Peer Review File

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Comment 1: Introduction; TNBC is usually symptomatic and rarely detected asymptomatically by mammographic screening due to the rapid growth pattern, so please comment on this.

Reply 1:

Thank you for your important suggestion. It is really true as you suggested that TNBC has rapid growth characteristics compared with other breast cancer subtypes, and therefore, rarely detected asymptomatically by mammographic screening (Won KA et al., Int J Oncol., 2020). Regarding the small TNBC, data showed that over the past decades, the proportion of detected small breast tumors dramatically increased from 36% to 68% from 1975 to 2012 and small TNBC accounted for about 10%-15% of these small BCs (Welch et al., N Engl J Med, 2016; Theriault RL et al., Clin Breast Cancer, 2011; Gorshein E et al., Clin Breast Cancer, 2014). So, we have added above points in our introduction.

"With the increased awareness of cancer screening and widespread application of mammography screening, an increasing number of small BCs are being detected (5, 6). Although TNBC has relatively rapid growth characteristics compared to other BC subtypes, *it still accounts for approximately 10-15% of patients diagnosed with small BCs (7, 8). Some research showed patients with small BC had a favorable prognosis (6, 9-11)."*

Changes in the text: We have added above points as your suggestion (see page 4 , line 94-96).

Comment 2: Results: Young age would normally be defined as <40 years not <55 years. The age grouping that you have chosen is a surrogate of menopausal status which you have also included in your analysis. Could the analysis be repeated with age <40 given this is a known independent prognostic variable please?

Reply 2:

Thank you for your kind advice. We totally agree with you that setting age <40 years as a group is meaningful. We have modified our age group to <40, 40-55 and >55 years as you advised. Similar with our previous results, age is not a prognostic factor affecting BCFI and OS both in full cohort and PSM cohort. Furthermore, in the new multivariable cox model tumor size is still the only factor affecting the BCFI and OS benefit of adjuvant chemotherapy in T1N0M0 TNBC. Relevant content has been modified in Table1, Table2, Table3, TableS1, TableS2, Figure 4 and also in corresponding text. Modified tables and figure are shown in the text below.

Changes in the text: we have modified our table, figure and text as advised (see page 7, line 161; page 8, line 182-184; page 8, line190-194; Table1; Table2; Table3; TableS1; TableS2; Figure 4).

Table 1. Baseline clinicopathological features of patients.

Characteristics	Full Cohort (N=1113)			Propensity Score Matched (N=441)		
	With Chemotherapy N=928 (%)	Without Chemotherapy N=185 (%)	*P* value	With Chemotherapy N=294 (%)	Without Chemotherapy N=147 (%)	*P* value
Age, years (median, range)	52.0 (23-83)	56.0 (27-85)	**0.004**	55.0 (31-83)	55.0 (27-85)	0.492
< 40	117 (12.6)	14 (7.6)		18 (6.1)	13 (8.8)	
40-55	454 (48.9)	77 (41.6)		142 (48.3)	65 (44.2)	
> 55	357 (38.5)	94 (50.8)		134 (45.6)	69 (47.0)	
Menstruation			**0.005**			
Premenopausal	399 (43.0)	59 (31.9)		96 (32.7)	53 (36.1)	0.477
Postmenopausal	529 (57.0)	126 (68.1)		198 (67.3)	94 (63.9)	
Histology			**<0.001**			
IDC	833 (89.8)	148 (80.0)		254 (86.4)	125 (85.0)	0.698
Non-IDC	95 (10.2)	37 (20.0)		40 (13.6)	22 (15.0)	
Tumor stage			**<0.001**			0.946
T1a-bN0M0	209 (22.5)	88 (47.6)		125 (42.5)	63 (42.9)	
T1cN0M0	719 (77.5)	97 (52.4)		169 (57.5)	84 (57.1)	
Grade			**<0.001**			0.800
I	20 (2.2)	4 (2.2)		7 (2.4)	2 (1.4)	

II	330 (35.6)	59 (31.9)		84 (28.6)	55 (37.4)	
III	464 (50.0)	53 (28.6)		135 (45.9)	49 (33.3)	
NA	114 (12.3)	69 (37.3)		68 (23.1)	41 (27.9)	
Ki67, %			**<0.001**			0.882
< 14	128 (13.8)	71 (38.4)		86 (29.3)	42 (28.6)	
≥ 14	800 (86.2)	114 (61.6)		208 (70.7)	105 (71.4)	
Breast surgery type			0.753			0.277
Lumpectomy	413 (44.5)	80 (43.2)		122 (41.5)	69 (46.9)	
Mastectomy	515 (55.5)	105 (56.8)		172 (58.5)	78 (53.1)	
Adjuvant radiotherapy			0.115			0.485
Yes	358 (38.6)	60 (32.4)		112 (38.1)	51 (34.7)	
No	570 (61.4)	125 (67.6)		182 (61.9)	96 (65.3)	

Abbreviations: IDC, invasive ductal carcinoma; NA, not available.

Table 2 Univariate analysis of prognostic factors affecting BCFI and OS in PSM cohort.

Characteristics	*P* value	
	BCFI	OS
Age (< 40 *vs.*40-55 *vs.* > 55)	0.589	0.293
Menstruation (Pre- *vs.* Post-menopausal)	0.993	0.467
Tumor stage (T1a-b *vs.* T1c)	**0.037**	0.060
Histology (IDC *vs.* Non-IDC)	0.280	0.115
Grade (Ⅰ *vs.* Ⅱ *vs.* Ⅲ)	0.900	0.073
Ki67 (< 14% *vs.* ≥ 14%)	0.418	0.766
Breast surgery type (Lumpectomy *vs.* Mastectomy)	0.457	0.235
Adjuvant chemotherapy (Yes *vs.* No)	0.241	0.509
Adjuvant radiotherapy (Yes *vs.* No)	0.370	0.110

Abbreviations: IDC: invasive ductal carcinoma.

Table 3 Multivariate Cox proportional regression analysis of prognostic factors affecting BCFI and OS in PSM cohort.

	BCFI		OS	
Characteristics	*HR* (95% CI)	*P* value	*HR* (95% CI)	*P* value
Age		0.650		0.771
< 40	1.00 (reference)		1.00 (reference)	
40-55	0.661 (0.188-2.331)	0.520	2490.501 (0-1.280E+51)	0.889
> 55	0.484 (0.102-2.291)	0.360	5266.136 (0-2.755E+51)	0.879
Menstruation		0.447		0.628
Pre-menopausal	1.00 (reference)		1.00 (reference)	
Post-menopausal	1.508 (0.523-4.346)		0.578 (0.063-5.288)	
Tumor stage [a]		**0.025**		0.073
T1a-bN0M0	1.00 (reference)		1.00 (reference)	
T1cN0M0	2.452 (1.120-5.366)		3.479 (0.890-13.606)	
Histology		0.216		0.865
IDC	1.00 (reference)		1.00 (reference)	
Non-IDC	0.413 (0.102-1.678)		0 (0-3.375E+36)	
Grade		0.638		0.335
Ⅰ	1.00 (reference)		1.00 (reference)	
Ⅱ	0.467 (0.056-3.919)	0.483	11575.021 (0-4.832E+127)	0.949

Ⅲ	0.302 (0.032-2.836)	0.295	3093.830 (0-1.301E+127)	0.956
Ki67		0.481		0.816
< 14%	1.00 (reference)		1.00 (reference)	
≥ 14%	1.368 (0.572-3.271)		1.159 (0.334-4.021)	
Breast surgery type		0.072		0.395
Lumpectomy	1.00 (reference)		1.00 (reference)	
Mastectomy	0.640(0.320-1.310)		0.475 (0.086-2.640)	
Adjuvant chemotherapy		0.187		0.521
Yes	1.00 (reference)		1.00 (reference)	
No	1.648 (0.785-3.459)		1.479 (0.447-4.896)	
Adjuvant radiotherapy		0.080		0.083
Yes	1.00 (reference)		1.00 (reference)	
No	1.490 (0.430-2.470)		8.823 (0.753-103.318)	

Abbreviations: HR: hazard ratio; IDC: invasive ductal carcinoma.

Table S1. Univariate analysis of prognostic factors affecting BCFI and OS in full cohort.

Characteristics	*P* value	
	BCFI	OS
Age (< 40 *vs.*40-55 *vs.* > 55)	0.338	0.193
Menstruation (Pre- *vs.* Post-menopausal)	0.148	0.555
Tumor stage (T1a-b *vs.* T1c)	0.102	0.350
Histology (IDC *vs.* Non-IDC)	0.920	0.275
Grade (Ⅰ *vs.* Ⅱ *vs.* Ⅲ)	0.639	0.219
Ki67 (< 14% *vs.* ≥ 14%)	0.964	0.708
Breast surgery type (Lumpectomy *vs.* Mastectomy)	0.581	0.383
Adjuvant chemotherapy (Yes *vs.* No)	**0.026**	0.060
Adjuvant radiotherapy (Yes *vs.* No)	0.536	0.156

Abbreviations: IDC: invasive ductal carcinoma.

Table S2. Multivariate Cox proportional regression analysis of prognostic factors affecting BCFI and OS in full cohort.

	BCFI		OS	
Characteristics	*HR* (95% CI)	*P* value	*HR* (95% CI)	*P* value
Age		0.531		0.273

< 40	1.00 (reference)		1.00 (reference)	
40-55	1.321 (0.584-2.986)	0.504	2.137 (0.252-18.089)	0.486
> 55	0.945 (0.323-2.766)	0.918	6.234 (0.493-78.761)	0.486
Menstruation		0.551		0.279
Pre-menopausal	1.00 (reference)		1.00 (reference)	
Post-menopausal	0.810 (0.405-1.620)		0.428 (0.093-1.985)	
Tumor stage [a]		**0.016**		0.123
T1a-bN0M0	1.00 (reference)		1.00 (reference)	
T1cN0M0	2.311 (1.167-4.578)		2.559 (0.775-8.452)	
Histology		0.185		0.430
IDC	1.00 (reference)		1.00 (reference)	
Non-IDC	0.533 (0.210-1.352)		0.388 (0.037-4.069)	
Grade		0.585		0.837
Ⅰ	1.00 (reference)		1.00 (reference)	
Ⅱ	0.932 (0.123-7.045)	0.946	4520.849 (0-1.237E+76)	0.921
Ⅲ	0.872 (0.114-6.659)	0.895	3799.301 (0-1.041E+76)	0.923
Ki67		0.950		0.793
< 14%	1.00 (reference)		1.00 (reference)	
≥ 14%	1.022 (0.524-1.990)		0.865 (0.294-2.552)	
Breast surgery type		0.141		0.694
Lumpectomy	1.00 (reference)		1.00 (reference)	
Mastectomy	0.563(0.262-1.209)		0.753 (0.183-3.092)	
Adjuvant chemotherapy		**0.011**		**0.023**
Yes	1.00 (reference)		1.00 (reference)	
No	2.336 (1.217-4.484)		3.427 (1.186-9.899)	
Adjuvant radiotherapy		0.147		0.301
Yes	1.00 (reference)		1.00 (reference)	
No	1.812 (0.812-4.042)		2.319 (0.471-11.411)	

Abbreviations: HR: hazard ratio; IDC: invasive ductal carcinoma.

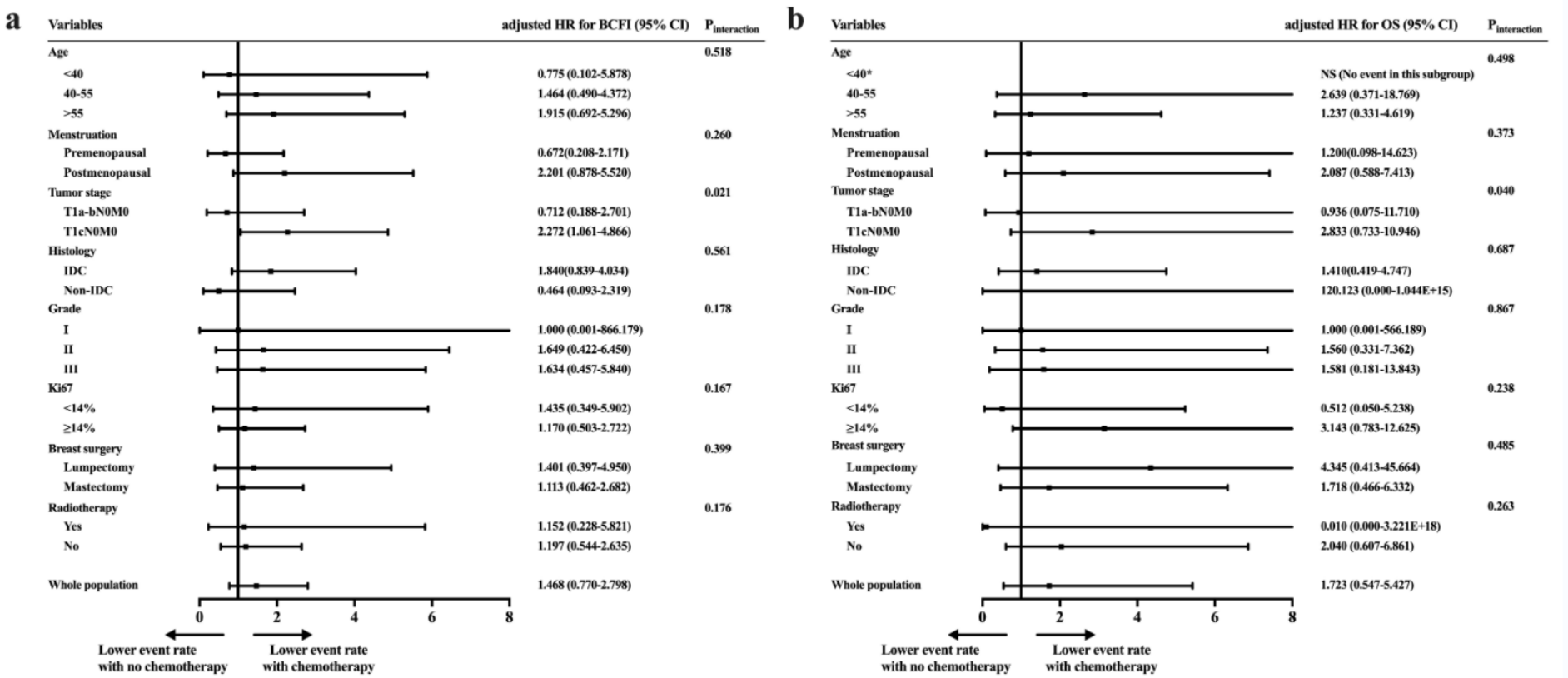

Figure 4. Forest plot of adjusted hazard ratios of breast cancer-free interval (a) and overall survival (b) of PSM cohort comparing chemotherapy and non-chemotherapy groups, stratified by clinical variables. Abbreviations: BCFI: breast cancer-free interval; OS: overall survival; HR: hazard ratio; IDC: invasive ductal carcinoma.

Comment 3: Results line 107; please re-phrase "more IDC tumor" as this doesn't read well.

Reply 3:

Thank you so much for the suggestion. We apologize for the inappropriate expression in our manuscript. **We have re-phrase "more IDC tumor" into "higher IDC tumor proportion" as follow:**

"Compared with untreated patients, patients who received adjuvant chemotherapy displayed unfavorable features, such as young age (<40 years old, 12.6% vs. 7.6%; P=0.004), premenopausal status (43.0% vs. 31.9%, P=0.005), higher IDC tumor proportion (89.8% vs. 80.0%, P<0.001), larger tumor size (T1cN0M0, 77.5% vs. 52.4%, P<0.001), higher tumor grade (grade III, 50.0% vs. 28.6%, P<0.001), and higher Ki67 index (Ki67 ≥ 14%, 86.2% vs. 61.6%, P<0.001)."

Changes in the text: we have modified our text as advised (see page 7, line 162).

Comment 4: Although the numbers are small, please define the BCFI and OS outcomes for T1a and T1b tumours separately and provide KM curves for these sub-groups to confirm no chemo benefit in T1b patients.

Reply 4:

Thank you for your important advice. As you suggest, we divided T1a-b patients into T1a and T1b patients and analyzed the adjuvant chemotherapy benefit in BCFI and OS inT1a and T1b tumours separately. **We found chemotherapy did not improve BCFI in either T1a or T1b patients. Regarding OS, we observed no events in T1a patients and no significant difference between T1b patients with and without chemotherapy. We had added the above point in "Result-3.3. Association between chemotherapy and survival outcomes in PSM cohort" as follow:**

"We further divided T1a-b patients into T1a and T1b groups. Chemotherapy was also not associated with improved BCFI both in T1a (P=0.138) and T1b population (P=0.691) (Figure 3a, b). As for OS, no events existed in T1a population and no significant difference was observed between T1b patients with and without chemotherapy (P=0.503) (Figure 3d, e)."

KM curves has been provided as Figure 3 and relevant content has also been added in corresponding text. Added figure are shown in the text below.

Changes in the text: we have added figure and text as advised (see page 9, line 207-212; Figure 3).

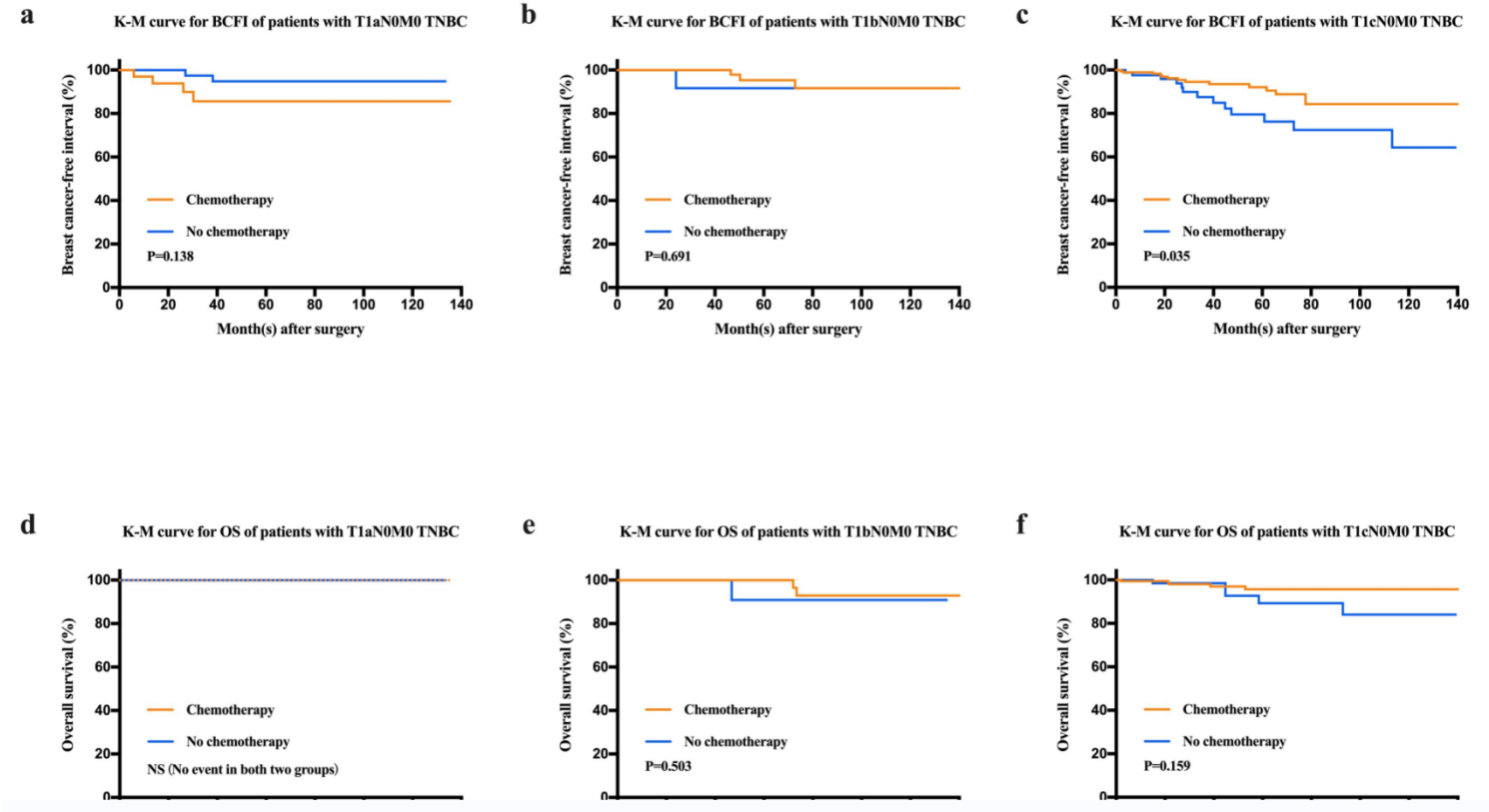

Figure 3. Kaplan-Meier curves of breast cancer-free interval (a, b, c) and overall survival (d, e, f) of the PSM cohort in T1aN0M0 (5-year BCFI: 85.6% vs. 94.8%; no OS events) (a, d), T1bN0M0 (5-year BCFI: 95.4% vs. 91.7%; 5-year OS: 100% vs. 90.9%) (b, e), and T1cN0M0 (5-year BCFI: 92.1% vs. 79.5%; 5-year OS: 95.7% vs. 89.3%) (c, f) patients. Abbreviations: BCFI: breast cancer-free interval; OS: overall survival; K-M: Kaplan-Meier.

Comment 5: Discussion: Your results are reassuringly similar to the larger SEER database study presented at ASCO earlier this month (Tarantino P, abstract 510). However, your reported BCF outcomes are inferior to their patients with and without chemotherapy, despite their longer follow up, especially for the T1c patients. Please add their results to your discussion and cover this point.'

Reply 5:

Thank you so much for your affirmation and suggestion. We have also noticed the study presented by Tarantino P at 2023 ASCO annual meeting. Similar with our result, Tarantino P et al. also found that chemotherapy improved BCSS only in T1c but not in T1a or T1b TNBC patients. **And we have added results of Tarantino P et al. 's study in our discussion.**

*"In addition, we have noticed that our results are similar with the SEER database study presented at ASCO in 2023, which showed that chemotherapy improved BCSS only in T1c but not in T1a or T1b TNBC pa*tients (31)."

Regarding the different survival data between our study and their study you mentioned , one possible explanation is that primary end point of their study is BCSS, presenting BC-specific death events, while our study 's primary end point is BCFI, which presents all BC-related reevents, including both recurrence and death events.

Changes in the text: we have added text as advised (see page 11, line 260-262).

Comment 6: Conclusion; I suggest you amend the second sentence to say that your data do not support the routine use of chemo in patients with T1a/b N0 TNBC in both the abstract and main manuscript.

Reply 6:

Thank you for your kind advice. We totally agree with your suggestion. **We have added the above points both in abstract and main manuscript as you advised.**

Abstract/conclusion

"The survival benefit of adjuvant chemotherapy was significantly associated with tumor size in T1N0M0 TNBC. A benefit of adjuvant chemotherapy was found in T1c, but not in T1a-b patients. Our data do not support the routine use of chemotherapy in patients with T1a-bN0 TNBC"

Main manuscript/conclusion

"Our study demonstrated that tumor size was significantly associated with the survival benefit of adjuvant chemotherapy in T1N0 TNBC patients. Our data do not support the routine use of chemotherapy in patients with T1a-bN0 TNBC, and benefit of adjuvant chemotherapy for T1a-bN0 patients needs further clinical evaluation."

Changes in the text: we have modified text as advised (see page 3, line 59-60; page12, line 298-299).