Research Article

Public Health Genomics

Public Health Genomics 2018;21:85–92
DOI: 10.1159/000495742

Received: April 4, 2018
Accepted: November 23, 2018
Published online: January 16, 2019

Use and Impact of the 21-Gene Recurrence Score in Relation to the Clinical Risk of Developing Metastases in Early Breast Cancer Patients in the Netherlands

Kay Schreuder[a, b] Anne Kuijer[c] Sanne Bentum[b] Thijs van Dalen[c]
Sabine Siesling[a, b]

[a]Department of Research, Netherlands Comprehensive Cancer Organisation (IKNL), Utrecht, The Netherlands; [b]Department of Health Technology and Services Research, Technical Medical Centre, University of Twente, Enschede, The Netherlands; [c]Department of Surgery, Diakonessenhuis Utrecht, Utrecht, The Netherlands

Keywords
Breast cancer · Systemic therapy · Gene profiling · Guideline adherence · Gene expression profile · 21-Gene recurrence score · Chemotherapy

Abstract
Background: The nationwide use of the 21-gene recurrence score (21-RS) and implications regarding chemotherapy administration in relation to clinical risk in early breast cancer patients are investigated. ***Methods:*** Breast cancer patients surgically treated between 2014 and 2016 were selected from the Netherlands Cancer Registry and categorized as having a clinical low, intermediate, or high risk of developing metastases. Deployment of the 21-RS is advocated in patients with an intermediate risk of developing metastases. The use and impact of the 21-RS test result on chemotherapy administration were assessed in relation to the clinical risk as well as patient and tumor characteristics; χ^2 tests were used for analysis. ***Results:*** Of all patients, 20,488 were considered as clinical low-, 4,309 as intermediate-, and 15,266 as high-risk patients. The 21-RS was deployed in 0.1% (n = 23), 3.2% (n = 137), and 0.6% (n = 90) of these categories, respectively. In the clinical intermediate-risk group, the 21-RS assigned 73.7, 13.1, and 13.1% of patients to the genomic low-, intermediate-, and high-risk category, respectively. Adherence to the 21-RS was 95.6% in these patients. ***Conclusion:*** In the Netherlands, the 21-RS test is applied both inside and outside the guideline-directed area. In case of discordance between the genomic and clinical risk, patients were treated in line with the result of the 21-RS.

Introduction

The use of adjuvant systemic therapy has considerably improved outcomes of breast cancer patients over the last 2 decades [1]. There is growing awareness that the selection of patients in whom the benefit of adjuvant chemotherapy (CT) outweighs the side effects of adjuvant CT can be optimized [2]. In addition to prognostic clinical factors, gene expression profiles (GEPs) have found their way in recent years into clinical practice to more accu-

KARGER

E-Mail karger@karger.com
www.karger.com/phg

Kay Schreuder
Department of Health Technology and Services Research
University of Twente, Hoedemakerplein 2
NL–7511 JP Enschede (The Netherlands)
E-Mail k.schreuder@iknl.nl

Table 1. Study population: surgically treated patients between 2014 and 2016 divided by the guideline-described clinical risk profiles

Clinical high risk (chemotherapy indicated) (n = 20,488)	Clinical intermediate risk (doubtful indication for chemotherapy) (n = 4,309)	Clinical low risk (chemotherapy not indicated) (n = 15,266)
a All patients with lymph node metastases (≥N1a), <70 years of age b Patients <70 years of age, without lymph node metastases (N0 or N1mi) and adverse prognostic factors: i Grade II tumors >2 cm ii Grade III tumors >1 cm iii Her2+ tumors (>0.5 cm) iv <35 years of age, regardless of other tumor characteristics (except grade I tumor <1 cm)	a Patients <70 years of age, without lymph node metastases (N0), with grade I tumors, tumor size >2 cm b Patients <70 years of age, without lymph node metastases (N0), with grade II tumors, tumor size 1–2 cm c Patients <70 years of age, with lymph node metastases (N1mi), grade I or II, tumor size up to 2 cm	a All patients who do not meet the earlier mentioned criteria: i ≥35 years of age, N0, grade I, tumor size <2 cm ii ≥35 years of age, N0, grade II or III, tumor size <1 cm iii Her2+ tumor, tumor size <0.5 cm, without other unfavorable characteristics iv Patients ≥70 years of age

rately distinguish between patients at low or high risk of disease recurrence [3].

Since 2012, the Dutch national breast cancer guideline (NABON) advocates the use of a GEP in patients in whom controversy exists about the benefit of adjuvant CT [3]. The latter group consists of patients with estrogen receptor (ER)-positive (+)/HER2-Neu-negative (–) disease of limited size and of low or intermediate malignance grade without overt lymph node metastasis (pT1c-2N0–1mi) [4]. There are several GEPs commercially available, of which the 70-gene signature (70-GS) and the 21-gene recurrence score (21-RS) are available in the Netherlands. The 70-GS and the 21-RS were both validated in large prospective trials [5, 6], and their prognostic value has been confirmed in ER+ breast cancer patients in a number of studies [7–11].

In a previous population-based study, we observed an increase in 70-GS use in Dutch breast cancer patients within the aforementioned guideline-directed indicated area in recent years [12]. When the 70-GS was used in accordance with the Dutch guideline, high adherence rates to the 70-GS test result were observed [13]. Remarkably, the 70-GS was frequently used in patients in whom the guideline was clear about the recommendation to administer or withhold CT. Although lower adherence rates to the GEP result were observed in these patients, use of a GEP significantly influenced CT decision-making [14].

The aim of the current study is to evaluate the use and clinical implications of 21-RS use in Dutch early-stage breast cancer patients on a nationwide level.

Material and Methods

Data Collection

Data were derived from the Netherlands Cancer Registry (NCR). The NCR registers data on patient, tumor, diagnostic, and treatment characteristics of all Dutch cancer patients. The information is collected by trained data managers and obtained directly from the patient records. Data concerning GEP use has been available since 2011. The 21-RS became available for clinical use in the Netherlands in 2013.

Study Population

From the NCR, all patients surgically treated for primary non-metastatic breast cancer between January 1, 2014, and December 31, 2016, were identified. Patients who were treated with CT or endocrine therapy prior to surgical treatment were excluded from the analysis. Since 2012, the NABON suggests the selective use of a GEP in ER+ breast cancer patients in whom controversy exists about the indication for adjuvant CT, since they are considered to have an intermediate risk of developing distant metastases. Following these Dutch breast cancer guideline directives, patients were categorized into clinical low, intermediate, or high risk of recurrence or distant metastases, which corresponded with the recommendation to omit or administer CT, respectively [3] (Table 1). The 70-GS and the 21-RS became available in Dutch clinical practice in 2011 and 2013, respectively. Patients in whom the 70-GS was deployed were excluded from the study population.

The deployment of the 21-RS in relation to the clinical risk profile was assessed as well as adherence to the test result for the respective clinical risk categories. The low, intermediate, and high 21-RS test results were based on the original 21-RS cutoffs of <18, 18–30, or ≥31, respectively. Discordance was defined as a disagreement between clinical risk estimation and genomic test result (i.e., either high clinical risk and low genomic risk or low clinical risk and high genomic risk). Adherence to the test result was defined as treating the patient in line with the 21-RS test result (i.e., CT administration or omission in patients with a genomic high or a genomic low risk, respectively). For patients with a genomic intermediate risk and a clinical low or intermediate risk, the omission of CT was seen as treatment in line with the test result. Further-

more, the administration of CT is considered to be in line with the test result in patients with an intermediate 21-RS in clinical high-risk patients.

In addition, the clinical impact of the 21-RS was evaluated in the group of patients with an intermediate clinical risk of developing metastases in terms of the proportion of patients who received CT or not in relation with 21-RS deployment.

Statistical Analysis

A flowchart was created to visualize the implications of the use of the 21-RS in terms of discordance between clinical and genomic risk estimate and adherence to the test result reflected in adjuvant CT use. To analyze trends in 21-RS use over time, the percentage of eligible patients actually receiving the 21-RS was set out against year of breast cancer diagnosis. χ^2 tests were performed, and a p value of <0.05 was considered to be statistically significant. Results are presented as actual numbers and percentages. A Cohen's kappa coefficient (k) was calculated to determine the agreement between clinical risk determination and 21-RS test result. Adherence to the 21-RS score was calculated per clinical risk category by dividing the number of patients assigned to the low-risk 21-RS result who did not receive CT plus the number of patients assigned to the high-risk 21-RS result who did receive CT by the total number of patients assigned to a 21-RS low- or high-risk test result. All analyses were performed using STATA© version 14.1.

Results

A total of 40,887 patients surgically treated for primary nonmetastatic breast cancer were identified during the study period: 50.1% were categorized as having a high clinical risk profile and 37.3% as having a low clinical risk profile, and the remaining 4,309 patients had an intermediate risk of developing metastases. In 3,921 patients, a GEP was used: in the majority of patients, the 70-GS was used, and the 21-RS was deployed in 254 patients, i.e., 6.5% of the patients who received a GEP. The 21-RS was deployed in 0.58, 1.24, and 0.73% of the patients in the study population (n = 29,935) in 2014, 2015, and 2016, respectively. The patient and tumor characteristics in relation to the clinical risk profile and 21-RS deployment are demonstrated in Table 2 and Figure 1. Overall, the 21-RS test result was in line with the clinical risk determination in 21.2% (n = 53) of patients, which reflects a poor agreement (Cohen's kappa: –0.01, 95% CI –0.07 to 0.05) (Table 3).

Use of the 21-RS in Patients in the Clinical Intermediate-Risk Group

In the clinical intermediate-risk category, the guideline-delineated group of patients for whom a GEP is indicated, the 21-RS assigned 73.7, 13.1, and 13.1% of patients to the genomic low-, intermediate-, and high-risk category, respectively (Fig. 1). Considering the omission of CT in patients with a genomic intermediate risk to be in line with the test result, overall adherence to the test result of the 21-RS was 95.6% in this category of patients. Outside the guideline-directed area, adherence to the 21-RS was higher in patients assigned to the genomic low-risk profile (98.0% did not receive CT) as compared to patients assigned to the genomic high-risk profile (88.9% of patients received CT). Twenty patients (14.6%) of the clinical intermediate-risk category received CT when a GEP was used compared to 21.2% of all patients who received CT in the intermediate-risk category irrespective of GEP use. In patients assigned to the genomic intermediate-risk category, 11.1% (n = 2) received adjuvant CT (Fig. 1).

Use of the 21-RS in Clinical Low- and High-Risk Patients

In the 23 clinical low-risk patients who received a 21-RS, 17.4% of patients were assigned to the high 21-RS test result (Fig. 1). Overall adherence to the 21-RS was 91.3% in these patients, considering the 4 patients who were assigned to the genomic intermediate-risk category and who did not receive adjuvant CT as being treated in line with the rest result. Four of the 23 clinical low-risk patients in whom the 21-RS was used received CT (17.4%) compared to 3.7% of all patients in the clinical low-risk category, irrespective of GEP use.

In the 90 patients categorized as clinical high risk, the 21-RS assigned 51.1% of patients to the genomic low-risk category (Fig. 1). Overall, CT administration was in line with the genomic risk in 81.1% of the patients in the clinical high-risk category, considering the administration of CT in patients with a genomic intermediate risk to be in line with the test result. Twenty-nine of these patients received CT (32.2%) compared to 52.2% of all patients in the high-risk category who received CT irrespective of GEP use.

Discussion

In this study, we aimed to gain insight into the use and impact of the 21-RS test in Dutch early-stage breast cancer patients following its introduction in Dutch clinical practice in 2013. The test was deployed in a limited number of patients, comprising <10% of the GEPs that were used during the study period [12]. Approximately half of the tests were used outside the intended indication area. The 21-RS test was in line with the clinical risk determi-

Table 2. Patient and tumor characteristics in relation to the clinical risk profile and 21-RS deployment (n = 29,935)

	Clinical low risk					Clinical intermediate risk					Clinical high risk				
	21-RS use (n = 23)		No 21-RS use (n = 17,075)		p value	21-RS use (n = 137)		No 21-RS use (n = 2,369)		p value	21-RS use (n = 90)		No 21-RS use (n = 9,644)		p value
	n	%	n	%		n	%	n	%		n	%	n	%	
Incidence per year															
2014	6	26.1	5,709	33.4		34	24.8	762	32.2		19	21.1	3,831	39.7	
2015	10	43.5	5,700	33.4		75	54.7	784	33.1		38	42.2	3,208	33.3	
2016	7	30.4	5,666	33.2	0.57	28	20.4	823	34.7	<0.05	33	36.7	2,605	27.0	<0.05
Age															
<35 years	0	0.0	11	0.1		0	0.0	2	0.1		2	2.2	317	3.3	
035–50 years	2	8.7	1,000	5.9		27	19.7	353	14.9		23	25.6	2,328	24.1	
050–70 years	13	56.5	6,532	38.3		110	80.3	2,014	85.0		65	72.2	6,999	72.6	
>70 years	8	34.8	9,532	55.8	0.25	0	0.0	0	0.0	0.30	0	0.0	0	0.0	0.825
Size															
000–10 mm	5	21.7	7,238	42.4		0	0.0	0	0.0		6	6.7	726	7.5	
011–20 mm	14	60.9	6,011	35.2		125	91.2	2,110	89.1		32	35.6	3,899	40.4	
021–30 mm	3	13.0	2,157	12.6		10	7.3	172	7.3		42	46.7	3,101	32.2	
>30 mm	1	4.3	1,567	9.2		2	1.5	61	2.6		10	11.1	1,743	18.1	
Unknown	0	0.0	102	0.6	0.12	0	0.0	26	1.1	0.53	0	0.0	175	1.8	<0.05
Estrogen receptor															
Negative	1	4.3	1,729	10.1		0	0.0	0	0.0		2	2.2	2,304	23.9	
Positive	22	95.7	15,255	89.3		137	100.0	2,369	100.0		88	97.8	7,292	75.6	
Unknown	0	0.0	91	0.5	0.61	0	0.0	0	0.0	na	0	0.0	48	0.5	<0.05
Progesterone receptor															
Negative	6	26.1	4,350	25.5		20	14.6	368	15.5		18	20.0	3,697	38.3	
Positive	17	73.9	12,631	74.0		117	85.4	2,001	84.5		72	80.0	5,892	61.1	
Unknown	0	0.0	94	0.6	0.94	0	0.0	0	0.0	0.77	0	0.0	55	0.6	<0.05
Her2 Neu															
Negative	20	87.0	15,352	89.9		137	100.0	2,369	100.0		88	97.8	7,262	75.3	
Positive	2	8.7	967	5.7		0	0.0	0	0.0		2	2.2	2,293	23.8	
Unknown	1	4.3	756	4.4	0.82	0	0.0	0	0.0	na	0	0.0	89	0.9	<0.05
Grade															
1	11	47.8	7,122	41.7		12	8.8	260	11.0		11	12.2	829	8.6	
2	8	34.8	6,894	40.4		125	91.2	2,109	89.0		56	62.2	4,158	43.1	
3	4	17.4	2,763	16.2		0	0.0	0	0.0		23	25.6	4,524	46.9	
Unknown	0	0.0	296	1.7	0.85	0	0.0	0	0.0	0.42	0	0.0	133	1.4	<0.05
Multifocality															
No	20	87.0	15,170	88.8		115	83.9	1,988	83.9		77	85.6	7,792	80.8	
Yes	3	13.0	1,875	11.0		22	16.1	378	16.0		13	14.4	1,807	18.7	
Unknown	0	0.0	30	0.2	0.93	0	0.0	3	0.1	0.92	0	0.0	45	0.5	<0.05

21-RS, 21-gene recurrence score; na, not applicable.

nation in 21.2% of all patients, and the test result was adhered to in over 90% of the patients irrespective of the deployment in relation to the indication area and a high or low clinical risk. Within the intended indication area, 15% received CT when the 21-RS was deployed.

While Dutch guidelines suggest the selective use of a GEP in ER+ breast cancer patients in whom controversy exists about the indication for adjuvant CT, we observed the use of the 21-RS test both inside and outside the guideline-directed area: half of the 21-RS tests (53.9%)

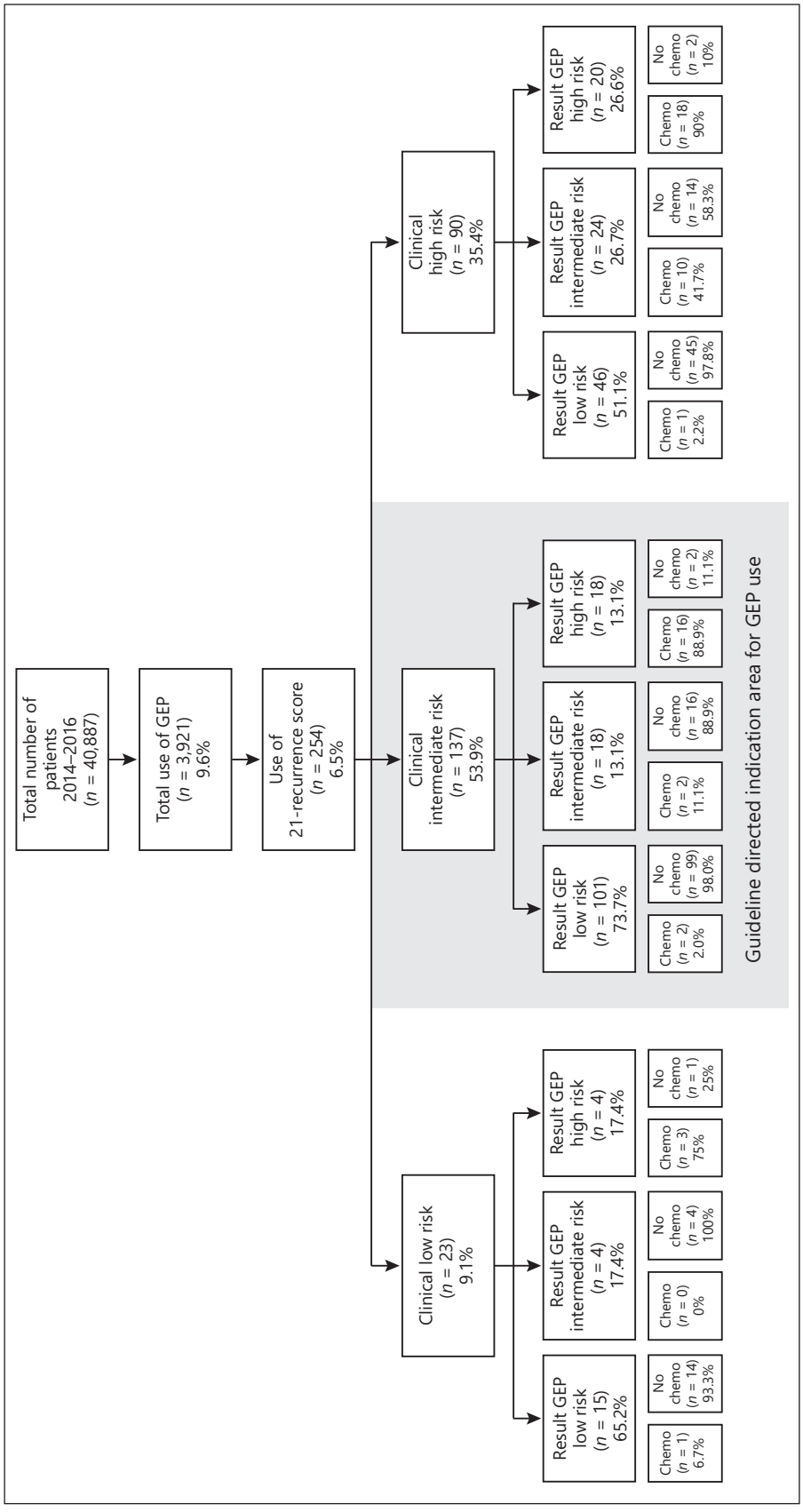

Fig. 1. Number of included patients grouped according to the clinical risk, GEP (21-gene recurrence score) result, and admittance to chemotherapy. GEP, gene expression profile.

Table 3. Clinical risk profile by result of the 21-RS

	Clinical risk profile				
	low	intermediate	high	unknown	total
21-RS low risk	15 (9.2)	101 (62.0)	46 (28.2)	1 (0.6)	163 (100.0)
21-RS intermediate risk	4 (8.2)	18 (36.7)	24 (49.0)	3 (6.1)	49 (100.0)
21-RS high risk	4 (9.5)	18 (42.9)	20 (47.6)	0 (0.0)	42 (100.0)

Values are *n* (%). Pearson $\chi^2(6) = 20.3918$, Pr = 0.002, k < 0 (clinical unknown risk category was excluded from kappa coefficient determination). 21-RS, 21-gene recurrence score.

were applied in patients who were considered candidates for gene expression profiling according to the current Dutch guideline based on doubt regarding CT benefit. This observation is in line with previous studies on the 70-GS where a similar frequent use of the 70-GS outside the guideline-directed area was observed [4, 14].

In the clinical intermediate-risk group of patients, adherence to the 21-RS was high (95%). In a previous study, focusing on the 70-GS, lower adherence rates to the genomic test result, varying between 83 and 89%, were observed [4]. We observed that in case of an intermediate genomic risk, patients were treated as having a clinical low risk, resulting in the omission of CT. A low and intermediate risk resulted in omission of CT in 85% of these clinical intermediate-risk patients. This compares to a proportion of 66% who did not receive CT following 70-GS use in the same proportion of patients [4]. Then again, an independent trend towards a more restrictive use of CT was observed over time, since in the latter study, conducted between 2011 and 2013, 45% of the clinical intermediate-risk patients received CT without the use of a GEP compared to 21% in the present study. The present study confirms that the genomic test result leads to lower implementation of CT, a finding that was also supported by a study where patients reported to be more reluctant to undergo CT when a genomic test indicated low recurrence risk [15].

When the 21-RS was deployed outside the indication area, the majority of patients were treated in line with the genomic risk, in both the clinical low- and the clinical high-risk group of patients. The adherence to the 21-RS test result was higher in the clinical high-risk group with a discordant GEP result than in the clinical low-risk patients, and this was in line with previous population-based studies of 70-GS use [14]. In clinical high-risk patients, this led to a 20% absolute reduction of administered CT when the 21-RS was applied, and this observation supports the observation by other studies that GEPs are mainly used for a substantiated decision to withhold CT in clinical high-risk patients [4, 14]. This partly explains why a high genomic risk in clinical low-risk patients is frequently disregarded, and in doing so, clinicians and patients may feel supported by the recent outcome results from the EORTC 10041/BIG 3-04 MINDACT trial [16]. Clinical low-risk patients had excellent outcomes irrespective of their genomic risk and the administration of CT. In the recently performed TAILORx trial, noninferiority of endocrine therapy alone compared to chemo-endocrine therapy for invasive disease-free survival was observed for patients with HR+, HER2–, axillary node-negative breast cancer with an intermediate 21-RS test result [17]. As these patients were mostly (approximately 75%) considered to be clinical low-risk patients, the omission of CT in patients with a genomic intermediate risk and a clinical low risk is in line with the findings in the current study.

In the current study, we considered the omission of CT to be in line with the test result in patients with an intermediate 21-RS test result and a clinical low- or intermediate-risk profile. This is assumed because both the clinical risk estimation and the 21-RS test result were not able to estimate a potential benefit of CT in these patients. Therefore, the omission of CT in these patients seems to be appropriate and is considered as in line with the test result. On the other hand, the administration of CT is considered to be in line with the test result in patients with an intermediate 21-RS in clinical high-risk patients. This is assumed because despite an intermediate 21-RS test result (and 21-RS use is disputed), the clinical risk estimation already appoints these patients as having a high risk of metastasis, and the administration of CT after an intermediate 21-RS result seems to be appropriate [3].

Although this study provides valuable insights into the use and the clinical implications of the 21-RS in Dutch clinical practice, it is important to keep in mind that, due to the retrospective observational nature of this study, a selection bias in this low number of patients could have introduced confounding by indication. Possibly, excluding patients that received a 70-GS has induced a selection bias, as this may have resulted in the exclusion of a specific patient group and has prevented these patients from receiving the 21-RS score.

It should be noted that the revised Dutch Guideline (2018) recommends different classification models to assess the likelihood of metastasis in individual patients with breast cancer [18]. Use of the risk calculation based on the updated and newly introduced clinical risk calculators would probably change the classification into the 3 clinical risk groups and, subsequently, the recommendations for GEP use.

The population-based character of this study enables us to provide an overview of the 21-RS use in all Dutch hospitals. The 21-RS is, in contrast to the 70-GS, not so much applied in the Dutch health-care setting, which resulted in a small study population. However, this study design gives a detailed analysis of 21-RS use and administration of CT in relation to the clinical risk of developing metastases in early breast cancer patients in the Netherlands. Despite the small patient number, this study can support further implementation of the 21-RS and implementation of innovations developed in the future.

Conclusion

In the Netherlands, the 21-RS test is applied both inside and outside the guideline-directed area. In all clinical risk categories, the majority of patients were assigned to the genomic low- and intermediate-risk categories, and adherence to the 21-RS was high. In case of discordance between the genomic and clinical risk, patients were treated in line with the result of the 21-RS, and a clinically relevant decrease in CT administration was observed after 21-RS use in clinical intermediate- and high-risk patients.

Acknowledgements

The authors would like to thank the data managers of the Netherlands Cancer Registry for collecting the data used in this study.

Statement of Ethics

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

Disclosure Statement

The authors do not declare any conflicts of interest.

References

1 Collaborative EB; Early Breast Cancer Trialists' Collaborative Group (EBCTCG). Effects of chemotherapy and hormonal therapy for early breast cancer on recurrence and 15-year survival: an overview of the randomised trials. Lancet. 2005 May;365(9472):1687–717.

2 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 Jun;6(2):85–93.

3 Landelijke Richtlijn Oncoline [Internet]. 2012 (revised in 2018). Available from: https://www.oncoline.nl/index.php?pagina=/richtlijn/pagina.php&fSelectNTG_181=182&fSelectedSub=181

4 Kuijer A, van Bommel AC, 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 Jul;18(7):720–6.

5 Sparano JA, Gray RJ, Makower DF, Pritchard KI, Albain KS, Hayes DF, et al. Prospective Validation of a 21-Gene Expression Assay in Breast Cancer. N Engl J Med. 2015 Nov;373(21):2005–14.

6 Sánchez-Forgach ER, Carpinteyro-Espín U, Alemán-Áviles JA, Sánchez-Basurto C. Validation and clinical application of MammaPrint® in patients with breast cancer. Cir Cir. 2017 Jul–Aug;85(4):320–4. Spanish.

7 Győrffy B, Hatzis C, Sanft T, Hofstatter E, Aktas B, Pusztai L. Multigene prognostic tests in breast cancer: past, present, future. Breast Cancer Res. 2015 Jan;17(1):11.

8 Saghatchian M, Mook S, Pruneri G, Viale G, Glas AM, Guerin S, et al. Additional prognostic value of the 70-gene signature (MammaPrint(®)) among breast cancer patients with 4-9 positive lymph nodes. Breast. 2013 Oct;22(5):682–90.

9 Mook S, Schmidt MK, Weigelt B, Kreike B, Eekhout I, van de Vijver MJ, et al. The 70-gene prognosis signature predicts early metastasis in breast cancer patients between 55 and 70 years of age. Ann Oncol. 2010 Apr;21(4):717–22.

10 Brufsky AM. Predictive and prognostic value of the 21-gene recurrence score in hormone receptor-positive, node-positive breast cancer. Am J Clin Oncol. 2014 Aug;37(4):404–10.

11 Albain KS, Barlow WE, Shak S, Hortobagyi GN, Livingston RB, Yeh IT, et al.; Breast Cancer Intergroup of North America. Prognostic and predictive value of the 21-gene recurrence score assay in postmenopausal women with node-positive, oestrogen-receptor-positive breast cancer on chemotherapy: a retrospective analysis of a randomised trial. Lancet Oncol. 2010 Jan;11(1):55–65.

12 Kuijer A, Schreuder K, Elias SG, Smorenburg CH, Rutgers EJ, 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 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 Aug;139(4):769–75.
14 Schreuder K, Kuijer A, Rutgers EJ, Smorenburg CH, van Dalen T, Siesling S. Impact of gene-expression profiling in patients with early breast cancer when applied outside the guideline directed indication area. Eur J Cancer. 2017 Oct;84:270–7.
15 Brewer NT, Edwards AS, O'Neill SC, Tzeng JP, Carey LA, Rimer BK. When genomic and standard test results diverge: implications for breast cancer patients' preference for chemotherapy. Breast Cancer Res Treat. 2009 Sep;117(1):25–9.
16 Cardoso F, van't Veer LJ, Bogaerts J, Slaets L, Viale G, Delaloge S, et al.; MINDACT Investigators. 70-Gene Signature as an Aid to Treatment Decisions in Early-Stage Breast Cancer. N Engl J Med. 2016 Aug;375(8):717–29.
17 Sparano JA, Gray RJ, Makower DF, Pritchard KI, Albain KS, Hayes DF, et al. Adjuvant Chemotherapy Guided by a 21-Gene Expression Assay in Breast Cancer. N Engl J Med. 2018 Jul;379(2):111–21.
18 Landelijke Richtlijn Oncoline [Internet]. 2018. Available from: https://www.oncoline.nl/richtlijn/item/pagina.php?id=41220&richtlijn_id=1069