Author's response to reviews

Title: St Gallen molecular subtypes in primary breast cancer and matched lymph node metastases - aspects on distribution and prognosis for patients with luminal A tumours. Results from a prospective randomised trial.

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Version: 4 Date: 1 November 2013

Author's response to reviews: see over
Dear Editor-in-Chief,

Enclosed please find the manuscript entitled “St Gallen molecular subtype in primary breast cancer and matched lymph node metastases. Aspects on distribution and prognosis for patients with luminal A tumours. Results from a prospective randomised trial.” by Falck et al which we kindly ask you to consider for publication in BMC Cancer. The manuscript has been rejected by Molecular Cancer after resubmission of a revised version without any comment of the revision of the manuscript.

Biomarker expression and molecular characteristics in primary tumours compared to metastatic lesions including synchronous lymph node metastases is a topic of interest in cancer research despite tumour type as it might serve as an vivo model for tumour progression. In primary breast cancer, the concordance of biomarker expression is generally high (80-95%) between primary tumours and matched lymph node metastases, although the prognostic implication for patients with discordant biomarker status is still not settled. In contrast, the fraction of patients with molecular discordance between primary tumours and relapses has repeatedly been shown to have an impaired prognosis compared to patients with an identical phenotype in the primary- and metastatic site. Consequently, biomarker status of the relapse is today guiding systemic treatment in metastatic breast cancer. In contrast no analysis of biomarkers are currently performed in lymph node metastases, despite that more than 10% of the patients has a shift in phenotype from the primary tumour to the node metastases. The discussion of biomarker classification in node metastases is also ongoing for other epithelial cancers as a tool for adjuvant treatment selection.

The present study aimed to classify primary breast cancer tumours and matched lymph node metastases into St Gallen surrogate molecular subtypes by immunohistochemistry including oestrogen receptor, progesterone receptor, human epidermal growth factor receptor and the proliferation marker Ki67 into luminal A, luminal B, HER2 type and triple-negative phenotype and compare the distribution and prognostic information. Patients with a luminal A subtype is today advocated systemic adjuvant treatment with endocrine therapy, whereas patients with all other subtypes will receive chemotherapy-containing regimens. The present cohort included 85 patients with available tumour tissue from both locations and is thus not powered to fully elucidate the issue, but can give additional important data in the field. We found that primary tumours classified as luminal A tumours shifted to a non- luminal A
subgroup in matched lymph node metastases in 7 of 45 cases (16%), whereas no shift in the opposite direction was observed (0/38) ($p=0.02$). In survival analysis using 5-year distant disease-free survival as primary endpoint all molecular subclasses had an increased hazard ratio, compared to the luminal A subclass. For patients diagnosed with a luminal A primary tumour and node positive disease, complementary molecular classification of the lymph node metastases could be helpful in tailoring adjuvant therapy and manage systemic disease since a subgroup of them are indicated to have a more aggressive phenotype in their lymph node metastases where chemotherapy is indicated.

All authors of this research paper have directly participated in the planning, execution, and analysis of the study. All authors of this paper have read and approved the final version submitted. The contents of this manuscript have not been copyrighted or published previously, are not now under consideration for publication elsewhere, and will not be copyrighted, submitted, or published elsewhere while acceptance by BMC cancerr is under consideration. There are no directly related manuscripts, published or unpublished, by one or more authors of this paper. An abstract was accepted for poster presentation at the San Antonio Breast Cancer symposium in 2011. The manuscript has been linguistically revised by Semantix AB, Malmö Sweden.

Lund 1st November 2013

On behalf of the authors

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