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Clonal alteration of breast cancer receptors between primary ductal carcinoma *in situ* (DCIS) and corresponding local events

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Abstract ***Background:*** Emerging data propose biomarker alteration due to clonal selection between the primary invasive breast cancer and corresponding metastases. In addition, impact on survival has been demonstrated. The present study investigates the relationship between the oestrogen receptor (ER), progesterone receptor (PR) and human epidermal growth factor receptor 2 (HER2) between primary ductal carcinoma *in situ* (DCIS) and intra-individually matched ipsilateral event.

Materials and methods: The cohort includes 1504 patients, diagnosed with a primary DCIS between 1986 and 2004. Of the 274 patients who developed a local relapse, 135 developed a new *in situ* carcinoma and 139 an invasive cancer up to 31st December 2011. ER and PR were identified by immunohistochemistry (IHC) and HER2 by silver-enhanced *in situ* hybridisation (SISH) as well as IHC.

Results: ER ($n = 112$), PR ($n = 113$) and HER2 ($n = 114$) status from both the primary DCIS and the corresponding relapse were assessed and were demonstrated to be discordant in 15.1%, 29.2% and 10.5% respectively. The receptor conversion was both from negative to positive and from positive to negative with no general pattern being seen in spite of sub-dividing into *in situ* relapse and invasive relapse. However, primary DCIS was HER2 positive in 40.3% whereas *in situ* and invasive relapses were HER2 positive in 42.9% and 34.5% respectively.

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Conclusions: Receptor conversion for ER, PR and HER2 status occurred between primary DCIS and corresponding local relapse in 10–30%. This study could not confirm that HER2 overexpression in primary DCIS had any impact on tumour progression to invasive cancer which has been proposed.

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1. Introduction

Primary ductal carcinoma *in situ* (DCIS) of the breast is a heterogeneous disease with different malignant potential. Altogether, DCIS has a good prognosis [1,2]. However, approximately half of the relapses developed after a primary DCIS will be invasive cancer [3,4]. The expression of oestrogen receptor (ER), progesterone receptor (PR), and human epidermal growth factor receptor 2 (HER2) have been shown to be associated with local relapse [5,6]. However there are conflicting data. Nevertheless, the optimal management of DCIS is controversial due to poor understanding of the natural history of DCIS and the poor understanding of those factors that are involved in tumour progression.

Biomarkers such as ER, PR and HER2 help clinicians to optimise and individualise management of patients with primary invasive breast cancer. ER and HER2 are of particular interest since they are both prognostic markers and predictors of treatment response. Moreover, emerging data propose biomarker alteration between the primary invasive breast cancer and the corresponding metastases [7–14] and indeed, some studies, including earlier data from our group have reported impact on survival due to such a change in receptor status [7–9].

In this study we wanted to perform a comparative analysis of ER, PR and HER2 status between primary DCIS and the corresponding local relapse (both *in situ* and invasive) and to investigate the role of adjuvant radiotherapy on any discordance.

2. Patients and methods

2.1. Study population

The study was approved by the Ethical committee at Uppsala University Hospital (Dnr 99442, Dnr 2005:118) and Umeå University (Dnr 05-065M, Dnr 2012-224-32M). The source population includes 1504 patients from two separate cohorts, diagnosed with a primary DCIS between 1986 and 2004. Of these 1504 patients, 458 were identified from a population based cohort diagnosed between 1986 and 2004 in Uppland and Västmanland regions of Sweden. The remaining 1046 were identified from the randomised SweDCIS trial of patients diagnosed between 1987 and 1999 [15]. A total of 274 patients developed a relapse/new cancer in the period up to and including 31st December 2011. Of these 274 patients, 135 (49.3%) patients developed an *in situ* relapse and 139 (50.7%) an invasive relapse. From these 274 patients, tissue samples from both the primary DCIS and the corresponding relapse were collected to perform analysis of ER, PR and HER2 status. Thirty patients (2%) out of the total cohort (1504 patients) died due to breast cancer up to the 31st December 2011. 28 of those patients had an invasive relapse as first event and two patients had an *in situ* relapse as first event (data not shown).

2.2. Tissue sample and biomarker measurement

Tissue microarray (TMA)-blocks were constructed from both primary DCIS and relapses. The detail of this process is described in an earlier publication [16]. ER and PR status were assessed by immunohistochemical (IHC) methods (DakoAutostainer), whereby tumours with >10% positive cells were classified as receptor positive. The antibodies used were NCL-6F11 (Novocastra) for ER and PgR NCL-1A6 (Novocastra) for PR analysis, respectively. Fixation and staining procedures were performed according to manufacturer's instructions. Positive and negative controls were included in all staining runs. HER2 status was assessed by using IHC analysis with antibody c-erb 2 poly rabbit, A0485 (DAKO) and Hercept-kit, which was confirmed by silver-enhanced *in situ* hybridisation (SISH). Using the Hercept-kit, tumours were classified as positive at the 3+ protein level. For HER2 status priority was given for SISH and if not available IHC was used for evaluation of HER2 levels. HER2 SISH was carried out in an automated instrument (Ventana Benchmark, Ventana Medical system, Tucson, AZ). Evaluation of HER2 gene amplification was performed according to the American Society of Clinical Oncology/College of American Pathologists guideline and Australian HER2 Advisory Board criteria for single HER2 probe testing. Both IHC methods and SISH are described in detail in an earlier publication [16]. Nuclear grade (NG) was evaluated in the primary DCIS prior to the TMA construction by one pathologist (K.J.). Tumour markers were scored by one single observer (W.Z.) and thus, we did not have a problem with inter-laboratory differences or intra-observer variability.

2.3. Statistical methods

Fisher's test was applied for comparison of ER, PR and HER2 status with baseline primary tumour

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