Reviewer's report

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

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Reviewer: Sabine Oldenborg

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Commends on Re-surgery plus chest wall re-irradiation for recurrent breast cancer- a second curative approach.

This article describes in retrospect the effect of re-irradiation +/- surgery as a curative treatment option for patients with recurrent breast cancer. In addition in 69% of patients hyperthermia was added to the re-irradiation. Although high local control and survival rates are reached, the number of patients is quite small and the actual treatment heterogeneous ( re-irradiation +/hyperthermia, +/ surgery, +/- systemic therapy) Good results are to be expected as a high radiation dose combined with hyperthermia is given to patients with a small tumor load and favourable prognostic factors. The merit of the paper lies in the toxicity analysis of re-irradiation with 60Gy, as only few data are published on this subject. The paper is very well written.

1. Abstract

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

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

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). “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”.

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.

2. Background

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.

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 mention in the discussion, hyperthermia has become a standard treatment for patients with recurrent breast cancer in previously irradiated area.

Paragraph 4: Sentence starting with "Therefore, this retrospective study..." you should mention here that you aim for curation. Sentence starting with "In our series, long-term local control was achieved......prognosis" is a result and does not belong here. Last sentence remove "including the value of hyperthermia". This has already been demonstrated in prospective trials.

3. Methods

Paragraph 1: Replace "other new primaries" by "other new primary tumors"

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

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

Table 2: What was the tumor size in patients with irresectable disease? Am I correct to assume that ~50% of patients received concurrent systemic therapy?

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? How and where did you measure temperature? 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? 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?

Paragraph 5: What were the specific toxicities that you investigated? What is your definition of late toxicity? "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? You included 3 patients with a regional recurrence, did you not include them in your local control analysis? How did you analyse local control for patients with irresectable disease?

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?

4. Results
Paragraph 1: “The median time to local recurrence …first recurrence (Table 2)“. This information belongs in the method section.
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.

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. 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 you patients received systemic therapy in addition to the re-irradiation, surgery and hyperthermia, how did this affect local control and survival?

Paragraph 3: Last sentence: replace “an insignificant increase” by “a statistically not significant increase”.

Paragraph 4: “Significant worse overall survival….”: replace “significant” by “significantly”. “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)?

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

5. Discussion
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!!
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. “Regarding the estimated 5-year overall survival of 75% in the combined treatment group, we arrive at the conclusion that durable local control converted into improved prognosis.” Insert “is” between “local control” and “converted”.
Paragraph 3: “Despite dose compromise…” how was the dose compromised?
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?
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.

6. Conclusion
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”.

Level of interest: An article of importance in its field

Quality of written English: Acceptable

Statistical review: No, the manuscript does not need to be seen by a statistician.

Declaration of competing interests:
I declare that I have no competing interests