JBUON 2017; 22(5): 1199-1208
ISSN: 1107-0625, online ISSN: 2241-6293 • www.jbuon.com
E-mail: editorial_office@jbuon.com

ORIGINAL ARTICLE

Impact of Oncotype DX on chemotherapy assignment: a retrospective single-center study on female breast cancer patients

Dimitris Panousis[1], Panagiota Ntasiou[1], Dimitris Grosomanidis[1], Konstantinos Chatzopoulos[1], Georgia Paraskevakou[1], Panagiota Kontogianni[1], Efstratia Charitidou[1,2], Grigoris Xepapadakis[1]

[1]Breast Clinic, "Rea" Maternity Hospital, Athens; [2]Department of Mathematics, National Technical University of Athens, Athens, Greece

Summary

Purpose: *This study was designed to determine the Recurrence Score (RS) distribution and its associated risk assessments based on traditional clinicopathologic characteristics in a single-center breast cancer (BC) deriving cohort in Greece, and to evaluate the impact of the RS results on adjuvant treatment decisions applied in this cohort.*

Methods: *This was a retrospective, single-center study regarding Greek female patients with early-stage breast cancer (ESBC). From 2009 to 2015, 114 cases lacking unanimity in the multidisciplinary breast meeting (MDM) fulfilled the inclusion criteria. The RS of the Oncotype DX (ODX) assay was the main outcome.*

Results: *The mean RS in the sample was 16.38 (SD=6.87). RS was positively correlated with Ki-67 (p=0.008). A negative progesterone receptor (PR) was associated with a higher RS (p<0.05). RS was higher for cases of chemotherapy assignment (p<0.001). According to the oncologists' pre-DX assay recommendations, 62.8% of the patients would have been 'wrongly' assigned to chemotherapy, while 14.3% of patients would have not been recommended this treatment even though they should have. The overall chemotherapy recommendation was significantly altered after the ODX RS assay was carried out (p=0.008) and, in the sample, it diminished by 39.5%.*

Conclusions: *The distribution of the ODX RS in the specific cohort of Greek women is similar to that reported in other geographic regions of the world. Knowledge of the RS resulted in a shift in treatment recommendations towards lower-intensity regimens and in a greatly reduced proportion of chemotherapy recommendations.*

Key words: *breast cancer, chemotherapy, oncotype assay, recurrence score*

Introduction

BC is the second most common cancer worldwide and, by far, the most frequent cancer among women [1]. In patients diagnosed with ESBC, treatment modalities include lumpectomy/mastectomy with the potential addition of radiotherapy and systemic therapy (e.g. endocrine, chemoendocrine, biologic therapy) for certain patients based on the patient/tumor characteristics [2-5]. BC is a heterogeneous disease considering that prognosis, survival and recurrence rates can vary widely [6-8]. They are influenced by a number of factors including TNM disease stage at diagnosis, presence of particular molecular markers embracing, specifically, the estrogen receptor (ER) and PR, respectively and the human epidermal growth factor receptor 2 (HER2) [9-12]. Decisions on whether to use adjuvant chemotherapy in patients with early, invasive, operable breast cancer have traditionally

Correspondence to: Dimitris Panousis, MD, PhD, FEBS. 383 Siggrou Ave. & 17 Pentelis, 17564 Palaio Faliro, Athens, Greece.
Tel: +30 210 9495922, Fax: +30 210 9495930, E-mail: d.panoussis@gmail.com
Received: 13/06/2016; Accepted: 08/07/2016

relied on such clinical, pathological and biological markers [13-15]. However, these indicators are imperfect in terms of reproducibility and often lack standardization (mentioning for example the Ki-67 marker), allowing room for misinterpretations [16]. Historically, the decision to treat ER-positive, lymph node (LN)-negative, BC patients with adjuvant chemotherapy (ACT) has been guided by clinical and pathological factors, in conjunction with the clinician and patient preferences [17,18]. In the absence of ACT, 15 % of patients relapse within 5 years [19]. However, under the traditional clinicopathological decision-making 75-92% of women receive ACT (current estimates indicate that more than 60% of patients with hormone receptor positive BC receive adjuvant chemotherapy) [17]. However, several studies have demonstrated that only 4–5% of patients are likely to benefit from chemotherapy [15,20].

The 21-gene ODX RS (Genomic Health, Redwood City, CA, USA) is a 21-gene reverse transcriptase-polymerase chain reaction assay first introduced in 2004 to provide additional clinical information regarding the risk of recurrence of ER-positive BCs. Tumor expression of these genes regulates basic functions of the malignant cell, such as proliferation and anti-apoptosis (Ki-67, serine/threonine kinase 15, survivin, cyclin-B1, MYB-2), HER2 (HER2, GRB-7), invasion (stromelysin-3, cathepsin-L2) and ER/PR status (ER/PR, SCUBE2, BCL2). The gene expression results from the assay are analyzed and converted, using a weighted formula, into a single RS, which is classified into one of 3 risk categories: low, RS ≤ 17; intermediate, RS 18-30; or high, RS ≥ 31 [21]. In 2006, an assay, aiming at suggesting a model to predict the 10-year survival benefit of chemotherapy based on the ODX RS, was published [22]. The standard pattern of adjuvant treatment consists of radiotherapy, chemotherapy and endocrine therapy for selected patients. There are several risk assessment tools such as the St Gallen consensus or Adjuvant Online and various guidelines issued by the European Society for Medical Oncology, the American Society of Clinical Oncology and the National Comprehensive Cancer Network, aimed at facilitating the treatment decision [23-25]. The most commonly used risk assessment tools are the St Gallen criteria and the adjuvant Online which take into account clinicopathologic parameters such as age, pathologic stage of primary tumor (Pt) grade, LN status, peritumoral vascular invasion (PVI), ER/PR status and HER2 expression. The former estimates the risk of recurrence, while the latter calculates the risk of BC-related death at 10 years. Both models are prognostic but not predictive in terms of the ACT benefit.

In particular, it is worth mentioning the numerous interpretations that can be given in the "intermediate categories", i.e. patients with intermediate clinicopathologic features, where there exists considerable uncertainty in discriminating which group of patients would benefit from adjuvant hormonotherapy treatment alone or chemotherapy plus hormonotherapy. Remarkable is the fact that while the absolute clinical benefit of ACT in the LN(-) breast cancer group is estimated at the level of 4% in terms of 10-year distant recurrence, more than 50% of these patients receive ACT.

Consequently, there is a clear need for updated prognostic-predictive models capable of providing useful information to support treatment decision-making for this particular group of patients. Concerning our institution, it is common practice since 2003 to discuss over BC cases at the MDM prior to making adjuvant treatment recommendations. In this context, cases are submitted for weekly review by a group of health care professionals including surgeons, oncologists, pathologists and experts from other specialties (plastic surgeons, gynecologists) who can contribute to optimizing the suggested treatment plan for each patient.

The current study was designed to determine the ODX RS distribution and its correlation with traditional clinicopathologic characteristics in a single-center cohort in Greece, as well as to evaluate the impact of the RS results on adjuvant treatment decisions in a specific group of BC patients where a unanimous decision of the MDM was not feasible. This was achieved by inspecting the characteristics of BC patients with regard to histopathological features. Focus was spotted on the comparison between the number of patients who would have been assigned to chemotherapy using traditional parameters of patient risk categorization and the number of patients that in practice were suggested to receive chemotherapy based on the RS.

Methods

This retrospective, single-center study included a total of 1935 operated breast cancer patients from 01/01/2009 to 30/12/2015. A set of 250 cases for which there was no unanimity in the MDM were reviewed, out of which 120 fulfilled the inclusion criteria for this study as described below. Subsequently, the names in our list and the respective assay results were cross-checked with the archives of the private molecular diagnostics laboratory that conducted the ODX assay. Given the initial set of 120 patient names, one patient

with non-valid ODX results was excluded from the study, and so there were 5 HER2-positive patients (after appropriately performing immunohistochemical tests for CerbB-2 and/or CISH-FISH tests). The final dataset designated for statistical analysis consisted of 114 patients, all of whom had positive ER status and 5 (4.4%) had one positive LN excised. The respective assays of ODX were conducted between February 2009 and May 2015. The study protocol and the database received approval from the ethics committee of the participating institution.

The initial database parameters were restricted to a shorter set including the following parameters of interest for this study: age at surgery, menopausal status, histological type, tumor grade, tumour size, p-53, Ki-67, number of positive LNs excised, as well as ER and PR status. The latter pair of parameters was measured in a scale of 0 up to 3+, as frequently met in the literature [26]. Information on the form of the assigned treatment (mastectomy, radiotherapy, hormonal therapy with tamoxifen) was also available.

The RS, i.e., the ODX main outcome, was the main parameter of interest. RS was presented in both quantitative and qualitative forms. A far as the latter form is concerned, scores were categorized as follows: low RS: 0 and 17 units; intermediate RS: 18 and 30 units; and high RS ≥31 units [27]. Due to the extremely small number of high RS patients in the sample, the quantitative rather than the qualitative form of RS was more reliable for the statistical analysis of the entire cohort. Nevertheless, the qualitative RS was also analyzed in appropriate subsamples of patients.

Statistics

Statistical analysis was performed using the R Statistical Software, version 3.1.2 (The R Foundation for Statistical Computing, Vienna, Austria). In particular, the figures were built using the *ggplot2* package of R. Since all quantitative parameters were skewed, apart from age at surgery, median (MED) and interquartile range (IQR) were mainly reported as descriptive statistics, though mean (M) and standard deviation (SD) values have been added in certain cases as well. Qualitative parameters were summarized by their absolute (n) and relative (%) frequencies. In case of missing values, these were explicitly mentioned for every parameter under investigation; no imputation technique was carried out.

The differentiation of quantitative parameters according to binary variables, such as dichotomized menopausal status or chemotherapy assignment, was tested using the two-samples t-test or Wilcoxon test as appropriate. The x^2 test or the Fisher's exact test were used to check the potential relationship between two independent qualitative parameters of interest, while the McNemar's test was employed to test for symmetry of rows and columns in a contingency table of two dependent qualitative variables. Moreover, the Pearson (r) or the Spearman (ρ) correlation test were used to measure the correlation between quantitative parameters and its statistical significance. The correlation coefficients were accompanied by 95% confidence intervals (95% CI) in the case of Pearson r and by bootstrapped 95% CI in the case of Spearman ρ. The results of ANOVA models were reported for the association of the RS with the quantitative parameters recorded. A significance level of 5% was used throughout the analysis.

Results

According to the medical records of the aforementioned referral breast clinic, 114 patients met the inclusion criteria, as described previously, to enter the current study. Figure 1 depicts the annual number of Oncotype DX assays conducted; note that 11 assays conducted in 2015 are omitted from the plot due to 2015 being a non-completed year. There is a clear pattern of this number rising over the years since Oncotype DX is regarded as of increasing significance in clinical decision-making. Specifically, the mean annual percent rise of the Oncotype DX assays conducted was 49.8% (min= -13.3%, max= 125.0%). Age at surgery in the sample ranged from 33 to 74 years with mean age equal to M= 51.1 years (SD= 9.0 years). Moreover, 63 women (55.3%) were pre-menopausal and 51 (47.7%) post-menopausal with 6 of them being peri-menopausal.

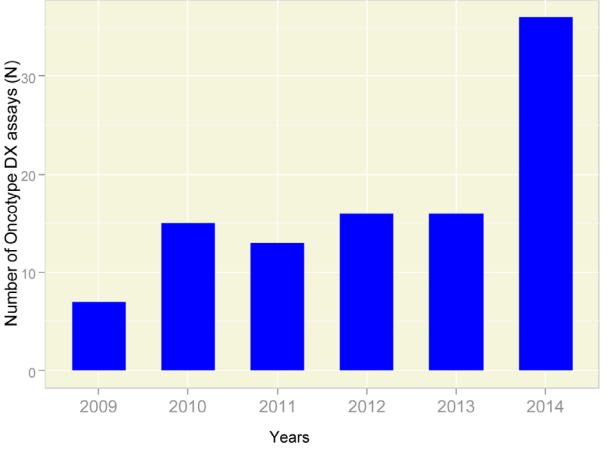

Figure 1. Distribution of the number of Oncotype DX assays conducted annually (11 cases of 2015 excluded since 2015 is a non-completed year).

Concerning the histological tumor grade, there were 9 cases (8.1%) of grade I, 80 cases (72.1%) of grade II and 22 (19.8%) of grade III. Three cases lacked grade information. The tumor diameter ranged from 3 to 60mm with a right skewed sample distribution as expected (MED=13.0mm; IQR=8.0mm) and there was 1 missing value. Moreover, Ki-67 was recorded in 112 cases with MED=15% and IQR=12%, indicating somewhat high levels of overexpression among the patients of this subsample; 82 patients (73.2%) had Ki-67

values ≥ the usual threshold of 10%. The expression of p-53 covered all the spectrum from 0 to 100% with MED=10.0% (IQR=35.0%, 9 missing values), indicating that half of the patients had p-53 overexpression considering a 10% threshold.

ER was strongly positive in 111 cases (97.4%) and weakly positive (ER=1) in 3 cases (2.6%). PR was strongly expressed in 75 cases (65.8%) and weakly or not at all expressed in 39 cases (34.2%). Multifocality, comedo necrosis and microcalcifications were noticed in 8 (7.0%), 2 (1.8%) and 10 patients (8.8%), respectively.

Regarding the kind of operations that were performed, 22 women (19.3%) underwent MRM, 83 (72.8%) underwent conservative surgery, while sentinel lymph node biopsy (SLNB) was carried out in all cases. The corresponding histological results revealed 25 women (21.9%) with lobular invasive cancer, 88 (77.2) with ductal invasive cancer, and one woman (0.9%) with tubular cancer.

Regarding the therapies assigned to the patients, 87 women (77.0%) were assigned to radiotherapy, 26 (23.0%) received chemotherapy and all of the 114 women of the study were recommended to receive hormone therapy. In particular, 22 patients (19.5%) followed a combination of radiotherapy and chemotherapy apart from the hormone therapy.

Summarizing the ODX outcome, the minimum and maximum RS were 0 and 44 respectively and the mean RS was M=16.38 (SD=6.87). Clarifying the RSs distribution, 68 women (59.6%) had low RS, 43 (37.7%) had intermediate RS and only 3 (2.6%) had high RS. As mentioned earlier, the very restricted number of high RS cases did not allow the extended use of the categorical RS form for the entire sample.

Table 1. Correlation between RS and the quantitative parameters of the sample

Parameters	*Sample correlation coefficient*	*95% CI*	*p value*
Age	0.14	-0.05, 0.31	0.14
Tumor size	0.13	-0.06, 0.30	0.18
p-53 ‡	0.02	-0.17, 0.19	0.84
Ki-67 ‡	0.25	0.07, 0.41	0.008 **

‡ the Spearman rather than the Pearson coefficient is reported along with the appropriate 95% CI

** significance at the 1% level

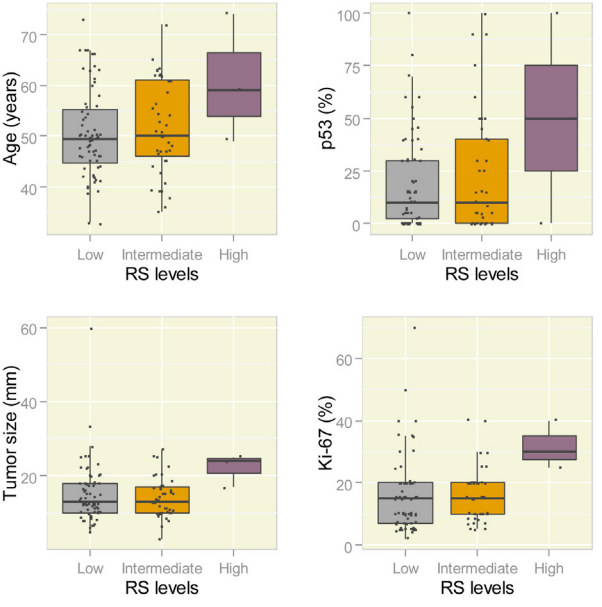

Figure 2. Boxplots showing the distribution of each quantitative parameter with each recurrence score (RS) level, also depicting the actual sample observations as single black points. For RS levels with age, tumor size and p53 values, p was 0.03, while p value for RS with Ki-67 was 0.008.

Exploration of RS-related associations

Regarding the quantitative parameters recorded, RS was significantly and positively correlated only with Ki-67 (p=0.008). The correlation coefficients of age, tumor size and p-53 with RS were not statistically significant (Table 1). Although there was no statistical significance with those parameters, this could be due to the very small proportion of high RS patients in the sample. In particular, the boxplots of Figure 2 show a hint that the high RS levels might be associated with older age, larger tumor diameter, higher p-53 and Ki-67 values, whereas patients of low and intermediate RS levels do not seem to be considerably differentiated in our sample.

It is of primary interest to explore the number of chemotherapies assigned to the sample patients relative to the respective RS levels. Only 4 out of 68 patients with low RS (5.9% of this subgroup) were assigned to chemotherapy. Moreover, 19 out of 42 patients with intermediate RS (45.2%) and all 3 patients of high RS (100%) received chemotherapy. The association between the RS level and the chemotherapy assignment was statistically significant (p<0.001).

Table 2 presents the sample distribution of RS (M±SD) over the categories of the qualitative parameters recorded. A negative PR expression seemed to be associated with a higher RS (all respective p values <5%). RS was statistically higher for cases of chemotherapy assignment (p<0.001). Grade III was barely not associated with a higher RS compared to highly differentiated tumors (p=0.08).

Due to the different prognostic value that the

qualitative RS represents in practice, we further explored the characteristics of low and intermediate RS patients in the sample (Table 3). PR and chemotherapy were statistically differentiated between low and intermediate RS patients (p<0.01), while the respective association with radiotherapy was barely non-significant (p=0.058). It was clear that low RS patients were more likely to show weaker expression of PR compared to the intermediate RS patients. The proportion of chemotherapy assignment in low RS patients in the sample was 5.9% vs 45.2% in intermediate RS patients. Finally, the proportion of radiotherapy assignment among low RS patients was 71% vs 88% for the intermediate RS patients.

Comparison with St. Gallen criteria

The following are regarded as unfavorable characteristics: tumor size >20mm, grade II or III, Ki-67≥10% and at least one positive lymph node. Seven patients (6.1%) had no unfavorable characteristics, 22 (19.3%) had one unfavorable characteristic, 72 (63.2%) had 2 unfavorable characteristics and 13 (11.4%) had 3 unfavorable characteristics. There was no patient bearing all 4 unfavorable characteristics simultaneously.

The number of unfavorable characteristics (#0 - #3 in our sample) did not seem to be statistically associated with RS in its dichotomous form, i.e., low vs intermediate RS (p=0.46). However, there was statistical association between the number of unfavorable characteristics and the continuous form of RS (p=0.03). In particular, the median RS slightly fell from MED=15 (range 9-27) for zero unfavorable characteristics to MED=14 (range 0-23) for one unfavorable characteristic, whereas for both two and three unfavorable characteristics it rose to MED=17 (range 0-44 and 13-43 respec-

Table 2. Mean and standard deviation of RS in each subgroup of patients, indicated by the qualitative characteristics, and one-way ANOVA results for the impact of the respective factors on RS

Factors	*RS (M ± SD)*	*Estimate*	*SE*	*p value*
Menopausal status				
Pre-menopause	15.8 ± 6.0	-	-	
Post/Peri-menopause	17.1 ± 7.8	1.30	1.29	0.32
Grade				
I	14.7 ± 6.1	-	-	
II	15.8 ± 6.3	1.11	2.40	0.64
III	19.4 ± 8.7	4.74	2.70	0.08
ER				
+1	16.7 ± 5.9	-	-	
+2	16.7 ± 4.6	0.03	4.25	0.99
+3	16.3 ± 7.4	-0.38	4.06	0.92
PR				
(-)	24.8 ± 11.8	-	-	
+1	18.3 ± 7.4	-6.53	3.10	0.03
+2	16.0 ± 4.1	-8.77	3.07	0.005
+3	13.7 ± 6.8	-11.06	3.09	<0.001
Histological type				
Ductal invasive	16.3 ± 7.2	-	-	
Lobular invasive	16.8 ± 5.5	0.59	1.56	0.71
MRM				
No	16.4 ± 6.7	-	-	
Yes	16.2 ± 7.6	-0.19	1.63	0.91
Radiotherapy				
No	15.7 ± 8.1	-	-	
Yes	16.5 ± 6.5	0.82	1.52	0.59
Chemotherapy				
No	14.2 ± 5.1	-	-	
Yes	23.4 ± 7.4	9.22	1.27	<0.001

ER: estrogen receptor, PR: progesterone receptor, MRM: modified radical mastectomy

tively). See also Figure 3 where the difference in the RS distribution across categories is illustrated.

Moreover, the association of the number of unfavorable characteristics with the assignment of chemotherapy showed a trend toward significance (p=0.053); therefore, it was of interest to explore the respective sample figures. Among the patients who did not receive chemotherapy, 5.7% had no unfavorable characteristics, 24.1% had one unfavorable characteristic, 60.9% had two unfavorable characteristics and 9.2% had three unfavorable characteristics. On the other hand, among the patients who were indeed assigned chemotherapy, 7.7% had no unfavorable characteristics, 3.8% had one unfavorable characteristic, 69.2% had two unfavorable characteristics and 19.2% had three unfavorable characteristics.

Recurrence score and decision making

Data from the corresponding medical decisions before carrying out the ODX test were available. Prior to performing the ODX assay, oncologists of our clinic provided their medical view on who certain patients should be eligible for receiving chemotherapy and who should be not. It was of great interest to explore how the ODX result had

Table 3. Characteristics of the sub-sample containing only low and intermediate RS patients

Characteristics	*RS*		*p value*
	Low (RS < 18)	Intermediate (RS 18 - 30)	
Mean age (SD), years	50.4 (8.7)	51.5 (9.1)	0.51
Median RS (IQR)	13.0 (5.0)	20.0 (3.5)	<0.001
Median tumor size (IQR), mm	13.0 (8.0)	13.0 (7.0)	0.72
Median p-53 (IQR), %	10 (27.5)	10 (40.0)	0.85
Median Ki-67 (IQR), %	15.0 (13.0)	15.0 (10.0)	0.20
Menopausal status, n (%)			1.00
Pre-menopause	38 (55.9)	24 (55.8)	
Post/Peri-menopause	30 (44.1)	19 (44.2)	
Grade, n (%)			0.37
I	7 (10.6)	2 (4.8)	
II	49 (74.2)	30 (71.4)	
III	10 (15.2)	10 (23.8)	
ER, n (%)			0.55
+1	1 (1.5)	2 (4.7)	
+2	13 (19.1)	10 (23.3)	
+3	54 (79.4)	31 (72.1)	
PR, n (%)			0.005
(-)	1 (1.5)	3 (7.0)	
+1	14 (20.6)	19 (44.2)	
+2	26 (38.2)	14 (32.6)	
+3	27 (39.7)	7 (16.3)	
Histological type, n (%)			1.00
Ductal invasive	53 (77.9)	34 (79.1)	
Lobular invasive	15 (22.1)	9 (20.9)	
MRM, n (%)			0.18
No	52 (76.5)	38 (88.4)	
Yes	16 (23.5)	5 (11.6)	
Radiotherapy, n (%)			0.058
No	20 (29.4)	5 (11.9)	
Yes	48 (70.6)	37 (88.1)	
Chemotherapy, n (%)			<0.001
No	57 (83.8)	23 (54.8)	
Yes	11 (16.2)	19 (45.2)	

MRM: modified radical mastectomy. For other abbreviations see text

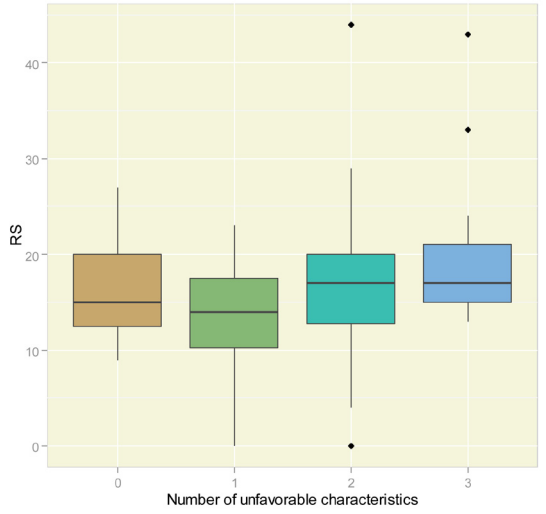

Figure 3. Distribution of recurrence score according to the number of patient unfavorable characteristics (p=0.03).

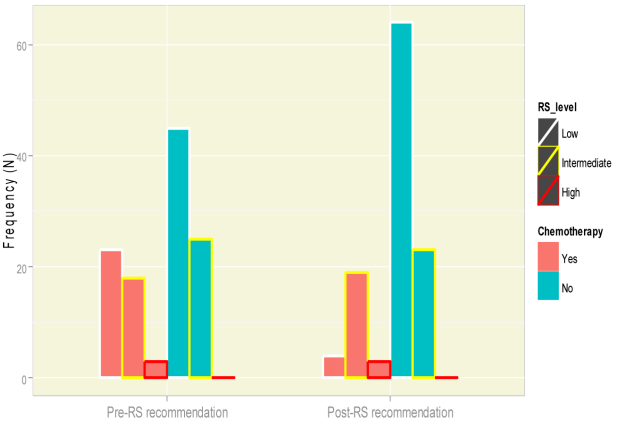

Figure 4. Distribution of the chemotherapy recommendation pre- and post-Oncotype DX assay, split by recurrence score (RS) level. The association between the changes in decision-making and the RS level was not statistically significant (p=0.73).

affected the decision-making that would otherwise solely rely on the traditional immunohistochemical parameters associated with each patient. According to the oncologists' recommendation prior to the test results, 70 patients would not have been given chemotherapy, 10 (14.3%; 95% CI=7.4-25.2%) of whom were finally assigned to chemotherapy after the ODX test. More interestingly, out of the 43 patients that would have been assigned to chemotherapy, only 16 (37.2%; 95% CI=23.4-53.3%) were finally recommended this treatment after reviewing the ODX results. This entails that 62.8% of the patients would have been 'wrongly' assigned to chemotherapy, while 14.3% of patients would have not been recommended this treatment even though they should have. Overall, chemotherapy recommendation was significantly altered after the ODX assay was carried out (p=0.008) and, in the sample, it diminished by 39.5%. There have been two relapses so far in the sample (median follow-up=31.9 months), after which cases chemotherapy was inevitably suggested later on.

In total, there was modification in the decision-making pre and post the ODX testing in 37 cases (32.7%). In an attempt to associate these findings with the RS level, we identified the following results (Figure 4): The ODX assay result altered the chemotherapy recommendation in 23 (33.8%) out of 68 low RS cases, in 14 (33.3%) out of 42 intermediate RS cases and in zero (0%) high RS cases. Nonetheless, the association between the changes in decision-making and the RS level was not statistically significant (p=0.73), although there was a pattern affecting only patients with low and intermediate RS scores.

Regarding the 27 patients who avoided chemotherapy due to an ODX-driven decision, we analyzed their respective number of unfavorable characteristics. None (0.0%) of these 27 patients had zero unfavorable characteristics, 3 patients (11.1%) had one unfavorable characteristic, 21 patients (77.8%) had two unfavorable characteristics and finally the remaining 3 patients (11.1%) had three unfavorable characteristics. However, there was no statistically significant association revealed between the status of the patient, i.e., whether a woman skipped chemotherapy or not, and the number of corresponding unfavorable characteristics (p=0.39).

Discussion

The main aim of this study was the determination of the RS distribution of this particular cohort of patients, its correlation with standard clinicopathologic parameters and, finally, the investigation of the consequences of the RS knowledge on the adjuvant treatment decisions by comparing the pre and post test decisions. Given the documented toxicity of the various chemotherapeutic regimens [28-31], it is very interesting to describe the effect of the RS in terms of chemotherapy spared. Retrospective inspection and analysis of all BC cases emerging from the medical records of the participating high-traffic breast clinic, with a large number of patients from all over the country, revealed that the distribution of the RS results in our group of patients was similar to that observed in other studies with a lower proportion of high RS 2.6% (e.g. in the NSABP B-14 and B-20 studies, 25–27% of patients were in the high RS category) , a fact that can be attributed to the selection criteria of the study which comprised mainly patients of low and intermediate risk [32]. Regarding the latter two categories, we identified 59.6% belonging in the low RS group and 37.7% in the intermediate one.

The pre-test recommendations, based on the St Gallen criteria, indicated that 6 out of 10 patients in our sample would not have been given chemotherapy; out of these patients, 14% were finally assigned to chemotherapy after the ODX test. Also, almost 63% of the patients that would have been assigned to chemotherapy, as a prior recommendation, finally avoided this treatment.

Overall, alteration in the decision-making pre and post the ODX testing was registered in one third of the cases. These findings are concordant with those reported in other retrospective and prospective studies conducted in different regions of the world (European countries, Japan, Australia and the United States) [19,33-48] and highlight the consistency of the impact of knowing the RS on adjuvant treatment decisions between regions and countries. The proportion of changes to chemotherapy or, in the other direction, to hormonotherapy, solely as a result of the ODX testing in BC was also similar to that of other studies, with the proportion of chemotherapy recommendations clearly decreasing and the proportion of hormonotherapy recommendations increasing [49]. Changes were observed largely towards lower-intensity treatments.

Adjuvant treatment for early-stage BC is an important and complex issue confronted by oncologists. For the patients this is a life-changing decision, the outcome of which will tremendously impact their everyday quality of life. The decision of whether to assign chemotherapy as part of adjuvant therapy to BC patients cannot be exclusively made based on traditional prognostic indicators, since they have often proven to be insufficient for the distinction between patients who are likely to benefit from chemotherapy and patients less likely to obtain a clear advantage from that. The additional information provided by the ODX assay result supplies the physician with unique-value information for the assessment of the risk of recurrence.

This study has several limitations arousing from its retrospective nature and the fact that data regarded a cohort from a single BC; therefore, the sample size of the study was relatively modest. However, the analysis has been as thorough as possible given the available data, without violating the statistical power of the respective analyses.

Conclusions

This study demonstrated that the distribution of the ODX RS in the specific cohort of Greek women with ESBC is similar to that reported in other geographical regions of the world. The impact of the RS information on adjuvant treatment decisions monitored in this study was also familiar to what has been reported by other researchers, with the main effect being a shift in treatment recommendations towards lower-intensity regimens. Finally, the proportion of chemotherapy recommendations was greatly reduced, suggesting that the RS can assist in making definitive treatment recommendations in cases for which physicians are ambivalent about selecting chemotherapy.

Conflict of interests

The authors declare no confict of interests.

References

1. International Agency for Research on Cancer (IARC) and World Health Organization (WHO). GLOBOCAN 2012. Estimated cancer incidence, mortality and prevalence worldwide in 2012. http://globocan.iarc.fr/Pages/fact_sheets_cancer.aspx, 2016.
2. Goldhirsch A, Wood WC, Coates AS, Gelber RD, Thurlimann B, Senn HJ. 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;22:1736-47.
3. Aebi S, Davidson T, Gruber G, Cardoso F. ESMO Guidelines Working Group. Primary breast cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol 2011;22:12-24.
4. NCCN Clinical Practice Guidelines in Oncology. Breast Cancer Version 2. [Cited 30 May 2013.] Available from URL: http://www.nccn.org/professionals/physician_gls/pdf/breast.pdf, 2013.
5. Harris L, Fritsche H, Mennel R et al. American Society of Clinical Oncology 2007 update of recommendations for the use of tumor markers in breast cancer. J Clin Oncol 2007;25:5287-312.
6. Polyak K. Heterogeneity in breast cancer. J Clin Invest 2011;121:3786-88.
7. Almendro V, Fuster G. Heterogeneity of breast cancer: etiology and clinical relevance. Clin Transl Oncol 2011;13:767-73.

8. Bertos NR, Park M. Breast cancer - one term, many entities? J Clin Invest 2011;121:3789-96.
9. Dunnwald LK, Rossing MA, Li CI. Hormone receptor status, tumor characteristics, and prognosis: a prospective cohort of breast cancer patients. Breast Cancer Res 2007;9:R6.
10. Park YH, Lee S, Cho EY et al. Patterns of relapse and metastatic spread in HER2-overexpressing breast cancer according to estrogen receptor status. Cancer Chemother Pharmacol 2010;66:507-16.
11. Gómez HL, Castaneda CA, Vigil CE et al. Prognostic effect of hormone receptor status in early HER2 positive breast cancer patients. Hematol Oncol Stem Cell Ther 2010;3:109-15.
12. Liu AN, Sun P, Liu JN et al. Clinicopathologic characteristics and prognostic factors in patients with operable HER-2 overexpressing breast cancer. Asian Pacific J Cancer Prev 2012;13:1197-201.
13. Sparano JA, Fazzari M, Kenny PA. Clinical application of gene expression profiling in breast cancer. Surg Oncol Clin N Am 2010;19:581-606.
14. Sotiriou C, Pusztai L. Gene-expression signatures in breast cancer. N Engl J Med 2009;360:790-800.
15. Paik S, Tang G, Shak S et al. Gene expression and benefit of chemotherapy in women with node-negative, estrogen receptor-positive breast cancer. J Clin Oncol 2006;24:3726-34.
16. Dowsett M, Nielsen TO, A'Hern R et al. International Ki-67 in Breast Cancer Working Group: Assessment of Ki67 in breast cancer: Recommendations from the International Ki67 in Breast Cancer Working Group. J Natl Cancer Inst 2011;103:1656-64.
17. Carlson JJ, Roth JA. The impact of the Oncotype Dx breast cancer assay in clinical practice: a systematic review and meta-analysis. Breast Cancer Res Treat 2013;141:13-22.
18. Tsai ML, Lillemoe TJ, Finkelstein MJ et al. Utility of Oncotype DX Risk Assessment in Patients With Invasive Lobular Carcinoma. Clin Breast Cancer 2016;16:45-50.
19. Jaafar H, Bashir MA, Taher A, Qawasmeh K, Jaloudi M. Impact of Oncotype DX testing on adjuvant treatment decisions in patients with early breast cancer: a single-center study in the United Arab Emirates. Asian Pac J Clin Oncol 2014;10:354-60.
20. Chereau E, Coutant C, Gligorov J et al. Discordance with local guidelines for adjuvant chemotherapy in breast cancer: reasons and effect on survival. Clin Breast Cancer 2011;11:46-51.
21. Paik S, Shak S, Tang G et al. A multigene assay to predict recurrence of tamoxifen-treated, node-negative breast cancer. N Engl J Med 2004;351:2817-26.
22. Habel LA, Shak S, Jacobs MK et al. A population-based study of tumor gene expression and risk of breast cancer death among lymph node-negative patients. Breast Cancer Res 2006;8:R25.
23. Goldhirsch A, Ingle JN, Gelber RD, Coates AS, Thürlimann B, Senn HJ; Panel members. Thresholds for therapies: highlights of the St Gallen International Expert Consensus on the primary therapy of early breast cancer 2009. Ann Oncol 2009;20:1319-29.
24. Aebi S, Davidson T, Gruber G, Castiglione M. ESMO Guidelines Working Group. Primary breast cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol 2010;21:9-14.
25. Hartmann LC, Ingle JN, Wold LE et al. Prognostic value of c-erbB2 overexpression in axillary lymph node positive breast cancer. Results from a randomized adjuvant treatment protocol. Cancer 1994;74:2956-63.
26. Harris L, Fritsche H, Mennel R et al. American Society of Clinical Oncology. American Society of Clinical Oncology 2007 update of recommendations for the use of tumor markers in breast cancer. J Clin Oncol 2007;25:5287-5312.
27. Markopoulos C. Overview of the use of Oncotype DX(®) as an additional treatment decision tool in early breast cancer. Expert Rev Anticancer Ther 2013;13:179-94.
28. Perry M, Koh D. The pulmonary toxicity of chemotherapeutic drugs. In: Perry M (Ed): The Chemotherapy Source Book. London: Williams and Wilkins, 1996 pp 665-7.
29. Perry M, Ewer M, Benjamin R. Cardiotoxicity of chemotherapeutic drugs. In: Perry M (Ed): The Chemotherapy Source Book. London: Williams and Wilkins, 1996, pp 649-59.
30. Pinder MC, Duan Z, Goodwin JS, Hortobagyi GN, Giordano SH. Congestive heart failure in older women treated with adjuvant anthracycline chemotherapy for breast cancer. J Clin Oncol 2007;25:3808-15.
31. Perry MC. Chemotherapeutic agents and hepatotoxicity. Semin Oncol 1992;19:551–65.
32. Mamounas EP, Tang G, Fisher B et al. Association between the 21-gene recurrence score assay and risk of locoregional recurrence in node-negative, estrogen receptor-positive breast cancer: results from NSABP B-14 and NSABP B-20. J Clin Oncol 2010;28:1677-83.
33. Lo SS, Mumby PB, Norton J et al. Prospective multicenter study of the impact of the 21-gene recurrence score assay on medical oncologist and patient adjuvant breast cancer treatment selection. J Clin Oncol 2010;28:1671-6.
34. Geffen DB, Abu-Ghanem S, Sion-Vardy N et al. The impact of the 21-gene recurrence score assay on decision making about adjuvant chemotherapy in early-stage estrogen-receptor-positive breast cancer in an oncology practice with a unified treatment policy. Ann Oncol 2011;22:2381-6.
35. Albanell J, Gonzalez A, Ruiz-Borrego M et al. Prospective transGEICAM study of the impact of the 21-gene Recurrence Score assay and traditional clinicopathological factors on adjuvant clinical decision making in women with estrogen receptor-positive (ER+) node-negative breast cancer. Ann Oncol 2012;23:625-31.
36. Klang SH, Hammerman A, Liebermann N, Efrat N, Doberne J, Hornberger J. Economic implications of 21-gene breast cancer risk assay from the perspective of an Israeli-managed health-care organization. Value Health 2010;13:381-7.
37. Ademuyiwa FO, Miller A, O'Connor T et al. The effects of oncotype DX recurrence scores on chemotherapy utilization in a multi-institutional breast cancer cohort. Breast Cancer Res Treat 2011;126:797-802.

38. Kamal AH, Loprinzi CL, Reynolds C et al. Breast medical oncologists' use of standard prognostic factors to predict a 21-gene Recurrence Score. Oncologist 2011;16:1359-66.
39. Henry LR, Stojadinovic A, Swain SM, Prindiville S, Cordes R, Soballe PW. The influence of a gene expression profile on breast cancer decisions. J Surg Oncol 2009;99:319-23.
40. Asad J, Jacobson AF, Estabrook A et al. Does oncotype DX recurrence score affect the management of patients with early-stage breast cancer? Am J Surg 2008;196:527-9.
41. Rayhanabad JA, Difronzo LA, Haigh PI, Romero L. Changing paradigms in breast cancer management: introducing molecular genetics into the treatment algorithm. Am Surg 2008;74:887-90.
42. Holt SDH, Bennett H, Bertelli G et al. A decision impact, decision conflict, and economic assessment of routine Oncotype DX testing of 146 women with node-negative or pNImi, ER-positive breast cancer in the UK. Br J Cancer 2013;108:2250-8.
43. de Boer RH, Baker C, Speakman D, Mann B. Australian decision impact study: the impact of Oncotype DX Recurrence Score (RS) on adjuvant treatment decisions in hormone receptor positive (HR+), node negative (N0) and node positive (N+) early stage breast cancer (ESBC) in the multidisciplinary clinic. Presented at San Antonio Breast Cancer Symposium (SABCS), San Antonio, TX, December 6-10, 2011, abstr no.24.
44. Yamauchi H, Nakagawa C, Yamashige S et al. Decision impact and economic evaluation of the 21-gene Recurrence Score (RS) assay for physicians and patients in Japan. Eur J Cancer 2011;47:S376.
45. Eiermann W, Rezai M, Kummel S et al. The 21-gene recurrence score assay impacts adjuvant therapy recommendations for ER-positive, node-negative and node-positive early breast cancer resulting in a risk-adapted change in chemotherapy use. Ann Oncol 2012;24:618-24.
46. Joh JE, Esposito NN, Kiluk JV et al. The effect of Oncotype DX recurrence score on treatment recommendations for patients with estrogen receptor-positive early stage breast cancer and correlation with estimation of recurrence risk by breast cancer specialists. Oncologist 2011;16:1520-6.
47. Oratz R, Kim B, Chao C et al. Physician survey of the effect of the 21-gene recurrence score assay results on treatment recommendations for patients with lymph node-positive, estrogen receptor-positive breast cancer. J Oncol Pract 2011;7:94-9.
48. Gligorov J, Pivot XB, Naman HL et al. Prospective study of the impact of using the 21-gene recurrence score assay on clinical decision making in women with estrogen receptor positive, HER2-negative, early-stage breast cancer in France. Presented at the American Society of Clinical Oncology (ASCO) Annual Meeting Chicago, IL, June 1–5, 2012, abstr no.568.
49. Cheung PS, Tong AC, Leung RC, Kwan WH, Yau TC. Initial experience with the Oncotype DX assay in decision-making for adjuvant therapy of early oestrogen receptor-positive breast cancer in Hong Kong. Hong Kong Med J 2014;20:401-6.