Author's response to reviews

**Title:** Re-surgery and chest wall re-irradiation for recurrent breast cancer - a second curative approach

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**Author's response to reviews:** see over
BMC Cancer
BioMed Central Editorial Board:
Dr. Diana Steinmann/ Mr. Jack Cochrane

Dear Dr. Steinmann,
Dear Mr. Cochrane,

thank you for the kind handling of our manuscript entitled “Re-surgery plus chest wall re-irradiation for recurrent breast cancer – a second curative approach!” by Arndt-Christian Müller, Franziska Eckert, Vanessa Heinrich, Michael Bamberg, Sara Brucker and Thomas Hehr.

Please find enclosed our revised manuscript which was carefully revised following the suggestions of all reviewers and the editors. Please find our replies to the reviewer’s comments in the attachment. We would like to thank the reviewers for their excellent suggestions that helped us to significantly improve the manuscript. We uploaded the revised manuscript and the manuscript with marked changes as additional file. The changes were highlighted with different colours and with the tool “Track changes”.

The data have not been published previously and all authors agreed to the submission of the revised manuscript. No conflict of interest does exist. We hope that the manuscript can now be accepted for publication in “BMC Cancer”.

If you have any further question, please don’t hesitate to contact me.

Sincerely,

Arndt-Christian Müller, MD

29/03/2011

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A) Comments to the editor:

We revised the manuscript according to the editorial requests and highlighted changed parts in grey.: 

a) Please add the following details to the Methods section of the manuscript: Ethics - Experimental research that is reported in the manuscript must have been performed with the approval of an appropriate ethics committee. Research carried out on humans must be in compliance with the Helsinki Declaration (http://www.wma.net/en/30publications/10policies/b3/index.html), and any experimental research on animals must follow internationally recognized guidelines. A statement to this effect must appear in the Methods section of the manuscript, including the name of the body which gave approval, with a reference number where appropriate. Informed consent must be documented. Manuscripts may be rejected if the editorial office considers that the research has not been carried out within an ethical framework, e.g. if the severity of the experimental procedure is not justified by the value of the knowledge gained.

=> We discussed this issue with the Ethic commission (Ethikkommission der Medizinischen Fakultät, Gartenstrasse 47, 72076 Tübingen). The Ethic commision decided that no approval is necessary for this retrospective analysis. The letter of the Ethic commision is attached (next to last page). As requested, we added the following sentences to the method part (paragraph 1): “After discussing the intended analysis, the institutional review board (Ethikkommission der Medizinischen Fakultät, Gartenstrasse 47, 72074 Tübingen) had no objections (Nr. 116/2011A).”

b) We recommend that you copyedit the paper to improve the style of written English. If this is not possible, you may need to use a professional copyediting service. Examples are those provided by the Manuscript Presentation Service (www.biomedes.co.uk), International Science Editing (http://www.internationalscienceediting.com/) and English Manager Science Editing (http://www.sciencemanager.com/). BioMed Central has no first-hand experience of these companies and can take no responsibility for the quality of their service.

=> The manuscript was copyedited by www.biomedes.co.uk. Modifications of the copyeditor Biomedes were highlighted in green. Biomedes was mentioned in the acknowledgement: “Copyediting was performed by Biomedes (www.biomedes.co.uk).” The certificate of Biomedes is attached (at the last page).

B) Comments to Reviewer 1 (Sabine Oldenborg)

We followed the suggestion of reviewer 1 and modified the requested paragraphs accordingly (marked by track changes).

B1. Abstract

a) In general: Why did you select patients with a favourable prognosis? This could also be a very worthwhile palliative treatment regimen.

=> Patients with favorable prognosis were chosen in cause of curative intent of treatment as stated in the method part (exclusion criterion palliative treatment intent). It is a good idea to treat patients with palliative intent, too. We will consider this protocol also for palliative situations in the future since side effects were tolerable. For clarification, we inserted “curative intent” in the introduction (as requested in B2.c), in the Abstract (line 2) and B2.a.

b) Paragraph 2 (Methods): Remove “due” in “The median exposure due to pre-radiation was 54Gy”.

=> We changed the sentence in “The median pre-radiation exposure was 54Gy”

c) Paragraph 3 (Results): Please include local control and survival rates for patients with and without surgery separately as you are comparing those groups in your conclusion. You...
can remove disease-free-survival rate, as this is not your main endpoint? Furthermore I would use 3-year estimated risk rates as your 5-year estimates are not reliable because of the small number of patients (large CI).

=> The data for patients with and without surgery were inserted in B1.d (see below). The conclusion was modified as requested. We focused on overall survival data dependent on residual tumor load and time to recurrence in the Abstract. The disease-free survival rate was removed as requested. We preferred 5-year estimates because median follow-up for survivors reached 48 months and a comparison with other publications is easier with this common definition. We discussed this issue with the Institute of Biostatistics in Tübingen. From statistician’s point of view this procedure is correct. Moreover, the requested three-year estimates are readily identifiable in the figures. The requested data on local control and performed surgery were inserted in the result section (B3.n last sentence; no sub-analysis of tumorsize was performed in accordance with B4.d). In cause of restrictions regarding character number/word count, we did not present or discuss sub-analysis data on local control in the Abstract (as done in the result part).

d) Paragraph 3 (Results): “Not performed resection and time to recurrence within two years were associated with significantly inferior survival” I would rephrase this sentence as follows: “Significantly inferior survival was associated with recurrence within two years and presence of macroscopic tumor load”.

=> We changed the sentence in “Significantly inferior survival was associated with recurrence within two years (40 vs. 71%, p<0.01) and presence of macroscopic tumour load (24 vs. 75%, p=0.03)”.

e) Paragraph 4 (Conclusions): You are neglecting the role that hyperthermia had in achieving long-term local control. It certainly had an important effect in your R1 and irresectable patients and you can not exclude a positive effect in your R0 group as all patients with poorer prognostic factors received hyperthermia (in your R0 group this concerned patients with close resection margins). "The local control rate is encouraging and translates into improved prognosis for the majority of patients”. Improved compared to...? Compared to historical control cases without reRT or compared to your irresectable patient group? Your irresectable patients were unable to receive surgery, so any comparison with that group does not make any sense. I think you should restrict yourself to answering your research question e.g. the effect of re-irradiation combined with hyperthermia +/- surgery, not the effect of preceding surgery as your patient group is too small and too heterogeneous to draw conclusions in that respect.

=> We agree with the reviewer and changed the conclusion of the Abstract part as suggested in point B6 (i.e. same conclusion in Abstract and Conclusion section): “Repeat radiotherapy for breast cancer recurrence, with total radiation doses of 60 Gy and the addition of hyperthermia in the majority of patients is feasible. This treatment has acceptable late morbidity and results in improved prognosis particularly in patients who have undergone previous resection of the recurrence.”

We comment, that hyperthermia did not have a sig. effect regarding local control or overall survival.

B2. Background

a) This part is quite long. You can skip the first 8 lines of paragraph 1 ("The local failure rate ....metachronous metastases") and start with data on recurrent breast cancer and describe the present problem.

=> The first 8 lines (paragraph 1) were removed and the problem description was brought forward:"Treatment of pre-radiated regions remains a therapeutic challenge in general. In particular in breast cancer, the curative potential of local (surgery, radio-therapy) and systemic (antihormonal therapy, chemotherapy) treatment of loco-regional recurrences remains unclear [1,2]."
b) I miss a paragraph dedicated to the role of hyperthermia combined with re-irradiation. Most of your patients received this treatment emerging from your methods. You should indicate the reason for this combination in your introduction; based on the results from the prospective trial, which you mentioned in the discussion, hyperthermia has become a standard treatment for patients with recurrent breast cancer in previously irradiated area.

=> We added two sentences explaining the role of hyperthermia: “For irresectable recurrences, re-irradiation combined with additional hyperthermia enhanced efficacy i.e. local control compared to radiotherapy alone by approximately 20% [8,9]. On the basis of the results from these prospective trials, thermoradiotherapy has become a standard treatment for patients with irresectable recurrent lesions particularly those in previously irradiated areas.”

c) Paragraph 4: Sentence starting with "Therefore, this retrospective study..." you should mention here that you aim for curation.

=> “with curative intent.” was inserted.

d) Paragraph 4: Sentence starting with “In our series, long-term local control was achieved.....prognosis” is a result and does not belong here.

=> Sentence was removed.

e) Paragraph 4: Last sentence remove “including the value of hyperthermia”. This has already been demonstrated in prospective trials.

=> Phrase "including the value of hyperthermia" was removed.

B3. Methods

a) Paragraph 1: Replace “other new primaries” by “other new primary tumors”

=> We changed this sentence in accordance with the copyeditor: “new primary tumors unrelated to their breast cancer or receiving palliative treatment were excluded.

b) Paragraph 2: "The median exposure due to pre-radiation was 54 Gy" remove “due”

=> We changed the sentence in “The median pre-radiation exposure …”

c) Paragraph 3: "Thereby, parasternal nodes were irradiated in 7 patients (17%) in mixed-beam-technique”. Remove "Thereby".

=> "Thereby" was removed.

d) Table 2: What was the tumor size in patients with irresectable disease?

=> Irresectable disease was defined as tumor infiltrating bony structures (i.e. ribs) or vessels or nerves. The tumor extent had to be restricted to the chestwall or regional lymphatics enabling a curative radiotherapy as stated in the inclusion criteria (treatment of complete tumor load). We did not measure or compare different tumor volumes because further subgroup analysis for 11 patients seemed not advisable.

e) Am I correct to assume that ~50% of patients received concurrent systemic therapy?

=> No, systemic chemotherapy was given sequentially to re-radiation treatment. Usually, chemotherapy was given after removal of recurrence before the start of re-irradiation or as Sandwich chemotherapy before and after Re-RT. In rare cases chemotherapy was given after Re-RT. For clarification, we added “sequential” in table 2 and in the method section and adapted the sentence in the next paragraph: “Further treatment before or after repeat radiotherapy consisted of sequential chemotherapy or hormonal therapy, as listed in Table 2.”
f) Paragraph 4: "In case of close or positive margins as well as definitive treatment superficial radiofrequency hyperthermia was offered". Why did not all patients with R1 or R2 resection or irresectable disease receive hyperthermia then?

=> We offered this treatment to all patients but some patients had contraindications (thrombosis, cardiac disease) and others refused hyperthermia. A sentence regarding treatment compliance was added as requested (see B4.a).

g) How and where did you measure temperature?

=> Temperature was measured by standard temperature probes at the surface (skin). We usually used 6 probes. The distance between each probe was 1cm.

h) What was the reason for restricting power to 10-25 watt in your study patients? We usually apply 50-150 watt when using 434 MHz applicators. According to the ESHO quality assurance guidelines treatment duration should be 60 minutes at 43°C, this implicates that some of your patients could not complete treatment as planned?

=> The quality assurance for superficial hyperthermia was done according to ESHO guidelines as published by our working group in the Int. Journal of Hyperthermia (Thermoradiotherapy for locally recurrent breast cancer with skin involvement T. Hehr, U. Lamprecht, S. Glocker, J. Classen, F. Paulsen, W. Budach, M. Bamberg Int J Hyperthermia 2001;17:291-301 IF 1.086). The applied power depends on the used applicator. We used a spiral shaped SA-115 applicator. The applied power of 10-25 Watt is a typical value for a spiral shaped applicator with one antenna. Presumably, the reviewer used another type of applicator (434 MHz). The total power of an applicator is calculated by the sum of power of each antenna. If the reviewer used an applicator with more antennas the higher power is explained. Another reason for higher power is the geometry of applicator and length of connection. We use short connections and therefore need lower power. That’s why, the power alone does not tell something about quality of hyperthermia. The quality assurance/maintenance is performed in Tübingen 6x/year including phantom measurements. For clarification and to avoid a too detailed description of hyperthermia (issue is re-irradiation), we deleted the sentence about power and referred to the mentioned publication in the method part. "Hyperthermia was performed in accordance with the ESHO-Guidelines. A detailed description of hyperthermia with SA-115 has been published [Hehr et al.].”

Some of the patients did not tolerate hyperthermia as planned for 60-90 minutes. This happened usually in the end of radiation treatment due to radiation skin toxicity and local pain due to hyperthermia. We added a sentence on treatment compliance in the result section as requested (B4.b). On the other hand, hyperthermia was given twice the week compensating shortened applications in comparison to other series with one hyperthermia per week.

i) What was the size of your BSD applicator? Was it capable of covering the entire re-RT field or at least the entire tumor volume?

=> The size of the BSD applicator was 15cm in diameter and covered at least the entire tumor volume. In case of larger or irregular tumor volumes, we treated patients at d1/d4 at main tumor volume and on d2/d5 at the remaining tumor volume, without overlapping each week.

j) Paragraph 5: What were the specific toxicities that you investigated? What is your definition of late toxicity?

=> We modified the paragraph about toxicity and added the specific measures: "The patient records and questionnaires were reviewed with respect to radiation-induced side effects according to CTC 3.0 [11] and LENT-SOMA [12]. Acute radiation dermatitis was investigated during and after re-irradiation and documented according to CTC 3.0. Late toxicity was defined as side effects occurring three months after treatment. Radiation dermatitis, induration/fibrosis, telangiectasia, pericarditis, pericardial effusion and pneumonitis were
investigated according to CTC 3.0. In addition, side effects related to skin (fibrosis/teleangiectasia) and lung (fibrosis) were documented according to LENT-SOMA.”

k) "Local failure was defined as any recurrence of tumor in the ipsi-lateral chest wall or in mastectomy scars. Regional failure was defined as any recurrence of tumor in the ipsilateral regional nodes". Did you not use the boundaries of your applied reRT field to define locoregional recurrences as this is the area you treated?

=> Generally, we used the boundaries of our RT-field. But a few patients received their first radiation treatment at other institutions. In these patients, the recurrence occurred in the scars or was located in a hyperpigmented area (typically treated by radiotherapy) at the chestwall or within the breast. That’s why, we used this more generous definition which was used by clinical trials, too.

l) You included 3 patients with a regional recurrence, did you not include them in your local control analysis?

=> Treatment of regional recurrences included always parts of the chestwall due to anatomical overlap (nodes in the axillar lobe of the breast etc.). Therefore, re-treatment of the chestwall occurred in all cases. Consequently, all patients with local treatment were included in the analysis.

m) How did you analyse local control for patients with irresectable disease?

=> For clarification, we added/modified the following sentences to/in the method part:” After re-treatment, senological examinations were performed every three to six months during the first two years and every six to twelve months thereafter. These investigations included clinical examination and imaging if required. After re-treatment, patients were monitored at least annually in terms of toxicity by a radiation oncologist.”

n) Paragraph 6: What were your main endpoints? What factors did you include in statistical analysis? For instance, did you include tumor size in case of irresectable disease? ~50% of you patients appear to have received systemic therapy in addition to the re-irradiation, surgery and hyperthermia, how did this effect local control and survival and how did time interval to recurrence effect local control?

=> As requested, we performed additional statistical analyses regarding local control (reviewer 2). We detected sig. differences for antihormonal treatment and number of recurrences until re-irradiation. All other factors (N-stage, nodal irradiation, grading, concurrent hyperthermia, surgery, margin status, time to recurrence, sequential chemotherapy) did not significantly affect local control. In cause of the requested additional analyses we extended the main endpoints. For clarification, we added:

“…were the main endpoints and these were…. Further subgroup analyses were performed for local control and overall survival. Initial tumor parameters (nodal stage, estrogen receptor status, time to first recurrence (≤2 years vs. >2years), number of recurrences until re-irradiation (one vs. more than one)), surgery of recurrence, margin status, concurrent hyperthermia, lymph node irradiation, sequential chemotherapy and antihormonal therapy were investigated as factors.”

We did not include tumour size due to the smallness and heterogeneity (different sizes combined with different risk profiles) of the patients with irresectable disease (please see above B3.d). As requested, we modified the paragraph about local control and inserted additional significant findings in the result section:

“Endocrine therapy increased local control (93 vs. 31%, p=0.01). However, local control decreased significantly from 91% to 31% (p=0.02) if at least two recurrences were experienced before re-irradiation was administered. A time period of less than two years to the first recurrence (<2 years vs. ≥2years: 16 vs. 68%, p=0.14) did not significantly lower local control. However, long-term local control at last follow-up improved to 70% (n=35/42) owing to curative resections of recurrences after re-irradiation in three patients.” … “A sub-
analysis of concurrent hyperthermia for R1-resected patients revealed a prolonged local control (86 vs. 50%, p=0.19; with one salvage treatment after re-irradiation 93 vs. 50%, p=0.05) but this was not significant. No other investigated factors significantly affected local control (data not shown).”
Consequently the discussion was adapted (see B5.b)

B4. Results
a)  Paragraph 1: “The median time to local recurrence …first recurrence (Table 2)”.
This information belongs in the method section.
=> This sentence was removed to the method section and the following sentence of the method section was replaced “Local recurrences occurred with a median time interval of 33 months.”

b) Did all your patients complete treatment as planned? I miss a paragraph on treatment compliance and one on treatment response for patients with irresectable disease.
=> For clarification, we added the following sentences: “With respect to total dose, patients completed radiation treatment as planned. For one patient, a treatment break of two weeks was required owing to acute radiation dermatitis. Concurrent hyperthermia was offered to all patients but some had contraindications (thrombosis, cardiac insufficiency and hypertension) and others refused hyperthermia, leading to an omission rate of 31%.” (paragraph 1)
“Local failures occurred in 10 patients (R0: 3/14, R1: 3/16; R2/irresectable: 4/12).” (paragraph 2)

c) Paragraph 2: You should use 3-year risk estimates as your 5-year rates are less reliable.
“In three patients local recurrences after re-irradiation were curatively resected. In one of the three patients additional brachytherapy was performed to a total dose of 30 Gy. Including patients with salvage treatment, seventy percent (n=35/42) achieved 5-year local control.” If I understand it correctly, these 3 patients developed a failure after your intended treatment. You should therefore sensor them at date of recurrence and exclude them from further analysis.
=> All data on local control were censored to the time of “first” recurrence after re-irradiation. Our intention was to demonstrate that even in case of recurrence after re-irradiation salvage surgery achieved curation in single cases. Therefore, these additional data including salvage after re-irradiation were provided (not censored for recurrence after re-irradiation but censored for recurrence after salvage).

d) The same goes for the section starting with “Evaluating the relevance of margin status….,” and the section starting with “More-over, concurrent hyperthermia….”. Furthermore, your patient group is too small to investigate the effect of subgroup of patients that received hyperthermia in a subgroup of resected patients. I would investigate the role of hyperthermia with respect to the whole study group. If you do decide to persist with subgroup analysis I would be interested in the effects of hyperthermia in patients with gross residual or irresectable disease and the effect of tumor size in this group. Furthermore, ~50% of your patients received systemic therapy in addition to the re-irradiation, surgery and hyperthermia, how did this affect local control and survival?
=> We agree with the reviewer and removed the subanalysis.

e) Paragraph 3: Last sentence: replace “an insignificant increase” by “a statistically not significant increase”.
=> The sentence was changed in “… a statistically not significant increase”.

f) Paragraph 4: “Significant worse overall survival….”: replace “significant” by “significantly”, was accordingly changed.
g) “Re-irradiation at second recurrence resulted in the lowest estimated survival curve with 34% overall survival” How did you analyse this? Did you create two groups (2 recurrences versus 1, 3-5)?

=> We performed a sub-analysis Re-RT at first vs. Re-RT at second recurrence (23 vs. 13 patients, patients with more than two recurrences were not included due to small subgroups). For clarification we added the patient number and the following phrase: “compared to 75% overall survival at first recurrence”

h) Paragraph 5: “Further treatment for any but local relapse after repeat radiotherapy consisted of chemotherapy or hormonal therapy, as listed in Table 2”. This should be part of the method section.

=> The sentence was modified for clarification (sequential chemotherapy) and moved to the method part:” Further treatment before or after repeat radiotherapy consisted of sequential chemotherapy or hormonal therapy (Table 2).”

i) It appears from table 2 that ~50% of you patients received concurrent systemic therapy (17 chemo, 19 hormonal treatment), whereas it is stated in the text that 15 patients received systemic treatment for regional relapse or distant metastases occurring after re-irradiation, or is this not true?

=> Please see above (B4.h). Systemic treatment was performed sequentially at time of re-treatment (before or after re-radiotherapy or both as Sandwich). The numbers in table 2 refer to the time period of re-treatment. The numbers of 15 patients with distant or regional failure refer to the time period after re-treatment i.e. failure after re-irradiation. We observed 12 local failures partially combined with regional (n=3) or distant failure (n=12) leading to 18 failing patients, i.e. DFS. The removal of the prior sentence (B4.h) clarified the time course of disease.

j) “Hence, the mean distant…..” remove “Hence”. “Merely, the mean disease-free survival....” remove “Merely”.

=> both words were removed.

B5. Discussion

a) Paragraph 1: “So, the optimal treatment procedures” remove “So”. “…because total re-treatment doses below 55 Gy give poor local control rates [21]”... not if you combine it with hyperthermia!!

=> “So” was removed. We added “without hyperthermia”.

b) Paragraph 2: “This series clearly demonstrates that best long-term local control was achieved in patients with a combined schedule i.e. surgery plus re-irradiation”. You can not ignore the effect of hyperthermia as most of your high risk patients received it, so mention it.

=> This series focused on re-irradiation. We did not find a significant effect for hyperthermia in cause of selection criterion. But, due to the high number (n=29) of patients treated with hyperthermia and a trend in subgroups, we add the effect of hyperthermia. Furthermore, we add the effect on local control for anti-hormonal treatment (additional requested sub-analysis B3. n):”predominately performed with hyperthermia and combined with anti-hormonal treatment. Reducing the risk of local relapse using endocrine therapy is in line with findings concerning primary treatment of breast cancer [18, 19].”

=> ”is” was inserted.
**Paragraph 3: “Despite dose compromise…” how was the dose compromised?**

We clarified the statement as follows: However, even in cases of re-irradiation and dose compromise, for exceptional patients (R0-resection of recurrence plus pre-radiation exposure of 60 Gy) the referred local control rate could be replicated.

**New paragraph: In your methods you state that: "Re-irradiation was not routinely performed in case of resected recurrence as “adjuvant” procedure. Preconditions of individual re-irradiation were close (#0.5 cm) or positive margins, perinodal involvement, multiple recurrences or other high-risk features...." What were the results without re-irradiation?**

This is a retrospective series on re-irradiation. Therefore, we do not have a control group without re-irradiation. But, if you consider patients not treated at first recurrence as “control group”, you can imagine that omission of early re-irradiation drops prognosis as already stated in the conclusion.

**Paragraph 8: remove this paragraph, it is too casuistic and too speculative as you already mentioned yourself and it has nothing to do with the effect of re-irradiation which is the scope of your research.**

We agree with the reviewer and deleted this paragraph on salvage after Re-RT.

**B6. Conclusion**

*a) Your conclusion is far too long and part of it belongs in the discussion section. You should simply end with your last paragraph and skip the rest. Add “and the addition of hyperthermia” after “with total radiation doses of 60 Gy”.*

The conclusion was shortened and modified taking the comments of reviewer 3 into account: “Standard of care for breast cancer recurrences is surgical resection, if possible. In general, due to the detrimental effect of recurrences, we recommend early re-irradiation if indicated at first recurrence and a fortiori in case of recurrence within two years, because both factors were associated in this investigation by a dramatically reduced local control or overall survival”.

The sentence of the last paragraph was accordingly changed: "Repeat radiotherapy for breast cancer recurrence with total radiation doses of 60 Gy and the addition of hyperthermia in the majority of patients were feasible with acceptable late morbidity and improved prognosis especially in patients with previous resection of the recurrence.”

**C) Comments to reviewer 2 (Wendy A Woodward)**

We also thank the reviewer 2 for the requested clarifications. The changes were highlighted in blue.

**C1. A few minor considerations:**

*a) Does ER status or chemotherapy use influence either recurrence or toxicity?*

We evaluated ER-status and influence of chemotherapy on recurrence and overall survival as shown in B3.n). Significant differences were only detected for anti-hormonal treatment but not for ER status. Some patients refused endocrine therapy and others received it with questionable ER-status explaining the different results.

We did not evaluate toxicity with subgroup analyses in cause of overlapping and interacting factors (total dose of first or second treatment, electrons vs. photons, hyperthermia, systemic treatment at first or second radiation course, palliative chemotherapy in case of local failure after re-treatment, different surgical procedures) and due to the moderate toxicity profile.

*b) Please be more explicit about which endpoint are measured from time of re-irradiation vs time of diagnosis throughout the manuscript.*

To easier understand the calculation, we modified the following sentence in the method section and Figure legend 2: Local control, distant-disease-free survival, disease-free sur-
vival and overall survival were the main endpoints and calculated from time of re-irradiation using the Kaplan-Meier method.

Legend 2 “All parameters were calculated from time of re-irradiation for recurrence.”

c) Was either the toxicity or control worse in patients initially treated with post-mastectomy radiation?

This part was deleted in the Introduction according to reviewer 1. Local control of patients with recurrence after breast conserving therapy was better in comparison to mastectomy.

d) Lastly, the manuscript would benefit from an editing by an editor who speaks English as a first language. The English is technically correct throughout but subtle editing would improve readability.

=> The manuscript was copyedited by www.biomedes.co.uk. Modifications of the copyeditor were highlighted in green.

D) Comments to reviewer 3 (John Yarnold)

We followed the suggestions of Reviewer 2 and included the requested information on radiation portals and toxicity (D1 a-c). Changes were highlighted in yellow.

D1. Major compulsory revisions

a) Detailed information on the treatment volumes irradiated at first treatment and at re-treatment must be provided, for example, how is 'chest wall' defined, and in how many patients was the brachial plexus re-irradiated, and to what dose precisely?

We precised the information on first treatment and inserted: “or a radiation boost ....” The first session of radiotherapy was carried out using 6MV photons with tangential fields or 4-12MeV electrons with one/multiple fields or an electron rotation. Gamma irradiation with cobalt 60 was rarely administered. Field definitions were standard definitions of the treatment time as published by Sack and Thesen [Sack et al.]. We also described re-irradiation and field definition: “Postoperative r” was deleted.

We inserted: “Re-irradiation was performed using 6MV photons (n=24) with tangential fields or 4-12MeV electrons with an electron beam rotation technique (n=18) as described elsewhere [11]. Chestwall was defined as thoracic wall extending from the second to the sixth/seventh intercostal space including a small portion of the underlying lung. Longitudinal field borders were orientated to the position of the contralateral breast (inferior/superior margin 2cm below palpable contralateral breast; the contralateral breast was not irradiated). Medial margin was 1cm over midline. Lateral margin was usually near midaxillary line. Resulting mean re-irradiation field size was 17x17cm (ranging from 8x8cm to 35x20cm). In most cases, the whole chestwall was covered (n=34) according to the above mentioned target volume definition. Eight patients were treated with involved field techniques with a lateral margin of ≥3cm. The brachial plexus and regional lymphatics were not re-irradiated.”

b) More information on the proforma used to record late adverse effects would be useful, including the specific features that were recorded.

=> The same question was asked by reviewer 1. The adaption’s were explained at point B3.j).

c) Table 3 is inadequate. The number of patients assessed at defined (annual) time points must be given, including an actuarial analysis.

=> Thank you for this comment. We would like to explain the reasons for the performed analysis. In a randomized controlled trial of both treatments (first and second radiotherapy) the requested analysis would be possible without limitations. But, the present manuscript is a retrospective analysis of patients only equally treated regarding second radiotherapy. Therefore, data about annual toxicity of first treatment are limited due to the long time period of first treatment (1968-2002). Therefore, the toxicity analysis concentrated on maxi-
ma l achieved acute/late toxicity because these data were available from medical reports. In addition, toxicity scores like RTOG criteria were developed in the eighties, CTC 3.0 criteria in 2003. We converted all toxicity descriptions (epitheliolysis etc.) and toxicity-scores into the corresponding CTC 3.0 grades. For patients treated initially at other institutions mostly medical reports as described in the method section were available. Consequently, some limitations due to the retrospective data acquisition persist and therefore an annual comparison of both treatments in this retrospective analysis is not feasible.

However, we wanted to compare cumulative toxicity at first radiotherapy with cumulative toxicity at second treatment. To achieve this aim, we concentrated on maximal reported acute and late toxicity after first radiotherapy and compared these data with the same parameters after re-irradiation in analogy to other retrospective series. The late effect of first treatment often corresponded to baseline examination before second treatment.

We hope, that we could explain the underlying reason for the performed cumulative toxicity analysis and added a sentence explaining the situation in legend of table 2:

“Since the first radiation treatment was performed before the definition of CTC criteria, all data from medical charts were reviewed and converted into CTC 3.0 criteria to compare maximal occurred cumulative toxicity at first and second radiation courses. Maximal accumulated late toxicity of the first radiation course was assessed at last follow-up before treatment or at baseline examination before re-treatment.”

We inserted “cumulative” in first sentence of legend of table 3 and corrected criteria in “CTC 3.0”.

D2. Minor compulsory revisions

a) It is not possible to conclude that the re-treatment described here impacted on prognosis as defined by overall survival (final sentence of Discussion). Main rationale and value relates to local control and quality of life

=> This sentence was changed in accordance with reviewer 1 (prognosis related to amount of surgery, please see B6.a): “Repeat radiotherapy for breast cancer recurrence with total radiation doses of 60 Gy and the addition of hyperthermia in the majority of patients were feasible with acceptable late morbidity and improved prognosis especially in patients with previous resection of the recurrence.”

b) Discretionary Revisions: Manuscript could be shortened, especially the Introduction

=> The introduction was shortened (see Reviewer 1, B2a)

Sincerely,

Arndt-Christian Müller, MD Thomas Hehr, MD
For: revision of manuscript as per contract.

INVOICE no: BMS-1313

To: Dr Mueller

For the English revision of manuscript.

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Banking details for transfers
Name of bank: Clydesdale Bank
Address of bank: 26, West High Street, Inverurie, Aberdeenshire AB51 3SL, UK
Sort code: 82-65-21
Account number: 10073789
Account name: Biomedes Ltd
IBAN: GB92CLYD82652110073789
BIC: CLYDGB21S21

The volume of business at present is such that BioMedES Ltd remains VAT exempt until further notice.

Many thanks,
Denys Wheatley (Chairman and Director, BioMedES Ltd)
Herrn 
Dr. med. Arndt-Christian Müller 
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nachrichtlich: 
Herrn Prof. Dr. med. Michael Bamberg 

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28.02.2011 
eingegangen am 

1. März 2011 
Datum 

Resurgery plus chest wall re-irradiation for recurrent breast cancer - a second curative approach. 
Schreiben vom 24.02.2011 

Sehr geehrter Herr Kollege, 

Ihre Anfrage bezüglich der retrospektiven Auswertung bereits vorhandener Daten von Patientinnen, die in der Vergangenheit unter der oben genannten Diagnose in Ihrer Klinik untersucht und behandelt wurden, hat der Ethik-Kommission zur Beratung vorgelegen. 

Die retrospektive, anonymisierte Auswertung individueller, in der Diagnostik und Therapie entstandener Daten eigener Patienten bedarf keiner Beratung durch die Ethik-Kommission gemäß der Berufsordnung für Ärzte und keiner informierten Einverständniserklärung der früher untersuchten Patienten. 

Gegen eine anonymisierte Zusammenstellung, Auswertung und Publikation der Daten bestehen seitens der Ethik-Kommission keine Bedenken. 

Mit freundlichen Grüßen 

Prof. Dr. med. Dieter Luft 
Vorsitzender der Ethik-Kommission 

Allgemeine Hinweise zum Votum der Ethik-Kommission Seite 2