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ORIGINAL ARTICLE

Where youth matters—clinicopathologic characteristics and emerging trends in treatment and outcomes in young Irish women with breast cancer

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Abstract

Background Young women with breast cancer (YWBC) represent 7–12% of breast cancer diagnoses and ostensibly have more biologically aggressive subtypes with higher relapse and mortality rates**.** We studied the clinical and pathological characteristics in YWBC and examined how outcomes and treatment have evolved.

Methods YWBC were identified from pathology databases at two tertiary centers. Patients were divided into two cohorts: those diagnosed from 2000 to 2005 (C1) and from 2006 to 2015 (C2). Data were retrieved from clinical, radiology, and histology databases. Statistical analysis was performed using R® (V3.2.0).

Results We identified 345 patients. Median age was 36 years (23–39 years). Mastectomy was performed in 232 patients (67.2%) and axillary lymph node clearance (ALNC) in 207 patients (60% [C1 82.7 vs. C2: 49.4%, $p < 0.001$]). One hundred-seventy patients (49%) were ER + HER2−, 88 (25.5%) were HER2+, and 58 (16.8%) were triple negative. Eighty patients (23.2%) received neoadjuvant therapy. Pathological complete response rates were statistically similar between C1 and C2 [C1 1 (0.9%) vs C2 16 (6.8%) $p = 0.1$]. Distant relapse occurred in 59 (19%) patients. There was a higher relapse rate (RR) in C1 [27 (32.1%) vs. 32 (15.7%), $p < 0.002$). HER2+ and ER+ HER2− patients in C1 had higher RRs than C2. Median overall survival in patients with metastatic disease was 29 months (range 2–119 months).

Conclusion Locally advanced disease was more prevalent in YWBC. Mastectomy and ALNC rates were high and most received multimodal treatment. The extent of axillary surgery declined over time. Outcomes were unchanged in triple negative patients. These remain a priority for research.

Keywords Axillary lymph node clearance · Breast cancer · Chemotherapy · Endocrine therapy · Locally advanced · Mastectomy · Triple negative · Young women

Introduction

Breast cancer in young women is defined as breast cancer occurring age 40 and under. It is a relatively rare disease accounting for approximately 7–12% of all breast cancers diagnosed while less than 4% occur in women under the age of 35 [1–3]. Although breast cancer in young women is uncommon, recent data indicates that the rate of advanced disease at diagnosis is increasing in this age group [4]. It is the leading cause of cancer death in women between 20 and 39 years in the USA [5].

Age-specific data on appropriate treatment and outcomes are lacking. Young women with breast cancer (YWBC) appear to present with more advanced disease [6–8]. It has previously been demonstrated that young age at diagnosis influences prognosis negatively [9, 10]. This may be partially explained by young women often being diagnosed at more advanced stage, and it has been reported that more than 90% of YWBC present to the symptomatic breast service [11, 12]. Potential reasons for

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this include a lack of awareness among young women, lack of reliable screening tools, and low index of suspicion among healthcare professionals. Also, pregnancy may hinder prompt diagnosis due to pregnancy-related breast changes.

In addition, YWBC also have more biologically aggressive subtypes and are more likely to develop triple-negative breast cancer (TNBC) and human epidermal growth factor receptor 2 (HER2)-positive breast cancer [13, 14]. Luminal-B breast cancers, defined as estrogen receptor (ER) positive, HER2 negative, Ki-67 high or progesterone receptor (PR) low, are also associated with an increased risk of relapse compared to patients with luminal-A breast cancer, defined as ER positive, HER2 negative, Ki-67 low, and PR high [15]. Data suggests that this subtype occurs more commonly in young women [16]. Two studies have reported rates of 35 and 33.6% of luminal-B breast cancer in YWBC while most series of breast cancer patients report a range of 5–16% in all patient cohorts [17–21]. Studies have also indicated that YWBC have higher proportions of high-grade disease, ductal histology, multifocality, node positivity, and lymphovascular invasion (LVI) positivity [6–8, 21]. There is also a higher risk of relapse and death, but it has not been established how much both stage at diagnosis and tumor biology contribute to prognosis [11, 13, 22].

YWBC are more likely to have multiple adjuvant therapies and therefore may experience significant morbidity. This has both societal and economic implications and often results in complex management issues. Special considerations in this patient group include age-related side effects such as menopausal symptoms, interference with fertility and family planning, change in body image, sexual dysfunction, bone morbidity, and genetic susceptibility [23].

In this study, we sought to evaluate the clinical and pathological characteristics in YWBC and examine how presentation, treatment strategies, and outcomes have evolved over time given the advances in breast cancer therapy over the past 10–15 years.

Methods

Patients diagnosed with invasive breast cancer aged 40 years and under between January 2000 to December 2015 were retrospectively identified from pathology databases at St. Vincent's Hospital (SVH), and patients diagnosed from January 2010 until December 2013 were retrospectively identified from pathology databases at the Mater Misercordiae University Hospital (MMUH).

Patient demographics, pathological characteristics, disease staging, type of surgery, association with pregnancy, use of Oncotype Dx (ODx) recurrence score (RS), and treatment administered were recorded. Follow-up data documenting recurrence and survival outcomes was gathered from medical oncology and breast surgery databases. This data was collected on a de-identified spreadsheet and then combined for analysis.

Women with bilateral disease were included only once with the most advanced cancer taken as the index tumor. Breast surgery involved a modified radical mastectomy or breast conserving surgery (BCS) combined with either a sentinel lymph node biopsy (SLNB) or axillary lymph node clearance (ALNC).

All patients underwent surgical management at SVH and MMUH, and all tumor samples were reviewed by breast pathologists at these institutions. Hormone receptor (ER and PR) and HER-2 status were determined by immunohistochemical (IHC) analysis. HER-2 was scored as 0, 1+, 2+, or 3+. IHC 0 and IHC 1+ were considered negative and IHC 3+ was considered positive. In SVH, fluorescent in situ hybridization (FISH) was performed on all pts. with an IHC score of 2+ and defined as amplified when dual-probe HER2/CEP17 ratio was greater than or equal to (≥) 2.0 while in MMUH, HER2/C17 DDISH (Dual-chromagen/Dual-hapten in situ hybridization) was performed using INFORM HER2 Dual ISH DNA and defined as amplified when ≥ 2.0. Tumors with ≥ 1% of cell nuclei stained were considered ER or PR positive, regardless of staining intensity. PR status was not routinely performed in SVH unless ER was 0%. Staging followed criteria of the American Joint Commission on Cancer (AJCC) Manual for Staging of Cancer, 7th edition [24]. Distant relapse was defined as recurrence of breast cancer beyond the ipsilateral or contralateral breast or regional lymph nodes including ipsilateral axillary, internal mammary, or supraclavicular lymph nodes. For women who underwent neoadjuvant therapy, staging and treatment was based on clinical, radiological, and histological data obtained at baseline biopsy.

To account for potential changes in outcome over time with the approval of anti-HER2 therapy at the end of 2005, patients were divided into two cohorts based on date of diagnosis; those diagnosed between 2000 and 2005 (C1) and those diagnosed between 2006 and 2015 (C2). Comparative analysis was performed.

Statistical analysis was performed using R® (V3.2.0). Summary statistics of continuous variables were given by mean (standard deviation) and frequencies (percentages) for categorical variables. Comparisons of continuous data were performed using *t* tests to compare C1 and C2. Comparisons for categorical data were performed using chi-squared tests and two-proportion tests. A p value less than 0.05 was deemed statistically significant.

Results

From January 2000 to December 2015, 300 women aged 40 years or less with invasive breast cancer treated in SVH and 45 women treated in MMUH between January 2010 and December 2013 were identified. In total, this retrospective analysis included 345 patients. Median age was 36 years

(range 23–39 years). Of 345 patients, 110 were diagnosed between 2000 and 2005 (C1) and 235 were diagnosed between 2006 and 2015 (C2). Patient and tumor characteristics are shown in Table 1.

Clinicopathological data

By histology, 313 tumors (90.7%) were invasive ductal carcinoma, no special type (IDC, NST), 15 (4.3%) invasive lobular carcinoma (ILC), 11 (3.2%) mixed IDC/ILC, and 6 other pathologies including mucinous ($n = 2$), metaplastic ($n = 1$), medullary ($n = 1$), tubular ($n = 1$), and carcinoma with focal squamous differentiation ($n = 1$).

The majority of tumors were grade 2 or 3; 319 (92.4%). Grade 3 disease was seen in 183 patients (53%), grade 2 in 136 (39.4%), and grade 1 in 21 (6.1%). Data regarding grade was unavailable in 5 (1.5%) patients. LVI was present in 171 cases (49.6%) and absent in 133 (38.6%), and LVI data was not available in 41 cases (11.9%). Multifocal disease occurred in 50 patients (14.5%).

When patients were evaluated by biomarker status (Fig. 1), ER+ HER2− breast cancer occurred in 170 patients (49.3%), 38 in C1 (34.5% of C1) and 132 in C2 (56.2% of C2); HER2+ ER+ status was seen in 55 patients (15.9%), 20 in C1 (18.2% of C1) and 35 in C2 (14.9% of C2); and HER2+ ER− status was identified in 33 patients (9.6%), 12 in C1 (10.9% of C1) and 21 in C2 (8.9% of C2). Finally, 58 tumors (16.8%) were characterized as triple negative, 11 in C1 (10% of C1) and 47 in C2 (20% of C2). There was incomplete receptor data in 29 (8.4%), all of whom were in C1 (26.4% of this group).

As described in Table 1, there were 33 cases (9.6%) of pregnancy-associated breast cancer and inflammatory breast cancer was diagnosed in 18 (5.2%) patients. Sixteen patients (4.6%) had BRCA-associated breast cancer, though many await genetic counseling and testing. In total, 186 patients (53.9%) had node-positive disease. Patients in C1 were more frequently node positive than those in C2: 62 (56.3%) in C1 and 123 (52.3%) in C2, with a median node count of 5 (range 1–37) in C1 versus (vs) 2 (range 1–44) in C2. Data on disease

Table 1 Patient and tumor characteristics

Tumor features		Cohort 1 ($n = 110$)	Cohort 2 ($n = 235$)	Total ($n = 345$)
Median size (mm)		25 (1.8–130)	22 (1–134)	23 (1.8–134)
Histology	IDC			313 (90.7%)
	ILC			15 (4.3%)
	Mixed IDC/ILC			11 (3.2%)
	Other			6 (1.8%)
Multifocal disease				50 (14.5%)
LVI	Present			171 (49.6%)
	Absent			133 (38.5%)
	Not available			41 (11.9%)
Grade	I			21 (6.1%)
	II			136 (39.4%)
	III			183 (53%)
	Not available			5 (1.5%)
Receptor status (RS)	ER+ HER2−	38 (34.5%)	132 (56.2%)	170 (49.3%)
	HER2+ ER+	20 (18.2%)	35 (14.9%)	55(15.9%)
	HER2+ ER−	12 (10.9%)	21 (8.9%)	33 (9.6%)
	TNBC	11 (10%)	47 (20%)	58 (16.8%)
	Missing data	29 (26.4%)		29 (8.4%)
Inflammatory BC				18 (5.2%)
Pregnancy associated				33 (9.6%)
BRCA associated				16 (4.9%)
Node positive		62 (56.3%)	123 (52.3%)	185 (53.6%)
Median node count		5 (1–37)	2 (1–44)	
Stage at diagnosis	I	26 (23.6%)	68 (28.9%)	94 (27.2%)
	II	44 (40%)	107 (45.5%)	151 (43.8%)
	III	32 (29.2%)	40 (17.1%)	72 (20.9%)
	IV	4 (3.6%)	19 (8.1%)	23 (6.7%)
	Missing	4 (3.6%)	1 (0.4%)	5 (1.4%)

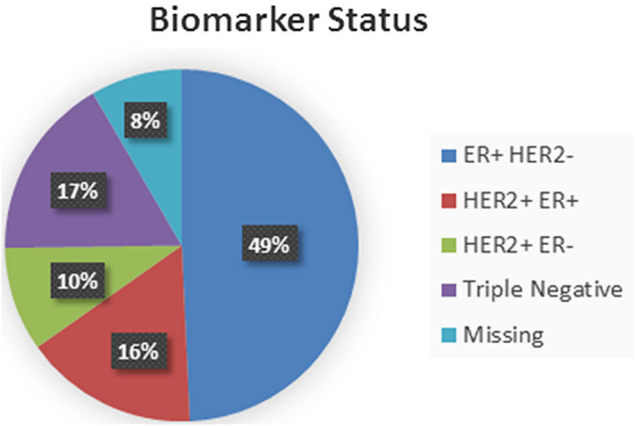

Fig. 1 Pie chart demonstrating breakdown by biomarker status

stage is shown in Table 1; stage II disease occurred in 151 patients (43.8%), the largest proportion of cases.

Treatment characteristics

As depicted in Fig. 2, the rate of mastectomy was significantly higher than wide local excision (WLE) in both groups. Mastectomy was carried out in 233 cases (67.5%) and unlike ALNC this did not decrease over time with 68 patients (61.8%) in C1 and 165 (70.2%) in C2 undergoing mastectomy. WLE was performed in 38 cases (34.5%) in C1 and 57 (24.2%) in C2. Thirteen patients did not undergo surgery due to locally advanced or metastatic disease at diagnosis, and data was unavailable for four patients. The proportion of patients undergoing ALNC was significantly higher in C1 than C2 (91 [82.7%] vs 116 [49.4%], $p < 0.001$). There was a concurrent increase in the use of SLN assessment (9 [16.9%] in C1 vs 103 [42.6%] in C2).

Systemic therapy

As shown in the consort diagram (Fig. 3), we observed that nearly all patients for which there was data available received systemic therapy. Of the patients who did not ($n = 6$), three declined therapy where it had been recommended. Of the 304 patients treated in the early stage setting, 80 patients (25.8%) received neoadjuvant therapy (NAT) and 199 (64.2%) adjuvant therapy; thus, 90.3% in this cohort received chemotherapy. Adjuvant endocrine therapy (ET) alone was prescribed in 25 patients (7.2%). The endocrine agents used included tamoxifen with or without a gonadotrophin-releasing hormone (GnRH) analogue or an aromatase inhibitor with a GnRH analogue. The use of ET alone without chemotherapy in the adjuvant setting increased over time with 21 patients (8.9%) receiving ET alone in C2 vs 4 (3.6%) in C1. Twenty-three patients (6.6%) were treated with palliative systemic therapy for de novo metastatic breast cancer.

The ODx RS was performed in 26 cases, all of whom were in C2 (12.7% of this group). The median RS was 17.5. Three patients had a high RS, 10 had intermediate scores, and 12 had a low RS. One patient (ODx score = 18) relapsed with liver metastases while on tamoxifen, underwent a metastasectomy, and subsequently completed 4 cycles of taxotere/cyclophosphamide (TC). She is currently in complete remission at 4 years of follow-up.

The most frequently used chemotherapy regimens in the adjuvant and neoadjuvant settings were TC, doxorubicin/cyclophosphamide and paclitaxel (AC/T), and taxotere/carboplatin/herceptin (TCH). Data on chemotherapy regimens utilized is shown in Table 2. Forty-eight patients (13.9%) were enrolled onto clinical trials.

NAT was given in 80 patients (23.2%); 33 (41.3%) were ER+ HER2−, 29 (36.2%) HER2+ [18 (22.5%) were HER2+ ER+ and 11 (13.7%) were HER2+ ER−], and 18 (22.5%) were triple negative. Of patients in C2, 16 (6.8%) achieved pathological complete response (pCR) while 1 patient (0.9%) obtained a pCR in C1. To date, no patients who achieved a pCR after NAT have relapsed (Table 3).

The use of non-anthracycline-based (NAB) therapy increased over time (Fig. 4). Of the patients treated in the

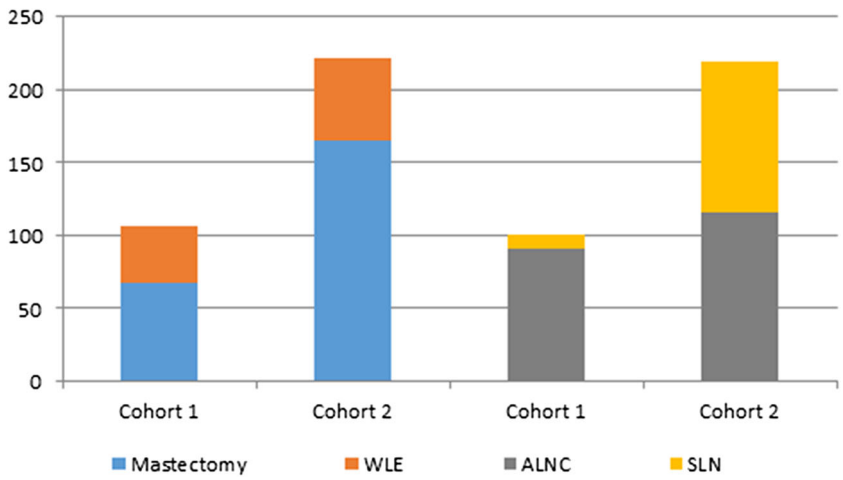

Fig. 2 Surgical management of breast and axilla

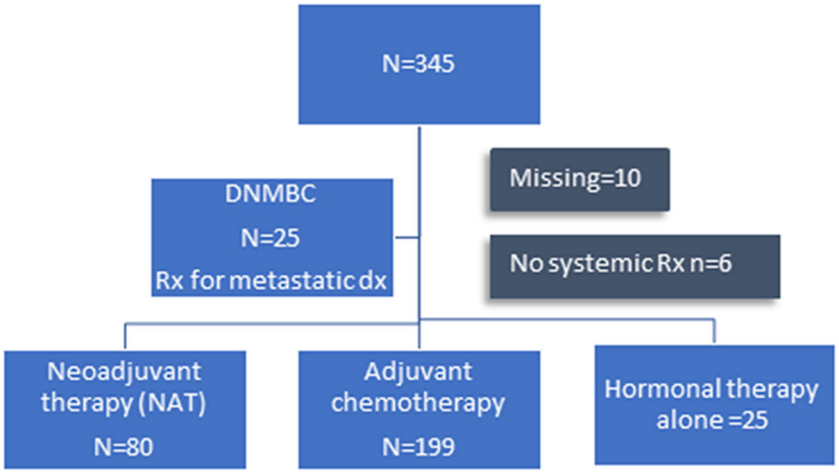

Fig. 3 Consort diagram showing treatment patterns for population (DNMBC: de novo metastatic breast cancer, rx treatment, dx disease)

(neo) adjuvant setting in C1, 45% ($n = 47$) received anthracycline-based (AB) therapy vs 32.5% ($n = 68$) in G2. Conversely, 12.5% ($n = 13$) received non-AB (NAB) therapy in C1 vs 46.4% ($n = 97$) in C2 ($p < 0.001$).

Distant relapse occurred in 59 patients, 19.4% of those treated in the (neo) adjuvant setting. There was a higher rate of relapse in C1 [27 (32.1%) in C1 vs 32 (15.7%) in C2, $p = <.002$). Relapse by biomarker status is demonstrated in Fig. 5. Fifteen (25.4%) patients who relapsed had HER2+ disease. Patients with HER2+ disease in C1 had a higher relapse rate (28.1%) compared to those in C2 (10.7%, $p = 0.036$). Relapse occurred in 12 (20.4%) and 32 (54.2%) of TN and ER+/HER− cases respectively. ER+ HER2− patients in C1 also had a higher relapse rate (36.8%) compared to those in C2 (13.6%, $p = 0.001$).

As seen in Fig. 6, median overall survival in all patients with stage IV disease was 29 months (range 2–119 months); 21 months in C1 and 29 months in C2, $p = 0.294$.

Discussion

Breast cancer in young women has been associated with a worse prognosis than breast cancer in older women. In line with existing data, our study, which evaluated nearly 350 women aged 40 years and under with breast cancer, demonstrates that YWBC present with more advanced stage at diagnosis and higher-grade disease. However, we identified that women diagnosed more recently (C2) had lower volume breast cancer at diagnosis which may suggest increasing awareness in this cohort.

Data from the Early Breast Cancer Trialist's Collaborative Group (EBCTG) 2005 meta-analyses found that of the 44% of patients for whom histology was available, 16 and 31% of women had grade 2 and grade 3 disease, respectively [25]. In contrast, in our study, only 6% had grade 1 disease while 53% had grade 3 disease. The rate of IDC was high in our cohort; studies have shown rates of IDC in the range of 56–80% while in our study, over 90% of women had IDC [26–28].

We also found that mastectomy and ALNC rates were significantly higher than reported in studies evaluating the general breast cancer population. This is likely, in part, due to more advanced disease at diagnosis. Two recent large studies utilizing SEER data quoted mastectomy rates of 43.4 and 30% in 87,504 and 132,149 women (of all ages), respectively, but in our population, 67.2% underwent mastectomy [29, 30]. However, like our study, SEER data have described mastectomy rates of 64–66% in women under 35 years [31, 32]. With more widespread use of SLNB, the extent of axillary surgery declined over time from 74.3% in C1 to 45.7% in C2. The decreased rate of ALNC surgery in C2 may also have been

Table 2 Chemotherapy regimens utilized in the neoadjuvant and adjuvant settings (*dd* dose dense, *NA* neoadjuvant, *adj* adjuvant, *RT* radiotherapy, *TNBC* triple negative breast cancer)

Chemotherapy regimen	N=	Chemotherapy regimen	N=
TC	59	CMF	7
AC/T	31	AT-CMF	5
TCH	41	A-CMF	4
TAC	14	FEC	4
dd AC/T	13	AC	4
NA (dd) AC/T → adj CMF/RT	7	CALGB 40603 regimen (TNBC)	3
TFAC	7	NA TC ➔ adj CMF/RT	3
ACTH	7	Miscellaneous	8

Table 3 Neoadjuvant therapy by biomarker status and pCR rates

NAT	$n = 80$ (23.2%)	
Biomarker status	ER+ HER2−	$n = 33$ (41.3%)
	HER2+ ER+	$n = 18$ (22.5%)
	HER2+ ER−	$n = 11$ (13.7%)
	TNBC	$n = 18$ (22.5%)
pCR ($n = 17$)	Cohort 1	$n = 1$ (0.9%)
	Cohort 2	$n = 16$ (6.8%)

impacted by the results of the ACOZOG Z0011 trial which demonstrated that patients with clinical T1-2N0 breast cancer, with no palpable axillary adenopathy and 1–2 sentinel lymph nodes containing metastases, treated with SLN dissection alone, had non-inferior overall survival to those treated with ALNC [33]. Like ODx testing resulting in reduced use of adjuvant systemic chemotherapy in women with node-negative ER-positive breast cancer (and increased use of hormonal therapy alone), the Z11 study results have led to a decline in more extensive axillary surgery.

Young age is associated with increased risk of locoregional recurrence; however, data indicate no difference in overall survival between BCS and mastectomy once radiation therapy is utilized and thus age should not be a contraindication to BCS [34–36]. Surgical mastectomy may be associated with psychological implications and a higher risk of complications which may result in treatment delays and worse cosmetic outcomes.

TN and HER2+ subtypes accounted for an expected proportion of breast cancer cases in this patient group; 17 and 25.5%, respectively. However, YWBC may also have a more aggressive phenotype within the more favorable HR+/HER2− breast cancer subtype. A study by Sheridan et al. demonstrated that young women with hormone receptor-positive breast cancer carried a worse prognosis than the same subtype in older women. Age under 40 predicted inferior survivals in the luminal subgroup, possibly driven by luminal-B cancer (though further subtyping of the luminal group was not available) [37]. In our study, 56% of the patients who relapsed in C2 had HR+/HER2− disease.

Most patients received multimodal therapy including surgery, radiotherapy, chemotherapy, and ET where appropriate. Therefore, these women generally undergo high-intensity treatment. In line with previous studies demonstrating high rates of chemotherapy administration in YWBC, 90% of women underwent chemotherapy in this study cohort [38]. The EBCTG meta-analysis demonstrated a reduction in breast cancer mortality in women younger than 50 who received chemotherapy independent of tumor features [25]. In addition, a large retrospective Danish study found that women aged under 40 who did not receive chemotherapy had a higher relative risk of death at 10 years of follow up compared to women aged 45–49 [39]. However, it is unclear in the era of molecular subtyping if age is an independent prognostic indicator. It has been demonstrated that select populations of young women can have good outcomes with ET alone [40]. In our study, we identified an increase in the use of adjuvant hormonal therapy alone, possibly due to the advent of ODx RS testing [41]. In C2, 8.9% received ET compared with 3.6% in C1. Of note, 26 patients underwent ODx RS testing. This assay was developed using populations of postmenopausal women so there have been concerns about whether they are reliable in young patients. However, accumulating international data indicate that this assay is prognostic, independent of patient age. Other than one patient with a low RS who received ET alone and relapsed, 11 patients with low RS remain in remission at a median follow up of 53 months.

Significant changes in systemic therapies have occurred over the past 10 years which have likely contributed to the improved outcomes over time seen in our population. These advances may be especially important in young women given that they more often present with higher-risk tumors which gain more relative benefit from chemotherapy and targeted therapies than older women. This study highlights that the use of non-anthracycline-based chemotherapy (i.e., TC) has become considerably more prevalent and does not appear to have had a negative impact on outcomes in our population.

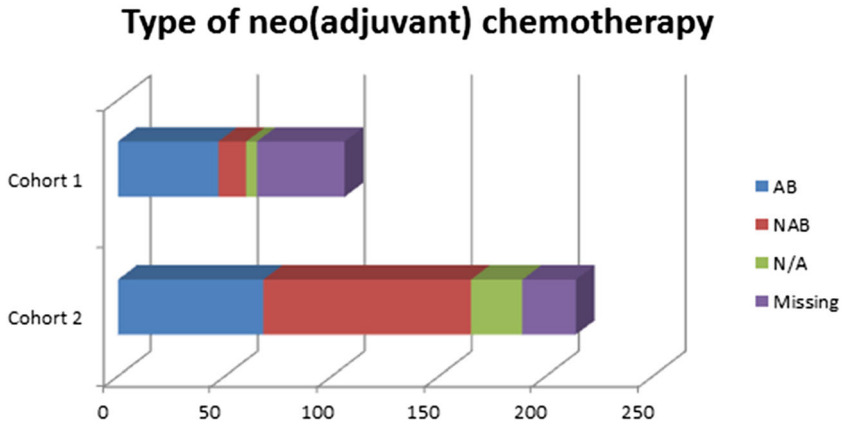

Fig. 4 Differences in chemotherapy regimens between C1 and C2. [AB anthracycline-based, NAB non-anthracycline based, N/A non-applicable (treated with hormonal therapy, received no neo (adjuvant) therapy or presented with *denovo* metastatic disease), missing: data on regimen received unavailable]

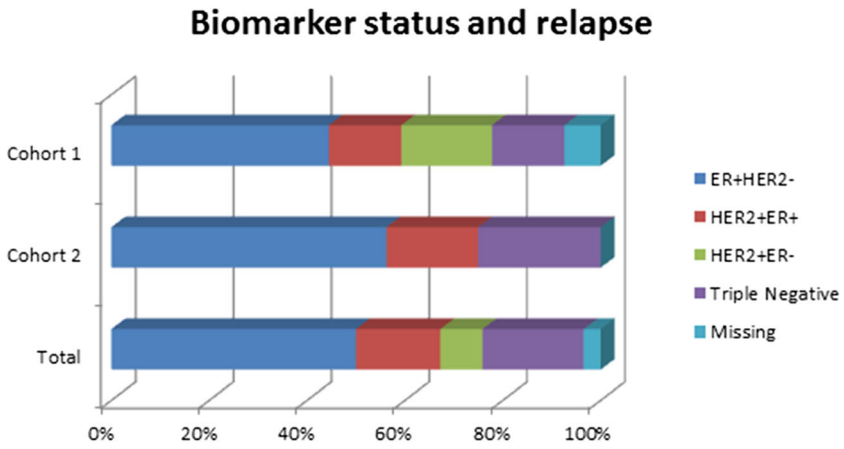

Fig. 5 Distant relapse data by biomarker status

We observed higher rates of PCR in C2, again reflecting advances in treatment regimens and trastuzumab use. PCR correlated with improved patient outcomes in certain biologic subtypes. The impact of anti-HER2 therapy administered in the neoadjuvant or adjuvant setting is highlighted by the reduced relapse rates in HER2+ patients in C2. Overall, 19.4% of patients relapsed with metastatic disease and including cases of de novo metastatic breast cancer, 24.3% of patients were treated in the metastatic setting. In line with international guidelines, women in our study received single-agent chemotherapy and ET where appropriate [42].

Our study has some limitations. Given its retrospective nature, variation in patient management over time is a potential bias. There was some incomplete data, mainly regarding receptor status and therapies received, particularly in C1. There is limited follow-up at 10 years for women in C2. Further follow-up is needed to verify that the improved outcomes over time are durable. Many patients are awaiting BRCA mutation testing so the current data reported is unlikely to be a true reflection of the prevalence of BRCA mutations in this population.

Results of our study indicate that outcomes remain suboptimal for young patients with ER+/HER2− and TN breast cancers. It is imperative that young women are viewed as a target group for intensified research so that new therapeutic targets and treatment modalities to counteract the worse

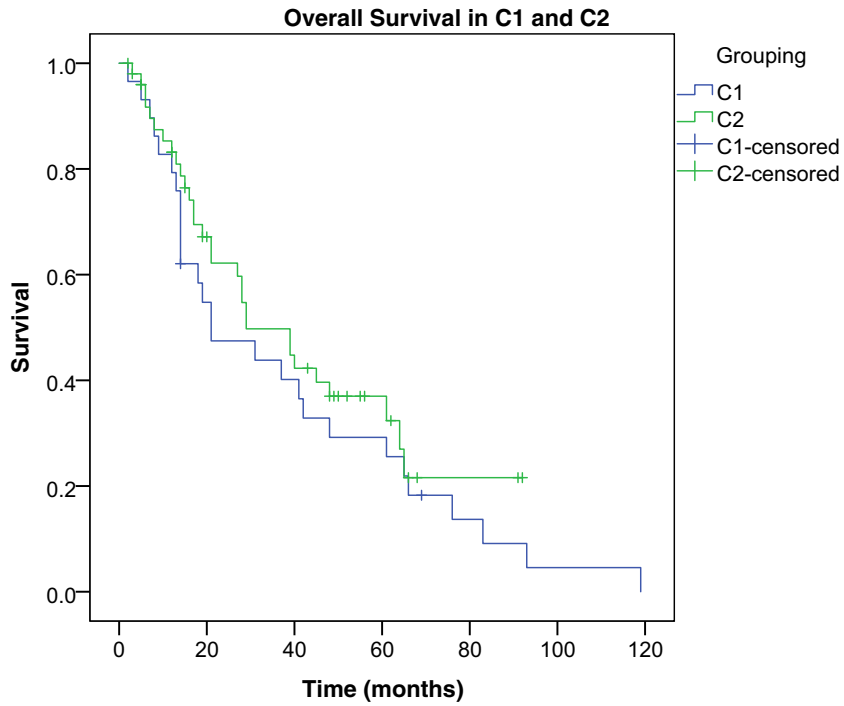

Fig. 6 Overall survival in months in patients with metastatic disease, by cohort

outcomes in this group are developed. We await with interest, investigation of agents such as the cyclin-dependent kinase (CDK) inhibitors, immunotherapy, and poly-ADP ribose polymerase (PARP) inhibitors in these patients. Despite some advances, little data exist regarding the optimal management of both early and advanced breast cancer in these particularly young patients and it remains unclear why young women develop more aggressive tumors and to what degree their treatment should be modified.

YWBC have potentially a long life expectancy on completion of therapy and therefore may encounter menopausal symptoms, fertility and family planning issues, sexual dysfunction, bone morbidity, and genetic susceptibility. Thus, tailoring adjuvant therapies so that benefit is maximized and toxicity minimized is of vital importance. Going forward, gene signature profiling may provide a mechanism of optimizing care for these women. Ongoing global collaborative initiatives remain the way forward to make progress in this patient group.

Compliance with ethical standards

Conflict of interest Dr. Janice M. Walshe has served as consultant in an advisory role to Roche, Genomic Health, Pfizer. Dr. Giuseppe Gullo has served as a consultant in an advisory role to Roche, Novartis, BMS.

There are no other potential conflicts of interest.

References

1. Hankey BF, Miller B, Curtis R et al (1994) Trends in breast cancer in younger women in contrast to older women. J Natl Cancer Inst 16:7–14
2. Ries LAG, Eisner MP, Kosary C, et al. (2005) SEER Cancer Statistics Review, 1975–2002, National Cancer Institute. Bethesda, MD, http://seer.cancer.gov/csr/1975_2002/, based on November 2004 SEER data submission, posted to the SEER web site 2005
3. Brinton LA, Sherman ME, Carreon JD, Anderson WF (2008) Recent trends in breast cancer among younger women in the United States. J Natl Cancer Inst 100(22):1643–1648. https://doi.org/10.1093/jnci/djn344
4. Johnson RH, Chien FL, Bleyer A (2013) Incidence of breast cancer with distant involvement among women in the United States, 1976 to 2009. J Am Med Assoc 309(8):800–805. https://doi.org/10.1001/jama.2013.776.
5. Siegel R, Naishadham D, Jemal A (2013) Cancer statistics. CA Cancer J Clin 63(1):11–30. https://doi.org/10.3322/caac.21166.
6. Maggard MA, O'Connell JB, Lane KE, Liu JH, Etzioni DA, Ko CY (2003) Do young breast cancer patients have worse outcomes? J Surg Res 113(1):109–113
7. Kheirelseid EAH, Boggs JM, Curran C et al (2011) Younger age as a prognostic indicator in breast cancer: a cohort study. BMC Cancer 11:383. https://doi.org/10.1186/1471-2407-11-383
8. Gnerlich JL, Deshpande AD, Jeffe DB, Sweet A, White N, Margenthaler JA (2009) Elevated breast cancer mortality in women younger than age 40 years compared with older women is attributed to poorer survival in early-stage disease. J Am Coll Surg 208(3):341–337. https://doi.org/10.1016/j.jamcollsurg.2008.12.001
9. de la Rochefordiere A, Asselain B, Campana F et al (1993) Age as prognostic factor in premenopausal breast carcinoma. Lancet 341(8852):1039–1043
10. Bonnier P, Romain S, Charpin C, Lejeune C, Tubiana N, Martin PM, Piana L (1995) Age as a prognostic factor in breast cancer: relationship to pathologic and biologic features. Int J Cancer 62(2):138–144
11. Fredholm H, Eaker S, Frisell J, Holmberg L, Fredriksson I, Lindman H (2009) Breast cancer in young women: poor survival despite intensive treatment. PLoS One 4(11):e7695. https://doi.org/10.1371/journal.pone.0007695
12. Ribnikar D, Ribeiro JM, Pinto D, Sousa B, Pinto AC, Gomes E, Moser EC, Cardoso MJ, Cardoso F (2015) Breast cancer under age 40: a different approach. Curr Treat Options in Oncol 16(4):16. https://doi.org/10.1007/s11864-015-0334-8
13. Azim HA, Partridge AH (2014) Biology of breast cancer in young women. Breast Cancer Res 16(4):427. https://doi.org/10.1186/s13058-014-0427-5
14. Keegan TH, DeRouen MC, Press DJ et al (2012) Occurrence of breast cancer subtypes in adolescent and young adult women. Breast Cancer Res 14(2):55. https://doi.org/10.1186/bcr3156
15. Yanagawa M, Ikemot K, Kawauchi S, Furuya T, Yamamoto S, Oka M, Oga A, Nagashima Y, Sasaki K (2012) Luminal A and luminal B (HER2 negative) subtypes of breast cancer consist of a mixture of tumours with different genotype. BMC Res Notes 5:376. https://doi.org/10.1186/1756-0500-5-376
16. Voduc KD, Cheang MC, Tyldesley S et al (2010) Breast cancer subtypes and the risk of local and regional relapse. J Clin Oncol 28(10):1684–1691. https://doi.org/10.1200/JCO.2009.24.9284
17. Collins LC, Marotti JD, Gelber S, Cole K, Ruddy K, Kereakoglow S, Brachtel EF, Schapira L, Come SE, Winer EP, Partridge AH (2012) Pathologic features and molecular phenotype by patient age in a large cohort of young women with breast cancer. Breast Cancer Res Treat 131(3):1061–1066. https://doi.org/10.1007/s10549-011-1872-9
18. Bacchi LM, Corpa M, Santos PP, Bacchi CE, Carvalho FM (2010) Estrogen receptor-positive breast carcinomas in younger women are different from those of older women: a pathological and immunohistochemical study. Breast 19(2):137–141. https://doi.org/10.1016/j.breast.2010.01.002
19. Caldarella A, Crocetti E, Bianchi S, Vezzosi V, Urso C, Biancalani M, Zappa M (2011) Female breast cancer status according to ER, PR and HER2 expression: a population based analysis. Pathol Oncol Res 17(3):753–758. https://doi.org/10.1007/s12253-011-9381-z
20. Tamimi RM, Baer HJ, Marotti J et al (2008) Comparison of molecular phenotypes of ductal carcinoma in situ and invasive breast cancer. Breast Cancer Res 10(4):R67. https://doi.org/10.1186/bcr2128
21. Carey LA, Perou CM, Livasy CA, Dressler LG, Cowan D, Conway K, Karaca G, Troester MA, Tse CK, Edmiston S, Deming SL, Geradts J, Cheang MCU, Nielsen TO, Moorman PG, Earp HS, Millikan RC (2006) Race, breast cancer subtypes, and survival in the Caroline breast cancer study. JAMA 295(21):2492–2502
22. Copson E, Eccles B, Maishman T, Gerty S, Stanton L, Cutress RI, Altman DG, Durcan L, Simmonds P, Lawrence G, Jones L, Bliss J, Eccles D, POSH Study Steering Group (2013) Prospective observational study of breast cancer treatment outcomes for UK women aged 18-40 years at diagnosis: the POSH study. J Natl Cancer Inst 105(13):978–988. https://doi.org/10.1093/jnci/djt134
23. Reyna C, Lee MC (2014) Breast cancer in young women: special considerations in multidisciplinary care. J Multidiscip Healthc 29(7):419–429. https://doi.org/10.2147/JMDH.S49994.
24. Edge SB, Byrd DR, Compton CC et al (2010) AJCC cancer staging manual. Springer, New York

25. Early Breast Cancer Trialists' Collaborative Group (EBCTCG) (2005) Effects of chemotherapy and hormonal therapy for early breast cancer on recurrence and 15-year survival: an overview of the randomised trials. Lancet 365(9472):1687–1717
26. Rakha EA, Putti TC, Abd El-Rehim DM et al (2006) Morphological and immunophenotypic analysis of breast carcinomas with basal and myoepithelial differentiation. J Pathol 208(4): 495–506
27. Louwman MW, Vriezen M, van Beek MW et al (2007) Uncommon breast tumors in perspective: incidence, treatment and survival in the Netherlands. Int J Cancer 121(1):127–135
28. Weigelt B, Geyer FC, Reis-Filho JS (2010) Histological types of breast cancer: how special are they? Mol Oncol 4(3):192–208. https://doi.org/10.1016/j.molonc.2010.04.004
29. Lizarraga I, Schroeder MC, Weigel RJ, Thomas A (2015) Surgical management of breast cancer in 2010-2011 SEER registries by hormone and HER2 receptor status. Ann Surg Oncol 22(Suppl 3): S566–S572. https://doi.org/10.1245/s10434-015-4591-3.
30. Agarwal S, Pappas L, Neumayer L, Kokeny K, Agarwal J (2014) Effect of breast conservation therapy vs mastectomy on disease-specific survival for early-stage breast cancer. JAMA Surg 149(3): 267–274. https://doi.org/10.1001/jamasurg.2013.3049
31. Han W, Kang SY, Korean Breast Cancer Society (2010) Relationship between age at diagnosis and outcome of premenopausal breast cancer: age less than 35 years is a reasonable cut-off for defining young age-onset breast cancer. Breast Cancer Res Treat 119(1):193–200. https://doi.org/10.1007/s10549-009-0388-z
32. de Deus Moura R, Carvalho M, Bacchi CE (2015) Breast cancer in very young women: clinicopathological study of 149 patients ≤25 years old. Breast 24(4):461–467. https://doi.org/10.1016/j.breast.2015.04.002
33. Giuliano AE, Ballman KV, McCall L, Beitsch PD, Brennan MB, Kelemen PR, Ollila DW, Hansen NM, Whitworth PW, Blumencranz PW, Leitch AM, Saha S, Hunt KK, Morrow M (2017) Effect of axillary dissection vs no axillary dissection on 10-year overall survival among women with invasive breast cancer and sentinel node metastasis: the ACOSOG Z0011 (alliance) randomized clinical trial. JAMA 318(10):918–926. https://doi.org/10.1001/jama/2017/11470
34. Kroman N, Holtveg H, Wohlfahrt J, Jensen MB, Mouridsen HT, Blichert-Toft M, Melbye M (2004) Effect of breast-conserving therapy versus radical mastectomy on prognosis for young women with breast carcinoma. Cancer 100(4):688–693
35. Mahmood U, Morris C, Neuner G, Koshy M, Kesmodel S, Buras R, Chumsri S, Bao T, Tkaczuk K, Feigenberg S (2012) Similar survival with breast conservation therapy or mastectomy in the management of young women with early-stage breast cancer. Int J Radiat Oncol Biol Phys 83(5):1387–1393. https://doi.org/10.1016/j.ijrobp.2011.10.075
36. Barton MK (2015) Mastectomy and breast-conserving therapy confer equivalent outcomes in young women with early-stage breast cancer. CA Cancer J Clin 65(5):335–336. https://doi.org/10.3322/caac.21289
37. Sheridan W, Scott T, Caroline S, Yvonne Z, Vanessa B, David V, Karen G, Stephen C (2014) Breast cancer in young women: have the prognostic implications of breast cancer subtypes changed over time? Breast Cancer Res Treat 147(3):617–629. https://doi.org/10.1007/s10549-014-3125-1
38. Lee MK, Varzi LA, Chung DU et al (2015) The effect of young age in hormone receptor positive breast cancer. Biomed Res Int 2015: 325715. https://doi.org/10.1155/2015/325715
39. Kroman N, Jensen MB, Wohlfahrt J et al (2003) Factors influencing the effect of age on prognosis in breast cancer: population based study. BMJ 320(7233):474–478
40. Gnant M, Mlineritsch B, Stoeger H (2015) Zoledronic acid combined with adjuvant endocrine therapy of tamoxifen versus anastrozole plus ovarian function suppression in premenopausal early breast cancer: final analysis of the Austrian breast and colorectal cancer study group trial 12. Ann Oncol 26(2):313–320. https://doi.org/10.1093/annonc/mdu544
41. Paik S, Shak S, Tang G, Kim C, Baker J, Cronin M, Baehner FL, Walker MG, Watson D, Park T, Hiller W, Fisher ER, Wickerham DL, Bryant J, Wolmark N (2004) A multigene assay to predict recurrence of tamoxifen-treated, node negative breast cancer. N Engl J Med 351(27):2817–2826
42. Partridge AH, Pagoni O, Abulkhair O et al (2014) First international consensus guidelines for breast cancer in young women (BCY1). Breast 23(3):209–220. https://doi.org/10.1016/j.breast.2014.03.011