Author’s response to reviews

Title: PRE-OPERATIVE AND INTRA-OPERATIVE DETECTION OF AXILLARY LYMPH NODE METASTASES IN 108 PATIENTS WITH INVASIVE LOBULAR BREAST CANCER UNDERGOING MASTECTOMY

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Version: 2 Date: 02 Jan 2018

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Editorial Board

BMC Cancer

I am sending you herewith an original manuscript of the paper PRE-OPERATIVE AND INTRA-OPERATIVE DETECTION OF AXILLARY LYMPH NODE METASTASES IN 108 PATIENTS WITH INVASIVE LOBULAR BREAST CANCER UNDERGOING MASTECTOMY by Jerica Novak, Nikola Besic, Radan Dzodic, Barbara Gazić and Andrej Vogrin.

We are thankful to the reviewers for their most useful and beneficial comments and suggestions which undoubtedly helped a lot to improve the paper.
We accepted all the comments of the reviewers. We indicated precisely the changes we made in response to the comments and we prepared a list in which we outlined all the suggestions raised by the reviewer and our response to each of these. The changes we made in response to the comments in the text are marked with red color.

All the authors have agreed to the submission of this manuscript in its present form. The work has not been published or submitted elsewhere.

Kindly consider this paper for publication in the BMC Cancer.

Sincerely yours

Jerica Novak

Answer to the Reviewer’s comments:

Reviewer 1:

1. The overall rate of identifying ILC patients who would require ALND was 43% in this study. This seems relatively low. First, it would be helpful if the authors’ could compare their finding with the rate of identifying patients who require ALND using other commonly used approaches as a control (e.g., intraoperative SLN frozen section only). Ideally, the most meaningful comparison is if the authors had a separate cohort at their institution who were not part of their algorithm to compare to, or alternatively by comparing it with figures in the literature.

Our data of IIC were compared with the data in the literature in the 5th, 6th and 7th paragraph of the Discussion section. We inserted the following text in the Discussion section in order to validate detection rate in our series. (page 9, lines 363-369):

“Ideally, the most meaningful comparison of our results for IIC would be to compare it with a separate cohort who was not a part of the treatment algorithm at our Institute. Unfortunately, at our Institute we don’t have experience with intraoperative SLN frozen section and there is no separate cohort. During the study period all our patients followed the same treatment protocol as was recommended by our national guidelines for breast cancer patients. Therefore our results were compared only with figures from the literature. “

2. It might be helpful if the authors could provide a cost-analysis, as identifying 43% of patients who require ALND must be considered in the context of what it would cost to perform AUS/US-FNAB/IIC in 100% of patients, versus the cost savings associated with avoiding a second operation in 43% of patients.
Data about cost effectiveness were included in the Results section as follows (page 6, lines 239-243):

“Charges for procedures in a cost-analysis were taken into account as follows: AUS investigation 60 EUR, US-FNAB 140 EUR, IIC 200 EUR and cALND 2500 EUR. Cost to perform AUS/US-FNAB/IIC in 100% of patients would be smaller (43.180 EUR) in comparison to total cost associated with avoiding a second operation in 43% of patients (115.000 EUR).”

Data about cost effectiveness were included in the Discussion section as follows (page 8, lines 293-295):

“Cost-analysis showed that our treatment algorithm was cost effective in comparison to cALND done as separate surgical procedure.”

3. It would be helpful to clarify the flow chart figure. First, including percentages as well as "n" would be helpful. Second, it would be helpful to separately present the outcomes of patients who did not undergo IIC, and those who did undergo IIC but had a negative result, rather than combining them.

A Flow chart figure 1 (page 3, line 115) was prepared as suggested by the reviewer.

4. The authors' approach had varying sensitivities and specificities depending on factors such as tumor stage. It would be helpful if the authors discuss whether they feel their approach, based on their results, should be used in all cases, or just select cases.

The following text was inserted in the Discussion section (page 9, lines 347-351):

“Our data suggest that the preoperative and intraoperative diagnostic approach should be done also in patients with small ILC. Another argument for this approach is cost-effective analysis which showed that our diagnostic algorithm has 2.66 times lower price in comparison to cALND done as a separate surgical procedure.”

5. It would be helpful for the authors to state the false-positive and false-negative rates of their approach.

False-positive and false-negative rates were included in the text in the Results section (page 5, lines 213-215 and page 6, line 230)

6. It would be helpful if the authors elaborated on what factors led surgeons to elect to perform IIC in some patients but not others. Furthermore, it would be helpful for the authors to discuss whether this may potentially act as a confounding factor (selection bias)?

In the Methods section the following text was inserted (page 3, lines 145-148):
“IIC was performed at the discretion of the surgeon. It was performed in patients with a palpable and/or large non-palpable breast lesion. IIC was not done in patients with a small non-palpable ILC.”

In the Discussion section the following text was inserted (page 9, lines 343-347):

“In our series IIC was not done in all patients. It was performed in patients with a palpable and/or large non-palpable breast lesion. IIC was not done in patients with a small non-palpable ILC. It might potentially act as a confounding factor (selection bias) for lower detection rate of CII in smaller tumors in our series in comparison to Creager’s series.”

Reviewer 2:

1. For a reason not explained they don't do a core biopsy preoperatively and don't do frozen section intraoperatively. Cytologist experience is very important and their results show that this is the case in their center however in light of ACOSOG Z011 trial I would anticipate less need for IIC in the future and less experience generated.

The following text was inserted in the AUS and US-FNAB section of the Methods (page 3 lines 126-130):

“Traditionally, surgeons relied on results of FNAB and cytology at our Institute since 1970-ies and only definitive samples obtained by surgical procedure were examined by pathologists. So, for patients included in our study core biopsies of lymph nodes or frozen section of sentinel lymph nodes have not been done.”

The following text was inserted in the 2nd paragraph of the Discussion section (page 7, lines 274-281):

“At our institution a core biopsy of axillary lymph nodes or intraoperative frozen section of SLN was not done at all because during that period according to our national guidelines for breast cancer, FNAB or US-FNAB were the standard of care for all breast cancer patients with palpable and/or US suspicious axillary lymph nodes. These two modalities represented the standard of care for breast cancer patients in our country. However, in light of ACOSOG Z011 trial there is less need for IIC and cytologists will in future generate less experience with IIC. “

2. The US identified 30 suspicious lymph nodes FNAB was done to all of them identifying 11 of them as positive. In 6 others final pathology identified metastasis. In a study by Horvath et al. comparing frozen section to IIC analysis they conclude that frozen section analysis of breast cancer patients should remain the standard of care (World J Surg Oncol. 2009).

The following paragraph was inserted in the Discussion section (page 8, lines 326-331):

“Another technique for detection of metastases in SNB is frozen section of SNB [23]. Horvath et al. reported that frozen section has sensitivity of 70% for detection of metastases in SNB in
patients with ILC, so they conclude that frozen section analysis of breast cancer patients should remain the standard of care [23]. However, Howard-McNatt et al. published even higher sensitivity (71%) using IIC for detection of metastases in SNB in a series of patients with ILC [22].”

3. The other question is the statement that IIC was performed at the discretion of the surgeon, which is not understood if the aim is to decrease the need of a second operation.

In the Methods section the following text was inserted (page 3, lines 145-148):

“IIC was performed at the discretion of the surgeon. It was performed in patients with a palpable and/or large non-palpable breast lesion. IIC was not done in patients with a small non-palpable ILC.” (page 3, line 145-148):

In the Discussion section the following text was inserted (page 9, lines 343-345):

“In our series IIC was not done in all patients. It was performed in patients with a palpable and/or large non-palpable breast lesion. IIC was not done in patients with a small non-palpable ILC.”

4. 26 patients needed a second operation assuming that some had immediate reconstruction. I hope that the axillary lymphadenectomy was done through a separate incision.

Data about immediate reconstruction and reoperations are presented in Flow chart figure 1. The following text was inserted in the Methods section (page 5, lines 185-189):

“In patients with immediate breast reconstruction an immediate ALND was done in 19 cases and delayed cALND was done in 10 cases. An immediate axillary lymphadenectomy was done whenever feasible through the same incision, while a delayed cALND was always done through a separate axillary incision.”

5. I do think that it should be clearly stated how many had second operation with no IIC, and how many had reconstruction and of them how many had second surgery.

Data about second operations with and without IIC and immediate reconstruction are presented in Flow chart figure 1. Furthermore, the following text was inserted in the Methods section (page 5, lines 186-189):

“In patients with immediate breast reconstruction an immediate ALND was done in 19 cases and delayed cALND was done in 10 cases. An immediate axillary lymphadenectomy was done whenever feasible through the same incision, while a delayed cALND was always done through a separate axillary incision.”

Also the following text was inserted (page 6, lines 234-237):
“Among 63 cases with IIC immediate ALND and another surgical procedure for cALND was done in 10 (16%) and 9 (14%) cases, respectively. On the other hand, among 28 cases with SLN biopsy but without IIC none cases had immediate ALND, while 3 (11%) cases had another surgical procedure for cALND.”