative therapy, one a second recurrence and 2 resec-tions and one 3 resections. This results in 10 surgeries and 2 conservative treat-ments. In 5 patients with primary disease 2 had conservative treatment of recur-rence and 3 a second resection. This results in 3 surgeries and 2 conservative treatments.

So we apologize for the confusion and clarified that now in the patient and meth-ods section with adding the sentence “5 of the recurrences developed in 5 patients with primary resections included also in this study. 7 patients had recurrences after first treatment elsewhere. From those 7 patients 3 there treated a second time for a further recurrence and one for a second and third recurrence.”

B) Radiotherapy was applied in 21 patients. One patient was lost to follow-up leaving 20 radiation treatments. 19 of those in surgically treated cases as described in Ta-ble 2. The one with radiation as final treatment of recurrence is as described in the text progressive. After surgery 13 treatments in primary disease (1 recurrence), 6 in recurrent disease (4 recurrences). We added that to now Table 2.
9. Description of R1 resection (Page 5, Alinea 26). Omit the term "capsula" when defining R1 resections, because DF tumors typically are not encapsulated. Prefer "R1 if the margins were contaminated by the tumour".

This is right and was changed.

10. Univariate/multivariate analysis. Replace your sentence "Neither in univariate nor in multivariate analysis margins, radiotherapy, sex, or size of the tumour showed a significant impact on local recurrence." by "In univariate analysis margins, radiotherapy, sex, or size of the tumour did not show a significant impact on local recurrence." Effectively, when variables are insignificant at univariate analysis, they are not included into the multivariate model. Your two significant independent prognostic factors for recurrence were recurrent disease and age. Why did you call recurrent disease a "surgical factor"? Specify also HR and CI for multivariate analysis results.

This is also right and was changed. To be honest, I can’t remember why we called recurrent disease a surgical factor. This was changed to “Recurrent disease was a negative factor on LR.” in both sentences. We added p, HR and CI values on page 7.

11. Did you get any information about morbidity or functional outcome, which are important endpoints in a surgical series concerning an indolent (not a "benign") disease?

We thought about that. But to be honest, it was a great effort to track those young and very mobile patients through Germany and in some cases also in Russia. The one lost was from the UAE. We had many letters to the German authorities and phone calls to patients and ancestors to get reliable results regarding local recurrence. So there was no really scientific satisfying way to get a representative and valid information on functional outcome as for example MSTS or Toronto score which we use in some other studies. This would have ended in 50% of patients with results without knowledge whether those results are really representative.

12. Discussion

A) Begin by commenting first your own findings. It is the high frequency of new recurrences after surgery for recurrence. For a better understanding, indicate in table 1 the number of recurrences by patients, not procedure. This may be followed by the quality of resection debate.
This was done. In the Table (now #2) we added as described above the information regarding radiotherapy in primary and recurrent disease. We found it rather difficult to focus on the patients and not on the procedures because margins or radio-therapy then could not longer be used as a factor because of mixing variables per patient. We hope that the clarifying statement at the patients and methods section will help for that.

B) Carefully discuss age as a prognostic factor. Effectively, the risk of recurrence also depends on tumor site which is age-dependent. For example harm-string/popliteal DF occur in young patients (16-18 years) and almost ever recur. In contrast, abdominal wall DF which also occur in young patients < 40 years (women # 36 years) almost never recur.

Done. Regarding location we have to less patients to draw any conclusion.

C) Discuss the place of radiotherapy PrimDF vs RecDF.

We added “Striking in our study was the high recurrence rate of 4/6 patients irradiated af-ter recurrent disease as compared to 1/13 in primary disease. The role of radiotherapy in DF management remains controversial and is extensively debated. [7]“

D) Avoid discussing colonoscopy (irrelevant)

Deleted.

E) or medical treatments (too seldom in your series), or pediatrics.

Deleted.

F) Contrary to your affirmation of a part location no clear prognostic factors being defined in DF (Page 8, Alinea 5), those have been discussed abundantly in the literature. You may cite Salas S, et al. JCO 2011;29:3553-3558. These authors identified age, size and site as being independent prognostic factors for PFS.
We added: “In the last years a number of clinical factors as e.g. age, size and site had been identified for progression free survival. [8] instead of “Despite clinical factors as e.g. location there are no clear prognostic factors.[9]”

G) There was no difference between resections R0 and R1 in PFS. Conclude that other treatment modalities should be preferred over surgery when DF ultimately recur.

In the conclusion it now reads: “If surgery is necessary, surgical margins are less important than keeping function for the patient. There was no difference between R0 and R1 resections in Local recurrence free survival. Other treatment modalities should be preferred over surgery when DF ultimately recurs.”

13. Restraine the number of references to 25 or 30.

Hard work. Reduced from 57 to 39.