The impact of progesterone receptor negativity on oncological outcomes in oestrogen-receptor-positive breast cancer

M. G. Davey, É. J. Ryan, P. J. Folan, N. O’Halloran, M. R. Boland, M. K. Barry, K. J. Sweeney, C. M. Malone, R. J. McLaughlin, M. J. Kerin and A. J. Lowery

Introduction

Contemporary multimodal breast cancer (BC) management is driven by tumour biology. Assessment of the steroid hormone receptors (oestrogen receptor (ER) and progesterone receptor (PgR)) and the human epidermal growth factor receptor-2 (HER2) are critical components of prognostication and targeted treatment planning. ER and PgR are expressed in 80 per cent and 60 per cent of BC respectively. These hormone receptors are commonly used as prognostic markers for BC, as hormone-receptor-positive (HR+) disease is typically associated with favourable patient outcomes, due to its less aggressive biology and because tumour expression of ER allows for targeted treatment with anti-oestrogen endocrine hormonal therapy (EHT). Current EHT primarily targets the ER, which predicts response to anti-oestrogen therapeutic strategies. The clinical importance of standard PgR assessment is less clear but it is likely that it provides valuable prognostic information at diagnosis, which may aid therapeutic decision making.

PgR is a ligand-activated nuclear transcription factor that mediates progesterone activity. ER+ cancers are typically PgR+, and PgR is an oestrogen-regulated gene with interplay between ER and PgR believed to be pivotal in biological responses to EHT. Additionally, PgR+ cancers depend upon oestrogen expression for tumour proliferation as well as acting as a function of the ER-alpha signalling pathway. The dependence of PgR expression on ER activity means that ER and PgR expression are typically concordant. However, 20 per cent of invasive BC demonstrates mixed hormone receptor status, with ER+/PgR- being the most common hormone receptor subgroup. Thus, when determining the prognostic significance of single HR positivity, the ER+/PgR- subgroup of breast cancers is the most clinically relevant group to investigate.

The importance of PgR status in clinical decision making remains a matter of debate when compared with ER status. While some authors argue that PgR provides invaluable prognostic information, others have questioned its value and have...
suggested removing standard PgR assessment in newly diagnosed BC\textsuperscript{15}. Despite the fact that PgR- tumours are likely to be more aggressive than PgR+ disease\textsuperscript{16}, ER+/PgR+ and ER+/PgR- cancers are typically treated in the same manner, and there have been limited developments in efforts to produce a potential therapeutic means of targeting the PgR\textsuperscript{17,18}. Decisions regarding cytotoxic neoadjuvant (NAC) and adjuvant chemotherapy (AC) are guided more often by pathological factors such as tumour size, nodal status and genomic testing, rather than PgR status\textsuperscript{19-21}. However, PgR expression is considered, as part of genomic panels such as OncotypeDX\textsuperscript{TM} (ODX, Genomic Health, Redwood City, CA, U.S.A.) in combination with other characteristics of tumour biology, in guiding personalized adjuvant therapies\textsuperscript{22,23}.

The primary aim of this study was to assess the impact of PgR negativity on oncological outcomes in ER- BC patients. The secondary aim was to compare the presentation and clinicopathological features of ER+/PgR+ and ER+/PgR- BCs and determine associations and predictors of PgR- disease.

**Methods**

**Study design and patient selection**

This study was granted institutional review board approval from the Galway University Hospitals (GUH) Clinical Research Ethics Committee. A single-centre, retrospective observational cohort study was undertaken. This study included all BC patients diagnosed and treated in GUH, a tertiary referral BC centre for the west of Ireland, over an 11-year period between January 2005 and December 2015. Included patients had a diagnosis of ER+ BC and were identified from a prospectively maintained institutional database. Detailed information regarding patient demographics, clinicopathological data, neoadjuvant treatment regimens, surgical management, ODX testing, adjuvant treatment regimens, disease recurrence and survival was collected using this database, and all data were cross-referenced with patient electronic and medical records.

**Patient process**

Patients presented either symptomatically or through BreastCheck, Ireland’s national mammography-based breast screening programme of women aged 50–70 years. Each patient underwent triple assessment. Clinical examination was conducted by a consultant breast surgeon. Standard radiological assessment consisted of mammography and ultrasonography; MRI was considered and used in select cases (i.e., dense breast tissue, invasive lobular carcinoma histological subtype, BRCA mutation carrier and diagnostic uncertainty after using other modalities). Imaging assessments were then reviewed by a dedicated breast radiologist. Diagnosis was confirmed by radiologically guided or clinical core biopsy reported on by a dedicated consultant breast pathologist. All breast tissue specimens were analysed in the accredited pathology laboratory. Staging was performed in accordance with the American Joint Committee on Cancer (AJCC), version 8 Guidelines\textsuperscript{24}.

**Histopathological assessment and immunohistochemistry**

ER and PgR status was routinely analysed using the Allred scoring system\textsuperscript{25}. HER2 status was assessed using immunohistochemistry (IHC), and those scoring 2+ were submitted for fluorescence in situ hybridization for confirmation of HER2 receptor status. Tumour specimens were graded using the Nottingham Histologic Score system (also termed the Elston-Ellis modification of Scarff-Bloom-Richardson grading system\textsuperscript{1}), as per the WHO Classification of Tumours Guidelines\textsuperscript{26}. Tumour lymphatic invasion was evaluated using IHC staining with D2-40 and vascular invasion using CD34\textsuperscript{27}. Tumour perineural invasion was evaluated using IHC staining with S-100 and a broad-spectrum keratin stain (AE1/AE3)\textsuperscript{28}. Ki67 was evaluated using MIB1 antibody testing\textsuperscript{29}.

**Multidisciplinary approach to care**

Each case was discussed at the breast multidisciplinary meeting held weekly at the tertiary referral centre. Multidisciplinary decisions regarding patient-specific treatment considered clinical, radiological and pathological factors as well as patient performance status, family history and genetic testing results. Adjuvant prescription of chemoendocrine therapies for a number of patients diagnosed with ER+/HER2-, lymph node negative (LN-) BC after 2007 were informed by recurrence score genomic panel-based testing (RS). Patients returned to the tertiary referral centre for examination by a specialized breast surgeon post-operatively and returned yearly for routine clinical and mammographic follow-up for 10 years following diagnosis.

**Follow-up**

Patient follow-up was recorded through a prospectively maintained database. The median and mean lengths of follow-up were calculated using the reverse Kaplan–Meier method\textsuperscript{30}. BC recurrence and overall survival data were calculated from a prospectively maintained institutional database. All data were cross-referenced with patient electronic and medical records. Survival status as well as cause of death were confirmed from data obtained from national registries. The authors defined disease-free survival (DFS) as ‘freedom from invasive disease recurrence’.

**Statistical analysis**

Clinicopathological and IHC correlates of PgR- were determined using independent Student’s t, χ\textsuperscript{2}, one-way ANOVA and Kruskal–Wallis tests as appropriate. Univariable logistic regression analysis was used to assess the association between variables and negative PgR status expressed in crude odds ratios (OR) with 95 per cent confidence intervals. Variables with P < 0.050 in univariable analysis were included in the multivariable logistic regression analysis. Binary logistic regression analysis was used to identify variables that contributed independently to negative PgR expression. Only patients undergoing surgical resection of their primary breast tumour were included for survival analyses. Kaplan–Meier curves, the log rank (Mantel–Cox) test, and Cox regression were used to assess relationship with clinical, pathological and IHC characteristics expressed as hazard ratios (HR) with 95 per cent confidence intervals. All tests of significance were two-tailed, with P < 0.050 indicating statistical significance. Data were analysed using SPSS\textsuperscript{TM} (IBM SPSS Statistics for Mac, Version 26.0. Armonk, NY) version 26.

**Results**

**Patient demographics**

There were 2660 consecutive patients diagnosed with and treated for ER+ BC between January 2005 and December 2015 included in this study. There were 2208 patients with PgR+ tumours (83.0 per cent) and 452 (17.0 per cent) were PgR-. (Appendix S1). The mean(s.d.) age at diagnosis was 59.6(13.3) years (range 21–99 years). At the time of BC diagnosis, 1900 patients (71.4 per cent)
were postmenopausal, and 2059 patients presented through the symptomatic breast pathway (77.4 per cent). The vast majority of cancers were invasive (2425, 91.2 per cent). The median follow-up was 97.2 (range 3.0–181.2) months.30

Clinicopathological characteristics associated with PgR status

Clinicopathological and molecular characteristics are shown in Table 1. Using binary logistic regression it was demonstrated that being postmenopausal at the time of diagnosis (OR 1.66), presenting with symptoms (OR 1.71), having IDC subtype (OR 1.51) and grade 3 tumours (OR 2.20) were all predictive of PgR- status (Table 2). Other patient and tumour features not associated with PgR status are outlined in Tables 1 and 2.

Table 1 Correlation of clinicopathological, immunohistochemical and molecular factors with progesterone receptor expression (n = 2660)

| Clinicopathological characteristics | PgR+ (n = 2208) | PgR- (n = 452) | P      |
|-------------------------------------|-----------------|----------------|--------|
| **Age at diagnosis (years)**        | 59.8 (21–99)    | 60.0 (30–92)   | 0.029<sup>†</sup> |
| **Menopausal status at diagnosis**  |                 |                |        |
| Premenopausal                       | 590 (26.7)      | 87 (19.2)      | <0.001<sup>§</sup> |
| Perimenopausal                      | 67 (23.0)       | 16 (3.5)       |        |
| Post-menopausal                     | 1551 (70.3)     | 349 (77.2)     |        |
| **Presentation**                    |                 |                |        |
| Symptomatic                         | 1700 (77.0)     | 359 (79.4)     | <0.001<sup>†</sup> |
| Screening                           | 508 (23.0)      | 93 (20.6)      |        |
| **Invasive tumour component**       |                 |                |        |
| Invasive                            | 2005 (90.8)     | 420 (92.9)     | 0.919<sup>†</sup> |
| Non-invasive                        | 203 (9.2)       | 32 (7.1)       |        |
| **Histological tumour type**        |                 |                |        |
| Invasive ductal carcinoma           | 1637 (74.1)     | 321 (71.0)     | 0.070<sup>§</sup> |
| Invasive lobular carcinoma          | 370 (16.8)      | 78 (17.3)      |        |
| Mucinous carcinoma                  | 53 (2.4)        | 10 (2.2)       |        |
| Other                               | 145 (6.6)       | 46 (10.1)      |        |
| **Tumour size (mm)**                |                 |                |        |
| Grade 1                             | 464 (21.0)      | 91 (20.1)      | <0.001<sup>§</sup> |
| Grade 2                             | 1297 (58.8)     | 227 (50.2)     |        |
| Grade 3                             | 447 (20.2)      | 134 (29.7)     |        |
| **Lymphovascular invasion**         |                 |                |        |
| Present                             | 558 (25.3)      | 108 (23.9)     | 0.027<sup>†</sup> |
| Absent                              | 1650 (74.7)     | 344 (76.1)     |        |
| **Perineural invasion**             |                 |                |        |
| Present                             | 167 (7.6)       | 16 (3.5)       | 0.724<sup>†</sup> |
| Absent                              | 2041 (92.4)     | 435 (96.5)     |        |
| **ER score**                        | 7.69 (0.07)     | 7.07 (0.16)    |        |
| **HER2 status**                     |                 |                |        |
| Negative                            | 2013 (91.2)     | 358 (79.2)     | <0.001<sup>‡</sup> |
| Positive                            | 195 (8.8)       | 94 (20.8)      |        |
| **Ki67**                            |                 |                |        |
| Low (<6%)                           | 65 (2.9)        | 7 (1.5)        | 0.013<sup>‡</sup> |
| Intermediate (6–14%)                | 145 (6.6)       | 19 (4.2)       |        |
| High (>14%)                         | 193 (8.7)       | 38 (8.4)       |        |
| **Clinical tumour stage**           |                 |                |        |
| 0–1                                 | 969 (43.9)      | 223 (49.5)     | 0.061<sup>§</sup> |
| 2                                   | 901 (40.8)      | 172 (38.1)     |        |
| 3                                   | 218 (9.8)       | 31 (6.9)       |        |
| 4                                   | 120 (5.4)       | 26 (5.8)       |        |
| **Clinical nodal stage**            |                 |                |        |
| 0                                   | 1307 (59.2)     | 265 (58.6)     | 0.846<sup>§</sup> |
| 1                                   | 630 (28.5)      | 126 (27.9)     |        |
| 2                                   | 189 (8.6)       | 36 (8.0)       |        |
| 3                                   | 82 (3.7)        | 25 (5.5)       |        |
| **Clinical metastatic stage**       |                 |                |        |
| 0                                   | 2086 (94.5)     | 425 (94.0)     | 0.186<sup>†</sup> |
| 1                                   | 122 (5.5)       | 27 (6.0)       |        |

Values in parentheses are percentages unless indicated otherwise; *values are median (range), mean(s.d.). PgR+, progesterone receptor positivity; PgR-, progesterone receptor negativity; ER, oestrogen receptor; HER2, human epidermal growth factor receptor; K, Kruskal-Wallis test.
Table 2 Significant clinical and pathological correlates of negative PgR expression following univariable and multivariable binary logistic regression analysis

| Parameter                  | Odds ratio Univariable | P       | Odds ratio Multivariable | P       |
|----------------------------|------------------------|---------|--------------------------|---------|
| Age >65 years              | 0.92 (0.73–1.17)       | 0.501   |                          |         |
| Being postmenopausal at diagnosis | 1.76 (1.31–2.35)   | <0.001  | 1.66 (1.25–2.20)         | <0.001  |
| Presentation (symptomatic) | 1.70 (1.34–2.14)       | <0.001  | 1.71 (1.30–2.25)         | <0.001  |
| Side affected              | 1.00 (0.98–1.01)       | 0.940   |                          |         |
| Invasive component         | 1.00 (1.00–1.00)       | 0.928   |                          |         |
| IDC subtype                | 1.27 (1.06–1.52)       | 0.099   | 1.51 (1.17–1.97)         | 0.002   |
| Size >50 mm                | 0.95 (0.66–1.37)       | 0.774   |                          |         |
| Grade 3                    | 1.76 (1.39–2.22)       | <0.001  | 2.12 (1.68–2.87)         | <0.001  |
| Lymphovascular invasion    | 1.00 (1.00–1.00)       | 0.533   |                          |         |
| Perineural invasion        | 1.00 (1.00–1.00)       | 0.533   |                          |         |
| HER2+                      | 1.00 (1.00–1.00)       | 0.533   |                          |         |
| Clinical T-stage           | 0.93 (0.68–1.27)       | 0.656   |                          |         |
| Clinical N-stage           | 0.93 (0.75–1.16)       | 0.532   |                          |         |
| Clinical M-stage           | 1.09 (0.68–1.73)       | 0.730   |                          |         |

Values in parentheses are 95% confidence intervals. PgR+, progesterone receptor positivity; PgR-, progesterone receptor negativity; ER, oestrogen receptor; HER2, human epidermal growth factor receptor-2; IDC, invasive ductal carcinoma.

Table 3 Treatment characteristics and their association with progesterone receptor expression (n = 2660)

| Treatment characteristics          | PgR+ (n = 2208) | PgR- (n = 452) | P       |
|------------------------------------|-----------------|----------------|---------|
| Neoadjuvant chemotherapy           |                 |                |         |
| Underwent treatment                | 247 (11.2)      | 61 (13.5)      | 0.361†  |
| Did not undergo treatment          | 1961 (88.8)     | 391 (86.5)     |         |
| Primary surgery (n = 2307)         |                 |                |         |
| Breast conserving surgery          | 1367 (61.9)     | 270 (59.7)     | 0.439†  |
| Mastectomy                         | 550 (24.9)      | 120 (26.6)     |         |
| None                               | 291 (13.2)      | 62 (13.7)      |         |
| Axillary surgery (n = 2307)        |                 |                |         |
| SLNB                               | 1100 (57.4)     | 222 (56.9)     | 0.439†  |
| ALND                               | 817 (42.6)      | 168 (43.1)     |         |
| ODX score (n = 341)                | 17.5 (7.2)      | 24.2 (10.1)    | <0.001§ |
| Low risk (score 0–10)              | 23 (7.9)        | 1 (2.0)        |         |
| Intermediate risk (score 11–25)    | 233 (80.3)      | 32 (62.7)      |         |
| High risk (score >25)              | 34 (11.7)       | 18 (35.3)      |         |
| Adjuvant chemotherapy              |                 |                |         |
| Underwent treatment                | 847 (38.4)      | 167 (37.0)     | 0.263†  |
| Did not undergo treatment          | 1361 (61.6)     | 285 (63.0)     |         |
| Adjuvant radiotherapy              |                 |                |         |
| Underwent treatment                | 1523 (69.0)     | 321 (71.0)     | 0.425†  |
| Did not undergo treatment          | 685 (31.0)      | 131 (29.0)     |         |
| EHT in invasive cases (n = 2425)   |                 |                |         |
| Underwent treatment                | 1968 (98.4)     | 410 (96.7)     | 0.008†  |
| Did not undergo treatment          | 33 (1.6)        | 14 (3.3)       |         |

Values in parentheses are percentages unless indicated otherwise. * mean(s.d.), median (range). ODX, OncotypeDX™ testing. SLNB, sentinel lymph node biopsy; ALND, axillary lymph node dissection; EHT, adjuvant endocrine hormone therapy. † Student independent t-test; §Fisher’s exact test; °one-way ANOVA test.

(40.3 per cent). Neoadjuvant chemotherapy (NAC) was prescribed in 11.2 per cent of PgR+ cases, and in 13.5 per cent of PgR- cases. Pathological complete response (pCR) rates were 10.1 per cent (25 of 247 patients) in those with PgR+ disease versus 18.0 per cent in those with PgR- disease (11 of 61) (P = 0.050). Of the HR+, HER2+ cohort, 67.5 per cent were PgR+ and 32.5 per cent PgR- respectively. Of those achieving pCR with PgR+ disease, 44.0 per cent had HER2+ disease (11 of 25 patients), and 36.4 per cent of those with PgR-/HER2+ disease achieved successful pCR (4 of 11). The vast majority of patients received EHT (98.2 per cent). Of the 47 patients who did not receive EHT, 19 (40.4 per cent) refused therapy, seven were considered a venous thromboembolic risk (14.9 per cent) and 21 were lost to follow-up (44.7 per cent). Patients with PgR+ disease were more likely to receive EHT than those with PgR- disease (98.4 versus 96.7 per cent). Twenty-seven of the 289 HER2+ patients (9.3 per cent) did not receive anti-HER2 therapy (i.e., Trastuzumab), as a result of poor tolerance, co-morbid state or patient preference. The impact of radiotherapy (XRT) and PgR status on survival is outlined in Appendix S2.

Oncological outcome based on PgR status

The median overall survival (OS) was 84 (range 3.0–280.6) months and 5-year OS was 88.8 per cent (2362 of 2660 patients). The median DFS was 81 (range 3.0–272.2) months and 5-year DFS was 90.3 per cent (2401 of 2660 patients). For patients with PgR+ disease, local recurrence rates were 2.0 per cent (45 of 2208) versus 2.4 per cent in those with PgR- disease (11 of 452) (P = 0.599). Distant recurrence rate was 11.7 per cent in those with PgR+ cancer (258 of 2208) versus 15.0 per cent in PgR- disease at median follow-up (68 of 452) (P = 0.049).
Kaplan–Meier analyses demonstrated significantly worse 5-year DFS (91.0 versus 85.8 per cent, P = 0.003) and OS (90.0 versus 83.9 per cent, P < 0.001) for patients with PgR- BC (Fig. 1). This survival difference remained in multivariable analysis, where PgR independently predicted worse DFS (HR 1.632) and OS (HR 1.774) (Tables 4 and 5).

On Kaplan–Meier analysis, treatment with systemic AC was not associated with DFS irrespective of PgR status, but it was associated with improved OS for both cohorts (Fig. 2). However, this did not reach statistical significance in multivariable analysis (Table 5). Subgroup analysis based on HER2 status demonstrated that patients with PgR-/HER2- disease had a worse DFS (5-year DFS 85.7 versus 89.6 per cent, P = 0.059) and OS (5-year OS 82.0 versus 91.0 per cent, P = 0.004) compared with their PgR+ /HER2− counterparts (Fig. 3). In patients with HER2+ disease, PgR status failed to impact survival outcomes significantly (Fig. 3). However, HER2 status was not an independent predictor of survival in multivariable analysis (Table 5).

Other factors associated with DFS and OS in multivariable analysis

Other independent predictors of worse DFS in multivariable analysis included age greater than 65 years at diagnosis (HR 1.499), being symptomatic at presentation (HR 2.810), grade 3 tumours (HR 1.546), clinical nodal stage (HR 1.907) and requiring mastectomy (HR 1.935) (Table 4). Similarly, age at diagnosis greater than 65 years (HR 2.249), being postmenopausal at diagnosis (HR 1.482), being symptomatic at presentation (HR 2.121),

Table 4 Univariable and multivariable Cox hazard regression analyses for clinicopathological patient and treatment factors associated with worse disease-free survival within oestrogen-receptor-positive breast cancer patients

| Parameter                        | Hazard ratio (95% CI) | P        | Hazard ratio (95% CI) | P        |
|----------------------------------|-----------------------|----------|-----------------------|----------|
| Age >65 years                    | 1.855 (1.462–2.353)   | <0.001   | 1.499 (1.152–1.950)   | 0.003    |
| Being postmenopausal at diagnosis| 0.976 (0.758–1.256)   | 0.849    |                       |          |
| Presentation (symptomatic)       | 4.799 (3.047–7.559)   | <0.001   | 2.810 (1.713–4.608)   | <0.001   |
| Left breast affected             | 1.000 (0.999–1.002)   | 0.789    |                       |          |
| Invasive component               | 0.996 (0.980–1.013)   | 0.646    |                       |          |
| IDC subtype                      | 1.102 (0.862–1.408)   | 0.440    |                       |          |
| Size >50 mm                      | 3.018 (2.294–3.971)   | <0.001   |                       |          |
| High grade                       | 2.040 (1.616–2.576)   | <0.001   | 1.546 (1.196–2.000)   | 0.001    |
| Lymphovascular invasion          | 1.000 (0.999–1.000)   | 0.007    |                       |          |
| Perineural invasion              | 1.000 (1.000–1.000)   | 0.178    |                       |          |
| PgR+                             | 1.354 (1.020–1.796)   | 0.036    | 1.632 (1.209–2.204)   | 0.001    |
| PgR−                             | 0.999 (0.999–1.000)   | 0.004    |                       |          |
| HER2+                            |                       |          |                       |          |
| HER2−                            |                       |          |                       |          |
| Clinical T-stage                 | 3.176 (2.442–4.132)   | <0.001   |                       |          |
| Clinical N-stage                 | 3.273 (2.578–4.157)   | <0.001   | 1.907 (1.437–2.530)   | <0.001   |
| Neoadjuvant chemotherapy         | 1.000 (0.999–1.001)   | 0.995    |                       |          |
| Mastectomy                       | 2.072 (1.735–2.476)   | <0.001   | 1.935 (1.468–2.551)   | <0.001   |
| High ODX                         | 1.934 (0.768–4.873)   | 0.162    |                       |          |
| Adjuvant chemotherapy            | 1.000 (1.000–1.000)   | 0.757    |                       |          |
| Adjuvant radiotherapy            | 0.661 (0.505–0.865)   | 0.003    |                       |          |
| SERM/AI                          | 1.507 (0.623–3.648)   | 0.363    |                       |          |

Values in parentheses are 95% confidence intervals. PgR+, progesterone receptor positivity; PgR−, progesterone receptor negativity; ER, oestrogen receptor; HER, human epidermal growth factor receptor-2; IDC, invasive ductal carcinoma; ODX, OncotypeDXTM genomic testing; SERM, selective oestrogen receptor modulator; AI, aromatase inhibitor.
Table 5 Univariable and multivariable Cox hazard regression analyses for clinicopathological patient and treatment factors associated with worse overall survival within oestrogen-receptor-positive breast cancer

| Parameter                           | Hazard ratio Univariable | P       | Hazard ratio Multivariable | P       |
|-------------------------------------|--------------------------|---------|---------------------------|---------|
| Age >65 years                       | 3.291 (2.655–4.080)      | <0.001  | 2.249 (1.652–3.060)       | <0.001  |
| Being postmenopausal at diagnosis   | 1.746 (1.336–2.284)      | <0.001  | 1.482 (1.035–2.121)       | 0.032   |
| Presentation (symptomatic)          | 3.921 (2.626–5.856)      | <0.001  | 2.121 (1.254–3.590)       | 0.005   |
| Left breast affected                | 1.000 (0.999–1.002)      | 0.838   |                           |         |
| Invasive component                  | 0.996 (0.983–1.010)      | 0.613   |                           |         |
| IDC subtype                         | 1.163 (0.917–1.475)      | 0.213   |                           |         |
| Size >50 mm                         | 3.007 (2.309–3.918)      | <0.001  |                           |         |
| High grade                          | 1.820 (1.449–2.285)      | <0.001  | 1.448 (1.112–1.885)       | 0.006   |
| Lymphovascular invasion             | 1.000 (0.999–1.001)      | 0.25    |                           |         |
| Perineural invasion                 | 1.000 (1.000–1.000)      | 0.475   |                           |         |
| PgR-HER2+                           | 0.999 (0.998–1.000)      | <0.001  | 1.774 (1.324–2.375)       | <0.001  |
| Clinical T-stage                    | 3.567 (2.786–4.568)      | <0.001  | 1.784 (1.004–3.170)       | 0.049   |
| Clinical N-stage                    | 2.973 (2.360–3.745)      | <0.001  | 2.016 (1.511–2.690)       | <0.001  |
| Neoadjuvant chemotherapy            | 1.000 (0.999–1.001)      | 0.452   |                           |         |
| Mastectomy                          | 2.003 (1.616–2.482)      | <0.001  | 1.341 (1.011–1.780)       | 0.042   |
| High ODX                            | 1.877 (0.602–5.852)      | 0.278   |                           |         |
| Adjuvant chemotherapy               | 1.000 (1.000–1.000)      | 0.287   |                           |         |
| Adjuvant radiotherapy               | 0.564 (0.440–0.723)      | <0.001  | 0.593 (0.440–0.799)       | 0.001   |
| SERM/AI                             | 1.142 (0.540–2.414)      | 0.729   |                           |         |

Values in parentheses are 95% confidence intervals. PgR+, progesterone receptor positivity; PgR-, progesterone receptor negativity; ER, oestrogen receptor; HER, human epidermal growth factor receptor 2; IDC, invasive ductal carcinoma subtype; ODx, Oncotype DX genomic testing; SERM, selective oestrogen receptor modulator; AI, aromatase inhibitor.

Discussion

This large retrospective cohort study analysed the clinical features and prognostic significance of PgR expression in patients diagnosed with ER+ BC in a tertiary referral centre. Patients with PgR- disease were more likely to be postmenopausal at the time of diagnosis, symptomatic at presentation and to have a high histological grade. Oncological outcomes were worse in patients diagnosed with PgR- BC versus their PgR+ counterparts, and this effect was independent of other clinicopathological and treatment factors. These results are consistent with other studies and a recent meta-analysis, where PgR negativity independently predicted worse oncological outcome in patients with ER+ BC.14,16

These data suggest that PgR assessment should remain part of routine work-up for all patients diagnosed with ER+ BC to inform patient prognosis better and aid the clinical decision-making process.

A number of studies have described PgR- BC independently predicting high RS21,32, and the present series highlights the increased incidence of high RS in PgR- BC (11.7 per cent in PgR- vs 3.5 per cent in PgR+). This is unsurprising as ODx score is derived from an equation which is largely dependent upon ER, PgR, ERBB2 (HER2) scores25, and it has been proposed that statistical models based on clinicopathological information such as PgR status could act as a surrogate in situations where ODx testing is not affordable or routinely available.19 While the Trial Assigning Individualized Options for Treatment (TAILORx trial) demonstrated the limited impact of chemotherapy in women with ER+, HER2-, LN- BC with an RS in the mid-range (11 to 25) there is evidence that low-grade, PgR- tumours should not be considered low risk regardless of RS.23 Moreover, the typical patient enrolled in TAILORx was 55 years old, had a 1.5-cm, intermediate-grade, PgR+ tumour with an RS of 17, making it difficult to extrapolate this data for younger women, with high-grade tumours or with PgR- disease. Consequently, PgR status may also help inform clinical decision-making when used in combination with ODx, particularly in intermediate-risk groups.24

One in eight patients in this study received NAC, and PgR expression significantly affected pathological response rates in those in receipt of this therapy. The use of NAC in HR+ BC is usually reserved for patients with locally advanced (IIb, IIIa, IIIb, or IIIc) disease, in those with HER2+ disease, in patients hoping to achieve breast conservation surgery (BCS) with increased tumour to breast ratio and in patients who require preoperative downstaging.33 Although ER+ cancers do respond to NAC, pCR rates are typically low, reaching only 10–15 per cent in most trials35, and results from this study mirror these reports (11.7 per cent). However, there is evidence that patients in the ER+/PgR-, HER-group are more likely to undergo BCS compared with the ER+, PgR+, HER-group (62 versus 29 per cent) after NAC.36 pCR results in this study are consistent with a pooled analysis of 10 prospective RCTs containing data from 5613 patients illustrating that ER+/PgR- cohorts have higher rates of pCR than those with ER+/PgR+ disease (PgR- 18.0 per cent versus PgR+ 10.1 per cent).36,37 PgR negativity is also an independent predictor of axillary nodal pCR in this group, which is associated with long-term clinical benefit in BC.39 While preliminary data suggest that genomic panel-based recurrence score tests, such as ODx,37 may be expanded to the neoadjuvant setting to help predict response to NAC for ER+ disease, these results require further validation. In the interim, PgR status should remain an important determinant in guiding NAC prescription and predicting response for this cohort of patients.38

The prognostic and predictive role of HER2 expression in BC is well described.39 In this study, HER2 positivity (HER2+) was found in 20.8 per cent of the ER+/PgR- group versus 8.83 per cent of the ER+/PgR+ group, consistent with other reports.36,40 PgR- mediated crosstalk with epidermal growth factor receptor has been provided as the rationale for the increased incidence of HER2.
expression in the ER+/PgR- group. Bae and colleagues previously demonstrated that there is little difference in survival outcomes based on PgR status in HER2+ patients, as they respond better to contemporary multimodal treatment, including systemic chemotherapy and targeted anti-HER2 therapy. In contrast, patients with ER+/PgR-/HER2- disease had worse oncological outcomes than their PgR+ counterparts. These results are confirmed in the present study, with PgR-/HER2- patients exhibiting significantly worse OS than PgR+/HER2- disease, while those with HER2+ disease displayed similar survival outcome irrespective of PgR status. These results reiterate that more aggressive treatment of patients with ER+/PgR-/HER2- disease is warranted in clinical practice, particularly given that survival outcomes for this cohort are equivalent to those with triple negative BC (TNBC) after 10 years.

Molecular cross-talk between ER and growth-factor-receptor signalling pathways leads to modulation of both ER and PgR function. It has been proposed that PgR negativity may indicate impaired growth factor signalling via the PI3K-Akt-MTOR pathway with resultant resistance to tamoxifen. At present PgR status is not considered to confer selective advantage between EHT types and ER status remains the only factor predictive of tamoxifen benefit. However, the absence of this synergistic response to EHT and relative endocrine resistance is a possible explanation for the worse outcomes associated with PgR- disease. These data, perhaps conscious consideration should be given to novel therapeutic strategies when treating patients with the PgR- subtype, particularly in cases of HER2- disease where the option of targeted anti-HER2 therapy or systemic chemotherapy may not be clinically indicated.

Alternative, the development of therapeutics capable of converting PgR- to PgR+ BC may offer a potential approach to ameliorate the worse prognosis of PgR- disease. Despite their worse prognosis, the authors advocate no change to surgical practice for patients with PgR- disease. Even in the analyses of the most aggressive of TNBCs, the introduction of more radical surgery has failed to improve prognosis and can cause increased morbidity. Relatedly, the association of mastectomy with worse survival is reflective of the underlying...
Mastectomy is typically indicated for tumours at advanced stages, where BCS is not feasible. In this study, patients undergoing mastectomy were more likely to have higher grade (30.6% versus 20.3% grade 3 tumours), more advanced nodal disease (25.0% versus 6.4% per cent) and distant metastasis (9.3% versus 2.6% per cent), and were more likely to require NAC (21.6% versus 7.4% per cent) than those undergoing BCS. It is somewhat surprising that receipt of XRT was associated with improved OS but not DFS in multivariable analysis, given it is an integral component of locoregional therapy. However, randomized data and meta-analyses demonstrate that the addition of XRT to surgery, regardless of surgical approach (BCS or mastectomy), appears to reduce the risk of distant recurrences and death. This may suggest an ‘abscopal’ or immunogenic effect beyond the immediate zone of locoregional irradiation that alters the natural history of distant micrometastases. However, the selection bias to spare older, more co-morbid patients the additional burden of XRT is an important confounder.

This study is subject to the inherent limitations of a single-centre, retrospective cohort study, including selection, ascertainment and confounding bias. The study time period also coincided with changes towards a refined approach to AC prescription within the ER+/HER2-/-LN- cohort, following publication of the results of the TAILORx study from Sparano and co-workers in 2018. Despite outlining the lack of consideration for the role PgR status in therapeutic decision making, the authors acknowledge that RS relies upon genomic information with regard to PgR receptor expression, which subsequently contributes to chemoendocrine prescription.

Acknowledgement
No funding was received for this study. M.G.D. and É.J.R. contributed equally to the manuscript.

Disclosure. The authors declare no conflict of interest.

Supplementary material
Supplementary material is available at BJS Open online.
References

1. Carey LA, Perou CM, Livasy CA, Dressler LG, Cowan D, Conway K et al. Race, breast cancer subtypes, and survival in the Carolina Breast Cancer Study. JAMA 2006; 295: 2492–2502
2. Lowery AJ, Kell MR, Glynn RW, Kerin MJ, Sweeney KJ. Locoregional recurrence after breast cancer surgery: a systematic review by receptor phenotype. Breast Cancer Res 2012; 133: 831–841
3. Sotiriou C, Neo S-Y, McShane LM, Korn EL, Long PM, Jazaeri A et al. Breast cancer classification and prognosis based on gene expression profiles from a population-based study. Proc Natl Acad Sci USA 2003; 100: 10393–10398
4. Fisher B, Costantino J, Redmond C, Poisson R, Bowman D, Couture J et al. A randomized clinical trial evaluating tamoxifen in the treatment of patients with node-negative breast cancer who have estrogen-receptor-positive tumors. N Engl J Med 1989; 320: 479–484
5. Slamon DJ, Fasching PA, Patel R, Verma S, Hurvitz SA, Chia SKL et al. NATALE: Phase III study of ribociclib (RIBO) + endocrine therapy (ET) as adjuvant treatment in hormone receptor-positive (HR+), human epidermal growth factor receptor 2-negative (HER2-) early breast cancer (EC). J Clin Oncol 2019; 37: TP5597
6. Thomas C, Gustafsson J. The different roles of ER subtypes in cancer biology and therapy. Nat Rev Cancer 2011; 11: 597–608
7. Bartlett JMS, Brookes CL, Robson T, van de Velde CJH, Billingham LJ, Campbell FM et al. Estrogen receptor and progesterone receptor as predictive biomarkers of response to endocrine therapy: a prospectively powered pathology study in the Tamoxifen and Exemestane Adjuvant Multinational trial. J Clin Oncol 2011; 29: 1531–1538
8. Daniel AR, Hagan CR, Lange CA. Progesterone receptor action: defining a role in breast cancer. Expert Rev Endocrinol Metab 2011; 6: 359–369
9. Howell A, Cuzick J, Baum M, Buzdar A, Dowsett M, Forbes JF, Hoctin-Boes G, Houghton J, Locker DY, Tobias JS; ATAC Trialists’ Group. Results of the ATAC (Arimidex, Tamoxifen, Alone or in Combination) trial after completion of 5 years’ adjuvant treatment for breast cancer. Lancet 2005; 365: 60–62
10. Diep CH, Ahrendt H, Lange CA. Progesterone induces progesterone receptor gene (PGR) expression via rapid activation of protein kinase pathways required for cooperative estrogen receptor alpha (ER) and progesterone receptor (PR) genomic action at ER/PR target genes. Steroids 2016; 114: 48–58
11. Cui X, Schiff R, Arpino G, Osborne CK, Lee AV. Biology of progesterone receptor loss in breast cancer and its implications for endocrine therapy. J Clin Oncol 2005; 23: 7721–7735
12. Colditz GA, Rosner BA, Chen WJ, Holmes MD, Hankinson SE. Risk factors for breast cancer according to estrogen and progesterone receptor status. J Natl Cancer Inst 2004; 96: 218–228
13. Foley NM, Coll JM, Sheehan M, van de Velde CJH, Billingham LJ, Campbell FM et al. Estrogen receptor and progesterone receptor as predictive biomarkers of response to endocrine therapy: a prospectively powered pathology study in the Tamoxifen and Exemestane Adjuvant Multinational trial. J Clin Oncol 2011; 29: 1531–1538
14. Diep CH, Ahrendt H, Lange CA. Progesterone induces progesterone receptor gene (PGR) expression via rapid activation of protein kinase pathways required for cooperative estrogen receptor alpha (ER) and progesterone receptor (PR) genomic action at ER/PR target genes. Steroids 2016; 114: 48–58
15. Cui X, Schiff R, Arpino G, Osborne CK, Lee AV. Biology of progesterone receptor loss in breast cancer and its implications for endocrine therapy. J Clin Oncol 2005; 23: 7721–7735
16. Colditz GA, Rosner BA, Chen WJ, Holmes MD, Hankinson SE. Risk factors for breast cancer according to estrogen and progesterone receptor status. J Natl Cancer Inst 2004; 96: 218–228
17. Foley NM, Coll JM, Lowery AJ, Hynes SO, Kerin MJ, Sheehan M et al. Estrogen receptor and progesterone receptor status on oncological outcomes in oestrogen receptor-positive breast cancer. Br J Surg 2019; 107: 33–43
18. Jonat W, Bachelot T, Ruhstaller T, Kuss I, Reimann U, Robertson JFR et al. Randomized phase II study of lonaprisan as second-line therapy for progesterone receptor-positive breast cancer. Ann Oncol 2013; 24: 2543–2548
19. Andre F, Ismaila N, Henry NL, Somerfield MR, Bast RC, Barlow W et al. Use of biomarkers to guide decisions on adjuvant systemic therapy for women with early-stage invasive breast cancer: ASCO clinical practice guideline update—integration of results From TAILORx. J Clin Oncol 2019; 37: 1956–1964
20. Senkus E, Kyrriakides S, Obnoh S, Penault-Llorca F, Poormans P, Rutgers E et al. Primary breast cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol 2015; 26:v8–v30
21. McVeigh TP, Kerin MJ. Clinical use of the Oncotype DX genomic test to guide treatment decisions for patients with invasive breast cancer. Breast Cancer (Dove Med Press) 2017; 9: 393–400
22. Paik S, Shak S, Tang G, Kim C, Baker J, Cronin M et al. A multi-gene assay to predict recurrence of tamoxifen-treated, node-negative breast cancer. N Engl J Med 2004; 351: 2817–2826
23. Amin MB, Edge S, Greene F, Byrd DR, Brookland RK, Washington MK et al. (eds) AJCC Cancer Staging Manual (8th edn). Cham: Springer International Publishing, 2017.
24. Allred DC. Issues and updates: evaluating estrogen receptor-alpha and HER2 in breast cancer. Breast Cancer (Dove Med Press) 2017; 9: 881–884
25. Gage MM, Mylander WC, Rosman M, Fujii T, Le Du F, Couture J et al. Combined pathologic–genomic algorithm for early breast cancer. Breast Cancer (Dove Med Press) 2017; 9: 881–884
26. Bloom HJ, Richardson WW. Histological grading and prognosis in breast cancer; a study of 1409 cases of which 359 have been followed for 15 years. Br J Cancer 1957; 11: 359–377
27. Chen Z, Xu S, Xu W, Huang JIAN, Zhang GU, Lei LEI et al. Expression of cluster of differentiation 34 and vascular endothelial growth factor in breast cancer, and their prognostic significance. Oncol Lett 2015; 10: 723–729
28. Brown IS. Pathology of perineural spread. J Neurol Surg B Skull Base 2016; 77: 124–130
29. Dowsett M, Nielsen TO, A’Hern R, Bartlett J, Coombes RC, Cuzick J et al., International Ki67 in Breast Cancer Working Group. Assessment of Ki67 in breast cancer: recommendations from the International Ki67 in Breast Cancer working group. J Natl Cancer Inst 2011; 103: 1656–1664
30. Xue X, Agalliu I, Kim MY, Wang T, Lin J, Ghavamian R et al. New methods for estimating follow-up rates in cohort studies. BMC Med Res Methodol 2017; 17: 155
31. Gage MM, Mylander WC, Rosman M, Fujii T, Le Du F, Couture J et al. Combined pathologic–genomic algorithm for early-stage breast cancer improves cost-effective use of the 21-gene recurrence score assay. Ann Oncol 2018; 29: 1280–1285
32. Chaudhary LN, Jawa Z, Szabo A, Visotcky A, Chitambar CR. Relevance of progesterone receptor immunohistochemical staining to Oncotype DX recurrence score. Hematol Oncol Stem Cell Ther 2016; 9: 48–54

Downloaded from https://academic.oup.com/bjsopen/article-lookup/doi/10.1093/bjsi/zxab040 by guest on 03 June 2021
33. Orucievic A, Bell JL, McNabb AP, Heidel RE. Oncotype DX breast cancer recurrence score can be predicted with a novel nomogram using clinicopathologic data. Breast Cancer Res Treat 2017; 163:51–61
34. Crolley VE, Marashi H, Rawther S, Sirohi B, Parton M, Graham J et al. The impact of Oncotype DX breast cancer assay results on clinical practice: a UK experience. Breast Cancer Res Treat 2020; 180:809–817
35. Cortazar P, Zhang L, Untch M, Mehta K, Costantino JP, Wolmark N et al. Pathological complete response and long-term clinical benefit in breast cancer: the CTNeoBC pooled analysis. Lancet 2014; 384:164–172
36. Petruolo OA, Pilewskie M, Patil S, Barrio AV, Stempel M, Wen HY et al. Standard pathologic features can be used to identify a subset of estrogen receptor-positive, HER2 negative patients likely to benefit from neoadjuvant chemotherapy. Ann Surg Oncol 2017; 24:2556–2562
37. van Mackelenbergh MT, Denkert C, Nekljudova V, Karn T, Schem C, Marmé F et al. Outcome after neoadjuvant chemotherapy in estrogen receptor-positive and progesterone receptor-negative breast cancer patients: a pooled analysis of individual patient data from ten prospectively randomized controlled neoadjuvant trials. Breast Cancer Res Treat 2018; 167:59–71
38. Pease AM, Riha LA, Gruner RA, Tung NM, James TA. Oncotype DX® recurrence score as a predictor of response to neoadjuvant chemotherapy. Ann Surg Oncol 2019; 26:366–371
39. Slamon D, Eiermann W, Robert N, Pienkowski T, Martin M, Press M et al. Adjuvant trastuzumab in HER2-positive breast cancer. N Engl J Med 2011; 365:1273–1283
40. Prat A, Cheang MCU, Martin M, Parker JS, Carrasco E, Caballero R et al. Prognostic significance of progesterone receptor-positive tumor cells within immunohistochemically defined luminal A breast cancer. J Clin Oncol 2013; 31:203–209
41. Bae SY, Kim S, Lee JH, Lee H-C, Lee SK, Kil WH et al. Poor prognosis of single receptor-positive hormone receptor breast cancer: similar outcome as triple-negative breast cancer. BMC Cancer 2015; 15:138–138
42. Robertson JF, Willsher PC, Winterbottom L, Blamey RW, Thorpe S. Onapristone, a progesterone receptor antagonist, as first-line therapy in primary breast cancer. Eur J Cancer 1999; 35:214–218
43. Cui X, Zhang P, Deng W, Oesterreich S, Lu Y, Mills GB et al. Insulin-like growth factor-I inhibits progesterone receptor expression in breast cancer cells via the phosphatidylinositol 3-kinase/Akt/mammalian target of rapamycin pathway: progesterone receptor as a potential indicator of growth factor activity in breast cancer. Mol Endocrinol 2003; 17:575–588
44. Petz LN, Ziegler YS, Schultz JR, Nardulli AM. Fos and Jun inhibit estrogen-induced transcription of the human progesterone receptor gene through an activator protein-1 site. Mol Endocrinol 2004; 18:521–532
45. Early Breast Cancer Trialists’ Collaborative Group (EBCTCG). Aromatase inhibitors versus tamoxifen in early breast cancer: patient-level meta-analysis of the randomised trials. Lancet 2015; 386:1341–1352
46. Davies C, Godwin J, Gray R, Clarke M, Cutter D, Darby S, McGale P, Pan HC, Taylor C, Wang YC, Dowsett M, Ingle J, Peto R. Relevance of breast cancer hormone receptors and other factors to the efficacy of adjuvant tamoxifen: patient-level meta-analysis of randomised trials. Lancet 2011; 378:771–784
47. Singhal H, Greene ME, Zarnike AL, Laine M, Al Abosy R, Chang Y-F et al. Progestosterone receptor isoforms, agonists and antagonists differentially reprogram estrogen signaling. Oncotarget 2018; 9:4282–4300
48. Lee A, Djamgoz M&A. Triple negative breast cancer: emerging therapeutic modalities and novel combination therapies. Cancer Treat Rev 2018; 62:110–122
49. Ahn S, Kim HJ, Kim M, Chung YR, Kang E, Kim E-K et al. Negative conversion of progesterone receptor status after primary systemic therapy is associated with poor clinical outcome in patients with breast cancer. Cancer Res Treat 2018; 50:1418–1432
50. Chen Q-X, Wang X-X, Lin P-Y, Zhang J, Li J-J, Song C-G et al. The different outcomes between breast-conserving surgery and mastectomy in triple-negative breast cancer: a population-based study from the SEER 18 database. Oncotarget 2017; 8:4773–4780
51. El-Tamer MB, Ward BM, Schiffner T, Neumayer L, Khuri S, Henderson W et al. Morbidity and mortality following breast cancer surgery in women: national benchmarks for standards of care. Ann Surg 2007; 245:665–671
52. Corradi S, Reitz D, Pazos M, Schönecker S, Braun M, Harbeck N et al. Mastectomy or breast-conserving therapy for early breast cancer in real-life clinical practice: outcome comparison of 7565 Cases. Cancers 2019; 11:160
53. Agarwal S, Pappas L, Neumayer L, Kokeny K, Agarwal J. Effect of breast conservation therapy vs mastectomy on disease-specific survival for early-stage breast cancer. JAMA Surg 2014; 149:267–274
54. Ragaz J, Olivotto IA, Spinelli JJ, Phillips N, Jackson SM, Wilson KS et al. Locoregional radiation therapy in patients with high-risk breast cancer receiving adjuvant chemotherapy: 20-year results of the British Columbia randomized trial. J Natl Cancer Inst 2005; 97:116–126
55. Early Breast Cancer Trialists’ Collaborative Group (EBCTCG); Darby S, McGale P, Correa C, Taylor C, Arriagada R, Clarke M et al. Effect of radiotherapy after breast-conserving surgery on 10-year recurrence and 15-year breast cancer death: meta-analysis of individual patient data for 10 801 women in 17 randomised trials. Lancet 2011; 378:1707–1716
56. Jatoi I, Benson JR, Kunkler I. Hypothesis: can the abscopal effect explain the impact of adjuvant radiotherapy on breast cancer mortality? NPJ Breast Cancer 2018; 4:8
57. Sparano JA, Gray RJ, Makower DF, Pritchard KI, Albain KS, Hayes DF et al. Adjuvant chemotherapy guided by a 21-gene expression assay in breast cancer. N Engl J Med 2018; 379:111–121