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 regarding 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 in an IRB-approved prospectively-maintained database of TNBC patients treated at two academic institutions in the United States from 1999-2018. Primary tumor size, histology, and nodal status were based upon definitive surgical pathology. Mean follow-up was 5.3 years.

Results: 756 TNBC cases were analyzed; 258 T1N0 TNBC patients were identified. Adjuvant chemotherapy was delivered to 30.5% of T1a, 64.7% T1b, and 83.9% T1c ($p < 0.0001$). Factors associated with delivery of adjuvant chemotherapy were age, histology, high-grade disease, and postoperative adjuvant radiation therapy. At a mean follow-up of 5.3 years, increase in overall survival was associated with use of chemotherapy in patients with T1c disease (93.2% v. 75.2% $p = 0.008$) but not in those with T1a (100% v. 100% $p = 0.3778$) or T1b (100% v. 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 cases of T1a and T1b disease, regardless of whether adjuvant chemotherapy was delivered.

Introduction

Most early stage, node-negative breast cancer patients face an excellent outcome with appropriately-selected locoregional and systemic therapy. Triple negative breast cancer (TNBC) represents a high-risk phenotype associated with a more advanced stage distribution and higher mortality rates compared to non-TNBC, even when detected early. Chemotherapy is the standard 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.

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 [1–3]. In contrast, others have shown that adjuvant chemotherapy is associated with improved outcomes even among cases of sub-centimeter disease [4]. Robust data regarding outcomes for T1bN0 TNBC are sparse, because of challenges with regard to early detection of TNBC.

Adjuvant chemotherapy is included as standard treatment in 2020 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 recommended for T1aN0 disease. 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 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%, and 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).

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 American Joint Committee on Cancer’s *AJCC Cancer Staging Manual*.

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. The primary endpoints were overall survival, local recurrence free survival, distant recurrence-free survival, and recurrence-free survival. The Kaplan-Meier plot and the 5-year survival probability was evaluated. Log rank test was used to assess the survival difference between patients who did and did not receive postoperative adjuvant chemotherapy. Multivariable Cox proportional hazards modelling was performed to jointly model the impact of adjuvant chemotherapy and adjuvant radiotherapy on overall survival. Survival data were censored at 15 years.

Results

Patient Characteristics

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. With regard to the two study sites, the population at HFHS was comprised of more African American patients compared to WCM, reflecting differences in the population demographics of metropolitan Detroit compared to Manhattan. There were also differences between the two sites with regard to histology; however, at both sites the majority of patients had invasive ductal carcinoma. A higher proportion of high-grade disease was seen at WCM than at HFHS (81.31% v. 71.43%; p = 0.048). Additionally, patients at WCM were more likely to undergo contralateral prophylactic mastectomy than at HFHS (19.19% v. 4.76%; p = 0.00357). Among the 282 T1N0 TNBC 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 15.0 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 (n = 282), adjuvant chemotherapy was delivered to 30.5% of T1a, 64.7% T1b, and 83.9% T1c (p < 0.0001). Factors associated with delivery of adjuvant chemotherapy were age ≤ 50 years (84.4% v. 65.5% p = 0.007), histology (p = 0.0337), high-grade disease (75.1% v. 51.0% p = 0.002), and delivery of postoperative adjuvant radiation therapy (RT) (p = 0.00733) (Table 2).

Overall Survival

For all T1N0 TNBC patients, 5-year overall survival was similar for patients both with (95.7%) and without (92.6%) 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 overall survival probability 100% v. 100% p = 0.3778) and T1b (5-year overall survival probability 100% v. 95.8% p = 0.2362) disease. Conversely, adjuvant chemotherapy did improve overall survival for patients with T1c disease (5-year overall survival probability 93.2% v. 75.2% p = 0.008) (Table 3).

Local Recurrence-Free Survival

No significant benefit was observed in local recurrence-free survival for the entire T1N0 TNBC cohort (84.6% with adjuvant chemotherapy v. 85.4% without, p = 0.6269). When stratified by tumor size, a numeric trend was observed favoring an association between adjuvant chemotherapy and improved local recurrence-free survival with increasing tumor size, but the differences were not statistically significant: T1a (81.8% with adjuvant chemotherapy v. 89.5% without), T1b (95.2% with adjuvant chemotherapy v. 87.7% without), and T1c (80.0% with adjuvant chemotherapy v. 69.1% without) (Table 4).

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 v. 89.7% without) or within the smallest-size subgroups: T1a (100% with adjuvant chemotherapy v. 95.5% without), T1b (93.8% with adjuvant chemotherapy v. 91.7% without), and T1c (88.5% with adjuvant chemotherapy v. 74.8% without). 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% versus 74.8%; p = 0.098).

Impact of Adjuvant Radiotherapy (RT) and Adjuvant Chemotherapy on Overall Survival

Table 5 demonstrates the results of multivariable Cox proportional hazards modelling to account for the effect of both adjuvant chemotherapy and adjuvant RT on overall survival. With joint modelling of both adjuvant chemotherapy and adjuvant 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.

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 size tumors.

The high 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) [1–3, 5]. In 2012, Memorial Sloan Kettering reported a series of 194 T1a/b N0 TNBC from 1999–2006 and demonstrated excellent 5-year locoregional and distant control among those that received and those that did not receive adjuvant chemotherapy [3]. 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 CTX was delivered [2].

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 therapy. [1]. In July 2020, An and colleagues published a single-center study of 351 TNBC patients with T1N0 disease, 88% of whom received postoperative 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 [4]. Ren and colleagues reported a 2019 single-institutional study of 354 triple negative T1N0 breast cancer 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 [6]. More recently in 2020, Zhai and colleagues reported on 7739 cases of T1N0 triple negative breast cancer and also found that adjuvant chemotherapy was associated with improved overall survival only in T1c patients [7].

In an effort to address the fact that most individual studies are underpowered to detect possible benefit from adjuvant 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 [8]. 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 [7, 10]. 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 of 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.[12]. These data suggest that RT might confer a survival advantage, perhaps due to abscopal antitumor effects [13]. In our study, to address this difference regarding delivery of RT, additional analyses were performed to account for the possible survival impact. This 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.

Our 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 featuring similar multidisciplinary management teams. Both of these sites 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. Clinical judgement regarding cases associated with higher-risk features (e.g. young age at diagnosis; histologic features consistent with more aggressive disease such as metaplasia) remains important in individualizing treatment plans.

Limitations

There are several limitations inherent to our study, given its retrospective nature and the prolonged time period 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 those reported in several other studies. Regarding the possible effect of RT, 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 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. 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 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.

Declarations

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Conflict of Interest Summary Statement

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

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Tables

Table 1
Characteristics of T1N0 TNBC patients stratified by site (HFHS = Henry Ford Health System and WCM = Weill Cornell Medicine)

		HFHS (n = 84)	WCM (n = 198)	P value
Race	African American	48 (57.1%)	22 (11.1%)	< 0.0001
	White American	36 (42.9%)	140 (70.7%)	
	NA	0 (0%)	36 (18.2%)	
Age 50	≤ 50	14 (16.7%)	54 (27.3%)	0.0798
	> 50	70 (83.3%)	144 (72.7%)	
Histology	IDC	71 (84.5%)	185 (93.43%)	< 0.0001
	IDC/ILC	7 (8.33%)	0 (0%)	
	ILC	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%)	
Any high-grade disease	No	22 (26.1%)	30 (15.15%)	0.048
	Yes	60 (71.4%)	161 (81.31%)	
	Unknown	2 (2.38%)	7 (3.54%)	
Any LVI	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%)	
CPM	No	79 (94.0%)	159 (80.30%)	0.00357
	Yes	4 (4.76%)	38 (19.19%)	
	Unknown	1 (1.19%)	1 (0.50%)	
Adjuvant XRT	Breast	56 (66.7%)	111 (56.06%)	0.917
	Breast/Regional	1 (1.19%)	2 (1.01%)	
	None	26 (30.9%)	53 (26.77%)	

		HFHS (n = 84)	WCM (n = 198)	P value
	PMRT	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%)	98 (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%)	

Table 2

Characteristics of 258 T1N0 TNBC 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
Race	African American	15 (19.5%)	51 (28.2%)	0.155
	White	54 (70.1%)	108 (59.7%)	
	NA	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	IDC	67 (87.01%)	168 (92.82%)	0.0337
	IDC/ILC	3 (3.90%)	4 (2.21%)	
	ILC	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%)	
Any High-Grade 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 LVI	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%)	
CPM	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	Breast	37 (48.05%)	125 (69.06%)	0.00733

		No Adjuvant Chemotherapy (n = 77)	Adjuvant Chemotherapy (n = 181)	P value
	Breast/Regional	2 (2.60%)	1 (0.55%)	
	PMRT	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%)	

Table 3
5-year overall survival probability of T1, T1a, T1b, and T1c node-negative TNBC patients treated with and without adjuvant chemotherapy (CTX)

Stage		5-year survival probability (%)	Hazard Ratio	Number of patients	P value
T1	No adjuvant CTX	92.6	1.0	90	0.07656
	Adjuvant CTX	95.7	0.4 (0.14–1.14)	182	
T1a	No adjuvant CTX	100	1.0	25	0.3778
	Adjuvant CTX	100	7.77e-10 (0.0 – Inf)	11	
T1b	No adjuvant CTX	95.8	1.0	30	0.2362
	Adjuvant CTX	100	0.26 (0.0236–2.87)	55	
T1c	No adjuvant CTX	75.2	1.0	22	0.00768
	Adjuvant CTX	93.2	0.208 (0.0579–0.744)	115	

Table 4
5-year local recurrence-free survival probability of T1, T1a, T1b, and T1c node-negative TNBC patients treated with and without adjuvant chemotherapy (CTX)

Stage		5-year survival probability	Hazard Ratio	Number of patients	P value
T1	No adjuvant CTX	85.4	1.0	90	0.6269
	Adjuvant CTX	84.6	0.844 (0.425–1.68)	182	
T1a	No adjuvant CTX	89.5	1.0	25	0.9856
	Adjuvant CTX	81.8	0.983	11	
T1b	No adjuvant CTX	87.8	1.0	30	0.160
	Adjuvant CTX	95.2	0.358 (0.08–1.6)	55	
T1c	No adjuvant CTX	69.1	1.0	22	0.1506
	Adjuvant CTX	80	0.492 (0.183–1.32)	115	

Table 5
Multivariable Cox proportional hazard modelling of adjuvant chemotherapy (CTX) and adjuvant RT on 5-year overall survival in T1N0 TNBC

Stage		Hazard Ratio	95% Confidence Interval	P value
T1	Adjuvant RT	0.41	0.13–1.2	0.112
	Adjuvant CTX	0.41	0.13–1.2	0.113
T1a	Adjuvant RT	6.4E-10	0.0 - Inf	1
	Adjuvant CTX	1.4E-09	0.0 – Inf	1
T1b	Adjuvant RT	0.23	0.021–2.6	0.234
	Adjuvant CTX	0.25	0.023–2.8	0.257
T1c	Adjuvant RT	0.66	0.164–2.62	0.5512
	Adjuvant CTX	0.21	0.053–0.86	0.0292

Table 6

Adjuvant chemotherapy (CTX) in early-stage triple negative breast cancer outcome studies

Study	Patient Sample	Median Follow-Up	Timeline	Adjuvant CTX Survival Benefit?
Ho (2012)	194 ≤ 1 cm node-negative TNBC T1mic: 16 T1a: 49 T1b: 129 Memorial Sloan Kettering Cancer Center (MSKCC)	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 OS 91–94% in patients without CTX and 96–100% in patients with CTX
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 (n = 7) T1b: No T1c: Yes
Bao (2019)	45 patients with pT1mi,a,b,N0M0 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

Study	Patient Sample	Median Follow-Up	Timeline	Adjuvant CTX Survival Benefit?
Zhai (2020)	7739 patients with T1N0M0 TNBC T1a: 755 T1b: 1979 T1c: 5005 SEER database	45 months	2010–2015	In T1N0, adjuvant CTX associated with significantly better BCSS
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	1998–2018	T1a/b: No T1c: Yes

Figures

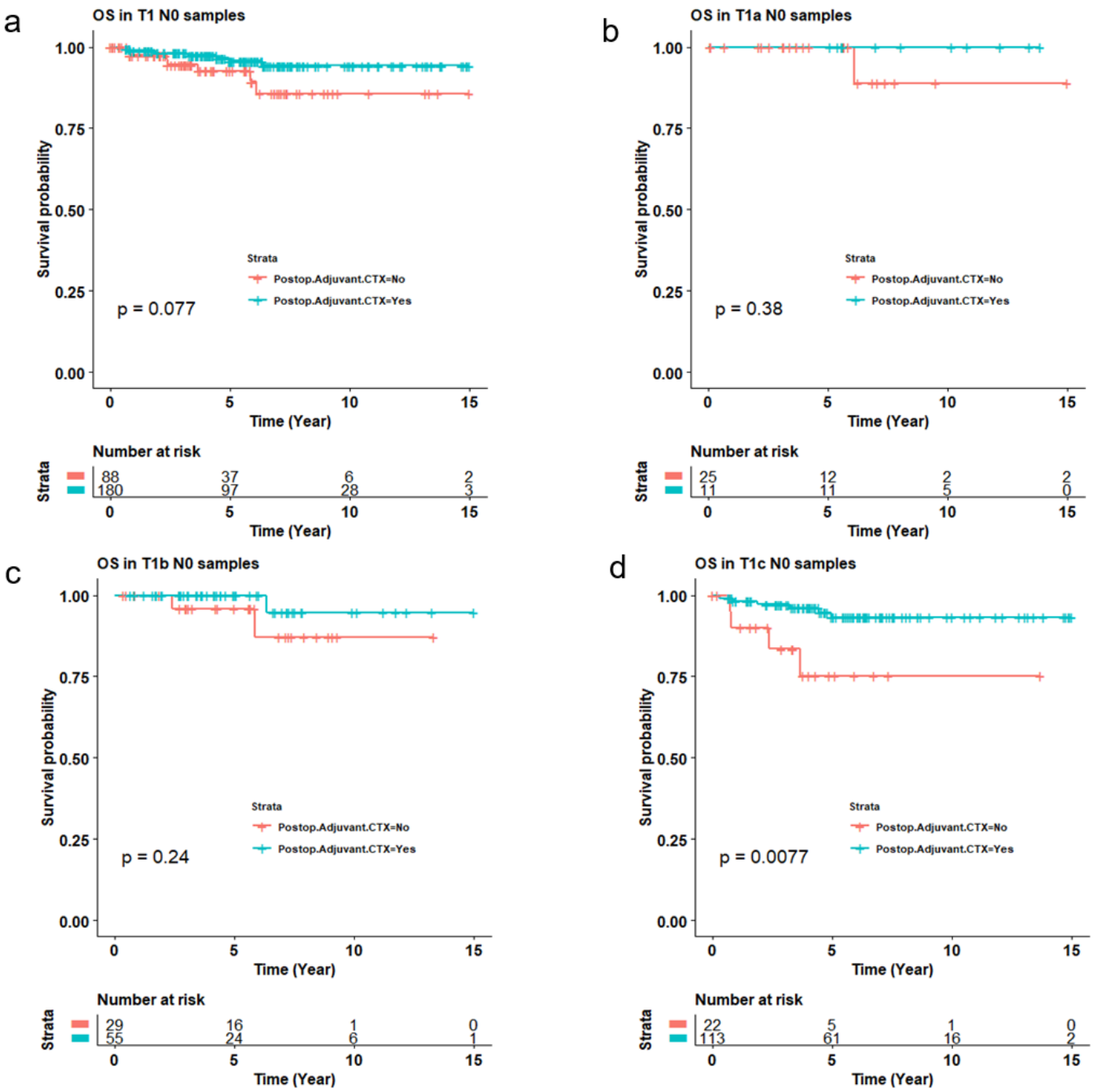

Figure 1

Overall survival of T1N0 TNBC 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).