Author's response to reviews

Title: High incidence of metastatic disease in primary high grade and large extremity soft tissue sarcomas treated without chemotherapy.

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Version: 2 Date: 18 April 2006

Author's response to reviews: see over
Dear Madam or Sir,

We appreciate the valuable comments of both reviewers and consider their statements while making the amendment of our work.

Please find attached the corrected version of our manuscript with the changes in the document highlighted.

Sincerely yours

Benedikt Leidinger MD
Reviewer 1:

Reviewer: Claus Belka

Reviewer's comment:
“The most severe problem I have with this paper is the fact that within the setting of already published randomized trial a completely different picture emerged. Although the authors discuss this fact I can not accept their conclusion that “The advantage of preoperative radiation therapy is lesser toxicity and probably a better patient function.”

Answer:
We expelled this statement from our conclusion. The reviewer correctly criticises our statement „The advantage of preoperative radiation therapy is lesser toxicity and probably a better patient function“. It is not meant to be our conclusion, but a citation from Davis AM, O’Sullivan B, Turcotte R, Bell R, Catton C, Chabot P, Wunder J, Hammond A, Benk V, Kandel R et al: Late radiation morbidity following randomization to preoperative versus postoperative radiotherapy in extremity soft tissue sarcoma. Radiother Oncol 2005, 75(1):48-53.

This question in this strong study upset is very well answered and we can only refer to this statement. Our data is a retrospective review and we cannot answer this question by our own data although wound infections and other combined therapy related complications were equally distributed (p=0.22). The statement is withdrawn from the conclusion.

Reviewer’s comment:
“Our data indicates that the elapsed time to tumour resection after preoperative radiation might play a role for the development of metastasis. This deteriorates our results in the preoperative study group.”

Answer:
There is a deterioration of the outcome in our preoperative study group. The overall (p=0.0248) and relapse free survival (p=0.104) were worse in this group. 56% (23/41) of the population developed metastatic disease. The risk of metastasis was higher in the group with preoperative irradiation: the preoperative radiotherapy group was associated with 7/8 (87.5%) and the postoperative group with 16/33 (49.5%) cases of metastatic disease (p=0.046, chi square). Occurrence of metastasis was not influenced by surgical margin (p=0.68) or local control status (p=0.24). Both groups did not receive chemotherapy. Average age, stage, tumour size, depth, anatomic localisation and the resection margin were equal in both groups. They only differed in the way when radiation therapy was applied. We do not believe that the deterioration of the results is caused by the kind of therapy but as we found out in the preoperative RTX group the delay to tumour resection amounted 8 weeks on average. This is a well described fact also by other authors due to soft tissue recovery e.g. (Virkus et al. 2002, Willet et al. 1987) and it may happen that a reduction in tumour volume may only be achieved in 40-60% with even tumour progression in 12-15% during RTX (Brant et al. 1990, Pitson et al. 2004) in the preoperative group. So the elapsed time to tumour resection may play a role for the development of metastasis because our study group had mainly <50% tumour necrosis after preoperative RTX.
Reviewer’s comment:
“When preoperative radiation has to be used, a combination of RTX and offensive chemotherapy with modern treatment protocols shows advantageous results.”

Answer:
This part of our statement has to be corrected for we have not applied offensive chemotherapy or other (neo)adjuvant treatment protocols in addition. We could only compare our high overall metastasis rate of 56% with other studies who used multimodal treatment protocols in high risk patients and showed by far better results.

We state:
“This outcome may support the thesis that a combination of RTX and offensive chemotherapy with multimodal treatment protocols is advantageous”

Summary

Our new title is:

Incidence of metastatic disease in primary high grade and large extremity soft tissue sarcomas treated without chemotherapy

Our new conclusion is:

Without chemotherapy there remains a high risk of metastasis in AJCC grade 3 extremity soft tissue sarcoma patients. Pre- or postoperative radiation seems to offer equal local control. When no chemotherapy is applied the elapsed time to tumour resection after preoperative radiation might contribute to the development of metastasis especially when the response to therapy is low. This outcome may support the thesis that a combination of RTX and offensive multimodal treatment protocols is advantageous in such high risk patients.
Reviewer's comments:
*Due to the limited total number of evaluable pts and small sample size for comparison (e.g. pre-RTX) no firm conclusion should be drawn upon the relevance of these factors on outcome.*

*In addition, selection bias for pre- vs. post-RTX might have a major influence (e.g. was initial irresectability independent of size of the tumor included for the therapeutic decision?).*

Answer:
An acknowledged deficiency of our study might be the preselection bias inherent in all review studies making validity and reliability of the results questionable. Although we did not intend to preselect patients for any of the two examined groups our patients are not equally proportioned (33-8) and smaller than other reported series. Despite, they are restricted to a well-defined cohort of patients treated in a uniform manner and relatively well balanced (see Table I-II).

**Average age, stage, tumour size, depth, anatomic localisation and the resection margin were equal in both groups.**

The decision whether to apply preoperative or postoperative RTX was not dependant on the size of the tumour for we have shown that both study groups had the same average tumour size and identical anatomical distribution.

With our work, we do not intend to state that postoperative radiotherapy is preferable in soft tissue sarcomas at all. We found that without chemotherapy there is a comparable high risk for metastasis in grade 3 and large tumour size patients. Not the kind of RTX but even more the elapsed time to tumour resection after preoperative radiation might contribute to the development of metastasis especially when the response to therapy is low.

Contributing to the distinguished criticism of the reviewer we corrected our conclusion and the title of the study:

**Title:** Incidence of metastatic disease in primary high grade and large extremity soft tissue sarcomas treated without chemotherapy

**Conclusion:** Without chemotherapy there remains a high risk of metastasis in AJCC grade 3 extremity soft tissue sarcoma patients. Pre- or postoperative radiation seems to offer equal local control. When no chemotherapy is applied the elapsed time to tumour resection after preoperative radiation might contribute to the development of metastasis especially when the response to therapy is low. This outcome may support the thesis that a combination of RTX and offensive multimodal treatment protocols is advantageous in such high risk patients.