Author's response to reviews

Title: Neoadjuvant chemotherapy in breast cancer significantly reduces number of yielded lymph nodes by axillary dissection.

Authors:

Thalia Erbes (thalia.erbes@uniklinik-freiburg.de)
Marzenna Orlowska-Volk (marzenna.orlowska-volk@uniklinik-freiburg.de)
Axel zur Hausen (axel.zurhausen@mumc.nl)
Gerta Rücker (ruecker@imbi.uni-freiburg.de)
Sebastian Mayer (sebastian.mayer@uniklinik-freiburg.de)
Matthias Voigt (Plastischer-Chirurg@dr-med-voigt.de)
Juliane Farthmann (Juliane.farthmann@uniklinik-freiburg.de)
Severine Iborra (severine.iborra@uniklinik-freiburg.de)
Marc Hirschfeld (marc.hirschfeld@uniklinik-freiburg.de)
Philipp T Meyer (philipp.meyer@uniklinik-freiburg.de)
Gerald Gitsch (gerald.gitsch@uniklinik-freiburg.de)
Elmar Stickeler (elmar.stickeler@uniklinik-freiburg.de)

Version: 2
Date: 19 November 2013

Author's response to reviews: see over
Authors response to reviewers

MS: 1876002016106930 Erbes et al.: Neoadjuvant chemotherapy in breast cancer significantly reduces number of yielded lymph nodes by axillary dissection

Corresponding author:

Elmar Stickeler, Department of Gynecology and Obstetrics, Head of Senology, University Medical Center Freiburg, Hugstetterstr.55, 79106 Freiburg, Germany, email: elmar.stickeler@uniklinik-freiburg.de, phone: 0049-761-270-31480, fax: 0049-761-270-31690

Version: 2; Date: 19 November 2013

We would like to thank the reviewers and the editor for their constructive comments.

Response to Reviewer 1 (Suzanne Coopey):

Minor Essential Revisions:

Comment 1

- "Title: would change “axillary staging” to “axillary dissection” since staging could simply mean sentinel node biopsy."

ad 1:
Thank you for the recommendation. The title of the article has been changed as the reviewer indicates.

Comment 2

- “Do you routinely evaluate the axilla prior to initiation of chemotherapy with either sentinel node biopsy or FNA/core biopsy? Please state in methods as this could affect your positive lymph node rate in the primary chemotherapy group."

ad 2:
All patients in our study exhibited a histologically proven axillary metastasis. The distinct algorithm for the confirmation of axillary involvement was as follows:
In the case of a clinical suspicious axilla (91.8%, 167/182) the lymph nodes status was evaluated by core biopsies of distinct nodes before neoadjuvant chemotherapy (NC). With the proven lymph node metastasis patients underwent the consecutive NC. In the case of a clinical negative axilla patients (8.2%, 15/182) underwent sentinel lymph node biopsy before NC. Finally all patients (182(182) underwent the consecutive ALND after NC. The total count of the lymph node yield includes both sentinel and non-sentinel count. Therefore we exclude that our staging procedures affect the positive lymph node rate.
Discretionary Revisions:

Comment 1
- “1. Results section, 2nd paragraph, 1st sentence—would change “significant” to “significantly.”

ad 1: done

Comment 2
- “Results section, 2nd paragraph—the term “primary neoadjuvant chemotherapy” seems redundant since neoadjuvant chemotherapy implies before surgery. Would suggest changing to primary chemotherapy or just neoadjuvant chemotherapy.”

ad 2: done

Comment 3
- “Table 1:
  --How did you determine tumor size in the PCG? Was this based on imaging? Perhaps include an explanation in Methods section.
  --Could you give age ranges and tumor size ranges?
  --For things like estrogen receptor, progesterone receptor, and Her2/neu receptors, I don’t think you need to include rows for both positive and negative. Positive would be sufficient.
  --Was presence of LVI based on surgical resection specimen or core biopsy? It would probably be more accurate for the PCG if you used the core biopsy prior to chemo.
  --Could you include what proportion of patients in each group took hormonal therapy, had radiation after breast conservation, and had post-mastectomy radiation? Since you later discuss recurrence rates.”

ad 3:
Table 1:
- In our study tumor size in the PCG was determined by ultrasound (on page 4 of the manuscript). This procedure is established as a routine measure for all patients treated in our breast center since 2001.
- We added age ranges, years: PCG (28-69), PSG (28-87) in table 1 (on page 16)
- We added tumor size ranges, mm: PCG (0-100), PSG (2-89) in table 1 (on page 16)
- For estrogen-, progesterone- and Her2/neu status we removed negative from the table as the reviewer suggested.
- In our study LVI was always based on surgical specimen.
- In the PCG 119/131 (90.8%) of hormone receptor positive patients received a antihormonal therapy, in the PSG 229/261 (87.7%).
Radiotherapy after breast conserving surgery was performed by 106/106 (100%) of the patients in the PCG and in 158/162 (97.5%) of patients in the PSG. Radiotherapy after mastectomy in 72/76 (94.7%) in the PCG and 182/189 (96.2%) in the PSG. The differences were statistically not significant (added on page 4 and 5 of the manuscript).

Comment 4

- “Discussion, 1st paragraph—I would remove the first 2 sentences. The first sentence is confusing.”

Response to Reviewer 2 (Laurie Kirstein):

Comment 1

- “This study raises an interesting topic: is a lower lymph node yield related to neoadjuvant chemotherapy and why. The value and strength of this article lies in the explanation of the morphology of the lymph nodes and provides an interesting suggestion for a reason for this phenomenon. That should be the main focus of this paper.”

Comment 2

- “Some of the clinical information and the suggestion of a correlation to lymph node yield, however, is confusing. For example, the NC group clearly had larger tumors and more advanced disease at presentation. It is logical that this group would have poorer outcome. Lymph node yield at surgery likely has nothing to do with it, and trying to tie these factors together weakens the paper.”

Comment 3

- “The other issue lies in a basic argument that “fewer nodes portend poorer prognosis” that is set forth in the introduction. The data presented showed no difference in DFS or OS in the group of patients who had <10 nodes retrieved after NC compared to those with >10 nodes retrieved after NC. It might be better to remove this concept from the paper, and simply focus on the fact that fewer nodes are retrieved after NC.”
The major focus of the paper is clearly the statement of a lower lymph node retrieval after NC:

However, the data in regards to OS and DFS are important in regards to the clinical impact of our therapeutic procedure. NC as a widely accepted and performed treatment option in early breast cancer (in Germany nearly 30-40% of all adjuvant chemotherapies) has still to proof its safety in specific clinical situations. The finding of lower number of lymph nodes after NC is an important topic in the daily routine. Therefore we performed this clinically based study. The outcome data do by far not weaken the paper, but they add clinical significance for the breast cancer community.

Comment 4

- "Likewise, while there were fewer nodes retrieved in the NC group, the majority of patients in this group still had >10 nodes retrieved. Since 10 is the cutoff the authors use in this study as having clinical significance, it calls into question the reason for trying to link these factors.

The removal of at least 10 axillary nodes represents the international gold standard for systematic axillary staging in currently accepted guidelines and is not an arbitrarily chosen number by our group! Of course the number is controversially discussed (ref. 11-13) as well as the potential clinical impact on outcome (ref. 4-10). These controversy represent the main hypothesis for the performance of our study and we were able to repute this theory.

Comment 5

- "Also, what is absent from this paper is the breakdown of lymph node yield in the NC group for patients with and without involved nodes at the time of surgery. Seeing the lymph node yield in NC patients with and without nodal involvement in table form would be informative. Is it nodal involvement and treatment effect that causes the lower yield, or the fibrosis? In addition, a breakdown of number of positive/total nodes retrieved per group should be included as well."

Due to the helpful comment of reviewer 2 we added the requested numbers, even if we already included data for the pCR patients (n=52, 28.6%) in the first submitted manuscript (page 6). The data clearly state that the status of lymph node positivity after NC at the time of surgery does not influence the number of retrieved lymph nodes. We found a median total number of 13 lymph nodes (interquartile range 10-17) for patients with nodal involvement compared to 14 nodes (interquartile range 11-18) in patients without nodal involvement (p=0.654), respectively (on page 6 of the manuscript). Multivariate analyses identified lymphoid depletion as an independent histomorphological parameter for a lower LNY after NC, not fibrosis, as stated by reviewer 2.

The median number of involved nodes/total nodes retrieved per group showed in the NC group a median number of 3.0 positive nodes (interquartile range 1-6)/13 total number of nodes and in the PSG 2.5 involved nodes (interquartile range 1-5)/17.0 total number of nodes (p=0.904) (on page 6 of the manuscript).

Table 5 will be added as follows (on page 21 of the manuscript)

Table 5: Influence of nodal involvement on total lymph node yield

<table>
<thead>
<tr>
<th></th>
<th>Median total number of lymph nodes for patients with nodal involvement</th>
<th>Median total number of lymph nodes for patients without nodal involvement</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
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</table>

4
Neoadjuvant chemotherapy in breast cancer significantly reduces number of yielded lymph nodes by axillary dissection

<table>
<thead>
<tr>
<th></th>
<th>PCG</th>
<th>PSG</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median number of involved lymph nodes</td>
<td>3.0 (1-6)*</td>
<td>2.5 (1-5)*</td>
<td>0.904</td>
</tr>
</tbody>
</table>

* interquartile range

Comment 6

- “I believe this paper should be limited to morphological characteristics of the nodes to explain a lower yield, and omit some of the clinico-prognostic suggestions. It would make this a stronger and clearer paper.”

ad 6: see comment ad 3,4,5!