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EPIDEMIOLOGY

Benefit of adjuvant chemotherapy in node-negative T1a versus T1b and T1c triple-negative breast cancer

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Abstract

Purpose National comprehensive cancer network guidelines recommend delivery of adjuvant chemotherapy in node-negative triple-negative breast cancer (TNBC) if the tumor is > 1 cm and consideration of adjuvant chemotherapy for T1b but not T1a disease. These recommendations are based upon sparse data on the role of adjuvant chemotherapy in T1a and T1b node-negative TNBC. Our objective was to clarify the benefits of chemotherapy for patients with T1N0 TNBC, stratified by tumor size.

Methods We performed a retrospective analysis of survival outcomes of TNBC patients at two academic institutions in the United States from 1999 to 2018. Primary tumor size, histology, and nodal status were based upon surgical pathology. The Kaplan–Meier plot and 5-year unadjusted survival probability were evaluated.

Results Among 282 T1N0 TNBC cases, the status of adjuvant chemotherapy was known for 258. Mean follow-up was 5.3 years. Adjuvant chemotherapy was delivered to 30.5% of T1a, 64.7% T1b, and 83.9% T1c ($p < 0.0001$). On multivariable analysis, factors associated with delivery of adjuvant chemotherapy were tumor size and grade 3 disease. Improved overall survival was associated with use of chemotherapy in patients with T1c disease (93.2% vs. 75.2% $p = 0.008$) but not T1a (100% vs. 100% $p = 0.3778$) or T1b (100% vs. 95.8% $p = 0.2362$) disease.

Conclusion Our data support current guidelines indicating benefit from adjuvant chemotherapy in node-negative TNBC associated with T1c tumors but excellent outcomes were observed in the cases of T1a and T1b disease, regardless of whether adjuvant chemotherapy was delivered.

Keywords Triple negative · Node-negative · Breast cancer · Adjuvant chemotherapy

Introduction

Most early-stage, node-negative breast cancer patients face an excellent outcome with appropriately-selected locoregional and systemic therapy [1]. Triple-negative breast cancer (TNBC) represents a high-risk phenotype associated with a more advanced stage distribution and higher mortality rate compared to non-TNBC, even when detected early [2–4]. Chemotherapy is the standard adjuvant systemic treatment offered for TNBC and because these tumors tend to be biologically more aggressive, the threshold for offering adjuvant chemotherapy to node-negative patients is lower for TNBC compared to non-TNBC patients. However, the minimum tumor size for which a node-negative TNBC patient should be routinely offered adjuvant chemotherapy has not yet been definitively established.

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Selective retrospective analyses suggest that TNBC patients with node-negative disease and primary tumors no larger than one centimeter achieve excellent 5-year locoregional and distant control, regardless of whether they receive adjuvant chemotherapy [1, 5, 6]. In contrast, others have shown that adjuvant chemotherapy is associated with improved outcomes even among cases of sub-centimeter disease [7]. Robust data regarding outcomes for T1a/T1bN0 TNBC are sparse, because of challenges regarding early detection of TNBC as TNBC is more difficult to detect mammographically compared to non-TNBC [8–10].

Adjuvant chemotherapy is included as standard treatment in 2021 National Comprehensive Cancer Network (NCCN) management algorithms for all node-positive TNBC and for node-negative TNBC when the primary tumor is larger than one centimeter. NCCN guidelines are ambiguous for cases of node-negative T1b TNBC, with a recommendation that adjuvant chemotherapy be "considered"; adjuvant chemotherapy is not usually recommended for T1aN0 disease [11]. In view of chemotherapy toxicity, cost, and risk of overtreatment, we sought to review our experience by investigating the survival benefits associated with adjuvant chemotherapy among women diagnosed with node-negative T1 TNBC stratified by tumor size.

Methods

Patient population

The study design and data collection methods were approved by the Weill Cornell Medicine (WCM) and Henry Ford Health System (HFHS) Institutional Review Boards. HFHS includes patients treated at two sites in metropolitan Detroit, Michigan and WCM includes patients treated at two sites in Manhattan, New York. We reviewed the electronic medical records of TNBC patients ages 18 and older seen at WCM and HFHS from December 1999 to June 2018. Patients meeting inclusion criteria for this study were those with pathologically confirmed TNBC defined as immunohistochemistry revealing estrogen receptor < 1%, progesterone receptor < 1%, HER2/neu immunohistochemistry (IHC) 1 + or 0; cases of HER2/neu 2 + were included if they were negative for amplification by fluorescence in situ hybridization (FISH) according to the guidelines of the American Society of Clinical Oncology [12].

Patients with tumors that were pathologic stage T1N0 (T1a: > 1 mm but ≤ 5 mm; T1b: > 5 mm but ≤ 10 mm; T1c: > 10 mm but ≤ 20 mm), undergoing primary surgical therapy without the receipt of any neoadjuvant treatment were reviewed. Patients with unknown or unverified hormone receptor and/or HER2 status, an incomplete clinical record or those in whom delivery of adjuvant chemotherapy could not be confirmed were excluded. Patient, disease, and treatment characteristics were retrospectively reviewed and entered into a RedCap database. Primary tumors and lymph nodes were staged based on pathology reports according to the pathological anatomic stage of the eighth edition of the American Joint Committee on Cancer's *AJCC Cancer Staging Manual* [13].

Statistical analysis

The statistical programming language R version 3.6.1 (R Foundation for Statistical Computing) was used. Chi-squared tests assessed association between categorical variables; student's *t* tests were used to compare difference of continuous variables within groups. Multivariable logistic regression was performed to evaluate demographic and clinical variables associated with receipt of adjuvant chemotherapy including age at diagnosis, tumor size, presence of grade 3 disease, lymphovascular invasion, receipt of adjuvant radiation therapy, and type of breast surgery. The primary endpoints were overall survival, local recurrence-free survival, distant recurrence-free survival, and overall recurrence-free survival. The Kaplan–Meier plot and the unadjusted 5-year survival probability were evaluated. Log-rank test and Cox proportional-hazard (CPH) modeling wre used to assess the survival differences between patients who did and did not receive postoperative chemotherapy. Time 0 was defined as the date of diagnosis, defined as date of biopsy-proven malignancy. Additionally, after exclusion of patients with unknown adjuvant chemotherapy and radiation status, joint CPH modeling was performed to analyze the impact of adjuvant chemotherapy and adjuvant radiation therapy on overall survival. Survival data were censored at 15 years. Additional survival analysis was performed on a subset of patients ages 18–80 at diagnosis with at least one year of follow-up time.

Results

We identified 756 TNBC cases at WCM and HFHS. Clinicopathologic characteristics of the 282 patients with T1N0 disease at each site are shown in Table 1. Regarding the two study sites, the population at HFHS was composed of more Black American patients compared to WCM (57.1% vs. 11.1%; $p < 0.0001$), reflecting differences in the population demographics of Detroit compared to Manhattan. There were also differences between the two sites regarding histology; however, at both sites the majority of patients had invasive ductal carcinoma (84.52% vs. 93.43%; $p < 0.0001$). A higher proportion of grade 3 disease was seen at WCM than at HFHS (81.31% vs. 71.43%; $p = 0.048$). Additionally, patients at WCM were more likely to undergo contralateral prophylactic

Table 1 Characteristics of 282 T1N0 triple-negative breast cancer patients stratified by site (HFHS = Henry Ford Health System and WCM = Weill Cornell Medicine)

	HFHS ($n=84$)	WCM ($n=198$)	p value
Race			
Black American	48 (57.1%)	22 (11.1%)	< 0.0001
White American	36 (42.9%)	140 (70.7%)	
Other	0 (0%)	36 (18.2%)	
Age 50			
≤ 50	14 (16.7%)	54 (27.3%)	0.0798
> 50	70 (83.3%)	144 (72.7%)	
Histology			
Invasive ductal carcinoma	71 (84.5%)	185 (93.43%)	< 0.0001
Invasive ductal/invasive lobular carcinoma	7 (8.33%)	0 (0%)	
Invasive lobular carcinoma	5 (5.95%)	3 (1.51%)	
Metaplastic	0 (0%)	3 (1.51%)	
Other	0 (0%)	6 (3.03%)	
Unknown	1 (1.19%)	1 (0.50%)	
Grade 3 disease			
No	22 (26.1%)	30 (15.15%)	0.048
Yes	60 (71.4%)	161 (81.31%)	
Unknown	2 (2.238%)	7 (3.54%)	
Any lymphovascular invasion			
No	77 (91.7%)	141 (71.2%)	0.119
Yes	6 (7.14%)	25 (12.63%)	
Unknown	1 (1.19%)	32 (16.16%)	
Mastectomy			
No	62 (73.8%)	131 (66.2%)	0.261
Yes	22 (26.2%)	67 (33.8%)	
Contralateral prophylactic mastectomy			
No	79 (94.0%)	159 (80.30%)	0.00357
Yes	4 (4.76%)	38 (19.19%)	
Unknown	1 (1.19%)	1 (0.50%)	
Adjuvant radiation therapy (RT)[a]			
Breast	56 (66.7%)	111 (56.06%)	0.917
Breast/regional	1 (1.19%)	2 (1.01%)	
None	26 (30.9%)	53 (26.77%)	
Post-mastectomy radiation	0 (0%)	1 (0.50%)	
Unknown	1 (1.19%)	31 (15.66%)	
Pathologic T stage			
T1a	7 (8.3%)	34 (17.17%)	0.115
T1b	27 (32.1%)	66 (33.33%)	
T1c	50 (59.5%)	998 (49.49%)	
Adjuvant chemotherapy			
No	19 (22.6%)	58 (29.29%)	0.146
Yes	63 (75.0%)	118 (59.60%)	
Unknown	2 (2.38%)	22 (11.11%)	

[a]Breast = patients undergoing lumpectomy + breast RT, Breast/regional = patients undergoing lumpectomy + breast/regional RT, None = patients undergoing no adjuvant RT, Post-Mastectomy Radiation Therapy = patients undergoing post-mastectomy RT

mastectomy than at HFHS (19.19% vs. 4.76%; $p=0.00357$ (Table 1). Among the 282 T1N0 patients, the receipt of adjuvant chemotherapy was unknown for 24; therefore, a total of 258 patients comprised the final study population. Mean follow-up was 5.3 years (median 4.7 years; range < 1 month to 15 years). Median age was 62 years (range 29–92). More than half of patients (137; 53.1%) had T1c tumors, with 36 (13.9%) having T1a and 85 (32.9%) having T1b disease.

Factors associated with delivery of adjuvant chemotherapy

Among T1N0 TNBC patients in whom adjuvant chemotherapy status could be confirmed ($n=258$), adjuvant chemotherapy was delivered to 30.5% of T1a, 64.7% T1b, and 83.9% T1c ($p<0.0001$). Patients receiving adjuvant chemotherapy were younger (age ≤ 50 years 29.8% vs. 13.0%; $p=0.007$), more likely to have grade 3 disease (83.43% vs. 64.94%; $p=0.00169$), and more likely to have received postoperative radiation therapy (70.2% vs. 50.6%; $p=0.00733$). In both groups, patients were most likely to have invasive ductal histology (92.8% vs. 87.0%; $p=0.0337$) (Table 2).

For the multivariable analysis, a strong correlation was demonstrated between type of breast surgery and receipt of adjuvant radiation where 76.4% of patients having mastectomy did not have adjuvant radiation and 82.4% of patients who did not have mastectomy had radiation ($p<0.0001$). Therefore, we built two separate models, one utilizing adjuvant radiation as a covariate and another with type of breast surgery as a covariate. On multivariable analysis, tumor size (OR 5.66, CI 2.787–12.194; $p<0.0001$), grade 3 disease (OR 2.75, CI 1.244–6.141; $p=0.0126$), and postoperative radiation therapy (RT) (OR 2.66, CI 1.329–5.392; $p=0.0059$) were associated with receipt of adjuvant chemotherapy. With inclusion of mastectomy as a covariate, only tumor size (OR 5.94, CI 3.006–12.457; $p<0.0001$) and grade 3 disease (OR 2.59, CI 1.218–5.589; $p=0.0014$) were associated with receipt of adjuvant chemotherapy (Table 3).

5-Year unadjusted overall survival

A total of 14 deaths occurred over the study period, with 71.4% (10/14) occurring in patients with T1c disease (Table 4). For all T1N0 TNBC patients, 5-year unadjusted overall survival was similar for patients both with (95.7%) and without (91.6%) the use of adjuvant chemotherapy (Fig. 1, log-rank p value = 0.077). When stratified by tumor size, there was no significant improvement in survival within the subcategories of T1a (5-year unadjusted overall survival probability 100% vs. 100%; $p=0.3778$) and T1b (5-year unadjusted overall survival probability 100% vs. 95.8%; $p=0.2362$) disease. Conversely, adjuvant chemotherapy

Table 2 Characteristics of 258 T1N0 triple-negative breast cancer patients stratified by receipt of adjuvant chemotherapy

	No adjuvant chemotherapy ($n=77$)	Adjuvant chemotherapy ($n=181$)	p value
Age at diagnosis	64 (38,92)	61 (29,85)	0.0035
Median follow-up time (years)	4.22	5.41	0.0278
Race			
Black American	15 (19.5%)	51 (28.2%)	0.155
White American	54 (70.1%)	108 (59.7%)	
Other	8 (10.4%)	22 (12.2%)	
Age 50			
≤ 50	10 (13.0%)	54 (29.8%)	0.0067
>50	67 (87.0%)	127 (70.2%)	
Histology			
Invasive ductal ccarcinoma	67 (87.01%)	168 (92.82%)	0.0337
Invasive ductal/invasive lobular carcinoma	3 (3.90%)	4 (2.21%)	
Invasive lobular carcinoma	2 (2.60%)	3 (1.66%)	
Metaplastic	0 (0%)	3 (1.66%)	
Other	5 (6.49%)	1 (0.55%)	
Unknown	0 (0%)	2 (1.10%)	
Grade 3 disease			
No	24 (31.17%)	25 (13.81%)	0.00169
Yes	50 (64.94%)	151 (83.43%)	
Unknown	3 (3.90%)	5 (2.76%)	
Any lymphovascular invasion			
No	63 (81.82%)	137 (75.69%)	0.332
Yes	6 (7.79%)	23 (12.71%)	
Unknown	8 (10.39%)	21 (11.60%)	
Mastectomy			
No	46 (59.7%)	127 (70.2%)	0.137
Yes	31 (40.3%)	54 (29.8%)	
Contralateral prophylactic mastectomy			
No	67 (87.0%)	148 (81.8%)	0.496
Yes	10 (13.0%)	31 (17.1%)	
Unknown	0 (0%)	2 (1.1%)	
Adjuvant radiation therapy (RT)[a]			
Breast	37 (48.05%)	125 (69.06%)	0.00733
Breast/regional	2 (2.60%)	1 (0.55%)	
Post-mastectomy radiation	0 (0%)	1 (0.55%)	
None	33 (42.85%)	45 (24.86%)	
Unknown	5 (6.94%)	9 (4.97%)	
Pathologic T stage			
T1a	25 (32.47%)	11 (6.08%)	<0.0001
T1b	30 (38.96%)	55 (30.39%)	
T1c	22 (28.57%)	115 (63.5%)	

[a]Breast = patients undergoing lumpectomy + breast RT, Breast/regional = patients undergoing lumpectomy + breast/regional RT, None = patients undergoing no adjuvant RT, Post-Mastectomy Radiation Therapy = patients undergoing post-mastectomy RT

Table 3 Multivariable association with receipt of adjuvant chemotherapy in T1N0 triple-negative breast cancer patients

Variable	OR	95% confidence interval	*p* value
Inclusion of adjuvant radiation as a covariate			
Age at diagnosis	0.956	0.928–0.984	0.0026
Tumor size	5.659	2.787–12.194	< 0.0001
Grade 3 disease	2.747	1.244–6.141	0.0126
Lymphovascular invasion	1.067	0.357–3.682	0.9111
Adjuvant radiation Therapy	2.660	1.329–5.392	0.0060
Inclusion of type of breast surgery as a covariate			
Age at diagnosis	0.960	0.933–0.986	0.0032
Tumor size	5.940	3.006–12.457	< 0.0001
Grade 3 disease	2.595	1.218–5.589	0.0137
Lymphovascular invasion	1.551	0.543–5.183	0.0437
Mastectomy surgery	0.655	0.332–1.299	0.223

did improve overall survival for patients with T1c disease (5-year unadjusted overall survival probability 93.2% vs. 75.2%; $p = 0.008$) (Table 5).

Unadjusted local recurrence-free survival

No significant benefit was observed in unadjusted 5-year local recurrence-free survival for the entire T1N0 TNBC cohort (84.5% with adjuvant chemotherapy vs. 83.3% without; $p = 0.3367$). When stratified by tumor size, a numeric trend was observed favoring an association between adjuvant chemotherapy and improved local recurrence-free survival with the increase in tumor size, but the differences were not statistically significant: T1a (81.8% with adjuvant chemotherapy vs. 89.5% without; $p = 0.9856$), T1b (95.2% with adjuvant chemotherapy vs. 87.7% without; $p = 0.160$), and T1c (80.0% with adjuvant chemotherapy vs. 69.1% without; $p = 0.1506$).

Unadjusted distant recurrence-free survival

Delivery of adjuvant chemotherapy was not significantly associated with improvements in distant recurrence-free survival for the entire T1N0 TNBC cohort (91.1% with adjuvant chemotherapy vs. 88.3% without; $p = 0.0927$) or within the smallest size subgroups: T1a (100% with adjuvant chemotherapy vs. 95.5% without; $p = 0.2505$), T1b (93.8% with adjuvant chemotherapy vs. 91.7% without; $p = 02{,}506$), and T1c (88.5% with adjuvant chemotherapy vs. 74.8% without; $p = 0.098$). Consistent with our findings regarding adjuvant chemotherapy and overall survival endpoints, distant recurrence-free survival was numerically higher for T1c patients receiving adjuvant chemotherapy compared to those not receiving systemic treatment, but the difference did not achieve statistical significance (88.5% vs. 74.8%; $p = 0.098$).

Unadjusted overall recurrence-free survival

A total of 37 recurrences occurred overall, with 64.9% (24/37) occurring in patients with T1c disease (Table 4). A similar pattern in unadjusted 5-year overall recurrence-free survival was seen for the entire T1N0 TNBC cohort (82.0% with adjuvant chemotherapy vs. 78.7% without; $p = 0.1304$). Within the subgroup of T1a and T1b, there was no statistically significant improvement for patients receiving adjuvant chemotherapy (T1a 81.8% with adjuvant chemotherapy vs. 84.8% without; $p = 0.7517$ and T1b 92.1% with adjuvant chemotherapy vs. 83.6% without; $p = 0.0713$). For T1c, although the difference was not statistically significant, there was a greater difference in unadjusted recurrence-free survival difference among T1c (77.4% with adjuvant chemotherapy vs. 64.8% without; $p = 0.1212$).

Adjusted multivariate outcomes

Joint modeling was performed on patients in whom adjuvant chemotherapy and RT status was known to account for the effect of both adjuvant chemotherapy and adjuvant RT on overall survival, given the substantial difference in receipt of adjuvant RT among patients who received adjuvant chemotherapy. With joint modeling of both adjuvant chemotherapy and RT, the delivery of RT did not change our results; overall survival was improved only in patients with T1c disease with receipt of adjuvant chemotherapy.

Table 4 Survival outcomes stratified by tumor size

	T1 ($n = 258$)	T1a ($n = 36$)	T1b ($n = 85$)	T1c ($n = 137$)	*p* value
Number of distant recurrences	17/258 (6.59%)	2/36 (2.78%)	4/85 (4.70%)	11/137 (8.03%)	0.602
Number of local recurrences	30/258 (11.63%)	5/36 (13.89%)	4/85 (4.70%)	21/137 (15.33%)	0.0506
Number of any recurrences	19/258 (76.00%)	6/36 (16.67%)	3/85 (3.53%)	10/137 (7.30%)	0.371
Number of deaths	32/258 (12.40%)	1/36 (2.78%)	7/85 (8.23%)	24/137 (17.52%)	0.145

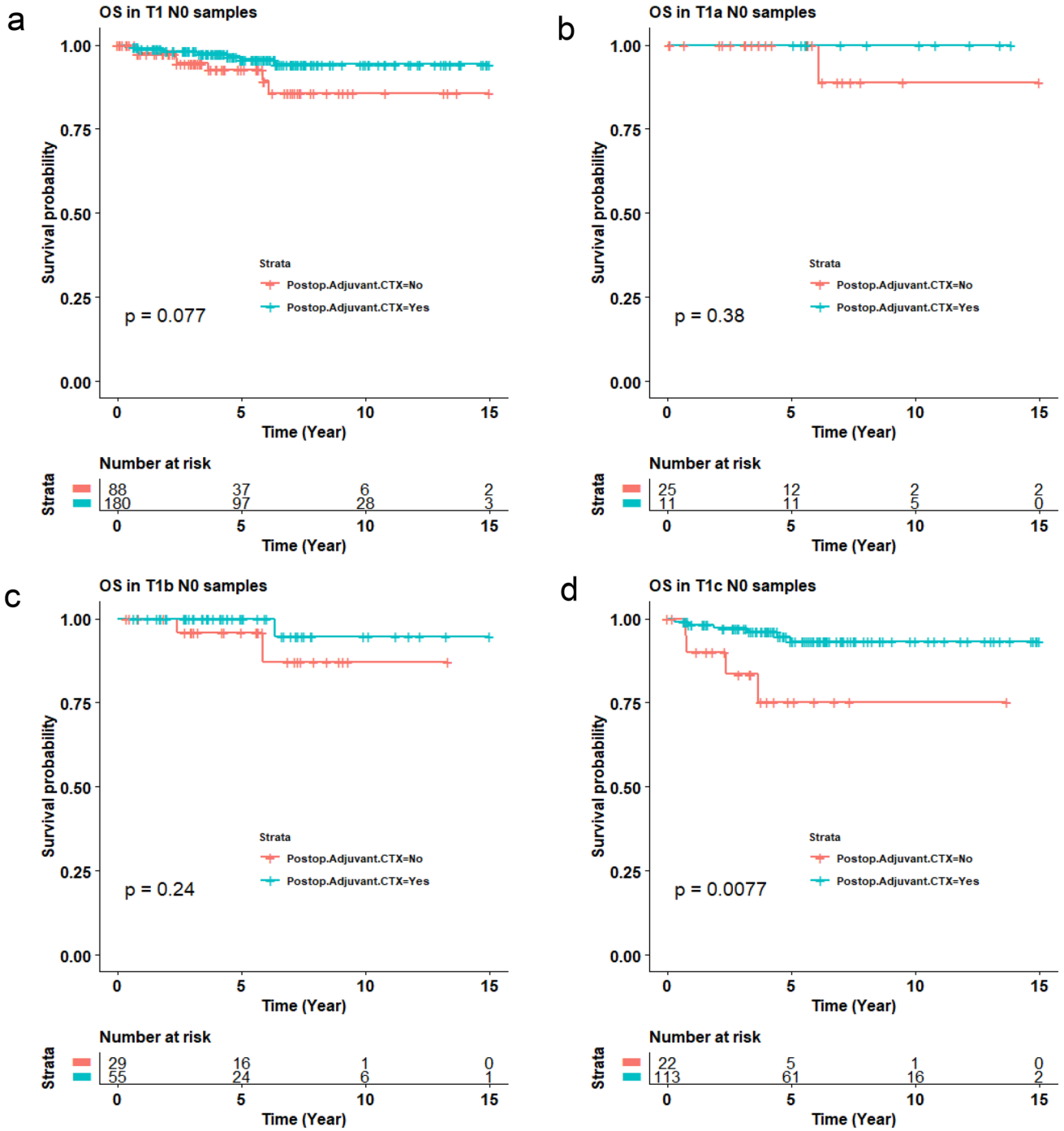

Fig. 1 5-year unadjusted overall survival of T1N0 triple-negative breast cancer patients treated with and without adjuvant chemotherapy stratified by tumor size **a** T1N0 **b** T1aN0 **c** T1bN0 **d** T1cN0. *Note* Figure created utilizing statistical programming language R version 3.6.1 (R Foundation for Statistical Computing)

Subset analysis of patients ages 18–80 with ≥ 1 year of follow-up

Subset analysis of patients with T1N0 TNBC ages 18–80 at time of diagnosis with at least one year of follow-up (but including four patients that died within one year of diagnosis) identified a total of 235 patients with a mean follow-up of 6.05 years (median 5.56 years, range 0.27 to 15.0 years). Mean follow-up for the 231 patients that were alive for at least one year was 6.14 years (median 5.57 years, range 1.17 to 15.0 years). Among these 235 patients, receipt of adjuvant chemotherapy was unknown for 7; therefore, a

Table 5 5-year unadjusted overall survival probability of T1, T1a, T1b, and T1c node-negative triple-negative breast cancer patients treated with and without adjuvant chemotherapy

Tumor size	*N*	5-Year survival probability	Hazard ratio (HR)	*p* value
T1				
No adjuvant chemotherapy	77	91.6% (84.8%, 99%)	Reference	0.04168
Adjuvant chemotherapy	181	95.7% (92.3%, 99.2%)	0.353 (0.123 – 1.01)	
T1a				
No adjuvant chemotherapy	25	100% (100%, 100%)	Reference	0.3778
Adjuvant chemotherapy	11	100% (100%, 100%)	7.77e-10 (0.0 – Inf)	
T1b				
No adjuvant chemotherapy	30	95.8% (88.2%, 100%)	Reference	0.2362
Adjuvant chemotherapy	55	100% (100%, 100%)	0.26 (0.0236 – 2.87)	
T1c				
No adjuvant chemotherapy	22	75.2% (56.2%, 100%)	Reference	0.0077
Adjuvant chemotherapy	115	93.2% (88%, 98.7%)	0.208 (0.0579 – 0.744)	

The 5-year survival probability was estimated from the Kaplan–Meier curve and the hazard ratio is derived from univariate Cox proportional hazards modeling; the p-value is associated with the hazard ratios through the Cox modeling

total of 228 patients were analyzed in this subset. Among these 228 patients, 32 (14.0%) had T1a disease, 77 (33.8%) had T1b disease, and 119 (52.0%) had T1c disease. Comparable to the larger cohort, a trend was seen for improved 5-year unadjusted distant recurrence-free survival and overall survival in patients with T1c disease that received adjuvant chemotherapy, but these differences were not statistically significant. Five-year distant recurrence-free survival rates for these groups were T1a, 100% with adjuvant chemotherapy versus 95.2% without ($p = 0.246$); T1b, 93.8% with adjuvant chemotherapy versus 91.3% without ($p = 0.213$); and T1c, 89.3% with adjuvant chemotherapy versus 76.2% without ($p = 0.074$). Five-year overall survival rates were T1a, 100% with and 100% without adjuvant chemotherapy ($p = 0.378$); T1b, 100% with adjuvant chemotherapy versus 95.7% without ($p = 0.205$); and T1c, 93.1% with adjuvant chemotherapy versus 85.7% without ($p = 0.118$).

Discussion

In this multi-institutional study, we sought to determine the benefit of adjuvant chemotherapy in early-stage, node-negative TNBC. With the limitation of retrospective data, the results generated from patients treated over the last two decades at two academic medical centers demonstrated that adjuvant chemotherapy was associated with improved 5-year overall survival in patients with stage T1c node-negative TNBC but not among those with smaller tumors.

The majority of screen-detected breast cancers are hormone receptor positive, resulting in a paucity of data detailing survival outcomes for cases of small, node-negative TNBC. Nonetheless, the favorable prognosis of patients with early-stage TNBC has been demonstrated by others (Table 6) [1, 5, 6, 14]. In 2012, Memorial Sloan Kettering reported a series of 194 T1a/b N0 TNBC from 1999 to 2006 and demonstrated excellent 5-year locoregional and distant control among those that received and those that did not receive adjuvant chemotherapy [6]. Similarly, a 2014 prospective multi-institutional cohort study from the National Comprehensive Cancer Network database involving 363 T1a/b N0 TNBC patients treated 2000–2009 reported excellent prognosis for T1aN0 and T1bN0 patients regardless of whether adjuvant chemotherapy was delivered [1].

Most studies looking at outcomes for cases of T1N0 TNBC are hampered by relatively small sample sizes of patients with T1a and T1b tumors. For example, a 2019 series of 45 TNBC and 71 hormone receptor-negative/HER2 + patients with early-stage, node-negative disease (T1mi/a/bN0M0) reported no difference in survival for those receiving chemotherapy compared to those not receiving adjuvant chemotherapy [5]. In July 2020, An and colleagues published a single-center study of 351 TNBC patients with T1N0 disease, 88% of whom received adjuvant chemotherapy. Adjuvant chemotherapy improved recurrence-free survival only in T1c disease, not in T1b and T1a. No difference in recurrence-free survival was noted for patients with T1c disease receiving different chemotherapy regimens. However, it should be noted that this study included only 19 T1a and 67 T1b TNBC patients [7]. Ren and colleagues reported a 2019 single-institutional study of 354 T1N0 TNBC patients and found that adjuvant chemotherapy improved recurrence-free survival for T1c but not T1a or T1b patients. Of note, however, only seven T1a and 44 T1b patients were included in this study [15]. More recently in 2020, Zhai and colleagues reported on 7739 cases of T1N0 TNBC and also found that adjuvant chemotherapy was associated with improved overall survival only in T1c patients [16].

In an effort to address the fact that most individual studies are underpowered to detect possible benefit from adjuvant

Table 6 Adjuvant chemotherapy in early-stage triple-negative breast cancer outcome studies (TNBC = triple-negative breast cancer)

Study	Patient sample	Median follow-up	Timeline	Adjuvant chemotherapy survival benefit?
Ho (2012)	194 ≤ 1 cm node-negative TNBC T1mic: 16 T1a: 49 T1b: 129 Memorial Sloan Kettering Cancer Center	73 months	1999–2006	T1mic/T1a: No T1b: No
Vaz-Luis (2014)	363 T1a,bN0M0 TNBC T1a: 99 T1b: 264 National Comprehensive Cancer Network	5.5 years	2000–2009	T1a/b: 5-year overall survival 91% to 94% in patients without chemotherapy and 96% to 100% in patients with chemotherapy
Colonna (2016)	49 T1a,bN0 TNBC T1a: 11 T1b: 38 Vanderbilt and Wake Forest	6.2 years	1997–2009	T1a/b: No
Ren (2019)	354 T1N0M0 TNBC T1a: 7 T1b: 44 T1c: 303 Fudan University Shanghai Cancer Center	45 months	2008–2015	T1a: NA T1b: No T1c: Yes
Bao (2019)	45 pT1mi,a,bN0M0 TNBC T1mi: 4 T1a: 9 T1b: 32 Cedars-Sinai Medical Center	4.9 years	2000–2013	T1mi: No T1a: No T1b: No
An (2020)	351 pT1N0M0 TNBC T1a: 19 T1b: 67 T1c: 265 Sun Yat-Sen University Cancer Center	68.5 months	2000–2016	T1a/b: No T1c: Yes
Zhai (2020)	7739 patients with T1N0M0 TNBC T1a: 755 T1b: 1979 T1c: 5005 SEER database	45 months	2010–2015	In T1N0, adjuvant chemotherapy associated with significantly improved breast cancer-specific survival
Steenbruggen (2020)	4366 pT1N0M0 TNBC patients T1a: 284 T1b: 923 T1c: 3159 Netherlands Cancer Registry	8.2 years	2005–2016	T1a/b: Yes T1c: Yes with better outcome most evident in T1c
Fasano (2021)	258 T1N0 TNBC T1a: 36 T1b: 85 T1c: 137 Weill Cornell Medicine and Henry Ford Health System	4.7 years	1999–2018	T1a/b: No T1c: Yes

chemotherapy in patients with T1a/bN0 TNBC, a nine-study meta-analysis was recently published, demonstrating that adjuvant chemotherapy was beneficial for the pooled cohort of over 750 T1bN0 patients [17]. Other national registry data from the United States and the Netherlands also indicated that adjuvant chemotherapy may improve outcomes for cases of node-negative TNBC associated with T1b tumors [16, 18]. A limitation of the large-scale registries, however, is the lack of standardized treatment approaches across the multiple institutions contributing data.

In this study, we noted that a significantly larger proportion of patients who received adjuvant chemotherapy were also recipients of postoperative adjuvant RT (70.16% vs. 50.65%; $p = 0.007$). A recent cohort study by de Boniface et al. comprised nearly 50,000 women examined survival after breast conservation versus mastectomy. At a median follow-up of 6.28 years, they found that breast conservation therapy with RT led to improved survival compared to mastectomy [19]. These data suggest that RT might confer a survival advantage, perhaps to due abscopal tumor effects [20]. In our study, to address this difference regarding receipt

of RT, joint modeling was performed to account for the possible impact on survival. Our analysis did not change our results that adjuvant chemotherapy improved overall survival in patients with T1c disease but did not significantly improve outcomes in patients with T1a and T1b disease.

Out study strengthens the existing literature regarding the role of adjuvant chemotherapy in early-stage TNBC because we evaluated the management of patients seen in two large tertiary referral cancer programs, both of which are certified by the National Accreditation Program for Breast Centers. We found that node-negative TNBC patients with tumors no larger than one centimeter have excellent survival rates and may be spared the toxicity of systemic therapy. While Oncotype and Mammaprint are available to predict chemotherapy response and likelihood of metastasis for hormone receptor-positive and HER2-negative breast cancers, Mammaprint does not risk stratify TNBC patients as precisely [21, 22]. TNBC remains a heterogeneous group of tumors that can be further categorized into subtypes based on gene expression analysis [23]. These subtypes have varying expression of other receptors and immune cells, conferring varying responses to chemotherapy. Specific to neoadjuvant chemotherapy, basal-like tumors exhibit the highest rates of pathologic complete response to carboplatin regimens, while luminal-androgen receptor lesions have the lowest pathologic complete response to all regimens [24]. These findings suggest that there may be utility in gene expression analysis for identifying patients who would benefit most from adjuvant chemotherapy and determining optimum regimens. In addition, ongoing research to develop new systemic therapies for TNBC, including targeted therapy for tumors with high expression of epidermal growth factor receptor, androgen receptor, and PDL-1 and immunotherapy with PARP inhibitors have the potential to impact adjuvant treatment decisions for TNBC and improve patient outcomes [25–27]. Ongoing work to examine the prognostic value of tumor infiltration leukocytes (TILs) both for survival outcomes as well as chemotherapeutic effects may also help to better identify early-stage cancers that may benefit most from adjuvant chemotherapy [28, 29]. Clinical judgment regarding cases associated with higher-risk features (e.g., young age at diagnosis, histologic features consistent with more aggressive disease such as metaplasia) remain important in individualizing treatment plans.

Limitations

There are limitations inherent to our study, given the retrospective nature and the prolonged time during which data were collected as adjuvant chemotherapy regimens have evolved. We also acknowledge the small sample sizes of subsets within the T1N0 category, albeit larger than reported in several other studies. Regarding the possible effect of adjuvant radiation therapy, we recognize that our sample size precluded exploration of the possibility that adjuvant RT may confer a survival advantage. Our analysis was also limited by the inability to provide details regarding chemotherapy schedules and content. Lastly, we recognize that given the retrospective nature of our study, selection bias may exist regarding which patients were offered adjuvant chemotherapy. There was also a small but statistically significant difference in the amount of follow-up time, in which patients receiving adjuvant chemotherapy had greater median follow-up than patients not receiving adjuvant chemotherapy. We did not collect data regarding performance status and comorbidities, and therefore cannot ascertain whether this may account for the overall benefit seen among patients with larger tumors.

Conclusion

Our findings support current guidelines indicating overall survival benefit from adjuvant chemotherapy in node-negative TNBC associated with T1c tumors. We found excellent survival outcomes in T1a/b node-negative patients regardless of whether adjuvant chemotherapy was delivered. Additional research is necessary regarding more precise methods to risk stratify patients with node-negative TNBC and tumors no larger than one centimeter in size.

Author contributions LN and YC designed the study. GF, SB, YC, LV, TC, RS, AS, JM, AM, EA, JN, AB, SF, HA, and MD were involved in the methodology. Data collection and analysis were performed by GF, SB, YC, and LN. The first draft of the manuscript was written by GF, and all authors commented on the previous versions of the manuscript. All authors have read and approved the final submitted manuscript.

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Data availability The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

Code availability Not applicable.

Declarations

Conflict of interest The authors declare that they have no conflict of interest.

Ethical approval Not applicable.

Consent to participate Not applicable.

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