Original Study

Are We Overtreating Patients With T1a HER2+ Breast Cancer? An Analysis of the National Cancer Database

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Abstract

The indications for chemotherapy in patients with T1aN0 HER2+ breast cancer have not been clearly defined. Currently, >50% of patients are receiving adjuvant chemotherapy. There are no overall survival differences noted based on receipt of chemotherapy.

Introduction: The potential benefit of systemic therapy in patients with T1a HER2+ cancers is not well understood, and no consensus guidelines exist. We sought to investigate practice patterns of chemotherapy use in this population. **Methods:** From the National Cancer Database (2013-2018), we identified female patients with HER2+ cancers staged as cT1aN0 or pT1aN0 and stratified by receipt of chemotherapy. Using univariate and multivariable analyses we assessed the clinicopathologic features associated with the receipt of chemotherapy. We also compared rates of overall survival (OS). **Results:** Of 5176 women with cT1aN0 HER2+ cancers, 88 (2%) received neoadjuvant chemotherapy. Younger age and hormone-receptor (HR) negative tumors were factors independently associated with receipt of neoadjuvant chemotherapy (all $P < .001$). Of 11,688 women with pT1aN0 HER2+ cancers, 5,588 (48%) received adjuvant chemotherapy. Rates of use increased over the analysis period from 39% in 2013 to 53% in 2018 ($P < .001$). Factors independently associated with receipt of adjuvant chemotherapy included younger age, having a poorly differentiated tumor, exhibiting lymphovascular invasion, undergoing adjuvant radiation (all $P < .001$). There were no differences in OS when comparing those who did and did not receive chemotherapy in either group. **Conclusions:** The use of chemotherapy in patients with HER2+ T1a cancers is increasing over time and is, as expected, more common among patients with unfavorable clinicopathologic features. Since no prognostic algorithm currently exists, more prospective data is needed to understand which of these patients may derive benefit from systemic therapy and which may safely avoid the morbidity of chemotherapy.

Clinical Breast Cancer, Vol. 22, No. 8, 828–839

Keywords: Neoadjuvant chemotherapy, Adjuvant chemotherapy, Breast cancer, HER2+ breast cancer, Early stage breast cancer

Introduction

Given the lack of consensus, clinical dilemmas around the appropriate use of systemic therapy in patients with early stage breast cancer persist and are increasing in frequency. With the improvement in technology and increased use of breast imaging for cancer screening, the proportion of patients diagnosed with early stage disease continues to increase.[1,2] The diagnosis of tumors <1 cm has seen the largest increase of any invasive tumor size since the advent of widespread screening mammography, constituting 23% of all invasive cancers diagnosed in 2010.[2]

Historically, patients with node-negative T1 breast cancers were treated with surgery alone since they experienced excellent outcomes without systemic therapy; 10-year breast cancer specific survival is reported to be >95%.[1,3,4] Additionally, the prospective studies of systemic therapy in patients with human epidermal growth factor receptor 2 (HER2) overexpressing cancers included only patients with tumors >2 cm, or smaller tumors with high risk clinical features[5-7] providing little randomized data on which to base the benefit of systemic therapy in patients with T1 tumors without high risk features.

More recently, investigators have identified factors associated with poorer outcomes in patients with early stage tumors for which

Accepted for presentation in poster format at the 23rd Annual Meeting of the American Society of Breast Surgeons, April 2022.

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Submitted: May 18, 2022; Revised: Jul 19, 2022; Accepted: Jul 24, 2022; Epub: 29 July 2022

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1526-8209/$ - see front matter
https://doi.org/10.1016/j.clbc.2022.07.013

Figure 1 Patient selection for analysis of neoadjuvant chemotherapy use among patients with cT1aN0 HER2+ cancer (A) and adjuvant chemotherapy use among patients with pT1aN0 HER2+ cancer (B).

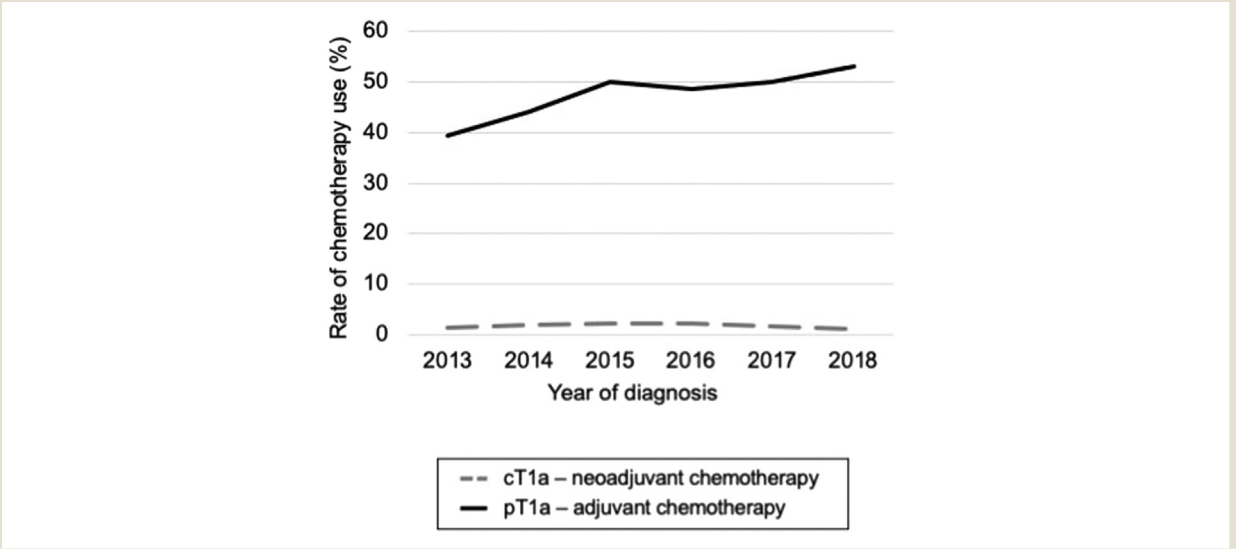
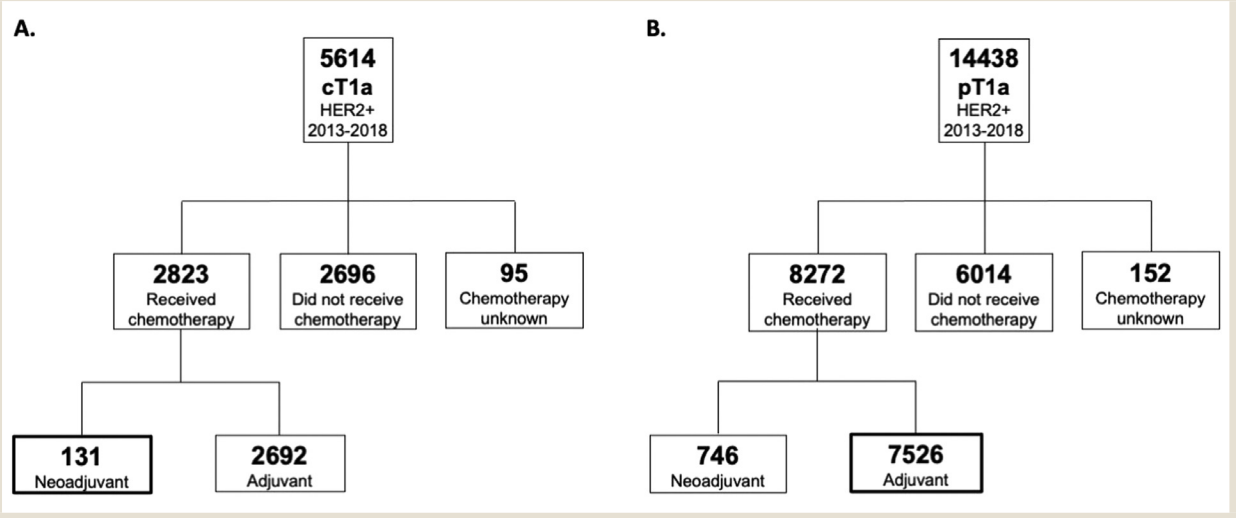


Figure 2 Rates of neoadjuvant (cT1aN0) and adjuvant (pT1aN0) chemotherapy over time among patients with HER2+ breast cancer.



systemic therapy may be indicated.[8-11] In addition to young age and high tumor grade, these studies highlight differences in receptor subtype, specifically those that are HER2 positive, are associated with a higher risk of recurrence and mortality when systemic therapy is not used. Without clear guidelines, clinicians are left to weigh the morbidity of systemic therapy with a small potential survival benefit in patients with high risk clinicopathologic features.[12]

Since systemic therapy has the most unfavorable risk:benefit ratio in patients with the earliest stage disease, we designed this study to assess the national practice patterns of the use of both neoadjuvant and adjuvant chemotherapy among patients with T1aN0 HER2+ breast cancer. We further sought to identify clinicopathologic features associated with the use of chemotherapy and compare overall survival (OS) between groups.

Materials and Methods

From the National Cancer Database (NCDB), we identified female patients with either cT1aN0 or pT1aN0 HER2+ breast cancer who were treated between 2013 and 2018. The NCDB is a joint collaboration between the American College of Surgeons and the American Cancer Society in which patient-level data are collected from all cancer patients seen at Commission on Cancer

Table 1 Clinicopathologic Features of Female Patients With cT1aN0 HER2+ Tumors (2013-2018) Stratified by Receipt of Neoadjuvant Chemotherapy.

	Overall	Chemotherapy		*P*
		No	*Yes*	
n	5092	2602	2490	
Age	60.8 ± 11.9	63.5 ± 12.0	57.9 ± 11.1	<.001
Facility type				
Community Cancer Program	328 (6.4)	180 (6.9)	148 (5.9)	.47
Comprehensive Community Cancer Program	2073 (40.7)	1091 (41.9)	982 (39.4)	
Academic/Research Program	1506 (29.6)	773 (29.7)	733 (29.4)	
Integrated Network Cancer Program	1011 (19.9)	511 (19.6)	500 (20.1)	
Unknown	174 (3.4)	47 (1.8)	127 (5.1)	
Race				
White	4190 (82.3)	2118 (81.4)	2072 (83.2)	.09
Black	539 (10.6)	280 (10.8)	259 (10.4)	
Other	315 (6.2)	179 (6.9)	136 (5.5)	
Unknown	48 (0.9)	25 (1.0)	23 (0.9)	
Insurance Status				
Not Insured	64 (1.3)	28 (1.1)	36 (1.4)	<.001
Private Insurance	2784 (54.7)	1241 (47.7)	1543 (62.0)	
Medicaid	243 (4.8)	106 (4.1)	137 (5.5)	
Medicare	1890 (37.1)	1172 (45.0)	718 (28.8)	
Other Government	58 (1.1)	29 (1.1)	29 (1.2)	
Unknown	53 (1.0)	26 (1.0)	27 (1.1)	
No High School Degree				
≥17.6%	741 (14.6)	403 (15.5)	338 (13.6)	.02
10.9%-17.5%	1031 (20.2)	548 (21.1)	483 (19.4)	
6.3%-10.8%	1241 (24.4)	641 (24.6)	600 (24.1)	
<6.3%	1365 (26.8)	655 (25.2)	710 (28.5)	
Unknown	714 (14.0)	355 (13.6)	359 (14.4)	
Median Income				
<$40,227	628 (12.3)	337 (13.0)	291 (11.7)	.005
$40,227-$50,353	856 (16.8)	443 (17.0)	413 (16.6)	
$50,354-$63,332	982 (19.3)	539 (20.7)	443 (17.8)	
≥$63,333	1904 (37.4)	921 (35.4)	983 (39.5)	
Unknown	722 (14.2)	362 (13.9)	360 (14.5)	
Charlson-Deyo Score				
0	4329 (85.0)	2181 (83.8)	2148 (86.3)	.06
1		606 (11.9)	328 (12.6)	278 (11.2)
2		114 (2.2)	67 (2.6)	47 (1.9)
≥3	43 (0.8)	26 (1.0)	17 (0.7)	
Year of Diagnosis				
2013	874 (17.2)	505 (19.4)	369 (14.8)	<.001
2014	864 (17.0)	460 (17.7)	404 (16.2)	
2015	835 (16.4)	410 (15.8)	425 (17.1)	
2016	875 (17.2)	428 (16.4)	447 (18.0)	
2017	840 (16.5)	397 (15.3)	443 (17.8)	
2018	804 (15.8)	402 (15.4)	402 (16.1)	

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Table 1 (*continued*)

	Overall	Chemotherapy		*P*
		No	*Yes*	
Histology				
Ductal	4548 (89.3)	2324 (89.3)	2224 (89.3)	.68
Lobular	404 (7.9)	202 (7.8)	202 (8.1)	
Other	140 (2.7)	76 (2.9)	64 (2.6)	
Tumor grade				
Well-differentiated	523 (10.3)	361 (13.9)	162 (6.5)	<.001
Moderately differentiated	2384 (46.8)	1282 (49.3)	1102 (44.3)	
Poorly differentiated	1813 (35.6)	755 (29.0)	1058 (42.5)	
Unknown	372 (7.3)	204 (7.8)	168 (6.7)	
Hormone receptor status				
Positive	3759 (73.8)	1998 (76.8)	1761 (70.7)	<.001
Negative	1331 (26.1)	604 (23.2)	727 (29.2)	
Unknown	2 (0.0)	0 (0.0)	2 (0.1)	
Lymphovascular invasion				
No	3901 (76.6)	2073 (79.7)	1828 (73.4)	<.001
Yes	420 (8.2)	106 (4.1)	314 (12.6)	
Unknown	771 (15.1)	423 (16.3)	348 (14.0)	
Adjuvant radiation				
No	2277 (44.7)	1245 (47.8)	1032 (41.4)	<.001
Yes	2684 (52.7)	1301 (50.0)	1383 (55.5)	
Unknown	131 (2.6)	56 (2.2)	75 (3.0)	
Anti-HER2 therapy				
No	2777 (54.5)	2399 (92.2)	378 (15.2)	<.001
Yes	2279 (44.8)	174 (6.7)	2105 (84.5)	
Unknown	36 (0.7)	29 (1.1)	7 (0.3)	
Endocrine therapy (denominator is HR+)				
No	811 (21.6)	501 (25.1)	310 (17.6)	<.001
Yes	2812 (74.8)	1437 (71.9)	1375 (78.1)	
Unknown	136 (3.6)	60 (3.0)	76 (4.3)	

accredited programs,[13] representing approximately 70% of United States cancer cases.[14]

For analysis, we stratified patients by whether they received systemic chemotherapy or not. For patients with cT1aN0 cancer, we selected patients who received NAC, which we defined as systemic chemotherapy initiated at least 30 days prior to first surgery. For patients with pT1aN0 cancer, we selected patients who received adjuvant chemotherapy. We assessed rates of chemotherapy use over time and compared facility, patient and tumor factors of those who received chemotherapy with patients who did not receive chemotherapy. For each group, we performed binary logistic regression to assess the clinicopathologic and demographic features associated with receipt of chemotherapy. We also compared OS between those who did and did not receive chemotherapy.

Statistical Analyses

All statistical analyses were carried out using SPSS statistical software (Version 28.0, IBM Corporation, Armonk, NY, USA). Comparisons of clinicopathologic features were performed using independent T-tests for continuous variables, and Chi square tests for categorical variables. Binary logistic regression models were used to assess factors associated with receipt of chemotherapy. Factors significant on univariate analysis were included in multivariable analysis. Kaplan-Meier survival analyses were used to compare OS between patients who did and did not receive chemotherapy.

Results

Neoadjuvant chemotherapy

We identified 5176 patients with cT1aN0 breast cancer; 2602 (50%) did not receive chemotherapy and 2490 (44%) received chemotherapy (Figure 1A). Among those who received chemotherapy, 88 (4%) received it in the neoadjuvant setting. The rate of NAC use was fairly consistent over time with 1.3% of patients receiving NAC in 2013, a slight increase to over 2% in 2015 and 2016, and a decrease to 1.1% in 2018 ($P = .82$, Figure 2).

Table 2 Factors Associated With the Initiation of Chemotherapy in the Neoadjuvant Setting in Patients With cT1aN0 Tumors

	Univariable			Multivariable		
	HR	*95% C.I.*	*P*	*HR*	*95% C.I.*	*P*
Age	0.97	0.95-0.99	**<.001**	0.97	0.95-0.99	**<.001**
Facility type						
Community Cancer Program						
Comprehensive Community (*ref*) Cancer Program	1.34	0.53-3.41	.54			
Academic/Research Program	0.70	0.26-1.93	.49			
Integrated Network Cancer Program	1.06	0.38-2.91	0.92			
Race						
White (*ref*)						
Black	0.41	0.15-1.14	.09			
Other	1.46	0.70-3.06	.31			
Insurance Status						
Not Insured (*ref*)						
Private Insurance	0.41	0.13-1.34	.14			
Medicaid	0.35	0.08-1.60	.18			
Medicare	0.24	0.07-1.01	.07			
Other Government	0.74	0.12-4.57	.74			
No High School Degree						
≥17.6% (*ref*)						
10.9%-17.5%	1.52	0.74-3.13	.26			
6.3%-10.8%	1.32	0.64-2.71	.45			
<6.3%	0.84	0.39-1.80	.65			
Median Income						
<$40,227 (*ref*)						
$40,227-$50,353	1.04	0.49-2.19	.93			
$50,354-$63,332	0.69	0.31-1.51	.35			
≥$63,333	0.90	0.46-1.75	.75			
Charleson-Deyo Score						
0 (*ref*)						
1	0.25	0.08-0.80	**.02**	0.33	0.10-1.06	.06
2	0.45	0.06-3.27	.43	0.63	0.09-4.66	.65
Year of Diagnosis						
2013 (*ref*)						
2014	1.47	0.68-3.17	.33			
2015	1.81	0.86-3.83	.12			
2016	1.84	0.88-3.87	.11			
2017	1.23	0.55-2.77	.61			
2018	0.88	0.36-2.14	.78			
Histology						
Ductal (*ref*)						
Lobular	0.55	0.20-1.51	.25			
Other	0.78	0.19-3.21	.73			
Tumor grade						
Well-differentiated (*ref*)						
Moderately differentiated	3.87	0.93-16.14	0.06	2.68	0.64-11.28	0.18
Poorly differentiated	5.57	1.34-23.15	**.02**	2.46	0.58-10.48	.23

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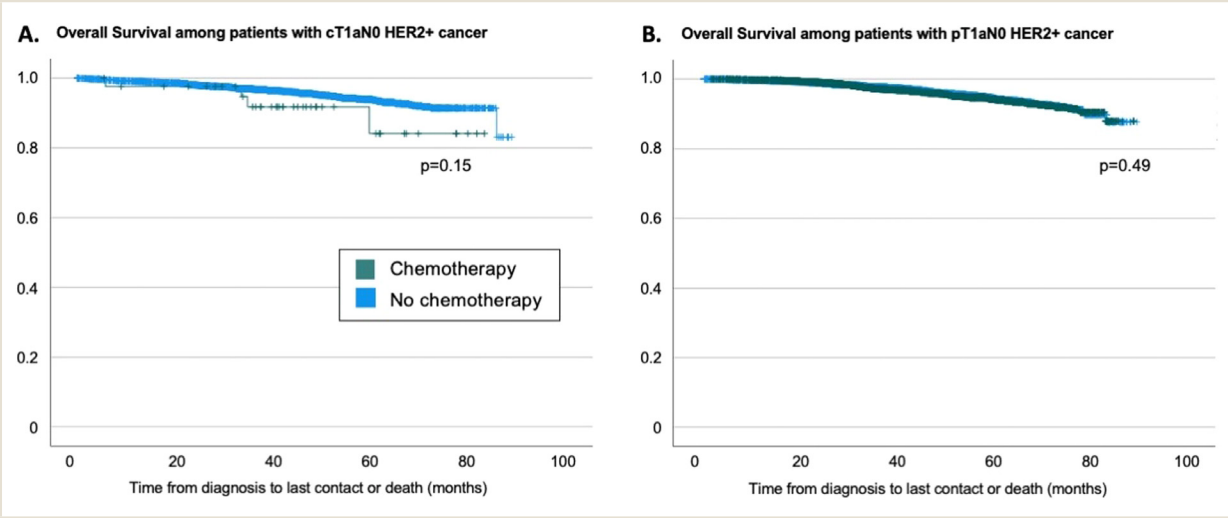
Table 2 (*continued*)

	Univariable			Multivariable		
	HR	*95% C.I.*	*P*	*HR*	*95% C.I.*	*P*
Hormone receptor status						
Positive (*ref*)						
Negative	4.55	3.03-7.14	**<.001**	5.56	3.33-9.09	**<.001**
Lymphovascular invasion						
No (*ref*)						
Yes	1.26	0.57-2.79	.57			

Figure 3 Kaplan-Meier curves for overall survival among patients with cT1aN0 HER2+ cancer (A) and pT1aN0 HER2+ cancer (B) stratified by receipt of chemotherapy.



Patients who received neoadjuvant chemotherapy were younger, more likely to have private insurance, poorly differentiated and hormone receptor (HR) negative tumors, and presence of lymphovascular invasion (all $P > .05$, Table 1). Patients who received neoadjuvant chemotherapy were also more likely to receive adjuvant therapy with radiation, anti-HER2 therapy and endocrine therapy (all $P < .001$).

Of the 85 patients who had clinical and pathologic tumor stages available, 32 (38%) had a breast pathologic complete response (pCR), which was defined as ypT0.

On univariate analysis, younger age, having a Charlson-Deyo score of 0, poorly differentiated and HR-negative tumor were factors associated with receipt of neoadjuvant chemotherapy (all $P < .05$, Table 2). Younger age (OR 0.97, 95% CI 0.95-0.99, $P < .001$) and HR-negative status (OR 5.56, 95% CI 3.33-9.09, $P < .001$) were the only two factors that persisted as independent predictors of receipt of neoadjuvant chemotherapy on multivariable analysis.

Median overall survival (OS) was similar between those who did and did not receive neoadjuvant chemotherapy (76.9 vs. 84.8 months, $P = .15$, Figure 3A).

Adjuvant chemotherapy

We identified 11,831 patients with pT1aN0 breast cancer; 5529 (47%) did not receive chemotherapy and 6159 (53%) received chemotherapy (Figure 1B). Among those who received chemotherapy, 5588 (91%) received it in the adjuvant setting. The rate of adjuvant chemotherapy use increased from 39% in 2013 to 53% in 2018 ($P < .001$, Figure 2).

Patients who received adjuvant chemotherapy were younger, more likely to have private insurance, a Charlson-Deyo score of 0, poorly-differentiated and hormone receptor negative tumors, and lymphovascular invasion (all $P \leq .05$, Table 3). Patients who received adjuvant chemotherapy were also more likely to receive adjuvant therapy with radiation, anti-HER2 therapy and endocrine therapy (all $P < .001$).

On univariate analysis, many clinicopathologic features were associated with the receipt of adjuvant chemotherapy (Table 4). Younger age (OR 0.96, 95% CI 0.95-0.97), poorly differentiated tumors (OR 2.08, 95% CI 1.46-2.98), presence of lymphovascular invasion (OR 2.80, 95% CI 1.91-4.11), and receipt of adjuvant anti-HER2 therapy (OR 143.69, 95% CI 118.63-174.05) were all independent predictors of receipt of adjuvant chemotherapy on

Table 3 Clinicopathologic Features of Female Patients With pT1aN0 HER2+ Tumors (2013-2018) Stratified by Receipt of Adjuvant Chemotherapy

	Overall	Chemotherapy		*P*
		No	*Yes*	
n	11,688	5529	6159	
Age	57.0 ± 12.2	60.8 ± 11.6	53.3 ± 11.7	**<.001**
Facility type				
Community Cancer Program	645 (5.5)	337 (6.1)	308 (5.0)	**.02**
Comprehensive Community Cancer Program	4324 (37.0)	2200 (39.8)	2124 (34.5)	
Academic/Research Program	3527 (30.2)	1679 (30.4)	1848 (30.0)	
Integrated Network Cancer Program	2349 (20.1)	1162 (21.0)	1187 (19.3)	
Unknown	843 (7.2)	151 (2.7)	692 (11.2)	
Race				
White	9306 (79.6)	4434 (80.2)	4872 (79.1)	.08
Black	1334 (11.4)	633 (11.4)	701 (11.4)	
Other	949 (8.1)	416 (7.5)	533 (8.7)	
Unknown	99 (0.8)	46 (0.8)	53 (0.9)	
Insurance Status				
Not Insured	207 (1.8)	69 (1.2)	138 (2.2)	**<.001**
Private Insurance	7181 (61.4)	3049 (55.1)	4132 (67.1)	
Medicaid	822 (7.0)	307 (5.6)	515 (8.4)	
Medicare	3236 (27.7)	1988 (36.0)	1248 (20.3)	
Other Government	132 (1.1)	70 (1.3)	62 (1.0)	
Unknown	110 (0.9)	46 (0.8)	64 (1.0)	
No High School Degree				
≥17.6%	1700 (14.5)	801 (14.5)	899 (14.6)	.22
10.9%-17.5%	2275 (19.5)	1112 (20.1)	1163 (18.9)	
6.3%-10.8%	2834 (24.2)	1302 (23.5)	1532 (24.9)	
<6.3%	3116 (26.7)	1471 (26.6)	1645 (26.7)	
Unknown	1763 (15.1)	843 (15.2)	920 (14.9)	
Median Income				
<$40,227	1420 (12.1)	688 (12.4)	732 (11.9)	.53
$40,227-$50,353	1845 (15.8)	869 (15.7)	976 (15.8)	
$50,354-$63,332	2177 (18.6)	1042 (18.8)	1135 (18.4)	
≥$63,333	4468 (38.2)	2077 (37.6)	2391 (38.8)	
Unknown	1778 (15.2)	853 (15.4)	925 (15.0)	
Charleson-Deyo Score				
0	10006 (85.6)	4635 (83.8)	5371 (87.2)	**<.001**
1	1329 (11.4)	703 (12.7)	626 (10.2)	
2	262 (2.2)	133 (2.4)	129 (2.1)	
≥3	91 (0.8)	58 (1.0)	33 (0.5)	
Year of Diagnosis				
2013	1710 (14.6)	971 (17.6)	739 (12.0)	**<.001**
2014	1858 (15.9)	943 (17.1)	915 (14.9)	
2015	1897 (16.2)	848 (15.3)	1049 (17.0)	
2016	2075 (17.8)	964 (17.4)	1111 (18.0)	
2017	2142 (18.3)	963 (17.4)	1179 (19.1)	
2018	2006 (17.2)	840 (15.2)	1166 (18.9)	

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Table 3 (*continued*)

	Overall	Chemotherapy		*P*
		No	*Yes*	
Histology				
Ductal	10655 (91.2)	5033 (91.0)	5622 (91.3)	.15
Lobular	702 (6.0)	323 (5.8)	379 (6.2)	
Other	331 (2.8)	173 (3.1)	158 (2.6)	
Tumor grade				
Well-differentiated	805 (6.9)	577 (10.4)	228 (3.7)	**<.001**
Moderately differentiated	4583 (39.2)	2539 (45.9)	2044 (33.2)	
Poorly differentiated	4053 (34.7)	1481 (26.8)	2572 (41.8)	
Unknown	2247 (19.2)	932 (16.9)	1315 (21.4)	
Hormone receptor status				
Positive	7987 (68.3)	3908 (70.7)	4079 (66.2)	**<.001**
Negative	3695 (31.6)	1618 (29.3)	2077 (33.7)	
Unknown	6 (0.1)	3 (0.1)	3 (0.0)	
Lymphovascular invasion				
No	9108 (77.9)	4660 (84.3)	4448 (72.2)	**<.001**
Yes	728 (6.2)	159 (2.9)	569 (9.2)	
Unknown	1852 (15.8)	710 (12.8)	1142 (18.5)	
Adjuvant radiation				
No	5157 (44.1)	2680 (48.5)	2477 (40.2)	**<.001**
Yes	6293 (53.8)	2771 (50.1)	3522 (57.2)	
Unknown	238 (2.0)	78 (1.4)	160 (2.6)	
Anti-HER2 therapy				
No	5791 (49.5)	5168 (93.5)	623 (10.1)	**<.001**
Yes	5822 (49.8)	296 (5.4)	5526 (89.7)	
Endocrine therapy (denominator is HR+)				
No	1522 (19.1)	849 (21.7)	673 (16.5)	**<.001**
Yes	6212 (77.8)	2958 (75.7)	3254 (79.8)	
Unknown	253 (3.2)	101 (2.6)	152 (3.7)	

multivariable analysis. Unlike in the neoadjuvant setting, HR status was not an independent predictor of adjuvant chemotherapy receipt.

Median overall survival (OS) was similar between those who did and did not receive adjuvant chemotherapy (85.1 vs. 85.7 months, $P = .49$, Figure 3B).

Discussion

In this study of national practice trends, we demonstrate an increase in the use of chemotherapy in patients with pT1aN0 HER2+ breast cancer, with rates exceeding 50% by the end of the study period.

The use of NAC in patients with locally advanced HER2+ breast cancer is well established as it provides the opportunity to downstage the breast and axilla to increase rates of breast conservation and avoidance of axillary lymph node dissection (ALND).[15,16] These benefits do not pertain to patients with cT1aN0 cancers. Breast conservation is almost universally an option (except in those for whom radiation is contraindicated and therefore would not require NAC for downstaging), and the rate of pathologic lymph nodes requiring ALND is extremely low.

Additionally, in patients with locally advanced disease, documentation of a pCR not only is prognostic for survival,[17,18] but identifies those who will benefit from adjuvant therapy as demonstrated in the KATHERINE trial.[19] Prospective trials of neoadjuvant chemotherapy and anti-HER2 therapy for patients with HER2+ cancers have documented pCR rates ranging from 46% to 52%.[20,21] None of these trials included patients with T1a disease, so the significance of the 38% pCR rate we observed in this study and its impact on survival outcomes in this group remain unclear.

Despite the unclear benefit of NAC, its use continues to increase in patients with cT1 HER2+ cancer.[22,23] Based on our study, though, it appears national rates of NAC remain low in patients with the earliest stage of disease.

The use of adjuvant chemotherapy plus anti-HER2 therapy has become standard of care, and its benefit in disease-specific and overall survival for patients with HER2+ node-positive or locally advanced cancers are supported by level 1 evidence.[24-26] Impor-

Table 4 Factors associated with the initiation of chemotherapy in the adjuvant setting in patients with pT1aN0 tumors

	Univariable			Multivariable		
	HR	*95% C.I.*	*P*	*HR*	*95% C.I.*	*P*
Age	0.95	0.95-0.95	**<.001**	0.96	0.95-0.97	**<.001**
Facility type						
Community Cancer Program						
Comprehensive Community Cancer Program	1.04	0.88-1.24	.64	1.46	0.97-2.20	.07
Academic/Research Program	1.24	1.04-1.47	**.02**	1.44	0.95-2.18	.09
Integrated Network Cancer Program	1.11	0.92-1.32	.28	1.22	0.80-1.88	.36
Race						
White						
Black	0.97	0.87-1.10	.67	0.91	0.67-1.22	.51
Other	1.19	1.04-1.37	**.01**	0.96	0.68-1.36	.82
Insurance Status						
Not Insured						
Private Insurance	0.73	0.54-0.99	**.04**	0.80	0.39-1.62	.53
Medicaid	0.87	0.63-1.22	.43	0.83	0.38-1.83	.65
Medicare	0.33	0.24-0.45	**<.001**	0.77	0.36-1.62	.48
Other Government	0.48	0.30-0.76	**<.001**	1.70	0.63-4.57	.30
No High School Degree						
≥17.6%						
10.9%-17.5%	0.93	0.82-1.06	.30			
6.3%-10.8%	1.07	0.95-1.21	.29			
<6.3%	1.05	0.93-1.18	.48			
Median Income						
<$40,227						
$40,227-$50,353	1.08	0.93-1.24	.31			
$50,354-$63,332	1.04	0.91-1.20	.55			
≥$63,333	1.13	1.00-1.28	.05			
Charleson-Deyo Score						
0						
1	0.77	0.69-0.87	**<.001**	0.89	0.66-1.20	.45
2	0.81	0.63-1.04	0.10	1.10	0.60-2.00	.76
≥3	0.51	0.33-0.79	**<.001**	0.63	0.19-2.10	.45
Histology						
Ductal						
Lobular	1.08	0.92-1.26	.34	1.03	0.70-1.52	.88
Other	0.78	0.62-0.98	**.03**	1.15	0.66-2.02	.63
Tumor grade						
Well-differentiated						
Moderately differentiated	2.01	1.70-2.38	**<0.001**	1.28	0.90-1.81	0.17
Poorly differentiated	4.11	3.47-4.87	**<.001**	2.08	1.46-2.98	**<.001**
Hormone receptor status						
Positive						
Negative	1.06	0.21-5.26	.94			
Lymphovascular invasion						
No						
Yes	3.60	3.00-4.33	**<.001**	2.80	1.91-4.11	**<.001**

(*continued on next page*)

Table 4 (*continued*)

	Univariable			Multivariable		
	HR	*95% C.I.*	*P*	*HR*	*95% C.I.*	*P*
Adjuvant radiation						
No						
Yes	1.38	1.28-1.49	**<.001**	1.12	0.93-1.36	.22
Anti-HER2 therapy						
No						
Yes	177.71	153.12-206.24	**<.001**	143.69	118.63-174.05	**<.001**
Endocrine therapy						
No						
Yes	1.19	1.10-1.28	**<.001**	0.91	0.75-1.11	.36

tantly, these trials did not include patients with T1 tumors, and so there are currently no consensus guidelines to support the use of any systemic therapy in patients with early stage disease. Our study, however, demonstrates that over half of patients with pT1aN0 HER2+ cancer are currently receiving adjuvant chemotherapy plus anti-HER2 therapy. Importantly, these prospective studies demonstrate that over 60% of patients experience a grade ≥3 adverse event and up to 7% suffer from a decrease in cardiac function due to the synergistic negative effects of these therapies.[25,26] Systemic therapy regimens that omit anthracyclines, such as those reported in the APT (adjuvant paclitaxel plus trastuzumab)[27] and ATEMPT (trastuzumab emtansine alone)[28] trials could be considered for patients with very early stage disease in order to minimize the potential risks of therapy.

This risk of morbidity must be weighed with an undefined benefit in breast cancer outcomes. Retrospective analyses of both the Surveillance, Epidemiology, and End Results (SEER) database[29] and the NCDB[30,31] failed to demonstrate breast-specific and overall survival benefits for patients with HER2+ T1a receiving systemic therapy. We similarly did not find any impact of chemotherapy on overall survival in our study. In a study of the Netherlands Cancer Registry, van Ramshorst et al. analyzed the use of systemic therapy in T1N0 HER2 positive cancers and, similar to our study, found an increase over time.[4] Additionally, they found that receipt of adjuvant systemic therapy was associated with a significant improvement of 5% in breast cancer specific survival in T1 patients, but the difference, although similar, was not significant in the T1a subgroup likely due to a small sample size. Similarly, a Canadian study of adjuvant chemotherapy and trastuzumab in patients with T1N0 HER2+ cancer by Ali et al. found improvements in disease-free and overall survival, but the results are challenging to interpret when it comes to T1a disease since only 8 patients with T1a tumors received systemic therapy.[32]

In light of the lack of a consistently demonstrable survival benefit, and in the era of de-escalation of many treatment modalities, the increase in the use of systemic therapy in patients with T1a HER2+ breast cancer is curious. One possible reason that the use of adjuvant therapy would increase is a change in the composition of the cancers diagnosed over time in which high risk features become more prevalent. We did not note any significant change over time of the main factors that predicted adjuvant chemotherapy use (analysis not shown). The other factors that could influence the increased use of systemic therapy in this population is an increase in the use of regimens with less toxic chemotherapy backbones, prompting higher rates of recommendation for systemic therapy by medical oncologists, and increase in uptake by patients due to reduced risk for toxicity. We do not have data on the tolerability of the chemotherapy regimens, adverse effects, nor of disease-specific outcomes, which are required to clearly define the risk and benefit in this population. A prospective trial documenting each of these findings would help clarify the risks and benefits of treatment, and may offer additional clinicopathologic factors that should be considered when considering adjuvant treatment in patients with very early stage disease. Given the already-favorable outcomes, and the risk/benefit ratio in the experimental arm, enrollment in such a trial may be challenging. However, several ongoing trials of limited or no chemotherapy with anti-HER2 therapy in Stage 1 HER2+ breast cancer, such as the ADEPT[33] and ATEMPT 2.0[34] trials, may help to clarify some of the questions related to benefit while minimizing the risk of systemic therapy. Additionally, as the use of genomic expression profiling for breast cancer increases, identification of patients whose tumor proliferation is actually driven by HER2 stimulation versus another biologic pathway may help to select patients for specific treatment regimens.

Our study has several strengths and limitations. The use of the NCDB allows us to analyze practice patterns across the spectrum of institution types and a diverse group of practitioners and patients. This provides an opportunity to assess trends in the use of systemic therapy over time, and to evaluate a large data set for factors associated with its use. The NCDB, like any large database, does not provide granular data related treatment decisions, so we are unable to assess the reasons for the use of chemotherapy in each instance, which would be helpful in more thoroughly understanding practice patterns. Additionally, the chemotherapeutic and anti-HER2 agents used are not documented individually, so we are not able to assess the specific regimens being used. There are also no data related to discontinuation of therapy, which prevents us from analyzing rates of completion, which may impact outcomes. While OS is documented, the NCDB does not provide data on any disease-

specific outcomes which, for early-stage cancer, are important in assessing the benefit of therapy.

Conclusion

The use of chemotherapy in patient with T1aN0 HER2+ breast cancer is increasing over time, mostly in the adjuvant setting. There are currently no genomic assays that predict a benefit of chemotherapy in these patients, and lack of data on the impacts on outcomes in very early stage disease make the risk:benefit analysis challenging. More investigation into clinicopathologic features that can help predict benefit of chemotherapy are needed in order personalize the systemic therapy recommendations for these patients.

Clinical Practice Points

Patients with T1aN0 breast cancer have often been treated without systemic therapy given their excellent survival outcomes. The majority of studies evaluating the effect of chemotherapy and targeted anti-HER2 therapy have been performed in patients with higher stage disease, but there may be evidence to suggest that even patients with the earliest stage HER2+ disease may benefit from systemic therapy. Using the National Cancer Database, we found that the use of adjuvant chemotherapy among patients with T1aN0 HER2+ breast cancer has been increasing, and currently exceeds 50%. We found no overall survival benefit among patients treated with systemic therapy. Since there are currently no genomic assays that can predict which patients with HER2+ disease may benefit from systemic therapy, and so future, large-scale studies to determine which factors predict a higher benefit than risk of chemotherapy in these patients is needed.

Disclosure

All authors report no disclosures.

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