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A 10 year service evaluation of the survival of 439 patients with early oestrogen receptor positive breast cancer who underwent initial OncotypeDX ® testing to guide adjuvant chemotherapy decisions

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ABSTRACT

Objective: To explore the long-term outcome of patients who underwent Oncotype DX® testing. The relationship between the RS, adjuvant treatments received, and clinical outcomes across the entire range of RS results are reported.

Methods: 10-year Kaplan–Meier estimates for distant recurrence/BC-specific survival (BCSS) in this cohort. The analysis included 439 patients. The follow-up time ranged from 14 to 142 months. All analyses were performed using the SPSS v20.

Results: More than half of patients had low RS (<18) (55.6%) and 15.3% had RS ≥ 31. Chemotherapy use was consistent with the RS with 4.4%, 7.1%, 28.0%, 71.4% and 91.0% receiving adjuvant chemotherapy in patients with RS < 11, 11–17, 18–25, 26–30, and ≥31, respectively. The overall chemotherapy rate was 27.6%. Distant metastasis free survival (DMFS) differed significantly (P < 0.001) between the RS groups with 10 year DMFS rates of 99% (SE +/- 0.01) in the RS<11, 97% (SE +/- 0.03) in the RS 11–17, 97% (SE +/- 0.02) in the RS 18–25, 85% (SE +/- 0.1) in the RS 26–30 and 74% (SE +/- 0.08) in the RS ≥ 31 group. Ten year breast cancer specific survival also differed significantly (P < 0.001) between the RS groups; this risk was 100% (no deaths from breast cancer reported in the first 10 years) in RS < 11, 95% (SE +/- 0.03) in RS 11–17, 94% (SE +/- 0.04) in RS 18–25, 93% (SE +/- 0.07) in RS 26–30, and 79% (SE +/- 0.07) in the RS ≥ 31 group.

Conclusions: Use of Oncotype DX RS does guide the treatment decisions and correlates with the BCSS and disease-free survival for ER positive, Her2 negative, early-stage, node negative breast cancer patients.

Introduction

Breast cancer is the most common type of cancer in women with its incidence increasing by 3.1% every year [1,2]. Approximately 80% of the patients present with early breast cancer [3,4]. Most of these cancers are oestrogen receptor (ER) positive and human epidermal growth factor 2 (HER2) negative, with estimated 10-to-15-year recurrence rate of 15% to 35% after adjuvant chemotherapy for those deemed to need it [5,6]. This translates into an overall five-year survival rate of more than 94% in early stage breast cancer [5]. The current NICE guidelines recommend surgery followed by endocrine therapy in patients with small tumours with low risk of recurrence (tumours <2 cm, grade 1 or 2, node negative, ER/PR positive) and addition of chemotherapy in patients with high risk tumours [6]. Chemotherapy offers a minimal clinical benefit in most patients with intermediate risk of recurrence.

Further stratification of these patients is important to guide systemic therapy. Individualized treatment plans based on patient stratification according to the risk of recurrence has become an effective strategy in the management of patients with intermediate risk [7,8].

The Oncotype DX® assay is one of the gene expression analyses available which was developed to guide treatment decisions in ER/ PR positive, HER2 negative breast cancer, based on prognostication of subsequent outcomes in clinical trials [7]. Prediction of benefit from chemotherapy was initially established in the prospective-retrospective validation study including samples of the primary tumour from 651 patients enroled in the B20 trial with hormone receptor–positive,

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Table 1
Baseline patient and tumour characteristics.

	All patients $N = 439$	RS<11 $N = 90$	RS 11–17 $N = 154$	RS 18–25 $N = 107$	RS 26–30 $N = 21$	RS >30 $N = 67$	P value
Median follow-up, months	60(14–142)	59 (14–142)	60 (19–137)	60 (25–138)	62 (25–128)	54 (20—137)	0.371
Mean (SD)	63.5 (28.3)	64.4 (30.2)	63.4 (27.3)	62.4 (25.0)	74.9 (35.8)	60.8 (30.4)	
Age; Mean (SD) years	58.3 (10.4)	59.0 (9.2)	58 (10.5)	58.3 (10.4)	57.4 (11.8)	58.9 (11.4)	0.920
Age; Median (range), years	59 (29–83)	59 (38–79)	59 (32–82)	59 (34–79)	57 (29–74)	62 (35–83)	
Age Category, n (%)							
<40 years	22 (5.0%)	1 (1.1%)	8 (5.2%)	7 (6.5%)	2 (9.5%)	4 (6.0%)	0.592
40–49 years	67 (15.3%)	15 (16.7%)	26 (16.9%)	12 (11.2%)	2 (9.5%)	12 (17.9%)	
50–59 years	137 (31.2%)	30 (33.3%)	44 (28.6%)	41 (38.3%)	8 (38.1%)	14 (20.9%)	
60–69 years	154 (35.1%)	35 (38.9%)	54 (35.1%)	33 (30.8%)	6 (28.6%)	26 (38.8%)	
>70 years	59 (13.4%)	9 (10.0%)	22 (14.3%)	14 (13.1%)	3 (14.3%)	11 (16.4%)	
Tumour size; Median (range), cm	2.1 (0.5–7.5)	2.1 (0.5–7.5)	2.0 (0.5–9.0)	2.1 (0.7–9.1)	2.0 (0.9–4)	2.2 (0.5–4.5)	0.452
Mean (SD), cm	2. (1.2)	2.2 (1.2)	2.3 (1.2)	2.5 (1.5)	2.1 (0.8)	2.2 (0.7)	
Tumour size category, *n* (%)							
≤1 cm	45 (10.3%)	13 (14.4%)	12 (7.8%)	14 (13.1%)	2 (9.5%)	4 (6.0%)	
>1 - 2 cm	160 (36.4%)	29 (32.2%)	65 (42.2%)	36 (33.6%)	10 (47.6%)	20 (29.9%)	0.130
>2–3 cm	165 (37.6%)	35 (38.9%)	52 (33.8%)	35 (32.7%)	7 (33.3%)	37 (53.7%)	
>3cm	69 (15.7%)	13 (14.4%)	25 (16.2%)	22 (20.6%)	2 (9.5%)	7 (10.4%)	
Grade 1; *n* (%)	60 (13.7%)	16 (17.8%)	27 (17.5%)	15 (14.0%)	1 (4.8%)	1 (1.5%)	
Grade 2; *n* (%)	300 (68.3%)	72 (80.0%)	116 (75.3%)	76 (71.0%)	13 (61.9%)	23 (34.3%)	*P*<0.001
Grade 3; *n* (%)	79 (18.0%)	2 (2.2%)	11 (7.1%)	16 (15.0%)	7 (33.3%)	43 (64.2%)	
Node status; 0	393 (89.5%)	77 (85.6%)	139 (90.3%)	96 (89.7%)	21 (100%)	60 (89.6%)	
Mic	46 (10.5%)	13 (14.4%)	15 (9.7%)	11 (10.3%)	0 (0.0%)	7 (10.4%)	0.646
NPI; Median (range)	3.4(2.1–5.5)	3.4 (2.1- 4.5)	3.4 (2.1–4.8)	3.4 (2.1–5.1)	3.5 (2.4–4.6)	4.4 (2.6–5.5)	<0.001
Mean (SD),	3.5 (0.6)	3.4 (0.5)	3.4 (0.6)	3.5 (0.6)	3.7 (0.6)	4.1 (0.6)	
Histology, *n* (%)							
IDC	352 (80.2%)	66 (73.3%)	120 (77.9%)	84 (78.5%)	19 (90.5%)	63 (94.0%)	0.105
ILC	66 (15.0%)	15(16.7%)	26 (16.9%)	20 (18.7%)	2 (9.5%)	3 (4.5%)	
Mucinous/colloid	10 (2.3%)	5 (5.6%)	2 (1.3%)	2 (1.9%)	0 (0.0%)	1 (1.5%)	
Other/unknown	11 (2.5%)	4 (4.4%)	6 (3.8%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	
ER positive	438(99.8%)	90 (100.0%)	154 (100.0%)	107 (100.0%)	21 (100.0%)	66 (98.5%)	0.234
PR Positive	381 (86.8%)	89 (98.9%)	145 (94.2%)	94 (87.9%)	15 (71.4%)	38 (56.7%)	<0.001
Lympho-vascular invasion; Yes	80 (19.3%)	16 (19.3%)	21 (14.4%)	21 (20.8%)	4 (21.1%)	18 (27.7%)	0.265
($n = 414$) No	334 (81.7%)	67 (80.7%)	125 (85.6%)	80 (79.2%)	15 (78.9%)	47 (72.3%)	
Chemotherapy; Yes	121 (27.6%)	4 (4.4%)	11 (7.1%)	30 (28.0%)	15 (71.4%)	61 (91.0%)	<0.001
No	318 (72.4%)	86 (95.6%)	143 (92.9%)	77 (72.0%)	6 (28.6%)	6 (9.0%)	

Abbreviations: IDC, invasive ductal carcinoma; ILC, invasive lobular carcinoma.

axillary node-negative breast cancer. In this trial, patients were randomized to tamoxifen or chemotherapy plus tamoxifen. Based on the expression levels of 21 genes, the test calculated a risk recurrence score (RS) from 0 to 100. In this initial validation study, high RS was defined as 31 to 100 irrespective of HER2 expression ($n = 651$), or 26 to 100 in tumour samples that had a low HER2 RNA expression score ($n = 569$), whereas, intermediate RS was defined as 18–30, and low-risk as 0–17 [9]. This study confirmed a correlation between the use of adjuvant chemotherapy treatment and increasing RS (likelihood ratio test on interaction, $P = 0.01$), which was statistically significant. Ten-year distant recurrence-free survival rates were 62% (95% CI, 48%−81%) with tamoxifen alone, and 88% (95% CI, 81%−95%) with chemotherapy plus tamoxifen. A high RS was found not only to be prognostic for a high distant recurrence rate, but was also predictive of benefit from adjuvant chemotherapy. In other cohorts, with low Oncotype Recurrence Scores, distant recurrence-free survival rates were similar with endocrine therapy alone [7,9].

Later, prospective trials and registry-based studies have consistently shown no benefit from the addition of chemotherapy in patients with low-risk Oncotype DX® [10–16]. Studies have also shown the benefit of chemotherapy in high-risk patients identified by the Oncotype DX® assay [14–16]. For the intermediate risk group, a large randomized trial, TAILORx, demonstrated that endocrine therapy alone was non-inferior to adjuvant chemotherapy plus endocrine therapy in the overall population with a RS of 11 to 25, the primary trial end point. An exploratory analysis of this trial did show some chemotherapy benefit for patients aged 50 years or younger with a RS of 16 to 25 [16]. TAILORx also demonstrated a low distant recurrence rate of 1% at 5 years and 3% at 9 years with endocrine therapy alone if the RS was 0 to 10 irrespective of age, and that integration of clinical features with RS provided additional prognostic information for recurrence but not prediction of chemotherapy benefit [14–17].

Many international guidelines endorse the use of Oncotype DX®; National Institute for Health and Care Excellence (NICE), American Society of Clinical Oncology (ASCO) and the National Comprehensive Cancer Network (NCCN) [6,18–21].

In this study, we report the outcome for all patients who underwent Oncotype DX® testing between 2010 and 2019. The relationship between the RS, adjuvant treatments received, and clinical outcomes across the entire range of RS results are reported. This analysis was conducted as a part of service evaluation of our current practices in managing early-stage breast cancer.

Materials and methods

We identified all ER positive/ HER2 negative, lymph node negative breast cancer patients who were diagnosed from 2010 to 2019 in Hywel Dda University Health Board using the Cancer Network Information System Cymru (CANISC) database ($n = 2524$). This data was linked with Oncotype DX® test results held on the Welsh Clinical Portal. This series includes all consecutive cases that had Oncotype DX® testing over this timeframe. The study was limited to women aged ≥18 years who were diagnosed with stage I to IIIA, first primary, hormone receptor (ER or PR)-positive, HER2-negative breast cancer (according to American Society of Clinical Oncology/College of American Pathologists guidelines) [22,23] and underwent Oncotype DX® testing. The study also includes data for 136 patients who were part of the initial trial to assess the cost effectiveness of Oncotype DX® in UK [24]. Patients with DCIS (stage = 0) were excluded from the study. Patients with node positive breast cancer diagnosed after 2016 were also excluded as they are part of the

nation-wide node positive Oncotype DX® trial. Patients with no follow-up were also excluded. The final data contained a total of 439 patients.

The CANISC database provided patient's clinical information including year of diagnosis, age, tumour type, grade, stage, and receptor status. The data on follow-up was extracted from the Welsh patient administration system (PAS).

Staging was determined using the 8th American Joint Committee on Cancer (AJCC) definitions [25]. ER positivity was defined as ≥1% of cancer cell nuclei staining positive [22]. All cases were HER2 negative defined by the initial and updated ASCO/CAP recommendations [24].

The eligible cohort was divided into five groups by age (≤ 35, 36–50, 51–65, 66–80, >80 years). These cut-offs were selected based on previously reported studies [14,26].

Oncotype DX® test results were provided as continuous recurrence-risk scores and during analysis were stratified into 5 categories: RS of 0–10, RS 11–17, RS 18–25, RS 26–30 and RS 31–100 in accordance with the stratification standard of the initial Oncotype DX® study and TAILORx trial [14–16].

The primary outcome of this study was breast cancer specific survival (BCSS) and secondary outcomes were distant metastasis free survival (DMFS) and loco regional recurrence free survival. To investigate the primary objective, in each age group, the percentages of patient in each of the RS risk categories were calculated. The rates of adjuvant chemotherapy were also assessed within each RS risk category according to the chemotherapy records obtained from CANISC database. Kaplan-Meier curves were plotted and compared for survival probability using the log-rank tests between patients with chemotherapy records of "Yes" and "No". P-values of <0.05 were considered significant. For the secondary outcome, distant metastasis free survival was defined as the time from initial diagnosis to the first distant recurrence. Locoregional recurrence was defined as recurrence of disease within the treated breast or axilla without any evidence of distant metastasis. We examined the distant metastasis free survival and its correlation with RS and other clinicopathologic features.

Estimates of ten-year overall survival (OS), BCSS and distant metastasis free survival with Standard Error (SE) were obtained by the Kaplan Meier method. Comparisons of DFS or BCSS amongst subgroups used pairwise log-rank tests (reported as significant for $p < 0.05$).

Univariate and multivariate Cox proportional hazard models for DFS were estimated; RS was coded as low, intermediate and high, age was coded as less than 50 versus 50 year or more, size as ≤2 cm and >2 cm and grades were coded as grade 3 versus grade 1–2.

All analyses were performed using the SPSS v20. Descriptive statistics were used to summarize the data according to patient and tumour characteristics. T-test and chi-squared test were performed to determine the differences in continuous and categorical patient characteristics. All tests were two-sided if applicable and statistical significance was assessed using an alpha of 0.05. The mean and standard deviations were calculated for normally distributed numeric covariates, while frequency and its percentage were shown for categorical variables. One-way ANOVA test or Kruskal–Wallis test was performed for numerical covariates if appropriate. Chi-square test or Fisher's exact test was employed for categorical covariates where appropriate.

Results

Patient characteristics

The final total number of patients with complete data was 439. Table 1 shows patient/tumour characteristics for the cohort. The median age was 59 (range: 29–83) years, 76.5% (336/439) were ≥ 50 years. Most of the tumours were grade 2 (300/439, 68.3%), 205/439 (46.7%) had tumours ≤ 2 cm in size, and 80.2% (352/439) had invasive ductal carcinoma Figs. 4–6.

Follow up ranged from 14 to 142 months (median 60 months). 250/439 (56.9%) of patients completed the 60 months of follow-up, whereas more than a quarter of patients (29.6%) had follow up of more than 60 months.

Table 2
Patient and Tumour Characteristics and use of Chemotherapy.

	All patients $N = 439$	Patients not treated with chemotherapy $N = 318$ (72.4%)	Patients treated with chemotherapy $N = 121$ (27.6%)	P value
Age; Mean (SD) years	58.4 (10.4)	59.3 (10.2)	56.1 (10.7)	0.004
Median (range), years	59 (29–83)	60.5 (32–83)	57 (29–76)	
Age Category, n (%)				
<40 years	22 (5.0%)	12 (3.8%)	10 (8.3%)	0.004
40–49 years	67 (15.3%)	42 (13.2%)	25 (20.7%)	
50–59 years	137 (31.0%)	100 (31.4%)	37 (30.6%)	
60–69 years	154 (35.1%)	117 (36.8%)	37 (30.6%)	
>70 years	59 (13.3%)	47 (14.8%)	12 (9.9%)	
Tumour size; Median (range), cm	2.1 (0.5–9.1)	2.1 (0.5–9)	2.2 (0.6–6)	0.767
Mean (SD), cm	2.3 (1.2)	2.3 (1.3)	2.3 (1.0)	
Tumour size category, *n* (%)				
≤1 cm	45 (10.3%)	34 (10.7%)	11 (9.1%)	
>1 - 2 cm	160 (36.4%)	123 (38.7%)	37 (30.6%)	0.201
>2–3 cm	165 (37.6%)	110 (34.6%)	55 (45.5%)	
>3cm	69 (15.7%)	51 (16.0%)	18 (14.9%)	
Grade 1	60 (13.7%)	52 (16.4%)	8 (6.6%)	<0.001
Grade 2	300 (68.3%)	238 (74.8%)	62 (51.2%)	
Grade 3	79 (18.0%)	28 (8.8%)	51 (42.2%)	
Node status; 0	393 (89.5%)	284 (89.3%)	109 (90.1%)	0.660
Mic	46 (10.5%)	34 (10.7%)	12 (9.9%)	
ER positive	438 (99.8%)	318 (100.0%)	120 (99.2%)	0.276
PR positive	381 (86.8%)	294 (92.5%)	87 (71.9%)	<0.001
Lymphovascular invasion (n = 414)				
Yes	80 (19.3%)	49 (16.4%)	31 (26.7%)	0.014
No	334 (80.7%)	249 (83.6%)	85 (73.3%)	
NPI; Median (range),	3.4 (2.1–5.5)	3. (2.1- 5.5)	3.8 (2.1–5.5)	<0.001
Mean (SD),	3.6 (0.6)	3.4 (0.6)	3.9 (0.6)	
Histology, *n* (%)				
IDC	352 (80.2%)	243 (76.4%)	109 (90.1%)	0.083
ILC	66 (15.0%)	57 (17.9%)	9 (7.4%)	
Mucinous/colloid	10 (2.3%)	8 (2.5%)	2 (1.7%)	
Other/unknown	11 (2.5%)	10 (3.2%)	1 (0.8%)	

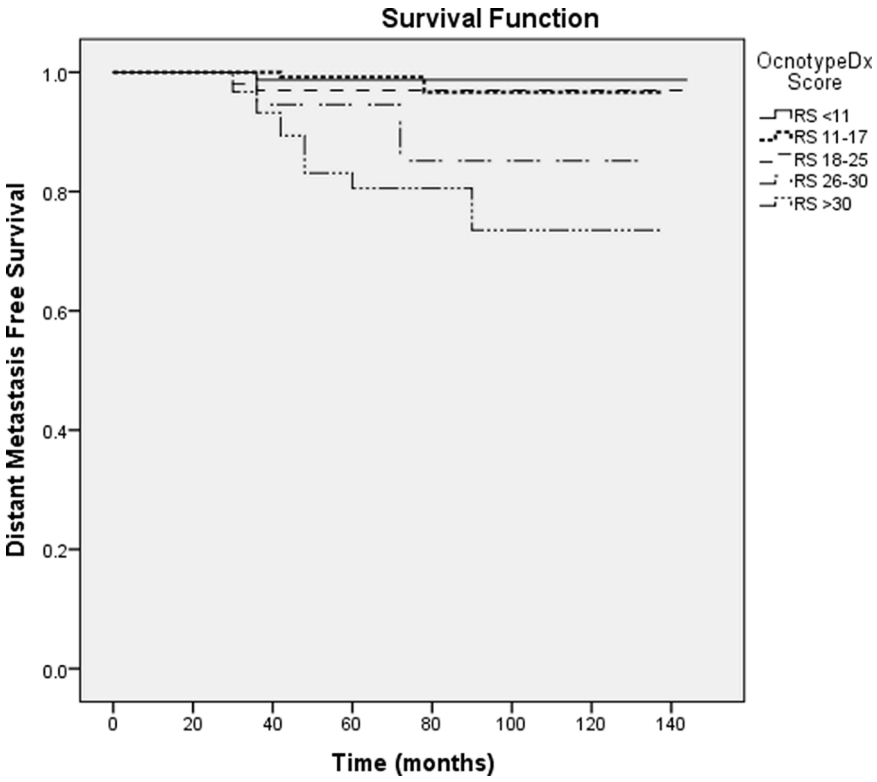

Fig. 1. Distant metastasis free survival.

RS distribution and patient characteristics within RS subgroups

Recurrence-Risk score distribution for the 439 patients is shown in Table 1. More than half of patients had low RS (<18) (55.6%, 244/439) and 15.3% (67/439) had RS ≥ 31. A wide RS distribution was observed within each level of clinic-pathological characteristic including age, tumour grade, and tumour size (Table 1). Patient characteristics in RS subgroups (<11,

11–17, 18–25, 26–30, and ≥31) were not statistically different with respect to age, tumour size or histological type (Table 1). The lower RS groups had a higher proportion of pathological grade 1 tumours and a lower proportion of grade 3 tumours. Lower RS was also noted in low Nottingham prognostic index (NPI) tumours. Patients with very low risk by clinic-pathological characteristics (grade 1 and tumour size ≤1 cm) ($n = 16$) were observed in all RS subgroups; RS<11 ($n = 6$), RS 11–17 ($n = 4$) RS 18–25 ($n = 6$).

Thirty patients had Oncotype DX® testing done for tumours which were less than 2 cm and grade 1. Of these 9/30 had micro-metastasis and 1/30 had bilateral breast cancer. Most of these tests on small (<1 cm), grade 1 tumours were done in the initial years of our experience with Oncotype DX® testing, with none in the last 3 years.

Chemotherapy use was consistent with the RS with 4.4% (4/90), 7.1% (11/154), 28.0% (30/107), 71.4% (15/21) and 91.0% (61/67) receiving adjuvant chemotherapy in patients with RS < 11, 11–17, 18–25, 26–30, and ≥31, respectively. The overall chemotherapy rate was 27.6% (121/439). Chemotherapy-treated and untreated patients were similar with respect to clinic-pathological characteristics except median grade distribution, PR positivity and median NPI scores (Table 2). A 3rd generation chemotherapy regimen containing both an Anthracycline and a Taxane was most common, accounting for 65.9% of cases, followed by an anthracycline only regime (26.8%).

In the RS group 26–30, six patients did not receive chemotherapy (2 refused and in 4 patients a mutual decision was made by the oncologist and patient for not proceeding with chemotherapy as the risks would have outweighed the benefits (age> 65 years and small tumours in 3 patients and small tumour in one patient). Similarly, in the RS group > 30, 4 patients refused chemotherapy and in 2 patients mutual decision was made by the oncologist and the patient (age >80 years in one patient and small tumour in the other patient).

Table 3
Univariate analysis on the entire cohort (chemotherapy-treated and untreated). The analysis evaluated the association between the variables and distant recurrence.

Variable	Comparison	Hazard Ratio for Distant recurrence (95% confidence intervals)	*P*-value
Age	≥50 versus <50 years	1.55 (0.574–4.210)	0.272
Size	≥2 versus <2cm	2.12 (0.731–6.175)	0.054
Grade	3 versus 1/2	1.71 (0.596–4.908)	0.244
RS group	≥31 versus <18	15.78 (4.261–58.440)	<0.001
	18–30 versus <18	3.24 (0.762–13.777)	0.097
	≥31 versus <31	8.321 (3.186–21.731)	<0.001

Abbreviation: RS, recurrence Score.

Distant metastasis free survival and loco regional recurrence free survival (Fig. 1)

With a median follow-up of 60 months, 19 distant metastases were documented: 1/90 (1.1%), 2/154 (1.3%), 3/107 (2.8%), 2/21 (9.5%), and 11/67 (16.4%) in patients with RS results <11, 11–17, 18–25, 26–30, and ≥31, respectively. Another 5 patients had loco-regional recurrences without any evidence of distant metastasis and 4 patients developed contralateral disease.

Kaplan–Meier (KM) estimates for distant metastasis free survival differed significantly ($P < 0.001$) between the RS groups with 10 year DMFS rates of 99% (SE +/- 0.01) in the RS<11, 97% (SE +/- 0.03) in the RS 11–17, 97% (SE +/- 0.02) in the RS 18–25, 85% (SE +/- 0.1) in the RS 26–30 and 74% (SE +/- 0.08) in the RS ≥ 31 group. KM estimates for

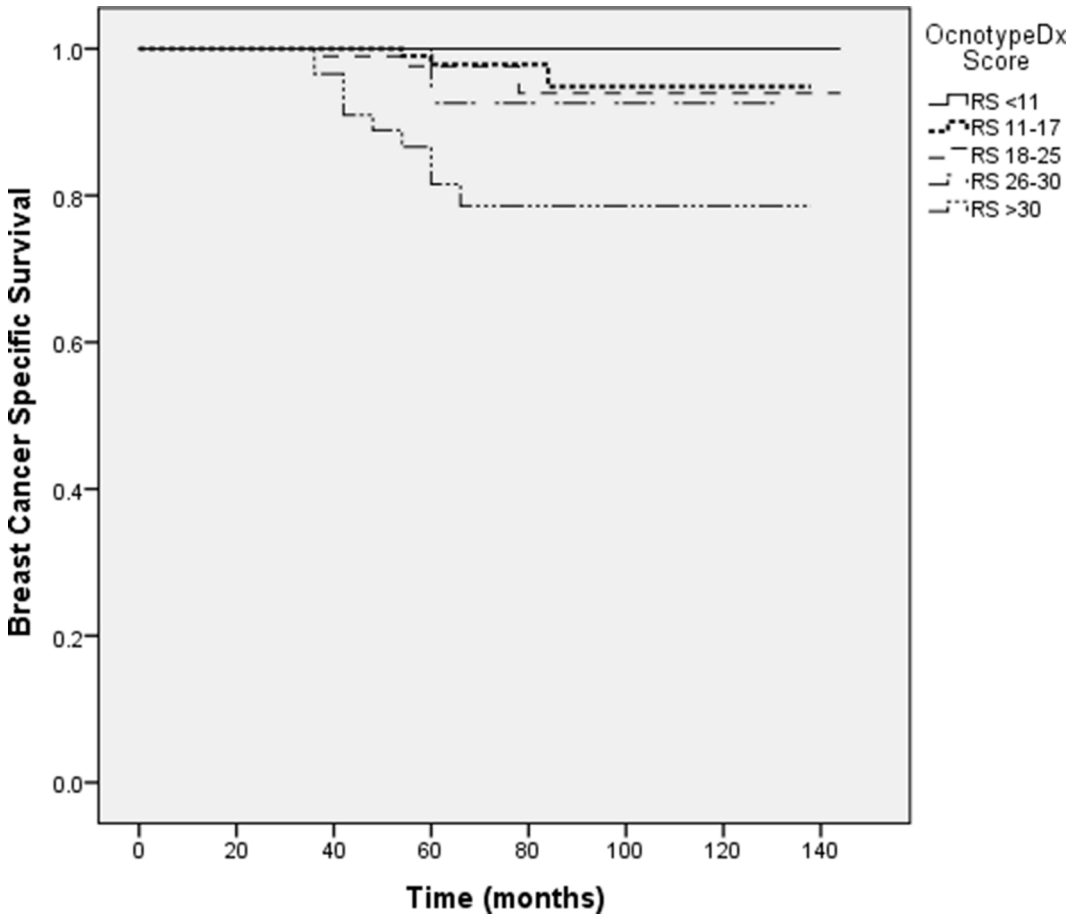

Fig. 2. Breast cancer specific survival.

distant metastasis free survival by recurrence score are presented in Fig. 1. It is important to emphasize that patients were not randomized to treatment and a selection bias for choice of therapy cannot be ruled out.

Table 3 presents subgroup analyses evaluating the rate of distant recurrence by age, tumour size, grade and recurrence score. Patients with high recurrence score were significantly more likely to develop distant metastasis.

Breast cancer death rates

Seventeen BC specific deaths were documented; 0/90 (0%), 3/154 (1.9%), 3/107 (2.8%), 1/21 (4.8%) and 10/67 (14.9%) in the RS $<$ 11, RS 11–17, RS 18–25, RS 26–30, and RS $\geq$ 31 groups, respectively. KM estimates for the 10 years breast cancer survival differed significantly ($P < 0.001$) between the RS groups (Fig. 2); Breast cancer specific survival rate was 100% (no deaths from breast cancer reported in the first 10 years) in RS $<$ 11, 95% (SE +/- 0.03) in RS 11–17, 94% (SE +/- 0.04) in RS 18–25, 93% (SE +/- 0.07) in RS 26–30, and 79% (SE +/- 0.06) in the RS $\geq$ 31 group.

Seven deaths were reported from other medical causes (severe aortic stenosis, cardiac failure, chronic liver disease). Overall survival is shown in Fig. 3.

Discussion

This study shows a statistically significant association between the RS and the BCSS and disease-free survival for ER positive, HER2 negative, node negative breast cancer patients with intermediate risk of recurrence. Use of Oncotype testing has become a key component in the clinical decision making in the above subgroup.

Our analysis included all RS-tested patients with node negative or micrometastatic disease in nodes, regardless of tumour size/grade. The pathological characteristics of the patients in our analysis is similar to those reported by others in the Western Hemisphere and in NSABP 20 and TAILORx [8,16,27,28,34]. The median age in our cohort was 56 years which was similar to that reported in Calilt data and other studies reported from UK [27–29,33]. The median age of patients in TAILORx, and plan B trial was lower, as the Oncotype was not done on patients older than 75 years in these trials [17,31].

Our cohort had a larger mean tumour size as compared to TAILORx cohort, Calilt data or SEER data [17,30,32]. In our series, mean tumour size was 2.3 cm (0.5–9.1 cm) which is similar to other studies from UK [27]. In our cohort only 47% of patients had tumour size less than 2 cm as compared to 75% in TAILORx and 77% in SEER data. 35/445 (7.8%) of patients in our cohort, with grade 1 tumours, less than 2 cm would not have been eligible for Oncotype based on NICE guidelines (which were published later). Our data shows that request for Oncotype testing is quite consistent with NICE guidelines which recommends gene profile testing done in the group with intermediate risk of recurrence, i.e., tumours >2 cm with grade 2/3 and smaller grade 3 tumours. Within the different RS groups, there was no statistically significant difference in the mean tumour size, highlighting the fact that gene profiling is more predictive of clinical outcome and response to chemotherapy as compared to size measurements. Our patients are a mix of screen detected and symptomatic patients and this may account for the larger mean tumour size.

Our cohort seems to have lower proportion of grade 1 tumours (14%) compared with TAILORx (25.8%) and SEER data (28.8%) however, it is consistent with grade distribution seen in Calilt data (14.3%) and more than those in plan B trial (5.1%) [17,30,31]. In our cohort, median NPI

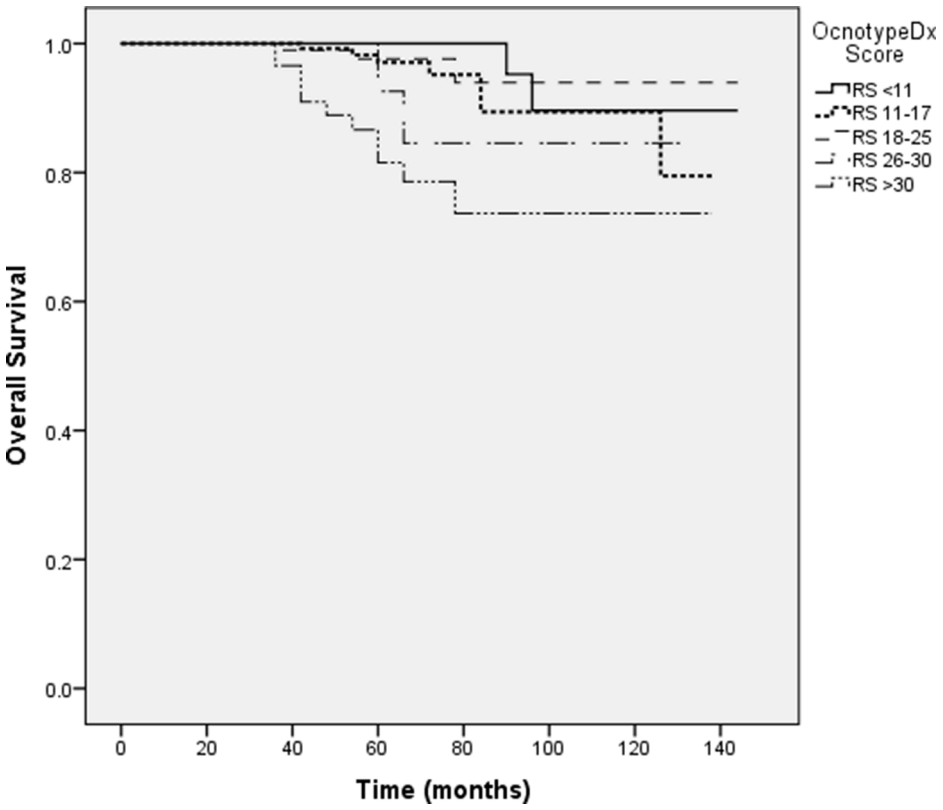

Fig. 3. Overall survival.

was lower than reported in the audit by Green et al. (3.4 vs. 3.69) [29].

The rate of chemotherapy use in our series is 27.6% in patients who underwent the Oncotype DX® testing which is similar to other UK studies [27,33], and to the results reported in a meta-analysis of international studies [35]. 4.4% of our patients with RS < 11 received chemotherapy which was consistent with real life data from Clalit registry (1.4% received chemotherapy) and National Cancer Data Base (NCDB) (4.8% received chemotherapy) [30,35]. Most of these patients received chemotherapy early on in our experience with Oncotype DX® testing (before 2016). The rate of chemotherapy use has decreased as we have gained more confidence in using Oncotype DX® testing. No patients have received chemotherapy in last 3 years where the RS was 11 or less. In our centre, prior to ordering Oncotype DX®, a cut-off of RS is decided in the Multi-disciplinary meeting dictated by patient's and tumour characteristics, such as age, performance status, tumour grade (for example 25 for post-menopausal women and 18 for premenopausal women), based on TAILORx results. Hence, we can see that a large proportion of patients with RS of < 18 did not receive chemotherapy and the rate of chemotherapy increased as the RS increased from 18–30.

For the RS < 11 group (which in our cohort included 1.4% chemotherapy-treated patients), the 5-year disease free survival rate was 99%, which is comparable to that reported in TAILORx [17]. Our findings are also similar to the findings reported in the SEER data, which demonstrated excellent 5-year BCSS survival in >11,000 node negative, HR+ HER2- BC patients with RS < 11 of 99.6% [36,37]. Similar outcome data were reported by the Nitz et al. for the WSG PlanB trial for patients with RS ≤ 11 who did not receive adjuvant chemotherapy (n = 348), where 3-year disease-free survival was 98% [31]. For patients with RS 12–25 and those with RS > 25, BCSS remain low in our study and is reasonably consistent with the rates reported in TAILORx trial; 10-year disease-free survival of 93%+/−0.07 and 78% +/- 0.06 vs. 93.8% ±0.5 and 89.3% ±1.4, respectively [17]. It is clear that if hormonal treatment compliance is excellent (and checked at follow up), its use in the low risk group provides excellent disease free survival and overall survival rates. Chemotherapy avoidance reduces the burden on an already stretched National Health Service in terms of cost of the drugs, hospital visits and admissions as well as avoiding the inconvenience, financial burden and side effects of chemotherapy for the patient.

The Oncotype DX® Recurrence Score is, and should always remain, an additional tool when consultant/patient discussion takes place. We believe that it should not be used as a sole arbiter for chemotherapy decisions. The patient's general health, personal preferences and traditional histopathological features should always play a part in the decision for or against chemotherapy. That 4.3% for those with recurrent score less than 11 and 27.8% for those with recurrent score 18 to 25 getting chemotherapy is evidence for this flexibility in clinical practice. Over time we have become more confident that Oncotype DX® provides a reliable prediction of chemotherapy benefit particularly in patients with an intermediate risk of recurrence.

We provide, with indirect evidence, that micro-metastatic disease in the sentinel lymph node(s) is suitable for RS testing regardless of the grade of the tumour, although, as mentioned above, a careful discussion with the patient is needed. Our cohort included lobular cancers which are considered less responsive to chemotherapy, and we plan a future sub analysis of this group. There remain several important unanswered questions. If the RS is high, which chemotherapy would be the best choice? There could be strong argument made to extend the Oncotype DX® test to include other genetic markers for resistance or susceptibility to specific chemotherapies where the RS is high.

Since Oncotype testing is only validated in HR positive breast cancers, there is need for a similar test to be developed to guide chemotherapy decisions in the 20% of patients who are HR negative. Other 2nd generation tests, for example Prosigna, provide additional information beyond dividing the tumour into low, intermediate or high risk, also provide 10-year risk of recurrence (ROR) score and intrinsic subtype of tumour which may be of benefit in patients with triple negative and HER2 positive breast cancer.

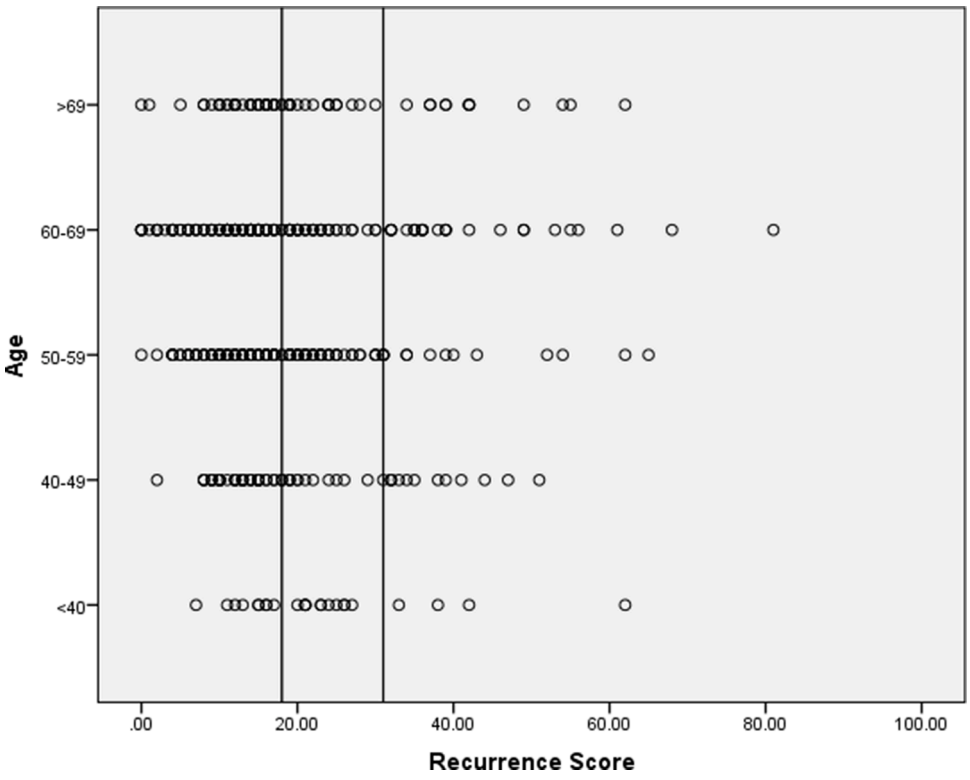

Fig. 4. Age vs. RS.

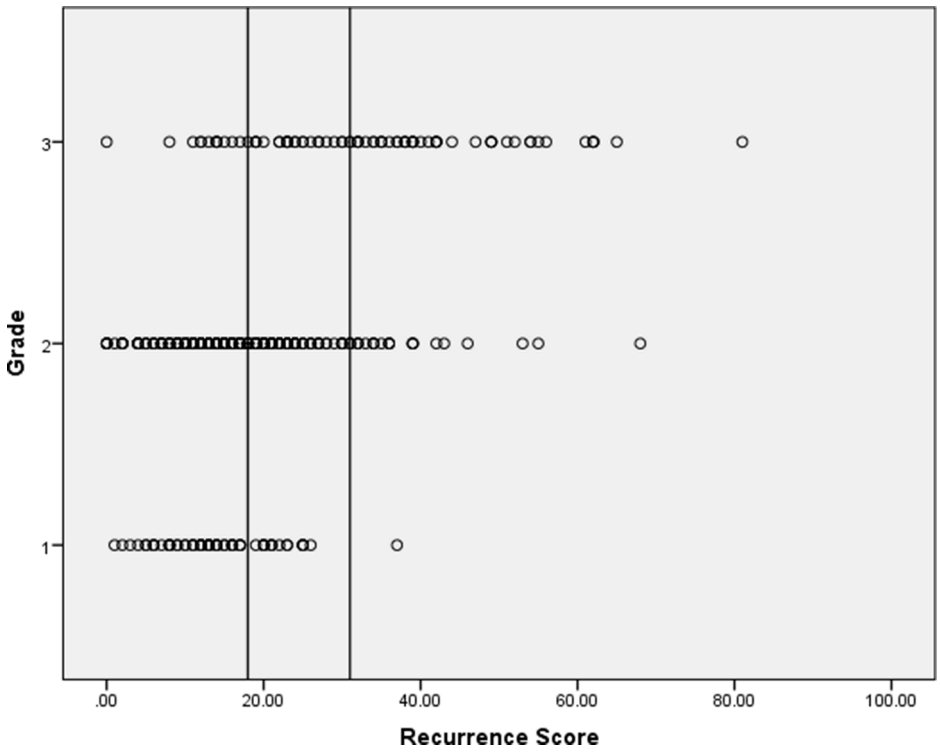

Fig. 5. Grade vs. RS.

Our results clearly demonstrate which patients can safely avoid chemotherapy but, in those needing chemotherapy, there are still a good proportion who do not benefit, either because they were never at risk of recurrence, or were given an ineffective chemotherapy regimen which did not prevent their recurrence.

Our study is based on prospectively maintained registry data and is representative of clinical practice at a local level. However, there are limitations to this study. The data are from a single health board/geographical area with a poorer, older and more uniform ethnic demographic than generally found in the UK. Moreover, the data were not

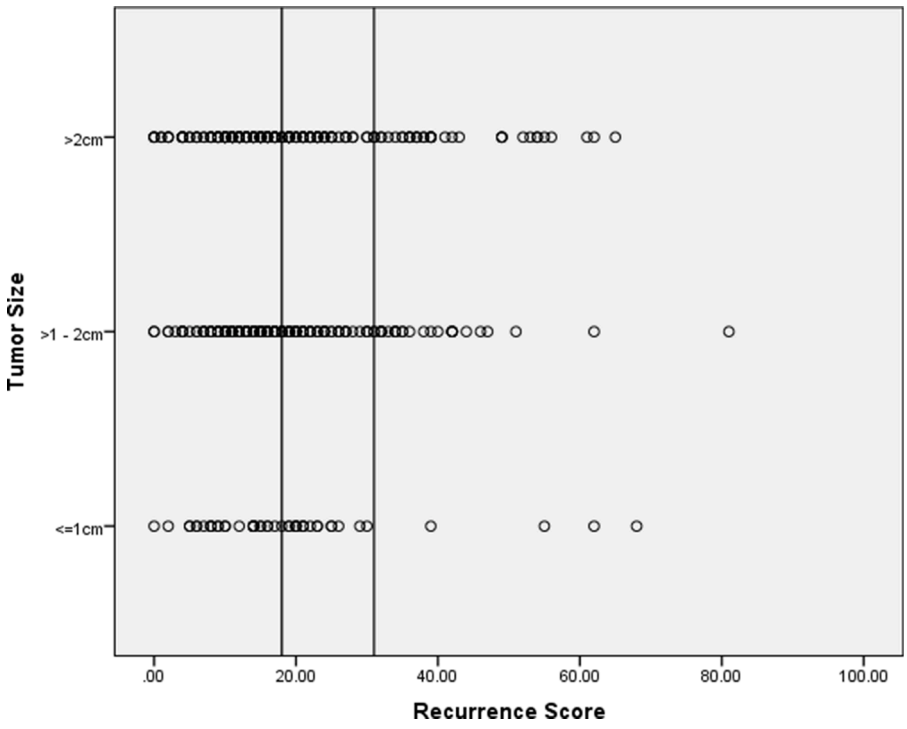

Fig. 6. Tumor Size vs. RS.

stratified according to the age, socio-economic or ethnicity, hence no inference can be made regarding its application in other parts of the world. Secondly, the patients were not randomized and chemotherapy decisions were not made uniformly, and, therefore, a selection bias exists both at the level of who got tested and how the RS was interpreted. Thirdly, the median follow-up of 60 months is relatively short for ER positive, HER2 negative, node negative breast cancer patients, where late recurrence remains a problem.

We conclude from this study that the RS does guide the treatment decisions and correlate with the BCSS and disease-free survival for ER positive, HER2 negative, early-stage node negative breast cancer patients.

Ethical approval

This study was part of service evaluation and was deemed exempt from human protection oversight by the Institutional Review Board as well as patient consenting was waived. (Service Evaluation form: appendix 1)

Author contributions statement

I can confirm that each author has contributed equally to the study, data collection and manuscript writing.

Declaration of Competing Interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests:

Simon Holt reports a relationship with Exact Sciences Corporation that includes: consulting or advisory. Mr Holt is on the advisory board of Exact Sciences and the test for the *initial* trial**,** in which some of these patients were involved were provided free of charge by them. Asma Munir, Anita Marie Huws, Sohail Khan, Dr Mark Davies, Saira Khawaja, Yousef Shariaha have no conflict of interest.

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