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ORIGINAL RESEARCH

Survival of the Patients With Breast Cancer Who Underwent Oncotype DX Recurrence Score Testing: Long-Term Survival Update of a Prospective Multicenter Study in Türkiye According to Different Cut-Offs

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ABSTRACT

Background: Seventy percent of early-stage breast cancers are hormone receptor positive. In this prospectively designed study, we aim to update the long-term survival outcomes of chemotherapy decision-making according to Oncotype DX Recurrence Score (ODX-RS) and its relation with different cut-offs.

Materials and Methods: Ten academic centers in Türkiye that routinely discuss all new cases at multidisciplinary tumor board participated. Consecutive patients who are pT1–3, pN0-N1mic, M0 were identified. Adjuvant treatment decisions were discussed at tumor board before and after ODX-RS results.

Results: Of the 165 patients (26–76, median 48 years) with a median follow-up of 108 months, ODX-RS ≤ 25 had significantly better overall survival (OS) than those with ODX-RS ≥ 26 ($p = 0.022$). When evaluated by age, OS and disease-free survival (DFS) was significantly better with ODX-RS ≤ 15 in patients aged ≤ 50 years and with ODX-RS ≤ 25 in patients aged > 50 years ($p = 0.034$ and $p = 0.024$). ODX-RS ≤ 20 in patients aged ≤ 50 years and ODX-RS ≤ 25 in patients aged > 50 years had significantly better OS ($p = 0.002$). There was no difference in OS between those who received chemotherapy before ODX-RS and those who did not ($p = 0.119$). Conversely in the post-ODX-RS, ODX-RS predicted survival better and OS was lower in patients who received chemotherapy compared to those who did not ($p = 0.020$) meaning that ODX-RS can predict OS. The

Abbreviations: DFS, disease free survival; ER, estrogen receptor; HER2, human epidermal growth factor receptor-2; HR, hormone receptor; LRFS, local-regional recurrence free survival; MFS, metastasis free survival; ODX-RS, Oncotype DX Recurrence Score; OS, overall survival; PR, progesterone receptor.

[Correction added on 14 August 2025, after first online publication: The copyright line was changed.]

ODX-RS test significantly reduced overall chemotherapy-related costs, yielding a favorable ICER of $3787.5 per QALY gained, thus demonstrating its cost-effectiveness.

Conclusions: The ODX-RS significantly influences treatment decisions resulting comparable survivals for patients who received chemotherapy and who did not. Different cut-offs have variable significant prognostic effect on survival prediction models.

1 | Introduction

Breast cancer is the most common malignancy among women worldwide [1]. The effective rollout of nationwide opportunistic screening initiatives at newly established cancer screening centers in Türkiye has led to an increase in the detection of early-stage breast cancers in recent years [2]. Specifically, a considerable percentage of newly diagnosed patients—27% and 45%—were identified at stages 1 and 2, respectively [2]. Among patients with early-stage breast cancer, approximately 70% exhibit hormone receptor (HR)-positive and human epidermal growth factor receptor-2 (HER2)-negative characteristics [3].

The management of breast cancer has seen significant advances over the past decade. One of the most significant advancements was the usage of genomic assays, such as the Oncotype DX Recurrence Score (ODX-RS) test, to guide treatment decisions and improve patient outcomes. The ODX-RS test, a 21-gene assay, has been widely adopted for its ability to assess the risk of recurrence in HR-positive, HER2-negative breast cancer patients, particularly those with node-negative disease [4].

The clinical utility of the test lies in its ability to stratify patients into low, intermediate, and high-risk categories based on the ODX-RS results. This stratification helps to determine the likely benefit of adjuvant chemotherapy. Several large-scale studies, including the landmark TAILORx trial, have demonstrated that patients with low to intermediate ODX-RS may safely forgo chemotherapy without compromising their survival outcomes [5, 6]. Consequently, the use of the ODX-RS test has led to a more personalized approach to breast cancer treatment, reducing the unnecessary exposure to chemotherapy and its associated toxicities [7].

Recent data also suggest that the use of the ODX-RS test not only influences treatment decisions but also has a significant effect on long-term survival rates. Studies have shown that patients stratified by the ODX-RS and treated accordingly, exhibit survival rates comparable to those who received more aggressive treatment without the test [8, 9]. This highlights the test's role in optimizing therapeutic strategies, thereby improving both quality of life and overall survival (OS) in breast cancer patients [10, 11].

In this prospectively designed study, we aim to update the long-term survival outcomes of chemotherapy decision-making according to genomic risk score, ODX-RS, and its relation with different cut-offs, in patients with HR-positive HER2-negative early-stage breast cancer.

2 | Materials and Methods

Ten academic centers in seven different regions of Türkiye that routinely discuss all new cases of breast cancer at weekly multidisciplinary tumor board participated in this prospective trial. The study was approved by a central ethics committee and by each participating institution's review board. Consecutive patients with breast cancer who had pT1–3, pN0-N1mic, M0, HR-positive, and HER2-negative tumors were identified. Tumors with ≥ 1% positively-stained cells for estrogen receptor (ER) or progesterone receptor (PR) were considered ER+ or PR+, respectively. A patient was considered to have HER2-negative disease if the primary tumor had a score of 0 or 1+ on HER2 immunohistochemical analysis or if silver or fluorescence in situ hybridization revealed no amplification of the HER2 gene. "Luminal subtypes" were defined based on PR and Ki-67 evaluation as follows: Luminal A (PR score ≥ 20% and Ki-67 < 20%) and Luminal B (PR < 20% or Ki-67 ≥ 20%). Adjuvant treatment decisions were made with careful consideration of clinical and pathologic factors by all of the tumor board members. This initial treatment decision (pre-ODX-RS assay decision) was recorded on a questionnaire form by site investigators, and baseline pathologic characteristics were recorded in an enrollment form. The patients identified at tumor board were individually contacted. The pre-ODX-RS assay decision was conveyed and informed consent was obtained. Formalin-fixed paraffin-embedded tissue blocks were sent to the central laboratory (Genomic Health Inc.; California, USA). Cases were discussed at tumor board once more when the ODX-RS became available. Results were categorized as low risk < 18, intermediate risk 18–30 and high risk > 30 during the study concordant with traditional cut-offs. Investigators filled the post-ODX-RS assay questionnaire forms with their final decision. The OS, disease free survival (DFS), local-regional recurrence free survival (LRFS), and metastasis free survival (MFS) were calculated at 5- and 9-years.

2.1 | Cost Effectiveness Analysis

Patients were subsequently analyzed for cost-effectiveness in the arms of chemotherapy + endocrine therapy or endocrine therapy alone, according to the results of ODX-RS. Those in perfect health were scored as 1, and death was scored as 0. The quality-adjusted life year (QALYs) was calculated as 0.68. The deterioration in the quality of life during chemotherapy, the period the patient was away from daily activities, the 6-month job loss within a year, and the cost of chemotherapy were considered. The European Quality 5 Dimension (EQ5D) scale was used for cost-effectiveness, and the Incremental Cost-Effectiveness Ratio (ICER) was calculated.

The chemotherapy costs used in adjuvant therapy were averaged, including the costs of AC (adriamycin 60 mg/m^2 + cyclophosphamide 600 mg/m^2), TC (docetaxel 75 mg/m^2, cyclophosphamide 600 mg/m^2), weekly paclitaxel 80 mg/m^2, FEC (5-Fluorouracil 500 mg/m^2 + cyclophosphamide 600 mg/m^2, epirubicin 100 mg/m^2), and docetaxel. Premedications were

calculated, and the average cost of Granulocyte colony-stimulating factor (G-CSF) use was added. The cost of hospitalization for complications was not included. Long-term chemotherapy toxicities and costs were not calculated. Costs were calculated based on December 2023 retail prices (Rx media).

2.2 | Statistical Analysis

Descriptive statistics were reported as mean, standard deviation, median, minimum, maximum, frequency, and percentage. The distribution of variables was checked with Kolmogorov–Simirnov test. Mann–Whitney *U* test was used for the comparison of quantitative data. Chi-square test (Fisher exact test) was used for the comparison of the qualitative data. Kaplan–Meier was used in the survival analysis. Statistical analyses on the ODX-RS were conducted using both nominal data based on the actual ODX-RS, and an ordinal scale with four ODX-RS categories (< 16, 16–21, 22–25, > 25) for survival analyses. SPSS 28.0 was used for statistical analyses. As this is a pre-planned multicenter study with a financial burden, the team statistician set a target of at least 15 patients per center for the study and did not calculate the sample size due to the design of the study.

3 | Results

The study included 165 breast cancer patients aged 26–76 (median 48) years. Most patients (81.2%; 134 out of 165) had a low ODX-RS (≤ 25), while 18.8% had a high ODX-RS (≥ 26). Clinic-pathologic details of the cohort is summarized in Table 1.

Prior to the ODX-RS results, 55.2% (92 out of 165 patients) of patients had a tumor board decision to receive chemotherapy. This rate decreased to 37% (61 out of 165 patients) after the availability of the ODX-RS results. For the remaining patients assessed before ODX-RS, 44.8% (73 out of 165 patients) of patients were decided by the tumor board not to receive chemotherapy, and the rate dropped to 38.2% (63 patients) after the availability of the ODX-RS result. Of the 92 patients in whom a decision for chemotherapy was taken, low risk was detected in 41 patients with ODX-RS and chemotherapy decision was abandoned. On the other hand, 73 patients in whom a decision for endocrine therapy was taken, high risk was detected in 10 patients with ODX-RS and chemotherapy decision was made. The results show that 6.1% (10 pts) of the patients would have been at risk for under treatment without the ODX-RS result, while 24.8% (41 pts) would have been at risk for overtreatment. As a result, in 30.9% of the patients, the treatment decision changed depending on the ODX-RS (Figure 1).

Tumor diameter, grade, Ki-67, and luminal B type were significantly higher and PR rate was significantly lower in the group receiving chemotherapy after ODX-RS than in the group not receiving chemotherapy according to ODX-RS (Table 2).

During a median follow-up period of 108 months (range 16–111), 11 (6.7%) patients had local recurrence or distant metastasis. Of those, nine (5.5%) had distant metastasis. Local recurrence was observed in 4 (2.4%) and regional recurrence in 6 (3.6%) patients. Three (1.8%) patients died due to breast cancer (Table 3).

There was no significant difference in local recurrence and metastasis rates between the groups receiving or not receiving chemotherapy, respectively based on their ODX-RS. Breast cancer-related mortality rate was significantly higher in the group that received chemotherapy after the ODX-RS than in the group that did not receive chemotherapy according to the ODX-RS. Three patients died due to breast cancer and all three had received chemotherapy (Table 4). Among the 104 patients who did not receive chemotherapy following ODX-RS, no breast cancer-related deaths were observed. In the multivariate analysis performed by adjusting significant factors (tumor size, grade, % PR, Ki-67, and Luminal A/B types as mentioned in Table 2), chemotherapy is found to be independently associated with poorer prognosis (HR = 7.23 [1.27–41.22 95% CI] $p = 0.026$).

In the Kaplan–Meier survival analysis, patients with ODX-RS ≤ 25 had significantly better OS than those with ODX-RS ≥ 26 ($p = 0.022$, Figure 2a). When evaluated according to age, OS was significantly better with ODX-RS ≤ 16 in patients aged ≤ 50 years and with ODX-RS ≤ 26 in patients aged > 50 years ($p = 0.034$, Figure 2b). ODX-RS ≤ 21 in patients aged ≤ 50 years and ODX-RS ≤ 26 in patients aged > 50 years had significantly better OS ($p = 0.002$, Figure 2c). There was no difference in OS between those who received chemotherapy before ODX-RS and those who did not ($p = 0.119$, Figure 2d). Conversely in the post-ODX-RS, ODX-RS predicted survival better and OS was lower in patients who received chemotherapy compared to those who did not ($p = 0.020$, Figure 2e) meaning that ODX-RS can predict OS.

The DFS did not differ significantly between patients who received chemotherapy and who did not after ODX-RS result ($p = 0.086$) (Figure 3a). When only age was evaluated in terms of DFS, ODX-RS ≤ 15 for ≤ 50 years and ODX-RS ≤ 25 for > 50 years significantly predicted better DFS ($p = 0.024$, Figure 3b). In survival analysis for LRFS, there was no significant association between ODX-RS and the decision to give or not to give chemotherapy ($p = 0.398$). The predicted MFS in the high-risk group that is recommended to receive chemotherapy according to the ODX-RS result was significantly shorter than the low-risk group that is not recommended to receive chemotherapy ($p = 0.030$, Figure 3c). When analyzed by age, ODX-RS ≤ 15 ($p = 0.002$) and ODX-RS ≤ 20 ($p = 0.028$) for patients aged ≤ 50 years and ODX-RS ≤ 26 for patients aged > 50 years significantly predicted improved MFS (Figure 3d,e).

In tumor board before ODX-RS, a chemotherapy decision was made for the 92 patients. For the 41 of those patients, whose decision to receive chemotherapy was changed to omitting chemotherapy after ODX-RS, there was no significant survival difference in OS, DFS, LRFS and MFS compared to the 51 patients who received chemotherapy ($p = 0.106$, $p = 0.595$, $p = 0.511$, and $p = 0.341$ respectively). Furthermore, no significant survival difference was detected in terms of OS, DFS, LRFS, and MFS when those 41 patients were compared with 63 patients who did not receive chemotherapy before and after ODX-RS ($p = 1$, $p = 0.622$, $p = 0.697$, and $p = 0.681$ respectively).

TABLE 1 | Clinic-pathologic features of the patients, distribution of ODX-RS, and difference in chemotherapy decision pre- and post-ODX-RS.

	Min–max	Median	Mean ± SD/ *n* (%)
Age	26.0–76.0	48.0	49.90 ± 10.36
≤ 50			96 (58.2%)
> 50			69 (41.8%)
Tumor size (cm)	0.5–8.0	2.0	1.99 ± 0.93
≤ 2			79 (47.9%)
> 2			86 (52.1%)
Grade			
I			29 (17.6%)
II			110 (66.7%)
III			26 (15.8%)
ER	5.0–100.0	90.0	82.70 ± 21.80
≤ 70%			30 (18.2%)
> 70%			135 (81.8%)
PR	0.0–100.0	60.0	50.30 ± 36.07
≤ 20%			54 (32.7%)
> 20%			111 (67.3%)
Ki-67	2.0–80.0	18.0	20.66 ± 15.53
≤ 20			76 (53.5%)
> 20			66 (46.5%)
Luminal			
A			59 (39.6%)
B			90 (60.4%)
HER2			
0			105 (63.6%)
I			36 (21.8%)
II			24 (14.5%)
Lymph node status			
pN0			154 (93.3%)
pN1mic			11 (6.7%)
ODX-RS	0.0–64.0	16.0	18.19 ± 10.09
≤ 25			34 (20.6%)
≥ 26			131 (79.4%)
Age ≤ 50 ODX-RS			
0–15			41 (42.7%)
16–20			25 (26.0%)
21–25			12 (12.5%)
≥ 26			18 (18.8%)
Age > 50 ODX-RS			
≤ 25			56 (81.2%)
≥ 26			13 (18.8%)
Pre ODX-RS			
CT (−)			73 (44.2%)
CT (+)			92 (55.8%)
Post ODX-RS			
CT (−)			104 (63.0%)
CT (+)			61 (37.0%)
Pre/post ODX-RS difference			
Pre (CT−)/post (CT−)			63 (38.2%)
Pre (CT−)/post (CT+)			10 (6.1%)
Pre (CT+)/post (CT−)			41 (24.8%)
Pre (CT+)/post (CT+)			51 (30.9%)

Abbreviations: CT: chemotherapy; ER: estrogen receptor; HER2: human epidermal growth factor receptor-2; ODX-RS: Oncotype-DX Recurrence Score; PR: progesterone receptor; SD: standard deviation.

The average chemotherapy cost was calculated as $1308, the cost of ODX-RS was $3300, and the average side effect cost was $468.5. According to NSABP 20 criteria, when chemotherapy was decided for 92 patients before ODX-RS determination, the average cost per patient among 165 patients was $1135.6, whereas after ODX-RS determination, when chemotherapy was decided for 43 patients, the average cost per patient in the cohort decreased to $530.8. The average side effect cost was $468.5. The difference per patient calculated as $2575.5 and the QALYs difference of 0.68 resulted in an ICER (USD per QALY gained) of $3787.5 (Table 5). When considering that patients received their salaries without working for 6 months of treatment, the ODX-RS cost imposes an additional financial burden of $1938 for a patient earning an average of one minimum wage, totaling 89,546 TL ($3198). For a patient earning an average of two minimum wages, the ODX-RS cost imposes an additional financial burden of $695, totaling 149,349 TL ($5334). These results demonstrate the cost effectiveness of the ODX-RS test.

4 | Discussion

This study evaluated the impact of the ODX-RS on treatment decision-making and long-term survival outcomes in HR-positive HER2-negative early-stage breast cancer patients. The results underscore the transformative role that genomic assays can play in guiding personalized treatment strategies and minimizing unnecessary chemotherapy.

A key observation from this study is the significant shift in treatment recommendations following the integration of the ODX-RS. Of the 92 patients in whom a decision for chemotherapy was taken, low risk (ODX-RS < 18) was detected in 41 patients with ODX-RS and chemotherapy decision was abandoned. On the other hand, 73 patients in whom a decision for endocrine therapy was taken, high risk (ODX-RS > 30) was detected in 10 patients with ODX-RS and chemotherapy

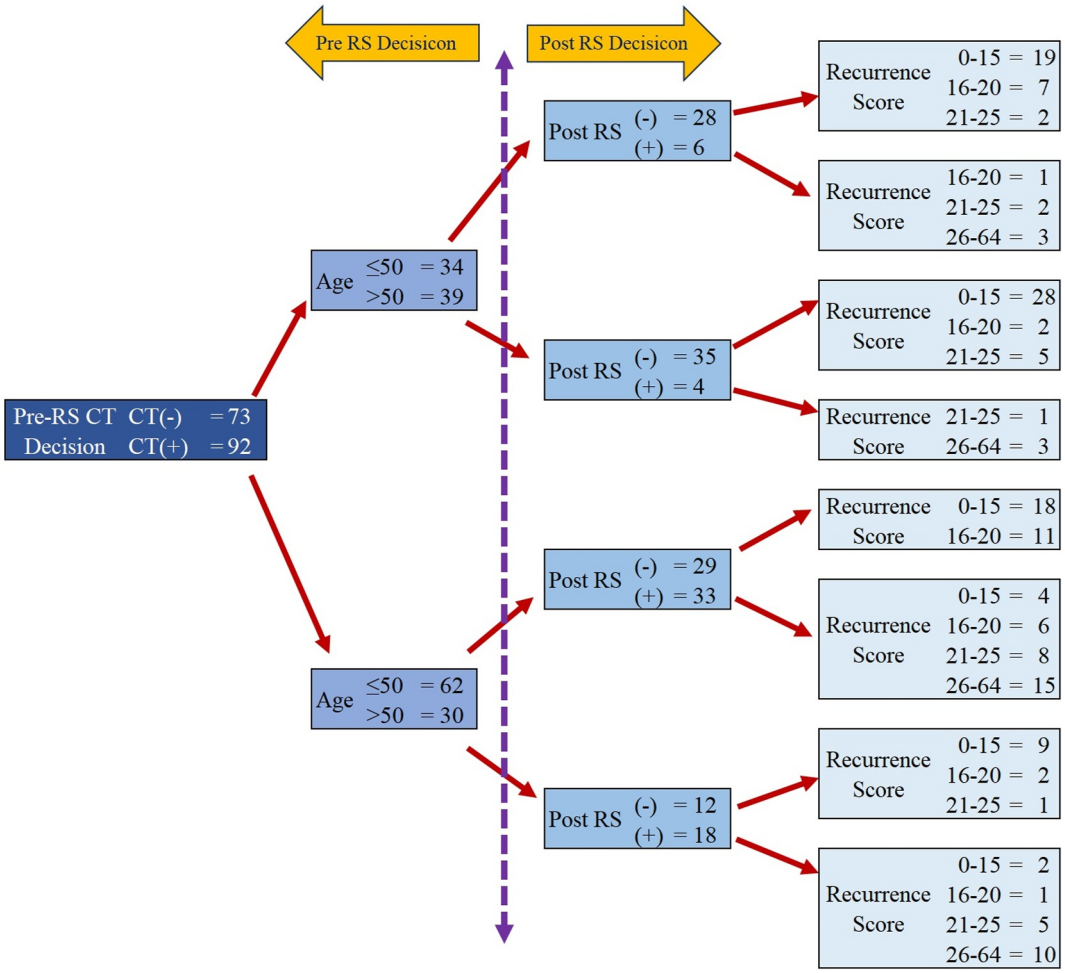

FIGURE 1 | Patient distribution in numbers in the Pre-ODX-RS group, Post-ODX-RS group and their recurrence score groups. CT: chemotherapy; RS: Oncotype-DX Recurrence Score. [Colour figure can be viewed at wileyonlinelibrary.com]

decision was made. The results show that 6.1% (10 pts) of the patients would have been at risk for under treatment without the ODX-RS result, while 24.8% (41 pts) would have been at risk for overtreatment. As a result, in 30.9% of the patients, the treatment decision changed depending on the ODX-RS. This shift demonstrates the critical role that genomic testing can play in refining treatment plans, potentially sparing patients from the adverse effects of chemotherapy while maintaining positive outcomes. These findings align with those from other major trials, such as the TAILORx study, which showed that patients with a low to intermediate ODX-RS could safely avoid chemotherapy without affecting survival outcomes [6, 10].

In their study, Schaafsma et al. highlighted that chemotherapy in patients with high-risk scores is associated with significantly longer OS and breast cancer-specific survival compared to high-risk patients who did not receive chemotherapy [12]. They also mentioned that patients with low-risk scores who were treated with chemotherapy tended to have shorter OS compared to low-risk patients who forwent chemotherapy. In our study, patients with a low ODX-RS ($\leq$ 25) exhibited significantly better OS compared to those with a high ODX-RS ($\geq$ 26) ($p = 0.022$). This significant difference was also valid for the different ODX-RS cut-offs and underscoring the ODX-RS as a reliable prognostic marker. These findings are consistent with prior research indicating that the ODX-RS test is effective in identifying patients who are likely to benefit from chemotherapy, as well as those who are unlikely to derive significant benefit from such treatment [8, 13–15]. Our study adds to the growing body of evidence supporting the ODX-RS test's predictive power in breast cancer management. Furthermore, if TAILORx cut-offs were applied to the cohort in this study, an additional 18 patients would have been spared from chemotherapy meaning that the rate of decision change would rise up to 41.8% from 30.9%.

A notable observation from our study was that breast cancer-specific mortality was higher among patients who received chemotherapy after being classified as high-risk based on ODX-RS results compared to those who did not receive chemotherapy. This could be due to the aggressive nature of high ODX-RS tumors and the potential risks associated with chemotherapy, especially in older patients or those with co-morbid conditions [16–18]. These findings highlight the importance of balancing the benefits and risks of chemotherapy, particularly in patients with high ODX-RS tumors, and suggest that the ODX-RS can help identify patients who would benefit most from chemotherapy while sparing others from its potential harms.

TABLE 2 | Comparison of the clinic-pathologic features of the patients who received chemotherapy and those who did not according to ODX-RS.

	Post- ODX-RS decision (no CT)		Post- ODX-RS decision (CT)		
	Mean ± SD/*n* (%)	**Median**	**Mean ± SD/*n* (%)**	**Median**	***p***
Age	51.24 ± 10.26	49.00	47.62 ± 10.21	48.00	0.067[a]
≤ 50	57 (54.8%)		39 (76.5%)		0.251[b]
> 50	47 (45.2%)		22 (43.1%)		
Tumor size (cm)	1.89 ± 0.85	1.80	2.18 ± 1.04	2.00	**0.017**[a]
≤ 2	56 (53.8%)		23 (45.1%)		**0.045**[b]
> 2	48 (46.2%)		38 (74.5%)		
Grade					
I	24 (23.1%)		5 (9.8%)		**0.008**[b]
II	69 (66.3%)		41 (80.4%)		
III	11 (10.6%)		15 (29.4%)		
ER	82.99 ± 21.99	90.00	82.21 ± 21.64	90.00	0.666[a]
≤ 70%	19 (18.3%)		11 (21.6%)		0.970[b]
> 70%	85 (81.7%)		50 (98.0%)		
PR	58.79 ± 33.28	70.00	35.82 ± 36.28	20.00	**0.000**[a]
≤ 20%	23 (22.1%)		31 (60.8%)		**0.000**[b]
> 20%	81 (77.9%)		30 (58.8%)		
Ki-67	16.37 ± 10.62	14.00	28.10 ± 19.53	21.50	**0.000**[a]
≤ 20	58 (55.8%)		18 (35.3%)		**0.001**[b]
> 20	32 (30.8%)		34 (66.7%)		
Luminal					
A	49 (47.1%)		10 (19.6%)		**0.000**[b]
B	45 (43.3%)		45 (88.2%)		
HER2					
0	68 (65.4%)		37 (72.5%)		0.352[b]
I	24 (23.1%)		12 (23.5%)		
II	12 (11.5%)		12 (23.5%)		
Lymph node status					
pN0	98 (94.2%)		56 (109.8%)		0.546[b]
pN1mic	6 (5.8%)		5 (9.8%)		

Note: The bold values are presenting statistically significant.
Abbreviations: CT: chemotherapy; ER: estrogen receptor; HER2: human epidermal growth factor receptor-2; ODX-RS: Oncotype-DX Recurrence Score; PR: progesterone receptor; SD: standard deviation.
[a]Mann–Whitney *U* test.
[b]Chi-square test.

The DFS did not differ significantly between patients who received chemotherapy and who did not after ODX-RS result ($p = 0.493$). In survival analysis for LRFS, there was also no significant association between ODX-RS and the decision to give or not to give chemotherapy ($p = 0.398$). This aligns with findings from other studies, such as the PlanB trial, which confirmed that patients with a low ODX-RS could be effectively treated with endocrine therapy alone, avoiding the toxicities associated with chemotherapy [16]. In a multicenter study by Tsuchida et al., there was no significant intergroup difference in local regional recurrence ($p = 0.139$) [15]. In another study that uses TAILORx cut-offs, local regional recurrence rates were similar for patients with ODX-RS 11–25 (RR: 1.120, 95% CI: 0.520–2.410); however, those with ODX-RS > 25 had an increased risk of local regional recurrence (RR: 2.490, 95% CI: 0.680–9.390) compared to those with ODX-RS < 11. There was a stepwise increase in local regional recurrence rates when applying traditional and TAILORx cut-offs (both $p < 0.050$) [19]. The lack of significant differences in DFS and LRFS between chemotherapy and non-chemotherapy groups reinforces the idea that the ODX-RS is effective in stratifying patients according to their risk of recurrence. This stratification enables clinicians to tailor treatment plans that are both effective and less toxic, optimizing patient outcomes and quality of life [20–22].

TABLE 3 | Survival details of the whole cohort.

		Min-max	Median	*n* (%)
Disease (metastasis & recurrence)	(−)			154 (93.3%)
	(+)			11 (6.7%)
Recurrence	(−)			157 (95.2%)
	(+)			8 (4.8%)
Metastasis	(−)			156 (94.5%)
	(+)			9 (5.5%)
Local recurrence	(−)			161 (97.6%)
	(+)			4 (2.4%)
Regional recurrence	(−)			159 (96.4%)
	(+)			6 (3.6%)
Exitus	(−)			156 (94.5%)
	(+)			9 (5.5%)
Exitus (breast cancer)	(−)			162 (98.2%)
	(+)			3 (1.8%)
				Mean ± SD
Follow up time (months)		16–111.0	108	106.0 ± 11.9

Abbreviation: SD: standard deviation.

TABLE 4 | Comparison of survival details of patients who received chemotherapy and those who did not according to ODX-RS.

		Post-ODX-RS decision (no CT)		Post-ODX-RS decision (CT)		
		n (%)	Median	*n* (%)	Median	*p*
Disease (metastasis & recurrence)	(−)	98 (94.2%)		56 (109.8%)		0.546[b]
	(+)	6 (5.8%)		5 (9.8%)		
Recurrence	(−)	100 (96.2%)		57 (111.8%)		0.434[b]
	(+)	4 (3.8%)		4 (7.8%)		
Metastasis	(−)	100 (96.2%)		56 (109.8%)		0.235[b]
	(+)	4 (3.8%)		5 (9.8%)		
Local recurrence	(−)	101 (97.1%)		60 (117.6%)		1.000[b]
	(+)	3 (2.9%)		1 (2.0%)		
Regional recurrence	(−)	102 (98.1%)		57 (111.8%)		0.125[b]
	(+)	2 (1.9%)		4 (7.8%)		
Exitus	(−)	102 (98.1%)		54 (105.9%)		**0.009**[b]
	(+)	2 (1.9%)		7 (13.7%)		
Exitus (breast cancer)	(−)	104 (100%)		58 (113.7%)		**0.049**[b]
	(+)	0 (0.0%)		3 (5.9%)		
		Mean ± SD		**Mean ± SD**		
Follow up time (months)		107.2 ± 10.2	108	103.8 ± 14.2	108	0.388[a]

Note: The bold values are presenting statistically significant.
Abbreviations: CT: chemotherapy; ODX-RS: Oncotype-DX Recurrence Score; SD: standard deviation.
[a]Mann–Whitney *U* test.
[b]Chi-square test.

The ODX-RS was a predictor for MFS in our cohort. MFS in the high-risk group that is recommended to receive chemotherapy according to the ODX-RS result was significantly shorter than the low risk group that is not recommended to receive chemotherapy. When analyzed by age, ODX-RS ≤ 15 and ODX-RS ≤ 20 for patients aged ≤ 50 years and ODX-RS ≤ 26 for patients aged > 50 years significantly predicted improved MFS. A multicenter study from Japan also supports these findings by highlighting that there was a trend for better MFS in the ODX-RS 0–25 group ($p = 0.08$) [15]. In addition, a recent meta-analysis by Sparona

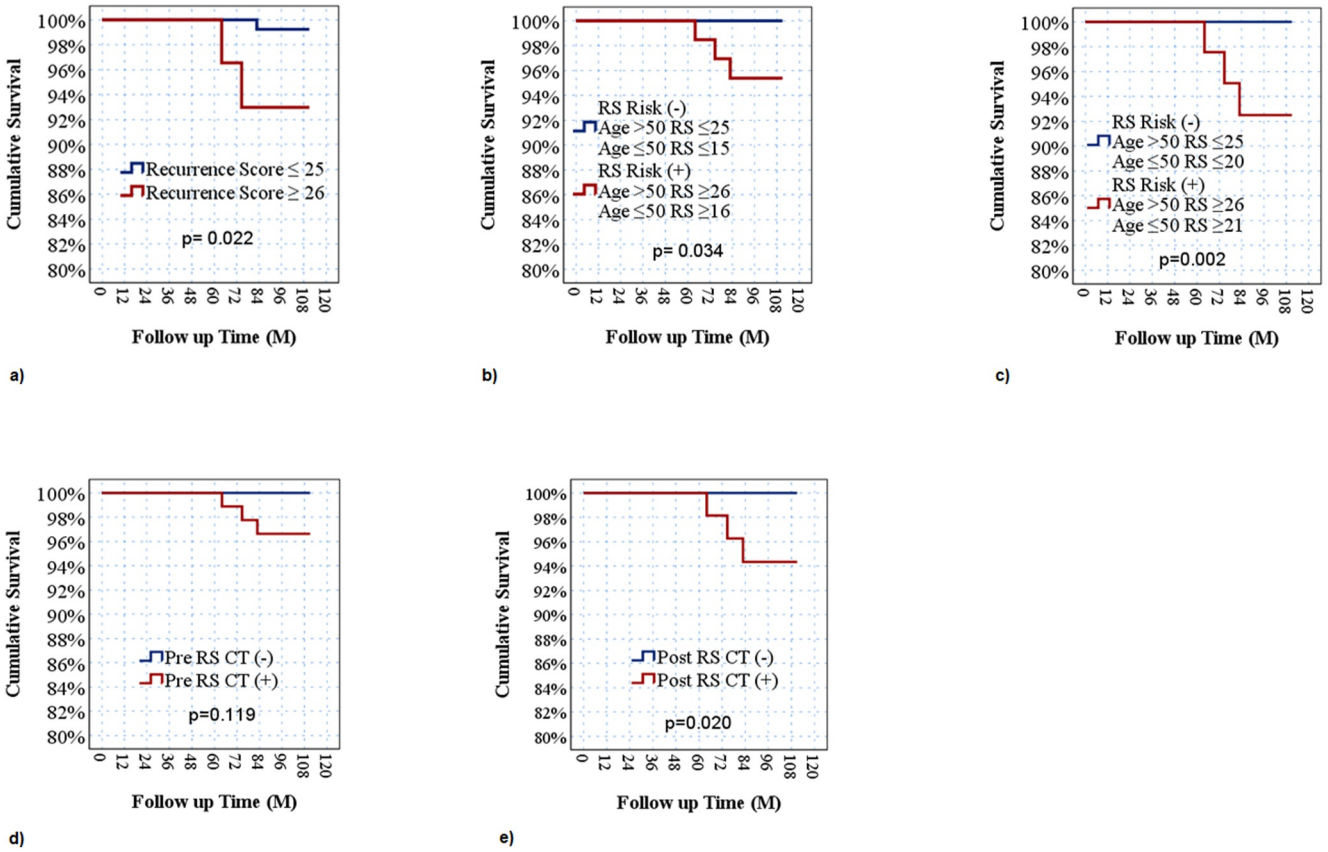

FIGURE 2 | Kaplan–Meier survival analysis: (a) overall survival of patients with ODX-RS ≤ compared with ODX-RS ≥ 26. (b) Overall survival for ages ≤ 50 and > 50 years with ODX-RS ≥ 16 and ODX-RS ≥ 26 cut-offs respectively. (c) Overall survival for ages ≤ 50 and > 50 years with ODX-RS ≥ 21 and ODX-RS ≥ 26 cut-offs respectively. (d) Overall survival of patients who received chemotherapy before ODX-RS and those who did not. (e) Overall survival of patients who received chemotherapy after ODX-RS and those who did not. M: months; RS: Oncotype-DX Recurrence Score. [Colour figure can be viewed at wileyonlinelibrary.com]

et al. updated the 12-year survival results of ODX-RS and concluded that ODX-RS is still prognostic for distant recurrence and OS [23]. The ability of the ODX-RS to predict long-term outcomes, such as MFS and OS, further supports its role in breast cancer management, allowing for more targeted and effective treatment plans.

This study raises important questions regarding the integration of genomic testing into clinical practice. The significant reduction in chemotherapy recommendations following ODX-RS testing underscores the need for oncologists to embrace genomic tools to enhance personalized treatment planning. However, the decision to utilize genomic testing should also consider factors such as cost, accessibility, and patient preferences, which may vary across different healthcare settings and populations [24–26]. As genomic testing becomes more prevalent, it is essential to ensure that these technologies are accessible to all patients, regardless of socioeconomic status, to avoid disparities in breast cancer care.

Despite the promising results, our study has several limitations. The relatively small sample size, resulting from the high cost of the test and funding limitations, may limit the generalizability of our findings and impede our ability to comprehensively capture late recurrences or long-term survival trends. Although our cost-effectiveness study found this test to be cost-effective in Türkiye, the Social Security Institution of Türkiye does not yet reimburse for it [26]. Additionally, the current database does not contain information on the presence or absence of ovarian function suppression. The results of the TAILORx and RxPONDER trials are also inconclusive as to the role of chemotherapy in inducing menopause [6, 10]. Therefore, it will be difficult to examine this effect in our study. Future research should aim to include larger, more diverse cohorts with longer follow-up periods and valid information about ovarian function suppression to validate these findings and explore the full potential of genomic assays in breast cancer treatment [27, 28].

Demonstrating the cost-effectiveness of ODX-RS test in developing countries is very important for its reimbursement by social security institutions. There are fewer studies in developing countries. Therefore, a further analysis was performed to investigate the cost effectiveness of the test. The use of the ODX-RS test reduced unnecessary chemotherapy and associated side effects, resulting in a cost saving of $2575.5 per patient and an ICER of $3787.5 per QALY gained, thereby demonstrating its cost-effectiveness in guiding adjuvant treatment decisions.

In conclusion, the ODX-RS significantly influences treatment decisions and serves as a valuable prognostic tool in HR-positive HER2-negative early-stage breast cancer patients. Different cut-offs has variable significant prognostic effect on survival prediction models. Its use in clinical practice enables a more personalized approach to treatment, reducing unnecessary

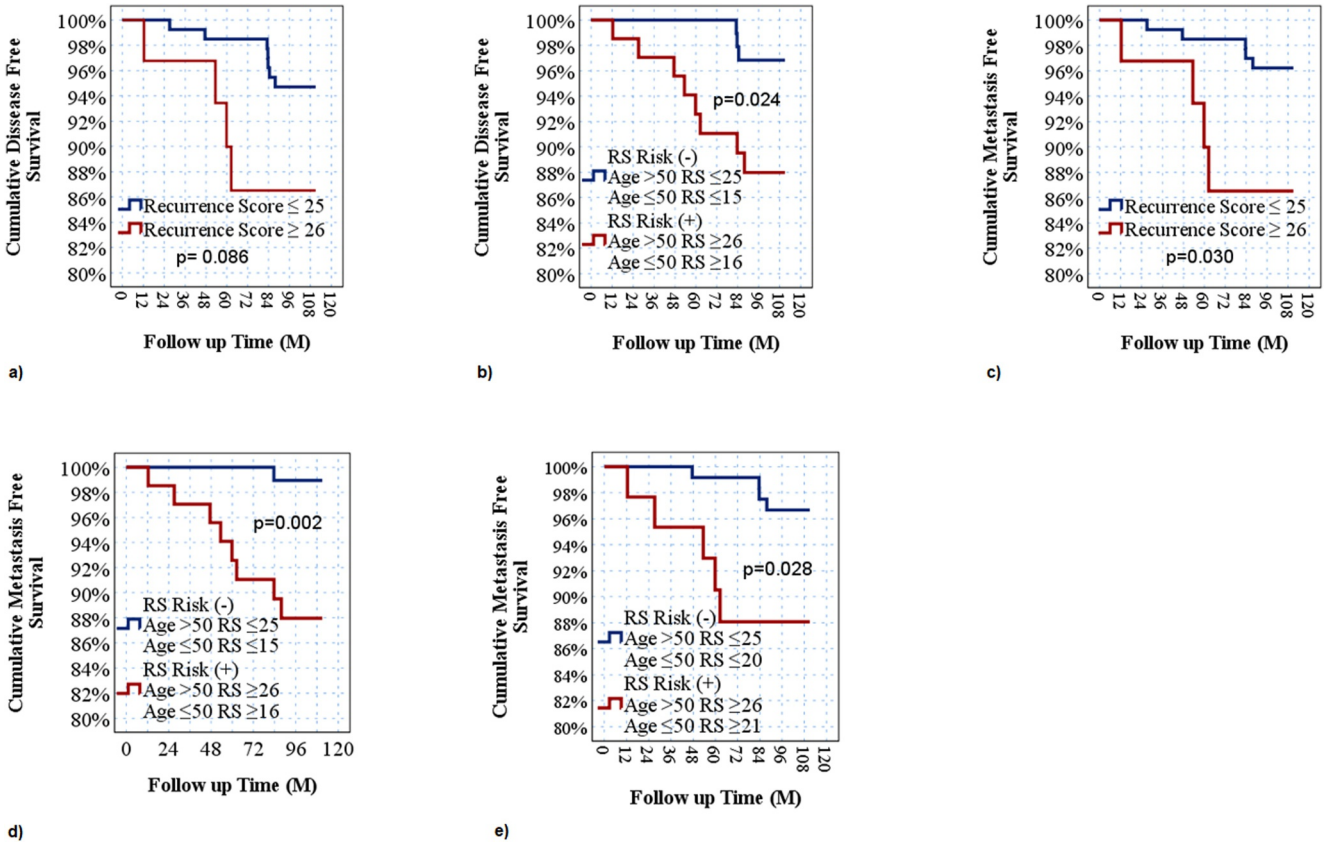

FIGURE 3 | Kaplan–Meier survival analysis: (a) disease-free survival of patients with ODX-RS ≤ compared with ODX-RS ≥ 26. (b) Disease-free survival for ages ≤ 50 and > 50 years with ODX-RS ≥ 16 and ODX-RS ≥ 26 cut-offs respectively. (c) Metastasis-free survival of patients with ODX-RS ≤ compared with ODX-RS ≥ 26. (d) Metastasis-free for ages ≤ 50 and > 50 years with ODX-RS ≥ 16 and ODX-RS ≥ 26 cut-offs respectively. (e) Metastasis-free for ages ≤ 50 and > 50 years with ODX-RS ≥ 21 and ODX-RS ≥ 26 cut-offs respectively. M: months; RS: Oncotype-DX recurrence score. [Colour figure can be viewed at wileyonlinelibrary.com]

TABLE 5 | Cost-effectiveness results for ODX-RS.

	Costs (USD)
Oncotype DX test	$3300.0
Mean pre-chemotherapy (92 patients)	$1135.6
Mean post-chemotherapy (43 patients)	$530.8
Chemotherapy adverse events	$468.5
Usual care-Oncotype DX test difference	$2575.5
QALY difference	0.68
ICER (USD per QALY gained)	$3787.5

Abbreviations: ICER: incremental cost-effectiveness ratio; QALY: quality-adjusted life year.

chemotherapy and its associated toxicities. A previous publication by Unal et al. with a median follow-up of 84 months ($n = 203$) also validated the reproducibility of the test in Turkish women [29]. Our study adds to the growing evidence supporting the integration of genomic testing into routine clinical decision-making, promoting tailored treatment strategies that enhance patient outcomes while minimizing harm. As genomic technologies continue to evolve, further research will be needed to explore their potential to improve cancer care and to address the challenges associated with their implementation in diverse healthcare settings.

Author Contributions

Enver Özkurt: data curation, formal analysis, investigation, validation, resources, writing – original draft, writing – review and editing. **Çetin Ordu:** writing – review and editing, resources, data curation, validation. **Ertan Koç:** data curation, formal analysis, software, writing – review and editing, visualization. **Erhan Gokmen:** writing – review and editing, resources, validation. **Mustafa Ozdogan:** validation, resources, writing – review and editing. **Nilufer Guler:** validation, resources, writing – review and editing. **Cihan Uras:** writing – review and editing, resources, validation. **Bahadır Öz:** writing – review and editing, resources, validation. **Orhan Demircan:** writing – review and editing, resources, validation. **Abdurrahman Isikdogan:** writing – review and editing, resources, validation. **Pinar Saip:** writing – review and editing, resources, validation, methodology, conceptualization. **Vahit Ozmen:** conceptualization, writing – review and editing, resources, funding acquisition, methodology, project administration, supervision, validation, visualization.

Conflicts of Interest

The authors declare no conflicts of interest.

Data Availability Statement

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

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