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EPIDEMIOLOGY

Suboptimal therapy following breast conserving surgery in triple-negative and HER2-positive breast cancer patients

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Abstract

Purpose To assess potential disparities in guideline-concordant care delivery among women with early-stage triple-negative and HER2-positive breast cancer treated with breast conserving therapy.

Methods Women ≥ 40 years old diagnosed with pT2N0M0 triple-negative or HER2-positive breast cancer treated with primary surgery and axillary staging between 2012 and 2017 were identified using the National Cancer Database (NCDB). The primary outcome was receipt of adjuvant systemic therapy and radiation concordant with current guidelines. Multivariable log-binomial regression was used to assess the prevalence of optimal therapy use across patient and cancer characteristics. Kaplan–Meier curves were used to assess 5-year overall survival. Multivariable Cox proportional hazards regression was used to compare the impact of optimal therapy on 5-year mortality.

Results 11,785 women were included with 7,843 receiving optimal therapy. Receipt of optimal therapy decreased with age even after adjusting for comorbidities and cancer characteristics; other sociodemographic factors were not associated with differences in receipt of optimal therapy. Among patients who did not receive adjuvant systemic therapy, most were not offered the treatment (49%) or refused (40%). Overall 5-year survival was higher among women who received optimal therapy (89% [95% CI 88.0–89.3] vs. 66% [95% CI 62.9–68.5]). Patients who received suboptimal therapy were over twice as likely to die within 5 years of their diagnosis (adjusted HR 2.44, 95% CI 2.12–2.82).

Conclusion Age is the primary determinant of the likelihood of a woman to receive optimal adjuvant therapies in high-risk early-stage breast cancer. Patients who did not receive optimal therapy had significantly diminished survival.

Keywords Adjuvant chemotherapy · Adjuvant radiotherapy · Healthcare disparities · HER2-positive breast cancer · Triple-negative breast cancer

Introduction

Over the last 25 years, breast cancer therapy has evolved dramatically with an increasing focus on tailoring treatment to cancer phenotype and individual patient characteristics [1, 2]. Although survival has generally improved for patients with breast cancer in the USA, disparities exist in the delivery of care and outcomes for patients when classified by clinicopathologic and socioeconomic factors [3–6]. The availability, accessibility, and implementation of the most recent evidence-based treatments are not equal for all patients, and adherence to guidelines may be limited by a number of factors, including patient characteristics and preferences, socioeconomic factors, systems factors, and physician bias [4, 7].

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The American Cancer Society, in setting the 2035 challenge goal to reduce cancer mortality by 40%, identifies the elimination of disparities in cancer screening and care across multiple demographic and socioeconomic categories as a critical component [8]. Instrumental to remedying such disparities is not only identifying patient groups with poorer relative outcomes but identifying which therapies are being neglected and the specific risk factors that drive suboptimal treatment.

Thus, the purpose of this study was to assess potential disparities in optimal care delivery (defined as the use of guideline-concordant adjuvant radiation and systemic therapy) among women with early-stage triple-negative (TN) and HER2-positive (HER2+) breast cancer treated with breast conserving therapy, a population for whom there are strong recommendations for the use of adjuvant therapies [1]. We hypothesized that demographic and socioeconomic measures would be associated with disparities in the optimal delivery of adjuvant radiation and systemic therapy in women with early TN and HER2+ breast cancer.

Methods

All women ≥ 40 years old diagnosed with TN or HER2 + breast cancer between 2012 and 2017 were identified using the National Cancer Database (NCDB). The NCDB is a database of incident cancer cases developed by the American Cancer Society and the Commission on Cancer of the American College of Surgeons. The NCDB was established in 1989 and is a nationwide, facility-based, comprehensive clinical surveillance oncology dataset that captures roughly 70% of all newly diagnosed cancer cases each year in the USA. Breast cancer patients were included in this study if they received primary surgery with partial mastectomy and axillary staging procedure and were ultimately staged pathologic T2 and node-negative (pT2N0M0). Women were excluded if they were treated with neoadjuvant therapy (radiation or systemic therapy) or were missing information on chemoradiation (Fig. 1).

The primary outcome of interest was whether a woman underwent optimal therapy in line with guidelines, defined as the following: For women treated in 2012, this included having undergone adjuvant chemotherapy and radiation. For women treated 2013–2017, this included having undergone adjuvant systemic therapy (chemotherapy for TNBC; chemotherapy and anti-HER2 therapy for HER2 +) and radiation. This difference in optimal therapy definition is due to a change in NCDB reporting: In 2013, six drugs previously classified as chemotherapy, including trastuzumab and pertuzumab, were reclassified as immunotherapy. Treatment did not have to be administered by the reporting facility.

Descriptive statistics were used to compare patient and cancer characteristics among women who did and did not receive optimal therapy as defined above. Multivariable log-binomial regression was used to assess the likelihood or prevalence of optimal therapy use across patient and cancer characteristics (prevalence ratio [PR]). Variables included in the model were age group, race/ethnicity, Charlson Comorbidity Index (CCI) score, primary insurance type, median income in the patient's ZIP code, educational ascertainment in the patient's ZIP code (measured as the percentage of adults ≥ 25 years old that did not graduate from high school), cancer histology, cancer subtype, facility type, and region. The model was also adjusted for year of diagnosis. Median income and educational ascertainment were measured using data from the 2016 American Community Survey (ACS), years 2012–2016. The Cochran–Armitage Trend Test was used to assess rates of optimal treatment by year between 2012 and 2017.

We also assessed the association of optimal therapy, compared to suboptimal, on overall 5-year survival. To account for the time needed to receive optimal treatment, follow-up began 8 months after diagnosis for all patients. Patients with < 8 months of follow-up time due to either early death or loss to follow-up were excluded. Kaplan–Meier curves were used to assess differences in 5-year overall survival. Multivariable Cox proportional hazards regression was used to compare the impact of optimal therapy, compared to suboptimal, on 5-year mortality after adjusting for age group, race/ethnicity, CCI score, primary insurance type, median income in the patient's ZIP code, educational ascertainment in the patient's ZIP code, cancer histology, cancer subtype, facility type, and region.

All analyses were conducted using SAS version 9.4 (SAS Inc., Cary, NC). The University of North Carolina IRB determined this study to be exempt (IRB# 20-1493).

Results

Overall, 11,785 women were included with 7843 (67%) receiving optimal therapy (both adjuvant systemic therapy and radiation). Among patients who did not receive optimal therapy ($n = 3,942$), 1638 (42%) received adjuvant radiation without adjuvant chemotherapy, 1045 (27%) received adjuvant chemotherapy without adjuvant radiation, and 1259 (32%) received neither adjuvant chemotherapy nor radiation (Fig. 1).

Table 1 shows receipt of optimal therapy by clinicopathologic and demographic factors including multivariable binomial regression by each variable. The likelihood of receiving optimal therapy was decreased for age deciles 70–79 years old (prevalence ratio [PR] 0.71, 95% CI 0.68–0.75) and 80–90 (PR 0.24, 95% CI 0.21–0.28) even after adjusting for

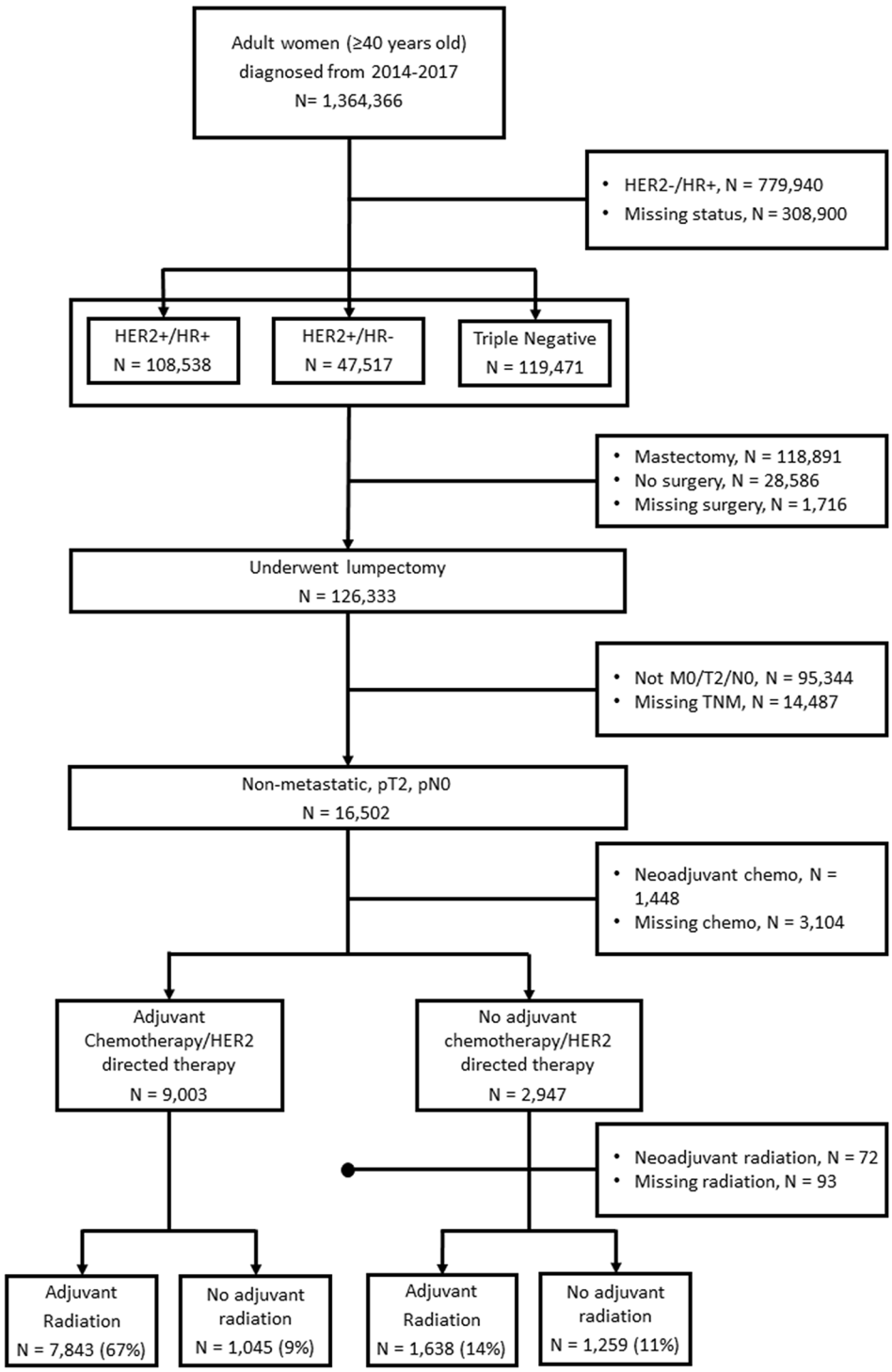

Fig. 1 STROBE Flow Chart. STROBE flow chart demonstrating inclusion/exclusion of patients identified in National Cancer Database

comorbidities and cancer characteristics. Patients over age 90 were excluded due to low numbers. Cancer phenotype was also significantly associated with likelihood of receiving optimal therapy. Compared to patients with hormone receptor-positive (HR+), HER2 + cancer, patients with hormone receptor-negative (HR−), HER2 + (PR 1.30, 95% CI 1.24–1.36) or TN cancer (PR 1.28, 95% CI 1.22–1.33) were more likely to receive optimal therapy. Patients with tumor histology other than ductal or lobular were also less likely to receive optimal therapy. No other variables demonstrated statistical significance.

Over the study period, the prevalence of women who had optimal therapy decreased significantly ($p < 0.0001$; Fig. 2). In 2012, 74% of patients received optimal therapy compared

Table 1 Patient demographics and association with receipt of optimal therapy

	Optimal treatment[a] 7841 (67%)	Suboptimal treatment[b] 3777 (33%)	PR (95% CI)[c]
Age, years, median (IQR)			–
Age groups, *n* (%)			
40–49 years old	1424 (18%)	327 (9%)	0.99 (0.97, 1.02)
50–59 years old	2516 (32%)	573 (15%)	1.0 (ref)
60–69 years old	2512 (32%)	814 (22%)	0.98 (0.95, 1.01)
70–79 years old	1184 (15%)	1083 (29%)	0.71 (0.68, 0.75)
80–89 years old	205 (3%)	980 (26%)	0.24 (0.21, 0.28)
Race/ethnicity, *n* (%)			
Non-Hispanic White	5122 (67%)	2657 (72%)	1.0 (ref)
Non-Hispanic Black	1764 (23%)	681 (18%)	0.99 (0.97, 1.02)
Hispanic	462 (6%)	209 (6%)	0.98 (0.93, 1.03)
Non-Hispanic other	310 (4%)	139 (4%)	0.97 (0.92, 1.03)
CCI score, *n* (%)			
0	6318 (81%)	2830 (75%)	1.0 (ref)
1	1168 (15%)	649 (17%)	1.01 (0.98, 1.04)
2	231 (3%)	193 (5%)	0.96 (0.89, 1.04)
≥ 3	124 (2%)	105 (3%)	0.94 (0.85, 1.04)
Primary insurance, *n* (%)			
Private insurance/managed care	4347 (56%)	1118 (30%)	1.0 (ref)
Medicare	2466 (32%)	2288 (61%)	0.90 (0.87, 0.93)
Medicaid	685 (9%)	244 (7%)	0.95 (0.92, 0.99)
Other government insurance	96 (1%)	34 (1%)	0.93 (0.84, 1.03)
Uninsured	157 (2%)	56 (2%)	0.93 (0.86, 1.01)
Median residential income[d], *n* (%)			
< $40,227	1365 (20%)	678 (21%)	0.97 (0.93, 1.01)
$40,227—$50,353	1491 (22%)	733 (22%)	0.99 (0.96, 1.02)
$50,354—$63,332	1549 (23%)	769 (23%)	0.98 (0.95, 1.01)
≥ $63,333	2394 (35%)	1128 (34%)	1.0 (ref)
Residential educational attainment[e], *n* (%)			
≥ 17.6%	1482 (22%)	729 (22%)	0.99 (0.95, 1.04)
10.9–17.5%	1871 (27%)	921 (28%)	1.01 (0.97, 1.04)
6.3–10.8%	1905 (28%)	908 (27%)	1.01 (0.98, 1.04)
< 6.3%	1549 (23%)	759 (23%)	1.0 (ref)
Cancer histology, *n* (%)			
Ductal	6714 (86%)	2961 (78%)	1.0 (ref)
Lobular	447 (6%)	349 (9%)	0.96 (0.91, 1.01)
Other	680 (9%)	467 (12%)	0.86 (0.82, 0.90)
Cancer subtype, *n* (%)			
HER2 + /HR +	1137 (15%)	1097 (29%)	1.0 (ref)
HER2 + /HR −	1106 (14%)	394 (10%)	1.30 (1.24, 1.36)
Triple-negative	5598 (71%)	2286 (61%)	1.28 (1.22, 1.33)
Current CoC accreditation, *n* (%)			
Community	830 (13%)	491 (11%)	0.97 (0.93, 1.01)
Comprehensive community	3509 (45%)	1702 (45%)	1.00 (0.98, 1.03)
Academic/research	2385 (30%)	1064 (28%)	1.0 (ref)
Integrated network	1117 (14%)	520 (14%)	1.00 (0.96, 1.03)
Facility region, *n* (%)			
Northeast	1666 (21%)	775 (21%)	1.0 (ref)
Midwest	1941 (25%)	833 (22%)	0.99 (0.96, 1.02)
South	3034 (39%)	1510 (40%)	0.98 (0.95, 1.01)

Table 1 (continued)

	Optimal treatment[a] 7841 (67%)	Suboptimal treatment[b] 3777 (33%)	PR (95% CI)[c]
West	1200 (15%)	659 (17%)	0.97 (0.94, 1.01)

PR prevalence ratio, *CI* confidence interval, *IQR* inter-quartile range, *CCI* Charlson comorbidity index, *HER2* human epidermal growth factor receptor 2, *CoC* Commission on cancer

[a]Optimal treatment is classified as receiving adjuvant chemotherapy/HER2-directed therapy and radiation

[b]Suboptimal treatment is classified as adjuvant chemotherapy/HER2-directed therapy without radiation, adjuvant radiation without chemotherapy/HER2-directed therapy, and no adjuvant therapy

[c]Estimated using log-binomial regression; model included all variables in the table, as well as year of diagnosis

[d]Median household income in patient's ZIP code; estimated and categorized into quartiles using the 2016 American Community Survey data, spanning 2012–2016

[e]Proportion of adults ≥ 25 years old in patient's ZIP code that did not graduate from high school; estimated and categorized into quartiles using the 2016 American Community Survey data, spanning 2012–2016

to 58% in 2017. In this cohort, 81% of patients received chemotherapy and/or HER2-directed therapy in 2012, compared to 70% in 2017. Likewise, 86% of patients received adjuvant radiation in 2012, compared to 72% in 2017.

Table 2 demonstrates the relationship of patient demographic and clinical variables with optimal therapy broken down into receipt of adjuvant systemic therapy or radiation therapy separately. Again, age was the only major difference demonstrated across treatment status. In the youngest deciles in our cohort, radiation was more likely to be omitted than systemic therapy, whereas in women 60 years of age and older, systemic therapy was more likely to be omitted than radiation.

Sociodemographic factors including race/ethnicity, median residential income, and residential educational attainment were not associated with differences in receipt of optimal therapy. Having non-private health insurance (including being uninsured) was associated with slightly lower prevalence of optimal therapy use, although due to small sample sizes the effects were not significant (Medicare: PR 0.90; 95% CI 0.87–0.93; Medicaid: PR 0.95; 95% CI 0.92–0.99; Other government insurance: PR 0.93, 95% CI 0.84–1.03; uninsured: PR 0.93, 95% CI 0.86–1.01). Facility characteristics, including Commission on Cancer accreditation and region, were also not associated with receipt of optimal therapy. Comorbidities also had minimal impact on receipt of optimal therapy.

Among patients who did not receive adjuvant chemotherapy or anti-HER2 therapy ($n = 2897$), 1442 (49%) were not offered the treatment, 1152 (40%) were offered treatment but refused, 325 (11%) had a documented contraindication, and < 1% died prior to treatment. Among those who did not receive adjuvant radiation, 1083 (55%) were not offered treatment, 764 (39%) refused, 129 (7%) had a documented contraindication (Table 3).

Overall survival was significantly different among women who did and did not undergo optimal therapy (Fig. 3). In the optimal therapy group, 5-year survival was 89% (95% CI 88.0–89.3) compared to 66% (95% CI 62.9–68.5) in the suboptimal therapy group. After adjusting for patient demographics including age and comorbidities, cancer characteristics, and facility type, patients who received suboptimal therapy were over twice as likely to die within 5 years of their diagnosis (HR 2.44, 95% CI 2.12–2.82). The association with suboptimal therapy and worse survival was true for patients both < 70 years old and ≥ 70 years old, although the separation of the survival curves is more pronounced for the older age group (Fig. 3b, c).

Discussion

We constructed a cohort of patients for whom the use of adjuvant systemic therapy and radiation therapy is strongly supported by guidelines [9]. We found that age was the primary determinant for whether a woman received this optimal vs. suboptimal care. Interestingly and importantly, socioeconomic factors like race/ethnicity, median residential income, and insurance status had minimal impact on treatment.

Efforts to limit overtreatment through widespread de-implementation of low-value care for older women with breast cancer has been slow and must be balanced with the risk of undertreatment leading to poorer outcomes, particularly with high-risk TN or HER2 + cancers. In older women with breast cancer, competing risks of non-cancer-associated mortality must be weighed against treatment options and the ability to tolerate treatment. Guidelines and expert recommendations have incorporated studies demonstrating the safety of scaling back of care for some older patients, including omitting radiation in women with early HR+, HER2-negative (HER2-) cancer, selective omission of axillary surgery, tailoring chemotherapy regimens, shorter radiation courses, and primary endocrine therapy for the particularly frail [9, 10]. In patients with high-risk

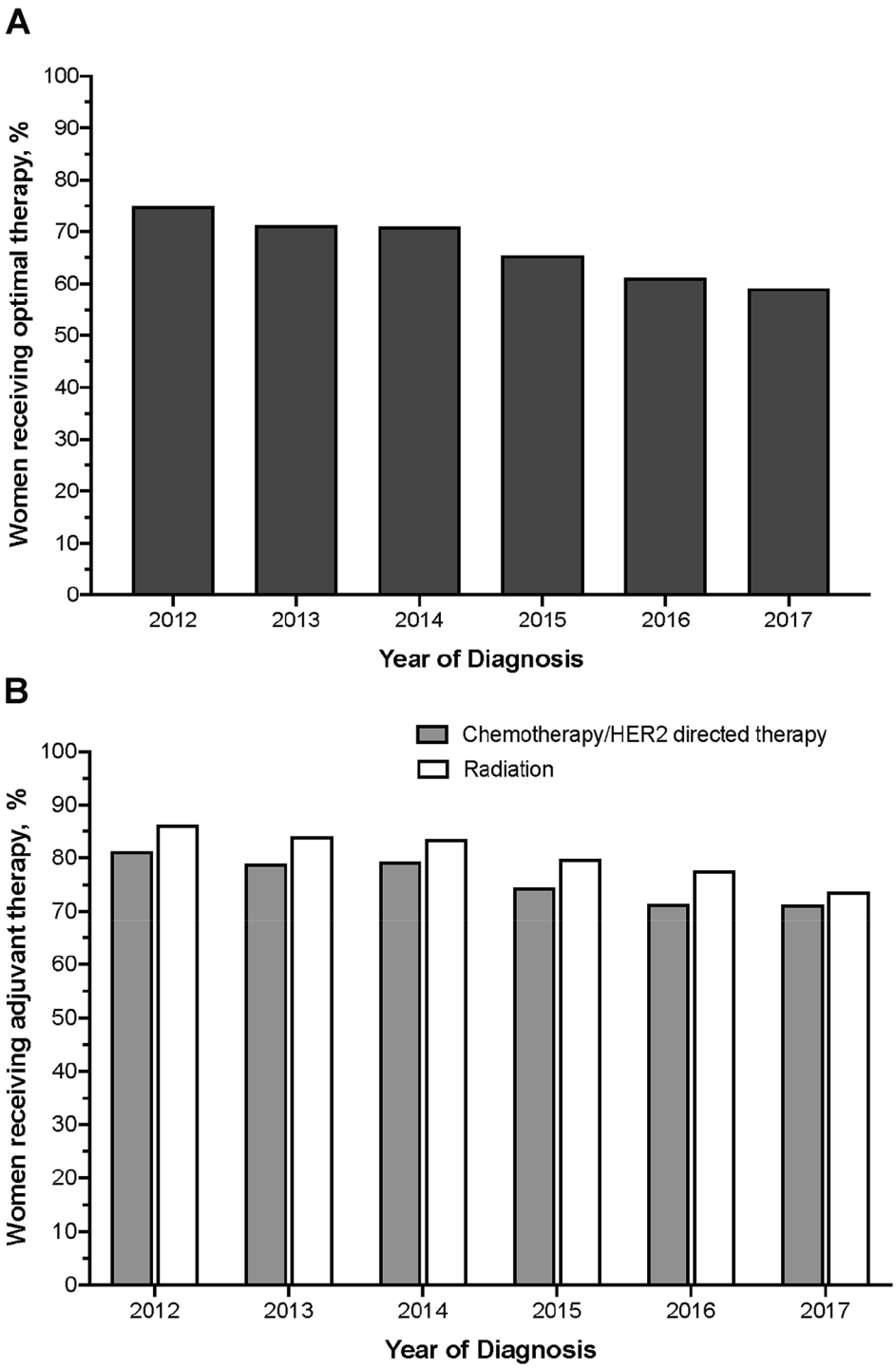

Fig. 2 Receipt of optimal therapy by year of diagnosis. **a** Percent of women receiving optimal therapy (systemic therapy and radiation therapy) by year of diagnosis. $p < 0.0001$ by Cochran–Armitage Trend test. **b** Percent of women receiving chemotherapy/HER2-directed therapy or radiation therapy by year of diagnosis

disease, however, there is no data to support omission of adjuvant systemic therapy and radiation. The benefits of adjuvant chemotherapy combined with targeted therapy for HER2 + breast cancer are well established, though notably age is the greatest risk factor for treatment-related cardiac events [11–16]. For women with TN breast cancer, adjuvant chemotherapy is recommended for all primary tumors larger than 1 cm or with node-positive disease [1]. The use of adjuvant chemotherapy in older patients presents additional challenges but is generally accepted for fit older patients with life expectancy greater than 10 years and may be tailored to patients with additional comorbidities or declining functional status [17, 18]. Adjuvant radiation may be safely omitted in older women with low risk hormone receptor-positive, HER2- tumors after BCS [1, 19, 20], although it

Table 2 Patient and cancer characteristics stratified by receipt of adjuvant chemotherapy/HER2-directed therapy and radiation

	Chemotherapy/HER2-directed therapy		Radiation	
	Yes	No	Yes	No
	8883 (76%)	2735 (24%)	9429 (81%)	2189 (19%)
Age, years, median (IQR)				
Age groups, *n* (%)				
40–49 years old	1577 (18%)	174 (6%)	1504 (16%)	247 (11%)
50–59 years old	2748 (31%)	341 (12%)	2677 (28%)	412 (18%)
60–69 years old	2789 (31%)	537 (20%)	2826 (30%)	500 (23%)
70–79 years old	1487 (17%)	780 (29%)	1714 (18%)	553 (25%)
80–89 years old	282 (3%)	903 (33%)	708 (8%)	477 (22%)
Race/ethnicity, *n* (%)				
Non-Hispanic White	5804 (67%)	1975 (74%)	6316 (69%)	1463 (69%)
Non-Hispanic Black	1989 (23%)	456 (17%)	2001 (22%)	444 (21%)
Hispanic	538 (6%)	133 (5%)	534 (6%)	137 (6%)
Non-Hispanic other	344 (4%)	105 (4%)	363 (4%)	86 (4%)
CCI score, *n* (%)				
0	7137 (80%)	2011 (74%)	7479 (79%)	1669 (76%)
1	1327 (15%)	490 (18%)	1464 (16%)	353 (16%)
2	275 (3%)	149 (5%)	314 (3%)	110 (5%)
≥ 3	144 (2%)	85 (3%)	172 (2%)	57 (3%)
Primary insurance, *n* (%)				
Private insurance/managed care	4766 (54%)	699 (26%)	4726 (51%)	739 (34%)
Medicare	2954 (34%)	1798 (66%)	3552 (38%)	1200 (55%)
Medicaid	776 (9%)	153 (6%)	755 (8%)	174 (8%)
Other government insurance	110 (1%)	20 (1%)	111 (1%)	19 (1%)
Uninsured	177 (2%)	36 (1%)	171 (2%)	42 (2%)
Median residential income[c], *n* (%)				
< $40,227	1575 (20%)	468 (20%)	1636 (20%)	407 (21%)
$40,227—$50,353	1683 (22%)	541 (23%)	1808 (22%)	416 (21%)
$50,354—$63,332	1768 (23%)	550 (23%)	1865 (23%)	453 (23%)
≥ $63,333	2712 (35%)	810 (34%)	2851 (35%)	671 (34%)
Residential educational attainment[d], *n* (%)				
≥ 17.6%	1703 (22%)	508 (21%)	1771 (22%)	440 (23%)
10.9–17.5%	2138 (28%)	654 (28%)	2247 (27%)	545 (28%)
6.3–10.8%	2164 (28%)	649 (27%)	2279 (28%)	534 (27%)
< 6.3%	1742 (22%)	566 (24%)	1876 (23%)	432 (22%)
Cancer histology, *n* (%)				
Ductal	7606 (86%)	2069 (76%)	7892 (84%)	1783 (81%)
Lobular	512 (6%)	284 (10%)	612 (6%)	184 (10%)
Other	765 (9%)	382 (14%)	925 (10%)	222 (10%)
Cancer subtype, *n* (%)				
HER2 + /HR +	1390 (16%)	844 (31%)	1611 (17%)	623 (28%)
HER2 + /HR −	1255 (14%)	245 (9%)	1215 (13%)	285 (13%)
Triple-negative	6238 (70%)	1646 (60%)	6603 (70%)	1281 (59%)
Current CoC accreditation, *n* (%)				
Community	987 (11%)	334 (12%)	1017 (11%)	304 (14%)
Comprehensive community	3973 (45%)	1238 (45%)	4225 (45%)	986 (45%)
Academic/research	2708 (30%)	741 (27%)	2827 (30%)	622 (28%)
Integrated network	1215 (13%)	422 (15%)	1360 (14%)	277 (13%)

Table 2 (continued)

	Chemotherapy/HER2-directed therapy		Radiation	
	Yes	No	Yes	No
	8883 (76%)	2735 (24%)	9429 (81%)	2189 (19%)
Facility region, *n* (%)				
Northeast	1890 (21%)	551 (20%)	2002 (21%)	439 (20%)
Midwest	2170 (24%)	604 (22%)	2296 (24%)	478 (22%)
South	3457 (39%)	1087 (40%)	3662 (39%)	882 (40%)
West	1366 (15%)	493 (18%)	1469 (16%)	390 (18%)

PR prevalence ratio, *CI* confidence interval, *IQR* inter-quartile range, *CCI* Charlson comorbidity index, *HER2* human epidermal growth factor receptor 2, *CoC* Commission on Cancer

[a]Optimal treatment is classified as receiving adjuvant chemotherapy/HER2-directed therapy and radiation

[b]Suboptimal treatment is classified as adjuvant chemotherapy/HER2-directed therapy without radiation, adjuvant radiation without chemotherapy/HER2-directed therapy, and no adjuvant therapy

[c]Median household income in patient's ZIP code; estimated and categorized into quartiles using the 2016 American Community Survey data, spanning 2012–2016

[d]Proportion of adults ≥ 25 years old in patient's ZIP code that did not graduate from high school; estimated and categorized into quartiles using the 2016 American Community Survey data, spanning 2012–2016

Table 3 Reason for omission of chemotherapy or radiation therapy

	No chemotherapy N = 2897[a]	No radiation N = 2304[a]
Reason, *n* (%)		
Not part of planned treatment	1291 (48)	1010(54)
Contraindicated[b]	298 (11)	117 (6)
Refused by patient or family[c]	1115 (41)	737 (40)
Recommended, unknown reason; or patient died prior to treatment	36	70
Unknown status	0	255

[a]Includes 1259 patients who received neither chemotherapy nor radiation

[b]Treatment was not recommended/administered because it was contraindicated due to other patient risk factors (comorbid conditions, advanced age, etc.)

[c]Treatment was recommended by the patient's physician, but was refused by the patient, the patient's family member, or the patient's guardian. The refusal was noted in patient record

remains the standard for women with TN or HER2 + tumors treated with partial mastectomy.

In 2009, the CALGB investigators randomized women ages 65 and older to standard chemotherapy or capecitabine and demonstrated that adjuvant chemotherapy was superior in this patient population [21]. Despite these and other data, studies have demonstrated disparities in the delivery of adjuvant chemotherapy in older adult women similar to what we have shown. In a 2019 study by Williams et al., one in six older women received guideline-discordant care (most commonly undertreatment) and this was associated with higher costs and rates of healthcare utilization [22]. A German study comparing adjuvant therapy in women older than 70 compared to their younger counterparts also demonstrated significant undertreatment with both systemic and local therapy despite similar distribution of tumor biology [23]. In a second European study, examining women over 80, 50% of women were undertreated, which was associated with decreased disease-specific survival [24]. In a study of data from the Surveillance, Epidemiology and Endpoints Registry (SEER), women over 67 had higher rates of mortality than younger controls when diagnosed with Stage 2 breast cancer, and this risk of mortality compared to controls increased when less aggressive therapy was given [25].

Our data also showed that patients who did not receive optimal therapy had significantly diminished survival compared with those receiving optimal, guideline-concordant therapy. This effect persisted after controlling for multiple demographic and clinicopathologic factors, including age and comorbidity. This is consistent with other recent analyses of NCDB in older patients with breast cancer. Crozier et al. showed that for women 70 years and older with surgically treated stage I–III TN breast cancer, propensity matched patients who received chemotherapy or were recommended but did not receive chemotherapy demonstrated an improvement in overall survival with administration of chemotherapy (hazard ratio [HR] 0.69, 95% CI 0.60–0.80) [26]. This effect persisted also for patients with increased comorbidity score (HR 0.74, 95% CI 0.59–0.94). Tamirisa et al. showed that adjuvant chemotherapy was associated with survival in a propensity matched cohort of patients with node-positive, HR + HER2 − breast cancer who were ≥ 70 years with Charlson/Deyo comorbidity score ≥ 2 [27]. From the data available in NCDB; however, it

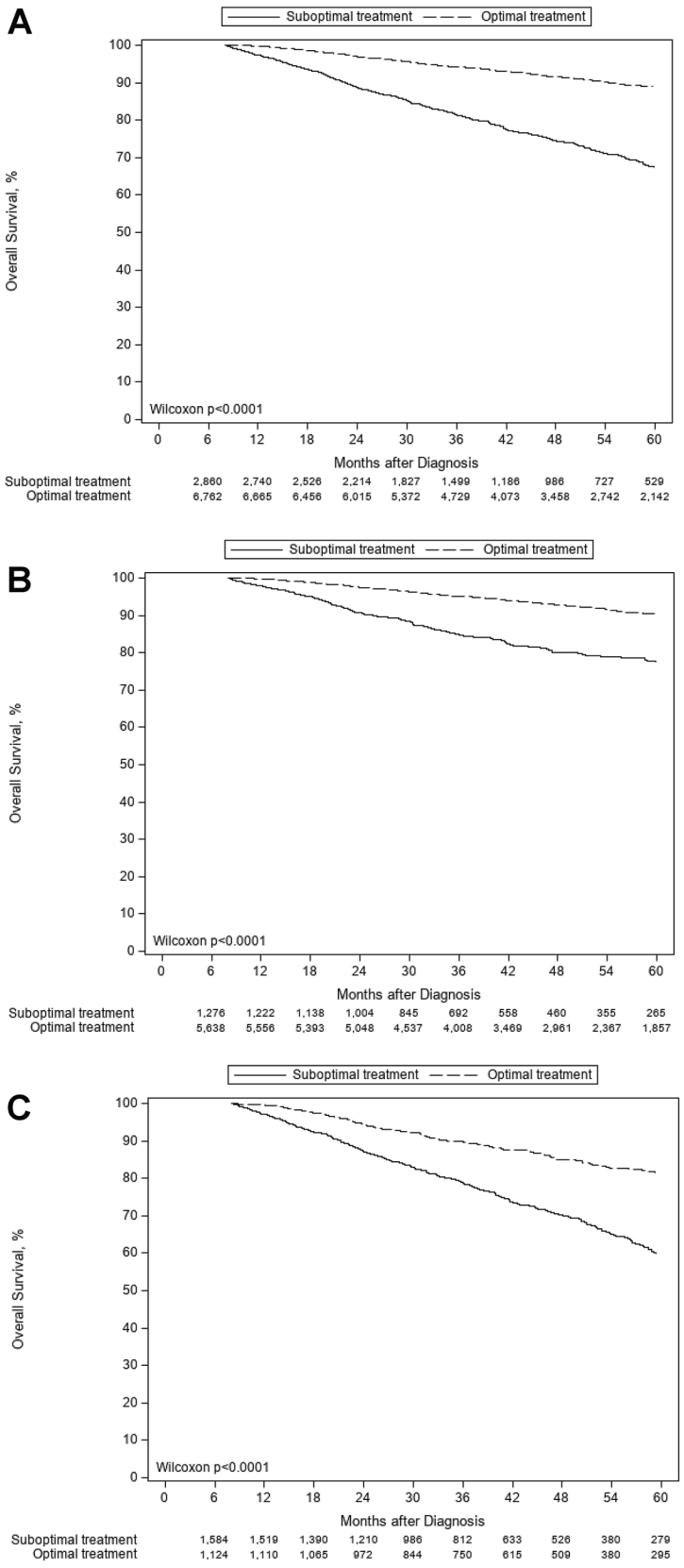

Fig. 3 Overall survival. **a** Overall survival for all patients by receipt of optimal vs. suboptimal treatment. **b** Overall survival for patients < 70 years old by receipt of optimal vs. suboptimal treatment. **c** Overall survival for patients ≥ 70 years old by receipt of optimal vs. suboptimal treatment

is impossible to estimate excess deaths attributable to breast cancer as opposed to uncaptured comorbid status or other determinants of health. Additionally, the depth of data fields present in the NCDB may not capture the level of detail needed to control for all patient selection factors and distinguish patient selection from treatment effects. Interestingly, we found that those patients with HER2+/HR+ cancers were least likely to receive optimal therapy (compared to TNBC and HR−/HER2 + patients). The mortality benefit of chemotherapy in older women has been shown to be greatest in those with HR− cancers, as well as patients with larger, node-positive cancers [28–30], and perhaps our data reflect a reliance on adjuvant endocrine therapy in HER2+/HR+ patients.

The reasons for patients not receiving optimal therapy in our study were similar for patients missing chemotherapy and/or radiation, with roughly 50% not offered treatment by providers, 40% refusing therapy, and 10% with a contraindication to therapy. Reasons that therapy was not offered or refused are not provided in more detail. Undertreatment may be contributing to older women not seeing the same improvement in outcomes compared to their younger counterparts [31]. Older patients of the same chronologic age may have strikingly different comorbidities [32] and different perspectives on the tradeoffs between quality of life and longevity [33] making decisions regarding adjuvant treatment complex [18]. Geriatric assessment tools exist to help make this decision [34, 35]. Online prediction tools such as Predict Breast Cancer may be used to help assess life expectancy and the marginal benefit of adjuvant chemotherapy [36]. Notably, in our data, the available measure of comorbidity likely underestimates frailty in the elderly, which may be contributing to the decisions for excluding adjuvant therapy [37]. This is evidenced in our overall survival curves in which suboptimal therapy is associated with worse overall survival in both younger and older patients, but the downward slope of the curve is much steeper in the older patients (and is not likely a reflection of unmeasured worse disease biology in this group).

Distance to treating facilities was not included in this analysis. Distance to an available radiation oncology facility has been associated with rates of BCT vs mastectomy [38]. Interpretation of distance data in NCDB, which includes great circle distance from a patient's ZIP code to a reporting facility, is more difficult.as not all patients are treated at their reporting facility, different elements of care (surgery, radiation, chemotherapy) are delivered at different locations, and this distance measure does not reflect closest available treatment facility and thus is a poor measure of access. Further, the relationship between distance and measures of adequacy of care and/or outcomes in NCDB is often not monotonic and may demonstrate improvement with increasing distance reflecting patient selection and regionalization of care [39, 40].

There was a significant decrease in the proportion of older patients receiving optimal therapy over time, from 74% in 2012 to 58% in 2017. The cause of this consistent, significant decline is not clear, though it may reflect the complexities of de-implementation such that therapies deemed inappropriate for one type of cancer (i.e. radiation for early-stage, HR+ breast cancer) may be applied to situations in which they might not apply. Alternatively, there may be increased awareness of ongoing efforts to fully evaluate our older adult patients, taking into careful consideration risks and benefits of therapy. It may represent a selection bias such that healthier patients were selected for neoadjuvant chemotherapy, which is increasingly more prevalent, and therefore our cohort represents a significantly frailer and/or sicker population than in earlier years. Finally, we cannot exclude an artifact of data collection or reporting creating this apparent decline.

We recognize several limitations to our study, most notably the lack of disease-specific survival data. Additionally, we lacked more granular data on the comorbid conditions of patients, which likely reflects an underestimation of morbidity, although this has not been shown to affect 5-year overall survival in a prior study [41]. NCDB participation is voluntary and likely underrepresents patients treated in rural hospitals. Finally, although we did not see evidence of racial disparities in delivery of optimal therapy in this patient population, this may be related to under-representation of Black women and Hispanic women in the NCDB.

In women who undergo breast conserving surgery for T2N0 TN and HER2 + breast cancer, guideline-concordant care includes adjuvant chemotherapy and radiation. As patients age, the competing risks of mortality as well as preferences regarding quality of life, including ability to tolerate toxic treatments and the life expectancy to see benefits, influence decision-making. Further study is needed to facilitate appropriate de-escalation of care while ensuring that older patients are not undertreated.

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Data availability The data that support the findings of this study are available from the National Cancer Database but restrictions apply to the availability of these data, which were used under license for the current study, and so are not publicly available. Data are however available from the authors upon reasonable request and with permission of the National Cancer Database.

Code availability The code used for analysis during the current study is available from the corresponding author on reasonable request.

Declarations

Conflict of interest The authors declare no conflicts of interest.

References

1. Network NCC: Invasive Breast Cancer (Version 6.2020) https://www.nccn.org/professionals/physician_gls/pdf/breast.pdf (2020)
2. Perou CM, Sørlie T, Eisen MB, van de Rijn M, Jeffrey SS, Rees CA et al (2000) Molecular portraits of human breast tumours. Nature 406(6797):747–752. https://doi.org/10.1038/35021093
3. Hsu CD, Wang X, Habif DV Jr, Ma CX, Johnson KJ (2017) Breast cancer stage variation and survival in association with insurance status and sociodemographic factors in US women 18 to 64 years old. Cancer 123(16):3125–3131. https://doi.org/10.1002/cncr.30722
4. Ward E, Jemal A, Cokkinides V, Singh GK, Cardinez C, Ghafoor A et al (2004) Cancer disparities by race/ethnicity and socioeconomic status. CA Cancer J Clin 54(2):78–93. https://doi.org/10.3322/canjclin.54.2.78
5. Jemal A, Robbins AS, Lin CC, Flanders WD, DeSantis CE, Ward EM et al (2018) Factors that contributed to black-white disparities in survival among nonelderly women with breast cancer between 2004 and 2013. J Clin Oncol 36(1):14–24. https://doi.org/10.1200/jco.2017.73.7932
6. Henley SJ, Ward EM, Scott S, Ma J, Anderson RN, Firth AU et al (2020) Annual report to the nation on the status of cancer, part I: national cancer statistics. Cancer 126(10):2225–2249. https://doi.org/10.1002/cncr.32802
7. Hoppe EJ, Hussain LR, Grannan KJ, Dunki-Jacobs EM, Lee DY, Wexelman BA (2019) Racial disparities in breast cancer persist despite early detection: analysis of treatment of stage 1 breast cancer and effect of insurance status on disparities. Breast Cancer Res Treat 173(3):597–602. https://doi.org/10.1007/s10549-018-5036-z
8. Ma J, Jemal A, Fedewa SA, Islami F, Lichtenfeld JL, Wender RC et al (2019) The American Cancer Society 2035 challenge goal on cancer mortality reduction. CA Cancer J Clin 69(5):351–362. https://doi.org/10.3322/caac.21564
9. Carlson RW, Moench S, Hurria A, Balducci L, Burstein HJ, Goldstein LJ, et al (2008) NCCN Task Force Report: breast cancer in the older woman. J Natl Compr Canc Netw 6(Suppl 4): S1–S25; quiz S6–S7.
10. Shachar SS, Hurria A, Muss HB (2016) Breast cancer in women older than 80 years. J Oncol Pract 12(2):123–132. https://doi.org/10.1200/jop.2015.010207
11. Advani PP, Ballman KV, Dockter TJ, Colon-Otero G, Perez EA (2016) Long-term cardiac safety analysis of NCCTG N9831 (Alliance) adjuvant trastuzumab trial. J Clin Oncol 34(6):581–587. https://doi.org/10.1200/jco.2015.61.8413
12. Piccart-Gebhart MJ, Procter M, Leyland-Jones B, Goldhirsch A, Untch M, Smith I et al (2005) Trastuzumab after adjuvant chemotherapy in HER2-positive breast cancer. N Engl J Med 353(16):1659–1672. https://doi.org/10.1056/NEJMoa052306
13. Romond EH, Perez EA, Bryant J, Suman VJ, Geyer CE Jr, Davidson NE et al (2005) Trastuzumab plus adjuvant chemotherapy for operable HER2-positive breast cancer. N Engl J Med 353(16):1673–1684. https://doi.org/10.1056/NEJMoa052122
14. Slamon D, Eiermann W, Robert N, Pienkowski T, Martin M, Press M et al (2011) Adjuvant trastuzumab in HER2-positive breast cancer. N Engl J Med 365(14):1273–1283. https://doi.org/10.1056/NEJMoa0910383
15. Perez EA, Romond EH, Suman VJ, Jeong JH, Davidson NE, Geyer CE Jr et al (2011) Four-year follow-up of trastuzumab plus adjuvant chemotherapy for operable human epidermal growth factor receptor 2-positive breast cancer: joint analysis of data from NCCTG N9831 and NSABP B-31. J Clin Oncol 29(25):3366–3373. https://doi.org/10.1200/jco.2011.35.0868
16. Joensuu H, Kellokumpu-Lehtinen PL, Bono P, Alanko T, Kataja V, Asola R et al (2006) Adjuvant docetaxel or vinorelbine with or without trastuzumab for breast cancer. N Engl J Med 354(8):809–820. https://doi.org/10.1056/NEJMoa053028
17. Shachar SS, Jolly TA, Jones E, Muss HB (2018) Management of triple-negative breast cancer in older patients: how is it different? Oncology (Williston Park) 32(2):58–63
18. Jolly TA, Williams GR, Bushan S, Pergolotti M, Nyrop KA, Jones EL, et al (2016) Adjuvant treatment for older women with invasive breast cancer. Womens Health (Lond) 12(1): 129–45; quiz 45–6. https://doi.org/10.2217/whe.15.92.
19. Hughes KS, Schnaper LA, Bellon JR, Cirrincione CT, Berry DA, McCormick B et al (2013) Lumpectomy plus tamoxifen with or without irradiation in women age 70 years or older with early breast cancer: long-term follow-up of CALGB 9343. J Clin Oncol 31(19):2382–2387. https://doi.org/10.1200/jco.2012.45.2615
20. Kunkler IH, Williams LJ, Jack WJ, Cameron DA, Dixon JM (2015) Breast-conserving surgery with or without irradiation in women aged 65 years or older with early breast cancer (PRIME II): a randomised controlled trial. Lancet Oncol 16(3):266–273. https://doi.org/10.1016/s1470-2045(14)71221-5
21. Muss HB, Berry DA, Cirrincione CT, Theodoulou M, Mauer AM, Kornblith AB et al (2009) Adjuvant chemotherapy in older women with early-stage breast cancer. N Engl J Med 360(20):2055–2065. https://doi.org/10.1056/NEJMoa0810266
22. Williams CP, Kenzik KM, Azuero A, Williams GR, Pisu M, Halilova KI et al (2019) Impact of guideline-discordant treatment on cost and health care utilization in older adults with early-stage breast cancer. Oncologist 24(1):31–37. https://doi.org/10.1634/theoncologist.2018-0076
23. Inwald EC, Ortmann O, Koller M, Zeman F, Hofstadter F, Evert M et al (2017) Screening-relevant age threshold of 70 years and older is a stronger determinant for the choice of adjuvant treatment in breast cancer patients than tumor biology. Breast Cancer Res Treat 163(1):119–130. https://doi.org/10.1007/s10549-017-4151-6
24. Bouchardy C, Rapiti E, Fioretta G, Laissue P, Neyroud-Caspar I, Schafer P et al (2003) Undertreatment strongly decreases prognosis of breast cancer in elderly women. J Clin Oncol 21(19):3580–3587. https://doi.org/10.1200/JCO.2003.02.046
25. Schonberg MA, Marcantonio ER, Ngo L, Li D, Silliman RA, McCarthy EP (2011) Causes of death and relative survival of older women after a breast cancer diagnosis. J Clin Oncol 29(12):1570–1577. https://doi.org/10.1200/JCO.2010.33.0472
26. Crozier JA, Pezzi TA, Hodge C, Janeva S, Lesnikoski BA, Samiian L et al (2020) Addition of chemotherapy to local therapy in women aged 70 years or older with triple-negative breast cancer: a propensity-matched analysis. Lancet Oncol 21(12):1611–1619. https://doi.org/10.1016/s1470-2045(20)30538-6
27. Tamirisa N, Lin H, Shen Y, Shaitelman SF, Sri Karuturi M, Giordano SH et al (2020) Association of chemotherapy with survival in elderly patients with multiple comorbidities and estrogen

receptor-positive. Node-Positive Breast Cancer JAMA Oncol 6(10):1548–1554. https://doi.org/10.1001/jamaoncol.2020.2388
28. Elkin EB, Hurria A, Mitra N, Schrag D, Panageas KS (2006) Adjuvant chemotherapy and survival in older women with hormone receptor-negative breast cancer: assessing outcome in a population-based, observational cohort. J Clin Oncol 24(18):2757–2764. https://doi.org/10.1200/JCO.2005.03.6053
29. Muss HB, Woolf S, Berry D, Cirrincione C, Weiss RB, Budman D et al (2005) Adjuvant chemotherapy in older and younger women with lymph node-positive breast cancer. JAMA 293(9):1073–1081. https://doi.org/10.1001/jama.293.9.1073
30. Du XL, Jones DV, Zhang D (2005) Effectiveness of adjuvant chemotherapy for node-positive operable breast cancer in older women. J Gerontol A Biol Sci Med Sci 60(9):1137–1144. https://doi.org/10.1093/gerona/60.9.1137
31. Smith BD, Jiang J, McLaughlin SS, Hurria A, Smith GL, Giordano SH et al (2011) Improvement in breast cancer outcomes over time: are older women missing out? J Clin Oncol 29(35):4647–4653. https://doi.org/10.1200/JCO.2011.35.8408
32. Piccirillo JF, Vlahiotis A, Barrett LB, Flood KL, Spitznagel EL, Steyerberg EW (2008) The changing prevalence of comorbidity across the age spectrum. Crit Rev Oncol Hematol 67(2):124–132. https://doi.org/10.1016/j.critrevonc.2008.01.013
33. Blinman P, King M, Norman R, Viney R, Stockler MR (2012) Preferences for cancer treatments: an overview of methods and applications in oncology. Ann Oncol 23(5):1104–1110. https://doi.org/10.1093/annonc/mdr559
34. Yourman LC, Lee SJ, Schonberg MA, Widera EW, Smith AK (2012) Prognostic indices for older adults: a systematic review. JAMA 307(2):182–192. https://doi.org/10.1001/jama.2011.1966
35. Mohile SG, Dale W, Somerfield MR, Schonberg MA, Boyd CM, Burhenn PS et al (2018) Practical assessment and management of vulnerabilities in older patients receiving chemotherapy: ASCO guideline for geriatric oncology. J Clin Oncol 36(22):2326–2347. https://doi.org/10.1200/jco.2018.78.8687
36. Wishart GC, Bajdik CD, Dicks E, Provenzano E, Schmidt MK, Sherman M et al (2012) PREDICT Plus: development and validation of a prognostic model for early breast cancer that includes HER2. Br J Cancer 107(5):800–807. https://doi.org/10.1038/bjc.2012.338
37. Jolly TA, Deal AM, Nyrop KA, Williams GR, Pergolotti M, Wood WA et al (2015) Geriatric assessment-identified deficits in older cancer patients with normal performance status. Oncologist 20(4):379–385. https://doi.org/10.1634/theoncologist.2014-0247
38. Schroen AT, Brenin DR, Kelly MD, Knaus WA, Slingluff CL Jr (2005) Impact of patient distance to radiation therapy on mastectomy use in early-stage breast cancer patients. J Clin Oncol 23(28):7074–7080. https://doi.org/10.1200/jco.2005.06.032
39. Ward EP, Unkart JT, Bryant A, Murphy J, Blair SL (2017) Influence of distance to hospital and insurance status on the rates of contralateral prophylactic mastectomy, a national cancer data base study. Ann Surg Oncol 24(10):3038–3047. https://doi.org/10.1245/s10434-017-5985-1
40. Wasif N, Chang YH, Pockaj BA, Gray RJ, Mathur A, Etzioni D (2016) Association of distance traveled for surgery with short- and long-term cancer outcomes. Ann Surg Oncol 23(11):3444–3452. https://doi.org/10.1245/s10434-016-5242-z
41. Wong ML, McMurry TL, Schumacher JR, Hu CY, Stukenborg GJ, Francescatti AB et al (2018) Comorbidity assessment in the national cancer database for patients with surgically resected breast, colorectal, or lung cancer (AFT-01, -02, -03). J Oncol Pract 14(10):e631–e643. https://doi.org/10.1200/jop.18.00175