

Original article

Recurrence in early breast cancer: Analysis of data from 3,765 Australian women treated between 1997 and 2015

Robin Stuart-Harris^{a, b, *}, Jane E. Dahlstrom^{b, c}, Ruta Gupta^c, Yanping Zhang^d, Paul Craft^{a, b}, Bruce Shadbolt^{b, e}

^a Medical Oncology Unit, The Canberra Hospital, Woden, ACT 2606, Australia

^b ANU Medical School, Australian National University, Barry Drive, Acton, ACT 0200, Australia

^c ACT Pathology, The Canberra Hospital, Woden, ACT 2606, Australia

^d ACT and SE NSW Breast Cancer Treatment Group, ACT Health, GPO Box 825, ACT 2601, Australia

^e Health Analytics Research Centre, ACT Health, GPO Box 825, ACT 2601, Australia



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ABSTRACT

Background: Evidence suggests recent improvements in outcome in early breast cancer (EBC).

Aim: To analyse recurrence in women with EBC from our region from 1997 to 2015.

Methods: We analysed recurrence in 3,765 women with EBC. Median follow up was 83.0 months. 62.5% had a symptomatic presentation. 81.8% were hormone receptor positive and 38.5% were node positive. Lymphovascular invasion (LVI) was present in 24.3%. Of the 2,686 women entered from 2002 onwards tested for HER2 status, 72.7% had a luminal tumour, 15.2% had a HER2+ tumour and 12.1% had a triple negative (TN) tumour.

Results: Recurrence occurred in 459 (12.2%), predominantly in distant sites (71.7%). In women entered from 2002 onwards, the five and 10 year recurrence rates were significantly lower in the luminal group than the HER2+ and the TN groups. Few recurrences occurred in HER2+ and TN cancers after 36 months. On multivariate analysis the following were associated with a significantly increased risk of recurrence: nodal involvement ($p < 0.0001$), tumour grade ($p < 0.0001$), symptomatic presentation ($p < 0.0001$), presence of LVI ($p = 0.001$), non-luminal tumour type ($p < 0.0001$) and tumour size >50 mm ($p = 0.02$).

Conclusion: The recurrence rate in this series was much lower than in previous older series. Lymph node involvement, tumour grade, symptomatic presentation, presence of LVI, non-luminal tumour type and tumour size (>50 mm) were associated with an increased risk of recurrence. We strongly recommend that clinicians include the presence of LVI and symptomatic presentation as well as the other established tumour factors, when assessing the risk of recurrence in women with EBC.

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1. Introduction

Between 1990 and 2000, there was a significant decrease in the mortality from breast cancer in Australia, where the mortality rate fell from approximately 50 per 100,000 in women aged 35–69 years in 1990 to about 38 per 100,000 by 2000 [1]. The cause of the reduction is multifactorial including breast screening and improvements in the management of EBC. Nevertheless, a significant proportion of women with EBC develop recurrence.

Factors previously reported to be associated with an increased

chance of recurrence and/or death from breast cancer include young age at diagnosis [2], tumour morphology (ductal versus lobular) [3], increased tumour size [4], higher tumour grade [5], the presence of LVI [6], axillary node involvement [7], negative hormone receptor (HR) status [8] and overexpressed tumour human epidermal growth factor receptor 2 (HER2) status [9].

In 2000, Perou reclassified breast cancers into luminal, HER2 enriched, normal breast like and basal subtypes, on the basis of molecular profiling [10]. Subsequently, Sorlie suggested that the luminal group be split into luminal A and luminal B [11]. This new classification has assisted clinicians to predict the natural history of breast cancers, more accurately. Genetic profiling of breast cancers has led to the identification of genetic signatures that help predict the risk of recurrence. However, there is still a need to establish

* Corresponding author. Medical Oncology Unit, The Canberra Hospital, Woden, ACT 2606, Australia.

E-mail address: robin.stuart-harris@act.gov.au (R. Stuart-Harris).

other prognostic factors for recurrence.

Different breast cancer types have different recurrence patterns. HER2 positive (HER2+) and basal like cancers recur earlier than luminal A cancers [12]. Luminal breast cancers recur at a low but steady rate and at 6–8 years following diagnosis, the risk of death from high risk breast cancers [13] may be lower than low risk breast cancers [13].

In 1997, we began an audit of the women with EBC from our region (the Australian Capital Territory and South East New South Wales). We investigated recurrence in women with EBC enrolled into this project from March 1997 to March 2015. Follow up was until March 2015.

2. Materials and methods

Eligibility criteria required subjects to be female, have invasive breast cancer without evidence of spread to distant sites. Outcome information was sought from the patient's clinicians or their General Practitioner.

Data collected included: age at diagnosis, menopausal status, how their breast cancer was discovered, their surgery, tumour histopathology, adjuvant treatment(s) received and their outcome at last follow up. Menopausal status was defined as premenopausal, postmenopausal, and perimenopausal if less than two years from their last menstrual period. Tumour histology was classed as invasive ductal cancer (IDC), invasive lobular cancer (ILC), special (mixed histologies, medullary, colloid, tubular and adenoid cystic carcinomas) and other (micropapillary, neuroendocrine, micro-invasive, metaplastic, clear cell, and apocrine carcinoma). A micrometastasis in a lymph node was classed as a positive node, but isolated tumour cells was classed as a negative node, consistent with the AJCC guidelines [14]. Testing for oestrogen receptor (ER) and progesterone receptor (PgR) status was by immunohistochemistry (IHC). Testing for tumour HER2 status by IHC began in December 2002 and testing for HER2 by in situ hybridisation began in July 2007. Testing for Ki67 by IHC began in March 2009. For mixed tumours or tumours with more than one Ki67 value, the highest value was used. Tumours were classified using IHC results as gene expression profiling was not available. Tumour groups were defined as recommended previously [15].

Data were analysed using SPSS version 23. In addition to descriptive statistics, Kaplan Meier curves and logrank tests were used to examine patient, tumour and treatments factors and recurrence and survival of subjects with metastatic disease. Other univariate analyses (UVAs) and multivariate analyses (MVAs) used Cox proportional hazards regression. A two-tailed p value of <0.05 was considered significant.

3. Data

Duration of follow up was from the date of the patient's (first) surgery to the date of their last follow up. Maximum follow up was from March 1997 to March 2015. Subject, tumour and treatment factors were examined to identify factors associated with an increased risk of recurrence. Initially, multiple UVAs were performed. Factors associated with an increased risk of recurrence by the UVAs were then examined in a MVA.

4. Results

4.1. Demographics of the women (Table 1)

Three thousand eight hundred and eighteen women with EBC were enrolled after written informed consent. Fifty-three women were excluded because of loss to follow up or missing date of last

follow up, leaving 3,765. The median age was 57.6 years (interquartile range 49.2–66.3 years) and the median follow up was 83.0 months (interquartile range 42–112 months). Two thousand four hundred and forty three women (64.9%) were postmenopausal and 999 (26.5%) were premenopausal and 323 (8.6%) were perimenopausal. Two thousand three hundred and fifty-five women (62.5%) had a symptomatic presentation.

4.2. Tumour characteristics (Table 1)

78.7% had IDC, 6.6% had ILC, 6.1% had a cancer of special type and 8.6% had a tumour classed as other. Tumour size and grade are listed in Table 1. LVI was present in 24.3%, absent in 72.4%, but unknown in 3.2%. 5.0% had no axillary surgery. Of the 3,575 who had axillary surgery, 61.7% were node negative and 37.3% were node positive but nodal status was unknown in 1.0%. Overall, 81.8% of the tumours were HR positive (ER+ and/or PgR+), and 17.6% were HR negative (ER-PgR-). 69.2% were ER + PgR + but 12.6% were single HR positive. Tumour HER2 status was available in 72.4% and was overexpressed in 15.3%. Ki67 results were available for only 19.9% of the tumours.

From 2002 onwards, tumour HER2 status was available in 2,686 of the 2,816 women (95.4%) but tumour Ki67 results were available in only 685 (24.3%). Because of lack of Ki67 results, we were unable to subclassify luminal tumours into luminal A or B. Of the 2,686, 72.7% were classed as luminal, 15.2% were HER2+ and 12.1% were triple negative (TN).

4.3. Treatment (Table 2)

Treatment provided was in accordance with published guidelines, as stated previously [16]. All women had surgery. 49.4% had breast conserving surgery (BCS) and 50.6% had a mastectomy. Of the 3,575 who had axillary surgery, 37.9% had a sentinel lymph node biopsy (SLNB) only, 2.5% had axillary lymph node sampling (1–4 nodes), 18.9% had a SLNB followed by an axillary clearance and 40.8% had an axillary clearance only. Thus, a total of 59.6% had an axillary clearance. Of those who had BCS, 95.7% were offered radiotherapy (RT) and 96.8% received RT. Of those who had a mastectomy, 39.8% were offered postmastectomy RT and 94.1% received postmastectomy RT.

4.4. Systemic adjuvant therapies

50.5% were offered adjuvant chemotherapy and of these, 90.2% accepted chemotherapy. The chemotherapy was cyclophosphamide, methotrexate and 5-fluorouracil (CMF) in 20.2%, anthracycline based in 39.7%, taxane based in 10.7%, anthracycline plus taxane in 29.0% and other in 0.4%. Of the 408 women with HER2+ cancers from 2002 onwards, 49.0% received trastuzumab. Of the 3,080 women with a HR positive tumour, 88.7% received adjuvant endocrine therapy (AET). Of these, 68.9% received tamoxifen, 37.0% received an aromatase inhibitor, 1.2% had an oophorectomy, 1.0% received an LHRH agonist and 0.1% received another form of AET. 8.2% received more than one form of AET.

4.5. Recurrence

Recurrence occurred in 459 (12.2%). Recurrence was local in 13.3%, local plus regional in 3.5%, regional in 8.9%, local or regional plus distant in 8.7%, distant only in 63.0%, but site of recurrence was unknown in 2.6%. Of all recurrences, 71.7% were distant recurrences. The five year recurrence rate was 2.5% for grade 1 cancers, 6.8% for grade 2 cancers and 17.0% for grade 3 cancers. Women with nodal involvement had a higher risk of recurrence in

Table 1
Demographics of the 3,765 subjects and their breast cancer.

| Age | Median 57.6 years | IQR 49.2–66.3 years | | |
|----------------------------------|------------------------------|--|-----------------------------|---|
| Menopausal status (3,765) | Postmenopausal 2,443 (64.9%) | Premenopausal 999 (26.5%) | Perimenopausal 323 (8.6%) | |
| Presentation (3,765) | Symptomatic 2,355 (62.5%) | Asymptomatic 1,410 (37.5%) | | |
| Tumour histology (3,765) | IDC 2,964 (78.7%) | ILC 250 (6.6%) | Special 228 (6.1%) | Other 323 (8.6%) |
| Tumour grade (3,765) | Grade 1 876 (23.3%) | Grade 2 1,478 (39.3%) | Grade 3 1,371 (36.4%) | Unknown 40 (1.1%) |
| Tumour size (3,765) | 1–10 mm (T1) 782 (20.8%) | 11–20 mm (T1) 1,481 (39.3%) | 21–50 mm (T2) 1,287 (34.2%) | >50 mm (T3) 209 (5.6%) Unknown 6 (0.2%) |
| Lymphovascular invasion (3,765) | Present 916 (24.3%) | Absent 2,727 (72.4%) Unknown 122 (3.2%) | | |
| Nodal status (3,575) | Node negative 2,205 (61.7%) | Node positive 1,334 (37.3%) | Unknown 36 (1.0%) | 1–4 nodes positive 963/1,334 (72.2%) >4 nodes positive 371/1,334 (27.8%) |
| ER status (3,765) | ER+ 3,041 (80.8%) | ER- 707 (18.8%) | Unknown 17 (0.4%) | |
| PgR status (3,765) | PgR+ 2,644 (70.2%) | PgR- 1,100 (29.2%) | Unknown 21 (0.6%) | |
| ER/PgR status (3,765) | ER+PgR+ 2,604 (69.2%) | ER-PgR- 664 (17.6%) | ER+PgR- 436 (11.6%) | ER-PgR+ 40 (1.1%) ERPgR unknown 21 (0.6%) |
| HR status (3,765) | Positive 3,080 (81.8%) | Negative 664 (17.6%) | Unknown 21 (0.6%) | |
| HER2 Status Overall (2,726) | Positive 417 (15.3%) | Negative 2,309 (84.7%) | | |
| Tumour type 2002 onwards (2,686) | Luminal 1,953 (72.7%) | HER2 Enriched 408 (15.2%) | Triple negative 325 (12.1%) | |

IQR = Interquartile range; IDC = invasive ductal cancer; ILC = invasive lobular cancer; ER = oestrogen receptor; PgR = progesterone receptor; + = positive; - = negative; HR = hormone receptor; HER2 = human epidermal growth factor receptor 2.

Table 2
Treatment of the 3,765 subjects.

| | | | | | |
|---|---|----------------------------------|---|---------------------------------------|--|
| Surgery (3,765) | Breast conserving surgery 1,861 (49.4%) | Mastectomy 1,904 (50.6%) | | | |
| Axillary surgery (3,575) | SLNB only 1,354 (37.9%) | Axillary sampling only 89 (2.5%) | SLNB followed by axillary clearance 675 (18.9%) | Axillary clearance only 1,457 (40.8%) | Total axillary clearance 2,321 (59.6%) |
| Radiotherapy (accepted/offered) (2,436) | BCS 1,724/1,781 (96.8%) | | Mastectomy 712/757 (94.1%) | | |
| Adjuvant chemotherapy (accepted/offered) (1,903) | 1,903/2,109 (90.2%) | | | | |
| Adjuvant chemotherapy (1,903) | CMF 385 (20.2%) | Anthracycline based 755 (39.7%) | Taxane based 204 (10.7%) | Anthracycline & taxane 551 (29.0%) | Other 8 (0.4%) |
| Trastuzumab 2002 onwards (408 HER2+) | 200/408 (49.0%) | | | | |
| Adjuvant endocrine therapy [†] (3,080 HR+) | Total 2,732 (88.7%) | Tamoxifen 1,882 (68.9%) | AI 1,010 (37.0%) | OFS* 61 (2.2%) | Other 2 (0.1%) |

SLNB = Sentinel lymph node biopsy; BCS = breast conserving surgery; HER2 = Human epidermal growth factor receptor 2; [†] = 223 women (8.2%) had more than one form of adjuvant endocrine therapy; + = Positive; HR = Hormone receptor; AI = aromatase inhibitor; OFS = Ovarian function suppression; * includes oophorectomy and LHRH agonist.

Table 3
Recurrence and survival by tumour type (2002 onwards, 2,686 subjects).

| | Luminal | HER2 Enriched | Triple Negative |
|------------------------------------|----------------------|---|---|
| Recurrence (268) | 139/1,953 (7.1%) | 70/408 (17.2%) | 59/325 (18.2%) |
| Five year recurrence rate | 6.4% ± 0.6% (SE) | 15.3% ± 1.9% (SE) (vs. luminal p < 0.0001) | 16.6% ± 2.2% (SE) (vs. luminal p < 0.0001) |
| Ten year recurrence rate | 10.6% ± 1.0 (SE) | 24.4% ± 3.6 (SE) (vs luminal p = 0.01) | 26.4% ± 4.1 (SE) (vs luminal p = 0.03) |
| Metastatic Disease | | | |
| Distant metastases | 102 (5.2%) | 57 (14.0%) (p < 0.0001) | 37 (11.4%) (p < 0.0001) |
| Median survival metastatic disease | 60.0 months, SE 3.65 | 54.0 months, SE 12.81 (HER2 vs. luminal p = 0.83) | 36.0 months, SE 4.19 (TN vs. luminal p = 0.005) |

SE = Standard error; HER2 = Human epidermal growth factor receptor 2.

the first five and 10 years than women without nodal involvement ($p < 0.01$). There was no significant difference in recurrence rates for the following periods of diagnosis: 1997–2001, 2002–2006 and 2007 onwards.

4.6. Tumour type, recurrence and survival (Table 3, Fig. 1 and 2)

Of the 2,686 women diagnosed from 2002 onwards, recurrence occurred in 268 (10.0%). Recurrence occurred in 7.1% of the luminal cancers, 17.2% of the HER2+ cancers, and 18.2% of the TN

cancers. The five year recurrence rate for the luminal group (6.4%) was significantly lower than the HER2+ (15.3%, $p < 0.0001$) and the TN (16.6%, $p < 0.0001$) groups. The 10 year recurrence rate (10.6%) for the luminal group was also significantly lower than the HER2+ (24.4%, $p = 0.01$) and the TN groups (26.4%, $p = 0.03$). For HER2+ and TN cancers, few recurrences occurred after 36 months. Metastatic disease occurred significantly less frequently in the luminal group (5.2%) than the HER2+ (14.0%) and the TN groups (11.4%) ($p < 0.0001$, respectively). In those who developed metastatic disease, the median survival of women with TN cancers (36.0

Table 4
Patient, tumour and treatment factors associated with recurrence (UVA).

| | | | | |
|---|---|---|--|---|
| Age (ref group 60–69 years) | 20–29 Years $p = 0.02$, HR 2.84, (95% CI 1.15–6.99) | 30–39 Years $p = 0.001$, HR 2.15, (95% CI 1.50–3.09) | 40–49 Years $p = 0.003$, HR 1.51, (95% CI 1.15–1.99) | 70–79 Years $p = 0.005$, HR 1.59, (95% CI 1.15–2.21) |
| Tumour detection (ref group asymptomatic) | Symptomatic $p < 0.0001$, HR 3.11, (95% CI 2.44–3.96) | | | |
| Menopausal status (ref group postmenopausal) | Premenopausal $p = 0.002$, HR 1.36, (95% CI 1.12–1.66) | | | |
| FH breast cancer (ref group at or slightly above) | Strong FH $p = 0.03$, reduced risk, HR 0.63, (95% CI 0.41–0.95) | | | |
| Tumour size (ref group up to 10 mm) | 21–50 mm $p < 0.0001$, HR 2.99, (95% CI 2.20–4.05) | >50 mm $p < 0.0001$, HR 6.24, (95% CI 4.32–9.01) | | |
| Tumour histology (ref group IDC) | Special reduced risk $p = 0.0001$, HR 0.28, (95% CI 0.15–0.54) | Other reduced $p = 0.05$, HR 0.66, (95% CI 0.44–1.01) | | |
| Tumour type 2002 Onwards (ref group luminal) | HER2 enriched $p < 0.0001$, HR 2.59, (95% CI 1.94–3.45) | Triple negative $p < 0.0001$, HR 2.81, (95% CI 2.07–3.81) | | |
| Tumour grade (ref group grade 1) | Grade 2 $p < 0.0001$, HR 2.04, (95% CI 1.48–2.83) | Grade 3 $p < 0.0001$, HR 4.66, (95% CI 3.43–6.33) | | |
| Lymphovascular invasion (ref group absent) | Present $p < 0.0001$, HR 3.92, (95% CI 2.73–3.97) | Unknown $p < 0.0001$, HR 2.21, (95% CI 1.42–3.42) | LVI present, node negative ($p < 0.0001$) | LVI present, node positive ($p < 0.0001$) |
| Nodal involvement (ref group not involved) | 1–4 involved nodes $p < 0.0001$, HR 2.49, (95% CI 1.99–3.11) | >4 involved nodes $p < 0.0001$, HR 6.63, (95% CI 5.23–8.40) | >4 involved nodes versus 1–4 involved nodes ($p < 0.0001$) | |
| Hormone receptor status (ref group positive) | Negative $p < 0.0001$, HR 2.45, (95% CI 2.01–2.99) | Negative versus single hormone receptor positive ($p < 0.0001$) | | |
| Ki67 (ref group <14%) | $\geq 14\%$ ($p = 0.009$) | $\geq 20\%$ ($p = 0.006$) | $\geq 25\%$ ($p = 0.002$) | |
| Surgery (ref group BCS) | Mastectomy $p < 0.0001$, HR 1.86, (95% CI 1.54–2.55) | | | |
| Chemotherapy (ref group no chemotherapy) | Chemotherapy $p < 0.0001$, HR 2.42, (95% CI 1.97–2.97) | | | |
| Postmastectomy radiotherapy (ref group no radiotherapy) | Radiotherapy $p < 0.0001$, HR 2.70, (95% CI 2.14–3.40) | | | |

UVA = Univariate analysis; ref group = reference group; HR = Hazard ratio; 95% CI = 95% confidence intervals; FH = family history; IDC = invasive ductal cancer; HER2 = human epidermal growth factor; BCS = breast conserving surgery.

Table 5
Multivariate analysis of factors associated with increased risk of recurrence on UVA (3,765).

| Step Entered | Factor | Hazard Ratio (95% CI) | p value |
|--------------|---|-----------------------|---------|
| 1 | Nodal involvement (ref group negative) | | |
| | 1–4 | 1.88 (1.47–2.39) | <0.0001 |
| | >4 | 3.19 (2.38–4.28) | <0.0001 |
| 2 | Tumour grade (ref group grade 1) | | |
| | Grade 2 | 1.44 (1.02–2.03) | 0.04 |
| | Grade 3 | 2.15 (1.51–3.06) | <0.0001 |
| 3 | Symptomatic presentation (ref group asymptomatic) | | |
| | Symptomatic | 1.70 (1.30–2.23) | <0.0001 |
| 4 | LVI (ref group absent) | | |
| | Present | 1.46 (1.16–1.83) | 0.001 |
| | Unknown | 2.17 (1.38–3.41) | 0.001 |
| 5 | Hormone receptor (ref group positive) | | |
| | Negative | 1.51 (1.20–1.90) | <0.0001 |
| 6 | Tumour size (ref group <11 mm) | | |
| | 11–20 mm | 0.81 (0.57–1.15) | NS |
| | 21–50 mm | 1.07 (0.75–1.53) | NS |
| | >50 mm | 1.64 (1.07–2.53) | 0.02 |

UVA = Univariate analysis; CI = Confidence intervals; ref group = reference group; LVI = lymphovascular invasion; NS = Not significant.

months, SE 4.19) was significantly shorter than for women with luminal cancers (60.0 months, SE 3.65, $p = 0.005$) but the survival of women with HER2+ cancers (54.0 months, SE 12.81) was not significantly different to that for women with luminal cancers.

4.7. Factors associated with an increased risk of recurrence: UVA (Table 4)

UVAs were performed to determine which patient, tumour and treatment factors were associated with an increased risk of recurrence. Patient factors were: age at diagnosis, type of presentation (symptomatic versus asymptomatic), menopausal status, and risk of breast cancer by the clinician's assessment. Tumour factors were: the presence of multiple tumours, tumour type, size, site, histology,

grade, HR status, Ki67 value, HER2 status, the presence of LVI, and nodal involvement. Treatment factors were: type of surgery, axillary surgery, systemic adjuvant therapies received (chemotherapy, AET, trastuzumab) and postmastectomy RT.

4.8. Patient factors

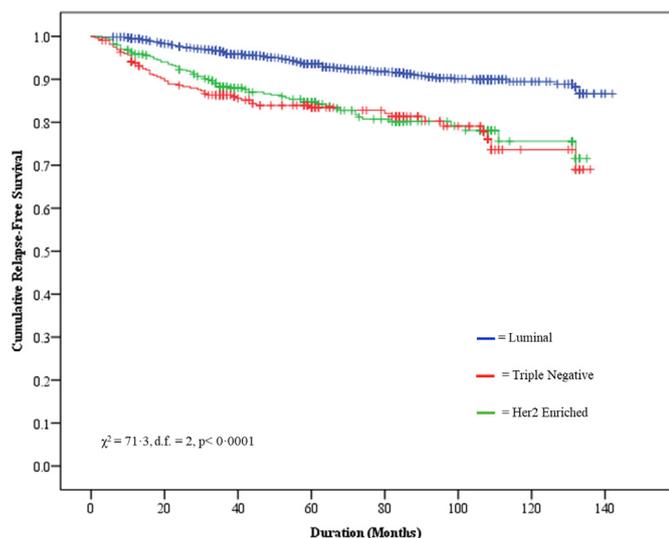
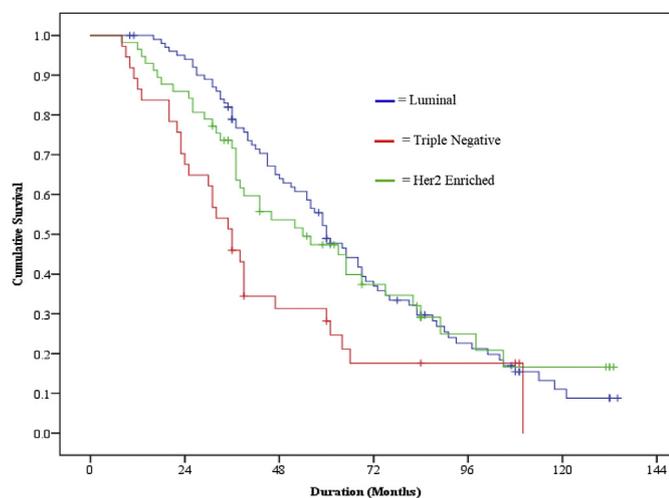
For age at diagnosis, 60–69 years was the reference group. Women in the following age groups had significantly increased risks of recurrence: 20–29 years, 30–39 years, 40–49 years and 70–79 years. Those with a symptomatic presentation were significantly more likely to develop recurrence than those asymptomatic at presentation ($p < 0.0001$). For menopausal status, the postmenopausal group was the reference group. Premenopausal

Table 6

Multivariate analysis of factors associated with increased risk recurrence on UVA (Year 2002 onwards, 2,686).

| Step entered | Factor | Hazard Ratio (95% CI) | p value |
|--------------|---|-----------------------|---------|
| 1 | Nodal involvement (ref group negative) | | |
| | 1–4 | 1.82 (1.33–2.50) | <0.0001 |
| 2 | Tumour grade (ref group grade 1) | | |
| | Grade 2 | 1.36 (0.80–2.31) | NS |
| 3 | Symptomatic presentation (ref group asymptomatic) | | |
| | Symptomatic | 2.42 (1.65–3.57) | <0.0001 |
| 4 | Luminal status (ref group non-luminal) | | |
| | Luminal | 1.66 (1.25–2.21) | 0.001 |
| 5 | LVI (ref group absent) | | |
| | Present | 1.48 (1.10–1.99) | 0.01 |
| | Unknown | 1.33 (0.49–3.61) | NS |

UVA = Univariate analysis; ref group = reference group; CI = confidence intervals; NS = Not significant; LVI = lymphovascular invasion.

**Fig. 1.** Cumulative recurrence free survival by tumour type (2002 onwards, 2,686 women).**Fig. 2.** Survival for women with metastatic disease by tumour type (2002 onwards, 2,686 women).

women had an increased risk of recurrence ($p = 0.002$). For family history, those at or slightly above average risk of breast cancer was

the reference group. Those with a strong family history of breast cancer had a significantly **reduced** risk of recurrence ($p = 0.03$).

4.9. Tumour factors

The presence of multiple tumours was not associated with an increased risk of recurrence. For tumour size, ≤ 10 mm was the reference group. Women with tumours ≥ 21 mm had a significantly increased risk of recurrence ($p < 0.0001$). For tumour histology, IDC was the reference group. IDC had the highest risk of recurrence, but the risk of recurrence for ILC was not significantly different. However, both the special and other groups had significantly **reduced** risks of recurrence ($p = 0.0001$, $p = 0.05$, respectively). Luminal cancers had a significantly lower five year recurrence rate than HER2+ cancers and TN cancers ($p < 0.0001$). For tumour grade, grade 1 cancer was the reference group. Grade 2 and grade 3 cancers had significantly higher risks of recurrence ($p < 0.0001$) and grade 3 cancers had a significantly higher risk of recurrence than grade 2 cancers ($p < 0.0001$). For LVI, no LVI was the reference group. LVI was associated with a significantly increased risk of recurrence ($p < 0.0001$), in both node negative ($p < 0.0001$) and also node positive tumours ($p < 0.0001$). For nodal involvement, no involvement was the reference group. Women with 1–4 involved nodes and >4 involved nodes had significantly increased risks of recurrence ($p < 0.0001$). Those with >4 involved nodes had an increased risk of recurrence compared with those with 1–4 involved nodes ($p < 0.0001$). Recurrence occurred significantly more frequently in HR negative tumours (21.8%) than in HR positive tumours (10.2%, $p < 0.0001$). The risk of recurrence for single HR positive cancers was not different to that of double HR positive tumours.

For the 2,816 women diagnosed from 2002 onwards, 685 (24.3%) had their tumour tested for Ki67 and we examined different cut points for Ki67 positivity and recurrence $<14\%$ versus $\geq 14\%$, $<20\%$ versus $\geq 20\%$ and $<25\%$ versus $\geq 25\%$. 25% was the best cut off with a sensitivity and specificity of 60%. Of the women with a tumour Ki67 of $\geq 25\%$, 14.5% developed recurrence compared with 7.5% of the women with a tumour Ki67 value of $<25\%$ ($p = 0.002$). Recurrence occurred significantly more frequently in HER2+ cancers (17.2%) than HER2 negative cancers (8.7%, $p < 0.0001$). In women with HER2+ cancers, the relapse rate was not significantly different between those who received trastuzumab (12.5%) and those that did not (21.6%). Of the 200 women who received trastuzumab, 11.5% developed distant metastases compared with 16.3% of those that did not ($p = NS$).

4.10. Treatment factors

Women who required a mastectomy and those that required an axillary clearance had significantly increased risks of recurrence compared with those that had BCS or no axillary clearance ($p < 0.0001$). Those recommended for postmastectomy RT and those recommended for chemotherapy also had a significantly increased risk of recurrence ($p < 0.0001$).

4.11. Factors associated with an increased risk of recurrence: MVA (Table 5)

Factors found to be associated with an increased risk of recurrence in the MVA, were entered into a MVA. Patient factors were: age, symptomatic presentation, menopausal status and risk of breast cancer. Tumour factors were: size, histology, type, grade, LVI, nodal involvement, and HR status. Treatment factors were: mastectomy, axillary clearance, chemotherapy and AET. In the MVA, only the following factors remained significantly associated with an increased risk of recurrence: nodal involvement, tumour grade, symptomatic presentation, presence of LVI, non-luminal (HR negative) tumour type and tumour size.

A separate MVA using the data from the 2002 onwards group was performed. The same factors remained associated with a significantly increased risk of recurrence, except for tumour size (Table 6).

5. Discussion

We report a relatively large study of 3,765 women with EBC, from one region in Australia, treated by one clinical group over a recent 15 year period and examined factors associated with recurrence. The strengths of this study are that majority of women were managed in a contemporary way. Nearly 50% of the women with HER2+ cancers received trastuzumab and nearly 80% of those who received chemotherapy received a modern chemotherapy regimen. In addition we included all patient groups and only a small proportion was excluded, solely due to missing data. However, only 18% of tumours were tested for Ki67, making it impossible to categorise luminal cancers into subgroups A or B. With respect to AET, the majority received tamoxifen and only 37% received an aromatase inhibitor and only 2% of premenopausal women received ovarian function suppression (OFS). Nowadays, the proportion of women who would receive an aromatase inhibitor and the proportion who would receive OFS would be higher. We also acknowledge that the median follow up of 83 months is relatively short and the recurrence rate will inevitably rise as more of the women with luminal cancers will develop recurrence, with more prolonged follow up. With respect to presentation, we categorised this as symptomatic or asymptomatic, but in future we will change this classification into screen detected and non-screen detected.

The MVA for the entire cohort showed that symptomatic presentation was the third most important prognostic factor for recurrence, followed by LVI, which was significant in both node negative and in node positive disease. We believe that symptomatic presentation is a prognostic factor for recurrence and not due to lead time bias as the follow up was 83 months. LVI can be difficult to detect and may not be present in sections examined. A strong family history of breast cancer was associated with a **reduced** risk of recurrence. Some of those individuals may have had BRCA mutations and may have had risk reducing surgery, which could explain this apparent reduction [17]. Unfortunately, we do not have data on BRCA status or risk reducing surgery.

We are aware of eight previous large scale studies that have

examined recurrence in women with EBC [4,8,18–23]. Two of these involved more than 3,500 subjects enrolled into clinical trials in the 1980s and noted recurrence rates of 45.3%⁴ and 59.7%.⁸ The recurrence rate in our study was only 12.2%, much lower than some of the older series. The median age of our subjects was younger than the median age of presentation of EBC in Australia [24], 38.5% were node positive and 50.5% received chemotherapy. These factors, coupled with the relatively short follow up of 83 months, may have influenced the low recurrence rate in our series. Two more recent studies [18] enrolled women from 1985–2001 and 1986–1999 [19]. In the first study, the patients were recurrence free at five years but 216 (7.6%) developed recurrence, subsequently. Stage, grade, HR status, and AET were associated with late recurrence. In the second study, 7.9% developed recurrence within 2.5 years. Node positivity, grade 3, and low ER positivity were associated with increased risks of recurrence. A further study [20] found that LVI and symptomatic presentation were associated with increased risk of recurrence. This study only enrolled HR+ postmenopausal women. An overview published recently [21] involved 62,293 women with EBC enrolled into 88 trials from 1976–2011. All received AET for five years and remained recurrence free. This study showed that the risk of distant recurrence was strongly correlated with tumour diameter and nodal status, but tumour grade, Ki67 and negative PgR status were also associated with increased risks of recurrence. Both these studies excluded patients who had recurrence in the first five years. Of these large retrospective studies, only one examined symptomatic presentation [20] and only two analysed the influence of LVI on recurrence [19,20]. Our study differs from these studies in the following ways: we included all eligible women with different tumour types, we did not exclude women with early recurrence and in our series many of the women received modern treatments.

The factors we identified as being associated with an increased risk of recurrence in the MVA have been described previously. However, we suspect that clinicians are using tumour size, tumour grade and nodal involvement but do not necessarily incorporate symptomatic presentation and LVI when assessing the probability of recurrence in women with EBC. Breast screening is one of the factors that has assisted in reducing breast cancer mortality in recent years [25] as screen detected cancers tend to be of lower grade, smaller size and more likely to be HR positive than symptomatic cancers [26].

We strongly recommend that clinicians include symptomatic presentation and LVI with known tumour factors when assessing risk of recurrence in women with EBC.

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Conflicts of interest

None declared.

Declarations of interests

None declared.

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Appendix A. Supplementary data

Supplementary data related to this article can be found at <https://doi.org/10.1016/j.breast.2019.02.004>.

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