Impact of 70-Gene Signature Use on Adjuvant Chemotherapy Decisions in Patients With Estrogen Receptor–Positive Early Breast Cancer: Results of a Prospective Cohort Study

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ABSTRACT

Purpose
Gene-expression profiles increasingly are used in addition to conventional prognostic factors to guide adjuvant chemotherapy (CT) decisions. The Dutch guideline suggests use of validated gene-expression profiles in patients with estrogen receptor (ER)–positive, early-stage breast cancer without overt lymph node metastases. We aimed to assess the impact of a 70-gene signature (70-GS) test on CT decisions in patients with ER-positive, early-stage breast cancer.

Patients and Methods
In a prospective, observational, multicenter study in patients younger than 70 years old who had undergone surgery for ER-positive, early-stage breast cancer, physicians were asked whether they intended to administer adjuvant CT before deployment of the 70-GS test and after the test result was available.

Results
Between October 1, 2013, and December 31, 2015, 660 patients, treated in 33 hospitals, were enrolled. Fifty-one percent of patients had pT1cN0, BRII, HER2-Neu-negative breast cancer. On the basis of conventional clinicopathological characteristics, physicians recommended CT in 270 (41%) of the 660 patients and recommended withholding CT in 107 (16%) of the 660 patients. For the remaining 43% of patients, the physicians were unsure and unable to give advice before 70-GS testing. In patients for whom CT was initially recommended or not recommended, 56% and 59%, respectively, were assigned to a low-risk profile by the 70-GS (kappa, 0.02; 95% CI, -0.08 to 0.11). After disclosure of the 70-GS test result, the preliminary advice was changed in 51% of patients who received a recommendation before testing; the definitive CT recommendation of the physician was in line with the 70-GS result in 96% of patients.

Conclusion
In this prospective, multicenter study in a selection of patients with ER-positive, early-stage breast cancer, 70-GS use changed the physician-intended recommendation to administer CT in half of the patients.

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INTRODUCTION

During the past two decades, treatment guidelines for adjuvant systemic therapy in breast cancer have changed considerably; today, chemotherapy (CT) is advised in the majority of patients. The recommendation to administer adjuvant CT is based on clinicopathological prognostic factors. There is growing awareness that conventional factors do not accurately estimate the prognosis or the benefit of CT in patients with estrogen receptor (ER)–positive breast cancer, which is reflected by a more reticent attitude toward CT administration in these patients in recent treatment guidelines.1

Several gene-expression profiles, such as the 70-gene signature (70-GS; MammaPrint, Amsterdam, the Netherlands), have been developed to aid adjuvant CT decision making in ER-positive, early-stage breast cancer.2,3 The 70-GS was validated in several retrospective studies4-9 and in a community-based feasibility study.10,11 Recently, the results of the MINDACT (microarray in node negative disease may avoid CT) trial provided the first level-1A evidence that

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omission of CT in patients assigned to the 70-GS low-risk category is safe.12 While the results of randomized clinical trials that compare the value of gene-expression profiles to clinicopathological factors when adjuvant chemotherapy is considered were awaited, national13 and international1,14 guidelines advised the use of a gene-expression profile in a selection of patients with early-stage ER-positive disease. The Dutch guideline has recommended use of a validated gene-expression profile since 2012 for patients with ER-positive invasive ductal carcinoma in whom doubt exists about CT benefit on the basis of clinicopathological factors.13 This guideline considers CT beneficial in patients who have an expected 10-year breast cancer–specific mortality of at least 15%, because these patients would have an absolute overall survival gain of 4% to 5% as a result of adjuvant CT administration. In common practice, gene-expression profiles in the Netherlands until now have been used mainly in patients with ER-positive, HER2-Neu-negative disease without overt lymph node metastases (pT1c-2N0-1mi).15 In the Netherlands, the 70-GS test accounts for 97% of all deployed gene-expression tests.16

The aim of this prospective, observational, multicenter study was to assess the impact of the 70-GS test on individual physician decisions when there was doubt about the benefit of adjuvant CT in patients with surgically treated, ER-positive, early-stage breast cancer.

**Study Design**

This study was an observational, prospective, multicenter study to assess the impact of 70-GS test use on adjuvant CT decision making. Patients for whom 70-GS test deployment was considered as part of routine clinical practice were eligible for participation. The Dutch national guideline suggests deployment of a validated gene-expression profile for patients with ER-positive ductal carcinomas in whom doubt exists about CT benefit. This guideline also states that, for patients with an expected 10-year overall survival of 85% or less, CT is indicated. It was expected that gene-expression profiles would be deployed only in patients with ER-positive, HER2-negative, low- or intermediate-grade tumors of stage T1c-2N0-1mi.15

Patients treated between January 1, 2013, and December 31, 2015, in 33 participating hospitals were enrolled after they provided informed consent before deployment of the 70-GS test. Exclusion criteria were a history of malignancy, distant metastasis, and neoadjuvant systemic treatment. The study was approved by the medical ethics committee of the University Medical Center Utrecht (12-450) and by institutional review boards of participating centers. The study protocol (protocol number 12-450) was registered in the clinicaltrial.gov database (NCT02209857).

Eligible patients were identified during postoperative multidisciplinary team meetings, in which a preliminary CT recommendation was formulated on the basis of the clinicopathological results (Fig 1). The treating physician completed the first clinical report form (CRF1), in which information on clinicopathological characteristics and the preliminary CT recommendation—to administer CT, withhold adjuvant CT, or state uncertainty and give no advice—were registered. The estimated 10-year overall survival without CT, which was based on the PREDICT tool from the United Kingdom National Health Service,17 was calculated for every patient to objectify the prognostic perspective of the preliminary CT recommendation. Unlike the Adjuvant! Online tool, PREDICT incorporates HER2 status in its model.18

After completion of CRF1, the tumor samples were sent for 70-GS analysis, and the results were disclosed to the oncologist within 10 working days. The posttest CT recommendation and the actually administered CT were recorded in a second CRF (CRF2).

**End Points**

The primary end point was the percentage of patients for whom 70-GS use led to an altered adjuvant CT recommendation. A secondary end point was the relationship between the preliminary recommendation by the physician and the proportion of patients who actually received CT. Both outcomes also were calculated by basing the recommendation of adjuvant CT on the estimated 10-year overall survival of 85% as a surrogate cutoff value, because the national guideline considers an estimated 10-year survival of less than 85% as a reason to recommend CT.

**Statistical Analysis**

Demographic and clinical characteristics of all patients were summarized in a baseline table. The differences in estimated median 10-year overall survival and CT benefit in relation to the recommendation before deployment of the test and in relation to the test result were compared with the Kruskall-Wallis test and the Mann-Whitney U test, respectively. The percentage of changes in CT recommendation was assessed with the McNemar test. Agreement between the preliminary CT recommendation and the 70-GS test result was assessed with the Cohen κ statistic, which can be interpreted as follows: values of 0 or lower indicate no agreement; of 0.01 to 0.20, no to slight agreement; of 0.21 to 0.40, fair agreement; of 0.41 to 0.60, moderate agreement; of 0.61 to 0.80, substantial agreement; and of 0.81 to 1.00, almost perfect agreement. All analyses were performed in R version 3.1.3.

**RESULTS**

A total of 698 patients with ER-positive, early-stage breast cancer were enrolled, and the mean number of patients per participating...
hospital was 21 (range, 2 to 60 patients). Thirty-eight patients were excluded from the study because of the following: no written informed consent (n = 5) and incomplete data on either the preliminary or the posttest CT recommendation at the closing date of the study (n = 33). A total of 660 patients (median age, 57 years) had evaluable data. The prevailing group was composed of postmenopausal women who had unifocal HER2-negative, low-grade tumors greater than 2 cm or intermediate-grade tumors of 1 to 2 cm without axillary lymph node involvement (pN0 or pN1mi; n = 405). On the basis of clinicopathological characteristics, the median estimated overall 10-year survival according to PREdict was 86.1% (range, 40.2% to 95.3%; interquartile range [IQR], 7.4%), and the expected CT benefit was 1.6% (range, 0.4% to 8.5%; IQR, 1.0%).

Before deployment of the 70-GS test, oncologists recommended CT in 41% and advised against it in 16% of patients. In the remaining 43% of patients, no preliminary CT recommendation was made, because physicians preferred to await the 70-GS test result (Fig 2). Patients to whom CT was recommended were younger and had larger tumors of higher grades than patients into whom physicians advised against adjuvant CT or patients to whom oncologists gave no advice (Table 1). There was no significant difference in median 10-year overall survival according to PREdict among the three pretest CT recommendation groups (P = .231).

The 70-GS test assigned 41% of all patients to the high-risk category. Of patients to whom CT was initially advised, 56% were assigned to the low-risk category by the 70-GS compared with 59% of the patients to whom CT was not recommended. The preliminary advice was in line with the 70-GS risk category in 48% of patients. There was no to slight agreement between this preliminary CT advice and the 70-GS test result (κ, 0.02; 95% CI, −0.08 to 0.11; P = 0.342; Fig 2).

By using the 10-year estimated survival of 85% as the cutoff value to administer CT or not, CT would have been considered beneficial in 289 patients (44%). In 37% of patients (n = 139) who had estimated 10-year survival rates greater than 85%, the 70-GS test indicated a high-risk result; in 46% of patients (n = 132) who had estimated 10-year survival rates less than 85%, the 70-GS test indicated a high-risk result. Again, no or only slight agreement between the 10-year survival categories and the 70-GS test results was observed (κ, 0.08; 95% CI, 0.01 to 0.16). A recommendation that was based on the estimated 10-year survival did not correspond to the 70-GS test result in almost half of the patients (45%; 95% CI, 41% to 49%). The physician adhered to the 70-GS test result in 96% (n = 357) and 96% (n = 276) of patients who had an estimated 10-year survival of greater than 85% or less than 85%, respectively.

A subgroup analysis in patients with tumors greater than 2 cm (n = 146) or in patients with axillary lymph node involvement (pN1mi or worse stage; n = 103) yielded similar proportions of patients assigned to the risk categories; discordance between the preliminary CT advice and the 70-GS test result occurred in 56% (κ, −0.04; 95% CI, −0.24 to 0.17) and 62% (κ = −0.10; 95% CI, −0.33 to 0.13) of patients, respectively.

The oncologist adhered to the 70-GS test result in 96% of patients: in 18 patients in the 70-GS low-risk category, oncologists recommended CT; in nine patients in the 70-GS high-risk category, oncologists advised against CT. Actually administered CT was the same as the posttest recommendations by oncologists in 94% of patients. Thirty patients to whom CT was recommended, of which 29 had a high-risk 70-GS test result, did not receive CT. Conversely, eight patients received CT despite the advice of the oncologists to withhold CT; seven of these patients had a low-risk 70-GS test result. Eventually administered CT was in line with the 70-GS test result in 91% of patients.

The recommendation was changed after 70-GS test use in 51% (95% CI, 46% to 56%; P < .001; Table 2) of patients for whom the clinician formulated a clear recommendation prior to the test (n = 377). Actually administered CT deviated from the preliminary CT recommendation in 52% of the patients.

Figure 2.

DISCUSSION

The results of this prospective, multicenter study demonstrated that 70-GS test use has substantial impact on CT decision making in patients with early-stage, ER-positive, HER2-negative breast cancer: 70-GS test use changed the premeditated advice from oncologists about adjuvant CT treatment in half of the patients. In addition, physicians were uncertain and unable to give advice without the 70-GS test in a substantial proportion of patients.

In this study, 70-GS test use led to altered advice about whether to administer CT or not in 51% of patients, and CT was administered in contradiction with the preliminary recommendation in a similar proportion of patients. Adherence of physicians and patients to the 70-GS test result was high and in line with recent studies.19,20 In studies in which multidisciplinary teams formulated advice before and after deployment of the 70-GS test, CT recommendation changes ranged from 16% to 38%.21,23 Similar results about the impact of Oncotype DX (Genomic...
Health, Redwood City, CA) and Prosigna (Nanostring Technologies, Seattle, WA) use have been reported. A recent meta-analysis was conducted to assess the impact of Oncotype DX on adjuvant CT decisions; the results demonstrated a change in CT decisions in 38% of recommendations to patients with early-stage, ER-positive, HER2-negative breast cancer. Two prospective, multicenter studies addressed the influence of Prosigna use on CT decision making and reported an impact on CT decisions in 18% and 20%

### Table 1. Baseline Demographic and Clinical Characteristics of All Patients Included in the Study

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>All Patients (N = 660)</th>
<th>Yes (n = 270)</th>
<th>No (n = 107)</th>
<th>No Advice Given (n = 283)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Patient characteristic</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean (SD) age, years</td>
<td>57.0 (8.1)</td>
<td>56.2 (7.9)</td>
<td>58.5 (8.0)</td>
<td>57.2 (8.3)</td>
</tr>
<tr>
<td>Menopausal status</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pre- or perimenopausal</td>
<td>218 (34)</td>
<td>102 (39)</td>
<td>28 (27)</td>
<td>88 (32)</td>
</tr>
<tr>
<td>Postmenopausal</td>
<td>428 (66)</td>
<td>162 (61)</td>
<td>76 (73)</td>
<td>190 (68)</td>
</tr>
<tr>
<td>Missing</td>
<td>14</td>
<td>6</td>
<td>3</td>
<td>5</td>
</tr>
<tr>
<td><strong>Tumor characteristic</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Unifocal disease</td>
<td>596 (90)</td>
<td>250 (93)</td>
<td>97 (91)</td>
<td>249 (88)</td>
</tr>
<tr>
<td>Invasive tumor grade</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>96 (15)</td>
<td>29 (11)</td>
<td>25 (23)</td>
<td>42 (15)</td>
</tr>
<tr>
<td>2</td>
<td>481 (73)</td>
<td>195 (72)</td>
<td>77 (72)</td>
<td>209 (74)</td>
</tr>
<tr>
<td>3</td>
<td>82 (12)</td>
<td>46 (17)</td>
<td>5 (5)</td>
<td>31 (11)</td>
</tr>
<tr>
<td>Mean (SD) tumor size, mm*</td>
<td>16.4 (7.0)</td>
<td>16.9 (5.7)</td>
<td>16.1 (12.0)</td>
<td>16.2 (5.3)</td>
</tr>
<tr>
<td>pT1</td>
<td>534 (81)</td>
<td>212 (79)</td>
<td>96 (90)</td>
<td>226 (80)</td>
</tr>
<tr>
<td>pT2</td>
<td>125 (19)</td>
<td>58 (22)</td>
<td>10 (9)</td>
<td>57 (20)</td>
</tr>
<tr>
<td>pT3</td>
<td>1 (0)</td>
<td>1 (1)</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>PR-positive disease</td>
<td>571 (87)</td>
<td>231 (86)</td>
<td>90 (84)</td>
<td>250 (88)</td>
</tr>
<tr>
<td>HER2-negative disease</td>
<td>638 (97)</td>
<td>259 (96)</td>
<td>105 (98)</td>
<td>274 (97)</td>
</tr>
<tr>
<td><strong>Axillary lymph node involvement†</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>pN0</td>
<td>552 (84)</td>
<td>224 (83)</td>
<td>95 (89)</td>
<td>233 (82)</td>
</tr>
<tr>
<td>pN1mi</td>
<td>65 (10)</td>
<td>27 (10)</td>
<td>5 (5)</td>
<td>33 (12)</td>
</tr>
<tr>
<td>pN1a</td>
<td>35 (5)</td>
<td>17 (6)</td>
<td>6 (6)</td>
<td>12 (4)</td>
</tr>
<tr>
<td>&gt; pN1a</td>
<td>3 (1)</td>
<td>—</td>
<td>—</td>
<td>3 (1)</td>
</tr>
<tr>
<td>Nx</td>
<td>5 (1)</td>
<td>2 (1)</td>
<td>1 (1)</td>
<td>2 (1)</td>
</tr>
<tr>
<td><strong>Treatment characteristic</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Surgery</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Breast-conserving surgery</td>
<td>532 (81)</td>
<td>211 (78)</td>
<td>91 (88)</td>
<td>230 (81)</td>
</tr>
<tr>
<td>Mastectomy</td>
<td>128 (19)</td>
<td>59 (22)</td>
<td>16 (15)</td>
<td>53 (19)</td>
</tr>
<tr>
<td>Axillary surgery</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SNP</td>
<td>621 (94)</td>
<td>258 (96)</td>
<td>96 (90)</td>
<td>267 (94)</td>
</tr>
<tr>
<td>ALND</td>
<td>6 (2)</td>
<td>1 (0)</td>
<td>4 (4)</td>
<td>1 (0)</td>
</tr>
<tr>
<td>SNP + ALND</td>
<td>12 (1)</td>
<td>3 (1)</td>
<td>1 (1)</td>
<td>8 (3)</td>
</tr>
<tr>
<td>No axillary surgery</td>
<td>21 (3)</td>
<td>8 (3)</td>
<td>6 (6)</td>
<td>7 (3)</td>
</tr>
<tr>
<td>Estimated median (IQR) 10-year survival</td>
<td>86.1 (7.4)</td>
<td>86.1 (7.6)</td>
<td>87.1 (6.6)</td>
<td>85.8 (7.9)</td>
</tr>
</tbody>
</table>

**NOTE.** All patients had estrogen receptor-positive disease. Data are presented as No. (%) unless otherwise indicated.

**Abbreviations:** ALND, axillary lymph node dissection; CT, chemotherapy; IQR, interquartile range; PR, progesterone receptor; SD, standard deviation; SNP, sentinel node procedure.

*Pathologic tumor size (pT) according to the TNM staging system.
†Pathologic lymph node involvement according to the TNM staging system.

### Table 2. CT Recommendation Before and After the 70-GS Test Result Was Obtained and CT Was Actually Administered

<table>
<thead>
<tr>
<th>Preliminary Recommendation</th>
<th>No. of Patients</th>
<th>Posttest Recommendation, No. (%)</th>
<th>Adherence to Test Result (%)</th>
<th>Actual Administration of CT, No. (%)</th>
<th>Adherence to Test Result (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>No CT</td>
<td>107</td>
<td>69 (65)</td>
<td>38 (35)</td>
<td>94</td>
<td>73 (68)</td>
</tr>
<tr>
<td>CT</td>
<td>270</td>
<td>156 (58)</td>
<td>114 (42)</td>
<td>97</td>
<td>162 (60)</td>
</tr>
<tr>
<td>Unsure</td>
<td>283</td>
<td>173 (61)</td>
<td>110 (39)</td>
<td>95</td>
<td>185 (65)</td>
</tr>
</tbody>
</table>

**NOTE.** There was in change in CT recommendation in 51% (95% CI, 46% to 56%; P < .001) of patients who had a clear pretest CT recommendation (ie, yes or no CT; n = 377). Actually administered CT differed from the preliminary CT recommendation in 52% (95% CI, 0.47% to 0.57%; P < .001) of patients who had a clear pretest CT recommendation.

**Abbreviations:** CT, chemotherapy; GS, gene signature.

*Percentage of patients in whom the posttest recommendation/actually administered CT was in line with the 70-GS test result (ie, no CT in patients with a low-risk profile and CT in patients with a high-risk profile).
Of patients, respectively. Unlike these two prospective studies, the oncologist could refrain from giving an advice before deployment of the 70-GS test in this study, which might have led to overestimation of the proportion of patients in whom the treatment advice was changed. In another large, prospective study to assess the impact of Oncotype DX use on CT decision making in patients with early-stage, ER-positive, HER2-negative breast cancer, the option to refrain from giving advice before deployment of a gene-expression test was available for participating physicians. This study reported a CT recommendation change in 50% of patients after Oncotype DX use, which is in concordance with our results.

In addition, an estimated 10-year overall survival of 85%, retrospectively estimated by PREDICT, was applied to the study group as a cutoff value to determine whether to administer adjuvant CT. Even when this cutoff value was used, the 70-GS test result differed from the surrogate recommendation that was based on PREDICT in almost half of the patients.

In this study, the oncologist recommended administration of adjuvant CT to 41% of all patients before 70-GS testing. This is in line with data from a nationwide study conducted by our research group, which used observational Netherlands Cancer Registry data: 45% of all Dutch patients with (pT1-2N0mi) ER-positive, HER2-negative breast cancer for whom no 70-GS test was deployed received adjuvant CT. This illustrates the current controversy about CT benefit in this specific patient population.

To our knowledge, this is the largest prospective study to date to evaluate the impact of 70-GS test use on CT decision making, and the design of this study mimics routine clinic practice. Nevertheless, the pretest CT recommendation by the oncologists remains an artificial statement made with the prospect of an obtained 70-GS test result. In addition, because of the observational design of the study, it is possible that oncologists used the 70-GS test only in a selection of eligible patients, which would result in an overestimation of adherence rates or percentages of treatment change. Despite these limitations, the impact of 70-GS test use on CT decision making in patients with ER-positive, HER2-negative disease was substantial.

The impact of the 70-GS test on CT decision making was assessed in patients with ER-positive, HER2-negative disease for whom controversy about CT benefit led to use of the 70-GS test. It is important to note that, in this study, the prognostic value of the 70-GS test was used to guide CT decisions. Future studies have to be conducted to provide outcome data that support the altered decisions. For that purpose, we intend to merge the data of this study with the Netherlands Cancer Registry database. Also, robust results of the recently presented European Organisation for the Research and Treatment of Cancer (EORTC) 10041/BIG 03-04 MINDACT trial indicate that 46% of patients with breast cancer who are identified as high risk for recurrence according to clinicopathological factors are assigned to the 70-GS low-risk category. These patients are unlikely to derive significant benefit from CT. The indication area for 70-GS test use, as stated in the current clinical guidelines, will likely extend to the clinical higher-risk categories of patients. This study demonstrates that the 70-GS test is supportive for CT decision making in assumed high-risk populations, such as patients who have larger tumors or lymph node metastases. At the same time, the MINDACT trial also indicates that, in patients identified as having a low risk of recurrence according to clinicopathological factors who are assigned to the 70-GS high-risk category, there is no significant difference in the 5-year distant metastasis–free survival between the patients who received adjuvant CT and those who did not receive CT. This suggests no clinical utility of the 70-GS test in patients with low clinical risks, and this may lead to less use of the 70-GS test in these patients.

In this study in patients with ER-positive, HER2-negative, low- or intermediate-grade, breast cancer of stage T1c-2N0-1mi, 70-GS test use changed the physician-intended recommendation to administer CT in half of the patients. The weak correlation between the pretest CT recommendation and the 70-GS result implies that oncologists encounter difficulties in the recommendation about whether to administer CT without use of a gene-expression profile in this group of patients. Although previous studies have demonstrated the existing controversy about the use of CT in this group of patients, this study demonstrates the inability of physicians to make an accurate chemotherapy recommendation on the basis of conventional prognostic factors alone.

**AUTHORS’ DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST**

Disclosures provided by the authors are available with this article at jco.org.

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AUTHORS’ DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

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