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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

breast cancer treatment guideline (Supplementary Table 1) [13].

2.3. Statistical analyses

Clinical low- and high-risk group were identified and further classified into different subcategories according to the Dutch guidelines based on grade, tumor size, and lymph-node involvement.

For both the clinical low- and high-risk group, patient and tumor characteristics as well as hospital type (district, teaching, and university) were compared between patients who did and did not received GEP testing by chi-square tests and an independent t-test for the normally distributed continuous variables age and size. Proportions of patients receiving a GEP in relation to the frequencies of the listed low- and high-risk categories are summarised and listed with the respective GEP test results and proportions of patients receiving adjuvant CT. Implications of GEP use, in terms of discordance between the clinical and genomic risk estimate and adherence to the test result reflected in adjuvant CT administration were evaluated in both the clinical low- and high-risk patients and the various subcategories. Subsequently, logistic regression analysis was performed to assess if GEP use was independently associated with the administration of adjuvant CT in clinical low- or high-risk patients after correction for confounders. The same approach was used to assess whether the GEP test result was independently associated with CT administration in clinical low- or high-risk patients who received GEP testing. Results are presented as odds ratios (OR) and 95% confidence intervals (95% CI). A p value of <0.05 was considered to be statistically significant. All statistical analyses were performed in STATA (version 13.1 2013, Texas).

3. Results

3.1. Study population

A total of 26,425 patients were identified in the NCR database: 35.4% of these patients were considered as clinical low risk and 64.6% as clinical high risk according to the guideline (Fig. 1). Overall, 3.9% patients in the clinical low-risk group received CT and 79.7% of clinical high-risk patients. A total of 1725 GEPs (6.5%) were deployed in the study population in 4.8% (n = 444) of the patients in the clinical low-risk group and in 7.5% (n = 1281) of patients in the clinical high-risk group received a GEP. Overall, 68.5% of patients with a discordant clinical and genomic risk estimation were treated in line with the GEP test result.

3.2. GEP use in clinical low-risk patients

GEPs assigned 20.3% of the clinical low-risk patients to a high genomic risk category. GEPs were more frequently deployed in patients under 35 years of age, with ER+/HER2-tumors of limited size without axillary lymph-node involvement. Furthermore, GEPs were more often deployed in patients treated in teaching hospitals (Table 1). GEP use was highest (32.2%) in the clinical low-risk patients <35 years of age with HER2-negative, grade 1 tumors ≤1 cm without axillary lymph-node involvement (group 1, Supplementary Table 2).

Overall, in 15.5% of clinical low-risk patients who underwent CT, a GEP was deployed compared to 4.3% who did not receive CT ($p<0.05$; Table 1). GEP use was independently associated with an increased risk of receiving CT in clinical low-risk patients on multivariate logistic regression analysis (OR = 2.12, 95% CI: 1.44–3.11, data not shown). The presence of axillary micro-metastases was the only clinicopathological factor that remained independently associated with CT administration in clinical low-risk patients who received GEP testing (pNmi versus pN0, OR = 10.75, 95% CI: 3.29–35.13, Table 2). In the subset of clinical low-risk patients with discordance between clinical and genomic risk assessment (n = 90; i.e. the GEP assigned patients to the high-risk category), CT was administered in 52.2% of patients (Fig. 1).

3.3. GEP use in clinical high-risk patients

The GEP assigned 449 patients to a low genomic risk category (35%). GEPs were more frequently deployed in clinical high-risk patients who were slightly older and more often had ER+/Her2-tumors <3 cm without axillary node involvement (Table 1). In 6.1% of clinical high-risk patients who received CT, a GEP was deployed compared to 12.8% of patients who did not receive CT ($p<0.001$, Table 1). GEP use in clinical high-risk patients remained independently associated with a decreased risk of CT administration in multivariate logistic regression analysis (OR = 0.55, 95% CI: 0.48–0.63, data not shown).

In clinical high-risk patients who received a GEP, a low-risk GEP result was strongly associated with a decreased risk of CT administration (OR = 0.05, 95% CI: 0.03–0.07). In 71.7% (n = 322) of these discordant patients, the administration of adjuvant CT was in line with the low-risk GEP test result (i.e. no CT was administered, Fig. 1). Young age, larger tumor size, higher grade, Her2+ disease, and (micro-)metastatic lymph-node involvement remained independently associated with an increased risk of CT administration in these patients (Table 3).

4. Discussion

Although the Dutch guideline suggests the use of a validated GEP in ER+ early breast cancer patients, in

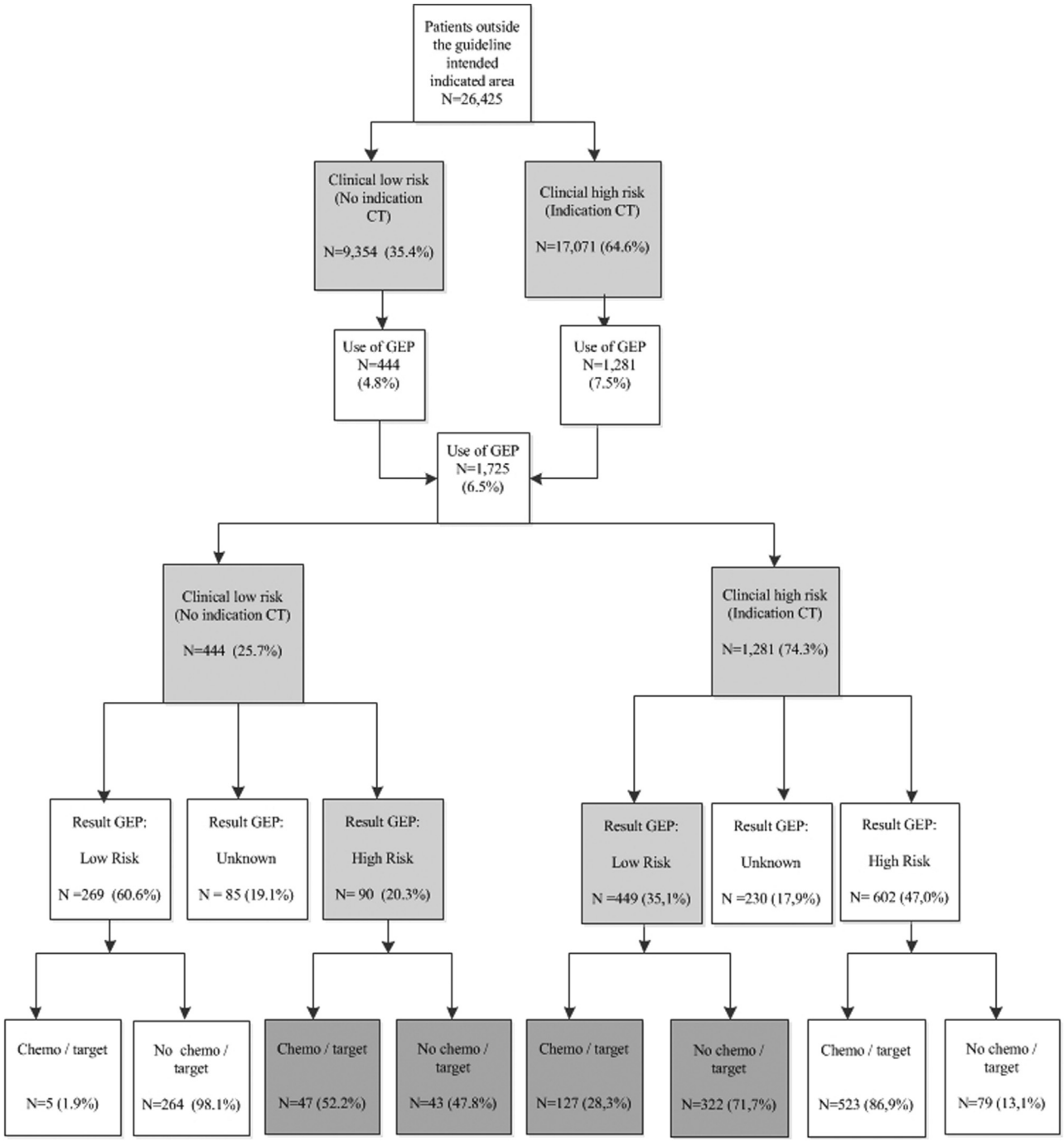

Fig. 1. Flowchart describing discordance between the clinical and genomic risk estimation and adherence to the genomic test result reflected in adjuvant CT administration.

whom benefit of CT is uncertain based on traditional prognostic factors alone [3,9], in the present population-based study, GEPs were used in 4.7% and 7.5% of patients who were considered as clinical low-risk and high-risk patients, respectively. In these groups, a discordance between the clinical and genomic risk-estimation was observed in 20.3% and 35.1%, respectively, and GEP use significantly influenced CT administration in these patients.

To our knowledge, this is the first report on the clinical impact of GEP use in patients in whom a GEP should be superfluous as the recommendation to administer or withhold CT is clear based on clinico-pathological factors. The observed frequency of 6.5% in the present group is remarkable and compares to a 15% deployment of GEPs in the category of patients in whom GEPs were advocated [10]. The relatively high incidence of GEP use in the present study and the

Table 1
Patient, tumor and hospital characteristics of patients outside the guideline directed indicated area for GEP use.

		Clinical low risk (n = 9354)					Clinical high risk (n = 17,071)				
		No GEP received (n = 8910)		GEP received (n = 444)		p-value[a]	No GEP received (n = 15,790)		GEP received (n = 1281)		p-value[a]
Age in years (mean, SD)		57.74	7.82	54.29	8.37	<0.05	53.69	9.87	54.32	9.22	<0.05
	<35	12	70.6%	5	29.4%		637	95.2%	32	4.8%	
	35–50	1812	92.5%	147	7.5%		5368	92.6%	429	7.4%	
	50–75	7086	96.0%	292	4.0%		9785	92.3%	820	7.7%	
Tumor size in mm (mean, SD)		9.15	4.05	11.46	4.41	<0.05	23.3	13.07	20.67	9.6	<0.05
	<10	6147	96.5%	221	3.5%		977	94.9%	52	5.1%	
	10–20	2763	92.5%	223	7.5%		6283	91.1%	614	8.9%	
	21–30	0	0.0%	0	0.0%		5315	91.8%	473	8.2%	
	>31	0	0.0%	0	0.0%		2800	95.6%	130	4.4%	
	Unknown	0	0.0%	0	0.0%		415	97.2%	12	2.8%	
Estrogene receptor	*ER−*	576	96.5%	21	3.5%	<0.05	3756	95.2%	188	4.8%	<0.05
	ER+	8245	95.1%	422	4.9%		11,793	91.5%	1092	8.5%	
	Unknown	89	98.9%	1	1.1%		241	99.6%	1	0.4%	
Progesterone receptor	*PR−*	1870	96.3%	71	3.7%	<0.05	5979	94.1%	375	5.9%	<0.05
	PR+	6945	94.9%	372	5.1%		9550	91.4%	904	8.6%	
	Unknown	95	99.0%	1	1.0%		261	99.2%	2	0.8%	
Her2 Neu	*Her2−*	8450	95.1%	434	4.9%	<0.05	11,862	91.7%	1068	8.3%	<0.05
	Her2+	268	97.8%	6	2.2%		3613	94.7%	203	5.3%	
	Unknown	192	98.0%	4	2.0%		315	96.9%	10	3.1%	
Node state	*Negative*	8177	95.9%	347	4.1%	<0.05	7129	89.7%	821	10.3%	<0.05
	Mi[b]	540	85.2%	94	14.8%		1127	92.3%	94	7.7%	
	N1	0	0.0%	0	0.0%		5358	94.9%	285	5.1%	
	N2	0	0.0%	0	0.0%		1283	96.5%	47	3.5%	
	N3	0	0.0%	0	0.0%		712	96.7%	24	3.3%	
	Unknown	193	98.5%	3	1.5%		181	94.8%	10	5.2%	
Grade	*1*	5703	95.1%	297	5.0%	<0.05	1417	92.3%	118	7.7%	0.05
	2	2481	95.9%	105	4.1%		6383	91.8%	567	8.2%	
	3	660	94.0%	42	6.0%		7663	92.9%	587	7.1%	
	Unknown	66	100.0%	0	0.0%		327	97.3%	9	2.7%	
Multifocality	*No*	7867	95.3%	388	4.7%	0.17	12,595	92.0%	1096	8.0%	<0.05
	Yes	989	94.6%	56	5.4%		2934	94.1%	184	5.9%	
	Unknown	54	100.0%	0	0.0%		261	99.6%	1	0.4%	
Hospital of surgery	*District*	2992	95.7%	133	4.3%	<0.05	5377	93.3%	388	6.7%	<0.05
	Teaching	5108	94.6%	293	5.4%		9081	91.4%	850	8.6%	
	University	810	97.8%	18	2.2%		1332	96.9%	43	3.1%	
Chemo/targeted therapy	No	8604	95.7%	388	4.3%	<0.05	3028	87.2%	445	12.8%	<0.05
	Yes	306	84.5%	56	15.5%		12,762	93.9%	836	6.1%	

[a] Chi-square test.
[b] Micrometastasis.

Table 2
Association between known GEP test result and the administration of adjuvant CT in clinical low-risk patients.

Factors associated with adjuvant chemotherapy administration in clinical low-risk patient who received a GEP (n = 359)[c]									
		No Chemo/targeted (N = 307)		Chemo/targeted (N = 52)		Univariable		Multivariate	
		n	*%*	*n*	*%*	*OR*	*95% CI*	*OR*	*95% CI*
GEP result	*Low risk*	264	86.0	5	9.6	Ref		Ref	
	High risk	43	14.0	47	90.4	57.71	21.73–153.26	90.95[a]	26.19–315.81
Age in years	*<35*	3	1.0	2	3.8	Ref		Ref	
	35–50	108	35.2	23	44.2	0.32	0.05–2.02		
	50–75	196	63.8	27	51.9	0.21	0.03–1.29		
Tumor size in mm	*<10*	136	44.3	32	61.5	Ref		Ref	
	11–20	171	55.7	20	38.5	0.50	0.27–0.91	0.82	0.20–3.33
Estrogen receptor	*ER−*	9	2.9	7	13.5	Ref		Ref	
	ER+	298	97.1	45	86.5	0.19	0.07–0.55	1.37	0.27–7.05
	Unknown	0	0.0	0	0.0				
Progesterone receptor	*PR−*	40	13.0	16	30.8	Ref		Ref	
	PR+	267	87.0	36	69.2	0.34	0.17–0.66	0.52	0.16–1.65
	Unknown	0	0.0	0	0.0				
Her2 Neu	*Her2−*	302	98.4	51	98.1	Ref		Ref	
	Her2+	2	0.7	1	1.9	2.96	0.26–33.25		
	Unknown	3	1.0	0	0.0	Omitted			
Node state	*Negative*	236	76.9	32	61.5	Ref		Ref	
	Mi[b]	69	22.5	20	38.5	2.14	1.15–3.97	10.75[a]	3.29–35.13
	Unknown	2	0.7	0	0.0	Omitted			
Grade	*1*	224	73.0	24	46.2	Ref		Ref	
	2	63	20.5	12	23.1	1.78	0.84–3.75	1.09	0.23–5.16
	3	20	6.5	16	30.8	7.47	3.42–16.30	3.13	0.62–15.65
	Unknown	0	0.0	0	0.0	Omitted			
Multifocality	*No*	267	87.0	41	78.8	Ref		Ref	
	Yes	40	13.0	11	21.2	1.79	0.85–3.77		
	Unknown	0	0.0	0	0.0				
Hospital of surgery	*District*	93	30.3	17	32.7	Ref		Ref	
	Teaching	201	65.5	31	59.6	0.84	0.44–1.60		
	University	13	4.2	4	7.7	1.68	0.49–5.78		

[a] Significant OR.
[b] Micrometastasis.
[c] Patients with an unknown GEP test results (n = 85) were excluded from these analyses.

apparent impact of GEP use on CT administration in these patients, suggests limited support among clinicians and patients for the current clinical guideline recommendations. The mere frequency of 'unintended' GEP use underscores that clinicians need reproducible and objective measures for the decision to administer CT. In both clinical low- and high-risk patients, GEP use was more frequent in patients with ER+/Her2-intermediate grade tumors of limited size, indicating uncertainty regarding CT administration especially in these subgroups of patients. Patients with micrometastatic axillary lymph-node involvement were more likely to receive a GEP in the clinical low-risk group, whereas GEPs were deployed mere frequently deployed in node-negative patients in the clinical high-risk group.

When a GEP was deployed, we observed an overall discordance between clinical and genomic risk estimation in 31.3% of patients assigned to the clinical low- or high-risk category. One of three clinical high-risk patients was assigned to the low-risk category by GEPs which led to omission of CT, despite a guideline indication to administer CT, in approximately 72% of these patients. The results of the MINDACT trial support the omission of adjuvant CT in stage I–III early-stage clinical high-risk breast cancer patients with up to three axillary lymph-node metastasis when the GEP categorises these patients as having a low genomic risk [14]. On the other hand, in the MINDACT trial, clinical utility of 70-gene signature use was not demonstrated for clinical low-risk patients as clinical low-risk patients assigned to the genomic high-risk profile who did not receive CT had similar 5-year disease free survival rates as patients who did receive CT. Therefore, the indication area for GEP use as stated in current clinical practice guidelines will probably be further broadened to clinical high-risk patients in coming years while its use will be discommended in clinical low-risk patients.

Overall, 68.5% of patients with a discordant clinical and genomic risk estimation were treated in line with the GEP test result (52.2% in low and 71.7% in high). This is substantially lower as compared to patients within the guideline intended area for GEP use, in whom adherence rates to the GEP result of up to 89% have been reported [10]. This observation is on the one hand not

Table 3
Association between known GEP test result and the administration of adjuvant CT in clinical high-risk patients.

Factors associated with adjuvant chemotherapy administration in clinical high-risk patient who received a GEP (n = 1051)[c]		No Chemo/targeted (N = 401)		Chemo/targeted (N = 650)		Univariable		Multivariate	
		n	*%*	*n*	*%*	*OR*	*95% CI*	*OR*	*95% CI*
GEP result	*Low risk*	322	80.3	127	19.5	0.06	0.04–0.08	0.05[a]	0.03–0.07
	High risk	79	19.7	523	80.5	Ref		Ref	
Age in years	*<35*	4	1.0	19	2.9	Ref		Ref	
	35–50	91	22.7	248	38.2	0.57	0.19–1.73	0.31	0.07–1.40
	50–75	306	76.3	383	58.9	0.26	0.09–0.78	0.12[a]	0.03–0.54
Tumor size in mm	*<10*	22	5.5	20	3.1	Ref		Ref	
	11–20	165	41.1	356	54.8	2.37	1.26–4.47	2.82[a]	1.11–7.16
	21–30	184	45.9	204	31.4	1.22	0.64–2.31	3.10[a]	1.17–8.25
	>31	26	6.5	65	10.0	2.75	1.29–5.86	6.84[a]	2.21–21.23
	Unknown	4	1.0	5	0.8	1.38	0.32–5.85	5.25	0.73–37.74
Estrogen receptor	*ER–*	14	3.5	124	19.1	Ref		Ref	
	ER+	387	96.5	525	80.8	0.15	0.09–0.27	0.54	0.25–1.16
	Unknown	0	0.0	1	0.2	Omitted			
Progesterone receptor	*PR–*	59	14.7	227	34.9	Ref		Ref	
	PR+	342	85.3	421	64.8	0.32	0.23–0.44	0.78	0.48–1.29
	Unknown	0	0.0	2	0.3	Omitted			
Her2 Neu	*Her2–*	365	91.0	535	82.3	Ref		Ref	
	Her2+	28	7.0	113	17.4	2.75	1.78–4.25	3.30[a]	1.68–6.52
	Unknown	8	2.0	2	0.3	0.17	0.04–0.81	0.30	0.02–5.11
Node state	*Negative*	286	71.3	430	66.2	Ref		Ref	
	Mi[b]	34	8.5	40	6.2	0.78	0.48–1.27	1.85	0.95–3.60
	N1	77	19.2	139	21.4	1.20	0.88–1.65	7.48[a]	4.27–13.13
	N2	0	0.0	22	3.4	Omitted		Omitted	
	N3	1	0.2	12	1.8	7.98	1.03–61.72	28.01[a]	3.15–249.41
	Unknown	3	0.7	7	1.1	1.55	0.40–6.05	1.17	0.23–5.95
Grade	*1*	55	13.7	42	6.5	Ref		Ref	
	2	232	57.9	240	36.9	1.35	0.87–2.10	2.19[a]	1.17–4.10
	3	113	28.2	361	55.5	4.18	2.66–6.59	3.93[a]	1.94–7.96
	Unknown	1	0.2	7	1.1	9.17	1.09–77.40	2.97	0.24–36.72
Multifocality	*No*	350	87.3	551	84.8	Ref		Ref	
	Yes	51	12.7	98	15.1	1.22	0.85–1.76		
	Unknown	0	0.0	1	0.2	Omitted			
Hospital of surgery	*District*	135	33.7	187	28.8	Ref		Ref	
	Teaching	246	61.3	444	68.3	1.30	0.99–1.71		
	University	20	5.0	19	2.9	0.69	0.35–1.33		

[a] Significant OR.
[b] Micrometastasis.
[c] ^Patients with an unknown GEP test results (n = 230) were excluded from these analyses.

surprising since the level of evidence for GEP use in clinical low- or high-risk patients was modest during our study period. On the other hand, it remains strange that the test was deployed for 'some' reason and subsequently not adhered to in 47.8% of patients with a low and 28.3% of patients with a high-risk test result. This may be explained by deployment of a GEP on a patients' request. Interestingly, GEP use was observed in 3–4% of N2/N3 high-risk patients. The use of GEPs in these patients can possibly be explained by patients' preferences to avoid CT. However, further qualitative psycho-oncological research is necessary to determine the influence of patients' preferences in undergoing CT in clinical low- and high-risk patients with (dis)cordant GEP results. On the other hand, physicians may seek more support for the recommendation or avoidance of CT instead of being in true doubt when deploying a GEP in the guideline intended indication area. The results of the MINDACT trial will probably strengthen the motivation for GEP use in clinical high-risk patients and may lead to a higher adherence to the low-risk GEP result. The observed higher adherence to the GEP result in clinical high-risk patients assigned to the low-risk GEP category (71.7%) in comparison to clinical low-risk patients assigned to the high GEP category (52.2%) is in line with previous studies which also report on GEPs being mainly used for a substantiated decision to withhold CT.

The population-based character of the present study makes our work unique and enables us to provide a nation-wide overview of GEP use (MammaPrint™ 70-gene signature). Implications of GEP use in ER+/Her2– early-stage breast cancer patients in whom uncertainty exists regarding CT benefit based on

traditional prognostic factors alone are increasingly studied. Reports on implications of GEP testing at a nation-wide level or in patients outside this guideline intended indication area are scarce. The strength of the population-based design is the weakness of the study as well. Although we assessed the association between GEP use and CT administration in multivariable logistic regression analysis correcting for all known clinico-pathological characteristics, confounding by indication cannot be ruled out completely.

5. Conclusion

GEPs are relatively quite frequently used to aid adjuvant CT decision-making in patients with a clear clinical guideline recommendation to administer or withhold CT in the Netherlands. Although adherence to the test result is limited in the categories of patients who are considered as having a low or high clinical risk of developing metastases, GEP use significantly influenced CT decision-making in these patients illustrating the clinicians need for reproducible and objective measures for the decision to administer CT.

Conflict of interest statement

The authors do not declare any conflicts of interest.

Ethics approval and consent to participate

According to the Central Committee on Research involving Human Subjects (CCMO), this type of study does not require approval from an ethics committee in the Netherlands. This study was approved by the Privacy Review Board of the NCR.

Availability of data and materials

The data that support the findings of this study are available from Netherlands Comprehensive Cancer Organization, but restrictions apply to the availability of these data, which were used under license for the present study, and so are not publicly available. Data are however available from the authors on reasonable request and with permission of Netherlands Comprehensive Cancer Organization.

Appendix A. Supplementary data

Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.ejca.2017.07.042.

References

[1] Early Breast Cancer Trialists' Collaborative, G. Effects of chemotherapy and hormonal therapy for early breast cancer on recurrence and 15-year survival: an overview of the randomised trials. Lancet 2005;365(9472):1687–717.
[2] Goldhirsch A, Ingle JN, Gelber RD, Coates AS, Thürlimann B, Senn HJ, et al. Thresholds for therapies: highlights of the St Gallen International Expert Consensus on the primary therapy of early breast cancer 2009. Ann Oncol 2009;20(8):1319–29.
[3] Paik S, Tang G, Shak S, Kim C, Baker J, Kim W, et al. Gene expression and benefit of chemotherapy in women with node-negative, estrogen receptor-positive breast cancer. J Clin Oncol 2006;24(23):3726–34.
[4] Beisecker A, Cook MR, Ashworth J, Hayes J, Brecheisen M, Helmig L, et al. Side effects of adjuvant chemotherapy: perceptions of node-negative breast cancer patients. Psychooncology 1997;6(2):85–93.
[5] Senkus E, Kyriakides S, Ohno S, Penault-Llorca F, Poortmans P, Rutgers E, et al. Primary breast cancer: ESMO clinical practice guidelines for diagnosis, treatment and follow-up. Ann Oncol 2013;24(Suppl 6):vi7–23.
[6] Goldhirsch A, Wood WC, Coates AS, Gelber RD, Thürlimann B, Senn HJ, et al. Strategies for subtypes–dealing with the diversity of breast cancer: highlights of the St. Gallen International Expert Consensus on the primary therapy of early breast cancer 2011. Ann Oncol 2011;22(8):1736–47.
[7] van de Vijver MJ, He YD, Van 't Veer LJ, Dai H, Hart AAM, Voskuil DW, et al. A gene-expression signature as a predictor of survival in breast cancer. N Engl J Med 2002;347(25):1999–2009.
[8] Filipits M, Rudas M, Jakesz R, Dubsky P, Fitzal F, Singer CF, et al. A new molecular predictor of distant recurrence in ER-positive, HER2-negative breast cancer adds independent information to conventional clinical risk factors. Clin Cancer Res 2011;17(18):6012–20.
[9] Kwaliteitsinstituut voor de gezondheidszorg CBO VvIK. In: Risicoprofilering. Richtlijn Mammacarcinoom; 2012. p. 81–3.
[10] Kuijer A, van Bommel ACM, Drukker CA, van der Heiden-van der Loo M, Smorenburg CH, Westenend PJ, et al. Using a gene expression signature when controversy exists regarding the indication for adjuvant systemic treatment reduces the proportion of patients receiving adjuvant chemotherapy: a nationwide study. Genet Med 2016;18(7):720–6.
[11] Kuijer A, Drukker CA, Elias SG, Smorenburg CH, Th. Rutgers EJ, Siesling S, et al. Changes over time in the impact of gene-expression profiles on the administration of adjuvant chemotherapy in estrogen receptor positive early stage breast cancer patients: a nationwide study. Int J Cancer 2016;139(4):769–75.
[12] Kuijer A, Schreuder K, Elias SG, Smorenburg CH, Rutgers EJT, Siesling S, et al. Factors associated with the use of gene expression profiles in estrogen receptor-positive early-stage breast cancer patients: a nationwide Study. Public Health Genomics 2016;19(5):276–81.
[13] Landelijke Richtijn Oncoline. 2012; 2.0. Available from: http://www.oncoline.nl/index.php?pagina=/richtlijn/item/pagina.php&id=34737&richtlijn_id=828.
[14] Cardoso F, van 't Veer LJ, Bogaerts J, Slaets L, Viale G, Delaloge S, et al. 70-Gene signature as an aid to treatment decisions in early-stage breast cancer. N Engl J Med 2016;375(8):717–29.