Reply to ‘Different outcome variables yield different results’, by O. Brouckaert et al.

We thank Brouckaert et al. [1] for their comments on our paper, in which they question our finding of a lack of effect of chemotherapy in postmenopausal patients with invasive lobular breast cancer (ILC).

The study by von Minckwitz et al. indeed seems to indicate that pathologic complete remission may not be a good predictor for the ultimate prognosis in patients with ILC [2]. But the fact remains that also in this study the likelihood of a pathologic complete response was rare (<10%) in patients with ILC and more than twofold lower than in those with invasive ductal cancer (IDC). And so far, we are still looking for the biological mechanisms which could explain this lack of response to neoadjuvant chemotherapy in patients with ILC.

For any factor to be a true confounder, it needs to be associated with the likelihood of receiving chemotherapy as well as with the overall survival. Unlike histological grade, for which we have adjusted in the multivariable analysis, vascular invasion and HER2 status have never been mentioned as criteria for the use of chemotherapy in the Dutch treatment guidelines, neither in patients with ILC nor in those with IDC. The same holds true for comorbidity, frailty or other factors that might limit general life expectancy. Although they may have influenced the decision to use chemotherapy in the patients observed in our study, it is very unlikely that that influence was dependent on the histological type of the study and could thus explain the differences observed between ILC and IDC with respect to the effect of chemotherapy.

We have tried to rule out the impact of the estrogen (ER) and progesterone receptor (PR) status on our findings by restricting our study population to patients who received hormonal treatment, assuming that they all had a positive ER and/or PR status. We agree with Brouckaert and colleagues that it would be interesting to see if and to what extent the levels of ER and PR expression are responsible for the differences in sensitivity to chemotherapy between ILC and IDC. Currently, we are planning such a study. A recent study of patients enrolled in the Tamoxifen Exemestane Adjuvant Multinational trial did not show any significant differences between ILC and IDC when looking at semi-quantitative ER expression levels according to the Allred score, but this score may not be sensitive enough [3].

As we have also clearly stated in the discussion of our paper, we are well aware of the limitations of the observational design of our study and thus, do not dispute the view that our results need to be validated by other studies before they can lead to a change in the treatment of patients with ILC. We hope that our findings and the clinical importance of the question are convincing enough to stimulate others to provide evidence from randomized data.

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disclosure

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references


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Staging for distant metastases in operable breast cancer: a suggested expansion of the ESMO guideline recommendation for staging imaging of node-negative, hormonal receptor-negative disease

We evaluated the impact of staging procedures to detect asymptomatic distant metastases (DM) in the management of women with operable invasive breast cancer (BC, entire cohort: n = 866). Out of 472 patients with lymph node (LN)-negative disease (pN0), DM were found in four cases (detection rate: 0.8%). All four patients presented with established risk factors: hormone receptor (HR)-negative status, HER2-positive status, n = 3; ‘triple-negative’ disease, n = 1. Considering the subgroup of LN-negative patients whose tumors showed the risk factor ‘negative HR status’ (n = 66), the detection rate of DM was 6%. The detection rates of DM in higher pN categories were as follows: pN1:1.7%; pN2:9.5%; pN3:13.5%. We generally support the international guidelines, including those published by the European Society for Medical Oncology (ESMO) which emphasize that patients with early-stage BC do not profit from radiological staging for the detection of DM and recommend refraining from this. However, we would expand these guidelines and propose that screening should be carried out in node-negative patients whose tumors show established tumor-related risk factors (e.g. HR-negative and HER2-positive status), since in this particular subcohort, the detection rate of DM is with 6% similarly high as that of patients with four to nine positive LNs.

The incidence of detectable metastatic disease at the time of breast cancer (BC) diagnosis is extremely small in patients with early-stage lymph node (LN)-negative disease. Regarding the question whether diagnostic procedures for the detection of