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Tamoxifen sensitivity and estrogen receptor mRNA levels

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To the editor,

In a recent letter, Smith et al. [1] respond to an article from Pentheroudakis et al. [2] in Breast Cancer Research and Treatment concerning the use of the quantitative RT-PCR (qPCR) for Estrogen Receptor alpha (ER) as an alternative for the immunohistochemical (IHC) determination of ER status in breast cancer tissue. Smith et al. state that the lack of correlation between qPCR and IHC shown in this article [2] might be due to the various regulatory translation mechanisms that will cause differences in efficiency of translation from mRNA to protein. They conclude that because of this poor relation between mRNA and protein, it is unlikely that transcriptional profiling can be used for predicting benefit from hormonal therapy in breast cancer.

We would like to make a few remarks on this issue.

Firstly, the correlation between a quantitative assay as qPCR and the semi-quantitative nature of IHC might be inherently low. The ligand binding assay (LBA) for measuring estradiol binding in tissue for which we have performed quality assurance [3] is much more quantitative than IHC. Indeed, in our patient cohort [4] ($n = 243$), we

found a strong significant correlation ($R_s = 0.776$, $P < 0.001$) between the LBA assay and qPCR data for ER. At a similar cut-off point for both LBA and qPCR, we found a Kappa of 0.76, which denotes substantial agreement [2].

Importantly, the amount of ER mRNA was specifically predictive for disease-free survival in the Tamoxifen-treated patients in our cohort ($n = 82$), when entered as a continuous factor in Cox regression (hazard ratio (HR) = 0.508, 95% confidence interval (CI) = 0.348–0.747, $P = 0.001$). At the cut-off point mentioned above, we find an HR = 0.251 (CI = 0.127–0.497, $P < 0.001$, Fig. 1).

Finally, we do not agree with the broad statement that “this casts doubt on the use of transcriptional profiling for predicting pathway activities or benefit from hormonal therapy in breast cancer.” We strongly believe that the rapidly expanding knowledge on how different ER ligands regulate gene expression [5–7] will soon allow us to quantitatively profile the expression levels of the target genes of the ER; thus, providing a sensitive and quantitative measure of estrogen sensitivity of the tumor.

P. N. Span (✉)
Department of Radiation Oncology 874, Radboud University
Nijmegen Medical Centre, P.O. Box 9101, 6500 Nijmegen,
The Netherlands
e-mail: p.span@rther.umcn.nl

P. N. Span · F. C. G. J. Sweep
Department of Laboratory Medicine, Radboud University
Nijmegen Medical Centre, Nijmegen, The Netherlands

H. W. van Laarhoven
Department of Medical Oncology, Radboud University
Nijmegen Medical Centre, Nijmegen, The Netherlands

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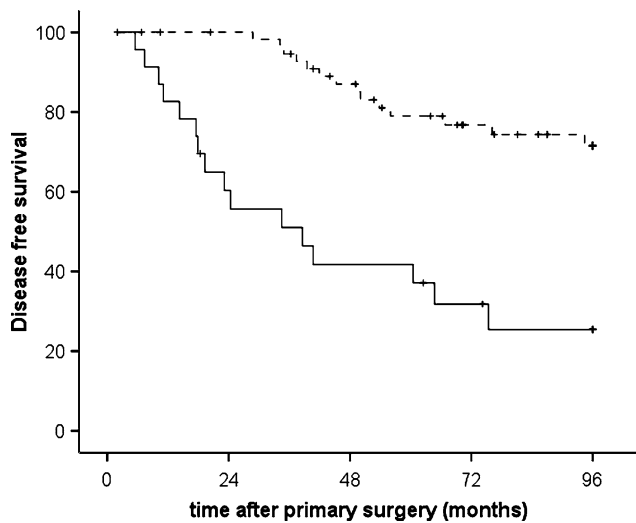


Fig. 1 Disease-free survival of patients treated with Tamoxifen, after dichotomization based on high (*dashed line*) or low (*straight line*) ER mRNA levels ($P < 0.001$ log-rank)

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