



Comparison of the Nottingham Prognostic Index and OncotypeDX[®] recurrence score in predicting outcome in estrogen receptor positive breast cancer

Eoin P. Kerin^a, Matthew G. Davey^{a,*}, Ray P. McLaughlin^b, Karl J. Sweeney^b, Michael K. Barry^b, Carmel M. Malone^b, Sami Abd Elwahab^{a,b}, Aoife J. Lowery^{a,b}, Michael J. Kerin^{a,b}

^a Discipline of Surgery, Lambe Institute for Translational Research, University of Galway, Galway, Ireland

^b Department of Surgery, Galway University Hospitals, Galway, Ireland

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ABSTRACT

Introduction: Traditionally, Nottingham prognostic index (NPI) informed prognosis in patients with estrogen receptor positive, human epidermal growth factor receptor-2 negative, node negative (ER+/HER2-/LN-) breast cancer. At present, OncotypeDX[®] Recurrence Score (RS) predicts prognosis and response to adjuvant chemotherapy (AC).

Aims: To compare NPI and RS for estimating prognosis in ER + breast cancer.

Methods: Consecutive patients with ER+/HER2-/LN- disease were included. Disease-free (DFS) and overall survival (OS) were determined using Kaplan-Meier and Cox regression analyses.

Results: 1471 patients met inclusion criteria. The mean follow-up was 110.7 months. NPI was calculable for 1382 patients: 19.8% had NPI ≤ 2.4 (291/1471), 33.0% had NPI 2.41–3.4 (486/1471), 30.0% had NPI 3.41–4.4 (441/1471), 10.9% had NPI 4.41–5.4 (160/1471), and 0.3% had NPI > 5.4 (4/1471). In total, 329 patients underwent RS (mean RS: 18.7) and 82.1% had RS < 25 (270/329) and 17.9% had RS ≥ 25 (59/329). Using multivariable Cox regression analyses (n = 1382), NPI independently predicted DFS (Hazard ratio (HR): 1.357, 95% confidence interval (CI): 1.140–1.616, P < 0.001) and OS (HR: 1.003, 95% CI: 1.001–1.006, P = 0.024). When performing a focused analysis of those who underwent both NPI and RS (n = 329), neither biomarker predicted DFS or OS. Using Kaplan Meier analyses, NPI category predicted DFS (P = 0.008) and OS (P = 0.026). Conversely, 21-gene RS group failed to predict DFS (P = 0.187) and OS (P = 0.296).

Conclusion: In our focused analysis, neither NPI nor RS predicted survival outcomes. However, in the entire series, NPI independently predicted both DFS and OS. On the 40th anniversary since its derivation, NPI continues to provide accurate prognostication in breast cancer, outperforming RS in the current study.

1. Introduction

Breast cancer is the most common malignancy in women [1]. Breast cancer prognosis is understood to be proportional to stage at presentation [2]. Among the most commonly used prognostic tools in breast oncology is the Nottingham Prognostic Index (NPI). First described by Haybittle and Blamey et al., in 1982 [3], NPI incorporates tumour size, histological grade, and degree of nodal burden to stratify patients into clinically distinct groups based on their prognosis [4,5]. Despite predating the molecular era, the NPI has stood the test of time as a predictor of survival and has been validated by several cancer registries

[6,7]. Not only does NPI provide prognoses for patients diagnosed with breast cancer, it also serves in selecting patients who may derive benefit from systemic therapies, based on the perception that all patients with breast cancer will derive a relative benefit proportional to their tumour stage at presentation. Notwithstanding, not all breast cancers will mandate the inevitable adverse effects associated with cytotoxic chemotherapy administration.

Approximately 80% of all breast cancers are classified as estrogen receptor positive (ER+). Robust prescription of endocrine agents (commonly Tamoxifen or aromatase inhibitors) have significantly improved oncological and survival outcomes for these patients [8].

* Corresponding author. Discipline of Surgery, Lambe Institute for Translational Research, National University of Ireland, Galway, Ireland.

E-mail address: m.davey7@nuigalway.ie (M.G. Davey).

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Despite ER + breast cancer representing a typically chemotherapy-insensitive disease [9], systemic chemotherapy prescription patterns peaked for these patients following the publication of the NSABP B-20 randomised trial in 1997, which was interpreted as proving that all patients with ER + breast cancer were ‘candidates’ for chemotherapy irrespective of age, tumour stage, or degree of nodal burden [10].

Translational research efforts during the molecular era have been focused on facilitating the identification of novel biomarkers which may successfully differentiate breast cancer patients based on their personal risk of relapse. Using the paraffin-embedded resected specimens from the NSABP B-20 study, Paik et al. designed and validated a 21-gene expression assay (commercially available as the OncotypeDX® Recurrence Score (RS) from Genomic Health Inc.®, Redwood City, CA, USA) which estimates prognoses and the derived benefit from chemoendocrine therapies in the setting of those with ER+/human epidermal growth factor receptor-2-negative (HER2-), lymph node negative (LN-) breast carcinoma [11,12]. Several large, prospective multicentre studies have validated the RS assay in predicting outcome for these patients [12–14], leading to the endorsement of this biomarker by several expert consensus statements and guidelines [15–17]. In fact, based on the recent results of the TAILORx and RxPONDER trials, it is now evident that a large proportion of those diagnosed with early-stage ER + breast cancers do not benefit from combined chemoendocrine therapies, refuting the conclusions of the previous NSABP-B20 study [13,14].

NPI and RS have become embedded into the management paradigm for estimating prognosis in those diagnosed with early-stage ER+/HER2-breast cancer. Nevertheless, establishing which biomarker more accurately informs prognosis for such patients is yet to be investigated. Accordingly, the aim of this study was to evaluate the role of NPI and RS in estimating patient-specific prognosis for those being treated with curative intent for ER+/HER2-/LN- breast cancer in a large European tertiary referral centre. In this study, an analysis was performed to estimate the value of NPI and RS testing to inform prognosis in the overall cohort of 1382 patients. Thereafter, a focused analysis of the 329 patients who underwent both NPI and RS testing was then performed to determine the value of these biomarkers in predicting long-term oncological and survival outcomes.

2. Methods

2.1. Patient selection

Local Hospital ethical approval was granted from the Galway Clinical Research Ethics Committee (C.A.: 2377). A single centre, retrospective observational cohort study was undertaken in accordance with the STROBE guidelines for observational studies [18]. Consecutive patients diagnosed and treated with curative intent between January 2005 and December 2015 for ER+/HER2-/LN- breast cancer in an Irish tertiary referral centre were included. Patients with nodal involvement (LN+) or metastatic (M1) disease at presentation were excluded. Patients were included via the symptomatic referral pathway and *BreastCheck* mammographic screening service, which is available to women aged 50–69 every two years in the Republic of Ireland. Patients were identified from a prospectively maintained database at the Department of Surgery. Detailed data regarding patient demographics, tumour and pathological information, RS testing, adjuvant treatment regimens, oncological surgical procedures, disease recurrence, and survival outcomes were collected using patient medical records. In this study, 1382 patients underwent NPI evaluation to inform prognosis. Of these, 329 patients underwent RS testing. For our Cox regression analyses, the entire cohort of 1382 patients were included in the analysis presented in the supplementary material while the refined cohort of 329 patients who underwent both RS and NPI testing are included in the tables presented in this manuscript. Importantly, RS testing was not performed as routine in the Republic of Ireland for the entirety of the recruitment of patients

to this study, with several of the included patients undergoing RS as part of the seminal TAILORx trial. Therefore, the test was not available to all included patients [14,16,19].

2.2. Multidisciplinary approach to treatment

Patients diagnosed with ER+/HER2-/LN- breast cancer were diagnosed after presenting to our specialised tertiary referral centre for breast cancer for triple assessment. Clinical breast examinations were performed by a consultant breast surgeon, radiological tumour evaluation was performed by a specialist breast consultant radiologist using mammography and/or ultrasound scanning. Core tissue biopsies were usually performed under image guidance by the radiologist and analysed by an expert consultant breast pathologist. Following triple assessment, all cases were discussed at the multidisciplinary meeting held weekly at the tertiary referral centre, where definitive treatment regimens for each patient were determined in accordance with standard best practice protocols. Following surgical resection with breast conservation surgery (BCS - wide-local excision with or without adjuvant radiotherapy) or mastectomy (as appropriate), tailored treatment strategies incorporated clinical, radiological, pathological, IHC, genomic testing (i.e.: RS testing), patient performance status, family history, as well as the patient’s own wishes regarding treatment. Patients returned to the tertiary referral centre for annual mammographic follow-up. Tumour staging was performed in accordance with the American Joint Committee on Cancer (AJCC), version 8 Guidelines [20] and standard of patient care was implemented in accordance with Internationally accepted best practice guidelines [21,22].

2.3. Histopathologic and immunohistochemistry appraisal

Resected tumour specimens were analysed using the 2010 American Society of Clinical Oncology/College of American Pathologists (ASCO/CAP) histopathological consensus guidelines for estrogen (ER) and progesterone (PgR) receptor status [23] and reported in accordance with the Allred scoring system [24]. Human epidermal growth factor receptor-2 (HER2) receptor status was identified by Herceptest™ (DAKO Agilent pathology solutions, Santa Clara, CA), with a score of 3+ considered positive. Any 2+ inconclusive results were confirmed using fluorescent *in situ* hybridization. Histopathological tumour grade was determined in accordance with the Elston-Ellis modification of the Scarff-Bloom-Richardson grading system (as per the World Health Organisation Classification of Tumours Guidelines) [25]. Appraisal of Ki-67 was performed using MIB1 antibody testing [26,27]. NPI categorization was performed in accordance with the work of Blamey et al. [4]: ‘excellent’ prognostic group had scores <2.4, ‘good’ prognostic group had scores 2.41–3.4, ‘moderate I’ prognostic group had scores 3.41–4.4, ‘poor’ prognostic group had scores 4.41–5.4 and ‘poor’ prognostic group had scores >5.4. RS 21-gene expression assay testing was performed at the Genomic Health Inc.® (Redwood City, CA) laboratory using paraffin-embedded tumour tissue samples [11].

2.4. Patient follow up

Each patient was followed-up and status recorded through a prospectively maintained institutional database. The median and mean lengths of follow-up were calculated using the reverse Kaplan-Meier method [28]. Data in relation to disease recurrence and survival were obtained from electronic patient medical records. Mortality status and cause of death was confirmed through the Republic of Ireland’s National Death Registry.

2.5. Definitions

- Recurrence was defined as relapse of a primary breast cancer following treatment with curative intent.

- Invasive disease-free survival (DFS) was defined as ‘freedom from invasive disease recurrence or death’ [29].
- Overall survival (OS) was defined as ‘death from any cause’ [29].

2.6. Statistical analysis

Clinicopathological, treatment and clinical outcomes were analysed using descriptive statistics. These included Fisher’s exact (†) and Chi-squared (χ^2) tests as appropriate [30]. Independent student’s t-test (‡) and one way analysis of variance (or ANOVA, §) was used to compare means among groups. Kaplan-Meier and Log-rank (Mantel-Cox) analyses were performed to determine the value of NPI and RS to act as a surrogate to improved survival. Cox-regression were used to associate recurrence, DFS, and OS with clinicopathologic characteristics expressed as hazard ratios (HR) with 95% confidence intervals (CIs). Variables with $P < 0.050$ in univariable analysis were included in the multivariable analysis. Data was analysed using Statistical Package for Social Sciences™ (SPSS™) version 26.0 (International Business Machines Corporation, Armonk, New York).

3. Results

3.1. Patient demographics and tumour features

In total, 1471 patients were diagnosed with ER+/HER2-/LN- breast cancer in our institution and met inclusion criteria. The mean age at diagnosis was 59.1 years (standard deviation (SD): 12.1 years, range: 27–96 years), median 58 years). NPI was calculated for 1382 patients: In total, 19.8% of patients were in the ‘excellent’ prognostic group (NPI ≤ 2.4) (291/1471), 33.0% were in the ‘good’ prognostic group (NPI 2.41–3.4) (486/1471), 30.0% were in the ‘moderate I’ prognostic group (NPI 3.41–4.4) (441/1471), 10.9% were in the ‘moderate II’ prognostic group (NPI 4.41–5.4) (160/1471), and 0.3% were in the ‘poor’ prognostic group (NPI > 5.4) (4/1471). Unfortunately, NPI was incalculable in 6.1% of patients (89/1471). In this study, 329 patients underwent RS testing (22.4%) and the mean RS was $18.7 \pm$ (SD: 8.0, range: 3–59). Of these, 82.1% had RS < 25 (270/329) and 17.9% had RS ≥ 25 (59/329). The mean RS for those with RS < 11 was 6.7 (SD: 2.7, range: 0–10), for those with RS 11–25 was 17.0 (SD: 4.1, range: 11–25), and for those with RS > 25 was 32.6 (SD: 7.3, range: 26–59) ($P < 0.001$, §). Clinicopathological and RS data are outlined in Table 1.

3.2. Treatment characteristics

In total, all patients received either BCS or mastectomy for excision of their cancer with curative intent (100.0%, 1471/1471). The vast majority of patients received adjuvant endocrine therapy (94.3%, 1387/1471) and most patients received adjuvant radiotherapy (70.7%, 1040/1471). Overall, 626 patients received adjuvant chemotherapy (42.6%). In relation to adjuvant endocrine therapy prescription, 357 patients received Tamoxifen (25.8%), 330 received Letrozole (23.9%), and 254 received Anastrozole (18.4%). The remaining 441 patients received a combination of the aforementioned endocrine agents or had missing details in relation to their endocrine therapy (31.9%). In relation to adjuvant chemotherapy prescription, 267 patients received taxane-based (19.3%), 281 received cyclophosphamide (20.3%), 254 received anthracycline-based chemotherapy (9.6%), and 17 patients received other chemotherapy drugs (1.2%).

NPI prognostic groups were associated with adjuvant chemotherapy and adjuvant radiotherapy prescription (both $P < 0.001$, χ^2). Patients with RS ≥ 25 were significantly more likely to receive adjuvant chemotherapy ($P < 0.001$, †). With respect to menopause status and treatment received for those who underwent RS testing ($n = 329$), 60.3% of patients who were premenopausal (35/58) received adjuvant chemotherapy while 41.7% of those who were postmenopausal received adjuvant chemotherapy (5/12) ($P = 0.168$, †). Adjuvant treatment

Table 1

Clinicopathological data of the 1471 patients included in this analysis.

Characteristic	N = 1471 (%)
Mean Age at diagnosis (\pm SD (range); median)	59.1 \pm 12.1, (27–96); 58
Pre/perimenopausal	306 (20.8%)
Postmenopausal	882 (60.0%)
Missing	283 (19.2%)
Symptomatic	463 (31.5%)
Screening detected	1008 (68.5%)
Invasive Ductal Carcinoma	930 (63.2%)
Invasive Lobular Carcinoma	176 (12.0%)
Other	365 (24.8%)
Grade 1	384 (26.1%)
Grade 2	794 (54.0%)
Grade 3	275 (18.7%)
Unknown	18 (1.2%)
Tumour Size (mm) (\pm SD (range); median)	19.0 \pm 15.0, (1–140); 18
Tumour Stage 0–1 (T0–1)	910 (62.0%)
Tumour Stage 2 (T2)	480 (32.7%)
Tumour Stage 3 (T3)	43 (2.9%)
Tumour Stage 4 (T4)	15 (1.0%)
TX (unclarified)	19 (1.0%)
Node Negative	1471 (100.0%)
Node Positive	0 (0.0%)
NPI ‘excellent’ prognostic group (≤ 2.4)	291 (19.8%)
NPI ‘good’ prognostic group (2.41–3.4)	486 (33.0%)
NPI ‘moderate I’ prognostic group (3.41–4.4)	441 (30.0%)
NPI ‘moderate II’ prognostic group (4.41–5.4)	160 (10.9%)
NPI ‘poor’ prognostic group (> 5.4)	4 (0.3%)
Missing	89 (6.1%)
ER Score (\pm SD (range); median)	7.6 \pm 1.0 [2–8]; 8
ER positive	1471 (100.0%)
ER negative	0 (0.0%)
PgR Score (\pm SD (range); median)	5.5 \pm 2.8 (2–8); 6
PgR positive	1210 (82.3%)
PgR negative	261 (17.7%)
Ki-67 proliferation indices (\pm SD (range); median) (N = 258)	14.7 \pm 9.0, (0–50), 10
Luminal A Molecular Subtype	946 (64.3%)
Luminal B Molecular Subtype	223 (15.2%)
Unknown	302 (20.5%)
21-gene Recurrence Score [®] (\pm SD (range); median) (N = 329)	18.4 \pm 8.0 (3–59)
21-gene Recurrence Score [®] less than 11	30 (9.1%)
21-gene Recurrence Score [®] between 11 and 25	240 (72.9%)
21-gene Recurrence Score [®] 25 or greater	59 (17.9%)

N; number, SD; standard deviation, ER; estrogen receptor, PgR; progesterone receptor, NPI; Nottingham prognostic index, RS; Recurrence Score[®].

prescription based on NPI and RS categories are outlined in Tables 2 and 3.

3.3. Oncological and survival outcomes

The mean and median follow-up were 110.7 months and 112.4 months (range: 3.0 months–200.3 months) respectively. At median follow-up, 9.3% of patients had experienced disease recurrence (137/1471) and 11.1% had experienced mortality (163/1471). For those who experienced recurrence, there were 22 patients who developed locoregional recurrence (LRR) (1.5%) and 115 distant disease recurrence (DDR) (7.8%). Increasing NPI category was associated with increased rates of recurrence ($P = 0.115$). Increasing NPI category was associated with poorer DFS ($P = 0.002$) and OS ($P = 0.001$, both χ^2 test) (Table 4). Similarly, RS group was associated with increased rates of recurrence ($P = 0.041$). At median follow-up, the proportion of patients experiencing recurrence or death increased with RS group (RS < 11 : 6.7% (2/30) vs. RS 11–25: 7.5% (18/240) vs RS > 25 : 17.0% (10/59)) ($P = 0.069$, χ^2). DFS and OS were similar for both RS groups ($P = 0.565$ and $P = 0.520$ respectively, both † test) (Table 5).

Table 2
Adjuvant treatment strategies based on Nottingham prognostic index categories.

Adjuvant Treatment	NPI 'excellent' prognostic group (n = 291)	NPI 'good' prognostic group (n = 486)	Moderate I NPI (n = 441)	Moderate II NPI (n = 160)	Poor NPI (n = 4)	P-value
Received adjuvant endocrine therapy	263 (90.4%)	455 (93.6%)	421 (95.5%)	154 (96.3%)	3 (75.0%)	1.000 χ^2
Did not receive adjuvant endocrine therapy	28 (9.6%)	21 (4.3%)	19 (4.3%)	5 (3.1%)	1 (25.0%)	
Missing	0 (0.0%)	10 (2.1%)	1 (0.2%)	1 (0.6%)	0 (0.0%)	
Received adjuvant chemotherapy	30 (10.3%)	141 (29.0%)	180 (40.8%)	89 (55.6%)	1 (25.0%)	<0.001 ^a χ^2
Did not receive adjuvant chemotherapy	255 (87.6%)	329 (67.7%)	241 (54.6%)	68 (42.5%)	3 (75.0%)	
Missing	6 (2.1%)	16 (3.3%)	20 (4.5%)	3 (1.9%)	0 (0.0%)	
Received adjuvant radiotherapy	186 (63.9%)	337 (69.3%)	324 (73.5%)	114 (71.2%)	1 (25.0%)	<0.001 ^a χ^2
Did not receive adjuvant radiotherapy	54 (18.6%)	114 (23.5%)	91 (20.6%)	40 (25.0%)	3 (75.0%)	
Missing	51 (17.5%)	35 (7.2%)	26 (5.9%)	6 (3.8%)	0 (0.0%)	

NPI; Nottingham prognostic index.

χ^2 denotes Chi-squared test.

^a Denotes statistical significance.

Table 3
Adjuvant treatment strategies based on 21-gene recurrence score categories.

Adjuvant Treatment	RS < 25 (n = 270)	RS > 25 (n = 59)	P-value
Received adjuvant endocrine therapy	257 (95.2%)	57 (96.6%)	0.635 ^b
Did not receive adjuvant endocrine therapy	13 (4.8%)	2 (3.4%)	
Received adjuvant chemotherapy	175 (64.8%)	51 (86.4%)	0.001 ^{b,a}
Did not receive adjuvant chemotherapy	95 (35.2%)	8 (13.6%)	
Received adjuvant radiotherapy	204 (75.6%)	47 (79.7%)	0.502 ^b
Did not receive adjuvant radiotherapy/Missing	66 (24.4%)	12 (20.3%)	

RS; 21-gene recurrence score.

^a Denotes Fisher's exact test.

^b Denotes statistical significance.

3.4. Disease-free survival based on Nottingham Prognostic Index and 21-gene recurrence score

Using univariable Cox regression analyses, NPI category (HR: 1.223, 95% CI: 1.047–1.429, P = 0.011) predicted disease recurrence. At multivariable analysis, NPI category (HR: 1.357, 95% CI: 1.140–1.616, P < 0.001) independently predicted DFS (Supplementary Material S1). When performing analysis with respect to the patients who underwent both RS testing and NPI (n = 329), neither RS nor NPI testing predicted DFS (Table 6). Using Kaplan Meier analyses, NPI category (P = 0.008) predicted DFS (Fig. 1). Conversely, 21-gene RS group failed to predict DFS (P = 0.775) (Fig. 2).

Table 4
Disease recurrence and overall survival based on Nottingham prognostic index.

	NPI 'excellent' prognostic group (n = 291)	NPI 'good' prognostic group (n = 486)	NPI 'moderate I' prognostic group (n = 441)	NPI 'moderate II' prognostic group (n = 160)	NPI 'poor' prognostic group (n = 4)	p-value
Recurrence	22 (7.6%)	41 (8.4%)	41 (9.3%)	24 (15.0%)	1 (25.0%)	0.115 χ^2
Alive with no active disease	269 (92.4%)	445 (91.6%)	400 (90.7%)	136 (85.0%)	3 (75.0%)	
Recurrence or Dead	36 (12.4%)	48 (9.9%)	69 (15.6%)	35 (21.9%)	0 (0.0%)	0.002 ^a χ^2
Alive with no active disease	255 (87.6%)	438 (90.1%)	372 (84.4%)	125 (78.1%)	4 (100.0%)	
Dead	32 (11.0%)	45 (9.3%)	51 (11.6%)	31 (19.4%)	0 (0.0%)	0.001 ^a χ^2
Alive	259 (89.0%)	438 (90.7%)	387 (88.4%)	129 (80.6%)	4 (100.0%)	

NPI; Nottingham prognostic index.

χ^2 denotes Chi-squared test.

^a Denotes statistical significance.

3.5. Overall survival based on Nottingham Prognostic Index and 21-gene recurrence score

Using univariable Cox regression analyses, NPI category (HR: 1.204, 95% CI: 1.022–1.417, P = 0.026) predicted survival. At multivariable analysis, NPI category (HR: 1.370, 95% CI: 1.139–1.646, P = 0.001) was identified as an independent predictor of survival (Supplementary Material S2). When performing analysis with respect to the patients who underwent both RS testing and NPI (n = 329), neither RS nor NPI testing predicted DFS (Table 7). Using Kaplan Meier analyses, NPI category predicted OS for those with ER+/HER2-/LN- disease (P = 0.026) (Fig. 3). Conversely, 21-gene RS group failed to predict OS (P = 0.574) (Fig. 4).

Table 5
Disease recurrence and overall survival based on 21-gene recurrence score categories.

Outcome	RS < 25 (n = 270)	RS > 25 (n = 59)	P-value
Recurrence	20 (7.6%)	10 (16.9%)	0.041 ^{b,a}
Alive with no active disease	250 (92.4%)	49 (83.1%)	
Recurrence or Dead	17 (6.3%)	4 (6.8%)	0.565 ^a
Alive with no active disease	253 (93.7%)	55 (93.2%)	
Dead	13 (4.8%)	4 (6.8%)	0.520 ^a
Alive	257 (95.2%)	55 (93.2%)	

RS; 21-gene recurrence score.

^a Denotes Fisher's exact test.

^b Denotes statistical significance.

Table 6

Univariable and multivariable Cox regression analyses to determine predictors of disease-free survival for the 329 patients who had undergone Oncotype DX® 21-gene Recurrence Score and Nottingham Prognostic Index testing.

Disease-Free Survival							
Parameter	HR	95% CI	P-value	HR	95% CI	P-value	
	Univariable			Multivariable			
Age	1.024	0.977–1.075	0.322				
Menopause Status	1.334	0.718–2.478	0.362				
Symptomatic	1.127	0.487–2.610	0.780				
Histology	1.002	1.000–1.004	0.063				
Grade	0.594	0.301–1.171	0.113				
Tumour Stage	0.996	0.953–1.042	0.872				
ER Score	1.119	0.592–2.427	0.614				
PgR Score	0.946	0.816–1.097	0.464				
Ki67 > 14%	3.163	0.285–35.084	0.348				
Molecular Subtype	1.003	1.001–1.005	0.015*	1.003	1.001–1.005	0.015*	
NPI Category	1.083	1.045–2.473	0.849				
21-gene RS	0.998	0.940–1.059	0.947				
Adjuvant ET	0.475	0.111–2.033	0.315				
Adjuvant Chemotherapy	0.947	0.398–2.256	0.903				
Adjuvant Radiotherapy	1.847	0.543–6.384	0.326				

HR; hazard ratio, CI; confidence interval, ER; estrogen receptor, PgR; progesterone receptor, NPI; Nottingham prognostic index, RS; Recurrence Score®, ET; endocrine therapy.

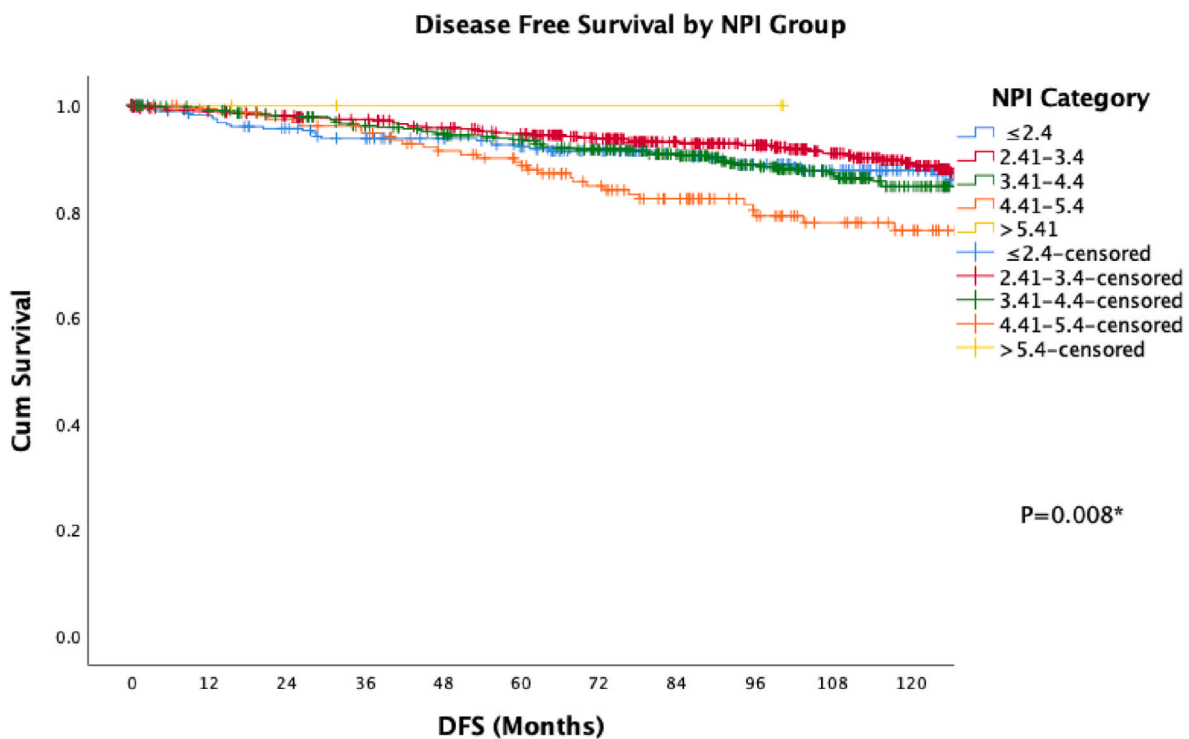


Fig. 1. Kaplan Meier curve of disease free survival based on Nottingham prognostic index category.

4. Discussion

This year marks 40 years since Haybittle and Blamey et al. first described the clinical application of a prognostic index designed by the Nottingham City Hospital group and later validated by several other institutions worldwide [4,6,14]. For decades, contemporary breast cancer management was heavily dependent upon the NPI to inform patient-specific prognostication, facilitating the tailoring of therapeutics in accordance with the perceived risk of recurrence, as detailed by the index. Importantly, the data presented in this study illustrates that the clinical application of NPI has stood the test of time, with NPI category independently predicting both DFS and OS in the independent multivariable Cox regression analyses performed within the entire cohort. NPI

category outperformed the RS genomic assay results in predicting long-term oncological and survival outcomes in these analyses. Notwithstanding, when performing a refined analysis for the patients who underwent both RS and NPI, neither biomarker predicted outcome in ER + disease. This unanticipated failure to predict survival outcomes may be best explained by a type II statistical error due to the favourable survival outcomes and few events of recurrence and mortality observed for the patients with early stage ER + disease in this series.

In the context of the series overall (where n = 1382), it is important to acknowledge that just 22.4% of patients in this series underwent RS testing compared to 93.9% of patients whom NPI was calculable for. There are several reasonable explanations for these findings: Firstly, during the early phases of this study, RS was initially unavailable for

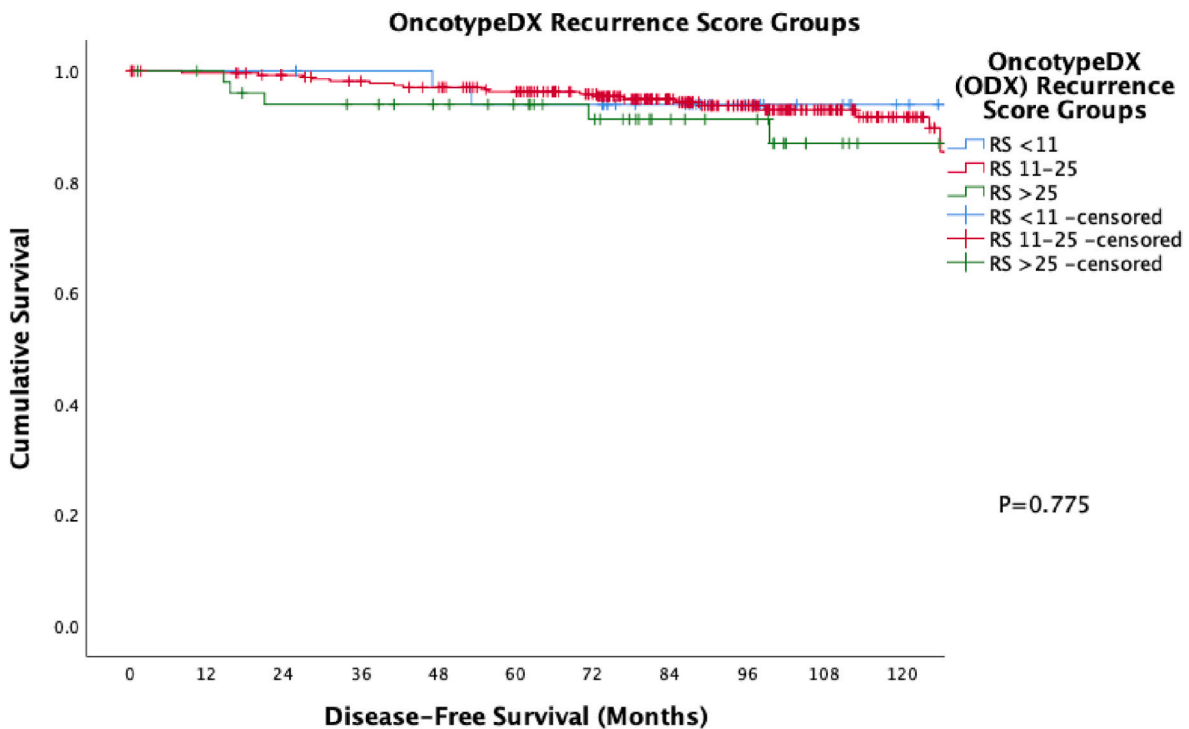


Fig. 2. Kaplan Meier curve of disease-free survival based on 21-gene recurrence score category.

Table 7

Univariable and multivariable Cox regression analyses to determine predictors of overall survival for the 329 patients who had undergone Oncotype DX® 21-gene Recurrence Score and Nottingham Prognostic Index testing.

Parameter	Disease-Free Survival			P-value	Disease-Free Survival		
	HR	95% CI	P-value		HR	95% CI	P-value
	Univariable				Multivariable		
Age	1.054	0.994–1.118	0.078				
Menopause Status	1.697	0.771–3.731	0.189				
Symptomatic	1.549	0.538–4.461	0.418				
Histology	1.003	1.000–1.005	0.032*				
Grade	0.591	0.261–1.341	0.209				
Tumour Stage	0.996	0.931–1.065	0.900				
ER Score	0.967	0.497–1.881	0.921				
PgR Score	0.954	0.799–1.139	0.604				
Ki67 > 14%	3.875	0.340–44.165	0.275				
Molecular Subtype	1.003	1.001–1.005	0.008*				
NPI Category	1.149	0.435–3.036	0.779				
21-gene RS	0.996	0.930–1.066	0.906				
Adjuvant ET	0.324	0.074–1.428	0.137				
Adjuvant Chemotherapy	0.712	0.251–2.019	0.523				
Adjuvant Radiotherapy	1.190	0.335–4.234	0.788				

HR; hazard ratio, CI; confidence interval, ER; estrogen receptor, PgR; progesterone receptor, NPI; Nottingham prognostic index, RS; Recurrence Score®, ET; endocrine therapy.

patients receiving treatment in the Republic of Ireland (2005–2007), before being made available on a trial basis only for those recruited to TAILORx (2007–2010) [16,19]. Thereafter, RS testing was not publicly reimbursed until from October 2011 onwards, meaning patients recruited to this study prior to this required private health insurance to undergo RS testing (2010–2011) [16,19]. Moreover, while NPI is calculable for tumours of all sizes, patient eligibility for RS testing is restricted to those with tumours less than 50 mm in size [16,19]. With the knowledge that larger breast cancers have an increased propensity to relapse than smaller tumours [9], this potentially confounds the results supporting NPI as a more sensitive biomarker of disease recurrence in the series overall.

While several studies highlight the prognostic and predictive

capabilities of the RS biomarker [12,31], it is of the utmost significance to ensure consideration for NPI subclassification when attempting to establish the true risk of disease recurrence in early-stage ER+/HER2-breast carcinoma. RS is a first generation multigene expression assay which has revolutionised the management of early-stage ER+/HER2-breast cancer, as evident from the recent landmark TAILORx and RxPONDER trials [13,14]. Based on these results, this study supports the continued application of NPI as a reliable means of providing patient specific prognostication in breast cancer. However, this also acknowledges the importance RS testing in disproving previous antiquated hypotheses, such as those which previously implicated the candidacy of all breast cancer patients to receive adjuvant chemotherapeutic regimens [10], irrespective of other important

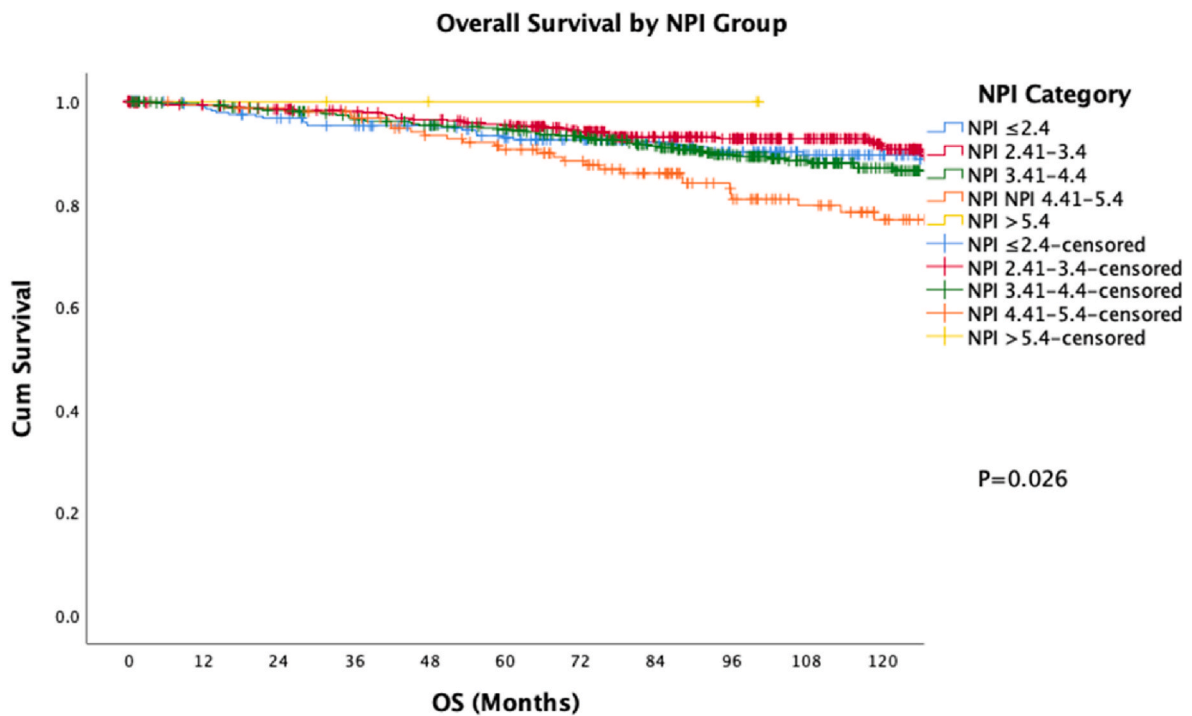


Fig. 3. Kaplan Meier curve of overall survival based on Nottingham prognostic index category.

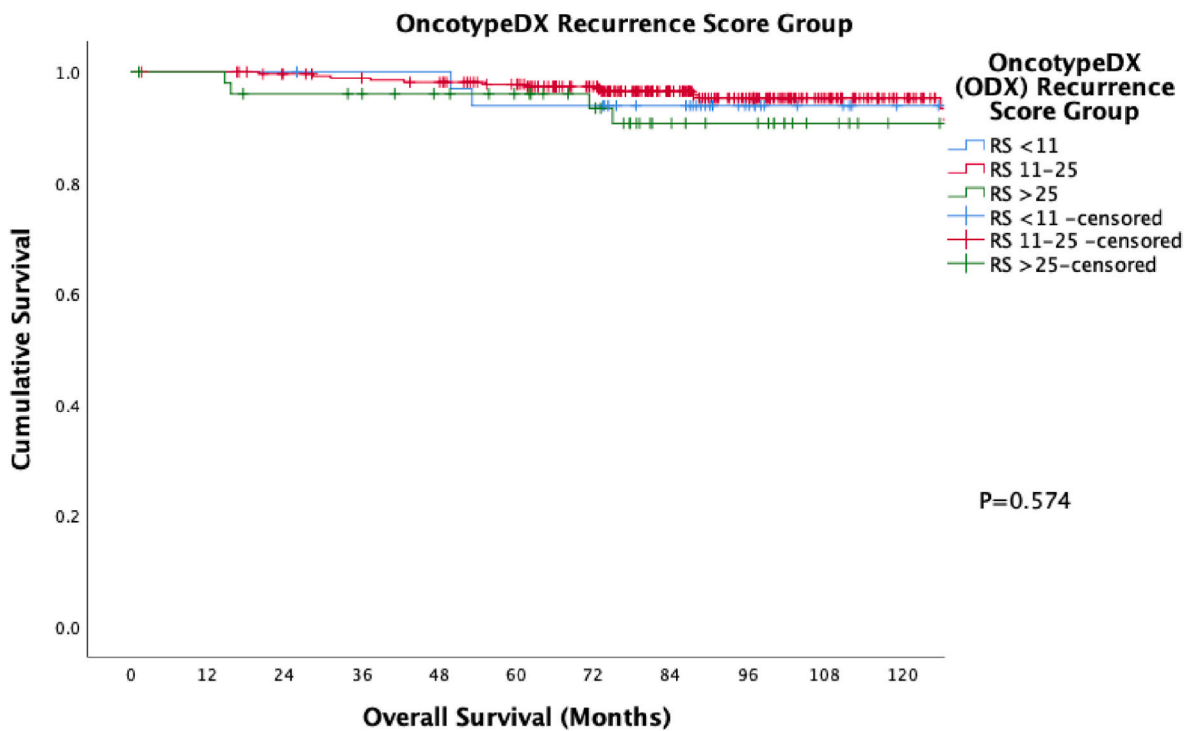


Fig. 4. Kaplan Meier curve of overall survival based on 21-gene recurrence score category.

clinicopathological and biomolecular parameters. Therefore, the modern multimodal approach to breast cancer therapeutics must consider both biomarkers in attempting to individualise treatment strategies to match the needs of each patient.

Traditionally, tumour burden in the breast, the extent of metastatic disease in ipsilateral lymph nodes, and tumour grade represented the key histopathological parameters used to inform breast cancer prognostication in early and locally advanced disease [32–34]. This dogma

was pragmatically investigated and validated in early NPI models [3–5], and has remained relevant in the molecular era, through the evolution of the traditional indices into more sophisticated and clinically applicable NPI models [35,36]. Notwithstanding these promising results, the work of Gray et al. has brought into question the reliability of NPI in accurately providing prognostication across extensive populations, due to a degree of heterogeneity among results reported [37]. The current analysis refutes this theory, given the sensitivity of NPI as a key

prognostic indicator of oncological outcome for those being treated for ER+/HER2-/LN- breast cancer in the analysis involving the entire patient series.

Recently, Kalinsky et al. published the 5-year results from the seminal RxPONDER trial and coherently indicated that the majority of patients with ER+/HER2-breast cancer with 0–3 positive lymph nodes should be spared adjuvant chemotherapy and would be best served with adjuvant endocrine agents prescribed in monotherapy [13]. RxPONDER fundamentally highlights the critical importance of routine RS testing in the contemporary multimodal approach to managing those with early-stage ER + disease, and we wish to emphasize that this work is not intended to discredit the landmark results from TAILORx and RxPONDER in recent times [13,14]. Thus, we await the opportunity to repeat the current analysis with a wider patient eligibility criteria to assess the validity of both NPI and RS testing in gauging patient specific prognostication using patient data from our tertiary referral centre. Furthermore, Kalinsky et al. demonstrated the importance of menopause status as a key parameter in the treatment algorithm for early stage ER + disease. This retrospective analysis fails to demonstrate the value of menopause status in determining long-term oncological outcomes for these patients, and it also failed to predict adjuvant chemotherapy prescription ($P = 0.168$). Therefore, the authors eagerly await the opportunity to evaluate the role of menopause status as a key determinant in guiding treatment decision making, based on the seminal work of Kalinsky et al. [13].

This study is subject to limitations. Primarily, this study suffers from the inherent limitations of being a retrospective cohort study, recruiting patients from a single centre. This presents certain unavoidable limitations including confounding, ascertainment and selection biases. Secondly, as previously outlined, it is plausible that the failure for RS and NPI to predict DFS and OS in our analysis is best explained by a type II statistical error due to just a subset of the 329 patients included in this analysis experiencing recurrence or mortality. Thirdly, RS has only recently become applicable to node positive disease, and as such only node negative patients were included in this study. Only 4 patients out of the 1471 included in this study had a NPI score that constituted inclusion in the ‘poor’ prognostic group. Certainly, in a study that included node positive patients, there would be a greater number of patients in this prognostic group, and as such this can be considered a limitation of this work. As described, the promising results of RxPONDER will provide the authors of this study a future opportunity to establish the prognostic role of RS relative to NPI in the setting of node positive disease, as is more relevant to the current management paradigm. Fourthly, while RxPONDER and TAILORx have reduced chemotherapy prescription for the majority with early-stage disease [13,14], this study transverses an era where robust chemoendocrine therapies were prescribed unnecessarily for the majority of such patients, and the implications of these treatments on patient quality of life have not been measured. Despite these limitations, this analysis provides novel data illustrating the importance of NPI as a relevant prognostic biomarker in modern breast cancer patient management.

In conclusion, while this study failed to illustrate the importance of NPI and RS in predicting long-term oncological and survival outcomes in a focused patient cohort who were treated in a large European tertiary referral centre, NPI did outperform RS in providing patient specific prognostication in the overall series. Thus, the authors wish to highlight the revolutionary role of NPI and the contemporary role of RS in personalising therapeutic decision making based on the individual needs of each patient. On the 40th anniversary of the NPI, this study illustrates the ever-present and evolving clinical utility of the biomarker in gauging patient prognosis, even in the molecular era where multigene assays such as RS dominate clinical decision making.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.breast.2022.11.001>.

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