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Original Research

Impact of gene-expression profiling in patients with early breast cancer when applied outside the guideline directed indication area

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Abstract ***Purpose:*** In Dutch guidelines, gene expression profiles (GEP) are indicated in estrogen receptor positive early breast cancer patients in whom benefit of chemotherapy (CT) is uncertain based on traditional prognostic factors alone. Aim of the present study is to assess the use and impact of GEP on administration of adjuvant CT in breast cancer patients who have according to national guidelines a clear indication to either use or withhold adjuvant chemotherapy (clinical high or low risk).

Methods: Clinical low- and high-risk patients, according to Dutch breast cancer guidelines, diagnosed between 2011 and 2014 were selected from the Netherlands Cancer Registry. Influence of GEP use and GEP test result on CT administration was assessed with logistic regression.

Results: Overall, 26,425 patients were identified; 4.8% of patients with clinical low risk (444/9354), 7.5% of the patients with a clinical high risk (1281/17,071) received a GEP. GEP use was associated with significantly increased odds of CT administration in clinical low-risk patients (OR = 2.12 95% CI: 1.44–3.11). In clinical high-risk patients, GEP use was associated with a decreased frequency of CT administration (OR = 0.55, 95% CI: 0.48–0.63). Adherence

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to the GEP result was higher in clinical high-risk patients with a discordant GEP result as compared to clinical low-risk patients with a discordant GEP result: 71.7% vs. 52.2%, respectively.

Conclusion: GEP is frequently used outside the indicated area and significantly influenced the administration of adjuvant CT, although adherence to the test result was limited.

1. Introduction

The use of adjuvant systemic therapy has considerably improved the prognosis of patients with breast cancer over the last 2 decades [1]. However, there is also a growing awareness that this broad application of adjuvant chemotherapy (CT) increases the risk of overtreatment as the threshold to use CT is difficult to determine [2]. Different biologic and clinical clues suggest that not all patients derive substantial benefit from CT [3]. Especially in estrogen receptor (ER) positive (+) early-stage breast cancer patients doubt exists regarding the benefit of adjuvant CT. Because of negative side effects of systemic therapies, effective use is important [4].

Gene expression profiles (GEPs) were developed a decade ago to enable a prediction of prognosis in addition to the prognostic information of conventional clinicopathological factors. Although the predictive value of GEPs in terms of a quantified benefit of administering CT is still disputed, national and international treatment guidelines currently suggest the use of a GEP complementary to clinicopathological factors in ER+ early-stage breast cancer patients [3,5–9]. The Dutch guideline (2012) suggests the use of a validated GEP in early breast cancer patients, in whom benefit of CT is uncertain based on traditional prognostic factors alone [3,9]. In a previous study, it was demonstrated that this category, in which GEP use is highest, consists of patients with ER+/HER2-Neu negative (−) disease without overt lymph-node metastasis (pT1c-2N0-1mi) [10].

Since all insurance companies fully reimburse GEP use in the Netherlands, and health-care insurance is mandatory, GEPs are available for every Dutch breast cancer patient. Within the guideline directed indicated area, an increase in GEP use over recent years and high adherence rates to the GEP test result were observed [11]. An unexpected observation in a previous population-based study was the frequent use of GEPs outside the guideline-intended indicated area, i.e. in patients in whom clinical guidelines state a clear recommendation to administer or withhold CT based on clinicopathological factors alone [12]. GEP use in this patient group raises the question whether the GEP test results influenced CT administration in these patients.

The aim of the present study is to evaluate the clinical implications (CT administration) of GEP use (MammaPrint™ 70-gene signature) and GEP test results when used outside the guideline intended GEP indication area. In this group, clinical risk estimation and the GEP test result were compared, and adherence rates to the test result were determined in case of discordance between the clinical and genomic risk assessment.

2. Material and methods

2.1. Data source

Data was derived from the Netherlands Cancer Registry (NCR) database. Since 1989, the NCR registers data on patient-, tumor-, diagnostic-, and treatment characteristics of all Dutch cancer patients, obtained by data managers directly from patient records. All surgically treated female patients diagnosed with primary non-metastatic invasive breast cancer between 1st January 2011 and 31st December 2014 were identified.

2.2. Study population

Patients with a prior history of malignancy or initially treated with CT or endocrine therapy prior to surgical treatment were excluded from the analysis. Patients >70 years of age were excluded since guidelines are inconclusive about the benefit of adjuvant CT advice in these patients. For the present study, patients were excluded for whom the current guideline advises to use a GEP as an adjunct to clinicopathological factors to guide adjuvant CT decision-making, i.e. patients with ER positive/HER2-Neu negative (−) disease without overt lymph-node metastasis (pT1c-2N0-1mi). The 70-GS is accountable for 97% of all deployed GEPs in the Netherlands, and we therefore decided to focus on the MammaPrint™ 70-gene signature only.

Patients for whom the current Dutch treatment guidelines state a clear advice to administer or withhold CT, so without an indication to perform a GEP, were included in the study. This includes patients ≤70 years of age, regarded as clinical low-risk, for which adjuvant CT is not recommended or high-risk based with recommendation to administer CT according to the Dutch